KEEPING TRAQ WITH PIQRAY CHECKLIST

Monitoring and considerations for cutaneous adverse reactions and hyperglycemia

This checklist does not cover all adverse reactions (ARs) associated with PIQRAY therapy, as there are other serious ARs to consider, including severe hypersensitivity, severe cutaneous adverse reactions (SCARs), pneumonitis, diarrhea or colitis, and embryo-fetal toxicity. The information presented here does not constitute medical advice and is not intended to take the place of your own clinical judgment based on a patient's particular presentation.

Before treatment

- ☐ **Assess fasting plasma glucose (FPG) and hemoglobin A1c (HbA1c), and optimize blood glucose**[1]
  - In SOLAR-1, patients with controlled type 2 diabetes and prediabetes were included if they had an FPG of ≤140 mg/dL (7.7 mmol/L) and HbA1c ≤6.4% (both criteria had to be met)[2]
- ☐ **Assess patient's past medical history**[1]
  - The safety of PIQRAY in patients with type 1 and uncontrolled type 2 diabetes has not been established as these patients were excluded from SOLAR-1. Patients with a medical history of controlled type 2 diabetes were included
  - Patients with a history of diabetes mellitus may require intensified hyperglycemic treatment. Closely monitor patients with diabetes
- ☐ **Consider prophylactic metformin to manage hyperglycemia**
  - 87% of patients (163/187) were managed with antihyperglycemic medication in the SOLAR-1 trial; 76% (142/187) used metformin as a single agent or in combination with other antihyperglycemic medications[1]
  - Consider premedication with metformin prior to the initiation of PIQRAY in combination with fulvestrant based on patient risk factors for hyperglycemia, gastrointestinal tolerability, and clinical situation[1]
  - In METALLICA (N=68), prophylactic use of metformin starting 7 days prior to the initiation of PIQRAY in combination with fulvestrant appeared to decrease the incidence and severity of hyperglycemia events, but increased the incidence and severity of nausea, vomiting, and diarrhea adverse reactions[1]
- ☐ **Consider prescribing a glucometer when starting patients on PIQRAY to begin regular monitoring of fasting glucose at home**
  - Including a glucometer prescription will ensure that your patients can do the required fasting glucose monitoring on a regular basis, with more frequent monitoring for patients with risk factors for hyperglycemia and at your clinical discretion[1]*
- ☐ **Consider prophylaxis with antihistamines prior to onset of rash**
  - Antihistamines administered prior to rash onset may decrease incidence and severity of rash based on a subgroup analysis of patients in the SOLAR-1 trial[1]

*Risk factors include obesity (BMI ≥30), elevated FPG, HbA1c at the upper limit of normal or above, use of concomitant systemic corticosteroids, or age ≥75. In addition to FPG, HbA1c levels should be monitored. Please refer to the PI for recommended monitoring intervals.

	Patients receiving prophylactic treatment prior to onset of rash (n=86)	Overall population (n=284)
All grades rash	27%	54%
Grade 3 rash	12%	20%
Rash leading to permanent discontinuation of PIQRAY	3.5%	4.2%

SOLAR-1 data[1,2]

15 days (range: 5-517 days)

Median time to first occurrence of grade ≥2 (FPG 160-250 mg/dL) **hyperglycemia**

12 days (range: 2-220 days)

Median time to first onset of grade 2 or 3 **rash**

Indication

PIQRAY® (alpelisib) tablets is indicated in combination with fulvestrant for the treatment of adults with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, PIK3CA-mutated, advanced or metastatic breast cancer as detected by an FDA-approved test following progression on or after an endocrine-based regimen.

Important Safety Information

PIQRAY is contraindicated in patients with severe hypersensitivity to it or any of its components.

Please see additional Important Safety Information on pages 2-4. Please click here for full Prescribing Information.

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During treatment with PIQRAY

☐ **Test FPG or fasting blood glucose as recommended[1]**

Monitor more frequently for the first few weeks during treatment in patients with risk factors for hyperglycemia such as obesity (body mass index ≥30), elevated FPG, HbA1c at the upper limit of normal or above, use of concomitant systemic corticosteroids, or age ≥75.

First 2 weeks:
At least 1x per week

After first 2 weeks:
At least once every 4 weeks and as clinically indicated for the duration of treatment

☐ **Test HbA1c[1]**

Once every 3 months and as clinically indicated for the duration of treatment

☐ **Advise patients of the signs and symptoms of hyperglycemia and to contact their health care provider immediately should they occur[1]**

- Excessive thirst, urinating more often than usual or higher amount of urine than usual, or increased appetite with weight loss

☐ **Advise patients of the signs and symptoms of SCARs and to contact their health care provider immediately should they occur[1]**

- A prodrome of fever, flu-like symptoms, mucosal lesions, progressive skin rash, or lymphadenopathy[1]

☐ **Monitor for different forms of rash**

- Rash may present as rash, rash macular, rash generalized, rash papular, rash pruritic, and maculopapular rash (one of the most common)[1,2]

If an AR occurs[1]

☐ **If a SCAR is confirmed, permanently discontinue PIQRAY. Do not reintroduce PIQRAY in patients who have experienced previous SCAR during treatment[1]**

☐ **If hyperglycemia occurs, adjust monitoring schedule**

- Monitor FPG or fasting blood glucose as clinically indicated and **at least 2x per week** until blood glucose or FPG decreases to normal levels[1]

☐ **Based on the severity of the hyperglycemia, PIQRAY may require dose interruption, reduction, or discontinuation[1]**

☐ **During treatment with antihyperglycemic medication, adjust monitoring schedule**

First 8 weeks:
Monitor FPG or fasting blood glucose at least 1x per week

After first 8 weeks:
Monitor FPG or fasting blood glucose every 2 weeks and as clinically indicated

Refer to PIQRAY Prescribing Information and/or Patient Management Brochure for management recommendations and medication used in SOLAR-1 trial.

Your Clinical Educator is available to answer any questions related to adverse reactions and dose modifications. They are dedicated to ensuring you have the right information so that you can optimize your patient's experience.

Important Safety Information (cont)

Severe Hypersensitivity: Severe hypersensitivity reactions, including anaphylaxis and anaphylactic shock, can occur in patients treated with PIQRAY. Severe hypersensitivity reactions were manifested by symptoms, including, but not limited to, dyspnea, flushing, rash, fever, or tachycardia. The incidence of grade 3 and 4 hypersensitivity reactions was 0.7%. Angioedema has been reported in the postmarketing setting in patients treated with PIQRAY. Advise patients of the signs and symptoms of severe hypersensitivity reactions. Permanently discontinue PIQRAY in the event of severe hypersensitivity.

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Severe Cutaneous Adverse Reactions (SCARs): SCARs, including Stevens-Johnson syndrome (SJS), erythema multiforme (EM), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS) can occur in patients treated with PIQRAY. In the SOLAR-1 study, SJS and EM were reported in 0.4% and 1.1% of patients, respectively. DRESS was reported in patients in the postmarketing setting. If signs or symptoms of SCARs occur, interrupt PIQRAY until the etiology of the reaction has been determined. Consultation with a dermatologist is recommended.

If a SCAR is confirmed, permanently discontinue PIQRAY. Do not reintroduce PIQRAY in patients who have experienced previous SCARs during PIQRAY treatment. If a SCAR is not confirmed, PIQRAY may require dose modifications, topical corticosteroids, or oral antihistamine treatment.

Advise patients of the signs and symptoms of SCARs (eg, a prodrome of fever, flu-like symptoms, mucosal lesions, progressive skin rash, or lymphadenopathy).

Hyperglycemia: Severe hyperglycemia, in some cases associated with hyperglycemic hyperosmolar non-ketotic syndrome (HHNKS) or ketoacidosis has occurred in patients treated with PIQRAY. Fatal cases of ketoacidosis have occurred in the postmarketing setting.

Hyperglycemia was reported in 65% of patients treated with PIQRAY. Grade 3 (FPG >250-500 mg/dL) and grade 4 (FPG >500 mg/dL) hyperglycemia was reported in 33% and 3.9% of patients, respectively. Ketoacidosis was reported in 0.7% of patients (n=2) treated with PIQRAY.

Among the patients who experienced Grade ≥ 2 (FPG 160 to 250 mg/dL) hyperglycemia, the median time to first occurrence of hyperglycemia was 15 days (range, 5 to 517 days).

In the 187 patients with hyperglycemia, 87% (163/187) were managed with anti-hyperglycemic medication, and 76% (142/187) reported use of metformin as single agent or in combination with other anti-hyperglycemic medication [ie, insulin, dipeptidyl peptidase-4 (DPP-4) inhibitors, and sulfonylureas]. In patients with Grade ≥ 2 hyperglycemia with at least 1 grade improvement (n = 153), median time to improvement from the first event was 8 days (range, 2 to 65 days).

In all patients with elevated FPG who continued fulvestrant treatment after discontinuing PIQRAY (n = 54), 96% (n = 52) of patients had FPG levels that returned to baseline.

Before initiating treatment with PIQRAY, test fasting plasma glucose (FPG), HbA1c, and optimize blood glucose. After initiating treatment, monitor fasting glucose (FPG or fasting blood glucose) at least once every week for the first 2 weeks, then at least once every 4 weeks, and as clinically indicated. Monitor HbA1c every 3 months and as clinically indicated. Monitor fasting glucose more frequently for the first few weeks during treatment in patients with risk factors for hyperglycemia such as obesity (BMI ≥30), elevated FPG, HbA1c at the upper limit of normal or above, use of concomitant systemic corticosteroids, or age ≥75.

If a patient experiences hyperglycemia after initiating treatment, monitor fasting glucose as clinically indicated, and at least twice weekly until fasting glucose decreases to normal levels. During treatment with anti-hyperglycemic medication, continue monitoring fasting glucose at least once a week for 8 weeks, followed by once every 2 weeks and as clinically indicated. Consider consultation with a health care practitioner with expertise in the treatment of hyperglycemia and counsel patients on lifestyle changes.

The safety of PIQRAY in patients with type 1 and uncontrolled type 2 diabetes has not been established as these patients were excluded from the SOLAR-1 trial. Patients with a medical history of controlled type 2 diabetes were included. Patients with a history of diabetes mellitus may require intensified hyperglycemic treatment. Closely monitor patients with diabetes.

Based on the severity of the hyperglycemia, PIQRAY may require dose interruption, reduction, or discontinuation. In the METALLICA study, prophylactic use of metformin starting 7 days prior to the initiation of PIQRAY demonstrated a decrease in the incidence and severity of hyperglycemia events. Advise patients of the signs and symptoms of hyperglycemia (eg, excessive thirst, urinating more often than usual or higher amount of urine than usual, or increased appetite with weight loss).

Pneumonitis: Severe pneumonitis, including acute interstitial pneumonitis and interstitial lung disease, can occur in patients treated with PIQRAY. Pneumonitis was reported in 1.8% of patients treated with PIQRAY.

In patients who have new or worsening respiratory symptoms or are suspected to have developed pneumonitis, interrupt PIQRAY immediately and evaluate the patient for pneumonitis. Consider a diagnosis of noninfectious pneumonitis in patients presenting with nonspecific respiratory signs and symptoms such as hypoxia, cough, dyspnea, or interstitial infiltrates on radiologic exams and in whom infectious, neoplastic, and other causes have been excluded by means of appropriate investigations.

Permanently discontinue PIQRAY in all patients with confirmed pneumonitis. Advise patients to immediately report new or worsening respiratory symptoms.

Diarrhea or Colitis: Severe diarrhea, resulting in dehydration and in some cases in acute kidney injury, can occur in patients treated with PIQRAY. Most patients (58%) experienced diarrhea during treatment with PIQRAY. Grade 3 diarrhea occurred in 7% (n=19) of patients. Among patients with Grade 2 or 3 diarrhea (n = 71), the median time to onset was 46 days (range, 1 to 442 days). In clinical trials, 63% of patients who experienced diarrhea required antidiarrheal medications (eg, loperamide) to manage symptoms. Dose reductions of PIQRAY were required in 6% of patients, and 2.8% of patients permanently discontinued PIQRAY due to diarrhea. Colitis has been reported in the postmarketing setting in patients treated with PIQRAY. Monitor patients for diarrhea and additional symptoms of colitis, such as abdominal pain and mucus or blood in the stool. Based on the severity of the diarrhea or colitis, PIQRAY may require dose interruption, reduction, or discontinuation. Advise patients to start antidiarrheal treatment, increase oral fluids, and notify their health care provider if diarrhea occurs while taking PIQRAY. For patients with colitis, additional treatment, such as enteric-acting and/or systemic steroids, may be required.

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Important Safety Information (cont)

Embryo-Fetal Toxicity: Based on findings in animals and its mechanism of action, PIQRAY can cause fetal harm when administered to a pregnant woman. Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with PIQRAY and for 1 week after the last dose. Advise male patients with female partners of reproductive potential to use condoms and effective contraception during treatment with PIQRAY and for 1 week after the last dose. Refer to the full Prescribing Information of fulvestrant for pregnancy and contraception information.

The most common adverse reactions (all grades, incidence ≥20%) were diarrhea (58%), rash (52%), nausea (45%), fatigue (42%), decreased appetite (36%), stomatitis (30%), vomiting (27%), weight decreased (27%), and alopecia (20%). The most common grade 3/4 adverse reactions (incidence ≥2%) were rash (20%), diarrhea (7%), fatigue (5%), weight decreased (3.9%), nausea (2.5%), stomatitis (2.5%), and mucosal inflammation (2.1%).

The most common laboratory abnormalities (all grades, incidence ≥20%) were glucose increased (79%), creatinine increased (67%), lymphocyte count decreased (52%), gamma-glutamyl transferase (GGT) increased (52%), alanine aminotransferase (ALT) increased (44%), hemoglobin decreased (42%), lipase increased (42%), calcium decreased (27%), glucose decreased (26%), and activated partial thromboplastin time (aPTT) prolonged (21%). The most common grade 3/4 laboratory abnormalities (incidence ≥5%) were glucose increased (39%), GGT increased (11%), lymphocyte count decreased (8%), lipase increased (7%), and potassium decreased (6%).

Please click here for full Prescribing Information.

References: 1. Piqray. Prescribing information. Novartis Pharmaceuticals Corp. **2.** Data on file. Novartis Pharmaceuticals Corp; 2018.

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