Fyarro™
sirolimus protein-bound particles
for injectable suspension (albumin-bound)

STOMATITIS MANAGEMENT HANDBOOK

Understanding the occurrence of stomatitis with FYARRO and suggested support measures

Indication

FYARRO™ (sirolimus protein-bound particles for injectable suspension) (albumin-bound) is an mTOR inhibitor indicated for the treatment of adult patients with locally advanced unresectable or metastatic malignant perivascular epithelioid cell tumor (PEComa).

Important Safety Information

Contraindication

FYARRO is contraindicated in patients with a history of severe hypersensitivity to sirolimus, other rapamycin derivatives, or albumin.

Warnings and Precautions

Stomatitis

Stomatitis, including mouth ulcers and oral mucositis, occurred in 79% of patients treated with FYARRO, including 18% Grade 3. Stomatitis was most often first reported within 8 weeks of treatment. Based on the severity of the adverse reaction, withhold, resume at reduced dose, or permanently discontinue FYARRO.

Please see additional Important Safety Information on pages 4-7 and full Prescribing Information in pocket.

STOMATITIS FOLLOWING TREATMENT WITH MECHANISTIC TARGET OF RAPAMYCIN (mTOR) INHIBITORS

Stomatitis commonly occurs during treatment with mTOR inhibitors. Stomatitis that occurs in association with the use of mTOR inhibitors usually resembles aphthous stomatitis rather than the mucositis seen with chemotherapy.[1]

Due to their distinct presentation, these ulcers are referred to as mTOR inhibitor–associated stomatitis.[1]

CTCAE SEVERITY GRADING FOR ORAL MUCOSITIS[2]*

SYMPTOMS	GRADE
Asymptomatic or mild symptoms; intervention not indicated	1
Moderate pain or ulcer that does not interfere with oral intake; modified diet indicated	2
Severe pain; interfering with oral intake	3
Life-threatening consequences; urgent intervention indicated	4
Death	5

*Based on the National Cancer Institute CTCAE v5.0; November 27, 2017. Accessed August 19, 2022. Oral mucositis is defined as a disorder characterized by ulceration or inflammation of the oral mucosa.[2]

STOMATITIS WAS THE MOST COMMON ADVERSE REACTION IN AMPECT

The safety and efficacy of FYARRO were studied in AMPECT, the first and only prospective study completed in advanced malignant PEComa.[3]

AMPECT was a multicenter, single-arm, open-label, phase 2 registrational study evaluating FYARRO in 34 patients (safety population).[3]

The adverse reaction term "stomatitis" in AMPECT included stomatitis, aphthous ulcer, mouth ulceration, and esophageal ulcer.

- Occurred in **27 patients (79%)**
- **Six (18%)** of the patients experienced **Grade 3** events
- Most commonly reported **within 8 weeks of treatment**

No Grade 4 adverse reactions were reported in the AMPECT trial after treatment with FYARRO. Stomatitis led to dose interruptions and dose reductions in 6 (18%) and 3 (9%) patients, respectively.

AMPECT=Advanced Malignant PEComa Trial; CTCAE=Common Terminology Criteria for Adverse Events; PEComa=perivascular epithelioid cell tumor.

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DOSE REDUCTIONS AND DOSAGE MODIFICATIONS MAY BE USED FOR ADVERSE REACTIONS INCLUDING STOMATITIS

RECOMMENDED FYARRO DOSAGE MODIFICATIONS FOR STOMATITIS

STOMATITIS SEVERITY	DOSAGE MODIFICATIONS
Grade 2 or 3	• Withhold FYARRO until Grade ≤1 • Restart at the same dose for first occurrence • If recurs, restart at reduced dose level
Grade 4	• Permanently discontinue FYARRO

RECOMMENDED DOSE REDUCTIONS OF FYARRO FOR ADVERSE REACTIONS

DOSE REDUCTION	DOSE
First dose reduction	**75 mg/m² (25% reduction from 100 mg/m²)**
Second dose reduction	**56 mg/m² (25% reduction from 75 mg/m²)**
Third dose reduction†	**45 mg/m² (20% reduction from 56 mg/m²)**

†**Permanently discontinue FYARRO in patients who are unable to tolerate FYARRO after 3 dose reductions.**

In AMPECT, most dose reductions (12/16) occurred within the first 3 months of treatment.[4]

Based on the severity of the adverse reaction, withhold, resume at a reduced dose, or permanently discontinue FYARRO.

CONCOMITANT TREATMENTS FOR TREATING STOMATITIS IN AMPECT

Full supportive care, including prescribing any concomitant medications or treatments, was determined by the study investigators as deemed appropriate in accordance with their institutional guidelines.[5]

Stomatitis was most commonly managed with steroid mouthwash, and 59% of all patients received stomatological preparations for local oral treatment, including[4]:

- **Magic mouthwash**
- **Sucralfate**
- **Nystatin**
- **Dexamethasone**

36% of mucositis events resolved without intervention, and the majority of stomatitis events (64%) were successfully managed with drug interruptions and/or concomitant medications.[4]

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Myelosuppression

FYARRO can cause myelosuppression including anemia, thrombocytopenia and neutropenia. Anemia occurred in 68% of patients; 6% were Grade 3. Thrombocytopenia and neutropenia occurred in 35% of patients each. Obtain blood counts at baseline and every 2 months for the first year of treatment and every 3 months thereafter, or more frequently if clinically indicated. Based on the severity of the adverse reaction, withhold, resume at reduced dose, or permanently discontinue FYARRO.

Infections

FYARRO can cause infections. Infections such as urinary tract infections (UTI), upper respiratory tract infections and sinusitis occurred in 59% of patients. Grade 3 infections occurred in 12% of patients, including a single case each of a UTI, pneumonia, skin, and abdominal infections. Monitor patients for infections, including opportunistic infections. Based on the severity of the adverse reaction, withhold, resume at reduced dose, or permanently discontinue FYARRO.

Hypokalemia

FYARRO can cause hypokalemia. Hypokalemia occurred in 44% of patients including 12% Grade 3 events. Monitor potassium levels prior to starting FYARRO and implement potassium supplementation as medically indicated. Based on the severity of the adverse reaction, withhold, resume at reduced dose, or permanently discontinue FYARRO.

Hyperglycemia

FYARRO can cause hyperglycemia. Hyperglycemia occurred in 12% of patients treated with FYARRO, all of which were Grade 3 events. Monitor fasting serum glucose prior to starting FYARRO. During treatment, monitor serum glucose every 3 months in non-diabetic patients, or as clinically indicated. Monitor serum glucose more frequently in diabetic patients. Based on the severity of the adverse reaction, withhold, resume at reduced dose, or permanently discontinue FYARRO.

Interstitial Lung Disease / Non-Infectious Pneumonitis

FYARRO can cause interstitial lung disease (ILD) / non-infectious pneumonitis. ILD / non-infectious pneumonitis occurred in 18% of patients treated with FYARRO, of which all were Grades 1 and 2. Based on the severity of the adverse reaction, withhold, reduce the dose, or permanently discontinue FYARRO.

Hemorrhage

FYARRO can cause serious and sometimes fatal hemorrhage. Hemorrhage occurred in 24% of patients treated with FYARRO, including Grade 3 and Grade 5 events in 2.9% of patients each. Monitor patients for signs and symptoms of hemorrhage. Based on the severity of adverse reaction, withhold, resume at reduced dose, or permanently discontinue FYARRO.

Hypersensitivity Reactions

FYARRO can cause hypersensitivity reactions. Hypersensitivity reactions, including anaphylaxis, angioedema, exfoliative dermatitis, and hypersensitivity vasculitis have been observed with administration of the oral formulation of sirolimus. Hypersensitivity reactions including anaphylaxis have been observed with human albumin administration. Monitor patients closely for signs and symptoms of infusion reactions during and following each FYARRO infusion in a setting where cardiopulmonary resuscitation medication and equipment are available. Monitor patients for at least 2 hours after the first infusion and as clinically needed for each subsequent infusion. Reduce the rate, interrupt infusion, or permanently discontinue FYARRO based on severity and institute appropriate medical management as needed.

Embryo-Fetal Toxicity

Based on animal studies and the mechanism of action, FYARRO can cause fetal harm when administered to a pregnant woman. In animal studies, mTOR inhibitors caused embryo-fetal toxicity when administered during the period of organogenesis at maternal exposures that were equal to or less than human exposures at the recommended lowest starting dose. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to avoid becoming pregnant and to use effective contraception while using FYARRO and for 12 weeks after the last dose.

Male Infertility

Azoospermia or oligospermia may be observed in patients treated with FYARRO. FYARRO is an anti-proliferative drug and affects rapidly dividing cells such as germ cells.

Immunizations and Risks Associated with Live Vaccines

No studies in conjunction with immunization have been conducted with FYARRO. Immunization during FYARRO treatment may be ineffective. Update immunizations according to immunization guidelines prior to initiating FYARRO, if possible. Immunization with live vaccines is not recommended during treatment and avoid close contact with those who have received live vaccines while on FYARRO. The interval between live vaccinations and initiation of FYARRO should be in accordance with current vaccination guidelines for patients on immunosuppressive therapies.

Risk of Transmission of Infectious Agents with Human Albumin

FYARRO contains human albumin, a derivative of human blood. Human albumin carries only a remote risk of transmission of viral diseases because of effective donor screening and product manufacturing processes. A theoretical risk for transmission of Creutzfeldt-Jakob Disease (CJD) also is considered extremely remote. No cases of transmission of viral diseases or CJD have ever been associated with albumin.

Adverse Reactions

Adverse Reactions in PEComa

The most common adverse reactions (≥30%) were stomatitis in 27 (79%) patients; fatigue and rash in 23 (68%) patients each; infection in 20 (59%) patients; nausea and edema in 17 (50%) patients each; diarrhea, musculoskeletal pain and decreased weight in 16 (47%) patients each; decreased appetite in 15 (44%) patients; cough in 12 (35%) patients; and vomiting and dysgeusia in 11 (32%) patients each.

Laboratory Abnormalities in PEComa

The most common Grade 3 to 4 laboratory abnormalities (≥6%) were decreased lymphocytes in 7 (21%) patients; increased glucose and decreased potassium in 4 (12%) patients each; decreased phosphate in 3 (9%) patients; and decreased hemoglobin and increased lipase in 2 (6%) patients each.

Dosage Interruptions

Dose interruptions of FYARRO due to an adverse reaction occurred in 22 (65%) patients. Adverse reactions which required dosage interruption in >5% of patients included stomatitis in 6 (18%) patients, pneumonitis in 5 (15%) patients, anemia in 3 (9%) patients, and dehydration, dermatitis acneiform, and thrombocytopenia in 2 (6%) patients each.

Dose Reduction

Dose reductions of FYARRO due to an adverse reaction occurred in 12 (35%) patients. Adverse reactions which required dose reductions in >5% of patients included stomatitis and pneumonitis in 3 (9%) patients each.

Drug Interactions

Reduce the dosage of FYARRO to 56 mg/m^2 when used concomitantly with a moderate or weak cytochrome P-450 3A4 (CYP3A4) inhibitor. Avoid concomitant use with drugs that are strong CYP3A4 and/or P-glycoprotein (P-gp) inhibitors and inducers and with grapefruit and grapefruit juice.

Use in Specific Populations

Pregnancy

Based on the mechanism of action and findings in animals, FYARRO can cause fetal harm when administered to a pregnant woman. Advise females of the potential risk to a fetus and to avoid becoming pregnant while receiving FYARRO.

Lactation

Sirolimus is present in the milk of lactating rats. There is potential for serious adverse effects from sirolimus in breastfed infants based on mechanism of action. Because of the potential for serious adverse reactions in breastfed infants from FYARRO, advise women not to breastfeed during treatment with FYARRO and for 2 weeks after the last dose.

Females and Males of Reproductive Potential

FYARRO can cause fetal harm when administered to a pregnant woman. Verify the pregnancy status of females of reproductive potential prior to starting treatment with FYARRO. Advise females of reproductive potential to use effective contraception and avoid becoming pregnant during treatment with and for at least twelve weeks after the last dose of FYARRO. Advise males with female partners of reproductive potential to use effective contraception and avoid fathering a child during treatment with FYARRO and for at least twelve weeks after the last dose of FYARRO. Although there are no data on the impact of FYARRO on fertility, based on available clinical findings with oral formulation of sirolimus and findings in animals, male and female fertility may be compromised by the treatment with FYARRO.

Pediatric Use

The safety and effectiveness of FYARRO in pediatric patients have not been established.

Geriatric Use

Of the 34 patients treated with FYARRO, 44% were 65 years of age and older, and 6% were 75 years of age and older. Clinical studies of FYARRO did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients.

Hepatic Impairment

FYARRO is not recommended for use in patients with severe hepatic impairment. Reduce FYARRO dosage in patients with mild or moderate hepatic impairment.

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ADDITIONAL RECOMMENDATIONS FOR PREVENTING OR MINIMIZING STOMATITIS

When treating a patient with FYARRO, the following steps may reduce the risk of developing, or the severity of, stomatitis:

RISK ASSESSMENT[6]

- Prophylactic, comprehensive oral examination before treatment initiation
- Determining an individual patient's risk for stomatitis/oral mucositis

ORAL HYGIENE[1,6,7]

- Regular brushing and flossing/dental examinations
- Mild toothpaste (avoid toothpastes containing sodium lauryl sulfate or strong flavors)
- Using a soft-bristled toothbrush
- Cleanse mouth with baking soda rinses

DIET[1,6,8]

- Avoid spicy/acidic foods/drinks
- Avoid hard/crunchy/crusty foods that could damage oral mucosa
- Eat and drink moderate-temperature food/drinks

EDUCATION[6]

- Advise patients of the risk of stomatitis with FYARRO
- Discuss likely signs and symptoms
- Instruct patients to contact HCP at first sign of mouth discomfort

Prepare your patients to help mitigate the risk and severity of stomatitis with FYARRO.

References 1. Pilotte AP, Hohos MB, Polson KMO, Huftalen TM, Treister N. Managing stomatitis in patients treated with mammalian target of rapamycin inhibitors. *Clin J Oncol Nurs*. 2011;15(5):E83-E89. doi:10.1188/11.CJON.E83-E89 **2.** Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. US Department of Health and Human Services. Published November 27, 2017. Accessed September 1, 2022. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf **3.** Wagner AJ, Ravi V, Riedel RF, et al. *nab*-Sirolimus for patients with malignant perivascular epithelioid cell tumors. *J Clin Oncol*. 2021;39(33):3660-3670. doi:10.1200/JCO.21.01728 **4.** Ganjoo KN, Dickson MAA, Ravi V, Riedel R, et al. Management of adverse events in the AMPECT trial of *nab*-sirolimus for the treatment of advanced malignant PEComa. Abstract presented at: CTOS Annual Meeting; September 9, 2022. **5.** AADi, LLC. A phase 2 multi-center investigation of efficacy of ABI-009 (*nab*-rapamycin) in patients with advanced malignant perivascular epithelioid cell tumors (PEComa). Protocol: PEC-001; 2015. [Supplementary Protocol for: Wagner AJ, Ravi V, Riedel RF, et al. *nab*-Sirolimus for patients with malignant perivascular epithelioid cell tumors. *J Clin Oncol*. 2021;39(33):3660-3670.] 2015. **6.** Brown TJ, Gupta A. Management of cancer-therapy associated oral mucositis. *JCO Oncol Pract*. 2020;16(3):103-109. doi:10.1200/JOP.19.00652 **7.** Kasi SR, Özcan M, Feilzer AJ. Side effects of sodium lauryl sulfate applied in toothpastes: a scoping review. *Am J Dent*. 2022;35(2):84-88. **8.** Stomatitis: types, causes, and treatments. WebMD. Accessed September 1, 2022. https://www.webmd.com/oral-health/guide/stomatitis-causes-treatment#1

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AADi bioscience

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Dose interruptions of FYARRO due to an adverse reaction occurred in 22 (65%) patients. Adverse reactions which required dosage interruption in >5% of patients included stomatitis in 6 (18%) patients, pneumonitis in 5 (15%) patients, anemia in 3 (9%) patients, and dehydration, dermatitis acneiform, and thrombocytopenia in 2 (6%) patients each.

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Lactation

Sirolimus is present in the milk of lactating rats. There is potential for serious adverse effects from sirolimus in breastfed infants based on mechanism of action. Because of the potential for serious adverse reactions in breastfed infants from FYARRO, advise women not to breastfeed during treatment with FYARRO and for 2 weeks after the last dose.

Females and Males of Reproductive Potential

FYARRO can cause fetal harm when administered to a pregnant woman. Verify the pregnancy status of females of reproductive potential prior to starting treatment with FYARRO. Advise females of reproductive potential to use effective contraception and avoid becoming pregnant during treatment with and for at least twelve weeks after the last dose of FYARRO. Advise males with female partners of reproductive potential to use effective contraception and avoid fathering a child during treatment with FYARRO and for at least twelve weeks after the last dose of FYARRO. Although there are no data on the impact of FYARRO on fertility, based on available clinical findings with oral formulation of sirolimus and findings in animals, male and female fertility may be compromised by the treatment with FYARRO.

Pediatric Use

The safety and effectiveness of FYARRO in pediatric patients have not been established.

Geriatric Use

Of the 34 patients treated with FYARRO, 44% were 65 years of age and older, and 6% were 75 years of age and older. Clinical studies of FYARRO did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients.

Hepatic Impairment

FYARRO is not recommended for use in patients with severe hepatic impairment. Reduce FYARRO dosage in patients with mild or moderate hepatic impairment.

Please see full Prescribing Information.