CLINICAL UPDATE

Brand Name	Fyarro™
Generic Name	sirolimus albumin bound nanoparticles
Drug Manufacturer	Aadi Bioscience, Inc

Clinical Update

TYPE OF CLINICAL UPDATE

New Formulation

FDA APPROVAL DATE

November 22, 2021

LAUNCH DATE

1st quarter 2022

REVIEW DESIGNATION

Type 5 - New Formulation or New Manufacturer; New Drug Application (NDA): 213312

TYPE OF REVIEW

Priority; Orphan

DISPENSING RESTRICTIONS

N/A

Overview

INDICATION(S) FOR USE

Fyarro™ is an mTOR inhibitor indicated for the treatment of adult patients with locally advanced unresectable or metastatic malignant perivascular epithelioid cell tumor (PEComa).

MECHANISMS OF ACTION

Sirolimus in Fyarro™ is an inhibitor of mechanistic target of rapamycin kinase (mTOR, previously known as mammalian target of rapamycin). mTOR, a serine threonine kinase, is downstream of the PI3K/AKT pathway, controls key cellular processes such as cell survival, growth, and proliferation, and is commonly dysregulated in several human cancers. In cells, sirolimus binds to the immunophilin, FK Binding Protein-12 (FKBP-12), to generate an immunosuppressive complex. The sirolimus-FKBP-12 complex binds to and inhibits activation of the mechanistic target of rapamycin complex 1 (mTORC1). Inhibition of mTOR by sirolimus has been shown to reduce cell proliferation, angiogenesis, and glucose uptake in in vitro and in vivo studies. In a nonclinical study in athymic mice bearing human tumor xenografts, intravenous administration of Fyarro™ resulted in higher tumor accumulation of sirolimus, inhibition of an mTOR target in the tumor, and tumor growth inhibition compared to administration of an oral formulation of sirolimus at the same weekly total dose.

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DOSAGE FORM(S) AND STRENGTH(S)

For injectable suspension: lyophilized powder containing 100 mg of sirolimus formulated as albumin-bound particles in single-dose vial for reconstitution.

DOSE & ADMINISTRATION

The recommended dosage of Fyarro™ is 100 mg/m2 administered as an IV infusion over 30 minutes on Days 1 and 8 of each 21-day cycle until disease progression or unacceptable toxicity.

EFFICACY

Perivascular Epithelioid Cell Tumor (PEComa) The efficacy of Fyarro™ was assessed in AMPECT (NCT02494570), a multicenter, single-arm clinical trial in 31 patients with locally advanced unresectable or metastatic malignant PEComa. Patients were required to have measurable disease at baseline, centrally confirmed diagnosis by pathology of malignant PEComa, and Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0 or 1. Patients with lymphangioleiomyomatosis and prior treatment with a mechanistic target of rapamycin (mTOR) inhibitor were excluded. Patients received Fyarro™ at a dose of 100 mg/m2 on Days 1 and 8 of 21-day cycles until disease progression or unacceptable toxicity. The efficacy population of 31 patients had the following demographic characteristics: median age 60 years (range 34 to 78), female (81%), White (74%), Black (10%), and ECOG PS of 0 (81%). Five (16%) patients had locally advanced disease and 26 (84%) had metastatic disease. Ninety-four percent of patients had prior surgery,19% had prior radiation therapy, and 13% had prior systemic therapy.

The major efficacy outcome measures were overall response rate (ORR) and duration of response (DOR) as assessed by blinded independent central review (BICR) using RECIST v.1.1.

Efficacy Results in AMPECT

Efficacy Endpoints	**FYARRO (N=31)**
Overall Response Rate (95% CI)*	39% (22%, 58%)
Duration of Response (DOR)	**(N=12)**
Median (95% CI) in months	NR (6.5, NE)
Range in months	5.6, 55.5+
% with duration ≥6 months	92%
% with duration ≥12 months	67%
% with duration ≥24 months	58%

* All responses were initially partial responses. Two patients with partial response converted to complete response during the follow up-period.
+ Denotes ongoing responses
CI = Confidence Interval; NR = Not Reached; NE = Not Estimable

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