ojemda™
(tovorafenib)
100 mg tablets
25 mg/mL for oral suspension

The first and only type II RAF inhibitor for BRAF alterations in relapsed or refractory pediatric low-grade glioma (R/R pLGG)[1]

Updated Data on Effect on Growth from FIREFLY-1

INDICATION

OJEMDA™ (tovorafenib) is indicated for the treatment of patients 6 months of age and older with relapsed or refractory pediatric low-grade glioma (LGG) harboring a BRAF fusion or rearrangement, or BRAF V600 mutation.

This indication is approved under accelerated approval based on response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

IMPORTANT SAFETY INFORMATION

Warnings and Precautions

Hemorrhage

Hemorrhage, including major hemorrhage defined as symptomatic bleeding in a critical area or organ, can occur with OJEMDA. Advise patients and caregivers of the risk of hemorrhage during treatment with OJEMDA. Monitor for signs and symptoms of hemorrhage and evaluate as clinically indicated. Withhold and resume at reduced dose upon improvement, or permanently discontinue based on severity.

Please see full Prescribing Information and full Important Safety Information throughout.

Tovorafenib is a type II RAF inhibitor that inhibits BRAF and CRAF[1]

Based on preclinical data, CRAF plays an essential role in chondrocyte maturation, a required step in linear bone growth.[2-4]

Growth velocity changes were observed in patients taking OJEMDA[1,5]

Primary analysis, as of June 5, 2023 data cutoff

15% (n=20/133)

of patients ≤18 years reported a decrease in growth velocity

Updated analysis, as of May 10, 2024 data cutoff*

46% (n=61/133)

of patients ≤18 years reported a decrease in growth velocity

No evidence of premature growth plate closure or bone age advancement[1,5]

In the primary analysis, 19 patients who experienced reductions in growth velocity had hand radiographs to assess bone age. In the updated analysis, 35 patients who experienced reductions in growth velocity had hand radiographs to assess bone age. In both analyses, there was no evidence of premature closure of the epiphyseal growth plates or advancement of bone age.

Growth-related discontinuation rates[1,5]

	Discontinuations
Primary analysis, as of June 5, 2023 data cutoff	2% (n=2/133)
Updated analysis, as of May 10, 2024 data cutoff	3% (n=4/133)

*The OJEMDA Prescribing Information includes data up to the primary June 2023 cutoff date. Updated analysis data is not currently included in the Prescribing Information.

BRAF=v-Raf murine sarcoma viral oncogene homolog B1; CRAF=rapidly accelerated fibrosarcoma; RAF=rapidly accelerated fibrosarcoma.

IMPORTANT SAFETY INFORMATION (cont'd)

Warnings and Precautions (cont'd)

Skin Toxicity Including Photosensitivity

OJEMDA can cause rash, including maculopapular rash and photosensitivity. Monitor for new or worsening skin reactions. Consider dermatologic consultation and initiate supportive care as clinically indicated. Withhold, reduce the dose, or permanently discontinue OJEMDA based on severity of adverse reaction.

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Tovorafenib is a type II RAF inhibitor that inhibits BRAF and CRAF[1] (cont'd)

Post hoc subgroup analysis, as of May 10, 2024 data cutoff

Decrease in growth velocity was observed to be a reversible event[5]

Growth velocity started to show recovery 3-6 months after stopping treatment

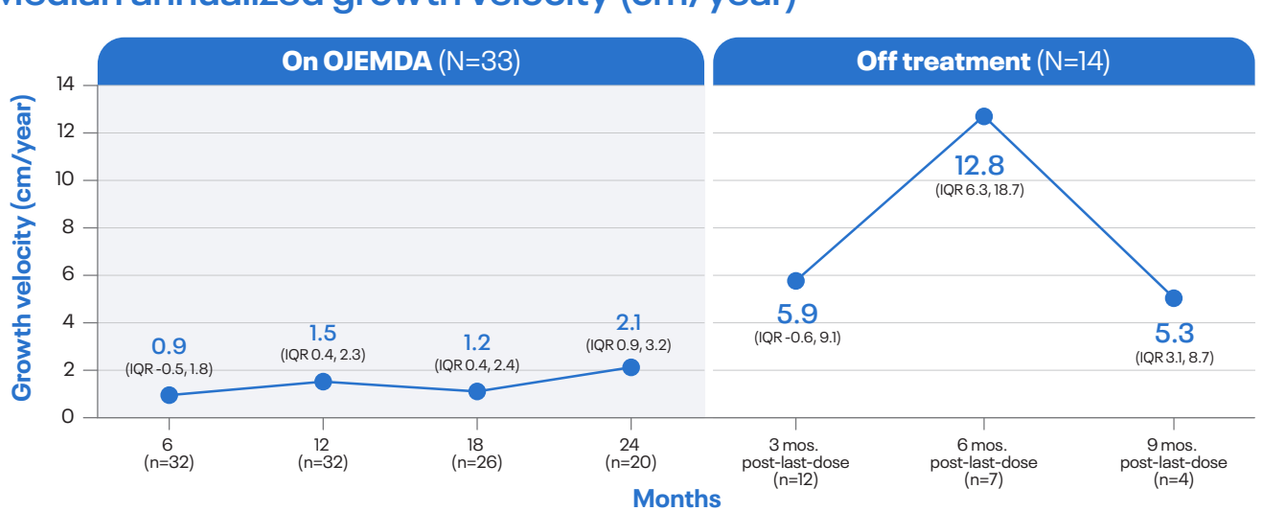
Of the 61/133 patients who reported decreased growth velocity as an adverse event, 33 either went off treatment or had a prolonged dose hold of three or more cycles and had at least one on-treatment height measurement at 6 months or later.

Among these 33 patients:

- 14 patients had at least one off-treatment height measurement taken at a minimum of 3 months after their last dose
- The remaining 19 patients either had not yet reached the 3-month post-treatment mark or lacked available post-treatment height measurements, rendering them ineligible for annualized growth velocity (AGV) recovery assessment at the time of the data cutoff
- 11 out of 14 patients had recovery in growth velocity*

*Recovery in growth velocity is defined as at least one AGV measurement taken while off therapy that is greater than the AGV measurement taken at the end of therapy.

Median annualized growth velocity (cm/year)[5]



Not every patient had height measurements documented at each time point.

Growth velocity data will become more robust as more patients go off treatment long enough to have had height assessments. Long-term follow-up is ongoing for patients continuing therapy or on drug holiday.

At the time of data cutoff, most patients (11/14) showed recovery in growth velocity including signs of catch-up growth[5]

Catch-up growth is characterized by a height velocity (rate of growth) that is above normal for age, occurring after a period when a child's growth was slower than expected.[6]

BRAF=v-Raf murine sarcoma viral oncogene homolog B1;
CRAF=rapidly accelerated fibrosarcoma; IQR=Interquartile range;
RAF=rapidly accelerated fibrosarcoma.

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IMPORTANT SAFETY INFORMATION (cont'd)

Warnings and Precautions (cont'd)

Skin Toxicity Including Photosensitivity

Photosensitivity

Advise patients to use precautionary measures against ultraviolet exposure such as use of sunscreen, sunglasses, and/or protective clothing during treatment with OJEMDA. Withhold, reduce the dose, or permanently discontinue OJEMDA based on severity of adverse reaction.

Hepatotoxicity

OJEMDA can cause hepatotoxicity. Monitor liver function tests, including ALT, AST and bilirubin, before initiation of OJEMDA, one month after initiation and then every three months thereafter and as clinically indicated. Withhold and resume at the same or reduced dose upon improvement, or permanently discontinue OJEMDA based on the severity.

Effect on Growth

OJEMDA can cause reductions in growth velocity. Growth velocity recovered after interruption of treatment with OJEMDA. Routinely monitor patient growth during treatment with OJEMDA.

Embryo-Fetal Toxicity

Based on findings from animal studies and its mechanism of action, OJEMDA may 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 nonhormonal contraception during treatment with OJEMDA and for 28 days after the last dose, since OJEMDA can render some hormonal contraceptives ineffective. Advise male patients with female partners of reproductive potential to use effective nonhormonal contraception during treatment with OJEMDA and for 2 weeks after the last dose.

NF1 Associated Tumors

Based on nonclinical data in NF1 models without BRAF alterations, tovorafenib may promote tumor growth in patients with NF1 tumors. Confirm evidence of a BRAF alteration prior to initiation of treatment with OJEMDA.

Adverse Reactions

The most common adverse reactions (≥30%) were rash, hair color changes, fatigue, viral infection, vomiting, headache, hemorrhage, pyrexia, dry skin, constipation, nausea, dermatitis acneiform, and upper respiratory tract infection.

Please see full Prescribing Information.

References: 1. OJEMDA™ [Package Insert]. Brisbane, CA; Day One Biopharmaceuticals, Inc.; 2024. **2.** Liu ES, Raimann A, Chae BT, Martins JS, Baccarini M, Demay MB. c-Raf promotes angiogenesis during normal growth plate maturation. *Development*. 2016;143(2):348-355. doi:10.1242/dev.127142 **3.** Provot S, Nachtrab G, Paruch J, Chen AP, Silva A, Kronenberg HM. A-raf and B-raf are dispensable for normal endochondral bone development, and parathyroid hormone-related peptide suppresses extracellular signal-regulated kinase activation in hypertrophic chondrocytes. *Mol Cell Biol*. 2008;28(1):344-357. doi:10.1128/MCB.00617-07 **4.** Papaioannou G, Petit ET, Liu ES, Baccarini M, Pritchard C, Demay MB. Raf kinases are essential for phosphate induction of ERK1/2 phosphorylation in hypertrophic chondrocytes and normal endochondral bone development. *J Biol Chem*. 2017;292(8):3164-3171. doi:10.1074/jbc.M116.763342 **5.** Data on file. Day One Biopharmaceuticals, Inc. **6.** Wit JM, Boersma B. Catch-up growth: definition, mechanisms, and models. *J Pediatr Endocrinol Metab*. 2002; 15(Suppl 5):1229-1241.

Day One BIOPHARMACEUTICALS

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