Koselugo® (selumetinib) – New orphan drug approval

- On April 10, 2020, the FDA announced the approval of AstraZeneca and Merck's Koselugo (selumetinib), for the treatment of pediatric patients, 2 years of age and older, with neurofibromatosis type 1 (NF1) who have symptomatic, inoperable plexiform neurofibromas (PN).

- NF1 is a rare, genetic disease characterized by skin pigmentation, neurologic and skeletal impairments, and an increased risk for development of other cancers. Symptoms begin during early childhood and appear in an estimated 1 out of 3,000 infants.

    — Approximately 30% to 50% of NF1 patients develop PNs, which are tumors that develop on the nerve sheaths that can lead to pain, motor dysfunction, airway dysfunction, bowel/bladder dysfunction, and disfigurement. These tumors also have the potential to transform into malignant peripheral sheath tumors.

- Koselugo is the first FDA-approved drug indicated for the treatment of patients with NF1 and inoperable PN. Koselugo is a MEK1/2 inhibitor, which blocks the MEK enzymes in the RAS/MAPK pathway, a cell-signaling pathway associated with tumor cell growth and proliferation in several cancers.

- The efficacy of Koselugo was established in an open-label, single arm study in 50 pediatric patients with NF1 and inoperable PN. Patients received Koselugo 25 mg/m^2 orally twice daily until disease progression or unacceptable toxicity. The major efficacy outcome measure was overall response rate (ORR). An additional efficacy outcome measure was duration of response (DOR).

    — The ORR was 66% (95% CI: 51, 79) and all patients had a partial response, meaning no patients had complete disappearance of the tumor.
    — In patients with a response, 82% had a DOR lasting 12 months or longer.

- Warnings and precautions for Koselugo include cardiomyopathy, ocular toxicity, gastrointestinal toxicity, skin toxicity, increased creatinine phosphokinase, increased levels of vitamin E and risk of bleeding, and embryo-fetal toxicity.

- The most common adverse reactions (≥ 40%) with Koselugo use were vomiting, rash, abdominal pain, diarrhea, nausea, dry skin, fatigue, musculoskeletal pain, pyrexia, acneiform rash, stomatitis, headache, paronychia, and pruritus.

- The recommended dose of Koselugo is 25 mg/m^2 orally twice daily (approximately every 12 hours) until disease progression or unacceptable toxicity. The recommended dose of Koselugo based on body surface area is shown in the table below.

    — Koselugo should be taken on an empty stomach, and food should not be consumed 2 hours before each dose or 1 hour after each dose

Body Surface Area	Recommended Dosage
< 0.55 m^2	Has not been established
0.55 to 0.69 m^2	20 mg in the morning and 10 mg in the evening
0.70 to 0.89 m^2	20 mg twice daily

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0.90 to 1.09 m^2	25 mg twice daily
1.10 to 1.29 m^2	30 mg twice daily
1.30 to 1.49 m^2	35 mg twice daily
1.50 to 1.69 m^2	40 mg twice daily
1.70 to 1.89 m^2	45 mg twice daily
$\geq$ 1.90 m^2	50 mg twice daily

- AstraZeneca's launch plans for Koselugo are pending. Koselugo will be available as 10 mg and 25 mg capsules.