**Background**

- The somatotropin receptor (SR) is a member of the class I receptor tyrosine kinase (RTK) superfamily, and plays a critical role in the growth and development of the fetus, as well as the maintenance of normal body mass in adults.

- MAP3K1 (also known as TAK1, TNF receptor-associated factor 2, or TRAF2) is a MAP3K that plays a critical role in the regulation of cell proliferation and survival.

- The somatotropin receptor is the key regulator of cell proliferation and survival.

**Chemotherapy remains a standard treatment for patients requiring systemic therapy.**

**RAS fusions are the most common oncogenic driver identified in pediatric low-grade gliomas (LGGs).**

- Approximately 30% of LGGs harbor RAS fusions, which are associated with a poor prognosis.

- Children with LGGs who are young (<3 years old) and have a poor performance status (Karnofsky/Lansky <70) are more likely to experience treatment-related side effects.

**Key inclusion criteria**

- Patients must be at least 1 year of age and have a Karnofsky/Lansky performance status of ≥50.

**Key exclusion criteria**

- Patients with a history of solid tumor malignancy (excluding cutaneous melanoma).

**Study design**

**Endpoints**

- **Primary endpoint:**
  - Objective response rate (ORR) for tovorafenib monotherapy or as second-line pharmacotherapy based on RANO criteria, as determined by the IRC.

- **Secondary and exploratory endpoints:**
  - ORR, CBR, PFS, OTR, TTR by investigator per RANO
  - Changes in body weight, appetite, performance status, or time to treatment discontinuation
  - Changes in Karnofsky/Lansky score
  - Time to next anti-epileptic therapy
  - Changes in QoL as assessed by QOL-6D score
  - Changes in QoL as assessed by the QLQ-C30 or the QLQ-P30

**Statistical methods**

- The primary analysis will include all randomized patients, and patients who are non-eligible for efficacy will be considered non-responders.

**Study design**

- **Arm 1:** RAS fusions as the sole driver of LGG, occurring in 30% of cases.

- **Arm 2:** Patients with LGGs who are young (<3 years old) and have a poor performance status (Karnofsky/Lansky <70) are more likely to experience treatment-related side effects.

**Assessments**

- **RAS fusions are the most common oncogenic driver found on a mutually exclusive basis in most pediatric low-grade gliomas (LGGs).**

- Patients with LGGs who are young (<3 years old) and have a poor performance status (Karnofsky/Lansky <70) are more likely to experience treatment-related side effects.

**Key inclusion criteria**

- Patients must be at least 1 year of age and have a Karnofsky/Lansky performance status of ≥50.

**Key exclusion criteria**

- Patients with a history of solid tumor malignancy (excluding cutaneous melanoma).

**Study design**

- **Arm 1:** RAS fusions as the sole driver of LGG, occurring in 30% of cases.

- **Arm 2:** Patients with LGGs who are young (<3 years old) and have a poor performance status (Karnofsky/Lansky <70) are more likely to experience treatment-related side effects.

**Assessments**

- **RAS fusions are the most common oncogenic driver found on a mutually exclusive basis in most pediatric low-grade gliomas (LGGs).**

- Patients with LGGs who are young (<3 years old) and have a poor performance status (Karnofsky/Lansky <70) are more likely to experience treatment-related side effects.