A Phase I Study of the MEK1 Inhibitor Selumetinib (AZD6244) Hydrogen Sulfate in Children with Neurofibromatosis Type 1 (NF1) and Inoperable Plexiform Neurofibromas (PNs)

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Background

Neurofibromatosis type 1 (NF1) and plexiform neurofibromas (PN): NF1 is an autosomal dominant disorder characterized by diverse, progressive manifestations, including the development of PN (25-40%), which are debilitating historically benign peripheral nerve sheath tumors. PN demonstrate the most rapid growth during early childhood, and morbidity develops as a result of PN growth. Surgery, the only standard treatment, is not feasible for most PNs due to their location next to vital structures, high vascularity, infiltrative nature, and large size. There are no standard medical therapies, and there is thus a great need for the development of effective medical therapies.

Figure 1: Progressive growth of left facial PN leading to visible disfigurement by the time the patient reaches 3 years of age.

Objectives

- We developed a phase I trial of selumetinib for pediatric patients with NF1 and inoperable PNs to determine acute and chronic toxicities, the maximum tolerated dose (MTD), pharmacokinetics, and preliminary activity of selumetinib.

Methods

- Eligibility: Children and adolescents (3-18 years old) with NF1 and inoperable, measurable PN (longest diameter ≥ 3 cm) with potential to cause substantial morbidity.
- Ability to swallow intact capsules
- Children and adolescents (3-18 years old) with NF1 and inoperable, measurable PN (longest diameter ≥ 3 cm) with potential to cause substantial morbidity.
- The maximum tolerated dose (MTD) is determined from cycle 1-3 toxicities.
- Cohorts of 3-6 patients are enrolled at each dose level (DL): Cycle 1, day 1 PK samples were obtained for 13 pts (8 DL1, 5 DL2). Cycle 2 patients were evaluated 6 weeks after study entry.
- The most frequent non DLTs are: Acneiform rash, CPK elevation, nausea, vomiting, abdominal pain, diarrhea, and fatigue. All DLTs have been reversible. Preliminary median (range) selumetinib C1 day 1 PK parameters were: AUC0-24h DL1 (n=8) 2118 (1872-3240) ng·h/mL; half-life DL1 6.8 h (5.6-14.3), DL2 7.6 h (5.4-9.8). Of 18 pts with ≥ 20% decreases in PN volume, 11 patients had a PR (8/12 patients at 20% decrease in PN volume).
- Of 18 patients with ≥ 20% within 15 months prior to enrollment) treatment with selumetinib is limited to a maximum of 2 years unless the patient experiences a PR.

Results

- The most frequent adverse events (AEs) include acneiform rash, diarrhea, nausea, vomiting, periorbital edema, mucositis, and dry skin.
- Of 18 patients with ≥ 20% decrease in PN volume, 11 patients had a PR (8/12 patients at 20% decrease in PN volume).
- The median cycle if ≥ 3 (range 3-34), and PD has not been observed to date.
- Responses were observed in progressive and non progressive PNs.

Conclusions

- The MTD of selumetinib for children and young adults with NF1 and PN is 25 mg/m2 dose BID on a continuous dosing schedule.
- The toxicity profile of selumetinib in children is broadly similar to that seen in adults.
- Selumetinib administration has been tolerated over multiple cycles. Shrinkage of progressive and non progressive PN has been observed at DL1 and DL2 with PR in 11/18 patients (PR rate of 61%).
- Selumetinib pharmacokinetics in children is similar to adults.
- A phase II expansion for children and young adults with NF1 and PN is in development to more fully evaluate activity, tolerability and clinical benefit of selumetinib.