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

Leigh Marcus[1], Michael J. Fisher[2], Brian Weiss[3], AeRang Kim[4], Eva Dombi[1], Andrea Baldwin[1], Trish Whitcomb[1], Staci Martin[1], Andrea Gillespie[1], Austin Doyle[5], Brigitte C Widemann[1].

NCI, Pediatric Oncology Branch, Bethesda, MD[1], Children's Hospital of Philadelphia, Philadelphia, PA[2], Cincinnati Children's Hospital, Cincinnati, OH[3], Children's National Medical Center, Washington, DC[4], NCI, Cancer Therapy Evaluation Program, Rockville, MD[5]

Pediatric ONCOLOGY BRANCH

Abstract

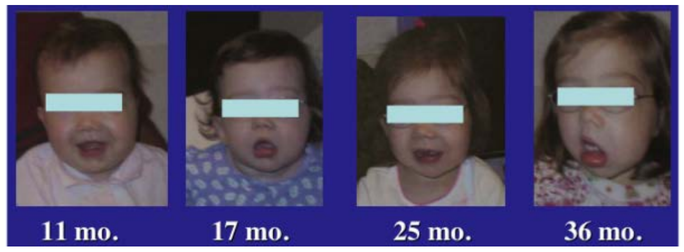
Background: Lack of functional neurofibromin in NF1 leads to dysregulated Ras signaling and tumorigenesis. Selumetinib (AZD6244; ARRY-142886), an oral selective inhibitor of MEK1/2, may inhibit PN growth by blocking Ras signaling. *Methods:* We are conducting a phase 1 trial (NCT01362803) to determine the maximum tolerated dose (MTD) and plasma pharmacokinetics (PK) of selumetinib in patients (pts) 3-18 years old with NF1 and inoperable PN. The MTD is determined based on cycle (C) 1-3 toxicities. Selumetinib is administered BID on a continuous dosing schedule (1C = 28 days) at dose level (DL) 1: 20, DL 2: 30, and DL 1.5: 25 mg/m2/dose. Response evaluation with volumetric MRI analysis occurs after C 5, 10, and then after every 6 C (partial response [PR] = ≥20% decrease in the PN volume). *Results:* Twenty-four pts (13 M:11 F, median age 10.9 years, range 3-18) with a median target PN volume of 1634 mL (range 47-10,269 mL) have enrolled. DL2 exceeded the MTD with DLT in 2/6 pts: grade (gr) 3 creatine kinase (CK) elevation (n=1), and gr 3 decrease in left ventricular ejection fraction (n=1). DL1 was tolerated with DLT in 2/12 pts: gr 3 cellulitis (n=1), and grade 3 urticaria (n=1). DL 1.5 was also tolerated with DLT in 1/6 pts: gr 3 rash. The most frequent toxicities (all grades) are acneiform rash, asymptomatic CK elevation, nausea, vomiting, abdominal pain, diarrhea, and fatigue. All DLTs have been reversible. Preliminary median (range) selumetinib C1 day 1 PK parameters were: $AUC_{0\text{-}24h}$ DL1 (n=8) 2118 (1872-3240) ng•h/mL, DL2 (n=5) 2702 (2088-6008) 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 ≥ 1 restaging MRI, 11 (61%) had a PR. *Conclusion*: In children with NF1 PN selumetinib is tolerated at 25 mg/m^2/dose BID on a continuous dosing schedule, approximately 60% of the adult recommended dose (75 mg BID). Activity is observed at DL1 and DL2. A phase II expansion is in development.

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 histologically 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 a left facial PN leading to visible disfigurement by the time the patient reaches 3 years of age.



- The *NF1* gene product neurofibromin accelerates Ras-GTP hydrolysis to Ras-GDP and thus functions as a potent negative regulator of Ras.
- Lack of functional neurofibromin in NF1 leads to dysregulated Ras and tumorigenesis.
- In a genetically engineered mouse NF1 neurofibroma model, evaluation of a MEK inhibitor (PD0325901) resulted for the first time in decreases in PN volumes using volumetric MRI analysis (*Jessen et al. JCI 2013*).
- There is a strong rationale for the evaluation of MEK inhibitors in NF1 PN.

Selumetinib (AZD6244) hydrogen sulfate:

- Selumetinib is an orally bioavailable specific MEK1/2 inhibitor in development for adult malignancies and pediatric low grade gliomas.
- The adult recommended dose is 75 mg BID (capsule formulation) on a continuous dosing schedule.
- The most common adverse events (AEs) include acneiform rash, diarrhea, nausea, vomiting, peripheral edema, oral mucosistis, and dry skin.

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:

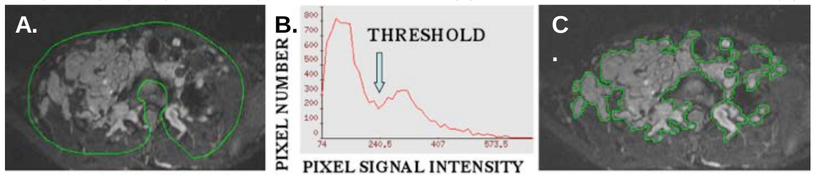
- Children and adolescents (3-18 years old) with NF1 and inoperable, measurable PN (longest diameter ≥ 3 cm) with potential to cause substantial morbidity
- Ability to swallow intact capsules

Design:

- Selumetinib (10, 25 mg capsules) BID, continuous dosing schedule (1 cycle =28 d).
- Cohorts of 3-6 patients are enrolled at each dose level (DL):
  DL1: 20 mg/m^2/dose (50% of solid tumor MTD) with planned escalations to DL2: 30, and DL3: 40 (=adult recommended dose) mg/m^2/dose .
- The maximum tolerated dose (MTD) is determined from cycle 1-3 toxicities.
- Toxicity evaluations with: Physical exams, laboratory studies, echocardiogram, EKG, ophthalmology, and adherence monitoring via capsule counts and patient diaries.
- Response evaluations with MRI and volumetric analysis after cy. 5, 10, 16, 22, etc.
  - Partial response (PR) = PN volume decrease ≥20%
  - Progressive disease (PD) = PN volume increase ≥ 20%
- Duration of treatment:
  - In absence of disease progression at enrollment (progression = PN volume increase ≥20% within 15 months prior to enrollment) treatment with selumetinib is limited to a maximum of 2 years unless the patient experiences a PR.

Figure 2: Automated volumetric MRI analysis:

On all MRI slices containing PN the tumor is roughly outlined manually including a rim of low signal intensity normal tissue (A) followed by automated histogram analysis, definition of threshold distinguishing high signal intensity PN from normal tissue (B), and determination of tumor borders (C).



Results

Patient characteristics:

- Twenty-four (13 M, 11 F) patients (median age 10.9, range 3-18 years) enrolled
- PN locations include orbit, face, neck/chest, abdomen, pelvis, lower and upper extremities, spine, and whole body
- Median PN volume at enrollment 1634 mL (range, 47–10,269 mL)

Table 1: Dose-limiting Toxicities (DLT) Cycles 1-3

Dose (mg/m^2)	Pt. #	Patients evaluable	Grade 3 DLT (N)
20	1-3	3	-
30	4-9	6	CPK (n=1), LVEF decrease (N=1)
20	10-18	9	Infection (N=1), Urticaria (N=1)
25 MTD	19-24	6	Maculo-papular rash (N=1)

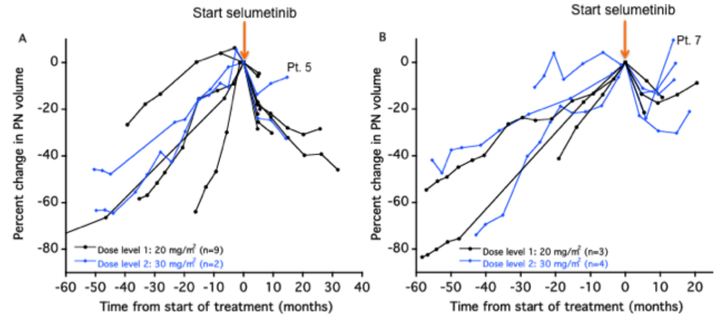
CPK=Creatine phosphokinase, LVEF= Left ventricular ejection fraction

- All DLTs were reversible after holding selumetinib.
- DLTs after cycle 3: Gr. 3 CPK (N=2), gr 3 mucositis (n=1) in patients enrolled at DL 2, and gr. 3 cellulitis (n=1) in a patient enrolled at DL1.
- The most frequent non DLTs are: Acneiform rash, CPK elevation, nausea, vomiting, diarrhea, abdominal pain, and fatigue.

Responses:

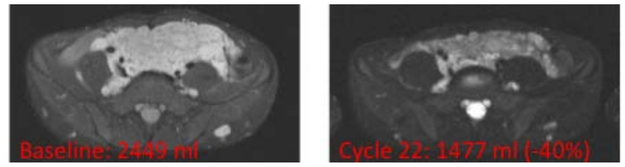
- Of 18 patients with ≥1 restaging MRI, 11 patients had a PR (8/12 patients at 20 mg/m^2, and 3/6 patients at 30 mg/m^2).
- The median cycle # is 9 (range 3-34), and PD has not been observed to date.
- Responses were observed in progressive and non progressive PNs.

Figure 3. Percent change in PN volume prior to and after start of treatment with selumetinib in patients without (A) and with (B) selumetinib dose reductions. Each symbol represents an MRI study



- With exception of patient 5, who has a PN with large nodular appearing lesions, PN reduction has been maintained in all patients not requiring dose reduction(s).
- Patient 7 had a PR, but the PN regrew while selumetinib was on hold for LVEF.

Figure 4: Example of a PR: Axial MRI of abdominal PN



Pharmacokinetics:

- Cycle 1, day 1 PK samples were obtained for 13 pts (8 DL1, 5 DL2).

Figure 5: Mean (standard deviation) plasma selumetinib concentrations

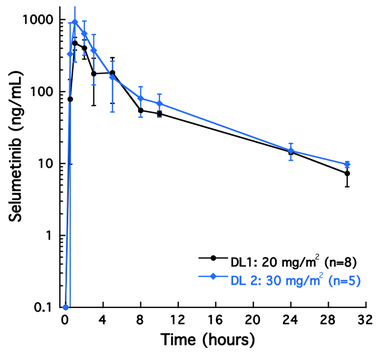


Table 2: Median (range) Selumetinib PK Parameters

	DL 1: n=8 20 mg/m^2	DL2: n=5 30 mg/m^2
T_{max} (h)	1 (1-3)	1 (1-2)
C_{max} (ng/mL)	513 (375-1590)	841 (576-1770)
$AUC_{0\text{-}24\ h}$ (ng•h/mL)	2118 (1872-3240)	2702 (2088-6008)
Half-life (h)	6.8 (5.6-14.3)	7.6 (5.4-9.8)

Conclusions

- The MTD of selumetinib for children and young adults with NF1 and PN is 25 mg/m^2/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 are 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.