Selumetinib (AZD6244; ARRY-142886) – Pediatric MATCH

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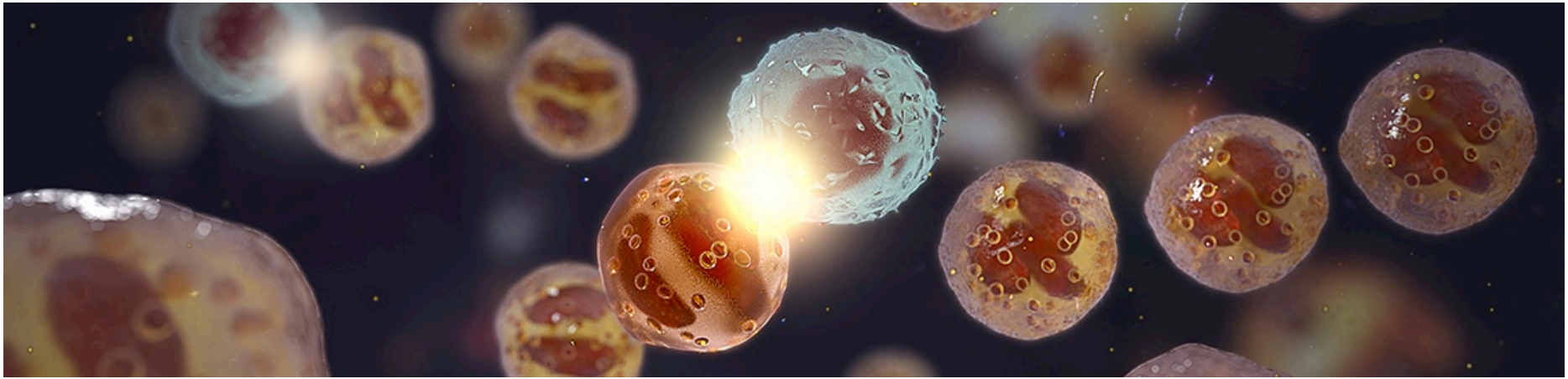
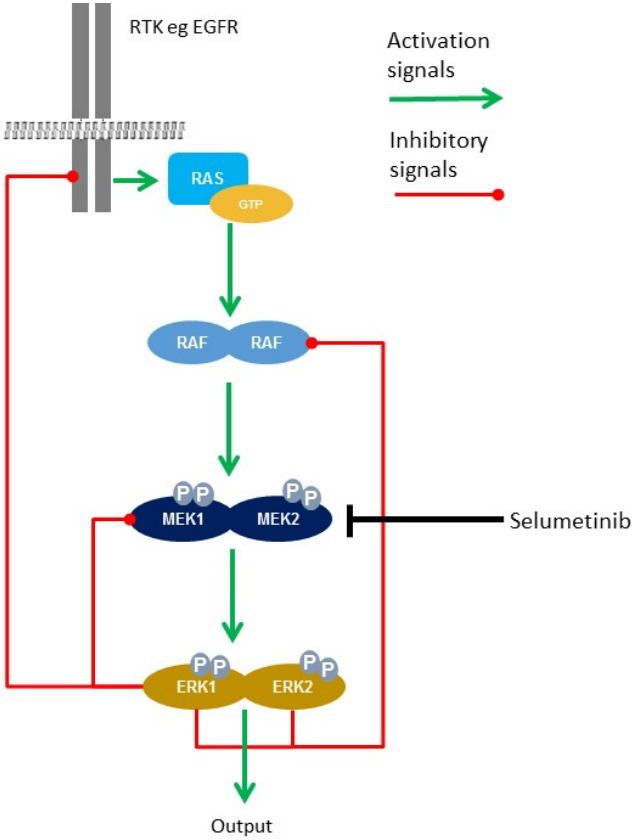


MEK activation and selumetinib MOA

- MEK is a fundamental component of the MAPK pathway – a central oncogenic signalling pathway frequently activated in tumours, either as a primary cause of tumour growth or as a cause of resistance to treatment
- The MAPK signalling pathway is activated by multiple mechanisms that converge on MEK, therefore inhibition of MEK also inhibits a number of upstream pathways
- Selumetinib is a MEK inhibitor, currently under investigation across a number of diverse (malignant and benign) tumour types resulting from activation of, and dependence on MEK:
  - As a result of cell mutation (e.g. *KRAS* in NSCLC, GNAQ in UM, KIAA1549-BRAF fusion gene in pilocytic astrocytoma)
  - Due to mutation present at birth (e.g. pediatric NF-1)



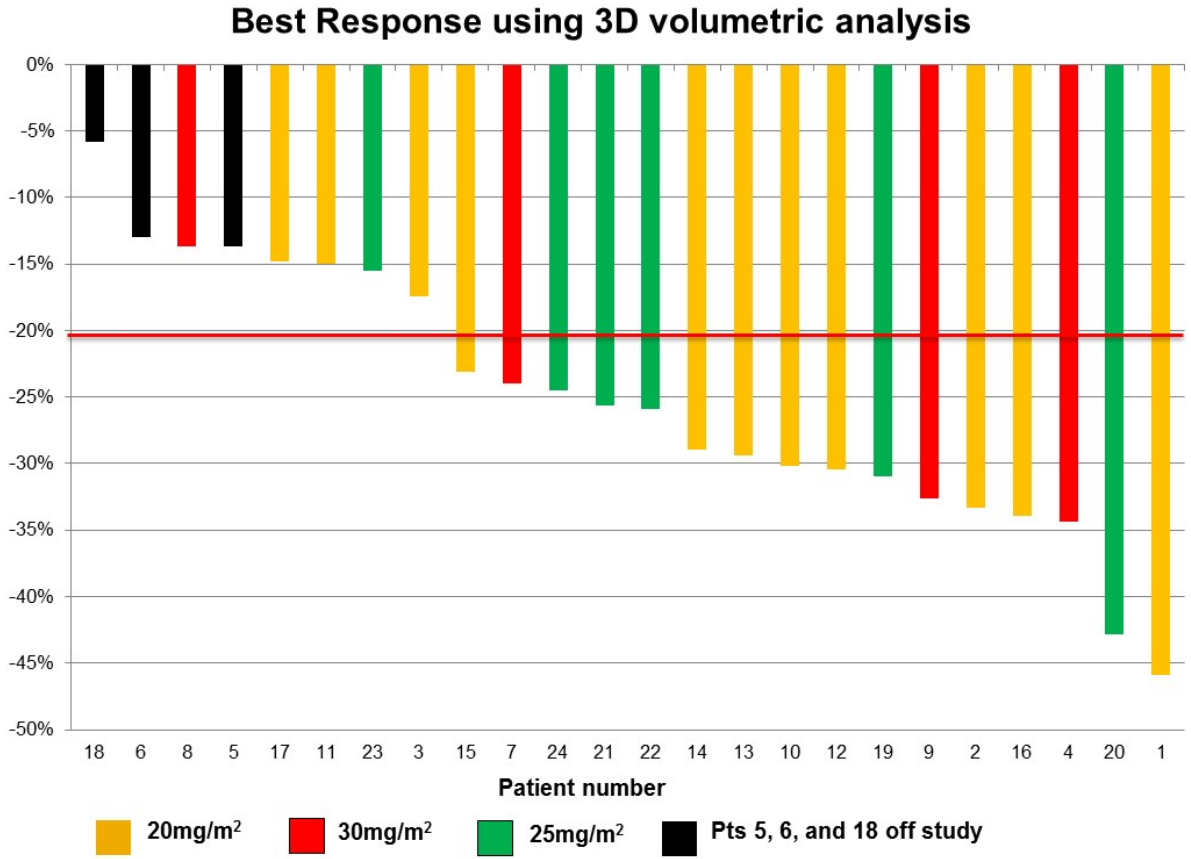
Selumetinib: Tolerability

- The recommended dose is 75mg BD continuous administration in combination with chemotherapies (i.e., docetaxel, dacarbazine)
- The established pediatric dose is 25mg/m^2 BD (monotherapy)
- Additional data on appropriate doses/schedules in combination is available
- The selumetinib clinical development programme currently provides safety data from >2,000 patients – almost half of whom received selumetinib in combination with other cancer therapies
- Appropriate use of AE management guidelines may result in patients remaining on therapy longer, potentially improving their response to treatment
  - Clear guidance is in place to manage any potential chemotherapy-related toxicities when selumetinib is used in combination with chemotherapy
- The short half-life of selumetinib (~5-7 hours) allows flexibility of scheduling – key to maximising the clinical effectiveness while controlling the side effect profile
  - Drug can easily be withdrawn and quickly removed from the system on onset of AEs

Selumetinib: Pediatric Experience

- Phase I/II study in NF1 PN (continuous dosing) – registration study (US)
- Phase II study in LGG – ongoing (US)
- Phase II study in NF1 PN (intermittent dosing) – planned (UK)
- Phase I study in ALL – planned (2017)
- Discussions ongoing with IGR (France) for pediatric study based on molecular profiling - planned

Phase I/II study in NF1 PN: Percentage Change in Tumor Volume)

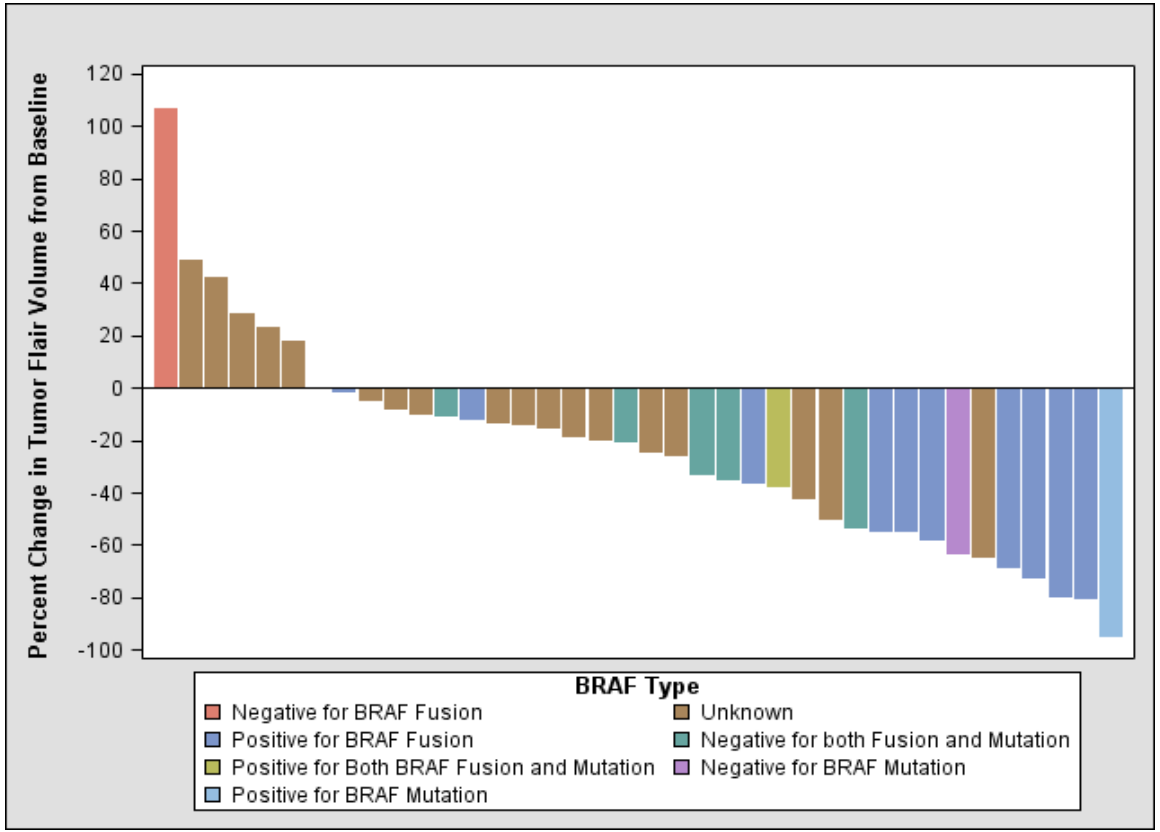


Phase I study of the MEK1/2 inhibitor selumetinib (AZD6244) hydrogen sulfate in children and young adults with neurofibromatosis type 1 (NF1) and inoperable plexiform neurofibromas (PNs); J Clin Oncol 32:5s, 2014 (suppl; abstr 10018);
Widemann B, Marcus LJ, Fisher MJ, Weiss BD, Kim A, Dombi E, Baldwin A, Whitcomb P, Martin S, Gillespie A, Doyle A. Phase I Study of the MEK1/2 inhibitor selumetinib (AZD6244 hydrogen sulfate) in children and young adults with neurofibromatosis type 1 (NF1) and inoperable plexiform neurofibromas (PNs). 50th Annual American Society for Clinical Oncology (ASCO); 2014 May 30-Jun3; Chicago, IL

Phase I/II study in LGG

- A Phase I and II and Re-treatment Study of Selumetinib for Recurrent or Refractory Pediatric Low Grade Astrocytoma

Phase I: Percent Change from Baseline Using Central Review Volumetric Analysis of FLAIR Images



- 9 PR by imaging; centrally reviewed
- Responses occurred between courses 2-15
- 7 of 9 responses occurred at 25 mg/m2/dose bid
- 5/9 subjects with responses had available tissue for BRAF analyses.
- 4/5 have BRAF aberration (3 fusion, 1 BRAFV600E mutation)
- Six of 9 patients with PR are still on therapy; 3 discontinued due to toxicity; 2 of 3 progressed within 3-6 months of stopping therapy

Ref: Banerjee A, Jakacki R, Onar-Thomas A, Wu S, Nicolaides T, Turner DC et al. A Phase 1 Study of AZD6244 in Children with Recurrent or Refractory Low Grade Gliomas: A Pediatric Brain Tumor Consortium Report. 50th Annual American Society for Clinical Oncology (ASCO); 2014 May 30-Jun3; Chicago, IL

Phase II Expansion: Strata

Stratum 1	Stratum 2	Stratum 3	Stratum 4	Stratum 5	Stratum 6
Patients with non NF-1 associated progressive, recurrent or refractory pilocytic astrocytoma **with** a BRAF aberration.	Patients with non NF-1 associated progressive, recurrent or refractory pilocytic astrocytoma **without** BRAF aberration.	Patients with NF-1 associated progressive, recurrent or refractory low grade glioma (WHO I or II)	Patients with non NF-1 associated progressive, recurrent or refractory optic pathway glioma (OPG).	Patients with non NF-1 associated progressive, recurrent or refractory low grade glioma (other than pilocytic astrocytoma or optic pathway glioma) with BRAF aberrations	Patients with non NF-1 associated progressive, recurrent or refractory low grade glioma who cannot be classified into Stratum 1, 2 or 5

Back-up slides

Selumetinib: External development program

- 51 studies either planned or ongoing

- Based on the preclinical data and on the PK profile, numerous indications explored either as single agent or in combination
  - **ALL, astrocytoma**, biliary, breast, colorectal, gall bladder, hepatobiliary, melanoma, multiple myeloma, non-hodgkins lymphoma, NSCLC, endometrial, ovarian, pancreatic, rectal, solid tumors, thyroid, kaposi sarcoma, soft tissue sarcoma, NF1 plexiform neurofibromas

Phase I/II study in NF1 PN: Safety

- DL1 (20mg/m^2 BID)
  - Safety (C1-3) DLTs: G3 infection, G3 urticaria
  - Safety (>C3) DLTs: G3 cellulitis
- DL2 (30mg/m^2 BID)
  - Safety (C1-3) DLTs: G3 CPK elevation, G3 LVEF decrease (C5*)
  - Safety (>C3) DLTs: 3 CPK (2 pts, one of them also had grade 3 CPK in cy 1), G2 mucositis
- DL1.5 (25mg/m^2 BID) – RP2D
  - Safety (C1-3): G3 rash (n=1)

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