

 TARGETED THERAPIES

Selumetinib MEKIng differences in NF1

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No effective therapies are available for children with inoperable neurofibromatosis type 1 (NF1) plexiform neurofibromas. These debilitating and painful tumours are characterized by elevated RAS and MAPK signalling. To date, therapeutic agents that target the RAS pathway have provided limited responses. This situation prompted the assessment of selumetinib, an oral inhibitor of MEK1 and MEK2 in children with NF1, on the basis of promising activity in adults with several types of advanced-stage cancers. Preclinical data from a mouse model of neurofibroma and results of a phase I study in children with NF1 and inoperable neurofibromas, now published in the *New England Journal of Medicine*, have demonstrated the long-term benefit of selumetinib.

The report indicates that decreases in neurofibroma tumour volume from baseline were noted in 12 of 18 mice treated with selumetinib. By contrast, neurofibroma volume increases were seen in 14 of 15 vehicle-treated control mice. In the clinical trial, a total of 24 children with a median tumour volume of 1,250 ml received a median of 30 cycles of

selumetinib, which was administered twice daily at a dose of 20–30 mg/m² in a continuous schedule in 28-day cycles. Responses to treatment were monitored using volumetric MRI to measure the change in size of neurofibromas. Results from pharmacokinetic evaluations of this agent were comparable to results observed in adults and thus, a maximum tolerated dose of 25 mg/m² was established.

Importantly, confirmed partial responses were noted in 17 children (71%). At the time of reporting of these trial results, no disease progression has been reported. Moreover, anecdotal clinical improvements in tumour-related pain, motor function, and reduced disfigurement were noted. The promising results of this phase I trial are now being tested in an ongoing prospective phase II study of selumetinib on patient reported outcomes (pain, quality of life) and functional changes related to the target plexiform neurofibromas.

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ORIGINAL ARTICLE Dombi, E. *et al.* Activity of selumetinib in neurofibromatosis type 1-related plexiform neurofibromas. *N. Engl. J. Med.* **375**, 2550–2560 (2016)