Good clinical response to alectinib, a second generation ALK inhibitor, in refractory neuroblastoma

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Abbreviations:

ALK	anaplastic lymphoma kinase
EKG	electrocardiogram
MIBG	metaiodobenzylguanine
NSCLC	non small cell lung cancer

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To The Editors,

We wish to report first use of alectinib (Alecensa; Roche Ltd), a second generation anaplastic lymphoma kinase (*ALK*) inhibitor, in a case of heavily pre-treated, refractory, metastatic neuroblastoma. Patients with refractory and or relapsed neuroblastoma have a poor outcome with conventional multimodality therapy. Activating mutations in the tyrosine kinase domain encoding regions of *ALK* have been identified as the most common cause of familial neuroblastoma and account for 10–15% of sporadic neuroblastoma cases [1]. Experience with the first-in-class *ALK* inhibitor crizotinib in children with refractory neuroblastoma has shown encouraging results. Crizotinib monotherapy achieved stable disease, with median progression free survival of over 12 months [2]. Alectinib is a second generation *ALK* tyrosine kinase inhibitor with greater potency against wildtype and mutant *ALK* and improved CNS penetration compared with crizotinib. A recent phase 3 study demonstrated the superiority of alectinib over crizotinib in *ALK* rearranged non small cell lung cancer (NSCLC) [3]. To our knowledge, the activity of alectinib in neuroblastoma has not been described.

Our patient, a 15-year-old female was diagnosed with stage III neuroblastoma without amplified *MYCN*. Initial disease sites included a left adrenal mass and regional lymph nodes. She achieved a complete remission after receiving treatment according to a standard high risk-neuroblastoma protocol. The patient remained disease free for 11 months, after which she relapsed with multiple nodal masses throughout the posterior mediastinum. Next generation sequencing of the relapsed tumor confirmed an *ALK* mutation at exon 24 F1245C. Treatment of the relapse included conventional salvage chemotherapy, surgical resection and external beam radiation. Persistent MIBG avid disease was treated with ceritinib monotherapy. A partial response was achieved and sustained for 12 months, before multiple new sites of disease (lung, supraclavicular nodes bilaterally) were detected. A repeat biopsy of supraclavicular nodes confirmed persistence of the known *ALK* mutation. Radionuclide therapy (MIBG and lutetium), together with external beam radiation

therapy resulted in temporary improvements before further disease progression within pleural and lung nodules occurred..

Because there is evidence for resistance to ceritinib with NSCLC cases harbouring the F1245C *ALK* mutation [5], treatment with an alternative second generation *ALK* inhibitor was offered. Alectinib therapy is generally well-tolerated and most common adverse events observed, which include fatigue, myalgias, peripheral edema and constipation, are minor [5]. Alectinib monotherapy was started after informed consent, with monitoring of blood counts, liver, and kidney function, muscle enzymes and cardiac function by EKG. Apart from some mild nausea, our patient tolerated the drug. There were no clinical or metabolic adverse effect at a dose of 600mg QID over 4 months. She improved symptomatically (severe pain requiring opiate analgesia resolved) and evaluation after 8 weeks revealed a very good partial response (Figure 1). She remained stable for a total of 16 weeks, at which time she presented with a new onset visible, right sided chest wall mass, contiguous with a known, pleurally based tumor. As with other tyrosine kinase inhibitors, use of alectinib as monotherapy leads to the emergence of resistance. Genetic analysis suggests that mutations within *ALK* kinase domain or up-regulation of an alternative signaling pathway are the likely mechanisms of resistance [6,7].

In summary, we observed a partial response with alectinib in a patient with chemotherapy-resistant *ALK* mutation positive metastatic neuroblastoma. We are unable to say in this case if the targeted mutation was present in the original tumor or developed at relapse. The excellent oral bioavailability and safety profile of the agent makes it ideal for use in heavily pretreated patients, although monotherapy is known to lead to resistance and undoubtedly short response times. Encouraging results in refractory tumors suggests there may be a role for its use in combination with other agents as frontline therapy for high-risk neuroblastoma.

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Nil.

Conflicts of interest

Dr Solomon serves as a medical consultant to Pfizer and Roche

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Figure 1 Comparative computerized tomography (CT) scans (A) pre-alectinib and (B) after three months treatment with alectinib monotherapy showing reduction in size of pleurally based metastatic neuroblastoma

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