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AACR – Loxo and Ignyta clash on novel kinase mechanism

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An early-stage showdown between Ignyta and Loxo Oncology has shone the spotlight on a genetic mutation that might gain prominence as cancer treatment increasingly embraces companion diagnostics.

So-called neurotrophic tyrosine receptor kinase (NTRK) gene fusions are a rare oncogenic driver that occurs across a range of cancers. With the two groups unveiling data from two similar phase I programmes Loxo might arguably have a tiny edge over Ignyta, though in reality the low patient numbers make this too close to call.

Loxo's LOXO-101 has shown partial responses in five of six patients with cancers driven by an NTRK fusion, while a seventh was not yet evaluable. In the case of Ignyta's entrectinib, three out of four had a partial response, one only just meeting the criteria.

Rational design

One difference is that LOXO-101 has been rationally designed specifically as an NTRK inhibitor. Entrectinib is also active across other, related, kinase-based oncogenic drivers.

Indeed, it is against one of these other mutations – Ros1 – that entrectinib efficacy looks particularly impressive: among 14 patients from Ignyta's dataset who had Ros1-driven tumours, 10 had a partial and two a complete response. The company also highlighted seven Alk-positive patients, five of whom had partial responses, though these were short-lived.

That said, these additional patients might cut little ice in the real world, given the availability of three approved drugs specifically for Alk-mutated NSCLC: Pfizer's Xalkori, Novartis's Zykadia and Roche's Alecensa. And just last month the US FDA extended Xalkori's label to Ros1-positive disease.

Both datasets came from larger studies – Ignyta's comprised two trials in a combined 119 patients, while Loxo had enrolled 43. But ultimately most patients did not have the specific mutation highlighted, or in Ignyta's case were not kinase inhibitor treatment-naive, and the vast majority of these others did not respond.

Presenting the Loxo data, Memorial Sloan Kettering Cancer Center's Dr David Hong pointed to the growing list of kinase fusion-based genetic alterations – including Abl and Braf in addition to Alk and Ros1 – that now had approved drugs, adding: "We believe NTRK fusions will soon join this list."

Both Alk and Ros1 mutations represent relatively tiny uses – Ros1 rearrangement occurs in just 1% of NSCLC – and require a companion diagnostic, but on the plus side this can justify orphan pricing. NTRK mutations are also present in roughly 1% of NSCLC patients, but have a higher incidence in sarcomas and papillary thyroid carcinoma.

As some cancer treatment gets carved up according to patients' genetics, regulatory approval of an NTRK inhibitor will have to be backed by a companion diagnostic. This will present problems, since varied fusion patterns make NTRK mutations very complex to assay, said Dr Hong.

Parallel existence

Loxo and Ignyta have led a parallel existence of sorts, both floating on Nasdaq in 2014. However, while Loxo's stock has since doubled, Ignyta has treaded water, and the latter's market cap stands at little more than half that of its rival.

Ignyta had licensed entrectinib from Nerviano Medical Sciences, and until it bought a portfolio of Teva castoffs this was its sole clinical asset (*Ignyta: boldly going where no one has gone before, March 18, 2015*). LOXO-101, meanwhile, is derived from Loxo's joint discovery alliance with Array Biopharma.

Sellside 2020 sales estimates, as computed by *EvaluatePharma*, are $203m for entrectinib and $198m for LOXO-101. Both projects are entering phase II studies in the specific patient populations identified in phase I.

Discussing the two datasets, Dana-Farber Cancer Institute's Dr Leena Gandhi endorsed work on the NTRK oncogene family, but ultimately would not choose between the two projects. Both showed high rates of response, she said, and broadly similar toxicity profiles.

However, she did point to entrectinib's ability to cross the blood-brain barrier and resulting activity in the CNS, which included one complete response.

She suggested that only when more became known about resistance mechanisms and efficacy in other settings would differentiation between entrectinib and LOXO-101 be easier. For now, though, it is good to have options, she stated.

Project	Company	Detail	Trial ID	AACR abstract
Entrectinib	Ignyta	Dose escalation in 175 pts with NTRK, Alk or Ros1 alterations (STARTRK-1)	NCT02097810	CT007
LOXO-101	Loxo Oncology	Dose escalation in 108 pts with NTRK alterations	NCT02122913	CT008

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