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Asco – Loxo nudges ahead of Ignyta with tumour-agnostic therapy

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Highly impressive initial signals of efficacy with larotrectinib have positioned Loxo Oncology as the next company to watch for a potential tumour-agnostic approval, and could see it steal a march on its archrival, Ignyta.

For investors there is one caveat: the cancer remission data, presented today as an Asco late-breaker, were locally assessed only, and are still subject to confirmation by independent review. However, should the results hold up they will serve as the basis for a US filing late this year or early in 2018.

Larotrectinib could gain a biomarker-based label, irrespective of cancer type. The project targets tumours harbouring tropomyosin receptor kinase (TRK) fusions, a rare genetic mutation; recently Merck & Co's Keytruda became the first drug to get a cancer type-agnostic US approval – in tumours with microsatellite instability or DNA mismatch repair deficiency.

Since larotrectinib and Ignyta's entrectinib, which also targets TRK as well as the related Ros1 and Alk fusions, burst onto the scene at last year's AACR meeting, Loxo stock has climbed 95%, while Ignyta has treaded water, creeping up just 6% (*AACR – Loxo and Ignyta clash on novel kinase mechanism, April 18, 2016*).

Pause for thought

Ignyta investors would do well to take note of the Asco data. These show that, in 50 subjects with TRK fusions identified by 15 different lab tests, 32 went into partial remission, while six had complete responses.

The pooled results come from three trials, and span 17 cancer types, including thyroid, lung, breast, colon and salivary gland. In a further five enrolled subjects there were four PRs and one CR, but these were too recent to have been confirmed, Loxo said.

Presenting the data, Memorial Sloan Kettering Cancer Center's Dr David Hyman highlighted the fact that there was no particular clustering of a single cancer type at either end of the response chart. He also highlighted the broad spread of subjects, between four months and 76 years of age.

In fact, he said, there was no single predictor of response beyond the fact that all subjects had a TRK gene fusion. However, to get the full benefit of this advance, broader adoption of tumour profiling was needed, he stressed, adding that the Keytruda approval might provoke such a change.

The data could also spell good news for Array Biopharma, Loxo's development partner for larotrectinib.

Meanwhile, Ignyta is not presenting data at Asco. Its most recent update, after AACR, showed entrectinib giving a 72% overall remission rate in 43 Ros1 fusion-positive NSCLC subjects; the group said its pivotal programme was over 85% enrolled, and was intended to back a TRK fusion-based, tissue-agnostic, NDA filing next year.

Entrectinib recently joined larotrectinib with a US breakthrough therapy designation, and Ignyta raised $88m gross last month. Loxo said it would look to file larotrectinib after central review later this year to confirm its initial findings.

Relapses

Interestingly, Loxo seems already to be heading off relapse problems by developing LOXO-195 specifically for patients who develop resistance to therapy with a TRK inhibitor like larotrectinib.

Specifically, in the trials presented at Asco, six initially responding patients progressed by way of a so-called solvent front mutation. These could be candidates for LOXO-195, for which data for the first two larotrectinib-relapsed patients – both responded to LOXO-195 – have just been published in Cancer Discovery.

Assuming that LOXO-195 works as intended, it could presumably also be used in patients who fail on Ignyta's

entrectinib. It is now vital for Loxo's data to be confirmed by central review – especially as five subjects in the local assessment are only just over the threshold for partial remission.

If the larotrectinib data do indeed hold up, Ignyta would have two things to worry about.

Trials to serve as the basis for larotrectinib's US filing		
Study	**Subjects in Asco presentation**	**Trial ID**
Phase I trial in adults	8	NCT02122913
Scout, phase I/II trial in adults and adolescents	12	NCT02637687
Navigate, phase II trial	35	NCT02576431

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