PINK SHEET
CITELINE REGULATORY

05 Jun 2017 | **Analysis**

Loxo Sees Larotrectinib As Model Form Of Oncology Drug Development

by Mary Jo Laffler

The pivotal data presented at ASCO showed a 76% response rate for the TRK inhibitor in patients with TRK fusion abnormalities, but there's still a lot left to prove about the tissue-agnostic model of drug development.

Delivering on the promise of precision medicine, *Loxo Oncology Inc.*'s larotrectinib could be the first of a modern form of oncology drug development – facilitated by US FDA's breakthrough designation program.

Larotrectinib is a targeted therapy that selectively inhibits the tropomyosin receptor kinase (TRK) fusion protein and is one of the first attempts at molecularly defined patient identification rather than traditional indications based on cancer location.

The first actual FDA approval for a molecularly defined cancer that does not specify tumor location recently went to *Merck & Co. Inc.*'s PD-1 inhibitor *Keytruda* (pembrolizumab), but the indication for microsatellite instability-high or mismatch repair deficient solid tumors was not the first approval for pembrolizumab and was based on retrospectively collected data. (Also see "*Biomarker-Led Claim Is Small Step For Merck's Keytruda, Giant Leap For Cancer Indications*" - Pink Sheet, 23 May, 2017.)

Larotrectinib could be the first novel drug

Oncology: Tissue-Agnostic Indications Advance Under US FDA's Breakthrough Umbrella

By Bridget Silverman

25 May 2017
Merck's Keytruda may not be only oncologic with indication for cancer patients defined by molecular signature, not tissue of origin, for long: Ignyta's entrectinib and Loxo Oncology's larotrectinib are positioned for breakthrough-

PINK SHEET
CITELINE REGULATORY

prospectively developed and approved for a tissue-agnostic claim, as well as the first with simultaneous approval in adults and children.

designated tissue-agnostic NDA submissions in NTRK fusion-positive cancers in 2018.

Read the full article here

The pivotal dataset of 55 patients, as agreed with FDA, was presented at the American Society of Clinical Oncology annual meeting June 3 in Chicago.

Lead investigator David Hyman, Memorial Sloan Kettering, described it as "a very efficient and focused development program" that is on "a very rapid path" from discovery to approval. Loxo intends to submit larotrectinib for approval late this year or early 2018, after the data go through independent central radiographic review.

The development process has been facilitated by FDA's breakthrough program. The agency, which has signaled its openness to tissue-agnostic claims for years, issued breakthrough therapy designations for the Keytruda claim and well as for larotrectinib and *Ignyta Inc.*'s entrectinib, another TRK-focused program.

"For a program like this which is moving so quickly, it's very helpful to be able to get meetings calendared more quickly, get feedback more quickly. I think that's been the largest benefit [from the breakthrough designation]," Loxo Chief Business Officer Jacob Van Naarden said in an interview at ASCO.

The company's efforts have also been facilitated by CEO Joshua Bilenker's background as an oncology reviewer at FDA. "He has the mind of a regulator," Van Naarden commented.

Looking At The Data

The TRK fusion mutation occurs in dozens of cancer types across patients' lifespans. According to ASCO, the abnormality occurs in about 0.5%-1% of many common cancers but in greater than 90% of certain rare cancers, such as salivary gland cancer, a form of juvenile breast cancer, and infantile fibrosarcoma. "At this point it is hard to find a cancer type where TRK fusions have not been reported," Hyman told a press briefing on the results.

There were 17 unique tumor types in the pivotal dataset, including common cancers as well as rare forms and pediatric cancers. Patient ages ranged from 4 months to 75 years, and patients had an average of two prior therapies.

Efficacy was seen regardless of tumor type and no one tumor type responded better than another. In the 50 patients with confirmatory response data, there was a 76% response rate. The other five patients were too early in treatment to have confirmatory scans, but Hyman said all

PINK SHEET
CITELINE REGULATORY

five had at least a partial response and remain on study awaiting their confirmatory scans.

Twelve percent had complete responses, and most partial responses exceeded the criteria with deep tumor regression; two patients moved forward to curative surgery and had pathologic complete responses, Hyman reported.

The median time of first response was 1.8 months, but Hyman explained that reflected the time the first scan was obtained. "In the clinic, patients report dramatic improvement of their symptoms within days of beginning therapy," he said.

The responses have been durable, with 79% of responses ongoing 12 months after starting treatment. Of the responders, 93% remain on therapy or had surgery with curative intent.

"More than three out of every four patients responded to therapy. You'd be hard pressed to find a targeted therapy even within a single disease context that has results like this," Hyman said.

Larotrectinib was also an "extremely well tolerated therapy," the investigator stated, with only 13% of patients requiring any dose modification and no patients discontinuing due to adverse events. The most common adverse events were fatigue (30%), dizziness (28%), and nausea (28%).

Testing Will Be Critical

"Not long ago it would have been a pipe dream to think that we could treat cancers independent of their site of origin," City of Hope's Sumanta Kumal Pal said in reaction to the larotrectinib data. While clinicians at major medical centers like Pal might be ready for "the era of treatment based on the patient not location," it won't be an easy transition, especially in community settings.

For all of the tissue-agnostic approaches, awareness and testing are essential to success. FDA approval of next-generation sequencing (NGS) panels should help – *Foundation Medicine Inc.*'s *FoundationOne* and *Thermo Fisher Scientific Inc.*'s *Oncomine* are both under review. (Also see "*Thermo Fisher Makes Final Push For 'Universal' Lung-Cancer Companion Dx*" - Medtech Insight, 14 Nov, 2016.)

Currently, limited testing makes it hard to be certain of population estimates, Van Naarden acknowledged. Loxo's commercial efforts will focus on diagnosis and awareness. It is also working on a companion diagnostic with *Roche*'s *Ventana Medical Systems Inc.*, an immunohistochemistry test that will come in at a lower price point than the NGS panels.

Loxo's Larotrectinib Requires Paradigm-Change In Clinical Practice

By Mary Jo Laffler

PINK SHEET
CITELINE REGULATORY

05 Jun 2017
The TRK inhibitor won over ASCO with deep and durable responses across 17 cancer types, but diagnostics will be the true test of the tumor-agnostic approach – and the focus of Loxo's commercial strategy.

Read the full article here

Pal also pointed out that it will be important to understand how to use larotrectinib in patients with tumor types that have a well-stocked armamentarium, although the drug will be easily adopted in rare cancers with no established standard of care. The same holds true for Keytruda, he noted. "With these mounting data there seem to be increasing calls to obtain molecular profiling in a wide variety of scenarios," Pal said. "It will be important to develop guidelines around testing for these expanding indications."

Physician use will be guided by FDA's labeling, which Van Naarden predicted would "be somewhat flexible ... and allow clinicians to make clinical judgement decisions." The breakthrough designations specify use in locally advanced or metastatic solid tumors in adult and pediatric patients who have either progressed following prior therapies or who have no acceptable standard therapies.

FDA will probably find additional data to be necessary, but that's another area where Van Naarden expects the agency to be flexible if accelerated approval is granted. "There's a lot of ways to build data packages in this modern era," he said, and the agency has expressed desire to see more real-world evidence.

Loxo is also running a clinical program for a follow-on TRK inhibitor, LOXO-195, which is intended as a therapeutic option for patients who develop resistance to larotrectinib. Van Naarden explained that research indicates that tumors can acquire point mutations in the TRK fusions that would prevent larotractinib from binding where it had been, but that the tumor would still be addicted to the same pathway and a new TRK inhibitor that binds differently would be effective. "The idea behind LOXO-195 is this sequential therapy extension of durable disease control," Van Naarden said, akin to EGFR inhibitors in lung cancer.

LOXO-195 is being studied in patients who progress on larotrectinib, and it worked in the first two patients that developed resistance. "Eventually patients will need it – we don't know when and hope it's a long time – but we want it to be there when they do," the exec said. It was a very deliberate effort, he noted, "and frankly we think this is how modern oncology drug development ought to happen."

Not A Universal Model

While NGS diagnostics will facilitate treatment based on molecular signature and help deliver on the promise of the genomics revolution, the histology-independent model is unlikely to

revolutionize oncology drug development.

In recent years, industry and non-industry groups have embraced "basket" trial designs driven by biomarkers, like *Novartis AG*'s SIGNATURE trial, ASCO's ongoing TAPUR trial and the NCI-MATCH trial from the National Institutes of Health. (Also see "*Genomics-Driven Trials Built To Be Fast And Flexible*" - Pink Sheet, 21 Sep, 2015.)

But some of the early basket trials to report have suggested tumor histology cannot be ignored.

Roche's VE-BASKET trial of *Zelboraf* (vemurafenib), a Phase II trial in patients with any type of nonmelanoma cancer who had BRAF V600 mutations, found that histologic context still mattered. Hyman was also lead author on VE-BASKET, and concluded in the New England Journal of Medicine that "an important implication" of the trial was that conventional treatment based on organ site, with molecular subtypes, "cannot be entirely replaced by molecular nosology (e.g. BRAF-mutated cancers)." (Also see "*Tissue-Agnostic Approach To Cancer Drug Development Takes A Hit*" - Pink Sheet, 14 Sep, 2015.)

Puma Biotechnology Inc. similarly found in its SUMMIT study of neratinib, also led by Hyman and presented at the American Association for Cancer Research annual meeting this April, that the drug had activity in some types of cancer with HER2-activating mutations but not others. (Also see "*Puma's Neratinib SUMMIT Study Shows Potential & Pitfalls Of Precision Medicine*" - Pink Sheet, 2 Apr, 2017.)

Probably the most likely application of tissue-agnostic drug development will be as a way to identify treatment for rare cancers.

Identification of targets is also easier said than done, but the increased information to come from greater use of less-expensive NGS will offer data mining opportunities. For example, TRK fusions were first discovered in 1982 but only gained practical attention with the development of next-generation sequencing.

But this sort of development poses a chicken-or-the-egg problem – does the detection of the mutation come first, or does the therapeutic that can target the mutation? "This is a real advance that we're seeing here today because it shows that it's important to look for it, because you have a treatment that could work for it," John Heymach, MD Anderson Cancer Center, pointed out during a discussion of the larotrectinib results.

"You only find what you look for," Heymach said.

Loxo's Van Naarden had a similar take. "You have to run the clinical trial and look," he said. "You really don't know a priori."