Patients with medullary thyroid cancer (MTC) may go long periods of time without any disease progression, but a majority of patients will enter an accelerated phase where the cancer becomes more aggressive, according to Jochen H. Lorch, MD, MS. There are 2 treatments currently approved by the FDA to treat MTC after progression; however, neither treatment provides a cure to patients, and the 2 drugs are often poorly tolerated by patients, according to Lorch, assistant professor of medicine at Harvard Medical School and director of the Thyroid Cancer Center at Dana-Farber Cancer Institute. New options are needed to treat MTC patients who progress and detect progression earlier on, says Lorch.

In an interview at the 2016 American Thyroid Association annual meeting, Lorch discussed with Targeted Therapies in Oncology (TTO) current approved treatment options for patients with MTC, the biology of the disease, managing potential progression, and future possibilities in the treatment of MTC.

**TTO: What is the standard treatment for MTC?**

**Lorch:** MTC is a rare disease among endocrine cancers; [it makes up] less than 4% of all thyroid cancers. Many times, MTC is stable and does not require treatment for many years. Eventually, though, most patients enter an accelerated phase where they do require systemic treatment.

There are currently 2 FDA-approved drugs for cases where the cancer progresses beyond the initial treatment of surgery or surveillance-vandetanib (Caprelsa) and cabozantinib (Cometriq). Both were based on phase III data. These were randomized trials, similar in size; however, the entry criteria were quite different. In the vandetanib trial, for example, there was no explicit requirement for disease progression. While in the cabozantinib study, progression was required for a little more than a year. Both trials showed a difference in progression-free survival (PFS). There was, however, no difference in overall survival, due to crossover. Subset analyses in the cabozantinib trial identified a subset of patients with a specific mutation in the RET proto-oncogene, the M918T mutation, which is typically associated with aggressive growth and a poor prognosis. Those patients actually had a survival benefit. **TTO:**

**How do you determine which drug to give each patient?**
**Lorch:** The big question is what are you going to use rst among these 2 drugs, and there is really no clear guide. Those 2 randomized trials were designed in quite different ways so you can’t directly compare the results. On the surface, vandetanib had much longer PFS than cabozantinib. However, the placebo arm in this trial also had PFS of a year and a half, which means that patients who received the placebo still had disease stability for more than a year. Patients might otherwise have been a good candidate for systemic treatment, so you might have been able to spare them the toxicity.

In the case of cabozantinib, the PFS in the study arm was roughly 11 months compared with approximately 4 months in the placebo arm. That sounds a little bit worse, but again, this was a different patient population with a more aggressive type of thyroid cancer. The type of RET mutation you detect does not influence the drug you’re using or tell you when to start treatment, [which] is really based on whether they have disease progression. Ultimately what counts is not calcitonin or CA levels, but radiographic progression.

**TTO:** Do all MTCs turn more aggressive?

**Lorch:** At this point, we don’t really know what prompts cancers to enter the accelerated phase. The vast majority of patients eventually enter that phase and it’s impossible to predict when that’s going to happen. There must be some additional genetic event that occurs. When that occurs is probably largely due to chance. It’s probably also not just one process but perhaps a number of events that trigger those tumors to become more aggressive.

At this point, outside of tumor marker measurements, we don’t really have anything to detect any early signs of potential progression. Even if tumor markers are starting to rise, that alone is not a reason to start treatment. It may prompt some additional imagining studies, alertness and more tight surveillance, but rising tumor markers by themselves do not mean that you have to put someone on these relatively morbid treatments.

**TTO:** What would you suggest for the maintenance of MTC?

**Lorch:** The unique feature about the biology of MTC is that there are often extended periods without any progression at all, or only a gradual progression. During that stage, sequential calcitonin and CA measurements, sequential imaging—such as thyroid or neck ultrasounds, CT
scans, and bone scans, are necessary to catch the moment when the disease is turning more aggressive, at which point systemic treatment should then be considered.

**TTO:** Where do you see treatment for MTC going in the future?

**Lorch:** In this day and age, you can’t talk about cancer without talking about immunotherapy, and there is no doubt that trials will be opening sooner or later for MTC. The other group of trials that will be coming are RET inhibitors. In many ways, they are similar to vandetanib and cabozantinib, but they more specifically block the RET proto-oncogene that’s driving MTC in the majority of cases. The hope is that this will add another line of treatment because none of the FDA-approved treatments are curative in any way. The best you can expect from them is to seize control for an extended period of time. Eventually, these patients progress and it’d be good to have another line of treatment available.

The other hope is that these drugs might be a little more favorable in terms of toxicity. The 2 drugs that are approved have rather significant toxicities. There are frequent dose reductions in the majority of cases with cabozantinib and a very significant number of cases with vandetanib have to be dose reduced, so the hope is that new drugs will be better tolerated because they may be more specific to the actual target that’s driving the cancer.

While we know that RET is driving those cancers, it’s not entirely clear whether these other 2 drugs act through inhibition of RET or if there’s other targets, such as VEGF, that also contribute to responses, so the hope is that they’ll be equally efficacious with less toxicity. But this will need to be tested and that will be the work of the next couple of years. - See more at: http://www.targetedonc.com/publications/targeted-therapy-news/2016/october-2016/expert-describes-need-for-new-options-for-medullary-thyroid-cancer#sthash.WLryW4yl.dpuf