Join A Clinical Trial: Casodex (bicalutamide) + Metformin

Dr. Marijo Bilusic is the director of the National Institutes of Health (NIH) Hematology Oncology Fellowship, and an Associate Research Physician in the Genitourinary Malignancies Branch, Center for Cancer Research, National Cancer Institute (NCI). He's keenly interested in tumor immunology and in developing prostate cancer treatments using novel target agents, therapeutic cancer vaccines, antibodies or immune modulations.

Prostatepedia spoke with him about a trial he's running that looks at men with prostate cancer on Casodex (bicalutamide) with or without metformin.

Would you walk us through the thinking behind your trial looking at Casodex (bicalutamide) with or without metformin?

Dr. Marijo Bilusic: A former prostate cancer patient of mine had had surgery and his prostate was removed. Then his PSA kept rising, and he was not very keen about hormonal therapy, which was recommended by other oncologists he'd seen before me. I met him, and we talked about what to do. "We're just going to observe you for now," I said. "Try to exercise, lose some weight, and make healthy lifestyle changes. We'll see you back in three months, and we'll see what your PSA's doing."

In three months, he came back, and his PSA was 50 percent less than before. It went from 4 to 2.

I was impressed. I asked him, "What did you do?" "I followed your instructions."

"Lots of people follow my instructions," I said, "but I've never seen anybody have PSA decline just with exercise and diet change. Any other changes from the last time we met?"

"I've also been taking metformin," he said. "I read that metformin can help people with prostate cancer and asked my primary care physician to prescribe it, even though I was not diabetic." It's important to note that metformin is not something that we would recommend to prostate cancer patients outside of a clinical trial, yet. That's why we're running this study-to learn more about how metformin works and who it may work for.

I was surprised, and grew curious about a potential link. After that, I did a literature review. I found one population based observational cohort study that included around 38,000 men with prostate cancer and diabetes from Ontario, Canada. Authors reported

that metformin treatment was associated with decreased prostate cancer mortality: 24% reduction for each additional 6 months of metformin use while use of other anti-diabetic medications did not significantly decrease mortality. This was a very interesting study. Two prospective studies tested metformin in non-diabetic patients with prostate cancer. First enrolled 42 patients with castration resistant prostate cancer who were treated with metformin, 1,000 mg twice daily. Two patients had ≥ 50% PSA decline and in 23 patients (52.3%) had a prolongation of PSA doubling time. Another study enrolled 24 men with newly diagnosed prostate cancer that were treated 500 mg of metformin three times a day before the surgery (neoadjuvant treatment). Metformin reduced
Ki67 proliferation index by 29%, compared to the baseline biopsy, meaning that the cancer became less aggressive with metformin use of about four weeks. That was very interesting.
Nobody knows how metformin works, exactly. Some studies have shown metformin also could help patients with breast cancer and pancreatic cancer, and also observational studies have shown decreased risk of the incidence of cancer, suggesting that metformin can help prevent cancer.
Though we are still trying to understand how metformin works, we do know it's inexpensive and it's very safe. Instead of having a treatment of prostate cancer that costs more than $100,000, it would be great to have one that costs only a couple of dollars. We're not there yet, but we're hopeful that this trial and others like it will help us continue to learn more about how to best treat prostate cancer.
To learn more about when metformin may work, we came up with the study design to test metformin in combination with Casodex (bicalutamide), an FDA-approved agent for prostate cancer. We selected Casodex (bicalutamide) because testing of this combination using animal model showed the synergistic effect of Casodex (bicalutamide) and metformin. The side effects profile is much better than from Lupron (leuprolide), so we thought that would be a reasonable alternative for people who have biochemically recurrent prostate cancer with rapidly rising PSA.

What can patients expect to happen in the trial?

Dr. Bilusic: First, we have to make sure they're eligible. When they contact us, we determine if they have a biochemical recurrence, which we define as somebody who's had prostatectomy followed by two rising PSAs above 0.2. If PSA doubling time is between three and nine months, those patients are potentially eligible for this trial. We are also looking for people who are not diabetic, but they should have a BMI of 25 or more because the mice models we tested were obese, and one of the side effects

of metformin is weight loss. We did not want to give somebody who is skinny to start with a drug that makes them lose weight. Eligible participants should also not have their testosterone suppressed by hormonal therapy. We don't allow prior hormonal therapy, unless it was given during the primary treatment as an adjuvant or neoadjuvant therapy.

Those are the main inclusion criteria: BMI more than 25, no history of diabetes (hemoglobin A1C should be less than 6.5), testosterone more than 150, no prior hormonal therapy, and PSA doubling time is three to nine months. Then we'll do a CAT scan and bone scan to confirm they don't have metastatic disease.

Once we determine they are eligible, we randomize them to one of the two groups. One group (control arm) will receive observation for two months, followed by Casodex (bicalutamide) alone for 6 more months. The other group will receive metformin alone for two months, followed by a combination of metformin and Casodex (bicalutamide) for 6 months. Because Casodex (bicalutamide) doesn't deprive testosterone, people have normal levels of testosterone, or sometimes higher levels. The total duration of treatment is 8 months or 32 weeks.

They come here to the NIH clinical center once a month, where we do blood work, a doctor evaluation, and we provide medication. During the trial, in addition to regular blood work, we research blood at the start, at the beginning of cycle three, and at the end of the trial. We're trying to understand the mechanism of how metformin works.

I know that you supply the medication, but are there any fees associated with participating in the trial?

Dr. Bilusic: No, there's really nothing else for the patient. Everything is provided, and all the care here at the NIH Clinical Center is free. Once a patient is enrolled on one of our protocols, we also support their trip to the NIH Clinical Center, so patients can come from all over the United States. We also provide a stipend for a hotel if they have to stay overnight. And we give them a meal voucher.

Subscribe to learn more about Dr. Bilusic's trial as well as others.