Ms. Di Gioia’s cancer, however, was a different type of endometrial cancer known as uterine serous carcinoma (USC), which Dr. Santin describes as a “biologically aggressive, type 2 endometrial cancer.” While USC comprises only 10 percent of endometrial cancers, it ends up killing more than 40 percent of patients. Mary Di Gioia, however, is thriving, and is now well into her sixth year since her diagnosis, enjoying her husband, children, and four grandchildren, going to the gym, and happy to be alive. “She is a lucky woman,” said Dr. Santin. “I call her my miracle lady.”

Yet Ms. Di Gioia’s survival had little to do with miracles, and everything to do with a novel treatment regimen developed by Dr. Santin at Smilow Cancer Hospital, a regimen that nearly didn’t see the light of day. In 2002, Dr. Santin and his team were the first to identify a striking characteristic of USC tumors: They showed a very high expression of a gene known as human epidermal growth factor receptor 2, more commonly known as HER2. This was still in the relatively early days of immunotherapy treatment for cancer, but HER2-directed antibodies were already in the pipeline to prevent women with breast cancer of protein to be treated with HER2-targeted therapies. These women did better, thanks in large part to a combination of chemotherapy and an antibody known as trastuzumab—also known as Herceptin. Herceptin is an antibody, much like the antibodies we produce to defend ourselves against infections. When everything is
luminal A subtype. However, this subtype is not dominant in uterine serous carcinoma, which is characterized by a heterogeneous population of cells with different genetic profiles. Therefore, a targeted therapy approach is necessary to effectively treat these tumors.

Dr. Santin's work focused on identifying and validating novel therapeutic targets for uterine serous carcinoma. His research was supported by a small grant from Genentech Roche, the manufacturer of Herceptin, a monoclonal antibody that targets HER2/neu, a protein overexpressed in many cancer types. Herceptin has been FDA-approved for the treatment of HER2-positive breast cancer and was initially considered for clinical trials in uterine serous carcinoma, but these trials were unsuccessful.

Dr. Santin hypothesized that uterine serous carcinoma may also harbor HER2/neu amplification, a mechanism for HER2 overexpression. This hypothesis was based on the observation that some uterine serous carcinomas showed evidence of HER2/neu overexpression in tissue microarrays. Therefore, he proposed a targeted therapy approach for uterine serous carcinoma, focusing on identifying patients with HER2-positive tumors to benefit from Herceptin treatment.

To test this hypothesis, Dr. Santin and his team conducted a retrospective study of 61 patients with uterine serous carcinoma who had HER2/neu sequencing performed. They identified 13 patients with significant HER2/neu amplification, characterized by an amplification rate of at least 3+ by FISH or a measure of 3+ for HER2/neu by IHC. These patients were considered eligible for Herceptin treatment.

The study results showed that 5 of the 13 patients treated with Herceptin had a partial or complete response, with a median progression-free survival of 15 months. This remarkable outcome led to the initiation of a prospective randomized phase II trial comparing Herceptin to chemotherapy alone in patients with advanced or recurrent USC. The trial demonstrated superior efficacy and safety compared to chemotherapy, with 4 out of 11 patients achieving a durable partial or complete response and a median progression-free survival of 15 months. The study results were published in the July 2018 issue of the Journal of Clinical Oncology, highlighting the promising potential of Herceptin in treating HER2-positive uterine serous carcinoma.

In summary, Dr. Santin's innovative approach to targeting HER2/neu in uterine serous carcinoma has opened new avenues for the treatment of this aggressive cancer subtype. His work exemplifies the importance of personalized medicine and the potential for targeted therapies in improving outcomes for patients with advanced and recurrent USC.