

# TARGETING DIFFICULT TO TREAT CANCERS OFFERING HOPE TO PATIENTS

FOR OVER A DECADE Cyclacel has focused on understanding the biology of the cancer cell cycle and discovering new drugs to block cancer growth and control the disease. Throughout 2009, Cyclacel's investigators reported important data from various clinical trials of the company's drugs that may have benefited certain participating patients in new and unique ways. Although much of 2009 focused on the development of sapacitabine, our other investigational Phase 2 stage drug, seliciclib, may have also made a difference in the lives of some patients.<sup>1</sup>

One such patient is Giacomo Cugliari, of Ontario, Canada, pictured with his wife Marianna on the front cover of this report. Giacomo first learned of his diagnosis of nasopharyngeal cancer (NPC) in 2003. His cancer journey began when his family physician, concerned about Giacomo's frequent nose bleeds, referred him to an Ear, Nose & Throat specialist in Toronto. Initially the specialist thought that Giacomo had a severe allergy to the carpeting in his home. However, this diagnosis was discarded after all carpeting was removed without stopping the bleeding episodes which increased in frequency.

Giacomo was then referred to an oncologist. After a number of tests, including biopsies, laboratory tests, an endoscopic nose exam, x-rays, MRI and CT scans, suggested a possible cancer diagnosis, Giacomo was eventually confirmed as having NPC.

NPC is a common disease in Asians but rare in Caucasians, in which malignant cancer cells form in the tissues of the upper part of the throat and behind the nose. Infection by certain viruses, such as the Epstein-Barr Virus, is considered a risk factor and a poor prognostic indicator. NPC can be difficult to diagnose and its symptoms may include sore throat, difficulty breathing, frequent nose bleeds, headaches, pain or ringing in the ear and hearing loss.

Giacomo's condition soon deteriorated to the point where he was experiencing nearly all of the symptoms, in addition to double vision or diplopia.

In 2003, the treatment options available to him included radiation and cytotoxic chemotherapy. According to Giacomo's recollection, his oncologist at a university hospital in Toronto, started him on a regimen of both radiation and cytotoxic chemotherapy. He recalls that his tumor responded and the cancer in his throat began to recede. He remembers that both he and his oncologist were satisfied with his initial response to therapy.

Unfortunately in 2005 the cancer returned. His physician adjusted the treatment schedule to a new

form of radiation therapy given concurrently with two cytotoxic chemotherapy drugs. An initially positive response only lasted about a year. Giacomo and his doctors knew that his chances for a long-term response were very low.

By August 2006, Giacomo recalls that his condition continued to deteriorate. The mass in his nasopharynx was growing, he had severe diplopia, and the cancer had spread to his lymph nodes. Running out of options, Giacomo's physician referred him to Princess Margaret Cancer Center in Toronto where he hoped to enroll in a

clinical trial and find new hope.

Under the care of a new physician, Dr. Lillian Siu, an experienced cancer specialist and clinical researcher, he was enrolled in a clinical trial involving gemcitabine, carboplatin and an epidermal growth factor inhibitor. However, he developed significant toxicity to this treatment regimen which resulted in his discontinuation from the clinical study. No longer a candidate for further chemotherapy, he was receiving supportive care for the symptoms caused by his cancer.



By March 2008, Giacomo's condition had become critically worse. His nose bleeds and headaches became more frequent and severe. His hearing began to decline. His diplopia had reduced his vision. He had lost 45 pounds. Just when all hope was nearly lost, Dr. Siu offered to enroll him in a clinical trial of seliciclib oral capsules, an experimental drug from Cyclacel. Dr. Siu was a Principal Investigator of this trial being conducted in certain Asian and North American hospitals. Giacomo agreed to participate.

Seliciclib inhibits cyclin dependent kinase enzymes or CDKs which were the subject of the 2001 Nobel Prize in Medicine. The drug's mechanism targets the biological clock of cancer cells or their cell cycle with the objective of stopping cancer from progressing and inducing cancer cells to commit suicide. It works without destroying the bone marrow and damaging the immune system. Seliciclib had been shown to have anti-tumor activity as a single agent in early stage trials in patients with a variety of solid tumors including lung cancer and NPC.

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Seliciclib capsules are taken by mouth. This was a nice change for Giacomo as nearly all previous cytotoxic chemotherapies were given as intravenous injections or infusions. He did not like infusions because, as he recalled, his veins were difficult to find by nursing staff. The seliciclib treatment regimen was easy by comparison as it involved taking the capsules twice a day for four days every week.

For Giacomo and Marianna the choice of treatment was stark: hospice care or the seliciclib trial. In April 2008, he began his first treatment with seliciclib. Within the first month of treatment, his nose bleeds stopped and his vision improved. His appetite returned and he felt better. The improvement in his condition was immediately apparent and he went on to achieve continuous seliciclib treatment for about two years without evidence of progression of his disease.

Recently published non-clinical studies show that seliciclib may be active in cancers that have failed to respond to cytotoxic chemotherapies, including lung cancers that express a gene mutation called K-Ras or N-Ras, and breast cancers that have failed to respond to hormonal therapy. Cyclacel and its collaborating scientists and physicians are intrigued by these results and continue to study the drug to determine why it would work in these difficult to treat cancers.

Giacomo is not interested in the science behind the drug. He simply knows that his response to the treatment is remarkable, perhaps miraculous, and he is grateful for it. In March 2010, he began his 23rd month on treatment. He has experienced very few toxicities from taking the drug over this long period. He looks and feels great and was able to return to his family home in Uruguay for a vacation in early 2010. With a smile, he recounts how he had the opportunity to eat figs from the family farm, a place that at one time he thought he would never see again.

When asked how he has managed through the years of treatment, he credits the two outstanding cancer centers in Toronto that looked after him, Dr. Siu, seliciclib, and of course Marianna, his wife of 24 years who has been there for him, loving and supporting him every day. He has returned to his regular activities and is grateful for every day that dawns. He and Marianna look forward to celebrating their silver anniversary. ●

<sup>1</sup>Sapacitabine and seliciclib are investigational drugs and are not approved as marketed agents for human use.