



ACUTE MYELOID LEUKEMIA (AML)

For over a decade Cyclacel has been dedicated to the understanding of the biology of the cancer cell cycle and translating advances in this area of science into novel therapeutics to benefit cancer patients. The recent opening for enrollment of the first Phase 3 trial in Cyclacel's history represents a culmination of the work of many employees, advisors and collaborators.

SEAMLESS PHASE 3 STUDY

The Phase 3 study, called SEAMLESS, is a pivotal, randomized trial of sapacitabine in elderly patients aged 70 years or older with newly diagnosed acute myeloid leukemia (AML) who are not candidates for intensive induction chemotherapy. SEAMLESS builds on promising one-year survival observed in elderly patients aged 70 years or older with newly diagnosed AML or AML in first relapse enrolled in a Phase 2 study of single agent sapacitabine.

The study is being conducted under a Special Protocol Assessment (SPA) agreement that Cyclacel reached with the U.S. Food and Drug Administration (FDA). The SEAMLESS study is chaired by Hagop M. Kantarjian, M.D., Chairman and Professor, Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, Texas. As the Principal Investigator of both Phase 1 and Phase 2 trials of sapacitabine in hematologic malignancies, Dr. Kantarjian has been instrumental in helping Cyclacel move sapacitabine to Phase 3 status for the front-line treatment of elderly patients suffering from AML.

AML: A LIFE-THREATENING DISEASE

AML is a cancer of the blood cells that progresses rapidly and if not treated, could be fatal in a few months. AML is generally a disease of older people and is uncommon before the age of 40. The average age at the time of AML diagnosis is about 67 years. There are more than 12,300 new cases of AML, of which about half occurred in older patients, and nearly 9,000 deaths caused by this cancer each year in the United States underscoring the high unmet medical need in this patient population.

Survival of older or elderly patients with AML is poor and has not improved in the last three decades. A recently published randomized study of patients with AML aged 70 years or older receiving front line treatment found that median overall survival in this group was approximately three months.¹ The reasons for poor survival include the inability to tolerate intensive therapy resulting from concomitant medical illnesses and organ dysfunction, and a greater resistance to therapy as a result of pre-existing or antecedent hematological disease (AHD), such as myelodysplastic syndromes (MDS) or myeloproliferative diseases (MPD). There are few treatment options for patients who are not candidates for standard induction chemotherapy.

¹ Harousseau JL, et al, *Blood* 2009 114 1166-1173.

INVESTIGATOR PERSPECTIVES

Following are excerpts from interviews with three investigators who took part in the recently reported Phase 2 study of sapacitabine in AML and are also participating in the SEAMLESS Phase 3 study. They are: David Claxton, M.D., Penn State Cancer Institute, Hershey, PA; Stuart Goldberg, M.D., John Theurer Cancer Center, Hackensack, NJ; and Karen Seiter, M.D., New York Medical College, Valhalla, NY. These investigators are leukemia experts who are also experienced investigators in clinical trials, specifically in acute myeloid leukemia, myelodysplastic syndromes, lymphoma, stem cell and bone marrow transplantation.

All three investigators agreed that there is a high unmet medical need in the population of elderly patients with AML. They noted that finding a therapeutic alternative to offer to their elderly patients who are unable to tolerate intensive chemotherapy was a significant factor which attracted them to consider the sapacitabine studies. "These patients have few options and are often too frail to make it through conventional 7+3 chemotherapy," commented Dr. Seiter.

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– KAREN SEITER, M.D.

Events over the past eighteen months have exacerbated this unmet patient need. Several drugs under clinical investigation in older or elderly patients with AML have failed in randomized Phase 2 or Phase 3 studies or encountered clinical or regulatory setbacks. Dr. Goldberg remarked that one of these drugs, gemtuzumab ozogamicin, was on the market after receiving accelerated approval for relapsed or refractory AML. However, as a confirmatory study failed to demonstrate an improvement in overall survival, it was voluntarily withdrawn from the market.

In light of the challenges posed by the disease and the decline in investigational drug protocols on offer for elderly patients with AML, what attracted these investigators to participate in sapacitabine clinical studies?

Dr. Seiter commented that "preclinical safety and efficacy demonstrated by the test drug, as well as unmet medical need, were important factors." In addition she noted that investigator enthusiasm for a new drug is often determined by their initial clinical experience with the new agent. Citing data she presented at a joint NCI-ASCO symposium on Cancer Trial Accrual in April 2010, it was shown that if investigators observed clinical benefit with few toxicities in their first few patients, they were more likely to continue contributing patients to the trial, as opposed to when they encountered difficulties.

Dr. Claxton agreed that manageable toxicities and clinical benefit of an investigational drug could increase investigator enthusiasm in entering patients into a clinical trial. "We saw reduced blast counts in a number of the first few patients we treated with sapacitabine. As long you can manage toxicities as they may come along and you see clinical benefit, you get excited as an investigator."

As is common with anticancer drugs in clinical trials, there is a learning curve for investigators treating patients with sapacitabine for the first time. All three investigators agreed that it is important to monitor patient blood counts, especially in the first few treatment cycles. Depending on baseline values, doses in some patients may need to be reduced or held until counts recover. After the initial cycles, patients who respond often do well with the dose adjustments. The investigators found this to be one of the most interesting aspects of sapacitabine therapy. They observed that while the agent has the ability to reduce excessive blast counts in AML patients who are often frail and have comorbidities, following the initial few cycles many patients can take the drug over long periods of time as an oral therapy.

Sapacitabine Orphan Drug Protection

Sapacitabine has been designated an Orphan Drug by FDA and EMA for use in the treatment of patients with both AML and MDS.

Under the Orphan Drug law, companies developing drugs for a disorder affecting fewer than 200,000 people in the United States may enjoy market exclusivity for seven years in parallel with available patent life and may be eligible for certain tax incentives. The European Union's orphan designation confers similar benefits and 10 years of exclusivity.

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– DAVID CLAXTON, M.D.

Dr. Goldberg noted that oral dosing allows patients to be followed by their community hematologists/oncologists in partnership with the clinical investigator, allowing local physicians to participate in the treatment plan. Unlike conventional chemotherapy, it may take several cycles of treatment for patients to achieve a response, which can sometimes occur as late as 9 cycles. This feature of the sapacitabine treatment experience provides a rationale for continuing treatment.

The investigators were eager to share anecdotal stories of patients they treated in sapacitabine trials:

Dr. Seiter shares the story of an elderly woman treated in the Phase 2 trial of sapacitabine who achieved 24 cycles of treatment with the drug. This patient often comes to the hospital while pushing her elderly husband who is wheel-chair bound and has to carry oxygen with him because of respiratory difficulties. New staff are frequently surprised to learn that it is not the husband but the wife who is the patient being treated for AML.

Dr. Claxton recounts his enthusiasm in reviewing the charts of some of his patients in the Phase 2 AML study showing remarkable declines in blasts in the first several cycles. He specifically recalls a 70-year old patient with secondary AML and a history of prior chemotherapy and radiation for lung cancer who entered remission on sapacitabine and then enjoyed a 14-month remission with excellent quality of life.

Dr. Goldberg recalls the case of an AML patient from the Phase 2 sapacitabine study. The patient was an 80-year old grandmother, who while on treatment with sapacitabine, was physically able to continue working at her job as a school crossing guard and also join her grandchildren on a family vacation in Florida. Dr. Goldberg believes that “the oral dosing of sapacitabine is a quality of life game changer”. “Subjecting elderly patients to 7 + 3 chemotherapy and probably prolonged hospitalization near the end of life is both unfair and unacceptable, and something that can be avoided with oral delivery of sapacitabine,” continued Dr. Goldberg.

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– STUART GOLDBERG, M.D.

All three investigators remain enthusiastic and are eager to participate in the SEAMLESS Phase 3 study. They have volunteered to mentor and share their experiences with new investigators that may participate in the Phase 3 trial who have no or limited experience with the drug.

Cyclacel is very grateful for the dedication and support of all clinical investigators who contributed their expertise in treating patients with AML to sapacitabine clinical trials, including the recently reported Phase 2 clinical trial of sapacitabine in AML, and those participating in the SEAMLESS Phase 3 study.