FLORIDA CANCER SPECIALISTS & Research Institute

CASE STUDY: The Development of Polatuzumab Vedotin (POLIVY®) into First-Line Therapy for Relapsed or Refractory Diffuse Large B-cell Lymphoma.

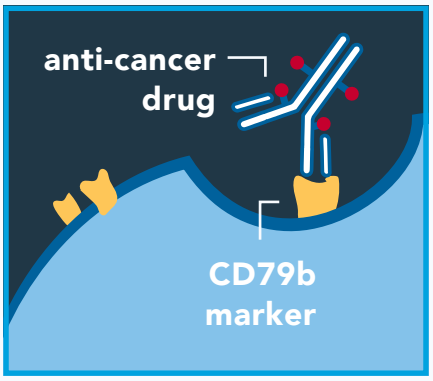
Phase 1 clinical trial conducted at Florida Cancer Specialists & Research Institute, LLC (FCS) ultimately leads to FDA approval of Polatuzumab vedotin, now considered first-line therapy for adult patients with relapsed or refractory (R/R) diffuse large B-cell lymphoma (DLBCL).

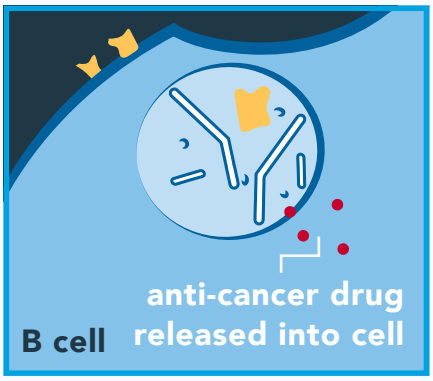
About DLBCL

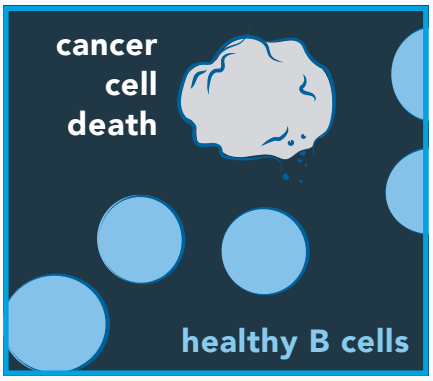
The most common form of non-Hodgkin lymphoma, DLBCL comprises 25 to 30 percent of all lymphomas diagnosed annually in the U.S. DLBCL is a fast-growing, aggressive form of lymphoma that occurs when cancerous white blood cells, also known as B cells or B lymphocytes, enlarge the lymph nodes; frequently migrating to other organs. Additionally, patients often experience "B-symptoms," which refers to fatigue, fever, night sweats and weight loss. Treatment is, most often, chemotherapy. The five-year survival rate is 73%.

Understanding Polatuzumab Vedotin (POLIVY®)

Almost all B cells (including cancerous ones) have a marker on their surface called CD79b. POLIVY is a type of targeted chemotherapy medicine called an antibody-drug conjugate, or ADC, with the ability to find dividing B cells, including cancerous B cells, and attach to them using the CD79b marker. A cytotoxin is then released into the cancer cell, causing it to die.







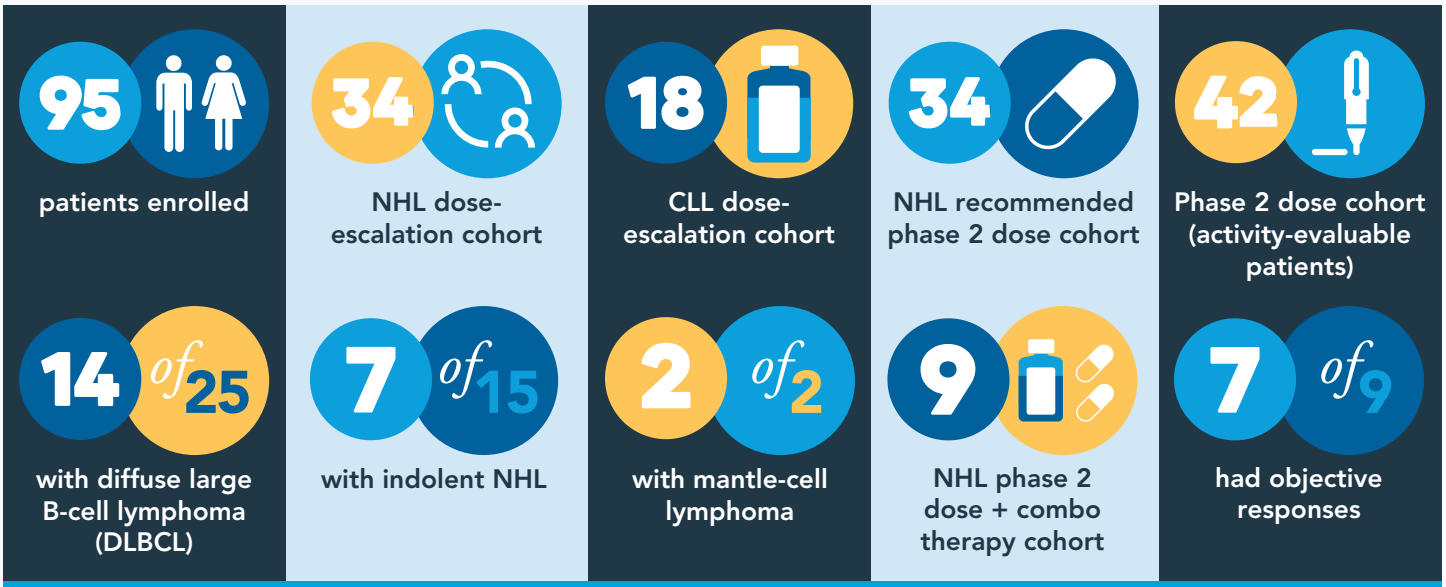
Determining the Effectiveness of Polatuzumab Vedotin (POLIVY)

The FCS Sarasota Drug Development Unit was one of 13 centers participating in the initial Phase 1 first in-human escalation monotherapy trial for polatuzumab vedotin. The purpose of this trial was to evaluate its effectiveness in R/R B-cell non-Hodgkin lymphoma (NHL) and chronic lymphocytic leukemia (CLL) based on safety, tolerability, maximum tolerable dose and recommended phase 2 dosage as a single agent and in combination with rituximab, a targeted immunotherapy for NHL.

FCS Director of Drug Development Manish R. Patel, MD was one of the early investigators for the trial.

"It's exciting to help develop drugs from the initial Phase 1 trial, including polatuzumab vedotin.

The observations that we made in this initial trial were the first steps to determining what is now part of the standard of care. Here we are, 12 years later, and POLIVY is now indicated as part of first-line therapy for R/R DLBCL patients," says Dr. Patel.



Phase 1 Trial Results

FDA Approval Timeline

On June 10, 2019, the U.S. Food and Drug Administration (FDA) granted accelerated approval to polatuzumab vedotin-piiq (POLIVY, Genentech, Inc.) for use in combination with two other cancer treatments: bendamustine and a rituximab product (BR).

This approval was based on findings from the Phase 1b/2 GO29365 trial (NCT02257567) an open-label, multicenter Phase 1 clinical trial that included a cohort of 80 patients with relapsed or refractory DLBCL who received at least one prior treatment regimen.

At the end point of the study, 40% of patients receiving the polatuzumab vedotin regimen achieved complete response (CR), meaning they experienced a disappearance of all signs of cancer, as compared with 18% of patients in the BR-alone arm.

Additionally, those who responded to the treatment remained in remission for a year or longer. This highly favorable response to POLIVY + BR treatment led to its accelerated FDA approval, making it available to all patients.

In August 2022, the FDA accepted a supplemental Biologics License Application (sBLA) for the combination of polatuzumab vedotin and R-CHP (a combination of rituximab, cyclophosphamide, doxorunicin, vincristine and prednisone) for the treatment for patients with previously untreated DLBCL.

FCS participated in the late-phase randomized Polarix study of 879 patients with previously untreated DLBCL led to a 27 percent reduction in

the risk of disease progression, relapse or death compared with only rituximab, cyclophosphamid, hydroxydaunorubicin, oncovin, and prednisone (R-CHOP) in patients with newly diagnosed DLBCL. Overall Survival at two years did not differ significantly between the Pola-R-CHP group and the R-CHOP group. The Phase 3 study results showed rapid and sustained improvements in symptoms and enhanced quality of life for adult patients with diffuse large B-cell lymphoma (DLBCL).

Both regimens led to rapid and sustained improvements in symptoms and improved health-related quality of life. Most patients had improvements in their lymphoma symptom scores after cycle 1, which may represent a benchmark in frontline DLBCL in the modern era.

> Quality of life (QOL) gains were not lost after treatment continued. It is reassuring to see that there is an improvement of the quality of life, functional status, and the lymphoma-associated symptoms. There was also no accumulated toxicity from the therapy. We're happy that there is no persistent toxicity from the patient's perspective, this type of QOL measurement is something that we should be more regularly involved in. Regulatory agencies can see that there is a persistence of a benefit to the patients from the patient's perspective.
>
> **Gustavo Fonseca, MD,** FCS Director of Clinical Research

Next Steps for Research

Evolved and advanced through international efforts, Pola-R-CHP was also approved in Europe in late 2022 and is considered first-line treatment for R/R DLBCL patients. Researchers are motivated by the fact the functional improvements and disease-free survival among patients has persisted. As such, polatuzumab vedotin is among the targeted therapies helping to transform chemotherapy.

A Leader in Cancer Care Advancements

With more than 300 clinical trials offered at three Phase 1 Drug Development Units and 37 locations statewide, FCS is involved in breakthrough cancer research that is advancing cancer screening, diagnosis, treatment and survivorship.

"It is rewarding to see the impact of our work in developing this drug and several others over the years. There are many others that expect to have the same trajectory," said Manish Patel, MD.

Additional References/Links

Study abstracts, FDA approvals:

- Safety and activity of the anti-CD79B antibody-drug conjugate polatuzumab vedotin in relapsed or refractory B-cell non-Hodgkin lymphoma and chronic lymphocytic leukaemia: a phase 1 study
- A Study of Polatuzumab Vedotin (DCDS4501A) in Combination With Rituximab or Obinutuzumab Plus Bendamustine in Participants With Relapsed or Refractory Follicular or Diffuse Large B-Cell Lymphoma
- FDA approves polatuzumab vedotin-piiq for diffuse large B-cell lymphoma (June 10, 2019)
- FDA Accepts Supplemental Biologics License Application for Genentech's Polivy Combination for People With Previously Untreated Diffuse Large B-Cell Lymphoma

Eventual FDA approved cancer treatments resulting from Phase 1 clinical trial FCS

participation: FLCancer.com/TBD

- Trifluridine/Tipiracil
- Entrectinib
- Avelumab
- Polatuzumab vedotin
- Enasidenib
- Pirtobrutinib
- Duvelisib
- Umbralisib
- Trametinib/Dabrafenib
- Niraparib
- Rucaparib
- Fostamatinib
- Margetuximab
  - Several of these were First in Human trials.
  - Polatuzumab vedotin is now part of 1st line therapy in Diffuse Large B Cell Lymphoma.

Types of Clinical Trials Phases

Phase I:

Primary goals to determine the activity in humans: the maximum tolerated dose, how the drug works in the body, side effects and duration of side effects.

Phase II:

Positive activity in Phase II trials may be approved for standard treatment or may require additional evaluation in Phase III trials.

Phase III:

Compare a new drug or therapy with a standard therapy in a randomized manner, providing a direct comparison to determine effectiveness.

Phase IV:

Once the drug or treatment becomes part of standard therapy, the manufacturer of the drug may elect to initiate Phase IV trials.

Conducted for ongoing evaluation of the treatment effectiveness and monitoring of side effects.

Current list of FCS clinical trials: **FLCancer.com/ClinicalTrials**