GLORIA
Phase 3 Trial in TNBC

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The GLORIA Study: A Phase 3, Randomized, Open-Label Study of the Anti–Globo H Vaccine Adagloxad Simolenin/OBI-821 in the Adjuvant Treatment of Patients With High-Risk, Early-Stage, Globo H–Positive, Triple-Negative Breast Cancer

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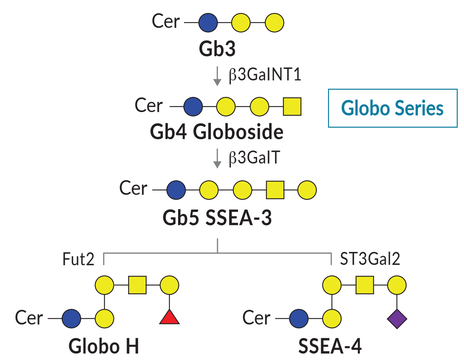
BACKGROUND

- Changes in glycosylation are associated with oncogenic transformation, and tumor cells display a wide range of aberrant glycosylation
- Lipid glycosylation results in the Lacto, Ganglio, and Globo series glycosphingolipids (GSLs) linked with ceramides in the cell surface membrane
- Globo series GSLs (stage-specific embryonic antigen (SSEA)-3, SSEA-4, and Globo H) are expressed on a wide range of tumor cells and are thought to be involved in early embryogenesis, tumor progression and metastasis, and immune suppression (**Figure 1**)

Figure 1. Globo Series



β3GalIT, β1,3-galactosyltransferase; β3GalNT1, β1,3-N-acetylgalactosaminyltransferase 1; cer, ceramide; Fut2, fucosyltransferase 2; Gb, globoside; SSEA, stage-specific embryonic antigen; ST3GAL2 ST3 beta-galactoside alpha-2,3-sialyltransferase 2.

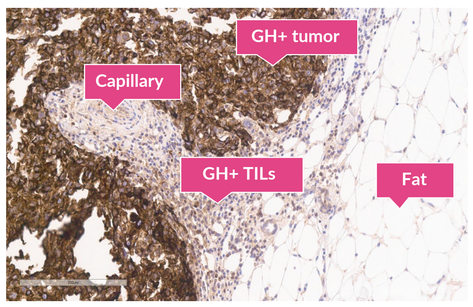
Globo H Expression in Patients With Breast Cancer

- A validated immunohistochemistry (IHC) assay (NeoGenomics) approved by the US FDA for use in clinical trials, measures the intensity and extent of Globo H expression microscopically using an H-score, defined as the sum of the products of the staining intensity (score of 0-3) multiplied by the percentage of cells (0-100) stained at a given intensity (**Figure 2**)
- 420 patients with triple-negative breast cancer (TNBC) have been screened across 4 separate clinical trials. 173 (41%) had an H-score of ≥15 (median 70) and in those patients 69/173 (40%) had an H-score of ≥100.

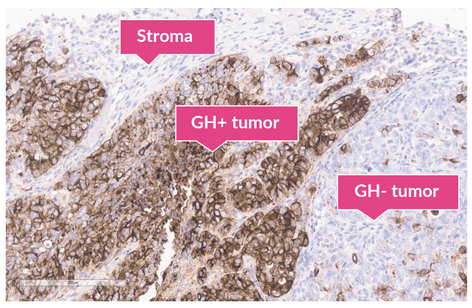
Figure 2. Globo H Expression in Patients With TNBC

GH expression level was assessed, and results are presented using an H-score system (0-300)

H-score = (% of weak intensity × 1) + (% of moderate intensity × 2) + (% of strong intensity × 3)



57-year-old female with infiltrating ductal carcinoma; H-score = 300



59-year-old female with papillary carcinoma; H-score = 185

GH, Globo H, GH-, GH-negative; GH+, GH-positive; TIL, tumor-infiltrating lymphocyte; TNBC, triple-negative breast cancer.

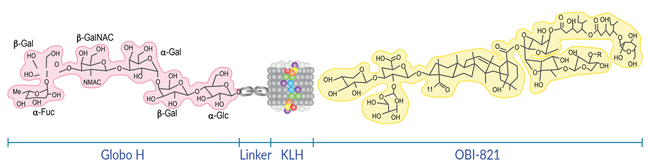
Triple-Negative Breast Cancer

- 10-20% of primary breast cancers are triple-negative breast cancers (TNBCs)[1] a heterogeneous group of tumors with the highest distant metastasis rate and lowest overall survival of all breast cancer subtypes[2]
- Patients with early-stage TNBC achieving a pathological complete response (pCR) after neoadjuvant chemotherapy demonstrate excellent recurrence-free and overall survival,[3] whereas patients with significant residual cancer burden after neoadjuvant chemotherapy have poor long-term outcomes[4]
- The presence and levels of stromal tumor–infiltrating lymphocytes (sTILs) have emerged as additional predictors of therapy response and disease-free and overall survival[5] in TNBC; the presence of sTILs in residual disease after neoadjuvant chemotherapy has also been found to be prognostic, especially in patients with large residual tumor burdens[6]
- Higher pCR rates are also achieved with the addition of immune checkpoint inhibitors to neoadjuvant chemotherapy[7,8]

Globo H Conjugate Vaccine

- Adagloxad Simolenin (AdaSim) is administered with the saponin adjuvant OBI-821 as a therapeutic vaccine targeting the tumor-associated carbohydrate antigen (TACA) Globo H ceramide (**Figure 3**)

Figure 3. Adagloxad Simolenin (AdaSim): Globo H Vaccine



Adagloxad simolenin is composed of a synthetic tumor antigen, Globo H, conjugated to a hemocyanin carrier protein (KLH) derived from the keyhole limpet

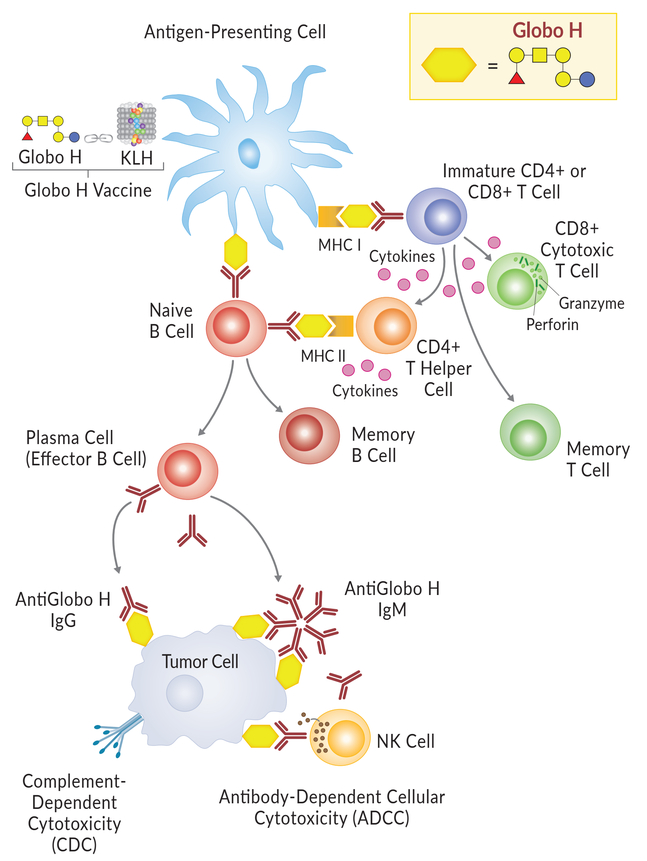
Adagloxad simolenin is administered with OBI-821—a saponin-based immune adjuvant purified from *Quillaja saponaria* tree bark—that induces humoral and cell-mediated responses

Quillaja saponaria

KLH, keyhole limpet hemocyanin.

- Following administration, the Globo H antigen is phagocytosed by dendritic cells, which process it and transport it to the lymph node where it activates an immature cluster of differentiation (CD)8+ T cells
- Dendritic cells also activate CD4+ T helper cells to support activation of B cells, which become plasma cells and induce anti-Globo immunoglobulin G (IgG) and immunoglobulin M (IgM)
- IgM and IgG antibodies recognize Globo H expressed on the tumor cell surface and recruit complements to attack the tumor cells (IgM) and guide natural killer cells to destroy the tumor (IgG) (**Figure 4**)

Figure 4. MOA of Therapeutic Vaccine Adagloxad Simolenin



CD, cluster of differentiation; IgG, immunoglobulin G; IgM, immunglobulin M; KLH, keyhole limpet hemocyanin; MHC, major histocompatibility complex; MOA, mechanism of action; NK, natural killer.

THE GLORIA STUDY

The GLORIA Study is presently enrolling patients in 13 countries. Of the 119 sites identified, 84 sites have been activated. A total of 900 patients have been prescreened as of May 2, 2022.

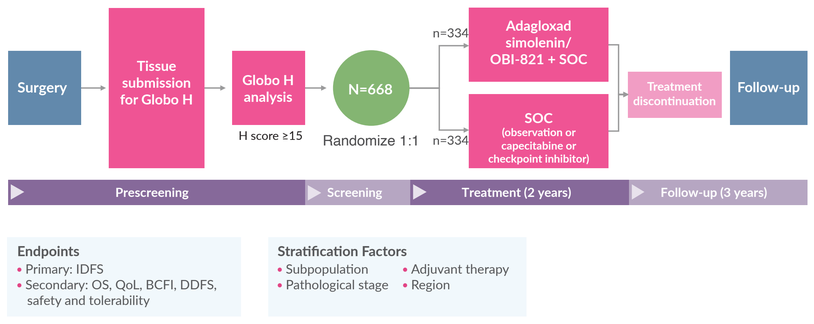
The protocol was recently amended with respect to patient eligibility and the definition of standard of care (SOC). Patients must have recovered from surgery and completed all planned neoadjuvant and/or adjuvant multiagent chemotherapy and/or radiation therapy. SOC in the AdaSim/OBI-821 arm is concomitant therapy of capecitabine or immune checkpoint inhibitor (in the US only). In the SOC arm patients will receive SOC therapy consisting of observation alone, or adjuvant capecitabine alone, or immune checkpoint inhibitor alone (in the US only).

THE GLORIA PHASE 3 STUDY DESIGN (NCT03562637)

A phase 3, randomized, open-label study of the anti-Globo H vaccine AdaSim /OBI-821 in the adjuvant treatment of patients with high-risk, early-stage Globo H–positive TNBC

GLORIA Protocol v 7.2 Study Schema

A Phase 3, Randomized, Open-Label Study of the Anti–Globo H Vaccine Adagloxad Simolenin/OBI-821 in the Adjuvant Treatment of High-Risk, Early-Stage, Globo H–Positive Triple-Negative Breast Cancer



Endpoints
- Primary: IDFS
- Secondary: OS, QoL, BCFI, DDFS, safety and tolerability

Stratification Factors
- Subpopulation
- Pathological stage
- Adjuvant therapy
- Region

BCFI, breast cancer–free index; DDFS, distant disease-free survival; IDFS, invasive disease-free survival; OS, overall survival; QoL, quality of life; SOC, standard of care.

Primary Endpoint: Invasive Disease-Free Survival

- 187 events required (3-year invasive disease free survival [IDFS]; hazard ratio, 0.66)
- 80% power; 2-sided alpha 0.05

Patients who complete the treatment phase without invasive disease recurrence should proceed to the IDFS follow-up phase

Key Eligibility Criteria

Key Inclusion Criteria	Key Exclusion Criteria
Histologically documented primary, localized, invasive TNBC	Previous history of invasive breast cancer within 10 years; history of other malignancies within 5 years
High-risk patients with no evidence of disease after completing standard treatment and meeting ***one*** of the following criteria: • Neoadjuvant chemotherapy followed by definitive surgery: – Residual invasive disease ≥1 cm in breast ***or*** ≥1 positive axillary node • Definitive surgery followed by adjuvant chemotherapy: pathological prognostic stage IIB, IIIA, IIIB, or IIIC (8th Ed AJCC)	• Received any or other anticancer vaccines – Neoadjuvant receipt of immune checkpoint inhibitors ***will not*** be exclusionary • Concomitant treatment with anticancer therapy other than capecitabine or checkpoint inhibitor, or other investigational therapy, if expected during the study
Must have completed ≥4 cycles of taxane and anthracycline-based chemotherapy, or taxane-containing regimen only if the patient is ineligible for anthracycline treatment in the neoadjuvant or adjuvant setting	Active autoimmune disease that requires systemic immunosuppressive/ immunomodulatory therapy
Globo H IHC H-score ≥15 from tumor tissue obtained at the time of definitive surgery or initial diagnosis (only if surgical tumor tissue sample is not available)	Prior receipt of a glycoconjugate vaccine for cancer immunotherapy
ECOG PS ≤1	

AJCC, American Joint Committee on Cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; IHC, immunohistochemistry; TNBC, triple-negative breast cancer.

- Randomization must occur within 16 weeks after definitive surgery and radiation therapy
- Concurrent capecitabine or checkpoint inhibition allowed

Stratification

Neoadjuvant vs Adjuvant only

If Neoadjuvant:

1. American Joint Committee on Cancer (AJCC) postneoadjuvant therapy pathological (yp) N status according to the 8th edition of the *AJCC Cancer Staging Manual* (ypNX/N0 I vs ypN1 vs ypN2/N3)
2. Receipt of adjuvant SOC therapy (capecitabine; immune checkpoint inhibitor) (Yes vs No)
3. Region (United States vs Mexico/Latin America vs Asia-Pacific vs China vs Eastern Europe vs Western Europe)

If Adjuvant:

1. AJCC pathological prognostic stage according to the 8th edition of the *AJCC Cancer Staging Manual* (stages IIB/IIIA vs IIIB/IIIC)
2. Region (United States vs Mexico/ Latin America vs Asia-Pacific vs China vs Eastern Europe vs Western Europe)

Patients who complete the treatment phase without invasive disease recurrence should proceed to the IDFS follow-up phase

Study Objectives

Primary Objective

To determine the effect of AdaSim/OBI-821 treatment on IDFS in the study population

Secondary Objectives

- To determine the impact of AdaSim/OBI-821 treatment, on:
  - Overall survival (OS)
  - Quality of life (QoL)
  - Breast cancer–free interval
  - Distant disease-free survival
- To determine safety and tolerability of AdaSim/OBI-821 in the study population

Exploratory Objectives

- To explore the association between the anti-Globo H antibody response to AdaSim/OBI-821 and IDFS and OS
- To evaluate the impact of tumor expression of Globo H on IDFS and OS
- To identify patient baseline characteristics and demographics that may be predictive of treatment outcomes with AdaSim/OBI-821
- To explore the association between baseline characteristics, including tumor pathological, molecular, and immune features, and tumor expression of Globo H

SUMMARY

- Patients with TNBC and residual disease after neoadjuvant chemotherapy have a poor prognosis
- Globo H is a glycosphingolipid expressed in early embryogenesis and aberrantly overexpressed in TNBC, including in cancer stem cells
- Globo H is thought to be involved with embryogenesis, tumor progression and metastasis, and immune suppression
- When administered with the adjuvant OBI-821, AdaSim results in IgM and IgG anti-Globo H humoral responses
- The phase 3 GLORIA Study is evaluating the effectiveness of AdaSim/OBI-821 as adjuvant therapy in patients with early-stage TNBC that has a high risk of progression
- In addition to safety, efficacy, and QoL, the study will evaluate the relationship between aberrant Globo H expression and baseline characteristics such as tumor pathology and immune factors

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