The GLORIA Study: A Phase 3, Randomized, Open-Label Study of the Anti-Globo H Vaccine Adagloxad Simolenin (OBI-822)/OBI-821 in the Adjuvant Treatment of Patients with High Risk, Early-Stage, Globo H-Positive, Triple Negative Breast Cancer

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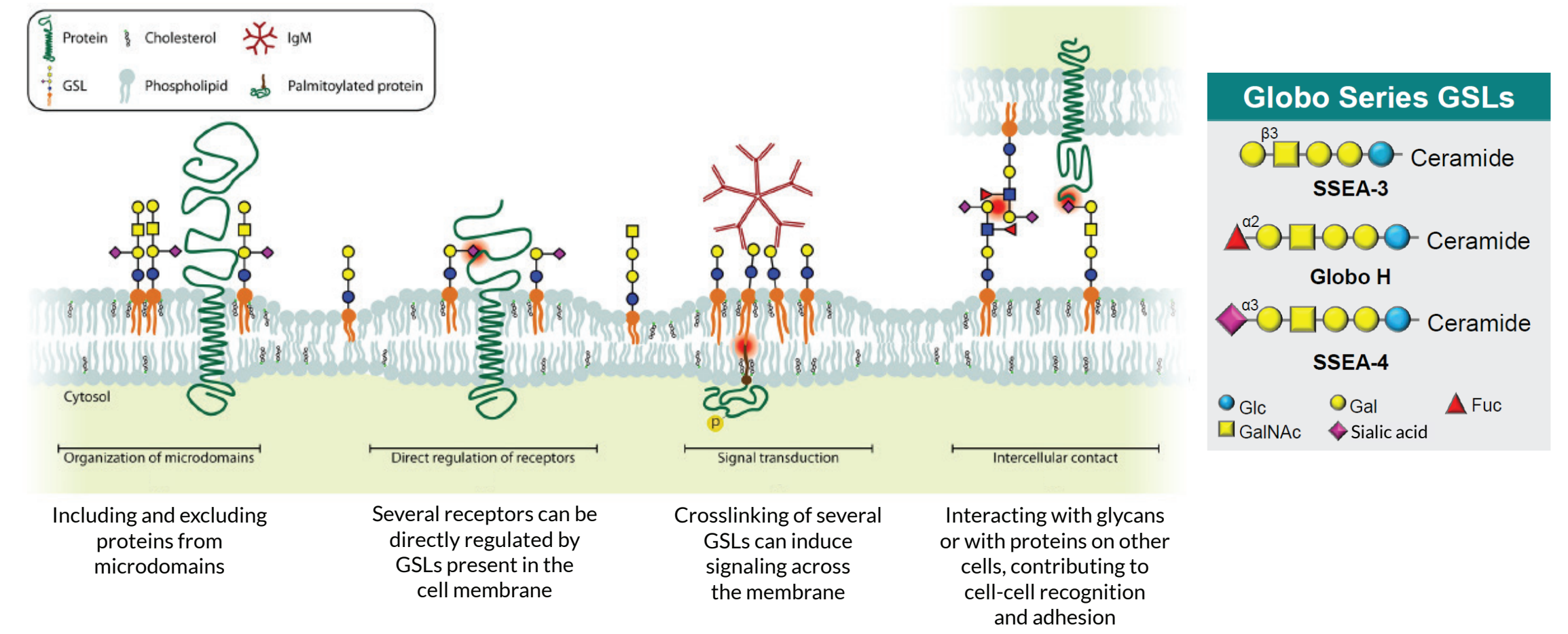
BACKGROUND

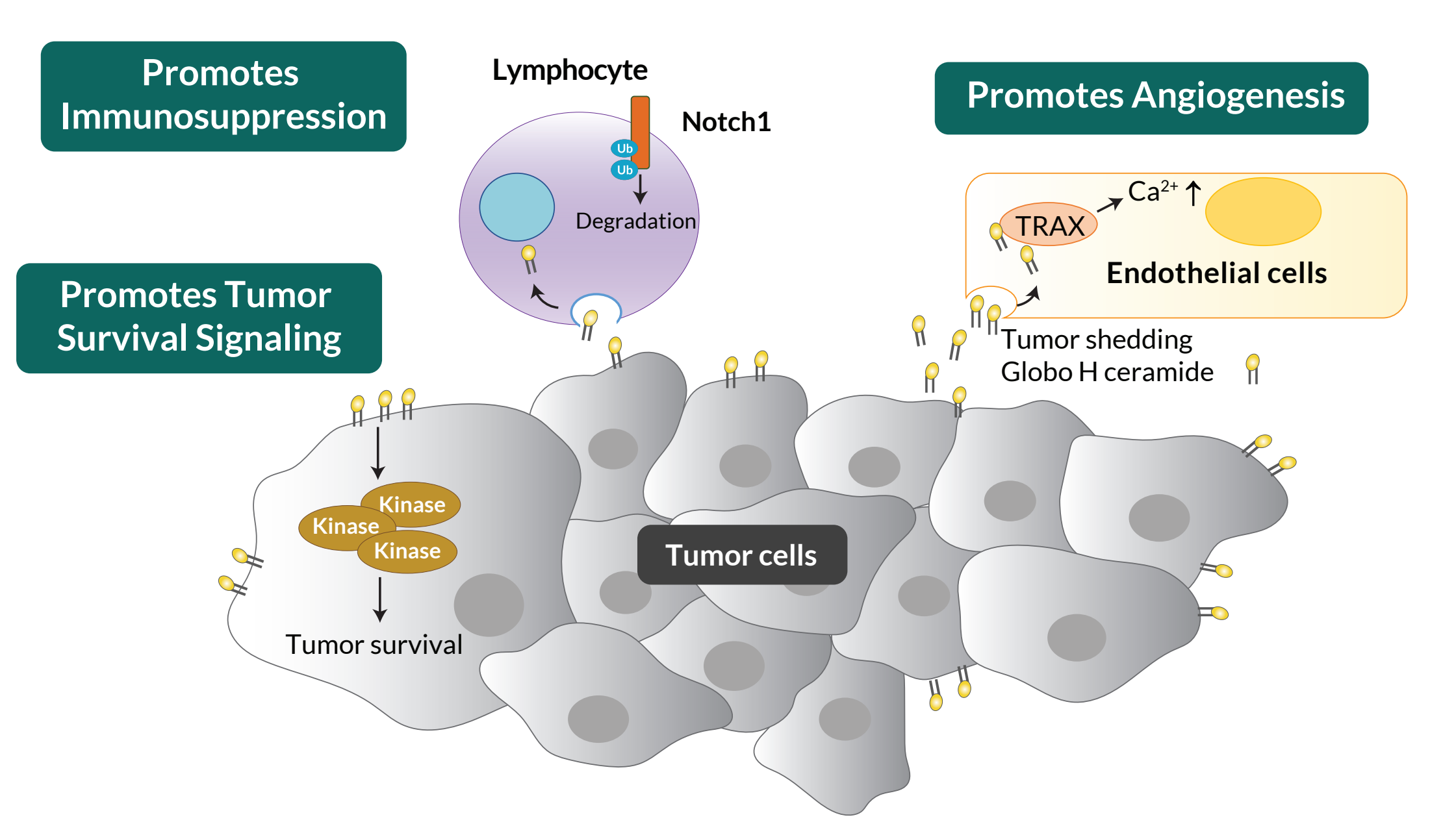
- Glycans and glycosphingolipids (GSLs) play a crucial role in tumor progression[1,2]
- Aberrant glycosylation is a hallmark of cancer cells[3]
- GSLs are glycans conjugated to a lipid (ceramide) core[4]
- Globo series is a unique class of GSLs involved in early embryogenesis and tumor development[5] (**Figure 1**)

Figure 1. Glycosphingolipids and Globo Series



- Globo H, a GSL, is a glycan isolated from the breast cancer cell line MCF-7 that is overexpressed on a variety of epithelial cell tumors such as colon, ovarian, gastric, pancreatic, lung, prostate, and breast cancers[6] and has limited expression in normal tissues[7]
- Experimental data suggest that Globo H promotes immunosuppression, tumor survival signaling, and angiogenesis (**Figure 2**).[5-7]
- Globo H expression in tumor stem cells and its function as an immune checkpoint makes it a target for immunotherapy[8]

Figure 2. Roles of Globo H



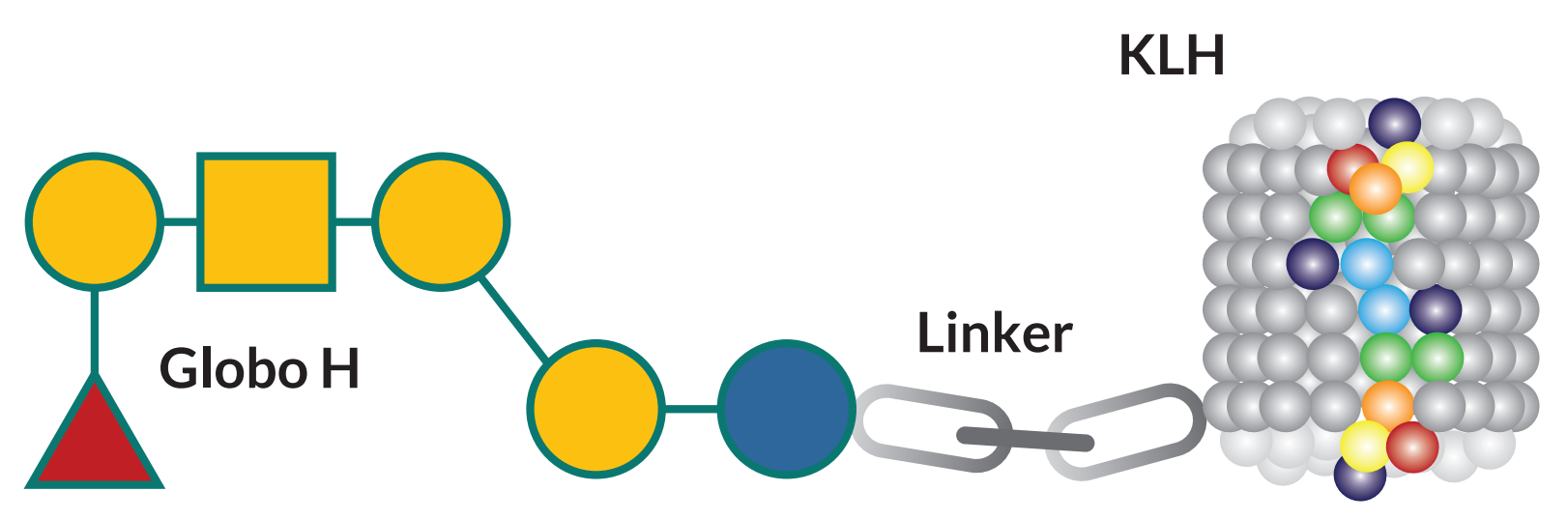
Triple-Negative Breast Cancer

- 10%-20% of primary breast cancers are TNBCs[9]
- This heterogeneous group of tumors has the highest distant metastasis rate and lowest overall survival of all breast cancer subtypes[10]
- Patients with early stage TNBC achieving a pathological complete response (pCR) after neoadjuvant chemotherapy demonstrate excellent recurrence-free and overall survival[11], whereas, patients with significant residual cancer burden after neoadjuvant chemotherapy have poor long-term outcomes[12]
- TNBC is a heterogenous disease with distinct molecular subtypes that differentially respond to chemotherapy and targeted agents[13,14] and that have variable long-term outcomes[15]; some of the more treatment-refractory subtypes reflect a more dedifferentiated or stem cell-like phenotype, such as the basal-like 2, mesenchymal stem-like, luminal androgen receptor, and unstable subtypes
- The presence and levels of stromal tumor infiltrating lymphocytes (sTILs) have emerged as additional predictors of therapy response[16] and disease-free and overall survival[17] in TNBC; the presence of TILs in residual disease after neoadjuvant chemotherapy has also been found to be prognostic, especially in patients with large residual tumor burdens[18]
- The immunologic nature of TNBC likely relates to the higher pCR rates achieved with the addition of immune checkpoint inhibitors to neoadjuvant chemotherapy[19,20]

Globo H Conjugate Vaccine

- OBI Pharma has initiated a global phase 3 trial in patients with TNBC, evaluating the safety and efficacy of adagloxad simolenin (OBI-822; **Figure 3**) administered with the saponin adjuvant OBI-821 as a therapeutic vaccine targeting the antigen Globo H ceramide

Figure 3. Adagloxad Simolenin (OBI-822)



Adagloxad Simolenin (OBI-822)

- Comprises a fully synthetic tumor antigen (Globo H) conjugated to a protein carrier (keyhole limpet hemocyanin [KLH])

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Potent Adjuvant (OBI-821)

- Saponin-based adjuvant
- Induces humoral and cell-mediated immune responses

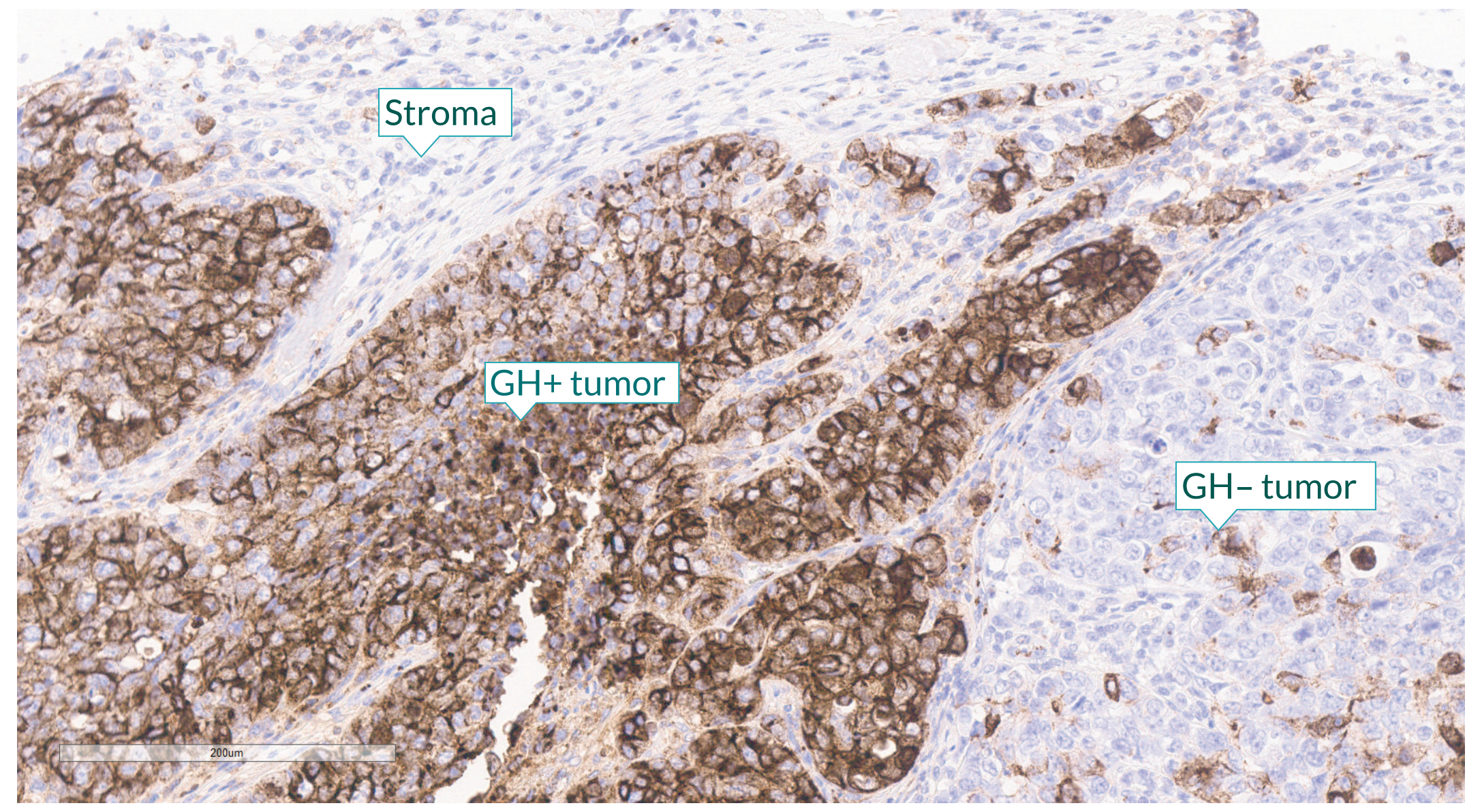
Globo H Expression in TNBC Patients by Validated Immunohistochemistry (IHC) Assay

GH expression level was assessed (**Figure 4A,B**) and results are presented using an H-score system (0 to 300): H-score = (% of weak intensity x 1) + (% of moderate intensity x 2) + (% of strong intensity x 3)

Figure 4. Global H (GH) Expression Level Assessments

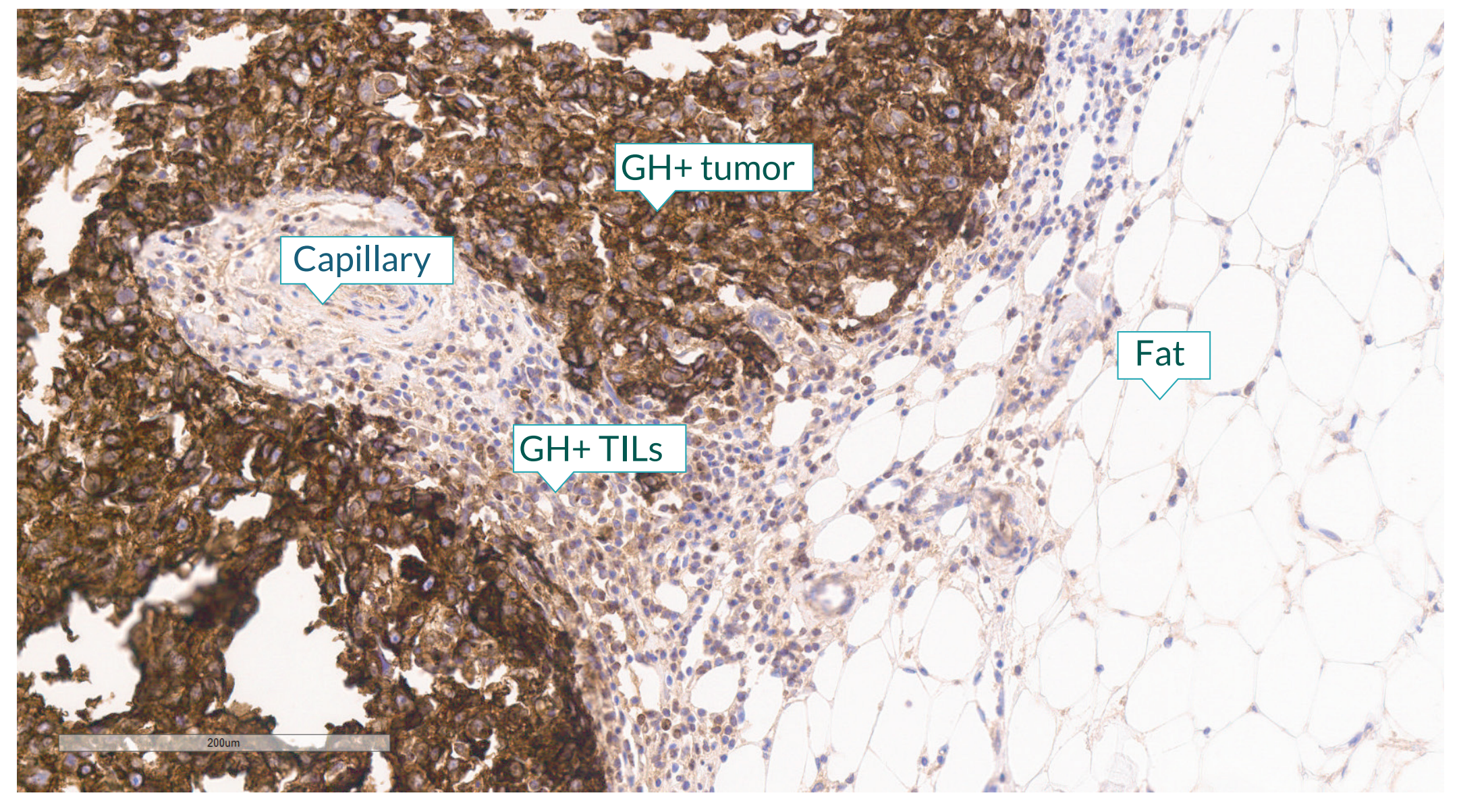
A. White 59-year-old female with papillary carcinoma; H-score = 185

Anti-GH monoclonal antibody (VK9) IHC staining 400×



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

Anti-GH monoclonal antibody (VK9) IHC staining 400×

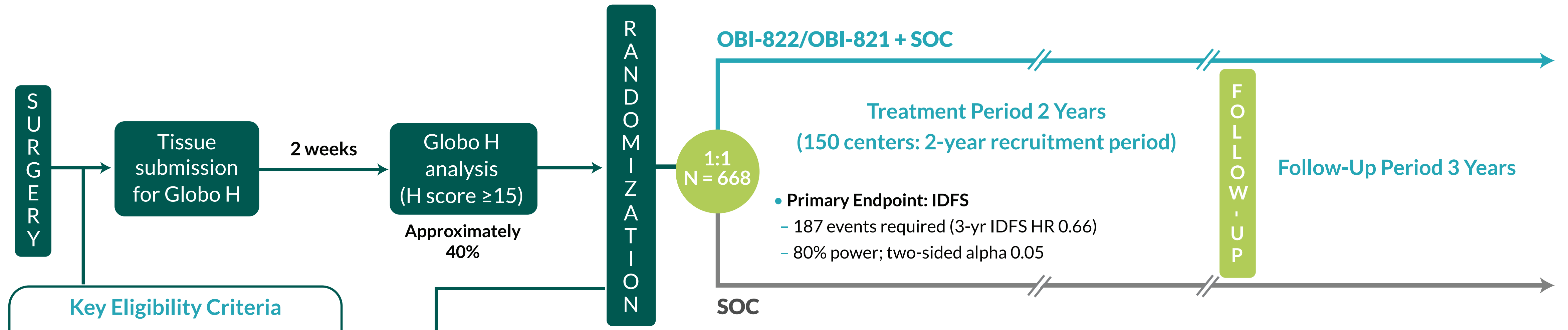


THE GLORIA PHASE 3 STUDY DESIGN (NCT03562637)

A phase 3, randomized, open-label study of the anti-Globo H vaccine adagloxad simolenin (OBI-822) OBI-821 in the adjuvant treatment of patients with high-risk, early-stage Globo H-positive TNBC (**Figure 5**)

Figure 5. Gloria Study Design

GLORIA Phase 3 Study



Treatment Period 2 Years
(150 centers: 2-year recruitment period)

- **Primary Endpoint: IDFS**
  - 187 events required (3-yr IDFS HR 0.66)
  - 80% power; two-sided alpha 0.05

Follow-Up Period 3 Years

Key Eligibility Criteria

- ECOG PS 0-1
- Histologically documented TNBC (ER/PR ≤5% cells)
- No evidence of metastatic disease on CT/MRI
- High risk defined as:
  - ≥1 cm residual primary or ≥1 residual axillary node after adequate neoadjuvant chemotherapy or
  - Pathological Stage IIB or III disease treated with adequate adjuvant chemotherapy alone
- Received ≥4 cycles of standard taxane- and/or anthracycline-based chemotherapy
- Randomized within 12 weeks of surgery, adjuvant multi-agent chemotherapy, or radiation therapy
  - Concurrent capecitabine, platinum, and/or radiation therapy allowed
  - Globo H IHC H-score ≥15 by central laboratory

	Baseline	Clinical Evaluations																					Follow-Up (FU) (every 26 weeks)							EOT
																							IDFS FU						OS FU (call)	
Week		1	2	3	4	6	8	10	12	16	20	24	28	36	44	52	60	68	76	84	92	100	126	152	178	204	230	256		
Month		1			2		3		4	5	6	7	8	9	11	13	15	17	19	21	23	25	32	38	45	51	58	64		
Year		Year 1															Year 2						Year 3		Year 4		Year 5			
822/821 Dosing		QW				Q2W				Q4W				Q8W																
822/821 Dosing		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X								
Physical Exam	X	X			X		X		X		X		X	X	X	X	X	X	X	X	X	X		X	X	X	X	X		X
Labs	X	X			X		X		X		X		X			X			X			X		X	X					X
Imaging	X															X						X			X					
QoL Questionnaire	X	X			X		X		X		X		X	X	X	X	X	X	X	X	X	X		X	X	X	X	X		X

Stratification

- Neoadjuvant vs Adjuvant only
- If Neoadjuvant:
  - yp Stage I vs II vs III
  - Adjuvant capecitabine or platinum (Yes/No)
  - Country
- If Adjuvant only:
  - p Stage II B/IIIA vs Stage III B/IIIC
  - Country

Phase 3 Study Inclusion and Exclusion Criteria

Inclusion	Exclusion
Documented radiographic and histopathologic confirmed primary localized invasive breast cancer documented as TNBC	Local recurrence of or previous history of contralateral invasive breast cancer within 10 years
Globo H IHC score ≥15 from primary site or lymph node	Definitive or radiologic evidence of metastatic disease
No evidence of metastatic disease in chest, abdomen, and pelvis by CT or other adequate imaging	Synchronous bilateral disease unless both are confirmed TNBC
High-risk patients defined as residual invasive disease following neoadjuvant chemotherapy; ≥4 axillary lymph nodes positive for invasive cancer; completed adjuvant chemotherapy	No immunotherapy within 4 weeks prior to study
Completed taxane ± platinum- and/or anthracycline-based chemotherapy	History of other malignancies
All treatment-related toxicities resolved to grade ≤1	Active autoimmune disease that requires systemic immunosuppressive/immunomodulatory therapy
Eastern Cooperative Oncology Group performance status 0 or 1	Prior glycoconjugate vaccine for cancer immunotherapy

Phase 3 Study Objectives

Primary Objective

- To determine the effect of adagloxad simolenin (OBI-822)/OBI-821 treatment on improving IDFS in the study population.

Secondary Objectives

- To determine the impact of adagloxad simolenin (OBI-822)/OBI-821 treatment in the study population, on:
  - Overall Survival (OS)
  - Quality of Life (QoL)
  - Breast cancer-free interval (BCFI)
  - Distant disease-free survival (DDFS)
- To determine safety and tolerability of adagloxad simolenin (OBI-822)/OBI-821 in the study population.

Exploratory Objectives

- To explore the association between the anti-Globo H antibody response to adagloxad simolenin (OBI-822)/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 adagloxad simolenin (OBI-822)/OBI-821
- To explore the association between baseline characteristics, including tumor pathological, molecular and immune features, and tumor expression of Globo H

SUMMARY

- TNBC patients with 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
- Experimentally, Globo H leads to tumor survival signaling, angiogenesis, and immunosuppression
- Adagloxad simolenin (OBI-822) is a Globo H conjugate vaccine that when administered in combination with the adjuvant OBI-821, results in IgM and IgG anti-Globo H humoral responses
- The ongoing randomized GLORIA phase 3 study is evaluating the effectiveness of OBI-822/OBI-821 as adjuvant therapy in subjects with high-risk early-stage TNBC
- Beyond the safety, efficacy, and QoL endpoints of this trial, exploratory endpoints will evaluate the relationship between aberrant Globo H expression and baseline characteristics including tumor pathology and immune factors

For information regarding this trial contact Dr Pei Hsu at peihsu@obipharma.com

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