A phase 1b/2 clinical investigation of invikafusp alfa (STAR0602), a first-in-class dual T-cell agonist, in combination with sacituzumab govitecan in patients with metastatic TNBC or HR+/HER2- MBC (START-002 trial)

Steven J Isakoff[1], Philippe L Bedard[2], Anastasia Martynova[3], Aditya Bardia[4] , Margaret E Gatti-Mays[5], Nathalie LeVasseur[6], Andreas Varkaris[1], William Randolph[7], Karunya Srinivasan[7], Shannon McCue[7], Andrew Bayliffe[7], Ke Liu[7], Zhen Su[7], Kevin Chin[7], Virginia Kaklamani[8], Kelly McCann[4], Erika Hamilton[9]

[1]Massachusetts General Hospital Cancer Center, Boston, MA; [2]Princess Margaret Cancer Centre, Toronto, Ontario, Canada; [3]USC Norris Comprehensive Cancer Center, Los Angeles, CA; [4]UCLA Health Jonsson Cancer Center, Los Angeles, CA; [5]The Ohio State University Comprehensive Cancer Center, Columbus, OH; [6]BC Cancer Vancouver Centre, Vancouver, BC, Canada; [7]Marengo Therapeutics, Inc., Cambridge, MA; [8]UT Health San Antonio, San Antonio, TX; [9]Sarah Cannon Research Institute, Nashville, TN

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Background

START-002 explores the hypothesis that combining sacituzumab govitecan's immunomodulatory potential with invikafusp alfa's selective activation and expansion of Vβ6/Vβ10 T-cells will enhance anti-tumor responses and improve clinical outcomes in breast cancer patients.



Invikafusp alfa ("Invika") is a novel, first-in-class dual T cell agonist that selectively targets subsets of T cells expressing the germline-encoded variable Vβ6 and Vβ10 variant TCRs that are enriched in tumor-infiltrating lymphocytes (TILs). Clinically, invika monotherapy generates a potent and selective expansion of mainly CD8+ Vβ6/ Vβ10 T cells. The completed Phase 1 dose escalation study of monotherapy invika (START-001) identified a recommended Phase 2 dose (0.08mg/kg) and demonstrated clinically meaningful single-agent anti-tumor activity in anti-PD(L)-1 resistant tumors, including objective responses in patients with TMB-H triple negative breast cancer (TNBC), colorectal cancer (CRC), non-small cell lung cancer (NSCLC), gastroesophageal junction cancer, gastric, and urothelial cancers. Based on these initial clinical results, the US FDA granted Fast Track Designation for invikafusp alfa in TMB-H CRC.

Sacituzumab govitecan (SG), an antibody drug conjugate (ADC), is FDA approved for patients with unresectable locally advanced or metastatic triple-negative breast cancer (mTNBC) and HR-positive/HER2-negative breast cancer (HR+/HER2- MBC). Preclinical studies indicate that ADCs enhance tumor immunogenicity by promoting immunogenic cell death, increased antigen presentation and tumor immune infiltration. These effects are likely mediated by cytotoxic tumor cell death and subsequent release of tumor-associated antigens. Recent clinical results from the ASCENT-04 trial demonstrated improved progression-free survival in previously untreated PD-L1+ mTNBC patients who received the combination of SG and pembrolizumab, thus confirming the clinical potential of combining an ADC with an IO agent in metastatic breast cancer.

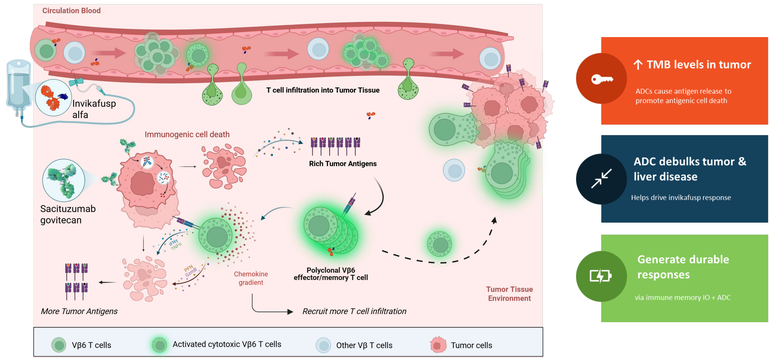


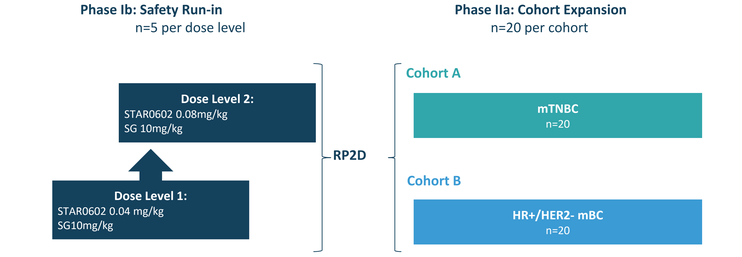
Figure 1. Invikafusp alfa, a bispecific agonist, reinvigorates anti-tumor T cell responses in vivo by selectively activating & expanding Vβ6 memory CD8 T cells in TILs. ADC (SG) increases immunogenic cell death priming for invika to amplify better quality T cell response.

Trial Design

START-002 is a Phase 1b/2, open label, multi-center study to determine the safety, feasibility, and anti-tumor activity of invikafusp alfa in combination with SG in patients with mTNBC or HR+/HER2- mBC.

- **Phase 1b**: Two safety run-in cohorts at dose levels of 0.04 mg/kg or 0.08mg/kg of invika in combination with the standard dose of SG (10mg/kg). The recommended Phase 2 dose was determined to be 0.08mg/kg invika + 10mg/kg SG.
- **Phase 2:** Expansion cohorts for patients with mTNBC or HR+/HER2- mBC. Phase 2 includes a Simon's 2-stage design and will enroll up to 20 participants into each expansion cohort.

The primary objectives of START-002 are to characterize the safety and tolerability of invikafusp alfa when given together with sacituzumab govitecan and to evaluate preliminary anti-tumor activity of the combination. The primary endpoints are safety and overall response rate per RECIST and iRECIST.



Patient Population

- **3L+ mTNBC:** Progression or recurrence of locally advanced or metastatic TNBC in participants who have received 2 or more prior systemic therapies, at least 1 of them for metastatic disease
- **2L+ HR+/HER2- mBC**: Progression or recurrence of locally advanced or metastatic HR+/HER2- breast cancer in participants who have received prior endocrine based therapy and at least 1 additional systemic therapy in the metastatic setting

Key Eligibility Criteria

- ECOG 0 or 1
- Measurable disease per RECIST
- Life expectancy ≥12 weeks
- Treated and asymptomatic CNS mets allowed

Bioanalytical and Biomarker Plan

Pharmacokinetics	STAR0602 population PK model-derived parameters including Cmax, AUC, CL, Vd
Pharmacodynamics	• Frequency of various immune cell subsets (including Vβ6/Vβ10 T cells) • Concentrations of soluble factors including cytokines • Changes in the expression of immune and tumor cell genes of interest (including individual TCR sequences)

Trial in Progress

START-002 is ongoing in the United States and Canada

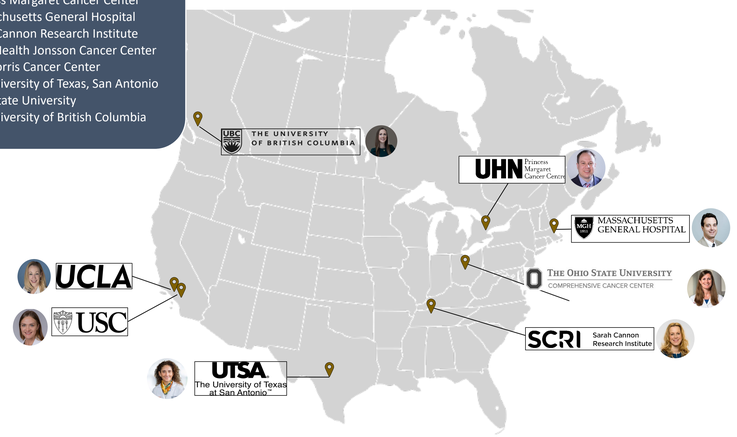
- Enrollment to the Ph1b safety run-in portion of START-002 was recently completed. No DLTs were observed and the 0.08mg/kg dose of invikafusp alfa was selected as the RP2D to be investigated in combination with SG in Ph2 expansion cohorts.
- Ph2a expansion cohorts for mTNBC and HR+/HER2- mBC patients are open and enrolling new patients.

Initial results from START-002 Ph1b are presented at SABC 2025:

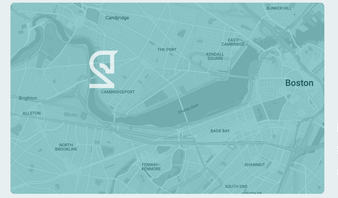
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Active Sites:

- Princess Margaret Cancer Center
- Massachusetts General Hospital
- Sarah Cannon Research Institute
- UCLA Health Jonsson Cancer Center
- USC Norris Cancer Center
- The University of Texas, San Antonio
- Ohio State University
- The University of British Columbia



Contact Us



General Inquiries: *info@marengotx.com*
Partnership Inquiries: *bd@marengotx.com*
Recruitment Inquiries: *peopleandculture@marengotx.com*

Marengo Therapeutics, Inc.
840 Memorial Drive, 4th Floor
Cambridge, MA 02139

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