DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
National Cancer Institute
Bethesda, Maryland 20892

July 29, 2024

Announcement of Availability to Investigators of IMC-F106C (Brenetafusp) (NSC 853198)

For Clinical and Nonclinical Study Proposals

The Cancer Therapy Evaluation Program (CTEP) is accepting Letters of Intent (LOIs) to conduct clinical studies using **IMC-F106C**, a T-cell receptor (TCR)/anti-CD3 fusion protein that targets tumor cell surface peptides in complex with human leukocyte antigen (HLA). IMC-F106C is being developed by CTEP as an anticancer agent in collaboration with Immunocore. CTEP will also consider requests to supply IMC-F106C for nonclinical studies. All clinical and nonclinical researchers possessing an interest in working with the agent are welcome to apply. Proposals for clinical trials should be supported by a strong rationale and when appropriate, robust preclinical data (see "Components of a Competitive Letter of Intent" at http://ctep.cancer.gov/protocolDevelopment/lois_concepts.htm). ***All proposals approved by CTEP will be sent to the industry collaborator for a commitment to supply drug for the study.***

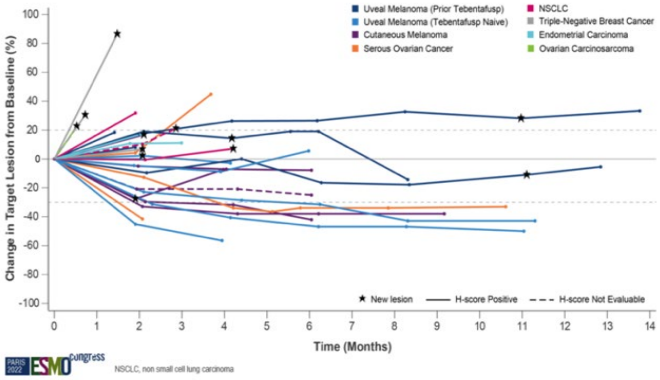
IMC-F106C is a TCR bispecific protein developed through Immunocore's Immune Mobilizing Monoclonal TCR Against Cancer (ImmTAC) platform. IMC-F106C is composed of a tumor-targeting domain and an scFv effector engaging domain (anti-CD3). It is designed to recognize a peptide of **PRAME** (Preferentially Expressed Antigen in Melanoma) **presented by HLA-A*02:01** (Moureau *et al.,* 2020). PRAME is a cancer/testis antigen that is highly expressed in a range of solid and hematological malignancies (Xu *et al.,* 2020; Kaczorowski *et al*., 2022). This technology was validated by the first-in-class ImmTAC, tebentafusp (Kimmtrak®), which targets the melanoma gp100 tumor-associated antigen and received FDA approval for the treatment of HLA-A*02:01-positive patients with metastatic uveal melanoma in January 2022 (Hassel *et al.,* 2023).

IMC-F106C is in clinical development for the treatment of PRAME-positive advanced cancers in A*02:01-positive patients. A phase 1 dose escalation trial (NCT04262466) enrolled 42 patients in nine dose cohorts from 0.3 to 160 mcg IMC-F106C (Hamid *et al.,* 2022). At doses >20 mcg weekly, there was strong and consistent pharmacodynamic activity (interferon γ induction and intratumoral T-cell trafficking). Durable objective responses were demonstrated in patients with various solid tumors, including uveal melanoma, cutaneous melanoma (CM), and platinum-resistant ovarian carcinoma (Figure 1). The most common treatment related adverse events (AEs) were Grade 1/2 cytokine release syndrome (CRS), Grade 3/4 AEs lymphopenia (14%), and aspartate aminotransferase increase (7%). There were no instances of treatment-related discontinuations or deaths, and the maximum tolerated dose was not reached. The trial was ongoing for four expansion cohorts: CM, non-small cell lung cancer, and endometrial and ovarian carcinoma.

Results for the CM cohort were presented at 2024 ASCO Annual Meeting (Hamid *et al.,* 2024). Of the 31 response-evaluable patients with CM, all with prior exposure to check point inhibitors, objective response rate was 13% and clinical benefit rate (partial response or stable disease) was 61%. PRAME-positive tumors (H-score ≥1) were associated with tumor reduction, better progression-free survival and overall survival, and circulating tumor DNA (ctDNA) responses.

The phase 2 dose selected for expansion cohorts was 160 mcg intravenous (IV) weekly following step-up dosing during cycle 1. An alternate lower dose of IMC-F106C is also being tested in the ongoing Phase 3 clinical trial for IMC-F106C in combination with nivolumab in first-line advanced CM (NCT06112314) (Long *et al*., 2024).

Figure 1. Responses were observed in multiple solid tumor types. PRAME expression was assessed by IHC H-score. Data was presented at ESMO Congress 2022.



Notably, the prevalence and level of PRAME expression are highly variable among tumors and histology subtypes. Several publications have identified PRAME as a potential cancer target in adult and pediatric tumors (Brohl *et al*., 2021, Kaczorowski *et al*., 2022). Box 1 listed references on PRAME expression in multiple tumors that may help selection of tumor types for clinical trials with IMC-F106C. Additional work on assessment of PRAME expression are ongoing and databases are rapidly evolving.

BOX 1: Select References on PRAME expression in tumors:

- Kaczorowski *et al*., (2022). PRAME expression in cancer. A systematic immunohistochemical study of >5800 epithelial and nonepithelial tumors. *Am J Surg Pathol.* 46(11):1467-1476.
- Brohl *et al.,* (2021). Immuno-transcriptomic profiling of extracranial pediatric solid malignancies. *Cell Rep.* 37(8):110047.
- Camarero *et al.,* (2023). PRAME immunohistochemistry in soft tissue tumors and mimics: A study of 350 cases highlighting its imperfect specificity but potentially useful diagnostic applications. *Virchows Archiv*, *483*(2), 145-156.

*Additional assessment of PRAME expression in more tumors and patients are ongoing using RNAseq, RT-PCR or IHC

Selected example from Kaczorowski *et al*., 2022

Epithelial tumors – % cases with PRAME+ tumors

- Germ cell seminoma – 78%
- Ovarian
  - Clear Cell 90%
  - Serous – 63%
  - Undifferentiated– 50%%
- Skin basal cell – 62%
- Salivary adenoid cystic carcinoma – 81%
- Thymic carcinoma -71%
- Uterine carcinosarcoma – 60%
- Uterine serous carcinoma – 82%

Mesenchymal and Neuroectodermal tumors

- Myxoid liposarcoma – 76%
- Synovial sarcoma – 70%
- Mucosal melanoma – 99%

.

Clinical Studies of Interest to CTEP for IMC-F106C

<u>The following approaches are of potential interest.</u>

1. Combination with IL-2 or IL-15 to evaluate safety and RP2D with the objective of increasing activity of the bispecific antibody thorough expanded effector T and NK cells.
2. Monotherapy signal seeking trials in rare tumors with high prevalence of PRAME expression or determined to be PRAME expressing by validated assay when available.
3. Monotherapy trials in sarcoma subtypes with high prevalence of PRAME expression with high prevalence of PRAME expression or when a validated assay is available, determined to be PRAME expressing.

4. Additional trial for high priority clinical settings and rational combinations may also be considered.

Biomarker and ancillary studies in clinical trials

- Until a validated biomarker of expression is available, selection of tumor types for efficacy studies should be limited to those with high prevalence of PRAME expression which would not require pre-screening. Phase 1 safety studies should preferably enroll HLA A2 patients from the same tumor types but would not require this restriction. However, all studies must include a plan for retrospective evaluation of PRAME expression.
- All patients should be screened for HLA for A*02:01. This assay could be covered by the pharmaceutical sponsor.
- Exploratory studies should include ctDNA monitoring and analysis for association with clinical benefit. Biomarkers plans should also consider studies for mechanisms of actions and resistance, immune profiles, tumor immune microenvironment (TIME), and their association with response.

Correlative and Nonclinical Studies of Interest to CTEP for IMC-F106C

CTEP would be interested in any translational studies, as well as any nonclinical studies that would advance the development of IMC-F106C through better understanding of the mechanisms of action and resistance, predictive markers and rational combinations.

Obtaining Forms and Contact Information

For clinical study proposals, the LOI Submission Form may be downloaded from the CTEP website at http://ctep.cancer.gov/protocolDevelopment/lois_concepts.htm.

If you are interested in obtaining the agent for nonclinical studies, whether alone or in association with a proposed clinical study, please complete the DCTD Nonclinical Request Form, which may be downloaded from the CTEP website at http://ctep.cancer.gov/industryCollaborations2/agreements_agents.htm.

Further instructions for completing and submitting the forms may be found within the respective documents.

Questions may be addressed to Howard Streicher, Medical Officer, Investigational Drug Branch, CTEP, DCTD, NCI at streicherh@ctep.nci.nih.gov.

A complete list of agents available for distribution by CTEP may also be found on the CTEP website at http://ctep.cancer.gov/industryCollaborations2/agreements_agents.htm.

References

Brohl, A.S., S. Sindiri, J.S. Wei, *et al.* (2021). Immuno-transcriptomic profiling of extracranial pediatric solid malignancies. *Cell Rep.* 37(8):110047.

Cammareri, C., F. Beltzung, M. Michal, *et al.* (2023). PRAME immunohistochemistry in soft tissue tumors and mimics: A study of 350 cases highlighting its imperfect specificity but potentially useful diagnostic applications. *Virchows Archiv*, *483*(2), 145-156.

Hamid, O., T. Sato, D. Davar, *et al.* (2022). Results from phase 1 dose escalation of IMC-F106C, the first PRAME x CD3 ImmTAC bispecific protein in solid tumors. *Annals of Oncol.* 33(7):S875.

Hassel, J.C., S. Piperno-Neumann, P. Rutkowski, *et al.* (2023). Three-year overall survival with tebentafusp in metastatic uveal melanoma. *N Engl J Med.* 389:2256-2266.

Hamid, O., A. Williams, J.S. Lopez, *et al.* (2024). Phase 1 safety and efficacy of IMC-F106C, a PRAME× CD3 ImmTAC bispecific, in post-checkpoint cutaneous melanoma (CM). *JCO.* 42(Suppl_16):9507.

Kaczorowski, M., M. Chlopek, A. Kruczak, *et al.* (2022). PRAME expression in cancer. A systematic immunohistochemical study of >5800 epithelial and nonepithelial tumors. *Am J Surg Pathol.* 46(11):1467-1476.

Long, G.V., V. Atkinson, P.A. Ascierto, *et al*. (2024). A phase 3 trial of IMC-F106C (PRAME x CD3) plus nivolumab versus standard nivolumab regimens in HLA-A*02:01+ patients with previously untreated advanced melanoma (PRISM-MEL-301). *JCO.* 42(Suppl_16):9602.

Moureau, S., A. Vantellini, F. Schlosser, *et al.* (2020). IMC-F106C, a novel and potent immunotherapy approach to treat PRAME expressing solid and hematologic tumors. *Cancer Res.* 80(Suppl_16):5572.

Xu, Y., R. Zou, J. Wang, *et al.* (2020). The role of the cancer testis antigen PRAME in tumorigenesis and immunotherapy in human cancer. *Cell Prolif.* 53(3):e12770.