Study Official Title:

Open Multi-cohort Study of the First Phase of Safety of a Drug Based on Double Recombinant Vaccinia Virus VV-GMCSF-Lact in Patients With Recurrent/Refractory Metastatic Breast Cancer With Single and Multiple Administration

Study NCT Number:

NCT05376527

Document Date:

12-MAR-2026

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To: ClinicalTrials.gov PRS Review Team

Date: 2026-03-12

Re: Protocol and SAP Submission for Study NCT05376527 / Oncolact2020

Subject: Clarification regarding the English versions of the Protocol and Statistical Analysis Plan

Dear PRS Review Team,

This letter is provided in response to the request for the English translation of the Protocol and the Statistical Analysis Plan (SAP) for the clinical study NCT05376527 / Oncolact2020.

The study is a local multicenter clinical trial conducted exclusively within the Russian Federation under the jurisdiction of the Ministry of Health of the Russian Federation. Consequently, the official versions of the Protocol and SAP were developed and approved by the National Regulatory Authority and the National Ethics Committee in the Russian language only.

To ensure transparency and fulfill the requirements of ClinicalTrials.gov, we are providing below an Extensive Integrated Summary of the Protocol and the Statistical Analysis Plan in English. This summary contains all essential technical and statistical information required for the scientific evaluation of the study design and results.

1. Key Protocol Information (Oncolact2020)

- **Study Design:** An open-label, multi-center, multi-cohort Phase I study utilizing a dose-escalation design to evaluate the safety, tolerability, and pharmacokinetics of the investigational product.
- **Investigational Product:** VV-GMCSF-Lact (recombinant vaccinia virus strain), solution for injection, 2 x 10^7 PFU/mL.
- **Target Population:** Patients with recurrent and/or refractory metastatic breast cancer who have exhausted standard-of-care treatment options.

- **Dosing Regimen:** The study involves both single and multiple intratumor administrations across sequential dose-escalation cohorts.

- **Objectives:**
    - Determination of the maximum tolerable dose of the drug;
    - Determination of the frequency, nature, intensity, and duration of adverse reactions associated with the use of the investigational drug when taken in increasing doses;
    - Identification of dose-limiting toxicity, its severity, duration, and reversibility;
    - Determining the pharmacokinetic profile of the virus and antibodies to it;
    - Evaluating the objective response to the treatment;
    - Evaluating the dynamics of changes in tumor size.

2. Statistical Analysis Plan (SAP) Summary

- **Sample Size Justification:** As a Phase I dose-escalation study, the sample size is determined by the number of dose cohorts and the observed toxicities (3+3 design or similar), rather than a formal power calculation for efficacy. This study will not test statistical hypotheses, so no formal justification of the sample size is required.

  It is estimated that up to 73 patients may be enrolled and screened, taking into account possible screening failures (up to 15 patients), up to 58 patients will receive the study drug, and no more than 54 patients will complete the study according to the protocol, with additional patients recruited at each stage and taking into account the possible inclusion of patients to replace those who drop out (no more than 4 patients in total in both stages).

- **Analysis Sets:**
    - **Intent-to-Treat:** The ITT dataset includes all subjects who received the study drug, regardless of their degree of adherence to the protocol during the study. This dataset is the primary dataset for analysis and will be used to evaluate all planned endpoints.
    - **Per Protocol:** All planned endpoints will be analyzed (in addition to the ITT analysis) using a data set of study participants selected according to the protocol (PP). A participant will be excluded from the PP data set in the following cases:
        - The patient's refusal to continue participating in the study.
        - Incorrect inclusion (i.e., non-compliance with the inclusion/exclusion criteria identified during the study).
        - Failure of the subject to comply with the rules of participation in the study.
        - The emergence of reasons/situations during the study that threaten the patient's safety (e.g., serious adverse reactions, detection of pregnancy in the patient).
        - The development of conditions in the patient described in the exclusion criteria.
        - The need to use drugs or therapies not permitted by the protocol during the study.
        - The patient is diagnosed with COVID-19.

- **Safety Population:** All patients received at least one dose of VV-GMCSF-Lact. This is the primary set for all safety and tolerability analyses.
- **Pharmacokinetic (PK) Population:** All patients who received the study drug and provided sufficient blood/biological samples for viral DNA/titer determination.
- **Full Analysis Set (FAS):** Used for the assessment of preliminary efficacy (ORR, DCR) in patients with at least one post-baseline tumor assessment.
- **PK set:** The analysis of pharmacokinetic and pharmacodynamic parameters will include data obtained from all patients who received the study drug, including those who withdrew early.

- **Statistical Methodology:**
  - **Safety:** Descriptive statistics for Adverse Events (AEs), coded via MedDRA, and laboratory abnormalities.
  - **PK:** A statistical plan for analyzing pharmacokinetic/pharmacodynamic data will be developed based on the actual values of virus concentration in the blood of patients. The statistical model will consider data from preclinical studies and the results of pharmacokinetic/pharmacodynamic evaluations of similar drugs. Based on the results of the development, a statistician will select and test a function describing the virus replication process over time, determining the replication coefficients and replication rate. The model will be constructed using a suitable software package (e.g., SAS). The developed model will be used to evaluate the entire set of data obtained, as well as individual patient data.
  - **Efficacy:** Efficacy parameters will be determined at Visits 10-12 in the first phase and Visits 6, 10, 11, 12 in the second phase based on computed tomography data. Objective response (rate of stabilization/progression) to treatment.
    The effectiveness of the treatment will be assessed using the RECIST 1.1 scale.
    The primary endpoint analysis will be performed by estimating the response rates with 95% CI for both the entire study population and all cohorts at all visits mentioned in this section for each phase.

- **Handling of Missing Data:**
  - Before performing statistical analysis, the database will be checked for missing, questionable, and non-analyzable data. All such data will be collected and forwarded to the researcher for verification and/or possible correction prior to finalizing the statistical report and database.
    In this study, there are no plans to replace missing data subject to statistical analysis.
    In the case of an incomplete date, the following replacement will be made:
    - if the day is missing, the date will be adjusted to the 15th day of the corresponding month and year (e.g., 02.2023 will be adjusted to 15.02.2023)
    - if the day and month are missing, the date will be adjusted to 01.07 of the corresponding year.

3. Commitment to Transparency

We confirm that the information provided in this summary is fully consistent with the original Russian-language Protocol ver. 2.2 of 13.03.2024 and SAP ver. 2.0 of 23.01.2025. Should a full

translation of specific sections be required for further review, we remain at your disposal to provide additional translated extracts.

We trust this comprehensive summary satisfies the current requirements for study registration/results publication.

Sincerely,

Elena V. Kuligina, PhD, authorized representative

Oncostar, LLC