Public Information

Boehringer Ingelheim

Study Title

A study to test different doses of BI 1831169 alone and in combination with ezabenlimab in people with different types of advanced cancer (solid tumors).

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Sponsor: SCS Boehringer Ingelheim Comm. V.

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1. General Information

1.1 Description of the Genetically Modified Organism

1.1.1 Introduction

In this clinical trial the safety and tolerability of an oncolytic virus (the investigational treatment) will be investigated in people with certain tumor types. It will take place in two parts, each with different participants.

- Part one will test the oncolytic virus (BI 1831169 or VSV-GP) by itself at different dose levels
- Part two will test the oncolytic virus (again at different dose levels) in combination with a checkpoint inhibitor (anti-PD1) another cancer medication called ezabenlimab

The oncolytic virus, called VSV-GP (BI 1831169) is given 5 times over a three-month period by injection directly into the tumor (i.t. or intratumoral), by injection directly into the bloodstream (i.v. or intravenous), or by a combination of both injections, intratumoral and intravenous.

1.1.2 Description of the GMO

VSV-GP is a recombinant Vesicular Stomatitis Virus (VSV), carrying the envelope glycoprotein (GP) of a non-neurotropic strain of the lymphocytic choriomeningitis virus, instead of its natural glycoprotein (G) to be utilised as an oncolytic therapeutic.

VSV-GP's therapeutic potential is not limited to pure lyses of tumor cells but is simultaneously capable to induce sustained anti-tumoral immune responses, which can be further enhanced by combination with other cancer therapeutics.

1.2 Nature and Purpose of the intended trial

The intended clinical study will serve to assess VSV-GP's therapeutic potential in cancer patients. The proposed clinical trial will be conducted in patients who have been diagnosed different types of advanced cancer (solid tumors). The trial start in Belgium is expected to be in Q2 2022 ("First patient in" in Belgium) and is expected to last until Q1 2025 ("Last patient last visit"). The clinical site in Belgium is the "Cliniques Universitaires Saint-Luc". Approximately 4 patients are expected to be enrolled in Belgium.

This is the first in human trial to be conducted using VSV-GP.

The trial is split into two parts. Part 1 investigates the use of VSV-GP as a monotherapy via three different routes of administration: intratumorally (i.t.), intravenously (i.v.) and as a combination of i.t. and i.v. (10% of the dose given first i.t. and then the remaining 90% given i.v.). Part 2 follows Part 1 to investigate the use of VSV-GP in combination with a checkpoint inhibitor (anti-PD1) ezabenlimab which is given intravenously.

The main purpose of this trial is to determine the safety and, tolerability of VSV-GP on its own as well as in combination with ezabenlimab, for the three different routes of administration.

Patients in Part 1 and Part 2 will receive VSV-GP as either i.t., i.v. or i.t.+i.v. on Day 1, Day 4, Day 22, Day 43 and Day 64. After their treatment, patients will be observed at the hospital for

28 hours following the first three treatments (Days 1, 4 and 22) and then for at least 6 hours following the fourth and fifth treatments (Days 43 and 64). After this they can leave the hospital, and are advised to follow biosafety measures, some for the 10 days following treatment, and others for the entire treatment duration.

Patients in Part 2 will additionally receive ezabenlimab starting on day 22 and continuing on a 3-weekly cycle for up to 1 year, or longer if the patient is clinically benefitting from treatment.

2. Research & Development Activities

2.1 Previous Development Activities

VSV-GP has not yet been used as a treatment in humans, meaning the above outlined trial will be a First-In-Human, or FIH, clinical trial. In previous research investigations VSV-GP has been proven to be safe and efficacious in non-clinical animal studies.

To understand potential risks of VSV-GP spreading into the environment, different animal species (pigs, rabbits, dogs and mice) were investigated for shedding. Shedding of infectious VSV-GP RNA was not detected in urine, feces or saliva but was detected at the intratumoral injection sites. However, no transmission was recorded in animal studies when infected mice were co-housed with healthy mice. This indicates that the potential for transmission of VSV-GP is considered very low.

2.2 Future Activities

Depending on the results of the above-described trial, future research and development activities might be triggered in order to inform and optimise future (non-)clinical trials.

2.3 Potential advantages of the deliberate release

Despite the continued advancements in cancer treatment, cancer remains a leading cause of death globally. In 2018, it was estimated that there were approximately 18 million new cancer cases and 9.2 million cancer-related deaths worldwide (Global cancer statistics 2018: GLOBOCAN database). If the disease is diagnosed in advanced or metastatic stage the vast majority of patients eventually progress on available treatments and succumb to their disease. These statistics highlight a substantial need for novel therapeutic agents and treatment strategies to improve the treatment outcome for cancer patients. Boehringer Ingelheim believes that the promising results from their non-clinical programme factored with the high unmet clinical need, support the initiation of a clinical trial with VSV-GP in patients. The administration of VSV-GP may drive an anti-tumor response or a disease stabilization and possibly improve the survival of patients with advanced cancers not eligible for available standard therapy options.

2.4 Risks

VSV-GP preferentially replicates in and lyse tumor cells and can stimulate adaptive immune responses directed against the tumor. In contrast, healthy cells can be infected by VSV-GP, but they recognize virus infection at an early stage and generate an antiviral state in the infected cell and in neighbouring cells. Thus, a VSV-GP infection in healthy cells is efficiently controlled.

Since replication of VSV-GP occurs in the cytoplasm and does not include a DNA synthesis step, there is negligible risk for integration in the genome of infected hosts.

In summary, risks to humans and the environment from exposure to VSV-GP are expected to be very low. Nevertheless, risk management measures will be implemented during the clinical trial to limit exposure of VSV-GP to the full extent possible. Such measures include but are not limited to the following procedures:

- VSV-GP will be prepared by staff who must use protective equipment.
- Staff must use standard procedures to protect themselves from "contamination" and apply careful management of needles and other sharps.
- Elimination or inactivation of left-overs of VSV-GP at the end of the clinical trial.
- Following their treatment with VSV-GP, the patient must be admitted to private room and remain in a private room until discharge; patient's movements within the hospital should be limited to the minimum necessary.
- When outside the room, the patient must wear a surgical grade mask and ensure that all injected and biopsied sites are covered with dressings.
- After patient's discharge, potentially contaminated surfaces should be disinfected following applicable local cleaning procedures.
- For a period of ten days following treatment, discharged patients:
    - must ensure that the injection/infusion site or any body fluids (including transmission via kissing) do not come into direct contact with any close contacts.
    - must avoid close contact with young children, pregnant women, immunocompromised people and livestock (e.g., pigs, cows, horses, etc.). When unavoidable, a surgical grade mask should be worn when within touching distance.
- Any spills or soiled material handled per standard procedures for infectious/ contaminated material.

3. Definitions

Word	Definition
VSV-GP (BI 1831169)	The oncolytic virus that will be tested in this trial
Shedding	The release of the tested virus through body secretions, excretions, or body surface lesions

4. Contact Details

Please contact us at the address below if you have any comments regarding this public record or our activities, or if you would like to receive additional information about this deliberate release.

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