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CLINICAL TRIAL PROTOCOL

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Open-label, phase Ia study of STING agonist BI 1703880 plus ezabenlimab for patients with advanced solid tumors

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ABSTRACT

BI 1703880, a novel STimulator of INterferon Genes (STING) agonist, has demonstrated preclinical antitumor activity. As STING activation can upregulate programmed death ligand 1 and human leukocyte antigen in tumor cells, a combination of BI 1703880 and an anti-programmed cell death protein 1-antibody, such as ezabenlimab, may improve efficacy. This first-in-human phase Ia study (NCT05471856) is evaluating BI 1703880 plus ezabenlimab in patients with advanced solid tumors. The study utilizes an innovative lead-in design; all patients receive BI 1703880 monotherapy in Cycle 1 and combination therapy from Cycle 2. The primary endpoint is dose-limiting toxicities during the maximum tolerated dose evaluation period. Results will inform the future development of BI 1703880 for treatment of metastatic or recurrent malignancies.

Clinical Trial number: NCT05471856

PLAIN LANGUAGE SUMMARY

There are many different types of treatments available for patients with cancer. One type of treatment aims to use the patient's own immune system to target and destroy the cancer, known as immunotherapy. BI 1703880 is a new drug that has been developed to activate the immune system for the treatment of cancer. This study is evaluating BI 1703880 for patients with advanced cancers based on its ability to destroy cancer cells in animal studies. BI 1703880 is being investigated on its own and in combination with another drug, ezabenlimab. The reason for testing these two drugs together is because sometimes cancer cells can become resistant to one type of immunotherapy, making proteins to "turn off" the immune response targeting the cancer. Similar to BI 1703880, ezabenlimab is also an immunotherapy. However, it turns the immune system on in a different way from BI 1703880, which means they may work together to produce a better anticancer result. The objective of the study is to determine a suitable dose of BI 1703880 alone and in combination with ezabenlimab and to see if any side effects occur.

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STING; STimulator of INterferon Genes; immunotherapy; cancer; phase I; DNA sensor; PD-1 antibody; immune checkpoint inhibitor

1. Introduction

Despite recent advances in cancer treatment, the prognosis for patients with advanced-stage disease or recurrent malignancies is poor. Immune checkpoint inhibitors are promising treatments for long-term response with a curative potential [1]. However, a majority of patients will have non-responsive tumors or develop resistance, highlighting a need for novel therapeutic agents and treatment regimens in this area [2]. In recent years, the STimulator of INterferon Genes (STING) pathway has been highlighted as an important target for activation of an antitumor immune response in cancer immunotherapy [3].

STING is the central molecule in the cyclic GMP–AMP synthase (cGAS)-STING innate immune pathway that senses cytosolic DNA. The presence of cytosolic DNA can be a result of viral or bacterial infection, mammalian DNA accessing the cytosol directly, mitotic failure, or mitochondrial dysfunction (Figure 1) [4,5]. Cytoplasmic DNA is recognized by cGAS, leading to the synthesis of 2′3′-cyclic GMP – AMP (2′3′-cGAMP), which acts as a second messenger to bind and activate STING [4,6–8]. The subsequent conformation changes result in the transcription of type I interferons (IFNs) and proinflammatory cytokines via NFκB [4,5]. Production of type I IFNs by antigen-presenting cells facilitates cross-priming of tumor-specific CD8+ T cells, which can lead to an adaptive antitumor immune response against tumor antigens

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Article highlights

- This is a first-in-human, dose-finding trial to determine the safety of BI 1703880 in combination with ezabenlimab in patients with advanced or metastatic solid tumors.
- The study utilizes an innovative intra-patient lead-in design, whereby patients will receive BI 1703880 monotherapy in the first cycle followed by BI 1703880 in combination with ezabenlimab from Cycle 2 onward.
- The primary endpoint is the occurrence of dose-limiting toxicities during the maximum tolerated dose evaluation period (defined as the first two treatment cycles of BI 1703880 administration).
- The results of this trial will inform the future development of BI 1703880 in combination with ezabenlimab for treatment of patients with metastatic or recurrent malignancies, for whom prognosis remains poor.
- The study is active, and patients are currently being recruited from approximately 10 sites across Japan, Spain, the United Kingdom, and the United States.

[9]. STING agonists have shown convincing antitumor effects across multiple preclinical models with several STING agonists tested in clinical settings in different tumors.

Cyclic dinucleotides (CDNs) administered intratumorally were the first class of STING agonists that entered drug development. The CDN-based STING agonist, ADU-S100/MIW815, was well tolerated in patients with advanced solid tumors and lymphomas, with no dose-limiting toxicity (DLT) reported [10]. However, further clinical trials were discontinued, and development was halted due to weak preliminary clinical results [11,12]. Similarly, MK-1454, a synthetic CDN analog in clinical development to treat advanced solid tumors or lymphomas, demonstrated some efficacy and manageable safety in preliminary studies when combined with pembrolizumab [10–12]. However, it has also been removed from development pipelines and recruitment for ongoing trials suspended [12]. Similarly, BI 1987446, an intratumorally administered STING agonist, was investigated as a monotherapy and in combination with an anti-PD-1 antibody in patients with advanced or metastatic solid tumors. However, development has been discontinued in favor of an agent that can be administered systemically [13].

BI 1703880 is a promising novel immune-directed second-generation STING agonist amenable for systemic administration, which offers a more convenient method of administration and facilitates combination with standard-of-care therapies. Systemic administration of BI 1703880 in combination with anti-programmed cell death protein 1 (PD-1) has demonstrated antitumor activity in animal models, including shrinkage or disappearance of tumors as well as durable antitumor immune memory [data on file]. Activation of the STING pathway induces programmed death ligand 1 (PD-L1) and human leukocyte antigen upregulation via IFN secretion. However, upregulation of PD-L1 promotes immune evasion, thus combination treatment with an anti-PD-1 antibody is likely to counteract this evasion and enhance the efficacy of cancer immunotherapy [14–18]. Ezabenlimab (BI 754091) is a humanized PD-1–targeting monoclonal antibody that is currently being investigated for the treatment of solid tumors [19]. Here, we describe the design of a phase Ia first-in-human, dose-finding study evaluating BI 1703880 monotherapy and in combination with ezabenlimab for patients with advanced solid tumors (NCT05471856).

2. Methods

2.1. Study design

This is a first-in-human phase Ia, open-label, non-randomized, single-arm, dose-escalation study evaluating the STING agonist BI 1703880 administered via intravenous infusion alone and in combination with a fixed dose of ezabenlimab. The study began enrolling patients in March 2023 and the primary completion is expected in 2025. As of 18 March 2024, 13 patients have been enrolled.

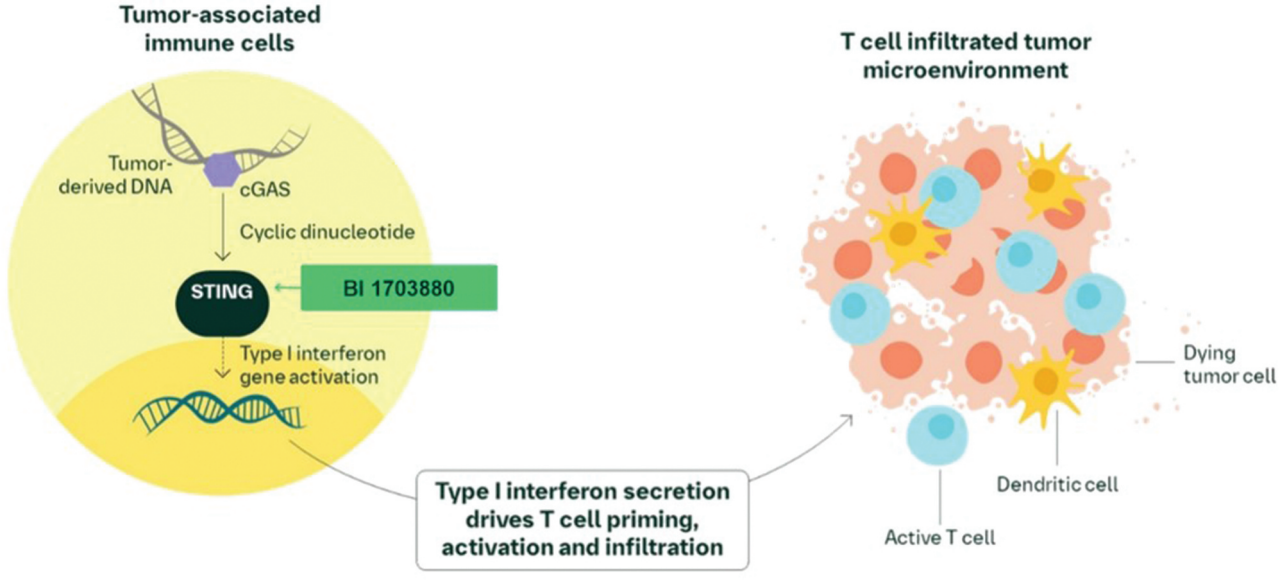

Figure 1. STING pathway.

cGAS: Cyclic GMP – AMP synthase; DNA: Deoxyribonucleic acid; STING: STimulator of INterferon Genes.

2.2. Participants

The study population consists of patients aged ≥18 years with a confirmed diagnosis of a locally advanced, metastatic, unresectable, or relapsed/refractory solid tumor, who have exhausted, refused, or who are not eligible for established treatment options for the malignant disease, and have at least one lesion measurable according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. Patients must have at least one lesion amenable to pre-treatment and on-treatment biopsy. Patients are eligible if they have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and have adequate organ function and bone marrow reserve. Patients must not have received prior STING agonist therapy or have a history of intolerability to a PD-1 or PD-L1 therapy. Patients must sign and date the informed consent form in accordance with International Conference on Harmonisation-Good Clinical Practice and local legislation. A full list of the eligibility criteria for this study is included in Supplementary Table S1 and Supplementary Table S2.

2.3. Treatment and dose escalation

In an innovative intra-patient lead-in design, BI 1703880 is administered by intravenous infusion to each patient as monotherapy for the first treatment cycle, followed by subsequent cycles of BI 1703880 in combination with ezabenlimab (Figure 2). Ezabenlimab 240 mg is administered as an intravenous infusion on Day 1 of every 3-week cycle beginning with Cycle 2. BI 1703880 and ezabenlimab are administered for up to 18 and 34 cycles, respectively, or until unacceptable toxicity or disease progression. Patients are treated beyond progression if there is evidence of clinical benefit.

To mitigate a potential safety risk, the first patient at the starting dose level is treated for the first cycle before the next patient at that dose level is enrolled. In subsequent dose levels, treatment of the second patient at that dose level is delayed until the first patient receives two BI 1703880 infusions.

Successive cohorts of patients will receive increasing doses of BI 1703880 until the maximum tolerated dose (MTD) is reached. Once a dose cohort is determined to be safe and allocation to the next highest dose level is completed, additional backfill patients may be enrolled at lower dose levels previously determined to be safe. A Bayesian logistic regression model with overdose control (BLRM-EWOC) is being used to determine the MTD by updating estimates of the probability of observing a DLT for each dose level. DLTs that occur during the MTD evaluation period (defined as the first two treatment cycles of BI 1703880 administration) will be used for dose-escalation decisions. If a dose does not fulfill the EWOC criteria, no escalation will be permitted. Skipping doses is not permitted, but intermediate dose levels that fulfill the EWOC criterion may be allowed. The Dose Escalation Committee (DEC) is responsible for reviewing the data from each dose cohort prior to escalation to the next dose level cohort. Initiation of each dose level cohort will only take place with approval from the DEC, guided by the BLRM-EWOC.

2.4. Study objectives and endpoints

The primary objective of the study is to characterize the safety of escalating doses of BI 1703880 in combination with a fixed dose of ezabenlimab in adult patients with advanced solid tumors in order to select an appropriate dose to be evaluated in subsequent trials. The primary endpoint is the occurrence of DLTs during the MTD evaluation period (defined as the first two cycles of BI 1703880 administration).

The secondary objectives are to further characterize the safety profile, particularly after additional cycles of treatment, and the pharmacokinetics of the escalating doses of BI 1703880. The secondary endpoints are the occurrence of DLTs during the entire treatment period, maximum measured concentration in plasma (C_{max}), time from dosing to maximum measured concentration (T_{max}), and area under the concentration–time curve ($AUC_{0\text{-}tz}$). Further objectives include efficacy, safety, pharmacokinetics, and pharmacodynamics (Table 1).

2.5. Assessments

2.5.1. Safety

Safety assessment involves continuous monitoring and review of adverse events (AEs), including serious AEs and AEs of special interest (AESIs), via physical examinations,

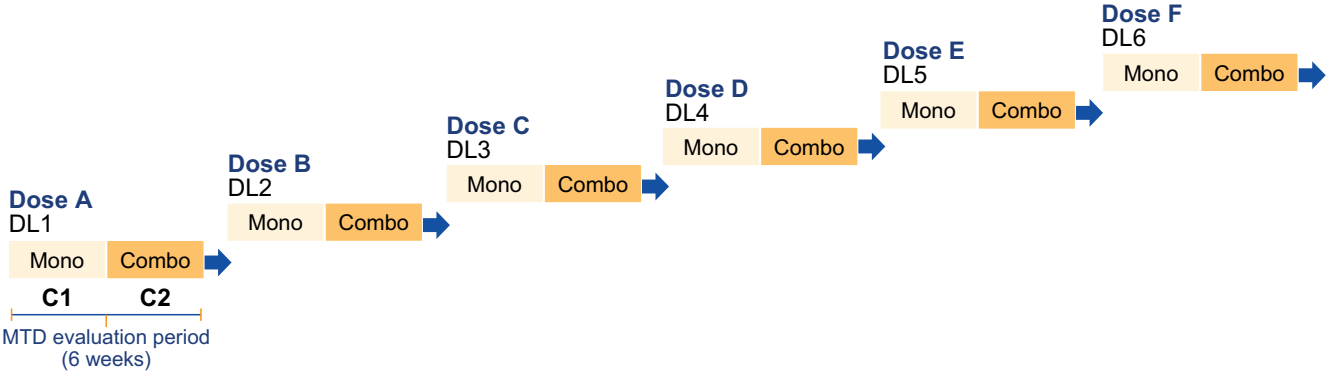

Figure 2. Study treatment design.

Combo: Combination; DL: Dose level; Mono: Monotherapy; MTD: Maximum tolerated dose.

Table 1. Study endpoints.

Study endpoint(s)	
Primary endpoint	
• Occurrence of DLTs during the MTD evaluation period	
Secondary endpoints	
• Occurrence of DLTs during the on-treatment period	
• PK parameters C_{max} and $AUC_{0\text{-}tz}$	
Further endpoints	
Efficacy	• OR based on RECIST 1.1 defined as BOR of confirmed CR or PR, where overall response is determined by the Investigator's assessment according to RECIST 1.1 • OR based on iRECIST, defined as BOR of confirmed CR or PR, where overall response is determined by the Investigator's assessment according to iRECIST
Safety	• Number of patients with Grade ≥3 CRS • Safety profile, including immune-related AEs, for monotherapy and combination with ezabenlimab
PK	• PK profiles and parameters of BI 1703880 and ezabenlimab • Characterization of BI 1703880 dose–exposure relationship • Immunogenicity of ezabenlimab
PD	• Change from baseline in peripheral cytokine levels • Change from baseline at C3D1 in number and density of tumor infiltrating T-lymphocytes in tumor tissue
PK/PD	• PK/PD correlations as appropriate and feasible

AE: Adverse event; AUC: Area under the curve; BOR: Best overall response; C3,D1: Cycle 3, Day 1; C_{max}: Maximum plasma concentration; CR: Complete response; CRS: Cytokine release syndrome; DLT: Dose-limiting toxicity; iRECIST: Response Criteria for use in trials testing Immunotherapeutics in Solid Tumors; MTD: Maximum tolerated dose; OR: Objective response; PD: Pharmacodynamic; PK: Pharmacokinetic; PR: Partial response; RECIST: Response Evaluation Criteria In Solid Tumors.

vital signs, laboratory tests (including blood and urine sampling), and electrocardiograms. Additional safety follow-up is being conducted during the post-treatment period, at 30 days and 90 days following the individual patient's end of treatment. All AEs and AESIs are collected and documented from the time of informed consent until a patient's end of trial. All AEs with an onset between start of treatment and 90 days after the last dose of trial medication are assigned to the on-treatment period for evaluation.

Physical health and vital signs are assessed at screening, on Days 1, 8, and 15 of Cycles 1 and 2, Day 1 of Cycle ≥3, at the end of treatment visit, and at the 30-day safety follow-up visit. ECOG performance status is assessed at screening, on Day 1 of Cycles 1, 2, and 3, on Day 1 of every other cycle beginning with Cycle 4 prior to trial medication intake, at the end of treatment visit, and at the 30-day safety follow-up visit.

2.5.2. Efficacy

Baseline tumor assessments are performed within 28 days before the start of trial treatment. Baseline imaging includes all known or suspected sites of disease using computed tomography or magnetic resonance imaging scan. Tumor assessments are then performed every 6 weeks (±3 days) for 6 months, then every 9 weeks (±3 days) until end of treatment. Tumor response is being evaluated at the sites according to RECIST 1.1 and Response Criteria for use in trials testing Immunotherapeutics in Solid Tumors (iRECIST). The same method of assessment and imaging technique is used for every evaluation.

2.5.3. Pharmacokinetics

Blood and urine samples are taken for pharmacokinetic analysis of BI 1703880 and ezabenlimab on Days 1, 8, and 15 of Cycles 1 and 2, and Day 1 for Cycle ≥3. Data are assessed to describe the concentration time course of BI 1703880.

2.5.4. Other assessments

Other assessments include the immunogenicity of ezabenlimab and BI 1703880 pharmacodynamics. Blood samples are analyzed for the presence of antidrug antibodies from Cycle 2 onward. Blood and tumor tissue samples are being collected to analyze the pharmacodynamic effects of BI 1703880 in the periphery and the target site. Biomarkers include, but are not limited to, cytokines and chemokines (e.g., IL-6, IL-2, TNFα, IFNβ, and IFNγ).

2.6. Statistical methods

Approximately 66 patients will be enrolled; six patients are expected to be enrolled in the dose escalation cohort, and five patients are expected to be enrolled in the backfill cohort, for each dose level. No formal sample size calculation was performed. However, simulation trials were conducted to evaluate the operating characteristics of the BLRM, whereby between 6 and 24 patients are expected to be treated on average before the criteria for the MTD determination are fulfilled per the model's recommendations. The BI 1703880 dose escalation is being guided by a BLRM-EWOC that is fitted to binary toxicity outcomes. The BLRM determines the MTD estimate by calculating estimates of the probability of observing a DLT for each dose level. The DEC may also recommend expansion of the size of the currently recruiting cohort or recommend the size for the next dose escalation cohort.

Intermediate dose levels are allowed upon review with the DEC, and a Fibonacci dose escalation scheme is implemented in consecutive dose cohorts if a DLT or a Grade ≥2 cytokine release syndrome AE is observed in any dose cohort during the MTD evaluation period. After all patients in a dose cohort have either been observed for the duration of the MTD evaluation period or have experienced a DLT, the BLRM will be updated with the newly accumulated data and the overdose risk calculated. Dose escalation is permitted to all dose combinations that fulfill the EWOC criterion.

AEs are coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA). Laboratory data are analyzed both quantitively as well as qualitatively; the latter are done via comparison of laboratory data to their reference ranges and assessment of Common Terminology Criteria for Adverse Events (CTCAE) grades, and values defined as clinically relevant will be summarized. Treatment groups are compared descriptively regarding distribution parameters as well as with regard to frequency and percentage of patients with abnormal values. Descriptive analyses are used to describe safety and efficacy endpoints.

3. Discussion

This study is evaluating the STING agonist BI 1703880 in combination with the anti-PD-1 antibody ezabenlimab in adult patients with advanced solid tumors. The aim of the study is to characterize the safety of escalating doses of BI 1703880 in combination with a fixed dose of ezabenlimab. The primary endpoint is the occurrence of DLTs during the first two cycles of treatment. The study will implement an innovative intra-patient lead-in design, whereby patients will receive BI 1703880 monotherapy in the first cycle followed by BI 1703880 in combination with ezabenlimab from Cycle 2 onward. The innovative study design allows for all patients to receive the potential optimal treatment regimen. The BLRM-EWOC design utilized for dose escalation with appropriate monitoring ensures the safety of the patients. The results of this study will guide the future development of BI 1703880. The study is active, and patients are currently being recruited from approximately 10 sites across Japan, Spain, the United Kingdom, and the United States.

Author contributions

Conception/design: NF, MS, JB, KH; Provision of study material or patients: NF, SK, VG, EEP, IM, GA, TD, DB, MEG, PL, KH Manuscript writing and revision: KH, SK, VG, EEP, IM, GA, TD, DB, MEG, NF, MS, JB, PL Final approval of manuscript: KH, SK, VG, EEP, IM, GA, TD, DB, MEG, NF, MS, JB, PL.

Disclosure statement

K Harrington participates in advisory boards/scientific advisory committees for Arch Oncology, AstraZeneca, Bristol Myers Squibb, Boehringer Ingelheim, Codiak, Inzen, Merck-Serono, MSD, Oncolys, Pfizer, Replimune, and Scenic; and has received research funding from AstraZeneca, Boehringer Ingelheim, MSD, and Replimune.

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I Moreno participates in advisory boards/scientific advisory committees for Ellipses Pharma, Ltd.

N Fernandez, M Schmohl, and J Barrueco are employees of Boehringer Ingelheim.

P LoRusso has participated in advisory boards for AbbVie, Takeda, Agenus, IQVIA, Pfizer, GlaxoSmithKline, QED Therapeutics, AstraZeneca, EMD Serono, Kyowa Kirin Pharmaceutical Development, Kineta Inc., Zentalis Pharmaceuticals, Molecular Templates, ABL Bio, STCube Pharmaceuticals, I-Mab, Seagen, imCheck, Relay Therapeutics, Stemline (a Menarini company), Compass BADX, Mekanistic, Mersana Therapeutics, BAKX Therapeutics, Scenic Biotech, Qualigen, NeuoTrials, Actuate Therapeutics, Atreca Development, Cullinan, Quanta Therapeutics, Schrodiner, and Boehringer Ingelheim; consultancy for SOTIO, I-Mab, Roivant Sciences; imCORE Alliance for Roche/Genentech; data monitoring committee for Amgen, DrenBio, and SOTIO.

G Alonso declares no conflict of interest.

D Berz reports personal fees from Jazz Pharma, Mirati, EMD, and Sun Pharma.

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Ethical declaration

The trial is being carried out in compliance with the protocol and in accordance with the Declaration of Helsinki, the International Conference on Harmonisation-Good Clinical Practice guidelines, relevant Boehringer Ingelheim standard operating procedures, the EU directive 2001/20/EC, the Japanese Good Clinical Practice regulations (Ministry of Health and Welfare Ordinance No. 28, 27 March 1997), and other relevant regulations. Investigators and site staff must adhere to these principles. This trial was initiated only after all required legal documentation was reviewed and approved by the respective Institutional Review Board/Independent Ethics Committee and competent authority according to national and international regulations (UK: The Yorkshire & The Humber – Sheffield Research Ethics Committee [ref: 22/YH/0255]). Patients must provide signed and dated written informed consent prior to enrollment. Deviation from the protocol, the principles of International Conference on Harmonisation-Good Clinical Practice, or applicable regulations are treated as "protocol deviation."

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Data availability statement

To ensure independent interpretation of clinical study results and enable authors to fulfil their role and obligations under the ICMJE criteria, Boehringer Ingelheim grants all external authors access to relevant clinical

study data. In adherence to the Boehringer Ingelheim Policy on Transparency and Publication of Clinical Study Data, scientific and medical researchers can request access to clinical study data, typically, one year after the approval has been granted by major Regulatory Authorities or after termination of the development program. Researchers should use the https://vivli.org/ link to request access to study data and visit https://www.mystudywindow.com/msw/datasharing for further information.

Previous presentation

This trial protocol was previously presented at the 37th Annual meeting of the Society for Immunotherapy of Cancer (SITC), Boston, MA, USA, November 10–12th 2022 (#626) and the 20th Anniversary meeting of the Japanese Society of Medical Oncology (JMSO), Fukuoka, Japan, March 16–18th 2023 (#e70268).

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