Protocol

Study ID: 213299

Official Title of Study: A Global, Molecular Disease Characterization Initiative (MDCI) in Oncology Clinical Trials

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TITLE PAGE

Protocol Title: A Global, Molecular Disease Characterization Initiative (MDCI) in Oncology Clinical Trials

Protocol Number: 213299/ Amendment 03

Compound Number or Name: None

Study Phase: Phase I/Phase II

Short Title: Molecular Disease Characterization Initiative **(MDCI)**

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May be found in the Study Reference Manual (SRM).

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Protocol Title: A Global, Molecular Disease Characterization Initiative (MDCI) in Oncology Clinical Trials

Protocol Number: 213299/ Amendment 03

Compound Number or Name: None

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The signed page is a separate document.

Medical Monitor Name and Contact Information can be found in the Study Reference Manual

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY List dates of original protocol and all amendments in reverse chronological order.		
Document	**Date**	**DNG or TMF Number**
Amendment 03	*25-OCT-2021*	*TMF-13855541*
Amendment 02	*25-NOV-2020*	*2019N418193_02*
Amendment 01	*15-JUN-2020*	*2019N418193_01*
Original Protocol	*09-MAR-2020*	*2019N418193_00*

Amendment 03 25-OCT-2021

This amendment is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

Overall Rationale for the Amendment: The overall rationale for this amendment is to clarify requirements on data collection and data entry, remove ICOS and epigenetic language, included the option for sites to send FFPE slides. Provided guidance on historical scans and image-guided biopsy. Updated the Introduction section to reflect GSK Oncology clinical trials and development updates. Schedule of activities table was updated to reflect changes made to the data collection and data entry requirements as well as provided guidance for combining Visit 1 and Visit 2 and option to have Visit 3 as a telehealth/phone visit. Included age requirement under inclusion criteria. Contraceptive use requirement for men was removed from inclusion criteria. Details on rationale are provided in the Table below.

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis	Removal of ICOS IHC requirement	To align with removal of ICOS studies from MDCI
Section 1.1 Synopsis	Added language for combining Visit 1 and Visit 2 as an option	To provide guidance on option to combine Visit 1 and Visit 2
Section 1.2 Schema and Section 4.1 Overall Design (Figure 2)	Updated study schema design	To align with updates to combine Visit 1 and Visits 2 as an option; allow for Visit 3 to be telehealth as an option; and provide flexibility to accommodate the sites for scheduling Visit 1 and 2
Section 1.3 Schedule of Activities (SoA)	Updated SoA Table 1: -Remove alcohol history requirement -Added radiation therapy under footnote 2 to be collected as part of medical history -Added footnotes to clarify option to combine Visit 1 and Visit 2; Visit 3 option for telehealth -Included footnote to allow transfer of HLA results from another GSK study to be used in MDCI -Removed vital signs from Visit 3 -Removed requirement for height and respiration rate -Removed requirement to collect prior and current anti-cancer therapies from Visit 3 -Added requirement to record weight at Visit 2 -Added haematology and coagulation labs to be collected at Visit 2; added footnote to clarify Visit 2 labs should be performed as close as possible as biopsy assessment where applicable	To align with changes in data collection and data entry requirements. Changes made to reflect feedback from sites.

Section # and Name	Description of Change	Brief Rationale
	-Added footnote to clarify that FFPE slides (details in SRM) can be sent instead of tissue block as per institutional guidance/policy -Added review of actionable results at Visit 3 - Added pre-study scans related to archived tumor specimen to the SoA to clarify scan requirements - Clarified that ECG should be done at baseline during Visit 1 and should be recorded in eCRF; removed ECG requirement from Visit 2 -Added footnote that if an ECG is done within 2 weeks of Visit 1, it can be used for this study, if the patient has not had any cardiac event. -Added footnotes to clarify withdrawal visit requirements. -For infectious disease biomarkers added footnote to include a window: Local test results are acceptable, if generated within 4 weeks from Visit 1.	
Section 2.2 Background	Removed ICOS language	To reflect GSK Oncology clinical trials and development updates
Section 2.2 Background	Added PVRIG, CD96 and TIGIT language	To reflect GSK Oncology clinical trials and development updates
Section 2.2 Background	Removed epigenetics language	To reflect GSK Oncology clinical trials and development updates
Section 5.1 Inclusion Criteria	Added language to clarify that FFPE slides can be sent instead of tissue block as per institutional guidance/policy	To clarify option for tissue sample being submitted for this study

Section # and Name	Description of Change	Brief Rationale
Section 5.1 Inclusion Criteria	Removed contraceptive use requirement for men	To align with IRB and safety feedback as this is not required as MDCI is a non-therapeutic study
Section 5.1 Inclusion Criteria	Added age requirement for eligibility under study	To align with requirement for age of consent
Section 7.2 Tumor Imaging	Added language on image-guided biopsy under Section 7.2.3 (Imaging from Image-Guided Biopsy) and historical scans under Section 7.2.4 (follow up imaging)	To provide guidance on historical scans and image-guided biopsy
Section 7.4.3 Electrocardiograms	Added language to ECG results requirements	To align with requirement of performing ECG and recording results into eCRF, only at baseline during Visit 1.
Section 8.2 Sample Size Determination	The following sentence was added: Expected to enroll 400 participants in this study	To include the expected number of participants to be enrolled in the study
Section 8.3 Population for analyses	Population for analyses definition was updated	To clarify the populations that will be included in the analyses
Section 9.3.2	Updated definition of SAE to: An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed	To align with updates from the global SAE template
Section 9.3.4 Reporting of SAE to GSK	Removal of bullet point for requirement to verify relationship of SAE to IP within 72 hours	To align with updates from the global SAE template
Section 10 References	New references were added and some references were updated or deleted	Updated references to align with changes in the main text

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Global, Molecular Disease Characterization Initiative (MDCI) in Oncology Clinical trials

Short Title: Molecular Disease Characterization Initiative **(MDCI)**

Rationale:

It is estimated that over 600,000 people will die from cancer in 2020 [American Cancer Society (ACS), 2020]; advancement is needed in further understanding biological mechanisms underpinning clinical outcomes and identification of novel pathways contributing to oncogenesis or treatment resistance.

The aim of this protocol is to leverage science and data, by comprehensively analyzing and compiling data from cancer patients' disease, in an effort to **reduce time-to-treatment for patients,** while learning of potentially **novel therapeutic regimens,** to address these two unmet needs for cancer patients; both of which lend to reducing the projections of cancer deaths. MDCI will accomplish this by looking at a patient's tumor specimen by validated clinical immunohistochemistry(IHC) assays coupled with whole exome and whole transcriptome sequencing. Based on IHC data, as well as previous medical history, all potential clinical trial options are returned; reducing time-to-treatment by supporting screening against all trial options, instead of one at a time. Sequencing data collected will allow researchers to correlate to outcome, potentially discovering novel targets/pathways, as well as co-expression of biomarkers; allowing for data-driven, novel treatment regimens.

Oncology, as a field, is moving away from 'universal treatment' and is evolving to a 'precision medicine' paradigm with therapy tailored to individual disease profile. The use of a precision medicine approach in oncology, however, also requires multiplex testing of tumor specimens at diagnosis and relapse, which presents challenges to timely evaluation thereby reducing the probability of a patient to participate in any one clinical trial. For oncology patients, the urgent need for timely treatment does not allow for a sequential, complex, and time-consuming process that is inherent in the tandem, focused screening for each individual clinical trial. Moreover, we have learned that determining a single analyte alone does not always correlate to clinical benefit [Blons, 2019]. While evaluating specimens for treatments available today, it is critical to understand, as well, the heterogeneity of a patient's disease and what molecular signatures may be present that do not have a targeted regimen, if we hope to impact cancer patient response/outcomes. Design and Data from trials such as the Lung-MAP study further emphasize this approach; 'as we begin to target less common genomic and immunotherapy subtypes, centrally coordinated clinical trial designs such as Lung-MAP are necessary to rapidly deliver effective therapies to patients, whereas also maximizing the quality of research data obtained'[Lam, 2018].

In this study, tumor specimens will be comprehensively evaluated both for patient-selection biomarkers relevant to the therapies within the GSK oncology clinical trials, as well as towards identifying novel targets. The data generated from validated clinical assays used in GSK investigational study protocols will be made available to help inform investigators and patients of clinical trials they may be best suited for. The results of this analysis will be shared with the investigator first, before being available to the patient (where not prohibited by local regulations), through individual portals (the investigator portal through the GSK sequencing partner; the patient portal, named 'Gather Share Know', is established by GSK in collaboration with an external partner). This study will involve many sites, located over a wide geographic footprint, with the intent of significantly expanding the opportunities for identifying participants and simplifying the screening process into clinical trials.

Expected Impact of MDCI Model

MDCI aims to create a platform to accelerate the availability of new therapeutic options for patients and increase participation in precision medicine clinical trials, while building a scientific database (GSK Clinical Science Database) to facilitate the investigation of biological mechanisms underpinning clinical outcomes in oncology.

This protocol design is expected to benefit patients, oncology healthcare providers, and clinical research:

- **Patient:**
  - Providing potential GSK trial options at the first testing timepoint; permitting efficient navigation of available trial options without the need for subsequent testing to screen for additional trials.
  - Returning a subset of data from validated clinical assays in a plain language summary, in real-time, as well as information to participants on MDCI study visits and what to expect through participant hub.
- **Physician:**
  - Providing a comprehensive view of all genetic and protein data, on patients' disease status
  - Reducing the need for repetitive screening in order to consider enrolling in multiple trials.
- **Oncology Research:**
  - Developing a GSK Clinical Science Database that may facilitate innovation, through further understanding of mechanisms of action or resistance leading to the identification of novel targets and potential combination approaches.
  - Leveraging artificial intelligence/machine learning (AI/ML) for algorithm builds of the data collected

Objectives and Endpoints:

Objectives	Endpoints
Primary	Primary
• To evaluate molecular and immunological profile of tumor and peripheral blood of all enrolled participants, across indications and within tumor subsets (Building a GSK Clinical Science Database for tumor profiling and correlative studies)	• Profile of patient specific selection biomarkers targeted by therapeutics with the GSK oncology pipeline, as well as other CCI biomarkers as detailed in the study reference manual (SRM).

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Overall Design:

This is a multicenter study, enrolling participants with advanced/metastatic disease for the purpose of biospecimen collection (tumor tissue and blood samples) for broad molecular profiling and examining the expression of specific antigens (e.g. NY-ESO-1, LAGE-1a), immune markers (e.g. PD-L1), tumor immune infiltrates, differentially expressed genes, and Human Leukocyte Antigen (HLA) genotype. Results from validated clinical assays will support the referral of eligible participants into an appropriate GSK Clinical trial. These results, paired with clinical & sequencing results, will facilitate the building of a scientific database (GSK Clinical Science Database) permitting investigation of mechanisms underpinning the activity of targeted agents, resistance to therapy, and conducting other correlative analyses.

- Participants who are HLA-A*02:01, HLA-A*02:05, HLA-A*02:06 positive and whose tumor tissue expresses NY-ESO-1 and/or LAGE-1a by a validated assay (based on relevant clinical cut-off detailed in SRM & other inclusion/exclusion criteria) may be referred to GSK3377794, GSK3845097, &/or GSK3901961 clinical trial(s)
- Participants whose tumor tissue is positive by validated PDL-1 (SP263) IHC (based on relevant clinical cut-off detailed in SRM & other inclusion/exclusion criteria) may be referred to GSK3359609 clinical trial(s).
- Based on BRCA 1 or 2 mutation, Homologous Recombination Deficiency (HRD) &/or PDL-1(SP263) tumor status, participants may be referred to Niraparib trial(s).

Validated clinical biomarker data will be returned to the physician, as well as a subset to the participant, through individual portal systems. This study will also utilize tumor and blood samples for CCI [redacted] research purposes, including potential biomarker, companion diagnostic, and investigational genetic research.

It is anticipated that this molecular disease characterization protocol will support screening for GSK Oncology trials, outlined within SRM.

Disclosure Statement: This is a single arm interventional molecular analysis study with no administration of investigational product and no masking.

Number of Participants: Approximately 400 participants will be enrolled into this molecular analysis study.

Study Groups and Duration:

Enrolled participants will be followed in two groups; (a) those enrolled onto a GSK clinical trial following Visit 3 and (b) those followed longitudinally, with disease re-analyzed at progression (Schedule of Activities Table 2). The total number of participants anticipated for this study is 400. Following consent, participants will have three initial study visits (further details on visits can be found in Schedule of Activities (SoA) and Section 4.1).

- **Visit 1:** Informed consent, review of medical history, targeted physical exam, information on Gather Share Know
- **Visit 2:** Biospecimen collection (e.g. tumor sample, blood), imaging
- **Visit 3:** Review results & trial matches with Physician, decide treatment options/treatment trial.

Note: Visit 1 and 2 may be combined, if appropriate, to reduce individual study visits. In the case that Visit 1 and 2 are combined, all corresponding samples must be collected per the SoA at this visit. In this scenario, following consent, all eligibility criteria should be confirmed prior to taking any Visit 2 assessments.

If a patient does not enroll onto a GSK study, or any other investigational study, the patient may remain under MDCI and be followed as per assessments on SoA Table 2.

Duration: It is expected that a majority of patients complete Visit 1 through Visit 3 in $\leq$8 weeks; Participants who are followed longitudinally (SoA Table 2) may be followed for 2 years.

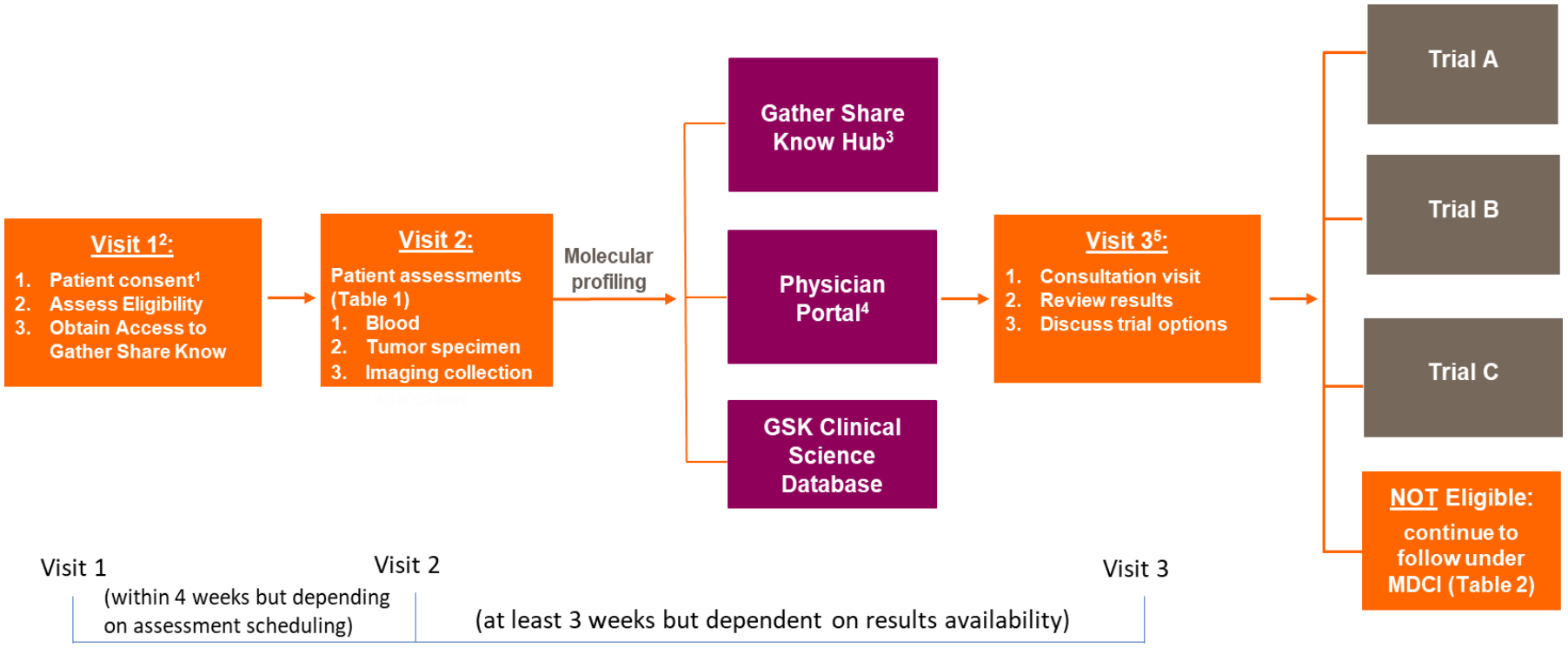
The study protocol will remain open until all designated GSK-sponsored impacted clinical trials (outlined in SRM) are closed to enrolment & all participants have completed this study or at the discretion of GSK.

Data Monitoring or Other Committee:

Study 213299 Translational Research Committee

This committee is composed of both internal and external disease-area experts. The objective of the Translational Research Committee for Study 213299 is to consult on trial design, development, and implementation of MDCI. Interim data will be reviewed to facilitate these efforts.

1.2. Schema



Footnotes: [1]MDCI will be an optional protocol under select GSK oncology protocols; [2]In the case that Visit 1 and 2 are combined, all corresponding samples must be collected per the SoA (Section 1.3 Table 1) at this visit and after eligibility is confirmed; [3]Subset of data to be shared on Gather Share Know; [4]Patient's molecular profile and medical history will be compared against the eligibility criteria of select GSK oncology protocols to identify potential trial options; [5]Visit 3 may occur remotely via telehealth/phone visit (optional).

1.3. Schedule of Activities (SoA)

Table 1 Schedule of Activities (SoA) for Study 213299

Procedures	Visit 1	Visit 2[1]	Visit 3/Withdrawal[1]	Withdrawal [17]	
Informed consent[15]	X				**Footnotes:**
Inclusion and exclusion criteria	X				**1.** Visit 2 should occur within 4 weeks of Visit 1 (dependent on assessment scheduling) or can be combined with Visit 1 assessments, if applicable. In the case that Visit 1 and 2 are combined, all corresponding samples must be collected per the SoA at this visit. Visit 3 is a Withdrawal visit for patients not continuing to be monitored under MDCI (Table 2) and may occur remotely via telehealth/phone visit (refer to SRM for details).
Demography	X				
Full physical examination	X			X	
Past /current medical conditions including Tobacco history and prior surgical history[2]	X				**2.** Past /current medical conditions, anti-cancer therapies, radiation therapy, and cancer-related prior surgical history will be collected for all participants.
Disease History Form	X				
Prior and Current anti-cancer therapies[2]	X	X		X	**3.** Woman of Childbearing Potential (WOCBP, see Appendix 4) must have a negative urine or serum pregnancy test a) at study start to be eligible for this study & b) prior to procedure(s)
Prior and Current Medications	X	X	X	X	
Vitals[14]	X	X		X	**4.** Includes HIV, HBV, HCV, HTLV, EBV, CMV, and syphilis (spirochete bacterium). Local test results are acceptable, if generated within 4 weeks from Visit 1.
Weight	X	X			**5.** HLA sample – one blood sample (see Section 7.7.4). HLA results from another GSK study may be transferred to be used in MDCI (see SRM and Study Laboratory Manual for details).
Disease Characteristics	X				
Single 12-Lead ECG[16]	X				**6.** Liquid Biopsies – two blood samples (see Section 7.7.5)
Pregnancy test[3]	X	X			**7.** Genetics sample – one blood sample (see Section 7.6)
Hematology	X	X[18]			**8.** Formalin-fixed, paraffin-embedded (FFPE) tumor block or fresh biopsy specimen, per Inclusion Criteria (see Section 5.1). Archival sample can be requested and sent after patient has consented. If an archival block cannot be sent as per
Coagulation	X	X[18]			
Infectious Disease Markers[4]	X				

Procedures	Visit 1	Visit 2[1]	Visit 3/Withdrawal[1]	Withdrawal [17]	
ECOG	X				institutional guidance/policy, slides can be sent instead, refer to the SRM and Study Laboratory Manual for further details.
HLA genotyping		X[5]			**9.** For participants with archived tumor specimen: Imaging by CT/MRI conducted for tumor assessment within ±4 weeks of tumor biopsy will be collected. Images from image-guided biopsy procedures (if conducted) will also be collected. See Section 7.2.
Liquid biopsy (blood)		X[6]		X	**10.** CT/MRI to assess tumor(s). Imaging visit window ±4 weeks (28 days), or -4 weeks if fresh tissue biopsy is conducted at Visit 2. Imaging for standard of care tumor assessment may be used if it was acquired within 28 days and conforms to the protocol imaging requirements in Section 7.2.3. Images from image-guided biopsy procedures (if conducted) will be collected.
Genetics sample		X[7]			**11.** Following completion of informed consent, patients will be provided credentials to log into the Gather Share Know Participant hub (see Section 7.1)
Tumor specimen		X [8]			**12.** For those participants who are not eligible for a GSK clinical trial, please refer to Table 2 SoA
Pre-study scans related to archived tumor specimen	X[9]				**13.** SAEs assessed as related to study procedure(s) or lead to study withdrawal
Tumor Imaging		X [10]			**14.** Blood Pressure, Pulse Rate, Temperature. If Visit 1 and 2 are combined, vital signs only need to be recorded once.
Review of AEs and SAEs that are related to study procedure(s) or lead to study withdrawal[13]	X	X	X	X	**15.** Must be signed before any study specific assessments are performed.
Gather Share Know Credentials	X [11]				**16.** ECG to be performed at baseline during Visit 1 and result to be entered into eCRF. An ECG done within 2 weeks of Visit 1 is acceptable, if the patient has not had any cardiac event.
Referral to intended GSK Treatment protocol			X [12]		**17.** Withdrawal Visit applicable only if participant withdraws from study prior to Visit 3.
Review of actionable results			X		**18.** Visit 2 haematology and coagulation laboratory tests to be performed as close as possible to the biopsy assessment.

Table 2 Schedule of Activities For Participants Ineligible for Treatment Trial

Note: For those participants not eligible for a GSK treatment trial or other clinical trial, and who receive Standard of Care (SoC), disease will continue to be monitored under MDCI following Table 2 assessments:

Procedures	Q26W until W104	Withdrawal/At Progression	
Visit Window	±4W	±4W	
Liquid Biopsy	X	X	**Footnotes:** **1.** Subsequent treatment and the associated clinical outcomes of interest will be collected for participants who do not enroll in a treatment protocol. **2.** Survival follow up will be conducted for participants who do not enroll in a treatment protocol. **3.** If patient progresses while on Standard of Care (SoC), a tumor biopsy may be taken for re-analysis & potential referral to a treatment trial based on results. Image guidance preferred when feasible. Images from guidance procedure will be collected (see Section 7.2.3). **4.** Any imaging for standard of care tumor assessment by CT, MRI, PET, nuclear medicine, Xray, or photography that was conducted will be collected. Visit window for imaging ±8 weeks. **5.** Imaging for tumor assessment conducted within 4 weeks prior to biopsy will be collected. Imaging conducted after biopsy is not required to be collected. **6.** Blood Pressure, Pulse Rate and Temperature
Tumor Specimen(3)		X	
Tumor Imaging	X(4)	X(5)	
Vitals(6)	X	X	
Review of AEs and SAEs that are related to study procedure(s) or lead to study withdrawal	X	X	
Current anti-cancer therapies(1)	X	X	
Survival Follow up(2)	X	X	

2. INTRODUCTION

2.1. Study Rationale

MDCI proposes to evaluate biomarkers on tumor specimens obtained from consenting cancer patients and thereby facilitate enrolment into clinical trials with agents that are targeted to the participant's tumor developed within the GSK therapeutic platforms. The tumor specimens and data collected during the course of this study will be stored in a GSK Clinical Science Database and utilized in CCI [redacted] nalysis to provide insights into mechanisms contributing to specific outcomes or resistance, and discovery of novel targets.

Oncology, as a field, is moving away from 'universal treatment' and is evolving to a 'precision medicine' paradigm with therapy tailored to each patient's disease. As the number of single-analyte tests has increased with the personalized medicine paradigm, oncologists are faced with deciding to use several single-analyte tests, or a single Next Generation Sequencing (NGS) test. Because immunohistochemistry (IHC) is a well-established method, evidence is needed to bridge or couple IHC with NGS to streamline testing and make this decision easier for oncologists. Recent data from NCI-MATCH supports the use of NGS coupled to IHC for molecular profiling; demonstrating 'feasibility of screening large numbers of patients at numerous accruing sites in a complex trial to test investigational therapies for moderately frequent molecular targets. Co-occurring resistance mutations were common and endorse investigation of combination targeted-therapy regimens' [Flaherty, 2020]. The Lung-MAP study, which has a similar approach, also supports this study design; 'As we begin to target less common genomic and immunotherapy subtypes, centrally coordinated clinical trial designs such as Lung-MAP are necessary to rapidly deliver effective therapies to patients, whereas also maximizing the quality of research data obtained' [Lam, 2018]. The central goal of the MDCI protocol is to further drive a shift in the direction of using broad molecular diagnosis to get the 'right patient to the right trial at the right time'.

This molecular characterization study will prospectively collect and examine each participant's tumor profile, along with clinical history, to use these data in providing appropriate trial option(s), when applicable. Further, data will be retrospectively analysed to advance our understanding of biological mechanisms underpinning clinical outcomes and discovering novel pathways contributing to treatment resistance or oncogenesis.

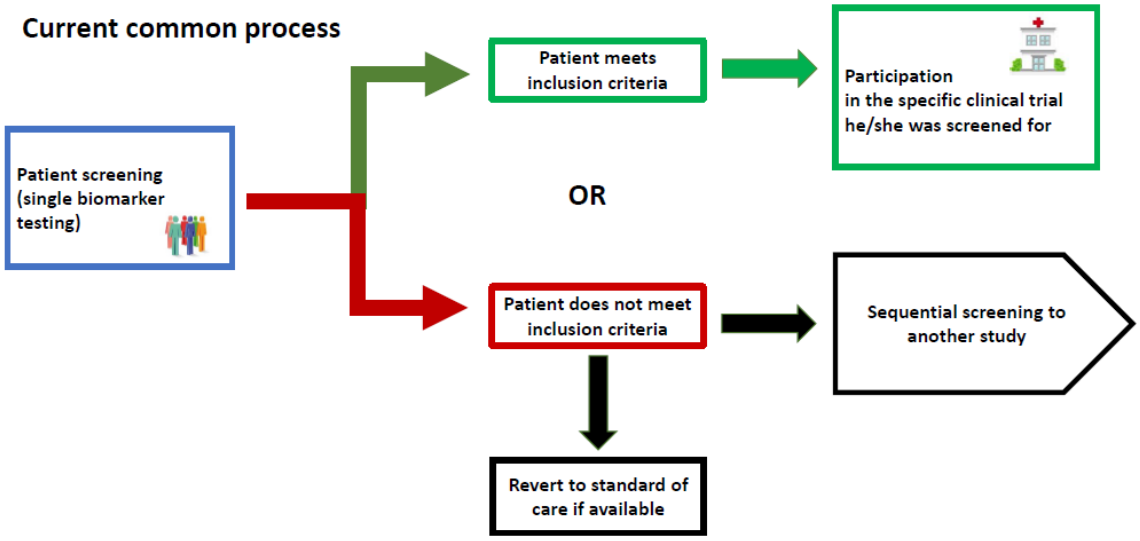
The scientific rationale for this study is three-fold:

- To collect several biological samples along with imaging, at current disease status, for correlative and diagnostic analyses; as an example, determining how closely circulating tumor cells (CTCs) mimic disease status, with the potential to move away from biopsy procedure.
- To collect data describing treatment patterns and corresponding treatment outcomes such as survival as documented by the treating physician; learning if medical history impacts molecular profile and mechanisms of resistance, and building algorithms to predict.

- To increase efficiency at GSK oncology trial sites, moving away from screening a patient for one single trial at a time; generating further evidence for use of broad molecular profiling.

Addressing Unmet Needs of Cancer Patients

Current common practice: patients undergo individual and sequential screening to be enrolled in a clinical trial. This can be very time-consuming, especially when the patient has to go through the screening process for multiple clinical trials with a low chance of being finally included in a precision medicine clinical trial (see schema below):



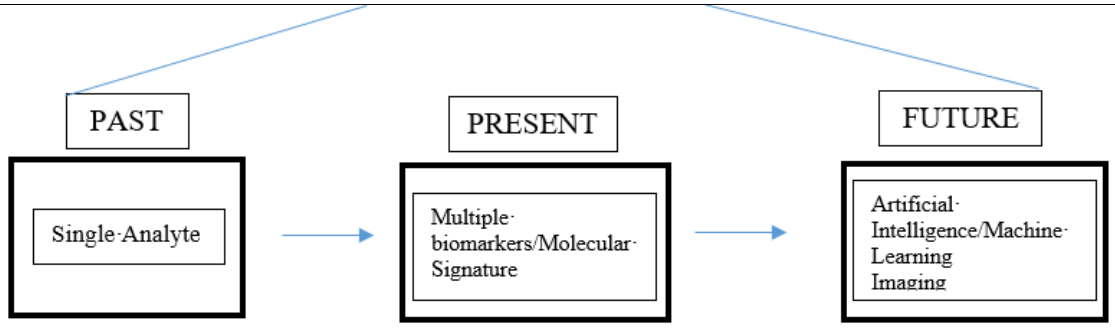
MDCI's envisaged solution is an operational model that would allow a secure and compliant sharing of patient data for those patients who have failed screening for a clinical trial, to be considered for an alternative clinical trial without having to undergo sequential rounds of biomarker characterization or requiring additional biopsy sampling.

It is expected that over 600,000 people will die from cancer in 2020; with lung & bronchus cancer accounting for most fatalities [American Cancer Society (ACS), 2020]. Through compiling a comprehensive dataset (clinical history, imaging, biomarker) for each of our patients, we hope to learn of correlative factors that may lend to novel therapies, combination strategies, and/or detection methods to address this unmet need for patients. Through a simple design, this molecular analysis protocol is expected to support participant enrollment into a range of oncology clinical trials within GSK, while advancing our understanding of this disease. This study will involve many sites, located over a wide geographic footprint, with the intent of significantly expanding the opportunities for participant identification and easing the current screening process.

2.2. Background

GSK oncology is focussed on developing cancer therapies within 4 scientific platforms: **immuno-oncology, cell and gene therapy, epigenetics, and synthetic lethality.** Each of these platforms provides the opportunity for a precision medicine approach through agents (e.g. small molecules, antibodies, engineered immune cells) targeting tumor expressed biomarkers, as well as potential for combination therapy. As we shift towards needing to know multiple biomarkers, molecular signatures and pathways to determine potential personalized treatments for our patients, comprehensive screening has become critical.

Immuno-oncology	Cell & Gene Therapy	Epigenetics	Synthetic Lethality
Stimulating anti-tumor immunity Checkpoint Blockade	Cells as medicines Target tumor-specific antigens	Molecular targeted therapies	Molecular targeted therapies
Combination Therapy			



2.2.1. Cancer immunotherapies

Cancer immunity is described as a cyclic multistep process that functions to elicit an effective antitumor response [Chen, 2013]. Each of the steps can be negatively regulated, thus providing the tumor with redundant mechanisms by which to block an antitumor immune response. In some cases, tumors will be highly dependent on a single mechanism, and in these cases, there is the potential to achieve significant clinical activity with single agent immunomodulatory therapy. However, it is expected that as tumors often utilize redundant mechanisms to block an antitumor immune response, combination therapy will likely be required.

Robust antitumor responses including complete cures in some cancers have been achieved by modulating patients' immune system. Antibodies targeting the checkpoint receptors and their cognate ligands engaged in negative regulation of T cell responses, such as cytotoxic t-lymphocyte-associated protein 4 (CTLA-4) and programmed death protein 1 (PD-1/PD) Ligand-1 (PD-L1), have demonstrated clinical efficacy and are proven effective as anticancer immunotherapies in a broad range of tumors including some solid tumors otherwise considered poorly immunogenic.

Dostarlimab (TSR-042) is a humanized mAb of the IgG4-κ isotype that binds with high affinity to PD-1, resulting in inhibition of binding to PD-L1 and programmed cell death-ligand 2 (PD-L2). This antibody was generated based on a proprietary platform that utilizes affinity maturation to select highly specific antibodies with desired functional characteristics. The functional antagonist activity of dostarlimab (TSR-042) was confirmed in a mixed lymphocyte reaction assay, demonstrating enhanced interleukin-2 (IL-2) production upon addition of dostarlimab (TSR-042).30 Furthermore, dostarlimab (TSR-042) has an acceptable safety profile based on toxicology studies in cynomolgus monkeys. The nonclinical development with dostarlimab (TSR-042) is discussed in the dostarlimab (TSR-042) Investigator's Brochure on file. Dostarlimab (TSR-042) has shown an acceptable clinical and nonclinical safety profile. No signals have been identified in clinical studies in patients with advanced solid tumors.

Dostarlimab (TSR-042) binds with high affinity to human and monkey PD-1. Dostarlimab (TSR-042) blocks the binding of soluble ligands to human PD-1 that is artificially expressed with a half-maximal inhibitory concentration of approximately 1 nM. Dostarlimab (TSR-042) enhances T cell activation as measured by the production of IL-2 from activated human cluster of differentiation 4+ T cells, with a half-maximal effective concentration of approximately 1 nM. Full PD-1 receptor occupancy by dostarlimab (TSR-042) in vitro is achieved at concentrations of approximately 1 μg/mL. Linear pharmacokinetics (PK) was observed for dostarlimab (TSR-042) over the range of 10 to 100 mg/kg in 18 cynomolgus monkeys. Sex had no effect on exposure. The volume of distribution at steady state was low and suggested minimal tissue penetration, which is consistent with other therapeutic monoclonal antibodies. Weekly administration resulted in approximately a 2- to 3-fold increase in dostarlimab (TSR-042) exposure.

Although antibodies directed against immune checkpoints such as PD-1 and its ligand, PD-L1, have proven effective across multiple indications, there is still a large unmet medical need for patients who do not respond or who develop resistance during

the course of treatment. There are several emerging hypotheses to explain the lack of response, including the overall presence and localization of immune cells in the tumor, the activity of immunosuppressive cells like regulatory T cells and myeloid-derived suppressor cells, as well as the up-regulation of additional T cell checkpoints on the tumor-infiltrating lymphocytes. TIM-3 is a novel immune checkpoint initially identified on IFN-γ-producing CD4+ T-helper 1 and CD8 T cells and has been implicated in the exhaustion of T cells. Up-regulation of TIM-3 expression on PD-1-positive tumor-infiltrating T cells in several cancers, such as NSCLC, is associated with reduced proliferation and secretion of cytokines important for T cell-mediated antitumor activity. Blocking TIM-3 therefore has the potential to restore tumor recognition by T cells and increase tumor killing. Studies have demonstrated that blockade of TIM-3 enhances T cell function, as evidenced by increased T cell proliferation and release of IFN-γ and IL-2, and this evidence supports targeting TIM-3 for tumor immunotherapy. Additionally, research has shown that TIM-3 blockade combined with paclitaxel promotes activation of dendritic cells, leading to increased CD8 T cell activation and antitumor activity [de Mingo Pulido, 2018].

Cobolimab is a novel, first-in-class anti-TIM-3 mAb that is in clinical development to treat solid tumors in combination with an anti-PD-1 antibody, dostarlimab. Although the mechanism of action of TIM-3 is not clearly understood, the current hypothesis is that cobolimab will work most effectively in conjunction with anti-PD-1 in tumors that either are refractory to anti-PD-(L)1 or have developed resistance after an initial response to anti-PD-(L)1.

The lack of benefit of current treatment options to patients with NSCLC may be due to additional immunosuppressive mechanisms, such as those mediated by TIM-3. Early combination treatment enables the assessment of TIM-3 and PD-1 blockade to address de novo resistance to anti-PD-1 blockade while preventing one of the mechanisms that may result in resistance to anti-PD-1 monotherapy.

Multiple immune checkpoints in addition to PD-(L)1 may regulate T cell anergy and modulate antitumor immunity [Topalian, 2011; Mellman, 2011]. Proteins of the nectin and nectin-like (Necl1) family, including TIGIT and CD96, have emerged as immune suppressing candidates that may prevent immune reactivation after PD (L)1 blockade. These co-regulatory receptors modulate the CD226 immune checkpoint, which is one of the major activating receptors for NK cells.

TIGIT is a T-cell immunoglobulin and immunoreceptor tyrosine-based inhibition motif domain. TIGIT's interaction with the ligand CD155 downregulates cytotoxic T and NK cells and is a critical regulator of antitumor T cell immunity [Harjunpää, 2020]. TIGIT may regulate antitumor immunity through a variety of mechanisms: by inhibiting NK cells from releasing tumor antigens, impairing T cell priming by dendritic cells, or inhibiting CD8+ effector tumor cell killing [Harjunpää, 2020; Johnston, 2014; Joller, 2014]. The interaction of TIGIT with its complementary costimulatory receptor, CD226, is analogous to the interaction of CTLA-4 and CD28. TIGIT competes with CD226 for its main ligand, CD155 [Stengel, 2012; Johnston, 2014], modulating antitumor immunity through multiple mechanisms. Binding of TIGIT on T cells with CD155 ligand on dendritic cells impairs CD4+ T cell function [Chauvin, 2020]. In addition, binding of TIGIT prevents homodimerization and activation of CD226 on CD8+ T cells [Johnston, 2014]. TIGIT also

interacts weakly with other co-regulatory inhibitors of the CD226 pathway including CD112, CD113, and CD114. TIGIT is upregulated on tumor infiltrating CD8+ T cells and a population of infiltrating CD4+ T cells in solid tumors in comparison to peripheral T cells from patients and normal donors. CD8+ and CD4+ TIGIT-expressing T cells also co-express PD-1.

CD96 represents a novel immune-checkpoint receptor target. Engagement of CD96 by a related ligand on antigen-presenting cells and cancer cells, CD155, functions as an 'off switch,' or immune checkpoint, to downregulate immune responses. GSK6097608 is a mAb checkpoint inhibitor designed to modulate this axis by forming a high-affinity complex with CD96, disrupting CD96:CD155 binding and redirecting CD155-mediated costimulatory signaling through the activating receptor CD226 to increase T-cell and NK-cell antitumor activity. Modulation of this axis via inhibition or deletion of CD96 has resulted in antitumor activity in mouse tumor models alone and in combination with PD-1 inhibition [Blake, 2016; Harjunpää, 2018].

An antibody currently in development by GSK, GSK4381562, is fully-human IgG1 antagonist antibody that binds to Poliovirus Receptor-related Immunoglobulin Domain Containing (**PVRIG**), preventing inhibitory CD112 (ligand) interactions, thereby promoting improved T and NK cell function. Blockade of PVRIG/CD112 interactions can also redirect CD112 to the co-stimulatory receptor CD226/DNAM-1, further promoting enhanced T/NK cell function. PVRIG binds to a distinct epitope on PVRIG and is also a fully Fc-competent backbone (IgG1), providing a potential functional advantage relative to the human IgG4 PVRIG antagonist COM701. Based on evidence supporting the molecular interplay between pathways and the utility of addressing diverse immune populations, GSK4381562 may not only work in concert with PD-(L)1 (programmed cell death protein 1 and/or programmed death ligand 1) inhibition, but also benefit patients who are refractory to, or have developed resistance to, current T cell-based therapeutics.

2.2.2. Cell and Gene Therapy (TCR engineered adoptive T-cell therapy targeting NY-ESO-1/LAGE-1a)

In contrast to indirect activation of host immune cells within the tumor microenvironment using checkpoint inhibitors, adoptive T‑cell therapy (ACT) is a personalized therapeutic approach involving direct infusion of cytotoxic T cells derived from the cancer patient (autologous) or another donor (allogeneic) that target a protein expressed on their cancer cells and can infiltrate the tumor, target and destroying tumor cells. T cells for ACT have been used in various forms: native unmodified (tumor infiltrating cells) or engineered T-cells targeting tumor antigens. Engineered T cells currently under evaluation either express a chimeric antigen receptors (CARs) or affinity-enhanced T cell receptors (TCRs). T cells are obtained from the participant by leukapheresis and can then be engineered to express CARs or affinity enhanced TCRs, that can target respectively, cancer cell surface expressed proteins, or epitopes of internal tumor-associated antigens (TAAs) presented in complex with HLA molecules to the cancer cell surface.

CAR engineered T-cell therapy directed at CD19 is approved for use in paediatric Acute Lymphoblastic Leukemia (ALL) and Diffuse Large B-cell Lymphoma (DLBCL).

For TCRs, the patient's T cells are engineered with a human lentivirus that expresses a tumor-specific TCR. These TCR-Ts are expanded in vitro and then re-infused into the participant. TCRs provide the opportunity to target intracellular antigens that are processed and presented by the major histocompatibility complex (MHC) known as Human Leukocyte Antigen (HLA) protein in humans [Schmitt, 2015]. Screening for both HLA and antigen is needed for TCR therapy. The TCR-modified T cell approach is also particularly suited for solid tumors due to their ability to recognize low concentrations of these intracellular cognate antigens. In addition, the TCR approach mimics the natural function of the T cell by recruiting the endogenous signalling molecules and adhering to correct spatial orientation between the T cell and its target. These aspects may contribute to a manageable safety profile, high anti-tumor activity and enhanced persistence of the infused TCR engineered T cells, providing ongoing anti-cancer protection.

2.2.2.1. Background for Current GSK TCR-T cells

GSK is developing a number of different TCR‑T cells, including GSK3377794 (NY-ESO-1 TCR engineered T-cells), GSK3901961 (NY-ESO-1 TCR engineered T-cells co-expressing the α-chain of the CD8 co-receptor) & GSK3845097 (NY-ESO-1 TCR engineered T-cells coexpressing the dnTGF-βRII receptor). These TCR‑T cells target the cancer testis antigens (CTAs) NY-ESO-1 and LAGE-1a, tumor-associated proteins found in several tumor types including synovial sarcoma and non-small cell lung cancer (NSCLC).

Treatment with GSK3377794 has demonstrated encouraging clinical responses in patients with SS, inducing a clinical response in 50% of treated SS patients with a manageable safety profile. This therapy is currently being explored in other tumors including NSCLC, Myxoid round cell liposarcoma (MRCLS), and multiple myeloma.

One requirement of all TCR-directed therapies is that the engineered TCR must recognize a peptide epitope of the TAA that is processed and presented on the tumor cell surface, in complex with the participant's own HLA protein. GSK TCR‑T GSK3377794 is engineered to recognize antigens complexed with HLA-A*02:01, HLA-A*02:05, and HLA-A*02:06, which means that only those participants with at least one of these HLA alleles potentially may respond to this TCR‑T.

The lentiviral vectors used for manufacturing of GSK3377794 trigger expression of the same affinity-enhanced TCR designated as clone NY-ESO-1^{c259} that is optimized to recognize the SLLMWITQC peptide, which is derived from the cancer testis antigens (CTAs) family members NYESO-1 and LAGE-1A. The final T‑cell product is comprised of autologous cluster of differentiation 4 (CD4) and cluster of differentiation 8 (CD8) T cells that have been transduced with this lentiviral vector. The product of this transduction is polyclonal T cells which are designed to target NY-ESO-1 and/or LAGE-la positive cells; consequently, only those participants with tumors positive for NY-ESO‑1 and/or LAGE-1a and the right HLA-A*02 allelic variant will potentially respond to

current GSK TCR‑T cells. Future versions of the GSK TCR‑T cells may target additional tumor antigens.

2.2.2.2. Background for HLA & Screening

Specific peptide epitopes of the NY-ESO-1 or LAGE-1a protein are processed and presented on the surface of the tumor cell in complex with an HLA molecule, which can be recognized by T cells. The enhanced affinity TCR-T cells recognize the target antigen peptide fragment when it is bound to any HLA-A*02 allelic variants HLA-A*02:01, HLA-A*02:05, and HLA-A*02:06. These variants are three of the most common subtypes and are carried by roughly 45% [Gonzalez-Galarza, 2015] of the world's population overall. Background for NY-ESO-1 TCR Target Antigens & Screening

NY-ESO-1 and LAGE-1a are members of the cancer-testis antigen (CTA) family of tumor-associated antigens and are expressed at different frequencies in different tumor types. These are cytoplasmic proteins detectable in multiple cancer types including non-small cell lung cancer (NSCLC), bladder cancer, melanoma, liver cancer, synovial sarcoma (SS), myxoid/round cell liposarcoma (MRCLS), multiple myeloma and many others. For example, about 76% of the patients with synovial sarcoma test positive for NY ESO 1 antigen [Lai, 2012; Endo, 2015]. In contrast, only roughly 10% of patients with NSCLC test positive for the NY ESO 1 and/or LAGE 1a antigens. NY-ESO-1 and LAGE-1a are expressed in tumor types other than those in current clinical trials. By analyzing all tumor types for these markers, we have the capability to better design our trials and have insight into potential combination therapies.

2.2.3. Synthetic Lethality Therapy

Niraparib is an orally available, potent, and highly selective poly (adenosine diphosphate-ribose) polymerase (PARP)-1 and PARP-2 inhibitor. Zejula™ (niraparib) was approved for the maintenance treatment of women with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete response (CR) or partial response (PR) to platinum-based combination chemotherapy by the United States (US) Food and Drug Administration (FDA) on 27 March 2017 and received a Marketing Authorization in the European Union (EU) on 16 November 2017. In an analysis of approximately 500 high-grade serous ovarian cancer tumors, approximately 50% contained homologous recombination defects, which could sensitize tumors to poly (adenosine diphosphate-ribose) polymerase inhibitors (PARPi) [TCGA, 2011].

Development of more efficacious treatment options for patients with NSCLC remains a high unmet need. Novel combination therapy regimens are needed with acceptable safety profile that deliver clinically meaning improvement in progression-free and overall survival when administered in the maintenance setting for patients with advanced/metastatic NSCLC whose disease did not progress with frontline pembrolizumab/platinum-based therapy. In the Phase 2 JASPER study (Study 3000-02-001), data provided support of the safety of the combination of niraparib and pembrolizumab in NSCLC. The combination of niraparib with pembrolizumab in this first-line treatment setting showed antitumor activity, with the highest response rate observed in participants with high PD-L1 expression.

In the TOPACIO/KEYNOTE-162 study, the combination of niraparib plus pembrolizumab provided promising antitumor activity in both advanced or metastatic triple-negative breast cancer, with numerically higher response rates in those with tumor breast cancer susceptibility gene (BRCA) and recurrent ovarian cancer [Konstantinopoulos, 2019; Vinayak, 2019]. The combination therapy was safe with a tolerable safety profile.

Please refer to related IB for up-to-date information on GSK therapies.

2.3. Benefit/Risk Assessment

A key benefit of MDCI is the use of one sampling strategy to determine current disease characteristics, and to screen participants for multiple clinical trials based on the results, eliminating the time and limitations involved in sequential screening. The broader dataset generated through the CCI analyses within this study will further inform the mechanisms of resistance and response and may also inform more appropriate next therapies for the patient, and discovery of additional therapeutic, prognostic or diagnostic biomarkers.

The results of clinical and non-clinical studies of GSK therapeutics can be found in the related IB.

2.3.1. Risk Assessment

No investigational therapeutic product is used in this study; consequently, there are no risks due to exposure to study drug. MDCI is primarily an CCI study that may inform subsequent clinical trial eligibility. Risk resulting from use of the investigational device results vary for each respective subsequent therapeutic CCI primary risk to patients presented by this protocol is the risk associated with specimen acquisition.

Tumor biopsy is a common procedure in cancer therapy as it is the cornerstone of diagnostic and therapeutic decisions in oncology. The risks of the biopsy may include pain, blood loss, infection, and other adverse events associated with surgery in general and associated with surgery at the given anatomical location. The sites are directed to take all appropriate safety measures to protect the well-being of the participant and to follow-up on any adverse event (AE) that would be related to the study procedure. Recent data published from pan-tumor study NCI-MATCH related to AEs due to biopsy procedure determined 'of 4,627 patients with data, 26 (0.6%) and 7 (0.2%) experienced grade 3 and 4 events, respectively. No deaths were related to the biopsy procedure' [Flaherty, 2020].

If a patient has had a biopsy prior to MDCI Visit 2 as part of standard of care, that biopsy may be accepted as the MDCI tumor specimen (See Section 7.7.1). If an archival tumor specimen is not available for screening, surplus tissue from standard of care procedures are acceptable before fresh biopsy may be obtained. For those patients undergoing a new biopsy, the location of the biopsy may be from either the primary tumor location or any other metastatic tumor site. Thus, physicians may choose an anatomic site for the biopsy

that presents an acceptable risk to the patient based on the overall status of the patient as well as the accessibility of the tumor. Radiologic guidance will be used for biopsy collection whenever possible. Biopsies will be collected using low-risk procedures that have an anticipated serious complication rate <2%. The informed consent form will clearly indicate that a biopsy may be needed and that participation on the study is optional so the patient is well-informed and may choose not to participate if he/she does not consent

Each patient is asked to provide 4 samples of whole blood at the second visit. There is a risk that the patient could experience complications due to these blood draws (e.g., pain, bleeding and/or bruising and possibly infection), although serious complications are likely to be very rare.

All procedures of blood collection and tumor biopsy must follow institutional standards.

Radiographic imaging for this study will cause no additional risk compared to standard of care radiological procedures typically conducted for participants with tumors. Imaging with computed tomography (CT) requires exposure to radiation. The effective radiation dose of a CT scan required for this study is approximately 20 mSv, which corresponds to about 10 times the average natural radiation a person is exposed to annually. The use of IV iodinated contrast is preferred for CT procedures in this study. Participants may be at risk of contrast sensitivity or an allergic reaction to the CT contrast agent. Magnetic resonance imaging (MRI) does not involve exposure to radiation, however due to the magnetic field there are risks for participants who may have metal implants, pacemakers, or other permanent magnetic devices which may shift or become dislodged and cause damage to surrounding tissue. Gadolinium-based contrast agents used in MRI are associated with the risk of nephrogenic systemic fibrosis in some participants who have reduced renal function. Any participant who will undergo an MRI should be screened by the institution for metal and contrast administration safety prior to scanning. All imaging procedures must be conducted following institutional standards and safety precautions.

Risk Assessment

Risks of Clinical Significance (Potential)	Summary of Data/Rationale for Risk	Mitigation Strategy
Tumor biopsy/Blood Samples	Bleeding, pain, swelling, infection, associated with the procedure &/or site of biopsy	Blood samples collected & biopsies are performed by trained personnel. Image-guided when necessary and performed only if deemed safe. Sites will utilize standard pre-biopsy screening measures (such as blood tests for platelets, and coagulation). The informed consent will identify any potential risks based on the site of the biopsy.
CT and MRI risks	Risk of contrast sensitivity or allergic reaction to the CT contrast agent. MRI - risks for participants who may have metal implants pacemakers, or other permanent magnetic devices which may shift or dislodged and cause damage to surrounding tissue.	All imaging procedures will follow institutional standards and safety precautions.
Assay Results	Risk of false positives and/or false negatives from assays used.	All assays used to determine protocol trial eligibility have demonstrated acceptable Negative Predictive Value (NPV) and Positive Predictive Value (PPV).

2.3.2. Benefit Assessment

The most direct potential benefit to participants in this study is to determine if they may be eligible to enter an intended treatment protocol based on clinical history and biomarker testing and analysis of their disease. Other benefits may include but not be limited to contributing to the understanding of disease, and having the opportunity to contribute to scientific knowledge overall via: providing data to support understanding of disease outcomes, the blood sample designated for genetics research, to the development of a liquid rather than solid tumor-based companion diagnostic via the liquid biopsy sample.

2.3.3. Overall Benefit: Risk Conclusion

The primary benefit to patients is providing the opportunity to be assessed for multiple treatment options (as opposed to one); potentially decreasing time-to-treatment, & multiple procedures. The MDCI protocol also gives patients access to trials for which they may otherwise not have been screened. Key risk in this pre-screening protocol are those associated with tumor biopsies. After balancing the risks associated with collection of a tumor biopsy (a standard procedure in the treatment of a cancer patient) with the benefits, it would appear the benefits outweigh the risks.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	Primary
• To evaluate molecular and immunological profile of tumor and peripheral blood of all enrolled participants, across indications and within tumor subsets (Building a GSK Clinical Science Database for tumor profiling and correlative studies)	• Profile of patient specific selection biomarkers targeted by therapeutics with the GSK oncology pipeline, as well as other CCI as detailed in the study reference manual (SRM).
CCI [redacted]	

CCI

[redacted]

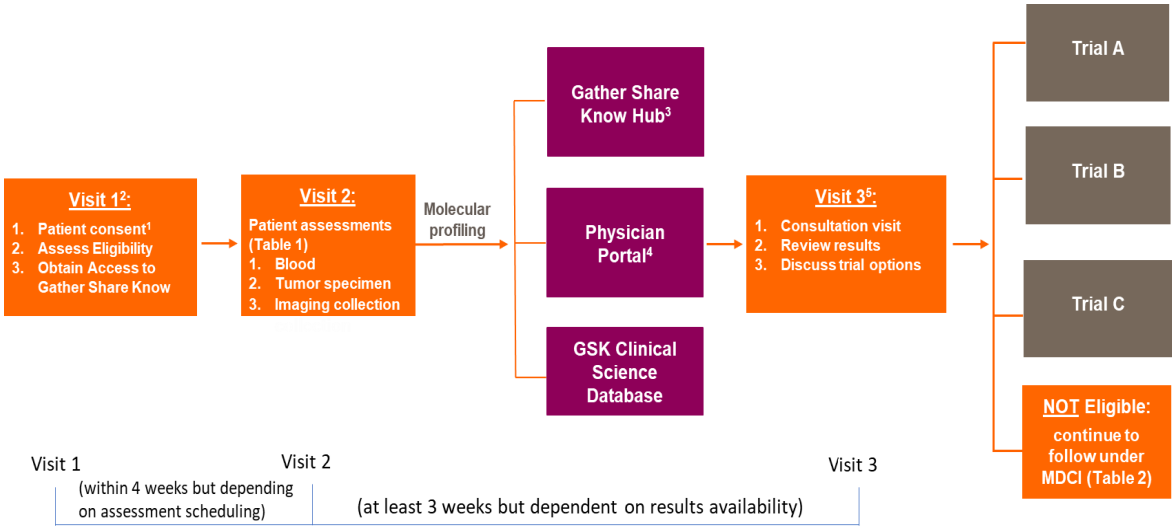
Taking into account the measures taken to minimize risk to participants participating in this study, the potential risks identified in association with this study are justified by the anticipated benefits that may be afforded to participants.

4. STUDY DESIGN

4.1. Overall Design

This is a multicenter study, enrolling patients with advanced/metastatic disease for the purpose of collecting tumor tissue and blood samples for broad molecular analysis and examining the expression of specific biomarkers using validated clinical assays. The study involves three primary visits (Figure 1).

Figure 1 Study Schema



Footnotes: [1]MDCI will be an optional protocol under select GSK oncology protocols; [2]In the case that Visit 1 and 2 are combined, all corresponding samples must be collected per the SoA (Section 1.3 Table 1) at this visit and after eligibility is confirmed; [3]Subset of data to be shared on Gather Share Know; [4]Patient's molecular profile and medical history will be compared against the eligibility criteria of select GSK oncology protocols to identify potential trial options; [5]Visit 3 may occur remotely via telehealth/phone visit (optional).

At **Visit 1**, informed consent will be obtained from participants to enroll in the study, specifically to undergo a multiplex biomarker characterization, and to store and share a subset of their data through a Participant Hub (Gather Share Know). Registering for Gather Share Know is optional; a standardized template will be created and included as an annexure to the regular ICF.

Upon consenting to participate in the MDCI screening process, the participant will continue with assessments per schedule of activities (SoA Table 1). For most participants, the expected duration between V1 and V3 is ≤8 weeks; which is dependent on the receipt and the type of tumor biopsy sample submitted.

During **Visit 2**, a tumor specimen will be collected or submitted, as per tumor specimen collection requirements (refer to SRM and Study Laboratory Manual). The specimen will be evaluated by IHC to determine the expression of tumor specific antigens and immune markers such as, but not limited to, NY-ESO-1 and PD-L1. A portion of the tumor specimen will also be analysed by whole exome sequencing (WES), as well as whole transcriptome sequencing (WTS) to determine patients' molecular profile; these sequencing data will not be used for trial referral.

A liquid biopsy (blood) will also be taken at Visit 2 to analyse CCI [redacted] circulating tumor DNA (ctDNA), CCI [redacted] and/or exosomes. In addition, participants will also provide mandatory blood samples for biomarker, validated clinical biomarker testing, and genetic research, as well as tumor imaging with CT/MRI. *HLA* genotype will be determined from whole blood DNA tested at a central laboratory.

CCI [redacted]

CCI [redacted] WES data from the blood will also be used in conjunction with the SNP genotyping data to assess the effect of host genetic variation in one or more candidate genes or across the genome on cancer risk, progression, and response to cancer treatments. Details of testing and management of all samples can be found in the respective sections of the SRM and Study Laboratory Manual.

A subset of the generated results will be uploaded to the Physician Portal for review, followed by the Gather Share Know Participant Hub. Physicians will review the results with participants at **Visit 3**. If the results indicate eligibility for a specific clinical trial, appropriate referrals to those trials will be made by physician for further screening. Participants will only be provided access to their selected results through the Gather Share Know Participant Hub after they have received information on the significance/benefits of the testing. Training will be provided to all participants who consent on how to access and navigate the hub.

All participants will undergo a follow-up safety assessment for any serious adverse events (SAEs) assessed as related to protocol-mandated study procedures or leading to study withdrawal.

The study protocol will remain open until all designated GSK-sponsored impacted clinical trials (outlined in SRM) are closed to enrolment & all participants have completed this study or at the discretion of GSK.

Participants ineligible for Clinical trials

If a patient does not enroll onto a GSK study, or any other investigational study, , and who procced to receive Standard of Care (SoC) therapy, disease will continue to be monitored under MDCI following a separate Schedule of Activities (SoA) for longitudinal follow-up (Table 2). Accordingly, physicians will be asked to enter/ report all anticancer therapies received and the participant's survival status during follow-up, in order to characterize treatment patterns and survival outcomes respectively.

The following portals will be used for this study:

1. ***Gather Share Know Participant Hub***
   The 'Gather Share Know' Participant Hub was designed and developed by the MDCI team in collaboration with an external partner. **This powerful tool has several objectives which include: connecting with our patients, directing our patients to credible sources, making our patients aware of 'what to expect' at study visits, returning invaluable validated clinical biomarker data (will not include germline sequencing data), providing them clinical trial options, and offering continued follow-up.** This tool also can also provide capability to allow participants to take part in surveys. Patients will be provided with training on the Gather Share Know Participant Hub prior to being given access. This training will

include an overview of the type of information that will be provided, how to use the portal and potential benefits.

2. ***Physician Portal***
   The 'Physician Portal' is a web-based compilation of a patient's clinical history and molecular data collected in this study, as well as a list of applicable clinical trials based on validated clinical assays that has been established by the sequencing vendor. A major benefit of this portal is the ability for physicians to compare the molecular profiles of all their patients that have enrolled into the MDCI study side-by-side.

GSK Clinical Science Database

To better understand our patients' disease, novel pathways/targets, mechanisms of action or resistance, disease progression and molecular change, clinical trial design, and potential combination strategies, all data collected (examples below) will be compiled into a GSK Clinical Science Database:

- Demographics
- Clinical disease & treatment history
- Tumor molecular profiling (IHC & sequencing)
- Liquid biopsy profiling
- Patient questionnaires

4.2. End of Study Definition

A participant will be determined to have completed the study for the primary objectives if:

- The participant signed consent to participate on one of the GSK treatment protocols
- After two years of longitudinal follow-up (Table 2)

The protocol will remain open until all designated GSK-sponsored clinical trials are closed to enrolment and the last participant in this study has completed their last visit or until a date otherwise determined at the discretion of GSK.

5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Intended and Alternative Treatment Protocols

1. Participant is a candidate for molecular screening for a GSK precision therapeutic clinical study (the Intended Treatment Protocol) that is being conducted in parallel at or nearby the MDCI recruitment site.

2. Participant is willing to travel to a site recruiting for the intended GSK treatment protocol (or alternative treatment protocol), if feasible, and if, in the investigator's opinion, the patient would benefit from enrolment into the intended GSK treatment protocol at an alternative clinical site. See 213299 Study Reference Manual (SRM) for the most recently updated lists of recruiting treatment trials.

Type of Participant and Disease Characteristics

3. Confirmed advanced/metastatic diagnosis of solid malignancy, as described in the Intended Treatment Protocol, including but not limited to the following disease-areas: NSCLC, HNSCC, Breast, Ovarian, CRC

4. Life expectancy of >6 months.

5. Able to provide blood samples (see Section 7.7 for blood volume requirements).

6. Able to provide an archival formalin-fixed paraffin-embedded (FFPE) tumor specimen from a current lesion/most current setting . If an archival tumor specimen is not available, surplus tissue from standard of care procedures is acceptable before fresh biopsy may be obtained. If an archival block cannot be sent as per institutional guidance/policy, slides can be sent instead, refer to the respective sections of the SRM and Study Laboratory Manual for further details.

Sex

Female

Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. Contraceptive use is a requirement for females as pregnancy is an exclusion for this study.

7. Female Participants:

- A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:
    - Is not a woman of childbearing potential (WOCBP)

      OR

    - Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), preferably with low user dependency, as described in Appendix 4.
    - A WOCBP must have a negative highly sensitive pregnancy test (urine or serum) as required by local regulations) within 24 hours before tumor biopsy.

- If a urine test cannot be confirmed as negative (e.g., an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.

- Additional requirements for pregnancy testing during and after study are located in Appendix 2.
- The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy

Informed Consent

8. Capable of giving signed informed consent as described in Appendix 1 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

9. Male or female, age ≥18 years; at the time consent is obtained (minimum age requirement per local regulatory requirements).

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1. ECOG Performance Status >2

2. History of myocardial infarction, acute inflammatory heart disease, unstable angina, or uncontrolled arrhythmia within the past 6 months.

3. For female participants, pregnancy

4. Any serious and/or unstable pre-existing medical, psychiatric disorder or other conditions that could interfere with the subject's safety, obtaining informed consent or compliance to the screening study procedures.

5.3. Screen Failures

Screen failures are defined as participants who consent to participate in Study 213299 but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, any protocol deviations and any serious adverse events (SAEs).

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened.

All samples (tumor and blood) and radiographic imaging collected from screen failure participants may be used for further biomarker, companion diagnostic, disease characterization, and/or genetic research.

Consent to another intended treatment protocol and tumor reanalysis are allowed after discussion with Sponsor.

6. STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

No investigational therapeutic product will be used in Study 213299. MDCI is primarily an CCI [redacted] study that may inform subsequent clinical trial eligibility. Therapeutic interventions resulting from use of the investigational device results vary for each respective subsequent therapeutic clinical study protocol and will therefore be described under those specific protocols. Consequently, the following sections are not applicable to this protocol:

Study Intervention(s) Administered
Preparation/Handling/Storage/Accountability
Measures to Minimize Bias: Randomization and Blinding
Study Intervention Compliance
Concomitant Therapy
Dose Modification
Intervention after the End of the Study

6.1. Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioural, compliance or administrative reasons. This is expected to be uncommon.
- At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA. See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- If the participant withdraws consent for disclosure of future information the sponsor may retain and continue to use any data and images collected before withdrawal of consent.
- If a participant withdraws from the study, they may request destruction of any samples taken and not tested, and the investigator must document this in the site study records and inform the sponsor.

6.2. Lost to Follow Up

A participant will be considered lost to follow-up if they repeatedly fail to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1.

7. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.
- Protocol waivers or exemptions are not allowed.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All Visit 1 evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (e.g., tumor imaging studies, blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time frame defined in the SoA.
    - The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 200 mL.
    - Repeat or unscheduled samples may be taken for safety reasons or for sampling issues.

7.1. Gather Share Know Participant Hub

The 'Gather Share Know' Participant Hub is an optional, web-based application with a patient facing solution will provide the following capability:

- A guide/overview of Gather Share Know platform: information provided, how to use and potential benefits.

- Patient Credentials: Following completion of informed consent, patients will be provided credentials to log into the Gather Share Know Participant Hub.
- Information about the Study: Study Site and PI information and study progress (e.g. enrolled, assessments, available results, study complete, etc.).
- Study Visits: List of visits and what to expect for each visit.
- Embedded and / or linked educational materials from credible sources (e.g. National Cancer Institute) with information specific to patient's diagnosis: This will be provided by GSK to participant hub vendor to populate based on diagnosis.
- Laboratory results (e.g. validated clinical biomarker data) in simple, easily understood, language: Results will come from the lab vendor conducting the analysis. Following agreed physician review period, this data will be published to participant hub.
- Trial Matching: The participant hub can recommend GSK Oncology trials that patients might be eligible for based on the MDCI lab and biomarker results and a subset of inclusion / exclusion criteria. Information about these trials and study PI or staff contacts will be provided to allow patients to follow up to express interest. These patients can also be notified as new GSK Oncology trials become available where they may be eligible.

  List of GSK trials to use for matching and associated enrolment timings will be provided by GSK and updated accordingly over time. Rules for trial matching based on biomarker results and a subset of inclusion / exclusion criteria will be provided. Biomarker results will come from lab vendor. Data to assess against subset of inclusion / exclusion criteria will come from InForm eCRF and where applicable, further information from the study site personnel. An outline of what data will be returned to patients, as well as directives & resources for counselling, can be found in the SRM.

7.2. Tumor Imaging

Imaging will be obtained by the site and transmitted to a central imaging vendor for CCI analyses. Instructions for tumor imaging and transmission to the central imaging vendor are detailed in the Imaging Manual provided to investigative sites.

7.2.1. Imaging Related to Archived Tumor Sample

For participants who provide archived tissue samples, associated imaging by CT/MRI that was acquired for standard of care tumor assessment within ±4 weeks of biopsy will be collected, to pair with the tissue sample. Images that capture the biopsied lesion and any other areas of disease will be used for CCI research. Refer to Section 7.2.2 for the types of imaging expected for this purpose.

7.2.2. Visit 2 Imaging

Tumor imaging must be completed at Visit 2 ± 4 weeks (28 days). If fresh biopsy is performed at Visit 2, imaging should be completed prior to the biopsy procedure, preferably on the same day, to avoid possible radiographic alterations due to tissue

sampling. Imaging conducted prior to enrollment may be used if acquired within 4 weeks of the visit and the requirements for tumor imaging are met.

The below imaging requirements are designed to best align with possible GSK Intended Treatment Protocols in order to reduce the potential need for re-scanning within the subsequently enrolled treatment study.

- Computed tomography (CT) scan with oral and/or IV contrast.

Indication	**CT[1,2] Anatomical Coverage Required**
NSCLC, CRC or breast	chest, abdomen, and pelvis
HNSCC	chest and abdomen, including liver head and neck region[3]
Ovarian	abdomen and pelvis

(1) In cases where contrast-enhanced CT is contraindicated, magnetic resonance imaging (MRI) with IV gadolinium is acceptable. When a chest scan is required, a non-contrast CT of the chest is preferred over non-contrast MRI.
(2) CT from a positron emission tomography (PET)-CT is permitted provided it is with CT contrast and is of diagnostic quality.
(3) CT or MRI accepted per site standard procedure.

- Contrast-enhanced CT or MRI of other sites of disease as indicated by the participant's underlying disease, following site standard procedures.
- Photography of any superficial skin lesions including a visible ruler.
- If completed at the site for SOC, positron emission tomography (PET) imaging, including FDG or other radiotracers, should also be collected. PET is not required for this protocol.

7.2.3. Imaging from Image-Guided Biopsy

Participants who provide archived tissue samples:

If the biopsy was performed under image guidance, images from the procedure will be collected, if available. Relevant modalities include CT, MRI, ultrasound, or medical photography. If images from the procedure are not available or if biopsy was not conducted under image guidance, an annotated image from a diagnostic CT/MRI may be requested, to identify the specific site of the biopsy. Additional detail is provided in the Imaging Manual.

Participants who provide fresh tissue samples:

It is preferred that all fresh tissue collection (Section 7.7.1) is performed under image guidance when clinically relevant. CT is the preferred modality for non-visible or non-palpable lesions. MRI or ultrasound is also accepted as relevant per tumor type. When imaging is conducted for biopsy guidance, images will be collected. The biopsied lesion should be well identified either by a visible needle depicted on imaging or an annotation to denote the lesion with anatomical location clearly identified on the image. Further guidance is provided in the Imaging Manual.

7.2.4. Follow Up Imaging

For participants who continue on the MDCI protocol for follow-up (Table 2) any imaging conducted for standard of care tumor assessment within ±8 weeks of each study visit will be collected. Disease assessment modalities may include imaging by CT, MRI, PET (FDG or other radiotracer), nuclear medicine, or plain radiography (Xray) and photography.

Upon withdrawal/progression, imaging for tumor assessment conducted within 4 weeks prior to biopsy will be collected. Imaging conducted after biopsy will not be collected. If biopsy is conducted under image guidance, imaging from the biopsy procedure will be collected in accordance with Section 7.2.3.

It is preferred that on-study biopsy (Section 7.7.1) is performed under image guidance when clinically relevant. CT is the preferred modality for non-visible or non-palpable lesions. MRI or ultrasound is also accepted as relevant per tumor type. When imaging is conducted for biopsy guidance, images will be collected. The biopsied lesion should be well identified either by a visible needle depicted on imaging or an annotation to denote the lesion with anatomical location clearly identified on the image. Further guidance is provided in the Imaging Manual.

7.3. Efficacy Assessments

Not Applicable.

7.4. Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

7.4.1. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the Skin, Cardiovascular, Respiratory, Gastrointestinal and Neurological systems. Weight will also be measured and recorded in eDC.
- A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).
- Investigators should pay special attention to clinical signs related to previous serious illnesses.
- Any specific conditions should be recorded under Medical History.

7.4.2. Vital Signs

- Oral temperature, pulse rate, and blood pressure will be assessed.
- Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.

- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g., television, cell phones).
- Vital signs (to be taken before blood collection for laboratory tests) will consist of 1 pulse and 1 blood pressure measurement. The readings will be recorded on the CRF.

7.4.3. Electrocardiograms

All cardiac assessments will be performed locally.
The following assessments will be conducted in order to monitor participant safety:

Single 12-lead electrocardiogram (ECG) will be obtained as outlined in the SoA (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. ECG to be performed only at baseline and result to be entered into eCRF. An ECG done within 2 weeks of Visit 1 is acceptable, if the patient has not had any cardiac event.

7.4.4. Clinical Safety Laboratory Assessments

Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.

- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered significantly abnormal by the investigator or medical monitor.
- All protocol-required laboratory assessments, as defined in Appendix 2 must be conducted in accordance with the laboratory manual and the SoA.

7.5. Adverse Events and Serious Adverse Events

The definitions of an AE or SAE can be found in Appendix 3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study, or that caused the participant to discontinue the study (see Section 6.1).

7.5.1. Time Period and Frequency for Collecting AE and SAE Information

- All SAEs will be collected from at the time points specified in the SoA (Section 1.3). However, any SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a participant consents to participate in the study.
- All AEs will be collected at the time points specified in the SoA (Section 1.3).
- Medical occurrences that begin before the start of procedures but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the case report form (CRF) not the AE section.
- All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.
- Investigators are not obligated to actively seek AEs or SAEs after the conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study participation, the investigator must promptly notify the sponsor.

7.5.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

7.5.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 6.2). Further information on follow-up procedures is given in Appendix 3.

7.5.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.
- For all studies except those utilizing medical devices investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

7.5.5. Pregnancy

- If a pregnancy is reported, the investigator should inform GSK within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAE.

7.5.6. Death Events

For all deaths, whether or not they are considered SAEs, specific Death sections of the CRF will be required to be completed.

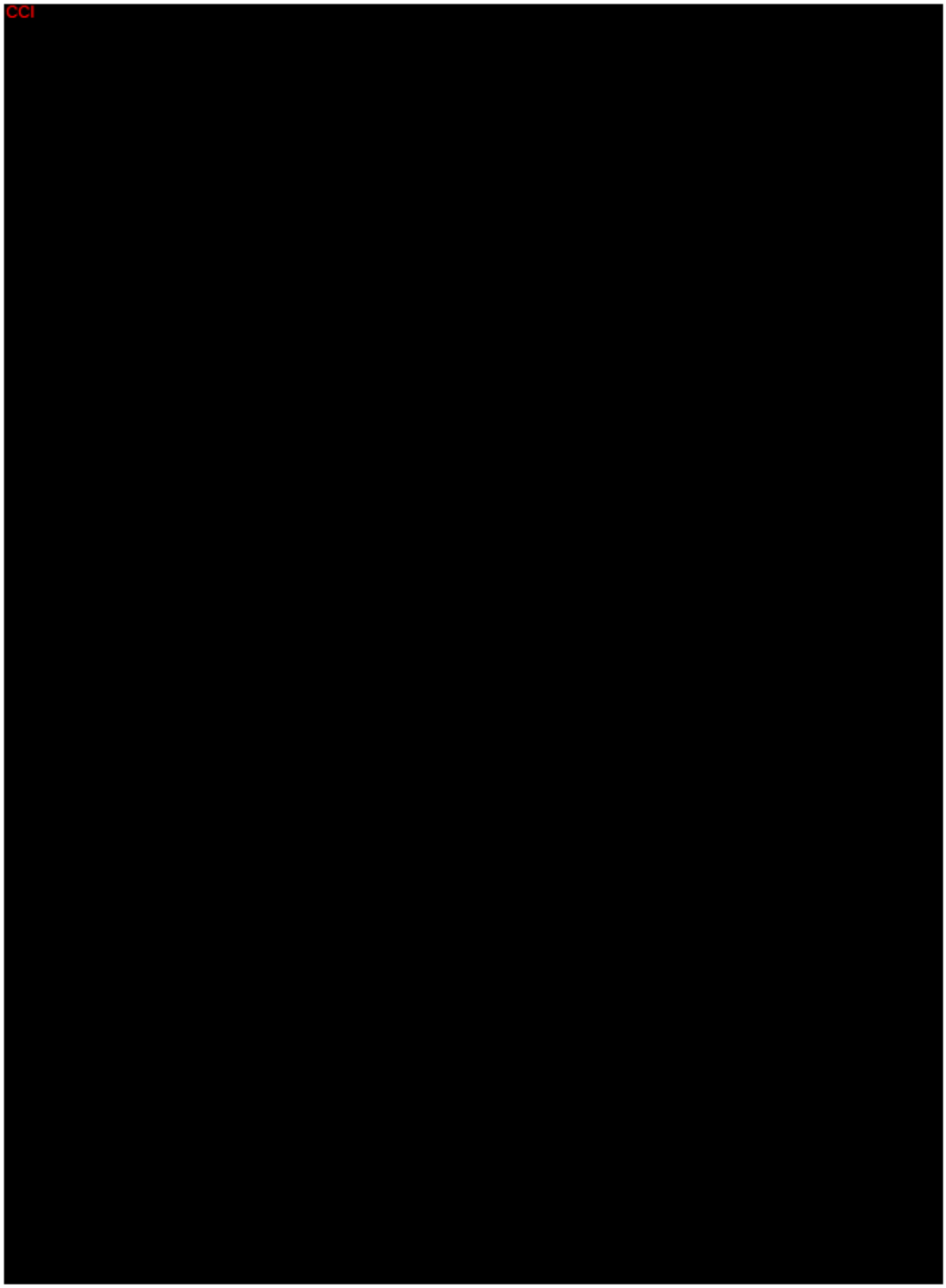
The Death CRF is provided immediately after the occurrence or outcome of death is reported. Initial and follow-up reports regarding death must be completed within one week of when the death is reported.

CCI

[redacted]

CCI

[redacted]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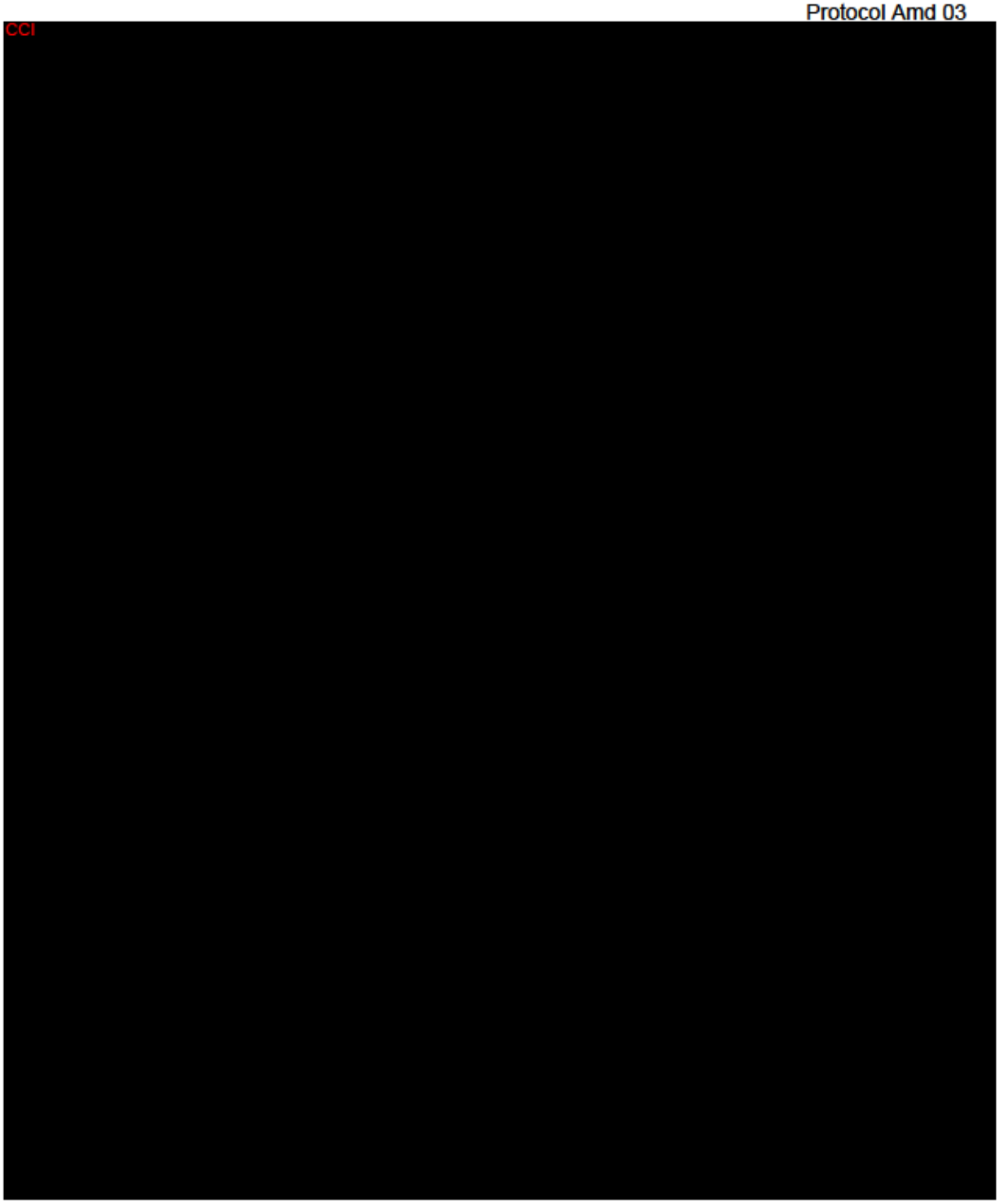

8. STATISTICAL CONSIDERATIONS

8.1. Statistical Hypotheses

MDCI is an CCI [redacted] study. No Hypothesis will be tested under this study.

8.2. Sample Size Determination

Since MDCI does not aim to test any specific hypothesis or answer any particular question, there is no statistical requirement to reach a specific number of samples and patients. It is expected to enroll 400 participants in this study.

8.3. Populations for Analyses

The following populations are defined:

Population	Description
Screened	All participants who sign the ICF
Enrolled	All participants who sign the ICF and meet inclusion/exclusion criteria
Ineligible for Treatment Trial	All participants who do not enrol onto a GSK treatment study
Randomized	NA
Safety	All participants who are enrolled and provided a tumor/blood sample

8.4. Statistical Analyses

Descriptive summary statistics of the key endpoints/markers (such as those considered for patient selection for various assets) will be tabulated and where relevant will be stratified by key baseline demographic and clinical characteristics.

Unsupervised clustering based on expression levels or mutation calls will be performed to identify cancer subtypes. The identified subtypes will be compared with subtypes found in previous research, such as TCGA (The Cancer Genome Atlas). For any phenotypic information of interest in the dataset, such as treatment outcome, the enrichment of phenotype in each subtype will be examined.

In addition, correlative and supervised analyses of molecular profiling data and other biomarker data in relation to specific phenotypes will be carried out via appropriate univariate (one marker at a time) analysis methods to assess and/or identify specific

markers for further investigation. A variety of multivariate statistical and machine learning methods may also be carried out to identify combinatorial signatures and generate insights of potential use for patient selection/stratification or enrichment and other purposes in ongoing and upcoming clinical projects.

8.4.1. Safety Analyse(s)

Adverse event (AE) data will be summarized overall and stratified by appropriate baseline & clinical characteristics (examples: gender, tumor type/grade/antigen expression, etc.). These summaries will be categorized by frequency and proportion of total subjects. All AEs will be coded using the standard MedDRA.

8.4.2. Other Analyse(s)

Demographic and baseline characteristics will be summarized by tumor type (i.e. NSCLC, HNSCC, breast, ovarian, CRC); and by clinical characteristics of interest to be described in a subsequent analysis plan. Medical history; history of cancer diagnosis and treatment; past and current medical conditions will be listed.

Percentage of participants and investigators utilizing the portal systems.

Results from single and multi-marker *in vitro* diagnostic assays will be summarized by tissue (i.e., tumor, blood) and tumor type.

HLA-subtypes for HLA-A locus will be listed and summarized by tumor type. Separate summaries of HLA-A may be given by ethnicity.

Number of participants who successfully provided a tumor sample will be summarized by tumor type. Separate summaries may be given by baseline demographics such as age and ethnicity.

Number of participants who have been referred into a treatment trial will be summarized by tumor type and treatment trial. Separate summaries may be given by baseline demographics such as age and ethnicity.

Treatment Patterns: Anti-cancer treatments received will be summarized for all participants stratified by tumor type and by line of therapy.

Time to Next Treatment (TTNT): The length of time from the initiation of an anticancer therapy to the date that the next systemic anticancer therapy is initiated. When subsequent treatment is not received, patients should be censored at last known activity (e.g. last physician visit).

Time to Progression (TTP): The length of time from the date the patient initiates an anticancer therapy to the date that a progression event or death due to progression is reported by the physician in the patient chart.

Overall Survival (OS): This is defined as the interval of time between the date of treatment initiation and the date of death due to any cause. For participants who do not

die, time of death will be censored at the date of last contact. Death due to any cause will be included.

8.5. Interim Analyses

Due to the continuous nature of this study, there is no interim analysis phase. Data will be continuously monitored and analysed in real-time during the course of the study.

8.6. Translational Research Committee

The Translational Research Committee (TRC) charter will describe the procedures related to TRC operations in greater detail.

8.7. Limitations

Patient population sampled may not be generalizable or comparable to participants who enrol in treatment protocols.

9. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

9.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

9.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC
  - Notifying the IRB/IEC of SAE or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

9.1.2. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

9.1.3. Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date on which the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- Copies of the ICF(s) must be provided to the participant or the participant's legally authorized representative.
- Participants who are rescreened are required to sign a new ICF.

The ICFs may contain a separate section that addresses the use of remaining mandatory samples for optional CCI research in accordance with SOP-GSKF-410. The Investigator or authorized designee will explain to each participant the objectives of the CCI research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow any remaining specimens to be used for CCI research. Participants who decline to participate will not provide this separate signature.

9.1.4. Data Protection

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection laws. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

9.1.5. Committees Structure

A Translational Research Committee (made up of both internal and external experts) has been formed around this protocol to meet quarterly to discuss protocol design, development, and status.

9.1.6. Dissemination of Clinical Study Data

- Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The Investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.
- GSK will also provide the Investigator with the standard report of the tumor biopsy results, and applicable clinical trials, from DNAseq and RNAseq analysis initially performed on tumor biopsy.
- GSK will also provide a subset of CLIA-validated results back to participants through Gather Share Know Participant Hub. List of results that will be shared can be found in SRM.
- The procedures and timing for public disclosure of the protocol and results summary and for development of a manuscript for publication for this study will be in accordance with GSK Policy.
- GSK intends to make anonymized participant-level data from this trial available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by trial participants are used to maximum effect in the creation of knowledge and understanding.
- A manuscript will be progressed for publication in the scientific literature if the results provide important scientific or medical knowledge.

9.1.7. Data Quality Assurance

- All participant data relating to the study will be recorded on eCRF unless transmitted to the Sponsor (or designee) electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The Sponsor (or designee) is responsible for the data management of this study including quality checking of the data.

- The Sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).
- Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the Investigator for 25 years from the issue of the final Clinical Study Report (CSR)/ equivalent summary unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

9.1.8. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported/entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

9.1.9. Study and Site Start and Closure

GSK or its designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of GSK. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines

- Inadequate recruitment of participants by the Investigator
- Discontinuation of further study intervention development

9.1.10. Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

9.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 3 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.
- Pregnancy testing (urine or serum as required by local regulations) should be conducted as indicated in the SoA (Section 1.3).
- Pregnancy testing (urine or serum as required by local regulations) should be conducted throughout the time frame for female participant contraception in Section 5.1, Inclusion Criteria.
- Additional serum or urine pregnancy tests may be performed, as determined necessary by the Investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study.

Table 3 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	**Parameters**		
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: • MCV • MCH • Reticulocytes	WBC count with Differential: • Neutrophils • Lymphocytes • Monocytes • Eosinophils • Basophils
Coagulation	INR, PT, and aPTT		
Other Tests	• Highly sensitive serum or urine hCG pregnancy test (as needed for women of childbearing potential)[a] • HIV, HBV, HCV, HTLV, EBV, and syphilis (spirochete bacterium).		

Abbreviations: aPTT = activated partial thromboplastin time; EBV = Epstein Barr virus; HBV = hepatitis B virus; HCV = hepatitis C virus; eCRF = electronic case report form; HIV = human immunodeficiency virus; HTLV = human T-lymphotropic virus; INR = international normalized ratio; MCH = mean corpuscular hemoglobin; MCV = mean corpuscular volume; PT = prothrombin time; RBC = red blood cells; WBC = white blood cells.

a. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.

Note: All study-required laboratory assessments listed on Table 3 will be performed by a local laboratory; The results of each test must be entered into the eCRF.

9.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

9.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.

Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events <u>NOT</u> Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.

- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

9.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:

- Results in death
- Is life-threatening

The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

Is a congenital anomaly/birth defect

Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

9.3.3. Recording and Follow-Up of AE and SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g. hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the GSK /AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to GSK.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AE and SAE can be assessed as severe.

An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Other measures to evaluate AE and SAE may be utilized (e.g. National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE).

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to** GSK**.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GSK to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide GSK with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.

- The investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information.

9.3.4. Reporting of SAE to GSK

SAE Reporting to GSK via Electronic Data Collection Tool

- The primary mechanism for reporting SAE to GSK will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the Medical Monitor by telephone.
- Contacts for SAE reporting can be found in SRM.

9.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

9.4.1. Definitions:

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

   For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

   Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.
3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
     - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
   - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrolment.

9.4.2. Contraception Guidance:

• **CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:**
• **Highly Effective Methods[b] That Have Low User Dependency**
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)[c]
• Bilateral tubal occlusion
• Vasectomized partner   • *Note: Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.*
• **Highly Effective Methods[b] That Are User Dependent**

• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c]
  • oral
  • intravaginal
  • transdermal
  • injectable

• Progestogen-only hormone contraception associated with inhibition of ovulation[c]
  • oral
  • injectable

• Sexual abstinence   • *Note: Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant*
a. Contraceptive use by women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies. b. Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly. c. Male condoms must be used in addition to hormonal contraception. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action. 1. Note: Periodic abstinence (calendar, sympto-thermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception for this study. Male condom and female condom should not be used together (due to risk of failure with friction)

9.4.3. Collection of Pregnancy Information

Female Participants who become pregnant

- Investigator will collect pregnancy information on any female participant, who becomes pregnant while participating in this study.
- The initial information will be recorded on the appropriate form and submitted to GSK within 24 hours of learning of a participant's pregnancy.
- Participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on participant and neonate, which will be forwarded to GSK Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion (occurring at <22 weeks gestational age) or still birth (occurring at >22 weeks gestational age) is always considered to be an SAE and will be reported as such.
    - Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study intervention by the investigator, will be reported to GSK as described in Appendix 3.
- While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating

- will discontinue study or be withdrawn from the study

9.5. Appendix 5: Abbreviations and Trademarks

Abbreviation	Definition or Explanation
ACT	Adoptive T-cell therapy
ADMA	Asymmetrical Dimethylated Arginine
AE	Adverse event
aPTT	Activated partial thromboplastin time
BRCA	Breast cancer susceptibility gene
CAR	Chimeric antigen receptor
CD4	Cluster of differentiation 4
CD8	Cluster of differentiation 8
CCI [redacted]	
CFR	Code of Federal Regulations (US)
CCI [redacted]	
CRC	Colorectal carcinoma
CRF	Case report form
CT	Computed tomography
CTA	Clinical Testis Antigen
ctDNA	Circulating tumor DNA
CTLA-4	Cytotoxic t-lymphocyte-associated protein 4
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram(s)
eCRF	Electronic Case Report Form
FFPE	Formalin-fixed, paraffin-embedded
GSK	GlaxoSmithKline
HLA	Human leukocyte antigen
HRD	Homologous Recombination Deficiency
IB	Investigator's brochure
ICF	Informed consent form
IHC	Immunohistochemistry
LAGE-1a	Cancer testis antigen 2
MATCH	Molecular Analysis for Therapy Choice
MDCI	Molecular Disease Characterization Initiative
MEP50	Methylosome protein 50
MMA	Monomethylarginine
MRCLS	Myxoid round cell liposarcoma
MRI	Magnetic resonance imaging
NA	Not applicable
NCI	National Cancer Institute
NGS	Next Generation Sequencing
NSCLC	Non-small cell lung cancer
NPV	Negative Predictive Value
NY-ESO-1	New York esophageal squamous cell carcinoma 1
PARP	Poly (adenosine diphosphate-ribose) polymerase
PD-1	Programmed death protein 1
PD-L1	PD-1 ligand
PD-L2	PD-1 ligand (another one)

Abbreviation	Definition or Explanation
PK	Pharmacokinetic(s)
PPV	Positive Predictive Value
PR	Partial Response (iPR = PR based on iRECIST)
PRMT	Protein arginine methyltransferase
PVRIG	Poliovirus Receptor-related Immunoglobulin Domain Containing
RNA	Ribonucleic acid
SAE	Serious adverse event
SDMA	Symmetrical Dimethyl Arginine
SNP	Single nucleotide polymorphism
SoA	Schedule of activities
SoC	Standard of care
SRM	Study Reference Manual
SS	Synovial Sarcoma
TCGA	The Cancer Genome Atlas
TIGIT	T-cell immunoglobulin and immunoreceptor tyrosine-based inhibition motif domain
CCI	[redacted]
WBC	White blood cell
WES	Whole exome sequencing
WOCBP	Woman of childbearing potential
WTS	Whole transcriptome sequencing

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
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Trademarks not owned by the GlaxoSmithKline group of companies
NONE

9.6. Appendix 6: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY List dates of original protocol and all amendments in reverse chronological order.		
Document	**Date**	**DNG Number**
Amendment 02	*25-NOV-2020*	*2019N418193_02*
Amendment 01	*15-JUN-2020*	*2019N418193_01*
Original Protocol	*09-MAR-2020*	*2019N418193_00*

Amendment 02 25 NOV 2020

Overall Rationale for the Amendment: The overall rationale for this amendment is to remove unnecessary sample and data collections, clarify rationale and conduct of MDCI study, expand the eligibility criteria related to tumor type, as well as archival tissue samples; removing the option of a mandatory fresh biopsy for enrollment. Tumor imaging for this study has also been revised to reflect this change. Stool and urine [redacted] samples were removed from Schedule of Activities, to better align with overall objective of the MDCI study. Medical Chart Review was also removed from protocol, as it was determined to be duplicative to data already being collected on study. Clarifications/updates were also provided regarding the expected impacts of this study. Updates to the Introduction section, as well as tumor types included, to reflect GSK Oncology clinical trials and development updates, were also included.

Section # and Name	Description of Change	Brief Rationale
Protocol Title	Updated	Protocol Title updated for clarification
1.1 Synopsis & 3 Objectives	Removal of objectives and clarifications made Addition of objective related to safety data collected	Some objectives were redundant and could be incorporated into one. Inclusion of objective related to summarizing safety data
1.3 Schedule of Activities	Table 1: Removed Stool Table 1: Removed Urine (except for pregnancy) Table 1: Revised Biopsy requirement Table 2: Added Review of AEs/SAEs	Table 1 changes: Simplifying of study conduct. Table 2 change: Because of procedures, Review of AEs/SAEs should be included
5.1 Inclusion Criteria	Revised sample acceptance & restrictions for tumor specimen	To align with treatment trial protocols
7.2 Tumor Imaging	Removed retrospective image collection. Updated timing of image collection related to tumor sample.	Alignment with tumor sample collection timing.
7.2.1 Imaging Related to Archived Tumor Sample	Added new section	Updated the section as per revised biopsy requirement
2 Introduction & Throughout	Updated information & study schema, corrected inconsistencies and typos Removed Medical Chart Review Added risk associated with assays	To improve quality of the protocol

Amendment 01 15-JUN-2020

Overall Rationale for the Amendment: The overall rationale for this amendment is the removal of two exclusion criteria (see table below), select local labs, and specific portions of the Medical Chart Review which are considered not applicable to the study population or the conduct of this study. Also, the primary objective related to the

development and usage of the participant hub was changed to an [CCI] objective since there is no scientific output to measure. Additional clarifications were also provided regarding patient travel to treatment sites, the total number of participants, and details related to the end of study.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis & 3. Objectives and Endpoints	Moved and revised the Primary Objective regarding the participant hub to the [CCI] Objectives section	Not a scientific output of study
1.1 Synopsis	Set the number of participants on study to approximately 400 participants.	Previous protocol did not provide an exact number
1.3 Schedule of Activities	Table 1: Removed lymphocyte local lab requirement. Table 2: Removed Questionnaire	Not necessary for this study population or study conduct. Questionnaire will not only be limited to patients who move onto Table 2.
4.2 End of Study Definition	Participant will be determined to have completed the study upon signing consent to another GSK study.	Documented evidence of study completion.
5.1 Inclusion Criteria	Clarity added that patient travelling to a treatment center can do so at discretion of physician.	Based on external physician feedback.
5.2 Exclusion Criteria	Removed two Exclusion Criteria stating, "Red blood cell transfusion within 2 weeks prior to anticipated start of study screening." And "Anticoagulation".	Criteria not applicable to the study population based on external physician and GSK medical monitor feedback.
8.0 Medical Chart Review	Parts of the medical chart review were removed	No longer a requirement for the study protocol.
9.10.4 Reporting of SAE to GSK	Removal of SAE reporting via paper eCRF	Study will use electronic reporting of SAEs
Throughout	Corrected inconsistencies and typos	To improve quality of the protocol

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