A STUDY EVALUATING THE CLINICAL ACTIVITY AND SAFETY OF APPROVED DRUGS WITHIN BIOMARKER-GUIDED PATIENTS WITH SOLID TUMORS

StrataPATH™: Precision Indications for Approved Therapies

Protocol Number:	STR-004-001
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SUMMARY OF CHANGES

Amendment 2	
Section Header	**Description/ Rationale**
Entire Protocol	• Updated version and date throughout • Added proprietary and confidentiality statement in footer • Corrected typos and revised wording to provide clarity as appropriate • Abbreviation list updated to reflect amendment text • Updated reference style for consistency
Title/ Title Page	• Added NCT number • Added and updated version, amendment and date list
Investigator Statement of Protocol Approval	• Text size reduced so all fits on 1 page to facilitate investigator's signature
1.1 Synopsis	• Updated approval date • Updated to reflect other changes made in document
3.1 Objectives and Endpoints	• Moved molecule response (ctDNA) monitoring from primary to secondary objective
4.3 End of Study Definition	• Clarified end of study definition
5.1 Inclusion Criteria	• Clarified that CGP test must be from CLIA certified lab and archival tissue needed to confirm CGP results from non-Strata tests or if otherwise indicated within a given cohort specific protocol criteria
5.2 Exclusion Criteria	• Added multiple primary cancers to exclusions • Added primary CNS tumors to exclusions • Added negative pregnancy test requirement to ensure women of child bearing potential are excluded from study
5.3 Contraception	• Added section to provide clarity on contraception use during study
5.4 Pregnancy	• Additional text to provide clarity on pregnancy during study
5.4.1. Use in Nursing Women	• Added section to provide clarity on study drug use in nursing women during study
5.6 Strategies for Recruitment and Retention	• Added StrataEXPress screening study to strategies for recruitment
7.1.1 Study Specific Procedures	• Included Echo with EKG for confirmation of eligibility and clarified that Echo and/or EKG may be study procedure if not done as part of SOC • Clarified additional procedures that are study-specific (i.e. review and sign informed consent)

7.1.2 Standard of Care Procedures	• Added COVID vaccination and disease history to medical history
7.2 Study Schedule	• Added review of medications to baseline and on-treatment visits for tdMeta and µMeta cohorts
9 Statistical Considerations	• Updated information with respect to sample size determination • Additional information provided for analysis of some efficacy endpoints
11.6 Safety Oversight	• Added Data and Safety Monitoring Board (DSMB)
12.4 Publication and Data Sharing Policy	• Added NCT number
Cohort Appendices	All Cohorts: • Added Inclusion Criteria to clarify that tumor needs to be measurable per RECIST 1.1 criteria • Inclusion criteria: ECOG updated to 0-1 from 0-2 • Review and update Safety Reporting Cohort A: • Removed ALK G1202R as a resistance mutation for lorlatinib based on current published preclinical and clinical data Cohorts D-F: • Updated biomarker names to be more consistent across cohorts Updated Cohort F: • Updated excluded tumor types • Updated Investigational product overview for conciseness • Updated from using Trop2 expression alone to improved model that comprises the expression of several genes related to expression of the drug antibody target and subsequent release and impact of the delivered drug • Updated biomarker raitonale • Added additional exclusion criteria • Updated adverse reactions with information from current package inserts • Added Cohort G and H

TABLE OF CONTENTS

INVESTIGATOR STATEMENT OF PROTOCOL APPROVAL

STR-004-001 – "Precision Indications for Approved Therapies (StrataPATH): A Study Evaluating the Clinical Activity and Safety of Approved Drugs within Biomarker-Guided Patients with Solid Tumors"

The information contained in this protocol and all other information relevant to this study are confidential and proprietary information of Strata Oncology Inc., except as may be required by federal, state or local laws or regulation, and may not be disclosed to others without prior written permission of Strata.

I have read and I understand protocol STR-004-001 (Amendment 2, DD-Mar-2023) and agree to conduct the study(ies) in accordance with the relevant, current protocol(s) and will only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, rights, or welfare of participants. I will conduct this protocol as outlined therein and will make all reasonable efforts to complete the study within the designated time and in accordance with all national, state, and local laws or regulations. I have read and understand all sections of the protocol.

I agree to personally conduct or supervise the described investigation(s).

I agree to inform any patients, or any persons used as controls, that the drugs are being used for investigational purposes and I will ensure that the requirements relating to obtaining informed consent in ICH GCP and institutional review board (IRB) review and approval in ICH GCP are met.

I agree to report the sponsor adverse experiences that occur in the course of the investigation(s) in accordance with ICH GCP. I have read and understand the information in the investigator's brochure, including the potential risks and side effects of the drug.

I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study(ies) are informed about their obligations in meeting the above commitments.

I agree to maintain adequate and accurate records in accordance with ICH GCP and to make those records available for inspection in accordance with ICH GCP.

I will ensure that an IRB that complies with the requirements of ICH GCP will be responsible for the initial and continuing review and approval of the clinical investigation. I also agree to promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human participants or others. Additionally, I will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to participants.

I agree to comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements in ICH GCP.

I will provide copies of the protocol and access to all information furnished by Strata to study personnel under my supervision. I will discuss material with them to ensure that they are fully informed about the study and study procedures.

I understand that the study may be terminated or enrollment suspended at any time by Strata Oncology Inc., with or without cause, or by me, if it becomes necessary to do so in the best interests of the study participants.

_____

Investigator Signature Date

_____

Investigator Printed Name

LIST OF ABBREVIATIONS

ABBREVIATION/TERM	DESCRIPTION
µMeta	Micro-metastatic
ADR	Adverse drug reaction
AE	Adverse event
ALK	Anaplastic lymphoma kinase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BRAF	B-Raf proto-oncogene, serine/threonine kinase
BUN	Blood urea nitrogen
CFR	Code of Federal Regulations
CGP	Complete genomic profile
CLIA	Clinical Laboratory Improvement Amendments of 1988
CMP	Clinical Monitoring Plan
CNS	Central nervous system
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Coronavirus disease of 2019
CR	Complete response
CRF	Case report form
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating tumor DNA
DFS	Disease-free survival
dMMR	Mismatch repair deficient
DNA	Deoxyribonucleic acid
DSMB	Data and Safety Monitoring Board
Echo	Echocardiogram
ECOG	Eastern Cooperate Oncology Group
EDC	Electronic data capture
EGFR	Epidermal growth factor receptor
EHR	Electronic health records

EKG	Electrocardiogram
ERBB2	Erb-b2 receptor tyrosine kinase 2
FDA	United States Food and Drug Administration
FFPE	Formalin-fixed, paraffin-embedded
GCP	Good Clinical Practice
HER2	Human epidermal growth factor 2
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonization
IEC	Independent ethics committee
IND	Investigational New Drug
IRB	Institutional Review Board
iRECIST	Response Evaluation Criteria in Solid Tumors in cancer immunotherapy trials
ITT	Intent to treat
LDH	Lactate dehydrogenase
LVEF	Left ventricular ejection fraction
mITT	Modified intent to treat
mL	Milliliter
MSI	Microsatellite instability
MSI-H	Microsatellite instability-high
NCI	National Cancer Institute
NSCLC	Non-small cell lung cancer
NTRK	Neurotrophic receptor tyrosine kinase
OHRP	Office for Human Research Protections
ORR	Objective response rate
OS	Overall survival
PD-1	Programmed death receptor-1
PD-L1	Programmed death-ligand 1
PI	Principal Investigator
PR	Partial response

QC	Quality control
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic acid
rwRR	Real world response rate
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SOA	Schedule of Activities
SOC	Standard of care
SOP	Standard Operating Procedure
tdMeta	Traditionally defined/advanced metastatic
TIA	Transient ischemic attack
TTD	Time to treatment discontinuation
TTnT	Time to next treatment
UP	Unanticipated problems
US	United States
VAF	Variant allele frequency

STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with International Conference on Harmonization Good Clinical Practice (ICH GCP) and applicable United States (US) Code of Federal Regulations (CFR). The Principal Investigator (PI) will assure that no deviation from, or changes to, the protocol will take place without prior agreement from the sponsor, funding agency and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s) (ICFs), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved form.

1 PROTOCOL OVERVIEW

1.1 SYNOPSIS

Title	Precision Indications for Approved Therapies (StrataPATH™): A Study Evaluating the Clinical Activity and Safety of Approved Drugs Within Biomarker-Guided Patients with Solid Tumors
NCT Identifier	NCT05097599
Protocol Number	STR-004-001
Sponsor	Strata Oncology
Approval Date	DD-Mar-2023
Primary Objectives	Traditionally Metastatic (tdMeta) Cohorts • Assess the clinical activity of anti-cancer therapies in participants with pre-specified biomarker profiles. Micrometastatic (μMeta) Cohorts • Evaluate ctDNA response rate at 6 months for participants who received an anticancer biomarker-guided therapy.
Secondary Objectives	tdMeta Cohorts • Assess the duration of response in anti-cancer therapies in participants with pre-specified biomarker profiles. • Evaluate ctDNA response rate at additional timepoints for participants who received anti-cancer therapies with pre-specified biomarker profiles. • Evaluate overall survival (OS) for participants who received an anticancer therapy with pre-specified biomarker profiles. • Monitor and characterize the overall safety for participants in each of the biomarker cohorts. • Assess the molecular response of anti-cancer therapies in participants with pre-specified biomarker profiles. μMeta Cohorts • Evaluate the ctDNA response rate at additional timepoints for participants who receive an anticancer biomarker therapy. • Evaluate disease-free survival (DFS) stratified by ctDNA status at different timepoints for participants who receive an anticancer biomarker therapy.

	• Assess the correlation between ctDNA and Disease-Free Survival (DFS). • Evaluate OS for participants who received an anticancer biomarker-guided therapy. • Monitor and characterize the overall safety for participants for participants in each of the biomarker cohorts.
Exploratory Objective	tdMeta Cohorts • Explore the relationship between serial ctDNA measurement and participant response to therapy.
Endpoints	tdMeta Cohorts *Primary:* • Objective response rate (ORR) *Secondary:* • Duration of response (DoR) • Time to treatment discontinuation (TTD) • Time to next treatment (TTnT) • ctDNA response • Overall survival (OS) • Incidence of SAEs µMeta Cohorts *Primary:* • ctDNA response *Secondary:* • ctDNA response • Disease-Free Survival (DFS) • Overall survival (OS) • Incidence of SAEs
Study Description	StrataPATH is a non-randomized, open-label platform study designed to explore the efficacy and safety of multiple FDA-approved and commercially available cancer therapies in new, biomarker-guided patient populations. This study intends to rapidly identify participants which have efficacy signals for possible expansion into adaptive or randomized studies. As this is a platform study, drug/biomarker cohorts may be added, changed, or discontinued over time. Eligible participants (≥ 18 years age) are those with a historically documented/pathologically confirmed solid tumor, have an eligible biomarker profile, and are planned for treatment. Study procedures will include: CT or MRI imaging (if enrolled in the tdMeta cohort) and repeat blood draws to support ctDNA assessment; study drug

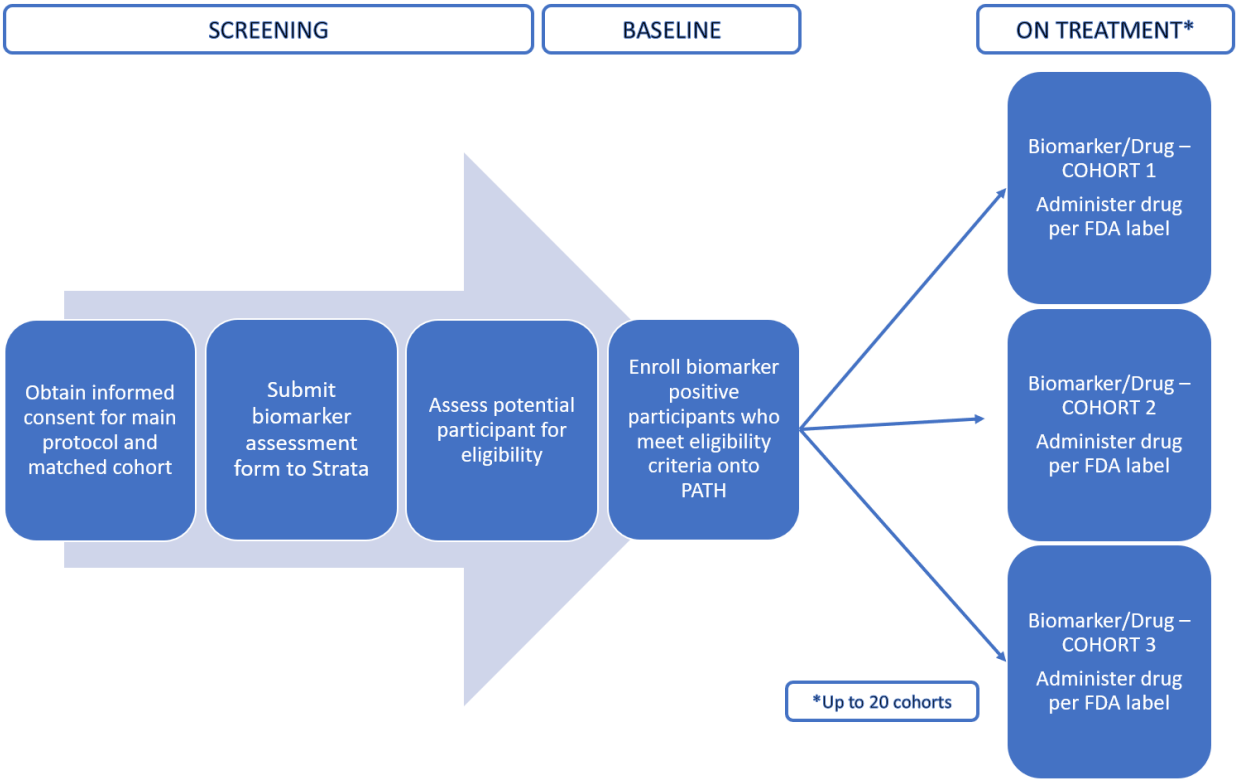
	dispensation, administration, and accountability; and data collection of standard of care procedures that may be done at regular clinic visits.
Study Population	35 participants per cohort for 20 cohorts (700 participants total) <u>Inclusion Criteria:</u> 1. Male or female ≥ 18 years of age. 2. Pathologically confirmed solid tumor. 3. Participants must be able to follow study visit schedule and be willing to provide peripheral blood samples at the indicated time points. 4. CGP results need to be from a test conducted in a CLIA approved laboratory and archival formalin-fixed, paraffin-embedded (FFPE) tumor tissue is required for confirmatory testing of non-Strata test results unless otherwise indicated within the cohort-specific protocol criteria. 5. Biomarker positive for the defined cohort. 6. Individuals with non-primary,treated or stable brain metastases must show no radiographic evidence of progression within 4 weeks prior to consent. 7. Adequate bone marrow, organ function & laboratory parameters as determined by the treating physician unless otherwise indicated within the cohort-specific protocol criteria. 8. Adequate cardiac function: a. Left ventricular ejection fraction (LVEF) ≥ 50%. b. QTc interval ≤ 470 ms (females) or ≤ 450 ms (males) average preferred. <u>Exclusion Criteria:</u> • Receiving another anticancer therapy. • Major surgery within 4 weeks prior to study entry. • Has received a systemic anticancer therapy within 3 weeks of first study dose. • Individuals with a history of a second malignancy are ineligible except for the following circumstances: a. Individuals with a history of other malignancies are eligible if they have been disease-free for at least 3 years or are deemed by the investigator to be at low risk for recurrence of that malignancy. b. Individuals with the following cancers that have been diagnosed and treated within the past 3 years are eligible: cervical/prostate carcinoma in situ, superficial bladder cancer, non-melanoma cancer of the skin. c. Patients with other cancers diagnosed within the past 3 years and felt to be at low risk of recurrence should be

	discussed with the study principal investigator to determine eligibility. • Participant has a primary central nervous system system tumor. • A woman of childbearing potential who has a positive urine pregnancy test (within 72 hours) prior to treatment. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. • Females who are pregnant or nursing or plan to become pregnant or anyone unwilling to use contraception for the duration of treatment. • Ongoing toxicity of CTCAE grade ≥2, other than peripheral neuropathy, related to anticancer therapy that was completed within 4 weeks of consent. • Ongoing peripheral neuropathy of CTCAE grade ≥3 • History of stroke including transient ischemic attack (TIA) or acute myocardial infarction within 6 months of consent. • Participant has a known history of human immunodeficiency virus (HIV), Hepatitis B or known active Hepatitis C virus infection. • Medical condition that would place the patient at risk as a result of blood donation, such as bleeding disorder. • Any other clinically significant medical condition that, in the opinion of the treating physician, makes participation undesirable, including but not limited to ongoing or active infection, significant uncontrolled hypertension, or severe psychiatric illness.
Study Duration	Approximately 5 years
Participant Duration	Up to 3 years
Description of Enrolling Sites	25-30 sites
Description of Study Intervention	The description of each cohort/study drug is included in the appendix.

1.2 STUDY SCHEMATIC

The study schema is outlined in **Figure 1** below.

Figure 1: Study Schematic for StrataPATH



2 INTRODUCTION

2.1 BACKGROUND

Cancer continues to be a significant cause of human disease, with an estimated 1.8 million new cancer cases diagnosed in the United States (US) in 2019.[1] Although survival rates vary widely across cancer types and disease stage, 5-year survival is approximately 68% across all cancer types.[2] When the disease can be diagnosed in the early-stage, standard adjuvant therapy following definitive therapy contributes to 5-year survival rates surpassing 90% (in select cancer types). It is estimated that there are 5.5 million patients living with cancer in the US that would have been diagnosed within the past 5 years. Many of these patients progress to late-stage cancer with over 600,000 deaths each year. As the second leading cause of US deaths,

identifying improved cancer treatment methods, is critical in reducing the extreme burden placed on patients, their families, health care systems, and society.[1]

The goal of precision medicine is to treat individuals based on the combination of their clinical and molecular characteristics resulting in an improved clinical benefit compared to standard or generic anticancer therapies. Pan-tumor targeted therapies are designed to focus on specific genomic changes rather than a site of origin. Identifying the precise set of patients who are most likely to respond to pan-tumor targeted therapies requires significant investment and motivation as the frequencies of particular genomic changes are low. This poses a challenge to the traditional model of drug development. Despite these challenges, precision therapies have seen some recent success. For example, some treatments previously approved for mutations in single tumor types (e.g., *HER2* [*ERBB2*] gene amplification in breast, *BRAF* mutations in melanoma, *EGFR* mutations and *ALK* translocations in lung) have broadened to pan-tumor approvals.

In 2017, the United States Food and Drug Administration (FDA) approved the first tumor-agnostic (or pan-tumor) indication in oncology. Pembrolizumab was approved for adult and pediatric patients with unresectable, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors who have progressed following prior treatment and who have no satisfactory treatment options. Efficacy was based on data from 149 patients enrolled across five uncontrolled trials. Overall response rate (ORR) was 39.6% (95%CI 31.7-47.9), including 11 complete responses and 48 partial responses.[3] Microsatellite instability (MSI) is estimated to occur in 3-5% of all solid tumors.[4]

Larotrectinib was approved in November of 2018. This precision therapy targets adult and pediatric solid tumors which have neurotrophic receptor tyrosine kinase (NTRK) fusions that are metastatic or where surgical resection is likely to result in severe morbidity, and who have no satisfactory alternative treatments or whose cancer has progressed following treatment. Efficacy was based on 55 patients treated across 3 different trials spanning 12 cancer types. ORR was 75% (95%CI: 61%-85%), including 22% complete responses and 53% partial responses.[5] While the clinical benefit is substantial and durable, NTRK fusions are also very rare occurring in less than 1% of most tumors.

While these study results are impressive, the reality is that only a fraction of eligible patients receive targeted therapies, and not until the overt metastatic stage when the potential for a cure may be improbable. There have been efforts to move these precision medicines earlier in the disease stage. For example, the EGFR inhibitor osimertinib, which is FDA approved for use in treatment naïve advanced non-small cell lung cancer (NSCLC), was tested for efficacy in patients with EGFR-mutated stage IB to IIIA NSCLC in the ADAURA trial.[6] Patients were randomized to receive either osimertinib or placebo. Patients in the treatment group had significantly longer disease-free survival (DFS) compared to patients in the placebo group (HR = 0.18; 95% CI 0.10 to 0.33).[6] The population was pre-selected based on biomarker status, and

patients were treated with osimertinib as adjuvant therapy. The data demonstrates the potential benefit of moving targeted therapies to earlier disease states.

Importantly, 44% of patients treated with placebo in ADAURA had not recurred after 24 months. In the paradigm of treating all early-stage patients with EGFR-mutant NSCLC with osimertinib, a substantial proportion may be cured prior to osimertinib treatment, and hence, cannot derive benefit while being exposed to osimertinib for 2 years. This indicates an opportunity to leverage newer technologies – specifically, liquid biopsies – to explore and refine who should be treated with targeted therapies based on if circulating tumor cells are present in the blood post-surgery.

With advancements in both tissue and blood-based molecular technologies, including genomic and transcriptomic profiling, there is an opportunity to expand the clinical benefit of approved therapies to earlier in the disease process where there is improved opportunity for durable disease-free survival.

2.2 STUDY RATIONALE

The cancer patient's treatment journey varies widely and is determined by stage and tumor type at diagnosis. Technology advances over the last few decades have provided physicians with improved information to better tailor patient treatment. These technologies now allow us to understand: 1) if genomic evidence of tumor cells remain in the blood after surgery; 2) how a tumor's genetic and transcriptomic make-up might impact a patient's response to therapy; and 3) if a personalized therapy is reducing disease burden.

StrataPATH is a non-randomized, open-label trial designed to explore efficacy and safety of multiple FDA-approved and commercially available cancer therapies in new, biomarker-guided patient populations. Aiming to increase clinical benefit for patients, this study will leverage technology advancements, scientific literature, and Strata's real-world evidence to define novel, highly responsive pan-tumor molecular indications for FDA-approved therapies in both the advanced and micro-metastatic settings. Strata will rapidly identify participants who have efficacy signals for possible expansion into adaptive or randomized studies.

StrataPATH is a platform study intended to study participants in both the overt metastatic setting and the circulating tumor deoxyribonucleic acid (ctDNA)-positive micro-metastatic setting. Due to potential population differences including, but not limited to, disease stage, Eastern Cooperate Oncology Group (ECOG) status, age, and prior treatments, these cohorts will be studied separately by design and in data analysis using different study endpoints.

2.3 RISK/BENEFIT ASSESSMENT

This study will evaluate the clinical benefit of existing FDA-approved therapies for off-label indications. Participants included in the measurable disease cohorts will have advanced or metastatic cancer that has progressed following standard therapy, have not adequately responded to standard therapy, have no existing standard therapy, have declined standard therapy, or, in the opinion of the Investigator, are not a candidate for or would be unlikely to tolerate or derive significant clinical benefit from standard therapy. These patients have limited to no treatment options, and the potential to select for an improved responder population based on known biomarkers within the drug class with plausible biologic rationale may provide tumor reduction and clinical benefit.

This study may also include separate cohorts of patients in the micro-metastatic setting (as defined by ctDNA positive liquid biopsy) post-standard of care adjuvant therapy, but not yet having been identified as traditionally advanced or metastatic using standard of care imaging or biochemical testing. All therapies are FDA-approved in oncology with demonstrated safety profiles in the traditionally advanced setting; the toxicity profile may be different in the micro-metastatic setting. The utility of targeted therapy in the early-stage setting has been demonstrated with the approval of osimertinib for patients with EGFR-mutated NSCLC. The ADAURA trial demonstrated that osimertinib was well tolerated post-resection in patients with stage IB-III NSCLC; dose reductions due to adverse events occurred in 9% of patients in the treatment group.[6] This was comparable to the 10% dose reduction rate observed in first-line patients with advanced NSCLC at the same recommended dose.[7] Comparatively, the toxicity profile of immunotherapies in early-stage disease may not be as favorable. Dose discontinuation due to adverse events occurred in only 9% of patients with advanced melanoma treated with pembrolizumab in KEYNOTE-001, while 14% of melanoma patients that received pembrolizumab as adjuvant therapy post resection in KEYNOTE-054 experienced adverse event related dose discontinuation.[8,9] Recently announced data from KEYNOTE-564, however, suggests that the toxicity profile of pembrolizumab when used as adjuvant therapy in patients with renal cell carcinoma following nephrectomy was consistent with previously reported studies with the anti-PD-1 therapy.[10] To monitor risk and capture any differences in toxicity profiles between patient populations, full safety data collection will be collected in this study.

More information on the clinical data associated with each therapeutic study arm and known and expected benefits, risks, and reasonably expected adverse events (Aes) may be found in the corresponding appendices.

3 OBJECTIVES AND ENDPOINTS

3.1 OBJECTIVES AND ENDPOINTS

All endpoints will be assessed independently for each biomarker-defined cohort. **Tables A and B** list the objectives and endpoints for this study. Cohorts are stratified based on disease

severity: (1) traditionally defined metastatic/advanced (tdMeta), and (2) micro-metastatic (μMeta).

Table A: StrataPATH Objectives and Endpoints for tdMeta Cohorts

tdMeta Cohorts	
OBJECTIVES	**ENDPOINTS**
Primary	
Assess the clinical activity of anti-cancer therapies in participants with pre-specified biomarker profiles.	ORR – Overall Response Rate is defined as the percentage of participants with a best overall response of CR or PR based on Response Evaluation Criteria in Solid Tumors (RECIST) 1.1, as assessed by the investigator.
Secondary	
Assess the duration of response in anti-cancer therapies in participants with pre-specified biomarker profiles.	• DoR – Duration of response is defined as the time from first documentation of disease response (CR or PR) until first documentation of progressive disease. • TTD – Time to treatment discontinuation is defined as length of time from the date the participant initiates the systemic treatment to the date the participant discontinues treatment • TTnT – Time to next treatment is defined as the length of time from the date the participant initiates study treatment to the date the participant initiates their next systemic treatment or death.
Evaluate ctDNA response rate at timepoints for participants who received anti-cancer therapies with pre-specified biomarker profiles.	ctDNA response – Proportion of participants with a <50% ratio of mean VAF will be defined as ctDNA responders. Molecular response is calculated as a ratio of mean VAF on-treatment at different timepoints compared to their baseline VAF.
Evaluate overall survival (OS) for participants who received an anticancer therapy with pre-specified biomarker profiles.	OS – Time from initiation of treatment until death from any cause.
Monitor and characterize the overall safety in the biomarker cohorts	The incidence of serious adverse events (SAEs).
Exploratory	
Explore the relationship between serial ctDNA measurement and participant response to therapy.	N/A

Table B: StrataPATH Objectives and Endpoints for μMeta Cohorts

μMeta Cohorts

OBJECTIVES	ENDPOINTS
Primary	
Evaluate ctDNA response rate at 6 months for participants who received an anticancer biomarker-guided therapy.	ctDNA response – Proportion of participants with a <50% ratio of mean VAF will be defined as ctDNA responders. Molecular response is calculated as a ratio of mean VAF on-treatment at 6 months compared to their baseline VAF.
Secondary	
Evaluate the ctDNA response rate at additional timepoints for participants who receive an anticancer biomarker therapy.	ctDNA response – Proportion of participants with a <50% ratio of mean VAF will be defined as ctDNA responders. Molecular response is calculated as a ratio of mean VAF on-treatment at additional timepoints compared to their baseline VAF.
Evaluate Disease-Free Survival (DFS) stratified by ctDNA status or response at different timepoints.	DFS – Time from initiation of treatment until disease recurrence or death from any cause.
Assess the correlation between ctDNA and Disease-Free Survival (DFS).	DFS – Time from initiation of treatment until disease recurrence or death from any cause.
Evaluate overall survival (OS) for participants who received an anticancer biomarker-guided therapy.	OS – Time from initiation of treatment until death from any cause.
Monitor and characterize the overall safety for participants in the biomarker cohorts	Incidence of serious adverse events (SAEs).

3.2 STUDY ENDPOINT RATIONALE

Study endpoints are stratified by disease severity (tdMeta or µMeta). Study endpoints include traditionally accepted trial endpoints in single-arm oncology studies including objective response rate (ORR), duration of response (DoR), disease-free survival (DFS), and overall survival (OS)[11]. The study also leverages real-world endpoints of time to next treatment (TTnT) and time to treatment discontinuation (TTD), and another potential surrogate endpoint of ctDNA response rate as defined in **Table A** and further described below.

3.2.1 REAL-WORLD ENDPOINTS

Increasingly, real-world evidence is being looked to as a complement to traditional clinical trial data collection. Real-world data is often easier and less expensive to collect, especially if it can be exported directly from electronic health record systems. The 21st Century Cures Act mandates the creation of regulatory pathways to support real-world evidence based regulatory approvals for the expanded use of existing FDA-approved therapies. For this study, we sought

to leverage both traditional and real-world data collection methodologies to reduce future data collection burden.

OS is well established as a standard measure of clinical benefit in cancer drug development. Additionally, surrogates are often used to support drug and/or medical device development as they have reduced event timelines. The changes “induced by a therapy on a surrogate endpoint are expected to reflect changes in a clinically meaningful endpoint”.[12]

TTnT and TTD will additionally be used as potential surrogates to OS. Khozin and colleagues looked at programmed death-ligand 1 (PD-L1) therapy outcomes for NSCLC participants within the Flatiron dataset and found that overall survival was strongly correlated with real world TTD (r^2=0.81, 95% CI 0.80-0.82) and also modestly correlated with TTnT (p = 0.60, 95% CI 0.56-0.64).[13] Similar results were observed across six different datasets (N=269-6,924) for NSCLC participants treated with immunotherapies. Correlations between the real-world endpoints of real-world TTD and real-world TTnT and OS were moderate to high and the authors concluded “real-world end points are generally consistent with each other and with outcomes observed in randomized clinical trials, which substantiates the potential validity of real-world data to support regulatory and payor decision making”.[14]

As high and significant correlation does not necessarily capture off-target effects and does not equal causation, Prentice has posited that it may be sufficient if the surrogate captures the net effect of the intervention on the clinical efficacy measure.[15] OS inherently captures not only the study drug’s efficacy, but also any downstream therapies the participant might have been administered.[13] Real-world TTnT and real-world TTD may provide more clinically meaningful endpoints as they also take into account why physicians and participants alter clinical care including toxicity and efficacy of the current drug under study. These surrogates are censored less commonly compared to OS.[14] While we may not have a comprehensive understanding of all factors, the most reliable evidence regarding the validity of a surrogate endpoint for a clinical efficacy measure might be provided by numerous trials which give reliable estimates of the net effects of the intervention on the clinically meaningful endpoint such as overall survival and the surrogate.[16] As in previous studies, this study will assess both the proposed surrogates (real-world TTNT and real-world TTD) and the known clinically meaningful endpoint of OS for the primary objectives.

3.2.2 CTDNA RESPONSE RATE

ctDNA clearance or response has been shown to be an early predictor of therapy response.[17,18] The current study will leverage ctDNA response rate as the secondary endpoint in both tdMeta and µMeta cohorts. ctDNA response rate is defined as the proportion of participants with a <50% ratio of mean VAF. An individual’s molecular response is calculated as a ratio of mean VAF on-treatment at 6 months to their baseline VAF. This is based on the tracer markers based

on the personalized ctDNA assay which are averaged together to create a mean VAF. Any participant who has a <50% ratio is defined as a responder.

3.2.3 DISEASE-FREE SURVIVAL

Disease-free survival (DFS) is defined as the time from date of first dose until disease recurrence or death from any cause. The most frequent use of this endpoint is in the adjuvant setting after definitive surgery or radiotherapy and is a recommended clinical endpoint based on FDA's guidance Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics.[11]

4 STUDY DESIGN

4.1 OVERALL DESIGN

Participants who are 18 years of age or older, have been diagnosed with histologically documented solid tumors, have an eligible biomarker profile, and are planned for treatment may be eligible for this study according to the criteria in **Sections 5.1-5.2** and the supplemental criteria in the specific biomarker/drug cohort appendix.

Each biomarker/drug cohort will be described in an appendix to this study protocol. Appendix information includes investigational product overview, rationale for biomarker/drug combination, additional cohort-specific eligibility criteria, study treatment including dosing and administration guidelines, along with known adverse reactions.

After obtaining informed consent, study staff shall assess individual participant eligibility using the criteria in **Sections 5.1-5.2** and the supplemental criteria in the specific appendix they are targeting for enrollment. The designated study staff will enter the participant's details into the electronic data capture (EDC) to support a sponsor-required confirmation of biomarker eligibility. Upon confirmation of eligibility and informed consent procedures, the participant will be formally enrolled into the study. Participants will be treated with the applicable cohort's study drug according to dosing instructions in the approved product labeling or provided Investigator's Brochure (IB).

For participants who exhibit more than 1 eligible biomarker result, the treating physician should determine the most appropriate cohort assignment. Factors for consideration include the drug's dosing and administration guidelines, as well as the commercially available product prescribing instructions or provided IB.

A leftover tumor specimen (if historical comprehensive genomic profiling (CGP) and/or ribonucleic acid (RNA) profiling results are not available for submission) and blood sample for ctDNA analysis will be collected at study entry (prior to therapy start). Blood samples will be

collected and CT/MRI scans will be performed until treatment discontinuation as outlined in the Study Schedule of Activities (SOA) (**Section 7.2**).

Tumor assessments to support ORR efficacy assessment will be completed as outlined in the Study Schedule of Activities (**Section 7.2**) and recorded in the study database. Study staff will also record information in the study EDC (either manually or through an integrated mechanism) which occur as part of standard of care visits. Standard of care details such as demographics, clinical characteristics, and concomitant medications will be recorded within the study database. Upon identification of any efficacy signal, additional real-world data collection may be requested (i.e., additional medical history and imaging) to support additional analysis and cohort expansion studies. Following completion of or discontinuation from drug, all active study participants will be followed for survival for 3 years from the date of consent.

This study will require reporting of Common Terminology Criteria for Adverse Events (CTCAE) grade 3 and 4 Aes that are possibly, probably, or definitely related to the study treatment. All SAEs, regardless of grade, relatedness to study drug, or expectedness, must be reported, including deaths.

Drug/biomarker cohorts may be added, changed, or discontinued over time. This study may enroll up to 700 participants.

4.2 JUSTIFICATION FOR DOSE

Each drug will be administered according to the FDA-approved dosing regimen listed in the approved product labeling or provided Investigator's Brochure (IB).

4.3 END OF STUDY DEFINITION

A participant is considered to have completed the study if they were treated for any duration of time, and were followed for survival for 3 years from the date of consent or until death.

5 STUDY ENROLLMENT AND WITHDRAWAL

5.1 INCLUSION CRITERIA

To be eligible to participate in this study, an individual must meet each of the criterion below **and** the criteria indicated in the selected biomarker/drug cohort appendix:

1. Male or female ≥ 18 years of age.

2. Pathologically confirmed solid tumor.
3. Participants must be able to follow study visit schedule and be willing to provide peripheral blood samples at the indicated time points.
4. CGP results need to be from a test conducted in a CLIA approved laboratory and archival formalin-fixed, paraffin-embedded (FFPE) tumor tissue is required for confirmatory testing of non-Strata test results unless otherwise indicated within the cohort-specific protocol criteria.
5. Biomarker positive for the defined cohort.
6. For individuals with non-primary, treated or stable brain metastases: No evidence of progression (defined as no radiographic evidence of progression) for at least 4 weeks prior to consent.
7. Adequate bone marrow, organ function & laboratory parameters as determined by the treating physician unless otherwise indicated within the cohort-specific protocol criteria.
8. Adequate cardiac function:
    8.1. Left ventricular ejection fraction (LVEF) ≥ 50%
    8.2. QTc interval ≤ 470 ms (females) or ≤ 450 ms (males) average preferred.

5.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Receiving another anticancer therapy.
2. Major surgery within 4 weeks prior to study entry.
3. Has received a systemic anticancer therapy within 3 weeks of first study dose.
4. Individuals with a history of a second malignancy are ineligible except for the following circumstances. Individuals with a history of other malignancies are eligible if they have been disease-free for at least 3 years or are deemed by the investigator to be at low risk for recurrence of that malignancy. Individuals with the following cancers that have been diagnosed and treated within the past 3 years are eligible: cervical/prostate carcinoma in situ, superficial bladder cancer, non-melanoma cancer of the skin. Patients with other cancers diagnosed within the past 3 years and felt to be at low risk of recurrence should be discussed with the study principal investigator to determine eligibility.
5. Participant has primary central nervous system tumor.
6. A woman of childbearing potential who has a positive urine pregnancy test (within 72 hours) prior to treatment. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
7. Females who are pregnant or nursing or plan to become pregnant or anyone unwilling to use contraception for the duration of treatment.
8. Ongoing toxicity of CTCAE grade ≥2, other than peripheral neuropathy, related to anticancer therapy that was completed within 4 weeks of consent.
9. Ongoing peripheral neuropathy of CTCAE grade ≥3.

10. History of stroke including transient ischemic attack (TIA) or acute myocardial infarction within 6 months of consent.
11. Participant has a known history of human immunodeficiency virus (HIV), Hepatitis B or known active Hepatitis C virus infection.
12. Medical condition that would place the patient at risk as a result of blood donation, such as bleeding disorder.
13. Any other clinically significant medical condition that, in the opinion of the treating physician, makes participation undesirable, including but not limited to ongoing or active infection, significant uncontrolled hypertension, or severe psychiatric illness.

5.3 CONTRACEPTION

Study medication may have adverse effects on a fetus in utero. Furthermore, it is not known if study medication has transient adverse effects on the composition of sperm.

Participants should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study, participants of childbearing potential must adhere to the contraception requirement from the day of study medication initiation (or 14 days prior to the initiation of study medication for oral contraception) throughout the study period up to 210 days after the last dose of study medication. Please refer to the cohort specific package insert for information on contraception requirements. If there is any question that a participant of childbearing potential will not reliably comply with the requirements for contraception, that participant should not be entered into the study.

5.4 PREGNANCY

If a participant inadvertently becomes pregnant while on treatment with study medication, the participant will be immediately discontinued from study treatment. The site will contact the participant at least monthly and document the participant's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor without delay and within 24 hours if the outcome is a serious adverse event (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor.

5.4.1 USE IN NURSING WOMEN

It is unknown whether study medication is excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, participants who are breastfeeding are not eligible for enrollment.

5.5 SCREEN FAILURES

Screen failures are defined as individuals who consented to participate in the clinical trial but were 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, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this trial (screen failure) because of the following may be considered for re-screening:

- Reversible causes of screening failure that have been adequately treated.
- Performance status.
- Stage of disease did not meet inclusion criteria at initial screen but have since progressed and may now meet eligibility criteria.
- Decline or delay in starting due to change in situation (availability, family situation, etc.).

Re-screened participants should be assigned the same study ID number as the initial screening (i.e., re-screened participants do not receive new study IDs).

5.6 STRATEGIES FOR RECRUITMENT AND RETENTION

Individuals will be screened and molecularly identified through standard of care (SOC) CGP testing or other available RNA profiling tests. StrataPATH will leverage the Strata Precision Oncology Network, a collective of >20 large hospital systems in the United States in addition to other academic and large research institutions familiar with biomarker-driven studies. Using this systematized approach, the pre-screened study population will be more likely to represent the demographics of the general advanced cancer population.

StrataEXPress (NCT05312307) is a parallel screening study that will be used to identify patients with RNA expression profiles or relevant algorithm scores consistent with eligibility requirements for StrataPATH biomarker/drug treatment cohorts. For StrataEXPress, archival tissue from solid tumors will be collected from eligible participants for RNA expression analysis using next-generation sequencing.

As many of these biomarkers are rare, other testing modalities are acceptable, if, sufficient detail is provided to support sponsor eligibility confirmation.

Pregnant women, those who lack consent capacity, including the mentally ill, prisoners, cognitively impaired participants, children, and employee volunteers will not be included in this study.

Participants will generally be seen and assessed for this research study during their regular clinic visits, reducing the burden to participants and their families.

5.7 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request.

An investigator may discontinue or withdraw a participant from the study for any of the following reasons:

- Pregnancy.
- Significant study intervention non-compliance.
- If any clinical AE, laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant.
- Disease progression which requires discontinuation of the study intervention.
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.
- Participant unable to receive therapy for greater than 2 weeks.
- Death.

The reason for participant discontinuation or withdrawal from the study will be recorded on the CRF. Participants who sign the ICF but do not receive the study intervention may be replaced. Participants who sign the ICF, receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, will be replaced if the reason for withdrawal is not due to failure to respond. Any participants who withdraw due to progression will be counted in efficacy calculations. Any participant withdrawal and replacement will be detailed in the Screening and Enrollment Log.

5.8 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if they fail to return for 2 consecutively scheduled visits and are unable or unwilling to be contacted by the study site staff.

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

- The site will attempt to contact the participant and reschedule the missed visit within a week and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will 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 or study file.
- Should the participant continue to be unreachable, they will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

6 STUDY AGENTS

6.1 DESCRIPTION OF STUDY AGENTS

Each specific drug/biomarker cohort appendix will describe study drug dosing and administration, any preparation and handling requirements separately.

6.2 ACQUISITION AND ACCOUNTABILITY

The study will utilize a combination of local pharmacy and central drug depot that will house and distribute all study drug on a per patient basis. Drug will be unblinded. Treatment cohort is determined by biomarker test results and will be communicated directly by Strata to the depot. When the central drug depot is used, study drug will be shipped from the drug depot of record to the study site. Visual confirmation of the shipment will be conducted by the PI or designee and documented according to the operations manual.

6.3 STUDY AGENT COMPLIANCE

Drug accountability will be performed by delegated study staff. The delegated study staff is responsible for ensuring that the participant is dosed according to the package insert. For applicable cohorts where participants are taking study drugs outside of the clinic, participants will be instructed to return all unused drug and empty packaging for accountability assessment. Used drug may be destroyed on site if sites SOPs support or returned to the drug depot. Details are outlined in the operations manual.

6.4 STUDY AGENT DISCONTINUATION

Discontinuation of dosing does not mean discontinuation from the study. Remaining study procedures should be completed as indicated by the study protocol regardless of whether the participant is on active treatment. If a clinically significant finding is identified (including, but not limited to, changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in study drug administration is needed. Any new, clinically relevant finding that is both unexpected and thought to be related to the drug will be reported as an SAE under Other Medically Important Event as described in Section 8.2.2. All AEs and SAEs will be reported and captured in the CRF.

7 STUDY PROCEDURES AND SCHEDULE

7.1 STUDY PROCEDURES

7.1.1 STUDY SPECIFIC PROCEDURES

All procedures listed here are specific to the study and are not part of standard clinical care:

- Review and sign informed consent
- Eligibility criteria review
- Biological specimen collection
    - Two 10 milliliter (mL) tube of blood (20 mL total) will be collected via venipuncture
- Archival FFPE tissue submission (if historical CGP and/or Strata RNA profiling results are unavailable or as otherwise indicated within the cohort-specific criteria)
- Biomarker confirmation (biomarker test results)
- Data collection of any standard of care procedures conducted as part of regular clinical visits
- Study drug dispensing
- Study drug administration
- CT/MRI scan of abdomen, chest, and pelvic area
- Tumor assessments (RECIST 1.1 or iRECIST)
- Drug administration and accountability
- Evaluation and documentation of adverse events (AEs) or serious adverse events (SAEs)
- Electrocardiograms (EKGs) and/or echocardiogram (Echo) are required for eligibility determination at screening. If not done as part of standard of care work-up or historical

EKG and/or Echo are not available, these tests should be performed as research procedures.

- A serum pregnancy test is required if the pre-treatment urine pregnancy test is positive or inconclusive. Pregnancy tests must be documented as negative within 3 days of study treatment.

7.1.2 STANDARD OF CARE PROCEDURES

All procedures listed here may be conducted as part of standard clinical care but are not required to be done for study purposes only (refer to **Tables C and D** for the Schedule of Activities). These SOC procedures are not billable to the study and should only be done if needed for clinical care.

Regardless of whether the following are performed during a standard of care clinical visit, or in combination with study procedures, all relevant data collected must be entered into the EDC system. The data entry of both SOC procedures and study-specific procedures is a required study activity to meet study objectives and endpoints.

- Demographics and disease/medical characteristics including:
  - Demographics
  - Disease history (date of first diagnosis, treatment history)
  - Current medical history (within the last 30 days) including medical illnesses and conditions, and surgical procedures not related to primary diagnosis.
  - COVID-19 vaccination and disease history
  - Previous and concomitant medication within the last 30 days before screening
- Complete or abbreviated physical examination
  - Information to be recorded may include results, abnormal findings, and clinical significance for various body systems examined.
- Performance Status (ECOG)
- Vital signs, including height, weight, blood pressure, heart rate, and respiration rate
- Standard local laboratory assessments including hematology, serum chemistry (albumin, alkaline phosphatase, total bilirubin, bicarbonate, blood urea nitrogen (BUN), calcium, chloride, creatinine, glucose, lactate dehydrogenase (LDH), phosphorus, potassium, total protein, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and sodium)
- Urine pregnancy test for females of childbearing potential within 3 days prior to treatment.

7.2 STUDY SCHEDULE

7.2.1 SCHEDULE OF ACTIVITIES

The schedules of activities (SOA) for both the tdMeta and µMeta cohorts are detailed in **Table C and Table D**. StrataPATH is designed to mimic real-world practice and will have a limited number of study-specific visits (**Section 7.1**). The visit schedules are comprised of a combination of study-specific visits and standard of care (SOC) visits. Participants will be followed for up to 3 years from the time of consent.

SOC procedures listed in the SOA typically occur during standard clinical visits and are to be documented within the EDC system at the timepoints outlined in the SOA.

Table C: StrataPATH Schedule of Activities – tdMeta Cohorts

SCHEDULE OF ACTIVITIES STR-004-001: StrataPATH tdMeta Cohorts	STUDY VISITS (participation up to 3 years)			
	Screening	Baseline	On Treatment	Post-Treatment[g]
Study Procedures				
Review and Sign Informed Consent Form	X			
Eligibility Criteria Review (Main and Cohort-Specific)	X	X		
Biomarker Confirmation	X			
CT Scan or MRI of Abdomen, Chest, and Pelvic Area		X[a]	X[b,c]	
RECIST 1.1 (or iRECIST) Assessment		X	X[b,c]	
Blood Draw: Whole Blood		X	X[b,c]	
FFPE Tissue Collection	X[d]			
Study Drug Administration		X[i]	X[i]	
Study Drug Accountability		X	X	X[h]
Study Drug Discontinuation				X[h]
Standard of Care (SOC) Procedures[e]				
Documentation of Biomarker Results	X[e]			
Demographics	X[e]			
Medical History	X[e,f]		X[e]	X[e]
Cancer Diagnosis	X[e]			
Prior and Concomitant Medications	X[e,f]		X[e]	X[e]
Physical Exam (Complete or Abbreviated)	X[e]		X[e]	X[e]
ECOG Performance Status	X[e]	X[e]	X[e]	X[e]
Height, Weight, Vital Signs	X[e]		X[e]	X[e]
Electrocardiogram (EKG)	X[j]		X[e]	X[e]
Echocardiogram (Echo)	X[j]			
Hematology	X[e]		X[e]	X[e]
Serum Chemistry	X[e]		X[e]	X[e]
Urine Pregnancy Test, Serum Pregnancy Test[k]	X[e]	X[e]	X[e]	
Safety Evaluation				
Adverse Events/Serious Adverse Events		X	X	X

[a] If a scan was performed within 28 days of the baseline visit, these results should be submitted to the study.

[b] Collect every 8 weeks (± 2 weeks) during year 1 on treatment. After year 1 of treatment, collect every 12 weeks (± 2 weeks). Collect upon disease progression.

[c] Confirmation of progression (e.g., confirmatory scan 4 weeks after initial progression assessment).

[d] Only required if historical comprehensive genomic or Strata RNA profiling results are not available or otherwise indicated within the cohort-specific criteria. Site should collect and submit a leftover tumor tissue specimen to the Strata Lab for confirmatory testing with a central next generation sequencing test.

[e] The specified SOC procedures should be conducted only if they are necessary for clinical care and should not be done for research purposes only. If any of these SOC activities are conducted at a regular clinic visit, the data obtained must be entered in the EDC for the study.

[f] Enter information from medical records obtained up to 30 days prior to the screening visit.

[g] Every 3 months for up to 3 years from the date of consent or until death, whichever comes first.

[h] Study drug will be discontinued upon progression or per physician discretion. Study drug discontinuation and accountability activities will only be performed once during post-treatment.

[i] The frequency of study drug dispensing and administration will be determined by the biomarker/study drug cohort in which the patient is enrolled.

[j] If not SOC and historical data not available, can be research activity.

[k] Only if urine test is positive or inconclusive; serum test can be research activity.

Table D: StrataPATH Schedule of Activities – µMeta Cohorts

SCHEDULE OF ACTIVITIES µMeta Cohorts STR-004-001 - StrataPATH	STUDY VISITS (participation up to 3 years)			
	Screening	Baseline	On Treatment	Post-Treatment[e]
Study Procedures				
Review and Sign Informed Consent Form	X			
Eligibility Criteria Review (Main and Cohort-Specific)	X	X		
Biomarker Confirmation	X			
Blood Draw: Whole Blood		X	X[b]	
FFPE Tissue Collection	X[a]			
Study Drug Administration		X[g]	X[g]	
Study Drug Accountability		X	X	X[f]
Study Drug Discontinuation				X[f]
Standard of Care (SOC) Procedures				
Documentation of Biomarker Results	X[c]			
Demographics	X[c]			
Medical History	X[c,d]		X[c]	X[c]
Cancer Diagnosis	X[c]			
Prior and Concomitant Medications	X[c,d]		X[c]	X[c]
Physical Exam (Complete or Abbreviated)	X[c]		X[c]	X[c]
ECOG Performance Status	X[c]	X[c]	X[c]	X[c]
Height, Weight, Vital Signs	X[c]		X[c]	X[c]
Electrocardiogram (EKG)	X[h]		X[c]	X[c]
Echocardiogram (Echo)	X[h]			
Hematology	X[c]		X[c]	X[c]
Serum Chemistry	X[c]		X[c]	X[c]
Urine Pregnancy Test, Serum Pregnancy Test[i]	X[c]	X[c]	X[c]	
Safety Evaluation				
		X	X	X

[a]Only required if historical comprehensive genomic or Strata RNA profiling results are not available or otherwise indicated within the cohort-specific criteria. Site should collect and submit a leftover tumor tissue specimen to the Strata Lab for confirmatory testing with a central next generation sequencing test.

[b]Collected every 8 weeks (± 2 weeks) during year 1 on treatment. Collect every 12 weeks (± 2 weeks) after year 1 on treatment. Collect upon disease progression.

[c]The specified SOC procedures should be conducted only if they are necessary for clinical care and should not be done for research purposes only. If any of these SOC activities are conducted at a regular clinic visit, the data obtained must be entered in the EDC for the study.

[d]Enter information from medical records obtained up to 30 days prior to the screening visit.

[e]Every 3 months for up to 3 years from the date of consent or until death, whichever comes first.

[f]Study drug will be discontinued upon progression or per physician discretion. Study drug discontinuation and accountability activities will only be performed once during the post-treatment phase.

[g]The frequency of study drug dispensing and administration will be determined by the biomarker/study drug cohort in which the patient is enrolled.

[h]If not SOC and historical data not availible, can be research activity.

[i]Only if urine test is positive or inconclusive; serum test can be research activity.

7.2.2 tdMETA COHORTS

7.2.2.1 SCREENING

- Obtain informed consent of potential participant verified by signature on written informed consent form
- Review medical history, including biomarker status and cancer diagnosis, to determine eligibility based on inclusion/exclusion criteria **(Sections 5.1-5.2**)
- Enter data from any standard of care procedures in the EDC
- Submit biomarker confirmation form
- If no historical Strata CGP or RNA profiling test results are available, submit a left-over FFPE tumor specimen for confirmation by a central lab

7.2.2.2 BASELINE

- Verify eligibility per inclusion/exclusion criteria
- Review of medications

- Negative pregnancy test (urine or serum)

- Obtain two 10 mL tubes of whole blood
  - Complete research blood collection form
- Conduct CT scan or MRI of abdomen, chest, and pelvic area
  - If a scan was conducted within 28 days of the baseline visit, these results should be submitted; an additional scan is not required for the baseline visit.
- Complete RECIST 1.1 (or iRECIST) assessment
- Dispense study drug and review dosing instructions
- Administer study drug and/or review administration instructions with participant
- Perform drug accountability
- Enter data from any standard of care procedures in the EDC, including ECOG status
- Document any AEs or SAEs

7.2.2.3 ON TREATMENT

- Review of medications

- Negative pregnancy test (urine or serum)
  - Obtain two 10 mL tubes of whole blood every 8 weeks during the first year of treatment and every 12 weeks thereafter and once upon disease progression

    - Complete research blood collection form
- Conduct CT scan or MRI of abdomen, chest, and pelvic area every 8 weeks during the first year of treatment and every 12 weeks thereafter
    - At progression, perform a confirmatory CT scan or MRI (e.g., 4 weeks after initial progression assessment)
- Complete RECIST 1.1 (or iRECIST) assessment every 8 weeks during the first year of treatment and every 12 weeks thereafter
    - At progression, perform RECIST 1.1 (or iRECIST) assessment (e.g., 4 weeks after initial progression assessment)
- Dispense study drug
- Administer study drug and/or review administration instructions with participant
- Perform drug accountability
- Enter data from any standard of care procedures in the EDC, including ECOG status
- Document any AEs or SAEs

7.2.2.4 POST-TREATMENT

Study drug will be discontinued upon disease progression or based on physician's discretion as described in **Section 5.5**. Site staff should collect unused study drug and any empty packaging and perform drug accountability upon study drug discontinuation. Participants that discontinue drug will remain on study for 3 years from the date of informed consent for follow-up data entry purposes only. No additional study specific procedures will occur following discontinuation. Participants will continue to see their physician for SOC clinic visits. Site staff will be responsible for collecting and entering the information below in EDC from the participants SOC clinic visits every 3 months.

- Medical history (specifically, disease recurrence and/or survival status)
- Concomitant medications (specifically, anticancer therapies)
- Standard of care procedures, including ECOG status

7.2.3 µMETA COHORTS

Note that µMeta cohorts will not have CT/MRI scans or RECIST 1.1 (or iRECIST) assessments performed.

7.2.3.1 SCREENING

- Obtain informed consent of potential participant verified by signature on written informed consent form
- Review medical history, including biomarker status and cancer diagnosis, to determine eligibility based on inclusion/exclusion criteria **(Sections 5.1-5.2**)

- Enter data from any standard of care procedures in the EDC, including ECOG status
- Submit biomarker confirmation form through the EDC
- If no historical CGP test results are available, submit an FFPE tumor specimen for confirmation by a central lab.

7.2.3.2 BASELINE

- Verify eligibility per inclusion/exclusion criteria
- Review of medications
- Negative pregnancy test (urine or serum)

- Obtain two 10 mL tubes of whole blood and complete research blood collection form
- Dispense study drug and review dosing instructions
- Administer study drug and/or review administration instructions with participant
- Perform drug accountability
- Enter data from any standard of care procedures in the EDC, including ECOG status
- Document any AEs or SAEs

7.2.3.3 ON TREATMENT

- Review of medications
- Negative pregnancy test (urine or serum)
- Obtain two 10 mL tubes of whole blood and complete research blood collection form every 8 weeks during the first year of treatment and every 12 weeks thereafter and once upon disease progression
    - Complete research blood collection form
- Dispense study drug
- Administer study drug and/or review administration instructions with participant
- Perform drug accountability
- Enter data from any standard of care procedures in the EDC, including ECOG status
- Document any AEs or SAEs

7.2.3.4 POST-TREATMENT

Study drug will be discontinued upon disease progression or based on physician's discretion as described in **Section 5.5**. Site staff should collect unused study drug and any empty packaging and perform drug accountability upon study drug discontinuation. Participants that discontinue drug will remain on study for 3 years from the date of informed consent for follow-up data entry purposes only. No additional study specific procedures will occur following discontinuation. Participants will continue to see their physician for SOC clinic visits. Site staff will be responsible

for collecting and entering the information below in EDC from the participants SOC clinic visits every 3 months.

- Medical history (specifically, disease recurrence and/or survival status)
- Concomitant medications (specifically, anticancer therapies)
- Standard of care procedures, including ECOG status

7.3 EFFICACY ASSESSMENTS

7.3.1 tdMETA COHORTS

Study procedures and evaluations to assess efficacy are listed below.

Response Assessment:
Participants will undergo tumor assessments as designated in the Schedule of Activities **(Table C, Section 7.2.1)** until disease progression (regardless of whether or not the participant is still receiving study treatment) or until the participant discontinues the study drug or starts alternative anticancer treatment. At the investigator's discretion, tumor assessments may be repeated at any time if progressive disease is suspected.

Confirmation assessment of progressive disease must be obtained at least 4 weeks after the initial disease assessment indicating progressive disease. After confirmation of progressive disease, participants must complete the end of treatment visit and enter the post-treatment follow-up period.

All active study participants who discontinue study drug for reasons other than disease progression (e.g., AEs) will continue tumor assessments until death, disease progression, initiation of another systemic anticancer therapy, lost to follow-up, withdrawal of consent, PI's decision, or study termination, whichever occurs first.

Measurable and evaluable lesions should be assessed and documented at baseline. Response assessments performed as standard of care prior to obtaining informed consent and within 28 days prior to enrollment do not have to be repeated at screening.

Baseline disease assessments will include a CT scan of the chest and abdomen/pelvis. CT scans of the neck and/or extremities should be performed as clinically indicated. Post-baseline disease assessments will include a CT scan of the chest and abdomen/pelvis for all participants. CT scans of the neck and/or extremities and brain MRIs should be repeated throughout the study if there is evidence of disease at screening or if clinically indicated. All scans should be performed in accordance with RECIST 1.1 and with contrast. If contrast is

contraindicated (i.e., in participants with known contrast dye allergy or impaired renal clearance), a chest CT without contrast and an abdomen/pelvis MRI without contrast may be performed.

If a CT scan for a tumor assessment is performed in a positron emission tomography/CT scanner, the CT acquisition must be consistent with the standards for a full contrast diagnostic CT scan.

Images will be collected and centrally stored to allow for retrospective review, if indicated.

All measurable and evaluable lesions should be reassessed at each subsequent tumor evaluation. The same radiographic procedures used to assess disease sites at screening should be used for subsequent tumor assessments (e.g., same modality and contrast protocol).

Response will be assessed by the Investigator using RECIST 1.1 (primary; see operations manual) and iRECIST (secondary; see operations manual). Assessments should be performed by the same evaluator, if possible, to ensure internal consistency across visits. Results must be reviewed by the investigator before dosing at the next cycle.

7.3.2 µMETA COHORTS

Post-SOC imaging or testing, investigators should denote disease-free status within the electronic health record (EHR). The physician note should also be entered into the EDC.

Please review the study's operations manual for specific instructions.

8 SAFETY ASSESSMENTS AND PROCEDURES

8.1 SAFETY AND OTHER ASSESSMENTS

Study procedures and evaluations to monitor safety and support the understanding of the study intervention's safety, or that are done for other purposes (e.g., screening, eligibility, enrollment), are listed below. Most assessments should be completed as per standard of care monitoring and data will be extracted from the electronic health records and entered in the EDC.

<u>Study-Specific Procedure</u>

- Assessment of adverse events

<u>Standard of Care Evaluation – Data prescribed in CRF and extracted from electronic health records.</u>

- Demographics and disease/medical characteristics including:
  - Participant demographics
  - Disease history (date of first diagnosis, treatment history)
  - Biomarker status (biomarker test results)
  - Medical history including documentation of prior and ongoing medical illnesses and conditions, and surgical procedures (those not related to primary diagnosis), previous diseases and concomitant diseases within the last 30 days before screening
  - Previous and concomitant medication
- Complete or abbreviated physical examination including a review of all body systems. Information to be recorded may include height, weight, organ systems, motor or vision assessment.
- Performance Status (ECOG).
- Vital signs should be assessed including blood pressure, heart rate, body temperature, and respiration rate.
- Standard local laboratory assessments, such as hematology, serum chemistry (albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, AST, ALT, and sodium).
- Urine pregnancy test for females of child-bearing potential.
- Electrocardiograms and Echocardiograms as indicated for the participant per standard of care guidelines.

Please review the study's operations manual for specific instructions.

8.2 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.2.1 DEFINITION OF ADVERSE EVENTS (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

8.2.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An AE or suspected adverse drug reaction is considered serious if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death,
- Life-threatening adverse event,
- Inpatient hospitalization or prolongation of existing hospitalization,
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or

- Congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

8.2.3 CLASSIFICATION OF AN ADVERSE EVENT

8.2.3.1 SEVERITY OF EVENT

All AEs will be assessed by the study investigator using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

8.2.3.2 RELATIONSHIP TO STUDY INTERVENTION

All AEs must have their relationship to study intervention assessed by the investigator who examines and evaluates the participant based on temporal relationship and their clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- **Possibly Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related"

soon after discovery, it can be flagged as requiring more information and later be upgraded to “probably related” or “definitely related”, as appropriate.

- **Unlikely to be Related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant’s clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the study investigator.

8.2.3.3 EXPECTEDNESS

The study physician will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information described in the package insert for each interventional product.

8.2.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs, including local and systemic reactions not meeting the criteria for SAEs, will be captured on the appropriate CRF. Information to be collected includes event description, time of onset, investigator’s assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. Regardless of relationship, all AEs occurring while on study must be documented and followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant’s condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

Study site will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.2.5 ADVERSE EVENT REPORTING

The investigator is responsible for reporting the information to the study sponsor and local regulatory authorities, as required.

8.2.6 SERIOUS ADVERSE EVENT REPORTING

The investigator will immediately report any SAE to the sponsor, whether or not it is considered study intervention related, including those listed in the protocol or package insert. The report must include an assessment of whether there is a reasonable possibility that the study intervention caused the event. Study endpoints that are SAEs (e.g., all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the study intervention and the event (e.g., death from anaphylaxis). In that case, the investigator must immediately report the event to the sponsor.

All SAEs will be followed until satisfactory resolution or until the investigator deems the event to be chronic or the participant is stable. Other supporting documentation of the event may be requested by the study sponsor and should be provided as soon as possible.

8.2.7 REPORTING EVENTS TO PARTICIPANTS

Section not applicable

8.2.8 EVENTS OF SPECIAL INTEREST

All deaths that occur during the study must be reported as follows:

- Death that is clearly the result of disease progression should be documented but not reported as an SAE.
- Where death is not due (or not clearly due) to progression of the disease under study, the AE causing the death must be reported as an SAE within 24 hours of knowledge of the event.
- Deaths with an unknown cause should always be reported as an SAE.

8.2.9 REPORTING OF PREGNANCY

Female participants with the ability to get pregnant will be required to be on a double barrier birth control method for the duration of the trial in all cohorts. Male participants with female partners of child-bearing potential should be advised on birth control approach based on the study drug cohort.

Participants who become pregnant during the study period should not receive any additional doses but will not be discontinued from the study to allow for tracking of event outcome. Participants will be asked the date of their last menstrual period in lieu of a pregnancy test at each visit. Pregnancy in a participant who has received study intervention is required to be reported within 24 hours of knowledge of the event to the sponsor.

8.2.10 REPORTING REQUIREMENTS

This study is investigational new drug (IND) exempt. The following criteria must be met in order for a clinical investigation to be considered IND-exempt:

(i) The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication for use nor intended to be used to support any other significant change in the labeling for the drug;

(ii) If the drug that is undergoing investigation is lawfully marketed as a prescription drug product, the investigation is not intended to support a significant change in the advertising for the product;

(iii) The investigation does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;

(iv) The investigation is conducted in compliance with the requirements for institutional review set forth in part 56 and with the requirements for informed consent set forth in part 50; and

(v) The investigation is conducted in compliance with the requirements of § 312.7.

StrataPATH meets the above criteria. This trial will be conducted in compliance with the requirements for review by an IRB (21 CFR part 56) and with the requirements for informed consent (21 CFR part 50).

8.3 UNANTICIPATED PROBLEMS

8.3.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems (UPs) involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** the following criteria:

- **Unexpected** in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied, **and**
- **Related or possibly related** to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research), **and**
- Suggests that the research places participants or others at a **greater risk of harm** (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.3.2 UNANTICIPATED PROBLEM REPORTING

The investigator will report unanticipated problems to the reviewing IRB and to the study sponsor. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number.
- A detailed description of the event, incident, experience, or outcome.
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP.
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are adverse drug reactions (ADRs) will be reported to the to the study sponsor within 24 hours of the investigator becoming aware of the event. The event must be ultimately reported to the IRB within 1 week from the time of identification of the event.
- Any other UP will be reported to the study sponsor within 5 business days of the investigator becoming aware of the problem. The event must be ultimately reported to the IRB within 2 weeks from the time of identification of the event.

9 STATISTICAL CONSIDERATIONS

9.1 SAMPLE SIZE DETERMINATION

The study design is similar to a basket trial with each basket molecularly defined. For both cohorts (tdMeta and μMeta), sample size calculations were completed under the following assumptions:

- Each cohort will enroll unique participants. Although participants may qualify for enrollment in more than one cohort, they will be enrolled in only one biomarker cohort (Refer to Section 10.2 for definitions).
- Each molecularly defined cohort will be evaluated independently.
- tdMeta and μMeta cohorts will be evaluated independently.

Sample size was determined using a two-stage design based on minimizing the risk of a false negative result. The binomial probability of observing an exact number of responses was used similar to that in a Simon's two-stage design.[19,20] The null hypothesis that the true response rate is 0.05 will be tested against a one-sided alternative. In the first stage, 12 patients will be accrued per cohort. If there are 1 or fewer responses in these 12 patients, the study will be stopped for that cohort. Response will be defined as partial response or complete response for tdMeta cohorts and <50% ctDNA mean VAF ratio for μMeta cohorts. Otherwise, 23 additional patients will be accrued for a total of 35. The null hypothesis will be rejected if 6 or more responses are observed in 35 patients. This design yields a type I error rate of 0.001 and a power of 88% when the true response rate is 0.30.

9.2 POPULATIONS FOR ANALYSES

The population for this study is defined separately by molecular cohort and disease severity (tdMeta and μMeta). The study includes participants diagnosed with both ctDNA positive recurrence, and those who are traditionally defined metastatic, relapsed, refractory, or advanced stage III or IV solid tumors that meet the entry criteria for one of the biomarker cohorts. In addition, subgroup analyses may be conducted to assess antitumor activity in cohorts of participants defined by the multiple molecular markers.

The analysis populations are defined in **Table E** according to cohort and disease severity.

Table E: Populations for Analyses

Population	Description
As-treated Population	All participants who receive at least 1 dose of assigned therapy
Intent-to-treat (ITT) Population	All participants who provide written informed consent and are assigned therapy
Modified ITT (mITT) Population	All participants belonging to the ITT Population who receive at least 1 dose of assigned therapy and 1 post-baseline scan

9.3 STATISTICAL ANALYSES

9.3.1 GENERAL APPROACH

This study will use an adaptive approach, with on-treatment data guiding trial adaptation and success or futility of each cohort. All statistical analyses will be pre-specified and finalized for each cohort prior to database lock. The statistical analysis plan (SAP) will describe the study populations to be included in the analyses and the procedures for accounting for missing, unused, and spurious data. High-level methods are described here.

9.3.2 EFFICACY ANALYSES

Efficacy analyses for ORR and DoR are based on the responses from Investigator-recorded measurements and assessments for target, nontarget, and new lesions according to RECIST 1.1.[21]

- ORR is defined as the percentage of participants with a best overall response of complete response (CR) or partial response (PR).
- DoR is defined as the time from first documentation of disease response (CR or PR) until first documentation of progressive disease.

Efficacy analyses for ctDNA response rate will be based on the proportion of participants considered responders compared to non-responder participants. Responders are defined as any participant with <50% ratio of mean VAF.

ORR and ctDNA response rate will be estimated by the proportion of participants with objective response and ctDNA response respectively and their 95% confidence intervals will be estimated using the exact binomial method. Other time-to-event efficacy analyses including TTD, TTNT, DFS and OS will be summarized using the Kaplan-Meier method with the appropriate time-defined cut-offs.

Additional supportive analyses of efficacy endpoints may be conducted using iRECIST.[22]

9.3.3 SAFETY ANALYSES

The safety analysis will be based on the as-treated population. The incidence of ADR/ADEs and changes in baseline in vital signs, clinical laboratory parameters, physical examination findings, ECOG performance status, will be analyzed as data are available.

9.3.4 BIOMARKER ANALYSES

If relevant data are available, relationships between biomarkers, biomarker changes and clinical outcomes may be explored.

9.3.5 BASELINE DESCRIPTIVE STATISTICS

Descriptive statistics will be used to summarize the analysis dataset based on all available clinical and biomarker data. For available quantitative measures such as age or biomarker expression values, the mean, median, standard deviation, minimum and maximum will be tabulated.

For the quantitative measures, histograms and/or side-by-side boxplots will be presented and used to evaluate the underlying form of the distribution as well as the presence of any extreme values. It is important to ensure that the analysis is robust to identify a small number of outlying, extreme values or skewed data distributions. For expression data, log transformations are commonly used to create more symmetric data out of distributions that are skewed right. Presentation of histograms before and after transformations are useful to gauge the appropriateness of the transformation.

9.3.6 PLANNED INTERIM ANALYSES

For each cohort, 12 participants will be enrolled initially. If there is one response or no responses in these 12 participants as defined by CR or PR (for tdMeta) and ctDNA response (for μMeta), the study will be stopped in that cohort. A minimum rwRR/ctDNA response of 10% and risk-benefit profile that the sponsor deems promising will be required before an additional 23 participants will be accrued for a total of 35 participants.

9.3.7 LIMITATIONS OF ANALYSES

The enrolled participants will be assigned to study cohorts based on molecular group status with hypothesized anti-tumor benefit. Consequently, any exploratory analyses for additional biomarker associations will be based on a potentially biased subset of the overall population. Statistical methodology will consider this potential bias.

10 QUALITY ASSURANCE AND QUALITY CONTROL

10.1.1 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure that the rights and well-being of participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the

conduct of the trial is in compliance with the currently approved protocol/amendment(s), with ICH/GCP, and with applicable regulatory requirement(s).

- Monitoring for this study will be performed by the study sponsor or designee.
- A combination of on-site and remote monitoring will be used for this study. Targeted/risk-based monitoring will be used to assess safety and key variables and verify endpoints.
- Details of clinical site monitoring are documented in a Clinical Monitoring Plan (CMP). The CMP describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports.
- Independent audits may be conducted by Strata Oncology to ensure monitoring practices are performed consistently across all participating sites and that monitors are following the CMP.

10.1.2 QUALITY ASSURANCE AND QUALITY CONTROL

Each clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation, and completion. The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities. Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted, data are generated, and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, ICH/GCP, and applicable regulatory requirements.

11 ETHICS/PROTECTION OF HUMAN PARTICIPANTS

11.1 INFORMED CONSENT PROCESS

Prior to the beginning of the trial, the investigator will ensure the IRB's written approval for the protocol and written ICF(s) as well as any other written information to be provided to the participants. The investigator must comply with applicable regulatory requirements (e.g., 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56) and must adhere to ICH GCP.

The investigator is responsible for obtaining written informed consent from each participant enrolled in the trial. The investigator or designee must explain the study objectives, methods, and potential benefits and potential risks of study participation. Participants will also be informed

by the investigator or designee that they may withdraw from the study at any time for any reason. Original, signed consent forms will be maintained at the site and will be made available for inspection, as needed.

11.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

The ICF describes in detail the study intervention, study procedures, risks, and benefits to study participation as well as a statement informing the participant of their right to withdraw from the study at any time for any reason. Written informed consent is required prior to starting intervention/administering study intervention.

11.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to an individual agreeing to participate in the study and continues throughout study participation. Consent forms will be IRB approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. A translated version of the ICF will be provided in the participant's primary language, as applicable. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the ICF prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of ICF will be given to the participants for their records.

The informed consent process will be conducted and documented in the source document (including the date of consent), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

11.2 STUDY DISCONTINUATION AND CLOSURE

The study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to all study participants, investigators, funding agency, sponsor, and regulatory authorities, as applicable. If the study is prematurely terminated or suspended, the PI will promptly inform study participants, the IRB,

and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

The study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and/or FDA and/or applicable regulatory bodies.

11.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly maintained by the investigator, their staff, the sponsor and affiliated institutions involved in the conduct of the trial. These entities are responsible for ensuring participant identity is protected from unauthorized parties. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. The participants will be informed that representatives of the sponsor, IRB/independent ethics committee (IEC), or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in accordance with local data protection laws. The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study, or the data will be released to any unauthorized third party without prior written approval of the sponsor. All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the IRB, regulatory agencies or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant’s contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored with the study sponsor or designee. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique participant identification number. The study data entry and study management systems used by clinical sites and by study sponsor research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived by the study sponsor or designee.

11.4 FUTURE USE OF STORED SPECIMENS AND DATA

Data collected for this study will be analyzed and stored at study sponsor or designee. After the study is completed, the de-identified, archived data will be stored at study sponsor or designee for potential use by other researchers including those outside of the study. De-identified data may be shared with third parties (including companies with which the sponsor has partnered for this study) or used by Strata Oncology for non-research purposes.

With the participant's consent and as approved by local IRBs, de-identified biological samples will be stored at the study sponsor's designated location. These samples could be used for other research, such as into the causes of cancer, its complications and other conditions for which individuals with cancer are at increased risk, and to improve treatment, including new test development. Study sponsor will have a code-link that will allow linking the biological specimens with the phenotypic data from each participant, maintaining the blinding of the identity of the participant.

During the conduct of the study, a participant can choose to withdraw consent to have biological specimens stored for future research. However, after the study is completed, a participant may not be able to withdraw consent to have their samples stored.

When the study is completed, access to study data and/or samples will be provided through the study sponsor.

11.5 KEY ROLES AND STUDY GOVERNANCE

Please refer to the operations manual for the list of study team roles and responsibilities of those involved in the conduct, management, or oversight of the trial.

11.6 SAFETY OVERSIGHT

Participant safety will be monitored by a Data and Safety Monitoring Board (DSMB) for this study. The DSMB is independent from the study sponsor and the DSMB's membership includes clinical oncology experts, a biostatistician, and investigators with expertise in clinical trial conduct and methodology. The DSMB will receive accrual reports every 3 months and meet every 6 months to review study participant demographic representation, baseline characteristics, protocol compliance, study safety, and any updates to the study protocol. The DSMB will also meet ad hoc as needed.

12 DATA HANDLING AND RECORD KEEPING

12.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the investigator. The investigator is responsible for ensuring the accuracy, completeness, attributability, legibility, originality and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Clinical data (including AE/SAEs, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered in a 21 CFR Part 11-compliant data capture system provided by the study sponsor. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

12.2 STUDY RECORDS RETENTION

Study documents should be retained until at least 2 years have elapsed since the formal discontinuation of clinical development of the study intervention. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

12.3 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, ICH/GCP, or operations manual requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the investigator to use continuous vigilance to identify and report deviations. All deviations must be addressed in study source documents and reported to Strata Oncology monitor and/or Site Management Associate. Protocol deviations must be sent to the reviewing IRB per their policies. The investigator/sponsor is responsible for knowing and adhering to the reviewing IRB requirements.

12.4 PUBLICATION AND DATA SHARING POLICY

This trial is registered at ClinicalTrials.gov (NCT05097599), and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals.

13 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such situations managed in a way that is appropriate to their participation in the design and conduct of this trial.

14 REFERENCES

1. American Cancer Society (2020). Cancer Statistics Center. *https://cancerstatisticscenter.cancer.org/#/*.

2. Miller, K.D., Nogueira, L., Mariotto, A.B., Rowland, J.H., Yabroff, K.R., Alfano, C.M., Jemal, A., Kramer, J.L., and Siegel, R.L. (2019). Cancer treatment and survivorship statistics, 2019. CA Cancer J Clin *69*, 363-385. 10.3322/caac.21565.

3. US Food and Drug Administration (2017). FDA grants accelerated approval to pembrolizumab for first tissue/site agnostic indication.

4. Le, D.T., Durham, J.N., Smith, K.N., Wang, H., Bartlett, B.R., Aulakh, L.K., Lu, S., Kemberling, H., Wilt, C., Luber, B.S., et al. (2017). Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. Science *357*, 409-413. 10.1126/science.aan6733.

5. US Food and Drug Administration (2018). FDA approves larotrectinib for solid tumors with NTRK gene fusions.

6. Wu, Y.L., Tsuboi, M., He, J., John, T., Grohe, C., Majem, M., Goldman, J.W., Laktionov, K., Kim, S.W., Kato, T., et al. (2020). Osimertinib in Resected EGFR-Mutated Non-Small-Cell Lung Cancer. N Engl J Med *383*, 1711-1723. 10.1056/NEJMoa2027071.

7. Ramalingam, S.S., Yang, J.C., Lee, C.K., Kurata, T., Kim, D.W., John, T., Nogami, N., Ohe, Y., Mann, H., Rukazenkov, Y., et al. (2018). Osimertinib As First-Line Treatment of EGFR Mutation-Positive Advanced Non-Small-Cell Lung Cancer. J Clin Oncol *36*, 841-849. 10.1200/JCO.2017.74.7576.

8. Garon, E.B., Rizvi, N.A., Hui, R., Leighl, N., Balmanoukian, A.S., Eder, J.P., Patnaik, A., Aggarwal, C., Gubens, M., Horn, L., et al. (2015). Pembrolizumab for the treatment of non-small-cell lung cancer. N Engl J Med *372*, 2018-2028. 10.1056/NEJMoa1501824.

9. Eggermont, A.M.M., Blank, C.U., Mandala, M., Long, G.V., Atkinson, V., Dalle, S., Haydon, A., Lichinitser, M., Khattak, A., Carlino, M.S., et al. (2018). Adjuvant Pembrolizumab versus Placebo in Resected Stage III Melanoma. N Engl J Med *378*, 1789-1801. 10.1056/NEJMoa1802357.

10. MSD (2021). *Merck's KEYTRUDA® (pembrolizumab) Demonstrated Superior Disease-Free Survival (DFS) Compared With Placebo as Adjuvant Therapy in Patients With Renal Cell Carcinoma (RCC) Following Surgery*. Press Release.

11. US Food and Drug Administration (2018). Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics Guidance for Industry.

12. Temple, R. (1995). A regualtory authority's opinion about surrogate endpoints. In Clinical Measurement in Drug Evaluation, W.T. Nimmo, ed. (J.Wiley).

13. Khozin, S., Miksad, R.A., Adami, J., Boyd, M., Brown, N.R., Gossai, A., Kaganman, I., Kuk, D., Rockland, J.M., Pazdur, R., et al. (2019). Real-world progression, treatment, and survival outcomes during rapid adoption of immunotherapy for advanced non-small cell lung cancer. Cancer. 10.1002/cncr.32383.

14. Blumenthal, G.M., Gong, Y., Kehl, K., Mishra-Kalyani, P., Goldberg, K.B., Khozin, S., Kluetz, P.G., Oxnard, G.R., and Pazdur, R. (2019). Analysis of time-to-treatment discontinuation of targeted therapy, immunotherapy, and chemotherapy in clinical trials of patients with non-small-cell lung cancer. Ann Oncol *30*, 830-838. 10.1093/annonc/mdz060.

15. Prentice, R.L. (1989). Surrogate endpoints in clinical trials: definition and operational criteria. Stat Med *8*, 431-440. 10.1002/sim.4780080407.

16. Fleming, T.R., and Powers, J.H. (2012). Biomarkers and surrogate endpoints in clinical trials. Stat Med *31*, 2973-2984. 10.1002/sim.5403.

17. Thompson, J.C., Carpenter, E.L., Silva, B.A., Rosenstein, J., Chien, A.L., Quinn, K., Espenschied, C.R., Mak, A., Kiedrowski, L.A., Lefterova, M., et al. (2021). Serial

Monitoring of Circulating Tumor DNA by Next-Generation Gene Sequencing as a Biomarker of Response and Survival in Patients With Advanced NSCLC Receiving Pembrolizumab-Based Therapy. JCO Precision Oncology, 510-524. 10.1200/po.20.00321.

18. Zhang, Q., Luo, J., Wu, S., Si, H., Gao, C., Xu, W., Abdullah, S.E., Higgs, B.W., Dennis, P.A., van der Heijden, M.S., et al. (2020). Prognostic and Predictive Impact of Circulating Tumor DNA in Patients with Advanced Cancers Treated with Immune Checkpoint Blockade. Cancer Discov *10*, 1842-1853. 10.1158/2159-8290.CD-20-0047.

19. Jung, S.H., Lee, T., Kim, K., and George, S.L. (2004). Admissible two-stage designs for phase II cancer clinical trials. Stat Med *23*, 561-569. 10.1002/sim.1600.

20. Simon, R. (1989). Optimal two-stage designs for phase II clinical trials. Control Clin Trials *10*, 1-10. 10.1016/0197-2456(89)90015-9.

21. Eisenhauer, E.A., Therasse, P., Bogaerts, J., Schwartz, L.H., Sargent, D., Ford, R., Dancey, J., Arbuck, S., Gwyther, S., Mooney, M., et al. (2009). New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer *45*, 228-247. 10.1016/j.ejca.2008.10.026.

22. Seymour, L., Bogaerts, J., Perrone, A., Ford, R., Schwartz, L.H., Mandrekar, S., Lin, N.U., Litiere, S., Dancey, J., Chen, A., et al. (2017). iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. Lancet Oncol *18*, e143-e152. 10.1016/S1470-2045(17)30074-8.

COHORT APPENDICES

See attached.

STR-004-001-PR (DOC-1513) Ver. 4

Approved By:

(CO-812) STRATA CHANGE ORDER

Description

Change Order 18-MAY-2023

Justification

Updating document description in Greenlight Guru to remove the number for the amendment.

Assigned To:	Initiated By:	Priority:	Impact:
Barb Holt	Barb Holt	Low	Minor

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Kat Corbitt	May 18, 2023 10:18 AM EDT	CO-782	3	Superseded
Ida Cao	August 20, 2021 12:35 PM EDT	CO-440	2	Superseded
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