Official Study Title:	**S**erial **M**easurements of **M**olecular and **A**rchitectural **R**esponses to **T**herapy (SMMART): **A**daptive **C**linical **T**reatment (ACT)
Protocol Short Title	SMMART-ACT
Protocol Number:	STUDY00026643
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Principal Investigator:	**Charles Lopez, MD, PhD** Division of Hematology & Oncology Oregon Health & Science University 3181 SW Sam Jackson Park Road Portland, OR 97239 Email: lopezc@ohsu.edu
Statistician:	**Byung S. Park, PhD** Knight Cancer Institute, Biostatistics Shared Resource Oregon Health & Science University 3181 SW Sam Jackson Park Road, KR-BSR Portland, Oregon 97239-3098 Telephone: 503-494-7062 Fax: 503-418-0125 Email: parkb@ohsu.edu
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SYNOPSIS

Study Title	Serial Measurements of Molecular and Architectural Responses to Therapy (SMMART): Adaptive Clinical Treatment (ACT)
Protocol Short Title:	SMMART-ACT
Protocol #	STUDY00026643
Coordinating Center	OHSU Knight Cancer Institute
Clinical Phase	Feasibility Phase II
Investigational Components	Refer to Drug Manufacturer-Specific Appendices (**Appendix A**). Drug Manufacturer-Specific Appendices will also be referred to as "drug-specific appendices(s)" throughout this document.
Study Description	The SMMART-Adaptive Clinical Treatment (ACT) trial is a study to assess the feasibility of a precision medicine approach for the treatment of patients with select advanced solid malignancies. To be considered enrolled in this trial, participants with breast, ovarian, prostate, or pancreatic malignancies, or sarcomas, will receive a treatment recommendation from the SMMART-ACT Tumor Board. Treatment recommendations will be based on case review and results of a suite of advanced multiplexed clinical assays comprising the SMMART Clinical Analytics Platform (SMMART-CAP) performed on a biopsy collected within 6 months of signing the ACT Tumor Board Informed Consent Form (ICF). ACT Tumor Board recommendations may or may not be an ACT Therapy regimen described in this protocol (Appendix A). If the participant is recommended an ACT Therapy regimen, they may continue and be approached for consent to ACT Therapy ICF and begin ACT Therapy screening. If the participant receives C1D1 of an ACT Treatment regimen, they will be considered on-therapy. If the ACT Tumor Board recommendation is not an ACT Therapy option listed in Appendix A, the participant will be moved to off-study. The SMMART-ACT Therapy regimens described in this protocol consist of one or more targeted drug agents, as part of mono- or combination regimens, which have established recommended phase 2 dose (RP2D) levels based on known maximum tolerated dose (MTD), maximum administered dose (MAD), or optimal biological dose (OBD). The assigned regimen will be administered to a participant for up to approximately 6 months, or until disease progression, unacceptable

	toxicity, or withdrawal of consent for participation. Participants can re-enter the study in the event of progressive disease or unacceptable toxicity. Upon reenrollment, another regimen will be selected in accordance with SMMART-ACT Tumor Board recommendations and up-to-date SMMART-CAP assay results from a recent biopsy (within 6 months). To provide an unprecedented look at the impact of a personalized, targeted therapy on the tumor and surrounding microenvironment, blood and tumor samples will be collected during therapy (On-Therapy Biopsy), and possibly at end-of-therapy (End-of-Therapy Biopsy), and characterized with SMMART exploratory research analytics (SMMART-ERA). This multi-omics-based platform is comprised of several multiplex platforms selected to characterize each participant's disease in terms of DNA mutations, RNA and protein expression, physical and molecular architecture of the cancer tissue, functions of relevant resident cells by sub-type, and the state of the tumor microenvironment. The SMMART-ACT Protocol (ACT) will serve as the guiding study document for this trial and provides the overall study design, general participant eligibility criteria, study-specific treatment plans and evaluations, and logistical and supporting documentation. Interventional ACT Therapies, including study drugs and combination therapy, are described in the accompanying drug-specific appendices (**Appendix A**). The drug-specific appendices contain drug-specific eligibility criteria, assessments, dosing and dose modification guidelines, management of treatment-related toxicities, expected adverse events for each investigational agent, and respective reporting requirements.
Primary Objective	Feasibility of the personalized SMMART-ACT strategy for five cancer types in advanced stages.
Secondary Objectives	1. Safety and tolerability; 2. Early indications of efficacy based on disease-specific response; 3. Estimated early indications of survival benefit.
Exploratory Objectives	1. Durability of response compared to the most recent therapy on which progression occurred; 2. Changes in ability to conduct activities of daily living (ADL); 3. Changes in quality of life (QoL); 4. Feasibility of SMMART 'centric' assessments of ongoing responses to treatment.

Primary Endpoint	Proportion of participants who receive an ACT Therapy (C1D1) based on a SMMART-ACT Tumor Board recommendation.
Secondary Endpoints	1. Incidence of treatment-emergent adverse events (TEAE) that are suspected or confirmed as attributable to study drug or procedure; 2. Rate of discontinuation from treatment due to intolerability and/or toxicities; 3. Objective Response Rate (ORR = CR +PR) per RECIST 1.1 at 24 weeks from C1D1 (+/- 2 weeks) by cancer type; 4. Progression-free survival (PFS), disease-specific survival (DSS), and overall survival (OS).
Exploratory Endpoints	1. Proportion of participants with a time-to-progression (TTP) ratio ≥1.3; 2. Time to decline (TTD) to ECOG performance status ≥3; 3. QoL assessments according to EORTC QLQ-C30, QLQ FA12, and QLQ INFO25 surveys; 4. Proportion of participants who have an On-Therapy Biopsy with sufficient tumor content for CLIA assays and RUO assays per cancer type and biopsy site; 5. Proportion of CLIA assay results obtained ≤14 business days of biopsy; and 6. Proportion of biopsies with RUO assay results that provide added biological understanding of treatment, per investigator discretion.
Key Inclusion Criteria	**The following key inclusion criteria must be met for <u>ACT Tumor Board eligibility</u>:** 1. Written informed consent prior to any screening activities, study-specific procedures, or interventions required for the ACT Tumor Board. 2. At least 18 years of age at time of informed consent. Persons of all gender identities, biological sexes, races, and ethnicities will be included. 3. A diagnosis of advanced sarcoma or advanced prostate, breast, ovarian or pancreatic cancer. 4. Biospecimen collection (Pre-Therapy Biopsy), as per institutional standards, must be consented to and collection must be feasible. a. Individuals with a prior tumor tissue sample (archival tissue) with successful SMMART-CAP assays, collected up to 6 months prior to signing the ACT Tumor Board ICF may be

	eligible, so long as ≤1 treatment has been received since the tissue collection. 5. ECOG performance status of ≤2. 6. Physician-assessed life expectancy of ≥ 6 months. **The following additional key inclusion criteria must be met for <u>ACT Therapy eligibility</u>:** 1. Documented progression after at least one line of prior therapy for advanced disease. Treating provider will confirm there are no standard of care treatments that will likely result in positive clinical benefit. If recurrence occurred within six months of the last dose of an adjuvant/neoadjuvant therapy, that adjuvant/neoadjuvant therapy will count as one line of therapy. 2. SMMART-ACT Tumor Board recommendation of at least one ACT Therapy regimen (Appendix A), based on the Tumor Board's review of SMMART-CAP results on the Pre-Therapy Biopsy. 3. Additional organ function and laboratory values must be met, as described in Section 4.2.1. 4. Additional drug-specific eligibility requirements must be met, per the specific ACT Therapy recommendation. 5. Additional cancer-specific eligibility criteria must also be met, as described in Section 4.3 *See **Section 4** for more details.*
Key Exclusion Criteria	**An individual who meets one or more of the following key exclusion points is not eligible for the <u>ACT Tumor Board</u>:** 1. Evidence of active malignancy of another cancer that may affect safety or efficacy of this study or impose unacceptable risk to the patient. 2. Absence of a biopsiable lesion, and unavailable/insufficient archival tissue. **An individual who meets one or more of the following key exclusion criteria is not eligible to receive <u>ACT Therapy</u>:** 1. Brain/CNS metastasis progressive within ≤ 4 weeks of CNS directed treatment, as evidenced by clinical and brain imaging assessments. 2. Other, concurrent anti-cancer therapy. 3. More than one intervening therapy for treatment of their cancer since the Pre-Therapy Biopsy.

	Note: Participants who have a Pre-Therapy Biopsy while receiving a standard of care (SOC) treatment will be ineligible if they receive any additional lines of treatment prior to the start of an ACT Therapy. 4. Untreated and/or uncured HCV infection, as evidenced by detectable HBC RNA by PCR. 5. Uncontrolled intercurrent illness and/or infection including, but not limited to: a. Symptomatic congestive heart failure (New York Heart Association [NYHA] class III or IV), b. Unstable angina pectoris or coronary angioplasty, or stenting within 6 months prior to enrollment, c. Cardiac arrhythmia (ongoing cardiac dysrhythmias of grade ≥2 [per NCI CTCAE v5.0]), d. Intra-cardiac defibrillators, e. Known cardiac metastases, f. History of abnormal cardiac valve morphology (≥grade 2), g. Chronic graft versus host disease (GVHD) or on systemic immunosuppressive therapy for the control of GVHD, h. Severe infection within ≤ 4 weeks prior to initiation of study therapy, including, but not limited to, hospitalization for complications of infection, bacteremia, or severe pneumonia. 5. Severe infection within 4 weeks of initiating study therapy. 6. Inability to take oral medication (if assigned ACT oral therapy) 7. Pregnant or plans to continue ongoing breastfeeding. 6. Any condition that, in the opinion of the investigator, could jeopardize the participant's safety or adherence to the study protocol. 7. Autoimmune disease or immune deficiency per **Section 4.2.2.1**. 8. Additional drug-specific exclusion criteria per **Appendix A**. *See **Section 4** for more details.*
Number of Participants	Total of 30 patients having diagnoses within the following cancer types: breast, ovarian, prostate, pancreatic, or sarcoma who receive an ACT Tumor Board recommendation. Accrual will occur over a 36-month period.
Duration of ACT Therapy	ACT Therapy may continue until disease progression, unacceptable toxicity, or withdrawal from study, up to a maximum of approximately 6 months.

Duration of Follow Up	Up to 5 years from a participant's last dose of the assigned ACT Therapy.
Statistical Analyses	The feasibility of the SMMART-ACT strategic approach will be assessed by the proportion of participants that receive an ACT Therapy regimen (i.e., C1D1) based on a SMMART-ACT Tumor Board therapy recommendation. The target threshold for feasibility is 75%. Bayesian Futility Monitoring Via Posterior Probability will be employed to monitor feasibility using the feasibility population set. Posterior toxicity probabilities are calculated to monitor the trial conduct. This feasibility study will enroll 30 participants. Historical experience in this setting suggests that ~20% of ACT Tumor Board reviews do not recommend an ACT therapy. To account for this, conservatively 38 individuals may be consented to achieve 30 patients who go on to receive an ACT Therapy recommendation in this study. With a sample size of 30, the 95% confidence interval width is 0.2742 using The Exact (Clopper-Pearson) formula when ORR assumes to be 0.14. An interim analysis of feasibility monitoring will be conducted after 15 participants receive a SMMART-ACT Tumor Board treatment recommendation. If > 9 of the first 15 SMMART-ACT Tumor Board recommendations result in participants receiving an ACT Therapy (i.e., if > 9 participants of the first 15 tumor board recommendations receive study therapy on C1D1 enrollment will continue until up to 30 total participants receive an ACT Therapy recommendation to assess feasibility. If at least 23 participants out of 30 receive C1D1 of an ACT Therapy based on the recommendation of a SMMART-ACT Tumor Board, the trial will be declared as feasible and efficacy will be evaluated. Secondary endpoints will summarize safety and tolerability and therapeutic intent as disease-specific ORR at 24 weeks from C1D1 (+/- 2 weeks) and estimates of survival benefit. Exploratory endpoints will estimate the quality of therapeutic benefit (TTP ratio, TTD, QoL), the feasibility of biopsy as the basis for time-sensitive clinical planning, and the informative value (e.g., mechanisms of response and resistance) of RUO assay results. The analyses of the exploratory endpoints will largely be descriptive. Categorical analyses will be applied to demographics.

SCHEMATIC OF STUDY DESIGN

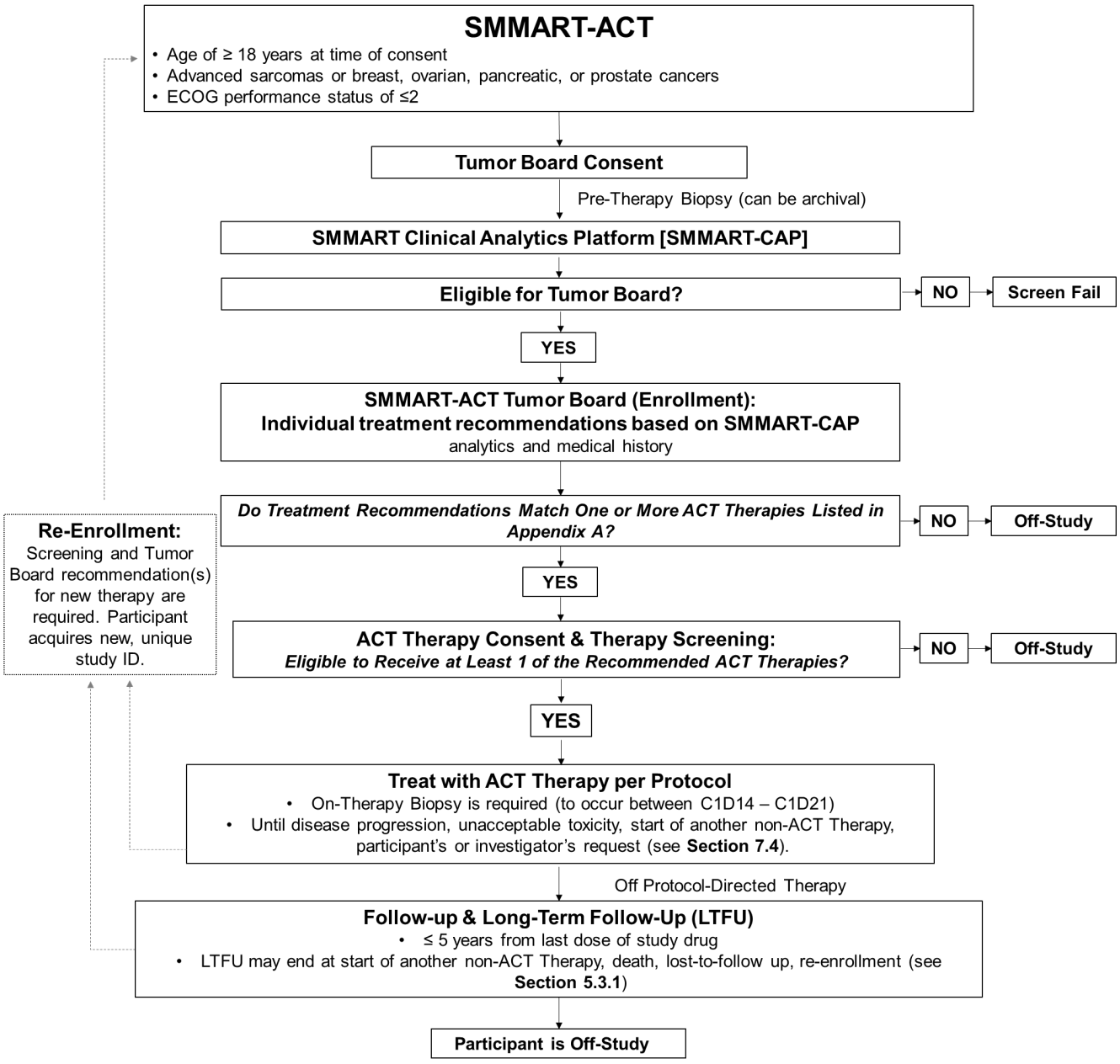

TABLE OF CONTENTS

SUMMARY OF CHANGES

Version #	Section	Summary of Changes	Justification
2.0	N/A	Minor formatting changes throughout protocol.	Visual consistency.
2.0	N/A	Changed "eCRIS" to "OnCore" throughout protocol.	This study will use OnCore.
2.0	N/A	Removed references to "investigator's brochure"	This study is utilizing package inserts as the source for all drug info.
2.0	5.3.1	Deleted "total withdrawal" option.	Total withdrawal was not intended to be included. Removal aligns the protocol with the intent of the study, and current consent form language.
2.0	5.3.2	Added text to state that previously accessed archival samples may continue to be accessed.	It is important to exploratory objectives to be able to continue performing tests on samples that were previously accessed. Some planned exploratory tests may not be able to be completed during the timeframe when a participant is On-Study.
2.0	5.4	Added text to state that previously accessed archival samples may continue to be accessed.	It is important to exploratory objectives to be able to continue performing tests on samples that were previously accessed. Some planned exploratory tests may not be able to be completed during the timeframe when a participant is On-Study.
2.0	5.5	Moved STUDY DISCONTINUATION AND CLOSURE subsection to the end of Section 5.	This subsection was previously above LOST TO FOLLOW-UP. It makes more sense for the flow of the protocol to move it to the end of the section.
2.0	8.1.3	Clarified that PET is only used when CT/MRI is not adequate.	Imaging should be done via CT/MRI, but some cancers cannot be adequately imaged with these modalities – PET is an option in these cases.
2.0	8.1.3.1	Revised language of bone scan timing to align with what is shown in the SOEs (e.g., every 12 weeks after start of treatment).	This timing aligns with what was recommended by the prostate team.
2.0	8.5.1	Changed timing of bone scan from Pre-Screening to Screening.	Change requested by prostate group.

2.0	10.1	Clarification of AEs that will be followed after EOT.	Limiting follow-up to only AEs that meet study collection criteria.
2.0	10.2.1	Updated AE definition to reflect current definition. Included AEs that may be related to clinical procedures.	Changes made for accuracy.
2.0	10.5	Revised AE collection to include "any grade" for those that impact stopping rules or that are AESI.	Previous collection language was limited to Grade 2+. Change made to expand collection.
2.0	10.5	Additional changes to reduce redundancy and consolidate repetitive paragraphs.	Reduce redundancy.
2.0	10.6	Revised AE collection to include "any grade" for those that impact stopping rules or that are AESI.	Previous collection language was limited to Grade 2+. Change made to expand collection.
2.0	Appendix A – All SOEs	Added line items for LDH and uric acid to all treatment SOEs in Appendix A.1 and A.2.	LDH and uric acid were previously mentioned in the CMP footnote but are not part of the CMP test. LDH and uric acid to be done as clinically indicated.
2.0	Appendix A – All SOEs	Changed timing of tumor imaging & disease assessment from Q6W to Q12W and as clinically indicated.	Change to accommodate disease groups with less frequent imaging schedules.
2.0	A.1	Updated "LOXO@Lilly" to "Eli Lilly and Company" at first mention, and "Lilly" thereafter.	Change made at the request of Eli Lilly and Company.
2.0	A.1.2.2.1	Revised CBC footnote.	Change made to align footnote with timing of events in the table.
2.0	A.1.2.2.2	Revised CBC/CMP footnotes.	Change made to align footnotes with timing of events in the table.
2.0	A.1.2.3.3	Added total cholesterol to Letrozole-specific SOE.	Addition to align SOE with A.1.3.4.2.
2.0	A.1.3.3.1	Removed breast cancer diagnosis from the Gemcitabine inclusion criteria.	This study seeks to recommend drugs beyond their current indications based on tumor characteristics.
2.0	A.1.3.6.1	Removed breast cancer diagnosis from the Tamoxifen inclusion criteria.	This study seeks to recommend drugs beyond their current indications based on tumor characteristics.
2.0	A.2	Addition of trastuzumab deruxtecan to all applicable subsections within A.2.	Addition of a new treatment option.
2.0	A.2.2.1	Phosphorus and magnesium added to Osimertinib screening.	Change made in response to WCG's coverage analysis.

2.0	A.2.2.3.6	Added Magnesium to D1 of each cycle to Osimertinib-specific SOE.	Change made in response to WCG's coverage analysis.
3.0	Throughout	Changes have been made throughout the protocol to redefine enrollment to be any participant who receives an ACT Tumor Board recommendation.	By redefining enrollment, participants who receive an ACT Tumor Board recommendation that does **not** match an ACT Therapy regimen will not be considered a Screen Fail and may be included in the analysis of this study.
3.0	Synopsis	Changes made to the Statistical Analyses section.	Changes were made by BSR in response to comments from CRRC review.
3.0	3.1	Revisions made throughout the entire section, including sub-sections.	Revisions made for clarity and completeness.
3.0	3.1.4	Clarified follow-up activities, and sub-divided Section 3.1.4.	LTFU disease and survivability status will be queried from medical records, not by in-person visits. Sub-divisions created for clearer separation.
3.0	4.1 4.2	Revisions made to clarify when various screening activities will occur.	Revisions made for clarity and accuracy.
3.0	4.2.2.1	Autoimmune disease & immune deficiency exclusion criteria were removed from A.1.5 and A.2.6 and inserted as Section 4.2.2.1.	These exclusions are not specific to the treatment arms contained within Appendix A.1 or A.2.
3.0	4.3	Revisions made to clarify when various screening activities will occur.	Revisions made for clarity and accuracy.
3.0	5.1.2 5.1.3	Swapped placement of Section 5.1.2 and 5.1.3.	Changes made to follow the flow of the study. Screen Fails can only occur after Pre-Screening and prior to Therapy Screening.
3.0	8.5.1	Removed LDH and uric acid from screening SOE. Autoimmune disease screening added to medical history footnotes.	LDH and uric acid were added during WCG coverage analysis review but were later determined not to be necessary. Autoimmune screening added for completeness.
3.0	9.1.4	Added target lesion evaluation metrics specific to Kaposi sarcoma (KS).	Evaluation criteria for KS are based on a recent clinical trial.
3.0	11.2	Language revisions.	Revisions made for clarity.
3.0	11.3.1	Language revisions.	Simplified definition of feasibility population.
3.0	11.4.2	Revisions to analysis of feasibility.	Revisions made by BSR.
3.0	11.4.3.1	Revisions to Disease-specific survival analysis.	Revisions made by BSR.

3.0	11.4.3.2	Revisions to Efficacy of Secondary Endpoint Analysis.	Revisions made by BSR.
3.0	11.4.5	Revisions to interim analysis.	Revisions made by BSR.
3.0	13.1.4.3	Added SMMART Repository as a location where data/samples will be stored.	SMMART Repository was recently IRB-approved. A primary purpose is to store all SMMART clinical trial data and samples.
3.0	A.1 & A.2	Removed LDH and uric acid from all SOEs.	These were added during WCG coverage analysis review but were later determined not to be necessary.
3.0	A.1 & A.2	Revised Footnote #12 in all SOEs.	Revisions made to clarify that LTFU is conducted via chart review, not in-person visits.
3.0	A.1.3.1.1	Removed reference to Appendix F.	Appendix F does not exist – the language was previously incorporated in Section 7.5.9.
3.0	A.1.3.5.1	Changed reference from Appendix D to Section 7.5.9.	Correction.
3.0	A.1.5	Removed and added as Section 4.2.2.1.	These exclusions are not specific to the arms contained in Appendix A.1.
3.0	Appendix A.2	Removed all drugs except for osimertinib from all relevant sections of Appendix A.2.	AstraZeneca withdrew use of all drugs except for osimertinib.
3.0	A.2.3.1	All changes throughout all sub-sections of A.2.3.1 made at the request of AstraZeneca.	Revisions made at the request of AstraZeneca.
3.0	A.2.4.2.2	Revised list of AESI.	Revisions made at the request of AstraZeneca.
3.0	A.2.4.2.4.3	Revised study close-out process.	Revisions made at the request of AstraZeneca.
3.0	A.2.6	Removed and added as Section 4.2.2.1.	These exclusions are not specific to the arms contained in Appendix A.2.
3.1	PI Change	PI change from Lara Davis, MD to Charles Lopez, MD, PhD.	Dr. Davis is leaving OHSU. Dr. Lopez agreed to take over as PI.

LIST OF DEFINITIONS:

ACT Therapy:	A drug regimen consisting of one or more drugs contained in one of the drug-specific sub-appendices in **Appendix A**, administered as recommended by the SMMART-ACT Tumor Board. All drugs used in an ACT Therapy have a recommended phase 2 dose (RP2D).
Drug Manufacturer-Specific Appendices:	Also referred to as “drug-specific appendices”. These sub-appendices are contained within **Appendix A**. Each drug-specific appendix contains all drugs, treatments, and other study-conduct information that is relevant to a single drug manufacturer.

Efficacy-evaluable:	An efficacy-evaluable participant is one who initiates an ACT Therapy (C1D1) and undergoes at least one On-Therapy disease assessment.
Enrollment:	Enrollment is defined as receiving a SMMART-ACT Tumor Board recommendation. The Tumor Board recommendation does not need to match an ACT Therapy option.
Main Study:	The study period that includes Therapy Screening, On-Therapy, and Follow-up/Long Term Follow-up. Main Study activities occur after the participant is enrolled and signs the ACT Therapy consent form.
On-Therapy:	The period during which a participant is receiving an ACT Therapy, beginning C1D1 and ending with the End-of-Therapy visit.
Tumor Board Screening:	The period starts when the ACT Tumor Board ICF is signed and ends when the participant receives an ACT Tumor Board recommendation, Screen Fails, or Withdraws, whichever comes first.
Screen Fail:	A participant who signs the ACT Tumor Board consent form, but who does not meet ACT Tumor Board eligibility criteria.
ACT Therapy Eligibility Fail:	A participant who receives an ACT Therapy recommendation, but who does not meet the therapy-specific eligibility criteria, and who therefore does not initiate their recommended ACT Therapy (C1D1).
Therapy Screening:	The period starts when the ACT Therapy ICF is signed and ends when the participant starts ACT Therapy (C1D1), fails Therapy Eligibility, or Withdraws, whichever comes first.

LIST OF ABBREVIATIONS:

AE	Adverse event
AESI	Adverse event of special interest
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
BEMS	BioLibrary Enterprise Management System
BID	Twice daily
BUN	Blood urea nitrogen
CAP	Clinical Analytics Platform
CBC	Complete blood cell (count)
CBR	Clinical benefit rate
CFR	United States Code of Federal Regulations
CMP	Comprehensive metabolic panel
COPD	Chronic obstructive pulmonary disease
CR	Complete response
CRMS	Clinical research management system
CRQA	Clinical Research Quality & Administration (OHSU)
CRRC	Clinical Research Review Committee (OHSU)
CRF	Case report form
CSF	Cerebral spinal fluid
CT	Computerized tomography

CTCAE	Common Terminology Criteria for Adverse Events
CTMS	Clinical trial management system
DFS	Disease-free survival
DLT	Dose limiting toxicity
DSMC	Data and Safety Monitoring Committee (OHSU)
DSMP	Data and Safety Monitoring Plan
DSS	Disease-specific survival
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic data capture
EMR	Electronic medical record
EOS	End-of-Study
EOT	End-of-Therapy
FDA	United States Food and Drug Administration
GCP	Good Clinical Practice
HBeAg	Hepatitis B “e” antigen
HBV	Hepatitis B virus
HCT	Hematocrit
HCV	Hepatitis C virus
HGB	Hemoglobin
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
IB	Investigator’s brochure
ICF	Informed consent form
ICH	International Conference on Harmonization
IM	Intramuscular injection
IND	Investigational new drug application
IP	Investigational product
IRB	Institutional Review Board
ITG	Informational Technology Group
IV	Intravenous
LVEF	Left ventricular ejection fraction
LFT	Liver function test
LTFU	Long-term follow-up
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
N/A	Not applicable
NCI	National Cancer Institute
OHRP	Office for Human Research Protections

OHSU	Oregon Health & Science University
ORR	Objective response rate
PCWG3	Prostate Cancer Working Group 3
PCBP	Participant of childbearing potential
PD	Progressive Disease
PET	Positron emission tomography
PI	Principle Investigator
PO	*Per os* (by mouth, orally)
PR	Partial response
PRO	Patient reported outcome
Q2W	Every 2 weeks
Q3W	Every 3 weeks
Q4W	Every 4 weeks
QD	Once daily
QoL	Quality of Life
RBC	Red blood cell (count)
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended Phase II Dose
RNI	Reportable new information
RT	Radiation therapy
SAE	Serious adverse event
SD	Stable disease
SMMART	Serial Measurements of Molecular and Architectural Responses to Therapy
SOC	Standard of care
SOE	Schedule of events
TEAE	Treatment emergent adverse events
TSMP	Trial Specific Monitoring Plan
TTD	Time-to-decline
TTP	Time-to-progression
UA	Urinalysis
ULN	Upper limit of normal
UP	Unanticipated problem
WBC	White blood cell (count)

1 BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

1.1 BACKGROUND

Cancer progression is driven by the acquisition of molecular aberrations that alter cellular function and institute biological programs underlying the “Hallmarks of Cancer”, including immune evasion, uncontrolled cell proliferation, resistance to cell death, and the ability to extravasate and metastasize[1]. The three basic modalities for treating cancer are surgery, radiation, and systemic therapy. For patients

with metastatic disease, these treatment approaches are rarely curative, and the associated therapeutic responses are limited in duration. Numerous mechanisms drive treatment failure, for example, the non-specific action of cytotoxic chemotherapeutic agents, molecular aberrations that confer drug resistance, and the activation of multiple redundant cell growth and survival pathways that cannot be targeted simultaneously by only one or two drugs. Furthermore, disease recurrence can be attributed to molecular heterogeneity among subclones of tumor cells. These minority cell populations frequently harbor molecular alterations that are refractory to the given treatment regimen and can expand to re-constitute the tumor.

In most advanced cancers, durable responses are therefore likely to be achieved only by combining multiple therapies that counter the spectrum of aberrations driving tumor progression or resistance. Identifying personalized combination therapies that will elicit a robust and beneficial response in individual patients, and predicting how best to adapt treatment regimens as drug-resistant tumors inevitably recur, is thus a crucial, and still unmet, need.

1.1.1 TARGETED THERAPIES

Recent advances in genomic, epigenomic, proteomic, and immune profiling have uncovered a large number of therapeutic targets that are transforming the field of cancer medicine. Rather than treating cancers with systemic cytotoxic regimens, these molecularly targeted agents aim to exploit key tumor-specific vulnerabilities, such as synthetic lethality or oncogene addiction.

Targeted therapies are agents that bind and alter the activity of specific proteins that enable cancer cell survival and disease progression. Gleevec®, which inhibits the kinase activity of BCR-ABL, was among the first developed targeted agents and has a dramatic and sustained clinical effect in individuals with CML[2]. Unfortunately, it was subsequently learned that the success of Gleevec® was an outlier, and that most targeted therapies lead to transient responses and rapid relapse. For example, vemurafenib, which inhibits activated B-RAF V600E, elicits dramatic clinical responses in patients with metastatic melanoma[3], but the cancer cells quickly become resistant by molecularly re-wiring themselves to activate the RAS/MAPK pathway through B-RAF V600E independent mechanisms[4,5]. Consequently, patients undergo a brief disease remission while the cancer cells are still sensitive to vemurafenib, followed by inevitable relapse and death upon the acquisition of resistance. Fortunately, combining BRAF inhibitors with agents that target MEK or immune checkpoints prolongs disease response and results in an improved two-year survival rate in patients with metastatic melanoma[6,7], demonstrating the need to target multiple pro-growth and survival signaling pathways that enable tumor growth and provide means of therapeutic escape.

Combining molecularly targeted agents with chemotherapy, radiation, immune modulators, or other targeted agents provides an opportunity to gain therapeutic control by simultaneously intervening in multiple aspects of tumor biology that cancers rely upon for growth and progression[8-13]. Unfortunately, a one-size-fits-all combination of cancer therapies is unlikely to be effective even for patients with the same pathological diagnosis. Moreover, the spectrum of targetable molecular alterations is likely to change within single patients as the tumor adapts to therapies and growth in different metastatic microenvironments. Therefore, processes for identifying candidate therapeutic targets for each individual across serial biopsies will be an essential part of any combination treatment program.

1.1.2 OHSU KNIGHT CANCER INSTITUTE SMMART PROGRAM CLINICAL ANALYTICS PLATFORM

The SMMART program is a patient-centric portfolio of observational and interventional studies aimed at optimizing an individual's treatment across all stages of the cancer continuum. The principal goal of SMMART is establishing a workflow that maximizes therapeutic response by obtaining and sharing in-depth molecular information about how a patient's cancer adapts to therapies. Central to the program is the SMMART clinical analytics platform (SMMART-CAP), a collection of assays that profile the cellular and molecular characteristics of an individual's cancer via RNA sequencing, immunohistochemistry, multiplexed proteomics, and genomic profiling (described in more detail in **Appendix B**). SMMART uses this platform for two primary purposes: 1) upon initial enrollment, to identify therapeutic targets in single biopsies and 2) in subsequent biopsies taken upon disease progression, to find new therapeutic targets that emerged in response to therapy and under selective pressure at different metastatic sites.

1.1.3 SMMART-ACT TUMOR BOARD

The SMMART-Adaptive Clinical Treatment (SMMART-ACT) Tumor Board is a multidisciplinary tumor board consisting of a panel of experts that convene to discuss the clinical history and cancer biology of an individual with the goal of providing treatment recommendations. SMMART-ACT Tumor Board attendees may include medical oncologists, radiologists, molecular pathologists, pharmacists, clinical genomics specialists, cancer biologists, bioinformatics experts, patient advocates, as well as basic and translational science researchers. Attendees who may participate in Tumor Board discussions include (1) clinicians who may or may not be study team members, and (2) non-clinicians who are study team members. All attendees who actively participate in SMMART-ACT Tumor Board discussions must comply with HIPAA rules and OHSU Information Privacy & Security guidelines.

Additional SMMART-ACT Tumor Board invitees may include researchers, collaborators, consultants, and students who are not considered study team members to passively observe, as long as they have agreed to comply with all HIPAA rules and OHSU Information Privacy & Security Guidelines. The participant's treating physician may attend or they can be represented by a proxy who is familiar with the participant's disease. The SMMART-ACT Tumor Board may be convened in-person, virtually, and/or via email.

Recommendations may include treatments that are described in this protocol (**Appendix A**), SOC, off-label, or part of a clinical trial. Treatment recommendations are advisory only, and the final treatment plan is ultimately the decision of the treating physician in consultation with the patient. If a potential SMMART-ACT Tumor Board-recommended treatment is part of a clinical trial (e.g., ACT Therapy, or another clinical trial), the treating physician is responsible for discussing possible trial participation with the patient, and routine clinical trial consent procedures will be followed. The SMMART-ACT Tumor Board recommendation will be documented in the participant binders as source documentation, and will contain information including, but not limited to, the final SMMART-ACT Tumor Board recommendation, voting summary, and date the SMMART-ACT Tumor Board meeting was held. Refer to **Section 13.1** for additional information regarding data storage.

The SMMART-ACT Tumor Board may issue up to two recommendations. If multiple recommendations are made, they will be ranked as "primary" and "secondary". Ranking will be done via vote of all voting members. The decision for which recommended treatment to use will ultimately be made by the treating physician and participant. If the ACT Tumor Board issues two recommendations that are both ACT Therapy options, and if during the course of the study the participant discontinues their primary

ACT Therapy, they may switch to the secondary SMMART-ACT Tumor Board recommended ACT Therapy without going Off-Study.

1.1.3.1 SMMART CLINICAL TUMOR BOARD PRINCIPLES

- The SMMART Clinical Tumor Board will attempt to recommend the most optimal treatment (or "best-choice" treatment option) that is in the best interest of the patient, does the least harm to the patient, and is supported by as much clinically credible evidence as possible.
- Therapeutic recommendations will be the best collective clinical judgement of the SMMART Clinical Tumor Board, based on as much biological information as is feasible, coupled with consideration of the patient's clinical information.
- All laboratory test information that is presented to the SMMART Clinical Tumor Board must be generated from a CLIA-licensed, College of American Pathologists-certified laboratory, or be an FDA-approved laboratory developed test (LDT) or in vitro diagnostic (IVD) result (e.g., SMMART-CAP, described in **Appendix B**). There may be instances in which analytics, in addition to those generated from the SMMART-CAP, may be considered by the SMMART Clinical Tumor Board if they meet these same requirements.
- Predicted toxicities of individual drugs and drug combinations will be taken into consideration, so that participant safety is always of highest consideration in a therapeutic option recommended by the SMMART Clinical Tumor Board.
- The conclusions from the SMMART Clinical Tumor Board will be made available to the treating physician. Investigational results from exploratory analytics are not discussed or considered.

1.1.3.2 APPLICATION OF SMMART CLINICAL TUMOR BOARD PRINCIPLES

The application of these principles in the multidisciplinary SMMART Clinical Tumor Board is aimed at identifying and matching therapies targeting genomic, genetic, and/or proteomic aberrations unique to a patient's cancer and that are associated with a given cellular process or processes on which cancer cells depend for survival and progression. Examples of treatment recommendations based on this approach are:

Example 1: A new ERBB3 activating mutation (i.e., $ERBB3^{E928A}$) is identified in the patient's tumor tissue. RNAseq shows that this mutation is expressed with a similar allele frequency as in the DNA, and protein profiling demonstrates downstream signaling through the PI3K pathway (including high phospho [p]-AKT, p-PRAS40, and p-GSK3b) and MAPK pathway (p-MEK and p-ERK1/2). The Tumor Board may suggest HER2-directed therapy that targets the HER2/3 heterodimer, such as trastuzumab/pertuzumab.

Example 2: A known pathogenic germline or somatic mutation in the DNA damage repair pathway (e.g., BRCA1, BRCA2, PALB2, RAD50, RECQL) is identified in the patient's tumor tissue. The SMMART Clinical Tumor Board may suggest a PARP inhibitor (e.g., olaparib, rucaparib, niraparib) alone or in combination.

Example 3: A PIK3CA mutation ($PIK3CA^{E545K}$) and PTEN loss are identified in the patient's tumor tissue. PTEN IHC shows no expression of PTEN in tumor cells. Protein profiling shows activation of the PI3K/AKT/mTOR pathway through high levels of p-AKT, p-PRAS40, and p-GSK3b. The Tumor Board may suggest a PI3K/mTOR or AKT inhibitor (e.g., copanlisib or alpelisib).

1.2 STUDY RATIONALE

Patients with advanced cancers that are resistant to SOC therapies quickly exhaust treatment options, with most practice guidelines recommending clinical trials. These clinical trials provide access to novel therapies, but often have restrictive eligibility requirements and endpoints that measure response criteria in large group cohorts with a shared pathological diagnosis, rather than tailoring treatments to the diverse and changing biology of tumors within individual patients[14,15]. In contrast with the existing treatment paradigm, this SMMART-ACT trial is an interventional study designed to assess the feasibility of treating advanced cancer patients with personalized therapy based on SMMART-ACT Clinical Tumor Board recommendation for one of the available ACT Therapies.

SMMART-ACT will combine each participant's medical and treatment history with the wealth of data derived from multiple SMMART-CAP tumor profiling technologies to build a personalized, multi-dimensional molecular profile of each participant's cancer. This data will then be used by the SMMART-ACT Tumor Board to recommend treatment options. Participants will include those who recently progressed on non-targeted, SOC drugs as well as those whose tumor adapted to prior targeted therapy, both of whom may benefit from a deeper interrogation of targetable molecular alterations.

This trial is built around a collection of investigational treatment regimens intended to optimally inhibit or perturb intrinsic or extrinsic biological pathways promoting the growth and/or survival of an individual participant's cancer. The investigational treatment regimens under study are comprised of targeted agents given alone, or in combination with other targeted therapies, immunotherapies, chemotherapies, or radiation therapy. Importantly, the investigational treatment regimens assessed in this study are required to have a recommended phase 2 dose (RP2D), thus, the dosing, frequency and safety profile of each therapeutic combination has already been established in a prospective clinical trial. By adopting this strategy, SMMART-ACT minimizes the toxicity of each personalized treatment recommendation. The available ACT Therapy options, in addition to details of each investigational agent, are described in the corresponding drug-specific appendices (**Appendix A**).

1.2.1 RATIONALE FOR INVESTIGATIONAL DRUG REGIMENS (ACT THERAPY OPTIONS)

The participants in this study will be diagnosed with one of five kinds of advanced cancer: breast, ovarian, prostate, pancreatic, or sarcoma. These cancers each have a unique underlying biology and are treated with therapeutic agents with widely varying mechanisms of action. Consequently, we anticipate that the SMMART-CAP assays will reveal a diverse array of targetable molecular alterations across enrolled participants, necessitating an extensive list of matching therapeutic agents.

The core investigational agents that make up the ACT Therapies are described in the corresponding drug-specific appendices (**Appendix A**). Each core investigational agent is required to have a known safety profile, with prior clinical studies establishing a RP2D for the single agent or the pre-specified combination treatment regimen (ACT Therapy) described herein. Some investigational agents may be administered as a single agent or as part of a pre-specified combination treatment regimen, as described in Appendix A. The RP2Ds may be based on a maximum tolerated dose (MTD), maximum administered dose (MAD), optimal biological dose (OBD), or the collective assessment of known toxicity, pharmacodynamics (PD), pharmacokinetics (PK), and efficacy profiles[16]. As investigational agents are

added to this study, they will be included and described in the corresponding drug-specific appendices (**Appendix A**).

Each drug-specific appendix may also identify potential therapeutic combinations for the core investigational agents and may include agents other than those core agents listed in the corresponding drug-specific appendices. These additional agents are specific to combination regimens and, like the core investigational agents, must have a RP2D. The RP2D of combination drugs are specific to their use in combination with the core investigational agent.

The potential therapeutic combinations listed in the drug-specific appendices are intended to be dynamic, with one or more drug agents anticipated to be revised or replaced based on the ever-growing body of scientific and clinical research data. Specific information regarding dosing guidelines for all potential therapeutic combinations are also described in corresponding drug-specific appendices. This study was found to be IND-exempt by the Food and Drug Administration (FDA). See **Section 6**.

1.3 EXPLORATORY STUDIES BACKGROUND

A series of analytics for research-use only (RUO) under the SMMART program's exploratory research analytics (SMMART-ERA) platform will be used within a comprehensive research program that aims to characterize underlying cancer biology and mechanisms of therapeutic resistance that arise post-treatment. In brief, these assays will be performed by an interdisciplinary team of OHSU scientists and outside collaborators with expertise in performing cutting-edge research on human tissue samples. These exploratory analytics may include the application of -omic technologies to characterize aspects of the tumor genome, transcriptome, and proteome as well as multiscale imaging technologies to investigate tumor cell architecture, ultrastructure, and microenvironment. Details of these exploratory analytics are described in **Appendix C**. Exploratory assays will not be discussed or considered in SMMART-ACT Tumor Board reviews.

1.4 RISK/BENEFIT ASSESSMENT

1.4.1 KNOWN POTENTIAL RISKS

The safety profile for each of the investigational treatment regimens in this study is based on prior clinical trial(s) observations (refer to **Section 10.4**). However, as some are still experimental therapies, there remains a risk that the combination of two or more drug agents may induce adverse events that have not been observed. As applicable, refer to the package insert or investigator's brochure of each individual drug agent for known potential risks.

1.4.2 KNOWN POTENTIAL BENEFITS

Given the lack of treatment options for treating patients with advanced cancers, the current study may provide access to a new treatment approach not otherwise available. It cannot, however, be guaranteed that participants in this study will directly benefit from treatment during participation.

2 OBJECTIVES AND ENDPOINTS

2.1 PRIMARY OBJECTIVE AND ENDPOINT

Objective	Endpoint	Start	End
Feasibility of utilizing a SMMART-ACT Tumor Board to select personalized advanced cancer treatment plans based on a pre-determined set of drug agents with RP2Ds (as described in drug-specific appendices [**Appendix A**]).	Proportion of participants who receive an ACT Therapy based on a SMMART-ACT Tumor Board recommendation.	SMMART-ACT Tumor Board review.	First dose of ACT study drug per unique treatment regimen (as described in drug-specific appendices).

2.2 SECONDARY OBJECTIVES AND ENDPOINTS

Objective	Endpoint	Start	End
1. Safety and tolerability of assigned ACT Therapy per cancer type;	a. Incidence of treatment-emergent adverse events (TEAEs) suspected or confirmed as attributable to study therapy; ***AND*** b. Rate of treatment discontinuation due to toxicities and/or intolerability.	First dose of study drug	a. 30 days after last dose of study drug(s). b. Last dose of study drug(s).
2. Preliminary indications of efficacy based on disease-specific responses;	a. Overall Response Rate (ORR = CR+PR) per RECIST 1.1.		At 24 weeks from C1D1 (+/- 2 weeks).
3. Estimated survival benefit per cancer type.	a. Progression-free survival (PFS) ***AND*** b. Disease-specific survival (DSS) ***AND*** c. Overall survival (OS)		a. First date of documented progression or recurrence (RECIST 1.1), end-of-study, or death due to any cause, whichever occurs first. b. Date of death as a result of the disease at time of last follow-up, up to end of LTFU.

			c. Date of death from any cause, up to end of LTFU.

2.3 EXPLORATORY OBJECTIVES AND ENDPOINTS

Objective	Endpoint	Start	End
1. Durability of response compared to the most recent therapy on which progression occurred;	Proportion participants with a TTP ratio ≥1.3.	First dose of study drug.	Date of disease progression after initiation of ACT Therapy. The baseline TTP ($TTP_{historic}$) is defined as time from start of prior line of treatment (i.e., last line of treatment before enrolling to this study) to the first documented date of progression on that treatment.
2. Changes in ability to conduct activities of daily living (ADL);	TTD to ECOG performance status ≥3.		Date of decline to ECOG ≥ 3.
3. Changes in QoL;	QoL, as measured by EORTC QLQC30, QLQ FA12, and QLQ INFO25 instruments.	Baseline (prior to first dose of C1D1 study drug)	Up to one year after discontinuing treatment.
4. Feasibility of SMMART-centric assessments of ongoing responses to treatment to identify mechanisms of therapy induced change, per investigator discretion. Such mechanisms may include, but will not be limited to, the following:	a. Proportion of participants who have an On-Therapy Biopsy with sufficient tumor content for assays. Analyzed per cancer type and biopsy site. b. Proportion of On-Therapy Biopsies with sufficient for tumor content assays. Analyzed by assay type (i.e., CLIA and RUO); and	First set of analytics performed on a biopsy for this study.	Last set of analytics performed on a biopsy for this study.

a. changes in tumor and tumor ecosystem biology; b. response and resistance to therapy.	c. Proportion of CLIA assay results obtained ≤14 business days of biopsy.		

2.4 SOLID TUMORS UNDER STUDY

Solid Tumor by Site
Breast Cancer, Metastatic (Stage IV)
Ovarian Cancer, Advanced (Stage III-IV)
Pancreatic Adenocarcinoma, Advanced (Stage III-IV)
Prostate Cancer, Metastatic (Stage IV)
Soft Tissue Sarcoma, Metastatic (Stage IV)

3 STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY DESIGN

This protocol describes the overarching design of the SMMART-ACT trial. The following list is a brief guide for navigating this protocol when a participant is identified as a potential SMMART-ACT candidate. More details may be found in the subsequent and referenced subsections:

1. *ACT Tumor Board ICF and eligibility [Section 4.1]*
    a. *Perform ACT Tumor Board eligibility assessments for all SMMART-ACT participants [Section 8.5.1]*
    b. *Pre-Therapy Biopsy (or archival tissue) [Section 8.4.1.1]*
    c. *If the participant does not meet Tumor Board eligibility, they are deemed a Screen Fail.*
2. *ACT Tumor Board is held [Section 1.1.3]*
    a. *If the ACT Tumor Board recommends an ACT Therapy option (listed in Appendix A), then participant may be considered for ACT Therapy Screening and Main Study participation.*
    b. *If the ACT Tumor Board does not recommend an ACT Therapy option, then participant is moved Off-Study.*
3. *ACT Therapy ICF packet and eligibility [Section 4.2]*
    a. *ACT Therapy consent packet includes: ACT Therapy ICF, Study Drug Plan & Acknowledgment Form, and Drug Information Sheet(s)*

   b. *Perform general therapy screening assessments, regardless of therapy assignment [Section 8.5.1];* ***plus***
   c. *Perform drug-specific screening assessments for the recommended ACT Therapy [Appendix A];* ***plus***
   d. *Perform disease-specific screening assessments for the recommended ACT Therapy [Section 4.3]*
   e. *If participant does not meet all ACT Therapy eligibility criteria, they will be moved Off-Study.*
4. *Initiate Study Therapy at C1D1*
   a. *Perform On-Therapy assessments specific for the SMMART-ACT recommended therapy [Appendix A]*
   b. *On-Therapy Biopsy [Section 8.4.1.2]*
5. *End-of-Therapy (EOT) is targeted approximately 6 months after C1D1 (i.e., 6 or 8 cycles, depending on the assigned cycle length).*
   a. *Perform EOT assessments for the specified ACT Therapy [Appendix A]*
   b. *An EOT biopsy is optional (prior to next line of treatment).*
6. *Follow-up visits will occur after EOT at Day 30, and Month 3, 6, 9, and 12.*
   a. *Perform follow-up assessments for the specified ACT Therapy [Appendix A]*
7. *Long-term follow-up (LTFU) will continue for up to 5 years.*
   a. *LTFU will be conducted via chart review every 6 months, for up to 5 years. Medical records will be used to assess disease status and survival status.*
   b. *See the appropriate SMMART-ACT recommended therapy schedule of events in Appendix A*

Details for each investigational study agent and corresponding combination treatment regimens are described in separate drug-specific appendices (**Appendix A**). The main body of this protocol must be used in conjunction with the drug-specific appendices containing the ACT therapy agent(s) for which the participant is assigned, based on a SMMART-ACT Tumor Board recommendation.

Refer to **Section 11**, Statistical Considerations, for additional information regarding statistical methods used in this study.

The SMMART-ACT trial is a single-center, open label, single arm, pilot study to primarily assess the feasibility of a personalized medicine approach utilizing molecularly guided targeted RP2D therapies for participants with the advanced malignancies of sarcomas and breast, ovarian, pancreatic, and prostate cancers. Up to 30 total enrolled participants are planned for accrual over 36 months.

3.1.1 ACT TUMOR BOARD / ENROLLMENT

After providing ACT Tumor Board informed consent, each participant must provide a tissue sample from a Pre-Therapy Biopsy that yields sufficient tissue for SMMART-CAP analytics. The Pre-Therapy Biopsy may be a fresh tissue collection or archival tissue collected within 6 months of signing the Tumor Board ICF. Tumor and/or blood biospecimens from each potential participant will be assessed with one or more SMMART-CAP clinical assays (unless already performed per institutional SOC and/or in another SMMART study). Clinically actionable recommendations for treatment will be generated based on these results. The multidisciplinary SMMART-ACT Tumor Board will follow SMMART Clinical Tumor Board Principles (**Section 1.1.3**) and will review case histories and the associated results of the analytics for each participant. The primary goal of the SMMART-ACT Tumor Board review is to formulate one or more

interventional recommendation(s) per participant, within the context of best practice treatment options for that individual.

Enrollment (On-Study) is defined as a participant who receives a SMMART-ACT Tumor Board **recommendation**.

If the ACT Tumor Board recommends an ACT Therapy (as listed in **Appendix A**) then the participant will be considered for participation in the Main Study. If the SMMART-ACT Tumor Board does not issue a recommendation that matches one of the ACT Therapy options, then the recommendation will be documented and the patient will be moved to Off-Study.

The primary endpoint for this feasibility study is the proportion of participants who are enrolled that receive the first dose of a SMMART-ACT Tumor Board recommended SMMART-ACT therapy.

3.1.2 ACT THERAPY SCREENING

Once an ACT Therapy regimen has been identified and the participant has signed the ACT Therapy ICF, the participant enters the next step of ACT Therapy screening. During ACT Therapy screening (1) all general screening (**Section 8.5.1**), (2) disease-specific screening (**Section 4.3**), and (3) drug-specific eligibility criteria (respective drug-specific appendices (**Appendix A**)) must be met. Distinct eligibility criteria apply to each of the drugs that may be included in an ACT Therapy regimen.

If the participant does not meet the necessary ACT Therapy inclusion criteria, or meets any exclusion criteria, they will be considered an ACT Therapy Eligibility Failure and moved Off-Study.

3.1.3 BASELINE / ON-THERAPY

Core investigational study agents may be administered in monotherapy or in combination with other targeted agents or immunotherapies, chemotherapies, or radiation (see respective drug-specific appendices in **Appendix A**). Details of dose levels and possible regimens for combinations are provided in the corresponding drug-specific appendices. Regardless of overall recommended treatment plan details, **each ACT Therapy must have an established RP2D that was determined in a prior clinical trial**.

The Baseline timepoint will occur on C1D1, according to the details listed within the Schedule of Events. Baseline assessments/labs shall occur prior to the initiation of study therapy.

All participants are required to undergo an On-Therapy Biopsy two weeks after initiating study therapy (C1D14). The On-Therapy Biopsy may occur up to three weeks after initiating study therapy (C1D21), but must occur before starting Cycle 2. Participants will continue to receive the study drug(s) after their On-Therapy Biopsy according to the biopsy results and the results of ongoing safety and clinical assessments.

3.1.4 END-OF-THERAPY (EOT), FOLLOW-UP, LONG-TERM FOLLOW-UP (LTFU) & RE-ENROLLMENT

3.1.4.1 END-OF-THERAPY (EOT)

An End-of-Therapy (EOT) Biopsy is optional but recommended. If an EOT Biopsy occurs, it must be before the participant starts a new therapy.

Participants will continue their assigned study intervention until discontinuation, up to a maximum of six months. See **Sections 5.3.1** and **Section 7.4** for specific guidelines. The discontinuation reason will be collected for all participants, and the date of discontinuation from study therapy is to be reported on the case report form (CRF) and in the participant's electronic medical record (EMR). Participants that discontinue may choose to have their disease managed and treated per institutional standards.

Participants will be asked for consent to an EOT Biopsy, if possible, as described above. Participants that discontinue will also undergo any applicable End-of-Therapy activities and events described in the drug-specific appendices (**Appendix A**), and will enter into a 5-year long-term follow-up (LTFU) period. All participants in LTFU will be considered Off-Treatment, but On-Study.

3.1.4.2 YEAR 1 FOLLOW-UP

Follow-up visits will be performed 30 days after EOT, and every 3 months after EOT, for 1 year.

If a participant has not shown signs of disease progression, then imaging should continue to be performed as clinically indicated (i.e., every 6-12 weeks), until disease progression, start of a new therapy, withdrawal from the study, or death, whichever occurs first. If participants do not return to the site for their routine clinical imaging assessments, disease status may be obtained via electronic health records, or follow-up contact may be made with the participant (e.g., by phone) or their treating physician.

See the therapy-specific SOE (**Appendix A**) for complete documentation of assessments to be performed during these visits.

3.1.4.3 LONG-TERM FOLLOW-UP (LTFU)

After the Year 1 Follow-up period, participants will enter long-term follow-up (LTFU) for up to 5 years. During LTFU participant medical records will be reviewed every 6 months for disease status and survival outcomes. If a participant has not shown signs of disease progression, then imaging should continue to be performed as clinically indicated (i.e., every 6-12 weeks), until disease progression, start of a new therapy, withdrawal from the study, or death, whichever occurs first. If participants do not return to the site for their routine clinical imaging assessments, disease status may be obtained via electronic health records, or follow-up contact may be made with the participant (e.g., by phone) or their treating physician.

3.1.4.4 RE-ENROLLMENT

A major effort within the SMMART program is to understand how tumors adapt to therapy by performing SMMART-CAP assays on Pre-Therapy and On-Therapy Biopsies. These analyses frequently reveal that cancer cells evade the actions of a drug by activating a new targetable biological pathway. Thus, at the discretion of the principal investigator, any participant with unacceptable toxicity or PD while On-Therapy or in LTFU, may re-enroll. Consent to a new ACT Tumor Board for an alternate therapy recommendation will define end of LTFU in cases of re-enrollment.

Re-enrollment will be considered a new accrual, and will require: new ACT Tumor Board informed consent, SMMART-ACT analytics performed on a new Pre-Therapy Biopsy, a new SMMART-ACT Tumor Board review to generate a new set of treatment recommendations, and a new ACT Therapy consent for treatment if the SMMART-ACT Tumor Board recommendation matches an ACT Therapy regimen. The requirements for a new Pre-Therapy Biopsy with accompanying ACT analytics for re-enrollment may be waived at the discretion of the investigator, in cases that may include, but are not limited to, recent biopsy and analytics (within 6 months of signing the new Tumor Board ICF). For all endpoints, analysis will be conducted for each enrollment (including re-enrollment).

3.2 JUSTIFICATION FOR RATIONALE OF STUDY DESIGN

Evidence-based methods to evaluate new and revised therapeutic approaches in the context of "one size fits all" clinical studies are clearly established and include head-to-head comparisons across multiple treatment arms and against placebo (or other controls). Conversely, best methods to clearly and unbiasedly judge feasibility, safety and tolerability, clinical benefit, etc., in the context of personalized treatment strategies, especially for the treatment of progressive, advanced and metastatic cancers, are unclear. Underlying the challenges within quality assessment are the inherent determinants and operational demands of a functional personalized therapy system, especially with respect to significance since the frequency at which any one single regimen is utilized may be low.

The primary endpoint of this study will assess the frequency at which a participant receives an ACT Therapy based on a SMMART-ACT Tumor Board recommendation. A 75% feasibility goal will be targeted. The success of this strategy will be evaluated after 15 participants have received a SMMART-ACT Tumor Board recommendation. If less than 9 participants receive a SMMART-ACT study therapy (i.e., take first dose of SMMART-ACT study drug(s) on C1D1); an interim feasibility review will be conducted.

Safety, tolerability, and early indications of efficacy will be evaluated through the incidences of TEAEs, compliance, and response. The impact of ACT Therapy regimens on time-to-event statistical measures such as time-to-progression and decline, and on QOL, will provide feedback on the value of aggressiveness within any ACT Therapy in the setting of advanced cancers. The SMMART molecular assessments will be evaluated in terms of productivity and value to inform on mechanisms of action, resistance, and response. The practicality of the analytical approach will be evaluated in terms of biopsy success, including tumor content and analytics turnaround times.

Given favorable early evaluations of feasibility, the foremost points of analysis of this study will be converted to address preliminary clinical benefit and efficacy in a phase II study.

3.2.1 JUSTIFICATION FOR DOSE

To minimize toxicity, each ACT Therapy described in this protocol (i.e., monotherapies or combination regimens) will be administered at an RP2D established in prior clinical trial(s) for the respective investigational regimen. Refer to corresponding drug-specific sub-appendices (**Appendix A**) for specific information regarding dosing guidelines.

3.3 END OF STUDY DEFINITION

The end of this study will be defined at the time at which all study data are collected. That may be prior to the completion of this protocol for all enrolled participants, if necessary, and/or prior to enrollment of the full number of participants that is stated herein as the target. This study protocol may be terminated when all data needed for the primary endpoint are collected.

4 STUDY POPULATION

4.1 ACT TUMOR BOARD ELIGIBILITY CRITERIA

4.1.1 ACT TUMOR BOARD INCLUSION CRITERIA

The following key inclusion criteria must be met for ACT Tumor Board eligibility:

1. Written informed consent prior to any study activities, study-specific procedures, or interventions.
2. At least 18 years of age at time of informed consent. Persons of all gender identities, biological sexes, races, and ethnicities will be included.
3. A diagnosis of advanced sarcoma or advanced prostate, breast, ovarian, or pancreatic cancer.
4. Biospecimen collection, as per institutional standards, must be consented to and collection must be feasible for SMMART-CAP analytics, with the following exceptions for tissue collections:
    a. Individuals with a prior tumor tissue sample , collected within 6 months of signing ACT Tumor Board consent may be eligible, so long as ≤1 treatment has been received since tissue collection and the tissue sample is sufficient for successful SMMART-CAP assays.
5. ECOG performance status of ≤2.
6. Physician-assessed life expectancy of ≥ 6 months.

4.1.2 ACT TUMOR BOARD EXCLUSION CRITERIA

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

1. Evidence of active malignancy of another cancer with a natural history or treatment history that may affect safety or efficacy assessments of this study or impose unacceptable risk to the participant. Guiding examples for those who can be enrolled include: individuals who have been disease free for ≥ two years; cancers with high cure rates (e.g., prior history of stage 1 rectal cancer and currently otherwise disease free); adequately treated, localized nonmelanomatous skin cancer.
2. Absence of biopsiable lesion, AND unavailable/insufficient archival tissue for SMMART-CAP analytics.

4.2 ACT THERAPY ELIGIBILITY CRITERIA

4.2.1 ACT THERAPY INCLUSION CRITERIA

To be eligible to receive ACT Therapy under this protocol, an individual must meet all of the following key inclusion criteria, as well as disease-specific eligibility criteria (**Section 4.3**) and drug-specific eligibility criteria (**Appendix A**).

1. Documented progression after at least 1 line of prior therapy for advanced disease. If recurrence occurred within 6 months of the last dose of an adjuvant/neoadjuvant therapy, that adjuvant/neoadjuvant therapy will count as 1 line of therapy.
2. SMMART-ACT Tumor Board recommendation of at least one ACT Therapy regimen defined within this protocol, based on the board's review of SMMART-CAP results on a Pre-Therapy biopsy.
3. Adequate organ function as defined in **Table 1**, assessed at Therapy screening, or by the time that study intervention commences:

Table 1. Adequate Organ Function Laboratory Values	
System	**Laboratory Value**
Hematological	
Absolute neutrophil count (ANC)	≥1,500/µL (1.5 K/cu mm)
Platelets	≥100,000/µL (100 K/cu mm)
Hemoglobin	≥9 g/dL (or ≥5.6 mmol/L)
Renal	
Creatinine **OR** Measured or calculated[a] creatinine clearance[b] (GFR can also be used in place of creatinine or CrCl)	≤1.5 x institutional ULN (IULN) **OR** ≥50 mL/min/1.73 m^2
Hepatic	
Total bilirubin	≤1.5 x IULN **OR** Direct bilirubin ≤ IULN for individuals with total bilirubin levels >1.5 x IULN
AST (SGOT) / ALT (SGPT)	≤3 x IULN
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT)	≤1.5xULN, unless individual is receiving anticoagulant therapy, as long as PT or PTT is within intended therapeutic range of intended anticoagulant therapy.
Activated Partial Thromboplastin Time (aPTT) or PTT	≤1.5xULN, unless participant is receiving anticoagulant therapy, as long as PT or PTT is within therapeutic range of intended anticoagulant therapy.
Body mass index (BMI)	
BMI[c]	>16.0 and <35.0 kg/m^2
[a] Creatinine clearance should be calculated per institutional standard. For participants with a baseline calculated creatinine clearance below normal institutional laboratory values, a measured baseline creatinine clearance should be determined. Individuals with higher values felt to be consistent with inborn errors of metabolism will be considered on a case-by-case basis.	

[b] Creatinine clearance of >30 mL/min may be considered given that renal toxicity is not at increased risk and excretion is not major route of clearance for any chosen SMMART-ACT therapeutic.
[c] Participants with a BMI of ≥30.0 will use ideal body weight indices in calculating the delivery of agents that are dosed based upon body surface area (i.e., mg agent/meter squared) or weight (i.e., mg agent/kg body weight).

4. Toxicities due to prior therapies should be resolved to baseline or Grade 1 (per CTCAE v5.0) before administration of study intervention. The following exceptions are permitted:
    a. Alopecia, fatigue, and lymphopenia due to prior therapies.
    b. Toxicities attributed to prior anti-cancer therapy that are not expected to resolve and to result in long lasting sequelae (e.g., neuropathy after platinum-based therapy), may be permitted.
5. Palliative radiation therapy completed ≥ two weeks prior to start of ACT Therapy to a measurable disease lesion(s).
6. Study intervention-specific eligibility criteria for the intended, recommended therapy (see corresponding drug-specific appendices (**Appendix A**)) must also be met.
7. Additional eligibility criteria specific to their disease, described in **Section 4.3**, must also be met.

4.2.2 ACT THERAPY EXCLUSION CRITERIA

An individual will be excluded from receiving ACT Therapy if any of the following criteria are met:

1. Any brain/CNS metastasis that progresses within ≤ four weeks of CNS directed treatment as ascertained by clinical examination(s) and MRI or CT during the Therapy Screening period.
2. One or more new, active brain/CNS metastasis or the presence of known leptomeningeal disease (LMD) that requires immediate treatment. If treatment within the first cycle of ACT Therapy is unlikely to be required, enrollment may be considered, as per the investigator.
3. Concurrent forms of anti-cancer therapy that have the potential to interfere with efficacy and safety assessments or that may pose increased risk to the participant while on an ACT Therapy, and as per the investigator. (Select hormone therapies are allowed. Refer to **Section 7.5.1** for concomitant medication exceptions.)
4. More than one intervening line of therapy for treatment of their cancer since the time of the Pre-Therapy Biopsy, exclusive of most maintenance hormone therapies (Refer to **Section 5.1.1** for Tumor Board screening parameters, and **Section 7.5.1** for concomitant medications exceptions). *Note: Participants who have a Pre-Therapy Biopsy while receiving a SOC treatment will not be eligible if they receive any additional lines of treatment prior to the start of ACT Therapy. This treatment will count as one line of intervening therapy.*
5. Untreated and/or uncured HCV infection, as evidenced by detectable HBC RNA by PCR. Prior treatment, concurrent treatment, and natural resolution of HCV infection are not exclusionary given (1) no risk for hepatic decompensation and (2) the intended ACT Therapy is not expected to exacerbate HCV infection.
6. Uncontrolled intercurrent illness and infection that may interfere with planned treatment, including, but not limited to, the following:
    a. Symptomatic congestive heart failure (New York Heart Association [NYHA] class III or IV) (**Appendix D**),
    b. Unstable angina pectoris or coronary angioplasty, or stenting within < six months prior to enrollment,

c. Cardiac arrhythmia (ongoing cardiac dysrhythmias of grade ≥2 [NCI CTCAE v5.0]),
d. Conditions that require intra-cardiac defibrillators,
e. Known cardiac metastases,
f. History of abnormal cardiac valve morphology (≥ Grade 2),
g. Chronic graft versus host disease (GVHD) or immunosuppressive therapy for the control of GVHD.

7. Severe infection within < four weeks prior to initiation of study therapy, including, but not limited to, hospitalization for complications of infection, bacteremia, or severe pneumonia.
8. Inability or unwillingness to take oral medication (only for assigned oral study interventions).
9. History of allergy to an assigned study agent or its excipients.
10. Current pregnancy, current breastfeeding, or unwillingness to not breastfeed while receiving study drug(s) or for the minimum required time after the last dose of study drug(s) as specified by the SMMART-ACT drug agents. See corresponding drug-specific appendices (**Appendix A**) for study drug-specific eligibility criteria related to pregnancy and breastfeeding.
11. Autoimmune disease or immune deficiency as outlined in **Section 4.2.2.1**.
12. Any condition that, in the opinion of the investigator, could jeopardize the participant's safety or adherence to the study protocol.

Drug-specific exclusion criteria are provided in corresponding drug-specific appendices (**Appendix A**).

4.2.2.1 AUTOIMMUNE DISEASE & IMMUNE DEFICIENCIES

Patients should be carefully questioned regarding their history of acquired or congenital immune deficiencies or autoimmune disease. Patients with any history of immune deficiencies or autoimmune disease listed in the table below are excluded from participating in the study.

Possible exceptions (*) to this exclusion could be patients with a medical history of such entities as atopic disease or childhood arthralgias where the clinical suspicion of autoimmune disease is low, patients with type I diabetes mellitus who are stable on insulin replacement, or patients with chronic fatigue syndrome. Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone may be eligible for this study. In addition, transient autoimmune manifestations of an acute infectious disease that resolved upon treatment of the infectious agent are not excluded (e.g., acute Lyme arthritis). Additionally, patients with a history of autoimmune disease with no exacerbations in the past 5 years and do not require immunosuppressive therapy may be considered on a case-by-case basis.

● Acute disseminated encephalomyelitis ● Addison disease ● Ankylosing spondylitis ● Antiphospholipid antibody syndrome ● Aplastic anemia ● Autoimmune hemolytic anemia ● Autoimmune hepatitis ● Autoimmune hypoparathyroidism ● Autoimmune hypophysitis ● Autoimmune myocarditis ● Autoimmune oophoritis ● Autoimmune orchitis ● Autoimmune thrombocytopenic purpura ● Behçet disease ● Bullous pemphigoid ● Chronic fatigue syndrome* ● Chronic inflammatory demyelinating polyneuropathy ● Churg-Strauss syndrome ● Crohn's disease	● Dermatomyositis ● Diabetes mellitus type 1* ● Dysautonomia ● Epidermolysis bullosa acquisita ● Gestational pemphigoid ● Giant cell arteritis ● Goodpasture syndrome ● Graves' disease ● Guillain-Barré syndrome ● Hashimoto disease ● IgA nephropathy ● Inflammatory bowel disease ● Interstitial cystitis ● Kawasaki disease ● Lambert-Eaton myasthenia syndrome ● Lupus erythematosus ● Lyme disease, chronic ● Meniere syndrome ● Mooren ulcer ● Morphea ● Multiple sclerosis ● Myasthenia gravis	● Neuromyotonia ● Opsoclonus myoclonus syndrome ● Optic neuritis ● Ord thyroiditis ● Pemphigus ● Pernicious anemia ● Polyarteritis nodosa ● Polyarthritis ● Polyglandular autoimmune syndrome ● Primary biliary cirrhosis ● Psoriasis ● Reiter syndrome ● Rheumatoid arthritis ● Sarcoidosis ● Scleroderma ● Sjögren syndrome ● Stiff-Person syndrome ● Takayasu arteritis ● Ulcerative colitis ● Vitiligo ● Vogt-Koyanagi-Harada disease ● Wegener granulomatosis

4.3 PARTICIPANT DISEASE-SPECIFIC ELIGIBILITY CRITERIA

4.3.1 CANCER-SPECIFIC INCLUSION/EXLUSION CRITERIA

The following disease-specific inclusion/exclusion criteria must also be met during ACT Therapy screening for participation for certain cancer types, as defined in the following sections:

4.3.1.1 BREAST CANCER - INCLUSION

1. Lesion(s) remain measurable after systemic therapies, as follows:

    a. At least one prior line of pharmacological therapy for ***hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2)-negative disease.***
    b. At least one prior line of targeted therapy for ***HER2-positive disease***.
    c. At least one prior line of combination therapy for ***triple negative disease lacking a BRCA1/2 mutation***.
    d. At least one prior line of therapy with a PARP inhibitor for ***triple negative disease with a BRCA1/2 mutation***.

4.3.1.2 PROSTATE CANCER - EXCLUSION

1. If the Therapy screening bone scan shows a "superscan" participants will be excluded from further participation and moved Off-Study. This is defined as an intense symmetric activity in the bones and diminished renal parenchymal activity, such that the presence of additional metastases in the future could not be evaluated.

4.4 STRATEGIES FOR RECRUITMENT AND RETENTION

This study will be conducted in the United States. Participants for this study will primarily be recruited from hematology and oncology practices within OHSU and its affiliated community hematology and oncology (CHO) partners, but additional collaborative study sites may also be invited to participate in this trial. Participants may be identified and referred to this study by their primary treating physician from within OHSU/CHO, collaborating study sites, or from the outside community. Participants may be identified by a member of the participant's treatment team, the PI, research team, or medical and surgical oncology clinics, as well as institutional tumor boards that are part of OHSU/CHO or collaborating study sites. As a member of the treatment team, the investigator(s) will screen their participant's medical records for suitable research study participants and discuss the study and their potential for enrolling in the research study. Referral of potential participants to investigator(s) of this study is made as part of SOC, with the referring physician seeking advice on the diagnosis, evaluation, and/or treatment of the participant's malignancy.

The investigator(s) may also screen the medical records of potential participants with whom the investigator does not have a treatment relationship. This will be done for the limited purpose of identifying participants who would be eligible to enroll in the study and to record appropriate contact information in order to approach these potential individuals regarding the possibility of participating in the study. Permission to review any records containing personal health information (PHI) as a preparatory step to research shall proceed only with the approval of the OHSU IRB. Such PHI will not be removed from OHSU.

Individuals interested in participating may contact the investigator from information on this study posted on the clinicaltrials.gov website or on the Knight Cancer Institute's study participant opportunities website, https://studypages.com/ohsu/cancercenter/home/.

4.4.1 ACCRUAL ESTIMATES

No OHSU Knight Cancer Institute study will focus on any particular gender, racial or ethnic subset. No participant will be excluded from the study on the basis of gender, racial or ethnic origin. Approximately 50% men and 50% women will be studied, with exceptions made for cancers of the reproductive system (i.e., ovarian and prostate). Participants identifying as male, female, gender non-conforming, gender-fluid and those of other minority backgrounds will be recruited for this study from the general population. The projected gender, racial, and ethnic composition of the study will represent that of the state of Oregon and the states of each participating collaborative site.

Thirty-six (36) months will be allowed for consent and screening of 38 participants to sign ACT Tumor Board consent in order to meet a total accrual goal of 30 enrolled participants (i.e., receive SMMART-ACT Tumor Board recommendation) with diagnosed advanced stage breast ($ER^+/HER2^-$, $HER2^+$, and triple

negative), ovarian, prostate, or pancreatic (adenocarcinoma) cancer or sarcoma. Any participant that re-enrolls for treatment under a new ACT Tumor Board recommendation will be counted towards a new enrollment accrual.

4.4.2 INCLUSION OF VULNERABLE POPULATIONS

Children are excluded from this study as the information pertaining to dosing and AEs for the investigational regimens listed in this study is very limited for individuals <18 years of age.

Individuals will be eligible and considered for enrollment regardless of their infection status with HIV and HBV. Individuals with evidence of HCV infection may be eligible. See **Section 4.2.2**.

5 STUDY ENROLLMENT AND WITHDRAWAL

5.1 PARTICIPANT SCREENING, AND ENROLLMENT

In order to participate in this study, signed informed consent must be obtained from the participant or the participant's legally acceptable representative. The current Institutional Review Board (IRB) approved informed consent must be signed and dated by each participant prior to undergoing any study procedures or before any prohibited medications are withheld from the participant. The informed consent discussion must be documented in the participant's medical record and a copy of their signed IRB-approved informed consent form must be scanned into their record.

Informed consent will be necessary for ACT Tumor Board and Main Study activities, regardless of the need for biopsy tissue. In addition, prior to starting an ACT Therapy regimen, participants will also be required to consent to the Study Drug Plan & Acknowledgement Form as part of the Main Study consenting process.

5.1.1 ACT TUMOR BOARD SCREENING

ACT Tumor Board Screening will begin once a participant is identified as a potential candidate for the study. Participants will sign an ACT Tumor Board informed consent form (ICF) that will allow for tumor tissue and blood to be collected for molecular profiling using one or more assays comprising the SMMART-CAP. Participants must also meet all ACT Tumor Board eligibility criteria per **Section 4.1**. The results of SMMART-CAP on the Pre-Therapy Biopsy tissue will be provided to the treating physician, as well as a multi-disciplinary tumor board (i.e., SMMART-ACT Tumor Board), which will review results of clinical assays and provide treatment recommendations for the participant's cancer.

In general, complete processing (including return of treatment recommendation) may take approximately 28 days from receipt of Pre-Therapy tissue, before results are available for discussion at a SMMART-ACT Tumor Board. *Note: a new Pre-Therapy Biopsy sample collection is not required for individuals who have undergone a prior tumor biopsy (archival tissue) within 6 months of signing the ACT Tumor Board ICF so long as the archival tissue sample is sufficient for assessment using SMMART-CAP or results of prior SMMART-CAP assays are available for review. Participants may receive up to one line of intervening therapy (per SOC) during or after undergoing a Pre-Therapy Biopsy. Participants that receive*

more than one line of intervening therapy after undergoing their Pre-Therapy Biopsy are considered a Screen Fail.

Any participant that receives an ACT Tumor Board treatment recommendation, whether or not the recommendation is an ACT Therapy option, will be considered enrolled.

If the treatment recommendation from Tumor Board matches one of the study intervention options listed in the SMMART-ACT drug-specific appendices (**Appendix A**), then the participant will be considered potentially eligible for ACT Therapy. Participants may then sign the ACT Therapy ICF (including Study Drug Plan & Acknowledgement Form) and undergo the interventional study assessments. Signing the ACT Therapy ICF will move the participant into the Therapy Screening phase of this study.

5.1.2 SCREEN FAILURES

Any participant who has signed the ACT Tumor Board ICF but does not meet the ACT Tumor Board eligibility criteria will be considered a Screen Fail and not counted towards the total number of planned enrollments.

The reason for Screen Failure should be captured in the database for each participant failing to meet the eligibility criteria. A minimal set of Screen Failure information is required to ensure transparent reporting of Screen Failure participants. Minimal information includes demography, Screen Failure details, eligibility criteria, and any study-procedure serious adverse event (SAE). Individuals who do not meet the criteria for participation in this trial may be re-screened no more than one time.

5.1.3 ACT THERAPY SCREENING

ACT Therapy Screening activities may begin once the participant has signed the ACT Therapy consent form. All Therapy Screening evaluations will be performed during this period and must be completed within 28 days prior to initiation of study drug (i.e., Day -28 to Cycle 1 Day 1, before drug). Preferably, all Therapy Screening assessments should be performed up to 3 days before the start of ACT Therapy (C1D1). Baseline assessments may occur on C1D1, *prior* to the initiation of study therapy.

Upon first dose of ACT Therapy study drug(s) (C1D1) the participant will be considered **"On-Therapy"**. If the participant was enrolled but does not meet all Therapy eligibility criteria, the participant will be moved to "**Off-Study**".

Any participant who has signed the ACT Therapy ICF but does not meet the Therapy study eligibility criteria, or meets Therapy study eligibility criteria but terminates their participation prior to receiving study therapy, will be moved to "**Off-Study**".

5.2 REGISTRATION AND ENROLLMENT PROCEDURES

5.2.1 REGISTRATION AND ENROLLMENT PROCEDURES

Participants will be required to give written informed consent to participate in the study before any study activities, tests, or evaluations are conducted that are not part of standard care. Registration from all consented participants must be entered into the OHSU electronic Clinical Research Management System (CRMS [e.g., OnCore]).

Eligibility must be confirmed and documented by the investigator prior to initiating both the ACT Tumor Board phase and ACT Therapy phase of the study. Materials required to complete the eligibility review include, at minimum:

- Current IRB-approved consent form and HIPAA Authorization for the study signed & dated by the participant (inclusive of the ACT Tumor Board ICF and ACT Therapy ICF).

- Documented (signed and dated) attestation by the investigator confirming participant's eligibility (including ACT Tumor Board Screening and ACT Therapy Screening), based on available source documentation and authorizing enrollment.

Participants will be considered enrolled after receiving a SMMART-ACT Tumor Board recommendation. Participants who receive a SMMART-ACT Tumor Board recommendation that matches an ACT Therapy detailed in **Appendix A** will be asked to sign the ACT Therapy ICF and will go into Therapy Screening to confirm eligibility prior to starting ACT Therapy. Participants who do not receive a recommendation that matches an ACT Therapy detailed in Appendix A will be moved to Off-Study.

Participants will be considered "On-Therapy" when they begin study therapy (i.e., Cycle 1 Day 1). "Re-enrollment" will be defined as instances in which the same individual receives a follow-on, unique ACT Therapy from an additional SMMART-ACT Tumor Board recommendation, after discontinuing an ACT Therapy regardless of reason (e.g., progression or intolerability).

See **Section 11** for information on statistical analyses for cases of re-enrollment.

5.3 PARTICIPANT WITHDRAWAL OR DISCONTINUATION FROM THE STUDY

A participant's End of Study (EOS) may be defined as time of completed collection of their data, or earlier. EOS may include a withdrawal that is requested by the participant and discontinuation initiated from another body, such as the investigator, local IRB, or regulatory authorities. Participants are free to withdraw consent and discontinue participation in the study at any time and without prejudice to further treatment.

5.3.1 PARTICIPANT WITHDRAWAL FROM THE STUDY

If a participant withdraws consent, the study team will document which level of withdrawal the participant requests. These include:

- **No Further Data or Specimen Collection**: End study contact with participant. No on-going or further collection of new data or specimens, continue using previously collected data/specimens.
- **No Further Procedures / Continued Data & Specimen Collection**: End study team contact with participant. No on-going or further collection of new fresh biopsy/blood specimens, but may

continue to collect new data as available, including using previously collected data and archival specimens created after withdrawal.

No further participant contact should be made if the participant withdraws consent. Information about the reason(s) for discontinuation and collection of any new or ongoing AEs should be collected at the time the participant withdraws consent.

5.3.2 PARTICIPANT DISCONTINUATION FROM THE STUDY

Reasons for regulatory- and protocol-determined discontinuation may include when requirements of the protocol are newly unmet by the participant, such as in the cases of the following:

- Pregnancy.
  Note: In the event of a pregnancy, the study therapy will be permanently discontinued. Refer to **Section 10.6.6** regarding reporting of pregnancy.
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.
- If the participant does not meet the eligibility criteria for the SMMART-ACT study therapy that was recommended by the Tumor Board.

EOS for a participant may be marked by any of following situations:

- A subsequent therapy is consented to (including ACT Tumor Board Screening for re-enrollment for another ACT study regimen);
- All of the participant's data has been collected per protocol;
- Death of any cause;
- Loss of contact with the participant (**Section 5.4**);
- Personal reasons, including, but not limited to, intolerability of a protocol therapy, unacceptable inconvenience, and economic hardship;
- Investigator's request, with or without a final disease assessment. Examples for investigator's request include, but are not limited to the following:
  - Significant study intervention non-compliance (e.g., participant is unable to adhere to study visit schedule, comply with drug regimen as self-reported from the medical drug diary and confirmation from study team via pill count, etc.)
  - Adverse event (AE), laboratory abnormality, or other medical condition or situation under which continued participation in the study would not be in the best interest of the participant;
- The request of a regulatory body.

If this study concludes prior to completion of this protocol (i.e., early termination of the study), then any participant's EOS may be defined as the date of termination of the study.

If a participant is Discontinued for any reason we may continue to access and collect previously uncollected data and specimens, provided that they are directly related to the research described within this protocol, and are from timepoints prior to the participants discontinuation. This includes re-accessing archival blood and tissue samples that were accessed prior to the participant being discontinued.

5.3.3 HANDLING PARTICIPANT WITHDRAWAL/DISCONTINUATION FROM STUDY

When a participant withdraws or is discontinued from the study, the reason the participant is no longer participating, the study name, IRB study number, and the date of withdrawal/discontinuation must be documented in the participant's medical record. The change in study status must be documented in the appropriate trial management system (i.e., OnCore).

5.3.2.1 PARTICIPANT REPLACEMENT

Participants in this study that withdraw prior to the completion of the ACT Tumor Board Screening period (i.e., prior to receiving a Tumor Board recommendation) may be replaced.

5.4 LOST TO FOLLOW-UP

Lost to follow-up is defined by the inability to reach the participant after a minimum of three documented phone calls, faxes, emails, and/or a registered mail letter over the course of approximately 12 months. The study team should show "due diligence" by documenting in the source documents the steps taken to contact the participant. If it is determined that the participant has died, the site may use permissible local methods to obtain date and cause of death.

If a participant is lost to follow-up we may continue to access and collect previously uncollected data and specimens, provided that they are directly related to the research described within this protocol, and are from timepoints prior to the participant being deemed as lost to follow-up. This includes re-accessing archival blood and tissue samples that were accessed prior to the participant being lost to follow-up.

5.5 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or stopped for any reason, in consideration of the rights, safety, and well-being of the participant(s), and in accordance with International Conference on Harmonization (ICH) / Good Clinical Practices (GCP) guidelines and local regulations.

Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study funder, local IRB, and other regulatory agencies (as required). If the study is prematurely terminated or suspended, the investigator will promptly inform the IRB and will provide the reason(s) for the termination or suspension. The study may resume once concerns about safety, protocol compliance, and data quality are addressed and satisfy the Sponsor, IRB and/or FDA.

6 STUDY INTERVENTION

Each core investigational study agent that is described in a corresponding drug-specific appendices (**Appendix A**) represents a unique product that may form the backbone of a SMMART-ACT study therapy. Each drug-specific appendix contains investigational study agent sub-sections that detail dose, timing, and frequency of administration, as well relevant guidelines for allowable dose modifications and adverse events, for that agent.

Pre-specified SMMART-ACT combination therapies are listed in the corresponding drug-specific appendices and consist of a core investigational agent in combination with one or more SOC agents, which include targeted drugs, chemotherapy(ies), radiotherapy, or combinations thereof. The SOC agents that may be combined with the core investigational agents are described in the respective drug-specific appendices. This includes pertinent dose, timing, and frequency of administration information, as well relevant guidelines for allowable dose modifications, and adverse events.

The SMMART-ACT trial is structured to allow for the seamless addition or removal of a study agent, study intervention, or both. If a study agent or study intervention is added or removed from a drug-specific appendices, amendments will be reasonably limited to the respective drug-specific appendices. Importantly, if a study drug is removed from a drug-specific appendix, then all relevant study interventions that are comprised of that study agent must also be removed from the drug-specific appendix. No new study agent or investigational regimen may be employed until the study site has received local IRB approval and, as applicable, notification to proceed from the appropriate regulatory authorities (per 21 CFR 312 for Investigational New Drug [IND] studies).

The acquisition, handling, preparation, administration of each study agent, and destruction is described in the most current version of the **SMMART-ACT Pharmacy Manual**.

6.1 INVESTIGATIONAL PRODUCT (IP)

Please reference the **SMMART-ACT Pharmacy Manual** for investigational product details and information (e.g., product formulation, storage, handling, preparation, administration, etc.). A list of the AEs and potential risks associated with the study agents administered in this study can be found in respective manufacturer package inserts or investigator's brochures. Administration of oral study agents will require the participant to maintain a study drug diary (refer to **Section 8.1.5**). Administration of intravenous study agents will be reconciled in the participant's EMR.

6.1.1 ACQUISITION – ALL STUDY AGENTS

All drug agents in this study will be supplied and/or prepared by the OHSU research pharmacy per manufacturer instructions. All other study agents in the respective drug-specific appendices (**Appendix A**) that are not core investigational products will be purchased commercially through the study.

6.1.2 ACCOUNTABILITY – ALL STUDY AGENTS

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of the study agent. (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage).

Responsibility for drug accountability at the study site rests with the investigator; however, the investigator may assign some of the drug accountability duties to an appropriate pharmacist or designee. Inventory and accountability records must be maintained and readily available for inspection by the study monitor and are open to inspection at any time by any applicable regulatory authorities or other oversight bodies.

The investigator or designee will collect and retain all used, unused, and partially used containers of study medication until full accounting has been completed. The investigator or designee must maintain records that document:

- Investigational product delivery to the study site.
- The inventory at the site.
- Use by each participant including pill/unit counts from each supply dispensed.
- Return of investigational product to the investigator or designee.
- Destruction or return of study agents for final disposal.

These records should include dates, quantities, batch/serial numbers (if available), and the unique code numbers (if available) assigned to the investigational product and study participants.

The investigational product must be used only in accordance with the protocol. The investigator will also maintain records adequately documenting that the participants were provided the correct study medication specified.

Completed accountability records will be archived by the site. At the completion of the study, the investigator or designee will oversee destruction of remaining study drug according to institutional standard operating procedures.

6.1.3 DESTRUCTION AND RETURN – ALL STUDY AGENTS

At the end of the study, or earlier upon approval from study management, unused supplies of each study agent should be destroyed according to institutional policies. Drug supplies will be counted and reconciled in full at the site with all monitoring procedures complete before destruction. Destruction will be documented in the Drug Accountability Record Form.

7 TREATMENT PLAN

This section only applies to participants who receive a SMMART-ACT Tumor Board recommendation that matches one of the ACT Therapies detailed in **Appendix A**.

Details of study therapies are described in each corresponding drug-specific appendix (**Appendix A**). Unless stated otherwise, study therapies will be administered on an *out-patient* basis. In general, treatment cycles will be 21 or 28 consecutive days, as denoted for each study therapy regimen. This will be described in the Study Drug Plan & Acknowledgment Form, specific to each participant and their personalized ACT Therapy regimen.

For participants receiving an ACT Therapy, no investigational or commercial agents or therapies other than those described in this protocol may be administered with the intent-to-treat the participant's malignancy. Unless otherwise stated, the allowable exceptions to this are the administration of hormone therapy (e.g., SERM, SERD, AI, and LHRH analogs), and androgen deprivation therapy (e.g., LHRH), HER2 targeted therapy (e.g., trastuzumab, pertuzumab), or anti-androgen therapy (e.g., LHRH, enzalutamide), which may be initiated or continued, at the discretion of the treating physician, as part of the standard management of the participant’s disease.

7.2 TREATMENT PERIOD AND MAINTENANCE

Participants will receive their assigned study therapy per the drug-specific dosing regimen described in the corresponding drug-specific appendix (**Appendix A**) for single-agent treatment, or combination treatment. Initial response, as judged by the investigator's clinical judgement, will be assessed after completion of the first three cycles of study intervention; however, additional assessments may occur more frequently if clinically indicated. Study assessments will be performed as outlined in the **Schedule of Events in the respective drug-specific appendix (Appendix A)**. Participants will be treated with their assigned study intervention until they complete the treatment period of this study (6 cycles if assigned to a 28-day regimen, or 8 cycles if assigned to a 21-day regimen – both being approximately 6 months), disease progression, withdrawal or discontinuation from study (see also **Section 7.4**), unacceptable toxicity, or death, whichever occurs first.

All ACT Therapy drugs will be provided by the study while the participant is On-Treatment. If a participant is continuing to receive benefit from study treatment at 6 months, the study team will assist the treating physician to attempt to obtain drug through the participant's insurance or via medication assistance program(s). However, the study will not be able to continue providing ACT Therapy drugs past the defined On-Therapy period (6 months), and the participant will be considered off study treatment and moved to follow-up.

7.3 DOSING DELAYS AND MODIFICATIONS

In general, interruptions and/or modifications are permitted in the case of medical/ surgical events or logistical reasons (i.e., elective surgery, unrelated medical events, vacation, and holidays) not related to study therapy. Participants should be placed back on study therapy within four weeks of the scheduled interruption unless otherwise approved by the investigator, and per drug-specific criteria. The reason for interruption should be documented in the participant's study record.

Dose modifications to an individual study agent (e.g., dose interruption, reduction, or termination) will be permitted in accordance with any safety parameters defined per study agent in the corresponding drug-specific appendices (**Appendix A**). In each drug-specific appendix, the allowable dose modifications and guidance for managing toxicities is described. For cases where the core agent has been incorporated into a combination regimen with one or more other anticancer modalities (e.g., targeted agent, chemotherapy, immunotherapy, and radiotherapy), allowable dose modification and guidance for managing toxicities during the course of the trial are also described in the corresponding drug-specific appendix. If, in cases of combination regimens, conflicting actions are recommended the more stringent action will be followed, or the discretion of the investigator will be followed.

While each drug within a given combination is to be administered at the established RP2D, the individual dose modification for each drug within a given combination should be guided by the package insert or investigator's brochure. In general, the dose reduction of each drug (in a combination) would be starting from the initial dose and decrease accordingly. If the RP2D of a drug combination has a drug at the lowest allowable dose level, then the study therapy should be halted or discontinued, in accordance with the package insert or investigator's brochure. Any allowable re-escalation of a dose for any drug should not be increased beyond the initial RP2D of that specific combination.

7.3.1 TOXICITY MONITORING OF INDIVIDUAL STUDY INTERVENTIONS

Given concern of excess toxicity of an individual study therapy, a formal toxicity assessment may occur in a joint data review of the Principal Investigator and Knight Data and Safety Monitoring Committee (DSMC). If it is established that a study therapy is too toxic, then that study therapy will be discontinued from the available list of study therapies in each respective drug-specific appendix (**Appendix A**).

See **Section 10.7** (Study Stopping Rules) for the criteria that will trigger a drug toxicity safety review.

7.4 DISCONTINUATION FROM STUDY THERAPY

A participant's discontinuation from their assigned study therapy (EOT) does not mean discontinuation from the study (EOS), and remaining study procedures should be completed as indicated by the study protocol (refer to the Schedule of Events in the applicable drug-specific appendices (**Appendix A**)). Further, discontinuation of one study drug does not necessitate discontinuation of all study drugs in an ACT Therapy regimen.

If a clinically significant finding is identified (including, but not limited to, changes from Baseline assessment), the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding must be reported as an adverse event (AE). Participants MUST discontinue study therapy (and non-investigational product at the discretion of the investigator) for any of the following reasons:

- Participant's request to stop study therapy. Participants who request to discontinue study therapy will remain On-Study. If a participant remains On-Study, they must continue to be followed for protocol specified follow-up procedures (refer to **Section 3.1.4.2 and 3.1.4.3**). The only exception to this is when a participant specifically withdraws consent for any further contact (refer to **Section 5.3**).
- Any clinical AE, laboratory abnormality, or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the participant.
- Termination of the study by Sponsor-Investigator.
- Disease progression in the absence of clinical benefit, as determined by the investigator.
- Specific study agent discontinuation criteria described in corresponding drug-specific appendices (**Appendix A**).
- Non-compliance of the participant with protocol-mandated procedures based on the judgment of the investigator.
- Participant becomes pregnant.

If a participant has not progressed following discontinuation of study drug(s), every effort should be made to continue to obtain disease assessments (e.g., radiographic or clinical laboratory testing, as applicable) until documented disease progression or until the participant has started an alternative cancer therapy.

The reason for study therapy discontinuation must be documented in the participant's medical records and entered on the appropriate CRF.

7.5 GENERAL CONCOMITANT MEDICATION AND SUPPORTIVE CARE GUIDELINES

Each participant assigned to an ACT Therapy will undergo review by research pharmacy, per institutional standards, to identify concomitant medications and to adjust or discontinue any medications accordingly. After enrollment, medications are continually reviewed throughout the study and before any new concomitant or supportive medications are prescribed. A description of precautionary and prohibited medications for each study drug is provided in the manufacturer's package insert or investigator's brochure for each drug, as well as the corresponding drug-specific appendices (**Appendix A**).

Supportive measures for optimal medical care are to be given throughout the study as indicated by the treating physician's assessment of the participant's medical need and institutional and general medical guidelines for the care of participants undergoing treatment of their cancer. Medications required to treat AEs and manage cancer symptoms and concurrent diseases and supportive care agents, such as pain medications, anti-emetics and anti-diarrheals, are allowed and will follow standard-of-practice medical guidelines.

The participant must be told to notify the investigational site about any new medications begun after the start of the study therapy. All medications (other than study agents) and significant non-drug therapies (including vitamins, herbal medications, physical therapy, and blood transfusions) administered during the study must be listed on the case report form (CRF).

7.5.1 CONCOMITANT ANTICANCER THERAPIES

Participants assigned to an ACT Therapy that are receiving hormonal therapy (e.g., LHRH analogs), or anti-angiogenic therapy (e.g., bevacizumab), as part of the standard management of their cancer may, at the discretion of the investigator, and in consultation with the clinical pharmacist and treating physician, continue to receive such therapies in addition to their assigned study intervention.

7.5.2 BLOOD PRODUCTS

All blood products are to be irradiated and leukocyte-reduced according to institution guidelines. Additionally, cytomegalovirus (CMV)-negative participants should receive CMV-negative blood products according to institution guidelines.

7.5.3 GROWTH FACTOR SUPPORT

Unless stated otherwise, the use of growth factors will be according to institutional guidelines and ASCO criteria[17]. Use of growth factors must be documented on the case report forms.

7.5.4 INFECTION PROPHYLAXIS

The use of prophylactic antibacterial, antifungal, and antiviral agents is recommended according to institutional guidelines. (Note: Certain antibiotics may have interactions with specific inhibitors, and thus

the assigned combination must be reviewed closely prior to initiating study therapy and while On-Therapy).

7.5.5 DIET

Participants should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea, or vomiting.

7.5.6 TREATMENT OF FEVER AND NEUTROPENIA

Neutropenic fever is defined (per CTCAE v5.0) as a disorder characterized by an ANC <1000/mm^3 and a single temperature of >38.3 °C [101 °F] or a sustained temperature of ≥38 °C [100.4 °F] for more than one hour. Neutropenic fever will be treated per institution guidelines.

7.5.7 GASTROINTESTINAL

Gastrointestinal symptoms will be treated with anti-emetics, anti-diarrheal agents, and acid suppressive therapies (e.g., antacids, H2 blockers, proton pump inhibitors) per institutional guidelines.

7.5.8 TUMOR LYSIS SYNDROME

Tumor lysis syndrome (TLS) should be managed per institutional guidelines. Appropriate prophylaxis for TLS, include hydration and anti-hyperuricemias.

7.5.9 CONTRACEPTION

One or more of the assigned drug agents in this study may/can cause embryo-fetal harm and may have adverse effects on a fetus in utero. Furthermore, one or more of the assigned drug agents may have adverse effects on the composition of sperm. Finally, the effect of otherwise untested combinations of agents on the embryo-fetus and/or sperm are unknown but constitute a justifiable concern. Please refer to corresponding drug-specific appendices (**Appendix A**) for drug-specific precautions. Sperm-producing participants and non-pregnant, non-breast-feeding participants may be enrolled if they are willing to use contraception as required by the SMMART-ACT study agent(s) and described below.

7.5.9.1 PARTICIPANT INFORMED CONSENT

Participants will be informed that taking the study medication(s) may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. For participants who are required to use adequate method(s) of contraception, the Study Drug Plan & Acknowledgement Form, specific to each participant and part of the informed consent process, will identify the potential methods and duration for which birth control must be used and is based on the specific study drug or combination of study drug(s). The Study Drug Plan & Acknowledgement Form will be in accordance with the requirements set forth in the respective appendices for each study drug used. For any combination of study drugs, the more conservative method(s) and timeline will be followed.

If there is any question that a participant will not reliably comply with the requirements for contraception, they should not receive ACT Therapy. If a participant becomes pregnant, the study drug(s) will be stopped immediately, and we will request to monitor the pregnancy until the baby is born. If a participant's partner becomes pregnant, we will request to monitor the partner's pregnancy until the baby is born.

7.5.9.2 PARTICIPANTS OF CHILDBEARING POTENTIAL

Persons of childbearing potential (PCBP) who are sexually active must agree to use two (except where noted below) effective methods of contraception for the duration of receiving ACT Therapy and for the minimum required time as specified by the ACT Therapy study agent(s). Highly effective methods of contraception include:

Acceptable non-hormonal birth control methods:

- Total/True abstinence: When the participant refrains from any form of sexual intercourse and this is in line with their usual and/or preferred lifestyle. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods, or declaration of abstinence solely for the duration of a trial) and withdrawal are not acceptable methods of contraception. No additional method will be required with this option.
- Vasectomized sexual partner with participant assurance that partner received post-vasectomy confirmation of azoospermia. No additional method will be required with this option unless otherwise specified by the ACT Therapy study agent(s).
- Tubal occlusion PLUS male condom.
- IUD PLUS male condom, provided coils are copper-banded.

Acceptable hormonal methods:

- Normal and low dose combined oral pills PLUS male condom.
- Cerazette (desogestrel) PLUS male condom. Cerazette is currently the only highly efficacious progesterone-based pill.
- Hormonal shot or injection (e.g., Depo-Provera) PLUS male condom.
- Etonogestrel implants (e.g., Implanon, Norplant) PLUS male condom.
- Norelgestromin/EE transdermal system PLUS male condom.
- Intrauterine system [IUS] device (e.g., levonorgestrel releasing IUS -Mirena®) PLUS male condom.
- Intravaginal device (e.g., EE and etonogestrel) PLUS male condom.

7.5.9.3 SPERM-PRODUCING PARTICIPANTS

If specified in the drug-specific sub-appendix (**Appendix A**), sperm-producing individuals must use an effective contraception method as listed below in order to be eligible for participation unless the participant has had a vasectomy (medical confirmation of successful surgery is required) and the ACT Therapy study agent(s) requires no additional methods (or if participant's partner is considered of non-childbearing potential). A participant's partner will be considered of nonchildbearing potential if they have received medical confirmation they are postmenopausal or they are surgically sterile (they have undergone a total hysterectomy, bilateral tubal ligation, bilateral oophorectomy, or bilateral salpingectomy).

- Total/True abstinence: When the participant refrains from any form of heterosexual intercourse and this is in line with their usual and/or preferred lifestyle. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and be the preferred and usual lifestyle of the participant. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of birth control; or
- Condom with spermicide.

7.5.9.3.1 HIGHLY TERATOGENIC DRUGS

For highly teratogenic drugs, the following methods will be considered acceptable if the participant's partner is of childbearing potential. It is important to note that a participant's partner is not a research participant and cannot be required to use a specific contraceptive method.

- Total/True abstinence: When the participant refrains from any form of heterosexual intercourse and this is in line with their usual and/or preferred lifestyle. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and be the preferred and usual lifestyle of the participant. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of birth control.
- Tubal occlusion PLUS male condom.
- IUD PLUS male condom, provided coils are copper-banded.
- Normal and low-dose combined oral pills PLUS male condom.
- Cerazette (desogestrel) PLUS male condom. Cerazette is currently the only highly efficacious progesterone-based pill.
- Hormonal shot or injection (e.g., Depo-Provera) PLUS male condom.
- Etonogestrel implants (e.g., Implanon, Norplant) PLUS male condom.
- Norelgestromin/EE transdermal system PLUS male condom.
- Intrauterine system [IUS] device (e.g., levonorgestrel releasing IUS -Mirena®) PLUS male condom.
- Intravaginal device (e.g., EE and etonogestrel) PLUS male condom.

7.5.9.4 SPERM DONATION AND EGG DONATION/RETRIEVAL

PCBP must agree to refrain from donating eggs, or retrieving eggs for their own use, for the duration of receiving study drug(s) and for the minimum required time after study drug(s) have been stopped as defined in the drug-specific appendices.

Sperm-producing participants must agree to refrain from donating sperm for the duration of receiving study drug(s) and for the minimum required time after study drug(s) have been stopped as defined in the drug-specific appendices.

7.5.10 USE IN PREGNANCY

If a participant inadvertently becomes pregnant while on ACT Therapy with one or more study agents, all on-study treatment will be stopped immediately and the participant will be followed. The participant will be followed per follow-up guidelines described below, with the exception that no tests shall be conducted as part of this study that will jeopardize the fetus and/or mother (e.g., radiographic studies will not be conducted, and study specific blood draws will not be performed). In addition, the site will

contact the participant at least monthly and document the participant's status until the pregnancy has been completed or terminated. The site will report the outcome of the pregnancy to the sponsor without delay and within 24 hours if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The pregnancy will be recorded on the CRF and reported by the investigator to the IRB.

If a participant impregnates their partner, the pregnancy will be recorded on the CRF and reported by the investigator to the IRB. Refer to **Section 10.6**.

7.5.11 USE IN NURSING PARTICIPANTS

Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, participants who are breast-feeding are not eligible to receive ACT Therapy.

7.6 PRECAUTIONARY AND PROHIBITED MEDICATIONS, TREATMENTS, AND PROCEDURES

Except as allowed in this protocol, no concomitant anti-cancer therapy or investigational anti-cancer therapy are allowed during the study (refer to specific inclusion criteria in **Section 4.2.1** and **Section 4.3**). Unless at the discretion of the investigator, the use of herbal or botanicals with anticancer activity is not permitted during the study.

A description of precautionary and prohibited medications for each study drug are provided in the manufacturer's package insert or investigator's brochure for each drug, as well as the corresponding drug-specific appendix (**Appendix A**). Participants must discontinue all prohibited medication(s) prior to initiating study therapy, and remain off these medications thereafter, unless permitted for the management of treatment related toxicity. Each participant assigned to ACT Therapy will undergo review by research pharmacy, per institutional standards, to identify concomitant medications and to adjust or discontinue any medications accordingly. After initiating study therapy, medications are continually reviewed throughout the study and before any new concomitant or supportive medications are prescribed.

For HIV-positive individuals that remain on antiretroviral drugs: If the planned study intervention has known CYP3A/4 interactions, alternative protease inhibitors may be considered (e.g., dolutegravir given with tenofovir/emtracitabine; raltegravir given with tenofovir and emtracitabine).

7.7 OTHER TREATMENT MODALITIES

Any surgery or radiation therapy that is in accordance with institutional standards may, at the discretion of the investigator and in consultation with the treating physician, be documented and used in the management of a participant's disease.

8 STUDY PROCEDURES/EVALUATIONS AND SCHEDULE

8.1 STUDY-SPECIFIC PROCEDURES

All study-specific procedures are described in the ACT Tumor Board Screening and Therapy Screening Schedule of Events (SOE) in **Section 8.5**, the Drug-Specific Screening Assessments in **Appendix A**, and the individual Therapy SOEs in **Appendix A**. The SOEs in **Section 8.5** describe all *general* procedures that occur for all patients during ACT Tumor Board Screening and Therapy Screening period, and the SOEs in **Appendix A** describes all ACT Therapy drug-specific procedures that occur during the Therapy Screening, Baseline, On-Therapy, and Follow-up periods.

8.1.1 DISEASE ASSESSMENT

The investigator, or qualified designee, will obtain prior and current details regarding the participant's cancer. Objective assessment of disease status and response to a study therapy will be assessed using appropriate disease-specific techniques. Efficacy assessments will be performed throughout the study as shown in the applicable Schedule of Events (SOE); however, additional assessments may be performed at any time if clinically indicated. The following disease-response criteria will be used, as applicable, for each of the malignancies included in this study (refer to **Section 9**):

- Solid tumors: RECIST v1.1[18]
- Prostate: RECIST v1.1 and Prostate Cancer Working Group 3 (PCWG3)[19]

8.1.2 PHYSICAL EXAMINATION

Physical exams must be performed by a medically qualified individual such as a licensed physician, Physician's Assistant, or Advanced Registered Nurse Practitioner as local law permits and per institutional standards, in alignment with SOE and endpoint assessments. The physical examination to be conducted may include an evaluation of general appearance; head, ears, eyes, nose, and throat; neck; skin; cardiovascular system; respiratory system; gastrointestinal system; lymphatic system, musculoskeletal system, and nervous system. All other physical exams after Baseline will include an evaluation of any AEs, or any previously reported symptoms, or prior physical examination findings. Clinically significant findings will be recorded as AEs, as described in **Section 10**, in the relevant CRF.

8.1.3 RADIOGRAPHIC OR OTHER IMAGING ASSESSMENTS

The timing of disease assessment that routinely utilizes imaging should be consistent with institutional standards. Imaging may be performed by one or more imaging modalities (e.g., computed tomography [CT], magnetic resonance imaging [MRI], X-ray, ultrasound), but the same imaging technique(s) should be used in a participant throughout the trial. All imaging will be performed according to institutional guidelines. Additional imaging modalities (e.g., bone scans, multi-gated radionucleotide angiography [MUGA]) may be performed as clinically indicated or as required by additional drug-specific appendix assessments.

Up to five index lesions will be identified for solid tumor cancers. These lesions will be followed throughout the study using CT and/or MRI (per institutional standard) and will provide the central basis for assessing responses that will be subject to RECIST 1.1 criteria.

Fluorodeoxyglucose (FDG) PET or PET/CT imaging will only be performed if clinically indicated for participants whose cancer cannot be adequately imaged using CT or MRI. The primary lesion must be ≥1 cm on the baseline anatomic imaging in order for an FDG-PET scan to be performed[18].

8.1.3.1 PROSTATE CANCER - BONE SCAN EVALUATION

Tumor response may also be assessed by standard Tc-99 bone scintigraphy. After the Therapy Screening assessment, the frequency of scans should be in accordance with institutional standards (e.g., every 12 weeks after initiation of the study treatment). PCWG3 criteria will be used to evaluate bone scans (see **Section 9.2**).

Progressive disease indicated by new bone lesions will consist of at least two new lesions verified at least three weeks thereafter in repeat imaging. Increased intensity of lesions on bone scan will not constitute disease progression. Only bone scans may be used to follow sites of disease within boney tissue.

Bone disease seen by CT only (i.e., not visible on bone scan) will not be taken to represent active disease and should not be documented as such since sclerotic lesions seen on CT may represent healed disease or nonmalignant confounders such as bone infarcts or other benign findings.

8.1.4 ASSESSMENT OF PARTICIPANT-REPORTED OUTCOMES (PROS)

Quality of Life (QoL) care metrics (e.g. also referred to as Patient Reported Outcomes "PROs") will be assessed according to the On-Therapy SOE (**Appendix A**). Study participants will be asked to complete a series of questionnaires, prior to receiving study agents (i.e., Baseline), and every three months thereafter for up to one year after discontinuing study therapy (**Table 2**). It may take approximately 15-30 minutes to complete the questionnaires. The surveys may be administered in-person, by phone, or electronically.

Table 2. QoL questionnaires

	Measurement	Baseline (prior to first dose C1D1)	Cycle 3, then every 3 cycles	EOT	Follow-up every 3 months after last dose of study therapy for up to 1 year
QoL	ORTC QLQ-C30	X	X	X	X
QoL	ORTC QLQ FA12	X	X	X	X
QoL	ORTC QLQ INFO25	X	X	X	X

8.1.5 ASSESSMENT OF STUDY AGENT ADHERENCE (DRUG DIARY)

Participants that self-administer (e.g., oral) study agents may be required to maintain a Drug Diary to assess compliance per treatment cycle. In such cases, participants will receive instruction on how to administer study agents from a physician, pharmacist, clinical research nurse, or other designated, qualified healthcare provider. This education will be provided prior to initiation of an ACT Therapy during the Therapy informed consent discussion, which will also utilize the **Study Drug Plan & Acknowledgement Form** and applicable **Drug Information Sheet(s)**. Participants will be provided with a Drug Diary and are required to record the date, dose, and the time of the administration.

8.2 LABORATORY PROCEDURES AND EVALUATIONS

All laboratory assessments will be performed as clinically indicated in accordance with institutional standards. Refer to **Section 8.5** and the drug-specific sub-appendices in **Appendix A** for a schedule of all laboratory tests and procedures. Note, "research blood" as designated in the schedule of events is considered separate and distinct from the clinical laboratory assessments on blood (e.g. CBCs, CMPs, biomarkers, etc., refer to **Section 8.4.2** for more detail on research blood collection).

8.3 SMMART CANCER ANALYTICS RESEARCH

A series of clinical and exploratory assays will be conducted on available participant biospecimens. These assays can be generally divided into clinical assays (SMMART-Clinical Analytics Platform [SMMART-CAP]) that are performed in a CLIA-certified/College of American Pathologists-accredited laboratory such as the Knight Diagnostic Laboratories (KDL), and exploratory assays (SMMART-Exploratory Research Analytics [SMMART-ERA]) performed by individual investigators within their respective laboratories or in research core facilities. If a particular assay is not clinically validated for use in a specific disease, then it will be considered exploratory. These exploratory assays are still considered to be of scientific interest to the investigators but will not be reported back to the participant or used to manage patient care. Exploratory assays will not be considered in SMMART-ACT Tumor Board reviews.

OHSU scientists will conduct or oversee the analysis of clinical and exploratory assay results as well as the integration of these data with patient clinical metadata. However, in some instances, in order to accomplish their scientific objectives, OHSU scientists may work with internal or external collaborators or core facilities who provide essential expertise or capabilities. Study biospecimens, data, or both may be released to co-investigators, collaborating institutions, and commercial laboratories for additional analyses aligned with achieving the aims of this study. All relevant policies and procedures for proper data and sample sharing will be followed, including requirements of de-identification of protected patient information or use of limited data set data. See **Section 13**.

8.3.1 SMMART CLINICAL ANALYTICS PLATFORM (SMMART-CAP)

The specific SMMART-CAP clinical assays to be performed on a study biospecimen sample will be dependent on sample availability and the participant's disease, and the selection of assays will be subject to investigator discretion. All laboratory-developed tests and FDA-approved in vitro diagnostic assays comprising the SMMART-CAP repertoire will be performed by a CLIA-licensed/College of American Pathologists-accredited laboratory. **Appendix B** provides details on SMMART-CAP clinical assays that may be performed. Details and steps of appropriate specimen handling are provided in the SMMART-ACT Laboratory Manual. At the discretion of the investigator, additional clinical assays not offered by the KDL may be requested from other CLIA-certified / College of American Pathologists-accredited laboratories.

8.3.2 SMMART EXPLORATORY RESEARCH ANALYTICS (SMMART-ERA)

The specific SMMART-ERA research assays performed on a study biospecimen sample will be dependent on sample availability, the participant's disease, and relevance to the scientific objectives of this study. The choice of individual SMMART-ERA assays will be subject to investigator discretion. SMMART-ERA

analytics will be performed, or overseen, by OHSU scientists affiliated with the SMMART Program, or performed by external collaborators for approved study-related purposes. **Appendix C** provides details on SMMART-ERA exploratory assays, including the laboratories in which they will be performed. Details and steps of appropriate specimen handling are provided in the SMMART-ACT Laboratory Manual.

8.4 BIOSPECIMEN COLLECTION

Biospecimens collected under this protocol may be fresh, frozen, fixed in formalin, or preserved by other designated methods, as appropriate, based on sample type and intended analyses. A board-certified pathologist will confirm and record tumor content of biopsy tissue. The methods of preservation and handling of biospecimens, as well as assay prioritization, are described in the **SMMART-ACT Laboratory Manual**.

All biospecimens will be given a specimen identification number generated by OHSU's approved Biobank Enterprise Management System (BEMS) and/or a study identification number. Biospecimen tracking procedures must be strictly adhered to under this protocol and should provide a secure and auditable chain of custody. Biospecimens for clinical purposes should be appropriately labeled with identifying information as described in the SMMART-ACT Laboratory Manual to assure adequate clinical reporting of SMMART-CAP assays, including, but not limited to, DNA and RNA analysis. Biospecimens for research purposes will be distributed to laboratories performing SMMART-ERA methods and will be research-labelled according to the SMMART-ACT Laboratory manual. Access to participant information for research assays will be restricted to protect participant confidentiality; researchers will only have access to a limited data set (i.e., dates of treatment, etc.), except in instances where individuals must sign chain of custody documentation during receipt of study biospecimen sample(s) from the study team. In this study, clinical data and remaining excess biospecimens (i.e., not distributed to research labs or consumed in SMMART-CAP assays) will be stored for future research (**Section 13.1.4**).

Participants will receive general information on risks and benefits of the biospecimen collection procedure(s) as part of the informed consent process, as well as a detailed review with the clinical staff performing the specific procedure(s). Designated study team members will work with clinical staff to acquire blood and tissue, process or prepare the biospecimens, and distribute the biospecimens to the appropriate clinical and research laboratories for analysis. Record of participant consent and tracking of the specimens will occur within BEMS and the study records. SMMART-CAP assays will receive priority in the distribution of blood and tissue biospecimens. Any remaining biological specimens may be utilized in other assays (**Section 8.3.2**) and/or stored for future research (**Section 13.1.4**).

Under this protocol, biospecimens that will be collected include samples from a participant's cancer and samples of their peripheral blood. All biospecimens will be collected per institutional guidelines, the timing of which is outlined in the ACT Tumor Board Screening and Therapy Screening Schedule of Events (SOE) in **Section 8.5,** and the drug-specific Therapy SOEs in **Appendix A**.

Archival tissue and the results of previous assays may also be acquired for use under this protocol; archival tissue may be used for clinical and research assays. The archived tissue sample(s) may be formalin-fixed and paraffin-embedded (FFPE) blocks on file within the local pathology department or may require requesting biospecimens from the outside facility that performed the initial diagnostic procedure.

8.4.1 TISSUE COLLECTION

Tumor tissue biopsies, isolated from primary and/or metastatic tumor sites, will be obtained from participants using the least invasive approach that is consistent with institutional standards. Tumor biospecimens will be processed according to the requirements of both the clinical and research assays being performed (e.g., fresh, formalin-fixed paraffin-embedded [FFPE], frozen, etc. [refer to SMMART-ACT Laboratory Manual]). Tumor biospecimens will be collected at time points as outlined in the ACT Tumor Board Screening and Therapy Screening Schedule of Events (SOE) in **Section 8.5,** and the drug-specific Therapy SOEs in **Appendix A**.

Biopsy procedures will be performed according to institutional guidelines and may be excisional, incisional, core needle (image-guided is recommended), or other modalities as appropriate; however, surgical procedures (e.g., EBUS, VATs, etc.) that occur in the operating room and/or that require full anesthesia sedation will not be performed for this study. Participant eligibility and fitness for a tumor tissue biopsy will be assessed on a case-by-case basis by the investigator(s) and radiologists/surgeons before every procedure. Participant safety will be a priority, and if a biopsy is not feasible or creates significant risk to the participant the procedure will not be performed. The investigator(s), in consultation with the radiology staff, must determine the degree of risk associated with the procedure and find it acceptable. Biopsies may be done with local anesthesia or conscious sedation. Institutional guidelines for the safe performance of biopsies should be followed.

In some cases, previously unresectable cancers may later become resectable, via surgery, biopsy, or other tissue collection method, if clinically indicated. In this scenario, participants consenting to this study agree to provide access to the collection of excess tumor tissue that is obtained as part of their clinical procedure performed under standard of care (per institutional standards).

Details for tissue collection parameters, timing, and distribution guidelines are described in the SMMART-ACT Laboratory Manual.

8.4.1.1 PRE-THERAPY BIOPSY

A Pre-Therapy Biopsy is required for all study participants and must be completed prior to the SMMART-ACT Tumor Board for treatment recommendation. If a fresh biopsy collection is not feasible, archival tissue (see **Section 8.4**) may be obtained to perform Pre-Therapy SMMART-CAP analytics, if the procedure occurred within 6 months prior to signing the Tumor Board ICF.

8.4.1.2 ON-THERAPY BIOPSY

An On-Therapy Biopsy is required for all participants approximately two weeks after the first dose of study drug(s) but must occur before starting Cycle 2 (e.g., between C1D14 – C2D1, before dose), regardless of whether the participant is on a monotherapy, or combination regimen. When possible, it is preferable that the On-Therapy Biopsy is collected from the same site as the Pre-Therapy Biopsy; however, it is not a deviation if an alternative site is biopsied. It is always at the clinical discretion of the radiologist to determine the specific anatomical location to biopsy, per patient safety. Note: applicable participants may be permitted to have an On-Therapy Biopsy on the same day as C2D1, as long as it occurs *before* receiving the first dose of C2 therapy. Participants may continue to receive the study agent(s) after their On-Therapy Biopsy in accordance with the biopsy results and the results of ongoing safety and clinical assessments.

Note: If the On-Therapy Biopsy yields insufficient tumor cells for the effective evaluation of planned analytics, including an inability to perform an On-Therapy Biopsy (e.g., due to safety reasons), the participant may:

1. Continue on the assigned study therapy; or
2. Proceed immediately with a second biopsy; or
3. Go off study therapy and enter follow-up period.

If the above situation occurs from insufficient tissue, this will be documented in the EDC.

8.4.1.3 OPTIONAL END-OF-THERAPY BIOPSY

Following disease progression, an End-of-Therapy (EOT) Biopsy is optional, but recommended, and will be acquired in the same way as the On-Therapy Biopsies from participants who have consented to have it. If a surgical procedure is performed for a clinical indication under standard of care (e.g., EBUS, VATS, etc.) or as part of a different research study, excess tumor tissue may be used for research purposes with the consent of the participant (e.g., tag-along or archival tissue). If an EOT Biopsy collection occurs, tissue must be obtained *before* the participant starts a new therapy.

8.4.2 RESEARCH BLOOD COLLECTION

In most cases, research blood samples may be drawn at the time of another scheduled blood collection for routine clinical purposes, via peripheral draw or central line (as applicable). When this is not possible, a research-only blood draw may be undertaken. Blood may be collected at the time points per the ACT Tumor Board Screening, ACT Therapy Screening, On-Therapy, End of Therapy, and Follow-up durations, as defined in **Section 8.5** and the drug-specific appendices in **Appendix A**. Research blood may also be collected any time a participant has a bone marrow biopsy and/or aspiration, biopsy, or other tissue collection procedure.

Under this protocol, up to approximately 65 mL of research blood may be collected at each blood draw, per the **SMMART-ACT Laboratory Manual**. Research blood collection volume is distinct from, and in addition to, the volume of blood required for general clinical labs and according to institutional SOC guidelines.

8.5 SCHEDULE OF EVENTS (SOE)

8.5.1 GENERAL SOE - ACT TUMOR BOARD SCREENING & ACT THERAPY SCREENING

General procedures and assessments that are required for all participants during the ACT Tumor Board Screening and ACT Therapy Screening periods, are described in the table below. **Additional Drug-Specific assessments** that must also be competed for ACT Therapy Screening are located in the Drug Manufacturer-Specific **sub-appendices of Appendix A**.

General Assessments / Procedures	ACT Tumor Board Screening[1]	ACT Therapy Screening[2]
Timeframe	**-90 days**	**-28 days to C1D1 (before drug)**

ACT Tumor Board Informed Consent Form (ICF)[A]	**X**	
General ACT Tumor Board Screening Eligibility Criteria	X (see Section 4.1)	
Disease-Specific Eligibility Criteria		X (see section 4.3)
Medical History	X[3]	X[4]
Concomitant Medications	X[5]	X[6]
Tumor Imaging	X[7]	X[8]
Bone scan (scintigraphy) (**for Prostate cancer only**)		X (see Section 8.1.3.1)
Biopsy Tissue Collection	X[9]	
Research Blood	X[10]	X[11]
Adverse Event Evaluation[12]	X[13]	
ACT Tumor Board	X[14]	
ACT Therapy Informed Consent Form (ICF)[B]		**X**
General ACT Therapy Screening Eligibility Criteria		X (refer to Section 4.2)
Drug-Specific Eligibility Criteria		X (refer to Appendix A)
Drug-Specific Screening Assessments		X (refer to Appendix A)
Disease Assessment[15]		X
Physical Exam[16]		X
Vital Signs[17]		X
ECOG PS		X
Hepatitis Screening[18]		X
Complete Blood Count (CBC) w/Diff[19]		X
Comprehensive Metabolic Panel (CMP)[20]		X
Coagulation Panel (PT/INR, aPTT)		X
Pregnancy Test		X[21]
Urinalysis[22]		X
ECG[23]		X
Serum Biomarkers[24]		X
PROs[25]		X

FOOTNOTES

A. ACT Tumor Board Screening ICF must be signed by the participant before undergoing any of the activities listed in Tumor Board Screening.

B. ACT Therapy ICF must be signed by the participant before undergoing any of the activities listed in ACT Therapy Screening, unless otherwise indicated.

1. Individuals must meet Tumor Board Screening criteria and fulfill all Tumor Board Screening requirements before they can proceed to sign the ACT Therapy ICF. Other testing may be necessary based on specific needs of cancer type.

2. A Therapy Screening Visit may occur as part of SOC. If a participant is eligible for the study after review of key inclusion/exclusion criteria, additional Therapy Screening Visits may be scheduled while study members are requesting insurance authorization to participate in a clinical trial. If laboratory or imaging procedures were performed for alternate reasons prior to signing consent, these results can be used for ACT study purposes (with consent of the participant). However, all Therapy Screening laboratory and imaging results must have been obtained within 28 days prior to C1D1, unless otherwise specified.

3. Medical history collection during Tumor Board Screening will include information on all active conditions, and any condition diagnosed within the prior 10 years, that are considered to be clinically significant by the investigator. Details regarding the participant's cancer will be recorded separately and not listed as medical history. Medical history must also be reviewed for pre-existing autoimmune diseases and immune deficiencies (Refer to **Section 4.2.2.1**).

4. Medical history will be collected/reconfirmed again during ACT Therapy Screening, prior to starting C1D1, in case any changes have occurred since the Tumor Board Screening collection. Medical history must also be reviewed for pre-existing autoimmune diseases and immune deficiencies (Refer to **Section 4.2.2.1**).
5. During Tumor Board Screening, review of concomitant medications will be collected in preparation for fresh tissue biopsy and safety considerations (e.g., anticoagulants and NSAIDs). If archival tissue is obtained in lieu of undergoing a fresh tissue biopsy, review of concomitant medications for this purpose will not be necessary.
6. Concomitant medications will be collected/reconfirmed again during ACT Therapy Screening, prior to starting C1D1, in case any changes have occurred since the Tumor Board Screening collection (if collected). Refer to Section 4.2.1, Section 4.3, Section 7.5, Section 7.5.1, and Section 7.6 for further detail.
7. During Tumor Board Screening, if recent scans are unavailable and new imaging is needed in order for radiology to assess feasibility to perform a biopsy (for fresh tissue collection), new scans may be ordered for RES biopsy purposes.
8. Tumor imaging scans are required during ACT Therapy Screening. If a tumor imaging scan was performed during Tumor Board Screening for biopsy, and it is within 28 days of C1D1, a new scan does not need to be repeated for the ACT Therapy Screening timepoint. If the Tumor Board Screening scan is beyond 28 days of C1D1, a new ACT Therapy Screening tumor imaging scan is required.
9. A Tumor Board Screening Biopsy collection is mandatory for participation and SMMART-CAP analytics. A fresh tissue biopsy is preferred; however, if a fresh biopsy collection is not feasible, archival tissue may be obtained for analysis. If archival tissue is used to fulfil the Tumor Board Screening requirement, the tissue collection procedure must have occurred within 6 months prior to signing the Tumor Board Screening ICF. Refer to **Section 8.4** for details regarding tumor sample. Complete processing of assays (including return of treatment recommendation) may take approximately 28 days from receipt of tissue.
10. Research blood should be collected during Tumor Board Screening if a fresh biopsy occurs, in which case research blood would be collected on the day of biopsy. If archival tissue is collected in lieu of a fresh-tissue biopsy, research blood may be collected during the ACT Therapy Screening period instead. See **Section 8.4.2** for information on research blood samples and their collection.
11. Research blood does not need to be collected during the ACT Therapy Screening period if it was already collected during a Tumor Board Screening Biopsy.
12. Adverse events will be assessed using the NCI CTCAE 5.0. Abnormal laboratory values will only be recorded as an AE if determined to be clinically significant by the investigator. Refer to **Section 10** for specific AE collection and reporting guidance.
13. During Tumor Board Screening, only AEs related to study specific interventions (e.g., Tumor Board Screening Biopsy, research blood collection) will be recorded. Refer to **Section 10.5** for additional guidance.
14. To move from ACT Tumor Board Screening to Therapy Screening, participants must have received a treatment recommendation from the SMMART-ACT Tumor Board, based on the results of one or more clinical assays comprising the SMMART-CAP from Pre-Treatment Biopsy, that matches one or more of the RP2D study interventions listed in corresponding drug-specific sub-appendices (**Appendix A**).
15. Participants must have objectively-assessable disease for study eligibility according to RECIST v1.1 or PCWG3 criteria.
16. Physical exams must be performed by a medically qualified individual such as a licensed physician, Physician's Assistant, or Advanced Registered Nurse Practitioner as local law permits and per institutional standards. A full physical exam will be performed at Screening, with a targeted physical exam at all other time points.
17. Routine vital signs to be performed include weight, blood pressure, heart rate, temperature, and oxygen saturation by pulse oximetry.
18. Hepatitis C testing does not need to be repeated if performed during Tumor Board Screening and not explicitly required for the assigned study intervention.
19. CBC with differential may include basophils, eosinophils, hematocrit, hemoglobin, lymphocytes, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, mean corpuscular volume, monocytes, neutrophils, platelet count, red blood cell count, and total white cell count.
20. CMP may include glucose, calcium, albumin, total protein, sodium, potassium, bicarbonate (total CO2), chloride, blood urea nitrogen (BUN), creatinine, alkaline phosphatase, alanine amino transferase (ALT, SGPT), aspartate amino transferase (AST, SGOT), and bilirubin.
21. In Participants of Childbearing Potential, a urine pregnancy test is required at ACT Therapy Screening and within 14 days prior to C1D1. If a urine pregnancy test is positive, a serum pregnancy test must be performed per institutional standards.

22. Dipstick urinalysis to include bilirubin, blood, glucose, ketones, pH, protein, specific gravity, color, and appearance, nitrite, leukocyte esterase. Microscopy should be used as appropriate to investigate white blood cells and use the high-power field for red blood cells.
23. Resting 12-lead ECG to be performed only as clinically indicated at ACT Therapy Screening.
24. Specific markers will be performed based on disease type (e.g., Cancer antigen [CA15-3/CA27-29], Carcinoembryonic antigen [CEA], Prostate-specific antigen [PSA]).
25. Study participants will be asked to complete a series of questionnaires. Refer to Table 2 for details.

8.5.2 GENERAL SOE - ON-THERAPY, END OF THERAPY, & FOLLOW-UP

Refer to the Drug-Specific sub-appendices of **Appendix A** for the schedule of events of procedures and assessments that are required for participants during On-Therapy (C1D1+), End of Therapy, and through Follow-up. There are two separate cycle lengths in this study: a **21-Day Cycle** and a **28-Day Cycle**. The assessment schedule duration shall be used according to each participants' specific cycle length, depending on the specific ACT therapy regimen assigned to that participant.

9 EFFICACY MEASURES

9.1 SOLID TUMOR EFFICACY MEASURES

Tumor response will be determined per the investigator's assessment, according to Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1)[25].

9.1.1 DEFINITION OF EFFICACY MEASURES

Measurable disease: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded for non-nodal lesions and short axis for nodal lesions) as >20 mm by breast x-ray, as >10 mm with CT scan, or >10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be >15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At Baseline and in Follow-Up, only the short axis will be measured and followed.

Non-measurable disease: All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

Cystic lesions thought to represent cystic metastases can be considered measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same participant, these are not preferred for selection as target lesions.

Target lesions: All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at Baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs but, in addition, should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the Baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The Baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions: All other lesions (or sites of disease) including any measurable lesions over and above the five target lesions should be identified as non-target lesions and should also be recorded at Baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout Follow-Up.

9.1.2 DISEASE EVALUATION

All measurements should be taken and recorded in metric notation using a ruler, calipers, or a digital measurement tool. All Baseline evaluations should be performed as closely as possible to the beginning of study therapy (prior to first dose of C1D1) and never more than 4 weeks before the beginning of the study therapy.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at Baseline and during Follow-Up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Breast x-ray. Lesions on breast x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung; however, CT is preferable.

Conventional CT. This guideline has defined measurability of lesions on CT scan based on the assumption that CT thickness is 5mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size of a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g., for body scans).

Endoscopy, Laparoscopy. Useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) is an endpoint.

Cytology, Histology. These techniques may be used to differentiate between partial responses (PR) and complete responses (CR).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during study therapy when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the study therapy) and progressive disease.

9.1.3 DISEASE-SPECIFIC MEASURES

Tumor markers (e.g., CA19-9, CA15-3, CA27-29, CEA) will be monitored as clinically indicated. Changes in tumor marker levels will be used to assist clinicians as part of their global assessment of clinical benefit.

Imaging response will be used as the primary determinant of response to study therapy. If radiographic images reveal progression of disease, then tumor assessment should be repeated ≥ 4 weeks later to confirm progression of disease. In the interval, clinicians have the option of continuing study therapy while awaiting radiographic confirmation. If the repeat scans fail to confirm progression of disease, study therapy may be continued/resumed as per protocol guidelines.

For prostate cancer (PCa), blood levels of PSA will be assessed monthly while on study therapy. This is considered a surrogate marker of disease status that historically has been used to make response determinations and will be used in this regard in the current study. PSA response will be determined per Prostate Cancer Working Group 3 Guidelines[19,26], as follows:

- Baseline PSA will be defined as the measurement obtained immediately *prior* to initiation of a given study therapy (prior to first dose of C1D1).
- PSA Response: a ≥50% reduction after the initiation of study therapy vs. Baseline.
- PSA Progression:
    - If PSA has declined from Baseline: progression is defined as time from start of study therapy to first PSA increase that is ≥25% and ≥2 ng/mL above the nadir and which is confirmed by a second value 3 or more weeks later.
    - If there is no decline from Baseline: progression is defined as PSA increase ≥25% and ≥2 ng/mL, which is confirmed by a second value 3 or more weeks later.
    - Nadir will be defined as the lowest PSA value that was confirmed by a second equal or lower measurement. (Thus, the nadir PSA is the second lowest PSA value measured.)
- Stable PSA: Does not meet criteria for response or progression.

9.1.4 EVALUATION OF TARGET LESION

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

- *Kaposi Sarcoma*: No detectable residual disease and no tumor-related edema for at least 4 weeks.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

- *Kaposi Sarcoma*: No new mucocutaneous lesions, visceral disease, or worsening tumor-related edema. Existing sites show a 50% reduction in (1) the number of lesions, (2) the form of lesions (i.e. flattening of raised lesions), and/or (3) the sum of the products of the largest perpendicular

diameters of five measurable lesions. If residual tumor-related edema is present despite meeting CR criteria, the response is still characterized as a PR.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

- *Kaposi Sarcoma*: Increase of more than 25% in (1) the size of existing lesions and/or (2) the number of existing lesions that have more nodular or plaque-like form, or the development of new sites of disease.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

- *Kaposi Sarcoma*: No PR, CR, or PD.

9.1.5 EVALUATION OF NON-TARGET LESION

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis). Note: If tumor markers are initially above the upper normal limit, they must normalize for a participant to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of non-target lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the lead sub-investigator or principal investigator.

9.1.6 EVALUATION OF NEW LESIONS

The finding of a new lesion should be unequivocal (i.e., not due to difference in scanning technique, imaging modality, or findings thought to represent something other than tumor, for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). However, a lesion identified on a follow-up scan in an anatomical location that was not scanned at Baseline is considered new and will indicate PD. If a new lesion is equivocal (because of small size, etc.), follow-up evaluation will clarify if it truly represents new disease and if PD is confirmed, progression should be declared using the date of the initial scan on which the lesion was discovered.

Overall Response: Participants with target (+/- non-target) disease

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD or NE	No	PR

CR	Note evaluated	No	PR
PR	Non-CR/non-PD or NE	No	PR
SD	Non-CR/non-PD or NE	No	SD
PD	Any	Yes or No	PD
Any	PD***	Yes or No	PD
Any	Any	Yes	PD

***In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.
Note: Participants with a global deterioration of health status requiring discontinuation of study therapy without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of study therapy.
Source: Eisenhauer, et al.[25]

Note: Participants receiving protocol-defined immune-modulated agents per the respective drug-specific appendix (**Appendix A**) will also be monitored for pseudoprogression. Pseudoprogression is the uncommon phenomenon in which an initial increase in tumor size occurs or new lesions appear, typically within 12 weeks from the start of immunotherapy, followed by a decrease in tumor burden. If pseudoprogression is suspected, the treating provider will bring any suspected pseudoprogression to the attention of the principal investigator, and at the PI's and treating provider's discretion, the participant will continue with immunotherapy. Participants may be allowed to continue immunotherapy when they meet PD based on RECIST v1.1 but pseudoprogression is suspected, as long as they do not have any deterioration in performance status or signs or symptoms of unequivocal PD or PD at sensitive sites.

9.2 PCWG3 PROCESS FOR ASSESSMENT OF BONE LESION

For prostate disease, rules for evaluation of response and progression based on bone lesions will be guided by Prostate Cancer Working Group 3 (PCWG3) criteria[19]. Bone disease will be classified as PD (progressive disease), PDu (progressive disease unconfirmed), Non-PD (no progressive disease), NED (no evidence of disease), or NE (non-evaluable). The definitions are summarized in Table 3.

Table 3. Bone Lesion Progression

Bone Response	Definition
PD	**Progressive disease:** 2 new lesions, not flare, persistent
PDu	**Progressive disease unconfirmed:** Temporary marker of possible PD, to be updated to PD or non-PD once a subsequent scan is available. If this is the final visit, the visit response will remain PDu, but is updated to PD during analysis
Non-PD	**Non-progressive disease:** At least one bone lesion present, but not enough to trigger PD
NE	**Non-evaluable:** Status of bone lesions cannot be determined (scan quality, scan missing, etc.)
NED	**No evidence of disease:** No lesions seen on bone scan

9.2.1 DESCRIPTIONS OF BONE RESPONSE CATEGORIES

9.2.1.1 NO EVIDENCE OF DISEASE

No lesions seen on bone scan at this visit. Either none were seen at Baseline, or all completely resolved on subsequent imaging.

9.2.1.2 NONPROGRESSION (NON-PD)

At least one bone lesion is present on the scan at this visit, but the conditions for progression have not been met, because there are not at least two new lesions present.

9.2.1.3 UNCONFIRMED PROGRESSIVE DISEASE (PDU)

At least two new bone lesions are present, but an additional scan is required for confirmation. This response category is meant as a placeholder that reflects temporary uncertainty and is updated to PD or non-PD once a subsequent bone scan is available.

9.2.1.4 PROGRESSIVE DISEASE (PD)

At least two new bone lesions are present, which have been confirmed to not represent flare or any other confounder (see below), and which are persistent for at least 6 weeks. The new bone lesions do not all have to appear at the same time. Thus, if one new lesion appears at visit N, and another new lesion at visit N+1, visit N+1 is considered to represent progressive disease.

9.2.1.5 CONFIRMATION OF PROGRESSION

Radiographic progression of bone lesions is defined as the appearance of ≥2 new bone lesions on radionuclide bone scan. When ≥2 new bone lesions are first observed, this is classified as PDu, which marks the possibility of progression that will be resolved by the next scan.

9.2.1.6 FOR NEW LESIONS WITHIN THE FLARE WINDOW (<12 WEEKS)

After a scan classified as PDu within the first 12 weeks of study therapy, if the next bone scan outside the flare window shows at least two additional new bone lesions (in addition to the new lesions seen on the prior scan), the initial progression is considered confirmed, and the bone scan response updated to PD. Because this requires at least 2 new lesions, followed by another 2 new lesions, this is known as the “2+2 rule”.

If the next bone scan outside the flare window does not show at least two additional new bone lesions, the lesions seen on the prior scan within the flare window are considered to be pre-existing lesions that became more visible because of the tumor flare phenomenon.

- The bone response at the prior visit is updated to non-PD.

- The bone lesions seen within the flare window are ignored for the purposes of counting new lesions at later time points, since they were not new. This may be referred to as “re-baselining”.

9.2.1.7 FOR NEW LESIONS OUTSIDE THE FLARE WINDOW (>12 WEEKS)

After a scan classified as PDu after the first 12 weeks of study therapy, if at least 2 of the new lesions seen on that scan persist on the next bone scan performed at least 6 weeks later, this confirms the initial progression. The prior response is then updated to PD. If the new lesions have disappeared on this later scan, the prior response is updated to non-PD because these lesions are presumed to be nonmalignant in nature. No re-baselining of lesions will occur in this scenario.

10 SAFETY

10.1 SPECIFICATION OF SAFETY PARAMETERS

The investigator is responsible for monitoring the safety of participants who have initiated study therapy. Safety assessments will be based on medical review of adverse events and the results of safety evaluations at specified time points as described in the Schedule of Events (SOE) in **Section 8.5** and the drug-specific sub-appendices in **Appendix A**. Any clinically significant adverse events that meet the collection criteria and parameters defined in the sections below that are persisting at the End-of-Therapy visit will be followed by the investigator until resolution/stabilization or death, whichever comes first.

10.2 DEFINITIONS

10.2.1 ADVERSE EVENT (AE)

An adverse event is defined as any untoward medical occurrence associated with the use of drug in humans, whether or not considered drug related (21 CFR 312.32 (a)). In general, this includes signs or symptoms experienced by the participant from the time of signing the informed consent to completion of the study. Adverse events will be assessed using the NCI CTCAE 5.0. Abnormal laboratory values will only be recorded as an AE if determined to be clinically significant by the investigator.

Clinical procedures may also result in AEs. Only AEs resulting from clinical procedures performed solely for research purposes of this clinical trial will be recorded.

AEs may include, but are not limited to:

- Subjective or objective symptoms spontaneously offered by the participant and/or observed by the investigator or medical staff.
- Clinically significant laboratory abnormalities.
- A significant worsening of the participant’s condition from study entry.

- Disease signs and symptoms and/or laboratory abnormalities existing prior to the use of the study therapy that resolve but then recur after treatment.
- Disease signs and symptoms and/or laboratory abnormalities existing prior to the use of the study therapy that increase in frequency, intensity, or a change in quality after treatment.

10.2.2 SERIOUS ADVERSE EVENT (SAE)

An AE or suspected adverse reaction is considered "serious" if, in the view of either the investigator or Sponsor-investigator, it results in *any* of the following outcomes:

- Death
- A life-threatening adverse event (i.e., the AE, in the view of the investigator, places the participant at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.)
- Inpatient hospitalization or prolongation of existing hospitalization.
- Persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the participant's ability to conduct normal life functions).
- A congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the IMP.

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/or the participant 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.
- The development of drug dependency or drug abuse.

10.2.3 TREATMENT EMERGENT ADVERSE EVENTS (TEAE)

TEAE is defined as an adverse event observed after starting study therapy that is related, or possibly related, to the study therapy, as assessed by the investigator.

10.2.4 UNANTICIPATED PROBLEMS (UP)

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

1. 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;
2. 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
3. Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than previously known or recognized.

This study will use the OHRP definition of UP.

10.2.5 SEVERITY OF EVENT

The investigator will grade the severity of each AE using, when applicable, the current version of the **CTCAE v5.0**.

In the event of an AE for which *no grading scale exists*, the investigator will classify the AE as defined below:

Grade 1:	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2:	Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.
Grade 3:	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
Grade 4:	Life-threatening consequences; urgent intervention indicated.
Grade 5:	Death related to AE.

Note: a semi-colon indicates 'or' within the description of the grade.

Please note that there is a distinction between **serious** and **severe** AEs: Severity is a measure of intensity whereas seriousness is defined by the criteria in Section **10.2.2**. For example, a mild degree of gastrointestinal bleeding requiring overnight hospitalization for monitoring purposes may be considered an SAE but is not necessarily severe.

10.2.6 ASSESSMENT OF CAUSALITY RELATIONSHIP TO STUDY INTERVENTION

For all collected AEs, the clinician who examines and evaluates the participant will determine the AE's causality based on temporal relationship and their clinical judgment. The degree of certainty about causality will be graded using the categories below:

Definitely Related:	There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.
Possibly Related:	There is some evidence to suggest a causal relationship.
Unrelated:	The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology.

10.3 EXPECTEDNESS

The investigator will be responsible for determining whether an AE is expected or unexpected.

Expected adverse events are those adverse events that are listed or characterized in the current package insert or investigator's brochure.

Unexpected adverse events are those not listed in the current package insert or investigator's brochure or not otherwise identified. This includes adverse events for which the specificity or severity is not consistent with the description in the package insert or investigator's brochure. For example, under this definition, hepatic necrosis would be unexpected if the current package insert or investigator's brochure only referred to elevated hepatic enzymes or hepatitis.

For participants receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

10.4 ADVERSE EVENT LISTS

Refer to the package insert or investigator's brochure for descriptions of AEs associated with each study intervention.

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

The occurrence of an UP, AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, upon review by a study monitor, or during an audit. Abnormal laboratory values will only be recorded as an AE if determined to be clinically significant by the investigator. All AEs grade 2+ that are related to study interventions, including local and systemic reactions not meeting the criteria for SAEs, will be captured on the appropriate CRF, as well as all AEs referenced in **Section 10.7** (inclusive of grade 1+ for a limited set), and all AESIs defined in **Appendix A** for each drug. Information to be collected includes event description, time of onset, clinician's assessment of severity, seriousness, expectedness, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and date of resolution/stabilization of the event. All AEs grade 2+ will be followed to adequate resolution, in addition to the limited set of AEs in **Section 10.7** and AESIs in **Appendix A**.

Any medical condition that is present at the time that the participant is screened for ACT Therapy will be considered as baseline and not reported as an AE.

Changes in the severity of an AE will be documented to allow an assessment to be performed of the duration of the event at each level of severity.

After informed consent has been obtained but prior to initiation of study therapy, only adverse events grade 2 or higher that are related to study-specific interventions (e.g., biopsy, blood collection) will be recorded, per investigator discretion. If a participant receives an interim line of treatment during the Tumor Board Screening phase (per SOC), then AEs related to the interim treatment will not be collected or reported.

After initiation of study therapy, adverse events will be reported until baseline is achieved, the event is assessed as stable by the investigator, initiation of new systemic anti-cancer therapy, the participant is lost to follow-up, or the participant withdraws consent, whichever occurs first. Participants removed from study therapy for unacceptable AE(s) will be followed until resolution or stabilization of the AE.

During follow-up, only serious adverse events that are assessed to be related or possibly related will continue to be reported until 90 days after the last dose of study therapy or until initiation of new systemic anti-cancer therapy, whichever occurs first. After this period, SAEs will only be reported if the investigator becomes aware of an event, and it is believed to be related to prior exposure to study therapy. In addition to these standard reporting guidelines, participants may also need to be monitored for specific AESIs, Special Situation Reports (e.g., pregnancy reports) and Product Complaints as designated by the manufacturer for the duration of study therapy and for 90 days after the last dose of study therapy or until initiation of new systemic anti-cancer therapy, whichever comes first. Please see corresponding drug-specific appendices (**Appendix A**) for AESIs, definitions of resolution for select AEs, and additional manufacturer reporting guidelines.

If the investigator should become aware of the development of cancer or a congenital anomaly in a subsequently conceived offspring of a participant (including pregnancy occurring in the partner of a study participant) who participated in the study, this should be reported as an SAE to the manufacturer as described in the corresponding drug-specific appendices.

10.5.1 PROCEDURES FOR ELICITING AND RECORDING ADVERSE EVENTS

A consistent methodology for eliciting AEs at all participant evaluation time points should be adopted. Examples of non-directive questions include:

- "How have you felt since your last clinical visit?"
- "Have you had any new or changed health problems since you were last here?"

10.5.2 SPECIFIC INSTRUCTIONS FOR RECORDING ADVERSE EVENTS

Investigators should use correct medical terminology/concepts when reporting AEs or SAEs. Avoid colloquialisms and abbreviations.

10.5.2.1 DIAGNOSIS VS. SIGNS AND SYMPTOMS

If known at the time of reporting, a diagnosis should be reported rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, it is acceptable to report the information that is currently available. If a diagnosis is subsequently established, it should be reported as follow-up information.

10.5.2.2 DEATHS

All deaths that occur during the protocol-specified AE reporting period as defined in the SOEs, regardless of attribution, will be reported to the appropriate parties. When recording a death, the event or condition that caused or contributed to the fatal outcome should be reported as a single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, report "Unexplained Death".

10.5.2.3 PREEXISTING MEDICAL CONDITIONS

A preexisting medical condition is one that is present prior to the start of the study therapy. Such conditions should be reported as medical and surgical history. A preexisting medical condition should be re-assessed throughout the trial and reported as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When reporting such events, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

10.5.2.4 HOSPITALIZATIONS FOR MEDICAL OR SURGICAL PROCEDURES

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE. If a participant is hospitalized to undergo a medical or surgical procedure as a result of an AE, the event responsible for the procedure, not the procedure itself, should be reported as the SAE. For example, if a participant is hospitalized to undergo coronary bypass surgery, record the heart condition that necessitated the bypass as the SAE.

Hospitalizations for the following reasons do not require reporting:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for preexisting conditions
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study
- Hospitalization or prolonged hospitalization for scheduled therapy of the target disease of the study

10.6 REPORTING PROCEDURES

For purposes of this study, *generally* only grade 2 and above adverse events related to study-specific interventions will be collected and reported. However, specific adverse events of any grade that impact the study stopping rules, as defined in **Section 10.7**, must also be collected, as well as any **AESIs as defined in Appendix A** for each study drug.

For collection of adverse events from research tissue and research blood collection procedures performed specifically for this study, the study team will collect and report any grade 2 or above adverse events that occur within two weeks of the procedure. Participants will be contacted by a member of the study team to assess for any research biopsy-related adverse events or if a research-only blood collection procedure was performed. If the study team does not learn of any adverse events related to the study procedures from participants within two weeks, or see any documented in the participant's study record, it will be concluded the participant did not experience any adverse events related to the research tissue or research blood collection procedures.

10.6.1 OHSU IRB REPORTING OF UNANTICIPATED PROBLEMS AND ADVERSE EVENTS

Unanticipated Problems and AEs will be reported to OHSU IRB according to the policies, procedures and guidelines posted on the OHSU IRB website.

Events that must be reported by the Investigator to the IRB are detailed in the OHSU IRB **Investigator Guidance: Prompt Reporting Requirements (HRP-801)**. Events that meet the criteria for OHSU Reportable New Information (RNI) must be reported to the IRB within 5 days of learning of the event. At a minimum, events requiring reporting to the IRB include:

- Any new or increased risk related to the research, including AEs or IND safety reports that require a change to the protocol or consent
- New FDA black box warning
- Publications identifying new risks
- Data Safety Monitoring Board/Committee letters recommending changes or discussing new risks
- Unanticipated adverse device effect
- Unauthorized disclosure of confidential participant information

10.6.2 FDA REPORTING

For studies conducted under an IND/IDE, the Sponsor Institution (OHSU) is required to report certain events to the FDA per applicable regulations.

MedWatch 3500A Reporting Guidelines
In addition to completing appropriate participant demographic (Section A) and suspect medication information (Section C and D), the report should include the following information within the Event Description (Section B.5) of the MedWatch 3500A form:

- Protocol number and title description
- Description of event, severity, treatment, and outcome if known
- Supportive laboratory results and diagnostics (Section B.6)
- Investigator's assessment of the relationship of the adverse event to each investigational product and suspect medication

Follow-up Information
Additional information may be added to a previously submitted report by any of the following methods:

- Adding to the original MedWatch 3500A report and submitting it as follow-up
- Adding supplemental summary information and submitting it as follow-up with the original MedWatch 3500A form
- Summarizing new information and sending it with a cover letter including participant identifiers (i.e., D.O.B. initial, participant number), protocol description and number, if assigned, brief adverse event description, and notation that additional or follow-up information is being submitted (the participant identifiers are important so that the new information is added to the correct initial report)

MedWatch 3500A (Mandatory Reporting) form is available at
https://www.fda.gov/media/69876/download

10.6.3 SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTIONS (SUSAR)

Per regulatory requirements, if an event is assessed by the Sponsor Institution as a Serious Unexpected Adverse Reaction (SUSAR), it is the responsibility of the Sponsor Institution (OHSU) to submit the SUSAR to Regulatory Authorities according to applicable regulations.

10.6.4 MANUFACTURER REPORTING REQUIREMENTS

Additional manufacturer reporting requirements are described in the respective drug-specific appendices (**Appendix A**).

10.6.5 REPORTING OF PREGNANCY

To ensure participant safety, each pregnancy in a participant on study therapy must be reported within 24 hours of learning of its occurrence. The pregnancy should be followed to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or any pregnancy- or childbirth-related and/or newborn complications.

The pregnancy should be recorded on the pertinent CRF and reported by the investigator to the manufacturer of the study drug as described in the corresponding drug-specific appendices (**Appendix A**). Pregnancy follow-up should be reported using the same form. Any SAE experienced during pregnancy (e.g., maternal serious complications, therapeutic abortion, ectopic pregnancy, stillbirth, neonatal death, congenital anomaly, birth defect) must be reported to the IRB and manufacturer of the study drug as described in the respective drug-specific appendices.

If while on study therapy a participant's sexual partner becomes pregnant, the pregnancy and pregnancy outcomes must also be reported as described above. Consent to report information regarding the pregnancy should be obtained from the pregnant individual.

10.7 STUDY STOPPING RULES

The overall study will be paused and appropriate authorities (e.g., IRB, Knight Data and Safety Monitoring Committee) notified if the following events occur:

- Life-threatening CTCAE grade 4 toxicity attributable to protocol therapy that is unmanageable, or unexpected.
- Death suspected to be related to a study agent.
- 30% of participants experience the toxicities in the following table:

Hematologic AEs	• CNS hemorrhage, any grade • Grade ≥2 hemorrhage (hemoptysis, as 2.5 mL bright red blood per episode) • Grade ≥3 hemorrhage (other)
Non-hematologic AEs	• Grade ≥3 laboratory increased serum transaminases (AST/ALT) in combination with Grade ≥3 laboratory hyperbilirubinemia • Grade ≥3 left ventricular dysfunction or absolute decrease from baseline of >10% for LVEF and/or LVEF is > institutional lower limit of normal (ILLN)

	• Grade ≥3 dysrhythmia AEs • Grade ≥2 ocular events including, but not limited to, serous retinopathy or retinal vein occlusion • Grade ≥3 cytokine release syndrome (CRS) • Grade ≥2 wound dehiscence • Grade ≥3 bronchospasm (allergy related edema/angioedema; hypotension) requiring intravenous intervention • Grade ≥3, Venous Thromboembolic Event (VTE) with thromboemboli that worsen/recur upon re-challenge • Grade ≥3 nephrotic syndrome • Unresponsive Grade ≥3 rhabdomyolysis which may include, but not be limited to, CPK elevation and myalgia
Suspected or confirmed adverse reactions to study drug	• Unresolved prolongation of QTc by > 500 ms and/or > 60 ms from baseline • Asymptomatic cardiomyopathy • Immune-mediated myocarditis • Interstitial lung disease (ILD) / pneumonitis • Arterial Thromboembolic Event (ATE), any grade • Suspected or confirmed hemophagocytic lymphohistiocytosis (HLH) or macrophage activation syndrome (MAS) • Drug reaction with eosinophilia and systemic symptoms (DRESS) • RPLS (Reversible Posterior Leukoencephalopathy syndrome or PRES (Posterior Reversible Encephalopathy Syndrome), any grade • Unresponsive Grade ≥3 dermatologic reactions to study drug including, but not limited to, severe cutaneous adverse reactions (SCARs), such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) • Perforation (GI, or any other organ), any grade • Fistula (in any internal organ), any grade • Drug reaction with eosinophilia and systemic symptoms (DRESS)

11 STATISTICAL CONSIDERATIONS

A separate Statistical Analysis Plan will provide details of the statistical analyses that are outlined in this protocol.

11.1 STATISTICAL HYPOTHESIS

This study will test the hypothesis that the SMMART-ACT strategy for the implementation and assessment of individualized therapies for advanced solid cancers based on a set of approved and investigational agents is feasible. The design of these treatment plans is based on a SMMART-ACT Tumor Board review of an individual's tumor biology and medical history.

The SMMART-ACT strategy will be considered feasible if at least 75% of participants who receive a SMMART-ACT Therapy recommendation from the ACT Tumor Board start their recommended SMMART-ACT Therapy (i.e., receive C1D1 of an ACT study therapy as part of this study).

11.2 SAMPLE SIZE DETERMINATION

This feasibility study will enroll 30 participants. To achieve 30 enrolled participants, and account for drop-out, we will consent up to 38 patients.

A formal power analysis is not applicable and has not been conducted for this descriptive feasibility pilot. With a sample size of 30, the 95% confidence interval width is 0.2742 using The Exact (Clopper-Pearson) formula when ORR assumes to be 0.14. An ORR of 14% based on three prior studies examining ORR of participants that did or did not receive matched targeted therapy for their refractory cancer may be considered as a benchmark for this study. An ORR of 14% based on three prior studies examining ORR of participants that did or did not receive matched targeted therapy for their refractory cancer may be considered as a benchmark for this study. The IMPACT study[20] reported an ORR of 16.4% and 5.4%, respectively, among participants that did or did not receive matched targeted therapy[20]. In the MOSCATO 01 study, 843 heavily pretreated patients with advanced solid tumors were offered molecular characterization of their tumors, of which 411 (49%) patients had an actionable target. Of that group, 199 participants were treated based on their genomic alteration, which resulted in an ORR of 11% (22 of 194 participants)[21]. In the SHIVA trial, 293 participants with a solid tumor carrying a molecular alteration that matched one of 10 targeted treatment groups were randomized to either a matched molecularly targeted agent (n=99), or control arm (n = 96). Of the evaluable population, four (4, or 4.1%) objective responses were observed among those that received a matched molecularly targeted agent (n=98), compared to three (3, or 3.4%) in the control group (n=89)[22].

11.3 POPULATIONS FOR ANALYSES

11.3.1 FEASIBILITY POPULATION

The feasibility population set includes participants discussed at an ACT Tumor Board who receive a SMMART-ACT Therapy recommendation.

11.3.2 SAFETY POPULATION

The safety population set includes participants who receive at least one dose of at least one of the study agent(s) comprising their recommended ACT Therapy. Analysis for demographics, baseline characteristics, disease history, and participant disposition will also be conducted using the safety population.

11.3.3 EFFICACY EVALUABLE POPULATION

The efficacy evaluable population set includes participants who receive at least one dose of at least one of the study agent(s) comprising their recommended ACT Therapy **and** who undergo at least one On-Therapy disease assessment. All efficacy analyses will be conducted using the efficacy evaluable population.

11.4 DESCRIPTION OF STATISTICAL METHODS

11.4.1 GENERAL APPROACH

Descriptive statistics will be used to summarize disposition, demographics, baseline characteristics, baseline disease characteristics, efficacy and safety outcomes. Descriptive summaries of discrete data will present the sample size and the incidence as frequency and percentage. Descriptive summaries of continuous data will present the sample size, group mean, standard deviation, median, and range. Confidence Intervals (CI) may be included as appropriate. The feasibility population set will be used for this general approach.

11.4.2 ANALYSIS OF PRIMARY ENDPOINT

The proportion of participants who receive an ACT Therapy regimen listed in Appendix A, based on a SMMART-ACT Tumor Board recommendation will be determined using the feasibility set.

The target threshold for feasibility is 75%. Bayesian Futility Monitoring Via Posterior Probability will be employed to monitor feasibility using the feasibility population set. Posterior toxicity probabilities are calculated to monitor the trial conduct. An interim analysis of feasibility will be conducted after 15 participants receive a SMMART-ACT Tumor Board treatment recommendation. If > 9 of the first 15 participants start an SMMART-ACT study therapy, the study enrollment will continue. If <10 of the first 15 participants start an SMMART-ACT therapy, enrollment will continue with a feasibility review (See Section 11.4.5).

11.4.3 ANALYSIS OF SECONDARY ENDPOINTS

The safety population will be used for analyses of safety and tolerability and early indications of survival benefit. The efficacy evaluable population will be used to analyze early indications of efficacy according to disease-specific response criteria (**Section 9**). Categorization of the secondary endpoints follows:

11.4.3.1 SAFETY, TOLERABILITY, AND ESTIMATES OF SURVIVAL BENEFIT

- The incidence of **TEAEs** experienced that are suspected or confirmed as attributable to a study drug or procedure will be tabulated (**Section 10.2.6**).
- The incidence of discontinuation from study therapy due to intolerability and/or toxicities will be reported.
- Overall survival (**OS**) will be estimated from the time of first dose of study drug until death from any cause (until the end of long-term follow-up). OS will be censored on the last date a participant is known to be alive and will be summarized descriptively using the Kaplan-Meier method. The median and 95% confidence interval will be included in the estimations, if possible.
- Progression-free survival (**PFS**) will be determined from the first dose of study drug until the earliest date of disease progression, as measured by investigator assessment, or death due to any cause (until the end of long-term follow-up). Participants with no observed death or progression, or discontinued from the study without disease progression, will be censored at the date of last adequate assessment visit. PFS will be estimated using the Kaplan-Meier method.
- Disease-specific survival **DSS:** The DSS is defined as the time from the first day of study therapy to death as a result of the disease at time of last follow-up (up to five years from time of last

dose of study therapy). Participants that die of causes other than study disease being assessed will be censored at the time of death. Cumulative incidence curves with 95% confidence interval will be estimated to determine the DSS risk, taking into account the competing risk of death.

11.4.3.2 EFFICACY

Early indications of efficacy, to support secondary endpoints of this study, will be evaluated as objective response rate (**ORR** = CR +PR) at 24 weeks from C1D1 (+/- 2 weeks). This will be determined and categorized by cancer type. An exact 95% confidence interval (CI) will be provided.

Refer to **Section 8.1.1** and **Section 9** for the disease-specific criteria that will be applied. Participants receiving protocol-defined immune-modulated agents per a drug-specific appendix (**Appendix A**) will also be monitored for pseudoprogression. Pseudoprogression is the uncommon phenomenon in which an initial increase in tumor size occurs or new lesions appear, typically within 12 weeks from the start of immunotherapy, followed by a decrease in tumor burden. Participants who meet PD based on RECIST v1.1, but may be experiencing pseudoprogression, may continue immunotherapy as long as they do not have any deterioration in performance status or signs or symptoms of unequivocal PD or PD at sensitive sites.

11.4.3.3 EXPLORATORY EFFICACY ENDPOINTS

- **Time to Progression (TTP) ratio:** The TTP ratio is a growth modulation index (GMI) in which TTP for each individual receiving their SMMART-ACT study therapy (i.e., TTP_{ACT}) will be compared with the failure time of their last therapy (i.e., $TTP_{historic}$)[23,24]. Where available the baseline TTP (i.e., $TTP_{historic}$) will be derived from the participant's EHR as the time from start of prior line of treatment (i.e., last line of treatment before initiating study therapy) to the first documented date of progression. The TTP_{ACT} is the time between starting the study therapy to time of any documented disease progression. In all cases, progression is assessed using disease-specific criteria for the relevant cancer type (refer to **Section 9**). The proportion of participants with a TTP ratio >1.3 will be descriptively summarized.
- **Quality of Life (QoL):** Standard instruments (EORTC QLQ-C30, QLQ FA12, and QLQ INFO25) will be used for participant-reported outcomes, which will be assessed at study-specific time points and summarized using descriptive statistics.
- **Time to Decline (TTD):** is measured from first dose of study drug until ECOG performance status ≥ 3. Those who fail to decline (ECOG status < 3) will be censored at last clinic evaluation or End-of-Therapy visit. Kaplan-Meier methods will be used to estimate TTD.
- **Feasibility of SMMART-centric assessments of ongoing responses**: Proportion of participants who have an On-Therapy Biopsy with sufficient tumor content for assays will be reported along with a 95% confidence interval. This will be summarized by cancer type and biopsy site. Proportion of On-Therapy Biopsies with sufficient for tumor content assays and its 95% confidence interval will be reported by assay type. Proportion of CLIA assay results obtained ≤14 business days of biopsy will be reported along with a 95% confidence interval.

11.4.4 SAFETY ANALYSES

Adverse events (AEs) will be tabulated by the MedDRA preferred term (PT) and system organ class. Severity of AEs will be based on the CTCAE v5.0 criteria and recorded in the EDC.

11.4.5 PLANNED INTERIM ANALYSES

An interim analysis will be performed after 15 participants receive a SMMART-ACT Tumor Board treatment recommendation (i.e., the denominator for feasibility proportion is the number of participants who receive a tumor board recommendation). The tumor board treatment recommendation *may or may not* be an ACT study therapy.

Bayesian Futility Monitoring Via Posterior Probability (https://trialdesign.org/one-page-shell.html#BEMPO) with the beta (0.5, 0.5) prior distribution and 75% as the reference response rate for futility monitoring and 90% as the probability confidence threshold for futility was used to monitor the feasibility of the trial. That is, if ≤ 9 of the first 15 participants receive C1D1 of an ACT Therapy based on the recommendation of a SMMART-ACT Tumor Board, the study will review the strategy design, but not pause, in order to consider an amendment of this protocol or a more extensive study re-design to improve feasibility. If > 9 of the first 15 SMMART-ACT Tumor Board recommendations result in participants receiving an ACT Therapy (i.e., if > 9 participants of the first 15 tumor board recommendations receive study therapy on C1D1 enrollment will continue until up to 30 total participants receive an ACT Therapy recommendation to assess feasibility. If at least 23 participants out of 30 receive C1D1 of an ACT Therapy based on the recommendation of a SMMART-ACT Tumor Board, the trial will be declared as feasible and efficacy will be evaluated. .

11.5 HANDLING OF MISSING DATA

Missing data will not be imputed. Whenever possible, the analysis will be conducted using all available data. Missing data will be reported in the descriptive summary, and it will be noted if participants were excluded from the analysis due to missing data.

12 CLINICAL MONITORING

12.1 OHSU KNIGHT CANCER INSTITUTE DATA & SAFETY MONITORING PLAN

All clinical trials at the Knight are required to have a Data and Safety Monitoring Plan (DSMP). This study is under the oversight of the Knight Cancer Institute's DSMC as described in the Knight institutional DSMP. The Knight DSMP outlines the elements required to ensure the safety of clinical trial participants, the accuracy and integrity of the data, and the appropriate modification of cancer-related clinical trials for which significant benefits or risks have been discovered or when the clinical trial cannot be successfully concluded. The Knight DSMP also describes the methods and procedures for ensuring adequate, risk-based oversight of cancer-related research at OHSU.

As described in the Knight DSMP, regardless of the trial's risk level and any specific Knight oversight in place, the investigator is singularly responsible for overseeing every aspect of the design, conduct, and final analysis of their investigation.

The Knight DSMC reviews and monitors study progress, toxicity, safety, and other data for this study. The DSMC will address any issue that raises questions about data integrity or trial participant safety with the investigator and study team. Should any major concern arise, the Knight DSMC may recommend corrective action and determine whether to suspend or terminate the study.

12.2 CLINICAL DATA & SAFETY MONITORING

The investigator is responsible for ensuring that the study is conducted in accordance with the protocol, Declaration of Helsinki, GCP, and applicable regulatory requirements, and that valid data are entered into the CRFs. To achieve this objective, the monitor's duties are to aid the investigator in the maintenance of complete, legible, well organized and easily retrievable data.

Monitoring visits will be performed during the study to ensure that the rights and well-being of human participants are protected, that the reported trial data are accurate, and that the conduct of the trial is in compliance with the protocol, GCP, and applicable regulatory requirements.

Details of monitoring activities, including designation of assigned monitoring entities, scope of monitoring visits, timing, frequency, duration of visits, and visit reporting, will be included in a separate Trial-Specific Monitoring Plan (TSMP).

The investigator will permit monitoring of the study as frequently as deemed necessary to determine that data recording and protocol adherence are satisfactory. The investigator agrees that the monitor will be permitted to conduct monitoring visits at appropriate intervals. The investigator agrees to provide all relevant information and documentation as requested by the monitor, including access to all original study documents and source data, including access to EMRs and/or source documents if necessary. The investigator and their staff will be expected to cooperate with the monitor and provide any missing information, whenever possible.

The monitor will conduct source data review and verification as outlined in the TSMP, and following each visit will generate a report summarizing the visit findings.

Regardless of monitoring entity, the OHSU Sponsor-Investigator is ultimately, singularly responsible for overseeing every aspect of the design, conduct, and final analysis of their investigation and for governing trial conduct at all sub-sites.

If at any time investigator noncompliance is discovered at OHSU, the Sponsor-Investigator shall promptly secure compliance.

Independent audits may be conducted by the Knight DSMC to verify that the rights and wellbeing of human participants are protected, that the reported trial data are accurate, that the conduct of the trial is in compliance with the protocol and applicable regulatory requirements, and that evidence of ongoing investigator oversight is present.

12.3 QUALITY ASSURANCE & QUALITY CONTROL

The investigational site will provide direct access to all trial related source data/documents, and reports for the purpose of monitoring by the monitor and/or sponsor, and auditing by the Knight DSMC and/or regulatory authorities.

All clinical trials at the Knight Cancer Institute are required to have a DSMP. All clinical work conducted under this protocol is subject to ICH GCP guidelines. This includes inspection of study-related records by the lead site, sponsor, its designee, or health authority representatives at any time.

Quality Assurance (QA) audit activities may occur and will be in accordance with the Knight's institutional DSMP. All discrepancies, queries, deviations, observations, and findings of non-compliance will be compiled into a final audit report. The PI must review and assess each finding and generate a response to the audit report that incorporates Corrective and Preventative Action (CAPA). A CAPA must analyze root cause(s) of non-compliance in order to identify and determine changes to correct and resolve issues and prevent recurrence.

Quality Control (QC) activities are designed to ensure the safety of study participants and the validity and integrity of data. Monitoring is designed to be a continuous, ongoing and multifaceted process. A review by the Knight DSMC and applicable IRB(s), as well as internal data quality control, review and evaluation may be included in the QC activities for this trial. Site monitoring visits are central to this process and will include reporting to appropriate individuals with oversight responsibilities.

The Sponsor-Investigator, or study monitor, will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the main and applicable drug-specific appendices (**Appendix A**), GCP, and the applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

13 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

13.1 SOURCE DATA/DOCUMENTS

The investigator will maintain adequate case histories of study participants, including accurate CRFs, and relevant electronic data capture (EDC) system(s), and all relevant source documentation. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents (e.g. chain of custody blood collection logs, chain of custody tissue collection logs, blood derivative logs, SMMART-ACT Tumor Board summary reports, etc.) should be completed in a neat, legible manner to ensure accurate interpretation of data.

The regulatory binder will document compliance with institutional regulatory obligations and good clinical practice (GCP) guidelines. Participant study binders will include documentation of consent, screening, eligibility (e.g., tumor board documentation), and study data source documents. Both will be stored in Florence, an eRegulatory platform that is 21 CFR Part 11 compliant.

Study data (i.e., outcome, disease assessment, AEs, diagnosis, and previous treatments) will be captured via a combination of CRFs and entry into Advarra, a 21 CFR Part 11 compliant EDC system. Details regarding the study EDC, data entry/correction, and data quality assurance will be included in a separate Data Management Plan.

13.1.1 PARTICIPANT & DATA CONFIDENTIALITY

The information obtained during the conduct of this clinical study is confidential, and unless otherwise noted, disclosure to third parties is prohibited. Information contained within this study will be maintained in accordance with applicable laws protecting participant privacy, including the provisions of the Health Insurance Portability and Accountability Act (HIPAA).

Participant confidentiality is strictly held in trust by the participating investigator(s) and study team. This confidentiality is extended to cover testing of biological specimens and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol (i.e., Main and drug-specific appendices (**Appendix A**)), 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.

The study monitor, other authorized representatives of the sponsor, representatives of the IRB, or manufacturers 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, per each drug-specific appendix (**Appendix A**), all records will continue to be kept in a secure location for as long a period as dictated by local IRB and institutional regulations. Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored within the Knight Cancer Institute per OHSU's Information Security Directives. Individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by Knight Cancer Institute research staff will be secured and password protected per OHSU's Information Security Directives. At the end of the study, per each drug-specific appendix, or after the appropriate period of record retention stated in **Section 13.1.5**, all study databases may be de-identified and archived within the Knight Cancer Institute.

13.1.2 DATA COLLECTION & STORAGE: PRIVACY, CONFIDENTIALITY & SECURITY

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. Standard institutional practices will be followed as described in the OHSU's Information Security Directives to maintain the confidentiality and security of data collected in this study. Study staff will be trained with regard to these procedures.

Loss of participant confidentiality is a risk of participation. Efforts will be made to keep study participant identities confidential except as required by law. Participants' biospecimens will be identified by code only. Specifically, each consenting participant will be assigned a unique coded identifier consisting of numbers. This identifier will be associated with the participant throughout the duration of their participation in the study. The coded identifier will also be used to identify any participant specific biospecimens.

Basic accrual tracking information (demographic, consent, visit information) will be captured in OHSU's electronic clinical information research system (OnCore), hosted on OHSU secure servers and managed by OHSU's information technology group at their data center in downtown Portland, Oregon. Any additional printed documents containing participant identifiers, such as those from the medical record to confirm eligibility, will be filed in binders and kept in a locked, secure location.

The web-accessible EDC system is password protected and encrypted with role-based security and is approved by OHSU's office of Information Privacy and Security. The EDC is administered by designated informatics staff within OHSU or Knight Cancer Institute. All users of the database are assigned a unique ID, username, and password and must complete training appropriate to their role before they are authorized to enter, access, and store data in the database.

Data to support exploratory analyses will be stored via LabKey, a data management platform that provides solutions for biological assay data, biological specimen tracking, and data visualization. The LabKey instance is housed behind the OHSU firewall. All web-based data transmissions are encrypted with industry-standard SSL methods. Access is integrated with OHSU's network such that users who are also OHSU employees are authenticated against their OHSU network credentials. LabKey is managed in accordance with OHSU Information Security Directives, ensuring fidelity of database configuration and back-ups.

All other electronic data extracts will be stored only on local study site computers and restricted drives, which are limited to only study investigators and staff with authorization to access the data. Quality assurance will be conducted as outlined in **Section 12.3**, Quality Assurance & Quality Control.

13.1.3 BIOSPECIMENS

Information about specimens collected, and associated clinical data, will be stored with the BEMS software, LABVANTAGE. This platform is a secure, commercial off-the-shelf, system that is hosted by OHSU's Information Technology Group (ITG) and managed by KDL.

13.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Because we are committed to making data and/or biospecimens from this study available to the broader research community to address scientific questions and/or to find new ways to prevent, detect or treat cancer and other diseases, participants who sign consent will be informed that their left-over biospecimens and data, including genetic data, may be stored indefinitely in a repository and shared for future research. The biospecimens and data collected for this study may be shared with the following repositories or databases listed below. *Please note*: If a participant co-consents to participation in the "Molecular mechanisms of tumor evolution and resistance to therapy (MMTERT, IRB# 16113)" any biospecimens and data may be stored and analyzed under MMTERT (IRB# 16113) indefinitely to address the scientific questions and/or development of biological tests related to cancer as described in MMTERT study protocol.

13.1.4.1 BIOLIBRARY, A TISSUE REPOSITORY (IRB# 4918)

Biospecimens (i.e., blood and tumor) and associated data may be submitted to IRB# 4918 OHSU BioLibrary for future management in accordance with relevant terms of consent and authorization. Details of any transferred materials will be documented in submission agreement(s). Biospecimens and associated data will be stored in the Knight Cancer Institute BioLibrary indefinitely and further analyzed to address scientific questions and/or development of biological tests related to cancer.

13.1.4.2 OREGON CLINICAL AND TRANSLATIONAL RESEARCH INSTITUTE (OCTRI) RESEARCH DATA WAREHOUSE (RDW) (IRB# 4076)

All data collected originally for research purposes in this study will be accompanied by a fully executed submittal agreement and appropriate IRB documents prior to deposition in the OCTRI RDW. This submittal agreement documents that providers of data to the OCTRI RDW agree to the stipulations of data submission, as specified in the RDW IRB protocol (IRB# 4076). Data providers remain the steward of the data.

13.1.4.3 SMMART REPOSITORY (IRB# 28065)

All data and samples originally collected for research purposes in this study will be stored in the SMMART Repository, indefinitely, for ongoing and future research. Once shared to the SMMART Repository use of the data and samples by the repository will be governed by the SMMART Repository protocol.

13.1.4.4 PUBLICLY ACCESSIBLE SCIENTIFIC DATABASES

The informed consent describes that biospecimens, data and genetic data collected under this study may be shared with others or placed into one or more publicly accessible scientific databases, such as the NIH Database for Genotypes and Phenotypes (dbGaP). Any personal information that could identify a participant will be removed or changed before it is shared with other researchers or results are made public. We will seek to share or deposit de-identified data into publicly accessible central repositories or databases that may be open or controlled access. Study data, including genomic data, will be deidentified according to the standards set forth in the HHS Regulations for the Protection of Human Subjects to ensure that the identities of research participants cannot be readily ascertained with the data before it is submitted.

13.1.5 MAINTENANCE OF RECORDS

Records and documents pertaining to the conduct of this study, source documents, consent forms, laboratory test results and medication inventory records, must be retained by the investigator for a period of two years following the date a marketing application is approved for the drug for the indication(s) for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication(s), until two years after the investigation is discontinued and FDA is notified. No records will be destroyed without the written consent of the sponsor-investigator. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

If the investigator relocates or for any reason withdraws from the study, the study records collected under this protocol must be transferred to an agreed upon designee, such as another institution or another investigator at OHSU. Records must be maintained according to institutional or FDA requirements.

13.2 PUBLICATION AND DATA SHARING

13.2.1 PUBLICATION

We will use data collected and created during this study in publications. Data and specimens collected and created during this study may be stored for future research, which may also be used in publications. Data and specimens collected and created during this study may be shared with other researchers, who may use it in publications.

Publications may include, but are not limited to, medical journals, newspapers, magazines, books, audio, video, or any other form of printed, digital, or broadcast media.

Except as allowed under the HIPAA Privacy Rule, no PHI will be used in any publications.

Participants will be informed of our intent to publish materials using data collected from and created about them. The intent to publish will be included in the informed consent form.

13.2.1.1 PUBLICATION POLICY

This study will adhere to the requirements set forth by the ICMJE and FDAAA that require all clinical trials to be registered in a public trial registry (e.g., ClinicalTrials.gov) prior to participant enrollment.

This study will comply with the NIH Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

13.2.2 BIOSPECIMEN AND DATA SHARING

Data and specimens that are collected and created during this study will be stored for future use, and may be shared with other OHSU researchers, external researchers, external vendors, other repositories both inside and external to OHSU, and public databases. Sharing of data and specimens will be permitted and managed as outlined in this section.

13.2.2.1 BIOSPECIMEN AND DATA SHARING POLICY

We are committed to making data and/or biospecimens from this study available to the broader research community while protecting the privacy and confidentiality of participants. The IRB-approved informed consent describes to the participant that their biospecimens, data and genetic data from this study may be shared with others or placed into one or more publicly accessible scientific databases, such as the NIH Database for Genotypes and Phenotypes (dbGaP). Any personal information that could

identify a participant will be removed or changed before it is shared with other researchers or results are made public. We will seek to share or deposit deidentified data into publicly accessible central repositories or databases that may be open or controlled access. Study data including genomic data will be deidentified according to the standards set forth in the HHS Regulations for the Protection of Human Subjects to ensure that the identities of research participants cannot be readily ascertained with the data before it is submitted.

Participants who sign consent will also be informed of potential sharing of their information and biospecimens with an OHSU repository for future use as described in **Section 13.1.4**. Biospecimens and associated clinical study data will be shared with investigators of the ongoing OHSU prospective observational study entitled "Molecular mechanisms of tumor evolution and resistance to therapy (MMTERT, IRB# 16113)" if they are consented to IRB# 16113.

Participants will not have access to experimental research data. Results of clinically validated tests may be obtained by request via the study investigator or treating physician.

13.3 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, 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 conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. OHSU has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

13.4 DELIVERY OF PROGRESS REPORTS TO STUDY FUNDERS

Upon the request of Study Funder(s), the Institution will submit oral or written reports on the progress of the study as provided by this protocol. Within one hundred and twenty (120) days following the completion or termination of the study, Institution will furnish Study Funder(s) with a final report detailing the results of the study. This reporting timeline will be superseded if a fully executed contract with a Study Funder differs from the above.

14 ETHICS/PROTECTION OF HUMAN PARTICIPANTS

14.1 ETHICAL STANDARD

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Participants of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR 312 (for IND studies), and/or the ICH E6.

14.2 INSTITUTIONAL REVIEW BOARD

The protocol, informed consent forms, recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of the protocols and the consent forms must be obtained before any participant is consented. Any amendment to the protocols, or changes to the consent forms or other participant materials, will require review and approval by the IRB before the changes are implemented to the study. A determination will be made regarding whether previously consented participants need to be reconsented whenever the consent form(s) are revised.

14.3 INFORMED CONSENT

Written informed consent will be obtained from all participants, or the legally authorized representative of the participant, participating in this trial, as stated in the Informed Consent section of 21 CFR Part 50. Documentation of the consent process and a copy of the signed consent shall be maintained in the participant's medical record.

14.3.1 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreement to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families, as appropriate. 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. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks/benefits of the study, alternatives to participation, and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. Participants will have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. Participants will sign the informed consent document prior to any procedures being done specifically for the study. Participants may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the participants for their records. 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 or withdraw from this study after initially agreeing to participate.

14.4 PROTOCOL REVIEW

This protocol and informed consent forms must be reviewed and approved in writing by the OHSU Knight Cancer Institute's Clinical Research Review Committee (CRRC) and the appropriate IRB prior to any participant being consented on this study.

14.5 CHANGES TO PROTOCOL

Any modification of this protocol must be documented in the form of a protocol revision(s) or amendment(s) submitted by the investigator and approved by the CRRC and IRB, before the revision or amendment may be implemented. The only circumstance in which the amendment(s) may be initiated without regulatory approval is for a change necessary to eliminate an apparent and immediate hazard to a participant. In that event, the investigator must notify the IRB (and sponsor/FDA if under an IND)

within five business days after the implementation. An investigator who holds an IND application (if applicable) must also notify the FDA of changes to the protocol per 21 CFR 312.

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APPENDIX A DRUG MANUFACTURER-SPECIFIC APPENDICES

This study includes drugs from multiple drug manufacturers. Data generated by this study will be shared with drug manufacturers who are providing drug(s) for use in this study. For confidentiality purposes we are including Drug Manufacturer-Specific Appendices to the Main Protocol. Drug manufacturers will only receive data that is directly related to their drug(s) and will only have access to the Main Protocol and their Drug Manufacturer-Specific Appendix.

Each Drug-Manufacturer-Specific Appendix will cover the following information:

- Summary of Study Drug(s)
- Study Regimen-Specific Schedule of Events (SOE)
- Summary of Study Interventions
- Manufacturer Reporting Requirements

Additional sections may be included, as appropriate.

APPENDIX B. SMMART-CLINICAL ANALYTICS PLATFORM

**Details regarding specimen collection, processing, tracking and shipping can be found in the SMMART-ACT Laboratory Manual **

B.1 TARGETED DNA SEQUENCING

Sequencing of a targeted panel of genes to identify clinically relevant genetic alterations for specific cancers will be performed on patient biospecimen at the Knight Diagnostic Labs (KDL). Solid tumors will be assessed using the GeneTrails® Solid Tumor Panel. Updated or alternative targeted panels may be used as they become available or if clinically appropriate.

B.2 WHOLE EXOME SEQUENCING

Whole exome sequencing (WES) may be performed on tumor/normal pair to identify genetic alterations. If performed, this assay may be subcontracted by the KDL to Tempus Labs, Inc., a CLIA-compliant, College of American Pathologists-accredited laboratory (CLIA# 14D21140007 and CAP# 9457450) or to another CLIA-compliant, College of American Pathologists/CAP-accredited laboratory. Tempus Labs, Inc. can perform high throughput sequencing, report the results back to the KDL, and provide raw sequencing files for download and analysis.

B.3 RNA SEQUENCING

Sequencing of RNA isolated from participant biospecimen to characterize the transcriptome and identify fusions will be performed at the KDL or, if logistically necessary, another CLIA-certified, College of American Pathologists-accredited laboratory. Regardless, processing of the raw sequencing data into gene-level expression values, including read alignment, recalibration, and quantification will be performed utilizing a computational pipeline constructed by the OHSU Bioinformatics Core and the KDL. Dependent upon sample availability, additional RNA sequencing work may be performed by Tempus Labs, Inc., who will provide raw sequencing files for download and analysis. In some cases, such as those with extremely limited sample availability, transcriptome sequencing may be replaced with a more limited RNA sequencing assay such as the GeneTrails® Solid Tumor Fusion Gene panel which identifies clinically actionable fusions in a limited set of genes.

B.4 IMMUNOHISTOCHEMISTRY

Immunohistochemistry (IHC) staining of individual protein targets will be sub-contracted by the KDL to OHSU Surgical Pathology or, if necessary, other CLIA-certified/CAP-accredited laboratories. The profiled proteins will relate to characteristics that are intrinsic to the cancer cells, such as growth, survival, death, motility, and DNA repair, as well as those that are extrinsic, such as the immune system and tumor microenvironment.

B.5 PROTEIN PROFILING

A multiplexed protein profiling test will be done on biopsy specimens through the KDL. The Nanostring DSP Tumor Signaling and I/O Panel will be used to measure the abundance and phosphorylation status of proteins related to characteristics intrinsic to the cancer cells, such as growth, survival, death, motility, and DNA repair. Additional, or alternative, protein profiling assays may be used as they become available.

B.6 ONCOLOGY MICROARRAY

Chromosomal microarray testing may be performed on patient biospecimen at the KDL. The Oncology Microarray – Targeted Gene and Region Panel can be used to detect copy number changes and copy-neutral loss of heterozygosity on a scale from genome-wide to individual genes. A homologous recombination deficiency (HRD) score may also be reported. Updated or alternative methods for generating genome-wide copy number profiles may be used as they become available or if clinically appropriate.

APPENDIX C. SMMART EXPLORATORY RESEARCH ANALYTICS PLATFORM

Details regarding specimen collection, processing, tracking, and shipping can be found in the SMMART-ACT Laboratory Manual

C.1 MULTIPLEX IMMUNOHISTOCHEMISTRY

Comprehensive in situ immune monitoring platform to audit immune composition and functionality with spatial context. Iterative cycles of IHC staining, scanning, and stripping will be performed on single, unstained slides from participant biospecimen at an OHSU laboratory. A validated antibody panel will be used to characterize tissue sample cell type composition, major immune group composition, as well as lymphoid and myeloid lineage and functional states. Additional antibody panels may be used to perform deeper profiling of specific aspects of the immune contexture.

C.2 CYCLIC IMMUNOFLUORESCENCE

Iterative rounds of multi-color immunofluorescent staining, imaging, and fluorophore quenching will be performed on single, unstained slides from participant biospecimen at an OHSU laboratory. Antibodies will be selected and validated to assess the cellular and extracellular composition, spatial organization, and molecular states (e.g., cell composition, functional protein levels, differentiation state, pathway activity) of tumor cells and their microenvironments.

C.3 REVERSE PHASE PROTEIN ARRAYS (RPPA)

Bulk characterization of basal protein expression and modification levels for greater than 400 independent analytes will be achieved using RPPA on participant biospecimen. This assay will be performed by the RPPA Core at MD Anderson. Briefly, frozen tissue will be lysed and protein will be extracted. Diluted lysates will be printed on nitrocellulose-coated slides and probed with validated primary antibodies followed by detection with Biotinylated secondary antibodies. Signal amplification will be achieved using the Vectastain Elite ABC kit from Vector Lab. The slides will be scanned, analyzed, and quantified to generate spot intensity values and estimate relative protein levels.

C.4 SINGLE CELL RNA SEQUENCING

Single- cell RNA sequencing to characterize the transcriptome of individual cells will be performed on participant biospecimen at an OHSU laboratory. Freshly collected or viably frozen tumor tissue will be processed and subjected to next-generation sequencing to assess for factors such as cellular composition, immune cell activity, and hallmark gene set enrichment. Additional methods that allow joint profiling of the DNA methylome, chromatin accessibility, and RNA may also be employed.

C.5 CELL CULTURE

Participant-derived cells will be subjected to short-term culture at an OHSU laboratory. Ex vivo culturing experiments will be used to investigate cancer cell growth/survival as well as mechanisms of therapeutic

response and resistance. Additional technologies such as next-generation sequencing or NanoString GeoMx DSP may be employed to characterize the DNA, RNA, or protein of the participant tissue samples.

C.6 EXPERIMENTAL TISSUE ANALYTICS

Exploratory Research Analytics still in development may be performed on excess participant biospecimens in order to develop, test, and/or validate the assays for eventual inclusion in the SMMART-ERA platform. Additional analyses of participant biospecimen may include advanced microscopy techniques such as 2D or 3D scanning electron microscopy as well as omic profiling techniques, including single cell next-generation sequencing.

C.7 EXPERIMENTAL BLOOD ANALYTICS

Research Analytics still in development may be performed on peripheral blood collected from research blood draws in order to develop, test, and/or validate the assays for eventual inclusion in the SMMART-ERA platform. This may include immunophenotyping by methods such as mass cytometry; characterization of cell free DNA, RNA, and proteins by methods such as next-generation sequencing; characterization of circulating tumor cells (CTCs) by methods such as fluorescence microscopy; as well as isolation and characterization of extracellular vesicles by methods such as fluorescence microscopy and next-generation sequencing.

APPENDIX D. NEW YORK HEART ASSOCIATION (NYHA) FUNCTIONAL CLASSIFICATION

NYHA Class	Symptoms
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath).
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea (shortness of breath).
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea.
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.
As published in: The Criteria Committee of the New York Heart Association. (1994). Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. (9th ed.). Boston: Little, Brown & Co. pp. 253–256.	