STATISTICAL ANALYSIS PLAN

TITLE:	**MYTACTIC: AN OPEN-LABEL PHASE II STUDY EVALUATING TARGETED THERAPIES IN PATIENTS WHO HAVE ADVANCED SOLID TUMORS WITH GENOMIC ALTERATIONS OR PROTEIN EXPRESSION PATTERNS PREDICTIVE OF RESPONSE**
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IND NUMBER:	152738
NCT NUMBER:	NCT04632992
TEST PRODUCT:	Entrectinib (RO7102122), Trastuzumab emtansine (RO5304020), Pertuzumab Trastuzumab Fixed Dose Combination Subcutaneous (PH FDC SC, RO7198574), Inavolisib (GDC-0077; RO7113755), Alectinib (RO5424802), Ipatasertib (RO5532961), Atezolizumab (RO5541267), Tucatinib, Pralsetinib (RO7499790), Tiragolumab (RO7092284)
MEDICAL MONITOR:	[redacted], M.D.
SPONSOR:	Genentech, Inc.
PREPARED BY:	[redacted]
DATE FINAL:	See electronic date stamp b[redacted]

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1. BACKGROUND

Oncology is rapidly evolving into a more personalized healthcare approach. Improved understanding of the role of cancer biomarkers, further development of molecular-targeted therapies, and the standardization of appropriate targeted treatment into treatment guidelines have shifted clinical practice to utilize genomic information as an integral component of clinical decision-making (Kris et al. 2014; Barlesi et al. 2016). Therapies that specifically target actionable oncogenic drivers have become the cornerstone of precision oncology.

Currently, targeted agents are approved for use in specific cancer types (as defined by primary site), or a subset of that population harboring the specific molecular alteration. Usually, targeted agents have been approved in the cancer types that most frequently carry the specific molecular target. However, it is now clear that molecular alterations can be found in cancers from other primary sites, although often at low incidence levels. The potential therapeutic importance of these abnormalities is not clear, although anecdotal reports have documented activity with the investigational use of appropriate targeted therapy (Cappuzzo et al. 2006; Masago et al. 2009; LoRusso et al. 2011; Masago et al. 2011; Kelly et al. 2012; Minor et al. 2012). With the relative rarity of these alterations (usually <= 5%) in any specific cancer type, it is difficult to identify sufficient patients for clinical trials.

With these recent advancements, numerous platforms have been developed to survey the cancer cell genome and detect critical molecular alterations. With increased molecular profiling, gene alterations for which a targeted agent exists, or are associated with improved efficacy of cancer immunotherapies, are being identified more frequently in tumor types for which these agents are currently not approved. These findings present a new opportunity to test the efficacy of available targeted agents and immunotherapies.

In addition, there have been recent drug approvals in pan-tumor indications paving the way for registration for molecular alterations in multiple tumor types.

For example, entrectinib (Rozlytrek®) was approved in the United States based on the results in 51 adult patients across three clinical trials. A pooled analysis of 3 Phase I-II studies investigating patients with locally-advanced or metastatic ROS1 fusion-positive non-small-cell lung cancer demonstrated that treatment with entrectinib induced a durable and clinically meaningful response. Among the efficacy-evaluable patients, 77% had an objective response, with a median duration of response of 24.6 months (95% CI 11.4-34.8) (Drilon et al. 2020). The same analysis investigated patients with metastatic or locally advanced solid tumors harboring a fusion in the NTRK gene (NTRK1, NTRK2, or NTRK3), comprising of 10 different tumor types and 19 different histologies. Similarly, treatment with entrectinib demonstrated a durable and clinically meaningful response, showing Entrectinib to be a viable treatment option for patients with NTRK fusion-

positive solid tumors. An objective response was observed in 57% of the evaluable patients (95%CI 43.2-70.8), with 4 complete responses and 27 partial responses. The median duration of response was 10 months (95% CI 7.1 to NE), (Doebele et al. 2019).

Tumor mutational burden has been associated with treatment outcomes with cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and programmed death-ligand 1 (PD-L1) inhibitors. Pembrolizumab (Keytruda®) was granted accelerated approval by the FDA for the treatment of adult and pediatric patients with unresectable or metastatic tumor mutational burden-high (TMB-H) solid tumors, defined as >= 10 mutations/megabase (mut/Mb). The Phase II basket study of pembrolizumab monotherapy in this patient population demonstrated that TMB-H was associated with higher response rates in a number of different unresectable or metastatic tumor types, suggesting that tumor mutational burden (TMB) may predict efficacy of pembrolizumab treatment.

In addition to testing targeted therapies in a pan-tumor setting, this study aims to expand study access to patients that are traditionally underrepresented in clinical trials. Classical registrational clinical trials often underrepresent patients of color, with data indicating that 88% of genetic sequencing/association studies have been done in individuals of European decent. In addition, industry study design standards may unintentionally prevent diverse patients from being enrolled, as most studies include certain inclusion/exclusion criteria that tend to exclude people of specific ethnicities. This study will focus on inclusion of underrepresented, understudied patients with broader entry criteria and with an emphasis on recruiting patients of color to ensure this study reflects the US population more accurately.

Specific biomarkers of interest for this protocol and their respective targeted therapies are outlined in Table 1. Background and rationale for the biomarkers and the associated targeted therapies, are provided in the sections below.

2. STUDY DESIGN

2.1 PROTOCOL SYNOPSIS

The Protocol Synopsis is in Appendix 1. The Protocol Synopsis includes the study objectives, inclusion and exclusion criteria, outcome measures, and statistical methods as stated in the protocol.

2.2 STUDY DESCRIPTION

MyTACTIC is a Phase II, multicenter, non-randomized, open-label, multi-arm study designed to evaluate the safety and efficacy of targeted therapies as single agents or in rational, specified combinations in patients with advanced unresectable or metastatic solid tumors determined to harbor specific biomarkers. Patients will be enrolled based on local testing performed at a Clinical Laboratory Improvement Amendments (CLIA)-certified or equivalently accredited diagnostic laboratory. For all patients whose positive biomarker result is from an assay other than a tissue-based assay conducted by

Foundation Medicine, Inc. (FMI), central testing of pre-treatment tissue (preferably from the most recent block) and blood is required after enrollment. Pre-treatment tissue will be submitted within 21 days after enrollment to a Sponsor-approved laboratory for central testing; this testing will not impact the study participation of enrolled patients.

The multi-arm structure of the MyTACTIC study allows patients with solid tumors to be treated with a drug or drug regimen tailored to their biomarker identified at screening. Each study treatment arm may have separate endpoints, screening, and treatment requirements, defined in the respective appendix. Futility analyses will be employed on all treatment arms to limit enrollment where evidence of very limited or lack of efficacy is observed.

During the study, the following biomarker samples will be collected:

Tumor tissue

- For patients with a positive biomarker result from an assay other than a tissue-based assay conducted by FMI, pre-treatment tissue samples (archival or recent resection or biopsy) must be submitted within 21 days of enrollment at baseline for central testing. If both archival and recent tissue is available, the recent tissue should be preferentially submitted.

Blood samples

- Mandatory blood samples will be collected at screening, 8 weeks after first treatment, and at disease progression for analyses including ctDNA

These samples will be used to evaluate predictive and/or prognostic biomarkers, including but not limited to biomarkers related to driver oncogene signaling, response to study treatment, tumor pathogenesis, and mechanisms of resistance.

The requirements for tissue and blood samples for screening and standardized testing purposes are described in Section 4.5.7 of the protocol

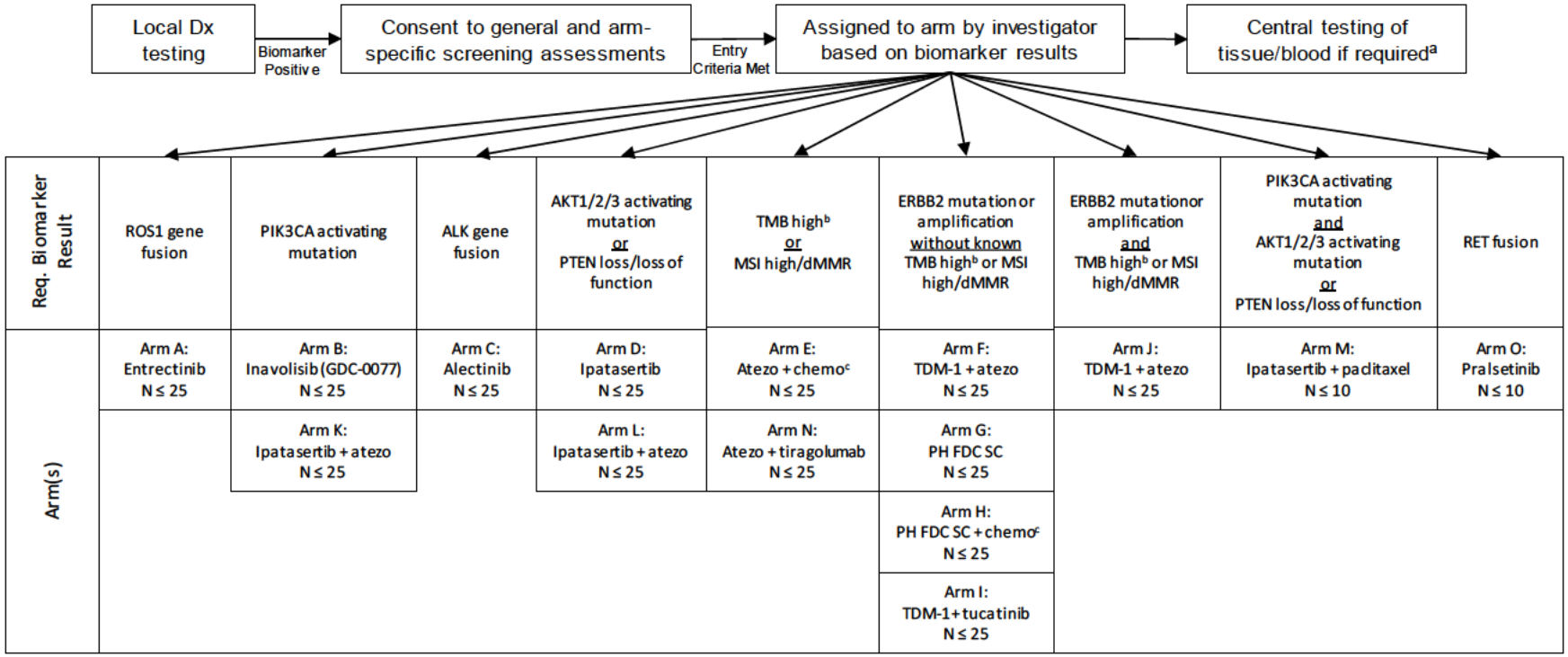
Treatment will be assigned by the treating investigator on the basis of relevant specified biomarkers, and will continue until radiographic disease progression (per RECIST v1.1 [Eisenhauer et al. 2009]; RANO Criteria for primary CNS tumors [Wen et al. 2017], or loss of clinical benefit for specific treatment arms, with Medical Monitor approval, see Section 3.1.2 of the protocol for treatment beyond disease progression); unacceptable toxicity; patient or physician decision to discontinue; or death, whichever occurs first. If a patient discontinues treatment prior to disease progression (because of adverse event or other reason), tumor assessments will continue as specified in the treatment-specific appendix until disease progression, death, withdrawal of consent, or arm/study closure by the Sponsor, whichever occurs first. Patients that have disease progression while on study may qualify for re-screening and enrollment into a different treatment arm if they have more than one documented biomarker and if the associated treatment arm is open and enrolling patients. Patients who qualify for more than one treatment arm and have

progressed on the first treatment must re-sign the informed consent form prior to re-screening and undergo screening for the second treatment arm.

Follow-up data, including survival and subsequent anti-cancer therapies, will be collected for each patient until death, loss to follow-up, withdrawal of consent, study/arm closure, or at least 1 year after end of treatment, whichever occurs first. Information regarding the nature and duration of subsequent therapies will be collected.

Patients who do not meet the criteria for participation in this study (screen failure) or the timeline for the screening window may qualify for re-screening at the investigator's discretion. Patients must re-sign the consent form prior to rescreening. The investigator will record reasons for screen failure in the screening log.

Figure 1 Study Schema



atezo=atezolizumab; chemo=chemotherapy; dMMR=deficient mismatch repair; Dx=diagnosis; MSI=microsatellite instability; PH FDC SC=fixed dose combination of trastuzumab and pertuzumab administered subcutaneously; TDM–1=trastuzumab emtansine; FMI=Foundation Medicine, Inc.; MSI=microsatelite; Req=required; *RET= Rearranged during Transfection;* TMB=tumor mutational burden.

Note: If more than one biomarker is identified, the investigator will decide which treatment the patient will receive.

[a] For all patients whose positive biomarker result is from an assay other than a tissue-based assay conducted by Foundation Medicine, Inc. (FMI), central testing of pre-treatment tissue (preferably from the most recent block) and blood is required after enrollment. Pre-treatment tissue will be submitted within 21 days after enrollment to a Sponsor-approved laboratory for central testing; this testing will not impact the study participation of enrolled patients.

[b] TMB high is defined as ≥ 10 mutations per megabase.

[c] Investigator's choice of docetaxel, paclitaxel, or capecitabine.

Table 1 Prevalences of Biomarkers for arms in MyTACTIC

Target *or Immune Marker*	**Biomarker Classification**	**Pan-tumor Prevalence**
ROS1	Fusion-positive (excluding NSCLC)	0.11%
PI3K	PIK3CA activating mutation(s)	11.2%
ALK	Fusion-positive (excluding NSCLC)	0.11%
AKT1/2/3	AKT-Activating mutation or PTEN-Loss (deletion)/LOF	12.6%
ERBB2 (HER2)	Activating mutation or amplification (excluding breast cancer)	4.9%
PD-L1	TMB ≥ 10 mut/Mb or MSI-H/dMMR	13.2%
ERBB2 (HER2) & CD274 (PD-L1)	ERBB2 Activating mutation or amplification & TMB ≥ 10 mut/Mb or MSI-H/dMMR	0.5%
AKT	*Co-mutations in PIK3CA and PTEN* *Co-mutation in PIK3CA and AKT*	*1.4%* *0.09%*
PD-L1 & TIGIT	*TMB ≥ 10 mut/Mb or MSI-H/dMMR*	*13.2%*
RET	*Fusion-positive (excluding NSCLC, thyroid cancer)*	*0.48%*

Table 2 Arm Alteration and Study Treatment

Biomarker alteration	**Study Treatment**
ROS1 gene fusion	Arm A: Entrectinib
PIK3CA activating mutation	Arm B: *Inavolisib (GDC-0077)*
	Arm K: Ipatasertib + atezolizumab
ALK gene fusion	Arm C: Alectinib
AKT activating mutations and/or *PTEN* loss/loss of function	Arm D: Ipatasertib
	Arm L: Ipatasertib + atezolizumab
Co-mutation in PI3KCA activating mutation and AKT activating mutation or PI3KCA activating mutation and PTEN loss/loss of function	*Arm M: Ipatasertib + paclitaxel*
TMB ≥ 10/MSI-H/dMMR	Arm E: Atezolizumab + chemotherapy[a]
	Arm N: Atezolizumab + tiragolumab

Biomarker alteration	Study Treatment
ERBB2 gene mutation or amplification without known TMB ≥ 10/MSI-H/dMMR	Arm F: Trastuzumab emtansine + atezolizumab
	Arm G: PH FDC SC
	Arm H: PH FDC SC + chemotherapy [a]
	Arm I: Trastuzumab emtansine + tucatinib
ERBB2 gene amplification or mutation and TMB ≥10/MSI-H/dMMR	Arm J: Trastuzumab emtansine + atezolizumb
RET gene fusion	*Arm O: Pralsetinib*

chemo=chemotherapy; dMMR=deficient mismatch repair; HER2=human epidermal growth factor receptor 2; PH FDC SC=fixed dose combination of trastuzumab and pertuzumab administered subcutaneously; MSI-H=microsatellite instability high; PI3K=phosphatidylinositol 3-kinase; RET *RET=Rearranged during Transfection*; TMB=tumor mutational burden. Investigator's choice of docetaxel, paclitaxel, or capecitabine.

2.2.1 DOSING BEYOND DISEASE PROGRESSION

In the absence of unacceptable toxicity, dosing of study treatment beyond radiographic disease progression may be permitted for patients in specific treatment arms with approval of the Medical Monitor if evidence of persistent clinical benefit is determined by the investigator and documentation is provided to the Sponsor.

If the above criteria are met, dosing of study treatment will continue until unacceptable toxicity, loss of clinical benefit (as determined by the investigator), or withdrawal of patient consent. Loss of clinical benefit is defined as the following:

- Appearance of signs and symptoms (including worsening of laboratory values) indicating disease progression
- Decline in ECOG performance status due to disease progression
- Presence of rapid progression of disease or of progressive tumor at critical anatomical sites (e.g. cord compression) requiring alternative medical intervention

2.2.2 NUMBER OF PATIENTS

Approximately 260 patients are anticipated to be enrolled at approximately 60 sites. Each arm will be limited to approximately 25 patients or <= 10 patients as indicated in the study. Given the hypothesis-generating nature of the study and the potential for a variable population of patients to enroll, potentially including diverse tumor types and later line patients, a minimum acceptable ORR of 10% will be considered for each arm for the purposes of nonbinding futility.

2.2.3 END OF STUDY AND LENGTH OF STUDY

The end of this study is defined as the date when the last patient, last visit (LPLV), occurs or the date at which the last data point required for statistical analysis or safety follow-up is received from the last patient, whichever occurs later. In order to obtain 1-year follow up for all patients, LPLV is expected to occur approximately 1 year after the last patient is enrolled.

2.3 OUTCOME MEASURES

2.3.1 Primary Efficacy Objective

The primary objective for this study is to evaluate the efficacy of various treatments and/or combinations of treatments in eligible patients with advanced unresectable or metastatic solid tumors, on the basis of the following endpoint:

- The primary endpoint for each arm of this study will be confirmed ORR (cORR) as assessed by the investigator and according to response evaluation criteria in solid tumors version 1.1 (RECIST v1.1), or Response Assessment in Neuro-Oncology [RANO] Criteria for primary CNS tumors [Wen et al. 2017]. The cORR is defined as the proportion of patients whose confirmed best response is a complete response (CR) or partial response (PR) for those with measurable disease and CR for those with non-measurable disease. Confirmation is defined by two consecutive evaluations at least 4 weeks apart for 3 week cycles and at least 6 weeks apart for 4 week cycles. This considers the patient measured within 2 weeks of the planned time between response evaluations.

2.3.2 Secondary Efficacy Objective

The secondary efficacy objectives for this study are to evaluate the efficacy of each targeted treatment on the basis of the following endpoints:

- PFS, defined as the time from start of treatment to the first occurrence of disease progression or death from any cause (whichever occurs first), as determined by the investigator according to RECIST v1.1.
- DOR, defined as the time from the first occurrence of a documented objective response to disease progression or death from any cause (whichever occurs first), as determined by the investigator according to RECIST v1.1.
- OS, defined as the time from start of treatment to death from any cause.
- PFS rate at 3 months during treatment and every 3 months thereafter for at least up to 1 year, defined as the proportion of patients who have not experienced disease progression or death from any cause as determined by the investigator, according to RECIST v1.1.
- OS rate every 3 months during treatment and every 3 months thereafter for at least up to 1 year, defined as the proportion of patients who have not experienced death from any cause.
- Disease control rate (DCR), defined as the proportion of patients whose best response is confirmed CR, confirmed PR, or SD, where SD is confirmed by two assessments a minimum of 6 weeks apart for 4 week cycles and 4 weeks apart for 3

week cycles. DCR will be summarized in the same fashion as the primary efficacy endpoint except, for DCR we will limit analysis to the subgroup in the analysis population consisting of those with measurable disease.

- ORR as assessed by the investigator and according to response evaluation criteria in solid tumors version 1.1 (RECIST v1.1), or Response Assessment in Neuro-Oncology [RANO] Criteria for primary CNS tumors [Wen et al. 2017]. The ORR is defined as the proportion of patients whose best response is a complete response (CR) or partial response (PR) for those with measurable disease and CR for those with non-measurable disease.

2.3.3 Exploratory Efficacy Objectives

Exploratory efficacy objectives are to evaluate efficacy based following the following:

- Analysis of primary and secondary efficacy endpoints when sub grouped by basket, tumor site of origin, and/or self-reported race and ethnicity.

2.4 SAFETY OBJECTIVE

The safety objective for this study is to evaluate the safety and tolerability of the study medications for the tumor types studied based on the following endpoints:

- Incidence and severity of adverse events, with severity determined according to National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 (NCI CTCAE v5.0)
- Change from baseline in targeted clinical laboratory test results

2.5 BIOMARKERS OBJECTIVE

The exploratory biomarker objective for this study is to identify and/or evaluate biomarkers that are early surrogates of efficacy or relapse, are associated with a more severe disease state (i.e., prognostic biomarkers), are associated with acquired resistance to study drug(s), or can increase the knowledge and understanding of disease biology and drug safety, on the basis of the following endpoint:

- The association of baseline and changes in circulating tumor DNA (ctDNA) levels with response and progression to therapy.
- Determination of baseline and changes in expression or levels of biomarkers in the tumor tissue or blood that may be associated with response or resistance to therapy.

2.6 ANALYSIS TIMING

Analysis will be done on an arm by arm basis. Interim analysis will be performed approximately 6 months after treatment initiation for the 12th patient. Primary analysis will be conducted approximately 12 months after LPI. Futility analysis will be performed approximately 2 months after the 12th patient has initiated treatment in order to allow time for at least one tumor assessment.

3. STATISTICAL METHODS

3.1 ANALYSIS POPULATION

The analysis population is defined as patients enrolled who have received at least one dose of study treatment. An efficacy-evaluable patient is defined as a patient in the analysis population.

3.2 ANALYSIS OF STUDY CONDUCT

Enrollment, major protocol deviations including major deviations of inclusion/exclusion criteria, and reasons for discontinuation from the study will be summarized for all patients. Study treatment administration and reasons for discontinuation from study treatment will be summarized.

3.3 EFFICACY ANALYSIS

3.3.1 PRIMARY EFFICACY ENDPOINTS

The primary endpoint for this study will be Confirmed Objective Response Rate (cORR) as assessed by the investigator and according to the corresponding assessment criteria (RECIST v1.1 or RANO). The cORR is defined as the proportion of patients whose confirmed best response is a CR or PR for those with measurable disease and CR for those with non-measurable disease. Confidence intervals at both 70% and 95% nominal levels will be reported using the Clopper-Pearson method. The primary efficacy endpoint will be computed for all treatment arms. If a patient receives at least one dose of study treatment and discontinues the study for any reason before confirmed response can be assessed, the patient will be considered a non-responder (not PR and not CR) and will be added to the denominator of the computation of cORR.

3.3.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints for each treatment arm will consist of DCR, PFS, 1-year OS, and DOR, which are listed and defined below. All secondary endpoints will be computed for all treatment arms.

- PFS, defined as the time from start of treatment to the first occurrence of disease progression or death from any cause (whichever occurs first), as determined by the investigator according to the corresponding assessment criteria (RECIST v1.1 or RANO). The PFS will be estimated using the Kaplan-Meier method. Median PFS and 95% confidence interval will be computed using the Brookmeyer-Crowley method.
- DOR, defined as the time from the first occurrence of a documented objective response to disease progression or death from any cause (whichever occurs first), as determined by the investigator according to the corresponding assessment criteria (RECIST v1.1 or RANO). The DOR will be estimated using the Kaplan-Meier method. Median DOR and 95% confidence interval will be computed using the Brookmeyer-Crowley method.

- OS, defined as the time from start of treatment to death from any cause. The OS will be estimated using the Kaplan-Meier method. OS will be estimated using the Kaplan-Meier method and Median OS and 95% confidence interval will be computed using the Brookmeyer-Crowley method.
- PFS rate at 3 months and every 3 months thereafter for at least up to 1 year, defined as the proportion of patients who have not experienced disease progression or death from any cause as determined by the investigator, according to RECIST v1.1. PFS rates will be computed using the Kaplan-Meier method with 95% confidence intervals for each rate given by Greenwood's formula.
- OS rate every 3 months during treatment and every 3 months thereafter for at least up to 1 year, defined as the proportion of patients who have not experienced death from any cause. OS rates will be computed using the Kaplan-Meier method with 95% confidence intervals for each rate given by Greenwood's formula.
- DCR is defined as the proportion of patients whose confirmed best response is CR, PR, or SD, where SD would require such assessment at least 98 days from treatment initiation for 4 week cycles and at least 70 days from treatment initiation for 3 week cycles and where PD has not been already designated. DCR will be summarized in the same fashion as the primary efficacy endpoint except, for DCR we will limit analysis to the subgroup in the analysis population consisting of those with measurable disease. 95% confidence interval will be determined using clopper-pearson method.
- ORR as assessed by the investigator and according to response evaluation criteria in solid tumors version 1.1 (RECIST v1.1), or Response Assessment in Neuro-Oncology [RANO] Criteria for primary CNS tumors [Wen et al. 2017]. The ORR is defined as the proportion of patients whose best response is a complete response (CR) or partial response (PR) for those with measurable disease and CR for those with non-measurable disease. 95% confidence interval will be determined using clopper-pearson method.

3.3.3 Exploratory Efficacy Analysis

See Subgroup Analyses

3.3.4 Biomarker Analyses

- For all treatment arms, descriptive statistics of biomarker data will include means medians, ranges, and standard deviations, as appropriate. For categorical analyses, frequency distributions will be tabulated as appropriate.
- Biomarker data in blood and tumor tissue and biomarker data collected over time (if available) will be used for additional subgroup analyses where primary and secondary efficacy endpoints and safety will be evaluated.

Although no formal statistical analysis of exploratory biomarkers will be performed, in an effort to understand the association of these markers with study treatment response, data may be analyzed in the context of this study and in aggregate with data from other studies. Results will be presented in a separate report.

Analysis will include but is not limited to concordance of local TMB assays with central testing by FMI and concordance of ctDNA detected mutations and mutations detected in tissue.

3.3.5 Sensitivity Analyses

Sensitivity analysis will be performed with arm-specific alterations confirmed by central re-testing.

Analyses excluding patients who switched arms will be performed.

3.3.6 Subgroup Analyses

The subgroups to be considered for efficacy analysis include but are not limited to the following:

- Tumor Type
- Age (≤ 65 years, > 65 years) at enrollment
- Race
- Gender
- ECOG performance status at randomization (0, 1)
- Prior therapies (number and types)

3.4 SAFETY ANALYSIS

The safety analysis population will include all patients who received at least one dose of study drug. Safety will be assessed through summaries of exposure to study treatment, adverse events, and changes in laboratory test results. Study treatment exposure (such as treatment duration, total dose received, and number of cycles and dose modifications) will be summarized with descriptive statistics. All verbatim adverse event terms will be mapped to Medical Dictionary for Regulatory Activities (MedDRA) thesaurus terms, and adverse event severity will be graded according to the NCI CTCAE (v5.0). All adverse events, serious adverse events, adverse events leading to death, adverse events of special interest, and adverse events leading to study treatment discontinuation that occur on or after the first dose of study treatment (i.e., treatment-emergent adverse events) will be summarized by mapped term, appropriate thesaurus level, and severity grade. For events of varying severity, the highest grade will be used in the summaries. Deaths and cause of death will be summarized. A shift table of selected laboratory tests will be used to summarize the baseline and maximum post baseline severity grade.

3.4.1 Exposure to Study Medication

Study drug exposure, including treatment duration, number of cycles, and dose intensity, will be summarized with descriptive statistics.

3.4.2 Adverse Events

Verbatim description of adverse events will be mapped to Medical Dictionary for Regulatory Activities (MedDRA) thesaurus terms. Adverse events will be graded by the investigator according to the NCI CTCAE v5.0. Treatment-emergent adverse events will be summarized by mapped term, appropriate thesaurus level, NCI CTCAE grade and treatment arm. Multiple occurrences of the same event will be counted once at the maximum grade. All reported AEs, SAEs, Grade 5 AEs, treatment-related AEs (as assessed by the investigator), severe AEs (Grade ≥ 3), AESIs, AEs leading to study drug discontinuation, and AEs leading to interruption or reduction will be summarized.

All listings of AEs will include all AEs with onset on or after the first study drug treatment up to the data cutoff date.

All deaths and causes of death will be summarized, during the study treatment period and those reported during the follow-up period after treatment completion/discontinuation.

3.4.3 Laboratory Data

Laboratory data will be graded according to NCI CTCAE and will be summarized descriptively, with shift tables from baseline to worst value post-baseline.

Changes in laboratory data over time will be summarized. Highest NCI CTCAE grade post-baseline will also be summarized. Values outside the normal ranges will be summarized.

3.4.4 Vital Signs

Changes from baseline in selected vital signs will be summarized.

3.5 FUTILITY ANALYSES

For some arms, limited data are available regarding the efficacy and safety of the treatment across the eligible tumor population(s). Therefore, data from the first 12 patients in a given arm will be used to conduct non-binding tumor agnostic futility analyses. Futility analyses for some arms maybe conducted with the integration of data from other ongoing studies, including TAPISTRY. These analyses will be used to identify whether a treatment may be ineffective in a tumor agnostic population due to limited or lack of efficacy, and further accrual into such an arm may be stopped. Enrollment will not be stopped while awaiting results of the tumor agnostic futility analysis.

The observed response rate (ORR), confirmation not necessary, will be the primary endpoint of the futility assessment. ORR is strictly lower than cORR but is faster to assess and allows for sufficient assessment of benefit to patients.

To perform the futility analyses we will use Bayesian gating with arm-specific gating criteria and non-informative prior where futility will be declared if there is a posterior probability of greater than 60% that the true ORR is less than the minimum acceptable level of 10%. In the case of our study, 0 out of 12 responses indicates futility. If an arm has 0 out of 12 responses,the arm may continue enrollment if it is determined that treatment is still likely to be beneficial to patients beyond what is currently available under standard of care. We thus consider the futility analysis to be non-binding.

POSTERIOR PROBABILITIES

Confidence intervals to exceed minimum acceptable levels of either 10% (arms B,E,F,G,H,I,J) or 30% (arms A,C,D) are given in Table 3 and Table 4.

Table 3 cORR confidence intervals for N = 25 that exceed 10%

confidence	Benchmark Estimate	left bound	right bound
70%	5/25	0.114	0.316
80%	5/25	0.101	0.34
90%	6/25	0.11	0.42
95%	7/25	0.121	0.494

Table 4 cORR confidence intervals for N = 25 that exceed 30%

confidence	Benchmark Estimate	left bound	right bound
70%	11/25	0.323	0.563
80%	11/25	0.301	0.587
90%	12/25	0.305	0.659
95%	13/25	0.313	0.722

For a projected sample size of 25, Table 5 provides probabilities of exceeding the benchmark estimates in Table 3 and Table 4, given the results after 12 patients

Table 5 Probabilities of equaling or exceeding the benchmark given results for 12 patients

Benchmark Estimate	0/12	1/12	2/12	3/12	4/12	5/12	6/12	7/12	8/12	9/12	10/12	11/12
5/25	0.02	0.162	0.497	0.84	0.981	1	1	1	1	1	1	1
6/25	0.008	0.08	0.321	0.678	0.919	0.992	1	1	1	1	1	1
7/25	0.003	0.036	0.188	0.5	0.812	0.963	0.997	1	1	1	1	1
11/25	0	0.001	0.008	0.054	0.213	0.499	0.784	0.945	0.992	0.999	1	1
12/25	0	0	0.002	0.023	0.119	0.348	0.652	0.882	0.977	0.997	1	1
13/25	0	0	0.001	0.008	0.057	0.215	0.503	0.782	0.942	0.991	0.999	1

Uniform prior is used to compute bayesian posterior at 12 patients. Probability of equaling or exceeding the benchmark after seeing 25 patients (13 more after the interim) is given in table.

3.6 OPTIONAL INTERIM ANALYSES

Given the hypothesis-generating nature of this study, the Sponsor may choose to conduct additional interim efficacy analyses. The decision to conduct an optional interim analysis and the timing of the analysis will be documented in the Sponsor's trial master file prior to the conduct of the interim analysis. The interim analysis will be performed and interpreted by Sponsor study team personnel.

Appendix 1 Protocol Synopsis

PROTOCOL SYNOPSIS

TITLE:	**MYTACTIC: AN OPEN-LABEL PHASE II STUDY EVALUATING TARGETED THERAPIES IN PATIENTS WHO HAVE ADVANCED SOLID TUMORS WITH GENOMIC ALTERATIONS OR PROTEIN EXPRESSION PATTERNS PREDICTIVE OF RESPONSE**
PROTOCOL NUMBER:	ML42439
VERSION NUMBER:	4
Eudract Number:	Not Applicable
IND NUMBER:	152738
NCT NUMBER:	NCT04632992
TEST PRODUCT:	Entrectinib (RO7102122), Trastuzumab emtansine (RO5304020), Pertuzumab Trastuzumab Fixed Dose Combination Subcutaneous (PH FDC SC, RO7198574), Inavolisib (GDC-0077; RO7113755), Alectinib (RO5424802), Ipatasertib (RO5532961), Atezolizumab (RO5541267), Tucatinib, Pralsetinib (RO7499790), Tiragolumab (RO7092284)
PHASE:	Phase II
INDICATION:	Solid tumors
SPONSOR:	Genentech, Inc.

Objectives and Endpoints

This study will evaluate the efficacy and safety of multiple therapies that are selected based on potential predictive biomarkers identified in patients with solid tumors.

Efficacy

Primary Efficacy Objective

The primary objective for this study is to evaluate the efficacy of various treatments and/or combinations of treatments in eligible patients with advanced unresectable or metastatic solid tumors, on the basis of the following endpoint:

- The primary endpoint for each arm of this study will be confirmed ORR (cORR) as assessed by the investigator and according to response evaluation criteria in solid tumors version 1.1 (RECIST v1.1), or Response Assessment in Neuro-Oncology [RANO] Criteria for primary CNS tumors. The cORR is defined as the proportion of patients whose confirmed best response is a complete response (CR) or partial response (PR) for those with measurable disease and CR for those with non-measurable disease.

Secondary Efficacy Objective

The secondary efficacy objectives for this study are to evaluate the efficacy of each targeted treatment on the basis of the following endpoints:

- Progression-Free Survival (PFS) defined as the time from start of treatment to the first occurrence of disease progression or death from any cause (whichever occurs first), as determined by the investigator according to RECIST v1.1.
- Duration of objective response (DOR), defined as the time from the first occurrence of a documented objective response to disease progression or death from any cause (whichever occurs first), as determined by the investigator according to RECIST v1.1.
- Overall survival (OS), defined as the time from start of treatment to death from any cause.
- PFS rate at 3 months during treatment and every 3 months thereafter for at least up to 1 year, defined as the proportion of patients who have not experienced disease progression or death from any cause as determined by the investigator, according to RECIST v1.1.
- OS rate every 3 months during treatment and every 3 months thereafter for at least up to 1 year, defined as the proportion of patients who have not experienced death from any cause.
- Disease control rate (DCR), defined as the proportion of patients whose best response is confirmed CR, confirmed PR, or SD where SD is confirmed by two assessments a minimum of 6 weeks apart. DCR will be summarized in the same fashion as the primary efficacy endpoint except, for DCR we will limit analysis to the subgroup in the efficacy population consisting of those with measurable disease.

Exploratory Efficacy Objective

Exploratory efficacy objectives are to evaluate efficacy based following the following:

- Analysis of primary and secondary efficacy endpoints when subgrouped by basket, tumor site of origin, and/or self-reported race and ethnicity.

Safety Objective

The safety objective for this study is to evaluate the safety and tolerability of the study medications for the tumor types studied based on the following endpoints:

- Incidence and severity of adverse events, with severity determined according to National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 (NCI CTCAE [v5.0])
- Change from baseline in targeted clinical laboratory test results

Biomarkers Objective

The exploratory biomarker objective for this study is to identify and/or evaluate biomarkers that are early surrogates of efficacy or relapse, are associated with a more severe disease state

(i.e., prognostic biomarkers), are associated wit h acquired resistance to study drug(s), or can increase the knowledge and understanding of disease biology and drug safety, on the basis of the following endpoint:

- The association of baseline and changes in circulating tumor DNA (ctDNA) levels with response and progression to therapy.
- Determination of baseline and changes in expression or levels of biomarkers in the tumor tissue or blood that may be associated with response or resistance to therapy.

Study Design

Description of Study

Overview of Study Design

MyTACTIC is a Phase II, multicenter, non-randomized, open-label, multi-arm study designed to evaluate the safety and efficacy of targeted therapies as single agents or in rational, specified combinations in patients with advanced unresectable or metastatic solid tumors determined to harbor specific biomarkers. Patients will be enrolled based on local testing performed at a Clinical Laboratory Improvement Amendments (CLIA)-certified or equivalently accredited diagnostic laboratory. For all patients whose positive biomarker result is from an assay other than a tissue-based assay conducted by Foundation Medicine, Inc. (FMI), central testing of pre-treatment tissue (preferably from the most recent block) and blood is required after enrollment. Pre-treatment tissue will be submitted within 21 days after enrollment to a Sponsor-approved laboratory for central testing; this testing will not impact the study participation of enrolled patients.

The multi-arm structure of the MyTACTIC study allows patients with solid tumors to be treated with a drug or drug regimen tailored to their biomarker identified at screening. Each study treatment arm may have separate endpoints, screening, and treatment requirements, defined in the respective appendix. Futility analyses will be employed on all treatment arms to limit enrollment where evidence of very limited or lack of efficacy is observed.

During the study, the following biomarker samples will be collected:

Tumor tissue

- For patients with a positive biomarker result from an assay other than a tissue-based assay conducted by FMI, pre-treatment tissue samples (archival or recent resection or biopsy) must be submitted within 21 days of enrollment at baseline for central testing. If both archival and recent tissue is available, the recent tissue should be preferentially submitted.

Blood samples

- Mandatory blood samples will be collected at screening, 8 weeks after first treatment, and at disease progression for analyses including ctDNA

These samples will be used to evaluate predictive and/or prognostic biomarkers, including but not limited to biomarkers related to driver oncogene signaling, response to study treatment, tumor pathogenesis, and mechanisms of resistance.

Treatment will be assigned by the treating investigator on the basis of relevant specified biomarkers, and will continue until radiographic disease progression (per RECIST v1.1; Response Assessment in Neuro-Oncology (RANO) Criteria for primary CNS tumors, or loss of clinical benefit for specific treatment arms, with Medical Monitor approval; unacceptable toxicity; patient or physician decision to discontinue; or death, whichever occurs first. If a patient discontinues treatment prior to disease progression (because of adverse event or other reason), tumor assessments will continue as specified in the treatment-specific appendix until disease progression, death, withdrawal of consent, or arm/study closure by the Sponsor, whichever occurs first. Patients that have disease progression while on study may qualify for re-screening and enrollment into a different treatment arm if they have more than one documented biomarker and if the associated treatment arm is open and enrolling patients. Patients who qualify for more than one treatment arm and have progressed on the first treatment must re-sign the informed consent form prior to re-screening and undergo screening for the second treatment arm.

Follow-up data, including survival and subsequent anti-cancer therapies, will be collected for each patient until death, loss to follow-up, withdrawal of consent, study/arm closure, or at least 1 year after end of treatment, whichever occurs first. Information regarding the nature and duration of subsequent therapies will be collected.

Patients who do not meet the criteria for participation in this study (screen failure) or the timeline for the screening window may qualify for re-screening at the investigator's discretion. Patients must re-sign the consent form prior to rescreening. The investigator will record reasons for screen failure in the screening log.

Number of Patients

Approximately 260 patients are anticipated to be enrolled at approximately 60 sites. Each arm will be limited to approximately 25 patients, with the exception of Arms M and O, which will be limited to approximately 10 patients.

Target Population

Inclusion Criteria

Patients must meet the following general inclusion criteria to be eligible to enroll in any treatment arm:

- Signed treatment-specific Informed Consent Form
- Positive biomarker results from a CLIA-certified or equivalently accredited diagnostic laboratory and availability of a full report of the testing results. This may be from a tissue or blood sample.
- For patients with a positive biomarker result from an assay other than a tissue-based assay conducted by FMI: Sufficient archival tissue or a recent pretreatment tissue sample must be available for central testing (i.e. at least 11 slides or equivalent block) unless approved by Medical Monitor. If both archival and recent tissues are available, the recent tissue should be preferentially submitted.
- Age ≥ 18 years at time of signing Informed Consent Form
- Participation in a clinical trial is an appropriate treatment option, in the opinion of the investigator
- Ability to comply with the study protocol
- Histologically or cytologically confirmed diagnosis of advanced unresectable or metastatic solid malignancy
- Evaluable or measurable disease (i.e., at least one target or non-target lesion per RECIST V1.1 or one measurable or non-measurable lesion per RANO criteria for patients with primary CNS tumors)
- Eastern Cooperative Oncology Group (ECOG) Performance Status 0–2
- Life expectancy ≥ 8 weeks
- Adequate hematologic and end-organ function, defined by the following laboratory test results, obtained within 14 days prior to initiation of study treatment:
  - ANC per arm-specific eligibility criteria
  - Platelet count $\geq 100 \times 10^9$/L (100,000/μL) without transfusion
  - Hemoglobin ≥ 90 g/L (9 g/dL)

    Patients may be transfused to meet this criterion.
  - AST, ALT, and alkaline phosphatase (ALP) $\leq 3 \times$ upper limit of normal (ULN), with the following exceptions:

    Patients with documented liver involvement: AST and ALT $\leq 5 \times$ ULN

    Patients with documented liver or bone involvement: ALP $\leq 5 \times$ ULN
  - Total bilirubin $\leq 1.5 \times$ ULN with the following exception:

Patients with known Gilbert disease: total bilirubin $\leq 3 \times$ ULN

- Serum creatinine $\leq$ 1.5 mg/dL or Glomerular filtration rate $>$ 50 mL/min/1.73 m2 as calculated through use of the Chronic Kidney Disease Epidemiology Collaboration equation

  Glomerular filtration rate (GFR) estimation: GFR=141 $\times$ min(Scr/κ, 1)α $\times$ max(Scr/κ, 1)-1.209 $\times$ 0.993Age $\times$ 1.018 [if female] $\times$ 1.159 [if black] where:
  Scr is serum creatinine in mg/dL,
  κ is 0.7 for females and 0.9 for males,
  α is -0.329 for females and -0.411 for males,
  min indicates the minimum of Scr/κ or 1, and
  max indicates the maximum of Scr/κ or 1

- Albumin $\geq$ 25 g/L (2.5 g/dL)

- Agrees to take measures to prevent pregnancy in the patient or partner
- In addition to the general inclusion criteria above, in order to be enrolled in a treatment arm of the study, patients must meet all of the treatment-specific inclusion criteria for the respective arm as detailed in the treatment-specific appendix.

  Note: The requirements for enrollment into a specific arm may be more stringent.

Exclusion Criteria

Patients who meet any of the following criteria will be ineligible and excluded from study entry in any arm:

- Current participation or enrollment in another therapeutic clinical trial
  - Re-screening for a different arm of this study is permitted after disease progression if another applicable mutation/biomarker is present
- Eligible for an approved indication included in the local prescribing information for the applicable study treatment
- Symptomatic or actively progressing CNS metastases

  Asymptomatic patients with treated or untreated CNS metastases are eligible, provided that all of the following criteria are met:

  --No ongoing requirement for corticosteroids as therapy for CNS metastases, unless noted otherwise in the arm-specific appendix

  --No evidence of interim progression between the completion of CNS-directed therapy and screening radiographic study

  --No history of intracranial hemorrhage or spinal cord hemorrhage

  --Evaluable disease must be present outside the CNS
- History of leptomeningeal disease, unless noted otherwise in the arm-specific appendix
- *Wide field* radiotherapy within 14 days prior to start of study treatment
- Stereotactic radiosurgery within 7 days prior to start of study treatment
- Severe infection within 4 weeks prior to initiation of study treatment, including, but not limited to, hospitalization for complications of infections, or any active infection that, in the opinion of the investigator, could impact patient safety
  - -- In the setting of a pandemic or epidemic, screening for active infections should be considered according to local or institutional guidelines or those of applicable professional societies (e.g., American Society of Clinical Oncology [ASCO] or European Society for Medical Oncology [ESMO]).
- Receipt of any anticancer drug/biologic or investigational treatment 21 days prior to Cycle 1, Day 1 except hormone therapy, which can be given up to 7 days prior to Cycle 1, Day 1; recovery of treatment-related toxicity consistent with other eligibility criteria
  - -- Androgen blockage may be continued for male patients with prostate cancer

- Patients known to be positive for HIV are excluded if they meet any of the following criteria:
  - -- CD4+ T-cell count of < 350 cells/μL
  - -- Detectable HIV viral load
  - -- History of an opportunistic infection within the past 12 months
  - -- On stable antiretroviral therapy for < 4 weeks
- Patients known to be positive for hepatitis C virus (HCV) antibody (Ab) are excluded with the following exceptions:
  - -- Patients who are HCV Ab positive but HCV RNA negative due to prior treatment or natural resolution are eligible
  - -- Patients with untreated HCV may be enrolled if the HCV is stable, the patient is not at risk for hepatic decompensation, and the intended treatment is not expected to exacerbate the HCV infection
  - -- Patients on concurrent HCV treatment may be enrolled if they have HCV below the limit of quantification
- Patients known to have active hepatitis B (chronic or acute; defined as having a positive hepatitis B surface antigen [HBsAg] test)
  - -- Patients with past hepatitis B virus (HBV) infection or resolved HBV infection (defined as the presence of hepatitis B core antibody [HBcAb] and absence of HBsAg) are eligible only if they are negative for HBV DNA
- History of or concurrent serious medical condition or abnormality in clinical laboratory tests that, precludes the patient's safe participation in and completion of the study or confounds the ability to interpret data from the study (e.g., clinically significant cardiovascular, pulmonary or metabolic disease; wound healing disorders; ulcers; bone fractures)
  - -- Patients with well-controlled comorbid disease on a stable treatment regimen for 4 weeks prior to screening are eligible for the study.
- History of malignancy other than disease under study within 3 years prior to screening, with the exception of malignancies with a negligible risk of metastasis or death (e.g., 5-year OS rate $> 90\%$), such as adequately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, localized prostate cancer, ductal carcinoma in situ, or Stage I uterine cancer
- Incomplete recovery from any surgery prior to the start of study treatment that would interfere with the determination of safety or efficacy of study treatment
- Major surgical procedure, other than for diagnosis, or significant traumatic injury within 4 weeks prior to initiation of study treatment, or anticipation of need for a major surgical procedure during the study
- Significant cardiovascular disease, such as New York Heart Association cardiac disease (Class II or higher), myocardial infarction, or cerebrovascular accident within 3 months prior to enrollment, unstable arrhythmias, or unstable angina
- Pregnant or breastfeeding, or intending to become pregnant during the study
- In addition to the general exclusion criteria above, in order to be enrolled in a treatment arm of the study, patients must meet all of the treatment-specific exclusion criteria for the respective arm as detailed in the treatment-specific appendix.

  Note: The requirements for enrollment into a specific arm may be more stringent

End of Study

The end of this study is defined as the date when the last patient, last visit (LPLV), occurs or the date at which the last data point required for statistical analysis or safety follow-up is received from the last patient, whichever occurs later. In order to obtain 1-year follow up for all patients, LPLV is expected to occur approximately 1 year after the last patient is enrolled.

Length of Study
In order to obtain 1-year follow up for all patients, LPLV is expected to occur approximately 1 year after the last patient is enrolled.

Investigational Medicinal Products

Test Products (Investigational Drugs)

Biomarker alteration	Study Treatment
ROS1 gene fusion	Arm A: Entrectinib
PIK3CA activating mutation	Arm B: *Inavolisib (GDC-0077)*
	Arm K: Ipatasertib + atezolizumab
ALK gene fusion	Arm C: Alectinib
AKT activating mutations and/or *PTEN* loss/loss of function	Arm D: Ipatasertib
	Arm L: Ipatasertib + atezolizumab
Co-mutation in PI3KCA activating mutation and AKT activating mutation or PI3KCA activating mutation and PTEN loss/loss of function	*Arm M: Ipatasertib + paclitaxel*
TMB ≥ 10/MSI-H/dMMR	Arm E: Atezolizumab + chemotherapy[a]
	Arm N: Atezolizumab + tiragolumab
ERBB2 gene mutation or amplification without known TMB ≥ 10/MSI-H/dMMR	Arm F: Trastuzumab emtansine + atezolizumab
	Arm G: PH FDC SC
	Arm H: PH FDC SC + chemotherapy [a]
	Arm I: Trastuzumab emtansine + tucatinib
ERBB2 gene amplification or mutation and TMB ≥10/MSI-H/dMMR	Arm J: Trastuzumab emtansine + atezolizumb
RET gene fusion	*Arm O: Pralsetinib*

chemo=chemotherapy; dMMR=deficient mismatch repair; HER2=human epidermal growth factor receptor 2; IV=intravenous; PH FDC SC=fixed dose combination of trastuzumab and pertuzumab administered subcutaneously; MSI-H=microsatellite instability high; PI3K=phosphatidylinositol 3-kinase; SC=subcutaneous; TMB=tumor mutational burden.

[a] Investigator's choice of docetaxel, paclitaxel, or capecitabine.

Statistical Methods

Primary Analysis

The primary endpoint for this study will be cORR as assessed by the investigator and according to the corresponding assessment criteria (RECIST v1.1 or RANO). The cORR is defined as the proportion of patients whose confirmed best response is a CR or PR for those with measurable disease and CR for those with non-measurable disease. Confidence intervals at both 70% and 95% nominal levels will be reported using the Clopper-Pearson method. The primary efficacy endpoint will be computed for all treatment arms. If a patient receives at least one dose of study treatment and discontinues the study for any reason before confirmed response can be assessed, the patient will be considered a non-responder (not PR and not CR) and will be added to the denominator of the computation of cORR.

Determination of Sample Size

The focus for this study will be estimation since the study is composed of many single arms specific to a targeted therapy. Estimation of the primary endpoint will be 95% confidence intervals using the Clopper-Pearson method. As such, the maximum margin of error for sample sizes 25, 50, and 75 are 20.7%, 14.5%, and 11.8%, respectively. On a per arm basis, if the lower bound of the confidence interval is larger than a benchmark specific to that arm, then we will consider the given treatment as a significant improvement over the benchmark.

Interim Analyses

Non-binding Futility Analyses

For some arms, limited data are available regarding the efficacy and safety of the treatment across the eligible tumor population(s). Therefore, data from the first 12 efficacy-evaluable patients in a given arm will be used to conduct non-binding interim tumor agnostic futility analyses. Futility analyses for some arms *may* be conducted with the integration of data from other ongoing studies (see the Statistical Analysis Plan [SAP] for details). These analyses may be used to identify whether a treatment may be ineffective in a tumor agnostic population due to limited or lack of efficacy, and further accrual into such an arm may be stopped. Enrollment will not be stopped while awaiting results of the tumor agnostic futility analysis. To perform the *analysis* we will use Bayesian gating with arm-specific gating criteria and non-informative prior where futility will be declared if there is a posterior probability of greater than 60% that the true cORR is less than an arm-specific unacceptable level.

Optional Interim Analyses

Given the hypothesis-generating nature of this study, the Sponsor may choose to conduct additional interim efficacy analyses. The decision to conduct an optional interim analysis and the timing of the analysis will be documented in the Sponsor's trial master file prior to the conduct of the interim analysis. The interim analysis will be performed and interpreted by Sponsor study team personnel.

ARM A: ENTRECTINIB IN PATIENTS WITH *ROS1* FUSION-POSITIVE TUMORS

Target Population

To be enrolled in Arm A: entrectinib treatment, patients must have met and continue to meet all general eligibility criteria, in addition to the arm-specific criteria below.

Additional Inclusion Criteria

Patients must meet the following additional inclusion criteria for entry into Arm A: entrectinib treatment:

- *ROS1* gene fusion positivity, except patients with non-small cell lung cancer (NSCLC), as determined by a Clinical Laboratory Improvement Amendments (CLIA) or equivalently certified next-generation sequencing (NGS) assay (tissue or blood)

  Gene fusion positivity is defined as a 3' *ROS1* fusion with a protein coding 5' gene fusion partner, which are predicted to be in frame with an intact kinase domain.
- ANC $\geq$ 1000/μL within 14 days prior to initiation of study treatment
- Ability to swallow entrectinib intact, without chewing, crushing, or opening the capsules/tablets
- For females of childbearing potential: Negative serum pregnancy test $\leq$ 7 days prior to initiating study treatment; agreement to remain abstinent (refrain from heterosexual intercourse) or use single or combined contraception methods that result in a failure rate of $<$ 1% per year during the treatment period and for at least 5 weeks after the last dose of entrectinib; and agreement to refrain from donating eggs during this same period.
- For males: Agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom plus an additional contraception method that together result in a failure rate of $<$ 1% per year during the treatment period and for at least 3 months after the last dose of entrectinib, and agreement to refrain from donating sperm during this same period.

Additional Exclusion Criteria

Patients who meet any of the following additional criteria will be excluded from entry into Arm A: entrectinib treatment:

- *ROS1* fusion-positive NSCLC
- Prior treatment with crizotinib
- Whole-brain radiotherapy and/or stereotactic radiosurgery for CNS disease within 14 days prior *to* the start of entrectinib treatment.
- Symptomatic or uncontrolled CNS involvement
  - -- Patients with CNS involvement, including leptomeningeal carcinomatosis or prior brain metastases, which are either asymptomatic or previously treated and controlled, are allowed.
  - -- Patients requiring corticosteroids must be at stable or decreasing doses for at least 2 weeks prior to the start of entrectinib treatment.
- Requirement for enzyme inducing anti-epileptic drugs (EIAEDs) or use within 14 days or 5 half lives (whichever is longer) prior to the start of entrectinib treatment
  - -- The use of seizure prophylaxis is allowed as long as patients are taking non-enzyme inducing anti-epileptic drugs (non-EIAEDs).
  - -- If patients require an anti-epileptic medication, a cytochrome (CYP) 3A4 non-EIAED can be used such as levetiracetam, valproic acid, gabapentin, topiramate, or lacosamide. Moderate inducers of CYP450, such as dexamethasone or other glucocorticoids, may be used at the discretion of the investigator.
- History of non-pharmacologically induced prolonged corrected QT (QTc) interval (e.g., repeated demonstration of a QTc interval $>$ 450 ms from ECGs performed at least 24 hours apart)
- History of recent (within the past 3 months) symptomatic congestive heart failure or ejection fraction $\leq$ 50% observed during screening for the study
- History of additional risk factors for torsade de pointes (e.g., family history of long QT syndrome)
- Grade $\geq$ 2 peripheral neuropathy
- Active gastrointestinal disease (e.g., Crohn's disease, ulcerative colitis, or short gut syndrome) or other malabsorption syndromes that would reasonably affect drug absorption

- Known interstitial lung disease, interstitial fibrosis, or history of tyrosine kinase inhibitor–induced pneumonitis

  Note: Radiation-induced lung disorders are not included in this exclusion criterion.

Test Product (Investigational Drug)

Entrectinib will be self-administered by patients orally at home (except on clinic days), at the same time each day, on a starting dose of 600 mg/day (three 200-mg capsules per day) once a day (QD) until disease progression, intolerable toxicity or consent withdrawal. Modification may be needed in cases of coadministration with moderate or strong CYP3A4 inducers. For more specific dosing instructions, refer to the pharmacy manual.

ARM B: *Inavolisib* (GDC-0077) IN PATIENTS WITH *PIK3CA* ACTIVATING MUTATION-POSITIVE TUMORS

Target Population

To be enrolled in Arm B: *inavolisib* (GDC-0077) treatment, patients must have met and continue to meet all general eligibility criteria, in addition to arm-specific criteria below.

Additional Inclusion Criteria

Patients must meet the following additional inclusion criteria for entry into Arm B: *inavolisib* (GDC-0077) treatment:

- *PIK3CA* mutation positivity, as determined by a Clinical Laboratory Improvement Amendments (CLIA) or equivalently certified next-generation sequencing (NGS) assay (tissue or blood)

  PIK3CA mutation positivity is defined by the presence of at least one nucleotide variant listed below:

  -- H1047D/I/L/N/P/Q/R/T/Y, G1049A/C/D/R/S, E545A/D/G/K/L/Q/R/V, E453A/D/G/K/Q/V, E542A/D/G/K/Q/R/V, K111N/R/E, Q546E/H/K/L/P/R, G106A/D/R/S/V, N345D/H/I/K/S/T/Y, G118D, C420R, R88Q, M1043I/T/V

  -- Other activating mutations with Medical Monitor approval
- ANC $\geq 1000/\mu L$ within 14 days prior to initiation of study treatment
- Fasting glucose < 126 mg/dL and glycosylated hemoglobin (HbA_{1c}) $< 5.7\%$
- Willingness and ability to swallow GDC-0077 intact, without chewing, or crushing the tablets
- For females of childbearing potential: Negative serum pregnancy test ≤ 7 days prior to initiating study treatment; agreement to remain abstinent (refrain from heterosexual intercourse) or use single or combined contraception methods that result in a failure rate of $< 1\%$ per year during the treatment period and for at least 60 days after the last dose of *inavolisib* (GDC-0077); and agreement to refrain from donating eggs during this same period. For all other women, documentation must be present in medical history confirming that patient is not of childbearing potential.
- For males: Agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom plus an additional contraception method that together result in a failure rate of $< 1\%$ per year during the treatment period and for at least 98 days after the last dose of *inavolisib* (GDC-0077), and agreement to refrain from donating sperm during this same period.

Additional Exclusion Criteria

Patients who meet any of the following additional criteria will be excluded from entry into Arm B: *inavolisib* (GDC-0077) treatment:

- Primary CNS tumors
- Type 2 diabetes requiring antihyperglycemic medication or any history of type 1 diabetes

  Patients with elevated fasting glucose at baseline (fasting glucose ≥ 126 mg/dL [≥ 7.0 mmol/L]) or HbA1c $\geq 5.7\%$ will be excluded from the study

- Malabsorption syndrome or other condition that would interfere with enteral absorption
- Uncontrolled pleural effusion or ascites requiring recurrent drainage procedures twice monthly or more frequently

  Indwelling pleural or abdominal catheters may be allowed provided the patient has adequately recovered from the procedure, is hemodynamically stable and symptomatically improved, and with prior approval from the Medical Monitor
- Any concurrent ocular or intraocular condition (e.g., cataract or diabetic retinopathy) that, in the opinion of the investigator and/or study ophthalmologist, would require medical or surgical intervention during the study period to prevent or treat vision loss that might result from that condition
- Active inflammatory (e.g., uveitis or vitritis) or infectious (e.g., conjunctivitis, keratitis, scleritis, or endophthalmitis) conditions in either eye or history of idiopathic or autoimmune-associated uveitis in either eye
- Patients requiring any daily supplemental oxygen
- History of or active inflammatory disease (e.g., Crohn's disease or ulcerative colitis) or any active bowel inflammation (including diverticulitis)

  Patients currently receiving immunosuppressants (e.g., sulfasalazines) are considered to have active disease and are, therefore, ineligible.
- Symptomatic hypercalcemia requiring continued use of bisphosphonate or denosumab therapy

  Bisphosphonate and denosumab therapy for bone metastases or osteopenia/osteoporosis is allowed.
- Clinically significant and active history of liver disease, including severe liver impairment (ChildPugh score B/C), current alcohol abuse, or cirrhosis
- Congenital long QT syndrome or QT interval corrected using Fridericia's formula (QTcF) $>$ 470 ms demonstrated by at least two ECGs $>$ 30 minutes apart, or family history of sudden unexplained death or long QT syndrome
- Current treatment with medications that are well known to prolong the QT interval
- Allergy or hypersensitivity to components of the *inavolisib (*GDC-0077*)* formulation
- Any symptomatic active lung disease, including pneumonitis

Test Product (Investigational Drug)

*Inavolisib (*GDC-0077*)* will be self-administered by patients orally at home (except on clinic days) at the same time each day, on a starting dose of 9 mg/day (one 9-mg tablet per day) once a day (QD) until disease progression, intolerable toxicity or consent withdrawal. For more specific dosing instructions, refer to the pharmacy manual.

ARM C: ALECTINIB IN PATIENTS WITH *ALK* REARRANGEMENT-POSITIVE TUMORS

Target Population

To be enrolled in Arm C: alectinib treatment, patients must have met and continue to meet all general eligibility criteria, in addition to the arm-specific criteria below.

Additional Inclusion Criteria

Patients must meet the following additional inclusion criteria for entry into Arm C: alectinib treatment:

- *ALK* gene fusion positivity, in indications other than non-small cell lung cancer (NSCLC), as determined by a Clinical Laboratory Improvement Amendments (CLIA) or equivalently certified next generation sequencing (NGS) assay (tissue or blood)

Gene fusion positivity is defined as a 3' *ALK* fusion with a protein coding 5' gene fusion partner, which are predicted to be in frame with an intact kinase domain.

- ANC ≥ 1000/μL within 14 days prior to initiation of study treatment
- For females of childbearing potential: Negative serum pregnancy test ≤ 7 days prior to initiating study treatment; agreement to remain abstinent (refrain from heterosexual intercourse) or use single or combined contraception methods that result in a failure rate of < 1% per year during the treatment period and for at least 90 days after the last dose of alectinib; and agreement to refrain from donating eggs during this same period.
- For males with female partners of childbearing potential: Agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom plus an additional contraception method that together result in a failure rate of < 1% per year during the treatment period and for at least 90 days after the last dose of alectinib, and agreement to refrain from donating sperm during this same period.

Additional Exclusion Criteria

Patients who meet any of the following additional criteria will be excluded from entry into Arm C: alectinib treatment:

- ALK-positive NSCLC
- Inability to swallow pills
- Any gastrointestinal disorder that may affect absorption of oral medications, such as refractory vomiting, malabsorption syndrome, external biliary shunt, or significant bowel resection that would preclude absorption of alectinib
- Detection of the following *ALK* point mutations: I1171N/S, G1202R
- Symptomatic or uncontrolled CNS involvement
  - -- Patients with CNS involvement, including leptomeningeal carcinomatosis or prior brain metastases, which are either asymptomatic or previously treated and controlled, are allowed.
  - -- Patients requiring corticosteroids must be at stable or decreasing doses for at least 2 weeks prior to the start of alectinib treatment.
- Liver disease, characterized by any of the following:
  - -- Impaired excretory function (e.g., hyperbilirubinemia) or synthetic function or other conditions of decompensated liver disease such as coagulopathy, hepatic encephalopathy, hypoalbuminemia, ascites, and bleeding from esophageal varices
  - -- Active autoimmune, alcoholic, or other types of acute hepatitis
- History of organ transplant
- Symptomatic bradycardia
- History of hypersensitivity to any of the additives in the alectinib drug formulation

  This includes, but is not limited to, patients with galactose intolerance, a congenital lactase deficiency, or glucose-galactose malabsorption.

Test Product (Investigational Drug)

Alectinib will be self-administered by patients orally at home (except on clinic days), at the same times each day, on a starting dose of 600 mg (four 150-mg capsules) twice a day (BID) until disease progression, intolerable toxicity or consent withdrawal. For more specific dosing instructions, refer to the pharmacy manual.

ARM D: IPATASERTIB IN PATIENTS WITH PTEN LOSS-OF-FUNCTION OR *AKT1/2/3* MUTANT-POSITIVE SOLID TUMORS

Target Population

To be enrolled in Arm D: ipatisertib treatment, patients must have met and continue to meet all general eligibility criteria, in addition to the arm-specific criteria below.

Additional Inclusion Criteria

Patients must meet the following additional inclusion criteria for entry into Arm D: ipatasertib treatment:

- *AKT1/2/3* mutant positivity or PTEN loss of function, as determined by a Clinical Laboratory Improvement Amendments (CLIA) or equivalently certified next-generation sequencing (NGS) assay (tissue or blood)

  AKT1/2/3 mutant positivity is defined by selected single nucleotide variants as listed below:

  -- *AKT1*: E17K; L52R; Q79K

  -- *AKT2*: E17K

  -- *AKT3*: E17K; L51R; Q78K

  PTEN loss of function is defined as PTEN dominant negative missense mutations or deleterious in-frame and missense mutations affecting protein function

  Other applicable mutations are eligible with Medical Monitor approval

  or PTEN protein loss as determined by a CLIA or equivalently certified immunohistochemistry assay
- ANC $\geq$ 1000/μL within 14 days prior to initiation of study treatment
- Fasting glucose $\leq$ 150 mg/dL and hemoglobin A_{1c} (HbA_{1c}) $\leq$ 7.5%
- Ability to swallow ipatasertib intact, without chewing, crushing, or opening the capsules
- For females of childbearing potential: Negative serum pregnancy test $\leq$ 7 days prior to initiating study treatment; agreement to remain abstinent (refrain from heterosexual intercourse) or use single or combined contraception methods that result in a failure rate of $<$ 1% per year during the treatment period and for at least 28 days after the last dose of ipatasertib; and agreement to refrain from donating eggs during this same period.
- For males: Agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom plus an additional contraception method that together result in a failure rate of $<$ 1% per year during the treatment period and for at least 28 days after the last dose of ipatasertib, and agreement to refrain from donating sperm during this same period.

Additional Exclusion Criteria

Patients who meet any of the following additional criteria will be excluded from entry into Arm D: ipatasertib treatment:

- Triple negative adenocarcinoma of the breast (TNBC)

  TNBC tumors are defined as HER2 negative, estrogen receptor (ER) negative, and progesterone receptor (PgR) negative:

  -- ER or PgR negativity is defined as $<$1% of tumor cell nuclei immunoreactive to the respective hormonal receptor

  -- HER2 negativity is assessed by IHC and/or in situ hybridization according to 2018 American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines
- History of malabsorption syndrome or other condition that would interfere with enteral absorption or results in the inability or unwillingness to swallow pills
- Known clinically significant history of liver disease consistent with Child-Pugh Class B or C, current drug or alcohol abuse, or cirrhosis

- New York Heart Association Class II, III, or IV heart failure; left ventricular ejection fraction (LVEF) $<$ 50%; or active ventricular arrhythmia requiring medication
- Congenital long QT syndrome or screening QT interval corrected using Fridericia's formula (QTcF) $>$ 480 milliseconds
- History or presence of an abnormal ECG that is clinically significant in the investigator's opinion (including complete left bundle branch block, second- or third-degree heart block, or evidence of prior myocardial infarction)
- Need for chronic corticosteroid therapy of $>$ 10 mg of prednisone per day or an equivalent dose of other anti-inflammatory corticosteroids or immunosuppressants for a chronic disease.
- History of Type I or Type II diabetes mellitus requiring insulin.

  Patients who are on a stable dose of oral diabetes medication $\geq$ 2 weeks prior to initiation of study treatment are eligible for enrollment.
- Grade $\geq$ 2 uncontrolled or untreated hypercholesterolemia or hypertriglyceridemia
- History of or active inflammatory bowel disease (e.g., Crohn's disease and ulcerative colitis) or active bowel inflammation (e.g., diverticulitis)
- Lung disease: pneumonitis, interstitial lung disease, idiopathic pulmonary fibrosis, cystic fibrosis, Aspergillosis, active tuberculosis, or history of opportunistic infections (pneumocystis pneumonia or cytomegalovirus pneumonia)
- Treatment with strong cytochrome P450 3A4 (CYP3A) inhibitors or strong CYP3A inducers within 2 weeks or 5 drug-elimination half-lives, whichever is longer, prior to initiation of study treatment
- Uncontrolled pleural effusion, pericardial effusion, or ascites

Test Product (Investigational Drug)

Ipatasertib will be self-administered by patients orally at home (except on clinic days), at the same time each day, on a starting dose 400 mg/day (two 200-mg tablets per day) once a day (QD) until disease progression, intolerable toxicity or consent withdrawal. For more specific dosing instructions, refer to the pharmacy manual.

ARM E: ATEZOLIZUMAB PLUS CHEMOTHERAPY IN PATIENTS WITH TMB-H/ MSI-H/DMMR-POSITIVE TUMORS

Target Population

To be enrolled in Arm E: atezolizumab plus chemotherapy treatment, patients must have met and continue to meet all general eligibility criteria, in addition to the arm-specific criteria below.

Additional Inclusion Criteria

Patients must meet the following additional inclusion criteria for entry into Arm E: atezolizumab plus chemotherapy treatment:

- Documentation of one of the following biomarkers, as determined by a Clinical Laboratory Improvement Amendments (CLIA) or equivalently certified assay (tissue or blood):
  - -- Tumor mutational burden-high (TMB-H), defined as $\geq$ 10 mutations per megabase
  - -- Microsatellite instability high (MSI-H)
  - -- Deficient mismatch repair (dMMR)
- ANC $\geq$ 1500/μL within 14 days prior to initiation of study treatment
- Lymphocyte count $\geq$ 500/μL

- For females of childbearing potential: Negative serum pregnancy test $\leq$ 7 days prior to initiating study treatment; agreement to remain abstinent (refrain from heterosexual intercourse) or use single or combined contraception methods that result in a failure rate of $<$ 1% per year during the treatment period and for at least 5 months after the last dose of atezolizumab or 6 months after the last dose of chemotherapy, whichever is later; and agreement to refrain from donating eggs during this same period.
- For males: Agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom plus an additional contraception method that together result in a failure rate of $<$ 1% per year during the treatment period and for 3 months after the last dose of chemotherapy and agreement to refrain from donating sperm during this same period.

Additional Exclusion Criteria

Patients who meet any of the following additional criteria will be excluded from entry into Arm E: atezolizumab plus chemotherapy treatment:

- Primary CNS tumors with any of the following characteristics:
  - -- History of intracranial hemorrhage or spinal cord hemorrhage
  - -- Neurosurgical resection or brain biopsy to the primary brain tumor within 28 days of Cycle 1, Day 1
- Metastases to the midbrain, pons, medulla, or spinal cord
- Uncontrolled tumor-related pain

  Patients requiring pain medication must be on a stable regimen at study entry.

  Symptomatic lesions (e.g., bone metastases or metastases causing nerve impingement) amenable to palliative radiotherapy should be treated prior to enrollment. Patients should be recovered from the effects of radiation. There is no required minimum recovery period.

  Asymptomatic metastatic lesions that would likely cause functional deficits or intractable pain with further growth (e.g., epidural metastasis that is not currently associated with spinal cord compression) should be considered for loco-regional therapy if appropriate prior to enrollment.
- Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once monthly or more frequently)

  Patients with indwelling catheters (e.g., PleurX®) are allowed.
- Uncontrolled or symptomatic hypercalcemia (ionized calcium $>$ 1.5 mmol/L, calcium $>$ 12 mg/dL, or corrected calcium $>$ upper linit of normal [ULN])
- Co-infection of hepatitis B virus (HBV) and hepatitis C virus (HCV)

  Patients with a history of HCV infection but who are negative for HCV RNA by PCR will be considered non-infected with HCV.
- Active or history of autoimmune disease or immune deficiency, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, antiphospholipid antibody syndrome, Wegener granulomatosis, Sjögren syndrome, Guillain-Barré syndrome, or multiple sclerosis, with the following exceptions:
  - -- Patients with a history of autoimmune-related hypothyroidism who are on a stable dose of thyroid replacement hormone are eligible for the study
  - -- Patients with controlled Type 1 diabetes mellitus who are on a stable insulin regimen are eligible for the study
  - -- Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis are excluded) are eligible for the study provided all of following conditions are met:
    - o Rash must cover $<$ 10% of body surface area

- Disease is well controlled at baseline and requires only low-potency topical corticosteroids
- No occurrence of acute exacerbations of the underlying condition requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high potency or oral corticosteroids within the previous 12 months

- History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, or idiopathic pneumonitis, or evidence of active pneumonitis on screening chest computed tomography (CT) scan

  History of radiation pneumonitis in the radiation field (fibrosis) is permitted.
- Active tuberculosis
- Treatment with therapeutic oral or intraveneous (IV) antibiotics within 2 weeks prior to initiation of study treatment

  Patients receiving prophylactic antibiotics (e.g., to prevent a urinary tract infection or chronic obstructive pulmonary disease exacerbation) are eligible for the study
- Prior allogeneic stem cell or solid organ transplantation
- Treatment with a live, attenuated vaccine within 4 weeks prior to initiation of study treatment, or anticipation of need for such a vaccine during atezolizumab treatment or within 5 months after the final dose of atezolizumab
- Prior treatment with CD137 agonists or immune checkpoint blockade therapies, including anti–PD-1, and anti–PD-L1 therapeutic antibodies

  Patients who have had prior anti-cytotoxic T–lymphocyte-associated protein 4 (CTLA-4) treatment may be enrolled, provided the following requirements are met:

  -- Last dose of anti-CTLA-4 at least 6 weeks prior to enrollment

  -- No history of severe immune-related adverse events from the anti-CTLA-4 (National Cancer Institute Common Terminology Criteria for Research Adverse Events version 5.0 [NCI CTCAE v5.0] Grade 3 and 4)
- Treatment with systemic immunostimulatory agents (including, but not limited to, interferon and interleukin 2 [IL-2]) within 4 weeks or 5 drug elimination half-lives (whichever is longer) prior to initiation of study treatment
- Treatment with systemic immunosuppressive medication (including, but not limited to, corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor-alpha [TNF-α] agents) within 2 weeks prior to initiation of study treatment, or anticipation of need for systemic immunosuppressive medication during study treatment, with the following exceptions:

  -- Patients who received acute, low-dose systemic immunosuppressant medication or a one-time pulse dose of systemic immunosuppressant medication (e.g., 48 hours of corticosteroids for a contrast allergy) are eligible for the study after Medical Monitor approval has been obtained

  -- Patients who received mineralocorticoids (e.g., fludrocortisone), corticosteroids for chronic obstructive pulmonary disease (COPD) or asthma, or low-dose corticosteroids for orthostatic hypotension or adrenal insufficiency are eligible for the study
- History of severe allergic anaphylactic reactions to chimeric or humanized antibodies or fusion proteins
- Known hypersensitivity to Chinese hamster ovary cell products or to any component of the atezolizumab formulation

Test Products (Investigational Drugs)

Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg for patients on Day 1 of each 21-day cycle until unacceptable toxicity or progressive disease (or loss of clinical benefit with approval of Medical Monitor).

Atezolizumab will be delivered in variable-size 0.9% NaCl IV infusion bags.

Docetaxel, paclitaxel, or capecitabine will be administered per package insert and institutional guidelines, including considerations for premedication, supportive medications, infusion times, infusion frequency, and total cycle count.

ARM F: TRASTUZUMAB EMTANSINE PLUS ATEZOLIZUMAB IN PATIENTS WITH *ERBB2* AMPLIFICATION OR MUTATION-POSITIVE TUMORS

Target Population

To be enrolled in Arm F: trastuzumab emtansine plus atezolizumab treatment, patients must have met and continue to meet all general eligibility criteria, in addition to the arm-specific criteria below.

Additional Inclusion Criteria

Patients must meet the following additional inclusion criteria for entry into Arm F: trastuzumab emtansine plus atezolizumab treatment:

- *ERBB2* mutation positivity, as determined by a Clinical Laboratory Improvement Amendments (CLIA) or equivalently certified next-generation sequencing (NGS) assay (tissue or blood)

  ERBB2 mutation positivity is defined by selected single nucleotide variants listed below:

  -- Furin-like domain: G222C; R226S; E265K; D277H; G292R; G309A/E; S310F/Y; C311R/S; E321G; C334S

  -- Kinase domain: T733I; L755P/S; *L755_T759del*; I767M; L768S; D769H/N/Y; Y772_A775dup; A775_G776ins(SVMA/VVMA/YAMA/YVMA/YVMD); G776delins(VC/VV/LC); V777L; G778_P780dup; V779A/L; T798M; L841V; V842I; N857S; T862A; L869R; H878Y; R896C

  -- Transmembrane domain: S653C; V659E; G660D; R678Q

  -- GFR domain IV: P551L; R552S

  -- Receptor L: S418T; A440T

  Other applicable mutations are eligible with Medical Monitor approval

  or evidence of ERBB2 gene amplification determined by CLIA or equivalently certified in-situ hybridization or NGS assay. Amplification is defined as a copy number of ≥ 6 for NGS assays or, for in-situ hybridization assays, as a HER2:CEP17 ratio ≥ 2.0 and average HER2 copy number/cell ≥ 4.0 signals/cell
- ANC $\geq 1200/\mu L$ within 14 days prior to initiation of study treatment
- For females of childbearing potential: Negative serum pregnancy test ≤ 7 days prior to initiating study treatment; agreement to remain abstinent (refrain from heterosexual intercourse) or use single or combined contraception methods that result in a failure rate of $< 1\%$ per year during the treatment period and for at least 7 months after the last dose of trastuzumab emtansine or 5 months after the last dose of atezolizuamb, whichever is longer; and agreement to refrain from donating eggs during this same period.
- For males: Agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom plus an additional contraception method that together result in a failure rate of $< 1\%$ per year during the treatment period and for at least 7 months after the last dose of trastuzumab emtansine and agreement to refrain from donating sperm during this same period.

Additional Exclusion Criteria

Patients who meet any of the following additional criteria will be excluded from entry into Arm F: trastuzumab emtansine plus atezolizumab treatment:

- Breast cancer
- Known tumor mutational burden (TMB) ≥ 10, microsatellite instability high (MSI-H), deficient mismatch repair (dMMR) status
- Metastases to the midbrain, pons, medulla, or spinal cord
- History of exposure to the following cumulative doses of anthracyclines as specified below:
  - -- Doxorubicin > 500 mg/m^2
  - -- Liposomal doxorubicin > 500 mg/m^2
  - -- Epirubicin > 720 mg/m^2
  - -- Mitoxantrone > 120 mg/m^2
  - -- Idarubicin > 90 mg/m^2

    If another anthracycline or more than one anthracycline has been used, the cumulative dose must not exceed the equivalent of 500 mg/m^2 doxorubicin.
- Patients who received prior trastuzumab, DS-8201, or other human epidermal growth factor receptor 2 (HER2)-targeting agents are eligible
- History of severe hypersensitivity to components of the trastuzumab emtansine formulation
- Cardiopulmonary dysfunction as defined by any of the following:
  - -- Uncontrolled hypertension (systolic > 150 mmHg and/or diastolic > 100 mmHg)
  - -- Inadequate left ventricular ejection fraction at baseline, $< 50\%$ by echocardiogram (ECHO) or multiple-gated acquisition (MUGA)
  - -- History of symptomatic congestive heart failure Grade ≥ 3 per National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0 (NCI CTCAE v5.0)
  - -- History of decrease in left ventricular ejection function to $< 40\%$ or symptomatic congestive heart failure (CHF) with prior trastuzumab treatment
  - -- Myocardial infarction or unstable angina within 6 months of enrollment
  - -- Current dyspnea at rest due to complications of advanced malignancy, or other disease requiring continuous oxygen therapy
  - -- Evidence of transmural infarction on ECG
  - -- Significant symptoms (Grade ≥ 2) relating to left ventricular ejection fraction (LVEF), cardiac arrhythmia, or cardiac ischemia
  - -- Serious cardiac arrhythmia not controlled by adequate medication
- Clinically significant history of liver disease, including cirrhosis, current alcohol abuse, autoimmune hepatic disorders, or sclerosis cholangitis
- Uncontrolled or symptomatic hypercalcemia (ionized calcium > 1.5 mmol/L, calcium > 12 mg/dL, or corrected calcium $>$ upper limite of normal [ULN])
- Co-infection of hepatitis B virus (HBV) and hepatitis C virus (HCV)
  - -- Patients with a history of HCV infection but who are negative for HCV RNA by PCR will be considered non-infected with HCV
- Grade ≥ 3 peripheral neuropathy, as defined by National Cancer Institute Common Terminology Criteria for Research Adverse Events version 5.0 [NCI CTCAE v5.0]
- Active or history of autoimmune disease or immune deficiency, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, antiphospholipid antibody syndrome, Wegener granulomatosis, Sjögren syndrome, Guillain-Barré syndrome, or multiple sclerosis, with the following exceptions:
  - -- Patients with a history of autoimmune-related hypothyroidism who are on a stable dose of thyroid replacement hormone are eligible for the study

-- Patients with controlled Type 1 diabetes mellitus who are on a stable insulin regimen are eligible for the study

-- Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis are excluded) are eligible for the study provided all of following conditions are met:

  - Rash must cover $<10\%$ of body surface area
  - Disease is well controlled at baseline and requires only low-potency topical corticosteroids
  - No occurrence of acute exacerbations of the underlying condition requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high potency or oral corticosteroids within the previous 12 months

- Uncontrolled autoimmune hemolytic anemia or immune thrombocytopenia
- Uncontrolled tumor-related pain

  Patients requiring pain medication must be on a stable regimen at study entry

  Symptomatic lesions (e.g., bone metastases or metastases causing nerve impingement) amenable to palliative radiotherapy should be treated ≥ 14 days prior to Cycle 1, Day 1. The patient must have recovered from any resulting acute toxicity (to Grade ≤ 1) prior to study treatment initiation

  Asymptomatic metastatic lesions that would likely cause functional deficits or intractable pain with further growth (e.g., epidural metastasis that is not currently associated with spinal cord compression) should be considered for loco-regional therapy if appropriate prior to enrollment

- Symptomatic pleural effusion, pericardial effusion, or ascites. History of idiopathic pulmonary fibrosis (including pneumonitis), drug-induced pneumonitis, organizing pneumonia (i.e., bronchiolitis obliterans, cryptogenic organizing pneumonia), or evidence of active pneumonitis on screening chest computed tomography (CT) scan. Patients with a history of radiation pneumonitis in the radiation field (fibrosis) are eligible.
- Active tuberculosis
- Treatment with therapeutic oral or intravenous (IV) antibiotics within 2 weeks prior to initiation of study treatment

  Patients receiving prophylactic antibiotics (e.g., to prevent a urinary tract infection or chronic obstructive pulmonary disease exacerbation) are eligible for the study

- Prior allogeneic stem cell or solid organ transplantation
- Treatment with a live, attenuated vaccine within 4 weeks prior to initiation of study treatment, or anticipation of need for such a vaccine during atezolizumab treatment or within 5 months after the final dose of atezolizumab
- Current treatment with anti-viral therapy for hepatitis B virus (HBV)
- Treatment with systemic immunostimulatory agents (including, but not limited to, interferon and interleukin 2 [IL-2]) within 4 weeks or 5 drug-elimination half-lives (whichever is longer) prior to initiation of study treatment
- Treatment with systemic immunosuppressive medication (including, but not limited to, corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor-alpha (TNF-α) agents) within 2 weeks prior to initiation of study treatment, or anticipation of need for systemic immunosuppressive medication during study treatment, with the following exceptions:

  -- Patients who received acute, low-dose systemic immunosuppressant medication or a one-time pulse dose of systemic immunosuppressant medication (e.g., 48 hours of corticosteroids for a contrast allergy) are eligible for the study after Medical Monitor confirmation has been obtained

-- Patients who received mineralocorticoids (e.g., fludrocortisone), corticosteroids for chronic obstructive pulmonary disease (COPD) or asthma, or low-dose corticosteroids for orthostatic hypotension or adrenal insufficiency are eligible for the study

- History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies, excipients of any drugs formulated in polysorbate 80 or 20 or fusion proteins
- Known hypersensitivity to Chinese hamster ovary cell products or to any component of the atezolizumab formulation

Test Products (Investigational Drugs)

Atezolizumab will be administered first followed by trastuzumab emtansine. Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle until unacceptable toxicity or progressive disease (or loss of clinical benefit with Medical Monitor approval). Atezolizumab will be delivered in variable-size 0.9% NaCl IV infusion bags. The size of the infusion bag for each dose is listed below and will accommodate fluid restrictions needed for smaller patients.

Trastuzumab emtansine is administered intravenously at 3.6 mg/kg by IV infusion every 21 days (unless dose reduction and/or dose delays are required) until disease progression or unacceptable toxicity. The dose of trastuzumab emtansine will be administered on the basis of the patient's baseline weight. Weight will be measured at each visit and dose must be re-adjusted for weight changes $>$ 10% compared to the previous visit or baseline. The investigator may choose to recalculate the dose at every cycle using actual weight at that time, according to their local practice.

ARM G: PH FDC SC IN PATIENTS WITH *ERBB2* AMPLIFICATION OR MUTATION-POSITIVE TUMORS

Target Population

To be enrolled in Arm G: fixed dose combination of trastuzumab and pertuzumab administered subcutaneously (PH FDC SC) treatment, patients must have met and continue to meet all general eligibility criteria, in addition to the arm-specific criteria below.

Additional Inclusion Criteria

Patients must meet the following additional inclusion criteria for entry into Arm G: PH FDC SC treatment:

- *ERBB2* mutation positivity, as determined by a Clinical Laboratory Improvement Amendments (CLIA) or equivalently certified next-generation sequencing (NGS) assay (tissue or blood)

  ERBB2 mutation positivity is defined by selected single nucleotide variants listed below:

  -- Furin-like domain: G222C; R226S; E265K; D277H; G292R; G309A/E; S310F/Y; C311R/S; E321G; C334S

  -- Kinase domain: T733I; L755P/S; *L755_T759del*; I767M; L768S; D769H/N/Y; Y772_A775dup; A775_G776ins(SVMA/VVMA/YAMA/YVMA/YVMD); G776delins(VC/VV/LC); V777L; G778_P780dup; V779A/L; T798M; L841V; V842I; N857S; T862A; L869R; H878Y; R896C

  -- Transmembrane domain: S653C; V659E; G660D; R678Q

  -- GFR domain IV: P551L; R552S

  -- Receptor L: S418T; A440T

  Other applicable mutations are eligible with Medical Monitor approval

  or evidence of ERBB2 gene amplification determined by CLIA or equivalently certified in-situ hybridization or NGS assay. Amplification is defined as a copy number of $\geq$ 6 for NGS

assays or, for in-situ hybridization assays, as a HER2:CEP17 ratio ≥ 2.0 and average HER2 copy number/cell ≥ 4.0 signals/cell

- Intact skin at planned site of subcutaneous (SC) injections (thigh)
- ANC ≥ 1000/μL within 14 days prior to initiation of study treatment
- Baseline and most recent (within 3 months) left ventricular ejection fraction (LVEF) ≥ 50% measured by echocardiogram (ECHO) or multiple-gated acquisition scan (MUGA)
- For females of childbearing potential: Negative serum pregnancy test ≤ 7 days prior to initiating study treatment; agreement to remain abstinent (refrain from heterosexual intercourse) or use single or combined contraception methods that result in a failure rate of < 1% per year during the treatment period and for at least 7 months after the last dose of PH FDC SC; and agreement to refrain from donating eggs during this same period.
- For males: Agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom plus an additional contraception method that together result in a failure rate of < 1% per year during the treatment period and for at least 7 months after the last dose of PH FDC SC, and agreement to refrain from donating sperm during this same period.

Additional Exclusion Criteria

Patients who meet any of the following additional criteria will be excluded from entry into Arm G: PH FDC SC treatment:

- Breast cancer
- Known tumor mutational burden (TMB) ≥ 10, microsatellite instability high (MSI-H), deficient mismatch repair (dMMR) status
- History of National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 (NCI CTCAE v5.0) Grade ≥ 3 symptomatic congestive heart failure (CHF)
- *In addition to the core exclusion criterion for significant cardiovascular disease, patients will be excluded if they have any of the following:*
  - -- *High-risk arrhythmias (i.e., atrial tachycardia with a heart rate ≥100/min at rest, significant ventricular arrhythmia [ventricular tachycardia], or higher-grade atrioventricular [AV]-block, such as second-degree AV-block Type 2 [Mobitz type II] or third-degree AV-block) not controlled by adequate medication*
  - -- *Evidence of transmural infarction on ECG*
  - -- *Evidence of myocardial infarction within 12 months prior to enrollment, cerebrovascular accident within 3 months prior to enrollment*
  - -- *Poorly controlled hypertension (e.g., systolic > 180 mmHg or diastolic > 100 mmHg)*
  - -- *Angina pectoris requiring anti-angina medication*
  - -- *Clinically significant valvular heart disease*
- History of ventricular dysrhythmias or risk factors for ventricular dysrhythmias, such as structural heart disease (e.g., severe left ventricular systolic dysfunction [LVSD], left ventricular hypertrophy), coronary heart disease (symptomatic or with ischemia demonstrated by diagnostic testing), clinically significant electrolyte abnormalities (e.g., hypokalemia, hypomagnesemia, hypocalcemia), or family history of sudden unexplained death or long QT syndrome
- Known active liver disease, for example, autoimmune hepatic disorders, or sclerosing cholangitis
- Current treatment with anti-viral therapy for hepatitis B virus (HBV)
- Known hypersensitivity to any of the study drugs, excipients, and/or murine proteins
- Previously experienced severe injection related reactions with pertuzumab plus trastuzumab IV and/or PH FDC SC

- Current chronic daily treatment with corticosteroids (dose > 10 mg methylprednisolone or equivalent excluding inhaled steroids)

Test Product (Investigational Drug)

PH FDC SC is given as a fixed dose (i.e. non-weight based) by SC injection. Two doses of PH FDC SC may be administered in the study: a 15 mL loading dose consisting of 1200 mg pertuzumab and 600 mg trastuzumab and a 10 mL maintenance dose consisting of 600 mg pertuzumab and 600 mg trastuzumab. Patients who have had ≥ 6 weeks since a prior dose of Perjeta and Herceptin intravenous (IV) or PH FDC subcutaneous (SC) at study entry, or have had ≥ 6 weeks since their last study treatment during the study treatment periods, must receive a loading dose before continuing with maintenance doses for subsequent administrations.

ARM H: PH FDC SC PLUS CHEMOTHERAPY IN PATIENTS WITH *ERBB2* AMPLIFICATION OR MUTATION-POSITIVE TUMORS-POSITIVE TUMORS

Target Population

To be enrolled in Arm H: fixed dose combination of trastuzumab and pertuzumab administered subcutaneously (PH FDC SC) plus chemotherapy treatment, patients must have met and continue to meet all general eligibility criteria, in addition to the arm-specific criteria below.

Additional Inclusion Criteria

Patients must meet the following additional inclusion criteria for entry into Arm H: PH FDC SC plus chemotherapy treatment:

- *ERBB2* mutation positivity, as determined by a Clinical Laboratory Improvement Amendments (CLIA) or equivalently certified next-generation sequencing (NGS) assay (tissue or blood)

  ERBB2 mutation positivity is defined by selected single nucleotide variants listed below:

  -- Furin-like domain: G222C; R226S; E265K; D277H; G292R; G309A/E; S310F/Y; C311R/S; E321G; C334S

  -- Kinase domain: T733I; L755P/S; *L755_T759del*; I767M; L768S; D769H/N/Y; Y772_A775dup; A775_G776ins(SVMA/VVMA/YAMA/YVMA/YVMD); G776delins(VC/VV/LC); V777L; G778_P780dup; V779A/L; T798M; L841V; V842I; N857S; T862A; L869R; H878Y; R896C

  -- Transmembrane domain: S653C; V659E; G660D; R678Q

  -- GFR domain IV: P551L; R552S

  -- Receptor L: S418T; A440T

  Other applicable mutations are eligible with Medical Monitor approval

  or evidence of ERBB2 gene amplification determined by CLIA or equivalently certified in-situ hybridization or NGS assay. Amplification is defined as a copy number of ≥ 6 for NGS assays or, for in-situ hybridization assays, as a HER2:CEP17 ratio ≥ 2.0 and average HER2 copy number/cell ≥ 4.0 signals/cell
- Intact skin at planned site of subcutaneous (SC) injections (thigh)
- ANC ≥ 1500/μL within 14 days prior to initiation of study treatment
- Baseline and most recent (witin 3 months) left ventricular ejection fraction (LVEF) ≥ 50% measured by echocardiogram (ECHO) or multiple-gated acquisition scan (MUGA)
- For females of childbearing potential: Negative serum pregnancy test ≤7 days prior to initiating study treatment; agreement to remain abstinent (refrain from heterosexual intercourse) or use single or combined contraception methods that result in a failure rate of < 1% per year during the treatment period and for at least 7 months after the last dose of PH FDC SC or 6 months after the last dose of chemotherapy, whichever is later; and agreement to refrain from donating eggs during this same period.

- For males: Agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom plus an additional contraception method that together result in a failure rate of < 1% per year during the treatment period and for at least 7 months after the last dose of PH FDC SC or for 3 months after the last dose of chemotherapy, whichever is longer, and agreement to refrain from donating sperm during this same period.

Additional Exclusion Criteria

Patients who meet any of the following additional criteria will be excluded from entry into Arm H: PH FDC SC plus chemotherapy treatment:

- Breast cancer
- Known tumor mutational burden (TMB) ≥ 10, microsatellite instability high (MSI-H), deficient mismatch repair (dMMR) status
- History of National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0 (NCI CTCAE v5.0) Grade ≥ 3 symptomatic congestive heart failure (CHF)
- *In addition to the core exclusion criterion for significant cardiovascular disease, patients will be excluded if they have any of the following:*
  - -- *High-risk arrhythmias (i.e., atrial tachycardia with a heart rate ≥100/min at rest, significant ventricular arrhythmia [ventricular tachycardia], or higher-grade atrioventricular [AV]-block, such as second-degree AV-block Type 2 [Mobitz type II] or third-degree AV-block) not controlled by adequate medication*
  - -- *Evidence of transmural infarction on ECG*
  - -- *Evidence of myocardial infarction within 12 months prior to enrollment, cerebrovascular accident within 3 months prior to enrollment*
  - -- *Poorly controlled hypertension (e.g., systolic > 180 mmHg or diastolic > 100 mmHg)*
  - -- *Angina pectoris requiring anti-angina medication*
  - -- *Clinically significant valvular heart disease*
- History of ventricular dysrhythmias or risk factors for ventricular dysrhythmias, such as structural heart disease (e.g., severe left ventricular systolic dysfunction [LVSD], left ventricular hypertrophy), coronary heart disease (symptomatic or with ischemia demonstrated by diagnostic testing), clinically significant electrolyte abnormalities (e.g., hypokalemia, hypomagnesemia, hypocalcemia), or family history of sudden unexplained death or long QT syndrome
- Known active liver disease, for example, autoimmune hepatic disorders, or sclerosing cholangitis
- Current treatment with anti-viral therapy for hepatitis B virus (HBV)
- Known hypersensitivity to any of the study drugs, excipients, and/or murine proteins
- Previously experienced severe injection related reactions with pertuzumab plus trastuzumab IV and/or PH FDC SC
- Current chronic daily treatment with corticosteroids (dose > 10 mg methylprednisolone or equivalent excluding inhaled steroids)

Test Products (Investigational Drugs)

PH FDC SC is given as a fixed dose (i.e. non-weight based) by SC injection. Two doses of PH FDC SC may be administered in the study: a 15 mL loading dose consisting of 1200 mg pertuzumab and 600 mg trastuzumab and a 10 mL maintenance dose consisting of 600 mg pertuzumab and 600 mg trastuzumab. Patients who have had ≥ 6 weeks since a prior dose of Perjeta and Herceptin intravenous (IV) or PH FDC SC at study entry, or have had ≥ 6 weeks since their last study treatment during the study treatment periods, must receive a loading dose before continuing with maintenance doses for subsequent administrations.

Docetaxel, paclitaxel, or capecitabine will be administered per package insert and institutional guidelines, including considerations for premedication, supportive medications, infusion times, infusion frequency, and total cycle count.

ARM I: TRASTUZUMAB EMTANSINE PLUS TUCATINIB IN PATIENTS WITH *ERBB2* AMPLIFICATION OR MUTATION-POSITIVE TUMORS

Target Population

To be enrolled in Arm I: trastuzumab emtansine plus tucatinib treatment, patients must have met and continue to meet all general eligibility criteria, in addition to the arm-specific criteria below.

Additional Inclusion Criteria

Patients must meet the following additional inclusion criteria for entry into Arm I: trastuzumab emtansine plus tucatinib treatment:

- *ERBB2* mutation positivity, as determined by a Clinical Laboratory Improvement Amendments (CLIA) or equivalently certified next-generation sequencing (NGS) assay (tissue or blood)

  ERBB2 mutation positivity is defined by selected single nucleotide variants listed below:

  -- Furin-like domain: G222C; R226S; E265K; D277H; G292R; G309A/E; S310F/Y; C311R/S; E321G; C334S

  -- Kinase domain: T733I; L755P/S; $L755\_T759del;$ I767M; L768S; D769H/N/Y; Y772_A775dup; A775_G776ins(SVMA/VVMA/YAMA/YVMA/YVMD); G776delins(VC/VV/LC); V777L; G778_P780dup; V779A/L; T798M; L841V; V842I; N857S; T862A; L869R; H878Y; R896C

  -- Transmembrane domain: S653C; V659E; G660D; R678Q

  -- GFR domain IV: P551L; R552S

  -- Receptor L: S418T; A440T

  Other applicable mutations are eligible with Medical Monitor approval

  or evidence of ERBB2 gene amplification determined by CLIA or equivalently certified in-situ hybridization or NGS assay. Amplification is defined as a copy number of ≥ 6 for NGS assays or, for in-situ hybridization assays, as a HER2:CEP17 ratio ≥ 2.0 and average HER2 copy number/cell ≥ 4.0 signals/cell
- ANC $\geq 1200/\mu L$ within 14 days prior to initiation of study treatment
- For females of childbearing potential: Negative serum pregnancy test ≤ 7 days prior to initiating study treatment; agreement to remain abstinent (refrain from heterosexual intercourse) or use single or combined contraception methods that result in a failure rate of $< 1\%$ per year during the treatment period and for at least 7 months after the last dose of trastuzumab emtansine or at least 1 week after last administration of tucatinib, whichever is longer; and agreement to refrain from donating eggs during this same period.
- For males: Agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom plus an additional contraception method that together result in a failure rate of $< 1\%$ per year during the treatment period and for at least 7 months after the last dose of trastuzumab emtansine or at least 1 week after last dose of tucatinib, whichever is longer and agreement to refrain from donating sperm during this same period.

Additional Exclusion Criteria

Patients who meet any of the following additional criteria will be excluded from entry into Arm I: trastuzumab emtansine plus tucatinib treatment:

- Breast cancer
- History of exposure to the following cumulative doses of anthracyclines as specified below:
  -- Doxorubicin > 500 mg/m^2
  -- Liposomal doxorubicin > 500 mg/m^2

-- Epirubicin > 720 mg/m^2

-- Mitoxantrone > 120 mg/m^2

-- Idarubicin > 90 mg/m^2

If another anthracycline or more than one anthracycline has been used, the cumulative dose must not exceed the equivalent of 500 mg/m^2 doxorubicin.

- Patients who received prior trastuzumab, DS-8201, or other human epidermal growth factor receptor 2 (HER2)-targeting agents are eligible
- History of severe hypersensitivity to components of the trastuzumab emtansine or tucatinib formulations
- Cardiopulmonary dysfunction as defined by any of the following:
  -- Uncontrolled hypertension (systolic > 150 mmHg and/or diastolic > 100 mmHg)
  -- Inadequate left ventricular ejection fraction at baseline, < 50% by echocardiogram (ECHO) or multiple-gated acquisition (MUGA)
  -- History of symptomatic congestive heart failure Grade ≥ 3 per National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0 (NCI CTCAE v5.0)
  -- History of decrease in left ventricular ejection function to < 40% or symptomatic congestive heart failure (CHF) with prior trastuzumab treatment
  -- Myocardial infarction or unstable angina within 6 months of enrollment
  -- Current dyspnea at rest due to complications of advanced malignancy, or other disease requiring continuous oxygen therapy
  -- Evidence of transmural infarction on ECG
  -- Significant symptoms (Grade ≥ 2) relating to left ventricular ejection fraction (LVEF), cardiac arrhythmia, or cardiac ischemia
  -- Serious cardiac arrhythmia not controlled by adequate medication
- Clinically significant history of liver disease, including cirrhosis, current alcohol abuse, autoimmune hepatic disorders, sclerosis cholangitis
- Have used a strong cytochrome P450 (CYP)2C8 inhibitor within 5 half-lives of the inhibitor, or have used a strong CYP3A4 or CYP2C8 inducer within 5 day prior to start of treatment
- Grade ≥ 3 peripheral neuropathy, as defined by NCI CTCAE v5.0
- Uncontrolled autoimmune hemolytic anemia or immune thrombocytopenia

Test Product (Investigational Drug)

Trastuzumab emtansine is administered intravenously at 3.6 mg/kg by IV infusion every 21 days (unless dose reduction and/or dose delays are required) until disease progression or unacceptable toxicity. The dose of trastuzumab emtansine will be administered on the basis of the patient's baseline weight. Weight will be measured at each visit and dose must be re-adjusted for weight changes > 10% compared to the previous visit or baseline. The investigator may choose to recalculate the dose at every cycle using actual weight at that time, according to their local practice.

Tucatinib drug product may be supplied as both a coated yellow oval-shaped tablet in a 150 mg dosage strength and a coated yellow round convex tablet in a 50 mg dosage strength. The tablets are manufactured from a drug product intermediate amorphous dispersion of tucatinib in polyvinylpyrrolidone-vinyl acetate copolymer, which is then combined with the pharmaceutical excipients (microcrystalline cellulose, sodium chloride, potassium chloride, sodium bicarbonate, silicon dioxide, crospovidone, and magnesium stearate), and compressed into tablets.

ARM J: TRASTUZUMAB EMTANSINE PLUS ATEZOLIZUMAB IN PATIENTS WITH *ERBB2*-AMLIFICATION or MUTATAION AND TMB-H/MSI-H/DMMR TUMORS

Target Population

To be enrolled in Arm J: trastuzumab emtansine plus atezolizumab treatment, patients must have met and continue to meet all general eligibility criteria, in addition to the arm-specific criteria below.

Additional Inclusion Criteria

Patients must meet the following additional inclusion criteria for entry into Arm J: trastuzumab emtansine plus atezolizumab treatment:

- *ERBB2* mutation positivity, as determined by a Clinical Laboratory Improvement Amendments (CLIA) or equivalently certified next-generation sequencing (NGS) assay (tissue or blood)

  ERBB2 mutation positivity is defined by selected single nucleotide variants listed below:

  -- Furin-like domain: G222C; R226S; E265K; D277H; G292R; G309A/E; S310F/Y; C311R/S; E321G; C334S

  -- Kinase domain: T733I; L755P/S; $L755\_T759del;$ I767M; L768S; D769H/N/Y; Y772_A775dup; A775_G776ins(SVMA/VVMA/YAMA/YVMA/YVMD); G776delins(VC/VV/LC); V777L; G778_P780dup; V779A/L; T798M; L841V; V842I; N857S; T862A; L869R; H878Y; R896C

  -- Transmembrane domain: S653C; V659E; G660D; R678Q

  -- GFR domain IV: P551L; R552S

  -- Receptor L: S418T; A440T

  Other applicable mutations are eligible with Medical Monitor approval

  or evidence of ERBB2 gene amplification determined by CLIA or equivalently certified in-situ hybridization or NGS assay. Amplification is defined as a copy number of ≥ 6 for NGS assays or, for in-situ hybridization assays, as a HER2:CEP17 ratio ≥ 2.0 and average HER2 copy number/cell ≥ 4.0 signals/cell
- Documentation of one of the following biomarkers, as determined by a CLIA or equivalently certified assay (tissue or blood):
  -- Tumor mutational burden high (TMB-H) high, defined as ≥ 10 mutations per megabase
  -- Microsatellite instability high (MSI-H)
  -- Deficient mismatch repair (dMMR)
- ANC $\geq 1200/\mu L$ within 14 days prior to initiation of study treatment
- For females of childbearing potential: Negative serum pregnancy test ≤ 7 days prior to initiating study treatment; agreement to remain abstinent (refrain from heterosexual intercourse) or use single or combined contraception methods that result in a failure rate of $< 1\%$ per year during the treatment period and for at least 7 months after the last dose of trastuzumab emtansine or 5 months after the last dose of atezolizuamb, whichever is longer; and agreement to refrain from donating eggs during this same period.
- For males: Agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom plus an additional contraception method that together result in a failure rate of $< 1\%$ per year during the treatment period and for at least 7 months after the last dose of trastuzumab emtansine and agreement to refrain from donating sperm during this same period.

Additional Exclusion Criteria

Patients who meet any of the following additional criteria will be excluded from entry into Arm J: trastuzumab emtansine plus atezolizumab treatment:

- Breast cancer

- Metastases to the midbrain, pons, medulla, or spinal cord
- History of exposure to the following cumulative doses of anthracyclines as specified below:
  - -- Doxorubicin > 500 mg/m^2
  - -- Liposomal doxorubicin > 500 mg/m^2
  - -- Epirubicin > 720 mg/m^2
  - -- Mitoxantrone > 120 mg/m^2
  - -- Idarubicin > 90 mg/m^2

  If another anthracycline or more than one anthracycline has been used, the cumulative dose must not exceed the equivalent of 500 mg/m^2 doxorubicin.
- Patients who received prior trastuzumab, DS-8201, or other human epidermal growth factor receptor 2 (HER2)-targeting agents are eligible
- History of severe hypersensitivity to components of the trastuzumab emtansine formulation
- Cardiopulmonary dysfunction as defined by any of the following:
  - -- Uncontrolled hypertension (systolic > 150 mmHg and/or diastolic > 100 mmHg)
  - -- Inadequate left ventricular ejection fraction (LVEF) at baseline, < 50% by echocardiogram (ECHO) or multiple-gated acquisition (MUGA)
  - -- History of symptomatic congestive heart failure Grade ≥ 3 per National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0 (NCI CTCAE v5.0) or Class ≥ II New York Heart Association
  - -- History of decrease in left ventricular ejection function to < 40% or symptomatic congestive heart failure (CHF) with prior trastuzumab treatment
  - -- Myocardial infarction or unstable angina within 6 months of enrollment
  - -- Current dyspnea at rest due to complications of advanced malignancy, or other disease requiring continuous oxygen therapy
  - -- Evidence of transmural infarction on ECG
  - -- Significant symptoms (Grade ≥ 2) relating to LVEF, cardiac arrhythmia, or cardiac ischemia
  - -- Serious cardiac arrhythmia not controlled by adequate medication
- Clinically significant history of liver disease, including cirrhosis, current alcohol abuse, autoimmune hepatic disorders, sclerosis cholangitis
- Uncontrolled or symptomatic hypercalcemia (ionized calcium > 1.5 mmol/L, calcium > 12 mg/dL, or corrected calcium > upper limite of normal [ULN])
- Co-infection of hepatitis B virus (HBV) and hepatitis C virus (HCV)
  - -- Patients with a history of HCV infection but who are negative for HCV RNA by PCR will be considered non-infected with HCV
- Grade ≥ 3 peripheral neuropathy, as defined by NCI CTCAE v5.0
- Active or history of autoimmune disease or immune deficiency, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, antiphospholipid antibody syndrome, Wegener granulomatosis, Sjögren syndrome, Guillain-Barré syndrome, or multiple sclerosis, with the following exceptions:
  - -- Patients with a history of autoimmune-related hypothyroidism who are on a stable dose of thyroid replacement hormone are eligible for the study
  - -- Patients with controlled Type 1 diabetes mellitus who are on a stable insulin regimen are eligible for the study

- -- Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis are excluded) are eligible for the study provided all of following conditions are met:
    - Rash must cover $<10\%$ of body surface area
    - Disease is well controlled at baseline and requires only low-potency topical corticosteroids
    - No occurrence of acute exacerbations of the underlying condition requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high potency or oral corticosteroids within the previous 12 months
- Uncontrolled autoimmune hemolytic anemia or immune thrombocytopenia
- Uncontrolled tumor-related pain

  Patients requiring pain medication must be on a stable regimen at study entry.

  Symptomatic lesions (e.g., bone metastases or metastases causing nerve impingement) amenable to palliative radiotherapy should be treated $\geq$14 days prior to Cycle 1, Day 1. The patient must have recovered from any resulting acute toxicity (to Grade $\leq$ 1) prior to study treatment initiation.

  Asymptomatic metastatic lesions that would likely cause functional deficits or intractable pain with further growth (e.g., epidural metastasis that is not currently associated with spinal cord compression) should be considered for loco-regional therapy if appropriate prior to enrollment.
- Symptomatic pleural effusion, pericardial effusion, or ascites. History of idiopathic pulmonary fibrosis (including pneumonitis), drug-induced pneumonitis, organizing pneumonia (i.e., bronchiolitis obliterans, cryptogenic organizing pneumonia), or evidence of active pneumonitis on screening chest computed tomography (CT) scan. Patients with a history of radiation pneumonitis in the radiation field (fibrosis) are eligible.
- Active tuberculosis
- Treatment with therapeutic oral or intravenous (IV) antibiotics within 2 weeks prior to initiation of study treatment

  Patients receiving prophylactic antibiotics (e.g., to prevent a urinary tract infection or chronic obstructive pulmonary disease exacerbation) are eligible for the study
- Prior allogeneic stem cell or solid organ transplantation
- Treatment with a live, attenuated vaccine within 4 weeks prior to initiation of study treatment, or anticipation of need for such a vaccine during atezolizumab treatment or within 5 months after the final dose of atezolizumab
- Current treatment with anti-viral therapy for hepatitis B virus (HBV)
- Treatment with systemic immunostimulatory agents (including, but not limited to, interferon and interleukin 2 [IL-2]) within 4 weeks or 5 drug-elimination half-lives (whichever is longer) prior to initiation of study treatment
- Treatment with systemic immunosuppressive medication (including, but not limited to, corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti–TNF-α agents) within 2 weeks prior to initiation of study treatment, or anticipation of need for systemic immunosuppressive medication during study treatment, with the following exceptions:
    - -- Patients who received acute, low-dose systemic immunosuppressant medication or a one-time pulse dose of systemic immunosuppressant medication (e.g., 48 hours of corticosteroids for a contrast allergy) are eligible for the study after Medical Monitor confirmation has been obtained

-- Patients who received mineralocorticoids (e.g., fludrocortisone), corticosteroids for chronic obstructive pulmonary disease (COPD) or asthma, or low-dose corticosteroids for orthostatic hypotension or adrenal insufficiency are eligible for the study

- History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies, excipients of any drugs formulated in polysorbate 80 or 20 or fusion proteins
- Known hypersensitivity to Chinese hamster ovary cell products or to any component of the atezolizumab formulation

Test Product (Investigational Drug)

Atezolizumab will be administered first followed by trastuzumab emtansine. Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle until unacceptable toxicity or progressive disease (or loss of clinical benefit with Medical Monitor approval). Atezolizumab will be delivered in variable-size 0.9% NaCl IV infusion bags. The size of the infusion bag for each dose is listed below and will accommodate fluid restrictions needed for smaller patients.

Trastuzumab emtansine is administered intravenously at 3.6 mg/kg by IV infusion every 21 days (unless dose reduction and/or dose delays are required) until disease progression or unacceptable toxicity. The dose of trastuzumab emtansine will be administered on the basis of the patient's baseline weight. Weight will be measured at each visit and dose must be re-adjusted for weight changes > 10% compared to the previous visit or baseline. The investigator may choose to recalculate the dose at every cycle using actual weight at that time, according to their local practice.

ARM K: IPATASERTIB PLUS ATEZOLIZUMAB IN PATIENTS WITH PIK3CA ACTIVATING MUTATION POSITIVE TUMORS

Target Population

To be enrolled in Arm K: ipatasertib in combination with atezolizumab treatment, patients must have met and continue to meet all general eligibility criteria, in addition to the arm-specific criteria below.

Additional Inclusion Criteria

Patients must meet the following additional inclusion criteria for entry into Arm K: ipatasertib in combination with atezolizumab treatment:

- *PIK3CA mutation positivity, as determined by a Clinical Laboratory Improvement Amendments (CLIA) or equivalently certified next-generation sequencing (NGS) assay (tissue or blood)*

  PIK3CA mutation positivity is defined by the presence of at least one nucleotide variant listed below:

  -- *H1047D/I/L/N/P/Q/R/T/Y, G1049A/C/D/R/S, E545A/D/G/K/L/Q/R/V, E453A/D/G/K/Q/V, E542A/D/G/K/Q/R/V, K111N/R/E, Q546E/H/K/L/P/R, G106A/D/R/S/V, N345D/H/I/K/S/T/Y, G118D, C420R, R88Q, M1043I/T/V*

  -- *Kinase domain: T733I; L755P/S; I767M; L768S; D769H/N/Y; Y772_A775dup; A775_G776ins(SVMA/VVMA/YAMA/YVMA/YVMD); L755P/S/_T759del; G776delins(VC/VV/LC); V777L; G778_P780dup; V779A/L; T798M; L841V; V842I; N857S; T862A; L869R; H878Y; R896C*

  Other activating mutations with Medical Monitor approval

- *No available acceptable treatment for malignancy that is expected to provide clinical benefit*
- *ANC ≥ 1000/μl within 14 days prior to initiation of study treatment*
- *Fasting glucose ≤ 150 mg/dL and hemoglobin A1c (HbA1c) ≤7.5%*
- *Ability to swallow ipatasertib intact, without chewing, crushing, or opening the capsules*

- *For females of childbearing potential: Negative serum pregnancy test ≤ 7 days prior to initiating study treatment; agreement to remain abstinent (refrain from heterosexual intercourse) or use single or combined contraception methods that result in a failure rate of < 1% per year during the treatment period and for at least 28 days after the last dose of ipatasertib and 5 months after the last dose of atezolizumab; and agreement to refrain from donating eggs during this same period.*
- *For males: Agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom plus an additional contraception method that together result in a failure rate of < 1% per year during the treatment period and for at least 28 days after the last dose of ipatasertib, and agreement to refrain from donating sperm during this same period.*

Additional Exclusion Criteria

Patients who meet any of the following additional criteria will be excluded from entry into Arm K: ipatasertib plus atezolizumab treatment:

- *Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once monthly or more frequently)*

  Use of an indwelling catheter (e.g., PleurX®) is allowed.
- *Uncontrolled tumor-related pain*

  Patients requiring pain medication must be on a stable regimen at study entry.

  Symptomatic lesions (e.g., bone metastases or metastases causing nerve impingement) amenable to palliative radiotherapy should be treated prior to enrollment. Patients should be recovered from the effects of radiation. There is no required minimum recovery period.

  Asymptomatic metastatic lesions that would likely cause functional deficits or intractable pain with further growth (e.g., epidural metastasis that is not presently associated with spinal cord compression) should be considered for loco-regional therapy if appropriate prior to enrollment.
- *Uncontrolled or symptomatic hypercalcemia (ionized calcium > 1.5 mmol/L, calcium > 12 mg/dL, or corrected serum calcium > ULN)*
- *Active or history of autoimmune disease or immune deficiency, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, antiphospholipid antibody syndrome, Wegener granulomatosis, Sjögren syndrome, Guillain-Barré syndrome, or multiple sclerosis, with the following exceptions:*

  Patients with a history of autoimmune-related hypothyroidism who are on thyroid-replacement hormone are eligible for the study.

  Patients with controlled Type 1 diabetes mellitus who are on a stable insulin regimen are eligible for the study.

  Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis are excluded) are eligible for the study provided all of following conditions are met:

  -- *Rash must cover < 10% of body surface area*

  -- *Disease is well controlled at baseline and requires only low-potency topical corticosteroids*

  -- *No occurrence of acute exacerbations of the underlying condition requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high-potency or oral corticosteroids within the previous 12 months*
- *History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, or idiopathic pneumonitis, or evidence of active pneumonitis on screening chest computed tomography (CT) scan*

History of radiation pneumonitis in the radiation field (fibrosis) is permitted.

- *Active tuberculosis*
- *Treatment with therapeutic oral or intravenous (IV) antibiotics within 2 weeks prior to initiation of study treatment*

  Patients receiving prophylactic antibiotics (e.g., to prevent a urinary tract infection or chronic obstructive pulmonary disease exacerbation) are eligible for the study
- *Prior allogeneic stem cell or solid organ transplantation*
- *Treatment with a live, attenuated vaccine within 4 weeks prior to initiation of study treatment, or anticipation of need for such a vaccine during atezolizumab treatment or within 5 months after the final dose of atezolizumab*
- *Prior treatment with anti-PD-1 or anti PD-L1 therapeutics unless approved by Medical Monitor*

  -- *Up to approximately 12 such patients may be enrolled*
- *Treatment with systemic immunostimulatory agents (including, but not limited to, interferon and interleukin 2 [IL-2]) within 4 weeks or 5 drug elimination half-lives (whichever is longer) prior to initiation of study treatment*
- *Treatment with systemic immunosuppressive medication (including, but not limited to, corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti–tumor necrosis factor-alpha [TNF-α] agents) within 2 weeks prior to initiation of study treatment, or anticipation of need for systemic immunosuppressive medication during study treatment, with the following exceptions:*

  -- *Patients who received acute, low-dose systemic immunosuppressant medication or a one-time pulse dose of systemic immunosuppressant medication (e.g., 48 hours of corticosteroids for a contrast allergy) are eligible for the study after Medical Monitor approval has been obtained*

  -- *Patients who received mineralocorticoids (e.g., fludrocortisone), corticosteroids for chronic obstructive pulmonary disease (COPD) or asthma, or low-dose corticosteroids for orthostatic hypotension or adrenal insufficiency are eligible for the study*
- *History of severe allergic anaphylactic reactions to chimeric or humanized antibodies or fusion proteins*
- *Known hypersensitivity to Chinese hamster ovary cell products or to any component of the atezolizumab formulation*
- *Prior treatment with ipatasertib or other Akt inhibitors*
- *History of malabsorption syndrome or other condition that would interfere with enteral absorption or results in the inability or unwillingness to swallow pills*
- *Known clinically significant history of liver disease consistent with Child-Pugh Class B or C, current drug or alcohol abuse, or cirrhosis*
- *New York Heart Association Class II, III, or IV heart failure; left ventricular ejection fraction (LVEF) < 50%; or active ventricular arrhythmia requiring medication*
- *Congenital long QT syndrome or screening QT interval corrected using Fridericia's formula (QTcF) > 480 milliseconds*
- *History or presence of an abnormal ECG that is clinically significant in the investigator's opinion (including complete left bundle branch block, second- or third-degree heart block, or evidence of prior myocardial infarction)*
- *Need for chronic corticosteroid therapy of > 10 mg of prednisone per day or an equivalent dose of other anti-inflammatory corticosteroids or immunosuppressants for a chronic disease.*
- *History of Type I or Type II diabetes mellitus requiring insulin.*

  Patients who are on a stable dose of oral diabetes medication ≥ 2 weeks prior to initiation of study treatment are eligible for enrollment.

Diabetic patients with fasting total serum glucose > 8.3 mmol/L (150 mg/dL) and/or HbA1C > 7.5 are not eligible for enrollment.

- *History of or active inflammatory bowel disease (e.g., Crohn's disease and ulcerative colitis) or active bowel inflammation (e.g., diverticulitis)*
- *Lung disease: pneumonitis, interstitial lung disease, idiopathic pulmonary fibrosis, cystic fibrosis, Aspergillosis, active tuberculosis, or history of opportunistic infections (pneumocystis pneumonia or cytomegalovirus pneumonia)*
- *Treatment with strong cytochrome P450 3A4 (CYP3A) inhibitors or strong CYP3A inducers within 2 weeks or 5 drug-elimination half-lives, whichever is longer, prior to initiation of study treatment*
- *Uncontrolled pleural effusion, pericardial effusion, or ascites*

Test Product (Investigational Drug)

Ipatasertib will be self-administered by patients orally at home (except on clinic days), at the same time each day, on a starting dose 400 mg/day (two 200-mg tablets per day) once a day (QD) until disease progression, intolerable toxicity or consent withdrawal. For more specific dosing instructions, refer to the pharmacy manual.

Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg for patients on Day 1 of each 21-day cycle until unacceptable toxicity or progressive disease (or loss of clinical benefit with Medical Monitor approval).

ARM L: IPATASERTIB PLUS ATEZOLIZUMAB IN PATIENTS WITH PTEN LOSS/ LOSS OF FUNCTION OR AKT ACTIVATING MUTATION–POSITIVE TUMORS

Target Population

To be enrolled in Arm L: ipatasertib in combination with atezolizumab treatment, patients must have met and continue to meet all general eligibility criteria, in addition to the arm-specific criteria below.

Additional Inclusion Criteria

Patients must meet the following additional inclusion criteria for entry into Arm L: ipatasertib in combination with atezolizumab treatment:

- *AKT1/2/3 mutant positivity, as determined by a Clinical Laboratory Improvement Amendments (CLIA) or equivalently certified next-generation sequencing (NGS) assay (tissue or blood)*

  AKT1/2/3 mutant positivity is defined by selected single nucleotide variants as listed below:

  - *AKT1: E17K; L52R; Q79K*
  - *AKT2: E17K*
  - *AKT3: E17K; L51R; Q78K*

  or PTEN protein loss of function or protein loss as determined by a CLIA or equivalently certified tissue-based NGS, in situ hybridization (ISH), or immunohistochemistry (IHC) assay
- *No available acceptable treatment for malignancy that is expected to provide clinical benefit*
- *ANC ≥ 1000/μl within 14 days prior to initiation of study treatment*
- *Fasting glucose ≤ 150 mg/dL and hemoglobin A1c (HbA1c) ≤7.5%*
- *Ability to swallow ipatasertib intact, without chewing, crushing, or opening the capsules*

- *For females of childbearing potential: Negative serum pregnancy test ≤ 7 days prior to initiating study treatment; agreement to remain abstinent (refrain from heterosexual intercourse) or use single or combined contraception methods that result in a failure rate of < 1% per year during the treatment period and for at least 28 days after the last dose of ipatasertib and 5 months after the last dose of atezolizumab; and agreement to refrain from donating eggs during this same period.*
- *For males: Agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom plus an additional contraception method that together result in a failure rate of < 1% per year during the treatment period and for at least 28 days after the last dose of ipatasertib, and agreement to refrain from donating sperm during this same period.*

Additional Exclusion Criteria

Patients who meet any of the following additional criteria will be excluded from entry into Arm L: ipatasertib plus atezolizumab treatment:

- *Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once monthly or more frequently)*

  Use of an indwelling catheter (e.g., PleurX®) is allowed.
- *Uncontrolled tumor-related pain*

  Patients requiring pain medication must be on a stable regimen at study entry.

  Symptomatic lesions (e.g., bone metastases or metastases causing nerve impingement) amenable to palliative radiotherapy should be treated prior to enrollment. Patients should be recovered from the effects of radiation. There is no required minimum recovery period.

  Asymptomatic metastatic lesions that would likely cause functional deficits or intractable pain with further growth (e.g., epidural metastasis that is not presently associated with spinal cord compression) should be considered for loco-regional therapy if appropriate prior to enrollment.
- *Uncontrolled or symptomatic hypercalcemia (ionized calcium > 1.5 mmol/L, calcium > 12 mg/dL, or corrected serum calcium > ULN)*
- *Active or history of autoimmune disease or immune deficiency, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, antiphospholipid antibody syndrome, Wegener granulomatosis, Sjögren syndrome, Guillain-Barré syndrome, or multiple sclerosis, with the following exceptions:*

  Patients with a history of autoimmune-related hypothyroidism who are on thyroid-replacement hormone are eligible for the study.

  Patients with controlled Type 1 diabetes mellitus who are on a stable insulin regimen are eligible for the study.

  Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis are excluded) are eligible for the study provided all of following conditions are met:

  -- *Rash must cover < 10% of body surface area*

  -- *Disease is well controlled at baseline and requires only low-potency topical corticosteroids*

  -- *No occurrence of acute exacerbations of the underlying condition requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high-potency or oral corticosteroids within the previous 12 months*
- *History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, or idiopathic pneumonitis, or evidence of active pneumonitis on screening chest computed tomography (CT) scan*

History of radiation pneumonitis in the radiation field (fibrosis) is permitted.

- *Active tuberculosis*
- *Treatment with therapeutic oral or intravenous (IV) antibiotics within 2 weeks prior to initiation of study treatment*

  Patients receiving prophylactic antibiotics (e.g., to prevent a urinary tract infection or chronic obstructive pulmonary disease exacerbation) are eligible for the study
- *Prior allogeneic stem cell or solid organ transplantation*
- *Treatment with a live, attenuated vaccine within 4 weeks prior to initiation of study treatment, or anticipation of need for such a vaccine during atezolizumab treatment or within 5 months after the final dose of atezolizumab*
- *Prior treatment with anti-PD-1 or anti PD-L1 therapeutics unless approved by Medical Monitor*
  - *Up to approximately 12 such patients may be enrolled*
- *Treatment with systemic immunostimulatory agents (including, but not limited to, interferon and interleukin 2 [IL-2]) within 4 weeks or 5 drug elimination half-lives (whichever is longer) prior to initiation of study treatment*
- *Treatment with systemic immunosuppressive medication (including, but not limited to, corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti–tumor necrosis factor-alpha [TNF-α] agents) within 2 weeks prior to initiation of study treatment, or anticipation of need for systemic immunosuppressive medication during study treatment, with the following exceptions:*
  - *Patients who received acute, low-dose systemic immunosuppressant medication or a one-time pulse dose of systemic immunosuppressant medication (e.g., 48 hours of corticosteroids for a contrast allergy) are eligible for the study after Medical Monitor approval has been obtained*
  - *Patients who received mineralocorticoids (e.g., fludrocortisone), corticosteroids for chronic obstructive pulmonary disease (COPD) or asthma, or low-dose corticosteroids for orthostatic hypotension or adrenal insufficiency are eligible for the study*
- *History of severe allergic anaphylactic reactions to chimeric or humanized antibodies or fusion proteins*
- *Known hypersensitivity to Chinese hamster ovary cell products or to any component of the atezolizumab formulation*
- *Prior treatment with ipatasertib or other Akt inhibitors*
- *History of malabsorption syndrome or other condition that would interfere with enteral absorption or results in the inability or unwillingness to swallow pills*
- *Known clinically significant history of liver disease consistent with Child-Pugh Class B or C, current drug or alcohol abuse, or cirrhosis*
- *New York Heart Association Class II, III, or IV heart failure; left ventricular ejection fraction (LVEF) < 50%; or active ventricular arrhythmia requiring medication*
- *Congenital long QT syndrome or screening QT interval corrected using Fridericia's formula (QTcF) > 480 milliseconds*
- *History or presence of an abnormal ECG that is clinically significant in the investigator's opinion (including complete left bundle branch block, second- or third-degree heart block, or evidence of prior myocardial infarction)*
- *Need for chronic corticosteroid therapy of > 10 mg of prednisone per day or an equivalent dose of other anti-inflammatory corticosteroids or immunosuppressants for a chronic disease.*
- *History of Type I or Type II diabetes mellitus requiring insulin.*

Patients who are on a stable dose of oral diabetes medication ≥ 2 weeks prior to initiation of study treatment are eligible for enrollment.

Diabetic patients with fasting total serum glucose > 8.3 mmol/L (150 mg/dL) and/or HbA1C > 7.5 are not eligible for enrollment.

- *History of or active inflammatory bowel disease (e.g., Crohn's disease and ulcerative colitis) or active bowel inflammation (e.g., diverticulitis)*
- *Lung disease: pneumonitis, interstitial lung disease, idiopathic pulmonary fibrosis, cystic fibrosis, Aspergillosis, active tuberculosis, or history of opportunistic infections (pneumocystis pneumonia or cytomegalovirus pneumonia)*
- *Treatment with strong cytochrome P450 3A4 (CYP3A) inhibitors or strong CYP3A inducers within 2 weeks or 5 drug-elimination half-lives, whichever is longer, prior to initiation of study treatment*
- *Uncontrolled pleural effusion, pericardial effusion, or ascites*

Test Product (Investigational Drug)

Ipatasertib will be self-administered by patients orally at home (except on clinic days), at the same time each day, on a starting dose 400 mg/day (two 200-mg tablets per day) once a day (QD) until disease progression, intolerable toxicity or consent withdrawal. For more specific dosing instructions, refer to the pharmacy manual.

Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg for patients on Day 1 of each 21-day cycle until unacceptable toxicity or progressive disease (or loss of clinical benefit with Medical Monitor approval).

ARM M: Ipatasertib Plus Paclitaxel In Patients With Co-Mutations In PIK3CA Activating Mutations And PTEN Loss/ Loss-of-Function or AKT Activating Mutation-Positive Tumors

Target Population

To be enrolled in Arm M: ipatasertib in combination with paclitaxel treatment, patients must have met and continue to meet all general eligibility criteria, in addition to the arm-specific criteria below.

Additional Inclusion Criteria

Patients must meet the following additional inclusion criteria for entry into Arm M: ipatasertib in combination with paclitaxel treatment:

- *A co-mutation of either PIK3CA activating mutation and AKT activating mutation or a PIK3CA activating mutation and PTEN loss or loss of function based on the following biomarkers:*
  - *PIK3CA mutation positivity, as determined by a Clinical Laboratory Improvement Amendments (CLIA) or equivalently certified next-generation sequencing (NGS) assay (tissue or blood)*

    PIK3CA mutation positivity is defined by the presence of at least one nucleotide variant listed below:
    - *H1047D/I/L/N/P/Q/R/T/Y, G1049A/C/D/R/S, E545A/D/G/K/L/Q/R/V, E453A/D/G/K/Q/V, E542A/D/G/K/Q/R/V, K111N/R/E, Q546E/H/K/L/P/R, G106A/D/R/S/V, N345D/H/I/K/S/T/Y, G118D, C420R, R88Q, M1043I/T/V*
    - *Other activating mutations with Medical Monitor approval*
  - *AKT1/2/3 mutant positivity, as determined by a Clinical Laboratory Improvement Amendments (CLIA) or equivalently certified next-generation sequencing (NGS) assay (tissue or blood)*

    AKT1/2/3 mutant positivity is defined by selected single nucleotide variants as listed below:
    - *AKT1: E17K; L52R; Q79K*

- *AKT2: E17K*
- *AKT3: E17K; L51R; Q78K*

or PTEN protein loss of function or protein loss as determined by a CLIA or equivalently certified tissue-based NGS, in situ hybridization (ISH), or immunohistochemistry (IHC) assay

- *ANC ≥ 1500/μl within 14 days prior to initiation of study treatment*
- *Fasting glucose ≤ 150 mg/dL and hemoglobin A1c (HbA1c) ≤ 7.5%*
- *Ability to swallow ipatasertib intact, without chewing, crushing, or opening the capsules*
- *For females of childbearing potential: Negative serum pregnancy test ≤ 7 days prior to initiating study treatment; agreement to remain abstinent (refrain from heterosexual intercourse) or use single or combined contraception methods that result in a failure rate of < 1% per year during the treatment period and for at least 28 days after the last dose of ipatasertib and 6 months after the last dose of paclitaxel, whichever occurs later, and agreement to refrain from donating eggs during this same period.*
- *For males: Agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom plus an additional contraception method that together result in a failure rate of < 1% per year during the treatment period and for at least 28 days after the last dose of ipatasertib, and 6 months after the last dose of paclitaxel, whichever occurs later and agreement to refrain from donating sperm during this same period.*

Additional Exclusion Criteria

Patients who meet any of the following additional criteria will be excluded from entry into Arm M: ipatasertib in combination with paclitaxel treatment:

- *History of malabsorption syndrome or other condition that would interfere with enteral absorption or results in the inability or unwillingness to swallow pills*
- *Known clinically significant history of liver disease consistent with Child-Pugh Class B or C, current drug or alcohol abuse, or cirrhosis*
- *New York Heart Association Class II, III, or IV heart failure; left ventricular ejection fraction (LVEF) <50%; or active ventricular arrhythmia requiring medication*
- *Congenital long QT syndrome or screening QT interval corrected using Fridericia's formula (QTcF) >480 milliseconds*
- *History or presence of an abnormal ECG that is clinically significant in the investigator's opinion (including complete left bundle branch block, second- or third degree heart block, or evidence of prior myocardial infarction)*
- *Need for chronic corticosteroid therapy of >10 mg of prednisone per day or an equivalent dose of other anti-inflammatory corticosteroids or immunosuppressants for a chronic disease*
- *Unresolved, clinically significant toxicity from prior therapy, except for alopecia and Grade 1 peripheral neuropathy*
- *Uncontrolled pleural effusion, pericardial effusion, or ascites*

  Patients with indwelling catheters (e.g., PleurX®) are allowed.
- *Uncontrolled tumor-related pain*
  - *Patients requiring pain medication must be on a stable regimen at study entry*
  - *Symptomatic lesions (e.g., bone metastases or metastases causing nerve impingement) amenable to palliative radiotherapy should be treated ≥ 14 days prior to Cycle 1, Day 1. The patient must have recovered from any resulting acute toxicity (to Grade ≤ 1) prior to study treatment initiation*
  - *Asymptomatic metastatic lesions that would likely cause functional deficits or intractable pain with further growth (e.g., epidural metastasis that is not currently*

associated with spinal cord compression) should be considered for loco-regional therapy if appropriate prior to enrollment

- *Uncontrolled hypercalcemia (> 1.5 mmol/L ionized calcium, > 12 mg/dL calcium, or corrected serum calcium > ULN) or symptomatic hypercalcemia requiring continued use of bisphosphonate therapy*
- *History of Type I or Type II diabetes mellitus requiring insulin.*

  Patients who are on a stable dose of oral diabetes medication ≥ 2 weeks prior to initiation of study treatment are eligible for enrollment.
- *Grade ≥ 2 uncontrolled or untreated hypercholesterolemia or hypertriglyceridemia*
- *History of or active inflammatory bowel disease (e.g., Crohn's disease and ulcerative colitis) or active bowel inflammation (e.g., diverticulitis)*
- *Lung disease: pneumonitis, interstitial lung disease, idiopathic pulmonary fibrosis, cystic fibrosis, Aspergillosis, active tuberculosis, or history of opportunistic infections (pneumocystis pneumonia or cytomegalovirus pneumonia)*
- *Treatment with strong cytochrome P450 3A4 (CYP3A) inhibitors or strong CYP3A inducers within 2 weeks or 5 drug-elimination half-lives, whichever is longer, prior to initiation of study treatment*
- *Prior treatment with an Akt inhibitor*
- *Note that prior PI3K or mTOR inhibitors are allowed.*
- *Known hypersensitivity or contraindication to any component of the study treatments, including the paclitaxel excipient macrogolglycerol ricinoleate*
- *Grade ≥ 2 peripheral neuropathy*
- *Prior treatment with paclitaxel treatment*

Test Product (Investigational Drug)

Ipatasertib will be self-administered by patients orally at home (except on clinic days), at the same time each day, on a starting dose 400 mg/day (two 200-mg tablets per day) once a day (QD) until disease progression, intolerable toxicity or consent withdrawal. For more specific dosing instructions, refer to the pharmacy manual.

The dose of paclitaxel in this study is 80 mg/m^2 administered by IV infusion on Days 1, 8, and 15 of each 28-day cycle. The paclitaxel infusion will be delivered over at least 60 minutes for each dose per institutional guidelines and administered after the oral dose of ipatasertib.

ARM N: Atezolizumab plus Tiragolumab in Patients with TMB-H/MSI-H/dMMR-Positive Tumors

Target Population

To be enrolled in Arm N: atezolizumab plus tiragolumab treatment, patients must have met and continue to meet all general eligibility criteria, in addition to the arm-specific criteria below.

Additional Inclusion Criteria

Patients must meet the following additional inclusion criteria for entry into Arm N: atezolizumab plus tiragolumab treatment:

- *Documentation of one of the following biomarkers, as determined by a CLIA or equivalently certified assay (tissue or blood):*
  - *Tumor mutational burden high (TMB-H) high, defined as ≥ 10 mutations per megabase*
  - *Microsatellite instability high (MSI-H)*
  - *Deficient mismatch repair (dMMR)*
- *ANC ≥ 1200/μL within 14 days prior to initiation of study treatment*

- *Lymphocyte count ≥500/μL*
- *Eastern Cooperative Oncology Group (ECOG) Performance Status 0–2*
- *For patients not receiving therapeutic anticoagulation: INR and aPTT ≤1.5 × ULN*
- *For females of childbearing potential: Negative serum pregnancy test ≤ 7 days prior to initiating study treatment; agreement to remain abstinent (refrain from heterosexual intercourse) or use single or combined contraception methods that result in a failure rate of < 1% per year during the treatment period and for at least 90 days after the final dose of tiragolumab or 5 months after the last dose of atezolizumab, whichever is later; and agreement to refrain from donating eggs during this same period.*
- *For males: Agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom during the treatment period and for 90 days after the last dose of tiragolumab and agreement to refrain from donating sperm during this same period.*

Additional Exclusion Criteria

Patients who meet any of the following additional criteria will be excluded from entry into Arm N: atezolizumab plus tiragolumab treatment:

- *Primary CNS tumors with any of the following characteristics:*
  - *History of intracranial hemorrhage or spinal cord hemorrhage*
  - *Neurosurgical resection or brain biopsy to the primary brain tumor within 28 days of Cycle 1, Day 1*
- *Metastases to the midbrain, pons, medulla, or spinal cord*
- *Uncontrolled tumor-related pain*

  Patients requiring pain medication must be on a stable regimen at study entry.

  Symptomatic lesions (e.g., bone metastases or metastases causing nerve impingement) amenable to palliative radiotherapy should be treated prior to enrollment. Patients should be recovered from the effects of radiation. There is no required minimum recovery period.

  Asymptomatic metastatic lesions that would likely cause functional deficits or intractable pain with further growth (e.g., epidural metastasis that is not currently associated with spinal cord compression) should be considered for loco-regional therapy if appropriate prior to enrollment.
- *Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once monthly or more frequently)*

  Patients with indwelling catheters (e.g., PleurX®) are allowed.
- *Uncontrolled or symptomatic hypercalcemia (ionized calcium >1.5 mmol/L, calcium >12 mg/dL, or corrected calcium >upper limit of normal [ULN])*
- *Patients known to be positive for hepatitis C virus (HCV) antibody (Ab) are excluded with the following exception (note that this is more stringent than the core criterion):*

  Patients who are HCV Ab positive but HCV RNA negative due to prior treatment or natural resolution are eligible
- *Co-infection of hepatitis B virus (HBV) and hepatitis C virus (HCV)*

  Patients with a history of HCV infection but who are negative for HCV RNA by PCR will be considered non-infected with HCV.
- *Positive EBV viral capsid antigen IgM test at screening*

  An EBV polymerase chain reaction (PCR) test should be performed as clinically indicated to screen for acute infection or suspected chronic active infection. Patients with a positive EBV PCR test are excluded.
- *Active or history of autoimmune disease or immune deficiency, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, antiphospholipid antibody syndrome, Wegener granulomatosis, Sjögren syndrome, Guillain-Barré syndrome, or multiple sclerosis, with the following exceptions:*

Patients with a history of autoimmune-related hypothyroidism who are on thyroid replacement hormone are eligible for the study.

Patients with controlled Type 1 diabetes mellitus who are on an insulin regimen are eligible for the study.

Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis are excluded) are eligible for the study provided all of following conditions are met:

- *Rash must cover <10% of body surface area*
- *Disease is well controlled at baseline and requires only low-potency topical corticosteroids*
- *No occurrence of acute exacerbations of the underlying condition requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high potency or oral corticosteroids within the previous 12 months*

- *History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, or idiopathic pneumonitis, or evidence of active pneumonitis on screening chest computed tomography (CT) scan*

  History of radiation pneumonitis in the radiation field (fibrosis) is permitted.
- *Active tuberculosis*
- *Treatment with therapeutic oral or intravenous (IV) antibiotics within 2 weeks prior to initiation of study treatment*

  Patients receiving prophylactic antibiotics (e.g., to prevent a urinary tract infection or chronic obstructive pulmonary disease exacerbation) are eligible for the study
- *Prior allogeneic stem cell or solid organ transplantation*
- *Live, attenuated vaccines (e.g., FluMist®) are prohibited within 4 weeks prior to initiation of study treatment, during study treatment, for 90 days after the final dose of tiragolumab, and for 5 months after the final dose of atezolizumab.*
- *Prior treatment with CD137 agonists or immune checkpoint blockade therapies, including anti-TIGIT, anti-LAG3, anti–PD-1, and anti–PD-L1 therapeutic antibodies*

  Patients who have had prior anti-CTLA-4 treatment may be enrolled, provided the following requirements are met:

  - *Last dose of anti-CTLA-4 at least 6 weeks prior to enrollment*
  - *No history of severe immune-related adverse events from the anti-CTLA-4 (National Cancer Institute Common Terminology Criteria for Research Adverse Events [NCI CTCAE] Grade 3 and 4)*
- *Treatment with systemic immunostimulatory agents (including, but not limited to, interferon and interleukin 2 [IL-2]) within 4 weeks or 5 drug elimination half-lives (whichever is longer) prior to initiation of study treatment*
- *Treatment with systemic immunosuppressive medication (including, but not limited to, corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti–tumor necrosis factor-alpha [TNF-α] agents) within 2 weeks prior to initiation of study treatment, or anticipation of need for systemic immunosuppressive medication during study treatment, with the following exceptions:*
  - *Patients who received acute, low-dose systemic immunosuppressant medication or a one-time pulse dose of systemic immunosuppressant medication (e.g., 48 hours of corticosteroids for a contrast allergy) are eligible for the study after Medical Monitor approval has been obtained*
  - *Patients who received mineralocorticoids (e.g., fludrocortisone), corticosteroids for chronic obstructive pulmonary disease (COPD) or asthma, or low-dose corticosteroids for orthostatic hypotension or adrenal insufficiency are eligible for the study*

-- *Any prior Grade ≥ 3 immune-mediated adverse event or any unresolved Grade > 1 immune-mediated adverse event while receiving any previous immunotherapy agent other than immune checkpoint blockade agents*

- *History of severe allergic anaphylactic reactions to chimeric or humanized antibodies or fusion proteins*
- *Known hypersensitivity to Chinese hamster ovary cell products or to any component of the atezolizumab or tiragolumab formulation*

Test Product (Investigational Drug)

Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle until unacceptable toxicity or progressive disease (or loss of clinical benefit with Medical Monitor approval). Atezolizumab should be administered prior to tiragolumab on days when both are administered.

Following the administration of atezolizumab and an observation period, patients will receive 600 mg tiragolumab at a fixed dose administered by IV infusion on Day 1 of each 21-day cycle. The tiragolumab dose is fixed and is not dependent on body weight.

ARM O: Pralsetinib in Patients with RET Fusion-Positive Tumors

Target Population

To be enrolled in Arm O: pralsetinib treatment, patients must have met and continue to meet all general eligibility criteria, in addition to the arm-specific criteria below.

Additional Inclusion Criteria

Patients must meet the following additional inclusion criteria for entry into Arm O: pralsetinib treatment:

- *RET fusion positivity, except patients with non-small cell lung cancer (NSCLC) or thyroid cancers, as determined by a Clinical Laboratory Improvement Amendments (CLIA) or equivalently certified next-generation sequencing (NGS) assay (tissue or blood)*

  Gene fusion positivity is defined as a 3′ RET fusion with a protein coding 5′ gene fusion partner, which are predicted to be in frame with an intact kinase domain.
- *ANC ≥ 1000/μL within 14 days prior to initiation of study treatment*
- *Ability to swallow pralsetinib intact, without chewing, crushing, or opening the capsules/tablets*
- *For females of childbearing potential: Negative serum pregnancy test ≤7 days prior to initiating study treatment; agreement to remain abstinent (refrain from heterosexual intercourse) or use single or combined contraception methods that result in a failure rate of < 1% per year during the treatment period and for at least 14 days after the last dose of pralsetinib; and agreement to refrain from donating eggs during this same period.*
- *For males: Agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom plus an additional contraception method that together result in a failure rate of < 1% per year during the treatment period and for at least 7 days after the last dose of pralsetinib, and agreement to refrain from donating sperm during this same period.*

Additional Exclusion Criteria

Patients who meet any of the following additional criteria will be excluded from entry into Arm O: pralsetinib treatment:

- *RET fusion-positive NSCLC*
- *RET fusion-positive thyroid cancer*
- *Patient's tumor has any additional known primary driver alterations other than RET, such as targetable mutations of EGFR, ALK, ROS1, MET, KRAS or BRAF.*
- *Known history of hypersensitivity to pralsetinib or any of its excipients*

- *Prior treatment with RET inhibitors (approved or investigational)*
- *Note: Other prior anti-cancer therapy is allowed*
- *Screening QT interval corrected using Fridericia's formula (QTcF) >480 milliseconds, history of prolonged QT syndrome or torsades de pointes, and/or familial history of prolonged QT syndrome*
- *History of pneumonitis during the prior 12 months*
- *Ongoing treatment with chronic immunosuppressants (e.g., cyclosporine) or systemic steroids >10 mg/day of prednisone (or equivalent)*
- *Active, uncontrolled infection (viral, bacterial, or fungal)*
  - -- *Participants with controlled infections who are stable on treatment may be eligible if the benefit–risk assessment is justified and permission is granted from the Sponsor.*
- *Clinically symptomatic interstitial lung disease or interstitial pneumonitis, including radiation pneumonitis (i.e., affecting activities of daily living or requiring therapeutic intervention)*
- *Neutrophil growth factor support within 14 days of the first dose of study drug*
- *Treatment with a prohibited medication or herbal remedy that cannot be discontinued at least 14 days before the start of study drug administration. Pralsetinib may be started within 14 days or 5 half-lives (whichever is longer) of prior therapy if this is considered by the investigator to be safe and in the best interest of the patient, with prior Sponsor approval.*

Test Product (Investigational Drug)

Pralsetinib will be self-administered by patients orally at home, at the same time each day, on a starting dose of 400 mg/day (four 100 mg capsules per day) once a day (QD) until disease progression, intolerable toxicity, or consent withdrawal. For more specific dosing instructions, refer to the pharmacy manual.