A **P**hase II circulating tumor DNA enriched, g**e**nomically di**r**ected post-neoadjuvant trial for patients with re**s**idual tripl**e** negati**ve** b**r**east canc**e**r (PERSEVERE)

HCRN BRE18-334

Sponsor Investigator
Bryan P. Schneider, MD
Indiana University Melvin and Bren Simon Comprehensive Cancer Center

Co-Investigators
Kathy D. Miller, MD
Tarah Ballinger, MD
Nawal Kassem, MD
Indiana University Melvin and Bren Simon Comprehensive Cancer Center

Statistician
Guanglong Jiang, MS
Indiana University School of Medicine

Pharmacist
Christopher A. Fausel, PharmD
Indiana University Melvin and Bren Simon Comprehensive Cancer Center

Trial Support and Funding Provided By
Genentech
Pfizer
Foundation Medicine
Epic Sciences
Vera Bradley Foundation for Breast Cancer Research
Indiana University Precision Health Initiative

Trial Management Provided by
Hoosier Cancer Research Network, Inc.
7676 interactive way, Suite 120
Indianapolis 46278

Investigational New Drug (IND): 151567

Initial Protocol Version: 08DEC2020
Amended Protocol Version Dates:
12JUL2021
11JAN2022
10AUG2022
14JUN2023

PROTOCOL SIGNATURE PAGE

A Phase II circulating tumor DNA enriched, genomically directed post-neoadjuvant trial for patients with residual triple negative breast cancer (PERSEVERE)

VERSION DATE: 14JUN2023

I confirm I have read this protocol, I understand it, and I will work according to this protocol and to the ethical principles stated in the latest version of the Declaration of Helsinki, the applicable guidelines for good clinical practices, whichever provides the greater protection of the individual. I will accept the monitor's overseeing of the study. I will promptly submit the protocol to applicable institutional review board(s).

_____ _____

Signature of Investigator Date

_____

Investigator Name (printed)

_____

Investigator Title

_____

Name of Facility

_____

Location of Facility (City and State)

_____ ❑ Not Submitting to IRB

Expected IRB Approval Date

COMPLETE AND EMAIL COPY TO HOOSIER CANCER RESEARCH NETWORK

SYNOPSIS

TITLE	A Phase II circulating tumor DNA enriched, genomically directed post-neoadjuvant trial for patients with residual triple negative breast cancer: PERSEVERE
SHORT TITLE	Circulating tumor DNA enriched, genomically directed post-neoadjuvant trial for patients with residual triple negative breast cancer
PHASE	Phase II
OBJECTIVES	**Primary Objective** • Demonstrate a 2-year disease-free survival (DFS) of > 50% for participants with residual disease and ctDNA positive triple negative breast cancer (TNBC) treated with a genomically directed therapy following preoperative chemotherapy (ARM 1) **Secondary Objectives** • Evaluate the 2-year DFS for participants with residual disease and ctDNA positive TNBC and no actionable genomic targets treated with a standard approach therapy following preoperative chemotherapy (ARM 2) • Evaluate the 2-year DFS for participants with residual disease and ctDNA negative TNBC treated with a standard approach therapy following preoperative chemotherapy (ARM 3) • Evaluate the overall DFS for ARMS 1, 2, and 3 • Evaluate the overall distant disease-free survival (DDFS) for ARMS 1, 2, and 3 • Evaluate 1-year DFS for ARMS 1, 2, and 3 • Determine 5-year overall survival (OS) for ARMS 1, 2, and 3 • Evaluate the DFS and OS for patients with markers associated with response to immune checkpoint inhibitor treatment vs. those without markers associated with response to immune checkpoint inhibitor treatment identified on residual disease. • Describe the toxicities associated with genomically directed therapy in this population • Describe patient preferences for return of ctDNA results • Evaluate the impact of ctDNA status and availability of genomically directed therapy on fear of recurrences (FCR) and health-related quality of life (HRQoL)
KEY ELIGIBILITY CRITERIA (See Section 3 for full eligibility criteria and See Section 4 for information regarding eligibility review and registration procedures.)	1. ECOG Performance Status 0 or 1 **within 28 days** prior to study registration. 2. Must have histologically or cytologically confirmed triple negative (ER-/PR-/HER2-) invasive breast cancer per pathology report. **NOTE:** ER and PR will be considered negative if ≤ 10% of cells stain weakly positive. HER2 will be considered negative if scored 0 or 1+ by immunohistochemistry (IHC) or 2+ by IHC associated with a fluorescence *in situ* hybridization (FISH) ratio of < 2.0 and < 6 copies per cell.

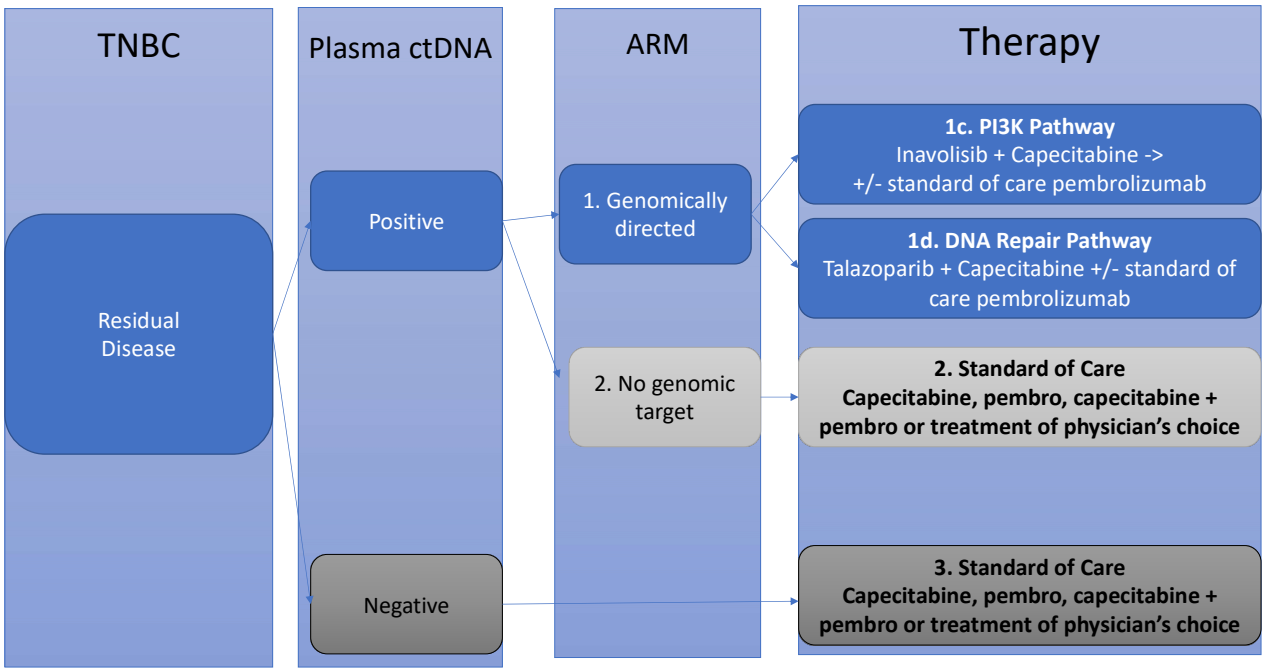
	3. Must have clinical stage I-III at diagnosis (AJCC 8th edition) based on initial evaluation by physical examination and/or breast imaging prior to neoadjuvant chemotherapy. 4. Must have completed preoperative (neoadjuvant) chemotherapy. **NOTE:** Acceptable preoperative regimens include an anthracycline or a taxane, or both. Participants who received preoperative therapy as part of a clinical trial may enroll. Participants may not have received adjuvant chemotherapy after surgery prior to arm assignment. Bisphosphonate use is allowed. 5. Subjects who received pembrolizumab in the neoadjuvant setting are eligible and may continue pembrolizumab treatment during the screening process. • Subjects assigned to Arm 1 will require a 3 week wash out period prior to initiation of study treatment. Subjects may resume pembrolizumab to complete the planned year of therapy (17 cycles) after completion of study therapy based on investigator discretion. • Subjects assigned to Arm 2 and Arm 3 may continue pembrolizumab treatment during the study based on investigator discretion. Total duration of pembrolizumab treatment should not extend beyond 17 cycles. 6. Must have completed definitive resection of primary tumor. Participants must begin assigned arm therapy no later than 96 days from the last local therapy (surgery or radiation). **NOTE:** Negative margins for both invasive and ductal carcinoma *in situ* (DCIS) are desirable, however participants with positive margins may enroll if the study site treatment team believes no further surgery is possible and participant has received radiotherapy. Participants with margins positive for lobular carcinoma *in situ* (LCIS) are eligible. Either mastectomy or breast conserving surgery (including lumpectomy or partial mastectomy) is acceptable. 7. Must have significant residual invasive disease at the time of definitive surgery following preoperative chemotherapy. Significant residual disease is defined as at least one of the following*:* • Residual invasive disease in the breast measuring at least 1 cm. The presence of DCIS without invasion does not qualify as residual disease in the breast. • Any macroscopic (> 2mm) residual lymph node involvement regardless of primary tumor site involvement (includes no residual disease in the breast). • Residual cancer burden (RCB) score 2 or 3. 8. Breast Radiotherapy • Radiotherapy is required for participants who underwent breast-conserving therapy, including lumpectomy or partial mastectomy unless deemed clinically inappropriate by treating provider.

	• Post mastectomy radiation is at the discretion of the treating physician. • If radiation was given prior to surgery, additional radiation after surgery is allowed but not required. • In all cases participants must begin arm assigned therapy no later than 96 days from the last local therapy (surgery or radiation) • Any acute toxicity must have resolved to grade < 2 prior to starting arm specific therapy. 9. Adequate laboratory values must be obtained **within 21 days** prior to study registration. • Hemoglobin (Hgb) ≥ 9.0 g/dL • Platelets ≥ 100 K/mm^3 • Absolute neutrophil count (ANC) ≥ 1.5 K/mm^3 • Calculated creatinine clearance of ≥ 50 cc/min using the Cockcroft-Gault formula: o Males: $\frac{(140 - \text{Age in years}) \times \text{Actual Body Weight in kg}}{72 \times \text{Serum Creatinine (mg/dL)}}$ o Females: Estimated creatinine clearance for males × 0.85 • Bilirubin ≤ 1.5 × ULN (except in participants with documented Gilbert's disease, who must have a total bilirubin ≤ 3.0 mg/dL) • Aspartate aminotransferase (AST, SGOT) ≤ 2.5 × ULN • Alanine aminotransferase (ALT, SGPT) ≤ 2.5 × ULN 10. Must consent to allow submission of blood and archived tumor tissue sample from definitive surgery for next generation sequencing of the tumor. Tumor block is preferred however 14 unstained slides + 1H&E can be submitted if necessary. **NOTE:** Due to possible false positives, ctDNA should not be drawn before completing radiation or less than 14 days from surgery if radiation is not required. 11. No stage IV (metastatic) disease, however no specific staging studies are required in the absence of symptoms or physical exam findings that would suggest distant disease.
STATISTICAL CONSIDERATIONS	This trial is designed to test the hypothesis that genomically directed therapy in the plasma ctDNA positive arm results in superior outcomes compared with the outcomes of those in BRE12-158. We propose a three-arm therapeutic design with the following characteristics: **ARM 1 (Patients who are ctDNA-positive and harbor a genomically directed target)** • Sample size: 90 • We assume a DFS probability of 50% at 24-months based on the historical control from BRE12-158. We also assume the DFS probability is at least 62.5% for patients with genomically directed therapy (ARM 1). • We will conclude that a DFS survival probability of >50% at 24-months in the genomically directed arm will be considered a positive trial.

	If a particular study drug is on shortage (ie, not available) for Arm 1 and a patient is assigned to that particular Arm they will be reassigned to Arm 2. Length of the follow-up period: 24 months • Alpha=0.05 for one-sided test • With 90 patients in Arm 1, we will have 80% power to demonstrate superiority in Arm 1 vs. 50% 2-yr DFS seen in the prior trial, BRE12-158 **ARM 2 (Patients who are ctDNA-positive and do not harbor a genomically directed target)** Assuming 90 patients are required for the primary endpoint and assuming 78% of those who are plasma positive will harbor a genomic target and be assigned to Arm 1, 25 patients will not have a genomic target and will be assigned to ARM 2. Prospective evaluation of capecitabine or the treatment of physician's choice will serve as an informal comparator for outcomes with contemporaneous traditional therapy in the ctDNA positive population. There will be insufficient numbers for formal comparisons and thus only descriptive statistics and comparisons will be made, including comparison with patients in BRE12-158. **ARM 3 (Patients who are ctDNA-negative)** Assuming 115 ctDNA positive patients will be required to fulfill the primary endpoint and assuming 65% of all patients screened in this population will be ctDNA positive, 62 patients will be ctDNA negative and be assigned to ARM 3. There will be insufficient numbers for formal comparisons and thus only descriptive statistics and comparisons will be made. **SCREENING** Assuming 177 patients will require a successful ctDNA test result and assuming 10% ctDNA testing failure + patient dropout, 195 patients will be needed to screen for this trial.
TOTAL NUMBER OF SUBJECTS	***Screen = 195 patients for ctDNA status (estimated number of subjects required to obtain the necessary 90 subjects in Arm 1)*** ctDNA test successful = 177 ctDNA-positive with successful ctDNA test = 115 • ctDNA-positive to receive genomically directed therapy = 90 (Arm 1) • ctDNA-positive without genomic target to receive treatment of physician's choice= 25 (Arm 2) ctDNA-negative to receive treatment of physician's choice = 62 (Arm 3)
ESTIMATED ENROLLMENT PERIOD	36 months

SCHEMA

A Phase II circulating tumor DNA enriched, genomically directed post-neoadjuvant trial for patients with residual triple negative breast cancer (PERSEVERE)



1: Experimental Arm (ctDNA-Positive, and harbor a genomically directed target)
Genomically directed therapy in conjunction with capecitabine. Arm 1a CLOSED based on FDA approval of pembrolizumab for high-risk early-stage triple-negative breast cancer in July 2021. Arm 1b will be closed due to a majority of patients receiving immunotherapy as standard of care. Arm 1c and Arm 1d are amended to now include targeted therapy with standard of care (vs. targeted therapy with atezolizumab and capecitabine) based on results of Impassion030 which demonstrate no benefit to atezolizumab in the adjuvant setting compared with placebo. For the standard of care in arm 1c, we recommend consideration of continued pembrolizumab per the KEYNOTE 522 after completion of inavolisib + capecitabine. If the patient has contra-indication to immunotherapy, we recommend no additional therapy after completion of inavolisib + capecitabine. For the standard of care in arm 1d, we recommend addition of pembrolizumab (per KEYNOTE 522) in combination with the talazoparib and capecitabine. If the patient has a contraindication to pembrolizumab, would recommend no additional therapy to be combined with the talazoparib and capecitabine. Pembrolizumab should not be extended beyond 17 cycles total (neoadjuvant + adjuvant).

2: Control Arm (ctDNA-Positive, and do not harbor a genomically directed target)
Capecitabine and pembrolizumab are considered standard options. Other therapies are not recommended but can be administered at treating physician's discretion. The use of no additional therapy is permitted if deemed appropriate by the treating provider, but not a recommended option.

3: Control Arm (ctDNA-Negative)
Capecitabine and pembrolizumab are considered standard options. Other therapies are not recommended but can be administered at treating physician's discretion. The use of no additional therapy is permitted if deemed appropriate by the treating provider, but not a recommended option.

If a particular study drug is on shortage for Arm 1 and a patient is assigned to that particular Arm, they will be reassigned to Arm 2.

1 BACKGROUND & RATIONALE

1.1 Primary (neoadjuvant) chemotherapy for breast cancer

Neoadjuvant chemotherapy has a well-established role in the management of both early-stage and locally advanced breast cancer. Providing treatment prior to definitive surgery not only improves the ability to achieve breast conservation, but also allows determination of in vivo sensitivity to therapy and offers an ideal platform for clinical research. Although many will experience shrinkage in tumor volume with neoadjuvant therapy, at the time of surgery only about 33% of patients will experience a pathologic complete response (pCR) with complete lack of invasive tumor tissue in the surgical specimen. Long-term follow-up of neoadjuvant studies consistently demonstrates significantly improved survival in individuals with pCR, with comparatively inferior outcomes in those with residual disease at surgery.[1-4] The impact of residual disease is more striking in patients with triple negative (ER-/PR-/HER2-) disease compared to patients with other molecular phenotypes.[5] Unfortunately, patients with triple negative disease who have substantial (Miller-Payne classification[6] 1 or 2 or residual cancer burden classification II or III[7]) residual disease at the time of surgery have a dismal prognosis with only 40-50% remaining free of recurrence at 2 years[4,8]. In short, the presence of viable invasive tumor after appropriate neoadjuvant chemotherapy reflects inherent resistance and portends an exceedingly high risk of subsequent recurrence.

A phase III trial, CREATE-X[9], randomized over 900 HER2-negative patients with residual disease in the breast or lymph node involvement after completion of standard neoadjuvant therapy of 8 cycles of capecitabine at 2500 mg/m^2/day (2 out of 3 weeks) vs. no additional therapy. Approximately 64% of the population had hormone receptor positive disease and 36% had triple negative disease. The capecitabine arm demonstrated an improvement in DFS from 74% in the control arm to 82% in the capecitabine arm (HR=0.70; p=0.005). The addition of capecitabine also improved OS from 89.2% to 94% (HR=0.60; p<0.01). The hazard ratios were highly significant in the triple negative subgroup (HR=0.58; 95% CI=0.39-0.87). Thus, capecitabine can be considered a standard option in this setting for triple negative breast cancer. A more recently reported meta-analysis at the 2019 San Antonio Breast Cancer Symposium supports the benefit for the addition of capecitabine to a standard backbone of adjuvant or pre-operative therapy.

While improvements were seen in CREATE-X, much work remains for improving outcomes for patients in this setting. We recently concluded a randomized phase II trial of genomically directed therapy vs. the treatment of physician's choice for this population; BRE12-158. The primary outcome is pending, but a preliminary assessment of DFS based on the status of circulating tumor DNA (ctDNA) performed at a single time point after surgery but prior to initiating post-neoadjuvant therapy was evaluated. The estimated 2-year DFS for those patients with plasma ctDNA negativity was approximately 76%. Conversely, those with ctDNA positivity had a DFS of 50%. This represents one of the most powerful stratification variables for patients with TNBC and residual disease after pre-operative therapy. Thus, we propose a novel trial to address the optimal approach for patients in this setting using plasma ctDNA status to stratify and high throughput genomic technology to identify and treat with highly active targeted agents.

KEYNOTE-522 randomized 602 patients to a traditional backbone of chemotherapy with or without pembrolizumab (200mg every 3 weeks) followed by continued post-neoadjuvant pembrolizumab for 9 cycles vs. placebo. The addition of pembrolizumab improved the pathological complete response from 51.2% in the chemotherapy alone arm to 64.8% in the pembrolizumab/chemotherapy arm.[27] A recent update has also demonstrated a statistically significant improvement in event free survival (EFS). The 36-month EFS improved from 76.8% in the chemotherapy alone arm to 84.5% in the pembrolizumab/chemotherapy arm.[28] In addition, there was a significant benefit seen with the addition

of pembrolizumab for those patients who did not achieve a pCR. Based on these data, pembrolizumab has now been approved by the FDA in combination with chemotherapy in the pre-operative setting with up to 9 cycles in the post-neoadjuvant setting.

1.2 Rationale for genomically directed approach

Currently, many of the therapies delivered in the neo-adjuvant and adjuvant setting for breast cancer are non-specific cytotoxic agents that are not selected based on specific characteristics from the tumor. Increasingly, molecular aberrancies have opened the door for potential design and use of drugs to capitalize on dysregulated pathways. Examples of successful drugs matched to genomic alterations include various categories of aberrancy.[10] When considering frequency and activity some of the most promising mutation/drug combinations for breast cancer include: ***PARP inhibition***, ***PI3K/AKT inhibition***, and ***checkpoint inhibition***.

Great activity has been demonstrated with the use of PARP inhibition for patients that harbor a germline pathogenic mutation in BRCA1 or BRCA 2. Both Olaparib and talazoparib are now approved for patients with HER2 negative metastatic breast cancer who have a germline BRCA mutation. Additionally, data support potential benefit for PARP inhibition in patients who harbor both somatic and germline mutations across the DNA repair pathway. Pi3K inhibition with alpelisib is FDA approved for patients with ER+, HER2- metastatic breast cancer who harbor an activating mutation in PI3K. Inhibition of the PI3K pathway has also been shown to improve outcomes in patients with TNBC with an activated PI3K pathway. It is known that patients with breast cancer who have gain-of-function mutations in PI3K-alpha (PIK3CA) respond to alpha-specific inhibitors. Inavolisib (GDC-0077) is a novel alpha-specific PI3K inhibitor that has demonstrated efficacy against PIK3CA mutated breast tumors.[13.] Checkpoint inhibition with pembrolizumab is approved across all solid tumors with microsatellite instability and elevated tumor mutation burden (>10 mutations per megabase). Pembrolizumab is also FDA approved for patients with metastatic TNBC with PD-L1 CPS $\geq$ 10% (using the Dako 22c3 antibody) and is FDA-approved in the first line setting in combination with chemotherapy. The use of pembrolizumab in the neoadjuvant (curative) setting and continuation in the post-neoadjuvant setting has shown benefit over chemotherapy alone based on the results from KEYNOTE 522. In KEYNOTE 522, all patients benefited from pembrolizumab regardless of PD-L1 status. The benefit of continued pembrolizumab in the post-neoadjuvant setting for those with residual disease is less clear as there was no re-randomization in the post-neoadjuvant setting. Further, there are no data to assess the impact of immune biomarkers from the residual disease specimen for post-neoadjuvant pembrolizumab (a secondary endpoint for those in arm 2 and arm 3). Atezolizumab was previously approved for the treatment of first line metastatic TNBC in combination with chemotherapy for patients with at least 1% PD- L1 positivity in immune cells infiltrating the tumor. More recently, however, the FDA-approval has been withdrawn due to lack of benefit in the confirmatory trial; Impassion131, and because of other approved options. Recent results from Impassion030 demonstrated no benefit for atezolizumab in the adjuvant setting, but atezolizumab continues to be tested in other settings with other drug partners. Its role in the neoadjuvant and post-neoadjuvant setting with other agents is under active investigation.

In general, the therapeutic index for these targeted approaches has been exceptionally high. This proposal will attempt to capitalize on this basic philosophy by matching the most promising targeted agents in TNBC with molecular aberrancies determined through cutting edge assessment of the tumor using massively parallel sequencing.

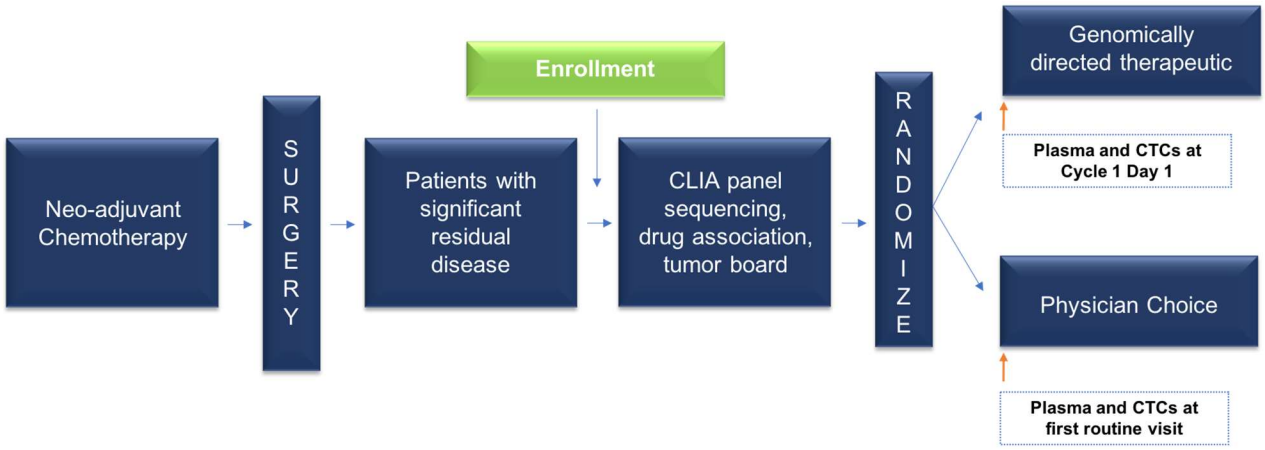
1.3 Rationale and Study Design

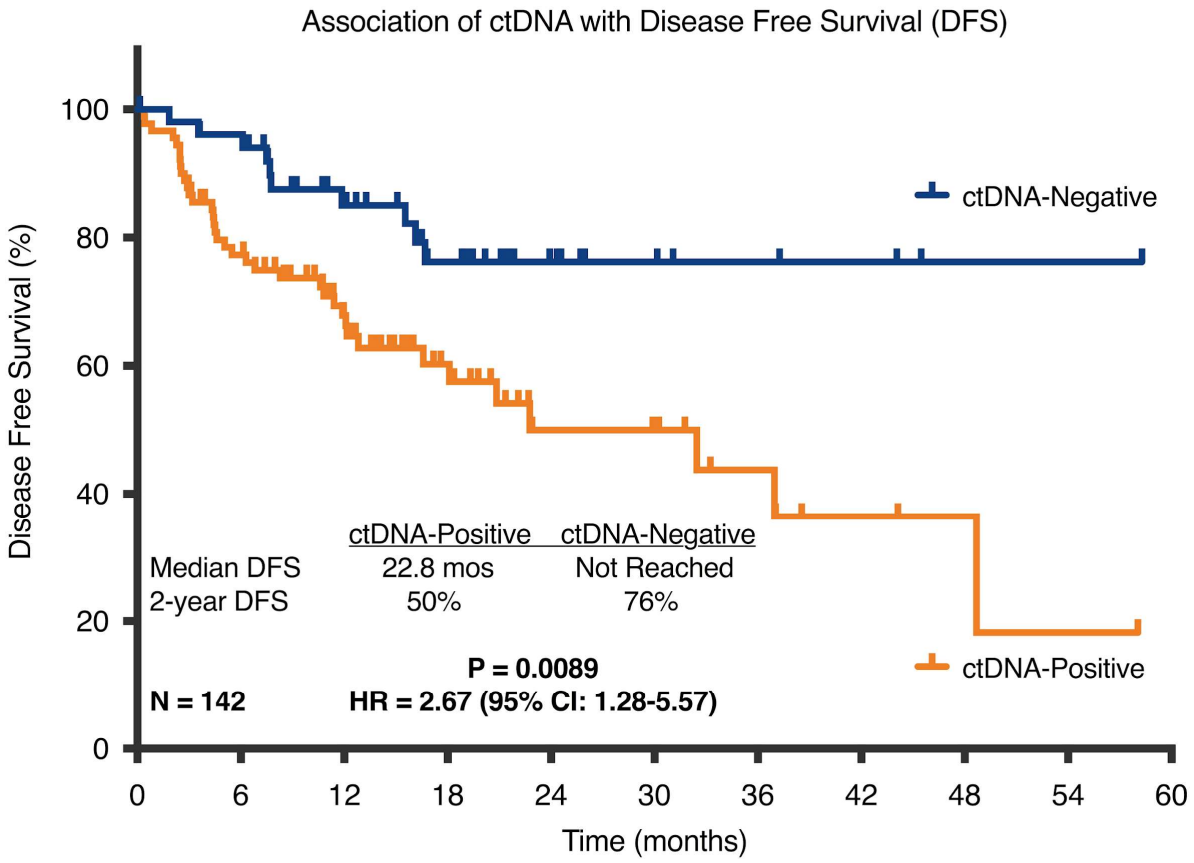
This study will capitalize on an exceptional setting to test a genomic approach and will enrich for participants who have already been exposed to standard non-specific chemotherapy in the neoadjuvant setting with substantial residual disease. This patient population, by definition, is resistant to traditional non-specific cytotoxic chemotherapy. Also, by nature of the high risk of relapse, they are clearly in need of additional, and hopefully superior, targeted therapy. In addition, there will be a focus on the impact of drug combinations to maximize therapeutic impact. For the patients who have both DNA repair deficiency and markers to suggest immune avidity, we will combine PARP inhibition with capecitabine and standard of care therapy (pembrolizumab if deemed appropriate by the treating provider). For those with an activated PI3K pathway, we will combine inavolisib (an alpha-specific PI3K inhibitor) with capecitabine followed by standard of care therapy (pembrolizumab if deemed appropriate by the treating provider). From a genomic standpoint, the use of these agents in a relatively early point in the tumor's life (i.e. adjuvant setting) will minimize some intrinsic concerns such as genomic drift. The premise of this trial is to test a personalized approach compared with historically non-personalized approach. This proposal, then, sets out to test the hypothesis that a genomically directed therapy will improve outcome over standard of care in a population that needs a better standard. The limitations of this approach include: 1. This is a non-randomized approach and thus, the historical value may be biased by other risk factors; and 2). This may have different results simply due to more contemporary treatment and managements when compared to the older trial, BRE12-158. That being said, these are the only preliminary data to date in this setting and represent the most scientifically valid assumptions.

1.4 Use of next generation sequencing to detect circulating tumor DNA (ctDNA)

An emerging method for non-invasive cancer detection is the analysis of "liquid biopsies" – the ability to detect tumor characteristics from the circulation, of which the most popular to date, is circulating tumor DNA (ctDNA). ctDNA is released into the circulation from the apoptosis or necrosis of tumor tissue, or from circulating tumor cells (CTCs) present in blood[14,15]. It has been demonstrated that ctDNA can be detected in many types of cancer, including: breast[16-19], prostate[20], gastric[21], and others[14]. The fraction of ctDNA compared to total cell-free DNA (cfDNA), can be quite small, in many cases less than 1%[22-24]. Highly sensitive next-generation sequencing techniques can be used to detect low amounts of ctDNA. Because somatic mutations provide intrinsic specificity for nucleic acid material derived from tumor tissue, the presence of ctDNA implies the presence of disease. Recently published data from our group demonstrated that ctDNA detected in the plasma of TNBC patients after neoadjuvant chemotherapy and surgery indicates rapid relapse[19]. A pivotal study by Garcia-Murillas et al., in a cohort of early breast cancer patients demonstrated that detection of ctDNA showed a similar pattern of rapid recurrence.[25] A similar study by Olsson et al.[26] showed that serial ctDNA sampling in patients with primary breast cancer can reach an average lead time of 11 months before the occurrence of metastatic disease. A prevailing theme among all these studies is that the presence of ctDNA predicts rapid relapse.

Congruent with previously published data, we recently analyzed plasma samples from TNBC patients who have completed neoadjuvant chemotherapy and surgery as part of a randomized phase II trial of genomically directed therapy vs. the treatment of physician's choice; BRE12-158 (Figure 1). The primary outcome is pending, but a preliminary assessment of DFS based on the status of circulating tumor DNA (ctDNA) performed at a single time point after surgery but prior to initiating post-neoadjuvant therapy was evaluated. The detection of ctDNA was significantly associated with an inferior DFS (median DFS: 22.8 months vs. Not Reached; HR=2.67, 95% CI:1.28-5.57; p=0.0089). At 24 months, the DFS probability was 50% in ctDNA-positive patients as compared to 76% in ctDNA-negative patients. As seen in the Kaplan-Meier curve (Figure 2), patients who were ctDNA-positive experienced a rapid relapse of their disease.





More recently, tissue informed assays have improved the sensitivity for detecting minimal residual disease. Specifically, the FoundationOne Tracker uses a trusted and clinically relevant tissue-informed CGP baseline paired with personalized ctDNA -based assessment that empowers informed biomarker-guided treatment decisions. CtDNA-based disease monitoring with FoundationOne Tracker can serve as a sensitive biomarker for MRD and can accurately assess risk to support additional adjuvant or perioperative treatment. In a retrospective analysis of resectable bladder cancer, FoundationOne Tracker exhibited a positive predictive value (PPV) of 91% for determining risk of relapse based on ctDNA assessment post resection. Additionally, the median disease-free survival (DFS) (3 months vs. not reached, hazard ratio (HR)=5.8 (95% confidence interval (CI) 3.8–8.7, p<0.0001)) and overall survival (OS) (13

months vs. not reached, HR=5.8 (95% CI 3.4–9.9, p<0.0001)) were significantly shorter for ctDNA-positive patients. In a separate retrospective study evaluating MRD detection in metastatic colorectal patients who underwent surgical resection with curative intent, FoundationOne Tracker exhibited a 94% PPV, and patients ctDNA detection post-surgery had shorter median DFS (3.2 vs 3.1 months, HR 4.97(95% CI 2.67-9.24)) and OS (31.6 months vs not reached, HR 27.05 (95% CI 3.60-203.46)) compared to those who were ctDNA negative. These studies demonstrate that post-operative MRD detection via FoundationOne Tracker is a strong prognostic biomarker that correlates with DFS and OS in patients with resected early-stage bladder cancer. Based on improved sensitivity, the FoundationOne Tracker will be used in this study to determine ctDNA status (positive vs. negative).

1.5 Definition of actionable mutations/pathways with recommended agent

1.5.1 Talazoparib + capecitabine (Arm 1a): patients with a deleterious somatic or germline mutation in BRCA1/2, PALB2, ATR, BARD1, BLM BRIP1, FANCA, FANCC, FANCD2, FANCF, MRE11A, RAD51, RAD51B, RAD51C, RAD51D, RAD54L, NBN, WRN, RECQL, ARID1A. This group in Arm 1 is **CLOSED**.

1.5.2 Atezolizumab + capecitabine (Arm 1b): patients whose tumors have PD-L1 immune cell staining (SP142 antibody) ≥ 1%, or a tumor mutation burden (TMB) ≥ 10 mutations/megabase, or MSI-high (determined by NGS). Since this arm represents therapy similar to standard of care therapy, this arm **will CLOSE**.

1.5.3 Inavolisib + capecitabine → +/- standard of care pembrolizumab (Arm 1c): patients whose tumors harbor gain-of-function mutations in PIK3CA.This group in Arm 1 will be updated to include the consideration of standard of care up to 9 cycles of pembrolizumab after completion of 8 cycles of inavolisib and capecitabine. Pembrolizumab should not be extended beyond 17 cycles total (neoadjuvant + adjuvant). If pembrolizumab is contraindicated, no therapy would be the preferred standard of care option. Capecitabine will be supplied by the study.

1.5.4 Talazoparib + capecitabine +/- standard of care pembrolizumab (Arm 1d): patients with a deleterious somatic or germline mutation in BRCA1/2, PALB2, ATR, BARD1, BLM BRIP1, FANCA, FANCC, FANCD2, FANCF, MRE11A, RAD51, RAD51B, RAD51C, RAD51D, RAD54L, NBN, WRN, RECQL, or ARID1A. Capecitabine will be administered with talazoparib. This group in Arm 1 will be updated to include the consideration for the addition of concurrent pembrolizumab with the talazoparib and capecitabine. The pembrolizumab should not be extended beyond 17 cycles total (neoadjuvant + adjuvant). Capecitabine and talazoparib will be supplied by the study. If pembrolizumab is contraindicated, the patient will receive the combination of capecitabine and talazoparib alone.

1.6 Protocol therapy

Participants that are plasma ctDNA positive (65%) with a genomic target will be assigned to one of the groups in **Arm 1** and receive genomically directed therapy in conjunction with standard of care therapy (n=90). There will be two groups in Arm 1. Arm 1a CLOSED based on FDA approval of pembrolizumab for high-risk early-stage triple-negative breast cancer in July 2021. Arm 1b will close as this arm mirrors the standard of care arm and based on results of IMPassion030.

- Arm 1a: DNA Repair pathway = talazoparib + capecitabine (n≈21) (CLOSED)
- Arm 1b: Immunotherapy pathway = pembrolizumab + capecitabine (n≈38) (to CLOSE)
- Arm 1c: PI3K Pathway = inavolisib + capecitabine → +/- standard of care pembrolizumab (n≈43)
- Arm 1d: DNA Repair = talazoparib + capecitabine +/- standard of care pembrolizumab (n≈47)

Participants that are plasma ctDNA positive (n≈25) without a pre-specified genomic target will be assigned to **Arm 2** and receive capecitabine and pembrolizumab or treatment of physician's choice. Capecitabine and pembrolizumab are considered standard options. Other therapies are not recommended but can be administered at treating physician's discretion. The use of no additional therapy is permitted if deemed appropriate by the treating provider, but not a recommended option.

Participants that are plasma ctDNA negative (about 35%; n≈62) will be assigned to **Arm 3** and receive capecitabine and pembrolizumab or treatment of physician's choice. Capecitabine and pembrolizumab are considered standard options. Other therapies are not recommended but can be administered at treating physician's discretion. The use of no additional therapy is permitted if deemed appropriate by the treating provider, but not a recommended option.

For all arms, we will plan to evaluate the impact of immune avidity on outcomes. We will compare outcomes for those tumors have PD-L1 immune cell staining ≥ 10%, or a tumor mutation burden (TMB) >10 mutations/megabase, or MSI-high (determined by NGS) vs. those with no markers of immunity.

1.6.1 Resolving ctDNA-positive patients with multiple actionable genomic mutations/pathways

Priority for the arm assignment will be given in the following order, based on known clinical evidence of highest likelihood of efficacy:

1. Patient with DNA repair mutations in BRCA1, BRCA2, or PALB2 will take priority over all other findings. They will be assigned to arm 1d.
2. PI3K mutations will take priority over all other DNA repair mutations (BRCA1, BRCA2, or PALB2). They will be assigned to arm 1c.

1.7. Fear of recurrence and patient reported outcomes

Fear of cancer recurrence (FCR) is a highly prevalent, persistent, and debilitating problem affecting breast cancer survivors. Defined as "fear, worry, or concern about cancer returning or progressing" (Lebel et al, Support Care Cancer, 2016), consequences of FCR include maladaptive coping skills, negative intrusive thoughts, and excessive distress. FCR amongst breast cancer survivors is often managed with either hypervigilance and excessive use of the medical system, or avoidance that becomes detrimental over time (Vachon et al Psycho-Oncology, 2020). Misunderstandings and unrealistic expectations for return of genomic sequencing in patients with metastatic cancer have been well characterized; however, understanding how this information is processed by patients in the curative setting is an unmet need to inform optimal delivery and minimize psychological distress. The PRESEVERE trial offers the opportunity to understand the psychological impact of additional prognostic and genomic information in a homogeneous population of patients who are at high risk of recurrence and are participating in a clinical trial.

Prior studies in early-stage breast cancer have found higher FCR to be associated with younger age, lower education, white race, increased physical symptoms, fatigue, pain, and lower health care satisfaction (Janz NK, BCRT, 2011; Liu BCRT, 2011). Interestingly, several studies have shown that FCR does not seem to correlate with actual determinants of risk of recurrence such as tumor stage, margin status, etc. The theoretical model of FCR based on Leventhal's Self Regulation Model of Illness proposes that FCR is a function of a) perception of personal risk for recurrence, which is influenced by cancer factors and treatment received, b) emotional status, in particular anxiety and excessive avoidant of reassurance-seeking behaviors, and c) greater perceived physical, economic, or social consequences of cancer (Lee-Jones, 1997). **It is hypothesized that knowledge of ctDNA positivity status may increase FCR through increased perception of personal risk; simultaneously, it is hypothesized that positive genomic testing results and additional systemic therapy will prolong FCR due to additional physical and social**

consequences of cancer. It is expected that these results will inform interventions to reduce FCR in this population and in those receiving genomic information in the early-stage breast cancer setting.

2 OBJECTIVES

2.1 Primary Objective

- Demonstrate a 2-year disease-free survival (DFS) of > 50% for participants with residual disease and ctDNA positive triple negative breast cancer (TNBC) treated with a genomically directed therapy following preoperative chemotherapy (ARM 1)

2.2 Secondary Objectives

- Evaluate the 2-year DFS for participants with residual disease and ctDNA positive TNBC and no actionable genomic targets treated with a standard approach therapy following preoperative chemotherapy (ARM 2)
- Evaluate the 2-year DFS for participants with residual disease and ctDNA negative TNBC treated with a standard approach therapy following preoperative chemotherapy (ARM 3)
- Evaluate the overall DFS for ARMS 1, 2, and 3
- Evaluate the overall distant disease-free survival (DDFS) for ARMS 1, 2, and 3
- Evaluate 1-year DFS for ARMS 1, 2, and 3
- Determine 5-year overall survival (OS) for ARMS 1, 2, and 3
- Evaluate the DFS and OS for patients with markers associated with response to immune checkpoint inhibitor treatment vs. those without markers associated with response to immune checkpoint inhibitor treatment identified on residual disease.
- Describe the toxicities associated with genomically directed therapy in this population
- Describe patient preferences for return of ctDNA results
- Evaluate the impact of ctDNA status and availability of genomically directed therapy on FCR and HRQoL

2.3 Exploratory Objectives

- Collect archived tumor specimens, genomic DNA, and circulating tumor samples to explore potential correlates of recurrence and toxicity
- Evaluate the drug specific effect on both efficacy outcomes (DFS and OS) and toxicity.
- Explore modifiers of FCR and HRQoL in this population, including patient preferences for return of results, coping strategies, anxiety, health literacy, self- efficacy, and disease characteristics.

3 ELIGIBILITY CRITERIA

3.1 General Inclusion Criteria

1. Written informed consent and HIPAA authorization for release of personal health information.
   NOTE: HIPAA authorization may be included in the informed consent or may be obtained separately.

2. Age ≥ 18 years at the time of consent.

3. ECOG Performance Status 0 or 1 **within 28 days** prior to study registration.

4. Must have clinical stage I-III at diagnosis (AJCC 8th edition) based on initial evaluation by physical examination and/or breast imaging prior to neoadjuvant chemotherapy.

5. Must have histologically or cytologically confirmed triple negative (ER-/PR-/HER2-) invasive breast cancer per pathology report. **NOTE:** ER and PR will be considered negative if ≤ 10% of cells stain weakly positive. HER2 will be considered negative if scored 0 or 1+ by immunohistochemistry (IHC) or 2+ by IHC associated with a fluorescence *in situ* hybridization (FISH) ratio of < 2.0 or < 6 copies per cell.

6. Must have completed preoperative (neoadjuvant) chemotherapy. **NOTE:** Acceptable preoperative regimens include an anthracycline or a taxane, or both. Participants who received preoperative therapy as part of a clinical trial may enroll. Participants may not have received adjuvant chemotherapy after surgery prior to registration. Bisphosphonate use is allowed.

7. Subjects who received pembrolizumab in the neoadjuvant setting are eligible and may continue treatment during the screening process. Subjects assigned to Arm 1 will require a 3 week wash out period prior to initiation of study treatment. Subjects may resume pembrolizumab to complete the planned year of therapy (17 cycles) after completion of study therapy based on investigator discretion. Subjects assigned to Arm 2 and Arm 3 may continue pembrolizumab treatment during the study based on investigator discretion. Total duration of pembrolizumab treatment should not extend beyond 17 cycles.

8. Must have significant residual invasive disease at the time of definitive surgery following preoperative chemotherapy. Significant residual disease is defined as at least one of the following*:*
    - Residual invasive disease in the breast measuring at least 1 cm. The presence of DCIS without invasion does not qualify as residual disease in the breast.
    - Any macroscopic, (> 2mm) residual, lymph node involvement regardless of primary tumor site involvement (includes no residual disease in the breast).
    - Residual cancer burden (RCB) score 2 or 3.

9. Must have completed definitive resection of primary tumor. Participants must begin assigned arm therapy no later than 96 days from the last local therapy. **NOTE:** Negative margins for both invasive and ductal carcinoma *in situ* (DCIS) are desirable, however participants with positive margins may enroll if the study site treatment team believes no further surgery is possible and participant has received radiotherapy. Participants with margins positive for lobular carcinoma *in situ* (LCIS) are eligible. Either mastectomy or breast conserving surgery (including lumpectomy or partial mastectomy) is acceptable.

10. Breast Radiotherapy
    - Radiotherapy is required for participants who underwent breast-conserving therapy, including lumpectomy or partial mastectomy unless deemed inappropriate by the treating provider.
    - Post mastectomy radiation is at the discretion of the treating physician.
    - If radiation was given prior to surgery, additional radiation after surgery is not required.
    - In all cases participants must and begin arm assigned therapy no later than 96 days from the last local therapy
    - Any acute toxicity must have resolved to grade < 2 prior to starting arm specific therapy.

11. Must consent to allow submission of blood and archived tumor tissue sample from definitive surgery for next generation sequencing of the tumor. Tumor block is preferred however 14 slides + 1H&E can be submitted if necessary. **NOTE:** Due to possible false positives, ctDNA should not be drawn before completing radiation or less than 14 days from surgery if radiation is not required.

~~13.~~12. Adequate laboratory values must be obtained **within 28 days** prior to study registration.
- Hemoglobin (Hgb) ≥ 9.0 g/dL
- Platelets ≥ 100 K/mm^3
- Absolute neutrophil count (ANC) ≥ 1.5 K/mm^3
- Calculated creatinine clearance of ≥ 50 cc/min using the Cockcroft-Gault formula:
  - Males: $\frac{(140 - \text{Age in years}) \times \text{Actual Body Weight in kg}}{72 \times \text{Serum Creatinine (mg/dL)}}$
  - Females: Estimated creatinine clearance for males × 0.85
- Bilirubin ≤ 1.5 ULN (except in participants with documented Gilbert's disease, who must have a total bilirubin ≤ 3.0 mg/dL)
- Aspartate aminotransferase (AST, SGOT) ≤ 2.5 ULN
- Alanine aminotransferase (ALT, SGPT) ≤ 2.5 ULN

~~14.~~13. Women of childbearing potential and their partners and male subjects and their partners must be willing to use effective contraception (as outlined in Section 5.6) from the time consent is signed until after protocol therapy discontinuation based on package insert or investigator brochure guidelines (See Section 5.6 for timeframes).

~~15.~~14. Women of childbearing potential must have a negative urine or serum pregnancy test within 7 days prior to study registration. Women should be counseled regarding acceptable birth control methods to utilize. If prior to treatment after discussion with the subject it is felt by the treating physician there is a possibility the subject is pregnant a pregnancy test should be repeated. **NOTE:** Women are considered not of childbearing potential if they are surgically sterile (they have undergone a hysterectomy, bilateral tubal ligation, or bilateral oophorectomy), or they are postmenopausal for at least 12 consecutive months.

~~16.~~15. Women must not be breastfeeding from the time of treatment initiation until the number of days after protocol therapy discontinuation based on package insert or investigator brochure guidelines (See Section 5.6 for timeframes).

3.1.1 Inclusion Criteria for patients assigned to Arm 1c ONLY

1. Adequate laboratory values must be obtained **within 21 days** prior to starting arm therapy.
   - Fasting total glucose ≤ 126 mg/dL
   - HbA1C ≤ 5.7%
   - Cholesterol < 300 mg/dL; 10.34 mmol/L
   - Triglycerides < 300 mg/dL; 3.42 mmol/L

3.2 General Exclusion Criteria

1. Clinically significant infections as judged by the treating physician.

2. Stage IV (metastatic) disease, however no specific staging studies are required in the absence of symptoms or physical exam findings that would suggest distant disease.

3. HIV-infected patients on effective anti-retroviral therapy with undetectable viral load within 6 months of registration are eligible for this trial. **NOTE:** Patients without a known history of being HIV positive do not require testing at screening. Patients who are known to be HIV positive will require testing as described to be eligible for this trial. Testing should be considered standard of care.

4. Patients with evidence of chronic hepatitis B virus (HBV) infection, with undetectable HBV viral load within 6 months of registration are eligible for this trial. They should be on suppressive therapy, if indicated. Patients with a history of hepatitis C virus (HCV) infection must have been treated and cured. For patients with HCV infection who are currently on treatment, the HCV viral load must be undetectable within 6 months of registration to be eligible for this trial. **NOTE:** Patients without a known history of being hepatitis positive do not require testing at screening. **Patients** who are known to be hepatitis positive will require testing as described to be eligible for this trial. Testing should be considered standard of care.

5. Participants with unstable angina or a myocardial infarction within 12 months of study registration.

6. Active second malignancy (except non-melanomatous skin cancer or incidental prostate cancer found on cystectomy): Active second malignancy is defined as a current need for cancer therapy or a high possibility (> 30%) of recurrence during the study. Previous contralateral breast cancer is allowable unless it meets “active” criteria as stated above.

7. Inability to swallow pills.

8. Evidence of significant uncontrolled concomitant disease that could affect compliance with the protocol, safety of participation, or interpretation of results. This includes significant liver disease (such as cirrhosis, uncontrolled major seizure disorder, or superior vena cava syndrome) or any other serious medical condition or abnormality in clinical laboratory tests that meet these criteria in the investigator’s opinion.

9. History of severe allergic, anaphylactic, or other hypersensitivity reactions to any of the study medications being used in this study.

10. Treatment with any investigational agent within 30 days prior to study registration.

3.2.1 Exclusion Criteria for patients assigned to Arm 1c ONLY

1. Any concurrent ocular or intraocular condition (e.g., cataract or diabetic retinopathy) that, in the opinion of the investigator, would require medical or surgical intervention during the study period to prevent or treat vision loss that might result from that condition.

2. Type 2 diabetes requiring ongoing systemic treatment at the time of study entry; or any history of Type 1 diabetes.

3. 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.

4. Symptomatic active lung disease, including pneumonitis

5. History of or active inflammatory bowel disease (e.g., Crohn's disease or ulcerative colitis). Patients currently receiving immunosuppressants for inflammatory bowel disease (e.g., sulfasalazine) are considered to have active disease and are therefore ineligible.

6. Any active bowel inflammation (including diverticulitis)

7. Symptomatic hypercalcemia requiring continued use of bisphosphonate or denosumab therapy. Bisphosphonate and denosumab therapy for bone metastases or osteopenia/osteoporosis is allowed.

4 PARTICIPANT REGISTRATION

Subjects will consent to participation in the trial. Sites will continue to enroll and the Foundation Medicine Assays will be used for both tissue and blood. Blood and tissue will be collected and submitted upon consent while eligibility is being determined. Once the amendment for utilization of the FoundationOneTracker assay is approved at the site, the FoundationOne® CDx assay for tissue will continue to be used and the FoundationOne Tracker assay for blood will be utilized. Tissue will be collected first and once a successful tissue test and the ability to select appropriate variants for tracking are confirmed, blood will be collected from the subject for the remainder of the required testing. **NOTE:** A successful tissue test is required to run the FoundationOneTracker. Subjects who have a tissue sample fail FoundationOne®CDx assay or primer design fails will not be able to have the FoundationOneTracker run for blood.

ctDNA should not be drawn before completing radiation or less than 14 days from surgery if radiation is not required. Once the sequencing results are received, subjects will be assigned to the appropriate Arm as described below (see registration process document provided by HCRN). An additional consent will be obtained for subjects assigned to Arm 1. The protocol therapy is not blinded to the participant or the treating investigator. All participants must be registered through HCRN's electronic data capture (EDC) system and begin assigned treatment within 96 days of last local therapy. If a particular study drug is on shortage for Arm 1 and a patient is assigned to that particular Arm, they will be reassigned to Arm 2.

NOTE: Treating investigators will receive sequencing results after completion of Arm assignment. ctDNA status will be discussed with the patient by the treating investigator. Genomic results will be discussed with the patient based on investigator discretion. Results will be flagged if a suspected germline mutation is found. It will be the responsibility of the treating investigator to follow-up with the subject regarding the results and need for additional genetic testing and/or genetic counseling as appropriate.

5 TREATMENT PLAN

This is a 3-arm study stratified by plasma ctDNA. Patients with residual TNBC disease after pre-operative therapy will be assigned to 1 of 3 Arms based on plasma ctDNA positivity and genomic marker(s). If a particular study drug is on shortage for Arm 1 and a patient is assigned to that particular Arm, they will be reassigned to Arm 2. Assignment to Arm 1a CLOSED based on FDA approval of pembrolizumab for high-risk early-stage triple-negative breast cancer in July 2021. Arm 1b will close due to its similarity to standard of care and based on results of IMPassion030. If a subject assigned to Arm 1c does not meet additional Arm 1c criteria, the subject will be reassigned to Arm 2.

Participants that are *plasma ctDNA positive* **with** a *genomic target* will be assigned to one of the 2 groups in **Arm 1** and receive genomically directed therapy.

- Arm 1a: DNA Repair pathway = talazoparib + capecitabine (CLOSED)
- Arm 1b: Immunotherapy pathway = atezolizumab + capecitabine (to CLOSE)
- Arm 1c: PI3K Pathway = inavolisib + capecitabine → +/- standard of care pembrolizumab
- Arm 1d: DNA Repair + Immunotherapy = talazoparib + capecitabine +/- standard of care pembrolizumab

Participants that are *plasma ctDNA positive* **without** *a genomic target* will be assigned to **Arm 2** and receive pembrolizumab and/or capecitabine (preferred option is pembrolizumab with capecitabine) or treatment of physician's choice. The use of no additional therapy is permitted if deemed appropriate by the treating provider, but not a recommended option.

Participants that are *plasma ctDNA negative* will be assigned to **Arm 3** and receive pembrolizumab and/or capecitabine (preferred option is pembrolizumab with capecitabine) or treatment of physician's choice. The use of no additional therapy is permitted if deemed appropriate by the treating provider, but not a recommended option.

Subjects receiving pembrolizumab are eligible and may continue treatment during the screening process. Subjects assigned to Arm 1 will require a 3 week wash out period prior to initiation of study treatment. Subjects assigned to Arm 2 and Arm 3 may continue pembrolizumab treatment during the study based on investigator discretion.

See Appendix C for information regarding contingency plans for COVID-19.

5.1 Arm 1 Drug Administration

Arm 1 subjects have plasma ctDNA positive (~65%) and a genomically driven treatment option. A ± 3 day window will be applied to all visits.

Arms 1c, and 1d will have a Safety Lead In Phase. Drug interaction and increased toxicity are not anticipated in these arms, however, there is limited experience with these combinations. To exclude prohibitive toxicity, the first six patients on these arms will be treated with combined therapy as outlined in each table below. If a patient goes off study before completing the dose-limiting toxicity (DLT) observation period for reasons other than DLT, then that patient should be replaced.

At pre-specified times during the safety lead in phase of Arm 1c and 1d, accrual will be paused to the relevant Arm for review of data by the study team. Subjects being screened during this time may be delayed in starting treatment due to this enrollment pause. The feasibility of this delay should be discussed by the site investigator with the subject to determine the subject's willingness to delay treatment initiation.

5.1.1 Arm 1a Treatment; CLOSED

Assignment to Arm 1a CLOSED based on FDA approval of pembrolizumab for high-risk early-stage triple-negative breast cancer in July 2021. DNA Repair pathway = patients with somatic or germline mutations, deletions or loss by fusions in DNA repair genes that are deemed to be deleterious. Patients are eligible for this arm if they have alterations in the pre-specified DNA repair genes, as follows: BRCA1/2, PALB2, ATR, BARD1, BLM, BRIP1, CHEK2, FANCA, FANCC, FANCD2, FANCF, MRE11A, RAD51, RAD51B, RAD51C, RAD51D, RAD54L, NBN, WRN, RECQL, ARID1A.

5.1.1.1 Capecitabine and Talazoparib

Drug[1]	Dose[2]	Route	Schedule	Cycle Length	Total # of Cycles
Capecitabine[2]	1000 mg/m^2 BID	Orally	14 days on and 7 days off	3 weeks (21 days)	8
Talazoparib[3]	Cycle 1: 0.75 mg	Orally	21 days on	3 weeks (21 days)	8
	Cycle 2-8: 1 mg				

1: Subjects will be asked to keep a diary to bring to each clinic visit in addition to all pill bottles for reconciliation.
2: All capecitabine doses will be based on the patient's actual weight. The actual weight at screening should be used for calculating body surface area (BSA). The BSA may be recalculated based on the actual weight at the start of each treatment cycle but recalculation is only required if a patient's weight changes by ≥ 10%. The calculated total daily dose should be rounded to the nearest 500 mg so treatment can be administered using only the 500 mg tablets. Morning (AM) and evening (PM) doses can be different if rounding the total daily dose to the nearest 500 mg requires.
3: Talazoparib dose is fixed, and as such, is not adjusted for changes in the patient's weight. Talazoparib dose should be increased to 1.0 mg for Cycles 2-8 in the absence of a DLT in Cycle 1. Capsules should be swallowed whole and must not be opened or dissolved. If the patient vomits or misses a dose, an additional dose should not be taken. The next prescribed dose should be taken at the usual time. Guidelines for management of talazoparib-specific adverse events can be found in Appendix A.

The current package insert and institutional guidelines should be utilized for capecitabine administration. The current investigator's brochure and institutional guidelines should be utilized for talazoparib administration. There is no particular sequence of administration to these medications but the way in which subjects are instructed should remain consistent throughout study treatment.

5.1.1.2 Safety Lead In

Weekly reviews will occur with the study team. A representative from each enrolling institution will be asked to attend a conference call or communicate by email each subject's status for appropriate monitoring of DLTs. Sites enrolling patients in the safety run-in must be willing to provide source documentation for all critical data within 5 business days of any subject visit. If at any time during enrollment of the first six patients, ≥ 2 patients experience a DLT, accrual will be suspended for review by the study team. If ≤ 1 of 6 patients experiences a DLT, a review will occur by the study team prior to Arm 1a re-opening for additional enrollment using the identical treatment doses. If 2 or more of 6 patients experience a DLT, enrollment to Arm 1a will be stopped and the study amended to explore lower starting doses. Please see Section 13 for additional information regarding study oversight during the Phase 1 component of the study.

The DLT monitoring period is Cycle 1 and Cycle 2. DLTs are defined as:

Toxicity Category	Criteria Defining a DLT
Hematological	Grade 4 neutropenia lasting for ≥ 7 days
	Febrile neutropenia
	Grade ≥ 3 thrombocytopenia of any duration associated with clinically significant bleeding of any duration or Grade 4 thrombocytopenia of any duration

Non-hematological	Grade ≥ 3 toxicity regardless of duration with the following exceptions: • Grade ≥ 3 electrolyte abnormality that lasts > 72 hours may be an exception as long as the patient has no has clinical symptoms, in which case all grade ≥ 3 electrolyte abnormality regardless of duration should count as a DLT. • Grade ≥ 3 fatigue that last < 1 week. • Grade ≥ 3 nausea, vomiting, diarrhea that < 72 hours with the use of adequate/maximal medical interventions and/or prophylaxis • Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law and based on the following observations: o Treatment-emergent ALT or AST > 3 ×ULN (or > 3 ×baseline value in disease states where LFTs may be elevated at baseline) in combination with total bilirubin > 2 ×ULN (of which ≥ 35% is direct bilirubin) o Treatment-emergent ALT or AST > 3 ×ULN (or > 3 ×baseline value in disease states where LFTs may be elevated at baseline) in combination with clinical jaundice
• Any toxicity that results in a > 14 day delay in Cycle 2 Day 1 or Cycle 3 Day 1 will be considered a DLT. • Death not clearly due to the underlying disease or extraneous causes will be considered a DLT. • The need for dose modification (see Section 6) based on toxicities not meeting the definition of DLT during Cycle 1 or Cycle 2 will NOT be considered DLT.	

5.1.2 Arm 1b Treatment (TO CLOSE)

Immunotherapy pathway = patients whose tumors have PD-L1 staining (SP142 antibody) ≥ 1%, immune cell staining, or a tumor mutation burden (TMB) ≥ 10 mutations/megabase, or MSI-high (determined by NGS).

5.1.2.1 Capecitabine and Atezolizumab

Drug[1]	Dose[2]	Route	Schedule	Cycle Length	Total # of Cycles
Capecitabine	1000 mg/m^2 BID	Orally	14 days on 7 days off	3 weeks (21 days)	8
Atezolizumab	1200 mg	IV over 1 hour[3]	Every 21 days	3 weeks (21 days)	9

1: Subjects will be asked to keep a diary to bring to each clinic visit in addition to all pill bottles for reconciliation.
2: All capecitabine doses will be based on the patient's actual weight. The actual weight at screening should be used for calculating body surface area (BSA). The BSA may be recalculated based on the actual weight at the start of each treatment cycle but recalculation is only required if a patient's weight changes by ≥ 10%. The calculated total daily dose should be rounded to the nearest 500 mg so treatment can be administered using only the 500 mg tablets. Morning (AM) and evening (PM) doses can be different if rounding the total daily dose to the nearest 500 mg requires.

3: Atezolizumab dose is fixed and as such, doses are not adjusted for changes in the patient's weight. The first dose of Atezolizumab will be delivered over 60 (± 15) minutes intravenously. Institutional standards will be used regarding the infusion and if the first infusion is tolerated, all subsequent infusions may be delivered over 30 (± 10) minutes. Guidelines for management of atezolizumab-specific adverse events can be found in Appendix B.

The current package insert and institutional guidelines should be utilized for capecitabine administration. The current investigator's brochure and institutional guidelines should be utilized for atezolizumab administration including premedications and infusion time windows. There is no particular sequence of administration to these medications but the way in which subjects are instructed should remain consistent throughout study treatment.

5.1.3 Arm 1c Treatment

PI3K Pathway = patients whose tumors harbor gain-of-function mutations in PIK3CA. If a subject assigned to Arm 1c does not meet additional Arm 1c criteria, the subject will be reassigned to Arm 2.

5.1.3.1 Capecitabine and Inavolisib followed by consideration for standard of care pembrolizumab

Drug[1]	Dose[2]	Route	Schedule	Cycle Length	Total # of Cycles
Capecitabine	1000 mg/m^2 BID	Orally	14 days on 7 days off	3 weeks (21 days)	8
Inavolisib[3]	Cycle 1: 6 mg Cycle 2-8: 9mg	Orally	21 days on	3weeks (21 days)	8
AFTER COMPLETION OF 8 CYCLES OF CAPECITABINE AND INAVOLISIB TREATMENT					
Pembrolizumab[4]	Pembrolizumab dose, route, schedule and cycle length per investigator discretion based on standard of care.				Up to 9

1: Subjects will be asked to keep a diary to bring to each clinic visit in addition to all pill bottles for reconciliation.
2: All capecitabine doses will be based on the patient's actual weight. The actual weight at screening should be used for calculating body surface area (BSA). The BSA may be recalculated based on the actual weight at the start of each treatment cycle but recalculation is only required if a patient's weight changes by ≥ 10%. The calculated total daily dose should be rounded to the nearest 500 mg so treatment can be administered using only the 500 mg tablets. Morning (AM) and evening (PM) doses can be different if rounding the total daily dose to the nearest 500 mg requires.
3: Inavolisib dose is fixed and as such, inavolisib dose is not adjusted for changes in the patient's weight. Inavolisib dose should be increased to 9 mg for Cycles 2-8 in the absence of dose limiting toxicity in cycle. **NOTE:** Verify dosage of tablets for Cycle 2 and subsequent as the dosage of tablets for Cycle 1 may be different. Ensure total dose for Cycle 2+ is 9 mg. If the patient vomits or misses a dose, an additional dose should not be taken. The next prescribed dose should be taken at the usual time. Guidelines for management of inavolisib-specific adverse events can be found in Appendix B.
4: Cycle 9 Day 1 standard of care therapy should occur 4 weeks (± 7 days) after completion of Cycle 8 study treatment.

The current package insert and institutional guidelines should be utilized for capecitabine administration. The current investigator's brochure and institutional guidelines should be utilized for inavolisib

administration. There is no particular sequence of administration to these medications but the way in which subjects are instructed should remain consistent throughout study treatment. The current package insert and institutional guidelines should be utilized for pembrolizumab administration including premedications and infusion time windows.

5.1.3.2 Arm 1c Safety Lead In

Once a subject is enrolled on Arm 1c weekly reviews will occur with the study team. A representative from each enrolling institution will be asked to attend a conference call or communicate by email each subject's status for appropriate monitoring of DLTs. Sites enrolling patients in the safety run-in must be willing to provide source documentation for all critical data within 5 business days of any subject visit. If at any time during enrollment of the first six patients, ≥ 2 patients experience a DLT, accrual will be suspended for review by the study team. If ≤ 1 of 6 patients experiences a DLT, a review will occur by the study team prior to Arm 1c re-opening for additional enrollment using the identical treatment doses. If 2 or more of 6 patients experience a DLT, enrollment to Arm 1c will be stopped and the study amended to explore lower starting doses. Please see Section for additional information regarding study oversight during the Phase 1 component of the study.

The DLT monitoring period is Cycle 1 and Cycle 2. DLTs are defined as:

Toxicity Category	Criteria Defining a DLT
Hematological	Grade 4 neutropenia lasting for ≥ 7 days
	Febrile neutropenia
	Grade ≥ 3 thrombocytopenia of any duration associated with clinically significant bleeding of any duration or Grade 4 thrombocytopenia of any duration
Non-hematological	Grade ≥ 3 toxicity regardless of duration with the following exceptions: • Grade ≥ 3 electrolyte abnormality that lasts > 72 hours may be an exception as long as the patient has no has clinical symptoms, in which case all grade ≥ 3 electrolyte abnormality regardless of duration should count as a DLT. • Grade ≥ 3 fatigue that last < 1 week. • Grade ≥ 3 nausea, vomiting, diarrhea that < 72 hours with the use of adequate/maximal medical interventions and/or prophylaxis
	• Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law and based on the following observations: o Treatment-emergent ALT or AST > 3 × ULN (or > 3 × baseline value in disease states where LFTs may be elevated at baseline) in combination with total bilirubin > 2 × ULN (of which ≥ 35% is direct bilirubin) o Treatment-emergent ALT or AST > 3 × ULN (or > 3 × baseline value in disease states where LFTs may be elevated at baseline) in combination with clinical jaundice
	• Grade ≥ 4 hyperglycemia (fasting) • Grade ≥ 3 hyperglycemia (fasting) that does not respond to insulin therapy within 3 days or that requires hospitalization
• Any toxicity that results in a > 14 day delay in Cycle 2 Day 1 or Cycle 3 Day 1 will be considered a DLT.	

- Death not clearly due to the underlying disease or extraneous causes will be considered a DLT.
- The need for dose modification (see Section 6) based on toxicities not meeting the definition of DLT during Cycle 1 or Cycle 2 will NOT be considered DLT.

5.1.4 Arm 1d Treatment

DNA Repair = patients who have genomic alterations that match to the criteria of both Arms 1a & 1b

5.1.4.1 Capecitabine + Talazoparib +/- consideration for standard of care Pembrolizumab

Drug[1]	Dose	Route	Schedule	Cycle Length	Total # of Cycles
Capecitabine[4]	1000 mg/m^2 BID	Orally	14 days on 7 days off	3 weeks (21 days)	8
Talazoparib[2]	Cycle 1: 0.75 mg	Orally	21 days on	3 weeks (21 days)	8
	Cycle 2-8: 1 mg				
Pembrolizumab[4]	Pembrolizumab dose, route, schedule and cycle length per investigator discretion based on standard of care.				Up to 9

1: Subjects will be asked to keep a diary to bring to each clinic visit in addition to all pill bottles for reconciliation.
2: Talazoparib doses are fixed and as such, doses are not adjusted for changes in the patient's weight. Talazoparib dose should be increased to 1.0 mg for Cycles 2-8 in the absence of DLT in Cycle 1. Capsules should be swallowed whole and must not be opened or dissolved. If the patient vomits or misses a dose, an additional dose should not be taken. The next prescribed dose should be taken at the usual time. Guidelines for management of talazoparib-specific adverse events can be found in Appendix A.
4: All capecitabine doses will be based on the patient's actual weight. The actual weight at screening should be used for calculating body surface area (BSA). The BSA may be recalculated based on the actual weight at the start of each treatment cycle but recalculation is only required if a patient's weight changes by ≥ 10%. The calculated total daily dose should be rounded to the nearest 500 mg so treatment can be administered using only the 500 mg tablets. Morning (AM) and evening (PM) doses can be different if rounding the total daily dose to the nearest 500 mg requires.

The current package insert and institutional guidelines should be utilized for capecitabine administration. The current investigator's brochure and institutional guidelines should be utilized for talazoparib administration. The current investigator's brochure and institutional guidelines should be utilized for pembrolizumab administration including premedications and infusion time windows. There is no particular sequence of administration to these medications but the way in which subjects are instructed should remain consistent throughout study treatment.

5.1.4.2 Arm 1d Safety Lead In

Once a subject is enrolled on Arm 1d weekly reviews will occur with the study team. A representative from each enrolling institution will be asked to attend a conference call or communicate by email each subject's status for appropriate monitoring of DLTs. Sites enrolling patients in the safety run-in must be willing to provide source documentation for all critical data within 5 business days of any subject visit. If at any time during enrollment of the first six patients, ≥ 2 patients experience a DLT, accrual will be suspended for review by the study team. If ≤ 1 of 6 patients experiences a DLT, a review will occur by the

study team prior to Arm 1d re-opening for additional enrollment using the identical treatment doses. If 2 or more of 6 patients experience a DLT, enrollment to Arm 1d will be stopped and the study amended to explore lower starting doses. Please see Section for additional information regarding study oversight during the Phase 1 component of the study.

The DLT monitoring period is Cycle 1 and Cycle 2. DLTs are defined as:

Toxicity Category	Criteria Defining a DLT
Hematological	Grade 4 neutropenia lasting for ≥ 7 days
	Febrile neutropenia
	Grade ≥ 3 thrombocytopenia of any duration associated with clinically significant bleeding of any duration or Grade 4 thrombocytopenia of any duration
Non-hematological	Grade ≥ 3 toxicity regardless of duration with the following exceptions: • Grade ≥ 3 electrolyte abnormality that lasts > 72 hours may be an exception as long as the patient has no has clinical symptoms, in which case all grade ≥ 3 electrolyte abnormality regardless of duration should count as a DLT. • Grade ≥ 3 fatigue that last < 1 week. • Grade ≥ 3 nausea, vomiting, diarrhea that < 72 hours with the use of adequate/maximal medical interventions and/or prophylaxis
	• Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law and based on the following observations: o Treatment-emergent ALT or AST > 3 ×ULN (or > 3 baseline value in disease states where LFTs may be elevated at baseline) in combination with total bilirubin > 2 ×ULN (of which ≥ 35% is direct bilirubin) o Treatment-emergent ALT or AST > 3 ×ULN (or > 3 ×baseline value in disease states where LFTs may be elevated at baseline) in combination with clinical jaundice
• Any toxicity that results in a > 14 day delay in Cycle 2 Day 1 or Cycle 3 Day 1 will be considered a DLT. • Death not clearly due to the underlying disease or extraneous causes will be considered a DLT. • The need for dose modification (see Section 6) based on toxicities not meeting the definition of DLT during Cycle 1 or Cycle 2 will NOT be considered DLT.	

5.2 Arm 2 Drug Administration

Arm 2 subjects have plasma ctDNA positive but do not have a genomically driven treatment option (~22%). Treatment of physician's choice will be given with consideration for capecitabine and/or pembrolizumab given the data from CREATE-X and KEYNOTE 522. Dose, schedule and duration of treatment to be determined by treating physician. Administration and management of side effects will be handled as standard of care per institutional guidelines. Information regarding treatment administration will be entered into the EDC system. The site investigator will be notified of the results to facilitate discussion of treatment options with the patient. If a particular study drug is on shortage for Arm 1 and a patient is assigned to that particular Arm, they will be reassigned to Arm 2. If a subject assigned to Arm 1c does not meet additional Arm 1c criteria, the subject will be reassigned to Arm 2.

5.3 Arm 3 Drug Administration

Arm 3 subjects have plasma ctDNA negative (~35%). Treatment of patient and physician's choice will be given with consideration for capecitabine and/or pembrolizumab given the data from CREATE-X and KEYNOTE 522. Dose, schedule and duration of treatment to be determined by treating physician. Administration and management of side effects will be handled as standard of care per institutional guidelines. Information regarding treatment administration will be entered into the EDC system. The site investigator will be notified of the results to facilitate discussion of treatment options with the patient. Consideration for no treatment can also be entertained if the patient and treating physician prefer.

5.4 Supportive Care

The use of supportive care including antibiotics, blood transfusions, etc. will be permitted as clinically indicated and according to institutional guidelines. Prophylactic use of white blood cell growth factors (i.e. Neulasta, Neupogen, Leukine, or biosimilar filgrastim or Pegfilgrastim agents) is not allowed. However, white blood cell growth factors may be used in accordance with ASCO guidelines if neutropenic fever occurs. Recombinant erythropoietin or similar compound may NOT be administered for anemia due to restrictions on their use in patients being treated with curative intent.

Arm 1c: Patients can receive loperamide (2 mg oral twice a day or 4 mg once a day) as anti diarrheal rescue if allowed by local guidance.

5.5 Concomitant Medications

The current package Insert should be utilized to determine use of concomitant medications for capecitabine and pembrolizumab. The current investigator's brochure should be utilized to determine use of concomitant medications for inavolisib and talazoparib. Bisphosphonate use is allowed.

5.6 Contraception Guidelines

Women of childbearing potential and their partners or male subjects and their partners, who are sexually active, must agree to the use of TWO highly effective forms of contraception in combination [as listed below], throughout the period of taking study treatment and for a designated time after last dose of study treatment based on the study treatment. Abstinence is considered an acceptable form of contraception if the subject totally/truly abstains from any form of sexual intercourse. This information is also applicable to breastfeeding.

Acceptable non-hormonal birth control methods:

- Total sexual abstinence ie, refrain from any form of sexual intercourse in line with the patients' usual and/or preferred lifestyle. Periodic abstinence (eg, calendar ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
- Vasectomised sexual partner PLUS male condom. With participant assurance that partner received post-vasectomy confirmation of azoospermia.
- Tubal occlusion PLUS male condom
- Intrauterine Device PLUS male condom. Provided coils are copper-banded.

Acceptable hormonal methods:

- Etonogestrel implants (eg, Implanon®, Nexplanon®) PLUS male condom
- Normal and low dose combined oral pills PLUS male condom
- Hormonal shot or injection (eg, Depo-Provera) PLUS male condom
- Intrauterine system device (eg, levonorgestrel-releasing intrauterine system - Mirena®) PLUS male condom

Timeframe after treatment discontinuation for continued contraception as described above:

- Inavolisib: 60 days (females) and 120 days (males)
- Atezolizumab: 5 months
- Capecitabine: 6 months
- Talazoparib: 7 months (females) and 4 months (males)
- Pembrolizumab: 4 months

5.7 Questionnaires

Patient reported outcome (PRO) measures will describe patient preferences for return of ctDNA results, and will quantify the impact of ctDNA status on fear of recurrence (FCR) and health- related quality of life (HRQoL). We will also characterize phenotypic modifiers of changes in FCR and HRQoL in this patient population. PRO measures to be administered are detailed in Appendix D.

PROs will be administered at screening, return of results, end of treatment, and at approximately 6 months surveillance follow up. These will be administered via a REDcap database. This study will utilize the secure, web-based, Research Electronic Data Capture (REDCap) system for PRO data input. The servers hosting REDCap are administered and supported by Indiana University's University Information Technology Services (UITS) and are physically located in IU's secured and environmentally structured data center on the IU Bloomington campus. To comply with HIPAA guidelines, physical, administrative, and technical safeguards and on ongoing risk management framework have been implemented and documented (NIST 800-53) to ensure the security and protection of the study data within the data center, the servers, and the database. REDCap is a software toolset developed by Vanderbilt University, with collaboration from a consortium of institutional partners, for electronic collection and management of research and clinical trial data. Indiana University has joined this consortium and has implemented REDCap within the Indiana University's central Information Technology Services (UITS) technical environment to enable rapid development and deployment of electronic data capture and reporting to support specific clinical and translational research projects. The implementation of these projects within REDCap depends on a thorough study-specific data dictionary that is defined in an iterative process by all members of the research team. The iterative development and testing process results in a well-defined data collection strategy for individual studies. The REDCap software

toolset provides a secure, web-based environment that is flexible enough to be used for a variety of types of research, provides an intuitive interface for users to enter data and have real time validation rules (with automated data type and range checks) at the time of entry. The system offers easy data manipulation with logged auditing, functionality for reporting, monitoring and querying patient records, and an automated export mechanism to common statistical packages such as SPSS, SAS, Stata, and R/S-Plus. REDCap App is a component of the overall REDCap platform that can be used for offline data capture and is synchronized with the primary REDCap database. It is available for download to iOS and Android devices and the REDCap App encrypts the data on the device.

6 DOSE MODIFICATIONS

The NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 5 will be used to grade adverse events. Participants enrolled in this study will be evaluated clinically and with standard laboratory tests before and at regular intervals during their participation in this study as specified in section 7 Schedule of Events.

6.1 Dose Level Reduction/Modification Tables

Arms 1a (CLOSED), 1b (TO CLOSE), 1c, and 1d will have a lower starting dose at Cycle 1 to ensure tolerability. Increased toxicities are not anticipated in these arms, however, there is limited experience with these combinations.

Arm 1a: (21 day Cycle); CLOSED

Dose level	Capecitabine	Talazoparib
1	1000 mg/m^2 BID for 14 days	1mg QD for 21 days
0 (Starting dose Cycle 1)	1000 mg/m^2 BID for 14 days	0.75 mg QD for 21 days
-1	750 mg/m^2 BID for 14 days	0.5 mg QD for 21 days
-2	500 mg/m^2 BID for 14 days	0.25 mg QD for 21 days

Arm 1b: (21 day Cycle) TO CLOSE

Dose level	Capecitabine	Atezolizumab
0 (Starting dose)	1000 mg/m^2 BID for 14 days	1200 mg IV every 21 days
-1	1000 mg/m^2 BID for 14 days	Discontinue
-2	750 mg/m^2 BID for 14 days	Discontinue
-3	500 mg/m^2 BID for 14 days	Discontinue

Arm 1c: (21 day Cycle)

Dose level	Capecitabine	Inavolisib
1	1000 mg/m^2 BID for 14 days	9 mg for 21 days
0 (Starting dose Cycle 1)	1000 mg/m^2 BID for 14 days	6 mg for 21 days
-1	750 mg/m^2 BID for 14 days	3 mg for 21 days
-2	500 mg/m^2 BID for 14 days	Discontinue

Arm 1d: (21 day Cycle)

Dose level	Capecitabine	Talazoparib
1	1000 mg/m^2 BID for 14 days	1mg QD for 21 days
0 (Starting dose Cycle 1)	1000 mg/m^2 BID for 14 days	0.75 mg QD for 21 days
-1	750 mg/m^2 BID for 14 days	0.5 mg QD for 21 days
-2	500 mg/m^2 BID for 14 days	0.25 mg QD for 21 days

6.2 General Delays and Dose Modifications

- Dose interruption and/or modification may be implemented due to hematologic or nonhematologic toxicities per dose modification tables after completion of Cycle 2 for safety lead in patients and as needed for all others.
- If toxicity causes treatment to be delayed, clinic visits (and study procedures) associated with each cycle of therapy, as defined by the administration of any of the Arm 1 investigational agents, will also be delayed (e.g., from Day 14 to Day 21). However, laboratory assessments and clinical visits shall be scheduled as needed for adverse events follow up. Once the toxicity has resolved to the required level, study treatment and study procedures will be resumed, according to the study cycle day count.
- If any observed toxicity is attributable to only one drug as assessed by the investigator, the dose of the other drug(s) may not require modification.
- Dose modifications for isolated abnormal hematologic laboratory values will be based on hematologic parameters at the start of a treatment cycle.
- Treatment may be delayed to manage toxicity. Delays up to 3 weeks (21 days) are permitted. A delay of longer than 3 weeks for an adverse event will require permanent discontinuation of the investigational agent but the patient may continue the capecitabine after discussion with the sponsor-investigator.

- No more than 2 total dose reductions will be permitted for any agent. If the patient has had two dose reductions and another toxicity requiring reduction is experienced, that agent will be permanently discontinued. For inavolisib in Arm 1c, there is only 1 total dose reduction in cycle 1.
- Special interest events are known toxicities attributable to specific drugs and will require customized dose modifications.
    - The non-hematologic toxicities listed in the special interest event dose modification table below should follow specified modifications.

6.2.1 Event Dose Modification Table

Event	Capecitabine	Talazoparib	Inavolisib
Hematologic Event Grade 3	Hold then, reduce to -1 dose level (750 mg/m^2 BID)	Hold then, reduce dose one level	Hold then, reduce dose one level
Hematologic Event Grade 4	Hold then, Reduce to -2 dose level (500 mg/m^2 BID)	Hold then, reduce dose one level	Hold then, reduce dose one level
Non-hematologic Event Grade 3**	Hold then, continue dose	Hold then, reduce dose one level	Hold then, reduce dose one level
Non-hematologic Event Grade 4**	Hold then, reduce to -1 dose level (750 mg/m^2 BID)	Hold then, reduce dose one level	Hold then, reduce dose one level

**See special interest event modifications are listed in the table below.

6.2.2 Special Interest Event Dose Modification Table

*Special Interest Events	Capecitabine	Talazoparib	Inavolisib
Adrenal insufficiency Grade 2–4	Hold then, continue dose	Hold then, reduce dose one level	Hold then, reduce dose one level
Hyperglycemia Grade 2 or Fasting blood glucose values 160 to 250 mg/dL or 8.9-13.9 mmol/L)	Continue dose	Continue dose	Hold then, continue dose
Hyperglycemia Grade 3 or 4 Fasting blood glucose values > 250 mg/dL or > 13.9mmol/L)	Hold then, continue dose	Hold then, reduce dose one level	Hold then, reduce dose one level
Hyperthyroidism Asymptomatic	Hold then, continue dose	Hold then, reduce dose one level	Hold then, reduce dose one level
Hyperthyroidism Symptomatic	Hold then, continue dose	Hold then, reduce dose one level	Hold then, reduce dose one level
Hypophysitis (pan-hypopituitarism) Grade 2 or 3	Hold then, continue dose	Hold then, reduce dose one level	Hold then, reduce dose one level
Hypophysitis (pan-hypopituitarism) Grade 4	Hold then, continue dose	Hold then, reduce dose one level	Hold then, reduce dose one level

*Special Interest Events	Capecitabine	Talazoparib	Inavolisib
Hypothyroidism Asymptomatic	Hold then, continue dose	Hold then, reduce dose one level	Hold then, reduce dose one level
Hypothyroidism Symptomatic	Hold then, continue dose	Hold then, reduce dose one level	Hold then, reduce dose one level
Diarrhea Grade 2	Continue	Continue	Hold then, continue dose
Diarrhea Grade 3	Hold then, reduce to -2 dose level (500 mg/m^2 BID)	Hold then, reduce dose one level	Hold then, reduce dose one level
Diarrhea Grade 4	Hold then, reduce to -2 dose level (500 mg/m^2 BID)	Hold then, reduce dose one level	Hold then, reduce dose one level
Nausea/Vomiting Grade 3	Hold then, reduce to -2 dose level (500 mg/m^2 BID)	Hold then, reduce dose one level	Hold then, reduce dose one level
Nausea/Vomiting Grade 4	Hold then, reduce to -2 dose level (500 mg/m^2 BID)	Hold then, reduce dose one level	Hold then, reduce dose one level
Mucositis Grade 2	Continue	Continue	Hold then, continue dose
Mucositis Grade 3	Hold then, reduce to -2 dose level (500 mg/m^2 BID)	Hold then, reduce dose one level	Hold then, reduce dose one level
Mucositis Grade 4	Hold then, reduce to -2 dose level (500 mg/m^2 BID)	Hold then, reduce dose one level	Discontinue
Colitis, Grade 2	Continue	Continue	Hold then, reduce dose or continue same dose
Colitis, Grade 3	Hold then, reduce to -2 dose level (500 mg/m^2 BID)	Hold then, reduce dose one level	Hold then, reduce dose one level
Colitis, Grade 4	Hold then, reduce to -2 dose level (500 mg/m^2 BID)	Hold then, reduce dose one level	Hold then, reduce dose one level
Major Organ Event Grade 3-4	Hold then, continue dose	Hold then, reduce dose one level	Hold then, reduce dose one level
Myocarditis Grade 2-4	Hold then, Reduce to -1 dose level (750 mg/m^2 BID)	Hold then, reduce dose one level	Hold then, reduce dose one level
Pneumonitis Grade 2-3	Hold then, continue dose	Hold then, reduce dose one level	Hold then, reduce dose one level
Pneumonitis Grade 4	Hold then, continue dose	Hold then, reduce dose one level	Discontinue

*Special Interest Events	Capecitabine	Talazoparib	Inavolisib
Skin/Dermatologic Event, Grade 2	Continue	Continue	Hold then, reduce dose or continue same dose
Skin/Dermatologic Event, Grade 3	Hold then, continue dose	Hold then, reduce dose one level	Hold then, reduce dose one level
Skin/Dermatologic Event, Grade 4	Hold then, continue dose	Hold then, reduce dose one level	Hold then, reduce dose one level
Skin-Palmar-plantar erythrodysesthesia syndrome (Hand Foot Syndrome) Grade 3	Hold then, reduce to -2 dose level (500 mg/m^2 BID)	Hold then, continue dose	Hold then, continue dose

- Hold all investigational agents until event resolves to 1 grade above baseline or better.
- Continue Dose-Continue agent listed at current dosing, consider management per institutional guidelines and/or Appendix A and B.
- Discontinue- Stop agent listed.

6.3 Dose Modifications for Capecitabine

Dose modifications for capecitabine will be made per package insert guidelines with site investigator discretion.

6.4 Dose Modifications for talazoparib

See section above for specific dose modifications.

6.4.1 Management of Talazoparib Specific Adverse Events

Toxicities related or possibly related with talazoparib treatment should be managed according to guidelines provided in the current investigator's brochure and standard medical practice. Management of talazoparib-specific adverse events can be found in Appendix A. If a diagnosis of Myelodysplastic Syndrome (MDS) or Acute Myeloid Leukemia (AML) is confirmed by a hematologist, the patient must permanently discontinue study treatment.

6.5 Dose Modifications for Inavolisib

See section 6 above for specific dose modifications. No more than two total dose reductions of inavolisib per patient (i.e., doses below 3 mg/day of inavolisib) will be allowed, and dose re-escalation of inavolisib may be permitted in the study after discussion with the sponsor-investigator. There is only 1 total dose reduction in cycle 1.

6.5.1 Management of Inavolisib-Specific Adverse Events

Toxicities related or possibly related with inavolisib treatment should be managed according to guidelines provided in the current investigator's brochure and standard medical practice. Management of inavolisib-specific adverse events can be found in **Appendix B**.

6.6 Discontinuation from Protocol Therapy

In addition to discontinuation from therapy related to toxicities as outlined in section above, a subject will also be discontinued from protocol therapy and followed per protocol under the following circumstances outlined below. The reason for discontinuation of protocol therapy will be documented on the electronic case report form (eCRF).

- Documented disease progression: (local, regional and/or distant), invasive contralateral breast cancer
- Site investigator determines a change of therapy would be in the best interest of the subject
- Subject requests to discontinue protocol therapy for any reason
    - In a subject decides to prematurely discontinue protocol therapy (“refuses treatment”), the subject should be asked if he or she may still be contacted for further scheduled study assessments. The outcome of that discussion should be documented in both the medical records and in the eCRF.
- Female subject becomes pregnant
- Protocol therapy is interrupted for > 21 days from the expected day of the next treatment.

6.7 Discontinuation from Protocol Activities

If a subject decides to discontinue from all protocol activities and not just from protocol therapy, a final evaluation should be completed at the time of the subject’s protocol withdrawal. An explanation of why the subject is withdrawing from the protocol will be recorded on the eCRF. A final assessment of adverse events will be recorded on the eCRF.

7 SCHEDULE OF EVENTS

NOTE: Please see Appendix C for additional information regarding protocol specific contingency plans for COVID 19

7.1 All Arms

	Screening[8]		Return of Results/Treatment Planning[10]
	-42 days-	28 days	
REQUIRED ASSESSMENTS			
Informed consent[1]	X		Arm 1 ONLY
Complete medical history and height	X		
Diagnosis and Staging[2]	X		
Complete physical examination	X		
Arm 1c only: Ophthalmic examination[9]			X[9]
Weight, BP and ECOG performance status	X	ECOG PS	
Adverse event & con med assessment	X		
LABORATORY ASSESSMENTS			
CBC with differential[3]		X	
CMP[3]		X	
Arm 1c only: HgBA1c, Fasting glucose, and Fasting Lipid Panel[9]			X[9]
Calculated creatinine clearance		X	
Urine pregnancy or serum HCG[3]		X	
CORRELATIVE SAMPLES			
Tumor from definitive surgery – Mandatory[4]	X		
Whole blood for genomic DNA – Mandatory[5]	X		
Whole blood for Plasma ctDNA – Mandatory[6]	X		
QUESTIONNAIRES[7]			
Preference for ctDNA results	X		X
Fear of cancer recurrence index (FCRI)	X		X
Assessment of survivor concerns (ACS)	X		X
Impact of Events scale (IES)	X		X
PROMIS-29 HRQoL	X		X
PROMIS Anxiety short form	X		X
Breast cancer self- efficacy scale	X		
Health literacy scale	X		
CDC BRFSS – physical activity, smoking, alcohol	X		

1: Subjects will consent to participation in the trial and proceed to formal study registration providing ALL of the eligibility criteria is met. Consent for Arm 1 specific treatment may be obtained prior to treatment C1D1 of the assigned Arm.

2: Diagnosis and staging information to include: confirmation of TNBC per pathology report (ER, PR and HER2 negative) Precise ER and PR status should be provided if available. Confirmation of clinical stage TNBC 1-3 per AJCC 8th edition.

3: CBC with platelet and differential (white blood cell count, absolute neutrophil count, hemoglobin and platelet count). Serum chemistries (creatinine, glucose, total bilirubin, aspartate transaminase [AST] and alanine transaminase [ALT]). Complete pregnancy testing only in women of childbearing potential. Urine pregnancy or serum HCG to be done 7 days prior registration. Women should be counseled regarding acceptable birth control methods to utilize from the time of screening, during treatment and after treatment completion. **NOTE:** If prior to treatment after discussion with the subject it is felt by the treating physician there is a possibility the subject is pregnant a pregnancy test should be repeated.

4: Mandatory collection of tumor tissue from definitive surgery to be identified at screening and shipped immediately after consent. This sample will be used to confirm the patient's triple negative breast cancer diagnosis. Also, extracted nucleic acids from this tumor sample will be used to perform next generation sequencing testing. Required for eligibility. Tissue can be collected and submitted upon consent while eligibility is being determined. Unused samples after protocol specific testing is complete will be stored for future research in minimal residual disease and cancer biomarkers.

5: Mandatory 8.5 mL whole blood for genomic DNA will be collected at screening after consent obtained. Unused samples after protocol specific testing is complete will be stored for future research in minimal residual disease and cancer biomarkers.

6: Mandatory: 17 mL whole blood for plasma ctDNA will be collected after a successful tissue test and the ability to select appropriate variants for tracking are confirmed. ctDNA should not be drawn before completing radiation or less than 14 days from surgery if radiation is not required. Required for eligibility. Unused samples after protocol specific testing is complete will be stored for future research in minimal residual disease and cancer biomarkers.

7: Questionnaires may be administered electronically or by paper. No protocol deviation will be incurred if patients do not return a response to the questionnaires. Patients must be made aware of their ctDNA results and assigned to a treatment arm BEFORE completing the questionnaires at "Return of Results/Treatment Planning" timepoint. Questionnaires completed during the screening period do not need to be repeated if they fall outside of the screening window.

8: Participants must register and begin assigned treatment no later than 96 days from the last local therapy. For those that do not require radiotherapy, the most recent surgery for breast cancer must have been completed no more than 96 days prior to study treatment initiation. A 42 day window may be applied from the time of screening to registration for required assessments, correlative specimen collection (unless otherwise specified) and questionnaire completion. A 28 day window may be applied from the time of screening to registration for laboratory assessments. See Section 4 for additional detail regarding FoundationOne assay use.

9: Ophthalmic examinations during study treatment and at treatment discontinuation are performed as clinically indicated per investigator discretion based on patient clinical status. If an ophthalmic exam is required during study treatment or study treatment discontinuation, the exam should consist of a full ophthalmic exam with dilation and refraction with specific attention paid to lens examination and detailed documentation. This exam may be performed after

assignment to Arm 1c and prior to treatment initiation on C1D1 but confirmation that there is no concurrent ocular or intraocular condition (e.g., cataract or diabetic retinopathy) that, in the opinion of the investigator, would require medical or surgical intervention during the study period to prevent or treat vision loss that might result from that condition is required for eligibility. HgBA1c, Fasting glucose, and Fasting Lipid Panel testing is required for eligibility for patients assigned to Arm 1c. Fasting means not having anything to eat or drink (except water) for 8-12 hours before the test.

10: Once the sequencing results are received, subjects will be assigned to the appropriate Arm and an additional consent will be obtained if the subject is assigned to Arm 1. The protocol therapy is not blinded to the participant or the treating investigator. **NOTE:** Treating investigators will receive sequencing results after arm assignment. ctDNA status (positive or negative) will be shared with subjects. Sequencing results will be shared with subjects at the treating investigator's discretion. Sequencing results will be flagged if a suspected germline mutation is found. It will be the responsibility of the treating investigator to follow-up with additional genetic testing and/or genetic counseling as appropriate. Subjects will be given the opportunity to ask questions regarding Arm assignment. A physician exam is not required during Return of Results/Treatment Planning. If a particular study drug is on shortage for Arm 1 and a patient is assigned to that particular Arm, they will be reassigned to Arm 2. If a subject assigned to Arm 1c does not meet additional Arm 1c criteria, the subject will be reassigned to Arm 2.

7.2 Arm 1 a: DNA Repair pathway = talazoparib + capecitabine

Assignment to Arm 1a **CLOSED** based on FDA approval of pembrolizumab for high-risk early-stage triple-negative breast cancer in July 2021. No patients were assigned to this Arm and the calendar was deleted.

7.3 Arm 1b: Immunotherapy pathway = atezolizumab + capecitabine (TO CLOSE)

Cycle = 3 weeks	**Cycles 1-9[1]**	**Safety Visit[2]**	**Surveillance[3]**
	D1 of each cycle (±7 days)	30/90 days (±7) after last dose	±1 month
REQUIRED ASSESSMENTS			
Informed consent for Assigned Arm	X[4]		
Complete physical examination	X	D30	X
Weight, BP and ECOG performance status	X	D30	X
Adverse event & con med assessment	X	X	
LABORATORY ASSESSMENTS			
CBC with differential[5]	X	D30	
CMP[5]	X	D30	
Calculated creatinine clearance	X		
Thyroid Function Testing[5]	X[5]	D30	
Urine pregnancy or serum HCG[5]	X[5]		
RADIOLOGY IMAGING			
Breast imaging (remaining native breast tissue only)	X[3]		Yearly
TREATMENT EXPOSURE			
Genomically directed atezolizumab + capecitabine[10]	X		
CORRELATIVE AND BANKING SAMPLES			
Tumor from initial diagnosis – Optional[6]	X[6]		
Tumor from progression – Optional[6]		@progression	
Whole blood for Plasma ctDNA – Mandatory[7]	X[7]	D30	X[7]
Whole blood for CTCs – Mandatory[8]	X[8]	D30	
QUESTIONNAIRES[9]			
Preference for ctDNA results		D30	X
Fear of cancer recurrence index (FCRI)		D30	X
Assessment of survivor concerns (ACS)		D30	X
Impact of Events scale (IES)		D30	X
PROMIS-29 HRQoL		D30	X
PROMIS Anxiety short form		D30	X

1: Cycle 1 Day 1 testing need not be repeated if obtained within 14 days of starting protocol therapy.

2: Participants in Arm 1 discontinued from the treatment phase of the study for any reason will have a safety visit 30 days (±7) after the last dose of protocol therapy. Subjects will also have an assessment of adverse events 90 days (±7) after the last dose of study treatment. This assessment may be accomplished via email, phone call or other avenues as appropriate.

3: Radiology imaging performed is per standard of care based on investigator discretion. If at any time during treatment, recurrence is suspected, imaging should be performed based on investigator's discretion. During surveillance, monitoring for the development of either local (chest wall, axillary, or supraclavicular nodes) or distant recurrent disease, is based on investigator's discretion. Complete physical exam including weight, and BP should be performed at least once every 3 months for the first two years, then at least every 6 months during years 3-5 after Treatment Discontinuation. At disease progression, participant should be followed for survival only. If there are concerns for recurrence upon physical exam, imaging should be performed to confirm per investigator's discretion. Surveillance visits are calculated from the last visit.

4: Participants will complete a treatment specific consent prior to Cycle 1 Day 1 based on the Arm they are assigned.

5: CBC with platelet and differential (white blood cell count, absolute neutrophil count, hemoglobin and platelet count). Serum chemistries (creatinine, glucose, total bilirubin, and aspartate transaminase [AST] and alanine transaminase [ALT]). Thyroid Function testing should be performed just prior to first dose of atezolizumab and then every 2 cycles. TSH and T4 will be obtained. T3 including free versus total testing is at the discretion of the site investigator. WOCBP should be counseled regarding acceptable birth control methods to utilize during treatment and after treatment completion. If prior to treatment after discussion with the subject it is felt by the treating physician there is a possibility the subject is pregnant a urine or serum pregnancy test should be repeated.

6: Optional collection of tumor tissue from initial diagnosis to be shipped prior to D30 safety visit. Optional collection of tissue for subjects undergoing a standard of care biopsy at progression. Subjects will be asked to consent to these collections.

7: Mandatory: 34 mL whole blood for plasma ctDNA will be collected prior to treatment on Cycles 1-8, Safety Visit, every 3 months for up to 2 years after treatment discontinuation and at progression.

8: Mandatory 20 mL whole blood for CTC will be collected at screening prior to C2D1 and C4D1 then at the Safety Visit.

9: Questionnaires may be administered electronically or by paper. No protocol deviation will be incurred if patients do not return a response to the questionnaires. Questionnaires will be completed at the safety visit and at +6 months surveillance visit, ± 1 month.

10: Participants will receive genomically directed therapy. Atezolizumab and capecitabine will be administered in combination for 8 cycles. Atezolizumab will be given alone on Cycle 9.

7.4 Arm 1c: PI3K Pathway = inavolisib + capecitabine → +/- standard of care pembrolizumab

Cycle = 3 weeks	**Cycle 1[1]**	**Cycles 2-8**	**Cycles 9-17[1]**	**Safety Visit[2]**	**Surveillance[3]**
	D1 (±3 days)	D1 of each cycle (±3 days)	Day 1 of each cycle (±3 days)	30/90 days (±7) after last dose	±1 month
REQUIRED ASSESSMENTS					
Informed consent for Assigned Arm[4]	X[4]				
Complete physical examination	X	X	X	D30	X
Ophthalmic examination[8]	X[8]				
Weight, BP and ECOG performance status	X	X	X	D30	X
Adverse event & con med assessment	X	X	X	X	
LABORATORY ASSESSMENTS					
CBC with differential[5]	X	X	X	D30	
CMP[5]	X	X	X	D30	
HgBA1c[5]	X	X[5]			
Fasting Glucose[5]	X	X[5]			
Calculated creatinine clearance	X				
Thyroid Function Testing[5]			X[5]	D30	
Urine pregnancy or serum HCG[5]	X[5]				
RADIOLOGY IMAGING					
Breast imaging (remaining native breast tissue only)[3]	X[3]	X[3]	X[3]		Yearly
TREATMENT EXPOSURE					
Genomically directed inavolisib + capecitabine[10]	X	X			
+/- Pembrolizumab[10]			X		
CORRELATIVE SAMPLES					
Tumor from initial diagnosis – Optional[6]	X[6]	X[6]			
Tumor from progression – Optional[6]				X[6]	
Whole blood for Plasma ctDNA – Mandatory[7]	X[7]	X[7]	X[7]	D30	X[7]
QUESTIONNAIRES[9]					
Preference for ctDNA results				D30	X
Fear of cancer recurrence index (FCRI)				D30	X
Assessment of survivor concerns (ACS)				D30	X
Impact of Events scale (IES)				D30	X
PROMIS-29 HRQoL				D30	X
PROMIS Anxiety short form				D30	X

1: Cycle 1 Day 1 and Cycle 9 Day 1 testing need not be repeated if obtained within 14 days of starting protocol therapy.

2: Participants in Arm 1 will have a safety visit 30 days (±7) after the last dose of protocol therapy. A safety follow up visit is not required for participants who complete the planned 8 cycles of inavolisib/capecitabine and proceed to standard of care treatment with pembrolizumab (preferred option) and no therapy is the preferred option if contraindication to pembrolizumab. Patients will have a Day 30 safety follow up visit after completion of standard of care treatment in addition to an assessment of adverse events 90 days (±7) after the last dose of standard of care therapy. The 90 day assessment may be accomplished via email, phone call or other avenues as appropriate.

3: Radiology imaging performed is per standard of care based on investigator discretion. If at any time during treatment, recurrence is suspected, imaging should be performed at investigator's discretion. During surveillance, monitoring for the development of either local (chest wall, axillary, or supraclavicular nodes) or distant recurrent disease is based on investigator's discretion. Complete physical exam including weight, and BP should be performed at least once every 3 months for the first two years, then at least every 6 months during years 3-5 after Treatment Discontinuation. At disease progression, participant should be followed for survival only. If there are concerns for recurrence upon physical exam, imaging should be performed to confirm per investigator's discretion. Surveillance visits are calculated from the last visit, not treatment discontinuation.

4: Participants will complete a treatment specific consent prior to Cycle 1 Day 1 based on the Arm they are assigned.

5: CBC with platelet and differential (white blood cell count, absolute neutrophil count, hemoglobin and platelet count). Serum chemistries (creatinine, glucose, total bilirubin, aspartate transaminase [AST] and alanine transaminase [ALT]). HgBA1c to be performed at screening, every 3 months during treatment and after completion of inavolisib. During inavolisib and capecitabine treatment fasting glucose monitoring is based on site investigator discretion and subject clinical status. Additional glucose monitoring may be required during Cycle 1 specifically around Day 4 and Day 15 and should be initiated based on investigator discretion. Fasting glucose monitoring is not required during pembrolizumab treatment. Thyroid Function testing should be performed just prior to first dose of pembrolizumab and then every 2 cycles. TSH and T4 will be obtained. Additional thyroid testing (such as T3 including free versus total testing) is at the discretion of the site investigator. WOCBP should be counseled regarding acceptable birth control methods to utilize during treatment and after treatment completion. If prior to treatment after discussion with the subject it is felt by the treating physician there is a possibility the subject is pregnant a urine or serum pregnancy test should be repeated.

6.Optional collection of tumor tissue from initial diagnosis to be shipped prior to D30 safety visit. Optional collection of tissue for subjects undergoing a standard of care biopsy at progression. Subjects will be asked to consent to these collections. Unused samples after protocol specific testing is complete will be stored for future research in minimal residual disease and cancer biomarkers.

7: Mandatory: 34 mL whole blood for plasma ctDNA will be collected prior to treatment on Cycles 1-8, Day 30 Safety Visit, every 3 months for up to 2 years after treatment discontinuation and at progression. Subjects that proceed to pembrolizumab after completion of capecitabine/inavolisib will have an additional sample drawn prior to treatment on Cycle 9 Day 1. Unused samples after protocol specific testing is complete will be stored for future research in minimal residual disease and cancer biomarkers.

8: Patients will undergo ophthalmic examinations during the study treatment period and at study treatment discontinuation as clinically indicated per investigator discretion based on patient clinical status. The ophthalmic examination should consist of a full ophthalmic exam with dilation and refraction with specific attention paid to lens examination and detailed documentation. In addition, patients will be asked if they have experienced any significant visual changes, pain, or sensitivity to light at each clinic visit. Any new eye-related symptoms including significant change in vision, eye pain, or photophobia will be evaluated by an ophthalmologist.

9: Questionnaires may be administered electronically or by paper. No protocol deviation will be incurred if patients do not return a response to the questionnaires. Questionnaires will be completed at the Day 30 safety visit then at +6 months surveillance visit, ± 1 month.

10: Participants will receive genomically directed therapy. Inavolisib and capecitabine will be administered Cycles 1-8. After completion of inavolisib and capecitabine, standard of care with pembrolizumab will be considered for Cycles 9-17 (Total of 9 cycles). Cycle 9 Day 1 study treatment should occur 4 weeks ± 7 days after completion of Cycle 8 study treatment. If a subject assigned to Arm 1c does not meet additional Arm 1c criteria, the subject will be reassigned to Arm 2.

7.5 Arm 1d: DNA Repair + Immunotherapy = talazoparib + capecitabine +/- standard of care pembrolizumab

	Cycles 1-9[1]	Safety Visit[2]	Surveillance[3]
	D1 of each cycle (±3 days)	30/90 days (±7) after last dose	±1 month
REQUIRED ASSESSMENTS			
Informed consent for Arm assignment[4]	X[4]		
Complete physical examination	X	D30	X
Weight, BP and ECOG performance status	X	D30	X
Adverse event & con med assessment	X	X	
LABORATORY ASSESSMENTS			
CBC with differential[5]	X	D30	
CMP[5]	X	D30	
Calculated creatinine clearance	X		
Thyroid Function Testing[5]	X[5]	D30	
Urine pregnancy or serum HCG[5]	X[5]		
RADIOLOGY IMAGING			
Breast imaging (remaining native breast tissue only)[3]	X[3]		Yearly
TREATMENT EXPOSURE			
Genomically directed talazoparib+ capecitabine +/-pembrolizumab[9]	X		
CORRELATIVE SAMPLES			
Tumor from initial diagnosis – Optional[6]	X[6]		
Tumor from progression – Optional[6]		@progression	
Whole blood for Plasma ctDNA – Mandatory[7]	X[7]	D30	X[7]
QUESTIONNAIRES[8]			
Preference for ctDNA results		D30	X
Fear of cancer recurrence index (FCRI)		D30	X
Assessment of survivor concerns (ACS)		D30	X
Impact of Events scale (IES)		D30	X
PROMIS-29 HRQoL		D30	X
PROMIS Anxiety short form		D30	X

1: Cycle 1 Day 1 testing need not be repeated if obtained within 14 days of starting protocol therapy.

2: Participants in Arm 1 will have a safety visit 30 days (±7) after the last dose of protocol therapy. Subjects on Arm 1d will also have an assessment of adverse events 90 days (±7) after the last dose of study treatment. This assessment may be accomplished via email, phone call or other avenues as appropriate.

3: Radiology imaging performed is per standard of care based on investigator discretion. If at any time during treatment, recurrence is suspected, imaging should be performed based on investigator's discretion. During surveillance, monitoring for the development of either local (chest wall, axillary, or supraclavicular nodes) or distant recurrent disease is based on investigator's discretion. Complete physical exam including weight, and BP should be performed at least once every 3 months for the first two years, then at least every 6 months during years 3-5 after Treatment Discontinuation. At disease progression, participant should be followed for survival only. If there are concerns for recurrence upon physical exam, imaging should be performed to confirm. Surveillance visits are calculated from the last visit, not treatment discontinuation.

4: Participants will complete a treatment specific consent prior to Cycle 1 Day 1 based on the Arm they are assigned.

5: CBC with platelet and differential (white blood cell count, absolute neutrophil count, hemoglobin and platelet count). Serum chemistries (creatinine, glucose, total protein, blood urea nitrogen [BUN], total carbon dioxide [CO2], albumin, total bilirubin, alkaline phosphatase, and aspartate transaminase [AST] and alanine transaminase [ALT]) and electrolytes (total calcium, chloride, potassium, sodium). Thyroid Function testing should be performed just prior to first dose of pembrolizumab and then every 2 cycles. TSH and T4 will be obtained. Additional thyroid testing (such as T3 including free versus total testing) is at the discretion of the site investigator. WOCBP should be counseled regarding acceptable birth control methods to utilize during treatment and after treatment completion. If prior to treatment after discussion with the subject it is felt by the treating physician there is a possibility the subject is pregnant a urine or serum pregnancy test should be repeated.

6: Optional collection of tumor tissue from initial diagnosis to be shipped prior to D30 safety visit. Optional collection of tissue for subjects undergoing a standard of care biopsy at progression. Subjects will be asked to consent to these collections. Unused samples after protocol specific testing is complete will be stored for future research in minimal residual disease and cancer biomarkers.

7: Mandatory: 34 mL whole blood for plasma ctDNA will be collected prior to treatment on Cycles 1-8, Treatment Discontinuation (Safety Visit), every 3 months for up to 2 years after treatment discontinuation and at progression. Unused samples after protocol specific testing is complete will be stored for future research in minimal residual disease and cancer biomarkers.

8: Questionnaires may be administered electronically or by paper. No protocol deviation will be incurred if patients do not return a response to the questionnaires. Questionnaires will be completed at treatment discontinuation at +6 months surveillance visit, ± 1 month.

9: Participants will receive genomically directed therapy. Talazoparib and capecitabine and standard of care pembrolizumab will be administered Cycles 1-8. An additional dose of standard of care pembrolizumab alone is permitted on Cycle 9 (per KEYNOTE 522) if deemed appropriate by treating provider.

7.6 Arm 2

	On Study[1]	Treatment Discontinuation	Surveillance[2]
	D1	30 days (±7) after last dose	±1 month
REQUIRED ASSESSMENTS			
Complete physical examination	Repeat as needed based on FDA label and standard practice		X
Weight and BP			X
Adverse event & concomitant medication assessment[6]			
LABORATORY ASSESSMENTS			
CBC with differential	Repeat as needed based on FDA label and standard practice		
CMP			
Calculated creatinine clearance			
RADIOLOGY IMAGING			
Breast imaging (remaining native breast tissue only)[2]	X[2]		Yearly
TREATMENT EXPOSURE			
Capecitabine or treatment of physician's choice[1]	X		
CORRELATIVE SAMPLES			
Tumor from initial diagnosis – Optional[3]	X[3]		
Tumor from progression – Optional[3]		@progression	
Whole blood for Plasma ctDNA – Mandatory[4]	X[4]	X[4]	X[4]
QUESTIONNAIRES[5]			
Preference for ctDNA results		X	X
Fear of cancer recurrence index (FCRI)		X	X
Assessment of survivor concerns (ACS)		X	X
Impact of Events scale (IES)		X	X
PROMIS-29 HRQoL		X	X
PROMIS Anxiety short form		X	X

1: Arm 2 subjects have plasma ctDNA positive but do not have a genomically driven treatment option. Pembrolizumab and/or capecitabine, or treatment of physician's choice will be given. Dose, schedule and duration of treatment to be determined by treating physician. Administration and management of side effects will be handled as standard of care per institutional guidelines. Information regarding treatment administration and laboratory data will be entered into the EDC system.

2: Radiology imaging performed is per standard of care based on investigator discretion. If at any time during treatment, recurrence is suspected, imaging should be performed based on investigator's discretion. During surveillance, monitoring for the development of either local (chest wall, axillary, or supraclavicular nodes) or distant recurrent disease is based on investigator's discretion. Complete physical exam including weight and BP completed at least once every 3 months for the first two years, then at least every 6 months during years 3-5 after Treatment Discontinuation. This information is required if available but if not collected does not constitute a deviation. At disease progression, participant should be followed for survival only. Surveillance visits are standard of care and are calculated from the last visit, not treatment discontinuation (with the exception of M3).

3: Optional collection of tumor tissue from initial diagnosis to be shipped prior to D30 safety visit. Optional collection of tissue for subjects undergoing a standard of care biopsy at progression. Subjects will be asked to consent to these collections. Unused samples after protocol specific testing is complete will be stored for future research in minimal residual disease and cancer biomarkers.

4: Mandatory 34 mL whole blood for plasma ctDNA will be collected at the 1st routine care visit, 3 month visit, 6 month visit, Treatment Discontinuation, and every 3 months for up to 2 years after treatment discontinuation. While ideally, all timepoints should be collected it will not be considered a deviation if the 1st routine care visit, 3 month visit, 6 month visit, Treatment Discontinuation and post-treatment samples are not drawn. Unused samples after protocol specific testing is complete will be stored for future research in minimal residual disease and cancer biomarkers.

5: Questionnaires may be administered electronically or by paper. No protocol deviation will be incurred if patients do not return a response to the questionnaires. Questionnaires will be completed at treatment discontinuation and at +6 months surveillance visit, ± 1 month.

6: Arm 2 subjects are undergoing treatment that is considered standard of care, recording and reporting of adverse events and concomitant medications will only be done when the AE requires dose modification of the standard of care drug.

7.7 Arm 3

	On Study[1]	Treatment Discontinuation	Surveillance[2]
	D1	30 days (±7) after last dose	±1 month
REQUIRED ASSESSMENTS			
Complete physical examination	Repeat as needed based on FDA labels and standard practice		X
Weight and BP			X
Adverse event & concomitant medication assessment[6]			
LABORATORY ASSESSMENTS			
CBC with differential	Repeat as needed based on FDA label and standard practice		
CMP			
Calculated creatinine clearance			
RADIOLOGY IMAGING			
Breast imaging (remaining native breast tissue only)[2]	X[2]		Yearly
TREATMENT EXPOSURE			
Observation, capecitabine or treatment of physician's choice[1]	X		
CORRELATIVE SAMPLES			
Tumor from initial diagnosis – Optional[3]	X[3]	X[3]	
Tumor from progression – Optional[3]		@progression	
Whole blood for Plasma ctDNA – Mandatory[4]	X[4]	X[4]	X[4]
QUESTIONNAIRES[5]			
Preference for ctDNA results		X	X
Fear of cancer recurrence index (FCRI)		X	X
Assessment of survivor concerns (ACS)		X	X
Impact of Events scale (IES)		X	X
PROMIS-29 HRQoL		X	X
PROMIS Anxiety short form		X	X

1: Arm 3 subjects have plasma ctDNA negative. Pembrolizumab and/or capecitabine, or treatment of physician's choice will be given. Dose, schedule and duration of treatment to be determined by treating physician. Administration and management of side effects will be handled as standard of care per institutional guidelines. Information regarding treatment administration and laboratory data will be entered into the EDC system.

2: Radiology imaging performed is per standard of care based on investigator discretion. If at any time during treatment, recurrence is suspected, imaging should be performed at investigator's discretion. During surveillance, monitoring for the development of either local (chest wall, axillary, or supraclavicular nodes) or distant recurrent disease is based on investigator's discretion. Complete physical exam including weight and BP should be performed at least once every 3 months for the first two years, then at least every 6 months during years 3-5 after Treatment Discontinuation. This information is required if available but if not collected does not constitute a deviation. At disease progression, participant should be followed for survival only. Surveillance visits are standard of care and are calculated from the last visit, not treatment discontinuation (with the exception of M3).

3: Optional collection of tumor tissue from initial diagnosis to be shipped prior to D30 safety visit. Optional collection of tissue for subjects undergoing a standard of care biopsy at progression. Subjects will be asked to consent to these collections. Unused samples after protocol specific testing is complete will be stored for future research in minimal residual disease and cancer biomarkers.

4: Mandatory 34 mL whole blood for plasma ctDNA will be collected at 1st routine care visit, 3 month visit, 6 month visit, Treatment Discontinuation, and every 3 months for up to 2 years after treatment discontinuation and progression. While ideally, all timepoints should be collected it will not be considered a deviation if the 1st routine care visit, 3 month visit, 6 month visit, Treatment Discontinuation and post-treatment samples are not drawn. Unused samples after protocol specific testing is complete will be stored for future research in minimal residual disease and cancer biomarkers.

5: Questionnaires may be administered electronically or by paper. No protocol deviation will be incurred if patients do not return a response to the questionnaires. Questionnaires will be completed at treatment discontinuation at +6 months surveillance visit, ± 1 month.

6: Arm 3 subjects are undergoing observation or treatment that is considered standard of care, recording and reporting of adverse events and concomitant medications will only be done when the AE requires dose modification of the standard of care drug.

8 CRITERIA FOR DISEASE EVALUATION

DFS is defined as the duration of time from assignment to an Arm to time of a DFS event, defined as local failure (invasive), regional failure, distant failure, contralateral breast cancer (invasive or non-invasive), or death from any cause. The diagnosis of local or distant recurrence should ideally be pathologically confirmed, however if biopsy if not possible, radiology confirmation by CT, MRI, or PET scan is acceptable.

9 BIOLOGICAL SAMPLES

HCRN will provide sample collection kits and shipping supplies for tissue sample submissions and for blood samples collected for genomic and correlative studies. All sample labels will only include the HCRN participant study ID#, date/time of collection and sample type. No personal identifiers will be included. Refer to the clinical laboratory manual (CLM) associated with this protocol for collection, processing, labeling, and shipping instructions.

9.1 Plasma for ctDNA Sequencing (Required)

Information for both Foundation One testing assays is included in this section. The original assay (FoundationOne® Liquid CDx) will be utilized by a site until IRB approval is obtained by that site for the protocol amendment in which the new assay is described.

9.1.1 FoundationOne® Liquid CDx assay; Plasma for ctDNA sequencing

ctDNA sequencing of plasma will be performed using the FoundationOne® Liquid CDx assay. This assay interrogates over 300 cancer genes as well as microsatellite instability (MSI) and tumor mutation (TMB). The presence or absence of somatic mutation in the results will be used to assign patients to the ctDNA positive or ctDNA negative arm.

9.1.1.1 To determine ctDNA-positivity when using this assay, the following rules will be applied:

The patient will be considered ctDNA-positive if any apply:

1. Detection of a circulating tumor fraction > 0% as determined by the FoundationOne® Liquid CDx tumor fraction algorithm.
2. Detection of point mutation(s) or insertion/deletion(s) present at a variant allele frequency (< 40% or > 60%).
3. Detection of point mutation(s) or insertion/deletion(s) present at a variant allele frequency between 40-60% if the mutation is not present in ClinVar or dbSNP as a known germline alteration.
4. Detection of copy number amplifications or deletions
5. Detection of a genomic rearrangement event
6. Detection of ctDNA as determined by aneuploidy model
7. The above will confer the status of ctDNA positive unless the ctDNA positivity call is uniformly felt to be the result of clonal hematopoiesis of indeterminate potential (CHIP); (See #9 below for definition of call for CHIP).
8. The co-occurrence of CHIP with other findings supporting ctDNA positivity, will retain a call of ctDNA positive.
9. A panel of experts lead by co-investigators will ultimately adjudicate the call of ctDNA positivity or negativity based on the above criteria. Confounding variables, such as the presence of these findings representing CHIP, will be considered by the expert panel and may result in a call of ctDNA negative.

9.1.2 FoundationOne Tracker Assay; Plasma for ctDNA sequencing

ctDNA sequencing of plasma will be performed using the FoundationOneTracker. The presence or absence of somatic mutation in the results will be used to assign patients to the ctDNA positive or ctDNA negative arm.

9.1.2.1 To determine ctDNA-positivity, the following rules will be applied:

The patient will be considered ctDNA-positive if any apply:

1. ctDNA status (detected/not detected) as determined by FoundationOne Tracker.
2. Detection of point mutation(s) or insertion/deletion(s) present at a variant allele frequency (< 40% or > 60%).
3. Detection of point mutation(s) or insertion/deletion(s) present at a variant allele frequency between 40-60% if the mutation is not present in ClinVar or dbSNP as a known germline alteration.
4. The above will confer the status of ctDNA positive unless the ctDNA positivity call is uniformly felt to be the result of clonal hematopoiesis of indeterminate potential (CHIP); (See #6 below for definition of call for CHIP).
5. The co-occurrence of CHIP with other findings supporting ctDNA positivity, will retain a call of ctDNA positive.
6. A panel of experts lead by co-investigators will ultimately adjudicate the call of ctDNA positivity or negativity based on the above criteria. Confounding variables, such as the presence of these findings representing CHIP, will be considered by the expert panel and may result in a call of ctDNA negative.

9.2 Tumor from Definitive Surgery for Next Generation Sequencing (Required)

9.2.1 Tumor tissue for NGS will be obtained as outlined in Section 7.

The patient's residual tumor at time of definitive surgery will undergo NGS using the FoundationOne®CDx test. This assay interrogates over 300 cancer genes, MSI, TMB, as well as immunohistochemistry for PD-L1 (F1CDx + Ventana SP142 + F1LCDx **OR** F1CDx + Dako 22C3 + F1Tracker monitoring test depending upon change in assay). PD-L1 CPS using the Dako 22c3 antibody. Results from this will be used to assign patients to genomically directed therapy in conjunction with the ctDNA results.

Subjects must consent to allow submission of archived tumor tissue sample from definitive surgery for next generation sequencing of the tumor. Tumor block is preferred however 14 unstained slides + 1H&E can be submitted if necessary.

9.3 FoundationOne Assays

9.3.1 FoundationOneLiquidCDx

The **FoundationOneLiquid®CDx** test is a liquid biopsy test for solid tumors that analyzes ctDNA in a CAP/CLIA laboratory. It uses a hybrid-capture, NGS test method combined with proprietary computational algorithms that enable accurate variant calls by discriminating sequencing artifacts from bona fide mutations. It identifies four classes of genomic alterations (base substitution, insertions and deletions, copy number alterations, and rearrangements) in over 300 commonly altered oncogenes along with the detection of MSI and TMB. The assay has robust clinical performance for sensitivity and positive predictive value (PPV) and will be used to determine whether a patient is ctDNA+ or ctDNA- and also to assign patients to a genomic targeted therapy (along with the FoundationOne®CDx test).

9.3.2 FoundationOne Tracker

With advances in platform, we plan to move to a more sensitive ctDNA assay, the FoundationOne Tracker. The FoundationOne Tracker is a tissue informed assay that has improved the sensitivity for detecting minimal residual disease. Specifically, the FoundationOne Tracker uses a trusted and clinically relevant tissue-informed CGP baseline paired with personalized ctDNA -based assessment that empowers informed biomarker-guided treatment decisions. CtDNA-based disease monitoring with FoundationOne Tracker can serve as a sensitive biomarker for MRD and can accurately assess risk to support additional adjuvant or perioperative treatment. The FoundationOne Tracker is performed exclusively as a laboratory service as a custom-built, patient-specific assay for oncology that is based on patient-specific somatic variants (PSVs; substitutions and select indels) identified from tumor tissue testing and used to longitudinally track plasma circulating tumor DNA (ctDNA) abundance as a biomarker for tumor burden dynamics. Subjects eligible for FoundationOne Tracker have received a separate baseline NGS assay that tests a patient's formalin-fixed, paraffin-embedded (FFPE) tumor tissue. DNA is extracted from formalin-fixed, paraffin-embedded (FFPE) tumor tissue is sequenced using a tumor-tissue next-generation sequencing (NGS) assay targeting a cancer-related gene panel to identify somatic variants specific to the patient's tumor. These PSVs are used to design a patient-variant-specific multiplex PCR NGS assay. Whole blood samples from the patient are collected at certain timed intervals for plasma ctDNA measurement. Cell free DNA is extracted and sequenced using the patient-specific FoundationOne Tracker for ctDNA measurement. ctDNA sequencing data are analyzed and results are reported, including detection of mutations in ctDNA and mean tumor molecules per mL of plasma.

9.4 Samples for future research in minimal residual disease and cancer biomarkers

Participant consent will be obtained for additional samples for future research in minimal residual disease and cancer biomarkers. These samples and any unused samples after protocol specific testing is complete will be stored until the research analysis can be performed. **NOTE:** Participants will be asked to consent to allow storage of their DNA and RNA for future studies.

This includes:

- Tumor from initial diagnosis (sample collected prior to neoadjuvant chemotherapy): **Optional**
    - Formalin-fixed paraffin embedded tissue will be obtained after the participant is formally registered to the trial.
- Tumor from definitive surgery:
  Required for all Arms
    - Formalin-fixed paraffin embedded tissue will be obtained after the participant is formally registered to the trial.
- Tumor from progression:
  Optional
    - Formalin-fixed paraffin embedded tissue will be obtained a standard of care biopsy is performed at progression.
- Whole blood for genomic DNA:
  Required for all Arms
    - Whole blood will be collected at screening after consent is signed for Arm 2 and Arm 3 participants.
- Whole blood for plasma ctDNA:
  Required for all Arms
    - Whole blood will be collected at Screening after consent, Day 1 of Cycles 1-8, D30 safety visit, every 3 months up to 2 years after treatment discontinuation visit and progression for Arm 1. For Arm 2 and Arm 3, samples will be collected after arm assignment at their next routine care visit (Day 1) and at the 3 month visit, 6 month visit and Treatment

Discontinuation. While ideally, all timepoints should be collected it will not be considered a deviation if the 3 month visit, 6 month visit or Treatment Discontinuation samples are missed for Arm 2 and Arm 3 subjects.

Refer to the CLM associated with this protocol for collection, processing, labeling, and shipping instructions.

10 DRUG INFORMATION

10.1 Talazoparib

See the investigator's brochure for complete details regarding this medication.

Talazoparib is an inhibitor of poly (ADP-ribose) polymerase (PARP) enzymes, including PARP1 and PARP2, which play a role in DNA repair. In vitro studies with cancer cell lines that harbored defects in DNA repair genes, including BRCA 1 and 2, have shown that talazoparib-induced cytotoxicity may involve inhibition of PARP enzymatic activity and increased formation of PARP-DNA complexes resulting in DNA damage, decreased cell proliferation, and apoptosis. Talazoparib anti-tumor activity was observed in human patient-derived xenograft breast cancer tumor models that expressed mutated or wild-type BRCA 1 and 2.

10.1.2 Supplier/How Supplied

Talazoparib capsules are supplied by Pfizer, Inc at no charge to subjects participating in this clinical trial as described in Section 5.

The drug product is a capsule formulation composed of a blend of talazoparib tosylate drug substance and silicified microcrystalline cellulose filled into a hypromellose capsule. The capsules are presented in strengths of 0.25 mg, and 1.0 mg (free base equivalent), distinguished by capsule color and described in milligrams per capsule. Capsules are provided in high-density polyethylene (HDPE) bottles, with induction-sealed closures, containing 30 drug product capsules of a single strength.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

10.1.3 Storage

Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F).

10.1.4 Adverse Events

See the current investigator's brochure for complete details regarding adverse events related to this medication. Most common adverse reactions (≥10%) were alopecia, diarrhea, dizziness, dysguesia, dyspepsia, fatigue, headache, hyperglycemia, increase liver function tests, hypocalcemia, loss of appetite, myelosuppression, nausea, vomiting, abdominal pain, and hyperbilirubinemia. Please see package insert for a detailed list of side effects.

Cases of MDS and AML have been reported in patients treated with talazoparib.

10.2 Inavolisib

See the current investigator's brochure for complete details regarding this medication.

Inavolisib (GDC-0077) is a potent selective inhibitor of the Class I PI3K α isoform (p110α) and a specific degrader of mutant p110α, as an anti-cancer agent. Nonclinical studies demonstrate that GDC-0077 specifically degrades mutant p110α, inhibits proliferation and induces apoptosis of *PIK3CA*-mutant breast cancer cell lines, inhibits tumor growth in human breast cancer xenograft models harboring *PIK3CA* mutations, and reduces downstream PI3K pathway markers, including phosphorylated form of protein kinase B (pAKT), PRAS40 phosphorylated at Threonine 246 (pPRAS40), and S6RP phosphorylated at Serine 235/236 (pS6RP). Efficacy was improved when GDC-0077 was used in combination with standard-of-care therapies for hormone receptor positive (HR+) breast cancer, including fulvestrant (endocrine therapy) or palbociclib (CDK4/6 inhibitor), in a *PIK3CA*-mutant human breast cancer xenograft model. Together, these data provide rationale for evaluating GDC-0077 as a single agent and in combination with standard-of-care endocrine and targeted therapies that may provide additional benefit to patients with locally advanced or metastatic, *PIK3CA*-mutant cancer, including HR+ breast cancer.

10.2.1 Supplier/How Supplied

Genentech will supply inavolisib at no charge to subjects participating in this clinical trial as described in Section 5.

Inavolisib (GDC-0077) drug product is intended for oral administration and will be supplied as film-coated tablets in two strengths (3 mg and 9 mg).

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

10.2.2 Storage and Stability

Recommended storage configuration at or below 86F (30C) when protected from light. For batch-specific instructions and information on shelf life, refer to the packaging.

10.2.3 Adverse Events

See the current investigator's brochure for complete details regarding adverse events related to this medication. The most common side effects of inavolisib occurring in more than 20% of patients are: gastrointestinal toxicity (nausea, vomiting, diarrhea, stomatitis/mucositis), hyperglycemia, decreased appetite, fatigue, neutropenia, dysgeusia, anemia, constipation and headache. Please see current IB for a detailed list of side effects.

10.3 Capecitabine

See the current package insert for complete details regarding this medication.

Enzymes convert capecitabine to 5-fluorouracil (5-FU) in vivo. Both normal and tumor cells metabolize 5-FU to 5-fluoro-2'-deoxyuridine monophosphate (FdUMP) and 5-fluorouridine triphosphate (FUTP). These metabolites cause cell injury by two different mechanisms. First, FdUMP and the folate cofactor, N5-10-methylenetetrahydrofolate, bind to thymidylate synthase (TS) to form a covalently bound ternary complex. This binding inhibits the formation of thymidylate from 2'-deoxyuridylate. Thymidylate is the necessary precursor of thymidine triphosphate, which is essential for the synthesis of DNA, so that a deficiency of this compound can inhibit cell division. Second, nuclear transcriptional enzymes can

mistakenly incorporate FUTP in place of uridine triphosphate (UTP) during the synthesis of RNA. This metabolic error can interfere with RNA processing and protein synthesis.

10.3.1 Supplier/How Supplied

Genentech will supply capecitabine at no charge to subjects participating in this clinical trial who are ctDNA positive and assigned to the genomically directed arm (Arm 1). Patients in Arm 2 (ctDNA positive but no actionable target) and Arm 3 (ctDNA negative) will receive the treatment of physician's choice and this will be considered standard of care; thus capecitabine will not be supplied. See Section 5 for additional details.

Tablets: 500 mg Color: Peach Engraving: XELODA on one side and 500 on the other 500 mg tablets are packaged in bottles of 120 (NDC 0004-1101-50). Only 500mg tablets will be used for this trial.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

10.3.2 Storage and Stability

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F). KEEP TIGHTLY CLOSED. Care should be exercised in the handling of capecitabine. Capecitabine tablets should not be cut or crushed. Procedures for the proper handling and disposal of anticancer drugs should be considered. Any unused product should be disposed of in accordance with local requirements, or drug take back programs. Several guidelines on the subject have been published see package insert.

10.3.3 Adverse Events

See the current package insert for complete details regarding adverse events related to this medication. Most common adverse reactions (≥30%) were diarrhea, hand and foot syndrome, nausea, vomiting, abdominal pain, fatigue/weakness, and hyperbilirubinemia. Please see package insert for a detailed list of side effects.

10.4 Pembrolizumab

Pembrolizumab is standard of care and thus will not be supplied to patients on this study.

11 ADVERSE EVENT MANAGEMENT

Adverse events will be collected and reported as described below for the experimental Arm 1 only. The descriptions and grading scales found in the NCI CTCAE v5 will be utilized for AE assessment. Arm 2 subjects are undergoing treatment that is considered standard of care, recording and reporting of adverse events will only be done when the AE requires dose modification of the standard of care drug. Arm 3 subjects are undergoing observation or treatment that is considered standard of care, recording and reporting of adverse events will only be done when the AE requires dose modification of the standard of care drug.

11.1 Definitions

Safety assessments will consist of monitoring and reporting adverse events (AEs) and serious adverse events (SAEs) per protocol. This includes all events of death, and any study specific issue of concern. The investigator is responsible for ensuring that all AEs and SAEs are observed or reported during the study are collected and reported to the FD, appropriate IRB(s), and Genentech, Inc. in accordance with CFR 312.32 (IND Safety Reports).

11.1.1 Adverse Event (AE)

An AE is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product (IMP) or other protocol-imposed intervention, regardless of attribution.

This includes the following:

- AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with TNBC that were not present prior to the AE reporting period.
- Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as cardiac catheterizations)
- If applicable, AEs that occur prior to assignment of study treatment associated with medication washout, no treatment run-in, or other protocol-mandated intervention.
- Preexisting medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period.

Hospitalization for elective surgery or routine clinical procedures that are not the result of an AE (e.g., surgical insertion of central line) should not be recorded as an AE.

Disease progression should not be recorded as an AE, unless it is attributable to the study regimen by the site investigator.

11.1.2 Definition of Serious Adverse Event (SAE)

A serious adverse event is any untoward medical occurrence resulting in one or more of the following:

- Results in death. All deaths that occur during the protocol-specified AE reporting period, regardless of attribution, will be reported to the appropriate parties. When recording a death, the event or condition that caused or contributed to the fatal outcome should be reported as the single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, report “Unexplained Death” **NOTE**: Death due to disease progression should not be reported as a SAE, unless it is attributable by the site investigator to the study drug(s).
- Is life-threatening (defined as an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization or prolongation of existing hospitalization. **NOTE:** Hospitalization for anticipated or protocol specified procedures such as administration of chemotherapy, central line insertion, metastasis interventional therapy, resection of primary tumor, or elective surgery, will not be considered serious adverse events.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly or birth defect.
- Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the participant or may require intervention (e.g., medical, surgical) to prevent one of the other serious outcomes listed in the definition above). Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions not resulting in hospitalization; or the development of drug dependency or drug abuse.

- If a subject is hospitalized to undergo a medical or surgical procedure as a result of an AE, the event responsible for the procedure, not the procedure itself, should be reported as the SAE. For example, if a subject is hospitalized to undergo coronary bypass surgery, record the heart condition that necessitated the bypass as the SAE.
    - Hospitalizations for the following reasons do not require reporting:
    - Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for preexisting conditions
    - Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study or
    - Hospitalization or prolonged hospitalization for scheduled therapy of the target disease of the study

11.1.3 Adverse Events of Special Interest (AESIs)

AESIs are a subset of Events to Monitor (EtMs) of scientific and medical concern specific to the product, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor is required. Such an event might require further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the trial Sponsor to other parties (e.g., Regulatory Authorities) may also be warranted.

Subjects will be monitored for AESIs from the time of signed informed consent until 90 days after discontinuation of inavolisib and/or atezolizumab. The following AEs are considered of special interest and must be reported to the Genentech Drug Safety utilizing the timeframe outlined in the SAE reporting section, irrespective of regulatory seriousness criteria:

Adverse events of special interest for this study include the following:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law and based on the following observations:
    - Treatment-emergent ALT or AST $> 3 \times$ ULN (or > 3 baseline value in disease states where LFTs may be elevated at baseline) in combination with total bilirubin $> 2 \times$ ULN (of which $\geq 35\%$ is direct bilirubin)
    - Treatment-emergent ALT or AST $> 3 \times$ ULN (or $> 3 \times$ baseline value in disease states where LFTs may be elevated at baseline) in combination with clinical jaundice
- Suspected transmission of an infectious agent by the study treatment, as defined below
- Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of study treatment is suspected.

The Inavolisib Events of Special Interest are:

- Grade ≥ 3 fasting hyperglycemia
- Grade ≥ 3 ALT/AST elevations
- Grade ≥ 2 colitis or enterocolitis
- Grade ≥ 3 diarrhea
- Grade ≥ 3 rash
- Grade ≥ 2 pneumonitis
- Grade ≥ 3 stomatitis or mucosal inflammation

11.1.4 Expectedness of Adverse Events

An adverse event not mentioned in the investigator's brochure or package insert or the specificity or severity of which is not consistent with the investigator's brochure or package insert is considered. Expected adverse events are those adverse events that are listed or characterized in the Package Insert (P.I) or current Investigator Brochure (I.B). Unexpected adverse events are those not listed in the P.I or current I.B or not identified. This includes adverse events for which the specificity or severity is not consistent with the description in the P.I. or I.B. For example, under this definition, hepatic necrosis would be unexpected if the P.I. or I.B. only referred to elevated hepatic enzymes or hepatitis.

11.1.5 Relatedness and Assessment of Adverse Events

All AEs and SAEs whether volunteered by the subject, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means will be reported appropriately. Each reported AE or SAE will be described by its duration (i.e., start and end dates), regulatory seriousness criteria if applicable, suspected relationship to inavolisib, talazoparib or capecitabine and actions taken.

To ensure consistency of AE and SAE causality assessments, investigators should apply the following general guideline:

Yes: There is a plausible temporal relationship between the onset of the AE and administration of the inavolisib, talazoparib or capecitabine, and the AE cannot be readily explained by the subject's clinical state, intercurrent illness, or concomitant therapies; and/or the AE follows a known pattern of response to the inavolisib, talazoparib or capecitabine or with similar treatments; and/or the AE abates or resolves upon discontinuation of the inavolisib, talazoparib or capecitabine or dose reduction and, if applicable, reappears upon re- challenge.

No: Evidence exists that the AE has an etiology other than the inavolisib, talazoparib or capecitabine (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the AE has no plausible temporal relationship to inavolisib, talazoparib or capecitabine administration (e.g., cancer diagnosed 2 days after first dose of study drug).

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

AEs will be categorized according to the likelihood that they are related to the study drug(s). Specifically, they will be categorized using the following terms:

Unrelated	Adverse Event is ***not related*** to the study drug(s)
Unlikely	Adverse Event is ***doubtfully related*** to the study drug(s)
Possible	Adverse Event ***may be related*** to the study drug(s)
Probable	Adverse Event is ***likely related*** to the study drug(s)
Definite	Adverse Event is ***clearly related*** to the study drug(s)

11.1.6 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE v5.0 will be used for assessing adverse event severity. Below Table should be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b,c]
4	Life-threatening consequences or urgent intervention indicated d
5	Death related to adverse event [d]

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.
Note: Based on the most recent version of NCI CTCAE v5.0 which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

- Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
- Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.
- If an event is assessed as a "significant medical event," it must be reported as a serious adverse event
- Grade 4 and 5 events must be reported as serious adverse events

11.2 Reporting

11.2.1 Adverse Event (AE) Reporting

- AEs will be recorded from time of initiation of study drug until 30 days after discontinuation of study drug(s) or until a new anti-cancer treatment starts, whichever occurs first. For subjects on Treatment Arm 1d the timeframe is 90 days.
- AEs will be recorded regardless of whether or not they are considered related to the study drug(s).
- All AEs will be recorded in the subject's medical record and on the appropriate study specific eCRF form within the EDC system.

11.2.2 Serious Adverse Event (SAE) Reporting

11.2.2.1 Study Center (Site) Requirements for Reporting SAEs to HCRN

- SAEs will be reported from time of signed informed consent until 30 days after discontinuation of study drug(s) or until a new anti-cancer treatment starts, whichever occurs first. For subjects on Treatment Arm 1d, the timeframe is 90 days.
- SAEs will be reported on the SAE Submission Form **within 1 business day** of discovery of the event.

- SAEs include events related and unrelated to the study drug(s).
- All SAEs will be recorded in the subject's medical record and on the appropriate study specific eCRF form within the EDC system.

The site will submit the completed SAE Submission Form to HCRN **within 1 business day** of discovery of the event**.** The form will be submitted to HCRN electronically to safety@hoosiercancer.org. The site investigator is responsible for informing the IRB and/or other local regulatory bodies as per local requirements.

The original copy of the SAE Submission Form and the email correspondence must be kept within the study file at the study site.

Once the SAE has resolved (see resolution guidelines listed above), sites must submit a follow-up SAE Submission Form within a reasonable timeframe to HCRN electronically to safety@hoosiercancer.org.

11.2.2.2 HCRN Requirements for Reporting SAEs to Genentech (GNE)

HCRN will report all SAEs to GNE **within 1 business day** of receipt of the SAE Submission Form from a site. Follow-up information will be provided to GNE as it is received from site. Genentech/Roche Drug Safety: Fax: (650) 225-4682 or (650) 225-4630 or email: usds_aereporting-d@gene.com.

11.2.2.3 HCRN Requirements for Reporting SAEs to Pfizer

HCRN will report all SAEs to Pfizer **within 1 business day** of receipt of the SAE Submission Form from a site. Follow-up information will be provided to Pfizer as it is received from site. Pfizer Drug Safety: Via fax: Pfizer U.S. Clinical Trial Department 1-866-997-8322 or email: USA.AEReporting@pfizer.com

11.2.3 Reporting AEs and SAEs in relation to COVID-19

For any study participants exhibiting symptoms consistent with COVID-19, these need to be captured as adverse events according to the established safety reporting system specified. Please consult with HCRN for questions related to the reporting of COVID-19 symptoms. In the event a participant tests positive for COVID-19, or if no testing is available, ensure appropriate documentation of the AE and/or SAE of COVID-19 is reflected in the eCRF.

11.3 Sponsor-Investigator Responsibilities

HCRN will send a SAE summary to the sponsor-investigator **within 1 business day** of receipt of SAE Submission Form from a site. The sponsor-investigator will promptly review the SAE summary and assess for expectedness and relatedness.

11.4 Procedures for Eliciting and Recording Adverse Events

11.4.1 Eliciting Adverse Events

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

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

11.4.2 Specific Instructions for Recording Adverse Events

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

11.4.2.1 Diagnosis vs. Signs and Symptoms

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

11.4.2.2 Post-Study Adverse Events

For studies involving collection of survival data/ follow up until progression free period/ Extended follow up period (2-years) the investigator after the end of the adverse event reporting period (defined as 30 days after the last dose of study drug) should report all deaths, (regardless of cause), and any serious adverse event including development of cancer or a congenital anomaly in a subsequently conceived offspring of a female subject [add if applicable-including pregnancy occurring in the partner of a male study subject] who participated in the study that is believed to be related to prior exposure to study drug.

11.5 Case Transmission Verification of Single Case Reports

Case Transmission Verification will be performed by both parties during this period to ensure successful transmission of Single case reports.

HCRN and the sponsor-investigator agrees to conduct the Case Transmission verification to ensure that all single case reports have been adequately received by Genentech via HCRN emailing Genentech a Quarterly line-listing documenting single case reports sent by HCRN to Genentech in the preceding time period. The periodic line-listing will be exchanged within seven (7) calendar days of the end of the agreed time period. Confirmation of receipt should be received within the time period mutually agreed upon. If discrepancies are identified, the sponsor-investigator, HCRN and Genentech will cooperate in resolving the discrepancies. The responsible individuals for each party shall handle the matter on a case-by-case basis until satisfactory resolution.

Following Case Transmission Verification, single case reports which have not been received by Genentech shall be forwarded by HCRN to Genentech within five (5) calendar days from request by Genentech. At the end of the study, a final cumulative Case Transmission Verification report will be sent to Genentech

11.6 Special Situation Reports

In addition to all SAEs, pregnancy reports and AESIs, the following other Special Situations Reports should be collected even in the absence of an Adverse Event and transmitted to Genentech **within thirty (30) calendar days** for Capecitabine and **one (1) business day** for Inavolisib:

- Data related to the Product usage during breastfeeding
- Data related to overdose, abuse, misuse or medication error (including potentially exposed or intercepted medication errors)
- In addition, reasonable attempts should be made to obtain and submit the age or age group of the patient, in order to be able to identify potential safety signals specific to a particular population

11.6.1 Pregnancy

If a female subject becomes pregnant while receiving the study drug or within 5 months after the last dose of study drug, or if the female partner of a male study subject becomes pregnant while the study subject is receiving the study drug or within 5 months after the last dose of study drug, or lactation exposure occurs, a report should be completed and expeditiously submitted to Genentech and Pfizer.

Follow-up to obtain the outcome of the pregnancy should also occur. Abortion, whether accidental, therapeutic, or spontaneous, should always be classified as serious, and expeditiously reported as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a female subject exposed to the study drug should be reported as an SAE.

Any reports of pregnancy (including pregnancy occurring in the partner of a male study subject), where the fetus may have been exposed to the Product, shall be transmitted to Genentech and Pfizer within thirty (30) calendar days of the awareness date. Pregnancies will be followed up until the outcome of the pregnancy is known, whenever possible, based upon due diligence taken to obtain the follow-up information.

11.6.2 Medication Overdose

Any overdose, or study drug administration error that results in an AE, even if it does not meet the definition of serious, requires reporting **within one 1 business day** to both Funders.

11.6.3 Product Complaints

All Product Complaints (with or without an AE) shall be forwarded to Genentech **within thirty (30) calendar days** for Capecitabine and **one (1) business day** for Inavolisib of the awareness date.

A Product Complaint is defined as any written or oral information received from a complainant that alleges deficiencies related to identity, quality, safety, strength, purity, reliability, durability, effectiveness, or performance of a product after it has been released and distributed to the commercial market or clinical trial.

11.7 HCRN Responsibilities to FDA

HCRN will manage the Investigational New Drug Application (IND) associated with this protocol on behalf of the sponsor-investigator. HCRN will cross-reference this submission to Genentech and Pfizer's parent INDs at the time of submission. Additionally, all written IND Safety Reports submitted to the FDA by HCRN on behalf of the sponsor-investigator must also be faxed to Genentech/Roche Drug Safety: Fax: (650) 225-4682 or (650) 225-4630 and/or Pfizer Drug Safety: Fax: Pfizer U.S. Clinical Trial Department 1-866-997-8322 or email: USA.AEReporting@pfizer.com

HCRN will be responsible for all communication with the FDA in accordance with 21CFR312 including but not limited to the 7 and 15 Day Reports, as well as an Annual Progress Report. A copy of these documents will be available to Genentech and/or Pfizer upon request.

11.8 IND Safety Reports Unrelated to this Trial

Genentech and Pfizer will provide to HCRN IND safety reports from external studies that involve the study drug(s) per their guidelines. HCRN will forward safety reports to the sponsor-investigator who will review these reports and determine if revisions are needed to the protocol or consent. HCRN will forward these reports to participating sites **within 1 business day** of receiving the sponsor-investigator's review. Based on the sponsor-investigator's review, applicable changes will be made to the protocol and informed consent document (if required). All IND safety reports will also be made available to sites via the EDC system. Upon receipt from HCRN, site investigators (or designees) are responsible for submitting these safety reports to their respective IRBs, as per their IRB policies.

12 STATISTICAL CONSIDERATIONS

12.1 Sample Size Justification

This trial was designed to demonstrate that genomically directed therapy in the plasma ctDNA positive arm results in superior outcomes compared with the outcomes of those in BRE12-158. We propose a three arm therapeutic design with the following characteristics to demonstrate superior outcome in the genomically directed arm as the primary endpoint. The sample size of 90 was calculated using the One-Arm Survival tool from SWOG based on survival probability. We took a conservative sample size from those two methods, to ensure we have enough power to reach our conclusion. Either the one-sample log-rank test or the same method (Brookmeyer-Crowley one-sample test) used in power calculation can be used in the statistical test. The assumptions underlying the power calculation are uniform accrual over time, no loss to follow-up and exponential distribution of event times.

ARM 1

- Sample size: 90
- We assume a DFS probability of 50% at 24-months in the historical control from BRE12-158. We also assume the DFS probability is at least 62.5% for patients with genomically directed therapy (ARM 1).
- We will conclude that a survival probability of >50% at 24-months in the genomically directed arm will be considered a positive trial.

Length of the accrual period: 36 months

Length of the follow-up period for the primary endpoint: 24 months

- Alpha=0.05 for one-sided test
- With 90 patients in Arm 1, we will have 80% power to demonstrate superiority in Arm 1 vs. 50% 2-yr DFS seen in the prior trial, BRE12-158

ARM 2

Assuming 90 patients are required for the primary endpoint and assuming 78% of those who are ctDNA positive will fit into a genomic basket, 25 patients will not fit into a basket and be placed into ARM 2. Prospective evaluation of the treatment of physician's choice will serve as an informal comparator for outcomes with traditional therapy in the plasma positive population. There will be insufficient numbers for formal comparisons and thus only descriptive statistics and comparisons will be made.

ARM 3

Assuming 115 ctDNA positive patients will be required to fulfill the primary endpoint and assuming 35% of all patients screened in this population will be ctDNA positive, 62 patients will be ctDNA negative and fall into ARM 3. There will be insufficient numbers for formal comparisons and thus only descriptive statistics and comparisons will be made.

SCREENING

Assuming 177 patients will require a successful ctDNA test result and assuming 10% ctDNA testing failure + patient dropout, 195 patients will be needed to screen for this trial.

12.2 Participant Characteristics

Participant characteristics will be summarized by treatment arms for demographics, baseline disease characteristics, and medical history. The three treatment arms will be compared using standard methods such as t-tests and chi-square tests.

12.3 Analysis of Primary Objective

- Demonstrate a 2-year disease-free survival (DFS) of > 50% for participants with residual disease and ctDNA positive triple negative breast cancer (TNBC) treated with a genomically directed therapy following preoperative chemotherapy (ARM 1). DFS is defined as the duration of time from arm assignment to time of a DFS event, defined as local failure (invasive), regional failure, distant failure, contralateral breast cancer (invasive or non-invasive), or death from any cause. The assumption from this trial is that a personalized approach will beat a historically non-personalized approach and we are powered to test that assumption. Thus, we will assume we have selected agents that will all have similar degree of effectiveness to support our hypothesis. We recognize the overt failure of any one arm may result in rejection of the hypothesis. We obviously will not have power to study the success or failure of each arm but will look at each in descriptive fashion for future hypothesis generation. Based on the preliminary data from our prior trial BRE12-158, the DFS probability at 24-month for ctDNA positive patients was 50.0% with a 95% confidence interval of 37.4% ~ 66.7%. The goal of this current trial is to demonstrate that we will beat a 50% 2-year DFS with genomically directed therapy. We will assume that the genomically directed therapy will improve the 24-month DFS probability from 50% to 62.5% in ctDNA positive patients. With 90 patients in Arm 1, we will have 80% power (alpha=0.05; one-sided test) to demonstrate superiority in Arm 1 vs. 50% 2-yr DFS seen in the prior trial, BRE12-158.
    - One-sample log-rank test will be used to determine significance of 2-year DFS >50% in Arm 1.

12.4 Analysis of Secondary Objectives

- Evaluate the 2-year DFS for participants with residual disease and ctDNA positive TNBC and no actionable genomic targets treated with a standard approach therapy following preoperative chemotherapy (ARM 2)
    - Kaplan-Meier curve will be used to evaluate the 2-year DFS in Arm 2.
- Evaluate the 2-year DFS for participants with residual disease and ctDNA negative triple negative breast cancer (TNBC) treated with a standard approach therapy following preoperative chemotherapy (ARM 3)
    - Kaplan-Meier curve will be used to evaluate the 2-year DFS in Arm 3.
- Evaluate the overall DFS for ARMS 1, 2, and 3
    - Kaplan-Meier curve will be used to evaluate the overall DFS in Arms 1,2,3.
- Evaluate the overall DDFS for ARMS 1, 2, and 3. DDFS is defined as the duration of time from registration to time of recurrence of breast cancer outside the breast and/or death from any cause. The diagnosis of local or distant recurrence should ideally be pathologically confirmed, however if biopsy is not possible, radiology confirmation by CT, MRI, or PET scan is acceptable.
    - Kaplan-Meier curve will be used to evaluate the overall DDFS in Arms 1,2,3.
- Evaluate 1-year DFS for ARMS 1, 2, and 3
    - Kaplan-Meier curve will be used to evaluate the 1-year DFS in Arms 1,2,3.
- Determine 5-year overall survival (OS) for ARMS 1, 2, and 3. Overall survival is defined as the time from date of treatment start until death from any cause.
    - Kaplan-Meier curve will be used to evaluate the 5-year OS in Arms 1,2,3.
- Evaluate the DFS and OS for patients with markers associated with response to immune checkpoint inhibitor treatment vs. those without markers associated with response to immune checkpoint inhibitor treatment identified on residual disease.
    - Kaplan-Meier curve will be used to evaluate
- Describe the toxicities associated with genomically directed therapy in this population
    - Safety and toxicity data will be tabulated and reported using CTCAE criteria v5.

- Describe patient preferences for return of ctDNA results
    - Patient preferences at ctDNA testing will be characterized using descriptive statistics and the trajectory of change in preferences following return of results and at treatment discontinuation will be descriptively summarized.
- Evaluate the impact of ctDNA status and availability of genomically directed therapy on FCR and HRQoL
    - Mixed effects model with a random subject effect will be used to model the PRO of interest by time and by study arm and their interaction. Each PRO will be described at each time point and by arm using least squares means, and linear contrasts will be used to describe changes over time and within or between arms.

12.5 Analysis of Exploratory Objectives

- Collect archived tumor specimens, genomic DNA, and circulating tumor samples to explore potential correlates of recurrence and toxicity
    - Correlative analyses that associate clinical or genomic data with survival outcomes will use the appropriate time-to-event analysis (including, Cox Proportional Hazards or Log-Rank Test). Correlative analysis that associate clinical or genomic data with categorical variables will use Chi-square or Fisher's exact test, as appropriate.
- Evaluate the drug specific effect on both efficacy outcomes (DFS and OS) and toxicity.
    - Drug-specific associations with survival outcomes will use the appropriate time-to-event analysis (including, Cox Proportional Hazards or Log-Rank Test). Drug-specific associations with toxicity variables will use Chi-square or Fisher's exact test, as appropriate.
- Explore modifiers of FCR and HRQoL in this population, including coping strategies, anxiety, health literacy, self- efficacy, and disease characteristics.
    - Mixed effects models will be adjusted for factors that may impact FCR and HRQoL

12.6 Assessment of Safety

All subjects who have received at least one dose of study treatment will be evaluable for safety. The National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5 will be used for toxicity assessment

12.7 Assessment of Efficacy

All subjects who have received at least one cycle of study treatment and have had at least one post baseline disease assessment or die of any cause before the first post baseline disease assessment will be evaluable for assessment of efficacy.

13 TRIAL MANAGEMENT

13.1 Data and Safety Monitoring Plan (DSMP)

The study will be conducted in accordance with the IU Simon Cancer Center's (IUSCC) DSMP for High Risk Safety Lead-In/Phase II Trials.

13.1.1 HCRN facilitated oversight activities for High Risk Safety Lead-In/Phase II Trials include:

- Review and processing of all AEs requiring expedited reporting as defined in the protocol
- Provide trial accrual progress, safety information, and data summary reports to the sponsor-investigator. For any increase in frequency of grade 3 or above adverse events (above the rate reported in the Investigator Brochure or package insert), the sponsor investigator will notify HCRN who will notify the DSMC Chair and Compliance Officer immediately. The notification will include the incidence of study adverse events, grades, and attributions, as well as investigator statements regarding comparison with risks per the IB/package insert.
- Notify participating sites of adverse events potentially requiring expedited reporting and subsequent DSMC recommendations for study modifications.
- Investigators will conduct continuous review of data and patient safety
- Coordinate, during safety lead-in, weekly (Phase I) meetings (Safety Calls), and subsequently, during the phase II portion, monthly (Phase II) meetings which will include representation from each accruing site.
    - These meetings should include review of data, the number of subjects and significant toxicities as described in the protocol. HCRN should maintain meeting minutes and attendance for submission to the DSMC upon request.
- Conduct the trial across all participating sites in accordance with the requirements set forth in the IUSCC DSMP.

13.2 IUSCC Data Safety Monitoring Committee Oversight

The IUSCC Data and Safety Monitoring Committee (DSMC) is responsible for oversight of subject safety, regulatory compliance, and data integrity for this trial. The DSMC will review this study to assess toxicity, compliance, data integrity, and accrual per the Institutional DSMP. Trials managed by HCRN are not routinely audited or monitored by IUSCC; however, the IUSCC DSMC retains the right to audit HCRN trials on a for cause basis.

13.2.1 IUSCC DSMC Review

The IUSCC DSMC will review study data twice annually per the IUSCC DSMP. In preparation for the IUSCC DSMC review, HCRN will provide the following:

- Monthly Summary Reports
- Reports of the following, if not already included in the Monthly Summary Report:
    - Adverse event summary report (including serious adverse events)
    - Study accrual patterns
    - Protocol deviations
- Audit and/or monitoring results, if applicable
- Data related to stopping/ dose decision rules described in study design
- HCRN weekly (Phase I) or monthly (Phase II) study update meeting minutes/ attendance

Documentation of DSMC reviews will be provided to sponsor-investigator (SI) and HCRN. The IUSCC DSMC will notify the sponsor-investigator and other regulatory bodies, as appropriate, for issues of immediate concern. The sponsor-investigator will work with HCRN to address the DSMC's concerns as appropriate.

At any time during the conduct of the trial, if it is the opinion of the sponsor-investigator that the risks (or benefits) to the patient warrant early closure of the study, this recommendation should be made in

writing to the DSMC Chair and Compliance Officer. Alternatively, the DSMC may initiate suspension or early closure of the study at any time based on its review of the study reports.

13.2.2 DSMC DLT Review

Prior to making dose escalation/expansion/de-escalation decisions, the SI and the study team will officially review all toxicity events for each subject for confirming treatment-related DLT. The study statistician will assist the determination of DLT and the interpretation of the statistical rule for dose escalation. Once a decision has been reached by the investigator, the official decision and toxicity data will be submitted to the DSMC via email (IUSCC-DLT-Review-L@list.iupui.edu). Treating additional subjects may not proceed until official DSMC correspondence confirms approval of dosing decisions for the next stage.

13.2.3 IND Information Review

For trials with an IND held locally by the IU principal investigator, the IND Annual Report will be prepared and submitted to the Compliance Team. This report will be reviewed by the DSMC at the time of FDA submission.

13.3 Data Quality Oversight Activities

Remote validation of the EDC system data will be completed on a continual basis throughout the life cycle of the study. Automated edit check listings will be used to generate queries in the EDC system and transmitted to the site to address in a timely fashion. Corrections will be made by the study site personnel.

13.3.1 Onsite Monitoring

Monitoring visits to the trial sites may be made periodically during the trial to ensure key aspects of the protocol are followed. For cause visits may occur as necessary. Selected source documents will be reviewed for verification of agreement with data entered into the EDC system. It is important for the site investigator and their relevant personnel to be available for a sufficient amount of time during the monitoring visits or audit, if applicable. The site investigator and institution guarantee access to source documents by HCRN or its designee.

Participating sites may also be subject to quality assurance audits by Genentech and/or Pfizer or its designee as well as inspection by appropriate regulatory agencies.

13.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the sponsor-investigator of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. All results of primary and secondary objectives must be posted to CT.gov within a year of completion. The sponsor-investigator has delegated responsibility to HCRN for registering the trial and posting the results on clinicaltrials.gov. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and study site contact information.

14. Data Handling and Record Keeping

14.1 Data Management

HCRN will serve as the Clinical Research Organization for this trial. Data will be collected through a web based clinical research platform (EDC system), a system compliant with Good Clinical Practices and Federal Rules and Regulations. HCRN personnel will coordinate and manage data for quality control assurance and integrity. Select data will be collected and entered into the EDC system by study site personnel from participating institutions.

14.2 Case Report Forms and Submission

Generally, clinical data will be electronically captured in the EDC system and correlative results will be captured in EDC system or other secure database(s). If procedures on the study calendar are performed for standard of care, at minimum, that data will be captured in the source document. Select standard of care data will also be captured in the EDC system, according to study-specific objectives.

The completed dataset is the sole property of the sponsor-investigator's institution and should not be exported to third parties, except for authorized representatives of appropriate Health/Regulatory Authorities, without permission from the sponsor-investigator and HCRN.

14.3 Record Retention

To enable evaluations and/or audits from Health Authorities/HCRN, the site investigator agrees to keep records, including the identity of all subjects (sufficient information to link records; e.g., hospital records), all original signed informed consent forms, copies of all source documents, and detailed records of drug disposition. All source documents are to remain in the subject's file and retained by the site investigator in compliance with the site contract with HCRN. No records will be destroyed until HCRN confirms destruction is permitted.

14.4 Confidentiality

There is a slight risk of loss of confidentiality of subject information. All records identifying the subjects will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. Information collected will be maintained on secure, password protected electronic systems. Paper files that contain personal information will be kept in locked and secure locations only accessible to the study site personnel.

Subjects will be informed in writing that some organizations including the sponsor-investigator and his/her research associates, HCRN, IRB, or government agencies, like the FDA, may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

If the results of the study are published, the subject's identity will remain confidential.

15. ETHICS

15.1 Institutional Review Board (IRB) Approval

The final study protocol and the final version of the informed consent form must be approved in writing by an IRB. The site investigator must submit written approval by the IRB to HCRN before he or she can enroll subjects into the study.

The site investigator is responsible for informing the IRB of any amendment to the protocol in accordance with local requirements. In addition, the IRB must approve all advertising used to recruit subjects for the study. The protocol must be re-approved by the IRB, as local regulations require.

Progress reports and notifications of serious and unexpected adverse events will be provided to the IRB according to local regulations and guidelines.

15.2 Ethical Conduct of the Study

The study will be performed in accordance with ethical principles originating from the Declaration of Helsinki. Conduct of the study will be in compliance with ICH Good Clinical Practice, and with all applicable federal (including 21 CFR parts 56 & 50), state, or local laws.

15.3 Informed Consent Process

The site investigator will ensure the subject is given full and adequate oral and written information about the nature, purpose, possible risks and benefits of the study. Subjects must also be notified they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The subject's signed and dated informed consent must be obtained before conducting any procedure specifically for the study. The site investigator must store the original, signed informed consent form. A copy of the signed informed consent form must be given to the subject.

16. REFERENCES

1. Fisher B, Bryant J, Wolmark N, et al: Effect of preoperative chemotherapy on the outcome of women with operable breast cancer. J Clin Oncol 16:2672-85, 1998
2. Bear HD, Anderson S, Smith RE, et al: Sequential preoperative or postoperative docetaxel added to preoperative doxorubicin plus cyclophosphamide for operable breast cancer:National Surgical Adjuvant Breast and Bowel Project Protocol B-27. J Clin Oncol 24:2019-27, 2006
3. Klauber-DeMore N, Ollila DW, Moore DT, et al: Size of residual lymph node metastasis after neoadjuvant chemotherapy in locally advanced breast cancer patients is prognostic. Ann Surg Oncol 13:685-91, 2006
4. von Minckwitz G, Untch M, Blohmer JU, et al: Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes. J Clin Oncol 30:1796-804, 2012
5. Carey LA, Dees EC, Sawyer L, et al: The triple negative paradox: primary tumor chemosensitivity of breast cancer subtypes. Clin Cancer Res 13:2329-34, 2007
6. Ogston KN, Miller ID, Payne S, et al: A new histological grading system to assess response of breast cancers to primary chemotherapy: prognostic significance and survival. Breast 12:320-7, 2003
7. Symmans WF, Peintinger F, Hatzis C, et al: Measurement of residual breast cancer burden to predict survival after neoadjuvant chemotherapy. J Clin Oncol 25:4414-22, 2007
8. Liedtke C, Mazouni C, Hess KR, et al: Response to neoadjuvant therapy and long-term survival in patients with triple-negative breast cancer. J Clin Oncol 26:1275-81, 2008
9. Masuda N, Lee SJ, Ohtani S, et al: Adjuvant Capecitabine for Breast Cancer after Preoperative Chemotherapy. N Engl J Med 376:2147-2159, 2017
10. McNeil C: NCI-MATCH launch highlights new trial design in precision-medicine era. J Natl Cancer Inst 107, 2015
11. Schmid P, Adams S, Rugo HS, et al: Atezolizumab and Nab-Paclitaxel in Advanced Triple-Negative Breast Cancer. N Engl J Med 379:2108-2121, 2018
12. Schmid P, Rugo HS, Adams S, et al: Atezolizumab plus nab-paclitaxel as first-line treatment for unresectable, locally advanced or metastatic triple-negative breast cancer (IMpassion130): updated efficacy results from a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 21:44-59, 2020
13. Gambardella V et al: PI3K pathway biomarkers and clinical response in a phase I/Ib study of GDC-0077 in hormone receptor-positive/HER2-negative breast cancer (HR+/HER2– BC). Poster 336P ESMO 2020 https://www.annalsofoncology.org/article/S0923-7534(20)40434-X/fulltext
14. Crowley E, Di Nicolantonio F, Loupakis F, et al: Liquid biopsy: monitoring cancer-genetics in the blood. Nat Rev Clin Oncol 10:472-84, 2013
15. Diaz LA, Jr., Bardelli A: Liquid biopsies: genotyping circulating tumor DNA. J Clin Oncol 32:579-86, 2014
16. Heidary M, Auer M, Ulz P, et al: The dynamic range of circulating tumor DNA in metastatic breast cancer. Breast Cancer Res 16:421, 2014
17. Dawson SJ, Rosenfeld N, Caldas C: Circulating tumor DNA to monitor metastatic breast cancer. N Engl J Med 369:93-4, 2013
18. Garcia-Murillas I, Schiavon G, Weigelt B, et al: Mutation tracking in circulating tumor DNA predicts relapse in early breast cancer. Sci Transl Med 7:302ra133, 2015
19. Chen YH, Hancock BA, Solzak JP, et al: Next-generation sequencing of circulating tumor DNA to predict recurrence in triple-negative breast cancer patients with residual disease after neoadjuvant chemotherapy. NPJ Breast Cancer 3:24, 2017

20. Schutz E, Akbari MR, Beck J, et al: Chromosomal instability in cell-free DNA is a serum biomarker for prostate cancer. Clin Chem 61:239-48, 2015
21. Hamakawa T, Kukita Y, Kurokawa Y, et al: Monitoring gastric cancer progression with circulating tumour DNA. Br J Cancer 112:352-6, 2015
22. Diehl F, Li M, Dressman D, et al: Detection and quantification of mutations in the plasma of patients with colorectal tumors. Proc Natl Acad Sci U S A 102:16368-73, 2005
23. Diehl F, Schmidt K, Choti MA, et al: Circulating mutant DNA to assess tumor dynamics. Nat Med 14:985-90, 2008
24. Holdhoff M, Schmidt K, Donehower R, et al: Analysis of circulating tumor DNA to confirm somatic KRAS mutations. J Natl Cancer Inst 101:1284-5, 2009
25. Garcia-Murillas I, Chopra N, Comino-Mendez I, et al: Assessment of Molecular Relapse Detection in Early-Stage Breast Cancer. JAMA Oncol, 2019
26. Olsson E, Winter C, George A, et al: Serial monitoring of circulating tumor DNA in patients with primary breast cancer for detection of occult metastatic disease. EMBO Mol Med 7:1034-47, 2015
27. Schmid P, Cortes J, Pusztai L, et al: Pembrolizumab for Early Triple-Negative Breast Cancer. N Engl J Med 382: 810-821, 2020
28. Schmid P, Cortes J, Dent R, et al: VP7-2021: KEYNOTE-522: Phase III study of neoadjuvant pembrolizumab + chemotherapy vs. placebo + chemotherapy, followed by adjuvant pembrolizumab vs. placebo for early-stage TNBC. ESMO Virtual Plenary Abstracts 21 (9): 1198-1200, 2021

APPENDIX A: MANAGEMENT OF TALAZOPARIB-SPECIFIC ADVERSE EVENTS

Toxicities associated or possibly associated with talazoparib treatment should be managed according to standard medical practice.

Hematologic Toxicity

Monitor complete blood counts monthly and as clinically indicated. Anemia (low hemoglobin), thrombocytopenia (low platelet count), neutropenia (low neutrophil count) and other hematologic events have been reported with talazoparib.

Management Guidelines for Blood/Investigation Events

Event	Management
Anemia event, Grade 1 or 2	● Hemoglobin ≥ 9 g/dL ● Continue talazoparib and monitor closely. ● Continue capecitabine
Anemia event, Grade 3	● Hemoglobin < 8 g/dL ● Hold talazoparib until Hemoglobin level resolves to grade 1 or less, then resume a reduced dose ● Hold capecitabine until Hemoglobin level resolves to grade 1 or less then resume at reduced dose 75%
Anemia event, Grade 4	● Hold talazoparib until Hemoglobin level resolves to grade 1 or less, then resume a reduced dose ● Hold capecitabine until Hemoglobin level resolves to grade 1 or less, then resume at reduced dose 50% dose reduction
Platelet count decrease event, Grade 1 or 2	● Platelet count ≥75,000/µL ● Continue talazoparib and monitor closely. ● Continue capecitabine
Platelet count decrease event, Grade 3	● Platelet count <50,000/µL ● Hold talazoparib until platelet level resolves to grade 1 or less, then resume a reduced dose ● Hold capecitabine until platelet level resolves to grade 1 or less, then resume at reduced dose 75%
Platelet count decrease event, Grade 4	● Hold talazoparib until platelet level resolves to grade 1 or less, then resume a reduced dose ● Hold capecitabine until platelet level resolves to grade 1 or less, then resume at reduced dose 50% dose reduction
Neutrophil count decrease event, Grade 1 or 2	● Neutrophil count ≥1500/µL ● Continue talazoparib and monitor closely. ● Continue capecitabine
Neutrophil count decrease event, Grade 3	● Neutrophil count <1,000/µL ● Hold talazoparib until neutrophil level resolves to grade 1 or less, then resume a reduced dose ● Hold capecitabine until neutrophil level resolves to grade 1 or less, then resume at reduced dose 75%

Neutrophil count decrease event, Grade 3 or 4	● Hold talazoparib until neutrophil level resolves to grade 1 or less, then resume a reduced dose ● Hold capecitabine until neutrophil level resolves to grade 1 or less, then resume at reduced dose 50% dose reduction
Other hematologic event, Grade 1 or 2	● Continue talazoparib and monitor closely. ● Continue capecitabine
Other hematologic event, Grade 3	● Hold talazoparib until event resolves to Grade 1 or less, then resume a reduced dose ● Hold capecitabine until event resolves to Grade 1 or less, then resume at reduced dose 75%
Other hematologic event, Grade 4	● Hold talazoparib until event resolves to Grade 1 or less, then resume a reduced dose ● Hold capecitabine until event resolves to Grade 1 or less, then resume at reduced dose 50%

Myelodysplasia/Acute Myeloid Leukemia

Myelodysplastic Syndrome/Acute Myeloid Leukemia (MDS/AML) have been reported in patients who received talazoparib. Overall, MDS/AML has been reported in 2 out of 584 (0.3%) solid tumor patients treated with talazoparib in clinical studies. The duration of talazoparib treatment in these two patients prior to developing MDS/AML was 4 months and 24 months, respectively. Both patients had received previous chemotherapy with platinum agents and/or other DNA damaging agents including radiotherapy.

Do not start talazoparib until patients have adequately recovered from hematological toxicity caused by previous chemotherapy. Monitor complete blood counts for cytopenia at baseline and monthly thereafter.

For prolonged hematological toxicities, interrupt talazoparib and monitor blood counts weekly until recovery. If the levels have not recovered after 3 weeks, refer the patient to a hematologist for further investigations, including bone marrow analysis and blood sample for cytogenetics. If MDS/AML is confirmed, discontinue talazoparib. Capecitabine should continue.

Non-hematologic Toxicity

Fatigue, increased blood glucose, nausea, vomiting, diarrhea, and headache have all been reported with talazoparib.

Management Guidelines for Gastrointestinal Events

Event	Management
Diarrhea event, Grade 1 or 2	● Continue talazoparib and monitor closely. ● Continue capecitabine
Diarrhea event, Grade 3	● Hold talazoparib until event resolves to ≤Grade 1 or baseline, then resume a reduced dose ● Hold capecitabine until event resolves to Grade 1 or less, then resume at reduced dose 50%
Diarrhea event, Grade 4	● Hold talazoparib until event resolves to Grade 1 or less, then resume a reduced dose ● Hold capecitabine until event resolves to Grade 1 or less, then resume at reduced dose 25%
Nausea/Vomiting event, Grade 1 or 2	● Continue talazoparib and monitor closely. ● Continue capecitabine
Nausea/Vomiting event, Grade 3	● Hold talazoparib until event resolves to ≤Grade 1 or baseline, then resume a reduced dose ● Hold capecitabine until event resolves to Grade 1 or less, then resume at reduced dose 50%
Nausea/Vomiting event, Grade 4	● Hold talazoparib until event resolves to Grade 1 or less, then resume a reduced dose ● Hold capecitabine until event resolves to Grade 1 or less, then resume at reduced dose 25%

Management Guidelines for Any Non-hematologic Events

Event	Management
Non-hematologic event, Grade 1 or 2	● Continue talazoparib and monitor closely. ● Continue capecitabine
Non-hematologic event, Grade 3	● Hold talazoparib until event resolves to ≤Grade 1 or baseline, then resume a reduced dose ● Continue capecitabine
Non-hematologic event, Grade 4	● Hold talazoparib until event resolves to Grade 1 or less, then resume a reduced dose ● Hold capecitabine until event resolves to Grade 1 or less, then resume at reduced dose 75%

APPENDIX B: MANAGEMENT OF INAVOLISIB-SPECIFIC ADVERSE EVENTS

FASTING HYPERGLYCEMIA

In general, patients with diabetes either requiring insulin therapy or with a baseline fasting glucose >126 mg/dL (7.0 mmol/L) or high HbA1c, suggesting poorly controlled diabetes, should be excluded from studies with inavolisib. Fasting is defined as abstaining from food and drink (with the exception of water) for at least 4 hours. Dosage modification guidelines for fasting hyperglycemia attributable to inavolisib are outlined below:

Event	Management
Hyperglycemia, Grade 1 > ULN to 160 mg/dL (8.9 mmol/L)	• Continue inavolisib. • Continue capecitabine • Encourage patients to adopt a diabetic diet • Initiate treatment with insulin if needed. • Monitor for glucose control. • Recheck in 3 days and adjust medications as needed
Hyperglycemia, Grade 2 > 160 to 250 mg/dL (> 8.9-13.9 mmol/L)	• Hold inavolisib, resume inavolisib when symptoms resolve to grade 1 or less and glucose levels are stable. ○ If fasting blood glucose persists > 200-250 mg/dL or > 13.9-27.8 mmol/L for 7 days despite above interventions, discuss with study PI. • Continue capecitabine • Encourage patients to adopt a diabetic diet • Initiate treatment with insulin. • Monitor for glucose control. • Recheck in 3 days and adjust medications as needed
Hyperglycemia, Grade 3 250 to 500 mg/dL (13.9-27.8 mmol/L)	• Hold inavolisib, resume inavolisib when symptoms resolve to: • If hyperglycemia resolves to Grade 1, >160 mg/dL or 8.9 mmol/L within 7 days, may resume at current dose level of inavolisib • If hyperglycemia resolves to Grade 1, >160 mg/dL or 8.9 mmol/L in ≥ 8 days, reduce inavolisib dose by one dose level when treatment resumes • If hyperglycemia > 250-500 mg/dL or > 13.9-27.8 mmol/L recurs within 30 days, reduce inavolisib dose by one dose level • Continue capecitabine • Manage hyperglycemia as per standard of care • Initiate or increase treatment with insulin. • Monitor for glucose control. • Recheck in 3 days and adjust medications as needed • Encourage patients to adopt a diabetic diet • Consider consultation with endocrinologist or diabetologist. Initiate fasting home glucose monitoring

Hyperglycemia, Grade 4 > 500 mg/dL (> 27.8 mmol/L)	• Hold inavolisib, resume inavolisib when: ○ *When hyperglycemia resolves to* Grade 1, > *160 mg/dL or 8.9 mmol/L, reduce* inavolisib *dose by one dose level when treatment resumes. If hyperglycemia > 500 mg/dL or > 27.8 mmol/L recurs within 30 days, permanently discontinue* inavolisib • Manage hyperglycemia as per standard of care • Assess for volume depletion and ketosis and administer appropriate intravenous or oral hydration • Initiate or increase treatment with insulin. • Monitor for glucose control. • Recheck in 3 days and adjust medications as needed • Encourage patients to adopt a diabetic diet • Consider consultation with endocrinologist or diabetologist

Fasting glucose should be checked by finger stick or lab value (if patient has scheduled appointment) PRIOR to dosing. Oral anti-diabetic medications should be titrated to the maximum allowed dosages to achieve control of blood glucose to < 160 mg/dL or 8.9 mmol/L. For example, metformin may be administered to a maximum dose allowed as per local prescribing information, given in divided doses, as tolerated. Please see local prescribing information of individual oral anti-diabetic agent for dosing guidelines.

There is a risk of hypoglycemia if insulin or sulfonylureas are used, particularly if these agents are started during periods of inavolisib exposure and doses are not adjusted appropriately during periods of treatment interruption, during which patients' insulin sensitivity may increase rapidly. Short-term insulin is allowed to control blood glucose levels, but goal should be to maintain on oral agents once acute episode resolves.

In order to diminish the risk of hypoglycemia, insulin should not be administered for asymptomatic hyperglycemia of any grade. Patients should be educated on the symptoms of hyperglycemia, so that patients can be promptly and appropriately managed.

GASTROINTESTINAL TOXICITY

Dose reductions for gastrointestinal toxicity should occur only if the symptoms persist despite adequate (combination) anti-emetic treatment(s), including ondansetron (or equivalent anti-emetic). For persistent nausea and/or vomiting attributable to the inavolisib and/or capecitabine, dosage modification guidelines for inavolisib, and/or capecitabine are outlined below:

Event	Management
Diarrhea event, Grade 1	• Continue inavolisib and monitor closely • Continue capecitabine • Adequate treatment with anti-diarrheals and maximum supportive care per institutional care
Diarrhea event, Grade 2	• Hold inavolisib and resume inavolisib when symptoms resolve to grade 1 or less • Continue capecitabine • Adequate treatment with anti-diarrheals and maximum supportive care per institutional care • If recurs within 30 days, reduce inavolisib by one dose level
Diarrhea event, Grade 3	• Hold inavolisib until event resolves to ≤Grade 1 or baseline, then resume a reduced dose • Hold capecitabine until event resolves to Grade 1 or less, then resume at reduced dose 50% • If recurs within 30 days after initiation of the first dose reduction, reduce inavolisib by one dose level. If recurs within 30 days from the second dose reduction, permanently discontinue inavolisib
Diarrhea event, Grade 4	• Permanently discontinue inavolisib until event resolves to Grade 1 or less, then resume a reduced dose • Hold capecitabine until event resolves to Grade 1 or less, then resume at reduced dose 25%
Nausea/Vomiting event, Grade 1 or 2	• Continue inavolisib and monitor closely • Continue capecitabine
Nausea/Vomiting event, Grade 3	• Hold inavolisib until event resolves to ≤Grade 1 or baseline, then resume a reduced dose • Hold capecitabine until event resolves to Grade 1 or less, then resume at reduced dose 50% • Dose re-escalation of the inavolisib and/or capecitabine may be permitted in subsequent cycles for patients who exhibit Grade < 1 nausea/vomiting through at least one cycle.
Nausea/Vomiting event, Grade 4	• Hold inavolisib until event resolves to Grade 1 or less, then resume a reduced dose • Hold capecitabine until event resolves to Grade 1 or less, then resume at reduced dose 25% • Dose re-escalation of the inavolisib and/or capecitabine may be permitted in subsequent cycles for patients who exhibit Grade < 1 nausea/vomiting through at least one cycle.

Any grade mucositis	• Intervene early • Initiate aggressive mouth care that includes dexamethasone (0.1 mg per mL) alcohol-free mouthwash. If that is not available, consider other mouthwash formulations (e.g., combinations of local anesthetic, antihistamine, corticosteroid, antacid, antifungal and/or antibiotics) • Avoid alcohol-, hydrogen peroxide-, iodine-, or thyme-containing products, as they may exacerbate the condition. Avoid harsh mouthwashes (e.g., Listerine®) • Diet should be modified (e.g., avoidance of spicy foods)
Mucositis event, Grade 1; asymptomatic or mild symptoms; intervention not indicated	• Continue inavolisib and monitor closely • Continue capecitabine • Maximum supportive care should be administered as needed at the discretion of the investigator
Mucositis event, Grade 2; Moderate pain or ulcer that does not interfere with oral intake; modified diet indicated	• Hold inavolisib until event resolves to ≤ Grade 1 or baseline, then resume at same dose • For recurrent Grade 2 stomatitis or oral mucositis within 30 days, reduce inavolisib dose by one dose level • Hold capecitabine until event resolves to Grade 1 or less, then resume at reduced dose 50%
Grade 3: Severe pain; interfering with oral intake	• Interrupt inavolisib until Grade ≤ 1 and reduce inavolisib dose by one dose level when dosing is resumed • Interrupt capecitabine until recovery to Grade ≤ 2; then may resume capecitabine as per local prescribing information
Grade 4: Life-threatening consequences; urgent intervention indicated	• Permanently discontinue inavolisib • Manage capecitabine as per local prescribing information
Grade 1; Inflammatory Colitis	• Close monitoring and treat as appropriate
Grade 2; Inflammatory Colitis	• If colitis-related symptoms do not improve to Grade ≤ 1 after 48 hours of anti-diarrheals, start treatment with oral corticosteroid [a] • Interrupt inavolisib until recovery to Grade ≤ 1, then may resume at the same dose or one dose level lower per investigator evaluation • If recurs within 30 days, reduce inavolisib by one dose level

Grade 3; Inflammatory Colitis	• Treat with high dose corticosteroids (IV solumedrol or PO prednisone) [b] • Interrupt inavolisib until recovery to Grade ≤ 1, then reduce by one dose level • Hold capecitabine until recovery to Grade ≤ 1 and manage as per local prescribing information • Consider colonoscopy • If Grade 3 recurs, permanently discontinue inavolisib
Grade 4; Inflammatory Colitis	• Permanently discontinue inavolisib • Manage capecitabine as per local prescribing information

SKIN TOXICITY

Dosage modification guidelines for skin toxicity attributable to the inavolisib and/or capecitabine are outlined below:

Management Guidelines for Dermatologic Events

Event	Management
Dermatologic event, Grade 1	• Continue inavolisib • Continue capecitabine • Consider treatment with topical corticosteroids and/or other symptomatic therapy (e.g., antihistamines).
Dermatologic event, Grade 2	• Interrupt inavolisib treatment • Treat rash per standard of care, including topical and/or oral corticosteroids, and/or antihistamines • When rash resolves to Grade ≤ 1, resume inavolisib at the same dose or one dose level lower per investigator evaluation • If Grade 2 rash recurs within 30 days, reduce inavolisib by one dose level when treatment resumes • Continue capecitabine
Dermatologic event, Grade 3	• Hold inavolisib • Interrupt capecitabine treatment until recovery to Grade ≤ 2 and manage as per local prescribing information • Treat rash with topical and/or systemic corticosteroids (oral or IV) and antihistamines • If rash resolves to Grade ≤ 1 within 30 days, reduce inavolisib by one dose level when treatment resumes • If rash does not resolve to Grade ≤ 1 within 30 days, discontinue inavolisib • Refer to dermatologist for consultation and skin biopsy
Palmar-plantar erythrodysesthesia syndrome (Hand Foot Syndrome), Grade 2	• Continue inavolisib. • Continue capecitabine
Palmar-plantar erythrodysesthesia syndrome (Hand Foot Syndrome), Grade 3-4	• Continue inavolisib. • Hold capecitabine until event resolves to Grade 1 or less, then resume at reduced dose 50%

Dose re-escalation of the inavolisib, and/or capecitabine may be permitted in subsequent cycles for patients who exhibit Grade ≤ 1 skin toxicity for at least one cycle after discussion with the sponsor-investigator. The inavolisib and/or capecitabine should be permanently discontinued for rash due to Stevens-Johnson syndrome, toxic epidermal necrolysis, or other suspected severe hypersensitivity or allergic reaction that is related to inavolisib and/or capecitabine.

Management of Pneumonitis

Grade 1	• No specific therapy required	• Chest CT scan • Repeat CT at least every 8 weeks until return to baseline • Consider pulmonologist/ respirologist consult • Advise patient to promptly report new or worsening respiratory symptoms	• No action
Grade 2	• Prescribe corticosteroids if infectious etiology is ruled out • Taper as clinically indicated	• Chest CT scan • Repeat CT at least every 8 weeks until return to baseline • Consider PFTs • Obtain pulmonologist/respirologis t consult	• Hold inavolisib and capecitabine as long as corticosteroids are being given. When pneumonitis improves to Grade ″ 1 and upon completion of any corticosteroid treatment, resume inavolisib and capecitabine dosing at the same dose or one dose level lower per investigator evaluation. For recurrent Grade 2 event, resume inavolisib and capecitabine dosing at one dose level lower
Grade 3	• Prescribe corticosteroids if infectious etiology is ruled out • Taper as clinically indicated	• Chest CT scan • Repeat CT at least every 8 weeks until return to baseline • Consider PFTs and bronchoscopy • Obtain pulmonologist/ respirologist consult	• Hold inavolisib and capecitabine as long as corticosteroids are being given. When pneumonitis improves to Grade ″ 1 and upon completion of any corticosteroid treatment, resume inavolisib and capecitabine dosing at one dose level lower
Grade 4	• Prescribe corticosteroids if infectious etiology is ruled out • Taper as clinically indicated	• Chest CT scan • Repeat CT at least every 8 weeks until return to baseline • Consider PFTs • Obtain pulmonologist/ respirologist consult • Bronchoscopy is recommended	• Permanently discontinue inavolisib • Permanently discontinue capecitabine
CT = computed tomography (scan); PFTs = pulmonary function tests.			

Management Guidelines for Any Non-hematologic Events

Event	Management
Non-hematologic event, Grade 1 or 2	• Continue inavolisib and monitor closely. • Continue capecitabine
Non-hematologic event, Grade 3	• Hold inavolisib until event resolves to ≤ Grade 1 or baseline, then resume a reduced dose • Continue capecitabine
Non-hematologic event, Grade 4	• Hold inavolisib until event resolves to Grade 1 or less, then resume a reduced dose • Hold capecitabine until event resolves to Grade 1 or less, then resume at reduced dose 75%

For Grade≤ 3 toxicities associated primarily with laboratory abnormalities only (e.g., elevation of ALT, AST, lipase, or amylase, or decreases in phosphorus without clinical or other evidence of pancreatitis or other hepatic dysfunction), study treatment may continue without interruption and/or dose-reduction at the discretion of the investigator per institutional practice.

APPENDIX C

COVID-19 Contingency Plans

New participant enrollment – HCRN and the study team are supportive of new patient enrollment if your site is confident that you will be able to conduct the protocol specified safety and efficacy monitoring required for the study. We recommend that investigators ensure the appropriate monitoring and follow-up of currently enrolled participants before considering recruitment of new participants.

Study participant site visits - For ongoing participants, where possible, and safe to do, please continue to prioritize scheduled study visits in order to keep the participants on the protocol defined regimen and facilitate full safety and efficacy monitoring. For ongoing participants who are unable to attend protocol-specified trial visits and procedures, please continue to assess adverse events/safety remotely (e.g., phone contact, virtual visit, alternative location for assessment, including local labs or imaging centers) and document all deviations to the study conduct, noting specifically if it is a result of COVID-19 control measures.

Anticipated Problem for Sites and Patients	**Recommended Contingency Plan or Alternative Procedure(s)**
Missed Protocol required physical exam(s)/ assessments	Exams and assessments unable to be conducted by a healthcare provider can be delayed or conducted remotely until it is deemed safe for patients to return to clinic.
Missed treatment Cycles	Missed treatments can be made up when it is safe for patients to return to clinic/infusion. Patients may have their oral medications mailed if feasible to maintain treatment cycle schedule.
Missed required specimen collections	Every effort should be made to collect specimens when patients return to clinic. Our team is working closely with sites to provide flexible shipment options to reduce patient appointments.
Missed PRO assessments	PRO questionnaires can be sent home with patients, e-mailed, or mailed and returned at the next safe timepoint.
Delays/Disruptions in Supply Chain	There may be unforeseen delays or disruptions in the supply chain related to the conduct of this trial as a result of COVID-19. If and when these instances arise, they will each be addressed on an individual basis.

APPENDIX D: Patient Reported Outcomes (PRO) Instructions

Patient Reported Outcomes (PRO) Instructions

In effort to reduce burden on sites and trial costs the Indiana University (IU) PERSEVERE Team will be managing the PRO questionnaires for BRE18-334 through RedCap.

1. Sites should ask patients their preference for paper or electronic surveys via email (preferred method)
    a. **Electronic:** Sites should complete or have patients complete the demographic information to initiate questionnaires for upon screening/enrollment
        i. https://redcap.link/PERSEVERE
        ii. The postcard below can be given to patients who are comfortable initiating the survey on their own.
        iii. IU PERSEVERE team will send patient automated emails to the patient to complete surveys
        iv. If a patient does not receive this email, please contact the IU team

    b. **Paper:** Sites should provide patient questionnaires at specified protocol timepoints.
        i. Patient should complete paper questionnaires
        ii. Site should fax questionnaires using the coversheet below.