DF/HCC Protocol #: *17-101*

TITLE: Palbociclib After CDK and Endocrine Therapy (PACE): A Randomized Phase II Study of Fulvestrant, Palbociclib, and Avelumab for Endocrine Pre-treated ER+/HER2- Metastatic Breast Cancer

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Industry (Pfizer)-Supplied Agents: Palbociclib, Avelumab
Other Agent(s): Fulvestrant, supplier: commercial

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SCHEMA

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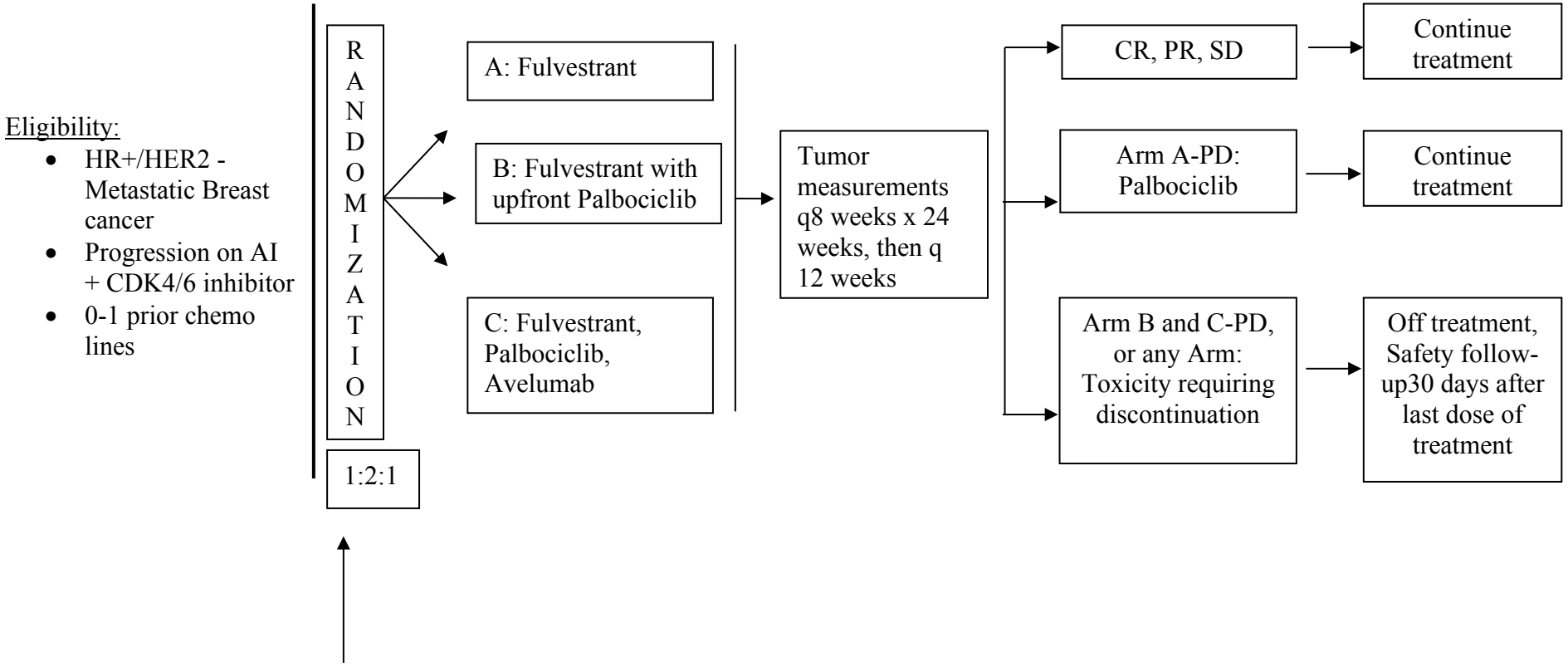
Eligibility:
HR+/HER2 - Metastatic Breast cancer
Progression on AI + CDK4/6 inhibitor
0-1 prior chemo lines
RANDOMIZATION
1:2:1
A: Fulvestrant
B: Fulvestrant with upfront Palbociclib
C: Fulvestrant, Palbociclib, Avelumab
Tumor measurements q8 weeks x 24 weeks, then q 12 weeks
CR, PR, SD
Continue treatment
Arm A-PD: Palbociclib
Continue treatment
Arm B and C-PD, or any Arm: Toxicity requiring discontinuation
Off treatment, Safety follow-up30 days after last dose of treatment
Stratification:
Exposure to a chemotherapy regimen between initial exposure to CDK4/6 inhibitor and entry on this study (Yes/No)

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1. OBJECTIVES AND ENDPOINTS

1.1 Study Design

This is a randomized phase II pilot study designed to evaluate the utility of palbociclib therapy (with fulvestrant) or PD-L1 checkpoint blockade (with fulvestrant) in patients with advanced ER+/HER2- breast cancer that has progressed despite prior CDK4/6 inhibition with endocrine therapy. At least 220 eligible patients will be randomized 1:2:1 to receive fulvestrant alone (Arm A: approximately 55 patients), fulvestrant plus palbociclib (Arm B: approximately 110 patients), or fulvestrant plus avelumab plus palbociclib (Arm C: approximately 55 patients). Patients will be stratified by whether there was exposure to a chemotherapy regimen between initial exposure to CDK4/6 inhibitor and entry on this study, to determine if a break from CDK4/6 inhibition increases CDK4/6 inhibitor sensitivity.

1.2 Primary Objective

To evaluate progression-free survival (PFS) using traditional RECIST criteria with the combination of fulvestrant and palbociclib vs. fulvestrant alone in patients with advanced HR+/HER2- breast cancer that has progressed despite prior CDK4/6 inhibition and endocrine therapy.

1.3 Secondary Objectives

- To assess the objective response rate (ORR) of fulvestrant + palbociclib vs fulvestrant alone in patients with advanced ER+/HER2- breast cancer that has progressed despite prior CDK4/6 inhibition and endocrine therapy
- To assess the PFS and ORR with addition of palbociclib after progression on fulvestrant alone in patients with advanced ER+/HER2- breast cancer that has progressed despite prior CDK4/6 inhibition and endocrine therapy using traditional RECIST criteria
- To assess the PFS and ORR for fulvestrant, palbociclib + avelumab vs fulvestrant alone in patients with advanced ER+/HER2- breast cancer that has progressed despite prior CDK4/6 inhibition and endocrine therapy using traditional RECIST criteria
- To assess the PFS and ORR for fulvestrant, palbociclib + avelumab vs fulvestrant + palbociclib in patients with advanced ER+/HER2- breast cancer that has progressed despite prior CDK4/6 inhibition and endocrine therapy using traditional RECIST criteria
- Safety and tolerability of all agents

1.4 Exploratory Objectives

[redacted]

1.5 Correlative Objectives

1.6 Endpoints

1.6.1 Primary Endpoint

- Progression-Free Survival (PFS)

1.6.2 Secondary Endpoints

- Objective Response (ORR: Complete Response or Partial Response)
- Duration of Response (DOR)
- Clinical Benefit Response (CBR)
- Type, incidence, severity (as graded by NCI CTCAE Version 4.0), seriousness and relationship to study medications of adverse events (AE) and any laboratory abnormalities

2. BACKGROUND

2.1 Hormone Receptor Positive Breast Cancer

Hormone receptor positive (HR+) breast cancer is the most commonly diagnosed subset of breast cancer, and affects thousands of patients every year. Endocrine therapy is highly effective for this subset of breast cancer, and standard adjuvant management for women with HR+ breast cancer includes adjuvant endocrine therapy for at least 5 years. Despite this effective therapy, a percentage of patients will relapse with incurable metastatic disease, likely related to the development of resistance to endocrine therapy.

A variety of novel agents are in development to improve the efficacy of endocrine therapy against HR+ breast cancer. These include compounds that halt progression through the cell cycle via inhibition of the CDK4/6 kinases. Palbociclib, a CDK4/6 inhibitor, has been approved for the treatment of metastatic HR+/HER2- negative breast cancer both in the first-line setting with concurrent aromatase inhibition (PALOMA-1, the findings were confirmed in PALOMA-2), as well as in patients previously treated with endocrine therapy in combination with fulvestrant (PALOMA-3). Palbociclib plus letrozole has been added to the NCCN guidelines as a treatment option for first-line therapy for postmenopausal patients with ER-positive, HER2-negative breast cancer (NCCN Guidelines). The most recently published ASCO on endocrine therapy for hormone receptor positive metastatic breast cancer also stated that a non-steroid aromatase inhibitor (AI) with palbociclib may be offered to treatment naïve HR+, HER2- metastatic breast cancer[50].). Since palbociclib was launched in US in February 2015, more than 35,000 women have been treated with palbociclib in routine clinical care. In addition, other CDK4, 6 inhibitors, including ribociclib and abemaciclib, are approved for metastatic HR+ HER2- breast cancer as well. .

However, patients progress on CDK4/6 inhibitor containing regimens. Mechanisms governing resistance to CDK4/6 inhibitor therapy have not been fully elucidated, and it is unclear whether ongoing palbociclib therapy might be of benefit even after the development of clinical progression.

2.2 Palbociclib Mechanism of Action

Cell cycle inhibition is a target of choice for novel cancer therapeutics. palbociclib, an orally active pyridopyrimidine, is a potent first-in-class, highly selective reversible inhibitor of CDK 4 and CDK6 (IC_{50} = 11 nM; Ki = 2 nM) with a molecular weight of 447.53. Data from nonclinical studies indicate that palbociclib may have cytoreductive as well as cytostatic effects on tumor cells.

The compound prevents cellular DNA synthesis by prohibiting progression of the cell cycle from G1 into the S phase, as demonstrated both in laboratory models and in early clinical trials. CDK4 and CDK6 control G1 to S phase transit by binding to D-type cyclins.[3-5] The CDK4/6/Cyclin D1 complex phosphorylates the retinoblastoma susceptibility (*RB1*) gene product (Rb), releasing the E2F and DP transcription factors that drive expression of genes required for S-phase entry.[5] CDK activity and G1 progression is negatively regulated by Cip-Kip and INK4 family, typified by p16.[6-10] Overexpression of p16 in cells with normal Rb inhibits both CDK4-and CDK6-associated kinase activity and Rb phosphorylation, with subsequent cell cycle arrest.[11,12]

There is a strong link between the actions of estradiol and the G1-S phase transition, where the estradiol effector is the cyclin D1-CDK4/6-Rb complex.[13] Cyclin D1 is a direct transcriptional target of ER[14-17] and microinjection of antibodies to cyclin D1 inhibits estrogen-induced S-phase entry.[18-22] In addition, anti-estrogen-induced growth arrest of ER+ breast cancer cells is accompanied by decreased cyclin D1 expression[23] while endocrine resistance is associated with persistent cyclin D1 expression and Rb phosphorylation.[24] Consistent with the notion that the main function of cyclin D1 is to activate CDK4/6, its oncogenic activity is dependent on CDK4/6-associated kinase activity[25] and CDK4/6 inhibitors are most effective in tumors with gene amplification and overexpression of cyclin D1,[26-28] which is common in ER+ breast cancer. For example, palbociclib was most effective for ER+ breast cancer in a cell line panel,[29] including those that exhibited anti-estrogen resistance. Genetic aberrations leading to hyperactivation of

cyclin D1-CDK4/6 is particularly common in ER+ breast cancer, consistent with its critical role in the tumorigenesis of this cancer subtype,[29] making CDK4/6 inhibitors particularly attractive agents for ER+ breast cancer.

Preclinical data, both Pfizer internal data and also from other laboratories, suggest that estrogen resistant models are exquisitely sensitive to the combination of palbociclib with antihormonal therapy or palbociclib alone. Blockade of the ER signaling pathway is synergistic with cell cycle arrest induction, as demonstrated by the more than doubling in median PFS observed in Study A5481003 (Study 1003; PALOMA-1) in combination with letrozole in post-menopausal women with ER-positive advanced breast cancer[34] which resulted in the accelerated approval in the US in February 2015.

2.3 Palbociclib Preclinical Data and Pharmacokinetic Studies

Palbociclib preclinical data indicate that it may be expected to have direct effect on growth arrest as well as potential secondary cytoreductive activity. Single agent palbociclib has shown antiproliferative effects (selective G_1 arrest) on Rb-positive cancer cells *in vitro* and *in vivo*[27] where palbociclib activity was associated with reduced Rb-phosphorylation and decreased expression of the cell proliferation marker Ki67. Palbociclib showed no activity in Rb-negative tumor cell xenografts, consistent with CDK4/6 inhibition as the sole mode of action.[27]

Treatment of cultured tumor cells with palbociclib causes growth arrest that is accompanied by the inhibition of specific pRb phosphorylation by CDK4 or CDK6 on residues serine -780 and -795 of pRb. The IC_{50} values for reduction of pRb phosphorylation at serine -780 and -795 in MDA-MB-435 breast carcinoma cells were 0.066 and 0.063 μM, respectively. The IC_{50} values for reduction of pRb phosphorylation are similar to the IC_{50} values of inhibition of thymidine incorporation across a range of cultured tumor and normal cells.

Palbociclib was tested in vitro on molecularly characterized human breast cancer cell lines. Results from these experiments indicate that those cell lines that are more sensitive to palbociclib (IC_{50} < 150 nM) have low levels of CDKN2A (p16) and high levels of Rb, while resistant cell lines show the opposite characteristics. Of note for this study, ER+ breast cancer seems to be particularly appropriate for treatment with palbociclib; sensitive cell lines in this panel represent mostly the luminal ER+ subtype.[29]

The combination of palbociclib with tamoxifen has been tested in vitro in ER+ human breast cancer cell lines indicating a synergistic interaction[29] and provided a biologic rationale for evaluating the combination of palbociclib with anti-hormonal therapy in the clinic. Also, most recent data from Julie Kan's group in hormone resistant models (MCF7-CYP19) indicate a significant benefit from the combination of palbociclib and letrozole as well as palbociclib and fulvestrant over single agent letrozole and fulvestrant (Pfizer, unpublished data).

Once daily oral administration of palbociclib was well tolerated in rats at levels of 10 mg/kg/day for males and up to 200 mg/kg/day for females[43].

Palbociclib has been evaluated in safety pharmacology, genetic toxicity, reproductive and

development (fertility and early embryonic development, embryofetal development), and repeat-dose toxicity studies of up to 15-weeks duration in the rat and dog. Based on the nonclinical safety studies conducted with palbociclib, the primary palbociclib-related systemic toxicities were observed in hematolymphopoietic tissues (decreased cellularity, increased iron pigment, decreases in peripheral leukocytes and RBC parameters) and male reproductive organs (degeneration of seminiferous tubules, secondary epididymal hypospermia and increased intratubular cellular debris). Partial to complete reversibility of toxicities was demonstrated following a 4 week recovery period, with the exception of the male reproductive organ findings in the dog. These toxicities occurred in both rats and dogs, and are consistent with the intended pharmacologic effect of palbociclib (i.e., cell cycle inhibition). (Fink et al, 2001; Arguello et al, 1998; Bartkova et al, 2003). Palbociclib was also identified with the potential to cause QT prolongation, developmental effects, and aneugenicity. Developmental effects that were considered adverse included a decrease in fetal body weights in rats and a low incidence of small phalanges on the forepaws in rabbits. A no effect level for aneugenicity was observed at approximately 7-fold higher than unbound systemic AUC24 exposures associated with the human clinical dose of 125 mg QD.

Palbociclib is being further evaluated for chronic toxicity in a 6-month rat and 9-month dog repeat-dose toxicity study. Cataracts have been identified in rats following 27-weeks of intermittent dosing. The minimal dose level for cataract formation has not been identified from the 27-week rat toxicity study, based on the histological data (lens degeneration was noted microscopically). Cataracts were identified from ophthalmic evaluations at the lower examined dose of 30 mg/kg/day in males but at no dose in females.

Further data from this toxicity study suggested a correlation between altered glucose metabolism and the formation of cataracts/lens degeneration. In dog toxicity studies (15-week and 39-week), no altered glucose levels or cataracts/lens degeneration have been observed (lack of lens degeneration not yet confirmed in the 39-week study; histopathology pending). Hyperglycemia and diabetes mellitus are not considered to be identified clinical risks and are not considered to be adverse drug reactions (ADRs) of palbociclib.

Human Pharmacokinetic (PK) Data

In the first-in-human Study A5481001, the exposure (area under the concentration-time curve from time 0 to 10 hours [$AUC_{(0-10)}$] and maximum concentration [C_{max}]) increased in a dose proportional manner over the dose range of 25 to 225 mg QD on Schedules 3/1 and 2/1 following palbociclib administration on Days 1 and 8 of Cycle 1, although some variability (low to moderate) around these doses was observed particularly at the 150 mg QD dose level. In Study 1003, following repeated daily dosing to steady state, palbociclib was absorbed with a median time to reach maximum concentration (T_{max}) of ~7.9 hours. The mean palbociclib apparent volume of distribution (V_z/F) was 2583 L, which is significantly greater than total body water (42 L), indicating that palbociclib extensively penetrates into peripheral tissues. Palbociclib was eliminated slowly; the mean elimination half-life ($t_{½}$) was 28.8 hours and the geometric mean CL/F (apparent clearance of drug from plasma) was 63.1 L/hour. Steady state was reached within 8 days after the start of palbociclib dosing. Palbociclib accumulated following repeated dosing with a median accumulation ratio (R_{ac}) of 2.4, which is consistent with the terminal half-life.

Food Effect

Study A5481021 was a randomized, open-label, single-dose, 4-sequence, 4-period crossover study to evaluate the effect of food on oral bioavailability of the palbociclib commercial free base capsule formulation in healthy subjects. The study results indicate that palbociclib absorption and exposure were very low in approximately 13% of the population under the fasted condition. Food intake increased the palbociclib exposure in this small subset of the population, but did not alter palbociclib exposure in the rest of the population to a clinically relevant extent. Administration of palbociclib with or in between meals significantly reduced the intersubject variability (%CV) of AUC_{inf} (area under the concentration-time curve from time zero to infinity) and C_{max}, from 39% for AUC_{inf} and 73% for C_{max} under overnight fasted conditions to 23% to 27% for AUC_{inf} and 21% to 24% for C_{max} under fed conditions, irrespective of the fat and calorie content of the food. Based on these findings, palbociclib should be taken with food.

Antacid Effect

The solubility of the palbociclib free base is pH dependent; palbociclib is water soluble at low pH (2.1 – 4.5), while the solubility dramatically decreases as pH rises above 4.5. Concomitant administration of agents which increase gastric pH can alter the solubility and absorption of palbociclib free base formulations.

In a drug-drug interaction study in healthy subjects (Study A5481038), coadministration of a single dose of 125 mg palbociclib free base capsule with multiple doses of a proton pump inhibitor (PPI), rabeprazole, under fed conditions decreased palbociclib C_{max} by 41% but had limited impact on AUC_{inf} (13% decrease) compared with a single dose of palbociclib administered alone. This 13% reduction in overall exposure is considered not clinically relevant. The results also indicated that administration of palbociclib under fed conditions with staggered dosing of an H2-receptor antagonist (H2RA), famotidine, and staggered dosing of a local antacid, Mi-Acid Maximum Strength Liquid, had no impact on the exposure of palbociclib. Given the reduced effect on gastric pH of H2RAs and local antacids compared to PPIs, the effect of these acid-reducing agents when given simultaneously with palbociclib free base capsules under fed conditions is expected to be minimal.[34,35] In another healthy subject study (Study A5481018), coadministration of a single dose 125 mg palbociclib free base capsule with multiple doses of rabeprazole under fasted conditions decreased palbociclib AUC_{inf} and C_{max} by 62% and 80%, respectively, when compared with a single dose of palbociclib administered alone.

Collectively, these antacid drug-drug interaction (DDI) data further support the requirement that the free base capsule of palbociclib should be taken with food.

Beginning in March-May 2020, Pfizer will be switching from a capsule to tablet formulation for palbociclib in the United States. The new tablet formulation of palbociclib may be taken with or without food, unlike the capsule formulation. Additionally, unlike the capsule formulation, the tablet formulation can be taken with proton pump inhibitors (PPI)/antacids and does not contain lactose (dairy) or gelatin, which may be important for patients with tolerability issues and/or dietary preferences.

Metabolic Drug Interaction

In vitro data indicate that CYP3A and SULT enzyme SULT2A1 are mainly involved in the metabolism of palbociclib. In vitro, palbociclib is not an inhibitor of CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, and 2D6, and is not an inducer of CYP1A2, 2B6, 2C8, and 3A4 at clinically relevant concentrations.

The effect of multiple dosing of palbociclib 125 mg QD on the single-dose PK of a sensitive CYP3A4/5 probe substrate, midazolam (2 mg), was evaluated in 26 healthy women of non-childbearing potential in Study A5481012. Coadministration of midazolam and palbociclib increased midazolam AUC_{inf} and C_{max} by 61% and 37%, respectively, relative to midazolam given alone. These results indicate that palbociclib is a weak time-dependent inhibitor of CYP3A.

An itraconazole DDI study in healthy subjects (Study A5481016) and a rifampin DDI study in healthy subjects (Study A5481017) were conducted to evaluate the potential for strong CYP3A inhibitors and inducers, respectively, to alter the PK of palbociclib. Coadministration of itraconazole and palbociclib increased palbociclib AUC_{inf} and C_{max} by approximately 87% and 34%, respectively, relative to when palbociclib was given alone. Coadministration of rifampin and palbociclib decreased palbociclib AUC_{inf} and C_{max} by approximately 85% and 70%, respectively, relative to when palbociclib was given alone. Based on these results, the concurrent administration of strong CYP3A inhibitors and inducers with palbociclib should be avoided.

Coadministration of Palbociclib and Fulvestrant

Study A5481023 was a randomized, double-blind, Phase 3 study conducted to assess the efficacy, safety, and PK of palbociclib administered in combination with fulvestrant with or without goserelin versus placebo plus fulvestrant with or without goserelin for the treatment of HR-positive/HER-2 negative advanced breast cancer that progressed on prior endocrine therapy. The study included limited PK sampling (steady-state trough samples) to confirm the lack of a clinically significant DDI between palbociclib and fulvestrant or between palbociclib and goserelin. The concurrent administration of fulvestrant did not have a clinically relevant impact on the plasma PK of palbociclib. Likewise, the concurrent administration of palbociclib did not have a clinically relevant impact on the plasma PK of fulvestrant. Therefore, there is no clinically relevant DDI between palbociclib and fulvestrant when they are coadministered.

Coadministration of Palbociclib and Goserelin

The concurrent administration of goserelin did not have a clinically relevant impact on the plasma PK of palbociclib in Study A5481023. Likewise, the concurrent administration of palbociclib did not have a clinically relevant impact on the plasma PK of goserelin. Therefore, there is no clinically relevant DDI between palbociclib and goserelin when they are coadministered.

2.4 Palbociclib Clinical Data

Palbociclib has been tested in a Phase 1 dose escalation trial (Study A5481001) in 74 patients with advanced cancer. Two dosing schedules were evaluated: Schedule 3/1 (3 weeks on treatment followed by 1 week off treatment; n=41) at doses ranging from 25 to 150 mg and Schedule 2/1 (2 weeks on treatment followed by 1 week off treatment; n=33) at doses ranging from 100 to 225 mg. All dose limiting toxicities (DLTs) observed in this study were related to myelosuppression and mainly consisted of Grade 3 neutropenia lasting more than 7 days after the end of the treatment cycle. However, neutropenia was reversible and non-cumulative. The most common non-hematological adverse events included fatigue, anemia, diarrhea, constipation, vomiting, and dyspnea, mostly mild to moderate severity. A greater proportion of patients on Schedule 2/1 had treatment-related adverse events during and after Cycle 1 than patients on Schedule 3/1 although the proportion of patients with treatment-related neutropenia was similar with respect to the 2 dosing schedules, both during and after Cycle 1. A total of 13/37 patients on Schedule 3/1 evaluable for efficacy experienced stable disease (SD), including 6 patients with SD lasting 40 weeks or longer. Based on the relatively improved safety profile of Schedule 3/1 and the efficacy results, Schedule 3/1 was selected for further clinical development and the Recommended Phase 2 Dose (RP2D) for this schedule was determined to be 125 mg/day.

Palbociclib has been investigated in the following pivotal studies for the treatment of advanced breast cancer: A5481003 (Study 1003), A5481008 (Study 1008), and A5481023 (Study 1023).

Study 1003 was a Phase 1/2, randomized, open-label study designed to assess the efficacy and safety of palbociclib (125 mg QD on Schedule 3/1) in combination with letrozole 2.5 mg QD versus letrozole 2.5 mg QD alone for the first-line treatment of post-menopausal women with ER-positive/HER2-negative advanced breast cancer. The results from the study demonstrated a statistically significant improvement in PFS for the palbociclib plus letrozole arm compared to the letrozole alone arm (20.2 vs. 10.2 months; HR=0.488 [95% CI: 0.319, 0.748]; p <0.001).**Error! Reference source not found.** The most common adverse events reported for the palbociclib plus letrozole arm were hematologic events, mostly neutropenia and leukopenia that were reversible. Based on the results from this study, palbociclib was granted accelerated approval in the US in combination with letrozole for the treatment of post-menopausal women with ER-positive/HER-2 negative advanced breast cancer as initial endocrine-based therapy for their metastatic disease.

Study 1008 was a Phase 3, randomized, double-blind, placebo-controlled study designed to assess the efficacy and safety of palbociclib (125 mg QD on Schedule 3/1) plus letrozole 2.5 mg QD versus placebo plus letrozole 2.5 mg QD for the first-line treatment of post-menopausal women with ER-positive/HER2-negative advanced breast cancer. The results from the study demonstrated a statistically significant improvement in PFS for the palbociclib plus letrozole arm compared to the placebo plus letrozole arm (24.8 vs. 14.5 months; HR=0.58 [95% CI: 0.46, 0.72]; p <0.000001)[37], confirming the significant clinical benefit and safety of palbociclib plus letrozole in ER-positive/HER2-negative advanced breast cancer who had not received prior systemic therapy for their advanced disease observed in Study 1003.

Study 01010 was a Phase 3, randomized, double-blind, placebo-controlled study designed to assess the efficacy and safety of palbociclib (125 mg QD on Schedule 3/1) plus fulvestrant 500

mg versus placebo plus fulvestrant 500 mg for the treatment of women with HR-positive/HER2-negative advanced breast cancer whose disease had progressed after prior endocrine therapy. The results from the study indicated that the addition of palbociclib to fulvestrant significantly prolongs PFS with the median PFS of 9.5 months (95% CI: 9.2, 11.0) for the palbociclib plus fulvestrant arm and 4.6 months (95% CI: 3.5, 5.6) for the placebo plus fulvestrant arm (HR=0.461 [95% CI: 0.360, 0.591]; p <0.0001)[38]. The adverse events observed in the study were consistent with the known safety profile of palbociclib. Overall, palbociclib was well tolerated with adverse events managed by dosing interruptions, dose reductions, and/or standard medical care. Based on the results from this study, palbociclib was approved in the US in combination with fulvestrant for the treatment of women with HR-positive/HER2-negative advanced breast cancer with disease progression following endocrine therapy.

2.5 Mechanisms of Resistance to Palbociclib and Endocrine Therapy

Despite the promising evidence of clinical efficacy outlined above, a subset of patients manifest de novo resistance to the anti-estrogen/palbociclib combination and those that do not invariably develop resistance at some point in the future. Insights into the mechanisms governing resistance to both anti-estrogen therapy as well as CDK 4/6 inhibition remain limited and constitute and active area of clinical and basic scientific research.

Early pre-clinical work with palbociclib revealed a set of 450 genes that were differentially expressed between resistant and sensitive cell lines[29].These results seemed to indicate that genes associated with luminal breast cancers were enriched in the sensitive group. Loss of the tumor suppressor Rb was associated with resistance, and this has been borne out in subsequent studies. In a recent in vitro study, ER+ cell lines were grown in long-term culture with palbociclib to induce acquired resistance (Lenihan C SABCS 2015). These resistant clones were then profiled via western blot assay, RNA sequencing, and mass spectrometry in an effort to identify mediators of resistance. Sustained downregulation of Rb was identified, which was reversible upon drug withdrawal. Hyperactivation of the PI3K/mTOR and Rho/Rac pathways was also identified. Targeted drug screening revealed increased sensitivity of palbociclib-resistant cell lines to various inhibitors of AKT, PI3K, and MEK. A second recent study confirmed this work in vitro, suggesting that in palbociclib-resistant T47D ER+ cells, loss of Rb acts as a primary driver of resistance (Lee NV SABCS 2015). This work also revealed upregulation of various transcriptional effectors including E2F, TGFB, WNT, MYC, and NF-kB in MCF7 palbociclib-resistant cell lines that had retained Rb expression. Interestingly, in these MCF7 palbociclib-resistant cell lines, both cyclin E1 and cyclin A2 were found to be upregulated downstream of E2F. Given the redundant role of cyclin E/CDK2 in the regulation of Rb, knockdown of cyclin E was attempted via shRNA. This intervention was able to restore palbociclib sensitivity, suggesting that cyclin E may be a key mediator of resistance in this context.

Mechanisms governing resistance to anti-estrogen blockade are also diverse and poorly understood. Many of the canonical signal transduction pathways alluded to above, including the PI3K/mTOR/AKT pathway, have been implicated in the development of estrogen-independence. Acquired mutations in the estrogen gene (ESR1) have also been described[46].These mutations rarely occur in primary breast cancer, but appear to be enriched via selective pressure during course of treatment with aromatase inhibitors. Tumors and cell lines that have acquired an ESR1 mutation

also appear to maintain at least some sensitivity to the selective estrogen degrader fulvestrant. ESR1 mutations have been identified via blood-based circulating free tumor DNA assays[51] and this may serve as a rapid, non-invasive measure of de novo or emerging resistance in ER+ breast cancer. In a recent retrospective-prospective analysis, plasma ESR1 levels were assessed in a subset of patients treated on the PALOMA-3 study outlined above[44]. The presence of ESR1 mutations (identified in more than 25% of patients) was associated with acquired resistance to prior aromatase inhibitor therapy. Both groups (with and without established ESR1 mutations) benefited from combination therapy with fulvestrant and palbociclib. Additional work is required to explore the role of CDK 4/6 inhibitor therapy in patients that have acquired anti-estrogen resistance via ESR1 mutation.

2.6 Immunotherapy in HR+/HER2- Breast Cancer

The emergence of immune therapy has revolutionized the treatment of multiple tumor types. Novel agents including the checkpoint inhibitors that impact PD-1 and PD-L1 signaling have been approved in multiple malignancies including melanoma, non-small cell lung cancer, and bladder cancer, with impressive results to date in other malignancies including various lymphomas, GI cancer, and squamous cell carcinoma of the head and neck. To date, early results with immune checkpoint blockade in breast cancer have been mixed. The majority of early clinical studies have incorporated single agent PD-1 or PD-L1 in the triple negative breast cancer population. This is based, in part, upon the knowledge that at least a subset of patients with triple negative breast cancer harbor a genomic signature enriched in immunomodulatory effectors[47]). Patients with triple negative breast cancer also seem to express higher relative levels of PD-L1 compared to non-triple negative controls[48].

Phase I studies of the PD-1 inhibitor pembrolizumab and the PD-L1 inhibitor atezolizumab have been reported in triple negative breast cancer[49]. Both of these studies reported overall response rates of approximately 18-19%, with a subset of durable, long-term responders. Limited experience exists to date in the HR+ breast cancer population though, per the Keynote 028 phase I study, PD-1 checkpoint blockade was well tolerated in the endocrine-resistant breast cancer population (Rugo HS SABCS 2015). The novel PD-L1 inhibitor avelumab, discussed in detail below, was assessed in a mixed population of patients with metastatic breast cancer in the phase I setting (Dirix SABC 2015). In this study, which included nearly 170 patients with up to three lines of prior chemotherapy, avelumab was well tolerated. The overall response rate was approximately 5%, with a range from 3% (in ER+/HER2- patients) to 9% (in triple negative patients). More than 20% of the patients on this study achieved stable disease. It is important to acknowledge that broad generalizations regarding the utility of immune therapy in breast cancer are hampered by relatively small sample sizes, differences amongst patient populations in the various studies, divergent inclusion criteria (including PD-L1 positivity), and arbitrary cut-points for PD-L1 expression. A larger study in a uniform population of HR+/HER2- metastatic breast cancer patients is needed to better assess the utility of PD-L1 blockade in the endocrine resistant population.

2.7 Avelumab Mechanism of Action

Avelumab (also referred to as MSB0010718C) is a fully human IgG1 antibody directed against PD-L1. Avelumab binds PD-L1 and blocks the interaction between PD-L1 and its receptors PD-1

and B7.1. This removes the suppressive effects of PD-L1 on anti-tumor CD8+ T cells, resulting in the restoration of cytotoxic T cell response.

The PD-1 receptor is expressed on activated CD4+ and CD8+ T cells. By interaction with its ligands, PD-L1 and PD-L2, PD-1 delivers a series of strong inhibitory signals through its cytoplasmic tail to inhibit T cell functions[52-54]. PD-L1 (also called B7-H1 and CD274) can be detected on resting and activated T cells, B cells, macrophages, dendritic cells, and mast cells; PD-L1 expression is greatly up-regulated after activation or interferon treatment[53].Numerous results from in vitro cellular assays have demonstrated that blockade of the PD-1/PD-L1 interaction enhances T cell responses, such as increases in proliferation and cytokine production[55-61].In PD-1–/–mice both T and/or B cells responses are unregulated resulting in an array of autoimmune pathologies[62,63]. Breaking tolerance through blocking PD-1 interaction with its ligands, and thus PD-1 signaling, can be applied to enhance Tcell activity towards chronic pathologies such as cancer[64].

External[63]and internal immunohistochemistry studies have demonstrated that PD-L1 is also expressed by a variety of human tumors, both by the tumor cells, as well as by the immune cells that are present in the tumor microenvironment. In contrast to very strong expression on syncytiotrophoblasts in the placenta and in cancer cells, low levels of PD-L1 expression were detected in some normal tissues including fetal cardiac tissue[58]. High levels of PD-L1 expression have been found to be associated with disease progression, increased metastasis, poor response to treatment, and decreased survival in a number of human cancers[63]. Importantly anti-PD-L1 blockade has demonstrated therapeutic efficacy in a variety of murine tumor models as monotherapy and has shown synergistic effect in combination therapy setting[56, 65-70].

The antitumor activity of avelumab has been investigated in various murine tumor models. Inhibition of the PD-1/PD-L1 interaction is proposed to exert a therapeutic effect by restoring anti-tumor CD8+ T cell responses.

To circumvent the need for a surrogate antibody, the lead candidate antibody was specifically selected for cross-reactivity to murine PD-L1, and, as consequence all of the nonclinical studies were conducted in syngeneic murine tumor models in which the immune system of the host is fully intact. It was demonstrated that the inhibition of the PD-1/PD-L1 interaction restores anti-tumor CD8+ T cell responses, which results in an anti-tumor activity.

Avelumab has demonstrated significant nonclinical activity as a monotherapy and in various combination therapy settings. In general, the anti-tumor immunotherapy via blockade of the PD-1/PD-L1 axis seems not to be limited to any specific tumor types, but there is recent evidence that PD-L1 tumor expression is a pre-requisite to achieve an objective response upon blockade of the PD-1/PD-L1 axis[71]. The clinical relevance of PD-1/PD-L1 blockade has been demonstrated in Phase I trials performed with antibodies targeting either PD-L1 or PD-1[71, 72].

Given the important role of PD-L1 in the suppression of T-cell responses, and the mode of action of avelumab which blocks the interaction between PD-L1 and its receptors, avelumab is being developed as a potential therapy for subjects with various tumors.

Clinical Phase I/II trials with MoAbs targeting either PD-L1 or PD-1 have shown promising hints for clinical efficacy, i.e., objective tumor response in indications such as NSCLC, melanoma, and ovarian cancer[71-73].

Avelumab has 2 main mechanisms of action for exerting its anti-tumor effects:

- PD-L1 on tumor cells can interact with PD-1 or B7-1 on activated T cells. These interactions have been shown to significantly inhibit T cell activities. Therefore, blocking PD-L1 interaction with PD-1 or B7-1 by anti-PD-L1 can release T cells from immunosuppression, and lead to elimination of tumor cells by T cells.
- Tumor cells may express high levels of PD-L1 on their surface compared with normal tissues. As a fully human IgG1 MoAb, avelumab has antibody-dependent cellular cytotoxicity (ADCC) potential. Upon binding to PD-L1 on tumor cells and binding with their Fcpart to Fc-gamma receptors on leukocytes, avelumab can trigger tumor-directed ADCC.

Therefore, blocking PD-L1 inhibitory mechanisms by interactions with not only PD-1 but also the other ligand, B7-1, avelumab offers unique therapeutic potential compared with MoAbs targeting PD-1.

2.8 Avelumab Pharmacokinetic Data and Dose Selection

A dose of 10 mg/kg of avelumab, intravenous (Iv) once every 2 weeks, was selected for the expansion cohorts of Phase I trials, the Phase II pivotal trial (EMR100070-003),and the ongoing Phase III trials based on the preliminary pharmacokinetic(PK),target occupancy, and preliminary clinical safety data collected in the clinical trials.

Avelumab plasma levels leading to full programmed death ligand 1 (PD-L1) receptor target occupancy (TO) on PBMCs resulted in tumor growth inhibition in a murine disease model. Therefore, full TO on PBMCs can be considered a PD marker for the ability of avelumab to act on its target and to show clinical activity.

Preliminary PK data from EMR 100070-001 show that the concentration at the end of dose interval (Cmin) increased more than proportionally to dose between 1 to 10 mg/kg, but proportionally for doses above 10 mg/kg. Consistently the t1/2 also increased with the dose. However, the average value was 102 and 120 hours for 10 mg/kg and 20 mg/kg, respectively, with no significant difference between these two dose groups. This PK characteristic suggests that target mediated drug disposition is involved in the clearance of avelumab and a high PD-L1 TO is likely achieved at the trough concentration for doses of 10mg/kg and 20mg/kg.

The in vitro target occupancy data further support that a high TO is likely achieved at 10 mg/kg and above.

Target occupancy was measured ex vivo by flow cytometry on peripheral blood CD3+ T cells from patients (n=9) treated with avelumab. After the first dose of the initial dose-escalation portion of Trial EMR 100070-001, the observed mean target occupancy reached a plateau of about 90% on Day 15 pre-dose for dose levels of 3 mg/kg and above.

In addition, in vitro target occupancy was measured using flow cytometry on peripheral blood CD3+ T cells from 8 healthy volunteers after spiking avelumab over a concentration range of 0.003 to 10 μg/mL. A 50% target occupancy was observed at a drug concentration (standard deviation [StD]) of 0.122 (0.042) μg/mL, and a concentration of 1 μg/mL avelumab was required for > 95% target occupancy. Based on these data and the trough serum levels observed in EMR 100070-001, target occupancy was projected to reach or exceed > 95% throughout the entire dosing interval for 10/13 subjects at 3 mg/kg, and for all (15/15) subjects at 10 mg/kg group from dose escalation group in EMR1000700-001.

Based on the ex-vivo peripheral blood CD3+ T cell and in vitro target occupancy results, the dose of 10 mg/kg every 2weeks is expected to achieve target saturation during the entire dosing interval in the majority of patients.

As of the safety cutoff date of 05 November 2015, 1353 subjects have received at least 1 dose of avelumab at doses ranging from 1.0 to 20 mg/kg in the Phase I Trial EMR 100070-001, of which 1315 have received the proposed dose of 10mg/kg (15 in the dose escalation part of the study and 1300 subjects in the pooled expansion cohort).

In the dose escalation portion of the Phase I study, there was no evidence of differences in the safety profile across all administered dose levels from 1 mg/kg to 20 mg/kg. The MTD was not reached. Ongoing review of the safety data by the Safety Monitoring Committee (SMC) suggests an acceptable safety profile of avelumab administered at the 10 mg/kg every 2 weeks dose and schedule. Treatment-related treatment-emergent adverse events (TEAEs) were observed in 813 (62.5%) subjects in the pooled expansion cohort. The most frequently observed treatment related TEAEs (incidence > 5%) were fatigue (212 subjects, 16.3%), infusion-related reaction (209 subjects, 16.1%), nausea (108 subjects, 8.3%), chills (102 subjects, 7.8%), diarrhea (79 subjects, 6.1%), and pyrexia (72 subjects, 5.5%).Grade ≥ 3 treatment-related TEAEs were observed in 124 subjects (9.5%) in the pooled expansion cohort. The most frequently reported Grade ≥ 3 treatment related TEAEs were gamma-glutamyl transferase increased (GGT) and infusion-related reaction (each occurred in 9 subjects; 0.7%). Infusion-related reactions including drug hypersensitivity reactions and immune-mediated adverse reactions have been identified as expected adverse drug reactions of avelumab. The safety profile of avelumab is consistent with findings reported for other anti-PD-1 or anti-PD-L1 antibodies.

In conclusion, preliminary data from EMR 100070-001 showed that avelumab at doses up to 20mg/kg Iv every 2 weeks was well tolerated, and the dose of 10 mg/kg Iv every 2 weeks was considered to have an acceptable safety profile for further investigation in clinical studies.

2.9 Avelumab Clinical Data

Avelumab is currently in clinical development across Phases I, II, and III. These include:

- EMR 100070-001: A Phase I, open-label, multiple ascending dose trial to investigate the safety, tolerability, pharmacokinetics, biological and clinical activity of avelumab in subjects with metastatic or locally advanced solid tumors and expansion to selected indications

- EMR 100070-002: A Phase I trial to investigate the tolerability, safety, pharmacokinetics, biological and clinical activity of avelumab in Japanese subjects with metastatic or locally advanced solid tumors, with expansion part in Asian subjects with gastric cancer
- EMR 100070-003: A Phase II, single arm, open-label, multicenter trial to investigate the clinical activity and safety of avelumab in subjects with Merkel cell carcinoma(MCC)
- EMR 100070-004: A Phase III open-label, multicenter trial of avelumab versus docetaxel in subjects with non-small cell lung cancer that has progressed after a platinum-containing doublet

EMR 100070-001 is a Phase I, open-label, multiple ascending dose trial to investigate the safety, tolerability, PK, biological and clinical activity of avelumab in subjects with metastatic or locally advanced solid tumors and expansion to selected indications. This trial consists of 2 parts. In the dose escalation part, sequential cohorts of subjects were enrolled at progressively higher dose levels (ranging from 1.0, 3.0, 10.0, and 20.0 mg/kg once every 2 weeks) with a 3 + 3 algorithm design for determination of the maximum tolerated dose (MTD) of avelumab; in the treatment expansion phase, subjects in different tumor cohorts are being treated with 10 mg/kg of avelumab once every 2 weeks until, confirmed progression, unacceptable toxicity, or any reason for withdrawal occurs. More than 1500subjects have been enrolled in the EMR100070-001 trial. The 3 + 3 dose escalation algorithm to determine the MTD is complete and a dose of 10 mg/kg once every 2 weeks was determined for the tumor expansion cohorts on the basis of safety, PK, and PD observations. The treatment expansion part of the trial consists of 16tumor treatment cohorts. As of 05 November 2015 (data cutoff for a pre-planned safety data review by the study Safety Monitoring Committee [SMC]), 53 subjects in the dose escalation part had received avelumab (4, 13, 15, and 21 subjects had received 1.0, 3.0, 10.0, and 20.0mg/kg of avelumab, respectively) and 1300 subjects in the pooled expansion part had received 10 mg/kg avelumab and were followed up for at least 4weeks.

The safety summary summarizes data from 1300subjects treated in the pooled treatment expansion cohort from the ongoing Phase I Trial EMR100070-001 (as of 05 November 2015). The pooled data included subjects treated in all tumor expansion cohorts, including non-small cell lung cancer (NSCLC), metastatic gastric cancer, breast cancer, colorectal cancer, castrate-resistant prostate cancer, adrenocortical carcinoma, melanoma, mesothelioma, urothelial carcinoma, ovarian cancer, renal cell carcinoma, and squamous cell cancer of the head and neck. Safety data are also summarized for 52 subjects in the ongoing Phase I Trial EMR 100070-002 and for 88 subjects in the ongoing Phase II Trial EMR100070-003 (as of 17December 2015). For TrialEMR100070-004, an overview of the serious adverse events (SAEs) is provided.

Most of the observed adverse events (AEs) were either in line with those expected in subjects with advanced solid tumors or with class effects of monoclonal antibody (mAb) blocking the PD-1/PD-L1 axis. Infusion-related reactions including drug hypersensitivity reactions and immune-mediated adverse reactions (immune-related pneumonitis, immune-related colitis, immune-related hepatitis, immune-related endocrinopathies (thyroid disorders, adrenal insufficiency, new onset type I diabetes mellitus, pituitary disorders), immune-related nephritis and renal dysfunction and other immune-related AEs (myositis, myocarditis, Guillain-Barré syndrome, uveitis, pancreatitis). Guidelines for the management of immune-mediated adverse

reactions and infusion-related reactions are implemented in all ongoing clinical studies with avelumab.

The clinical efficacy information summarized in the Investigator's Brochure includes data from the following expansion cohorts of the ongoing Phase I TrialEMR100070-001, NSCLC (second line and first line cohorts), ovarian cancer, GC/GEJ, UC, mesothelioma, and adrenocortical carcinoma. In addition, efficacy results for 20 subjects in the gastric cancer expansion cohort of the ongoing Phase I Trial EMR 100070-002 and 88 subjects in Part A of the ongoing Phase 1 Trial EMR 100070-003 in mMCC are summarized.

The NSCLC expansion cohort in the ongoing Phase I Trial EMR100070-001 had a cutoff date of 15 January 2015, 6 months after start of avelumab treatment of the last subject in this expansion cohort (a total of 184 treated subjects). The objective response rate (ORR) based on confirmed and unconfirmed responses for subjects treated in the NSCLC expansion cohort was 14.1% (26 of 184 NSCLC subjects). Progression free survival (PFS) and overall survival (OS) were all evaluated for all NSCLC subjects treated in the expansion phase. As of 15 January 2015, the median PFS and OS for the NSCLC treatment expansion cohort were 11.6 weeks and 8.4 months, respectively.

The clinical activity of avelumab was also evaluated by subjects' tumor PD-L1 expression status in the NSCLC expansion cohort. An objective response was observed in 20 of 122 subjects (16.4%) who were PD-L1 positive (defined as having at least 1% PD-L1 positive tumor cells) compared with 2 of 20 subjects (10.0%) who were considered PD-L1 negative (defined as having less than 1% PD-L1 positive tumor cells). A longer median PFS (12.0vs 5.9 weeks) and OS (8.9 vs 4.6months) were both observed in PD-L1 positive compared with PD-L1 negative subjects.

The ovarian cancer expansion cohort had a data cutoff of 13 February 2015, approximately 13 weeks after the start of avelumab treatment on the last subject who was included in this pre-planned interim analysis on this expansion cohort. The ORR based on confirmed and unconfirmed responses for subjects treated in the ovarian cancer expansion cohort was 10.7% (8 of 75 subjects). The median PFS for the ovarian cancer expansion cohort was 11.4 weeks (95%confidence interval (CI): 6.3 to 12.0weeks).

The preliminary efficacy data for the ongoing Phase I Trial EMR 100070-002 are based on a data cutoff of 11 March 2015. As of the data cutoff, 3 of 20 subjects responded to trial treatment (all responses were partial responses [PRs] and all responses were confirmed responses), and the best overall response (BOR) was 15.0% (95%CI: 3.2%to 37.9%). The median PFS of this group was 11.9 weeks (95% CI: 6.0 to 12.3weeks).

Avelumab was approved by the FDA in March 2017 for treatment of Merkel-cell carcinoma.

The results of a Phase I cohort expansion trial in patients with metastatic breast cancer were presented at the 2015 San Antonio Breast Cancer meeting (Dirix et al, SABCS 2015). In this trial, 168 patients with metastatic breast cancer with up to 3 prior lines of therapy in the metastatic setting were treated with avelumab 10 mg/kg every 2 weeks until disease progression. Overall, treatment was well tolerated, with the primary grade >3 clinically significant toxicities

including autoimmune hepatitis (3 patients, 1.8%), GGT increase (3 patients, 1.8%) and fatigue (3 patients, 1.8%). Eight patients (4.8%) experienced grade 1/2 hypothyroidism, and one patient each experienced grade 3 pneumonitis, or grade 4 thrombocytopenia. The overall response rate in this unselected population was 4.8% (95% CI 2.1, 9.2) with one complete and 7 partial responses. An additional 23.2% of patients had stable disease. The median time to response was 11.4 weeks (range, 5.7-17.7 weeks), the median duration of response was 28.7 weeks (95% CI: 6.1, ne), and responses were ongoing in 5/8 patients at time of the analysis. Tumor shrinkage of ≥30% was observed in 16 patients (9.5%), including 2 patients with progressive disease by RECIST who had partial responses by modified Immune RECIST Criteria (irRC). Responses were seen in all molecular subtypes. PD-L1 status in 136 evaluable patients did not appear to correlate with response, although small numbers and varying cut-offs make this data difficult to interpret.

Response rates of ER-positive breast cancers to immune checkpoint blockade agents (e.g. anti-PD1 therapy) have been limited in clinical trials reported so far. This is likely because ER-positive breast cancers generally show low rates of lymphocytic infiltration and/or because they do not present a significant antigenic load to cytotoxic T cells. Possible strategies to increase the susceptibility of ER-positive breast cancers to immunotherapy thus include those that increase T cell activity within these tumors, or those that increase the "antigenicity" of tumor cells. Preliminary lab data suggests that the combination of CDK4/6 inhibition and anti-PD1 therapy is more effective than either monotherapy alone, and that this effect is potentially mediated by one or both of these mechanisms[76].

2.10 Rationale

Palbociclib has an established role in the treatment of metastatic HR+/HER2- breast cancer, both in the first-line setting (in combination with an aromatase inhibitor) as well as in patients who have been previously treated with endocrine therapy (in combination with fulvestrant). The combination of antihormonal therapy with the CDK4/6 inhibitor palbociclib has emerged as the FDA-approved standard of care for patients with metastatic HR+/HER2- breast cancer based upon the results of the PALOMA-1 and PALOMA-3 studies. The mechanisms governing resistance to these regimens (both de novo and acquired) remain poorly understood. The therapeutic paradigm of continuation of target blockade beyond progression is pursued in anti-estrogen and anti-HER2 approaches for breast cancer, but it is not clear if continuation of palbociclib beyond prior progression on a CDK4/6 containing regimen is of clinical value as well. Furthermore, the role of immune therapy and checkpoint blockade following the development of CDK inhibitor resistance has not yet been explored. Given the expanding patient population that has developed resistance to the combination of anti-estrogen therapy and CDK 4/6 blockade, we set out to assess both of these questions in this clinical protocol.

As outlined above, early data has implicated the loss of Rb in the development of resistance to CDK 4/6 inhibition. Upregulation of cyclin E via various signal transduction cascades (including the PI3K/AKT/mTOR pathway) has also been observed. Activating events in the PI3K signal transduction pathway, as well as acquisition of ESR1 mutations, have been identified as putative factors in the development of resistance to endocrine therapy. How these alterations, as well as previously unidentified mechanisms, might impact the development of clinical resistance constitutes an important exploratory endpoint of the current study. Additional tumor- or host-

specific factors, such as intratumoral heterogeneity and genomic instability, might also impact the rate at which resistance develops, the magnitude of benefit gleaned by the application of ongoing CDK 4/6 blockade, and response to immune checkpoint blockade.

As widespread use of CDK 4/6 inhibitors continues in the clinical arena, elucidation of the biologically-relevant mechanisms leading to resistance constitutes a critically important problem for investigation in the clinical trial setting. Insight into factors leading to progression on these regimens will assist in the development of rational second- and third-line approaches for the large group of patients receiving therapy for metastatic HR+/HER2- breast cancer.

3. PARTICIPANT SELECTION

3.1 Eligibility Criteria

3.1.1 Participants must have histologically confirmed hormone receptor positive (HR+) HER2 negative metastatic or locally recurrent unresectable invasive breast cancer. Both measurable and non-measurable disease are allowed. ER, PR and HER2 measurements should be performed according to institutional guidelines, in a CLIA-approved setting. Cut-off values for positive/negative staining should be in accordance with current ASCO/CAP (American Society of Clinical Oncology/College of American Pathologists) guidelines.

3.1.2 Men and pre- and postmenopausal women are eligible. Ongoing monthly GNRH agonist is required in pre-menopausal women or male participants for at least 4 weeks prior to study entry.

3.1.3 Participants must have radiological or objective evidence of progression on an endocrine and CDK 4/6 inhibitor regimen in the metastatic setting, and/or relapse/progression during or within 12 months of completion of an endocrine and CDK4/6 inhibitor regimen in the adjuvant setting.

- Participants must have previously been exposed to CDK4/6 inhibitor therapy in combination with endocrine therapy. Exposure to any prior CDK4/6 inhibitor, (including palbociclib, abemaciclib, and ribociclib) is allowed. Patients may have a line of endocrine therapy after combination endocrine and CDK4/6 inhibitor exposure.
- Participants must have remained on prior endocrine and CDK4/6 therapy in the metastatic setting without progression for at least 6 months prior to study entry.
- It is not mandatory to have a CDK 4/6 inhibitor containing regimen as the most recent treatment.
- Participants may have had no more than 1 prior line of endocrine and CDK4/6 inhibitor therapy in the metastatic setting

3.1.4 Participants may have 0-1 prior lines of cytotoxic chemotherapy in the metastatic setting.

3.1.5 Prior endocrine therapy in the metastatic setting may include any aromatase inhibitor (AI) or tamoxifen. In the metastatic setting, 1-2 prior lines of endocrine therapy are allowed. Prior Fulvestrant is permitted if the participant received ≤2 doses without concurrent endocrine therapy prior to enrollment and without evidence of disease progression.

3.1.6 Participants may have received radiotherapy for palliative purpose, but must not be experiencing > grade 1 treatment related toxicities and must have completed treatment > 14 days prior to registration.

3.1.7 Age ≥18 years. Because no dosing or adverse event data are currently available on the use of study agents in participants <18 years of age, children are excluded from this study.

3.1.8 ECOG performance status 0-1 (see Appendix A).

3.1.9 Participants must have normal organ and marrow function as defined below:

- Absolute neutrophil count ≥ 1,500/μL
- Platelets ≥ 100,000/μL
- Hemoglobin ≥ 9g/dL
- Total bilirubin ≤ 1.5 x institutional upper limit of normal (ULN)
- AST (SGOT)/ALT (SGPT) ≤ 2.5 x institutional ULN, or ≤ 5 x ULN for subjects with documented metastatic disease to the liver.
- Creatinine ≤ institutional ULN or creatinine clearance ≥ 30 mL/min/1.73 m^2 for subjects with creatinine levels above institutional ULN.

3.1.10 Women of childbearing age, women who are made postmenopausal through use of GNRH agonists, and men must agree to use adequate contraception for the duration of protocol treatment and for at least 90 days after the last dose of palbociclib if the risk of contraception exists.

Adequate contraception is defined as one highly effective non-hormonal form of contraception or two effective forms of non-hormonal contraception by the participant and/or partner.

Highly Effective Non-Hormonal Contraception
Methods of birth control which result in a low failure rate (i.e., less than 1% per year) when used consistently and correctly are considered highly-effective forms of contraception.
The following non-hormonal methods of contraception are acceptable:

- True abstinence when this is in line with the preferred and usual lifestyle of the participant. [Periodic abstinence (e.g., calendar, ovulation, symptothermal post-ovulation methods) and withdrawal are not acceptable methods of contraception].
- Male sterilization (with appropriate post-vasectomy documentation of the absence of sperm in the ejaculate). For female participants, the vasectomized male partner should be the sole partner.

OR

Effective Non-Hormonal Contraception
Alternatively two of the following effective forms of contraception may be used instead:

- Placement of non-hormonal intrauterine device (IUD) or intrauterine system (IUS). Consideration should be given to the type of device being used, as there is higher failure rates quoted for certain types, e.g., steel or copper wire.
- Condom with spermicidal foam/gel/film/cream/suppository.
- Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository.
- The use of barrier contraceptives should always be supplemented with the use of spermicide. The following should be noted:
- Failure rates indicate that, when used alone, the diaphragm and condom are not highly effective forms of contraception. Therefore, the use of additional spermicides does confer additional theoretical contraceptive protection.
- However, spermicides alone are ineffective at preventing pregnancy when the whole ejaculate is spilled. Therefore, spermicides are not a barrier method of contraception and should not be used alone.

It should be noted that two forms of effective contraception are required. A double barrier method is acceptable, which is defined as condom and occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository.

3.1.11 Premenopausal women must have a negative serum or urine pregnancy test. Pregnancy testing does <u>not</u> need to be pursued in female participants who are:

- Age > 60 years; or
- Age < 60 with intact uterus and amenorrhea for 12 consecutive months or more AND estrogen (estradiol) levels within postmenopausal range; or
- Status-post bilateral oophorectomy, total hysterectomy, or bilateral tubal ligation.

3.1.12 Participant must be able to swallow and retain oral medication.

3.1.13 Ability to understand and the willingness to sign a written informed consent document.

3.2 Exclusion Criteria

3.2.1 Participants who have had endocrine, chemotherapy, and/or biologic therapy < 7 days (other than fulvestrant) prior to entering the study or those who have not recovered from any prior treatment-related toxicities (must recover to no more than grade 1. Alopecia, sensory neuropathy Grade ≤ 2, or other Grade ≤ 2 toxicity not constituting a safety risk based on investigator's judgment are acceptable).

3.2.2 Participants who have had prior therapy with any anti-PD-1, anti-PD-L1, L2, or anti-

CTLA4 immunotherapy

3.2.3 Participants who are receiving concurrent therapy with other investigational agents.

3.2.4 Rapidly progressive, symptomatic, visceral spread of disease placing participant at risk of life-threatening complications in the short term.

3.2.5 Participants with active brain metastases. Stable treated brain metastases are allowed (this includes participants who have documented radiologic stability at least 4 weeks after radiotherapy, and do not require systemic steroids for management of symptoms from CNS metastatic lesions).

3.2.6 Participants who have discontinued prior palbociclib for toxicity, or have needed more than two dose reductions for toxicity from prior palbociclib therapy. If a participant previously required dose reductions during prior palbociclib therapy and tolerated it well, for example prior dosing at 100 mg or 75 mg qd 3 weeks on 1 week off schedule, then that dose may be selected for this trial.

3.2.7 History of allergic reactions to palbociclib or attributed to compounds of similar chemical or biologic composition to palbociclib.

3.2.8 Known prior severe hypersensitivity to investigational product or any component in its formulations, including known severe hypersensitivity reactions to monoclonal antibodies (NCI CTCAE v4.03 Grade ≥ 3)

3.2.9 Participants receiving any medications or substances that are strong inhibitors or inducers of CYP3A isoenzymes are ineligible. Lists including medications and substances known or with the potential to interact with the CYP3A isoenzymes are provided in Appendix B, and can also be found within Section 5.4. Because the lists of these agents are constantly changing, it is important to regularly consult a frequently-updated list such as http://medicine.iupui.edu/clinpharm/ddis/table.aspx; medical reference texts such as the Physicians' Desk Reference may also provide this information. As part of the enrollment/informed consent procedures, the participant will be counseled on the risk of interactions with other agents, and what to do if new medications need to be prescribed or if the participant is considering a new over-the-counter medicine or herbal product.

3.2.10 Prior organ transplantation including allogenic stem-cell transplantation

3.2.11 Current use of immunosuppressive medication, except for the following: a. intranasal, inhaled, topical steroids, or local steroid injection (e.g., intra-articular injection); b. Systemic corticosteroids at physiologic doses ≤ 10 mg/day of prednisone or equivalent; c. Steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication).

3.2.12 Uncontrolled intercurrent illness including, but not limited to: ongoing or active

infection requiring systemic therapy, clinically significant cardiovascular disease including: cerebral vascular accident/stroke (< 6 months prior to enrollment), myocardial infarction (< 6 months prior to enrollment), unstable angina, congestive heart failure (≥ New York Heart Association Classification Class II), or serious cardiac arrhythmia requiring medication, uncontrolled diabetes mellitus, or psychiatric illness/social situations that would limit compliance with study requirements. Ability to comply with study requirements is to be assessed by each investigator at the time of screening for study participation.

3.2.13 Active autoimmune disease that might deteriorate when receiving an immuno-stimulatory agent. Participants with diabetes type I, vitiligo, psoriasis, or hypo- or hyperthyroid diseases not requiring immunosuppressive treatment are eligible.

3.2.14 Known history of testing positive for HIV or known acquired immunodeficiency syndrome, or need to receive combination antiretroviral therapy for HIV

3.2.15 Known history of colitis, inflammatory bowel disease, pneumonitis, or pulmonary fibrosis.

3.2.16 Hepatitis B virus (HBV) or hepatitis C virus (HCV) infection at screening (positive HBV surface antigen or HCV RNA if anti-HCV antibody screening test positive)

3.2.17 Live vaccination within 4 weeks of the first dose of avelumab

3.2.18 Pregnant women are excluded from this study because effect of palbociclib and avelumab on a developing fetus is unknown. Breastfeeding should be discontinued prior to entry onto the study.

3.2.19 Individuals with a history of a different malignancy are ineligible except for the following circumstances. Individuals with a history of other malignancies are eligible if they have been disease-free for at least 3 years and are deemed by the investigator to be at low risk for recurrence of that malignancy. Individuals with the following cancers are eligible if diagnosed and treated within the past 5 years: ductal carcinoma *in situ* of the breast, cervical cancer *in situ*, and basal cell or squamous cell carcinoma of the skin.

3.3 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial.

4. REGISTRATION PROCEDURES

4.1 General Guidelines for DF/HCC and DF/PCC Institutions

Institutions will register eligible participants in the Clinical Trials Management System (CTMS) OnCore. Registrations must occur prior to the initiation of protocol therapy. Any participant not registered to the protocol before protocol therapy begins will be considered ineligible and

registration will be denied.

An investigator will confirm eligibility criteria and a member of the study team will complete the protocol-specific eligibility checklist.

Following registration, participants may begin protocol therapy. Issues that would cause treatment delays should be discussed with the Overall Principal Investigator (PI). If a participant does not receive protocol therapy following registration, the participant's registration on the study must be canceled. Registration cancellations must be made in OnCore as soon as possible.

4.2 Registration Process for DF/HCC and DF/PCC Institutions

DF/HCC Standard Operating Procedure for Human Subject Research Titled *Subject Protocol Registration* (SOP #: REGIST-101) must be followed.

4.3 General Guidelines for Other Investigative Sites

Eligible participants will be entered on study centrally at the Dana-Farber Cancer Institute by the Project Manager. All sites should email or call the Project Manager to verify slot availability. The required forms in Section 4.4 should be emailed or faxed to the Project Manager.

Following registration, participants should begin protocol therapy within 7 business days. Issues that would cause treatment delays should be discussed with the Overall PI. If a participant does not receive protocol therapy following registration, the participant's registration on the study must be canceled. The Project Manager should be notified of cancellations as soon as possible.

4.4 Registration Process for Other Investigative Sites

To register a participant, the following documents should be completed by the research nurse or data manager and emailed to the Project Manager at [redacted]

- Clinic visit note documenting history and physical exam
- Copy of required laboratory tests including: Hematology (CBC with differential), serum chemistries (creatinine clearance, bilirubin, ALT, and AST), hepatitis testing, pregnancy testing if necessary.
- Pathology report and documentation of ER/PR status and HER2 status.
- ECG report
- Signed participant consent form
- HIPAA authorization form (if separate from the informed consent document)
- Completed DF/HCC Eligibility Checklist with stratification

To complete the registration process, the Project Manager will

- follow the DF/HCC Standard Operating Procedure for Human Subject Research Titled *Subject Protocol Registration* (SOP #: REGIST-101) and register the participant on the protocol

- call or email the research nurse or data manager at the participating site with the participant study number, and to confirm registration

NOTE: Registration can only be conducted during the business hours of 8:00 AM and 5:00 PM Eastern Time Monday through Friday. Same day treatment registrations will only be accepted with prior notice and discussion with the DF/HCC Project Manager.

5. TREATMENT PLAN

Agents will be administered per the table below. Cycles last 4 weeks (28 consecutive days) and the start of a cycle is defined as the day when palbociclib administration begins. Treatment will be administered on an outpatient basis. Expected toxicities and potential risks as well as dose modifications for study medications are described in Section 7 (Expected Toxicities and Dosing Delays/Dose Modification). No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy.

5.1 Treatment Regimen

This is a phase II, randomized study of fulvestrant alone versus fulvestrant and palbociclib versus fulvestrant, palbociclib, and avelumab in patients with metastatic or locally advanced/unresectable HR+/HER2- breast cancer that have demonstrated prior progression on a combination of endocrine therapy + CDK 4/6 inhibitor. Each subject will be assigned a unique identification number during screening, which will be used on all case report forms (CRFs) and correspondence regarding the subject.

Arm A: Fulvestrant Alone. Upon progression, patients may begin Palbociclib.
Arm B: Fulvestrant, Palbociclib
Arm C: Fulvestrant, Palbociclib, Avelumab

Table 1. Treatment Description

Treatment Description					
Agent	**Premedications/ Precautions**	**Starting Dose**	**Route**	**Schedule**	**Cycle Length**
Palbociclib	Given with food	125 mg*	PO	Daily on days 1-21, followed by one week off	28 days (4 weeks)
Fulvestrant	N/A	500mg (two injections of 250 mg each)	IM	Cycle 1: Day 1, 15; Subsequent cycles: Day 1	

Avelumab	Premedicate with antihistamine and acetaminophen, or per local guidelines guidelines for the first 4 infusions. Premedication should be administered for subsequent avelumab doses based upon clinical judgment and presence/ severity of prior infusion reactions. This regimen may be modified based on local treatment standards and guidelines as appropriate; however, the prophylactic use of systemic corticosteroids is not permitted.	10mg/kg	IV	Every 14 days	

*Patients may continue at same dose if previously treated with palbociclib at 100 mg or 75 mg

Day 1 of each cycle begins with fulvestrant dosing.

5.2 Pre-Treatment Criteria

Informed consent will be obtained after the study has been fully explained to the subject and before the conduct of any screening procedures or assessments. If screening assessments occur within 7 days before start of study treatment, then they may serve as the baseline Cycle 1 Day 1 study tests do not need to be repeated.

Pre-treatment criteria will be assessed within 14 days of the first dose of study treatment to establish eligibility and baseline values. This will be considered the baseline clinical evaluation. Additional pre-treatment evaluations, also found in Section 3.1.6, are CBC with differential, chemistries, and EKG. Pregnancy testing for screening should be obtained in appropriate patients, as defined in Eligibility. Required results for initiation of protocol therapy include:

- Absolute neutrophil count $\geq$ 1000/μL

- Platelets $\geq$ 100,000/μL
- Hemoglobin $\geq$ 9g/dL
- Total bilirubin < 1.5 x institutional upper limit of normal (ULN)
- AST (SGOT)/ALT (SGPT) $\leq$ 2.5 x institutional ULN, or AST and ALT levels $\leq$ 5 x ULN (for subjects with documented metastatic disease to the liver).
- Creatinine $\leq$ institutional ULN or creatinine clearance $\geq$ 30 mL/min/1.73 m^2 for subjects with creatinine levels above institutional ULN.
- Baseline negative hepatitis testing (HBV sAg and anti HCV antibody)
- Negative pregnancy test (in appropriate patients)
- Thyroid testing with free T4 and TSH

Refer to Section 6.2.1 for treatment parameters required after dose delays and re-treatment.

5.3 Agent Administration

5.3.1 Palbociclib

Palbociclib 125 mg should be taken orally, once per day, with food. Patients who previously required a dose reduction of palbociclib to 100 or 75 mg daily and tolerated it well can begin with that dose. If a dose is vomited, a replacement dose should NOT be taken. If a dose is missed, and it is less than 6 hours from usual time of dosing, then patients may take that dose. Otherwise that dose should be skipped and NOT retaken; patients should resume regular dosing the following day. Patients who inadvertently take 1 extra dose during a day must skip the next day's dose. Treatment is continuous daily for 21 days, and then 7 days off, to complete a 28 day cycle.

On days when patient is scheduled for a clinic visit, the patient may take palbociclib at home or in the clinic prior to addition investigational therapy.

Patients will be required to return all bottles of palbociclib at each study visit for drug accountability. The number of remaining capsules/tablets will be documented and recorded.

5.3.2 Fulvestrant

Fulvestrant 500 mg will be administered in the clinic as two IM injections of 250 mg each on Cycle 1 Days 1 and 15, and Day 1 of each subsequent 28-day (4-week) cycle. For participants who have had at least 1 dose of fulvestrant prior to enrollment, subsequent fulvestrant injections will administered on Day 1 of each 28-day cycle (no Day 15 dose).

An administration window of +/- 2 days is allowable. Fulvestrant must be administered at the participating study site.

For participants in Arm C, fulvestrant should be administered prior to avelumab infusion. For details regarding the dosing instructions and safety profile of fulvestrant, refer to the fulvestrant package insert or SmPC.

5.3.3 Avelumab

Avelumab will be administered as10 mg/kg body weight IV once every 2 weeks. An administration window of +/- 2 days is allowable. For participants in Arm C, fulvestrant should be administered prior to avelumab infusion. Avelumab is administered as a 1-hour IV infusion, diluted with 0.9% saline solution.

Premedication: In order to mitigate infusion-related reactions, a premedication with an antihistamine and with acetaminophen 30 to 60 minutes prior to the first 4 infusions of avelumab is mandatory (for example, 25-50 mg oral diphenhydramine and 500-650 mg oral acetaminophen). Premedication should be administered for subsequent avelumab doses based upon clinical judgment and presence/severity of prior infusion reactions. This regimen may be modified based on local treatment standards and guidelines as appropriate; however the prophylactic use of systemic corticosteroids is not permitted.

Setting: Avelumab should be administered in a setting that allows for immediate access to an intensive care unit or equivalent environment and administration of therapy for anaphylaxis, such as the ability to implement immediate resuscitation measures. Steroids (dexamethasone 10 mg), epinephrine (1:1,000 dilution), allergy medications (IV antihistamines), bronchodilators, or equivalents, and oxygen should be available for immediate access.

Observation period: Following avelumab infusions, patients must be observed for 30 minutes post-infusion for potential infusion-related reactions.

5.4 General Concomitant Medication and Supportive Care Guidelines

All prior treatment or medication administered during the 30 days preceding the first dose of study treatment and any concomitant therapy administered to the subject throughout the study until 30 days after the final dose of study treatment must be recorded on the Prior and Concomitant Therapy page of the eCRF. The generic name of the drug (or trade name for combination drugs) must be specified along with the duration of treatment and indication for use. If concomitant medication/therapy is administered for an adverse event (AE), investigators will record that AE on the AE page of the eCRF.

Supportive care medications are allowed at any time on trial. Specifically, the following agents are permitted:

- Antiemetics
- Antidiarrheal therapy
- Antiallergic measures such as corticosteroids and antihistamines
- Bisphosphonates: Subjects being treated with bisphosphonates when they enter the study may continue the medication as long as the dose is stable. Subjects may also initiate bisphosphonate therapy while on protocol therapy if it is thought to be medically necessary.

- Agents to assist in management of endocrine therapy-induced side effects (NSAIDs, gabapentin, duloxetine, venlafaxine, citalopram, etc)

Growth factors, including GCSF, are not allowed on trial. The use of concurrent investigational or other antitumor therapies, other than endocrine therapy, is not permitted. Concurrent palliative radiotherapy is not allowed on trial, except in circumstances when the need for radiotherapy does not reflect progressive disease. If radiotherapy is necessary, all agents except for fulvestrant should be held during radiation.

Strong CYP3A inhibitors/inducers are not allowed on study. Palbociclib is metabolized to multiple metabolites in a qualitatively similar manner in rat, dog and human liver microsomes. In vitro, Palbociclib is primarily metabolized by CYP3A4 enzymes. Co-administration with drugs that are CYP3A inhibitors and inducers may change the plasma concentrations of palbociclib in humans. The concurrent use of CYP3A inhibitors, including amprenavir, atazanavir, boceprevir, clarithromycin, conivaptan, delavirdine, diltiazem, erythromycin, fosamprenavir, indinavir, itraconazole, ketoconazole, lopinavir, mibefradil, miconazole, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, verapamil, voriconazole, and grapefruit, grapefruit juice or any product containing grapefruit, are not allowed in the study. The concurrent use of CYP3A inducers, including carbamazepine, felbamate, nevirapine, phenobarbital, phenytoin, primidone, rifabutin, rifampin, rifapentin, and St. John's wort, are not allowed in the study. This medication list may also be found in Appendix B.

Concomitant use of moderate CYP3A inducers and CYP3A substrates is allowable on study, however precaution should be exercised for use of any concomitant medication.

Patients taking proton pump inhibitors must take palbociclib capsules with food. The new tablet formulation of palbociclib may be taken with or without food and can be taken with proton pump inhibitors (PPI)/antacids.

Chronic immunosuppressive therapies should be avoided, including systemic corticosteroids. Steroids given for physiological replacement, as anti-emetics or inhaled as well as short course of oral/topical steroids given for allergic reactions or asthma flares are allowed.

The use of herbal medicine is not recommended during protocol treatment.

Surgery is allowed during protocol therapy, however it is suggested to avoid nadir of counts at time of surgery. Patients pursuing surgery must hold palbociclib (and avelumab if in Arm C) therapy 7 days before the surgery and up to 2 weeks after surgery. Patients may resume palbociclib (avelumab if in Arm C) therapy once satisfactory wound healing and recovery have occurred. Patients should continue endocrine therapy if other agents are held for surgery.

5.4.1 Timing and use of contraception

The effects of palbociclib and avelumab on the developing human fetus are unknown. If, for any reason, a woman should become pregnant or suspect that she is pregnant while participating in this study, she should inform her treating physician immediately.

Females of childbearing potential, women who are made postmenopausal through use of GNRH agonists, and men should use adequate contraceptive methods during therapy and for at least **90 days** after last dose of palbociclib. Adequate contraception is defined as one highly effective non-hormonal form of contraception or two effective forms of non-hormonal contraception by the patient and/or partner.

Highly Effective Non-Hormonal Contraception
Methods of birth control which result in a low failure rate (i.e., less than 1% per year) when used consistently and correctly are considered highly-effective forms of contraception.
The following non-hormonal methods of contraception are acceptable:

- True abstinence when this is in line with the preferred and usual lifestyle of the participant. [Periodic abstinence (e.g., calendar, ovulation, symptothermal post-ovulation methods) and withdrawal are not acceptable methods of contraception].
- Male sterilization (with appropriate post-vasectomy documentation of the absence of sperm in the ejaculate). For female participants, the vasectomized male partner should be the sole partner.

Effective Non-Hormonal Contraception
Alternatively two of the following effective forms of contraception may be used instead:

- Placement of non-hormonal intrauterine device (IUD) or intrauterine system (IUS). Consideration should be given to the type of device being used, as there is higher failure rates quoted for certain types, e.g., steel or copper wire.
- Condom with spermicidal foam/gel/film/cream/suppository.
- Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository.
- The use of barrier contraceptives should always be supplemented with the use of spermicide. The following should be noted:
- Failure rates indicate that, when used alone, the diaphragm and condom are not highly effective forms of contraception. Therefore, the use of additional spermicides does confer additional theoretical contraceptive protection.
- However, spermicides alone are ineffective at preventing pregnancy when the whole ejaculate is spilled. Therefore, spermicides are not a barrier method of contraception and should not be used alone.

It should be noted that two forms of effective contraception are required. A double barrier method is acceptable, which is defined as condom and occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream /suppository.

5.5 Crossover Therapy

For patients on Arm A, fulvestrant alone, patients may cross over to palbociclib monotherapy at time of confirmed disease progression. Decision on crossover will be made at the discretion

of the patient and provider. Treatment may continue until one of the criteria listed in Section 5.6.

5.6 Criteria for Removal from Treatment

Duration of therapy will depend on individual response, evidence of disease progression and tolerance. In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies:

- Progression/Relapse based on RECIST 1.1
- Progression/Relapse NOT based on RECIST 1.1, but with need to change systemic therapy
- Intercurrent illness that prevents further administration of combination treatment,
- Unacceptable toxicity to protocol therapy,
- Participant demonstrates an inability or unwillingness to comply with the medication regimen and/or documentation requirements, as determined by the treating provider
- Participant decides to withdraw consent from the protocol therapy
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the opinion of the treating investigator (physician discretion).
- Death

Participants will be removed from the protocol therapy when any of these criteria apply. The reason for removal from protocol therapy, and the date the participant was removed, must be documented in the case report form (CRF).

If a patient discontinued study therapy due to toxicity, tumor assessments will continue to be performed at a minimum of 12-week intervals throughout long-term follow-up until documented disease progression, death, or withdrawal of consent.

In the event of unusual or life-threatening complications, participating investigators must immediately notify the Principal Investigator Erica L. Mayer MD MPH [redacted]

5.7 Follow Up

Participants in Arms A or B will be followed for safety follow-up for 30 days after removal from protocol therapy or until death, whichever occurs first. For Arm C patients (Fulvestrant, Palbociclib, and Avelumab), given the potential risk for delayed immune-related toxicities, safety follow-up must be performed at least 90 days after the last dose of avelumab administration. The extended safety follow-up beyond 30 days after last study drug administration may be performed either via a site visit or via a telephone call with subsequent site visit requested in case any concerns noted during the telephone call. SAEs which occur after occur any time after the 30-day or 90-day period, respectively, will be followed to resolution if the Principal Investigator suspects a causal relationship between palbociclib or avelumab and the SAE.

If a patient discontinued study therapy for reason other than disease progression, tumor

assessments will continue to be performed at a minimum of 12-week intervals throughout long-term follow-up until documented disease progression, death, or withdrawal of consent.

At time of disease progression, patients will be followed for survival at least every 6 months until time of death or withdrawal of consent. This will occur via telephone call if the site is unable to confirm status via chart review. If a patient withdraws consent to follow-up, attempts should be made to contact the patient to determine the reason for discontinuation.

Subsequent anti-cancer medications, including dose and regimen, or cancer-related radiotherapy or cancer-related surgery since end of study treatment will be collected and recorded in the CRF for all patients, regardless of reason for treatment discontinuation.

A subject who has ceased to return for visits will be followed up by mail, phone, or other means as much as possible to gather information such as the reason for failure to return and the status of treatment compliance, presence or absence of AEs, the clinical course of signs and symptoms, and survival.

The end of study (EOS) will occur as of the date of the last visit of the last patient undergoing the study. In the event that the EOS is declared earlier, investigational product(s) will be available to patients who continue to receive clinical benefit.

The reason for taking a participant off-treatment and off-study, and the date the participant was removed, must be documented in the case report form (CRF).

6. DOSING DELAYS/DOSE MODIFICATIONS

Dose delays and modifications will be made as indicated in the following table(s). The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for dose delays and dose modifications. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. See Appendix D for an overview of CTCAE.

All adverse events experienced by participants will be collected from the time of the first dose of study treatment, through the study and until 30 days (90 days for Arm C) after removal from study or death, whichever occurs first. Participants continuing to experience toxicity at the off protocol therapy visit may be contacted for additional assessments until the toxicity has resolved or is deemed irreversible.

In the event of significant treatment-related toxicity, dosing may be interrupted or delayed and/or reduced as described below. If treatment is held for toxicity, study assessments should stay on schedule according to the required data table. In the event of multiple toxicities, dose modification should be based on the worst toxicity observed. Patients are to be instructed to notify Investigators at the first occurrence of any adverse sign or symptom.

6.1 Palbociclib

6.1.1 Palbociclib Toxicity management

Every effort should be made to administer study treatment on the planned dose and schedule. However, in the event of significant treatment-related toxicity, administration of palbociclib may need to be adjusted. In the event treatment interruption is deemed necessary for palbociclib, treatment with the other medication(s) will continue as planned.

As per Section 5.4, treatment with growth factors is not allowed on trial.

If the retreatment parameters (see Section 6.1.3) are met within 3 weeks of treatment interruption or cycle delay, palbociclib may be resumed. Please refer to Dose Reduction section for adverse events requiring dose reduction at the time of treatment resumption.

If the retreatment parameters have not been met after 3 weeks of dose interruption (including the scheduled 1 week off treatment), the patient should permanently discontinue palbociclib treatment.

For participants enrolled on Arm C, there is no required dose modification for palbociclib for grade 3 uncomplicated neutropenia at Day 15 after Cycle 2 [Cycle 3 and beyond].

Patients holding palbociclib for surgery are allowed to hold 7 days before and up to 2 weeks after surgery and are allowed to resume palbociclib therapy once satisfactory wound healing and recovery have occurred. Patients should continue fulvestrant and/or avelumab if palbociclib is held for surgery.

Patients permanently discontinuing palbociclib treatment due to treatment-related toxicity should continue on fulvestrant and/or avelumab as per the investigator's discretion and followed accordingly per protocol.

6.1.2 Palbociclib Dosing Interruptions/Delays

Patients experiencing the following adverse events should have their treatment of palbociclib interrupted/delayed until criteria for retreatment are met:

- Uncomplicated Grade 3 or 4 neutropenia (ANC<1000/mm3);
- Grade 3 or 4 neutropenia (ANC<1000/mm3) associated with a documented infection or fever ≥38.5°C, 100.4°F;
- Platelet <75,000/mm3);
- Grade ≥3 non-hematologic toxicity (including, nausea, vomiting, diarrhea, and hypertension only if persisting despite optimal medical treatment);
- Intolerable grade 2 non-hematologic toxicity persisting despite optimal medical treatment and lasting more than 3 weeks;
- In case of concurrent > 3x ULN ALT and 2x ULN Total Bilirubin, palbociclib will be permanently discontinued.

Patients should not hold or discontinue palbociclib for side effects potentially or likely related to concomitant fulvestrant therapy as per the investigator's judgment.

Appropriate follow up assessments should be performed until adequate recovery occurs before treatment can resume.

Missed doses are not made up. When the adverse event resolves, the cycle will continue as scheduled.

The need for a dose reduction at the time of treatment resumption should be based on the criteria defined in Dose Reductions Section unless expressly agreed otherwise following discussion between the investigator and the sponsor. If a dose reduction is applied, the patient may need to return to the clinic to receive new drug supply.

6.1.3 Palbociclib Retreatment criteria

Retreatment with palbociclib following treatment interruption for treatment related toxicity or at the start of any new cycle may not occur until all of the following parameters have been met:

- Platelet count ≥ 75,000/mm3;
- ANC ≥ 1000/mm3 and no fever;
- Any persistent grade 3 or higher treatment-related non-hematologic AEs considered related to palbociclib have recovered to Grade ≤ 1 or baseline.

If a treatment delay results from decline in hematologic parameters, the frequency of blood count assessments should be adjusted as clinically indicated.

If the retreatment parameters are met within 3 weeks of treatment interruption or cycle delay, palbociclib may be resumed. Please refer to Dose Reductions Section for adverse events requiring dose reduction at the time of treatment resumption.

If these parameters have not been met after 3 weeks of dose interruption (including the scheduled 1 week off treatment), the patient should permanently discontinue palbociclib treatment.

6.1.4 Palbociclib Dose Reductions

Following dose interruption or cycle delay the palbociclib dose may need to be reduced when treatment is resumed.

No specific dose adjustments are recommended for Grade 1 or short lasting Grade 2 (<3 weeks) treatment-related toxicity. However, investigators should always manage their patients according to their medical judgment based on the particular clinical circumstances.

Palbociclib will be dose reduced for treatment-related non-hematologic Grade 2 toxicity lasting for >3 weeks, despite optimal medical treatment. Palbociclib will be discontinued for subjects experiencing a persistent grade 2 treatment-related non-hematologic toxicity after 2 dose reductions, in the presence of maximum supportive care, as judged by the

investigator.

Taking palbociclib according to recommendation (i.e., with food) should be reinforced and confirmed. Dose reduction of palbociclib may be recommended depending on type and severity of the toxicity encountered (Table 2). Patients who start palbociclib therapy at 100mg (Dose level -1) or 75 mg (Dose level -2) can use the lower dose levels if dose reduction is necessary. Once a dose has been reduced for a given patient, all subsequent cycles should be administered at that dose level, unless further dose reduction is required. Dose re-escalation is not allowed. Patients who cannot tolerate the lowest dose level will be discontinued from the study.

Table 2. Dose Levels

Dose Level	Palbociclib
Starting dose	125 mg/d, 3 weeks on/1 week off
-1	100 mg/d, 3 weeks on/1 week off
-2	75 mg/d, 3 weeks on/1 week off
-3	75 mg/d, 5 days on 2 days off
	Discontinue Study Treatment

Recommended dose modifications for treatment-related toxicities requiring treatment interruption/delay or persisting despite optimal medical treatment are described in Table 3.

Table 3. Palbociclib Dose Modifications for Treatment Related Toxicities Requiring Treatment Interruption/Delay or Persisting Despite Optimal Medical Treatment.

Toxicity	Intervention with Palbociclib
Uncomplicated Grade 3 neutropenia *(ANC ≥500 - <1000/mm^3)*	• 1st occurrence: Hold drug. If ANC recovers (ANC ≥ 1000) within 2 weeks, resume at same dose. • If ANC takes longer than 2 weeks to recover (ANC≥1000), but within 3 weeks, then resume drug and decrease drug by 1 dose level. • Recurrent uncomplicated Grade 3: Hold drug. If ANC recovers (ANC ≥ 1000) within 2 weeks, resume drug and decrease drug by 1 dose level. • For participants enrolled on Arm C, there is no action to palbociclib required for grade 3 uncomplicated neutropenia at Day 15 after cycle 2 [cycle 3 and beyond]
Grade 3 neutropenia *(ANC<1000/mm^3)* **associated with a documented infection or fever ≥38.5°**	• Hold drug. If ANC recovers (ANC ≥ 1000) within 2 weeks, resume drug and decrease drug by 1 dose level. • If ANC takes longer than 2 weeks to recover (ANC≥1000), but within 3 weeks, then resume drug and decrease drug by 2 dose levels. • If these parameters have not been met after 3 weeks of dose interruption (including the scheduled 1 week off treatment), the patient should permanently discontinue Palbociclib.

Toxicity	Intervention with Palbociclib
Grade 4 neutropenia (ANC < 500/mm3)	• First occurrence: Hold drug. Resume once ANC ≥ 1000 and decrease dose by 1 dose level. • Recurrent Grade 4 neutropenia: Hold drug. Resume once ANC ≥ 1000 and decrease dose by an additional dose level.
Grade 3 or 4 thrombocytopenia (platelet count < 75,000)	• 1st occurrence: Hold drug until plt ≥ 75,000, then resume drug and decrease by 1 dose level. • Recurrent Grade 3 thrombocytopenia: hold drug until plt ≥75,000, then decrease drug by an additional dose level.
Grade ≥3 non-hematologic toxicity *(including, nausea, vomiting, diarrhea, and hypertension only if persisting despite optimal medical treatment)*;	• 1st occurrence: Hold drug until toxicity decreases to ≤ Grade 1 or to baseline, then resume drug and decrease by 1dose level. • If toxicity takes longer than 2 weeks to recover to ≤ Grade 1, but within 3 weeks, then resume drug and decrease drug by 2 dose levels. • Recurrent toxicity: Hold drug until toxicity decreases to ≤ Grade 1 or to baseline, then decrease drug by an additional dose level.
Grade 2 non-hematologic toxicity persisting despite optimal medical treatment, deemed unacceptable in the investigator's judgment, and lasting at least 2 weeks;	• 1st occurrence: Hold drug until toxicity decreases to ≤ Grade 1 or to baseline, then resume drug at same dose level. • Recurrent toxicity: Hold drug until toxicity decreases to ≤ Grade 1 or to baseline, then resume drug and decrease by 1 dose level.
LFTs Concurrent > 3XULN SGPT/ALT and 2X ULN total bilirubin	Discontinue Palbociclib permanently.

6.2 Fulvestrant

Discontinuation of fulvestrant for adverse events is very rare. However, in the unlikely event that the patient discontinues fulvestrant and is able to continue on palbociclib and/or avelumab, the investigator should contact the Medical Monitor to discuss the benefit-risk assessment of continuing with palbociclib and/or avelumab.

There are no expected significant overlapping toxicities between fulvestrant and either palbociclib or avelumab.

6.2.1 Fulvestrant Dose modifications/delays

No dose reduction for fulvestrant is permitted.

6.3 Avelumab

In the event that the participant holds or discontinues avelumab, therapy with other study medications may continue.

6.3.1 Management of Immune-Related Adverse Events (irAEs)

Since inhibition of PD-L1 stimulates the immune system, irAEs may occur. Treatment of irAEs is dependent upon severity (NCI-CTCAE grade) and in general consist of:

- Grade 1 to 2: treat symptomatically or with moderate dose steroids, more frequent monitoring
- Grade 1 to 2 (persistent): manage similar to high grade AE (Grade 3 to 4)
- Grade 3 to 4: treat with high dose corticosteroids

Please see Section 6.3.4 for more information about dose modifications and toxicity management with avelumab.

6.3.2 Management of Severe Hypersensitivity or Flu-like Reactions Related to Avelumab

In order to mitigate infusion-related reactions, premedication with an antihistamine and with acetaminophen is mandatory prior to the first 4 infusions of avelumab. Management of infusion-related reactions should follow guidelines set forth in Table 4.

Table 4: Treatment Modification for Symptoms of Infusion-Related Reactions Caused by Avelumab

NCI-CTCAE Grade	Treatment Modification for Avelumab
Grade 1 – mild • Mild transient reaction; infusion interruption not indicated; intervention not indicated	• Decrease the avelumab infusion rate by 50% and monitor closely for any worsening
Grade 2 – moderate • Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (for example, antihistamines, NSAIDs, narcotics, Iv fluids); prophylactic medications indicated for ≤ 24 h	• Temporarily discontinue avelumab infusion • Resume infusion at 50% of previous rate once infusion-related reaction has resolved or decreased to at least Grade 1 in severity, and monitor closely for any worsening
Grade 3 or Grade 4 – severe or life-threatening • Grade 3: Prolonged (for example, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae • Grade 4: Life-threatening consequences; urgent intervention indicated	• Stop the avelumab infusion immediately and disconnect infusion tubing from the subject • Subjects have to be withdrawn immediately from avelumab treatment and must not receive any further avelumab treatment

Once the avelumab infusion rate has been decreased by 50% or interrupted due to an infusion-related reaction, it must remain decreased for the next scheduled infusion. If no infusion reaction is observed in the next scheduled infusion, the infusion rate may be returned to baseline at the subsequent infusions based on investigator's medical judgment. If a subject experiences a Grade 3 or 4 infusion-related reaction at any time,

the subject must discontinue avelumab.

6.3.3 Severe Hypersensitivity Reactions

If hypersensitivity reaction occurs, the subject must be treated according to the best available medical practice. Subjects should be instructed to report any delayed reactions to the investigator immediately.

Symptoms
- Impaired airway
- Decreased oxygen saturation (< 92%)
- Confusion
- Lethargy
- Hypotension
- Pale/clammy skin
- Cyanosis

Management
- Epinephrine injection and dexamethasone infusion
- Subject should be placed on monitor immediately
- Alert intensive care unit for possible transfer if required

6.3.4 Avelumab Dose modification/delays

Treatment of immune related Adverse Events (irAEs) should follow guidelines set forth in the following Table (per Investigator's Brochure):

Table 5. Management of Immune-related Adverse Events

Gastrointestinal irAEs		
Severity of Diarrhea / Colitis (NCI-CTCAE v4.03)	**Initial Management**	**Follow-up Management**
Grade 1 Diarrhea: < 4 stools/day over Baseline Colitis: asymptomatic	Continue avelumab therapy Symptomatic treatment (for example, loperamide)	Close monitoring for worsening symptoms Educate subject to report worsening immediately If worsens: Treat as Grade 2 or 3/4

Grade 2 Diarrhea: 4 to 6 stools per day over Baseline; IV fluids indicated < 24 hours; not interfering with ADL Colitis: abdominal pain; blood in stool	Hold avelumab therapy Symptomatic treatment	If improves to Grade 1: Resume avelumab therapy If persists > 5 to 7 days or recur: Treat as Grade 3 to 4
Grade 3 to 4 Diarrhea (Grade 3): ≥ 7 stools per day over Baseline; incontinence; IV fluids ≥ 24 hrs.; interfering with ADL Colitis (Grade 3): severe abdominal pain, medical intervention indicated, peritoneal signs Grade 4: life-threatening, perforation	Hold avelumab for Grade 3. Permanently discontinue avelumab for grade 4 or recurrent grade 3. 1.0 to 2.0 mg/kg/day methylprednisolone IV or equivalent Add prophylactic antibiotics for opportunistic infections Consider lower endoscopy	If improves: Continue steroids until ≤ Grade 1, then taper over at least 1 month, resume avelumab therapy following steroids taper for initial Grade 3 If worsens or persists > 3 to 5 days, or recurs after improvement: Add infliximab 5 mg/kg (if no contraindication), Note: Infliximab should not be used in cases of perforation or sepsis
Dermatological irAEs		
Grade of Rash (NCI-CTCAE v4)	**Initial Management**	**Follow-up Management**
Grade 1 to 2 Covering ≤ 30% body surface area	Continue avelumab therapy Symptomatic therapy (for example, antihistamines, topical steroids)	If persists > 1 to 2 weeks or recurs: Withhold Avelumab therapy Consider skin biopsy Consider 0.5 to 1.0 mg/kg/day methylprednisolone IV or oral equivalent. Once improving, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume avelumab therapy following steroids taper If worsens: Treat as Grade 3 to 4
Grade 3 to 4 Grade 3: Covering > 30% body surface area; Grade 4: life threatening consequences	Hold Avelumab for grade 3 Permanently discontinue avelumab for grade 4 or recurrent grade 3 Consider skin biopsy Dermatology consult	If improves to Grade ≤ 1: Taper steroids over at least 1 month; resume Avelumab therapy following steroids taper (for initial grade 3

	1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent Add prophylactic antibiotics for opportunistic infections	
Cardiac irAEs		
Myocarditis	**Initial Management**	**Follow-up Management**
New onset of cardiac signs or symptoms and / or new laboratory cardiac biomarker elevations (e.g. troponin, CK-MB, BNP) or cardiac imaging abnormalities suggestive of myocarditis.	hold avelumab therapy Hospitalize. In the presence of life threatening cardiac decompensation, consider transfer to a facility experienced in advanced heart failure and arrhythmia management. Cardiology consult to establish etiology and rule-out immune-mediated myocarditis. Guideline based supportive treatment as appropriate per cardiology consult.* Consider myocardial biopsy if recommended per cardiology consult.	If symptoms improve and immune-mediated etiology is ruled out, re-start avelumab therapy. If symptoms do not improve/worsen, viral myocarditis is excluded, and immune-mediated etiology is suspected or confirmed following cardiology consult, manage as immune-mediated myocarditis.
Immune-mediated myocarditis	Permanently discontinue avelumab. Guideline based supportive treatment as appropriate per cardiology consult.* Methylprednisolone 1-2 mg/kg/day or equivalent. Add prophylactic antibiotics for opportunistic infections	Once improving, taper steroids over at least 1 month If no improvement or worsening, consider additional immunosuppressants (e.g. azathioprine, cyclosporine A)
*Local guidelines, or eg. AHA guidelines		

Pulmonary irAEs		
Grade of Pneumonitis (NCI-CTCAE v4)	**Initial Management**	**Follow-up Management**
Grade 1 Radiographic changes only	Consider holding avelumab therapy Monitor for symptoms every 2 to 3 days Consider Pulmonary and Infectious Disease consults	Re-image at least every 3 weeks If worsens: Treat as Grade 2 or Grade 3 to 4
Grade 2 Mild to moderate new symptoms	Delay avelumab therapy Pulmonary and Infectious Disease consults Monitor symptoms daily, consider hospitalization 1.0 to 2.0 mg/kg/day methyl-prednisolone IV or oral equivalent Add prophylactic antibiotics for opportunistic infections. Consider bronchoscopy, lung biopsy	Re-image every 1 to 3 days If improves: When symptoms return to ≤ Grade 1, taper steroids over at least 1 month and then resume avelumab therapy following taper If not improving after 2 weeks or worsening: Treat as Grade 3 to 4
Grade 3 to 4 Grade 3: Severe new symptoms; New / worsening hypoxia; Grade 4: life-threatening	Permanently discontinue avelumab therapy Hospitalize Pulmonary and Infectious Disease consults 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent Add prophylactic antibiotics for opportunistic infections Consider bronchoscopy, lung biopsy	If improves to ≤ Grade 1: Taper steroids over at least1 month If not improving after 48 hours or worsening: Add additional immunosuppression (for example, infliximab, cyclophosphamide, IV immunoglobulin, or mycophenolate mofetil)
Hepatic irAEs		
Grade of Liver Test Elevation (NCI-CTCAE v4)	**Initial Management**	**Follow-up Management**
Grade 1	Continue avelumab therapy	Continue liver function monitoring If worsens: Treat as Grade 2 or 3 to 4

Grade 1 AST or ALT > ULN to 3.0 x ULN and / or total bilirubin > ULN to 1.5 x ULN		
Grade 2 AST or ALT > 3.0 to ≤ 5 x ULN and / or total bilirubin > 1.5 to ≤ 3 x ULN	Hold avelumab therapy Increase frequency of monitoring to every 3 days	If returns to ≤ Grade 1: Resume routine monitoring, resume avelumab therapy If elevations persist > 5 to 7 days or worsen: Treat as Grade 3 to 4.
Grade 3 to 4 AST or ALT > 5 x ULN and / or total bilirubin > 3 x ULN	Permanently discontinue avelumab therapy Increase frequency of monitoring to every 1 to 2 days 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent Add prophylactic antibiotics for opportunistic infections Consult gastroenterologist/hepatologist Consider obtaining MRI/CT scan of liver and liver biopsy if clinically warranted	If returns to Grade ≤ Grade 1: Taper steroids over at least 1 month If does not improve in > 3 to 5 days, worsens or rebounds: Add mycophenolate mofetil 1 gram (g) twice daily If no response within an additional 3 to 5 days, consider other immunosuppressants per local guidelines
Renal irAEs		
Grade of Creatinine Increase (NCI-CTCAE v4)	**Initial Management**	**Follow-up Management**
Grade 1 Creatinine increased > ULN to 1.5 x ULN	Continue avelumab therapy	Continue renal function monitoring If worsens: Treat as Grade 2 to 3 or 4.
Grade 2 to 3 Creatinine increased > 1.5 and ≤ 6 x ULN	Hold avelumab therapy Increase frequency of monitoring to every 3 days 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections Consider renal biopsy	If returns to Grade ≤1: Taper steroids over at least 1 month, and resume avelumab therapy following steroids taper. If worsens: Treat as Grade 4.
Grade 4 Creatinine increased > 6 x ULN	Permanently discontinue avelumab therapy Monitor creatinine daily 1.0 to 2.0 mg/kg/day prednisone or equivalent.	If returns to Grade ≤1: Taper steroids over at least 1 month.

	Add prophylactic antibiotics for opportunistic infections Consider renal biopsy Nephrology consult	
Endocrine irAEs		
Endocrine Disorder	**Initial Management**	**Follow-up Management**
Grade 1 or Grade 2 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus)	Continue avelumab therapy Endocrinology consult if needed Start thyroid hormone replacement therapy (for hypothyroidism), anti-thyroid treatment (for hyperthyroidism), corticosteroids (for adrenal insufficiency) or insulin (for Type I diabetes mellitus) as appropriate. Rule-out secondary endocrinopathies (i.e. hypopituitarism / hypophysitis)	Continue hormone replacement/suppression and monitoring of endocrine function as appropriate.
Grade 3 or Grade 4 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus)	Hold avelumab therapy Consider hospitalization Endocrinology consult Start thyroid hormone replacement therapy (for hypothyroidism), anti-thyroid treatment (for hyperthyroidism), corticosteroids (for adrenal insufficiency) or insulin (for type I diabetes mellitus) as appropriate. Rule-out secondary endocrinopathies (i.e. hypopituitarism / hypophysitis)	Resume avelumab once symptoms and/or laboratory tests improve to Grade ≤ 1 (with or without hormone replacement/suppression). Continue hormone replacement/suppression and monitoring of endocrine function as appropriate.
Hypopituitarism/Hypophysitis (secondary endocrinopathies)	If secondary thyroid and/or adrenal insufficiency is confirmed (i.e. subnormal serum FT4 with	Resume avelumab once symptoms and hormone tests improve to Grade ≤ 1 (with or without hormone replacement). In addition, for hypophysitis with

	inappropriately low TSH and/or low serum cortisol with inappropriately low ACTH) Refer to endocrinologist for dynamic testing as indicated and measurement of other hormones (FSH, LH, GH/IGF-1, PRL, testosterone in men, estrogens in women) Hormone replacement/suppressive therapy as appropriate Perform pituitary MRI and visual field examination as indicated If hypophysitis confirmed: Continue avelumab if mild symptoms with normal MRI. Repeat the MRI in 1 month Hold avelumab if moderate, severe or life-threatening symptoms of hypophysitis and/or abnormal MRI. Consider hospitalization. Initiate corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) followed by corticosteroids taper during at least 1 month. Add prophylactic antibiotics for opportunistic infections.	abnormal MRI, resume avelumab only once shrinkage of the pituitary gland on MRI/CT scan is documented. Continue hormone replacement/suppression therapy as appropriate.

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial.

The study period, during which AEs and SAEs must be reported, begins after starting the first dose of study treatment and ends 30 days (90 days for Arm C) following the last administration of study treatment or study discontinuation/termination, whichever is earlier. After this period, investigators should only report SAEs that are attributed to study treatment. 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 assessed and reported, when appropriate. Abnormal laboratory values will not be reported unless deemed to be clinically significant based on the criteria listed in section 7.7. Each reported AE or SAE will be described by its CTCAE Version 4.0 term, grade, duration (i.e., start and end dates), regulatory

seriousness criteria if applicable, suspected relationship to Fulvestrant, Palbociclib or Avelumab, expectedness, and actions taken.

The following list of reported and/or potential AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting **in addition** to routine reporting.

7.1 Expected Toxicities

7.1.1 Adverse Event List(s) for Palbociclib

The primary anticipated toxicity of palbociclib is neutropenia. In the phase I, dose-escalation trial of palbociclib alone in advanced cancers[42], neutropenia was the only dose-limiting toxicity (DLT). Grade 3 neutropenia during cycle 1 was observed in 3/22 patients receiving palbociclib 125 mg PO daily, with no grade 4 neutropenic events observed. Based on this result, 125 mg PO daily became the recommended phase 2 dose (RP2D). Other hematologic AEs of grade 3 or greater during cycle 1 were anemia and leukopenia, occurring in 1 and 4 of 41 patients, respectively. The most common non-hematologic AEs of grade 3 or greater during cycle 1 were fatigue, nausea, and abdominal pain (each occurring in 2 of 41 patients). Of note, there were no complicated hematologic AEs documented, and all hematologic AEs resolved during the off-drug period of a 3 week on/1 week off schedule and were non-cumulative.

In a phase II trial of palbociclib alone for advanced breast cancer, the only toxicities $\geq$ grade 3 observed were transient neutropenia (50%) and thrombocytopenia (21%).[30] In a phase II trial of palbociclib plus letrozole for first-line therapy of hormone receptor positive breast cancer, the most common AEs reported were neutropenia, leukopenia, and fatigue.[31,32] The median time to first treatment delay for neutropenia was 58 days, and the median duration of treatment delay until recovery was 5 days (range 1-16 days). (Pfizer internal data). In general, hematologic abnormalities were adequately managed with standard supportive care, were not complicated, and resolved during the drug hold with no cumulative toxicity noted.
In the phase I, dose-escalation trial of palbociclib alone in advanced cancers,[42] QT interval changes were also evaluated in detail. While 26 of 41 patients had a maximum increase of <30 msec from baseline QTc, zero patients had an on-treatment value exceeding 500 msec.

The following toxicities have been observed with some frequency in patients given palbociclib: neutropenia, leukopenia, infections, fatigue, low hemoglobin, thrombocytopenia, inflammation of the mouth, diarrhea, constipation, nausea, vomiting, joint pain, back pain, pain in hands and feet, hair loss, rash, cough, dyspnea, headache, dizziness, anorexia, hot flush, insomnia, abdominal pain, indigestion, dry mouth, fever, asthenia, swelling of the hands and feet, irritation or sores in the lining of hollow organs like mouth, throat, stomach, bowels; pain, flu-like illness, muscle pain, pain in the muscles and bone including around the chest, muscle cramps, increases in blood liver markers that may indicate liver damage, dry skin, itching, mouth/throat pain, nosebleed, impaired sense of taste, high blood pressure, depression, fall, febrile neutropenia, lymphocytopenia,

blurred vision increased tearing and dry eye.

Palbociclib is considered to have the potential to impair reproductive function and fertility in male humans based on nonclinical findings in rats and dogs. In a male rat fertility study, there were no effects on mating or fertility, but palbociclib-related findings in the testis and epididymis were consistent with repeat-dose toxicity findings, and correlated with lower sperm motility and density. Men should consider sperm preservation prior to beginning therapy with palbociclib.

7.1.2 Adverse Event List(s) for Fulvestrant

Fulvestrant is an ER antagonist indicated for the treatment of HR+ MBC in postmenopausal women with disease progression following anti-estrogen therapy.

In a study with postmenopausal women with advanced breast cancer who had disease recurrence on or after adjuvant endocrine therapy or progression following endocrine therapy for advanced disease, the most frequently reported adverse events were injection-site pain (11.6% of patients), nausea (9.7%), and bone pain (9.4%). Because fulvestrant is administered intramuscularly, it should be used with caution in patients with bleeding diatheses, thrombocytopenia, or anticoagulant use. For details regarding the safety profile of fulvestrant, refer to the fulvestrant package insert or SmPC.

7.1.3 Adverse Event List(s) for Avelumab

For the purpose of regulatory reporting requirements during clinical development, the following AEs will be considered as expected and met the threshold of causal association (based on comprehensive medical evaluation considering the mechanism of action and temporal relationship after excluding other possible etiologies) defined by the Sponsor.

The following side effects have been observed among 1738 patients treated with avelumab according to the results from studies EMR100070-001 in various solid tumors (N=1650) and EMR100070-003 Part A in Merkel cell carcinoma (N=88) where avelumab was administered intravenously (IV) as single agent at a dose of 10 mg/kg every 2 weeks (Q2W)

Three types of risks are associated with avelumab: general signs and symptoms, reactions that occur during or following the infusion, and immune-mediated side effects:

- General signs and symptoms including fatigue, nausea, diarrhea, constipation, anorexia, weight loss, vomiting, anemia, abdominal pain, cough, shortness of breath, edema of the feet and legs, back pain, joint pain
- Infusion related symptoms including hypersensitivity reactions which may include chills, shaking, fever, back pain, belly pain, shortness of breath or wheezing, decrease in blood pressure or hives.
- Immune-mediated adverse reactions including immune-mediated colitis, pneumonitis, immune-mediated thyroid disorders including hyperthyroidism, hypothyroidism, thyroiditis and autoimmune thyroiditis; immune-mediated skin

reactions including rash, pruritis, redness, blisters, pemphigoid or peeling; other immune-mediated reactions including myocarditis, hepatitis, pneumonitis, pancreatitis, adrenal insufficiency, diabetes, uveitis, myosistis, Guillain-Barre syndrome

7.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- **For expedited reporting purposes only:**
  - AEs for the agent(s) that are listed above should be reported only if the adverse event varies in nature, intensity or frequency from the expected toxicity information which is provided.
  - Other AEs for the protocol that do not require expedited reporting are outlined in the next section (Expedited Adverse Event Reporting) under the sub-heading of Protocol-Specific Expedited Adverse Event Reporting Exclusions.

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

Expectedness:

- **Expected** adverse events are those adverse events that are listed or characterized in the current adverse event list, the Package Insert, the Investigator Brochure or is included in the informed consent document as a potential risk.

- **Unexpected** adverse events are those not listed in the Package Insert (P.I.) or current Investigator Brochure (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.

7.3 Serious Adverse Event Reporting

7.3.1 In the event of an unanticipated problem or life-threatening complications treating investigators must immediately notify the Overall PI.

7.3.2 Investigators **must** report to the Overall PI any serious adverse event (SAE) that occurs

after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment on the local institutional SAE form.

7.3.3 For Multi-Center Trials where a DF/HCC investigator is serving as the Sponsor, each participating institution **must** abide by the reporting requirements set by the DF/HCC. This applies to any medical event equivalent to an unexpected grade 2 or 3 with a possible, probable or definite attribution, unexpected grade 4 toxicities, and grade 5 (death) regardless of study phase or attribution.

7.4 DF/HCC Adverse Event Expedited Reporting Guidelines

The following adverse events must be reported to the DFCI IRB according to the expedited reporting guidelines:

- **CTCAE Grade 2 and Grade 3 Events** – that are *Unexpected* and there is a *Reasonable Possibility* that the *Adverse Event* is related to the study Intervention.
- **CTCAE Grade 4 Events –** Report all events that are *Unexpected*. Events that are *Expected* and listed within the protocol and/or current consent form do not need to be reported to the DFCI IRB. Please note, an event that presents at a higher severity than what is currently listed within the protocol and/or current consent as expected would be considered unexpected and reportable.
- ALL CTCAE Grade 5 Events.

Investigative sites within DF/HCC will report SAEs directly to the DFCI Office for Human Research Studies (OHRS) per the DFCI IRB reporting policy. For all events that meet the expedited reporting criteria, a full written adverse event report must be submitted to the DFCI IRB **within 10 working days** from notification of the event.

Other investigative sites will report SAEs to their respective IRB according to their local IRB's policies and procedures for reporting adverse events. A copy of the submitted institutional AE form will be forwarded to the Coordinating Center.

The Coordinating Center will submit AE reports from outside institutions to the DFCI IRB according to DFCI IRB policies and procedures in reporting adverse events.

7.5 Expedited Reporting to the Food and Drug Administration (FDA)

The Overall PI, as study sponsor, will be responsible for all communications with the FDA. The Overall PI will report to the FDA, regardless of the site of occurrence, any serious adverse event that meets the FDA's criteria for expedited reporting following the reporting requirements and timelines set by the FDA.

7.6 Expedited Reporting to Pfizer

Within 24 business hours of first awareness of the event (or immediately upon awareness if the event is fatal or life-threatening), the study team will report to Pfizer by facsimile any Serious Adverse Event ("SAE," as defined below) for which reporting is required under this provision

(as described below). Such SAEs are to be reported for study subjects or individuals otherwise exposed to the Pfizer Product (Palbociclib and/or Avelumab) as described below. The study teams should report SAEs as soon as they are determined to meet the definition, even if complete information is not yet available.

Study teams will report SAEs using Form FDA 3500A (MedWatch). The *Reportable Event Fax Cover Sheet* provided by Pfizer must also be included with each SAE submitted.

7.6.1 SAE Definition for Reporting to Pfizer

An SAE is any adverse event, without regard to causality, that is life-threatening (ie, causes an immediate risk of death) or that results in any of the following outcomes: death; in-patient hospitalization or prolongation of existing hospitalization; persistent or significant disability or incapacity (i.e., substantial disruption of the ability to conduct normal life functions); or a congenital anomaly or birth defect. Any other medical event that, in the medical judgment of the Principal Investigator, may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed above is also considered an SAE. A planned medical or surgical procedure is not, in itself, an SAE.

7.6.2 Exposure During Pregnancy, Exposure During Lactation, Occupational Exposure

Even though there may not be an associated SAE, exposure to Palbociclib or Avelumab during pregnancy, exposure to Palbociclib or Avelumab during lactation, and occupational exposure to Palbociclib or Avelumab are reportable to Pfizer.

7.6.3 Hy's Law Cases

Cases of potential drug-induced liver injury as assessed by laboratory test values ("Hy's Law Cases") are also reportable to Pfizer. If a participant develops abnormal values in aspartate transaminase (AST) or alanine transaminase or both, concurrent with abnormal elevations in total bilirubin and no other known cause of liver injury, that event would be classified as a Hy's Law Case.

7.6.4 Exclusions from SAE Reporting Requirements

Specifically excluded from the reporting requirements for SAEs under this provision is any SAE identified in the protocol as anticipated to occur in the study population at some frequency independent of drug exposure, unless the Principal Investigator assesses such an event as related to study medication. Also, specifically excluded from the reporting requirements is any SAE judged by the Overall Investigator to represent disease progression, unless it results in death within the SAE Reporting Period.

7.6.5 SAE Reporting Period

SAEs that are subject to reporting to Pfizer provisions are those that occur from after the first dose of study medication through 30 calendar days after the last administration of medication

in Arm B and at least 90 days of study medication in Arm C. SAEs should be reported to Pfizer after the 30-day and/or 90-day period, respectively, if the Principal Investigator suspects a causal relationship between Palbociclib OR Avelumab and the SAE. SAEs occurring on Arm A are not reported to Pfizer.

7.7 Expedited Reporting to Hospital Risk Management

Participating investigators will report to their local Risk Management office any participant safety reports or sentinel events that require reporting according to institutional policy.

7.8 Routine Adverse Event Reporting

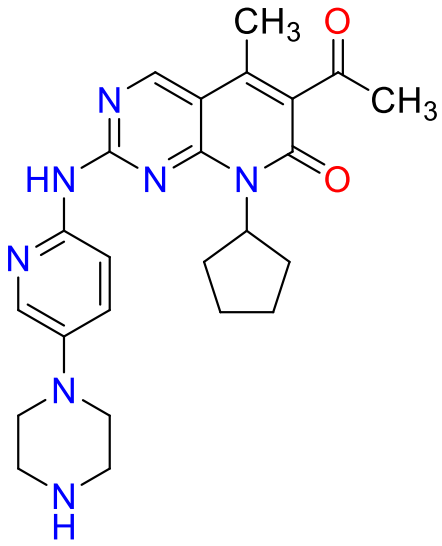
All adverse events **must** be reported in routine study data submissions to the Overall PI on the toxicity case report forms. Grade 1 hematologic toxicity will not be reported on the case report forms unless they induce clinical signs or symptoms, require treatment or further diagnostic tests, or result in a dose hold or modification. All AEs on Cohort A and B must be followed until resolution or for 30 days after the subject's last study visit, whichever comes first. Adverse events for patients on Cohort C will be followed until resolution or for at least 90 days after the subject's last study visit, whichever comes first. **AEs reported through expedited processes (e.g., reported to the IRB, FDA, etc.) must also be reported in routine study data submissions.**

8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational or other agents administered in this study can be found in Section 7.1.

8.1 Palbociclib

8.1.1 Description



Chemical name: 6-acetyl-8-cyclopentyl-5-methyl-2-(5-(piperazin-1-yl)pyridin-2-ylamino)pyrido[2,3-d]pyrimidin-7(8H)-one.
Chemical formula: C24H29N7O2
Molecular weight: 447.53.
Half life: ~27 hours.
Plasma protein binding of palbociclib: ~85%
Plasma protein binding of PF-05089326 (the lactam of palbociclib, one of the main metabolites present in plasma): 95%

Palbociclib (IC_{50} = 11 nM; Ki = 2 nM) is metabolized to multiple metabolites in a qualitatively similar manner in rat, dog and human liver microsomes. In vitro, Palbociclib is primarily metabolized by CYP3A4 and SULTA2A1 enzymes. Information on potential drug interactions can be found in Section 6.4.

8.1.2 Form

Beginning in March-May 2020, Palbociclib will be supplied by Pfizer in a tablet formulation. There is no change to the active ingredient, dosage strengths or dosing schedule. The tablets will be packed in blister packs. The new packaging features basic calendarization and detailed patient instructions on how to take palbociclib throughout the treatment schedule.

The new monthly box will contain 3 weekly blister packs of 7 tablets each along with the USPI for the tablet formulation. Each strength of tablet has a different shape or color as well as a different color carton similar to the way the current bottles have different colored labels (see below).

Prior to the change to the tablet formulation, palbociclib is supplied by Pfizer as capsules containing 75 mg, 100 mg, or 125 mg equivalents of palbociclib free base. Pfizer will supply the oral drug formulation to sites in High Density Polyethylene (HDPE) bottles containing 75 mg, 100 mg, or 125 mg capsules. The capsules can be differentiated by their size and color (see below).

Table 6. Palbociclib capsule characteristics

Dosage	Capsule color	Capsule size
75 mg	Sunset Yellow/Sunset Yellow	2

100 mg	Caramel/Sunset Yellow	1
125 mg	Caramel/Caramel	0

8.1.3 Storage and Stability

Storage conditions stated in the Single Reference Safety Document (i.e., Investigator's Brochure (IB), United States Package Insert (USPI), Summary of Product Characteristics (SPC), or Local Product Document (LPD)) will be superseded by the label storage.

Palbociclib capsules or tablets should be stored at controlled room temperature (20-25°C, 59-86°F) in their original container.

Investigators and site staff are reminded to check temperatures daily (i.e. manually or by using alarm systems to alert of any excursions) and ensure that thermometers are working correctly as required for proper storage of investigational products. These include thermometers for room storage. Any temperature excursions must be reported to Pfizer. The investigational products must be stored as indicated. Deviations from the storage requirements, including any actions taken, must be documented and reported to Pfizer.

Once a deviation is identified, the investigational products (palbociclib) must be quarantined and not used until Pfizer provides documentation of permission to use the investigational product.

Medication should be kept in a secured locked area at the study site in accordance with applicable regulatory requirements. Returned medication should be stored separately from medication that needs to be dispensed.

8.1.4 Handling

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment.

8.1.5 Availability

Palbociclib is an investigational agent and will be supplied free-of-charge from Pfizer using a commercial supply.

8.1.6 Administration

Beginning in March-May 2020, Palbociclib will be supplied by Pfizer in a tablet formulation. The tablets will be packed in blister packs containing either 75 mg, 100 mg or 125 mg tablets. Patients will be dispensed a monthly box containing 3 weekly blister packs of 7 tablets each along with the USPI for the tablet formulation.

The new smooth-coated tablet formulation offers patients the flexibility to take IBRANCE with or without food,

Palbociclib will be provided in non-patient-specific bottles containing either 75 mg, 100 mg or 125 mg capsules.

Site personnel must ensure that patients clearly understand the directions for self-medication. Patients should be given a sufficient supply to last until their next study visit. Unused drug and/or empty bottles should be returned to the site at the next study visit. Unused returned medication MUST NOT be re-dispensed to patients. All empty bottles or unused medication returned by the patient will be destroyed on site after verification from the study team and the outpatient pharmacist.

Palbociclib is an agent that must be handled and administered with care. Patients should be instructed to keep their medication in the bottles provided and not transfer it to any other container. Due to possible unknown hazards associated with topical and environmental exposure to experimental agents, capsules must not be opened and/or emptied into any vehicle for oral ingestion; capsules must be swallowed intact.

Only a single capsule or tablet strength will be dispensed to the patient at each dispensing visit. In the event of dose modification, request should be made of the patient to return all previously dispensed medication to the clinic and new capsules or tablets will be dispensed.

8.1.7 Ordering

Qualified personnel at participating sites will order the drug directly from Pfizer.

8.1.8 Accountability

To ensure adequate records, palbociclib capsules/tablets will be accounted for as instructed by Pfizer. Patients are requested to return previously dispensed containers as well as their completed drug diary to the clinic at each visit for accountability purposes even if they will not be issued with new medication at that visit.

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of the agent (investigational or free of charge) using the NCI Drug Accountability Record or another comparable drug accountability form. (See the CTEP website at http://ctep.cancer.gov/protocolDevelopment for the "Policy and Guidelines for Accountability and Storage of Investigational Agents" or to obtain a copy of the drug accountability form.)

8.1.9 Destruction and Return

Sites will document and destroy unused investigational product per their local policies. The site primary investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer. Destruction must be adequately documented.

8.2 Fulvestrant

8.2.1 Description

Fulvestrant injection for intramuscular administration is an estrogen receptor antagonist. The chemical name is 7-alpha-[9-(4,4,5,5,5-penta fluoropentylsulphinyl) nonyl]estra-1,3,5-(10)- triene-3,17 beta-diol. The molecular formula is C32H47F5O3S and its structural formula is: OH OH (CH2)9SO(CH2)3CF2CF3 Fulvestrant is a white powder with a molecular weight of 606.77. The solution for injection is a clear, colorless to yellow, viscous liquid.

Fulvestrant is commercially available and considered standard-of-care for patients with hormone receptor positive, metastatic breast cancer. The dose, schedule, and mode of administration used in this trial are identical to the dose, schedule, and mode of administration approved for use for this indication by the U.S. FDA.

Fulvestrant will be charged to the patient and/or insurance company as it is considered standard-of-care.

8.2.2 Form

Fulvestrant injection is commercially available as a sterile, single patient, prefilled syringe containing 250 mg at a concentration of 50 mg/mL. The solution is a clear, colorless to yellow, viscous liquid. In addition to the fulvestrant, each injection contains as inactive ingredients alcohol, USP, benzyl alcohol, NF, and benzyl benzoate, USP, as co-solvents and castor oil, USP, as a co-solvent and release rate modifier.

8.2.3 Storage and Stability

Syringes of fulvestrant should be stored in the original container and refrigerated at 2-8°C.

8.2.4 Handling

Fulvestrant requires no specific handling precautions. Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment.

8.2.5 Preparation

Remove syringe from tray and check that it is not damaged. Peel open the safety needle outer packaging. Break the seal of the white plastic cover on the syringe luer connector to remove the cover with the attached rubber tip cap. Twist to lock the needle to the luer lock connector. Remove needle sheath. Remove excess air from the syringe (a small bubble may remain).

8.2.6 Administration

Fulvestrant will be administered at a dose of 500 mg (2 x 250 mg injections) IM on Cycle 1 Day 1, Cycle 1 Day 15, Cycle 2 Day 1, and on Day 1 of each subsequent cycle. Cycle length = 28 days.

Fulvestrant will be administered slowly into each buttock. Immediately upon withdrawal of syringe from patient activate needle protection device by pushing lever arm forward until needle tip is fully covered. Visually confirm that the needle arm has advanced and that the needle tip is fully covered. If unable to activate, discard immediately into an approved sharps container.

Fulvestrant must be administered at the study site.

8.2.7 Ordering

Fulvestrant is commercially available and will be ordered by each prescribing provider for the duration for the study.

8.2.8 Accountability

Fulvestrant is commercially available and therefore accountability should be performed as standard policy in the investigational site.

8.2.9 Destruction

Fulvestrant is commercially available and therefore destruction should be performed as standard policy in the investigational site.

8.3 Avelumab

8.3.1 Pharmaceutical Properties

Avelumab drug product is a sterile, clear, and colorless concentrate for solution for infusion presented at the concentration of 20 mg/mL in European Pharmacopeia (Ph. Eur.) and United States Pharmacopeia (USP) type I glass vials closed with a rubber stopper and sealed with an aluminum Flip Offiaronmp crimp seal closure.

8.3.2 Description of the Formulations

Each single-use vial contains 200 mg of avelumab as a preservative-free acetate-buffered solution(pH 5.2) containing Mannitol, and Polysorbate 20 (Tween□20).

8.3.3 Instructions for Storage

Avelumab drug product must be stored at 2°C to 8°C until use. The storage condition is based on data from ongoing long term stability studies with avelumab. Avelumab drug product stored at room (23°C to 27°C) or higher temperatures for extended periods of time might be subject to degradation. Avelumab drug product must not be frozen. Rough shaking of the solution must be avoided. For administration in clinical trials, avelumab drug product must be diluted with 0.9% saline solution (sodium chloride injection) supplied in an infusion bag. The immediate administration of the prepared solution for dosing kept at room temperature is preferred. In case the aseptically prepared dosing solution cannot be administered immediately after preparation, the acceptable holding time is: not more than 24 hours under refrigerated conditions (2-8°C, 36-46°F) with no more than 8 of those hours at room temperature (15-25°C, 59-77°F), including infusion time.

No other drugs should be added to the solution for infusion containing avelumab.

8.3.4 Handling of the Dosage Forms

For administration in clinical trials, avelumab drug product must be diluted with 0.9% saline solution (sodium chloride injection) supplied in an infusion bag. Detailed information on infusion bags and medical devices to be used for the preparation of the dilutions and subsequent administration will be provided in the IP Manual.

To prepare the dilutions, subsequent preparation steps must be accomplished by adequate trained personnel under a laminar flow box using aseptic techniques:
Prior to the preparation of the dilution for final infusion, allow each vial to equilibrate to room temperature for a minimum of 30 minutes. Use a disposable syringe equipped with a needle of suitable size to remove a volume of sodium chloride solution to be replaced by avelumab from the infusion bag and discard the removed solution. Use a new disposable syringe equipped with a needle of suitable size to inject a volume of avelumab drug product identical to the discarded volume of sodium chloride solution into the infusion bag. Gently invert the mixture 10 times. Infusion bags must not be shaken, in order to avoid foaming or excessive shearing of the protein solution. The preparation must be carefully inspected as it should result in a homogeneous looking clear solution, free of visible particles.

8.3.5 Compatibility

There are no known compatibility issues for co-administration of avelumab with any of the other agents.

8.3.6 Availability

Avelumab is an investigational agent and will be supplied free-of-charge from Pfizer.

8.3.7 Preparation and Administration

Only clinical site personnel who are appropriately trained on the procedures may perform the preparation and administration step specified in the IP Manual. Clinical site personnel

involved in these procedures must comply with all applicable regulations and standards. The preparation and administration of all sterile products must be performed using aseptic technique. Utilize local site procedures as appropriate.

Avelumab) infusion solutions must be prepared in 0.9% Sodium Chloride (Normal Saline) and the final concentration of MSB0010718C (avelumab) in the infusion solutions must be between 0.016 mg/mL to 8 mg/mL. Total volume of final prepared solution must be 250 mL. Investigational drug products must be inspected visually for particulate matter and discoloration (i.e. change in color) prior to administration, whenever the solution and container permit. If particulates or discoloration are observed, do not use the vial(s) and notify the Principal Investigator or designee. Do not shake or freeze the vial(s). The final IP must be administered within 24 hours of preparation stored at room temperature 15 to 25 °C, 59 to 77 °F. Dose preparation must be performed using sterile handling techniques in compliance with local, state, and national laws/regulations. Avelumab MUST be administered with a low protein binding 0.2 micron PES filter. Each vial is for single-use only. Each vial is for use in a single patient, for a single dose. Avelumab is administered over 1 hour (-10/+20 minutes).

8.3.8 Ordering

Qualified personnel at participating sites will order the drug directly from Pfizer.

8.3.9 Accountability

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of the agent (investigational or free of charge) using the NCI Drug Accountability Record or another comparable drug accountability form. (See the CTEP website at http://ctep.cancer.gov/protocolDevelopment for the "Policy and Guidelines for Accountability and Storage of Investigational Agents" or to obtain a copy of the drug accountability form.)

8.3.10 Destruction and Return

All opened (i.e. aluminum overseal broken) vials (full, partially used, and empty) may be destroyed at the site by the appropriate site personnel local environmental requirements and institutional policies. Discarded volumes of IP solutions must be disposed of as pharmaceutical waste according to local site procedures. Destruction must be adequately documented.

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

9.1 Correlative Studies Background

The following outline provides a brief overview of the correlative studies.

[redacted]

9.2 Specimen Submission Requirements

The following specimens are to be submitted to the indicated lab. Refer to the separate PACE Study Manual for additional processing and shipping instructions. Sample collection kits will be provided to sites by Core Prognostex. Guardant Health will provide the sample collection and shipping materials for the Guardant cfDNA sample.

Required Specimen Submissions

Specimen Type	Collection Time Point					Shipping Condition	Ship to
	Baseline	C2 D1	C3D1	C5 D1	Progression / EOS		

Paraffin block (or 15 unstained slides) [a]	X					Ambient temperature	DFCI Smith Laboratory
1 H&E stained slide	X					Ambient temperature	DFCI Smith Laboratory
Streck Tubes (circulating cfDNA) [b]	X	X	X	X	X	Ambient temperature	DFCI Smith Laboratory
Guardant Health 360 cfDNA sample	X		X		X	Ambient temperature	Guardant Health 360
Plasma (EDTA tube)	X				X	Frozen	DFCI Smith Laboratory
2 Lavender Top EDTA Tubes (germline DNA)[c]		X				Thermos provided by Core Prognostex	DFCI Smith Laboratory
CTC sample (2 10 mL CellSave tubes)	X		X		X	Ambient temperature	Northwestern Lab
Fresh and frozen tumor tissue (optional biopsy)[d]	X				X	Frozen in OCT & ambient in formalin	DFCI Smith Laboratory

a. Preference for metastatic sample if available. Archival tissue can be collected at any time point throughout the study.
b. 2 Streck top tubes will be collected for cfDNA at baseline, time of each restaging, and progression or treatment discontinuation.
c. Sample for germline mutation should be collected at C2D1 or at any time during treatment
d. Baseline and Off-Treatment research biopsies are optional, but strongly encouraged, for patients with "easily accessible disease" and "accessible disease".

9.3 Translational Research Blood

Streck Tube (blood sample for cell-free DNA)
Blood will be collected for ctDNA analysis via 2 10 mL Streck tubes prior to dosing at Cycle 1 Day 1, Cycle 2 Day 1, at every restaging, and at time of disease progression or study discontinuation visit, whichever comes first. Collection tubes for research blood samples will be in the research sample collection kit provided by Core Prognostex. Instructions for collection, labeling, and shipment are included within the PACE Study Manual.

Guardant Health cfDNA
An additional single 10 mL Streck tube will be collected at baseline, C3D1, and off-treatment for Guardant Health 360. This sample kit will be provided by Guardant Health and the instructions for collection, labeling, and shipment are included within the Guardant Lab Manual.

DO NOT FREEZE OR REFRIGERATE STRECK TUBES.

Plasma Sample
Blood will be collected for plasma via a 10 mL EDTA tube (lavender top) at baseline and at time of progression or study discontinuation visit, whichever comes first. Instructions for collection,

labeling, and shipment are included within the PACE Study Manual.

Germline DNA Blood Collection
Two 10 mL Lavender top [EDTA] tubes of whole blood will be collected at Cycle 2 Day 1 for extraction of germline DNA. If it is missed, the sample may be drawn at any time during treatment. Collection tubes for research blood samples will be in the research sample collection kit provided by Core Prognostex. Instructions for collection, labeling, and shipment are included within the PACE Study Manual.

DO NOT REFRIGERATE/FREEZE OR CENTRIFUGE.

CTC Collection
Two 10 mL CellSave tubes will be collected at baseline, at time of first restaging (C3D1), and off-treatment for CTC analysis. Collection tubes for research blood samples will be in the research sample collection kit provided by Core Prognostex. Instructions for collection, labeling, and shipment are included within the PACE Study Manual.

DO NOT REFRIGERATE/FREEZE OR CENTRIFUGE.

9.4 Tumor Biopsies

Optional Tumor Biopsy will be performed at the following time-points:

- Baseline (Pre-Treatment): to be performed up to 2 weeks prior to starting treatment. Optional for patients with accessible disease or easily accessible disease.
- Off-Study/Disease Progression: to be performed after disease progression has been determined prior to initiation of subsequent therapy. Optional for patients with easily accessible and accessible disease

Fresh and frozen tumor samples from research biopsy will be shipped with the Specimen Requisition form found in the PACE Study Manual. Instructions for collection, labeling, and shipment are included within Appendix E and the PACE Study Manual.

9.5 Archival Tissue Collection

The following archival tissue specimens are required for gene profiling:

- 1 paraffin block (or 20 unstained slides 4-5μm thick)
- 1 H&E slide

Archival tissue will be collected for all participants. Preference is for tissue from metastatic biopsy or surgery rather than primary breast cancer diagnosis. Archival tissue sample is shipped ambient in conventional paraffin block or slide shipper to the DFCI PACE study team with the Specimen Requisition form found in the PACE Study Manual. The PACE Study Manual contains additional information on labeling and shipment of archival tissue to DFCI. Paraffin blocks will be returned after completion of correlative research. Unstained slides will not be returned.

10. STUDY CALENDAR

All subjects must sign an informed consent document prior to initiation of any study related procedures. The consenting individual for the clinical trial must be an MD listed as a co-investigator on the trial.

Baseline evaluations are to be conducted ≤ 14 days prior to start of protocol therapy. Scans must be done ≤4 weeks (+7 days) prior to the start of therapy. If performed at baseline < 7 days of C1D1, procedures do not need to be repeated to initiate treatment.

All assessments must be performed prior to administration of any study medication. Day 15 study assessments must be performed within +/- 3 days of the protocol-specified date, unless otherwise noted. Day 1 study assessments for Cycle 2 and beyond must be performed within +/- 3 days of the protocol-specified date. Day 14 Avelumab dose must be administered within +/- 2 days. Restaging CT or MRI scans and bone scans may be done +/- 7 days of the protocol-specified date, though it is preferred that they occur within the +/- 3 day window if possible.

Cycle 2 Day 15 laboratory assessments may be performed locally if appropriate plan is in place for the study site to receive and review results in a timely manner.

If treatment is held, the calendar of assessments should remain on schedule. Restaging scans should not be delayed.

After time of progression, patients will be followed for survival at least every 6 months until time of death. If a patient is taken off protocol treatment for any reason other than progression or death, then the patient should also be followed for progression with staging scans no less than every 12 weeks until disease progression, start of alternative anti- cancer therapy, death, or withdrawal of consent, whichever comes first. These patients should also be followed for survival every 6 months until time of death.

Table 7. Study Calendar

	Pre-Study	Cycle 1		Cycle 2		Subsequent Cycles		Follow-up	
	≤ 14 days of registration	D1	D15 ± 3 days	D1 ± 3 days	D15 ± 3 days	C3 D1 ± 3 days	D1 of each cycle ± 3 days	At time of progression or off treatment	Safety Follow-up[i]
Physical exam, ECOG PS	X	X[f]		X		X	X	X	
Vital signs, weight	X	X[f]		X		X	X	X	
Height	X								
CBC w/diff[a]	X	X[f]	X	X	X	X	X	X	
Serum chemistry[a]	X	X[f]	X	X	X	X	X	X	
Free T4, TSH, ACTH	X			X			X[g]		
HBV sAg , HCV Ab	X								
12-lead EKG	X								
B-HCG[b]	X								
Concomitant medication	X	X		X		X	X		
AE evaluation	X			X		X	X[h]	X	
Tumor measurements[c]	X					X	X		
Bone scan[d]	X								
Research blood, biopsy, or tissue[e]	X	X		X		X	Every 2 cycles	X	
Survival/safety follow-up								X	X

a. Serum chemistry: sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, glucose (random), total bilirubin, alkaline phosphatase, ALT, AST, albumin, calcium, magnesium, phosphorus, and CK [CK required for Arm C only]. **CBC and chemistries are required prior to each Avelumab dose in Arm C.** C2 Day 15 laboratory assessments are not required for Arm A.
b. In women of childbearing potential only (including premenopausal women with intact uterus and ovaries on GnRH agonist).
c. Baseline tumor assessments ≤4 (+7 days) weeks prior to the start of therapy. Subsequent assessments every 8 weeks (2 cycles, +/- 7 days) until 24 weeks at which point the interval may be extended to every 12 weeks, (3 cycles +/- 7 days). See Section 11.

d. Baseline whole body bone scan ≤4 (+7 days) weeks prior to the start of therapy. For patients with measurable disease, skeletal lesions identified on the whole body bone scan at baseline, which are not visible on the chest, abdomen and pelvis CT (or MRI) scan should be imaged at baseline and followed using localized CT, MRI or x-ray. Whole body bone scans need not be repeated after baseline unless clinically indicated. For patients with bone only disease, whole body scans will be performed every 6 months to confirm response, or earlier if clinically indicated.
e. See Section 9.
f. If performed at baseline ≤ 7 days of C1D1, procedures do not need to be repeated to initiate treatment. In the event that the participant's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.
g. After Cycle 4, endocrine tests are required every 2 cycles
h. Adverse events must be evaluated prior to every Avelumab infusion for patients on Arm C prior to infusion.
i. Adverse events will be collected until 30 days (Arms A and B) or at least 90 days (Arm C) after last dose of study treatment. AE collection after participants have come off treatment can occur within a +2-week window of the defined period. Patients will be followed for long term survival every 6 months or until death either via a site visit or via a telephone call. See Section 5.7.

11. MEASUREMENT OF EFFECT

For the purposes of this study, participants should be evaluated within 4 weeks of treatment start and re-evaluated for response every 8 weeks (2 cycles). After 24 weeks (cycle 6), tumor measurements can be performed every 12 weeks (3 cycles).

Confirmation of CR or PR are not required for best overall response determination in this trial. All primary and secondary endpoints based on radiological assessments of tumor burden will be derived using the local radiologist's/investigator's assessment.

Contrast computed tomography (CT) (or without contrast if contraindicated) of chest and abdomen is preferred. Magnetic resonance imaging (MRI) of chest and abdomen is an acceptable alternative. Note: PET-CT scans are not allowed per protocol for primary assessment of response. PET-CT scans may be done according to clinical judgment to supplement CT or MRI scans in cases where results of the PET-CT may clarify or resolve a clinical question. If palpable/visible lesions (e.g. chest wall nodule, etc) is being used as a target lesions, measurements and photographs should be taken as well.

11.1 RC: RECIST Criteria

Response and progression will be primarily evaluated in this study using the criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

11.1.1 Definitions

Evaluable for Target Disease response. Only those participants who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for target disease response. These participants will have their response classified according to the definitions stated below. Bone only disease, if there are lytic lesions, is also allowed and treatment response will be evaluated based on the MD Anderson criteria. (Note: Participants who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response. Participants who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

Evaluable for PFS. All participants randomized on this study are considered to be evaluable for PFS (whether or not they are eligible, have measurable disease, or receive protocol therapy).

11.1.2 Disease Parameters

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

A lesion in a previously irradiated area is not eligible for measurable disease unless there is objective evidence of progression of the lesion prior to study enrollment. Lesions in previously irradiated areas must be clearly identified as such.

Clinical lesions. Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

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

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

Lytic bone lesions or mixed lytic-blastic lesions, *with identifiable soft tissue components*, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered target lesions if the *soft tissue component* meets the definition of measurability as defined above. These lesions will be evaluated by the RECIST 1.1 criteria. Lytic bone lesions or mixed lytic-blastic lesions that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered target lesions and response will be evaluated using the MD Anderson (MDA criteria) [41]. 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same participant, these are preferred for selection as target lesions. Lesions in previously irradiated areas or areas subject to other loco-regional therapy are usually not considered measurable unless there has been demonstrated progression of that lesion.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but

in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow up.

11.1.3 Methods for Evaluation of Disease

All measurements should be taken and recorded in metric notation, using a ruler, calipers, or digital measurement tool. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 2 weeks before the beginning of the treatment.

Measurements are based on the sum of a perpendicular, bidimensional measurement of the greatest diameters of each individual lesion.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the anti-tumor effect of a treatment.

Clinical lesions. Clinical lesions will only be considered measurable when they are superficial (*e.g.*, skin nodules and palpable lymph nodes) and ≥10 mm in diameter as assessed using calipers (*e.g.*, skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Conventional CT and MRI. These techniques should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen, and pelvis. Head and neck tumors and those of extremities usually require specific protocols.

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should

be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

Ultrasound (US). When the primary endpoint of the study is objective response evaluation, US should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions, and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

FDG PET and PET/CT. The acquisition of FDG PET and FDG PET/CT scans should follow the NCI Guidelines for using FDG PET as an indicator of therapeutic response (L.K. Shankar et al, Consensus recommendations for the use of 18F- FDG PET as an indicator of therapeutic response in patients in National Cancer Institute Trials. J Nucl Med, 47(6):901-903, 2006). Patients should avoid strenuous exercise and be on a low carbohydrate diet for 24 hours prior to the scan. Patients should fast for 4 hours or longer prior to the FDG injection and should have a serum glucose of less than 200 mg/dL at the time of FDG injection. A 10-20 mCi dose of FDG should be injected for typical adult patients. For longitudinal studies with multiple scans, particular attention should be paid to ensure consistent patient preparation and acquisition parameters between the follow-up scan and the baseline scan. When designing a study where PET scans are going to be utilized as one of the modalities to evaluate efficacy, it is important to consult with physicians in nuclear medicine in designing the appropriate criteria to be utilized. *In this protocol, PET or PET/CT should NOT be used as the primary modality to evaluate objective response, but may be used in an adjunctive fashion together with either CT or MRI in cases of uncertainty, as clinically indicated.*

Endoscopy, Laparoscopy. The utilization of these techniques for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in reference centers. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained. *In this protocol, endoscopy or laparoscopy will not be used for evaluation of response.*

Tumor markers. Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a subject to be considered in complete clinical response.

Cytology, Histology. These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).
The cytological confirmation of the neoplastic origin of any effusion that appears or

worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

11.1.4 Response Criteria

a. Evaluation of Target Lesions

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

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

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

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

Unknown (UN): Assessment of target lesions cannot be made due to insufficient or unevaluable data. In this case, a concise explanation must be given.

b. Evaluation of Lytic Bone Lesion Target Lesion (MDA criteria)

Response category	**Criteria**
Complete response	Complete sclerotic fill-in of lytic lesions on x-ray or CT scan. Normalization of bone density on x-ray or CT scan. Normalization of signal intensity on MRI. Normalization of tracer uptake on skeletal scintigraphy

Partial Response	Development of a sclerotic rim or partial sclerotic fill-in of lytic lesions on x-ray or CT scan. Osteoblastic flare - Interval visualization of lesions with sclerotic rims or new sclerotic lesions in the setting of other signs of PR and absence of progressive bony disease. ≥ 50% decrease in measurable lesions on x-ray, CT, or MRI. ≥ 50% subjective decrease in the size of ill-defined lesions on x-ray, CT, or MRI. ≥ 50% subjective decrease in tracer uptake on skeletal scintigraphy.
Progressive Response	≥ 25% increase in size of measurable lesions on x-ray, CT, or MRI. ≥ 25% subjective increase in the size of ill-defined lesions on x-ray, CT, or MRI. ≥ 25% subjective increase in tracer uptake on skeletal scintigrap New bone metastases.
Stable Disease	No change < 25% increase or < 50% decrease in size of measurable lesions < 25% subjective increase or < 50% subjective decrease in size of ill-defined lesions No new bone metastases

c. Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Incomplete Response/Stable Disease (SD): Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

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

Unknown (UN): Assessment of non-target lesions cannot be made due to insufficient or unevaluable data. In this case, a concise explanation must be given.

Note: If tumor response data is missing for target lesions, the overall assessment must be Unknown (UN) unless there is new disease that would result in an overall assessment of PD. However, if there is missing or unevaluable data for non-target lesions, but data is available for all target lesions, the overall response for that time point will be assigned based on the sum LD of all target lesions. Additionally, the assessment of CR cannot be made if there is missing or unevaluable data for non-target lesions. In this case, the overall assessment would be PR.

Overall level of substantial worsening that merits discontinuation of therapy. A useful test that can be applied when assessing non-targets for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease.
Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

d. Evaluation of New Lesions

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

e. Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on measurement criteria.

Objective response will be defined as best overall response of CR or PR. Otherwise, the patient will be considered as non-responder; this includes patients with inadequate data for tumor assessment.

Clinical benefit will be defined as best overall response of CR or PR or stable disease of at least 24 weeks duration. Otherwise, the patient will be considered as non-responder; this includes patients with inadequate data for tumor assessment.

Table 8. For Participants with Measurable Disease (*i.e.*, Target Disease)

Target Lesions	Non-Target Lesions	New Lesions*	Overall Response
CR	CR	No	CR
CR	SD	No	PR
CR	UN	No	PR
PR	SD or UN	No	PR
SD	SD or UN	No	SD
PD	Any	Yes or No	PD
Any	PD***	Yes or No	PD
Any	Any	Yes	PD

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Participants with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration."* Every effort should be made to document the objective progression even after discontinuation of treatment.

Table 9. For Participants with Non-Measurable Disease

Non-Measurable Lesions	New Lesions	Overall Response
CR	No	CR
PR	No	PR
SD or UN	No	SD
PD	Yes or No	PD
Any	Yes	PD

Note: Participants with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration."* Every effort should be made to document the objective progression even after discontinuation of treatment.

11.1.5 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started, or

death due to any cause. Participants without events reported are censored at the last disease evaluation.

Duration of overall complete response: The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent or progressive disease is objectively documented, or death due to any cause. Participants without events reported are censored at the last disease evaluation.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progressive disease is objectively documented, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

11.1.6 Progression-Free Survival

Progression-Free Survival: Progression-Free Survival (PFS) is defined as the time from randomization to the earlier of progression or death due to any cause. Participants alive without disease progression are censored at date of last disease evaluation. The Statistical Analysis Plan will document special cases of PFS definition and censoring criteria.

11.2 irRC: Immune-Related Response Criteria

Definition of Tumor Response Using irRC

NOTE: This section is for secondary endpoint assessment to be used only for patients in Arm C.

RECIST 1.1 has its shortcomings for targeted immunotherapy in oncology, as RECIST may not accurately capture the 'flare effect' - pseudo-progression effect – which can be seen with immunotherapy agents, and may declare progressive disease too early, when the treatment effect is not yet fully evident. Immune related Response Criteria (irRC) were created to provide better assessment of the effect of immunotherapeutic agents. (Wolchok et al, CCR 2009)

The sum of the products of the two largest diameters of lesions (SPD) at tumor assessment using the immune-related response criteria (irRC) for progressive disease incorporates the contribution of new measurable lesions. Each net Percentage Change in Tumor Burden per assessment using irRC criteria accounts for the size and growth kinetics of both old and new lesions as they appear.

11.2.1 Definition of Target Lesions Response Using irRC

• **irComplete Response (irCR):** Complete disappearance of all target lesions. This category
encompasses exactly the same subjects as "CR" by the mWHO criteria.

• **irPartial Response (irPR):** Decrease, relative to baseline, of 50% or greater in the sum of the products of the two largest perpendicular diameters of all target and all new

measurable lesions (i.e., Percentage Change in Tumor Burden). Note: the appearance of new measurable lesions is factored into the overall tumor burden, but does not automatically qualify as progressive disease until the SPD increases by > 25% when compared to SPD at nadir.

• **irStable Disease (irSD):** Does not meet criteria for irCR or irPR, in the absence of progressive disease.

• **irProgressive Disease (irPD):** At least 25% increase Percentage Change in Tumor Burden (i.e., taking SPD of all target lesions and any new lesions) when compared to SPD at nadir.

11.2.2 Definition of Non-Target Lesions Response Using irRC

• **irComplete Response (irCR):** Complete disappearance of all non-target lesions. This category encompasses exactly the same subjects as "CR" by the mWHO criteria.

• **irPartial Response (irPR):** Non-target lesion(s) are not considered in the definition of PR; this term does not apply.

• **irStable Disease (irSD):** Does not meet the criteria for irCR or irPD.

• **irProgressive Disease (irPD):** Increases in number or size of non-target lesion(s) does not constitute progressive disease unless/until the Percentage Change in Tumor Burden increases by 25% (i.e., the SPD at nadir of the target lesions increases by the required amount).

11.2.3 Impact of New Lesions on irRC

New lesions in and by themselves do not qualify as progressive disease. However their contribution to total tumor burden is included in the SPD which in turn feeds into the irRC criteria for tumor response. Therefore, new non-measurable lesions will not discontinue any subject from the study.

11.2.4 Definition of Overall Response Using irRC

Overall response using irRC will be based on these criteria:

• **Immune-Related Complete Response (irCR):** Complete disappearance of all tumor lesions (target and non-target together with no new measurable/unmeasurable lesions) for at least 4 weeks from the date of documentation of complete response.

• **Immune-Related Partial Response (irPR):** The sum of the products of the two largest perpendicular diameters of all target lesions is measured and captured as the SPD baseline. At each subsequent tumor assessment, the SPD of the two largest perpendicular diameters of all target lesions and of new measurable lesions are added together to

provide the Immune Response Sum of Product Diameters (irSPD). A decrease, relative to baseline of the irSPD compared to the previous SPD baseline, of 50% or greater is considered an immune Partial Response (irPR).

• **Immune-Related Stable Disease (irSD):** irSD is defined as the failure to meet criteria for immune complete response or immune partial response, in the absence of progressive disease.

• **Immune-Related Progressive Disease (irPD):** It is recommended in difficult cases to confirm PD by serial imaging. Any of the following will constitute progressive disease:
− At least 25% increase in the SPD of all target lesions over nadir SPD calculated for the target
lesions.
− At least a 25% increase in the SPD of all target lesions and new measurable lesions (irSPD) over the nadir SPD calculated for the target lesions.

Table 10: Immune-Related Response Criteria Definitions

Target Lesion Definition	Non-Target Lesion Definition	New Measurable Lesions	New Non-measurable lesions	Percent change in tumor burden (including measurable new lesions when present)	Overall irRC Response
Complete Response	Complete Response	No	No	-100%	irCR
Partial Response	Any	Any	Any	≥ 50 %	irPR
				< -50% to +25%	irSD
				> +25%	irPD
Stable Disease	Any	Any	Any	< -50% to +25%	irSD
				> +25%	irPD
Progressive Disease	Any	Any	Any	≥ 25 %	irPD

11.2.5 Immune-Related Best Overall Response Using irRC (irBOR)

irBOR is the best confirmed irRC overall response over the study as a whole, recorded between the date of first dose until the last tumor assessment before subsequent therapy (except for local palliative radiotherapy for painful bone lesions) for the individual subject in the study. For the assessment of irBOR, all available assessments per subject are considered.

irCR or irPR determinations included in the irBOR assessment must be confirmed by a second (confirmatory) evaluation meeting the criteria for response and performed no less than 4 weeks after the criteria for response are first met.

11.2.6 Confirmation of Progressive Disease in Arm C Avelumab Arm

Avelumab, like other immunotherapeutic agents, may produce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen

with such an approach may extend beyond the typical time course of image responses seen with cytotoxic agents, and can manifest as a clinical response after an initial increase in tumor burden or even the appearance of new lesions.

For any subject in Arm C who showed first radiologic evidence of progressive disease (PD) by RECIST 1.1 and is deemed clinically stable, it is at the discretion of the investigator to continue treating the subject until progression is confirmed at least 4 weeks from the date of the first radiologic evidence of PD. If progression is confirmed, the subject will be discontinued from study treatment. Otherwise, the subject will continue treatment and radiographic scans. Any subject who had initial radiologic progression and is deemed clinically unstable should be discontinued from both study drugs and no subsequent scan for confirmation is required.

Further details are as below:

For purposes of PFS assessment on this trial, in addition to radiographic assessment of tumor
response or progression, the investigator should into account the clinical condition/stability of subjects.

Clinically stable is defined by the following criteria:

- Absence of signs and symptoms (including worsening of laboratory values) indicating disease progression
- No decline in ECOG performance status
- Absence of rapid progression of disease
- Absence of progressive tumor(s) at critical anatomical sites (eg, cord compression) requiring urgent alternative medical intervention

Any subject who showed first radiologic evidence of progressive disease and is deemed clinically unstable should be discontinued from study drugs and is not required to have repeat imaging for confirmation.

For a clinically stable subject with first radiologic evidence of progressive disease (ie, unconfirmed progression of disease), it is at the discretion of the investigator to continue treating the subject with the assigned treatment per protocol until progression of disease is confirmed on a subsequent scan at least 4 weeks later. If progression is not confirmed on the subsequent scan, the subject should continue to receive study treatment and have radiographic scans performed every 8 weeks if the patient has been on study for less than 24 weeks, or every 12 weeks for patients who have been on study greater than 24 weeks to monitor disease status. If radiologic progression is confirmed by subsequent scans, then the subject will be discontinued from study treatment. Exceptions may be considered to continue treatment in the presence of clinically stable or improved condition only after consultation with the principal investigator.

12. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

12.1 Data Reporting

12.1.1 Method

The Office of Data Quality (ODQ) will collect, manage, and perform quality checks on the data for this study.

12.1.2 Responsibility for Data Submission

Investigative sites are responsible for submitting data and/or data forms to the Office of Data Quality in accordance with DF/HCC SOPs.

12.2 Data Safety Monitoring

The DF/HCC Data and Safety Monitoring Board (DSMB) will review and monitor study progress, toxicity, safety and other data from this study. The board is chaired by a medical oncologist from outside of DF/HCC and has external and internal representation. Information that raises any questions about participant safety or protocol performance will be addressed by the Overall PI, statistician and study team. Should any major concerns arise, the DSMB will offer recommendations regarding whether or not to suspend the study.

The DSMB will meet twice a year to review accrual, toxicity, response and reporting information. Information to be provided to the DSMB may include: participant accrual; treatment regimen information; adverse events and serious adverse events reported by category; summary of any deaths on study; audit results; and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

12.3 Multicenter Guidelines

This protocol will adhere to the policies and requirements of the DF/HCC Multi-Center Data and Safety Monitoring Plan. The specific responsibilities of the Overall PI, Coordinating Center, and Participating Institutions and the procedures for auditing are presented in Appendix H.

- The Overall PI/Coordinating Center is responsible for distributing IND Action Letters or Safety Reports to all participating institutions for submission to their individual IRBs, if applicable

- Mechanisms will be in place to ensure quality assurance, protocol compliance, and adverse event reporting at each site.

- Except in very unusual circumstances, each participating institution will order the study

agent(s) directly from supplier. A participating site may order the agent(s) only after the initial IRB approval for the site has been forwarded to the Coordinating Center.

12.4 Collaborative Research and Future Use of Data and Biospecimens

Tissue, blood, bodily fluids, and other materials derived from these will be collected in this study to analyze genes, DNA, RNA, proteins and cells for the study's correlative endpoints and potential future research, utilizing new types of biomarker testing as it becomes available.

These samples and any data generated as a part of these clinical trials may be used for future research studies and may be provided to collaborating investigators both within and outside of the DF/HCC for either correlative endpoints or secondary use. Samples and data may be shared with outside non-profit academic investigators, as well as with for-profit pharmaceutical investigators or commercial entities, with whom we collaborate. When samples or data are sent to collaborators and when any research is performed on them, all information will be identified with a code, and will not contain any PHI, such as name, birthday, or MRNs.

In order to allow the greatest amount of research to be performed on the specimens and information generated as a part of this trial, researchers in this study may share results of genetic sequencing with other scientists. De-identified specimen or genetic data may be placed into one of more publicly-accessible scientific databases, such as the National Institutes of Health's Database for Genotypes and Phenotypes (dbGaP). The results from the correlative research on this study will be shared with these public databases. Through such databases, researchers from anywhere will have access to de-identified samples or data for future research. More detailed information, beyond the public database, may only be accessed by scientists at other research centers who have received special permission to review de-identified data.

13. STATISTICAL CONSIDERATIONS

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a Statistical Analysis Plan (SAP). This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition and/or its analysis will also be reflected in a protocol amendment.

13.1 Accrual and Sample Size Determination

It is planned to stratify (as defined in Section 1.1) and randomize a total of 220 patients, in a 1:2:1 ratio, to have 110 patients randomized to receive fulvestrant+palbociclib (arm B) and 55 patients randomized to each of the control arm, fulvestrant (arm A), and the exploratory arm, fulvestrant+palbociclib+avelumab (arm C).

An accrual duration of 30 months is expected, with accrual during the first 6 months averaging 2.7 patients/month for a total of 16 patients while participating centers are activated, then uniform accrual of 8.5 patients per month for 24 months.

The sample size for the primary objective comparing fulvestrant+palbociclib versus fulvestrant (arm B versus arm A) was determined based on prior published experience of PALOMA-3 [Cristofanilli et al, Lancel Oncol 2016] that the median PFS for patients receiving fulvestrant alone after prior endocrine therapy is estimated to be approximately 4 months, and a risk reduction by 38.5% (hazard ratio [HR]=0.6154) to a median PFS of 6.5 months (assuming exponential distribution of PFS) in the fulvestrant+palbociclib arm is a clinically-meaningful improvement in PFS with the combination. A total of 119 events are required to have 80% power to detect this improvement in PFS using a log-rank test with a one-sided alpha level of 0.05 and assuming 5% drop-out (i.e., PFS event never documented) by 6 months in each arm. Under the design assumptions, 119 PFS events in arms B+A would be expected after 32 months since start of enrollment.

The sample size for the exploratory objective comparing fulvestrant+palbociclib+avelumab versus fulvestrant (arm C versus arm A) was determined based on the median PFS of 4 months for patients receiving fulvestrant alone, and a risk reduction by 47% (HR=0.53) to a median PFS of 7.5 months in the fulvestrant+ palbociclib+ avelumab is a clinically-meaningful improvement in PFS with triplet therapy. A total of 63 events are required to have 80% power to detect this improvement in PFS using a log-rank test with a one-sided alpha level of 0.05 and assuming 5% drop-out by 6 months in each arm. Under the design assumptions, after 32 months when the primary objective could be analyzed, 80 PFS events in arms C+A would be expected and power would be about 88%.

13.2 Analysis Populations

Intent-to-Treat (ITT) Population: The ITT population will include all patients who are randomized, according to treatment assignment. The ITT population will be the primary population for evaluating all efficacy endpoints and patient characteristics.

Safety Population: The safety population will include all patients who receive at least 1 dose of study treatment(s), according to actual study treatment received.

13.3 Analysis of Efficacy Endpoints

Combination fulvestrant+palbociclib versus fulvestrant (arm B vs. arm A)

For the primary objective, the distributions of PFS (as defined in Section 11.1.16) will be compared between fulvestrant+palbociclib versus fulvestrant (arm B versus arm A) using a stratified log-rank test with one-sided alpha level of 0.05. A stratified Cox proportional hazards model will be fitted to estimate the treatment hazard ratio and the corresponding two-sided 90% CI. The PFS distributions will be summarized according to treatment arm using the Kaplan-Meier method and displayed graphically, along with estimates of median and other percentiles of the PFS distributions and with estimates of 6-month and 12-month PFS (with two-sided 90% CI to accompany each estimate).

For the secondary objective, the OR rate (ORR) will be estimated according to treatment arm (fulvestrant+palbociclib versus fulvestrant) as the number of patients with objective response (as

defined in Section 11.1.4.e) divided by the number of patients randomized to the respective treatment arm, with two-sided 90% CI for the ORRs. ORRs will be compared between the two treatment arms (arm B vs. arm A) using a Cochran-Mantel-Haenszel test with the same stratification factor as for the PFS analysis.

Secondary measures based on radiological assessments of tumor burden (as defined in Sections 11.1.4.e and 11.1.5) will also be estimated and summarized according to treatment arm. Among the subset of patients with objective response, duration of response will be summarized using the Kaplan-Meier method. Best overall response will be summarized descriptively; the percent change in tumor burden corresponding to best overall response may be summarized graphically as a waterfall plot. Clinical benefit rate will be estimated and summarized similarly to ORR.

As secondary and exploratory objectives, the treatment effects on PFS and OR will be estimated in subgroups defined according to predefined molecular subgroups, including ESR mutation, PI3K mutation, loss of Rb gene and/or function, and the stratification factor of whether or not there was exposure to a chemotherapy regimen between initial exposure to CDK4/6 inhibitor and entry on this study. In addition to HR and ORR estimates (with CIs), the p-value for test of subgroup-by-treatment interaction from Cox PH and logistic regression models will be reported though power for test of interaction is limited.

For the primary endpoint, PFS is based on traditional RECIST 1.1 criteria with date of progressive disease (PD) as first radiologic evidence of PD. Per section 11.2.6, for any subject in Arm C who showed first radiologic evidence of progressive disease (PD) by RECIST 1.1 and is deemed clinically stable, it is at the discretion of the investigator to continue treating the subject until progression is confirmed at least 4 weeks from the date of first radiologic evidence of PD.

Palbociclib after fulvestrant (arm A crossover)

For the secondary objective to assess PFS and ORR with the addition of palbociclib after progression on fulvestrant alone, the analysis will include the subset of patients from the ITT population for arm A who initiate palbociclib after progression on fulvestrant alone. The PFS distribution will be summarized using the KM method, and the ORR will be estimated as the number of patients with objective response divided by the number of patients who initiate palbociclib after progression on fulvestrant alone.

Fulvestrant+palbociclib+avelumab versus fulvestrant (arm C vs. arm A)
For the exploratory objective to assess PFS and ORR for fulvestrant+palbociclib+avelumab versus fulvestrant alone, the analyses will follow as described above for the comparison of arms B vs. A.

Fulvestrant+palbociclib+avelumab versus fulvestrant+palbociclib (arm C vs. arm B)

For the exploratory objective to assess PFS and ORR for fulvestrant+palbociclib+avelumab versus fulvestrant+palbociclib, the analyses will follow as described above for the comparison of arms B vs. A, however the focus will be on estimation of treatment effects rather than testing.

13.4 Comparison of RECIST versus irRC (arm C)

As an exploratory objective, among patients assigned to fulvestrant+palbociclib+avelumab (arm C), the best overall response assessments by RECIST and irRC will be cross-tabulated to summarize concordance/discordance of the two assessments. Details of the cases of discordance will be described.

13.5 Safety

The maximum grade of each adverse event (AE) type will be summarized as frequency (and %) of patients experiencing the AE, tabulated according to body system and AE type, separately according to treatment group. The summaries may be without regard to relation and in the subset considered as related to study treatment(s). Laboratory data will be summarized descriptively by cycle and treatment.

Supplemental Safety Monitoring of Fulvestrant+Palbociclib+Avelumab (Arm C)

In addition to regular reporting of AEs to the DSMB, sequential boundaries will be used to monitor safety of patients receiving fulvestrant+palbociclib+avelumab (arm C) in case of unexpectedly high treatment-related grade 3-5 non-hematologic AE rate, providing guidance to pause enrollment to arm C for further safety review if excessive numbers of these AEs are observed. The criteria are defined such that the probability of pausing is at most 0.05 if the true rate of these AEs is 33%, and the probabilities of pausing are 0.71 or 0.98 if the true rates are 50% or 60%[74]. . The Table gives the criteria for pausing enrollment to arm C in order to more fully evaluate safety.

Table. Criteria for pausing enrollment because of all/treatment-related grade 3-5 non-hematologic AEs to more fully evaluate safety, for sample size up to 55 patients in arm C, with 0.05 probability of pausing when the true AE rate is 33% (pause if number of AEs is $\geq b_n$ of N patients in the safety-evaluable population)

Boundary (b_n)	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
N pts in safety-eval. population	5	6-7	8-9	10-11	12-13	14-15	16-17	18-19	20-22	23-24	25-26	27-29	30-31	32-33	34-36
Boundary (b_n)	20	21	22	23	24	25	26	27							
N pts in safety-eval. population	37-38	39-40	41-43	44-45	46-48	49-50	51-53	54-55							

The safety-evaluable population will include patients randomized to arm C for whom AEs of at least the first cycle of protocol therapy have been recorded in the database or an SAE has been reported.

13.6 Interim Efficacy/Inefficacy Monitoring

The study is designed to have one interim analysis and the final analysis for the primary objective, on the basis of the primary endpoint of PFS. The purpose of the interim analysis is to

allow early stopping of the study for futility. The interim analysis will be planned to correspond to the DSMB meeting after 50% of PFS events have been recorded, using the linear inefficacy boundary approach LIB20[75]. Under the design assumptions, 60 PFS events in arms B+A would be expected after 21 months since start of enrollment, at which point about 70% of enrollment would be expected

14. PUBLICATION PLAN

It is understood that any manuscript or releases resulting from the collaborative research will be circulated to all participating sites prior to submission for publication or presentation. The Primary Investigator will be the final arbiter of the manuscript content.

The outcome results of this trial will be made public within 24 months of the end of data collection. Interim results of this trial may also be periodically presented at meetings of the American Society of Clinical Oncology and the San Antonio Breast Cancer Symposium. Results of the formal interim analysis will be made available for presentation after analysis is complete. A full report of the outcomes will be made public no later than two (2) years after the end of data collection.

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APPENDIX A: EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG) PERFORMANCE STATUS CRITERIA

Description	Grade
Fully active, able to carry on all pre-disease performance without restriction.	0
Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature, i.e., light house work, office work.	1
Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.	2
Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	3
Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	4

APPENDIX B: STRONG CYP3A INDUCERS/INHIBITORS AND INFORMATION ON POSSIBLE DRUG INTERACTIONS

Medications that strongly inhibit CYP3A:
Amprenavir
Atazanavir
Boceprevir
Clarithromycin
Conivaptan
Delavirdine
Diltiazem
Erythromycin
Fosamprenavir
Indinavir
Itraconazole
Ketoconazole
Lopinavir
Mibefradil
Miconazole
Nefazodone
Nelfinavir
Posaconazole
Ritonavir
Saquinavir
Telaprevir
Telithromycin
Verapamil
Voriconazole
Grapefruit, grapefruit juice, or any product containing grapefruit

Medications that strongly induce CYP3A:
Carbamazepine
Felbamate
Nevirapine
Phenobarbital
Phenytoin
Primidone
Rifabutin
Rifampin
Rifapentin
St. John's wort

APPENDIX C: PALBOCICLIB DRUG DIARY

Participant Identifier: _____ Cycle Number:_____
Your MD: _____ Phone: _____
Your RN: _____ Phone: _____

Palbociclib Instructions

How much: Your dose is _____

When: You should take your dose within 1 hour of a meal at the same time each day.

Special Instructions

If it is more than 6 hours after your regularly scheduled time, do not take that days dose.
If you inadvertently take 1 extra dose during a day, you must skip the next days dose.
If you vomit your dose, do not retake the dose.
The Palbociclib is to be swallowed whole, and not to be chewed, crushed or opened.
Please avoid eating grapefruit.
Remember to bring any unused drug, all empty containers, and this diary with you to your next visit.

Palbociclib Dosing Log

	Date	Amount Taken	Time Taken	Taken within 1 hr of a meal
Day 1				
Day 2				
Day 3				
Day 4				
Day 5				
Day 6				
Day 7				
Day 8				
Day 9				
Day 10				
Day 11				
Day 12				
Day 13				
Day 14				
Day 15				
Day 16				
Day 17				
Day 18				
Day 19				
Day 20				
Day 21				
Day 22				
Day 23				
Day 24				
Day 25				
Day 26				
Day 27				
Day 28				

APPENDIX D: COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS (VERSION 4.0)

Cancer Therapy Evaluation Program, NCI CTCAE v 4.0. Available from http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev 4.pdf.

APPENDIX E: RESEARCH SPECIMEN COLLECTION GUIDELINES

[redacted]

[redacted]

APPENDIX F: DANA-FARBER/HARVARD CANCER CENTER MULTI-CENTER DATA AND SAFETY MONITORING PLAN

TABLE OF CONTENTS

1. INTRODUCTION

The Dana-Farber/Harvard Cancer Center Multi-Center Data and Safety Monitoring Plan (DF/HCC DSMP) outlines the procedures for conducting a DF/HCC Multi-Center research protocol. The DF/HCC DSMP serves as a reference for any sites external to DF/HCC that are participating in a DF/HCC clinical trial.

1.1 Purpose

To establish standards that will ensure that a Dana-Farber/Harvard Cancer Center Multi-Center protocol will comply with Federal Regulations, Health Insurance Portability and Accountability Act (HIPAA) requirements and applicable DF/HCC Standard Operating Procedures.

1.2 Multi-Center Data and Safety Monitoring Plan Definitions

DF/HCC Multi-Center Protocol: A research protocol in which one or more outside institutions are collaborating with Dana-Farber/Harvard Cancer Center where a DF/HCC investigator is the sponsor. DF/HCC includes Dana-Farber/Partners Cancer Care (DF/PCC) Network Clinical Trial Affiliates.

Lead Institution: One of the Dana-Farber/Harvard Cancer Center consortium members (Dana-Farber Cancer Institute (DFCI), Massachusetts General Hospital (MGH), Beth Israel Deaconess Medical Center (BIDMC), Boston Children's Hospital (BCH), Brigham and Women's Hospital (BWH) responsible for the coordination, development, submission, and approval of a protocol as well as its subsequent amendments per the DFCI IRB and applicable regulatory guidelines (CTEP, Food and Drug Administration (FDA), Office of Biotechnology Activities (OBA) etc.). The Lead Institution is typically the home of the DF/HCC Sponsor. The Lead Institution also typically serves as the Coordinating Center for the DF/HCC Multi-Center Protocol.

DF/HCC Sponsor: The person sponsoring the submitted Multi-Center protocol who takes responsibility for initiation, management and conduct of the protocol at all research locations. In applicable protocols, the DF/HCC Sponsor will serve as the single liaison with any regulatory agencies. The DF/HCC Sponsor has ultimate authority over the protocol and is responsible for the conduct of the study at DF/HCC and all Participating Institutions. In most cases the DF/HCC Sponsor is the same person as the DF/HCC Overall Principal Investigator; however, both roles can be filled by two different people.

Participating Institution: An institution that is outside the DF/HCC and DF/PCC consortium that is collaborating with DF/HCC on a protocol where the sponsor is a DF/HCC Investigator. The Participating Institution acknowledges the DF/HCC Sponsor as having the ultimate authority and responsibility for the overall conduct of the study.

Coordinating Center: The entity (i.e. Lead Institution, Medical Monitor, Contract Research Organization (CRO), etc) that provides administrative support to the DF/HCC Sponsor in order that he/she may fulfill the responsibilities outlined in the protocol document and DSMP, and as

specified in applicable regulatory guidelines (i.e. CTEP Multi-Center Guidelines). In general, the Lead Institution is the Coordinating Center for the DF/HCC Multi-Center Protocol.

DF/HCC Office of Data Quality (ODQ): A group within DF/HCC responsible ensuring high-quality standards are used for data collection and the ongoing management of clinical trials, auditing, and data and safety monitoring. ODQ also coordinates quality assurance efforts related to multi-center clinical research.

DF/HCC Research Informatics Office (RIO): A group within DF/HCC responsible for providing a comprehensive data management platform for managing clinical trial data.

2. GENERAL ROLES AND RESPONSIBILITIES

For DF/HCC Multi-Center Protocols, the DF/HCC Sponsor, the Coordinating Center, and the Participating Institutions are expected to adhere to the following general responsibilities:

2.1 DF/HCC Sponsor

The DF/HCC Sponsor, Erica Mayer, MD, MPH, will accept responsibility for all aspects of conducting a DF/HCC Multi-Center protocol which includes but is not limited to:

- Oversee the coordination, development, submission, and approval of the protocol as well as subsequent amendments.
- Ensure that the investigators, study team members, and Participating Institutions are qualified and appropriately resourced to conduct the protocol.
- Include the Multi-Center Data and Safety Monitoring Plan as an appendix to the protocol.
- Ensure all Participating Institutions are using the correct version of the protocol.
- Ensure that each participating investigator and study team member receives adequate protocol training (and/or a Site Initiation Visit prior to enrolling participants) and throughout trial's conduct as needed.
- Ensure the protocol will be provided to each participating site in a language understandable to all applicable site personnel when English is not the primary language.
- Monitor progress and overall conduct of the study at all Participating Institutions.
- Ensure all DFCI Institutional Review Board (IRB), DF/HCC and other applicable reporting requirements are met.
- Review data and maintain timely submission of data for study analysis.
- Act as the single liaison with FDA, as applicable.
- Ensure compliance with all requirements as set forth in the Code of Federal Regulations, applicable DF/HCC requirements, HIPAA requirements, and the approved protocol.
- Commit to the provision that the protocol will not be rewritten or modified by anyone other than the DF/HCC Sponsor.
- Identify and qualify Participating Institutions and obtain accrual commitments prior to extending the protocol to that site.
- Monitor accrual and address Participating Institutions that are not meeting their accrual requirements.

2.2 Coordinating Center

The general responsibilities of the Coordinating Center may include but are not limited to:

- Assist in protocol development.
- Review registration materials for eligibility and register participants from Participating Institutions in the DF/HCC clinical trial management system (CTMS).
- Distribute protocol and informed consent document updates to Participating Institutions as needed.
- Oversee the data collection process from Participating Institutions.
- Maintain documentation of Serious Adverse Event (SAE) reports and deviations/violation submitted by Participating Institutions and provide to the DF/HCC Sponsor for timely review and submission to the DFCI IRB, as necessary.
- Distribute serious adverse events reported to the DF/HCC Sponsor that fall under the DFCI IRB Adverse Event Reporting Policy to all Participating Institutions.
- Provide Participating Institutions with information regarding DF/HCC requirements that they will be expected to comply with.
- Carry out plan to monitor Participating Institutions either by on-site or remote monitoring.
- Maintain Regulatory documents of all Participating Institutions which includes but is not limited to the following: local IRB approvals/notifications from all Participating Institutions, confirmation of Federalwide Assurances (FWAs) for all sites, all SAE submissions, Screening Logs for all sites, IRB approved consents for all sites
- Conduct regular communications with all Participating Institutions (conference calls, emails, etc) and maintain documentation all relevant communications.

2.3 Participating Institution

Each Participating Institution is expected to comply with all applicable federal regulations and DF/HCC requirements, the protocol and HIPAA requirements.

The general responsibilities for each Participating Institution may include but are not limited to:

- Document the delegation of research specific activities to study personnel.
- Commit to the accrual of participants to the protocol.
- Submit protocol and/or amendments to their local IRB.
- Maintain regulatory files as per sponsor requirements.
- Provide the Coordinating Center with regulatory documents or source documents as requested.
- Participate in protocol training prior to enrolling participants and throughout the trial as required (i.e. teleconferences).
- Update Coordinating Center with research staff changes on a timely basis.
- Register participants through the Coordinating Center prior to beginning research related activities.
- Submit Serious Adverse Event (SAE) reports to local IRB per institutional requirements and to the Coordinating Center, in accordance with DF/HCC requirements
- Submit protocol deviations and violations to local IRB per institutional requirements and to the DF/HCC Sponsor in accordance with DF/HCC requirements.

- Order, store and dispense investigational agents and/or other protocol mandated drugs per federal guidelines and protocol requirements.
- Have office space, office equipment, and internet access that meet HIPAA standards.
- Participate in any quality assurance activities and meet with monitors or auditors at the conclusion of a visit to review findings.
- Promptly provide follow-up and/or corrective action plans for any monitoring queries or audit findings.

3. DF/HCC REQUIREMENTS FOR MULTI-CENTER PROTOCOLS

The following section will clarify DF/HCC Requirements and further detail the expectations for participating in a DF/HCC Multi-Center protocol.

3.1 Protocol Distribution

The Coordinating Center will distribute the final DFCI IRB approved protocol and any subsequent amended protocols to all Participating Institutions.

3.2 Protocol Revisions and Closures

The Participating Institutions will receive notification of protocol revisions and closures from the Coordinating Center. It is the individual Participating Institution's responsibility to notify its IRB of these revisions.

- **Non life-threatening revisions:** Participating Institutions will receive written notification of protocol revisions regarding non life-threatening events from the Coordinating Center. Non-life-threatening protocol revisions must be IRB approved and implemented within 90 days from receipt of the notification.

- **Revisions for life-threatening causes:** Participating Institutions will receive immediate notification from the Coordinating Center concerning protocol revisions required to protect lives with follow-up by fax, mail, e-mail, etc. Life-threatening protocol revisions will be implemented immediately followed by IRB request for approval.

- **Protocol closures and temporary holds:** Participating Institutions will receive notification of protocol closures and temporary holds from the Coordinating Center. Closures and holds will be effective immediately. In addition, the Coordinating Center, will update the Participating Institutions on an ongoing basis about protocol accrual data so that they will be aware of imminent protocol closures.

3.3 Informed Consent Requirements

The DF/HCC approved informed consent document will serve as a template for the informed consent for Participating Institutions. The Participating Institution consent form must follow the consent template as closely as possible and should adhere to specifications outlined in the DF/HCC

Guidance Document on Model Consent Language for PI-Initiated Multi-Center Protocols. This document will be provided separately to each Participating Institution upon request.

Participating Institutions are to send their version of the informed consent document and HIPAA authorization, if a separate document, to the Coordinating Center for review and approval prior to submission to their local IRB. The approved consent form must also be submitted to the Coordinating Center after approval by the local IRB for all consent versions.

The Principal Investigator (PI) at each Participating Institution will identify the physician members of the study team who will be obtaining consent and signing the consent form for therapeutic protocols. Participating institutions must follow the DF/HCC requirement that only attending physicians obtain informed consent and re-consent for all interventional drug, biologic, or device research.

3.4 IRB Documentation

The following must be on file with the Coordinating Center:

- Initial approval letter of the Participating Institution's IRB.
- Copy of the Informed Consent Form(s) approved by the Participating Institution's IRB.
- Participating Institution's IRB approval for all amendments.
- Annual approval letters by the Participating Institution's IRB.

3.5 IRB Re-Approval

Verification of IRB re-approval from the Participating Institutions is required in order to continue research activities. There is no grace period for continuing approvals.

The Coordinating Center will not register participants if a re-approval letter is not received from the Participating Institution on or before the anniversary of the previous approval date.

3.6 Participant Confidentiality and Authorization Statement

In 1996, congress passed the first federal law covering the privacy of health information known as the Health Insurance Portability and Accountability Act (HIPPA). Any information, related to the physical or mental health of an individual is called Protected Health Information (PHI). HIPAA outlines how and under what circumstances PHI can be used or disclosed.

In order for covered entities to use or disclose protected health information during the course of a study, the study participant must sign an authorization statement. This authorization statement may or may not be separate from the informed consent document. The Coordinating Center, with the approval from the DFCI IRB, will provide a consent template, with information regarding authorization for the disclosure of protected health information.

The DF/HCC Sponsor will use all efforts to limit its use of protected health information in its trials. However, because of the nature of these trials, certain protected health information must be

collected. DF/HCC has chosen to use authorizations, signed by the participant in the trial, rather than limited data sets with data use agreements.

3.6.1 DF/HCC Multi-Center Protocol Confidentiality

All documents, investigative reports, or information relating to the participant are strictly confidential. Whenever reasonably feasible, any participant specific reports (i.e. Pathology Reports, MRI Reports, Operative Reports, etc.) submitted to the Coordinating Center should be de-identified. It is recommended that the assigned protocol case number (as described below) be used for all participant specific documents. Participant initials may be included or retained for cross verification of identification.

3.7 DF/HCC Multi-Center Protocol Registration Policy

3.7.1 Participant Registration and Randomization

Please refer to Protocol Section 4 for participant registration information. Treatment cannot begin until site has received confirmation that participant has been registered with DF/HCC CTMS.

3.7.2 Initiation of Therapy

Participants must be registered with the DF/HCC CTMS before the initiation of treatment or other protocol-specific interventions. Treatment and other protocol-specific interventions may not be initiated until the Participating Institution receives confirmation of the participant's registration from the Coordinating Center. The DF/HCC Sponsor and DFCI IRB must be notified of any violations to this policy.

3.7.3 Eligibility Exceptions

No exceptions to the eligibility requirements for a protocol without DFCI IRB approval will be permitted. All Participating Institutions are required to fully comply with this requirement. The process for requesting an eligibility exception is defined below.

3.8 DF/HCC Protocol Case Number

At the time of registration, the following identifiers are required for all subjects: initials, date of birth, gender, race and ethnicity. Once eligibility has been established and the participant successfully registered, the participant is assigned a unique protocol case number. Participating Institutions should submit all de-identified subsequent communication and documents to the Coordinating Center, using this case number to identify the subject.

3.8.1 Protocol Deviations, Exceptions and Violations

Federal Regulations require an IRB to review proposed changes in a research activity to ensure that researchers do not initiate changes in approved research without IRB review and approval, except when necessary to eliminate apparent immediate hazards to the

participant. DF/HCC requires all departures from the defined procedures set forth in the IRB approved protocol to be reported to the DF/HCC Sponsor, who in turn is responsible for reporting to the DFCI IRB.

For reporting purposes, DF/HCC uses the terms "violation", "deviation" and "exception" to describe departures from a protocol. All Participating Institutions must adhere to these requirements for reporting to the DF/HCC Sponsor and will follow their institutional policy for reporting to their local IRB.

3.8.2 Definitions

Protocol Deviation: Any departure from the defined procedures set forth in the IRB-approved protocol which is *prospectively approved* prior to its implementation.

Protocol Exception: Any protocol deviation that relates to the eligibility criteria, e.g. enrollment of a participant who does not meet all inclusion/exclusion criteria.

Protocol Violation: Any protocol departure that was not *prospectively approved* by the IRB prior to its initiation or implementation.

3.8.3 Reporting Procedures

DF/HCC Sponsor: is responsible for ensuring that clear documentation is available in the medical record and/or regulatory documents to describe all protocol exceptions, deviations and violations. The DF/HCC Sponsor will also be responsible for ensuring that all protocol violations/deviations are promptly reported per DFCI IRB guidelines.

Participating Institutions: Protocol deviations require prospective approval from the DFCI IRB. The Participating Institution must submit the deviation request to the Coordinating Center who will then submit the deviation request to the DFCI IRB. Upon DFCI IRB approval the deviation is submitted to the Participating Institution IRB, per institutional policy. A copy of the Participating Institution's IRB report and determination will be forwarded to the Coordinating Center within 10 business days after the original submission. The deviation may not be implemented without all required approvals.

All protocol violations must be sent to the Coordinating Center in a timely manner. The Coordinating Center will provide training for the requirements for the reporting of violations.

Coordinating Center: Upon receipt of the violation/deviation report from the Participating Institution, the Coordinating Center will submit the report to the DF/HCC Sponsor for review. Subsequently, the Participating Institution's IRB violation/deviation report will be submitted to the DFCI IRB for review per DFCI IRB reporting guidelines. DF/HCC will forward all violation reports to CTEP via an internal DF/HCC process, as applicable.

3.9 Safety Assessments and Toxicity Monitoring

The study teams at all participating institutions are responsible for protecting the safety, rights and well-being of study participants. Recording and reporting of adverse events that occur during the course of a study help ensure the continuing safety of study participants.

All participants receiving investigational agents and/or other protocol mandated therapy will be evaluated for safety. The safety parameters include all laboratory tests and hematological abnormalities, physical examination findings, and spontaneous reports of adverse events reported by participants. All toxicities encountered during the study will be evaluated according to the NCI criteria specified in the protocol. Life-threatening toxicities must be reported immediately to the DF/HCC Sponsor via the Coordinating Center.

Additional safety assessments and toxicity monitoring will be outlined in the protocol.

3.9.1 Guidelines for Reporting Serious Adverse Events

Guidelines for reporting Adverse Events (AEs) and Serious Adverse Events (SAEs) are detailed in protocol Section 7.3.

Participating Institutions must report the SAEs to the DF/HCC Sponsor and the Coordinating Center following the DFCI IRB Adverse Event Reporting Policy.

The Coordinating Center will maintain documentation of all Participating Institution Adverse Event reports and be responsible for communicating to all participating investigators, any observations reportable under the DFCI IRB Reporting Requirements. Participating Institutions will review and submit to their IRB according to their institutional policies and procedures

3.9.2 Guidelines for Processing IND Safety Reports

The DF/HCC Sponsor will review all IND Safety Reports per DF/HCC requirements and ensure that all IND Safety Reports are distributed to the Participating Institutions as required by DF/HCC policy. Participating Institutions will review/submit to their IRB according to their institutional policies and procedures.

3.10 Data Management

DF/HCC RIO develops case report forms (CRF/eCRFs), for use with the protocol. These forms are designed to collect data for each study. DF/HCC RIO provides a web-based training for all eCRF users.

3.10.1 Data Forms Review

Data submissions are monitored for timeliness and completeness of submission. If study forms are received with missing or questionable data, the submitting institution will receive

a written or electronic query from the DF/HCC Office of Data Quality, Coordinating Center, or designee.

Responses to all queries should be completed and submitted within 14 calendar days.

Responses may be returned on the written query or on an amended paper case report form, or in the case of electronic queries, within the electronic data capture (eDC) system. In the case of a written query for data submitted on a paper case report form, the query must be attached to the specific data being re-submitted in response.

If study forms are not submitted on schedule, the Participating Institution will periodically receive a Missing Form Report from the Coordinating Center noting the missing forms.

4. REQUISITIONING INVESTIGATIONAL DRUG

The ordering of investigational agent is specified in the protocol Section 8.

Participating Institutions should order their own agent regardless of the supplier.

If the agent is commercially available, check with the local Director of Pharmacy and/or the Research Pharmacy to ensure that the agent is in stock. If the agent is not stocked, ensure that the agent can be ordered once the protocol is approved by the local IRB.

If the agent is investigational, ensure that the pharmacy will be able to receive and store the agent according to state and federal requirements. The local IRB should be kept informed of who will supply the agent (i.e., NCI or a pharmaceutical company) so that any regulatory responsibilities can be met in a timely fashion.

5. MONITORING: QUALITY CONTROL

The quality control process for a clinical trial requires verification of protocol compliance and data accuracy. The Coordinating Center, with the aid of the DF/HCC Office of Data Quality, provides quality control oversight for the protocol.

5.1 Ongoing Monitoring of Protocol Compliance

The Participating Institutions may be required to submit participant source documents to the Coordinating Center for monitoring. Participating Institution may also be subject to on-site monitoring conducted by the Coordinating Center.

The Coordinating Center will implement ongoing monitoring activities to ensure that Participating Institutions are complying with regulatory and protocol requirements, data quality, and participant safety. Monitoring practices may include but are not limited to source data verification, and review and analysis of eligibility requirements, informed consent procedures, adverse events and all associated documentation, review of study drug administration/treatment, regulatory files, protocol departures reporting, pharmacy records, response assessments, and data management.

Additionally, a plan will be formulated to provide regular and ongoing communication to Participating Institutions about study related information which will include participation in regular Lead Institution initiated teleconferences. Teleconferences will occur every 2 weeks and will continue regularly until completion of accrual. Upon completion of accrual, teleconferences will occur monthly until all patients complete protocol therapy. Upon completion of protocol therapy, teleconferences will occur every 3 months until study completion. Additional communication may be distributed via "Newsletter" or email as deemed appropriate by DF/HCC Sponsor.

On-Site Monitoring: On-site monitoring will occur on an as-needed basis. Participating Institutions will be required to provide access to participants' complete medical record and source documents for source documentation verification during the visit. In addition, Participating Institutions should provide access to regulatory documents, pharmacy records, local policies related to the conduct of research, and any other trial-related documentation maintained by the Participating Site. On-site monitoring visits can be substituted with remote (virtual) monitoring visits at the discretion of the Principal Investigator.

Remote Monitoring: Remote monitoring will be performed on an as-needed basis by the Clinical Trial Monitor. Sites will be asked to provide source documentation via fax, email, or mail as specified by the Clinical Trial Monitor for virtual monitoring.

5.2 Monitoring Reports

The DF/HCC Sponsor will review all monitoring reports to ensure protocol compliance. The DF/HCC Sponsor may increase the monitoring activities at Participating Institutions that are unable to comply with the protocol, DF/HCC Sponsor requirements or federal and local regulations.

5.3 Accrual Monitoring

Prior to extending a protocol to an external site, the DF/HCC Sponsor will establish accrual requirements for each participating institution. Accrual will be monitored for each participating institution by the DF/HCC Sponsor or designee. Sites that are not meeting their accrual expectations may be subject to termination.

A minimum of 3 participants per site annually is recommended for Phase II trials. However, given the additional regulatory burden and cost of overseeing each site, a consideration of 5 per site/annually should be a minimum target for each site.

6. AUDITING: QUALITY ASSURANCE

Auditing is a method of Quality Assurance and involves the systematic and independent examination of all trial related activities and documents. Audits determine if evaluated activities were appropriately conducted and whether data was generated, recorded and analyzed, and accurately reported per the protocol, applicable Standard Operating Procedures (SOPs), and the Code of Federal Regulations (CFR).

6.1 DF/HCC Internal Audits

All Participating Institutions are subject to audit by the DF/HCC Office of Data Quality (ODQ). Typically, approximately 3-4 participants would be audited at the site over a 2 day period. If violations which impact participant safety or the integrity of the study are found, more participant records may be audited.

6.2 Audit Notifications

It is the Participating Institution's responsibility to notify the Coordinating Center of all scheduled audit dates (internal or NCI) and re-audit dates (if applicable), which involve this protocol. All institutions will forward a copy of final audit and/or re-audit reports and corrective action plans (if applicable) to the Coordinating Center, within 12 weeks after the audit date.

6.3 Audit Reports

The DF/HCC Sponsor will review all final audit reports and corrective action plans, if applicable. The Coordinating Center, must forward any reports to the DF/HCC ODQ per DF/HCC policy for review by the DF/HCC Audit Committee. For unacceptable audits, the DF/HCC Audit Committee would forward the final audit report and corrective action plan to the DFCI IRB as applicable.

6.4 Participating Institution Performance

The DF/HCC Sponsor, with the DFCI IRB, charged with considering the totality of an institution's performance in considering institutional participation in the protocol.

Participating Institutions that fail to meet the performance goals of accrual, submission of timely and accurate data, adherence to protocol requirements, and compliance with state and federal regulations, may be recommended for a six-month probation period. Such institutions must respond with a corrective action plan and must demonstrate during the probation period that deficiencies have been corrected, as evidenced by the improved performance measures. Participating Institutions that fail to demonstrate significant improvement will be considered by the DF/HCC Sponsor for revocation of participation. A DF/HCC Sponsor and/or the DFCI IRB may terminate a site's participation if it is determined that a site is not fulfilling its responsibilities as described above.