MSK PROTOCOL COVER SHEET

A Phase 1b / 2a, Open-label Platform Study to Evaluate Mirdametinib as Monotherapy or in Combination with Other Anticancer Agents in Patients with Advanced Solid Cancers Harboring MAPK-activating Mutations

Principal Investigator/Department:
Ezra Rosen, MD PhD
Early Drug Development, Department of Medicine

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1.0 PROTOCOL SUMMARY AND/OR SCHEMA

1.1 Targeting the MAPK Pathway in Hormone Resistant ER+ Breast Cancer

Approximately 70% of all metastatic breast cancers (MBCs) are dependent on the estrogen receptor. Hormonal therapies targeting ER are highly active in this group of cancers and have been remarkably successful in dramatically improving outcomes in this group of patients. Unfortunately, resistance to targeted therapy is a nearly universal phenomenon, and over 90% of patients eventually develop resistance to this class of therapy. Therefore, a molecular map of resistance and strategies designed specifically against these mechanisms are necessary to prolong clinical benefit in this group of patients.

To determine the cause of this resistance, an MSK-led study (under IRB#06-107 and IRB#12-245) sequenced a total of 1,918 patients with MSK-IMPACT, including 1,501 hormone positive tumors, 692 of which had previously been exposed to hormonal therapy[1]. This study identified mutations in three non-overlapping gene sets that associated with the hormone-resistant phenotype: (1) ESR1, (2) MAPK pathway, and (3) Transcription Factors. The finding of mutations that might serve to activate MAPK signaling was particularly striking given the known oncogenic function of this pathway in other cancers and the potential to target this pathway with selective and potent inhibitors of the MEK or ERK kinases.

Indeed, in preclinical models, loss of NF1 function was associated with reduced sensitivity to fulvestrant, and this phenotype was reversed with treatment with an ERK inhibitor[1]. Moreover, this finding implicating the MAPK pathway in endocrine resistant MBC has been validated by other groups in independent patient cohorts, and the combination of the MEK inhibitor selumetinib and the ER antagonist fulvestrant was sufficient to rescue the phenotype conferred by NF1 loss[2,3]. In our genomic analysis of patients with ER+ MBC, we find that over 15% of cases of hormone resistance are associated with alterations whose principal effector pathway is likely to be the ERK pathway – but no single mutation predominates. Instead, we have identified genomic alterations which by class may be implicated:

(1) **RAS modulators:** NF1 loss (6%) and KRAS + HRAS (3%) mutations. Work by multiple groups have demonstrated that these genomic alterations can promote hormone independent tumor growth in laboratory models. We have also observed these to be sensitive to MEK kinase inhibition.

(2) **Receptor tyrosine kinase:** EGFR amplification (2%) and HER2 somatic mutations (7%). We have previously demonstrated that these specific alterations can promote ERK activation and hormone resistant tumor growth in laboratory models. We have also observed these to be sensitive to MEK kinase inhibition.

(3) **RAF/MEK kinase cascade:** BRAF mutation (1%) and MEK1 (1%) mutation are both observed in our series.

We hypothesize that alterations in the MAPK pathway promote resistance to ER targeted therapies in ER+ MBC, and that this resistance can be overcome through the use of MAPK targeted therapies in combination with hormonal therapy. We will therefore propose an integrated clinical and translational research plan centered around the following clinical trial:

We will perform a phase IB/IIA clinical trial of the selective estrogen receptor degrader (SERD) fulvestrant with the allosteric MEK1/2 inhibitor mirdametinib. Responders will be stratified based on their enrolling alteration. Primary endpoints will be safety and toxicity, and secondary endpoints will focus on efficacy, including progression free survival. Responses to therapy will be based on RECIST assessment. As secondary, exploratory endpoints, we will additionally explore longitudinally collected MSK-ACCESS samples to chart treatment response and to identify potential mechanisms of resistance to therapy. We will utilize these biomarkers to investigate the way in which MAPK pathway alteration type, heterogeneity, clonality, baseline MAPK and ER transcriptional output, and co-mutational pattern condition pre-treatment sensitivity to the drug combination. Further, pre-treatment biopsies from the patients on this study will be used to make PDX and cell culture models, and these will be utilized to assess whether measures of MAPK pathway output or MAPK pathway effectors can stratify likely responders. Exploiting the mechanisms of acquired resistance in solid tumors has facilitated the development of multiple therapeutic strategies that can dramatically extend clinical benefit, and we propose this combination therapy as a novel therapeutic drug combination in this genomically selected population of ER+ MBC patients.

1.2 Utilizing MEK Inhibitor Monotherapy with Mirdametinib in all solid tumor types

The MAPK pathway is one of the most commonly mutated pathways in human cancer and this pathway has been targeted at multiple nodes along this pathway, including RAF, MEK, and ERK, and MEK1 and MEK2 have been validated as oncogenic targets. However, the RTK dependent feedback mechanisms to kinase inhibition and the allele-specific dependence of MEK mutants to upstream pathway effectors has only been elucidated.

In particular, MEK mutants have recently been characterized and divided into three distinct classes[4,5]. Class 1 MEK alterations are RAF dependent and they increase ERK activation only in the setting of activated RAF. These mutants are most sensitive to RAF feedback inhibition, and thus almost always occur with additional alterations in upstream MAPK alterations. Class 2 RAF MEK alterations are RAF regulated and have some ERK activation at baseline, but with activated RAF the pathway output is activated further. Class 3 MEK alterations activate the pathway in the absence of any upstream pathway activation. These alterations share an in-frame deletion in which a potent negative regulatory segment of MEK is removed. These can drive MAPK pathway activation in RAF-less cells, and these strongly activate this pathway.

This classification is elucidated in a series of preclinical experiments utilizing mirdametinib[4]. They show that class 1 MEK1 mutants (D67N, P124L, P124S) and class 2 MEK1 mutants (K57N, C121S, F53L, and Q56P) were sensitive to mirdametinib with severely reduced IC50 of pERK, however class 3 MEK1 mutants (ΔL98-I103, ΔI99-K104, ΔE102-I103) were not affected. This result was replicated using an alternative MEK inhibitor, trametinib. Based on these data, we propose to investigate the utility of MEK inhibitor monotherapy utilizing mirdametinib in class 1 and class 2 MEK1/2 mutant tumors in this Phase 1/2 study.

2.0 OBJECTIVES AND SCIENTIFIC AIMS

Table 1 Study Objectives and Endpoints

Objectives	Endpoints
Primary	
Arm 1: • To evaluate the safety and tolerability of mirdametinib in combination with fulvestrant in postmenopausal patients with estrogen receptor positive metastatic breast cancer harboring NF1 loss of function mutation or another alteration of the MAPK pathway Arm 2: • To evaluate the safety and tolerability of mirdametinib as single agent in adult patients with advanced solid cancers driven by the alteration of the MAPK pathway	All arms: • Type, incidence and severity of adverse events (including the dose limiting toxicities in Cycle 1) • Abnormal results of laboratory safety assessments, vital signs, ECGs, LVEF assessments, and physical and ophthalmological exams
Secondary	
Arm 1:	All arms:

• To evaluate the efficacy of mirdametinib in combination with fulvestrant in postmenopausal patients with estrogen receptor positive metastatic breast cancer harboring NF1 loss of function mutation or another alteration of the MAPK pathway • To evaluate the pharmacokinetics of mirdametinib in combination with fulvestrant in the eligible population Arm 2: • To evaluate the efficacy of mirdametinib as single agent in adult patients with advanced solid cancers driven by alterations of the MAPK pathway • To evaluate the pharmacokinetics of mirdametinib as the single agent in the eligible population	• Efficacy endpoints will be the best objective response (BOR) by RECIST 1.1, disease control rate (DCR), duration of response (DOR), and progression-free survival (PFS) • Pharmacokinetic endpoints will be Plasma concentration-time profiles and derived PK parameters of PD-0325901 and PD-0315209, including but not limited to AUC0-last, Cmax, and Tmax, and other PK parameters if deemed appropriate
Exploratory	
All arms: • To evaluate the changes from baseline in the biomarkers of tumor biology and anti-tumor activity	All arms: • The biomarker endpoints will be: ▪ Genomic molecular profile (NGS by MSK-IMPACT) on the fresh tumor biopsy of metastatic tumor ▪ RNA sequencing on the fresh tumor biopsy of metastatic tumor ▪ Cell-free DNA in serial plasma samples (NGS by MSK-ACCESS) ▪ pMEK and pERK changes in the cytoplasm and nucleus

3.0 BACKGROUND AND RATIONALE

3.1 Mirdametinib

Mirdametinib is a highly selective and potent, non-ATP-competitive oral inhibitor of MEK1 and MEK2 kinases. It significantly inhibits the phosphorylation of the MAP kinases ERK1 and ERK2, leading to impaired tumor cell growth in vitro and in vivo with an IC50 of approximately 0.3 nM based on in vitro cellular assays and PK/PD of mouse xenograft

tumor models. Mirdametinib has exhibited anti-tumor activity against a broad spectrum of human tumors in cell lines and animal xenograft models.

The plasma PK profile of mirdametinib is characterized by rapid absorption with the Cmax achieved by approximately 1-hour post-dose and bi-phasic elimination with a terminal elimination half-life ranging from 22 to 30 hours. Mirdametinib (PD-0325901) is largely eliminated by conversion to a primary active metabolite (PD-0315209) which has a half-life ranging from 30 to 40 hours. Generally, exposure of mirdametinib (both Cmax and AUCtau) increases proportionally with increases in dose from 1 to 30 mg QD or BID. Mirdametinib exposure following multiple doses exhibited a small degree of accumulation exhibiting accumulation ratios for AUCtau ranging from 1.3 to 1.9 after 21 days of BID dosing. Accumulation of the primary metabolite, PD-0315209, was higher at approximately 3-fold.

Mirdametinib is a substrate of CYP3A4, CYP1A2, CYP2C9 and CYP2C19, however, conversion of mirdametinib to the primary metabolite PD-0315209 is largely mediated by non-CYP enzymes. Therefore, inhibition of CYP enzymes is unlikely to significantly alter the pharmacokinetics of mirdametinib. Mirdametinib is a substrate of both P-gp and BCRP. Inhibition of P-gp may increase the absorption of mirdametinib. However, in the absence of P-gp inhibitors, mirdametinib is extensively and rapidly absorbed due to its high permeability and solubility. Only small amounts of mirdametinib are eliminated in urine and feces unchanged. Therefore, inhibition of P-gp is not likely to have a significant impact on the systemic exposure of mirdametinib. Mirdametinib is not a significant inhibitor of CYP enzymes or major drug transporters with the exception of OAT1 which may be inhibited at clinically relevant concentrations.

Mirdametinib at the dose of 2.0 mg/m^2 BID (up to the total of 4 mg BID) given 3 weeks on / 1 week off is being explored as a monotherapy in Phase IIB clinical trial for the treatment of adult and pediatric patients with plexiform neurofibromas associated with neurofibromatosis Type 1 (NF1-PN) [NCT03962543]. In addition, mirdametinib in combination with lifirafenib is in a Phase IB clinical study for the treatment of advanced solid cancers driven by the KRAS/NRAS mutations or other MAPK pathway alterations [NCT03905148]. In this study mirdametinib is being explored in combination with this RAF dimer inhibitor at doses ranging from 2 mg to 8 mg QD.

A detailed description of the chemistry, pharmacology, efficacy, and safety of mirdametinib (PD-0325901) is provided in the Investigator's Brochure.

3.2 Additional Background on Mirdametinib

Clinical Experience with mirdametinib

Phase 1/2 Trial A4501001 in Advanced Solid Cancers

A4581001 is a completed Phase 1/2 trial conducted by Pfizer to evaluate the safety and anti-tumor efficacy of mirdametinib in 79 patients with advanced, refractory breast cancer, colorectal cancer, non-small cell lung cancer or non-ocular melanoma. The maximum administered dose (MAD) was 30 mg twice daily (BID) for the intermittent (3 weeks on/1 week off or 3/1) schedule and 20 mg BID for the continuous schedule. Initially, 20 mg BID administered on a 3/1 schedule was selected for further investigation in the Phase 2 component of this study. However, this dose was not well tolerated and was therefore reduced to 15 mg BID. The Phase 2 component of this study was terminated prematurely because of an unexpectedly high incidence of musculoskeletal and neurological adverse events.

For the continuous dosing schedule, the MTD was found to be 15 mg BID. However, 10 mg BID administered on a 5 days on/2 days off schedule that was selected as the recommended Phase 2 dose to mitigate the safety risk. This was based on the observation of significant ocular toxicities that occurred after Cycle 1 (retinal vein occlusion [RVO]) at 15 mg BID and 10 mg BID on the continuous schedule.

Mirdametinib exhibited dose-limiting toxicities at dose levels ≥ 20 mg BID administered on the 3/1 schedule and ≥ 10 mg BID on both the continuous and 5/2 schedules. The main adverse events at mirdametinib doses ≥10 mg BID on both the intermittent (3/1) and continuous dosing schedules were Grade 3-4 neurologic and neuromuscular disorders (most notably, muscle weakness, confusion, slurred speech, seizure / convulsions) and ocular disorders (most notably, RVO). Other frequently reported treatment-related AEs included diarrhea, acneiform skin rash, edema, nausea, and fatigue. These toxicities resulted in frequent treatment interruptions, dose reductions and treatment discontinuations in individual patients and eventually led to the study termination.

The RVO occurred after Cycle 1 at the 15 mg BID and 10 mg BID dose levels administered on the continuous dosing schedule. Of note, 1 subject presented with RVO after 9 cycles of therapy. This subject was initially treated at 10 mg BID administered 5 days on/2 days off but had a dose-decrease to 5 mg BID in Cycle 2 after experiencing binocular diplopia post oral prednisone therapy for a Grade 2 rash. At lower doses of 5-8 mg BID, one patient experienced a case of grade 2 iridocyclitis and grade 1 subfoveal retinal detachment. Based on the review of ocular data, these events occurred after escalation to $\underline{\geq}$ 15mg BID. From 1 to 8 mg BID, 1 patient experienced a G1 visual disturbance definitely not related and 1 patient experienced G1 scleral disorder and G1 eye disorder at least possibly related to mirdametinib. A subsequent analysis found predisposing factors for retinopathy in all

subjects with RVO and no correlation with cumulative dose. Other visual disturbances included blurred vision, reduced acuity, halos, floaters, colored spots, or flashes of light.

Phase 2 Trial A4581002 in Advanced NSCLC

A4581002 is a terminated Phase 2 trial conducted by Pfizer that evaluated the safety and anti-tumor efficacy of mirdametinib in 34 patients with advanced non-small cell lung cancer. A mirdametinib dose of 20 mg BID on the continuous schedule was originally chosen as the starting dose. However, later experience gained with this dose in an ongoing study (Protocol A4581001, Phase 1 portion) revealed that this dosing regimen was not well tolerated without regular treatment breaks. Consequently, this study was amended to change the starting dose to 15 mg BID on an intermittent dosing schedule consisting of 3 weeks on/1 week off in 28-day cycles (Schedule 1). Mirdametinib was initially administered at 15 mg twice daily (BID) on the 3/1 intermittent dosing schedule (Schedule 1); no subjects were dosed on a continuous dosing regimen. Schedule 1 however was not well tolerated. Thirteen subjects were treated according to Schedule 1 and significant AEs were experienced (fatigue and myalgia which occurred in a single subject, and 1 case each of blurred vision and hallucinations). Consequently, this study was again amended to change the dose to 15 mg BID administered on a different intermittent schedule (5 days on/2 days off for 3 weeks, followed by 1 week off) in 28-day cycles (Schedule 2). The 13 subjects dosed according to Schedule 1 were replaced. Twenty-one subjects were dosed according to Schedule 2, but on 31 July 2006 additional enrollment into this study was suspended following the finding of a second case of retinal vein occlusion (RVO) in the Phase 1 trial A4581001. The most frequently reported treatment-related AEs included diarrhea, rash, fatigue, reversible visual disturbances (primarily on the 3/1 schedule), nausea, and vomiting.

Phase 1 Trial A4581004 in Healthy Subjects

A4581004 is a completed Phase 1 trial conducted by Pfizer to evaluate the effect of food on the safety and pharmacokinetics of a single 20 mg dose of mirdametinib in healthy Asian subjects. No notable adverse events have been reported from this trial.

Phase Trial 2a NF106 Trial in Plexiform Neurofibroma

NF106 is a completed investigator-initiated single-arm Phase 2a trial NF106 (NCT02096471) supported by the Neurofibromatosis Clinical Trials Consortium (NFCTC) that evaluated mirdametinib in 19 patients with growing or symptomatic NF1-PN. This trial showed an objective response rate (ORR) of 42% using MRI volumetric response criteria after 1 year of therapy. Patients received mirdametinib at a dose of 2 mg/m^2 BID (maximum dose = 4.0 mg BID). The results of the NF106 NFCTC study have been presented[6].

The most common AEs of any grade were acneiform rash (94.7%), fatigue (57.9%), and nausea (52.6%). One subject developed two treatment-related grade 3 adverse events (back and abdominal pain) simultaneously during course 1; the pain resolved upon drug interruption and did not recur at the reduced dose of 2mg BID, or 1.4mg/m^2/dose (notably

pain is a common disease related adverse event given nerve sheath growth). There were no grade 4 AEs and no subjects died during the study. Five subjects (26.3%) required dose reductions while on study: for grade 3 abdominal/back pain (as described above), grade 1 rash (n=2), grade 2 nausea (n=1) and grade 2 fatigue (n=1). A total of five subjects withdrew from protocol therapy; four due to low grade rash perceived to be intolerable and one who felt the study commitments were too challenging. Overall, mirdametinib had good tolerability at the dose of 2 mg/m^2 BID in the study NF106.

This trial showed an objective response rate (ORR) of 42% after 1 year of therapy using MRI volumetric response criteria. Patients received mirdametinib at a dose of 2 mg/m^2 BID (maximum dose = 4 mg BID). However, the ORR results in this study may have been confounded by the inclusion of a provision in the protocol which removed patients from treatment if they did not achieve at least a 15% reduction in tumor volume by Cycle 8 or 20% by Cycle 12. Some patients may have been removed from the Weiss study prior to achievement of their maximum tumor response and therefore, some patients may have achieved a PR had they been allowed to remain on study beyond Cycle 8.

Phase 2b MEK-NF-201 (ReNeu) Trial in Plexiform Neurofibroma

The original proposal for Study MEK-NF-201 was a single arm study of mirdametinib in approximately 50 patients ≥12 years of age with NF1-PN. At the pre-IND meeting for IND# 139883 in August 2018, the FDA recommended expanding the age eligibility criteria to include patients less than 12 years of age who can swallow capsules, considering the growth patterns of NF1-PN (i.e., decreased growth rate after adolescence). In January 2019, the FDA agreed that the trial may include 50 pediatric patients ≥2 years of age) with NF1-PN.

The modified MEK-NF-201 trial is ongoing as a non-randomized, open-label, multi-center, Phase 2b trial in 100 patients with NF1-PN (50 patients ≥2 and ≤17 years of age and 50 patients ≥18 years of age). Eligible patients must have NF1-PN that is causing significant morbidity, such as head and neck lesions that are compromising the airway or great vessels, brachial or lumbar plexus lesions that are causing nerve compression and loss of function, lesions causing major deformity or are significantly disfiguring, lesions of the extremity that cause limb hypertrophy or loss of function, and painful lesions.

Interim data from the ReNeu trial were disclosed in February 2021, which were comprised of data from the first 20 adult patients enrolled and which utilized a January 22, 2021 data cutoff. Objective responses were defined as a ≥ 20% reduction in target tumor volume measured by MRI and were assessed by blinded independent central review (BICR). Patients received mirdametinib at a dose of 2 mg/m2 twice daily (maximum dose: 4 mg twice daily) without regard to food on a three weeks-on, one week-off intermittent schedule, with patients being allowed to stay on treatment for up to 24 cycles (approximately two years). The median time on treatment for the 20 adult patients evaluated for this analysis was 10.1

cycles (approximately 10 months), with an initial efficacy assessment performed following cycle five and then every four cycles thereafter.

The preliminary efficacy and safety analysis showed 10/20 (50%) of patients had achieved an objective response by BICR. For seven of the 10 patients who achieved an initial objective response, subsequent scheduled scans were available, and six of these seven patients had confirmed responses. Sixteen (16/20, 80%) of these patients remain on study and only one patient required a dose reduction due to an AE. Reasons for discontinuation included one each of progressive disease, participant decision, AE (Grade 1 diarrhea), and a patient being unable to undergo required MRI imaging due to a titanium rod implant from non-treatment-related worsening of scoliosis. Lastly, mirdametinib displayed a generally well-tolerated safety profile. The majority of TRAEs were Grade 1 or 2 with only one Grade 3 TRAE reported. No Grade 4 or 5 AEs have been reported. The most common TRAEs were rash, nausea and diarrhea.

3.3 Fulvestrant

Fulvestrant has a long history of use in estrogen receptor positive breast cancer as a selective estrogen receptor degrader (SERD) that blocks the action of estrogen.[35] Fulvestrant is currently standard of care for women with metastatic breast cancer. It can be used as monotherapy, where time to progression at a dose of 250mg was shown to be comparable to anastrazole (5.5 months vs 5.1 months).[36] Additionally, fulvestrant is now standard of care when used in combination with other agents for this group of patients, such as in the Solar-1 trial where alpelisib was combined with fulvestrant for PIK3CA mutant ER+ breast cancers, yielding a PFS of 11 months. As described in section 1.1, there are preclinical data suggesting that blocking the estrogen receptor in combination with blocking the MAPK pathway causes regression of these MAPK-altered ER+ breast cancers. Therefore, as has been performed with CDK4/6 inhibitors and PIK3CA inhibitors previously, in this trial we will combine fulvestrant with the MEK inhibitor mirdametinib to concurrently block both pathways.

3.4 Benefit/Risk Assessment

To date, the safety profile of single-agent mirdametinib (PD-0325901) in patients with advanced cancer (doses < 10 mg BID, intermittent schedule) has been characterized by mostly manageable and reversible toxicities. The most frequently reported adverse events have been rash, nausea, vomiting, diarrhea, and fatigue. The majority of the events were mild-to-moderate intensity. Other events that have been reported in lesser frequency include ocular disorders (visual disturbances, blurred vision, retinal vein occlusion), nervous system disorders (including confusion, slowed ideation, slurred speech, and hallucinations), musculoskeletal and connective tissue disorders (general weakness, as well as neck muscle weakness associated with mild and moderate elevations in creatine kinase [CK]), and cardiac disorders (decreased left ventricular ejection fraction [LVEF], congestive heart failure). These events primarily occurred in patients receiving doses ≥ 10 mg (up to 30 mg) BID.

In order to minimize potential risk during study participation, subjects will be carefully monitored for the development of toxicities throughout the study and guidelines for dose modification/discontinuation for selected adverse events are provided.

Based on the available nonclinical and clinical trial data, the benefit-risk balance is considered favorable for further development in patients with NF.
More detailed information about the known and expected benefits and risks and reasonably expected adverse events of mirdametinib (PD-0325901) may be found in the Investigator's Brochure.

3.5 MAPK Pathway and Estrogen Receptor Signaling in Breast Cancer

70% of all invasive breast cancers are dependent on the estrogen receptor. Hormonal therapies targeting ER are highly active in this group of cancers and has been remarkably successful in dramatically improving outcomes in this group of patients. Unfortunately, resistance to targeted therapy is a universal phenomenon, and over 90% of patients eventually develop resistance to this class of therapy. These patients with hormone-resistant metastatic breast cancer (MBC) suffer significant morbidity and mortality from their disease as their cancer spread becomes more recalcitrant to therapy, all while physicians are forced to use less effective and more toxic chemotherapies. Therefore, effective strategies and novel or new combinations of drugs are necessary to prolong clinical benefit in this group of patients.

We have pioneered efforts to understand the molecular underpinnings to the development of resistance to ER targeted therapies[7–9]. Additionally, the breast medicine group at MSKCC has been at the forefront of developing rational approaches to overcoming hormone resistance[10–12]. More specifically, we have utilized genomic sequencing to characterize the molecular basis by which breast cancers evolve from primary, hormone-responsive tumors into metastatic, hormone-refractory tumors. We first identified mutations in the gene for ERα (ESR1) in 35-40% of patients with ER+ MBC and prior progression on an aromatase inhibitor. The role of these mutations in promoting resistance to estrogen deprivation therapy in the form of aromatase inhibitors has since been validated mechanistically and clinically by us and others.

More recently we have conducted a study of a total of 1,918 patients utilizing MSK Impact, including 1,501 hormone positive tumors, 692 of which had previously been exposed to hormonal therapy[1]. This study identified mutations in three non-overlapping gene sets that associated with the hormone-resistant phenotype: (1) ESR1, (2) MAPK pathway, and (3) Transcription Factors. Strikingly, the aggregate group of tumors with MAPK alterations was nearly as large as the group of patients with ESR1 mutation in this cohort and the alterations appeared to be mutually exclusive. The finding of mutations that might serve to activate MAPK signaling was particularly striking given the known oncogenic functions of this pathway in other cancers and the potential to target this pathway with selective and potent inhibitors of the MEK or ERK kinases.

Indeed, in their preclinical model, loss of NF1 function was associated with reduced sensitivity to fulvestrant, and this phenotype was reversed with treatment with an ERK inhibitor[1]. Moreover, this finding implicating the MAPK pathway in endocrine resistant MBC has been validated by other groups in independent patient cohorts[3], and the combination of the MEK inhibitor selumetinib and fulvestrant was sufficient to rescue the phenotype conferred by NF1 loss[2]. This finding of mutations that might serve to activate MAPK signaling was particularly striking given the known oncogenic functions of this pathway in other cancers and the potential to target this pathway with selective and potent inhibitors of MEK.

The MAPK pathway has been previously implicated in both modulating ER signaling and cooperating with ER to potentially drive breast cancer growth[13–17]; however targeting this pathway has not been investigated in part due to the lack of patient selection markers. In our genomic analysis of patients with ER+ MBC, we have identified a number of alterations whose principal effector pathway is likely to be the ERK pathway – but no single mutation predominates. Instead, we have identified genomic alterations which by class may be implicated:

(1) RAS modulators – NF1 loss (6%) and KRAS + HRAS (3%) mutation are both commonly observed in our series. Work by our group as well as the lab of Matthew Ellis has demonstrated that these genomic alterations can promote hormone independent tumor growth in laboratory models. We have also observed these to be sensitive to MEK kinase inhibition.

(2) Receptor tyrosine kinase (RTK) – EGFR amplification (2%) and HER2 somatic mutation (7%) are both commonly observed in our series. We have previously demonstrated that these specific alterations can promote ERK activation and hormone resistant tumor growth in laboratory models. We have also observed these to be sensitive to MEK kinase inhibition.

(3) RAF/MEK kinase cascade – BRAF mutation (1%) and MEK1 (1%) mutation are both observed in our series. We are currently modeling the impact of these alterations on hormone sensitivity but by virtue of their canonical effects, hypothesize they may be similar to the other groups.

Beyond these relatively common alterations that promote ERK activity, there are some other genomic alterations (rare or common) that may be relevant in this disease and may be considerations including FGFR1, MET, ERBB3, ERBB4 in the RTK group; RASAL1, NRAS in the RAS group; and CRAF, PAK in the kinase cascade group.

Beyond the association of this group of tumors with resistance to aromatase inhibitors, we have also observed this group to have shortened response to SERM/SERD therapies as well. By contrast, the group of patients with ESR1 mutations has comparable outcomes to the group of patients with wild type ESR1. Moreover, mechanistic studies conducted by our group and others have demonstrated that mutant estrogen receptors can be potently

inhibited by SERMs and SERDs that have reasonably good pharmacokinetic properties. However, preclinical research has found that MAPK-altered ER+ tumors only have partial sensitivity to SERM/SERD compounds and combined inhibition of MEK or ERK with ER is superior to either alone in this group. This data along with older data on cooperativity of ER and MAPK in breast cancers is the basis for our consideration for combination therapy rather than single agent anti-estrogen or MEKi/ERKi in this population.

Taken together, the emerging data on genomic alterations in hormone-resistant ER+ MBC point to a large population of patients with mutations leading to activation of the MAPK pathway and potentially causal of hormone resistance. Preclinical studies support the concept that targeting MEK or ERK kinase can synergize with antiestrogens in these cancers in blocking tumor proliferation. We do note the failure of a fulvestrant and selumetinib combination in postmenopausal patients[18], however in an unselected population, MEK inhibition may predominantly have the effect of causing feedback induction of the PI3K pathway that is often activated in breast cancer. Indeed, our preliminary data demonstrates a lack of activity for MEK inhibition in most breast cancers but markedly increased activity in those cancers that have activating mutations such as NF1 loss (Chandarlapaty lab, manuscript in prep).

Given the wealth of clinical experience of safely combining antiestrogens with targeted therapies including many ATP competitive kinase inhibitors, untoward effects of combining fulvestrant and MEK inhibitors is not anticipated. At our institution, we have pioneered basket studies[19–21] in which genomically or histologically selected vulnerable subpopulations are treated with selective targeted agents. As we have identified a number of different genomic alterations promoting MAPK activation, we propose to study the effect of combined MEK inhibition with fulvestrant in three different classes of MAPK-altered tumors (RAS, RTK, and RAF/MEK) in a Phase 1/2 study.

3.6 MAPK Pathway and MEK mutations as oncogenic drivers

The activated, GTP-bound RAS (RAS–GTP) drives the formation of high-activity homodimers or heterodimers of the RAF protein kinases (ARAF, BRAF or CRAF), which directly phosphorylate and activate MEK1 and MEK2 (also known as MAPKK1 and MAPKK2). MEK1 and MEK2 are dual-specificity kinases that activate ERK1 and ERK2 by phosphorylating them.

Many human cancers harbor gain-of-function mutations in the genes encoding RAS, BRAF, CRAF, MEK1 or MEK2, which act as oncogenes driving deregulated activation of ERK1 and ERK2 signaling. In this way, MEK1 or MEK2 mutations can lead to inappropriate cell proliferation and survival in multiple cancers. In addition, MEK1 and MEK2 mutations have also been associated with the acquired resistance of BRAF V600E mutant tumors to RAF/MEK inhibitors. MEK1 and MEK2 have been validated as drug targets in cancer treatment.

At the current time, MEK inhibitors are famously used in conjunction with RAF inhibitors, for example in BRAF mutant melanoma[22] and in BRAF V600E mutated colorectal cancer[23]. Further, it is well-known that MEK1 mutations are sufficient to cause resistance to MEK and BRAF inhibition in melanoma, showcasing that these tumors are MEK dependent[24]. In addition to MEK1 mutations, additional upstream alterations in the MAPK pathway, including KRAS and NRAS mutations and amplification of BRAF V600E allele, are sufficient to cause activation of MEK and reduced efficacy of MEK inhibitors in these tumors[25].
While the groundwork for the use of MEK inhibitors in RAF driven tumors is now well established, the therapeutic potential of this class of drugs in treating solid tumors with MEK1/2 gain of function mutations is currently not known. This clinical study seeks to utilize and study the utility of an ATP-dependent MEK inhibitor mirdametinib (PD-0325901) in the treatment of patients with advanced solid tumors harboring MEK1/2 mutations. In the past two years, gain of function mutations in MEK1 and MEK2 have been categorized and divided into three classes based on their dependence on RAF activation and their sensitivity to MEK inhibition. The use of MEK inhibition as monotherapy in these MEK1/2 mutant tumors remains an open question.

There is a growing body of data showing that different MEK mutants are differentially sensitive to MEK inhibitors, and this sensitivity varies by class of MEK mutant[4,25]. Class I MEK mutants, or RAF dependent MEK mutants, can be repressed either with MEK or ERK inhibitors. These MEK mutants almost always coexist with upstream additional activating alterations in the MAPK pathway. Strategies to target these alterations may lie in MEK inhibitor monotherapy or in dual therapy with MEK inhibitor with additional inhibition of the upstream activating node in the pathway. Class II MEK mutants are RAF regulated, and these are sensitive to MEK inhibitors as well[4]. There is additionally patient-level evidence of the above, in a colorectal cancer patient who developed resistance to cetuximab who developed a MEK1 K57T mutation, treatment with the MEK inhibitor trametinib led to a clinical response and a reduction in the allele frequency of MEK1 K57T[26]. The delineation of these MEK alleles which are sensitive to MEK inhibition has now allowed for the rational design of a clinical trial only enrolling patients with sensitizing MEK1/2 alleles to be treated with an allosteric MEK inhibitor, mirdametinib.

Notably, class III MEK mutant alleles are not sensitive to allosteric MEK inhibitors. These alterations (typically in-frame deletions) constrain the MEK kinase in the “αC-in” conformation, reducing the binding affinity of allosteric MEK inhibitors. This resistance to allosteric MEK inhibitors has been shown clinically, for example in a BRAF V601E colorectal cancer patient treated with the MEK inhibitor binimetinib and the EGFR anti-EGFR antibody panitumumab[27]. This patient developed resistance to therapy after development of a MEK1 V211D mutation, however this mutant remains sensitive to newer ATP-competitive MEK inhibitors.

A deep understanding of the biology and the unique properties of this pathway is necessary to design and develop a well-reasoned clinical trial in this space. Given the preclinical data

above, a significant fraction of which was developed at Memorial Sloan Kettering, we are well positioned to spearhead this trial using mirdametinib as monotherapy in advanced solid tumors harboring MEK1/2 mutations. Further, we will simultaneously perform an integrated translational research plan in which we will focus on identifying mechanisms of primary and acquired resistance in mirdametinib in these oncogene-addicted tumors. In our experience, this has facilitated the development of multiple therapeutic strategies that can (1) dramatically extend clinical benefit and can (2) further elucidate the underlying biology of these tumors. We propose to leverage our clinical leadership of targeted therapies in the MAPK pathway to the development of mirdametinib in this clinical space. Moreover, our expertise in cell biology, translational genomics, and principled computational analysis to define these mechanisms in future correlative work.

3.7 Study Rationale

This is an open-label, parallel-design platform study to evaluate mirdametinib (PD-0325901) as monotherapy or in combination with other anticancer agents in patients with advanced solid cancers that express the genomic alterations of the MAPK pathway. The first arm will enroll patients with the estrogen receptor (ER) positive metastatic breast cancer harboring the NF1 loss of function or other MAPK-activating mutations. The second arm will enroll patients with advanced solid cancers expressing MEK1 or MEK2 mutations. CRC, small bowel, biliary and ampullary cancers will be excluded from both arms.

Rationale for Arm 1
The current treatment paradigm in the management of metastatic breast cancer (MBC) typically offers endocrine therapy in conjunction with a CDK4/6 inhibitor as standard of care in the first-line setting. These patients inevitably progress and at this point in their disease trajectory, fulvestrant is commonly used as a second-line agent. The second-line setting in this genomically selected population is an ideal fit for the combination of fulvestrant with mirdametinib in that we anticipate an acceptable side effect profile of the addition of mirdametinib to fulvestrant. We will also recruit MBC patients further in their disease course who have received multiple previous lines of therapy.

Taken together, the emerging data on genomic alterations in hormone-resistant ER+ MBC point to a large population of patients with mutations leading to activation of the MAPK pathway and potentially causal of hormone resistance. Preclinical studies support the concept that targeting MEK or ERK kinase can synergize with antiestrogens in these cancers in blocking tumor proliferation. We do note the failure of a fulvestrant and selumetinib combination in postmenopausal patients[18], however in an unselected population, MEK inhibition may predominantly have the effect of causing feedback induction of the PI3K pathway that is often activated in breast cancer. Indeed, our preliminary data demonstrates a lack of activity for MEK inhibition in most breast cancers but markedly increased activity in those cancers that have activating mutations such as NF1 loss (Chandarlapaty lab, manuscript in prep).

Given the wealth of clinical experience of safely combining antiestrogens with targeted therapies including many ATP competitive kinase inhibitors, untoward effects of combining fulvestrant and MEK inhibitors is not anticipated. At our institution, we have pioneered

basket studies[19–21] in which genomically or histologically selected vulnerable subpopulations are treated with selective targeted agents. As we have identified a number of different genomic alterations promoting MAPK activation, we propose to study the effect of combined MEK inhibition with fulvestrant in three different classes of MAPK-altered tumors (RAS, RTK, and RAF/MEK) in a Phase 1/2 study.

Rationale for Arm 2
Downstream effectors of the MAPK pathway including MEK1 and MEK2 are targetable oncogenes that are mutated across a wide range of human cancers. MEK mutants have recently been characterized and divided into three distinct classes. Class 1 MEK alterations are RAF dependent and they increase ERK activation only in the setting of activated RAF. Class 2 RAF MEK alterations are RAF regulated and have some ERK activation at baseline, but with activated RAF the pathway output is activated further. Class 3 MEK alterations activate the pathway in the absence of any upstream pathway activation. We propose to investigate the utility of MEK inhibitor monotherapy utilizing mirdametinib in class 1 and class 2 MEK1/2 mutant tumors in a Phase 1/2 study.

We hypothesize that these MEK1 and MEK2 mutants may be targetable in a variety of solid tumors, therefore this arm of the protocol is designed as a basket study for any patient harboring a class 1 or class 2 MEK1 or MEK2 alteration regardless of computational pattern. Indeed, preclinical data suggests that class 1 mutations with additional upstream mutations are a hallmark of the RAF dependence of this class of MEK mutants. Gastrointestinal malignancies will be largely excluded from this study given the prevalence of high levels of EGFR activation, and our prediction that adaptive feedback reactivation of EGFR-mediated reactivation of MAPK signaling will render monotherapy with a MEK inhibitor ineffective, as has been previously observed with BRAF V600E colorectal cancers[28,29].

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

This will be a Phase 1b / 2a open label, parallel design, platform study to evaluate the safety and tolerability, efficacy, PK and biomarkers of mirdametinib in two arms, where each arm will include two parts:

- Arm 1: mirdametinib in combination with fulvestrant in postmenopausal patients with estrogen receptor positive metastatic breast cancer harboring NF1 loss of function or another alteration of the MAPK pathway
    - Part 1: safety run-in (confirmation of the RP2D for mirdametinib in combination with the standard recommended dose of fulvestrant). This part may include the mirdametinib dose de-escalation according to the 3+3 design if necessary
    - Part 2: dose expansion cohorts where the mirdametinib RP2D will be administered in combination with the standard recommended dose of fulvestrant
- Arm 2: mirdametinib as single agent in adult patients with advanced solid cancers driven by the alteration of the MAPK pathway

- Part 1: mirdametinib dose escalation to MTD or RP2D according to the 3+3 design
- Part 2: dose expansion cohorts

4.2 Intervention

Study Periods

Each subject will undergo 3 periods (screening, treatment, and post-study follow-up).

Screening

The screening period will be from the signing of the informed consent until the first dose of the first study drug on Day 1 of Cycle 1 (C1D1). The screening period should not exceed 28 calendar days before C1D1.

Treatment

A treatment cycle lasts 28 days. The treatment period will be from the first dose of the first study drug until the last dose of the last study drug.

The treatment will continue until the disease progression, death, unacceptable toxicity, withdrawal of consent, or another reason for permanent discontinuation of treatment. Patients with documented progression of disease may be allowed to continue on study if the patient is tolerating treatment, and in the opinion of the investigator, the patient is deriving clinical benefit from continuing study treatment and continuation of treatment is approved by the principal investigator. If said patient continues treatment post progression, they will require reconsent.

Dose levels of mirdametinib are summarized in section 10.2.

Post-study Follow-up

The post-study follow-up will include the end of treatment (EoT) visit, the safety follow-up visit, and the long-term follow-up.

An End of Treatment (EoT) visit will be performed within 7-14 days after the administration of the last dose of the last study drug.

The safety follow-up (FU) visit will be performed 30 days after the last dose of the last study drug treatment (except for subjects who died, withdrew consent, and objected to further data collection or were lost to follow up). The safety FU assessment can be done via the clinic visit (recommended) or via a phone call (if subject cannot attend the clinic visit or has started a new anti-cancer treatment). The investigator may order unscheduled FU visits after the 30-day safety FU visit if the adverse events ongoing at the safety FU are deemed to be clinically significant and related to the study drug(s).

The long-term follow-up will aim to obtain the information necessary for the duration of response (DOR) and the progression-free survival (PFS) endpoints. The long-term follow-up visits will be performed via clinic visit or phone call about every 3 months for 12 months

after the last dose of the last study drug (except for subjects who died, withdrew consent and objected to further data collection or were lost to follow up).

There will be no formal assessment of the overall survival in this study.

Arm 1 - Part 1 (Safety Run-in of Mirdametinib in Combination with Fulvestrant)

If permitted by the acceptable safety profile of mirdametinib 4 mg BID in combination with the standard recommended dose of fulvestrant, the Part 1 in Arm 1 of the study will be conducted as a single dose level. Patients with any MAPK pathway activating alteration as listed in section 6.1 will be included in this safety run-in, however patients harboring NF1 loss of function mutations will be prioritized, at the discretion of the principal investigator.

If mirdametinib 4 mg BID in combination with the standard recommended dose of fulvestrant is not tolerated well in the initial Dose Level, then a Dose Level de-escalation will be evaluated with mirdametinib 2 mg BID in combination with the standard recommended dose of fulvestrant. The Dose Level de-escalation will be evaluated according to the 3+3 design based on the incidence of dose-limiting toxicities (DLT) and the overall safety profile of the study treatments. The DLT definitions are listed in Section 15.3.

At each step of the 3+3 design, the investigators will review all available safety and PK data at the current dose level and decide about the appropriate next step. The subjects will become evaluable for the 3+3 decisions if they complete Cycle 1 and receive at least 80% of doses at their assigned mirdametinib doses and all of their fulvestrant doses, or if they exhibit a DLT in Cycle 1.

Dose Selection: We note that the dosing of mirdametinib in the most recent phase II trial[6] is 2 mg/m^2 twice daily, which translates to 4 mg twice daily in an adult population. However, the aforementioned study used an intermittent 3 weeks on / 1 week off schedule. This protocol is slightly different in that we are initiating a continuous dosing schedule of mirdametinib rather than intermittent. We believe that this schedule remains quite safe given that this dose is far below the MTD (15 mg BID) at which intermittent dosing was necessary to avoid toxicity.

More specifically, continuous dosing of mirdametinib was utilized at doses ranging from 10 mg BID to 20 mg BID in advanced cancer but transitioned to alternative intermittent schedules following the occurrence of 2 events of retinal vein occlusion (RVO) at 10 mg BID and 15 mg BID on the continuous schedule. Subsequent analysis of relevant visual adverse events found predisposing risk factors for retinopathy in both subjects experiencing an RVO. Notably, as mentioned previously, the next dose and schedule evaluated was both significantly dose reduced (2 mg/m^2 BID; maximum dose 4 mg BID) and given on an intermittent schedule (3 weeks on, 1 week off). As a result, an evaluation of mirdametinib at doses between 2 mg/m^2 – 10 mg/m^2 on a continuous basis has not been performed leaving a wide gap in the safety and tolerability information of this agent. Further, on the aforementioned study above (4 mg BID dosing) showed general good tolerability (see section 3) with no RVOs reported.

Last, we also note the low likelihood of interaction between fulvestrant and mirdametinib as their toxicity profiles are orthogonal, and fulvestrant is generally extremely well tolerated.

Due to the knowledge gained in this retrospective review, the implementation of screening for RVO risk factors prior to the initiation of mirdametinib therapy and the class experience of other MEK inhibitors administered on a continuous schedule, we propose the evaluation of mirdametinib beginning at 4 mg BID, on a continuous schedule in a controlled clinical trial setting. To ensure that the dose selected is feasible, tolerable, and beneficial, we are planning a phase 1 dose escalation in standard 3+3 design. However, to be conservative with this clinical trial design, in addition to dose de-escalation, we additionally have added intermittent dose dosing levels on mirdametinib de-escalation, in the case that continuous dosing is poorly tolerated.

The starting dose of mirdametinib in combination with fulvestrant in each Dose Level will be as follows:

- Dose Level 1: mirdametinib 4 mg BID PO + fulvestrant
- (Only to be triggered pending DLTs on higher Dose Levels as described below)
    - Dose Level -2: mirdametinib 2 mg BID PO continuous + fulvestrant, and Dose Level -2INT: mirdametinib 2 mg BID PO on 3 weeks on, 1 week off + fulvestrant

The 3+3 decisions in Part 1 of Arm 1 will be made as follows.

1. Mirdametinib starting dose Dose Level 1 (4 mg BID PO given continuously)
    a. Up to 3 subjects will be treated with mirdametinib 4 mg BID PO given continuously in combination with the recommended dose of fulvestrant.
    b. If ≤1 of the first 3 evaluable subjects in Dose Level 1 exhibit a DLT in Cycle 1, then Dose Level 1 will be expanded (see #2 below).
    c. Mirdametinib dose in combination with fulvestrant will not be escalated above the 4 mg BID dose level.
2. Dose Level 1 expansion:
    a. A sufficient number of subjects will be treated with mirdametinib 4 mg BID PO given continuously in combination with the recommended dose of fulvestrant to accrue 6 evaluable subjects.
    b. If ≤1 of 6 evaluable subjects in the starting Dose Level exhibit a DLT in Cycle 1, then **mirdametinib 4 mg BID PO** given continuously will be declared as the recommended dose for Part 2 (RP2D) in combination with fulvestrant.
    c. If ≥2 of the first 3 evaluable subjects or ≥2 of the 6 evaluable subjects in Dose Level 1 exhibit a DLT in Cycle 1, then the mirdametinib dose will be de-escalated (see #3 below, Dose Level -2).

3. Mirdametinib Dose Level -2 (de-escalation Dose Level at 2 mg BID PO given continuously)
    a. Up to 3 subjects will be treated with mirdametinib 2 mg BID PO given continuously in combination with the recommended dose of fulvestrant in Dose Level -2
    b. If 1 of the first 3 evaluable subjects in Dose Level -2 exhibit a DLT in Cycle 1, then a sufficient number of subjects will be treated with mirdametinib 2 mg BID PO given continuously in combination with the recommended dose of fulvestrant to accrue 6 evaluable subjects.
    c. If ≤1 of 6 evaluable subjects in Dose Level -2 exhibit a DLT in Cycle 1, then **mirdametinib 2 mg BID PO** given continuously will be declared as the recommended dose for Part 2 (RP2D) in combination with fulvestrant.
    d. If ≥2 of the first 3 evaluable subjects or ≥2 of the 6 evaluable subjects in Dose Level -2 exhibit a DLT in Cycle 1, then the Arm 1 will be further de-escalated (see #4 below).
4. Mirdametinib Dose Level -2INT (de-escalation Dose Level at 2 mg BID PO on a 3 weeks on, 1 week off schedule)
    a. Up to 3 subjects will be treated with mirdametinib 2 mg BID PO given intermittently in combination with the recommended dose of fulvestrant in Dose Level -2INT
    b. If 1 of the first 3 evaluable subjects in Dose Level -2INT exhibit a DLT in Cycle 1, then a sufficient number of subjects will be treated with mirdametinib 2 mg BID PO, intermittently dosed, in combination with the recommended dose of fulvestrant to accrue 6 evaluable subjects.
    c. If ≤1 of 6 evaluable subjects in Dose Level -2INT exhibit a DLT in Cycle 1, then **mirdametinib 2 mg BID PO**, intermittently dosed, will be declared as the recommended dose for Part 2 (RP2D) in combination with fulvestrant.
    d. If ≥2 of the first 3 evaluable subjects or ≥2 of the 6 evaluable subjects in Dose Level -2 exhibit a DLT in Cycle 1, then the Arm 1 will be discontinued. The reason for discontinuation of Arm 1 will be that 2 mg BID PO, dosed intermittently, is deemed to be the minimum dose required for sufficient clinical benefit from mirdametinib in combination with fulvestrant in the refractory metastatic breast cancer.

Arm 1 - Part 2 (Expansion Cohorts)

The following expansion treatment groups (up to 28 subjects each). Both cohorts are planned and the rationale for sample size is included in section 14.5. These will initially be started, either in parallel or sequentially depending on the results of Part 1:

1. Subjects with hormone receptor-positive, HER2-negative metastatic breast cancer exhibiting NF1 loss defined as homozygous deletion of NF1 by NGS assay; truncating or nonsense mutations in NF1; OncoKB defined pathogenic missense mutation; OncoKB defined activating mutation in KRAS or HRAS.
2. Subjects with hormone receptor-positive, HER2-negative metastatic breast cancer exhibiting EGFR amplification defined as >1.9 copies of EGFR by NGS assay; ERBB2 hotspot somatic mutation defined as activating by OncoKB.

The above expansion treatment groups are prioritized for this study, however as an exploratory treatment group to be considered in the future is the following cohort:

1. Subjects with hormone receptor-positive, HER2-negative metastatic breast cancer exhibiting OncoKB defined activating mutations in BRAF, CRAF, or MEK1/2

Arm 2 – Part 1 (Dose escalation of mirdametinib as single agent)

Part 1 will be conducted in three sequential Dose Level escalations according to the 3+3 design based on the incidence of dose-limiting toxicities (DLT) and the overall safety profile of the study treatments. The DLT definitions are listed in Section 15.3.

At each step of the 3+3 design, the investigators will review all available safety and PK data in the current Dose Level and decide about the appropriate next step. The subjects will become evaluable for the 3+3 decisions if they complete Cycle 1 and receive at least 80% of assigned drug doses, or if they exhibit a DLT in Cycle 1.

The starting dose of mirdametinib as single agent in each Dose Level escalation will be as follows:

- Dose Level 1: **mirdametinib 4 mg BID PO**, given continuously
- Dose Level 2: **mirdametinib 6 mg BID PO**, given continuously
- Dose Level 3: **mirdametinib 8 mg BID PO**, given continuously
- The de-escalation (Dose Level -1) may evaluate **mirdametinib 3 mg BID** given continuously, and (Dose Level -1INT) may evaluate **mirdametinib 3 mg BID** given on a 3 weeks on, 1 week off schedule. These de-escalation Dose Levels will be evaluated at investigator's discretion after the higher dose of mirdametinib is not tolerated. The de-escalation Dose Levels will be started only if the benefit-risk ratio is acceptable at the investigator's opinion.

The 3+3 decisions in Part 1 of Arm 2 will be made as follows.

1. Dose Level 1 (**mirdametinib 4 mg BID PO** given continuously)
    a. Up to 3 subjects will be treated with mirdametinib as single agent at the dose of **4 mg BID PO** given continuously.

b. If 1 of the first 3 evaluable subjects in Dose Level 1 exhibit a DLT in Cycle 1, then Dose Level 1 will be expanded (see #2 below)

c. If 0 of the first 3 evaluable subjects in Dose Level 1 exhibit a DLT in Cycle 1, then the dose of mirdametinib as single agent will be escalated to Dose Level 2 (**6 mg BID** given continuously) (see #4 below)

2. Dose Level 1 expansion:

   a. A sufficient number of subjects will be treated with mirdametinib as single agent at the dose of **4 mg BID PO** given continuously to accrue 6 evaluable subjects.

   b. If ≤1 of 6 evaluable subjects in the starting Dose Level exhibit a DLT in Cycle 1, then then the dose of mirdametinib as single agent will be escalated to Dose Level 2 (**6 mg BID** given continuously) (see #5 below).

   c. If ≥2 of the first 3 evaluable subjects or ≥2 of the 6 evaluable subjects in Dose Level 1 exhibit a DLT in Cycle 1, then the mirdametinib dose will be de-escalated (see #3 below).

3. Dose Level -1 (de-escalation Dose Level **3 mg BID PO** given continuously)

   a. Up to 3 subjects will be treated with mirdametinib as a single agent at the dose of 3 mg BID PO in Dose Level -1

   b. If ≤1 of the first 3 evaluable subjects in Dose Level -1 exhibit a DLT in Cycle 1, then a sufficient number of subjects will be treated with **mirdametinib 3 mg BID PO** given continuously to accrue 6 evaluable subjects.

   c. If ≤1 of 6 evaluable subjects in Dose Level -1 exhibit a DLT in Cycle 1, then **mirdametinib 3 mg BID PO** given continuously will be declared as the recommended dose for Part 2 (RP2D).

   d. If ≥2 of the first 3 evaluable subjects or ≥2 of the 6 evaluable subjects in the de-escalation Dose Level exhibit a DLT in Cycle 1, then the Arm 2 will be further de-escalated (see #4 below).

4. Dose Level -1INT (de-escalation Dose Level **3 mg BID PO** on a 3 weeks on, 1 week off schedule)

   a. Up to 3 subjects will be treated with mirdametinib as a single agent at the dose of 3 mg BID PO intermittently in Dose Level -1INT

   b. If ≤1 of the first 3 evaluable subjects in Dose Level -1INT exhibit a DLT in Cycle 1, then a sufficient number of subjects will be treated with **mirdametinib 3 mg BID PO** intermittently to accrue 6 evaluable subjects.

   c. If ≤1 of 6 evaluable subjects in Dose Level -1INT exhibit a DLT in Cycle 1, then **mirdametinib 3 mg BID PO** intermittently will be declared as the recommended dose for Part 2 (RP2D).

d. If ≥2 of the first 3 evaluable subjects or ≥2 of the 6 evaluable subjects in the de-escalation Dose Level exhibit a DLT in Cycle 1, then the Arm 2 will be discontinued. The reason for discontinuation of Arm 2 would be that **3 mg BID** PO intermittently is deemed to be the minimum dose required for sufficient clinical benefit from mirdametinib as single agent in the refractory advanced cancer.

5. Dose Level 2 (Dose Level escalation **6 mg BID PO** given continuously)
    a. Up to 3 subjects will be treated with mirdametinib as a single agent at the dose of 6 mg BID PO given continuously in Dose Level 2
    b. If ≤1 of the first 3 evaluable subjects in Dose Level 2 exhibit a DLT in Cycle 1, then a sufficient number of subjects will be treated with mirdametinib 6 mg BID PO given continuously to accrue 6 evaluable subjects.
    c. If ≤1 of 6 evaluable subjects in Dose Level 2 exhibit a DLT in Cycle 1, then the dose of mirdametinib as single agent will be escalated to Dose Level 3 (**8 mg BID** given continuously) (see #6 below).
    d. If ≥2 of the first 3 evaluable subjects or ≥2 of the 6 evaluable subjects in Dose Level 2 exhibit a DLT in Cycle 1, then **mirdametinib 4 mg BID PO** given continuously will be declared as the recommended dose for Part 2 (RP2D).
6. Dose Level 3 (Dose Level escalation 8 mg BID PO given continuously)
    a. Up to 3 subjects will be treated with mirdametinib as a single agent at the dose of 8 mg BID PO in Dose Level 3
    b. If ≤1 of the first 3 evaluable subjects in Dose Level 3 exhibit a DLT in Cycle 1, then a sufficient number of subjects will be treated with mirdametinib 8 mg BID PO given continuously to accrue 6 evaluable subjects.
    c. If ≤1 of 6 evaluable subjects in Dose Level 3 exhibit a DLT in Cycle 1, then **mirdametinib 8 mg BID PO** given continuously will be declared as the recommended dose for Part 2 (RP2D).
    d. If ≥2 of the first 3 evaluable subjects or ≥2 of the 6 evaluable subjects in Dose Level 3 exhibit a DLT in Cycle 1, then **mirdametinib 6 mg BID PO** given continuously will be declared as the recommended dose for Part 2 (RP2D).
    e. The dose of mirdametinib as single agent will not be escalated above 8 mg BID PO given continuously.

Arm 2 – Part 2 (expansion cohorts for mirdametinib as single agent)
One or more expansion cohorts (up to 30 subjects each) will be started, either in parallel or sequentially depending on the results of Part 1. The purpose will be to evaluate the efficacy and safety of the RP2D of mirdametinib as single agent (as determined in Part 1 of Arm 2) in the subjects with advanced solid cancers (with the exception of colorectal, small bowel, biliary and ampullary cancers) harboring activating mutations in MEK1/2.

In the dose escalation portion of part 2, we anticipate accruing both class 1 and class 2 MEK alterations. Both of these MEK alteration types are seen commonly and when mature, this dose escalation cohort will comprise patients harboring both mutation types. However, we cannot anticipate the order of accrual on this cohort. If a clear preponderance of one MEK alteration type is accrued first and promising activity is seen, then that expansion cohort will be opened initially, and the other expansion cohort will be opened later, pending clinical activity. If, on the other hand, both class 1 and class 2 MEK alterations accrue at equal rates and promising clinical activity is observed for both alteration types, these will expansion cohorts will open in parallel.

The following expansion treatment groups (up to 30 subjects each) will initially be started, either in parallel or sequentially depending on the efficacy and safety results of Part 1:

1. Class 1 MEK1/2 alterations.
2. Class 2 MEK1/2 alterations.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS & NON-THERAPEUTIC ASSESSMENTS

5.1 Mirdametinib

This study utilizes the investigational agent PD-0325901 (mirdametinib) to be supplied by SpringWorks. The IND # for PD-0325901 (mirdametinib) is 139883 (Neurofibromatosis Type 1).

On January 19, 2018, SpringWorks Subsidiary 3, PBC (SpringWorks) accepted an IND transfer and agreed to assume all sponsor and regulatory responsibilities for IND 066809 (Cancer) and drug product, PD-0325901, previously held by Pfizer.

Only subjects enrolled in the study, who meet study entry criteria (Sections 6.1 and 6.2) may receive study treatment. Only authorized Site personnel may supply or administer study treatment.

Treatment Name	Mirdametinib (PD-0325901)
Type	Drug
Dose Formulation	Capsule
Unit Dose Strength(s)	1 mg and 2 mg
Dosage Level(s)	See the planned doses for each Dose Level escalation (Section 4.2)
Route of Administration	Oral
Frequency of Administration	Twice daily (BID)

Sourcing	SpringWorks will provide MSK with mirdametinib for individual subject distribution.
Packaging and Labeling	Mirdametinib will be provided in 75 count bottles. Each bottle will be labeled as required per country requirement.
Former Names	PD-0325901-00, PD-0325901-0000, PF-00192513-00

Preparation:

- Mirdametinib does not require special preparation by pharmacy personnel prior to dispensing to subjects.
- Mirdametinib will be supplied as hard gelatin capsules (1- and 2-mg) for oral administration.
- Mirdametinib will be packaged in high-density polyethylene bottles.
- Subjects will be instructed to keep their mirdametinib in the original bottles and not transfer it to any secondary containers.

Handling:

- No special handling of mirdametinib is required.

Storage:

- Mirdametinib must be stored at 15°C to 25°C (59°F to 77°F).
- The Investigator must confirm appropriate temperature conditions have been maintained during transit for all mirdametinib received and any discrepancies are reported and resolved before use of the study treatment.
- All mirdametinib must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

Accountability:

- The Investigator or designee is responsible for mirdametinib accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
- Subjects will be instructed not to dispose of any mirdametinib treatment bottles, and to bring all bottles (used and unused) back to the site at every visit.
- Accountability will be performed by site personnel at each dispensing visit as described in the SoA (Section 11). If issues with the subject's compliance with mirdametinib are detected, subjects will be re-educated about the importance of following the prescribed dosing regimen.
- Returned mirdametinib will not be re-dispensed to the subjects.

5.2 Fulvestrant (Faslodex)

Fulvestrant will be administered in Arm 1 by intramuscular (IM) injection at the dose and regimen approved by the FDA for the treatment of ER-positive metastatic breast cancer (500mg on Day 1 and Day 15 of Cycle 1 and on Day 1 of all subsequent cycles).

Fulvestrant is supplied as two 5 mL clear neutral glass (Type 1) barrels, each containing 250 mg/5 mL of Fulvestrant solution for intramuscular injection and fitted with a tamper evident closure. The single-dose prefilled syringes are presented in a tray with polystyrene plunger rod and safety needles (SafetyGlide™) for connection to the barrel. Discard each syringe after use. If a patient dose requires only one syringe, unused syringe should be stored as directed below.

Storage: REFRIGERATE, 2°-8°C (36°-46°F). TO PROTECT FROM LIGHT, STORE IN THE ORIGINAL CARTON UNTIL TIME OF USE.

Refer to the package insert for additional details regarding Fulvestrant administration.

5.3 FDA Application

This study utilizes the investigational agent PD-0325901 (mirdametinib) to be supplied by SpringWorks. The IND # for PD-0325901 (mirdametinib) is 139883 (Neurofibromatosis Type 1) and 066809 (Cancer). Memorial Sloan Kettering Cancer Center will submit a Cross Reference Application to the FDA for the investigational use of PD-0325901 (mirdametinib) as monotherapy and in combination with fulvestrant.

6.0 CRITERIA FOR PARTICIPANT ELIGIBILITY

Eligible patients must meet all of the inclusion criteria and cannot meet any of the exclusion criteria before the start of treatment.

Where applicable, the CTCAE V.5.0 classification should be used to interpret the severity grades used as limits for eligibility.

6.1 Participant Inclusion Criteria

Subjects are eligible to start the treatment in the study only if all of the following criteria apply:

Arm 1 (metastatic breast cancer):

- Female adults (≥18 years of age on the date of informed consent)
- Postmenopausal or receiving ovarian suppression (including GnRH agonists such as goserelin)
- Histologically confirmed hormone receptor-positive metastatic breast cancer with evidence of progression on at least 1 prior line of therapy for metastatic disease which should have included a CDK4/6 inhibitor in combination with endocrine therapy. Prior chemotherapy is permitted.
- ER+ as defined by immunohistochemistry (IHC) ≥1% by local laboratory testing (as per the ASCO-CAP guidelines)

- HER2-negative, as defined by the negative in situ hybridization test (FISH, CISH, or SISH) or an IHC status of 0, 1+ or 2+ by local laboratory testing. If IHC is 2+ (i.e. indeterminate), then a negative in situ hybridization test (FISH, CISH, or SISH) is required (as per the ASCO-CAP guidelines).
- NF1 loss of function or another MAPK-activating genomic alteration documented by a CLIA-certified NGS assay at any time before the start of treatment. Note: archival tissue, if available and collected within 6 months of enrollment, may be used for this testing in lieu of fresh tissue.

Arm 2 (advanced solid cancers):

- Male or female adults (≥18 years of age on the date of informed consent)
- Histologically confirmed advanced, metastatic solid tumor cancer for which there is no available therapy known to confer clinical benefit. Colorectal, anal, small bowel, biliary or ampullary cancers are not eligible.
- Class 1 or class 2 MEK1 or MEK2 mutations, as described below, documented by a CLIA-certified NGS assay at any time before the start of treatment. Class 3 MEK1 or MEK2 mutations as described in that paper are excluded. A complete list of the mutations allowed based on that paper can be found below, however, rare mutations not listed in this table may be permitted at the discretion of the principal investigator of the study. Note: archival tissue, if available and collected within 6 months of enrollment, may be used for this testing in lieu of fresh tissue.

Class 1 – Permitted	**Class 2 – Permitted**	**Class 3 - Excluded**
MEK1 D67N	MEK1 K57N	MEK1 ∆L98-I103
MEK1 P124L	MEK1 C121S	MEK1 ∆I99-K104
MEK1 P124S	MEK1 F53L	MEK1 ∆E102-I103
	MEK1 Q56P	

The permitted mutations shown above are for MEK1. MEK1 and MEK2 are closely related, are structurally similar, share 79% amino acid identity, and they share equal ability to phosphylate their ERK substrates[30]. While the experiments performed above classify individual MEK1 mutations only, the class 3 mutations in MEK1 all share in-frame deletions that remove a potent negative regulatory element of MEK1. These are easily distinguishable from other mutations in MEK1. Therefore, the identification of exclusionary class 3 MEK2 alterations will be straightforward as well, with paralogous mutant residues in MEK1 and MEK2 defined in the manuscript above. A table showing the permitted enrolling paralogous class 1 and class 2 residues are shown in the table below, again with the caveat that rare mutations in MEK2 not listed in the table below may be eligible at the discretion of the principal investigator.

MEK1	**MEK2**
F53	F57
Q56	Q60
K57	K61

V60	V64
D67	D71
C121	C125
P124	P128
Y130	Y134
E203	E207

All Arms:

- Patient (or Legally Authorized Representative [LAR]) must sign written informed consent form before any study-specific procedure is performed
- ECOG performance score of 0 or 1
- Life expectancy of ≥3 months
- At least one tumor lesion measurable by RECIST 1.1. A lesion in a previously irradiated area may be considered as measurable disease if there is objective evidence of progression of the lesion by RECIST 1.1 (*Eisenhauer EA et al, 2009*) between the prior radiotherapy and the screening CT or MRI scan.
- Adequate bone marrow function at screening, as determined by:
    - Absolute neutrophil count (ANC) >1,500/mm^3 (CTCAE Grade ≤1)
    - Platelet count >100,000 mm^3
    - Hemoglobin >9.0 mg/dL
- Adequate kidney function at screening, as determined by
    - Estimated glomerular filtration rate (eGFR) >60 mL/min/1.73 m^2 calculated by the CKD-EPI equation (CTCAE Grade ≤ 1).
- Adequate hepatic function at screening, as determined by:
    - Total bilirubin ≤1.5 x ULN if baseline was normal or ≤1.5 x baseline if baseline was abnormal (CTCAE Grade ≤1). Patients with previously documented Gilbert's Syndrome may have total bilirubin ≤3 x ULN.
    - AST ≤3.0 x ULN if baseline was normal or ≤3.0 x baseline if baseline was abnormal (CTCAE Grade ≤1).
    - ALT ≤3.0 x ULN if baseline was normal or ≤3.0 x baseline if baseline was abnormal (CTCAE Grade ≤1).
- Adequate coagulation function at screening, as determined by:
    - INR ≤1.5 x ULN if not on anticoagulant therapy or >1.5 x baseline if on anticoagulant therapy (CTCAE Grade ≤1). If the patient receives anticoagulant therapy, the dose must be stable for at least 2 weeks before the start of treatment.
    - PTT ≤1.5 x ULN
- Adequate cardiac function at screening, as determined by:
    - Systolic blood pressure <150 mmHg and diastolic blood pressure <90 mmHg (CTCAE Grade ≤1).
      Note: Anti-hypertensive medications are permitted, and if a patient does not meet these eligibility criteria at time of screening, treatment with additional anti-hypertensive agents is permissible at the discretion of the investigator,

and blood pressure can be rechecked at a subsequent visit. Measured blood pressures that fall out of this range after screening do not render patients ineligible, however every effort should be made to medically manage these elevated blood pressures at the investigator's discretion.
    - LVEF ≥50% by MUGA or ECHO.
    - No clinically significant ECG waveform abnormalities at the investigator's discretion
    - QTcF ≤470 ms
- Adequate serum lipid profile at screening, as determined by
    - Serum cholesterol <300 mg/dL
    - Serum triglycerides <300 mg/dL
- Adequate glycemic control at screening, as determined by
    - Fasting blood glucose <140 mg/dL **or**
    - Random blood glucose <250 mg/dL

  Note: Anti-hyperglycemic medications are permitted if a patient does not meet these eligibility criteria at time of screening. Blood glucose measurements that fall out of this range do not render patients ineligible, and appropriate glycemic control at subsequent visits is at the discretion of the investigator.
- Blood calcium and phosphate levels within normal levels per institutional lab standard at screening (calcium level may be corrected for albumin at the investigator's discretion)
- Adequate ophthalmological exam in both eyes at screening, as determined by
    - Intraocular pressure ≤21 mmHg
    - No clinically significant abnormalities on the ocular tomography (OCT), including no evidence of ocular abnormality that would be considered a significant risk factor for central serous retinopathy, retinal vein occlusion (RVO), or neovascular macular degeneration (mild and controlled / stable age-related macular degeneration may be acceptable at the investigator's discretion).
- Able and willing to comply with all aspects of the protocol

Contraception and Pregnancy Testing

<u>Arm 1 (ER-positive metastatic breast cancer):</u>

- Not applicable (subjects must be female and postmenopausal or receiving ovarian suppression)

<u>Arm 2 (advanced solid cancers with MEK1 or MEK2 mutations):</u>

- Male subjects must agree to the following during the treatment period and **for at least 6 months** after the last dose of study treatment:
    - Refrain from donating sperm

      AND either:

- Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent

  OR

- Must agree to use a male condom when having sexual intercourse with a woman of childbearing potential (WOCBP).

- Women of childbearing potential (WOCBP) must
  - Have a negative pregnancy test at screening and within 72 hours before the start of treatment

    AND

  - Must agree to use a contraceptive method that is highly effective during the treatment period and for at least 6 months after the last dose of study treatment. Suitable methods of contraception are described in Section 11.5

    AND

  - Must agree not to donate eggs (ova, oocytes) for the purpose of reproduction during the study and for a period of 6 months after last dose of study treatment.

6.2 Participant Exclusion Criteria

Subjects are excluded from the study if any of the following criteria apply:

Medical and surgical history

- History of HIV with the following exceptions:
  - Patients with CD4+ T-cell (CD4+) counts ≥ 350 cells/uL
- History of AIDS-defining opportunistic infection with the following exceptions:
  - Patients without opportunistic infection within the past 12 months
  - Patients on prophylactic antimicrobials unless the specific antimicrobial drug(s) has an interaction or overlapping toxicity with the proposed treatment as determined by the investigator
- History of active Hepatitis B or Hepatitis C infection at screening with the following exceptions:
  - Patients with Hepatitis B on a suppressive antiviral therapy
  - Patients with Hepatitis C who have completed curative antiviral treatment and have an undetectable viral load
- History (within 5 years) or current evidence of neoplastic disease other than the cancer under study, except cervical carcinoma in situ, superficial noninvasive bladder tumors, curatively treated Stage I-II non-melanoma skin cancer, or any other previous cancer curatively treated <5 years before the start of treatment.

- Current evidence of untreated/unstable symptomatic primary CNS tumor, metastases, leptomeningeal carcinomatosis, or spinal cord compression. Exception: Patients are eligible if neurological symptoms are stable for 14 days prior to the first treatment dose and no CNS surgery or radiation has been performed for 28 days, or 14 days of SRS.
- Current evidence of CTCAE Grade >1 toxicity before the start of treatment, except for hair loss.
    - Subjects with Grade 2 neuropathy may be eligible at the investigator's discretion.
- History or current evidence of ocular abnormalities on ophthalmologic examination that would be considered a risk factor for central serous retinopathy, RVO or neovascular macular degeneration (mild and controlled age-related macular degeneration may be acceptable at the investigator's discretion)
- Current evidence of incomplete recovery from surgery or radiotherapy at screening or planned major surgery or radiotherapy during the treatment. Minor elective surgery may be acceptable at the investigator's discretion.
- History or current evidence of significant (CTCAE Grade ≥2) infection or wound within 2 weeks before the start of treatment.
- History or current evidence of significant cardiovascular disease within 6 months before the start of treatment. This includes, but may not be limited to: unstable angina, new-onset angina, myocardial infarction, arterial thrombosis, pulmonary embolism, CVI/TIA/stroke, pericarditis (any CTCAE grade), pericardial effusion (CTCAE Grade ≥2), non-malignant pleural effusion (CTCAE Grade ≥2), malignant pleural effusion (CTCAE Grade ≥3), congestive heart failure (NYHA Class II - IV) or cardiac arrhythmia requiring anti-arrhythmic therapy, except the following
    - Subjects receiving digoxin, calcium channel blockers, or beta-adrenergic blockers may be eligible at the investigator's discretion if the dose has been stable for ≥2 weeks before the start of treatment.
    - Subjects with sinus arrhythmia and infrequent premature ventricular contractions may be eligible at the investigator's discretion.
- History or current evidence of malabsorption syndrome, major surgical GI resection or other GI conditions that may impair absorption of mirdametinib
- Known or suspected hypersensitivity or allergy to any of the study drugs or excipients contained in the study drug formulations. In addition, allergy to other medications or other type of hypersensitivity may warrant exclusion at the investigator's discretion.
- Female subjects who are pregnant or breastfeeding.
- History or current evidence of any other medical or psychiatric condition or addictive disorder, or laboratory abnormality that, in the opinion of the investigator, may increase the risks associated with study participation, or require treatments that may interfere with the conduct of the study or the interpretation of study results.

<u>Prior or concomitant treatments</u>

- Prior therapy with mirdametinib or any other MEK1/2 inhibitor (e.g., selumetinib, trametinib, cobimetinib, binimetinib) at any time before the start of treatment

- Prior systemic any anti-cancer therapy within five half-lives or two weeks (whichever is shorter), excluding hormonal therapy for metastatic breast cancer, before the start of treatment.
- Prior radiotherapy to the orbital region at any time before the start of treatment
- Prior radiotherapy to tumor lesion(s) that will be chosen as target lesions within 4 weeks before the start of treatment, unless the lesion(s) exhibited objective progression between the prior radiotherapy and the screening CT or MRI scan.
    - Prior palliative radiotherapy to non-target lesions may be allowed at the investigator's discretion at any time before the start of treatment.
- Prior therapy with a live vaccine(s) within 4 weeks before the start of treatment or likely to require live vaccine(s) at any time during the treatment.
    - Injectable flu vaccine (inactivated or recombinant) may be permitted at the investigator's discretion at any time before or during the treatment.
    - Covid-19 vaccination (any type) is permitted either before or during this protocol and does not preclude trial enrollment, at the discretion of the investigator.
- Prior antibiotic therapy for active infection ≤2 weeks before the start of treatment
- Prior therapy with platelet or blood transfusion for the treatment of thrombocytopenia within 2 weeks before the start of treatment.
    - Blood transfusion for the treatment of anemia within 2 weeks before the start of treatment may be acceptable at the investigator's discretion.
    - EPO for the treatment of anemia within 2 weeks before the start of treatment may be acceptable at the investigator's discretion
- Prior therapy with G-CSF or GM-CSF for the treatment of leukopenia within 2 weeks before the start of treatment
- Prior therapy with systemic or topical ophthalmic glucocorticosteroids within 2 weeks before the start of treatment (except for subjects who receive glucocorticosteroid replacement therapy at physiologic doses and / or inhaled or non-ophthalmic topical corticosteroids)

7.0 RECRUITMENT PLAN

This is an investigator initiated trial run at Memorial Sloan Kettering Cancer Center. Cancer patients at Memorial Sloan Kettering harboring the mutations listed in the inclusion criteria will be screened and recruited utilizing automated Darwin queries and through consults placed to the Early Drug Development Service.

Potential research subjects will be identified by a member of the patient's treatment team, the protocol investigator, or research team at Memorial Sloan-Kettering Cancer Center (MSKCC). If the investigator is a member of the treatment team, s/he will screen their patient's medical records for suitable research study participants and discuss the study and their potential for enrolling in the research study. Potential subjects contacted by their treating physician will be referred to the investigator/research staff of the study.

The principal investigator may also screen the medical records of patients with whom they do not have a treatment relationship for the limited purpose of identifying patients who would

be eligible to enroll in the study and to record appropriate contact information in order to approach these patients regarding the possibility of enrolling in the study.

During the initial conversation between the investigator/research staff and the patient, the patient may be asked to provide certain health information that is necessary to the recruitment and enrollment process. The investigator/research staff may also review portions of their medical records at MSKCC in order to further assess eligibility. They will use the information provided by the patient and/or medical record to confirm that the patient is eligible and to contact the patient regarding study enrollment. If the patient turns out to be ineligible for the research study, the research staff will destroy all information collected on the patient during the initial conversation and medical records review, except for any information that must be maintained for screening log purposes.

In most cases, the initial contact with the prospective subject will be conducted either by the treatment team, investigator or the research staff working in consultation with the treatment team. The recruitment process outlined presents no more than minimal risk to the privacy of the patients who are screened and minimal PHI will be maintained as part of a screening log. For these reasons, we seek a (partial) limited waiver of authorization for the purposes of (1) reviewing medical records to identify potential research subjects and obtain information relevant to the enrollment process; (2) conversing with patients regarding possible enrollment; (3) handling of PHI contained within those records and provided by the potential subjects; and (4) maintaining information in a screening log of patients approached (if applicable).

7.1 Research Participant Registration

Confirm eligibility as defined in the section entitled Inclusion/Exclusion Criteria. Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures. During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist. The individual signing the Eligibility Checklist is confirming whether the participant is eligible to enroll in the study. Study staff are responsible for ensuring that all institutional requirements necessary to enroll a participant to the study have been completed. See related Clinical Research Policy and Procedure #401 (Protocol Participant Registration).

7.2 Randomization

Study treatment blinding and randomization are not applicable in this open-label study.

8.0 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved

to participants prior to their inclusion in the study. Participants*/LAR* will also be informed that they are free to withdraw from the study at any time. All participants*/LAR* must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form. Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

9.0 PRE-TREATMENT/INTERVENTION

Patients must have a screening tumor assessment by computed tomography (CT) (preferred to assess target lesions) or magnetic resonance imaging (MRI) scans of known sites of disease as clinically indicated. If the patient has had appropriate imaging scans (e.g., routine clinical management) performed within 28 days prior to Cycle 1 Day 1, then the results of those scans may be used if they are of diagnostic quality. Subsequent post-screening tumor assessments will be done following RECIST v1.1 guideline. Response will be assessed as per RECIST v1.1 by the investigator.

Prior to enrollment, tumor tissue samples with sufficient tumor cell content must be provided during the Screening Period. Patients without satisfactory archival tumor samples, or with an archival tumor sample older than 6 months, will be required (pending the safety of obtaining this additional biopsy) to consent to a tumor biopsy prior to dosing with study drug. If the biopsy is deemed unsafe, the patient may be eligible at the discretion of the principal investigator.

Each potential research patient will provide written informed consent ≤45 days prior to initiation of treatment and prior to starting any study-specific procedures. Upon signature of

the ICF, patients will be assigned a unique patient number as enrollment (Screening) occurs. All screening procedures are listed in Table 3.

10.0 TREATMENT/INTERVENTION PLAN

In all arms of this study, mirdametinib is defined as investigational product (IP) and refers to 1 mg and 2 mg capsules of mirdametinib (PD-0325901). Mirdametinib will be administered by mouth twice daily at the doses specified below.

For Arm 1 of this study, fulvestrant (Faslodex) will be administered by intramuscular (IM) injection at the dose and regimen approved by the FDA for the treatment of ER-positive metastatic breast cancer (500mg on Day 1 and Day 15 of Cycle 1 and on Day 1 of all subsequent cycles).

10.1 Mirdametinib Study Treatment

- Subjects will be instructed to take mirdametinib at home and record the time of intake for both daily doses in the patient dosing diary. Missed doses will also be recorded in the dosing diary. Subjects will be instructed to **not** take their planned morning dose of mirdametinib prior to each study visit during the treatment period. Instead, the morning dose will be taken following the pre-dose PK blood draw or any other assessment scheduled to be obtained at pre-dose during the visit.
- Mirdametinib treatment will be dispensed to subjects every two Cycles during scheduled study visits as described in the SoA or at an unscheduled visit if mirdametinib treatment is damaged/lost.
- Throughout the treatment period, subjects will self-administer study treatment BID utilizing a continuous dosing schedule in 28-day Cycles.
- Subjects will be instructed to swallow capsules whole and not to open or chew them prior to swallowing.
- No capsule should be ingested if it is broken, cracked, or otherwise not intact.
- Subjects should be encouraged to take their dose approximately every 12 hours
- Subjects can take mirdametinib capsules without regard to food intake.
- Delivery of mirdametinib via nasogastric tube or gastrostomy tube is not allowed.
- If a subject misses a scheduled dose of study treatment, and it is within 6 hours of the scheduled dose, the subject should immediately administer the missed dose and resume study treatment in accordance with the normal administration schedule. If more than 6 hours has elapsed since the time of scheduled administration, the subject will **not** be instructed to administer the missed dose and to resume study treatment as prescribed.
- Subjects should not take 2 doses together to “make-up” for a missed dose.
- If a subject vomits any time after taking a dose, then they must be instructed not to take another dose to “make up” for vomiting, but rather, to resume subsequent doses as prescribed.

- If a subject inadvertently takes 1 extra dose, then the subject should not take the next scheduled dose of study treatment. Only one dose should be skipped in this context.

The dose levels for mirdametinib are summarized as follows:

Dose Level -2INT	2mg PO BID, 3 weeks on/1 week off
Dose Level -2	2mg PO BID given continuously
Dose Level -1INT	3mg PO BID, 3 weeks on/1 week off
Dose Level -1	3mg PO BID given continuously
Dose Level 1	4mg PO BID given continuously
Dose Level 2	6mg PO BID given continuously
Dose Level 3	8mg PO BID given continuously

In arm 1, dose level 1 of mirdametinib will be used in the safety run-in with fulvestrant and this dose will be used as the RP2D, otherwise dose de-escalation will be carried out. In this arm if that dose is not tolerated, this will proceed to dose level -2 with fulvestrant. If dose level -2 is not tolerated, dose level -2INT will be initiated. Arm 2 will follow a dose escalation 3+3 standard design, in which dose level 1 is the initial dose of mirdametinib, with additional dose levels 2 and 3. Pending DLTs in dose levels 1-3, this arm will proceed to dose level -1 using mirdametinib as monotherapy. If dose level -1 is not tolerated, dose level -1INT will be initiated.

10.2 Study Treatment Errors

- Mirdametinib treatment errors may result in this study from the administration or consumption of the study treatment by the wrong subject or at the wrong dosage strength. Subjects will be instructed to call their treating physician or nurse immediately in the event of such a treatment error. If this happens, the treating physician or nurse will re-review the dose instructions with the subject to ensure compliance. If the subject is experiencing any side effects from the treatment error, they will be treated as clinically indicated based on symptoms. Treatment errors occurring to a study subject are to be captured in the electronic case report form (eCRF) when appropriate.
- Study treatment errors are reportable irrespective of the presence of an associated AE/SAE, including errors involving subject exposure to the mirdametinib product.
- If the study treatment error is accompanied by an AE (as determined by the Investigator), the study treatment error (if applicable), and any AE(s), must be captured on an AE eCRF page.

10.3 Study Treatment Compliance

Subject compliance with mirdametinib treatment will be assessed at each visit where study treatment is dispensed. Compliance will be assessed by counting returned capsules/dispersible tablets in addition to reviewing the dosing diary entries. At each study visit, any discrepancies or deviations will be discussed with the subject and will be recorded in the source documentation. The number of capsules/dispersible tablets dispensed, and the number of capsules/dispersible tablets returned will be recorded in the eCRF, as well as any deviations.

10.4 Concomitant Therapy

Prior/Concomitant Medications and/or Procedures
Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the subject is receiving at the time of signing informed consent/assent or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The subject should contact their doctor if they have any questions regarding concomitant or prior therapy.

Prohibited or Restricted Concomitant Medications/Treatments

- Prior therapy with mirdametinib or any other MEK1/2 inhibitor (e.g., selumetinib, trametinib, cobimetinib, binimetinib) at any time before the start of treatment
    - Any other MEK 1 / 2 inhibitors are prohibited during the treatment until the EOT visit.
- Systemic anti-cancer therapy within 5 half-lives or two weeks (whichever is shorter), excluding hormonal therapy for metastatic breast cancer, before the start of treatment and during the treatment until the EOT visit.
- Radiotherapy to the orbital region at any time before the start of treatment and during the treatment until the EOT visit.
- Radiotherapy to tumor lesion(s) that will be chosen as target lesions within 4 weeks before the start of treatment, unless the lesion(s) exhibited objective progression between the prior radiotherapy and the screening CT or MRI scan.
    - Radiotherapy to tumor lesion(s) chosen as target lesions is further prohibited during the treatment until the EOT visit
    - Palliative radiotherapy to non-target lesions may be allowed at the investigator's discretion at any time before the start of treatment and during the treatment until the EOT visit.
- Live vaccine(s) within 4 weeks before the start of treatment and during the treatment until the EOT visit.
    - Injectable flu vaccine (inactivated or recombinant) may be permitted at the investigator's discretion at any time before or during the treatment until the EOT visit.

  - Inactivated, protein-based, RNA-based or DNA-based COVID vaccines may be permitted at the investigator's discretion.
- Antibiotic therapy for active infection within 2 weeks before the start of treatment
- Platelet or blood transfusion for the treatment of thrombocytopenia within 2 weeks before the start of treatment and during the DLT assessment period (Cycle 1), except when the thrombocytopenia has been identified DLT.
  - RBC or blood transfusion for the treatment of anemia within 2 weeks before the start of treatment and during the treatment may be acceptable at the investigator's discretion if the chronic anemia has been persistent within 4 weeks before the start of treatment.
  - EPO for the treatment of anemia within 2 weeks before the start of treatment may be acceptable at the investigator's discretion if the dose has been stable within 4 weeks before the start of treatment
- G-CSF or GM-CSF for the treatment of leukopenia within 2 weeks before the start of treatment and during the DLT assessment period (Cycle 1)
- Systemic or topical ophthalmic glucocorticosteroids within 2 weeks before the start of treatment and during the treatment until the EOT visit
  - Systemic glucocorticosteroids are permissible are permitted during the screening and treatment for blood product transfusions, or as pulse treatment for an acute allergic reaction or bronchospasm, or as replacement therapy at physiologic doses
  - Topical inhaled or non-ophthalmic glucocorticosteroids are permitted during the screening and treatment.

Supportive Care
Supportive / symptomatic therapy for management of adverse events or co-morbidities is permitted at the investigator's discretion as long as the therapy is not listed among the prohibited medications.

11.0 EVALUATION DURING TREATMENT/INTERVENTION

11.1 Clinical Safety Laboratory Analytes

Table 2

Hematology	Serum or Plasma Chemistry	Urinalysis
• White blood cell count with differential (including at minimum: neutrophils, basophils, eosinophils, lymphocytes, monocytes) • Red blood cell count • Hemoglobin • Hematocrit • Platelet count • Reticulocyte count	• Albumin • Alkaline phosphatase • ALT • AST • Bicarbonate • BUN or urea • Calcium • Chloride • Creatinine	• Specific gravity • Leukocyte esterase • Ketones • Protein • Glucose • Nitrite • Occult blood • Microscopy (if clinically indicated)

<table>
<tr><th colspan="3">Table 2</th></tr>
<tr><th>Hematology</th><th>Serum or Plasma Chemistry</th><th>Urinalysis</th></tr>
<tr><td></td><td rowspan="3">Creatine kinase
Glucose
Lactate dehydrogenase
Phosphate
Potassium
Sodium
Total bilirubin
Total protein
Triglycerides
Total cholesterol
LDL
Uric acid</td><td></td></tr>
<tr><td>Coagulation</td><td>Virology (screening only)</td></tr>
<tr><td>PT/INR
aPTT</td><td>HBV: HBsAg and HBV-DNA
HCV: anti-HCV antibody and HCV-DNA</td></tr>
</table>

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen

11.2 Physical Examinations and Vital Sign Measurements

Physical examinations, including height (required at screening only), weight, and vital signs (blood pressure [BP], heart rate, pulse, and temperature), will be performed in accordance with the Schedule of Assessments.

Any physical examination or vital signs assessed as clinically significant should be recorded as an AE or SAE. If SAE criteria are met the event should be recorded and reported according to the SAE reporting process.

All on treatment visits have a +/-3 day window.

11.3 ECOG Performance Status

Performance status will be assessed using the ECOG scale in accordance with the Schedule of Assessments.

11.4 Electrocardiograms (ECGs)

To evaluate the QT/QTc interval in patients treated with mirdametinib, either with or without fulvestrant, will be monitored with a standard 12-lead ECG performed in triplicate (≥1 minute apart) at different timepoints. Patients should be in supine position and resting for at least 10 minutes before study-related ECGs. ECG monitoring should be performed prior to PK blood draws. Details can be found in the Schedule of Assessments.

The ECG parameters (heart rate, PR interval, QRS interval, QT interval, and corrected QT [QTc] interval) at each time recorded, as well as the change from screening will be listed and summarized. These parameters will be determined electronically by the ECG machine at

the clinical site. The QT interval will be corrected by both the Bazett and Frederica methods as follows:

- Bazett: QTcB = QT/(RR)1/2
- Fridericia: QTcF = QT/(RR)1/3

The overall ECG assessment will be reported as “Normal” or “Abnormal” with respect to relevant abnormalities by the investigator. A shift table comparing the ECG assessment over the study drug administration period to screening will be presented.

The QTc data obtained by using the Bazett and Frederician corrections will be categorized separately into the following classifications and summarized by time after study drug dosing:

- QTc interval >450 msec and ≤480 msec
- QTc interval >480 msec and ≤500 msec
- QTc interval >500 msec

The change of the QTc values obtained by using the Bazett’s and Frederica’s correction will also be categorized separately as follows:

- QTc interval increases from baseline by >30 msec and ≤60 msec
- QTc interval increases from baseline by >60 msec

The calculated QTc average of the 3 ECGs must be <480 msec for eligibility.

The average of triplicate 12-lead ECG results will be summarized by treatment at each time point using descriptive statistics (number of subjects, mean, SD, median, minimum, and maximum).

11.5 Pregnancy Testing

For females of childbearing potential, negative serum pregnancy test is required at screening and within 72 hours of starting treatment. Serum pregnancy testing will be performed on Day 1 of each cycle and at EOT for females of childbearing potential. If the clinic standard is to do a serum pregnancy test more frequently, that is acceptable with the protocol as written.

Male and female patients should start using birth control from screening throughout the study period up to 6 months after the last dose of study drug. If there is any question that a patient will not reliably comply with the contraception requirements, they should not be enrolled in the study, and any patient who becomes pregnant should be withdrawn from the study. Any pregnancies that occur within 6 months post-treatment discontinuation are to be reported.

Patients of childbearing potential, who are sexually active, and their partners must agree to the use of a highly effective form of contraception throughout their participation during the study treatment and for 6 months after the last dose of study drug(s):

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:

- Progestogen-only hormonal contraception associated with inhibition of ovulation
- Intrauterine device (either copper or hormone-based)
- Bilateral tubal occlusion
- Vasectomized partner
- Sexual abstinence if it is the preferred and usual lifestyle of the patient

11.6 Demographics and Baseline Characteristics

Patient demography consists of age, race, ethnicity, and gender at screening. In addition, history of smoking and alcohol consumption will be collected and documented in the medical record.

For disease history the following will be documented:

- Date of first diagnosis
- Tumor type
- Stage at time of initial diagnosis
- Histology and grade of disease at diagnosis and most recent biopsy if additional biopsy performed
- Information on first anticancer treatment, if applicable:
  - Intent (adjuvant, neoadjuvant, curative, palliative)
  - Date of start of first treatment
  - Agents used in first treatment
  - Date of last dose of first treatment
- Information on second and subsequent anticancer treatments, if applicable:
  - Intent (adjuvant, neoadjuvant, curative, palliative)
  - Dates of start of all subsequent treatments
  - Agents in all subsequent treatments
  - Dates of last dose of all subsequent treatments
- Best response and toxicities for each prior anticancer treatment
- Date of recurrence for each prior anticancer treatment

For medical and surgical history, the following will be documented:

Major medical and surgical history (including medication history), including history of thrombocytopenia, neutropenia, leukopenia, or anemia will be collected. Details of any prior invasive malignancy will be collected. Medical and surgical history will be obtained by interviewing the patient or by reviewing the patient's medical records.

11.7 Concomitant Medications and Procedures

Concomitant treatment and medication information will be collected from the Screening Visit until 30 days after their last dose of study drug. Medications will be coded using World Health Organization (WHO) Anatomical Therapeutic Chemical classification. The generic name of the drug (or trade name for combination drugs) must be specified along with the reason for use, and duration of treatment.

All concomitant procedures (including transfusions) will be recorded from the Screening Visit through the EOT Visit (occurring 7-14 days after the last dose of study drug).

Any changes in documented, permitted concomitant treatments already being taken at the beginning of the clinical study must be recorded in the eCRF.

11.8 Additional Anticancer Treatment and Radiotherapy

Subjects should not receive additional therapeutic anticancer treatment until after PD has been documented on study per RECIST v1.1. If a subject requires additional anticancer treatment, study drug will be discontinued, and the subject will enter the Post-Treatment Period and followed by clinic visit or phone call every 12 weeks for up to 1 year.

Palliative radiotherapy for pre-existing non-target lesions and bone metastases may be allowed during the study with the approval of the principal investigator. However, if the indication for palliative radiation is the appearance of a new lesion, the subject will be declared to have progressive disease and study drug will be discontinued and subject have an End of Treatment visit and will enter the Post-Treatment Period and be followed monthly by clinic visit or phone call every 12 weeks.

11.9 Correlatives

11.9.1 Pharmacokinetics

Blood samples for PK assessment for mirdametinib will be drawn per the Schedule of Assessments. Instructions for the collection and processing of PK samples are provided below. Collection time of previous dose, time of dose on the sample day and sample time will be entered in the eCRF.

Whole blood samples of approximately 4 mL will be collected in K2EDTA tube (purple top) for measurement of plasma concentrations of Mirdametinib and the active metabolite PD-0315209. Whole blood samples will be processed to plasma and each plasma sample will be divided into 2 aliquots (1 each for PK and a back-up sample). Samples should be processed and stored as described in Appendix I and II.

Mirdametinib and PD-0315209 will be analyzed in plasma using validated liquid chromatography- mass spectrometry bioanalytical methods.

PK parameters of interest will be estimated by non-compartmental analysis (NCA) as described in Section 14.7 and may include AUC_{last}, $AUC_{last, ss}$ C_{max}, $C_{max, ss}$ and $C_{trough, ss}$.

Plasma concentrations and PK parameter estimates will be presented using descriptive statistics by dose level and by arm.

Additional blood PK samples may be drawn at any time during the study, at the discretion of the investigator, if knowledge of plasma drug concentrations for mirdametinib is considered to be helpful in interpretation of AEs that may affect the safety of study subjects.

11.9.2 Biomarkers

11.9.2.1 Biomarker Sample Collection

The following patient samples are required for biomarker assessment:

- To meet primary and secondary objectives, a tumor tissue sample must be provided during the Screening Period. Patients without archival material or tumor tissue that does not meet minimum requirements (< 12 months old from time of enrollment, tumor block or 20 slides, will undergo a tumor biopsy before beginning treatment to obtain the sufficient tumor material.
- Paired biopsies (collected at screening and on treatment) are suggested but not mandatory for a subset of consenting patients with accessible tumors. To minimize the risk, investigators will preferably choose patients who have easily accessible tumors and in whom an outpatient procedure without general anesthesia is possible.
- Blood samples for the analysis of circulating tumor DNA (ctDNA) will be obtained at screening, during treatment and at EOT.

Details on blood and tissue sample collection, processing, storage, shipping, and handling instructions can be found in Appendix I.

11.9.2.2 Biomarker Analysis based on Tumor Tissue

Baseline tumor tissue will be collected prior to initiating treatment. Sensitizing biomarkers (genomic and protein) will be measured and correlated with clinical efficacy. Nucleic acids will be extracted for exploratory biomarker analysis to determine if genomic features associate with sensitivity or resistance to mirdametinib.

During screening, the investigator will assess the feasibility of obtaining pre-treatment and on-treatment tumor tissue biopsies from the patient. As described above, pre-treatment tissue is obligatory as long as this tissue can be obtained safely (and archival tissue from within 6 months is not available). On-treatment tumor biopsies are encouraged whenever possible but are optional. In all cases this will typically require that the tumor lesions be superficially accessible. Details on collection are provided in Appendix I. Biopsies are an integral component of this study. Patients will be approached to sign IRB#06-107. This will allow for tumor tissue samples and tumor derived samples including but not limited to DNA, RNA, protein lysates, and tumor cells to be collected and stored for the purpose of potential testing and study, including but not limited to the future diagnostic development of biomarkers and the future development of cancer models.

11.9.2.3 Biomarker Analysis from Blood Samples

Baseline blood samples may be used to evaluate a liquid biopsy approach for patient selection and diagnostic methods. Longitudinal blood will be collected for ctDNA monitoring and correlation with clinical response. Blood samples collected at time of progression or after end of treatment may be used to evaluate genomic profiles associated with resistance. Any remaining blood samples may be stored via 06-107 and may be utilized for future research and diagnostic development related to mirdametinib.

In the course of this research it is possible that some patients whose tumors are analyzed through investigational "next-generation" profiling in a research (non-CLIA) environment will be found to have somatic or germline mutations in genes that are known to be associated with an increased risk of cancer or other diseases. It will be stated in the consent that the participants will not receive any specific results from research tests. The consent will tell participants that if they wish to have genetic testing done for personal reasons than they should make an appointment with the MSK Clinical Genetics Service.

If in the course of this research a research finding is obtained that, in the opinion of the investigator, may be critical to the preventive care of the participant or their family, the investigator can communicate that finding to the IRB Genomic Advisory Panel (GAP). The finding will be reviewed by the GAP to determine whether the incidental finding should be discussed with the participant. For MSK, in the event that the GAP determines that the finding should be discussed with the participant, and the participant has consented to be re-contacted, then the treating/consenting physician shall be contacted by the panel and asked to refer the participant to the Clinical Genetics Service for further discussion of the research finding.

The following information must be provided to GAP for review:

- Participant Name/MRN #
- Type of Biospecimen (tissue, blood, saliva)
- Incidental Finding
- Collection Protocol #
- Contact: rtmgapirb@mskcc.org

11.10 Post-study Follow-up

The post-study follow-up will include the end of treatment (EoT) visit, the safety follow-up visit, and the long-term follow-up. The purpose of these additional visits post follow-up is for safety. No additional biomarkers will be collected for study purposes after the EoT visit.

An End of Treatment (EoT) visit will be performed within 7-14 days after the administration of the last dose of the last study drug.

The safety follow-up (FU) visit will be performed 30 days after the last dose of the study drug (except for subjects who died, withdrew consent, and objected to further data collection or were lost to follow up). The safety FU assessment can be done via the clinic visit (recommended) or via a phone call (if subject cannot attend the clinic visit or has started a new anti-cancer treatment). The investigator may order unscheduled FU visits after the 30-day safety FU visit if the adverse events ongoing at the safety FU are deemed to be clinically significant and related to the study drug(s).

The long-term follow-up visits will be performed via clinic visit or phone call every 3 months for 12 months after the last dose of the study drug (except for subjects who died, withdrew consent and objected to further data collection or were lost to follow up).

Schedule of Assessments (SOA) Table 3

Study Procedures	Treatment Visits (+/- 3 day window)						Follow-up		
	Screening (within 28 days of C1D1)	Cycle 1[14]		Cycle 2		Cycle 3+	EOT +/- 3 days	Safety Follow-up +/- 3 days	Long term follow-up +/- 14 days
		Day 1	Day 15	Day 1	Day 15	Day 1	7-14 days of last dose	30 days of last dose	Q3 months for 1 year after last dose
Informed Consent	Within 45 days								
Demographics	X								
Complete medical history	X								
Pre-Treatment Core Biopsy or Archival tissue	X[4]								
Genomic molecular profile (historic report)	X								
Abbreviated medical history		X							
Concomitant medications	X	X	X	X	X	X	X	X	
Toxicities	X	X	X	X	X	X	X	X	X[14]
Physical exam	X	X		X		X		X	
ECOG performance status	X	X	X	X	X	X	X	X	
Vital signs[1]	X	X	X	X	X	X	X	X	
12-lead ECG, in triplicate[12]	X	X		X		Cycle 5 and every odd Cycle thereafter	X		
NYHA classification	X	X		X		Cycle 5 and every odd Cycle thereafter	X		
Hematology[15]	X	X	X	X	X	X	X	X	
Chemistry[15]	X	X	X	X	X	X	X	X	
Urinalysis (Dipstick) [15]	X	X	X	X	X	X			
Total cholesterol, LDL, Triglycerides[15]	X	X		X		X			

Coagulation (aPTT and PT or INR)[15]	X	X		X		Cycle 5 and every odd Cycle thereafter	X	X	
Thyroid function (TSH, FT3, FT4)[15]	X	X		X		Cycle 5 and every odd Cycle thereafter	X	X	
Virology[2]	X								
Pregnancy test (only WOCBP)[4]	X	X		X		X	X		
Mirdametinib dosing[5]		Twice daily (Morning dose will be taken in the clinic on Cycle 1 Days 1 and 15, and Cycle 2 Day 1)							
Fulvestrant IM injection		X	X	X		X			
PK sampling for mirdametinib[6]		X	X	X					
Ophthalmological examination[7]	X					Cycle 3 and every odd Cycle thereafter (+/- 7 days)	X		
Echocardiogram[8]	X					Cycle 3 and every odd Cycle thereafter (+/- 7 days)	X		
Tumor assessment by RECIST 1.1[9]	X					C3, then every 8 weeks (+/- 5 days) until cycle 11, then every 12 weeks (+/- 7 days) on cycles 12 and above	X		
On-Treatment Tumor biopsy – Core Needle (Optional)[10]				Within 7 days of C2D1					
Tumor markers		X		X		Day 1 of every cycle until the first scan, and then coinciding with imaging time points	X		
MSK-Access cfDNA		X					X		
cfDNA collection				X		X			

1. Vital signs should include body temperature, height (required at screening, only) and weight, blood pressure, heart rate, and pulse oximetry.
2. Virology at screening will include the following assessments:
   - HBV: HBsAg and HBV-DNA
   - HCV: anti-HCV antibody and HCV-DNA
3. Archival tumor: Sufficient if within 6 months of trial enrollment. If archival tissue is not available a core needle biopsy is mandatory, as long as the investigator deems the procedure to be safe and accessible. A sample of the archival tumor tissue from the primary or metastatic tumor (block preferred, or at least 5 FFPE slides) will be

collected at screening.

4. **Pregnancy test:** women of childbearing potential must have a negative serum pregnancy test within 3 days before dosing on Day 1 in each cycle
5. **Study drug administration**:
   a. Mirdametinib dosing at home: twice daily by mouth on every day of each 28-day cycle except for the morning dose on Day 1 and Day 15 in each cycle.
   b. Mirdametinib dosing in the clinic: the clinic staff will administer the morning dose of mirdametinib on Cycle 1 Days 1 and 15 and Cycle 2 Day 1.
6. **PK sampling**: Blood samples for mirdametinib concentration in plasma will be drawn at the following time points:
   a. Day 1 and Day 15 of Cycle 1: pre-dose and at 0.5h, 1.0h, 2.0h and 4.0h after the mirdametinib dose
   b. Day 1 of Cycle 2: pre-dose
7. **Ophthalmological exam**: must include visual acuity, tonometry, slit lamp exam and optical coherence tomography (OCT); fundoscopy with pupil dilation is not mandatory but may be performed at the discretion of the ophthalmologist. For cycles that do not have a scheduled ophthalmological exam, the treating physician will evaluate the participant for ocular toxicity and refer them to an ophthalmologist if clinically indicated.
8. **LVEF assessment by echocardiogram (Echo),** where the exam may be limited only on the measurement of LVEF without other aspects (global and regional contractility, stroke volume etc.), unless requested at the investigator's discretion. Results from a MUGA scan can also be used if it is performed as part of the patient's routine care.
9. **Imaging** to be performed within five-day window up to cycle 12, then within 7-day window for cycles 12 and above
10. **Paired tumor on-treatment biopsy – Core Biopsy (Optional).** If tumor lesion is accessible at acceptable risk and the patient has consented, the core biopsy will be obtained from the primary or metastatic tumor within 7 days before C2D1.
11. Clinical/local lab tests are listed in Table 2
12. The triplicate ECG will be done pre-dose and at 4 hours post-dose on C1D1 and C2D1. All other triplicate ECGs will be obtained pre-dose.
13. The long-term follow-up visits may be done in clinic or via telehealth
14. Baseline characteristics of these patients will utilize laboratory and clinical studies performed on C1D1.
15. Laboratory Assessments and Urinalysis: must be completed within 3 days before dosing on Day 1 of each cycle except for on Cycle 1 Day 1 (which must be completed on same day)

12.0 CRITERIA FOR REMOVAL FROM STUDY

Patients will begin dosing on Cycle 1 Day 1 (C1D1) according to assigned dose level and arm with cycle length of 28 days. Individual patients will continue on mirdametinib or mirdametinib with fulvestrant until progression of disease, unacceptable toxicity, or other reason for treatment discontinuation. Patients with documented progression of disease may be allowed to continue on study if the patient is tolerating treatment, and in the opinion of the investigator, the patient is deriving clinical benefit from continuing study treatment and continuation of treatment is approved by the investigator. If said patient continues treatment post progression, they will require reconsent.
Patients may be removed from study for the following reasons, including but not limited to:

- Progression of Disease (with exception as above)
- Unacceptable toxicity, with attention to DLT as described in Section 15.3
- Noncompliance with protocol
- Concurrent illness compromising ability to fulfill protocol requirements
- Requirement for alternative treatment in the opinion of the investigator
- Pregnancy
- Loss to Follow up
- Withdrawal of Consent
- Death
- Study Termination

The clinical trial may be discontinued or terminated in case of an unacceptable risk, any relevant toxicity, or a negative change in the risk/benefit assessment. This might include the occurrence of AEs which character, severity or frequency is new in comparison to the existing risk profile. In addition, any data deriving from other clinical trials or toxicological studies which negatively influence the risk/benefit assessment might cause discontinuation or termination of the study.

13.0 CRITERIA FOR OUTCOME ASSESSMENT AND ENDPOINT EVALUABILITY

13.1 Safety Endpoints

Tolerability and safety of mirdametinib and mirdametinib plus fulvestrant combination, endpoints of the study, will be evaluated by assessment of AEs, TEAEs, SAEs, DLTs, concomitant medications, PEs, vital sign measurements, clinical safety laboratory evaluations (hematology, serum chemistry, and urinalysis), ECOG scores, electrocardiograms (ECGs), and other assessments.

All safety parameters will be performed in accordance with the Schedules of Assessments presented in each arm.

13.2 Efficacy Endpoints

Efficacy will be assessed by confirmed ORR, DOR, clinical benefit rate (CR + PR + SD ≥4 months), and PFS. Tumor response will be evaluated by the investigator using RECIST version 1.1. OS is not an endpoint of this study. Arms 1 and 2 we be analyzed completely separately.

13.3 Evaluable subjects

Patients who achieve sufficient compliance with the study drug intake in Cycle 1 (received at least 45 of 56 [greater than 80%] doses of mirdametinib (in Arm 1 only, also both doses of fulvestrant) **or** experience a DLT will be considered as evaluable for the assessment of the DLT rate for the particular dose level.

Additional patients should be enrolled at the same dose level as necessary to ensure an adequate number of DLT-evaluable patients.

13.4 Evaluation of Tumor Response

13.4.1 Overview

The efficacy of both study arms will be evaluated by assessment of tumor response to treatment according to RECIST v1.1 [Eisenhauer 2009] per investigator assessment.

Response to treatment will be based on investigator evaluation of radiographic images. All radiographic images/scans at the time points specified as well as any unscheduled images/scans should be archived for potential future evaluation.

CT or MRI scans will be performed on each patient. Baseline images should encompass all areas of known predilection for metastasis of the disease under evaluation and should additionally investigate areas that may be involved based on signs and symptoms of individual patients. The imaging method used for the patient at screening will be used at each subsequent visit.

Any other sites at which new disease is suspected should also be appropriately imaged. If an unscheduled assessment is performed and the patient has not progressed, every attempt should be made to perform subsequent assessments at the scheduled visits while the patient remains on study drug.

13.4.2 Timing of Radiographic Evaluations

All patients will undergo serial radiographic assessments to assess tumor response. Initial tumor imaging at screening must be performed within 28 days prior to the date of the first dose of study drug. Scans performed prior to the signing of the ICF as part of routine clinical management are acceptable for use as initial tumor imaging if they are of diagnostic quality and performed within 28 days prior to the date of first dose.

Radiographic evaluations to assess extent of disease will be conducted at screening and every 8 weeks (56 ± 5 days) from Cycle 1 Day 1 for the first 12 cycles on study (or sooner if clinically indicated). Thereafter tumor assessments will be performed every 12 weeks (84 ± 7 days). Per RECIST v1.1, CR or PR should be confirmed; tumor imaging for confirmation of response must be performed at least 4 weeks after the first indication of response.

Imaging should not be delayed for delays in cycle starts or extension of combination treatment cycle intervals.

Radiographic evaluations will continue until PD, start of alternate anticancer therapy, withdrawal of consent to study participation, becoming lost to follow-up or death. If a patient discontinues treatment for a reason other than radiographic disease progression, withdrawal of consent to study, lost to follow-up, or death, scans should continue at the specified intervals until progression is confirmed or until the start of subsequent anticancer treatment.

If a patient discontinues treatment for clinical progression and does not meet RECIST v1.1 criteria for progression, scans should continue at the specified intervals until progression is confirmed or until the start of subsequent anticancer treatment.

13.4.3 Assessment of Response by RECIST

RECIST v1.1 will be used by the investigator as the primary measure for assessment of tumor response, date of disease progression, and as a basis for all protocol guidelines related to disease status.

14.0 BIOSTATISTICS

14.1 Analysis Populations

The following analysis populations will be used:

- **DLT Evaluable Population** consists of patients who receive at least 80% of planned total doses of mirdametinib in cycle 1 (in Arm 1 only, also both doses of fulvestrant) and are observed within 28 days following the first dose of mirdametinib or patients who experience a DLT.
- **Efficacy Population**, used for the assessment of efficacy for each arm, will consist of all patients in Part 2 who received at least 1 dose of study drug and who have at least 1 post-baseline tumor assessment. Arms 1 and 2 will be analyzed separately. In addition, patients treated at the MTD in the dose escalation portion of the protocol (both arms 1 and 2) will be included in the efficacy analyses for the expansion cohorts in part 2 if they meet the requirements for efficacy population as defined above. Additionally, the RP2D will be determined pending the clinical data obtained in the dose escalation portion of the protocol. If the RP2D is less than the MTD, then patients treated at the RP2D in the dose escalation portion of the protocol (both arms 1 and 2) will be included in the

efficacy analyses for the expansion cohorts in part 2 if they meet the requirements for efficacy population as defined above.

- **Pharmacokinetic Population**, used for the assessment of pharmacokinetic endpoints, will consist of all patients who have sufficient pharmacokinetic concentration data recorded to derive pharmacokinetic endpoints.
- **All treated population or safety population:** consisting of all patients who receive any amount of drug

Arms 1 and 2 will be analyzed separately throughout the study.

Arm 1

The study will follow a standard 3+3 dose escalation schema. As described previously in section 4.2, the 3+3 decisions in Part 1 of Arm 1 will be made starting with a mirdametinib starting dose level (4 mg BID PO), where subjects will be treated with mirdametinib 4 mg BID PO given continuously in combination with the recommended dose of fulvestrant. If ≤1 of the first 3 DLT evaluable subjects in Dose Level 1 exhibit a DLT in Cycle 1, then Dose Level 1 will be expanded. Mirdametinib dose in combination with fulvestrant will not be escalated above the 4 mg BID given continuously dose level.

A sufficient number of subjects will be treated with mirdametinib 4 mg BID PO given continuously in combination with the recommended dose of fulvestrant to accrue at least 6 evaluable subjects. If ≤1 of 6 evaluable subjects in the starting dose level exhibit a DLT in Cycle 1, then **mirdametinib 4 mg BID PO** given continuously will be declared as the recommended dose for Part 2 (RP2D) in combination with fulvestrant. If ≥2 of the first 3 evaluable subjects or ≥2 of the 6 evaluable subjects in Dose Level 1 exhibit a DLT in Cycle 1, then the mirdametinib dose will be de-escalated (Dose Level -2). If dose de-escalation is not required there will be six evaluable patients total.

In the case of de-escalation, Mirdametinib Dose Level -2 (de-escalation dose level 2 mg BID PO) will be given to up to 3 subjects, treated with mirdametinib 2 mg BID PO given continuously in combination with the recommended dose of fulvestrant. If 1 of the first 3 evaluable subjects in Dose Level -2 exhibit a DLT in Cycle 1, then a sufficient number of subjects will be treated with mirdametinib 2 mg BID PO given continuously in combination with the recommended dose of fulvestrant to accrue 6 evaluable subjects. If 1 of 6 evaluable subjects in Dose Level -2 exhibit a DLT in Cycle 1, then **mirdametinib 2 mg BID PO** given continuously will be declared as the recommended dose for Part 2 (RP2D) in combination with fulvestrant. If ≥2 of the first 3 evaluable subjects or ≥2 of the 6 evaluable subjects in Dose Level -2 exhibit a DLT in Cycle 1, then the Arm 1 will be further de-escalated.

In this case, Mirdametinib Dose Level -2INT (de-escalation dose level at 2 mg BID PO on a 3 weeks on, 1 week off schedule) will be given to up to 3 subjects, treated with mirdametinib 2 mg BID PO on a 3 weeks on 1 week off schedule, in combination with the recommended dose of

fulvestrant. If 1 of the first 3 evaluable subjects in Dose Level -2INT exhibit a DLT in Cycle 1, then a sufficient number of subjects will be treated with mirdametinib 2 mg BID PO on a 3 weeks on, 1 week off schedule, in combination with the recommended dose of fulvestrant to accrue 6 evaluable subjects. If 1 of 6 evaluable subjects in Dose Level -2INT exhibit a DLT in Cycle 1, then **mirdametinib 2 mg BID PO on a 3 weeks on, 1 week off schedule,** will be declared as the recommended dose for Part 2 (RP2D) in combination with fulvestrant. If ≥2 of the first 3 evaluable subjects or ≥2 of the 6 evaluable subjects in Dose Level -2INT exhibit a DLT in Cycle 1, then Arm 1 will be discontinued. In the case of de-escalation there will be at least 18 evaluable patients (6 from dose level 0, and 6 on two separate dose levels of de-escalation).

Arm 2

Part 1 will be conducted in three sequential Dose Level escalations according to the 3+3 design based on the incidence of dose-limiting toxicities (DLT) and the overall safety profile of the study treatments. At each step of the 3+3 design, the investigators will review all available safety and PK data in the current Dose Level and decide about the appropriate next step. The subjects will become evaluable for the 3+3 decisions if they complete Cycle 1 and receive at least 80% of assigned drug doses, or if they exhibit a DLT in Cycle 1. The starting dose of mirdametinib as single agent in each dose escalation dose level will be as follows: mirdametinib 4 mg BID PO given continuously, mirdametinib 6 mg BID PO given continuously, mirdametinib 8 mg BID PO given continuously. The de-escalation Dose Levels (Dose Level -1) may evaluate mirdametinib 3 mg BID given continuously and (Dose Level -1INT) may evaluate mirdametinib 3 mg BID given on. 3 weeks on, 1 week off schedule.

The 3+3 decisions in Part 1 of Arm 2 will be made similar to the above. Up to 3 subjects will be treated with mirdametinib as single agent at the dose of **4 mg BID PO** given continuously. If ≤1 of the first 3 evaluable subjects in Dose Level 1 exhibit a DLT in Cycle 1, then Dose Level 1 will be expanded. If 0 of the first 3 evaluable subjects in Dose Level 1 exhibit a DLT in Cycle 1, then the dose of mirdametinib as single agent will be escalated to Dose Levels 2 and 3 (**6 mg BID** given continuously **and 8 mg BID** given continuously) following the same rules as above. There will thus be as many as 18 evaluable patients on this arm.

The following table shows the corresponding probability of escalating given five hypothetical true risk for DLT.

True risk of DLT	0.1	0.2	0.3	0.4	0.5
Probability of escalation	0.9	0.7	0.5	0.3	0.2

14.2 General Principles

The majority of the analysis will be descriptive in nature. Unless stated otherwise, continuous variables will be summarized using descriptive statistics (number of patients, mean, standard deviation, median, lower and upper quartile, minimum and maximum values) and the number and percentage of patients will be used for categorical variables.

14.3 Safety Analysis

All AEs will be listed, including the verbatim description per CTCAE v5.0. This analysis will be done on the safety population.

TEAEs are defined as those occurring after the first dose of study drug and within 30 days following the cessation of treatment, whether or not they are considered related to the study medication.

The following key safety parameters will be evaluated:

- Incidence of TEAEs, treatment-related TEAE, TEAEs leading to death, SAE, treatment-related SAE, TEAE leading to study drug discontinuation, TEAE leading to dose modifications (e.g., dose reduction) and TEAE leading to study discontinuation
- TEAEs will be further summarized by severity (according to NCI CTCAE Version 5.0)
- Changes in clinical laboratory parameters (hematology, chemistry, urinalysis), CTCAE graded laboratory toxicities, vital signs, ECOG performance status, ECG parameters, physical examinations, ophthalmology examinations, and usage of concomitant medications

14.4 QTc Analyses

Descriptive statistics and categorical analyses of ECG variables will be provided.

14.5 Efficacy Analyses

The primary efficacy analyses will be performed using the Efficacy Population.

Efficacy endpoints will be based on RECIST v1.1 by investigator's assessment:

- **Objective Response Rate (ORR)** is defined as the proportion of patients with confirmed CR or PR (i.e., 2 visit responses of either CR or PR at least 4 weeks apart) according to RECIST v1.1 criteria.
    - The maximum percent reduction in tumor size will also be presented as a waterfall plot.
- **Clinical Benefit Rate (CBR**) is defined as the proportion of patients with a confirmed best response of CR or PR, or SD that is sustained for at least 4 months after the first dose of mirdametinib according to RECIST v1.1 criteria.

- **Duration of Response (DOR)** (applicable only to patients with confirmed CR or PR) is defined as the time interval between the date of the earliest qualifying response (CR or PR) and the date of disease progression or death for any cause, whichever occurs earlier.
    - For patients who are alive without disease progression following response, DOR will be censored on the date of last evaluable tumor assessment or last follow-up for disease progression.
- **Progression-Free Survival (PFS)** is defined as the time from the first day of study drug administration (Day 1) to disease progression as defined by RECIST v1.1 criteria, or death from any cause.
    - Patients who are alive and free from disease progression will be censored at the date of their last tumor assessment.

For ORR and CBR, patients without a post-baseline tumor assessment will be excluded as they are not efficacy evaluable. The ORR and CBR calculation will include only efficacy evaluable patients.

An exact binomial 95% confidence interval for CBR and ORR will be calculated in each treatment group using the Clopper-Pearson method.

For PFS, Kaplan-Meier curves will be generated, and the median time-to-event and the associated 95% CIs will be provided. In addition, the rate of PFS at 6 months will be derived from the corresponding Kaplan-Meier curves and the associated 95% CIs calculated using Greenwood's formula on the ln[-ln(survival scale)] and back transformed. This analysis will include the patients in the efficacy population.

Depending on responses seen, a central review of all images may also be performed by an independent reviewer as a sensitivity analysis.

Sample size justification and patient numbers.

For the initial parts of both arms, these utilize 3+3 design with arm 1 utilizing dose de-escalation as necessary, and arm 2 utilizing this design to escalate to MTD or RP2D. In the dose expansion cohorts of arm 1, the mirdametinib RP2D will be administered in combination with the standard recommended dose of fulvestrant with the primarily efficacy endpoint, and in dose expansion cohorts of arm 2, the mirdametinib will be given as monotherapy at the RP2D. Per MSKCC clinical research guidelines in CR426, "Expansion Cohorts in Phase I Clinical Trials", for expansion cohorts of size less than 30, a sample size justification is not required. Further, requirements for stopping rules for lack of efficacy (futility) are also not required for cohorts of less than 30 patients. Assuming a 10% low unpromising response rate (null hypothesis), and a response rate >= 25% as a promising rate of response (alternative hypothesis), and n = 28 in each expansion cohort, this will provide 86% power to reject the null hypothesis if at the end of the trial at least 5 / 28 responses are observed in each cohort. Type I error is 14% for each

expansion cohort. The 10% null response rate is justified as an approximation of the standard historical rate in breast tumors treated with fulvestrant. For example, the null response rate in Solar-1 trial was 12.8%[33] and the null response rate in the Paloma-3 trial was 6.3%.[34]

The two arms of the study will be statistically analyzed separately. Given the type I error above of 14% for any one expansion cohort, each arm (with at most two cohorts) yields a family wise error rate of 1-(1-0.14)^2 = 26%. If one chooses to consider the (at most) four expansion cohorts simultaneously, this yields an overall family wise error rate of 1-(1-0.14)^4 = 45%. While we acknowledge that this is high when all expansion cohorts are considered, first these cohorts are exploratory and second the two arms are clearly biologically different and are being treated with differing drug regimens, therefore they will be analyzed separately, thus the appropriate family wise error rate to consider for this study is that of 2 expansion cohorts, or 26%.

In the safety run in of arm 1, a minimum of six and as many as 12 DLT-evaluable patients are required. In the dose expansion cohorts of arm 1, the mirdametinib RP2D will be administered in combination with the standard recommended dose of fulvestrant with the primarily efficacy endpoint, and in dose expansion cohorts of arm 2, the mirdametinib will be given as monotherapy at the RP2D. For these expansion cohorts, as explained above, each will be deemed promising if at the end of the study at least 5 / 28 responses (CR or PR) are observed. This part of the study will enroll 2 * 28 = 56 efficacy evaluable patients (28 patients on each of two expansion cohorts). Exploratory future cohorts, such as subjects with hormone receptor-positive, HER2-negative metastatic breast cancer exhibiting OncoKB defined activating mutations in BRAF, CRAF, or MEK1/2 (section 4.2) are not included in this analysis. To account for non-evaluable patients, we will have a goal total enrollment of 60 patients. This part of the study is planned to accrue approximately 2 patients per month and it is expected to complete accrual in 3 years.

In the dose escalation part of arm 2 (mirdametinib monotherapy in MEK1/2 mutant patients), we anticipate as few as 6 DLT-evaluable patients and as many as 18 DLT-evaluable evaluable patients will be required, the precise number of patients enrolled in this arm is pending the observed toxicity of mirdametinib monotherapy in dose escalation. This part of the study will take approximately nine months to complete accrual, assuming two patients per month are accrued. The specific expansion cohorts for this arm of the trial are pending the observed responses by genotype and cancer lineage in this arm of the protocol. However, as with arm 1, as explained above, each expansion cohort will be deemed promising if at the end of the study at least 5 / 28 responses (CR or PR) are observed. As we also anticipate as many as two expansion cohorts of patients on this arm of the study, this arm will also require as many as 2 * 28 = 56 efficacy evaluable patients with a goal total enrollment of 60 patients which will take 3 years to accrue.

14.6 Demographics, Medical History, Baseline Characteristics and Concomitant Medications

Demographics, baseline disease characteristics and medical history information will be summarized for the safety population by dose level in order to assess the comparability of the treatment groups descriptively. Data to be tabulated will include demographic features such as age, sex and race, as well as disease-specific characteristics.

The number and percentages of patients screened, treated, completed the treatment/study, and withdrawn from treatment/study for any reasons will be presented overall and by treatment group/dose level.

14.7 Pharmacokinetic Analyses

PK parameters for mirdametinib and PD-0315209 will be calculated using non-compartmental analysis with appropriate software such as Phoenix WinNonlin (Version 8.1 or higher, Certara, Inc.). Only plasma concentrations greater than or equal to the validated lower limit of quantitation (LLQ) will be used in the PK analyses. Actual blood sampling times will be used in all PK analyses. Per-protocol times will be used to calculate mean plasma concentrations for graphical displays.

The following PK parameters will be determined as appropriate:

C_{max}	Maximum concentration, determined directly from individual concentration-time data (Cycle 1, Day 1 only)
$C_{max, ss}$	Maximum concentration at steady-state, determined directly from individual concentration-time data (Cycle 1, Day 15 only)
$C_{trough, ss}$	Minimum concentration at steady-state, determined directly from individual concentration-time data (Cycle 1, Day 15 and Cycle 2, Day 1 only)
T_{max}	Time to reach maximum concentration, determined directly from individual concentration-time data.
AUC_{last}	Area under the concentration-time curve from time-zero to the time of the last quantifiable concentration; calculated using the linear-up/log-down trapezoidal rule (Cycle 1, Day 1 only)
$AUC_{last, ss}$	Area under the concentration-time curve from time-zero to the time of the last quantifiable concentration at steady-state; calculated using the linear-up/log-down trapezoidal rule (Cycle 1, Day 15 only)

Additional PK parameters may be calculated if data allows. Population PK modeling may be performed on the mirdametinib concentration-time data collected from this study to quantitatively describe the PK, explore the PK variability, and identify any covariate effects such as demographic, intrinsic or extrinsic factors, or co-medication on the PK. The exposure-response relationship between measures of mirdametinib exposure and measures of efficacy, including, but not limited to, ORR, PFS, and DOR may also be explored. The relationship between mirdametinib exposure and key safety variables, including EKG, may be explored. In addition, tumor biopsy biomarkers may be explored in the exposure / response analyses.

14.8 Biomarker Analyses

For each patient in the study, blood and tumor tissue samples will be collected, evaluated and archived to support exploratory biomarker analysis. Gene mutations and other genomic features, and other exploratory biomarkers will be correlated with response.

As data warrants, exploratory analysis may be performed on each exploratory endpoint listed. In addition, exploratory analyses may be performed to examine the relationship between exposure to mirdametinib and clinical and safety endpoints (including tumor size or change in tumor size from baseline).

These translational endpoints will include biomarkers associated with response, such as pre-treatment and on-treatment MSK-IMPACT, and cell free DNA dynamics using MSK-ACCESS. MSK-IMPACT will be performed on all solid tumor biopsies, and MSK-ACCESS will be performed serially at timepoints specified in the Schedule of Assessments. These samples will be banked. Any prioritized findings arising clonally in tissue will be cross-validated in cfDNA from the same patient. In addition to confirming tissue findings, cfDNA sequencing will allow for (1) the assessment of response prior to imaging, (2) an analysis of the differential response of heterogenous subclones to treatment, and (3) the acquisition of sequencing data where tissue collection was not possible.

In parallel with the above, the solid tumor biopsies will be utilized for additional translational work, and this line of inquiry includes the generation of PDX models and/or tumor derived cell lines and transcriptomic and protein analyses.

15.0 TOXICITIES/RISKS/SIDE EFFECTS

Adverse Events

CTCAE Version 5 will be utilized for toxicity evaluation.
An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered casually related to the product. In clinical studies, an AE can include an undesirable medical condition occurring at any time, including baseline or washout periods, even if no study drug has been administered.

The intensity and causality of each AE will be assessed by the investigator as outlined in the following sections.

Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated; easily tolerated

Grade 2: Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADLs). (Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, or managing money.)

Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL. (Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.)

Grade 4: Life-threatening consequences; urgent intervention indicated.

Grade 5: Death related to AE

Treatment-Emergent Adverse Events

A TEAE is any event that was not present prior to the initiation of study drug or any event that worsens in either intensity or frequency following exposure to study drug.

Collecting and Recording Adverse Events

AEs spontaneously reported by the patient and/or in response to an open question from the study personnel or revealed by observation will be recorded in the EDC.

Information about AEs/SAEs will be collected from the first treatment through 30 days after the last dose of study drug or until alternate anticancer treatment has been initiated (whichever occurs earlier).

The AE term should be reported in standard medical terminology when possible. For each AE, the investigator will evaluate and report the onset (date and time), resolution (date and time), intensity, causality, action taken, serious outcome (if applicable), and whether or not it caused the patient to discontinue the study.

Concomitant illnesses that existed before entry into the study will not be considered AEs unless the illness worsens during the Treatment Period. Pre-existing conditions will be recorded as medical history in the eCRF.

Reporting Disease Progression

The event of disease progression is an efficacy criterion and is therefore not considered an AE. Disease progression should be reported within the EDC. If AEs/SAEs occur in relation to disease progression, the AEs/SAEs must be reported per AE/SAE reporting requirements.

Follow-Up of Adverse Events

Investigators must follow subjects with AEs/SAEs until event resolution or stabilization, withdrawal of consent, subject loss to follow-up, or death, whichever occurs first.

If an investigator becomes aware of an SAE after the specified follow up- period and considers the SAE related to the study drug, the investigator should report the SAE to SpringWorks according to timelines for reporting SAEs.

Withdrawal due to Adverse Events

Withdrawal due to AEs should be distinguished from withdrawal due to other causes, according to the definition of AE noted earlier, and recorded on the appropriate AE eCRF page. When a patient withdraws because of an SAE, the SAE must be reported in accordance with the reporting requirements.

15.1 Serious Adverse Event (SAE) Reporting

An adverse event is considered serious if it results in ANY of the following outcomes:

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition
- *List any additional events that require SAE reporting (pregnancy, AEs of special interest (AESI), secondary malignancies, etc.)*

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

SAE reporting is required as soon as the participant starts investigational treatment/intervention. SAE reporting is required for 30-days after the participant's last investigational treatment/intervention. Any event that occur after the 30-day period that is unexpected and at least possibly related to protocol treatment must be reported.

Please note: Any SAE that occurs prior to the start of investigational treatment/intervention and is related to a screening test or procedure (i.e., a screening biopsy) must be reported.

All SAEs must be submitted in PIMS. If an SAE requires submission to the HRPP office per IRB SOP RR-408 'Reporting of Serious Adverse Events', the SAE report must be submitted within 5 calendar days of the event. All other SAEs must be submitted within 30 calendar days of the event.

The report should contain the following information:

- The date the adverse event occurred
- The adverse event
- The grade of the event
- Relationship of the adverse event to the treatment(s)
- If the AE was expected
- Detailed text that includes the following
    - An explanation of how the AE was handled
    - A description of the participant's condition
    - Indication if the participant remains on the study
- If an amendment will need to be made to the protocol and/or consent form
- If the SAE is an Unanticipated Problem

15.2 External SAE Reporting

All SAEs/SUSARs (related and unrelated) will be recorded from the time of starting treatment until 30 days following the end-of-treatment exposure. Any SAEs/SUSAR considered possibly or probably related to the investigational product and discovered by the investigator at any time after the study should be reported.

All SAEs/SUSARs must be reported to SpringWorks within 5 business day of the first awareness of the event. MSK will provide a copy of the redacted MSK SAE report by fax or email to the assigned drug safety vendor below:

United BioSource Corporation
920 Harvest Drive, Suite 200
Blue Bell, PA 19442
Fax: 866-750-4514
PV@springworkstx.com

Additional follow-up information, if required or available, should all be reported to the assigned drug safety vendor within 5 business day of receipt. This should be completed on a follow-up MSK SAE form and faxed or emailed to the drug safety vendor with the original SAE/SUSAR information and kept with the appropriate section of the CRF and/or study file.

For IND/IDE protocols:
The SAE report should be completed as per above instructions. If appropriate, the report will be forwarded to the FDA by the IND Office.

15.3 Dose Limiting Toxicities

The severity of adverse events (AEs) reviewed as potential dose-limiting toxicity (DLT) will be graded according to the CTCAE V.5.0. classification.

The occurrence of any of the following AEs during Cycle 1 (Day 1 – Day 28) will be considered a DLT, except for those AEs clearly related to disease progression or intercurrent illness.

Hematologic:

1. Grade 4 or greater hematologic toxicity (neutropenia, thrombocytopenia, or anemia)
2. Grade 3 febrile neutropenia (absolute neutrophil count [ANC] < 1000/mm^3 with a single temperature of > 38.3^oC (101°F) or a sustained temperature of ≥ 38^oC (100.4°F) for > 1 hour)
3. Grade 3 thrombocytopenia with clinically significant bleeding

Non-hematologic:

1. Grade 2 or greater ocular toxicities leading to reduced visual acuity limiting ADL, glaucoma, retinal detachment, or retinal vascular disorder
2. NYHA class III or IV left ventricular dysfunction
3. Grade 3 or greater non-hematologic toxicity that is clinically significant with the following exceptions:
    a. Toxicity (other than rash) that starts to resolve within 3 days of initiating optimal supportive care
    b. Grade 3 rash that resolves to grade 1 or less within 7 days of initiating optimal supportive care
    c. Grade 3 laboratory abnormalities that are not associated with clinical sequelae (e.g., isolated lactose dehydrogenase elevation) and resolves to Grade ≤1 within 3 days of initiating optimal supportive care
    d. Grade 3 or 4 electrolyte laboratory abnormalities that last up to 72 hours, are not clinically complicated, and resolve spontaneously or respond to conventional medical interventions
    e. Grade 3 or 4 amylase or lipase elevation that is not associated with symptoms or clinical manifestations of pancreatitis
    f. Alopecia
4. Grade 4 non-hematologic toxicity, with the exception of those listed above, regardless of clinical significance or duration
5. Hy's law criteria (Grade ≥ 2 bilirubin in conjunction with grade ≥2 transaminase and without elevation of alkaline phosphatase)

In addition, clinically important or persistent toxicities not included above may also be considered a DLT at the discretion of the investigator after consultation with the SpringWorks physician.

A DLT may require temporary interruption or permanent discontinuation of mirdametinib. Mirdametinib treatment may be restarted at the same or reduced dose after the DLT has resolved to Grade ≤1. See the mirdametinib treatment modification guidelines in Table 4 below.

15.4 Dose Modification

The Investigator may temporarily interrupt, reduce the dose or permanently discontinue one or more study drugs at their discretion due to treatment-emergent adverse event that – in the Investigator's opinion – warrants treatment modification.

The treatment with fulvestrant in Arm 1 should be modified according to the USPI (where applicable) or at the investigator's discretion.

The treatment with mirdametinib in all arms should be modified according to the guidelines provided in Table 4 and Table 5below.

Treatment should remain interrupted until the AE has resolved to Grade ≤1 (of Grade ≤2 in the event of rash). In addition, the AE resolution to Grade 2 may be acceptable at the Investigator's discretion if same toxicity was ongoing at Grade 2 since the pre-treatment baseline). The study treatment may be re-started at the same or lower dose (see Table 4 and Table 5) if the has reached satisfactory resolution in ≤21 days. If the AE has taken >21 to reach satisfactory resolution, then the study treatment should be permanently discontinued, unless the Investigator has determined that re-starting the treatment has acceptable benefit-risk ratio (e.g. continued objective response or stable disease after AE resolution).

Once a dose of the study treatment has been reduced due to an AE, the subject must remain on the reduced dose for the duration of the study. One subject may have up to 2 dose reductions due to AE. Dose re-escalation after the AE resolution is not permitted.

Table 4 Guideline for Mirdametinib Dose Modification for Related Adverse Events

RELATED ADVERSE EVENTS (Worst Grade by CTCAE V. 5.0)	INTERVENTION
NEUTROPENIA (ANC DECREASE)	
Grade 3 (ANC <1.0x to 0.5x 10^9/L)	Interrupt mirdametinib until resolution to Grade ≤1, then • If resolved in ≤7 days, may re-start mirdametinib at the same dose at the Investigator's discretion • If resolved in >7 days, re-start mirdametinib at the next lower dose (seeTable 5).
Grade 4 (ANC <0.5x 10^9/L)	Interrupt mirdametinib until resolution to Grade ≤1, then • If resolved in ≤7 days, may re-start mirdametinib at the next lower dose (see Table 5) at the Investigator's discretion • If resolved in >7 days, permanently discontinue mirdametinib.
Grade 3 febrile neutropenia (ANC <1.0x 10^9/L with a single temperature of >38.3 degrees C [101 degrees F] or a sustained temperature of ≥38 degrees C [100.4 degrees F] for more than one hour)	Interrupt mirdametinib until complete resolution of fever and ANC resolution to Grade ≤1. After satisfactory resolution, re-start mirdametinib at the next lower dose (see Table 5).
Grade 4 febrile neutropenia (ANC and temperature criteria as listed above PLUS life-threatening signs or symptoms including septic shock, hypotension and/or acidosis)	Permanently discontinue mirdametinib.
THROMBOCYTOPENIA (PLATELET COUNT DECREASE)	
Grade 3 thrombocytopenia (Platelets <50x to ≥25x 10^9/L)	Interrupt mirdametinib until resolution to Grade ≤1, then • If resolved in ≤7 days, may re-start mirdametinib at the same dose at the Investigator's discretion • If resolved in >7 days, re-start mirdametinib at the next lower dose (seeTable 5).
Grade 4 thrombocytopenia (Platelets <25x 10^9/L)	Interrupt mirdametinib until resolution to Grade ≤1, then • If resolved in ≤7 days, may re-start mirdametinib at the next lower dose (see Table 5) at the Investigator's discretion • If resolved in >7 days, permanently discontinue mirdametinib.
OPHTHALMOLOGICAL	

Any Grade ≤2 event not leading to reduced visual acuity limiting ADL.	Continue mirdametinib at the same dose. Perform ophthalmologic exams at least monthly or more frequently at the Investigator's discretion until resolution to Grade ≤1.
Any Grade 2 event reduced visual acuity limiting ADL, or any Grade ≥3 event.	For events different from RVO or retinal detachment, interrupt mirdametinib until resolution to Grade ≤1. Perform ophthalmologic exams at least biweekly or more frequently at the Investigator's discretion until satisfactory resolution. After resolution to Grade ≤1, re-start mirdametinib treatment at the next lower dose (see Table 5). For Grade ≥3 RVO or retinal detachment, permanently discontinue mirdametinib.
NEUROLOGICAL	
Grade ≤2 seizure / convulsion, hallucination, confusion or delirium or similar events lasting >24 hours AND after ruling out other possible causes.	Interrupt mirdametinib until resolution to Grade ≤1. After resolution to Grade ≤1, re-start mirdametinib at the next lower dose (see Table 5).
Any Grade ≥3 event	Interrupt mirdametinib until resolution to Grade ≤1. After resolution to Grade ≤1, the Investigator may re-start mirdametinib at the next lower dose (see Table 5) or permanently discontinue mirdametinib, depending on the Investigator's benefit-risk assessment.
MUSCULOSKELETAL	
Grade ≥3 muscle weakness (symptomatic and interfering with ADL).	Interrupt mirdametinib until resolution to Grade ≤1. After resolution to Grade ≤1, re-start mirdametinib at the next lower dose (see Table 5).
DERMATOLOGICAL	
Grade ≥3 rash	Interrupt mirdametinib until resolution to Grade ≤1. After resolution to Grade ≤1, re-start mirdametinib at the next lower dose (see Table 5).
LVEF	
Grade 2 LVEF decrease (post-baseline LVEF of 40-49%)	If asymptomatic, interrupt mirdametinib until LVEF resolves to ≥50%. Perform LVEF exams at least biweekly or more frequently at the Investigator's discretion until satisfactory resolution After resolution to Grade ≤1, re-start mirdametinib at the next lower dose (see Table 5).

	If symptomatic, permanently discontinue mirdametinib.
Grade 3 LVEF decrease (post-baseline LVEF of 20-39% or ≥20% difference between the post-baseline vs. baseline LVEF)	If asymptomatic, interrupt mirdametinib and repeat LVEF exam in one week. If repeat exam shows persistent Grade 3 LVEF decrease, then permanently discontinue mirdametinib. If repeat exam shows Grade 2 LVEF decrease or better, then apply the guideline listed above for Grade 2 LVEF decrease. If symptomatic, permanently discontinue mirdametinib.
Grade 4 LVEF decrease (post-baseline LVEF <20%)	Permanently discontinue study treatment.
QTcF	
Grade 3 QTcF prolongation (absolute QTcF >500 msec or QTcF change from baseline >60 msec)	Repeat ECG in triplicate approximately 1 hour after the initial ECG and consult with a cardiologist. The three ECGs must be recorded in close succession and not more than 2 minutes apart, and after at least 5 minutes of quiet supine rest. Calculate the mean QTcF from the three ECGs. If the absolute QTcF is <480 msec or QTcF change from baseline is ≤30 msec on repeat ECG triplicate, and the cardiologist agrees, then mirdametinib may be re-started immediately at the same dose. If the absolute QTcF is >480 msec to ≤500 msec or QTcF change from baseline is >30 msec to ≤60 msec on repeat ECG triplicate, and the cardiologist confirms that the result is drug-related, then mirdametinib should be temporarily interrupted during the follow up by weekly repeat ECG triplicates. When the absolute QTcF is <480 msec or QTcF change from baseline is ≤30 msec on repeat ECG triplicate, then mirdametinib should be re-started at the next lower dose (see Table 5). If the absolute QTcF is >500 msec or QTcF change from baseline is >60 msec on repeat ECG triplicate, and the cardiologist confirms that the result is drug-related, then mirdametinib should be permanently discontinued.
TOTAL BILIRUBIN	
Grade 2 total bilirubin increase (>1.5x to 3.0x ULN if baseline was normal; >1.5x to 3.0x baseline if baseline was abnormal)	Interrupt mirdametinib until resolution to baseline, then • If resolved in ≤7 days, re-start mirdametinib at the same dose • If resolved >7 days, re-start mirdametinib at the next lower dose (see Table 5)
Grade 3 total bilirubin increase (>3.0x to 10.0x ULN if baseline was normal; >3.0x to 10.0x baseline if baseline was abnormal)	Interrupt mirdametinib until resolution to baseline, then • If resolved in ≤7 days, may re-start mirdametinib at the next lower dose (see Table 5) at the Investigator's discretion • If resolved >7 days, permanently discontinue mirdametinib
Grade 4 total bilirubin increase (>10.0x ULN if baseline was normal; >10.0x baseline if baseline was abnormal)	Permanently discontinue mirdametinib

AST or ALT	
Grade 3 AST or ALT increase (>5.0x to 20.0x ULN if baseline was normal; >5.0x to 20.0x baseline if baseline was abnormal)	Interrupt mirdametinib until resolution to Grade ≤1 (or Grade ≤2 if the subject has liver metastases). After resolution to Grade ≤1, re-start mirdametinib at the next lower dose (see Table 5).
Grade 4 AST or ALT increase (>20.0x ULN if baseline was normal; >20.0x baseline if baseline was abnormal)	Permanently discontinue mirdametinib
Potential DILI / Hy's Law (pending clinical adjudication)	
Total bilirubin increase ≥2.0x ULN and ALT or AST increase ≥3.0x ULN	Permanently discontinue mirdametinib. If clinical adjudication confirms DILI / Hy's Law, then report DILI as SAE.
OTHER	
Grade ≥ 3 hematologic toxicities or clinically significant Grade 2 hematologic abnormalities that do not resolve within 72 hours after initiation of medical management.	Interrupt dosing, after resolution to Grade ≤ 1, restart study treatment at the next lower dose following Table 5.
Grade ≥ 3 nonhematologic toxicity that is not controlled by optimal supportive medication.	Interrupt dosing; after resolution to Grade ≤ 1 or baseline, restart study treatment at the next lower dose following **Error! Reference source not found.**.
Other Grade 2 toxicity that is subjectively intolerable (except alopecia) and not controlled by optimal supportive medication.	Interrupt dosing; after resolution to Grade ≤ 1 or baseline, re-start study treatment at the same dose.
Recurrent subjectively intolerable toxicity (at least a week interruption on 2 occasions) that is not controlled by optimal supportive medication.	Interrupt dosing; after resolution to Grade ≤ 1 or baseline, restart study treatment at the next lower dose using **Error! Reference source not found.**. If toxicity is still intolerable, permanently discontinue study treatment (unless otherwise discussed with the Principal Investigator).

ADL=activities of daily living; LVEF=left ventricular ejection fraction

In the event a dose reduction is required, the study treatment total daily dose will be reduced as shown in Table 5:

Table 5 Mirdametinib Dose Reduction

Dose at the time of the event	Reduced dose
2 mg BID	1 mg BID
4 mg BID	2 mg BID
6 mg BID	4 mg BID

BID = twice daily

15.5 Side Effects of Fulvestrant

Fulvestrant (Faslodex) Injection is an estrogen receptor antagonist used to treat some hormone-related breast cancer. Fulvestrant is also used in postmenopausal women whose breast cancer has progressed after treatment with other anti-estrogen medication.

Per the package insert provided on the FDA website, the following adverse reactions (ARs) were calculated based on the safety analysis of the CONFIRM study comparing the administration of fulvestrant 500 mg intramuscularly once a month with fulvestrant 250 mg intramuscularly once a month[31]. The most frequently reported adverse reactions in the fulvestrant 500 mg group were injection site pain (11.6% of patients), nausea (9.7% of patients), and bone pain (9.4% of patients); the most frequently reported adverse reactions in the fulvestrant 250 mg group were nausea (13.6% of patients), back pain (10.7% of patients), and injection site pain (9.1% of patients).

The safety of fulvestrant 500 mg versus anastrozole 1 mg was evaluated in the FALCON study[32]. The data described below reflect exposure to fulvestrant in 228 out of 460 patients with HR-positive advanced breast cancer in postmenopausal women not previously treated with endocrine therapy who received at least one (1) dose of treatment in the FALCON study[32]. Permanent discontinuation associated with an adverse reaction occurred in 4 of 228 (1.8%) patients receiving fulvestrant and in 3 of 232 (1.3%) patients receiving anastrozole. Adverse reactions leading to discontinuation for those patients receiving fulvestrant included drug hypersensitivity (0.9%), injection site hypersensitivity (0.4%), and elevated liver enzymes (0.4%). The most common adverse reactions occurring in ≥5% of patients receiving 500 mg fulvestrant were: injection site pain, nausea, bone pain, arthralgia, headache, back pain, fatigue, pain in extremity, hot flash, vomiting, anorexia, asthenia, musculoskeletal pain, cough, dyspnea, and constipation.

Increased hepatic enzymes (ALT, AST, ALP) occurred in >15% of Fulvestrant users and were not dose-dependent.

Because Fulvestrant is administered intramuscularly, it should be given with caution in patients with bleeding diathesis, thrombocytopenia, or anticoagulant use. For further details regarding the safety profile of fulvestrant, refer to the fulvestrant package insert.

COMMON, SOME MAY BE SERIOUS In 100 people receiving Fulvestrant, more than 20 and up to 100 may have:
• Cough • Infection, especially when white blood cell count is low • Anemia which may require transfusion • Bruising, bleeding • Constipation • Diarrhea • Nausea • Vomiting • Loss of appetite • Pain • Tiredness • Flushing • Headache

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Fulvestrant, from 4 to 20 may have:
• Change in the heart rhythm • Swelling of the body • Shortness of breath • Blood clot which may cause swelling, pain • Liver damage which may cause yellow eyes and skin, swelling • Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat

15.6 Side Effects of Mirdametinib

As described in section 3.2, the ReNeu study (MEK-NF-201) utilized mirdametinib at a dose of 2 mg/m^2 BID (maximum dose = 4.0 mg BID). This is the dose of mirdametinib that we are using in this study.

Per the Investigator's Brochure for Mirdametinib, NF Study 106 was a Phase 2 study with mirdametinib conducted patients with a NF1-associated plexiform neurofibroma[6]. This Phase 2, open-label study evaluated 19 patients (range 16-39 years) with symptomatic or growing plexiform neurofibromas. Quantitative radiographic response in a target lesion after administration of mirdametinib at a dose of 2mg/m2 twice daily (maximum dose of 4 mg twice daily) on a 3 weeks on / 1 week off schedule was assessed. Mirdametinib was well tolerated with the most common dose limiting toxicity being acneiform rash in 3/19 patients (16%). Five subjects (26.3%) developed Grade 3 toxicities, with four of those subjects (21%) reporting a Grade 3 toxicity of pain. No subjects developed Grade 4 or higher toxicities and 1 subject experienced an SAE. This subject experienced Grade 2 Constipation, Abdominal distention, Cyst and Grade 3 Abdominal pain and Back pain. The Grade 2 Constipation, Grade 3 Abdominal pain, and Grade 3 Back pain were all considered possibly related to drug. No deaths were reported in this study.

The intermittent dosing schedule along with the maximum daily dose of 4 mg abrogated the ocular toxicities that have been reported with this compound. In addition, there were no reports of cardiac toxicities reported.

The table below contains a list of adverse reactions considered to be expected for regulatory reporting purposes for mirdametinib in advanced cancer studies.

System Organ Class	Adverse Reaction
Eye disorders	Retinal vein occlusion Retinal hemorrhage Optic ischemic neuropathy
Nervous system disorders	Dizziness Paraesthesia
Gastrointestinal disorders	Diarrhea
Skin and subcutaneous tissue disorders	Rash
Musculoskeletal and connective tissue disorders	Muscle disorder (neck drop) Muscular weakness
Psychiatric disorders	Confusional state

15.6.1 Known Drug Class Effects and Other Human Experience

In addition to side effects common to small-molecule kinase inhibitors such as rash, fatigue, and diarrhea, events unique to MEK inhibitors as a class have also been identified.

Ocular toxicity has been associated with MEK inhibitors. Although retinal vein occlusion has been reported, the more frequent underlying pathology for visual changes is central serous retinopathy. Unlike retinal vein occlusion, which can result in permanent loss of vision, central serous retinopathy usually resolves spontaneously after interruption of treatment and does not preclude retreatment.

Peripheral edema, particularly periorbital edema, and markedly elevated serum levels of CPK without underlying pathology have also been observed after MEK-inhibitor therapy. Dropped-head syndrome, an uncommon progressive weakness of neck extensor muscles that is characterized by focal non-inflammatory myopathy, moderately elevated serum CPK levels, lack of response to corticosteroids, and resolution after discontinuation of the agent, has been reported in patients exposed to MEK inhibitors. Cases of left ventricular dysfunction have also been reported after therapy with MEK inhibitors, as have CNS effects, including hallucinations and confusion, presumably attributable to a subset of MEK-targeted agents with good CNS penetration.

The drug manufacturer SpringWorks considers the available safety data from clinical studies of mirdametinib in patients with advanced cancer to be consistent with the known safety profile of other MEK inhibitors. The available data supports the continued assessment of the benefit/risk profile of mirdametinib in indications where an overactivation of the MAPK pathway exists. Reference the investigators brochure for more information.

16.0 PROTECTION OF HUMAN PARTICIPANTS

16.1 Privacy

MSK's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals/entities described in the Research Authorization form. A Research Authorization form must be approved by the IRB and Privacy Board (IRB/PB).

The consent indicates that individualized de identified information collected for the purposes of this study may be shared with other qualified researchers. Only researchers who have received approval from MSK will be allowed to access this information which will not include protected health information, such as the participant's name, except for dates. It is also stated in the Research Authorization that their research data may be shared with others at the time of study publication.

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice and applicable regulatory requirements.

Patient confidentiality is strictly held in trust by the sponsor and/or their designee(s), participating investigators, and any staff. This confidentiality includes the clinical information relating to patients, as well as any genetic or biological testing.

The principal investigator(s) at each center will ensure that the patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Patients must also be notified that they are free to discontinue from the study at any time. The patient should be given the opportunity to ask questions and allowed time to consider the information provided.

The patient's signed and dated informed consent must be obtained before conducting any study procedures. The principal investigator(s) must maintain the original signed ICF.

16.2 Data Management

Source documents will be maintained by MSK and used to enter data and complete the eCRFs in the clinical database. Medidata will be the Electronic Database Captures (EDC) for this study. Any entered, changed, and final data will be available with a validated audit trail report or data extract report. The eCRFs will be considered complete when all expected data has been entered and all discrepancies have been resolved or documented. The investigator must sign all eCRFs according the requirements of the EDC.

Patient records, source documents, IP inventory, regulatory documents, and other correspondence must be maintained in the appropriate study files according the ICH GCP, and these records will be retained for the period required by institution.

16.3 Quality Assurance

Before the start of the study, the study personnel will meet to discuss the protocol and data collection procedures, and applicable training of site personnel will be conducted. During the conduct of the study, site monitoring will occur (which will include on-site visits) in accordance with applicable regulations and Good Clinical Practices (GCP). During these contacts, the monitoring activities will include the following:

- Checking and assessing the progress of the study
- Reviewing study data collected to date for completeness and accuracy
- Conducting source document verifications by reviewing each patient's eCRF against source documents
- Identifying any issues and addressing resolutions
- Recording and reporting protocol deviations to the IRB
- Confirming that SAEs have been properly reported to the drug manufacturer (SpringWorks) and submitted to the IRB if appropriate

Upon completion of the study, the principal investigator will ensure all data and IP reconciliation is complete.

16.4 Data and Safety Monitoring

The Data and Safety Monitoring Plan utilized for this study will be aligned with the MSK DSM Plan, where applicable.

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan Kettering were approved by the National Cancer Institute in August 2018. The plans address the new policies set forth by the NCI in the document entitled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials."

There are several different mechanisms by which clinical studies are monitored for data, safety and quality. At a departmental/PI level there exists procedures for quality control by the research team(s). Institutional processes in place for quality assurance include protocol monitoring, compliance and data verification audits, staff education on clinical research QA and two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: *Data and Safety Monitoring Committee (DSMC)* for Phase I and II clinical trials, and the *Data and Safety Monitoring Board (DSMB)* for Phase III clinical trials, report to the Deputy Physician-in-Chief, Clinical Research.

The degree of monitoring required will be determined based on level of risk and documented.

The MSK DSMB monitors phase III trials and the DSMC monitors non-phase III trials. The DSMB/C have oversight over the following trials:

- MSK Investigator Initiated Trials (IITs; MSK as sponsor)
- External studies where MSK is the data coordinating center
- Low risk studies identified as requiring DSMB/C review

This clinical trial falls under the oversight of the DSMC.

The DSMC will initiate review following the enrollment of the first participant/or by the end of the year one if no accruals and will continue for the study lifecycle until there are no participants under active therapy and the protocol has closed to accrual. The DSMB will initiate review once the protocol is open to accrual.

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18.0 APPENDICES

I. Summary of Biospecimens
II. PK sample collection and shipping
III. Investigational Scan Considerations

Appendix I: Summary of Biospecimens

Specimen	Collection Time Points	Mandatory or Optional?	SOC or Research?	Collection Amount	Specimen Processing Location	Shipping Details	Analysis (reason for specimen collection)
Tumor tissue	SCR, On-Treatment	Screening (Mandatory), On Treatment (optional)	Research	**TISSUE SECTIONING REQUESTS ARE TO BE MADE IN BATCH ONLY** One core for FFPE, Diagnosis and MSK-Impact Two fresh cores for PDX generation (1 required and 1 optional) Three frozen cores for RNA-seq (1), protein lysates (1), and further sequencing (1 in reserve)	Diagnosis and MSK-Impact: MSK Pathology Lab PDX Generation: PDX Core Frozen cores: Chandarlapaty lab and Solit lab	N/A	Diagnosis Confirmation MSK-Impact PDX Generation Frozen tissue for assessment of RNA, protein, and further sequencing
Blood for SOC labs	SCR, all D1, EOT	Mandatory	SOC	Variable	MSK	N/A	CBC, chemistry, thyroid function, pregnancy test (as required)

Specimen	Collection Time Points	Mandatory or Optional?	SOC or Research?	Collection Amount	Specimen Processing Location	Shipping Details	Analysis (reason for specimen collection)
Plasma for ctDNA	C1D1, C2D1, imaging timepoint, EOT, Follow-up	Mandatory	Research	4x 10mL cell free DNA BCT tubes (screening) 2x 10mL cell free DNA BCT tubes (all other time points)	Department of Molecular Pathology at MSK	Ambient, shipped immediately by courier to Department of Molecular Pathology at MSK	ctDNA
Plasma for Pharmacokinetics	Refer to SOA (Table 3)	Mandatory	Research	1x 4 mL blood processed for plasma in K2EDTA tube	MSK; Process and store in freezer within 60 min of blood collection. Invert 8-10 times gently and immediately place on wet ice. Maintain samples on wet ice throughout processing. Centrifuge appx 3000 rpm for 10 min at 4deg C. Transfer 2 aliquots into 2- or 3-mL polypropylene screw-cap tubes for storage (-20deg C) and shipping (dry ice).	Q2 Solutions ATTN: Kimberly Norwood 19 Brown Rd Ithaca, NY 14850 T: +1 607.330.9871 Kimberly.Norwood@Q2LabSolutions.com Dry Ice shipment on Monday, Tuesday, or Wednesday.	PK analysis

Appendix II: PK sample collection and shipping

Plasma/Serum Collection for the PD-0325901 assay:

- Collection tube type needed for PK sample tubes with K2EDTA anticoagulant for blood collection. If possible, ≥4 mL of blood would be sufficient for analysis (we need at least 600 uL of plasma/sample).
- Preferred tube type for plasma is **Sarstedt order number 72.694.406** (2.0 mL SC Micro Tube PCR-PT, polypropylene, 10.8 mm diameter, 44 mm length). https://www.sarstedt.com/en/products/laboratory/screw-cap-micro-tubes-reaction-tubes/screw-cap-micro-tubes/product/72.694.406/
- temperature for storage and shipping: -20°c
- processing instructions: **collect plasma within 1 hour after draw blood. Samples should be stored on wet ice during processing.**
- flash freeze samples in an upright position and then transfer to a -20°c freezer as appropriate.
- shipment and storage temperature: storage temperature is 20°c freezer, samples should be shipped on dry ice

Some notes on shipping samples

Labeling

- Tube labels must be of a laminated, durable material
- Tube labels must include:
    - Barcode ID
    - Protocol/ Study #
    - Cycle/ Treatment #
    - Subject #
    - Day and timepoint
    - Matrix

Packaging: whenever possible, samples should be shipped in tube size appropriate white 9 x 9 storage boxes (VWR: Part Number 89214-766 (2 inch) or Part Number 89214-770 (3 inch)

An electronic manifest in an excel file format with the following data should be provided to Q2 labs:

- Protocol
- Site Number
- Subject Number
- Timepoint
- Collection Date
- Sample Type, i.e. Matrix

A paper manifest must be included in each sample shipment.

All samples must be frozen prior to packaging and during shipment.

Ship the plasma/serum sample aliquots per the shipment schedule on dry ice to:

Q-SQUARED SOLUTIONS
ATTN: Kimberly Norwood-Colwell
19 BROWN RD
ITHACA, NY 14850

Phone: +1 607.330.9871
Fax: +1 607.266.0749
Email: Kimberly.Norwood@Q2LabSolutions.com

Email manifest and shipment tracking information to the following:
Kimberly.Norwood@Q2LabSolutions.com and Jorge.Benitez@Q2LabSolutions.com

Shipment schedule:

- Domestic: Ship Monday, Tuesday, or Wednesday only to ensure arrival by Thursday/Friday
- The lab is not typically staffed on weekends (Saturday or Sunday) or holidays. Special arrangements must be made at least 2 weeks in advance if a weekend/holiday receipt is necessary. **A weekend/holiday receipt fee may be charged.**

Appendix III: Investigational Scan Considerations

Patients on study may have biopsies performed at screening and during treatment (within 7 days of C2D1). Patients may also have an investigational CT scan of the chest, abdomen and pelvis at screening (if performed sooner than clinically indicated). In addition, one of the CT scans performed prior to Cycle 11 (at a schedule of every 8 weeks), may be considered investigational depending on the patient's status. Patients undergoing investigational CT guided biopsies are exposed to an additional 0.626 Gy (+/- 0.132) dermatologically, an additional 29.9 mSv in for scan done in helical mode and an additional 18.9 mSv for scans done in axial mode. Patients undergoing investigational CT scans of the chest/abdomen/pelvis are exposed to an additional 1.5 rem.

It is estimated that each patient will have up to 2 additional scans for CT-guided biopsies and up to 2 additional diagnostic CT scans of the chest/abdomen/pelvis.

The informed consent will include the necessary risk language on contrast use and low-level radiation.