Academic and Community Cancer Research United (ACCRU)

Combination of MEK Inhibitor Binimetinib and CDK4/6 Inhibitor Palbociclib in KRAS and NRAS Mutant Metastatic Colorectal Cancers

For any communications regarding this protocol, please contact the person listed on the Protocol Resource page. This is a stand-alone document found on the ACCRU web site (www.ACCRU.org).

Study Chairs

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Statistician: [redacted]

√ Study contributor(s) not responsible for patient care.

Drug Availability

Commercial Agents: Trifluridine/Tipiracil (TAS-102), Binimetinib (MEK162) and Palbociclib -IND Exempt

Research Coordinating Center

Academic and Community Cancer Research United

[redacted]

Document History	**(effective date)**
Initial Version	April 22, 2019
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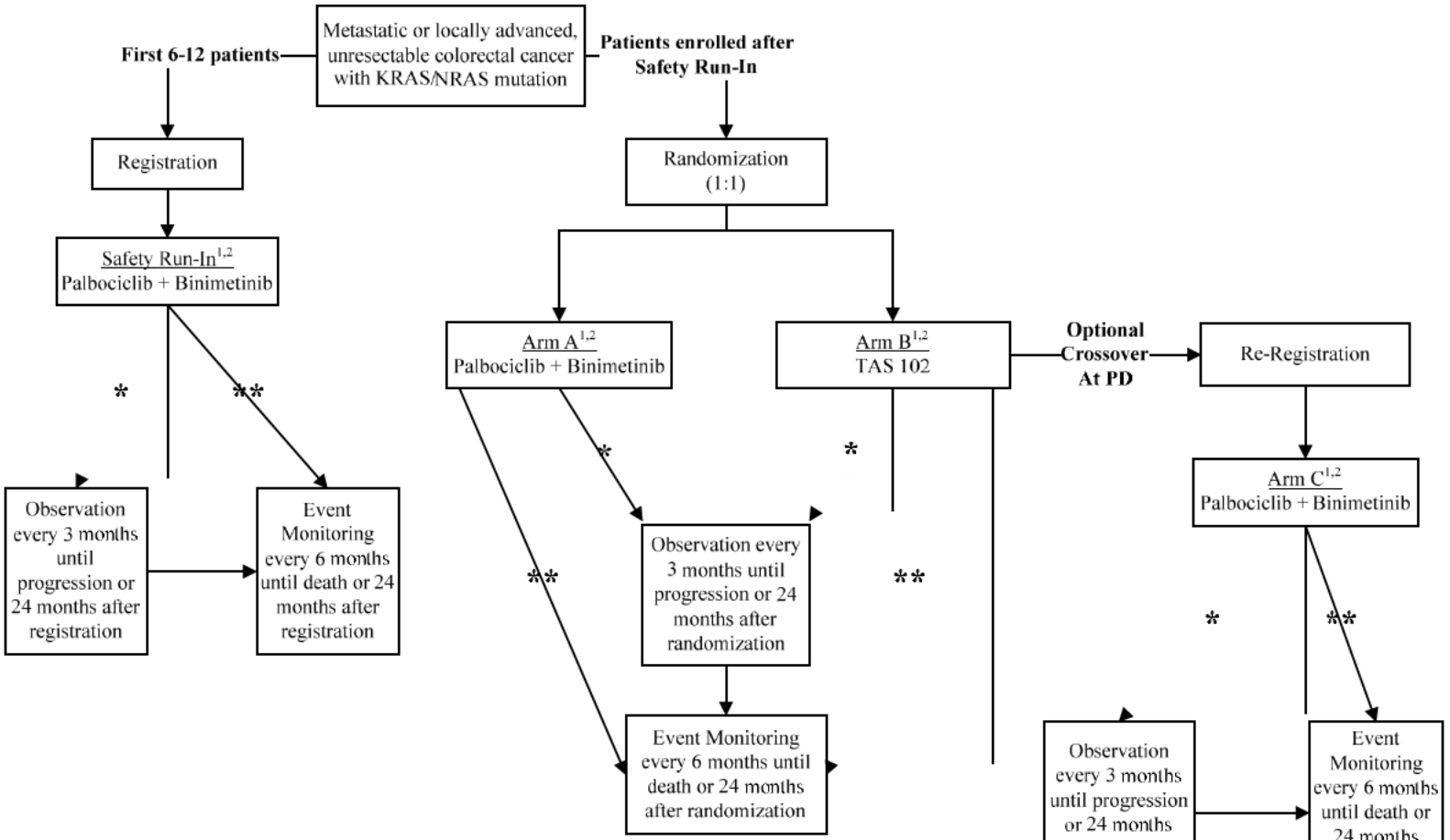
For first 6-12 patients during Part 1 (Safety Run-In): prior to discussing protocol entry with subjects, call the ACCRU Registration Office (507-284-4130) for dose level and to ensure that a place on the protocol is open to the patient.

Patient Schema



[1]Cycle length = 28 days; refer to Section 7.0 for dosing information
[2]Treat until progression or maximum 24 cycles

*Off-treatment for any reason **other than** disease progression, alternative therapy, or withdrawal/refusal

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Definitions:

Observation: Part of the Active Monitoring phase of a study; the time period following the active treatment phase when the participant continues to receive cycles of evaluation in compliance with the Test Schedule and will be required to return to the consenting site for protocol tests.

Event Monitoring: Not part of the Active Monitoring phase of a study; the time period when the participant is no longer following the protocol test schedule. During Event Monitoring, the data collection schedule is dictated by the protocol but the visit schedule is determined by clinical practice at each participating site. During the Event Monitoring Phase of the study, the participant is being monitored for key study events such as progression, new primaries, and death. Participants will not be required to return to the consenting site for study-related reasons or required to have research-related tests performed. Samples from biospecimens collected in the course of clinical care may be requested but cannot be required of the participant.

Generic name: Binimetinib Brand name(s): MEKTOVI Availability: RxCrossroads by McKesson Clinical Research Services	Generic name: Palbociclib Brand name(s): IBRANCE Availability: RxCrossroads by McKesson Clinical Research Services	Generic name: Trifluridine/Tipiracil (TAS-102) Brand name(s): LONSURF Availability: Commercially available

1.0 Background

1.1 KRAS and NRAS mutant colorectal cancers

Colorectal cancer (CRC) is the third most common cancer in men and women in the United States, afflicting approximately 4.8% of men and women during their lifetimes and causing an estimated 50,310 deaths in 2014. Mortality is primarily driven by the 20% of CRC patients with metastatic disease, who suffer 5-year overall survival (OS) of only 12.9% [1]. Patients with metastatic CRC have experienced improvements in median OS, from 14.2 months for those diagnosed in 1990-1997 to over 29 months for those diagnosed after 2004 [2]. Much of these improvements are attributable to development of novel therapies. Previously, only fluoropyrimidines like 5-fluorouracil were standard options for patients with CRC, but starting in the mid-2000s, increasing numbers of patients were treated with irinotecan, oxaliplatin, bevacizumab, and the monoclonal antibodies targeting the epidermal growth factor receptor (EGFR), and more widespread use of these agents contributed to improvements in survival [2]. Nevertheless, barring surgical resection of oligometastatic disease, inevitably metastatic cancers develop resistance to therapies, resulting in clinical progression and ultimately death. There remains a great unmet need to better understand biologic mechanisms of susceptibility to therapies and use this knowledge to personalize therapy choices for individual patients.

EGFR and proteins involved in its downstream signal transduction play important roles in oncogenesis and tumor progression in CRC. EGFR is a transmembrane receptor tyrosine kinase, with an ectodomain that can bind known ligands such as epidermal growth factor (EGF), transforming growth factor alpha (TGF-α), amphiregulin, epiregulin, heparin-binding EGF, betacellulin, and epigen. Upon ligand binding, EGFR homodimerizes to activate downstream intracellular signal transduction cascades, notably including the mitogen activated protein kinase (MAPK) pathway via RAS, RAF, and mitogen-activated protein kinase kinase (MEK), to ultimately promote cell proliferation and survival [3]. There are three RAS genes in humans encoding homologous proteins, *HRAS*, *NRAS*, and *KRAS* [4]. Mutations in exons 2, 3, and 4 of *KRAS* and *NRAS* are found in 37-43% of CRC patients [5],and contribute to oncogenesis by driving cell proliferation in a growth factor-independent fashion [3]. The RAS proteins are G proteins that are in active conformation when bound to guanosine triphosphate (GTP) and in inactive conformation when bound to guanosine diphosphate (GDP). Oncogenic *KRAS* mutations hinder hydrolysis of GTP to GDP and thus keep KRAS in an active conformation [4]. The active conformation of GTP-bound KRAS can then bind other effector proteins, such as the RAF family of serine/threonine kinases, to activate them and facilitate activation of MEK. MEK also functions as a kinase that, when active, phosphorylates and activates ERK, ultimately activating a variety of transcriptions factors to drive cell proliferation.

1.2 Rationale for combination MEK and CDK4/6 inhibitors in RAS mutant cancers

Although patients with *KRAS* and *NRAS* mutant metastatic CRC do not benefit from treatment with anti-EGFR monoclonal antibodies, these tumors are appealing targets for inhibition of signal transduction molecules downstream of RAS in the EGFR signaling cascade, such as MEK. Several preclinical studies have demonstrated that RAS mutated malignancies may be susceptible to MEK inhibitors, but that monotherapy with MEK inhibitors is unlikely to yield a durable and clinically meaningful response. Seven CRC cell lines with mutations in exon 4 of *KRAS* were found to rely on MEK activity for proliferation, as they had IC_{50} values <100 nM to the MEK inhibitor PD0325901 [6].

CRC cell lines with mutations in exon 2 of *KRAS* also demonstrated heterogeneous responses to MEK inhibitor monotherapy, with seven cell lines showing sensitivity to PD0325901 with IC_{50}<20 nM, and seven cell lines showing resistance to anti-proliferative effect [6]. Thus, in vitro data suggests that *KRAS* mutant CRC cell lines may be susceptible to MEK inhibitors, although there are additional mechanisms of resistance that need to be elucidated.

Several small molecule inhibitors of MEK have been in clinical trials in malignancies harboring mutations in *BRAF*, *KRAS*, or *NRAS*, including CRC. However, results with MEK inhibitor monotherapy have been unimpressive to date. Monotherapy with the MEK inhibitor trametinib (GSK1120212) in 12 *KRAS* mutated CRC patients yielded no responses. Four of the 12 patients had stable disease, with duration on study of 31, 28, 16, and 16 weeks [7]. Preclinical in vivo work and early phase clinical studies investigating combination MEK inhibitor and inhibitors of the PI3K/AKT/MTOR pathways have also been disappointing. For example, combination treatment with the MEK inhibitor selumetinib and the PI3K/MTOR inhibitor BEZ235 in murine patient derived xenografts from metastatic CRC patients showed no tumor responses [8].

Although MEK inhibitor monotherapy has not yielded significant responses in early clinical trials of *KRAS*-mutant CRC, it was able to yield significant duration of disease stability in one-third of *KRAS*-mutant CRC subjects. Combining MEK inhibitors with cyclin dependent kinase (CDK) 4/6 inhibitors is a rational combination to augment response. Alterations in cell cycle pathways including CDKs, p16INK4A, and retinoblastoma protein (Rb) are increasingly implicated in oncogenesis in RAS-mutated malignancies. Mitogenic signals lead to increased synthesis of cyclin D and binding to CDK4 or CDK6, which phosphorylate Rb. Hypophosphorylated Rb is bound to the transcription factor E2F, but phosphorylated Rb releases E2F, increasing transcription of genes promoting progression from G1 into S phase of the cell cycle. The protein p16INK4A induces senescence in G1 by leading to dissociation of the complex of cyclin D and CDK4/6. While loss of the Rb tumor suppressor is a common event in carcinogenesis, *RB1* mutations are very uncommon in CRCs. Non-silent *RB1* mutations are found in only about 2.7% of CRCs, which does not represent a significant increase over the expected background rate of mutations as detected by the MutSig algorithm [5]. Furthermore, since Rb is a tumor suppressor, both alleles of *RB1* would need to be mutated in order to result in loss of Rb, which is extremely uncommon. In fact, the majority of CRCs have higher amounts of Rb detectable by immunohistochemistry [9]. Nevertheless, loss of functional Rb is vital to maintain ongoing cell proliferation, via a mechanism independent of the PI3K/AKT/MTOR pathway [10]. RAS mutated malignancies often dysregulate the p16/CDK/Rb pathway upstream of Rb. Methylation of p16 and subsequent loss of expression is common in *KRAS* mutant CRCs[11], and concomitant p16 methylation and *KRAS* mutation is associated with worse prognosis in CRCs [12]. Thus, CDK4/6 inhibition to restore the tumor suppressor ability of intact Rb is a potential strategy to inhibit proliferation in RAS-mutated malignancies, particularly in combination with MEK inhibition, and there is accumulating preclinical evidence supporting this strategy.

Combination of MEK inhibitor and CDK4/6 inhibitor is a rational pairing in RAS mutant malignancies given the associations between the EGFR/MAPK pathway and the cell cycle machinery. Some of the activity of MEK inhibitors is likely mediated by affecting the cell cycle. LS1034 and CCCL-18 colon cancer cell lines, which both have mutations in *KRAS* A146T, demonstrated marked decrease in cyclin-D and hypophosphorylation of

Rb when treated with the MEK inhibitor PD0325901[6]. Mechanisms of resistance to MEK inhibitors may use alternative pathways to uncouple the cell cycle effects from MEK inhibition. For example, concomitant *PIK3CA* mutations and *KRAS* mutations in HCT-15 and DLD-1 cell lines were associated with lack of decrease in cyclin D1 level or G1 cell cycle arrest, suggesting that concomitant *PIK3CA* mutations may decouple cell cycle regulation from the MAPK pathway [13]. Combination of MEK inhibitor and CDK4/6 inhibitor has yielded strong evidence of efficacy in murine models of RAS-mutated malignancies as well. A genetically engineered mouse model utilizing inducible *NRAS* Q61K mutation leads to spontaneous formation of *NRAS*-mutant melanomas. In these models, monotherapy with the MEK inhibitor GSK1120212 only caused cytostatic effect but did not cause tumor regression, as extinction of the mutant *NRAS* did. In an unbiased screen to determine differentially expressed genes between the *NRAS*-extinguished mice and the MEK inhibitor-treated mice, genes involved in cell cycle regulation were most significant, with *CDK4* identified by pathway analysis as driving the differential gene regulation. Combination treatment with the CDK4/6 inhibitor palbociclib and either of the MEK inhibitors selumetinib or trametinib had synergistic effects in vivo in both the inducible *NRAS* melanoma model and in *NRAS*-mutant human melanoma xenograft models [14].

1.21 Preliminary data supporting combination MEK and CDK4/6 inhibitors in RAS mutant CRC

Indeed, the combination of MEK and CDK4/6 inhibitors has synergistic efficacy in *KRAS* mutant models of CRC in vitro and in vivo. Our work at the University of Texas MD Anderson Cancer Center demonstrated that the combination of binimetinib and palbociclib synergistically impaired cell viability and growth in vitro in a panel of 11 *KRAS* mutant CRC cell lines[15]. Reverse phase protein arrays performed on cell lines after 24 hours of treatment with binimetinib and palbociclib demonstrated that combination treatment synergistically decreased the level of phosphorylated ribosomal protein S6, which we confirmed on immunoblotting. Though this decrease was blunted in two cell lines with concomitant mutated *PIK3CA*, another cell line with mutated *PIK3CA* had brisk synergistic decrease of phosphorylated ribosomal protein S6, suggesting that *PIK3CA* mutation alone is not a biomarker of resistance to combination therapy. Additionally, the combination of palbociclib and trametinib caused tumor regression in *KRAS* mutant CRC cell line xenograft models and in KRAS mutant patient-derived xenograft (PDX) models, including notably a model with atypical *KRAS* A146T mutation [15]. Immunohistochemistry from the PDX model showed marked decrease in staining for the proliferative marker Ki67 with combination therapy. RPPA from PDX-derived tissues after 21 days of treatment showed greater downregulation of phospho-S6, polo-like kinase 1 (PLK1), and cyclin B1 (Ccnb1).

Figure 1.21

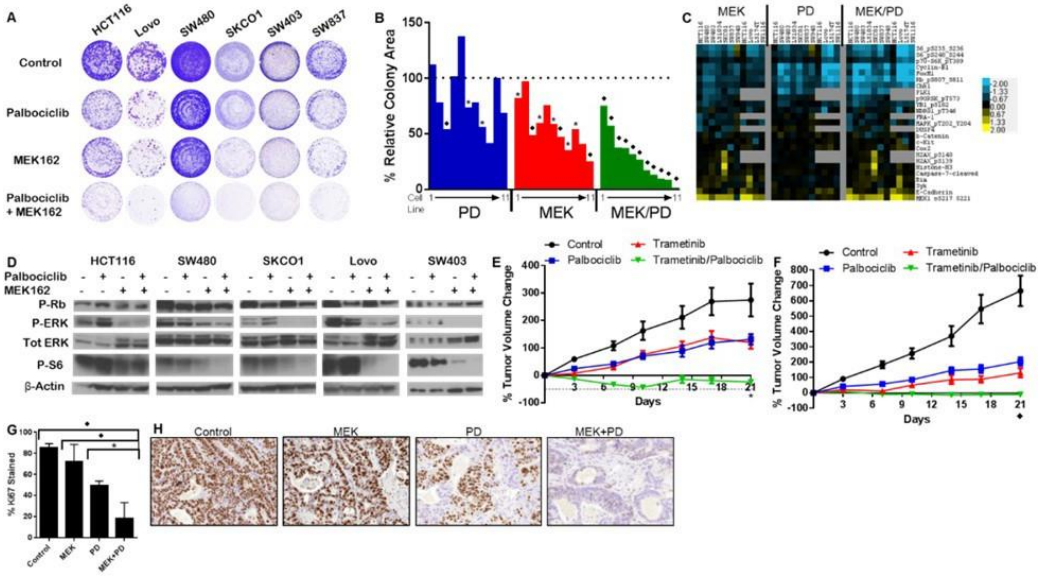

Figure 1.21: A, Clonogenic assay for six representative cell lines treated with palbociclib, binimetinib (MEK162), the combination, or with DMSO control for 10-14 days. B, Summary colony assay results for a panel of 11 KRAS mutant CRC cell lines treated with DMSO control, PD, MEK, or MEK/PD at concentrations approximating the IC50 for MEK monotherapy for 10-14 days. Results here are normalized to DMSO control. A waterfall plot is depicted showing values, with cell lines consistently depicted in the same order of T84, LS174T, SW1116, SW948, LS1034, HCT116, SW837, SW403, SW480, Lovo, and SKCO1. The data represent mean values for 3-4 independent experiments. * $p<0.05$, ♦ $p<0.006$. All p-values were generated by Student's t-test. C, Protein lysates were obtained from a panel of 9 KRAS mutant CRC cell lines after treatment with DMSO control, palbociclib (PD) 400 nM, MEK162 (MEK) 200 nM, or MEK162 200 nM + palbociclib 400 nM (MEK/PD) for 24 hours, and RPPA was performed. Protein levels were normalized to DMSO controls of each cell line, and a log2 heatmap of the most differentially expressed proteins was generated. D, Western blotting of the indicated antibodies for KRAS mutant cell lines HCT116, SW480, SKCO1, Lovo, and SW403 treated with palbociclib 400 nM and/or MEK162 200 nM for 24 hours. E, Lovo cell line xenografts were treated with vehicle control daily, palbociclib 100 mg/kg daily, trametinib 3 mg/kg every 2 days, or palbociclib 100 mg/kg daily + trametinib 3 mg/kg every 2 days, and tumor volume was measured twice per week. Data are mean ± SEM, with 10 mice/arm. * $p<0.01$ on day 21 for combination vs. each other arm by Student's t-test. F, Xenografts implanted with patient-derived CRC cells harboring *KRAS* A146T mutation were treated with vehicle control daily, palbociclib 100 mg/kg daily, trametinib 3 mg/kg every 2 days, or palbociclib 100 mg/kg daily + trametinib 3 mg/kg every 2 days, and tumor volume was measured twice per week. Data are mean ± SEM, with 9-10 mice/arm. ♦ $p<0.001$ on day 21 for combination vs. any other arm by Student's t-test. Dotted lines represent 50% decrease in tumor volume. G, Percentage of nuclear area stained by Ki67 antibody after KRAS A146T mutant PDX was treated with trametinib (MEK) alone, palbociclib (PD) alone, the combination (MEK/PD), or vehicle-treated control for 21 days. Data represent mean ± SD of samples from 3-4 mice. * $p\leq0.02$, ♦ $p<0.003$ by Student's t-test. H, Representative immunohistochemistry images for Ki67 staining.[15]

Additional work performed at the University of Michigan demonstrated the efficacy of palbociclib and trametinib in a wider variety of *KRAS* mutant CRC PDX models[16]. This work independently also found synergistic activity of

palbociclib and trametinib in vitro in HCT116 *KRAS*-mutant CRC cell lines and found that the combination potentiated cell cycle arrest. Additionally, 18/18 CRC-derived PDX models had RB expression, confirming that RB loss is an exceedingly rare event in CRC. Three KRAS mutant PDX models were tested for efficacy of the combination of trametinib and palbociclib in vivo, and objective responses were observed in all three models with combination trametinib/palbociclib. These models were varied in their genotypes and were $KRAS^{G12V}$ $PIK3CA^{WT}$, $KRAS^{G12D}$ $PIK3CA^{Q546L}$, and $KRAS^{Q61H}$ $PIK3CA^{E542K}$. [16]. The combination of trametinib and palbociclib indeed significantly reduced phospho-RB as seen on immunohistochemistry and immunoblotting. This strong preclinical evidence motivated the current clinical trial.

1.3 Investigational Agent Binimetinib (MEK162 / ARRY-438162)

Binimetinib is an oral, ATP non-competitive, highly selective inhibitor of MEK1/2. The compound has nanomolar activity against purified MEK enzyme (IC_{50} = 12 nM) and inhibits both basal and induced levels of ERK phosphorylation in numerous cancer cell lines with IC_{50} values as low as 5 nM. Binimetinib is undergoing clinical evaluation for the treatment of a range of *BRAF* V600E and RAS-mutated solid-tumor indications including melanoma, colorectal and biliary cancers. Binimetinib was approved by the U.S. Food and Drug Administration in June 2018 for treatment of unresectable or metastatic melanoma with a BRAF V600E or V600K mutation when combined with the BRAF inhibitor encorafenib.

Binimetinib potently inhibits the cell proliferation of mutant *BRAF* and RAS human cancer cell lines in vitro. Binimetinib has demonstrated in vitro and in vivo antitumor activity in several cancer models driven by the MAPK pathway (melanoma, CRC, pancreatic, non-small cell lung) with tumor regressions in some. Tumor growth inhibition correlated with decreased phospho-ERK levels in all tumor xenografts. Binimetinib has also shown significant anti-tumor activity in xenograft models in combination with the CDK 4/6 inhibitor LEE011, targeted agents like LGX818, RAF265, and standard-of-care agents such as cisplatin, 5 FU, and taxanes.

1.31 Preclinical pharmacology and toxicology

Preclinical toxicological studies indicated that binimetinib was well-tolerated. The most prominent findings were dose-related, reversible hair loss and/or scabbing in rats and dose-related, reversible loose or watery stools in monkeys. Administration of binimetinib to rats was associated with microscopic findings of soft tissue mineralization, skin effects, and minimal to mild clinical pathology changes. Gastric mucosal lesions were associated with binimetinib administration to rats at 100 mg/kg. In cynomolgus monkeys, administration of binimetinib was associated with soft stools, moderate clinical pathology changes in some animals and reversible histopathologic changes in the gastrointestinal tract.

There was no evidence of genotoxicity. Embryo-fetal development studies showed evidence of teratogenicity in rabbits (ventricular septal defects and outflow tract defects) and decreased ossification that is considered to be secondary to decreased fetal body weights at maternally toxic doses in rats.

1.32 Clinical Experience with Binimetinib

As of 20 January 2018, a total of 2816 healthy subjects and patients have received at least 1 dose of binimetinib, either as a single agent or in combination with other targeted agents, standard chemotherapy agents or immunomodulating agents. These patients constitute the binimetinib safety population, which includes 229 healthy subjects, 17 subjects with hepatic dysfunction, 6 subjects with renal dysfunction, 164 patients with rheumatoid arthritis and 2400 patients with advanced cancer.

Overall, binimetinib has demonstrated an acceptable safety profile. Available clinical data indicates a safety profile consistent with those reported for other allosteric MEK1/2 inhibitors. The adverse events observed are generally reversible and manageable by appropriate supportive medical care and/or dose modification. The most frequent treatment-related AEs in patients receiving binimetinib include rash, dermatitis acneiform, nausea, vomiting, diarrhea, peripheral edema, fatigue, and CPK elevation. Other clinically relevant toxicities are retinal events, increase of blood pressure, decrease of ejection fraction, and noninfectious pneumonitis which are monitored closely.

Important potential adverse effects associated with the administration of the binimetinib have been established primarily from safety data from the phase 3 COLUMBUS study in which it was combined with the *BRAF* inhibitor encorafenib in patients with unresectable or metastatic melanoma (https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210498lbl.pdf), and include:

- **Left ventricular dysfunction**: Symptomatic or asymptomatic decreases in ejection fraction occurred in 7% of patients, with Grade 3 left ventricular dysfunction occurring in 1.6% of patients.
- **Hemorrhage**: Hemorrhage occurred in 19% of patients, with events ≥ Grade 3 occurring in 3.2% of patients. Fatal intracranial hemorrhage in the setting of new or progressive brain metastases occurred in 1.6% of patients. The most frequent hemorrhagic events were gastrointestinal, including rectal hemorrhage (4.2%), hematochezia (3.1%), and hemorrhoidal hemorrhage (1%).
- **Venous thromboembolism**: Occurred in 6% of patients, including 3.1% of patients who developed pulmonary embolism.
- **Ocular toxicities**: Serous retinopathy is a class effect of MEK inhibitors. It is generally asymptomatic or mildly symptomatic and reversible [22]. Serous retinopathy occurred in 20% of patients. Symptomatic serous retinopathy occurred in 8% of patients with no cases of blindness. The median time to onset of the first event of serous retinopathy (all grades) was 1.2 months. RVO is a known class-related adverse reaction of MEK inhibitors and may occur in patients treated with binimetinib in combination with encorafenib. In patients with BRAF mutation-positive melanoma across multiple clinical trials, 0.1% of patients experienced RVO.
- **Pneumonitis/Interstitial Lung Disease:** Pneumonitis occurred in 0.3% of patients with BRAF mutation-positive melanoma across multiple clinical trials.

- **Hepatotoxicity**: The incidence of Grade 3 or 4 increases in liver function laboratory tests was 6% for alanine aminotransferase (ALT), 2.6% for aspartate aminotransferase (AST), and 0.5% for alkaline phosphatase. No patient experienced Grade 3 or 4 serum bilirubin elevation.
- **CK Elevation/Rhabdomyolysis**: Asymptomatic elevations of laboratory values of serum CK occurred in 58% of patients. Rhabdomyolysis was reported in 0.1% of patients with BRAF mutation-positive melanoma across multiple clinical trials.
- **Embryo-Fetal Toxicity**: Binimetinib can cause fetal harm when administered to pregnant women.

1.4 Investigational Agent Palbociclib (PD-0322991)

1.41 Preclinical pharmacology and toxicity

Altered glucose metabolism (glycosuria, hyperglycemia, decreased insulin) associated with changes in the pancreas (islet cell vacuolation), eye (cataracts, lens degeneration), teeth (degeneration/necrosis of ameloblasts in actively growing teeth), kidney (tubule vacuolation, chronic progressive nephropathy), and adipose tissue (atrophy) were identified in the 27-week repeat-dose toxicology study in rats and were most prevalent in males at doses ≥30 mg/kg/day (approximately 11 times the human exposure [AUC] at the recommended dose). Some of these findings (glycosuria/hyperglycemia, pancreatic islet cell vacuolation, and kidney tubule vacuolation) were present in the 15-week repeat-dose toxicology study in rats, but with lower incidence and severity. The rats used in these studies were approximately 7 weeks old at the beginning of the studies. Altered glucose metabolism or associated changes in pancreas, eye, teeth, kidney, and adipose tissue were not identified in dogs in repeat-dose toxicology studies up to 39 weeks duration.

Carcinogenicity studies have not been conducted with palbociclib.

Palbociclib was aneugenic in Chinese Hamster Ovary cells in vitro and in the bone marrow of male rats at doses ≥100 mg/kg/day for 3 weeks. Palbociclib was not mutagenic in an in vitro bacterial reverse mutation (Ames) assay and was not clastogenic in the in vitro human lymphocyte chromosome aberration assay.

In a fertility study in female rats, palbociclib did not affect mating or fertility at any dose up to 300 mg/kg/day (approximately 4 times human clinical exposure based on AUC) and no adverse effects were observed in the female reproductive tissues in repeat-dose toxicity studies up to 300 mg/kg/day in the rat and 3 mg/kg/day in the dog (approximately 6 times and similar to human exposure [AUC], at the recommended dose, respectively).

The adverse effects of palbociclib on male reproductive function and fertility were observed in the repeat-dose toxicology studies in rats and dogs and a male fertility study in rats. In repeat-dose toxicology studies, palbociclib-related findings in the testis, epididymis, prostate, and seminal vesicle at ≥30 mg/kg/day in rats and ≥0.2 mg/kg/day in dogs included decreased organ weight, atrophy or degeneration, hypospermia, intratubular cellular debris, lower sperm motility and

density, and decreased secretion. Partial reversibility of male reproductive organ effects was observed in the rat and dog following a 4- and 12-week non-dosing period, respectively. These doses in rats and dogs resulted in approximately ≥10 and 0.1 times, respectively, the exposure [AUC] in humans at the recommended dose. In the fertility and early embryonic development study in male rats, palbociclib caused no effects on mating but resulted in a slight decrease in fertility at 100 mg/kg/day with projected exposure levels [AUC] of 20 times the exposure in humans at the recommended dose.

1.42 Clinical Experience with Palbociclib

The most extensive clinical trials of palbociclib to date have been performed in combination with letrozole or fulvestrant in hormone receptor positive breast cancer patients.

In a study of palbociclib 125 mg/day plus letrozole 2.5 mg/day versus letrozole alone, in which 83 out of 160 patients with ER-positive, HER2-negative advanced breast cancer received at least 1 dose of treatment with palbociclib/letrozole, the median duration of treatment for palbociclib was 13.8 months while the median duration of treatment for letrozole on the letrozole-alone arm was 7.6 months. Dose reductions due to an adverse reaction of any grade occurred in 36% of patients receiving palbociclib plus letrozole. Permanent discontinuation associated with an adverse reaction occurred in 7 of 83 (8%) patients receiving palbociclib plus letrozole and in 2 of 77 (3%) patients receiving letrozole alone. Adverse reactions leading to discontinuation for those patients receiving palbociclib plus letrozole included neutropenia (6%), asthenia (1%), and fatigue (1%). The most common adverse reactions (≥10%) of any grade reported in patients in the palbociclib plus letrozole arm were neutropenia, leukopenia, fatigue, anemia, upper respiratory infection, nausea, stomatitis, alopecia, diarrhea, thrombocytopenia, decreased appetite, vomiting, asthenia, peripheral neuropathy, and epistaxis. The most frequently reported serious adverse reactions in patients receiving palbociclib plus letrozole were pulmonary embolism (3 of 83; 4%) and diarrhea (2 of 83; 2%). An increased incidence of infections was observed in the palbociclib plus letrozole arm (55%) compared to the letrozole alone arm (34%). Febrile neutropenia has been reported in the palbociclib clinical program, although no cases were observed in this study. Grade ≥3 neutropenia was managed by dose reductions and/or dose delay or temporary discontinuation consistent with a permanent discontinuation rate of 6% due to neutropenia.

In another study of palbociclib 125 mg/day plus fulvestrant 500 mg versus placebo plus fulvestrant, in which 345 out of 517 patients with HR-positive, HER2-negative advanced or metastatic breast cancer received at least 1 dose of treatment with palbociclib/fulvestrant, dose reductions due to an adverse reaction of any grade occurred in 36% of patients receiving palbociclib plus fulvestrant. Permanent discontinuation associated with an adverse reaction occurred in 19 of 345 (6%) patients receiving palbociclib plus fulvestrant, and in 6 of 172 (3%) patients receiving placebo plus fulvestrant. Adverse reactions leading to discontinuation for those patients receiving palbociclib plus fulvestrant included fatigue (0.6%), infections (0.6%), and thrombocytopenia (0.6%). The most common adverse reactions (≥10%) of any grade reported in patients in the

palbociclib plus fulvestrant arm were neutropenia, leukopenia, infections, fatigue, nausea, anemia, stomatitis, headache, diarrhea, thrombocytopenia, constipation, vomiting, alopecia, rash, decreased appetite, and pyrexia. The most frequently reported serious adverse reactions in patients receiving palbociclib plus fulvestrant were infections (3%), pyrexia (1%), neutropenia (1%), and pulmonary embolism (1%).

1.5 Control Agent Trifluridine/Tipiracil (TAS-102)

1.51 Preclinical pharmacology and toxicity

TAS-102 is an orally administered chemotherapeutic drug comprised of the combination of trifluridine, a cytotoxic thymidine-based nucleic acid analogue, and tipiracil, a thymidine phosphorylase inhibitor that prevents overly rapid degradation of trifluridine to allow for therapeutic plasma concentrations for longer durations. No long-term studies evaluating the carcinogenic potential of trifluridine/tipiracil in animals have been performed. Trifluridine/tipiracil was genotoxic in a reverse mutation test in bacteria, a chromosomal aberration test in mammalian-cultured cells, and a micronucleus test in mice. Animal studies did not indicate an effect of trifluridine/tipiracil on male fertility in rats. Dose-related increases in the corpus luteum count and implanted embryo count were observed, but female fertility was not affected.

1.52 Clinical experience with TAS-102

TAS-102 is currently FDA approved for the treatment of metastatic CRC after prior treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF biologic therapy, and an anti-EGFR therapy if wild-type in RAS. In a randomized (2:1), double-blind, placebo-controlled trial, 533 patients (median age 63 years; 61% men; 57% White, 35% Asian, 1% Black) with previously treated metastatic colorectal cancer received TAS-102 as a single agent at a dose of 35 mg/m^2/dose administered twice daily on Days 1 through 5 and Days 8 through 12 of each 28-day cycle. The mean duration of TAS-102 therapy was 12.7 weeks. The median progression-free survival on this trial was 2.0 months (95% confidence interval 1.9-2.1 months)[17]. These results were also true in the *KRAS* mutant subgroup (n=407), with median PFS of 1.9 mo [18]. The most common adverse drug reactions or laboratory abnormalities (all Grades and greater than or equal to 10% in incidence) in patients treated with TAS-102 at a rate that exceeds the rate in patients receiving placebo were anemia, neutropenia, asthenia/fatigue, nausea, thrombocytopenia, decreased appetite, diarrhea, vomiting, abdominal pain, and pyrexia. In the study, 3.6% of patients discontinued TAS-102 for an adverse event and 13.7% of patients required a dose reduction. The most common adverse reactions leading to dose reduction were neutropenia, anemia, febrile neutropenia, fatigue, and diarrhea.

2.0 Goals

2.1 Primary Objective

2.11 The primary objective is to compare the progression-free survival (PFS) between those randomized to palbociclib/binimetinib and those randomized to TAS-102

in patients with refractory *KRAS*- or *NRAS*-mutant metastatic CRC.

2.2 Secondary Objectives

2.21 To compare the overall response rate by RECIST 1.1 criteria between those randomized to palbociclib/binimetinib and those randomized to TAS-102 in patients with refractory *KRAS*- or *NRAS*-mutant metastatic CRC.

2.22 To compare the overall survival (OS) between those randomized to palbociclib/binimetinib and those randomized to TAS-102 in patients with refractory *KRAS*- or *NRAS*-mutant metastatic CRC.

2.23 To determine the safety and tolerability of the recommended phase II dose of palbociclib in combination with binimetinib in patients with refractory KRAS- or NRAS-mutant metastatic CRC.

2.3 Correlative Research

2.31 To determine the tumor mutational profiles that characterize groups of patients that predict for response or resistance to combination of palbociclib/binimetinib.

2.32 To determine the correlation between circulating tumor DNA and tumor response or resistance to therapy with palbociclib/binimetinib or TAS-102.

2.33 To determine the association between Consensus Molecular Subtype based on gene expression profiling and response or resistance to combination of palbociclib/binimetinib.

3.0 Patient Eligibility (Safety Run-In and Randomized Phase II)

NOTE: Waivers to eligibility criteria are not allowed per ACCRU policy.

For first 6-12 patients during Part 1 (Safety Run-In): Prior to discussing protocol entry with subjects, call the ACCRU Registration Office (507-284-4130) for dose level and to ensure that a place on the protocol is open to the patient.

3.1 Inclusion Criteria

3.11 Age ≥18 years.

3.12 Histological confirmation of colorectal cancer that is metastatic and/or unresectable.

3.13 Documented mutation in *KRAS* or *NRAS* (codon 12, 13, 59, 61, 117, or 146) in tumor tissue from primary or metastatic site, tested by a CLIA-certified laboratory.

3.14 Measurable disease as defined in Section 11.0.

3.15 ECOG Performance Status (PS) of 0 or 1.

NOTE: Form is available on the ACCRU web site.

3.16 Previously treated with fluoropyrimidine, oxaliplatin, and irinotecan based chemotherapy, and an anti-VEGF biological therapy

3.17 The following laboratory values obtained ≤14 days prior to registration/randomization unless otherwise noted.

- Absolute neutrophil count (ANC) ≥1.5 x 10^9/L
- Platelet count ≥75 x 10^9/L without transfusions
- Hemoglobin (Hgb) ≥9 g/dL
- Total bilirubin ≤1.5 x upper limit of normal (ULN)
- Aspartate transaminase (AST) and alanine aminotransferase (ALT) ≤2.5 x ULN; ≤5.0 x ULN if known liver metastases
- Serum creatinine ≤1.5 mg/dL OR calculated creatinine clearance ≥50 mL/min using the Cockcroft-Gault formula below:

Cockcroft-Gault Equation:	
Creatinine clearance for males =	(140 - age)(weight in kg) / (72)(serum creatinine in mg/dL)
Creatinine clearance for females =	(140 - age)(weight in kg)(0.85) / (72)(serum creatinine in mg/dL)

3.18 Negative serum β-HCG pregnancy test done ≤7 days prior to registration/randomization for women of childbearing potential only.

3.19a Able to swallow capsules with no surgical or anatomic conditions that would preclude the patient from swallowing and absorbing oral medications.

3.19b Able and willing to provide informed written consent and able to comply with protocol requirements.

3.19c Able and willing to return to enrolling institution for follow-up (during the Active Monitoring Phase of the study).

NOTE: During the **Active Monitoring** Phase of a study (i.e., active treatment and observation), participants must be willing to return to the consenting institution for follow-up.

3.19d Willing to provide blood and tissue samples for mandatory correlative research

purposes (see Sections 6.0, 14.0, and 17.0).

3.19e Patient is deemed by the Investigator to have the initiative and means to be compliant with the protocol (treatment and follow-up).

3.2 Exclusion Criteria

3.21 Prior treatment with drug targeting BRAF, MEK, ERK, or CDK family.

NOTE: For the purpose of this protocol, prior treatment with regorafenib is allowed.

3.22 Prior treatment with trifluridine/tipiracil (TAS-102).

3.23 Pregnant or nursing (lactating women), where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test.

3.24 Women of child-bearing potential.

NOTE: defined as all women physiologically capable of becoming pregnant, **unless** they agree to use highly effective methods of contraception throughout the study and for 8 weeks after study drug discontinuation. Refer to Appendix III: Study Contraception Guidelines for acceptable forms of highly effective methods of contraception.

NOTE: Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation ≥42 days prior to registration/randomization. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment is she considered not of child bearing potential.

3.25 Sexually active males.

NOTE: unless they agree to use highly effective methods of contraception throughout the study and for 12 weeks after study drug discontinuation and should not father a child in this period. Refer to Appendix III: Study Contraception Guidelines for acceptable forms of highly effective methods of contraception.

3.26 Any symptomatic brain metastasis.

NOTE: Patients previously treated or untreated for this condition who are asymptomatic in the absence of corticosteroid and anti-epileptic therapy are allowed. Brain metastases must be stable for ≥ 4 weeks prior to registration/randomization, with imaging (e.g., magnetic resonance imaging [MRI] or computed tomography [CT]) demonstrating no current evidence of progressive brain metastases at registration/randomization.

3.27 Prior treatment ≤21 days prior to registration/randomization with any other chemotherapy, small molecule inhibitor (e.g. regorafenib), monoclonal antibody, immunotherapy, or radiotherapy.

NOTE: All toxicities from prior therapy must be ≤ Grade 1 (or ≤ Grade 2 for peripheral neuropathy or alopecia).

3.28 Impaired cardiovascular function or clinically significant cardiac diseases, including any of the following:

- History of acute coronary syndromes (including myocardial infarction, unstable angina, coronary artery bypass grafting, coronary angioplasty, or stenting) <6 months prior to registration/randomization.
- Symptomatic chronic heart failure (i.e. Grade 2 or higher), history or current evidence of clinically significant cardiac arrhythmia and/or conduction abnormality <6 months prior to registration/randomization except atrial fibrillation and paroxysmal supraventricular tachycardia.
- Left ventricular ejection fraction (LVEF) <50% as determined by a multigated acquisition (MUGA) scan or echocardiogram ≤28 days prior to registration/randomization.

3.29a Uncontrolled hypertension, defined as persistent elevation of systolic blood pressure ≥150 mmHg or diastolic blood pressure ≥100mmHg despite current therapy.

3.29b History of thromboembolic or cerebrovascular events ≤ 12 weeks prior registration/randomization. Examples include transient ischemic attacks, cerebrovascular accidents, hemodynamically significant (i.e. massive or sub-massive) deep vein thrombosis or pulmonary emboli.
Note: Patients with either deep vein thrombosis or pulmonary emboli that does not result in hemodynamic instability are allowed to enroll as long as they are on a stable dose of anticoagulants for at least 4 weeks.
Note: Patients with thromboembolic events related to indwelling catheters or other procedures may be enrolled.

3.29c Known history of acute or chronic pancreatitis ≤ 6 months prior to registration/randomization.

3.29d Known positive serology for HIV (human immunodeficiency virus), active hepatitis B, and/or active hepatitis C infection.

3.29e Patients who have neuromuscular disorders that are associated with elevated CPK (e.g. inflammatory myopathies, muscular dystrophy, amyotrophic lateral sclerosis, spinal muscular atrophy).

3.29f History of chronic inflammatory bowel disease or Crohn's disease requiring medical intervention (immunomodulatory or immunosuppressive medications or surgery) ≤12 months prior to registration/randomization.

3.29g Impaired GI function or disease that may significantly alter the absorption of binimetinib or palbociclib (e.g., ulcerative disease, uncontrolled vomiting, malabsorption syndrome, small bowel resection with decreased intestinal absorption) in the opinion of the investigator.

3.29h History or current evidence of retinal vein occlusion (RVO) or current risk factors to RVO (e.g. uncontrolled glaucoma or ocular hypertension, history of hyperviscosity or hypercoagulability syndromes).

3.29i Leptomeningeal disease.

3.29j Known hypersensitivity to the components of study drugs or its analogs.

3.29k Known medical, psychiatric, substance abuse, or cognitive disorder that may compromise the patient's ability to understand the patient information, give informed consent, comply with the study protocol or complete the study.

3.29l Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements in the opinion of the investigator.

3.29m Patients who have undergone major surgery ≤21 days prior to registration/randomization or who have not recovered from side effects of such procedures.

3.29n Any other co-morbid, systemic illnesses or other severe concurrent disease which, in the judgment of the investigator, would make the patient inappropriate for entry into this study or interfere significantly with the proper assessment of safety and toxicity of the prescribed regimens.

3.29 o Previous or concurrent malignancy ≤3 years prior to registration/randomization with the following exceptions:

- adequately treated basal cell or squamous cell carcinoma of the skin
- superficial bladder cancer
- prostate intraepithelial neoplasm
- in situ carcinoma of the cervix
- other solid tumors treated curatively without evidence of recurrence for ≥3 years prior to registration/randomization

NOTE: If there is a history or prior malignancy, must not be receiving other specific anti-cancer treatment such as anti-estrogen, anti-androgen, or other tyrosine kinase inhibitor therapy.

3.3 Re-Registration Procedure for Part 2 Optional Crossover Participants

NOTE: Re-registration must occur ≤28 days from Part 2 TAS-102 disease progression (PD).

Upon confirmation of progression for patients in Arm B (TAS-102) of randomized portion of the trial, patients may elect to cross-over to treatment with binimetinib + palbociclib as long as the following criteria are met:

3.31 Crossover Inclusion Criteria

3.311 Age ≥18 years.

3.312 Histological confirmation of colorectal cancer that is metastatic and/or unresectable.

3.313 Documented mutation in *KRAS* or *NRAS* (codon 12, 13, 59, 61, 117, or 146) in tumor tissue from primary or metastatic site, tested by a CLIA-certified laboratory.

3.314 Measurable disease as defined in Section 11.0.

3.315 ECOG Performance Status (PS) of 0 or 1.

3.316 Previously treated with fluoropyrimidine, oxaliplatin, and irinotecan based chemotherapy, and an anti-VEGF biological therapy.

3.317 The following laboratory values obtained ≤28 days of Re-registration unless otherwise noted

- Absolute neutrophil count (ANC ≥1.5 x 10^9/L)
- Platelet count ≥75 x 10^9/L without transfusion
- Hemoglobin (Hgb) ≥9 g/dL
- Total bilirubin ≤1.5 x upper limit of normal (ULN)
- Aspartate transaminase (AST) and alanine aminotransferase (ALT) ≤2.5 x ULN; ≤5.0 x ULN if known liver metastases
- Serum creatinine ≤1.5 mg/dL OR calculated creatinine clearance ≥50 mL/min using the Cockcroft-Gault formula below:

Cockcroft-Gault Equation:

$$\text{Creatinine clearance for males} = \frac{(140 - \text{age})(\text{weight in kg})}{(72)(\text{serum creatinine in mg/dL})}$$

$$\text{Creatinine clearance for females} = \frac{(140 - \text{age})(\text{weight in kg})(0.85)}{(72)(\text{serum creatinine in mg/dL})}$$

3.318 Negative serum β-HCG pregnancy test done ≤7 days prior to Re-registration for women of childbearing potential only.

3.319a Able to swallow capsules with no surgical or anatomic conditions that would preclude the patient from swallowing and absorbing oral medications.

3.319b Able and willing to provide informed written consent and able to comply with protocol requirements.

3.319c Able and willing to return to enrolling institution for follow-up (during the Active Monitoring Phase of the study).

NOTE: During the **Active Monitoring** phase of a study (i.e., active treatment and observation), participants must be willing to return to the consenting institution for follow-up.

3.319d Willing to provide blood samples for mandatory correlative research purposes (see Section 14.0).

3.319e Patient is deemed by the Investigator to have the initiative and means to be compliant with the protocol (treatment and follow-up).

3.32 Crossover Exclusion Criteria

3.321 Prior treatment with drug targeting BRAF, MEK, ERK, or CDK family.

NOTE: For the purpose of this protocol, prior treatment with regorafenib is allowed.

3.322 Pregnant or nursing (lactating women), where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test.

3.323 Women of child-bearing potential.

NOTE: Defined as all women physiologically capable of becoming pregnant, **unless** they agree to use highly effective methods of contraception throughout the study and for 8 weeks after study drug discontinuation. Refer to Appendix III: Study Contraception Guidelines for acceptable forms of highly effective methods of contraception.

NOTE: Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation ≥42

days of Re-registration. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment is she considered not of child bearing potential.

3.324 Sexually active males.

NOTE: unless they agree to use highly effective methods of contraception throughout the study and for 12 weeks after study drug discontinuation and should not father a child in this period. Refer to Appendix III: Study Contraception Guidelines for acceptable forms of highly effective methods of contraception.

3.325 Any symptomatic brain metastasis.

NOTE: Patients previously treated or untreated for this condition who are asymptomatic in the absence of corticosteroid and anti-epileptic therapy are allowed. Brain metastases must be stable for ≥4 weeks, with imaging (e.g., magnetic resonance imaging [MRI] or computed tomography [CT]) demonstrating no current evidence of progressive brain metastases at Re-registration.

3.326 Impaired cardiovascular function or clinically significant cardiac diseases, including any of the following:

- History of acute coronary syndromes (including myocardial infarction, unstable angina, coronary artery bypass grafting, coronary angioplasty, or stenting) <6 months prior to Re-registration
- Symptomatic chronic heart failure (i.e., Grade 2 or higher), history or current evidence of clinically significant cardiac arrhythmia and/or conduction abnormality <6 months prior to Re-registration except atrial fibrillation and paroxysmal supraventricular tachycardia
- Left ventricular ejection fraction (LVEF) <50% as determined by a multigated acquisition (MUGA) scan or echocardiogram.

3.327 Uncontrolled hypertension, defined as persistent elevation of systolic blood pressure ≥150 mmHg or diastolic blood pressure ≥100 mmHg despite current therapy.

3.328 History of thromboembolic or cerebrovascular events ≤ 12 weeks prior re-registration. Examples include transient ischemic attacks, cerebrovascular accidents, hemodynamically significant (i.e. massive or sub-massive) deep vein thrombosis or pulmonary emboli.
Note: Patients with either deep vein thrombosis or pulmonary emboli that does not result in hemodynamic instability are allowed to enroll as long as they are on a stable dose of anticoagulants for at least 4 weeks.
Note: Patients with thromboembolic events related to indwelling catheters or other procedures may be enrolled.

3.329a Known history of acute or chronic pancreatitis ≤ 6 months prior to re-registration.

3.329b Known positive serology for HIV (human immunodeficiency virus), active hepatitis B, and/or active hepatitis C infection.

3.329c Patients who have neuromuscular disorders that are associated with elevated CPK (e.g., inflammatory myopathies, muscular dystrophy, amyotrophic lateral sclerosis, spinal muscular atrophy).

3.329d History of chronic inflammatory bowel disease or Crohn's disease requiring medical intervention (immunomodulatory or immunosuppressive medications or surgery) ≤12 months prior to Re-registration.

3.329e Impaired GI function or disease that may significantly alter the absorption of binimetinib or palbociclib (e.g., ulcerative disease, uncontrolled vomiting, malabsorption syndrome, small bowel resection with decreased intestinal absorption) in the opinion of the investigator.

3.329f History of retinal vein occlusion (RVO) or current risk factors to RVO (e.g., uncontrolled glaucoma or ocular hypertension, history of hyperviscosity, or hypercoagulability syndromes).

3.329g Leptomeningeal disease.

3.329h Known hypersensitivity to the components of study drugs or its analogs.

3.329i Known medical, psychiatric, substance abuse, or cognitive disorder that may compromise the patient's ability to understand the patient information, give informed consent, comply with the study protocol, or complete the study.

3.329j Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements in the opinion of the investigator.

3.329k Patients who have undergone major surgery ≤21 days prior to Re-registration or who have not recovered from side effects of such procedures.

3.329l Any other co-morbid, systemic illnesses or other severe concurrent disease which, in the judgement of the investigator, would make the patient inappropriate for entry into this study or interfere significantly with the proper assessment of safety and toxicity of the prescribed regimens.

3.329m Previous or concurrent malignancy ≤3 years prior to Re-registration with the following exceptions:

- adequately treated basal cell or squamous cell carcinoma of the skin
- superficial bladder cancer
- prostate intraepithelial neoplasm
- in situ carcinoma of the cervix
- other solid tumors treated curatively without evidence of recurrence for ≥3 years prior to Re-registration

NOTE: If there is a history or prior malignancy, must not be receiving other specific anti-cancer treatment such as anti-estrogen, anti-androgen, or other tyrosine kinase inhibitor therapy.

4.0 Test Schedule

Tests and procedures	Screening[1]	Active Treatment Phase[2]								
		Cycle length = 28 days						Optional Crossover at PD[20] (Arm B only)	End of Treatment (30-37 days from last dose)	For off treatment reasons other than PD or alternative therapy (For Patients with PD, follow Section 13.3 Event Monitoring)
		Cycle 1		Cycle 2		Cycles 3-24 (until PD)				
	≤28 days prior to Registration/ Randomization	Day 1 (Prior to Treatment)[3]	Day 15 (Prior to Tx)	Day 1 (Prior to Tx)	Day 15 (Prior to Tx)	Day 1 (Prior to Tx)	Day 15 (Prior to Tx)	≤28 days prior to Re-Registration		Observation† every 12 weeks (±7 days) until PD or 24 months from Registration/ Randomization/ Re-Registration
Medical history	X							X		
Physical exam, vitals, weight, ECOG PS	X	X	X	X		X		X	X	X
Assessment of concomitant medications	X	X	X	X		X		X	X	X
Height	X							X		
Adverse event assessment	X	X	X	X	X	X		X	X	X
Hematology: CBC with differential	X[4]	X	X	X	X	X	X[5,6]	X	X	X
Chemistry: SGOT (AST), ALT, alkaline phosphatase, total bilirubin, creatinine, calcium, phos, glucose, sodium, potassium, glucose, albumin, total protein, chloride, bicarbonate, BUN, and magnesium	X[4]	X		X		X		X	X	X
Creatine phosphokinase (CK/CPK) [8], troponin I or troponin T		X[7]	X[7]	X[7]	X[7]	X[7]			X[7]	X[7]
Carcinoembryonic antigen (CEA)		X		X		X			X	
HIV Ab, HBsAg, HCV Ab	X									

Serum β-HCG[9]	X	X		X		X		X		
Urinalysis		X[7]		X[7]		X[7]			X[7]	

Tests and procedures	Screening[1]	Active Treatment Phase[2]								
		Cycle length = 28 days						Optional Crossover at PD[21] (Arm B only) ≤28 days prior to Re-Registration	End of Treatment (30-37 days from last dose)	Observation† every 12 weeks (±7 days) until PD or 24 months from Registration/ Randomization/ Re-Registration For off treatment reasons other than PD or alternative therapy
		Cycle 1		Cycle 2		Cycles 3-24 (until PD)				
	≤28 days prior to Registration/ Randomization	Day 1 (Prior to Treatment)[3]	Day 15 (Prior to Tx)	Day 1 (Prior to Tx)	Day 15 (Prior to Tx)	Day 1 (Prior to Tx)	Day 15 (Prior to Tx)			
Tumor measurement[10]	X					X[11]		X		X[12]
Ophthalmic exam [13]	X[R]									
2-D echocardiogram or MUGA[14]	X[R]			X[7]		X[7,15]			X[7]	
Mandatory archival tumor tissue sample (see Section 17.1)[16,R]	X									
Mandatory blood sample (see Section 14.1) [17, R]		X[7]	X[7,18]	X[7]					X[7,19]	
Patient Medication Diaries			X	X	X	X			X	

† Observation Phase: Part of the Active Monitoring Phase of a study; the time period following the active treatment phase when the participant continues to receive cycles of evaluation in compliance with the Test Schedule. Participants will be required to return to the consenting site for follow-up.

1. Clinical testing may be used for screening purposes if within visit window. Patient must sign consent for any tests or procedures performed solely for the purpose of this research trial.
2. Unless otherwise specified, may be performed ±3 days of the day indicated on the table.
3. Protocol treatment must begin ≤21 days from Registration/Randomization/Re-Registration.
4. Must be completed ≤14 days prior to Registration/Randomization
5. Applicable to Arm B (TAS-102) patients ONLY
6. Performed Day 15 (±3 days) on Cycle 3 and subsequent cycles.
7. Not applicable to Arm B (TAS-102) patients. However, patients initially randomized to arm B who subsequently cross over to receive binimetinib/palbociclib do need to undergo the listed assessments.
8. Follow-up for total creatine phosphokinase (CPK) ≥3.0 X ULN will include weekly assessment of isoenzymes and myoglobin in blood or urine and troponin as applicable.
9. For women of childbearing potential only. Must be done ≤7 days prior to registration/randomization/re-registration and ≤72 hours prior to EACH cycle.
10. Tumor measurement must be performed using CT scan or MRI. The same imaging assessment method performed at baseline should be used at subsequent required timepoints.

11. Performed on Day 1 (±3 days) on Cycles 3, 5, 7, 9, and subsequent odd cycles.
12. In Observation, CT and/or MRI scans are required to obtain tumor measurements (every 12 weeks ±7 days after last on-treatment tumor assessment) until documented radiographic disease progression, death, withdrawal of consent, study closure, or 24 months from Registration/Randomization/Re-Registration, whichever occurs first.
13. Full ophthalmic examination including slit lamp examination, visual acuity testing, intraocular pressure (IOP), and indirect fundoscopy with attention to retinal abnormalities, especially RPED-like events and RVO. For patients with clinical suspicion of retinal abnormalities (e.g., photopsia, metamorphopsia, impairment of visual acuity, etc.) or RVO, additional assessments of optical coherence tomography (for RPED) and fluorescein angiography (for RVO) is **mandatory**. For patients on Arm A, any new or worsening visual impairment requires repeat ophthalmic evaluation.
14. Limited echocardiogram only to assess left ventricular ejection fraction is acceptable. MUGA scan is also permitted. Whichever modality was used at baseline should be continued throughout the study.
15. Performed on Cycle 5 Day 1 (±3 days) and then every 12 weeks after Cycle 5 Day 1 (±7 days).
16. Submission of tissue ≤60 days after registration/randomization. Refer to Section 17.0 for additional information.
17. Collect tubes as defined in Section 14.1. Kits are required for this collection.
18. Thymidine kinase activity assay only. Refer to Section 14.1
19. Mandatory blood samples should be collected as soon as possible upon knowledge of treatment cessation for reasons including but not limited to disease progression, withdrawal, etc. This sample can be collected ≤37 days after progression.
20. Re-registration for Arm B (TAS-102) patients interested in optional crossover must occur ≤28 days from documentation of progression. After re-registration, patients follow Test Schedule beginning with Cycle 1 Day 1. Crossover treatment will continue until progression for up to 24 cycles.

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5.0 Stratification and Grouping Factors

5.1 Stratification Factors (In Randomized groups only)

5.11 Mutation in KRAS codon 12/13: Yes vs No

5.12 Previously received regorafenib: Yes vs No

5.2 Grouping Factors

5.21 Group: Safety Run-in vs. Randomized

6.0 Registration/Randomization Procedures

6.1 Registration Procedure for Part 1: Safety Run-in

Prior to discussing protocol entry with subjects, call the ACCRU Registration Office ([redacted] for dose level and to ensure that a place on the protocol is open to the patient.

6.11 To register a patient, fax ([redacted]) a completed Eligibility Checklist to the Academic and Community Cancer Research United (ACCRU) Registration Office between 8 a.m. and 4:30 p.m. central time Monday through Friday.

6.2 Randomization Procedure for Part 2: Phase II

6.21 To register a patient, access the ACCRU web page at [redacted], go to the Application section and click on "Registration" and enter the registration/randomization application. The registration/randomization application is available 24 hours a day, 7 days a week. Back up and/or system support contact information is available on the Web site. If unable to access the Web site, call the Academic and Community Cancer Research United (ACCRU) Registration Office at [redacted] between the hours of 8 a.m. and 4:30 p.m. Central Time (Monday through Friday).

Instructions for the registration/randomization application are available on the above web page under the Study Resources section, "Application Training."

Prior to initiation of protocol study intervention, this process must be completed in its entirety and a ACCRU subject ID number must be available as noted in the instructions. It is the responsibility of the individual and institution registering the patient to confirm the process has been successfully completed prior to release of the study agent. Patient registration via the registration/randomization application can be confirmed in any of the following ways:

- Contact the ACCRU Registration Office [redacted]. If the patient was fully registered, the ACCRU Registration Office staff can access the information from the centralized database and confirm the registration.
- Refer to "Application Training" at www.ACCRU.org; click on "Registration, Installation & Entry Instructions".

6.22 Randomization Procedures: Phase II

6.221 The factors defined in Section 5.0 will be used as stratification factors.

6.222 After the patient has been registered into the study, the values of the stratification factors will be recorded, and the patient will be assigned to one of the following treatment groups using the Pocock and Simon dynamic allocation procedure which

balances the marginal distributions of the stratification factors between the treatment groups [21].

Arm A:
Binimetinib 30 mg twice daily + Palbociclib using recommended dose as determined in Part 1 component

Arm B:
TAS-102 35 mg/m^2 twice daily for days 1-5 and 8-12; off days 6-7 and 13-28

6.3 Safety Run-In and Phase II

6.31 Correlative Research

A mandatory correlative research component is part of this study, the patient will be automatically registered onto this component (see Sections 3.0, 14.0, and 17.0).

6.32 Prior to accepting the registration, the following will be verified:

- IRB approval at the registering institution
- Patient eligibility
- Existence of a signed consent form
- Existence of a signed authorization for use and disclosure of protected health information

6.33 Documentation of IRB approval must be on file in the Registration Office before an investigator may register any patients. Approvals should be uploaded using the online ACCRU Regulatory Management System (ARMS).

In addition to submitting initial IRB approval documents, ongoing IRB approval documentation must be on file (no less than annually) with ACCRU. Approvals should be uploaded using the online ACCRU Regulatory Management System (ARMS). If the necessary documentation is not submitted in advance of attempting patient registration, the randomization will not be accepted and the patient may not be enrolled in the protocol until the situation is resolved.

Submission of annual IRB approvals is required until the study has been closed through your IRB.

6.34 At the time of registration, the following will be recorded:

- Patient has/has not given permission to store and use his/her leftover tissue sample(s) for future research to learn about, prevent, or treat cancer.
- Patient has/has not given permission to store and use his/her leftover tissue sample(s) for future research to learn, prevent, or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).
- Patient has/has not given permission to store and use his/her leftover blood sample(s) for future research to learn about, prevent, or treat cancer.
- Patient has/has not given permission to store and use his/her leftover blood sample(s) for future research to learn, prevent, or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).
- Patient has/has not given permission for ACCRU to give his/her leftover tissue sample(s) to outside researchers.

- Patient has/has not given permission for ACCRU to give his/her leftover blood sample(s) to outside researchers.

6.35 Treatment cannot begin prior to registration and must begin ≤21 days after registration.

6.36 Pretreatment tests/procedures (see Section 4.0) must be completed within the guidelines specified on the test schedule.

6.37 All required baseline symptoms (see Section 10.0) must be documented and graded.

6.38 Treatment on this protocol must commence at an ACCRU institution under the supervision of a medical oncologist.

6.39 Blood draw kit is available on site.

6.4 Re-Registration Procedure for Part 2 Optional Crossover

NOTE: Re-registration must occur ≤28days from Part 2 TAS-102 disease progression (PD).

Upon confirmation of progression for patients in Arm B (TAS-102) of randomized portion of the trial, patients may elect to cross-over to treatment with binimetinib + palbociclib as long as the following criteria are met:

6.41 To re-register a patient, fax ([redacted]) or email ([redacted]) a completed crossover eligibility checklist to the Academic and Community Cancer Research United (ACCRU) Registration Office between 8 a.m. and 4:30 p.m. central time Monday through Friday.

6.42 Correlative Research

A mandatory correlative research component is part of this study, the patient will be automatically registered onto this component (see Sections 3.0 and 14.0).

6.43 Prior to accepting the registration, the following will be verified:

- IRB approval at the registering institution
- Patient eligibility
- Existence of a signed consent form
- Existence of a signed authorization for use and disclosure of protected health information

6.44 At the time of re-registration, the following will be recorded:

- Patient has/has not given permission to store and use his/her leftover blood sample(s) for future research to learn about, prevent, or treat cancer.
- Patient has/has not given permission to store and use his/her leftover blood sample(s) for future research to learn, prevent, or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).
- Patient has/has not given permission for ACCRU to give his/her leftover blood sample(s) to outside researchers.

6.45 Crossover treatment cannot begin prior to re-registration and must begin ≤21 days after crossover re-registration.

6.46 Treatment on this protocol must commence at an ACCRU institution under the supervision of a medical oncologist.

6.47 Blood draw kit is available on site.

7.0 Protocol Treatment

This is a Phase II, open-label, multicenter study designed to evaluate the safety, tolerability, and efficacy of the combination of binimetinib and palbociclib in patients with metastatic *KRAS* or *NRAS* mutant colorectal adenocarcinoma.

This study consist of two parts: Part 1 is a safety run-in to confirm the safety and tolerability of the doses of binimetinib and palbociclib determined in a preceding independent Phase I study; and Part 2 is a 1:1 randomized, open-label, Phase II clinical trial. The primary aim is to determine the clinical efficacy of the combination of palbociclib and binimetinib administered at the confirmed safe and tolerable dose as confirmed in Part 1, compared to the efficacy of standard of care therapy TAS-102 (trifluridine/tipiracil). Subjects randomized to the TAS-102 arm will have the option of crossing over to therapy with the combination of palbociclib and binimetinib upon progression.

7.1 Part 1: Safety Run-In

In Part 1, an initial cohort of 6 patients will receive palbociclib orally once daily on days 1-21 out of a 28 day cycle and binimetinib orally twice per day continuously per Dose Cohort 1 in the table below. The starting dose of palbociclib will be 100 mg orally once daily on days 1-21 out of a 28 day cycle (Dose Cohort 1; see Table 7.1).

Dose Cohort	Binimetinib Dose	Palbociclib Dose**
-1	30 mg BID daily	75 mg daily Days 1-21
1*	30 mg BID daily	100 mg daily Days 1-21

* Starting dose level

** Dose levels as listed in Table 1 are provisional, and actual dose levels will be determined per discussion with participating investigators during dose escalation teleconferences and may differ from those presented in Table 1. If the starting dose is not well tolerated, with 2 or more subjects experiencing excessive toxicity as defined in Section 7.15, then dose de-escalation will be studied to determine a safe and tolerable dose in this population of colorectal cancer patients.

7.11 Rules for Dose De-escalation

Dose de-escalation will be considered if Dose Cohort 1 per Table 7.1 proves excessively toxic, with 2 or more subjects having excessive toxicity as defined in Section 7.15. If this is the case, an additional 6 patients will be enrolled at Dose Cohort -1 with dose de-escalation.

Dose de-escalation will proceed per the tables below:

Dose Cohort 1

If there are…	Then…
0-1/6 subjects with excessive toxicity per Section 7.15	Proceed to Part II
≥2/6 subjects with excessive toxicity per Section 7.15	Enroll 6 subjects at Dose Cohort -1

Dose Cohort -1

If there are…	Then…
0-1/6 subjects with excessive toxicity per Section 7.15	Proceed to Part II
≥2/6 subjects with excessive toxicity per Section 7.15	STOP. Will need to reconsider dosing scheme

7.12 Patient Cohorts

Six patients will be treated at each dose level and observed for a minimum of 28 days from the day that treatment is initiated with binimetinib and palbociclib (Cycle 1 Day 1 to Cycle 1 Day 28), to assess toxicities, before new patients are treated. Doses will not be escalated in any individual patient.

All patients who receive the assigned treatment will be considered evaluable for toxicities to make a dose escalation decision.

If any patient in Part 1 withdraws from the study for any reason other than study drug toxicity or adverse event prior to completing one 28-day cycle of treatment with the study drugs, then he/she may be replaced. Otherwise, patients will not be replaced on study.

7.13 Reporting of Excessive Toxicities

Whenever a patient experiences toxicity that fulfills the criteria for excessive toxicity per Section 7.15 treatment with the study drugs will be interrupted and the toxicity will be followed up.

Investigators are to contact the ACCRU Operations Office (507-266-0800) as soon as any event comprising excessive toxicity per Section 7.15 occurs.

7.14 Re-Starting Patients on Treatment Following Excessive Toxicity event

For all toxicity grades, if the toxicity resolves to Grade 1 or baseline within 1 week of onset, treatment may be resumed at the same or a lower dose level at the investigator's discretion and following discussion with the study chair. For toxicities that result in treatment delays of more than 7 but not more than 21 days, treatment may be resumed at a lower dose level.

If a patient requires a dose interruption of >21 days from the intended day of the next scheduled dose, then the patient must be discontinued from the study. In this event, more frequent follow up as outlined in cycle 1 to monitor this toxicity may be appropriate.

7.15 Definitions of Excessive Toxicity during Safety Run-In

Definitions of excessive toxicity events reflect the known and expected toxicities of binimetinib and palbociclib. Events meeting criteria for excessive toxicity during the safety run-in will be defined as an adverse event or abnormal laboratory value assessed as at least possibly related to binimetinib and/or palbociclib that occurs during the first 28 days of treatment and fulfills any of the criteria in the table below. Toxicity is evaluated according to the NCI CTCAE v4.03.Whenever a patient experiences toxicity that fulfills the criteria for an excessive toxicity event, treatment with the study drug will be interrupted and the toxicity will be followed up.

For this protocol, excessive toxicity events will be defined as follows:

- Grade 3+ Febrile Neutropenia
- Grade 4 neutrophil count decreased > 7 consecutive days
- Grade 4 platelet count decreased
- Grade 4+ anemia
- Non-hematologic AE: Any Grade ≥4; Grade 3 requiring dose modification (dose reduction per section 8.0)
    - In addition:
        - Ejection fraction decreased: Grade ≥2
        - Retinal vascular disorder if comprised of retinal vein occlusion as assessed by ophthalmologist: Grade ≥2

If 2 or more patients (out of 6) experience any of the above, then we will a) de-escalate or b) temporarily stop the trial to re-assess the drug dose.

7.2 Part 2: Randomized Phase II Study and Optional Crossover

After confirming the optimal safe and tolerable doses of combination binimetinib and palbociclib in Part 1, eligible patients will be enrolled in an open-label, 1:1 randomized clinical trial of binimetinib/palbociclib (arm A) vs. TAS-102 monotherapy (arm B).

Subjects in arm B who discontinue study therapy due to disease progression per RECIST 1.1 criteria may choose to undergo crossover to treatment with binimetinib and palbociclib as in arm A. Those subjects who elect to cross over will need to re-register ≤28 days from progression on TAS-102 and will undergo monitoring as per subjects in arm A. Up to 24 cycles of crossover treatment is allowed.

Part 2 Treatment Schedule (Randomized)

Arm	Agent	Dose Level	Route	Day	Re-Rx#
A	Binimetinib	30 mg twice daily	Oral	Daily	Every 28 days
A	Palbociclib	100 mg once daily	Oral	Days 1-21	
B	TAS-102	35 mg/m^2 twice daily*	Oral	Days 1-5 and 8-12	

* Based on trifluridine component. Doses should be rounded to the nearest 5-mg increment. Dose should be capped at 80 mg per dose of trifluridine component, consistent with standard practice and the label. Use actual weight or estimated dry weight if fluid retention. No change in dose will be required for <10% weight change.

\# Plus or minus 3 days

Part 2 Treatment Schedule (Optional Crossover)

Agent	Dose Level	Route	Day	Re-Rx#
Binimetinib	30 mg twice daily	Oral	Daily	Every 28 days
Palbociclib	100 mg once daily	Oral	Days 1-21	

\# Plus or minus 3 days

7.21 Patients can be instructed in administration techniques and granted treatment independence with nursing staff approval.

7.22 Return to consenting institution

For this protocol, the patient must return to the consenting institution for evaluation at least

every 28 days during treatment and at 30-37 days after discontinuation of investigational therapy if in Arm A during observation (Active Monitoring Phase).

7.23 Treatment by a local medical doctor (LMD) is not allowed.

7.24 Missed/skipped/vomited doses will not be made up (i.e. the patient should not double their dose if the previous dose was missed).

8.0 Dosage Modification Based on Adverse Events

Strictly follow the modifications in this table for the first **two** cycles, until individual treatment tolerance can be ascertained. Thereafter, these modifications should be regarded as guidelines to produce mild-to-moderate, but not debilitating, side effects. If multiple adverse events are seen, administer dose based on greatest reduction required for any single adverse event observed. Reductions or increases to treatment given are based on adverse events observed in the preceding cycle.

If a subject experiences more than one toxicity, dose reduction should be according to the toxicity with the highest grade.

In the case of two or more toxicities of the same grade, the investigator may dose reduce according to that deemed most causally related to study treatment.

ALERT: ADR reporting may be required for some adverse events (See Section 10.0)

8.1 Binimetinib Dose Levels (Based on Adverse Events)

Patients will be monitored for adverse events at each visit with the NCI CTCAE version 4.03 used for all grading. All AEs should be followed at each visit until resolution or stabilization of the event, whichever comes first.

Appropriate clinical experts such as an ophthalmologist, cardiologist, or dermatologist should be consulted as deemed necessary.

Doses of binimetinib should be adjusted for AEs throughout the study. In general, doses should not be reduced or interrupted for Grade 1 AEs unless the AE is a specific treatment-related ocular AE. Treatment to control symptoms should be provided as appropriate. All dose modifications should be based on the worst preceding toxicity (CTCAE version 4.03).

An individual patient may have their dose of binimetinib reduced to the dose levels specified in Table 8.1 below. When the AE that resulted in a dose reduction improves to and remains stable at the patient's Baseline for a minimum of 14 days, the dose can be re-escalated to the next dose level at the discretion of the Investigator, provided there are no other concomitant binimetinib-related toxicities that would prevent drug re-escalation.

There is no limit to the number of times the patient can have their dose reduced or re-escalated (in 15 mg increments); however, no dose re-escalation is allowed after a dose reduction due to LVEF dysfunction.

Dose interruptions of more than 28 days are not allowed.

Refer to the tables in Section 8.4 for specific dose adjustment recommendations for binimetinib-induced toxicities.

Dose Level	Drug	Dose**
0*	Binimetinib (MEK 162)	30 mg BID

Dose Level	Drug	Dose**
-1	Binimetinib (MEK 162)	15 mg BID***

* Dose level 0 refers to the starting dose.
** Dose reduction should be based on the highest AE grade.
*** Dose reduction below 15 mg BID is not allowed

8.2 Palbociclib Dose Levels (Based on Adverse Events)

Dose Level	Drug	Dose
0*	Palbociclib	100 mg
-1	Palbociclib	75 mg

* Dose level 0 refers to the presumed starting dose.

Please refer to Section 8.5 for dose adjustment recommendations for palbociclib induced toxicities.

8.3 TAS-102 Dose Levels (Based on Adverse Events)

Dose Level	Drug	Dose
0*	TAS-102	35 mg/m^2
-1	TAS-102	30 mg/m^2
-2	TAS-102	25 mg/m^2
-3	TAS-102	20 mg/m^2

* Dose level 0 refers to the starting dose.

Please refer to Section 8.6 for dose adjustment recommendations for TAS-102 induced toxicities.

8.4 Binimetinib Dose Modifications Based on Specific Adverse Events

→ → Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03* unless otherwise specified ← ←			
CTCAE System/Organ/ Class (SOC)	ADVERSE EVENT	GRADE	ACTION**
BASED ON INTERVAL ADVERSE EVENT			
Investigations	Ejection fraction decreased	Asymptomatic grade 2: Absolute decrease in left ventricular ejection fraction of >10 through 20% compared to baseline and below the institutional lower limit of normal (LLN)	WITHHOLD for up to 28 days, with repeat LVEF evaluation every 2 weeks. RESUME at DECREASED dose level# if all the following are present: • LVEF at or above the LLN and • Absolute decrease from baseline is 10% or less and

→ → Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03* unless otherwise specified ← ←			
CTCAE System/Organ/ Class (SOC)	ADVERSE EVENT	GRADE	ACTION**
			• Patient is asymptomatic If the LVEF does not recover within 4 weeks, **permanently DISCONTINUE** treatment
Cardiac disorders	Left ventricular systolic dysfunction	Grade 3-4: Symptomatic due to drop in ejection fraction (either responsive to or refractory to intervention)	**Permanently DISCONTINUE** Closely monitor LVEF until resolution or up to 16 weeks
Investigations	Ejection fraction decreased	Grade 3-4: Absolute decrease in left ventricular ejection fraction of >20% compared to baseline and below the institutional lower limit of normal (LLN)	
Eye disorders	Retinopathy	Grade 1	• MAINTAIN dose level • Repeat ophthalmologic monitoring including visual acuity assessment and OCT within 10 (±3) days. If remains asymptomatic (Grade 1), maintain dose level and continue schedule of visual assessments established per protocol. If becomes symptomatic or visual acuity assessment shows grade 2, follow Grade 2 guidelines below
Eye disorders	Retinopathy	Grade 2	• Interrupt treatment • Repeat ophthalmologic monitoring including visual acuity assessment and OCT

→ → Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03* unless otherwise specified ← ←			
CTCAE System/Organ/ Class (SOC)	ADVERSE EVENT	GRADE	ACTION**
			within 10 (±3) days. If resolved to baseline or Grade ≤1, within 10 days, resume treatment at current dose level and continue schedule of visual assessments established per protocol. If not resolved to baseline or Grade ≤1, resume treatment at REDUCED dose level# and continue schedule of visual assessments established per protocol
Eye disorders	Retinopathy	Grade 3	• Interrupt treatment • Repeat ophthalmologic monitoring including visual acuity assessment and OCT within 10 (±3) days. If resolved to baseline or Grade ≤2, resume treatment at REDUCED dose level# and continue schedule of visual assessments established per protocol. If not resolved to baseline or Grade ≤2, continue to hold treatment and repeat ophthalmologic assessment in 10 (±3) days - If then resolves to baseline or Grade ≤2, resume treatment at REDUCED dose level# and continue schedule of visual assessments established per protocol. - If remains Grade 3, permanently

→ → Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03* unless otherwise specified ← ←			
CTCAE System/Organ/ Class (SOC)	ADVERSE EVENT	GRADE	ACTION**
			discontinue and proceed with immediate follow-up with ophthalmologic monitoring
Eye disorders	Retinopathy	Grade 4	• **Permanently DISCONTINUE** treatment • Initiate immediate follow-up with ophthalmic monitoring until stabilization or resolution
Eye disorders	Retinal vascular disorder	Retinal vein occlusion – ANY GRADE	**Permanently DISCONTINUE** treatment Continue ophthalmologic monitoring
Eye disorders	Uveitis	Grade 1 Asymptomatic; clinical or diagnostic observations only	• MAINTAIN dose level • Repeat ophthalmologic monitoring including visual acuity assessment and OCT within 10 (±3) days. If remains asymptomatic (Grade 1), maintain dose level and continue schedule of visual assessments established per protocol. If becomes symptomatic or visual acuity assessment shows grade 2, follow Grade 2 guidelines below
Eye disorders	Uveitis	Grade 2 Medical intervention indicated	• Interrupt treatment • Repeat ophthalmologic monitoring including visual acuity assessment and OCT within 10 (±3) days. If resolved to baseline or Grade ≤1, resume treatment at current dose level and continue

→ → Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03* unless otherwise specified ← ←			
CTCAE System/Organ/ Class (SOC)	ADVERSE EVENT	GRADE	ACTION**
			schedule of visual assessments established per protocol. If uveitis lasts >6 weeks, permanently discontinue.
Eye disorders	Uveitis	Grade 3 Posterior or pan-uveitis	• Interrupt treatment • Repeat ophthalmologic monitoring including visual acuity assessment and OCT within 10 (±3) days. If resolved to baseline or Grade ≤2, resume treatment at REDUCED dose level[#] If not resolved to baseline or Grade ≤2, continue to hold treatment and repeat ophthalmologic assessment in 10 (±3) days If remains Grade 3, permanently discontinue.
Eye disorders	Uveitis	Grade 4 Blindness (20/200 or worse) in the affected eye	• **Permanently DISCONTINUE** treatment • Initiate immediate follow-up with ophthalmic monitoring until stabilization or resolution
Eye disorders	Eye disorders – Other, specify	Grade 1-2	• MAINTAIN dose level • Increase frequency of ophthalmologist monitoring to at least every 14 days until stabilization or resolution • Images/results of the ophthalmic examinations (at a minimum, OCT, color fundus photography and/or fluorescein

→ → Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03* unless otherwise specified ← ←			
CTCAE System/Organ/ Class (SOC)	ADVERSE EVENT	GRADE	ACTION**
			angiography) must be made available upon Sponsor request.
Eye disorders	Eye disorders – Other, specify	Grade 3	• Interrupt treatment • Refer patient to ophthalmologist within 1 week: o If resolved to ≤ Grade 1 in ≤21 days, REDUCE[#] dose level o If not resolved to ≤ Grade 1 in ≤21 days, **permanently DISCONTINUE** treatment and initiate close follow-up with ophthalmic monitoring until stabilization or resolution Images/results of the ophthalmic examinations (at a minimum, OCT, color fundus photography and/or fluorescein angiography) must be made available upon Sponsor request.
Eye disorders	Eye disorders – Other, specify	Grade 4	• **Permanently DISCONTINUE** treatment • Initiate immediate follow-up with ophthalmic monitoring until stabilization or resolution
Gastrointestinal disorders	Diarrhea	Grade 1-2 (increase of up to 6 stools per day over baseline, or mild to moderate increase in ostomy output compared to baseline) IF uncomplicated (NO concomitant moderate to severe	Consider temporary interruption of binimetinib until resolved to Grade ≤ 1. Then resume treatment at current dose level of binimetinib.

→ → Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03* unless otherwise specified ← ←			
CTCAE System/Organ/ Class (SOC)	ADVERSE EVENT	GRADE	ACTION**
		abdominal cramping, grade ≥2 nausea/vomiting, decrease in performance status, fever, bleeding, or dehydration)	
Gastrointestinal disorders	Diarrhea	Grade 1-2 (increase of up to 6 stools per day over baseline, or mild to moderate increase in ostomy output compared to baseline) IF complicated (has concomitant moderate to severe abdominal cramping, grade ≥2 nausea/vomiting, decrease in performance status, fever, bleeding, or dehydration)	Interrupt dosing of binimetinib until resolved to Grade ≤ 1. Then resume treatment at reduced dose
Gastrointestinal disorders	Diarrhea	Grade 3-4	Interrupt dosing of binimetinib until resolved to Grade ≤ 1. Then resume treatment at reduced dose[#]
Gastrointestinal disorders	Nausea OR Vomiting	Grade 1-2	Maintain dose of binimetinib. Promptly initiate antiemetics
Gastrointestinal disorders	Nausea OR Vomiting	Grade 3	Ensure patient is taking optimal antiemetics. If optimal antiemetics do not control grade 3 nausea/vomiting, interrupt dosing with binimetinib until resolved to Grade ≤1. May resume treatment at same dose level if toxicity is unrelated to binimetinib, or else resume at reduced dose
Gastrointestinal disorders	Nausea OR Vomiting	Grade 4	Permanently discontinue
Investigations	Alanine aminotransferase increased	AST or ALT > ULN	Continue treatment with maintained dose level

→ → Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03* unless otherwise specified ← ←			
CTCAE System/Organ/ Class (SOC)	ADVERSE EVENT	GRADE	ACTION**
	OR Aspartate aminotransferase increased	to 3 × ULN if baseline was normal, or 1.5-3 x baseline value if had abnormal baseline)	
Investigations	Alanine aminotransferase increased OR Aspartate aminotransferase increased	(AST or ALT > 3 to 5 × ULN, or > 3 to 5 x baseline value if had abnormal baseline)	Maintain dose level of binimetinib Reassess within ≤ 14 days. If no improvement within 14 days, interrupt dosing of binimetinib until resolved to Grade ≤ 1 or to pretreatment/ baseline levels. Then resume treatment at current dose level binimetinib
Investigations	Alanine aminotransferase increased OR Aspartate aminotransferase increased	(AST or ALT > 5 to 20 × ULN if baseline was normal, or >5 to 20 × baseline if had abnormal baseline	<u>1st occurrence:</u> Interrupt dosing of binimetinib for up to 28 days until resolved to Grade ≤ 1. If improves to Grade 0-1 or to pretreatment/baseline levels, resume at 1 reduced dose level of binimetinib. If no improvement, PERMANENTLY DISCONTINUE binimetinib <u>2nd occurrence:</u> Consider permanently discontinuing binimetinib

Investigations	Alanine aminotransferase increased OR Aspartate aminotransferase increased	AST or ALT >20 × ULN if baseline was normal, or >20 × baseline if had abnormal baseline	PERMANENTLY DISCONTINUE binimetinib

→ → Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03* unless otherwise specified ← ←			
CTCAE System/Organ/ Class (SOC)	ADVERSE EVENT	GRADE	ACTION**
Investigations	CPK increased	Grade 1-2 (CPK > ULN – 5x ULN)	Maintain dose of binimetinib. Ensure patient is adequately hydrated. Closely monitor CK and serum creatinine. If total CK ≥ 3 × ULN, measure CK isoenzymes and myoglobin in blood or urine.
Investigations	CPK increased	Grade 3 (CPK >5 – 10 x ULN) WITHOUT renal impairment (serum creatinine <1.5x ULN or 1.5 x	If asymptomatic, maintain dose of binimetinib. Ensure patient is adequately hydrated. Monitor and measure isoenzymes and

→ → Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03* unless otherwise specified ← ←			
CTCAE System/Organ/ Class (SOC)	ADVERSE EVENT	GRADE	ACTION**
		baseline)	myoglobin in blood or urine and serum creatinine. If symptomatic (muscle pain/spasms/muscle weakness), interrupt dosing of binimetinib until resolved to CTCAE Grade ≤ 1 and monitor closely, then: •If resolved in ≤ 28 days, resume treatment at 1 reduced dose level of binimetinib[#] •If not resolved in ≤ 28 days permanently discontinue binimetinib.
Investigations	CPK increased	Grade 4 (CPK >10 x ULN) WITHOUT renal impairment (serum creatinine <1.5x ULN or 1.5 x baseline)	If asymptomatic, interrupt dosing of binimetinib. Ensure patient is adequately hydrated. Monitor and measure isoenzymes and myoglobin in blood or urine and serum creatinine •If resolved in ≤ 28 days, resume treatment at 1 reduced dose level of binimetinib[#] •If not resolved in ≤ 28 days, permanently discontinue binimetinib. If symptomatic (muscle pain/spasms/muscle weakness), interrupt dosing of binimetinib until resolved to CTCAE Grade ≤ 1 and monitor closely, then: •If resolved in ≤ 28 days,

			resume treatment at 1 reduced dose level of binimetinib[#] If not resolved in ≤ 28 days permanently discontinue
Investigations	CPK increased	Grade 3-4 WITH renal impairment (serum creatinine ≥1.5x ULN or 1.5 x baseline)	Interrupt dosing of binimetinib until resolved to Grade ≤ 1 or baseline level. Ensure patient is adequately hydrated. Monitor closely and measure isoenzymes and myoglobin in blood or urine and serum creatinine, then: •If resolved in ≤ 28 days,

→ → Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03* unless otherwise specified ← ←			
CTCAE System/Organ/ Class (SOC)	ADVERSE EVENT	GRADE	ACTION**
			resume treatment at 1 reduced dose level of binimetinib[#] •If not resolved in ≤ 28 days, permanently discontinue binimetinib. <u>2nd occurrence:</u> Permanently discontinue binimetinib.
Skin and subcutaneous tissue disorders	Any	Grade 1	Maintain dose level of binimetinib. Initiate Initial Rash Treatment Regimen and closely monitor rash
Skin and subcutaneous tissue disorders	Any	Grade 2	<u>1st occurrence:</u> •Maintain dose level of binimetinib •Initiate Initial Rash Treatment Regimen if it was not already started and rash should be closely monitored •Reassess within ≤ 14 days. If rash worsens or does not improve, interrupt dosing of binimetinib until resolved to Grade ≤ 1. Then resume treatment at current dose level binimetinib. <u>2nd occurrence:</u> •Maintain dose level of binimetinib •Continue Initial Rash Treatment Regimen and rash should be closely monitored •Reassess within ≤ 14 days. If rash worsens or does not improve, interrupt dosing of binimetinib until resolved to Grade ≤ 1. Then resume treatment with a dose reduction[#].
Skin and subcutaneous	Any	Grade 3	<u>1st occurrence:</u> •Interrupt dosing of

→ → Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03* unless otherwise specified ← ←			
CTCAE System/Organ/ Class (SOC)	ADVERSE EVENT	GRADE	ACTION**
tissue disorders			binimetinib until resolved to Grade ≤ 1. Reassess weekly. Then resume treatment at current dose level of binimetinib. •Consider referral to dermatologist and manage rash per dermatologist's recommendation. <u>2nd occurrence:</u> •Interrupt dosing of binimetinib until resolved to Grade ≤ 1. Then resume treatment at 1 reduced dose level of binimetinib[#]. •Consider referral to dermatologist and manage rash per dermatologist's recommendation.
Skin and subcutaneous tissue disorders	Any	Grade 4	**DISCONTINUE permanently**
Vascular disorders	Thromboembolic event	Grade 2 or 3: Uncomplicated DVT or PE	WITHHOLD for up to 3 weeks • If improved to Grade 0 or 1 and is symptomatic, RESUME at same dose[#]. • If not improved, resume at reduced dose level or **permanently DISCONTINUE**
Vascular disorders	Thromboembolic event	Grade 4: Life-threatening pulmonary embolism	**Permanently DISCONTINUE**
Respiratory, thoracic, and mediastinal disorders	Pneumonitis	Grade 1	MAINTAIN dose level of binimetinib and monitor weekly
Respiratory, thoracic, and mediastinal disorders	Pneumonitis	Grade 2	WITHHOLD for up to 4 weeks • If improved to Grade 0 or 1, RESUME at DECREASED dose[#]. • If not resolved within 4 weeks, **permanently**

→ → Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03* unless otherwise specified ← ←			
CTCAE System/Organ/ Class (SOC)	ADVERSE EVENT	GRADE	ACTION**
			DISCONTINUE
Respiratory, thoracic, and mediastinal disorders	Pneumonitis	Grade 3-4	**Permanently DISCONTINUE**

* Located at [redacted]

** Use the following to describe actions in the Action column:
- Omit = Treatment is not given for thiscycle
- Hold/Delay = Treatment can be made up as part of this cycle
- Discontinue = Treatment is totally stopped

Do not re-escalate.

For adverse events NOT otherwise identified above that are suspected to be related to binimetinib, the following general recommendations should be used as guidelines for clinically significant dose modifications:

GRADE	ACTION
Recurrent Grade 2	Withhold BINIMETINIB for up to 4 weeks. If improved to Grade 0 or 1, or pretreatment/baseline level, resume at reduced dose *. *NOTE: dose reduction below 15 mg BID is not allowed. Dose may be re-escalated when AE improves and remains stable at ≤ Grade 1 for ≥14 days. There is no limit to the number of times dose can be reduced or re-escalated in 15-mg increments.
Grade 3 or 4	Withhold BINIMETINIB for up to 4 weeks. • If improved to Grade 0 or 1 or pretreatment/baseline level, resume at reduced dose*. If not improved, permanently discontinue. *NOTE: dose reduction below 15 mg BID is not allowed.
Grade 4	Permanently discontinue binimetinib

NOTE: If the patient experiences a significant adverse event requiring a dose reduction at the start of the next cycle, then the dose will remain lowered for that entire subsequent cycle. If that cycle is completed with no further adverse events > Grade 2, then the dose may be increased, at the investigator's discretion, one level at a time, in the following cycles, for the adverse events that are not marked with # in the table above (Section 8.4).

8.5 Palbociclib Dose Modifications Based on Specific Adverse Events

→ → Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03* unless otherwise specified ← ←			
CTCAE System/Organ/Class (SOC)	ADVERSE EVENT	GRADE	ACTION**
BASED ON INTERVAL ADVERSE EVENT			
Blood and lymphatic system disorders	Anemia	Grade 3: Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated	• No dose adjustment is required. • Consider repeating complete blood count monitoring one week later. • Withhold initiation of next cycle until recovery to Grade ≤2.
Blood and lymphatic system disorders	Febrile neutropenia	Grade 3: ANC <1000/mm^3 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	• OMIT treatment and initiation of next cycle until recovery to Grade ≤2 • Resume at next lower dose.
Investigations	Neutrophil count decreased	Grade 3: 500/mm^3 - <1000/mm^3	• No dose adjustment is required. • Consider repeating complete blood count monitoring one week later. • Withhold initiation of next cycle until recovery to ≤ Grade 2.

→ → Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03* unless otherwise specified ← ←			
CTCAE System/Organ/Class (SOC)	ADVERSE EVENT	GRADE	ACTION**
Investigations	Neutrophil count decreased	Grade 4: <500/mm^3	• OMIT treatment and initiation of next cycle until recovery to ≤ Grade 2 • Resume at next lower dose.
Investigations	Platelet count decreased	Grade 3: 25,000/ mm^3 - <50,000/mm^3	• No dose adjustment is required. • Consider repeating complete blood count monitoring one week later. • Withhold initiation of next cycle until recovery to ≤ Grade 2.
Investigations	Platelet count decreased	Grade 4: <25,000/ mm^3	• OMIT treatment and initiation of next cycle until recovery to ≤ Grade 2 • Resume at next lower dose.
Respiratory, thoracic, and mediastinal disorders	Pneumonitis	Grade 3	• Omit treatment and initiation of next cycle until recovery to ≤ Grade 2
Respiratory, thoracic, and mediastinal disorders	Pneumonitis	Grade 4	• Permanently Discontinue

* Located at [redacted]

** Use the following to describe actions in the Action column:

- Omit = Treatment is not given for this cycle
- Hold/Delay = Treatment can be made up as part of this cycle
- Discontinue = Treatment is totally stopped

For clinically relevant adverse events that are suspected to be related to palbociclib NOT otherwise identified above, the following general recommendations should be used as guidelines for dose modifications:

GRADE	AGENT	ACTION
Grade ≥3 Non-hematologic toxicity (if persisting despite medical treatment)	PALBOCICLIB	• OMIT treatment until symptoms resolve to Grade ≤1 or ≤2 if not clinically significant. • Resume at next lower dose.

NOTE: If the patient experiences a significant adverse event requiring a dose reduction at the start

of the next cycle, then the dose will remain lowered for that entire subsequent cycle. If that cycle is completed with no further adverse events > Grade 2, then the dose may be increased, at the investigator's discretion, one level at a time, in the following cycles.

NOTE: Adverse events requiring a dose-reduction step for any or all drugs beyond the two dose-reduction steps (levels –1 and –2) will be at the discretion of the treating physician, if the decision is made for the patient to be kept on study. These dose reductions must be clearly recorded in reported clinical data.

NOTE: Asymptomatic lab abnormalities that is not clinically significant (i.e. electrolyte abnormalities, ALC decrease.

8.6 TAS-102 Arm Dose Modifications Based on Specific Adverse Events

Take the following actions for the following hematologic adverse events occurring on Day 1 of any cycle

→ → Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03* unless otherwise specified ← ←			
CTCAE System/Organ/Class (SOC)	ADVERSE EVENT	GRADE	ACTION**
BASED ON INTERVAL ADVERSE EVENT			
Blood and lymphatic system disorders	Febrile neutropenia	Grade 3: ANC <1000/mm^3 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	• DELAY treatment until recovery and ANC≥1500/mm^3 • Reinitiate treatment at REDUCED dose level
Investigations	Neutrophil count decreased	Grade 2: 1000/mm^3 - 1500/mm^3	• DELAY treatment until ANC ≥1500/mm^3 • Reinitiate treatment at SAME dose level
Investigations	Neutrophil count decreased	Grade 3: 500/mm^3 - 1000/mm^3	• DELAY treatment until ANC ≥1500/mm^3 • Reinitiate treatment at SAME dose level
Investigations	Neutrophil count decreased	Grade 4: <500/mm^3	• DELAY treatment until ANC ≥1500/mm^3 o If recovery ≤1 week, reinitiate at SAME dose level o If recovery >1 week, reinitiate at REDUCED dose level
Investigations	Platelet count decreased	Grade 2: 50,000/ mm^3 - <75,000/mm^3	DELAY treatment until platelets ≥75,000/mm^3. Reinitiate treatment at SAME dose level
Investigations	Platelet count decreased	Grade 3: 25,000/ mm^3 - <50,000/mm^3	DELAY treatment until platelets ≥75,000/mm^3. Reinitiate treatment at SAME dose level

→ → Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03* unless otherwise specified ← ←			
CTCAE System/Organ/Class (SOC)	ADVERSE EVENT	GRADE	ACTION**
Investigations	Platelet count decreased	Grade 4: <25,000/ mm^3	• DELAY treatment until platelets ≥75,000/mm^3 o If recovery ≤1 week, reinitiate at SAME dose level o If recovery >1 week, reinitiate at REDUCED dose level

* Located at [redacted]

** Use the following to describe actions in the Action column:
- Omit = Treatment is not given for this cycle
- Hold/Delay = Treatment can be made up as part of this cycle
- Discontinue = Treatment is totally stopped

Take the following actions for the following hematologic adverse events occurring within the treatment cycle (after day 1)

→ → Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03* unless otherwise specified ← ←			
CTCAE System/Organ/Class (SOC)	ADVERSE EVENT	GRADE	ACTION**
BASED ON INTERVAL ADVERSE EVENT			
Blood and lymphatic system disorders	Febrile neutropenia	Grade 3: ANC <1000/mm^3 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	• OMIT treatment until recovery and ANC≥1500/mm^3 • Reinitiate treatment at REDUCED dose level
Investigations	Neutrophil count decreased	Grade 4: <500/mm^3	• OMIT treatment until improved to ≤ Grade 1 o If recovery ≤1 week, reinitiate at SAME dose level o If recovery >1 week, reinitiate at REDUCED dose level

→ → Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03* unless otherwise specified ← ←			
CTCAE System/Organ/Class (SOC)	ADVERSE EVENT	GRADE	ACTION**
Investigations	Platelet count decreased	Grade 3: 25,000/ mm^3 - <50,000/mm^3	OMIT treatment until platelets ≥75,000/mm^3. Reinitiate treatment at SAME dose level
Investigations	Platelet count decreased	Grade 4: <25,000/ mm^3	• OMIT treatment until resolved to ≤ Grade 1 o If recovery ≤1 week, reinitiate at SAME dose level o If recovery >1 week, reinitiate at REDUCED dose level

* Located at [redacted]

** Use the following to describe actions in the Action column:
- Omit = Treatment is not given for this cycle
- Hold/Delay = Treatment can be made up as part of this cycle
- Discontinue = Treatment is totally stopped

For clinically significant adverse events that are suspected to be related to TAS-102 NOT otherwise identified above, the following general recommendations should be used as guidelines for dose modifications at all points within a cycle:

GRADE	ACTION
Grade ≥3 Non-hematologic toxicity	• OMIT treatment until resolved to ≤ Grade 1 • For Grade 3 nausea/vomiting controlled by antiemetics, reinitiate at SAME dose level • For Grade 3 diarrhea responsive to antidiarrheal medication, reinitiate at SAME dose level • For all other, reinitiate at REDUCED dose level

9.0 Ancillary Treatment/Supportive Care

Patients should receive full supportive care while on this study. This includes blood product support, antibiotic treatment, and treatment of other newly diagnosed or concurrent medical conditions. All blood products and concomitant medications such as antidiarrheals, analgesics, and/or antiemetics received from the first day of study treatment administration until 30 days after the final dose will be recorded in the medical records.

9.1 Permitted concomitant therapy requiring caution and/or action with binimetinib therapy

Binimetinib potently inhibits CYP2B6 (Ki of 1.67 μM). Based on these *in vitro* findings, binimetinib may inhibit the metabolic clearance of co-medications metabolized by CYP2B6 if sufficiently high concentrations are achieved *in vivo.* At 45 mg BID, the maximum concentrations achieved in plasma are normally <1.5 μM so the risk of drug interaction is limited. Caution should be used in patients receiving concomitant treatment with other drugs that are substrates of this enzyme.

Binimetinib induced CYP3A4 *in vitro;* however no clinically relevant inhibition or induction was

observed in a clinical midazolam-based drug interaction study [CMEK162A2105] following 14 days of repeat dosing of binimetinib.

Binimetinib is primarily metabolized via glucuronidation by UGT1A1. It is advised that inhibitors or inducers of UGT1A1 should be taken with caution when co-administered with binimetinib.

In vitro data showed that binimetinib is a substrate of P-gp as well as a substrate of BCRP. Thus, the use of drugs that are known to inhibit or induce P-gp and BCRP should be used with caution.

The solubility of binimetinib is pH-dependent, and a 10-fold decrease in solubility is observed between pH 1 and 2. However, the extent of binimetinib exposure (AUC) was not altered in the presence of a gastric acid reducing agent (rabeprazole) [Clinical Study ARRAY-162-105].

Drugs with a conditional, possible, or known risk to induce Torsade de Pointes (TdP) should be used with caution. Patients receiving such medications must be carefully monitored for potentiating of toxicity due to any individual concomitant medication, and may require dose titration of the drug substance. Investigators should use caution when prescribing co-medications, as clinical experience with these compounds in patients with cancer is often limited.

Refer to Appendix I for list of medications to be used with caution when administered with binimetinib.

9.2 Management of nausea and/or vomiting (on binimetinib arm)

Because nausea and vomiting have been reported for binimetinib, it is recommended that patients are educated on the possibility of occurrence of these side effects prior to starting study treatment. Patient education as well as proper management of nausea and/or vomiting at the first sign is important.

Clinical judgment and experience of the treating physician should guide the management plan of each patient. Patients experiencing nausea and/or vomiting ≥ Grade 1 by CTCAE v4.03 will receive antiemetics at the discretion of the treating physician (as per local guidelines). It is recommended that patients be provided a prescription for antiemetics, and are instructed on the use of antiemetics on the first day of study drug treatment. Prophylactic antiemetics such as dexamethasone 8 mg, prochlorperazine, or metoclopramide may be administered to patients on an "as needed" basis.

Dose interruption/reduction decisions for nausea and/or vomiting should be based on the CTCAE grade of the toxicity and the guidelines provided in Section 8.4.

As a guidance for recommendations on supportive measures for the prevention and/or management of nausea and/or vomiting, the published recommendation from American Society of Clinical Oncology (ASCO), the European Society of Medical Oncology (ESMO) and Multinational Association of Supportive Care (MASCC) can be used [19, 20].

9.3 Diarrhea (on binimetinib arm)

9.31 Proactively investigate for occurrence of diarrhea and educate patients

- Remind patients at each visit to contact the Investigator immediately upon the first sign of loose stool or symptoms of abdominal pain. Additionally, at each study visit, each patient should be asked regarding occurrence of diarrhea or diarrhea-related symptoms. If the patient had symptoms, the patient should be asked regarding the actions taken for these symptoms and re-instruct if indicated.

- The patients should be instructed on dietary modifications and on early warning signs of diarrhea and potentially life-threatening illnesses (e.g. severe cramping might be a sign for severe diarrhea, fever with diarrhea might be a sign for infection, fever and dizziness on standing might be a sign for shock).

- Patients should be educated about what to report to the Investigator (i.e., number of stools, stool composition, stool volume).

9.32 Anti-diarrheal therapy

- In order to effectively manage diarrhea and mitigate the escalation in severity or duration of diarrhea, patient education as outlined above as well as proper management of diarrhea is important.

- Management of diarrhea should be instituted at the first sign of abdominal cramping, loose stools or overt diarrhea. All concomitant therapies used for treatment of diarrhea must be recorded on the Concomitant Medications section of the patient record. It is recommended that patients be provided loperamide tablets and are instructed on the use of loperamide at on the first day of binimetinib treatment. In addition to the binimetinib induced-diarrhea dosing guidelines, these instructions should be provided at each visit and the site should ensure that the patient understands the instructions.

- Explain the frequency of diarrhea and its relationship to NCI CTCAE grading.

- Determine if diarrhea is complicated or uncomplicated.

9.33 Rule out other or concomitant causes

These may include:

- Infection with Candida, Salmonella, Clostridium difficile, Campylobacter, Giardia, Entamoeba and Cryptosporidium species can lead to severe infections in immunosuppressed patients
- Medication-induced diarrhea
- Malabsorption/lactose intolerance
- Fecal impaction, partial bowel obstruction

9.34 For uncomplicated Grade 1/2 diarrhea

- Stop all lactose-containing products, alcohol and eat frequent small meals that include bananas, rice, applesauce or toast

- Stop laxatives, bulk fiber (i.e. Metamucil®) and stool softeners (e.g. docusate sodium; Colace®)

- Stop high-osmolar food supplements such as Ensure® Plus and Jevity® Plus (with fiber)

- Drink 8 to 10 large glasses of clear liquids per day (e.g. water, Pedialyte®, Gatorade® or broth)

- Consider administration of standard dose of loperamide: initial administration 4 mg, then 2 mg every 4 hours (maximum of 16 mg/day) or after each unformed stool.

- Discontinue loperamide after 12-hours diarrhea-free (Grade 0) interval.

- If uncomplicated Grade 1 to 2 diarrhea persists for more than 24 hours, escalate to high dose loperamide: 2 mg every 2 hours (max. of 16 mg/day) or after each unformed stool.

NOTE: Oral antibiotics may be started as prophylaxis for infections under the discretion of the physician.

- If uncomplicated Grade 1 to Grade 2 diarrhea persists after 48 hours of treatment with loperamide, discontinue loperamide and begin a second-line agent which can be an opiate (opium tincture or paregoric), octreotide acetate or steroid (budesonide)

9.35 For complicated Grade 1/2 diarrhea or any Grade 3 to 4 diarrhea

- The patient must call the investigator immediately

- If loperamide has not been initiated, initiate loperamide immediately. Initial administration 4 mg, then 2 mg every 4 hours (maximum of 16 mg/day) or after each unformed stool

- Administer IV fluids and electrolytes as needed. In case of severe dehydration, replace loperamide by octreotide.

- Monitor/continue IV fluids and antibiotics as needed. Intervention should be continued until the patient is diarrhea free for at least 24 hours.

- Hospitalization may need to be considered.

9.4 Skin Toxicity (on binimetinib arm)

Clinical judgment and experience of the treating physician should guide the management plan of each patient. In general, the following interventions are in addition to the rash dosing guidelines in Section 8.4:

- Prophylaxis of skin toxicity to be initiated 24 hours prior to the first treatment with study drug or later as needed

- Application of topical agents to the most commonly affected skin areas such as face, scalp, neck, upper chest and upper back

Topical agents include non-oily sunscreen (PABA free, SPF ≥30, UVA/UVB protection), topical steroids (preferably mometasone cream i.e. Elocon®) and topical erythromycin evening (i.e. Eryaknen® or topical pimocrolimus)

NOTE: Topical agents should be applied on a daily basis starting on Day 1 of study treatment or 24 hours prior to the first dose, and more often as needed.

- Possibly oral doxycycline (100 mg twice daily) for the first 2-3 weeks of study drug administration.

Other effective medications are antihistamines, other topical corticosteroids, other topical antibiotics and low-dose systemic corticosteroids.

The treatment algorithm based on CTCAE grade is as follows:

9.41 Mild rash (CTCAE Grade 1)

- Consider prophylactic rash treatment if not already started
- Topical or other topical corticosteroid (i.e. mometasone cream) and/or topical antibiotic (i.e. erythromycin 2%) are recommended.
- The patient should be reassessed within a maximum of 2 weeks or as per investigator opinion.

9.42 Moderate rash (CTCAE Grade 2)

- Use of topical erythromycin or clindamycin (1%) plus topical mometasone or pimecrolimus cream (1%) plus oral antibiotics such as: doxycycline (100 mg BID) or minocycline (50 to 100 mg QD).
- Although there has been no evidence of phototoxicity or photosensitivity in patients being treated with binimetinib, doxycycline (or minocycline as second-line) should be used with thorough UV protection (i.e., avoidance of direct exposure to sunlight, use of sunscreen and sunglasses, etc.).
- Use of acitretin is not recommended

9.43 Severe rash (CTCAE Grade 3)

- In addition to the interventions recommended for moderate rash, consider oral prednisolone at a dose of 0.5 mg/kg. Upon improvement, taper the dose in a stepwise manner (25 mg for 7 days, subsequently decreasing the dose by 5 mg/day every day).
- Alternatively, in addition to the interventions recommended for moderate rash, consider oral isotretinoin (low doses, i.e. 0.3 to 0.5 mg/kg) (Lacouture et al 2011)
- Use of acitretin is not recommended

9.44 Severe rash (CTCAE Grade 4)

- Immediately discontinue the patient from study drug and treat the patient with oral and topical medications (see recommendation CTCAE Grade 3).

9.45 Symptomatic treatment

It is strongly recommended that patients who develop rash/skin toxicities receive symptomatic treatment

- For pruritic lesions, use cool compresses and oral antihistaminic agents
- For fissuring, use Monsel's solution, silver nitrate, or zinc oxide cream. If not sufficient use mild steroid ointments or combinations of steroids and antibiotics such as Fucicort®
- For desquamation, use emollients with mild pH 5/neutral (best containing urea 10%)
- For paronychia, antiseptic bath and local potent corticosteroids, use oral antibiotics and if no improvement is seen, refer to a dermatologist or surgeon
- For infected lesions, obtain bacterial and fungal cultures and treat with topical or systemic antibiotics based on sensitivity of culture

9.5 Blood products and growth factors should be utilized as clinically warranted and following institutional policies and recommendations. The use of growth factors should follow published guidelines of the American Society of Clinical Oncology (ASCO), Recommendations for the Use of WBC Growth Factors: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol 2015;33:3199-3212.

10.0 Adverse Event (AE) Reporting and Monitoring

Definitions

Adverse Event
Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Suspected Adverse Reaction
Any adverse event for which there is a reasonable possibility that the drug caused the adverse event.

Expedited Reporting
Events reported to sponsor within 24 hours, 5 days or 10 days of study team becoming aware of the event.

Routine Reporting
Events reported to sponsor via case report forms

Events of Interest
Events that would not typically be considered to meet the criteria for expedited reporting, but that for a specific protocol are being reported via expedited means in order to facilitate the review of safety data (may be requested by the FDA or the sponsor).

10.1 Adverse Event Characteristics

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.03. A copy of the CTCAE version 4.03 can be downloaded from the CTEP web site: ([redacted]

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

b. Identify the grade and severity of the event using the CTCAE version 4.03.

c. Determine whether the event is expected or unexpected (see Section 10.2).

d. Determine if the adverse event is related to the study intervention (agent, treatment or procedure) (see Section 10.3).

e. Determine whether the event must be reported as an expedited report. If yes, determine the timeframe/mechanism (see Section 10.4).

f. Determine if other reporting is required (see Section 10.5).

g. Note: All AEs reported via expedited mechanisms must also be reported via the routine data reporting mechanisms defined by the protocol (see Sections 10.5 and 18.0).

Each CTCAE term in the current version is a unique representation of a specific event used for medical documentation and scientific analysis and is a single MedDRA Lowest Level Term (LLT). NOTE: A severe AE, as defined by the above grading scale, is NOT the same as serious AE which is defined in the table in Section 10.4.

10.2 Expected vs. Unexpected Events

Expected events - are those described within the Section 15.0 of the protocol, the study specific consent form, package insert (if applicable), and/or the investigator brochure, (if an investigator brochure is not required, otherwise described in the general investigational plan).

Unexpected adverse events or suspected adverse reactions are those not listed in Section 15.0 of the protocol, the study specific consent form, package insert (if applicable), or in the investigator brochure (or are not listed at the specificity or severity that has been observed); if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan.

Unexpected also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs but have not been observed with the drug under investigation.

10.3 Assessment of Attribution

When assessing whether an adverse event is related to a medical treatment or procedure, the following attribution categories are utilized:

Definite - The adverse event *is clearly related* to the agent(s)/treatment.
Probable - The adverse event *is likely related* to the agent(s)/treatment.
Possible - The adverse event *may be related* to the agent(s)/treatment.
Unlikely - The adverse event *is doubtfully related* to the agent(s)/treatment.
Unrelated - The adverse event *is clearly NOT related* to the agent(s)treatment.

Events determined to be possibly, probably or definitely attributed to a medical treatment suggest there is evidence to indicate a causal relationship between the drug/device and the adverse event.

10.31 Protocol-Specific Exceptions to Expedited Reporting

10.311 The following hospitalizations are not considered to be SAEs because there is no "adverse event" (i.e., there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations for respite care
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed post study drug administration)
- Hospitalization for routine maintenance of a device (e.g., battery replacement) that was in place before study entry

10.312 Death

- Any death occurring within 30 days of the last dose, regardless of attribution to an agent/intervention under an IND/IDE requires expedited reporting within 24-hours.

- Any death occurring greater than 30 days with an attribution of possible, probable, or definite to an agent/intervention under an IND/IDE requires expedited reporting within 24-hours.

- **Reportable categories of Death**

  - Death attributable to a CTCAE term.

  - Death Neonatal: A disorder characterized by cessation of life during the first 28 days of life.

  - Death NOS: A cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.

  - Sudden death NOS: A sudden (defined as instant or within one hour of the onset of symptoms) or an unobserved cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.

  - Death due to progressive disease should be reported as **Grade 5 "Neoplasms benign, malignant and unspecified (including cysts and polyps) – Other (Progressive Disease)"** under the system organ class (SOC) of the same name. Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

10.313 Secondary Malignancy

- A ***secondary malignancy*** is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

- All secondary malignancies that occur following treatment with an agent under an IND/IDE to be reported. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (e.g., AcuteMyeloctyic Leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

- Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

10.314 Second Malignancy

- A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting.

10.315 Pregnancy

To ensure patient safety, pregnancies or lactation (both those of female patients and female partners of male patients) occurring while the patient is on study treatment must be reported to ACCRU within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on the MedWatch Form 3500A and reported by the investigator to ACCRU. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the MedWatch Form 3500A.

If a pregnancy occurs while on study treatment, the newborn will be followed for at least 3 months following the expected delivery date.

Prior to obtaining private information about a pregnant woman and her infant, the investigator must obtain consent from the pregnant woman and the newborn infant's parent or legal guardian. A consent form will need to be submitted to the IRB for these subjects if a pregnancy occurs. If informed consent is not obtained, no information may be collected.

In cases of fetal death, miscarriage or abortion the mother is the patient. In cases where the child/fetus experiences a serious adverse event other than fetal death, the child/fetus is the patient.

NOTE: When submitting the MedWatch Form 3500A reports for "Pregnancy", "Pregnancy loss", or "Neonatal loss", the potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section. Include any available medical documentation.

10.4 Expedited Reporting Requirements for Commercial Agent(s) – Palbociclib + Binimetinib or TAS-102

Expedited Reporting Requirements for or Adverse Events that Occur within 28-30 Days of the Last Administration of a **Commercial** Agent [1,2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) 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 subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the sponsor within the timeframes detailed in the table below.

Hospitalization	Grade 1 Timeframes	Grade 2 Timeframes	Grade 3 Timeframes	Grade 4 & 5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	7 Calendar Days			24-Hour; 3 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required		7 Calendar Days	

Expedited AE reporting timelines are defined as:

- "24-Hour; 3 Calendar Days" - The AE must initially be reported within 24 hours of learning of the AE, followed by a complete expedited report within 3 calendar days of the initial 24-hour report.
- "7 Calendar Days" - A complete expedited report on the AE must be submitted within 7 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:
Expedited 24-hour notification followed by complete report within 3 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 7 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

[2] For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

Additional Instructions:

1. An increased incidence of an expected adverse event (AE) is based on the patients treated for this study at their site. A list of known/expected AE's are reported in the package insert or the literature, including AE's resulting from a drug overdose.
2. Follow site-specific reporting guidelines.
3. Submit MedWatch form 3500A ([redacted] or found on the ACCRU web site) along with the MedWatch Fax Cover Sheet (found on the ACCRU website) to the ACCRU SAE Coordinator via email to [redacted] The ACCRU SAE Coordinator will forward SAEs for patients who received at least one dose of binimetinib to Pfizer (email: [redacted] using the Serious Adverse Event Notification Form Fax Cover Sheet (Appendix VI) within 1 business day of receipt.

4. The ACCRU SAE Coordinator will forward to [redacted] as appropriate. The ACCRU IND Coordinator will assist the sponsor-investigator in notifying the FDA if required.

10.5 Other Required Reporting

10.51 Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSOS) in general, include any incident, experience, or outcome that meets **all** of the following criteria:

1. Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;

2. Related or possibly related to participation in the research (in this guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and

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

Some unanticipated problems involve social or economic harm instead of the physical or psychological harm associated with adverse events. In other cases, unanticipated problems place subjects or others at increased *risk* of harm, but no harm occurs.

10.52 Baseline and Adverse Events Evaluations

The following pre-treatment symptoms/conditions are to be graded at baseline and adverse events are to be graded at each evaluation using CTCAE v4.03 grading.

System Organ Class (SOC)	Adverse event/Symptoms	Baseline	Each evaluation
Blood and lymphatic symptom disorders	Anemia	X	X
	Febrile neutropenia	X	X
Eye disorders	Blurred vision	X	X
	Flashing lights	X	X
	Floaters	X	X
	Retinal vascular disorder	X	X
Investigations	Ejection fraction decreased	X	X
	CPK increased	X	X
	Neutrophil count decreased	X	X
	Platelet count decreased	X	X
	White blood cell decreased	X	X
Musculoskeletal and connective tissue disorders	Arthralgia	X	X
	Myalgia	X	X
Skin and subcutaneous tissue disorders	Photosensitivity	X	X
	Rash acneiform	X	X
	Rash maculo-papular	X	X

10.53 **Case Report Forms** - Academic and Community Cancer Research United (ACCRU)

Submit via appropriate ACCRU Case Report Forms (i.e., paper or electronic as applicable) the following AEs experienced by a patient and not specified in Section 10.5:

10.531 Grade 1 and 2 AEs deemed *possibly, probably, or definitely* related to the study treatment or procedure.

10.532 Grade 3 and 4 AEs regardless of attribution to the study treatment or procedure.

10.533 Grade 5 AEs (Deaths)

10.5331 Any death within 30 days of the patient's last study treatment or procedure regardless of attribution to the study treatment or procedure.

10.5332 Any death more than 30 days after the patient's last study treatment or procedure that is felt to be at least possibly treatment related must also be submitted as a Grade 5 AE, with a CTCAE type and attribution assigned.

10.54 Follow-up for Toxicities

Patients whose treatment is interrupted or permanently discontinued due to an adverse

event or clinically significant laboratory value must be followed up at least once a week (or more frequently if required by institutional practices, or if clinically indicated) for 4 weeks, and subsequently at approximately 4-week intervals, until resolution or stabilization of the event, whichever comes first. Appropriate clinical experts should be consulted as deemed necessary.

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has been registered on the trial and until at least 30 days after the patient has stopped study treatment must be reported to ACCRU as per timeframe outlined in protocol sections 10.4 and 10.5.

Any SAEs experienced after this 30-day period should only be reported to ACCRU if the investigator suspects a causal relationship to the study treatment. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all SAEs is collected and recorded on the MedWatch 3500A Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the MedWatch 3500A Form, and send the completed form to ACCRU.

Follow-up information is sent to the same contact(s) to whom the original SAE Report Form was sent, using a new MedWatch 3500A Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, and whether the patient continued or withdrew from study participation.

10.55 Late-Occurring Adverse Events

Refer to the instructions in the Forms Packet (or electronic data entry screens, as applicable) regarding the submission of late occurring AEs following completion of the Active Monitoring Phase (i.e., compliance with Test Schedule in Section 4.0).

10.56 Quarterly Report: Research Coordinating Center will provide Pfizer with accrual and a toxicity report on a quarterly basis.

11.0 Treatment Evaluation Using RECIST Guideline

NOTE: This study uses protocol RECIST v1.1 template dated 2/16/2011. See the footnote for the table regarding measureable disease in Section 11.44, as it pertains to data collection and analysis.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (version 1.1) (26). Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the short axis measurements in the case of lymph nodes are used in the RECIST guideline.

11.1 Schedule of Evaluations

For the purposes of this study, patients should be reevaluated every 8 weeks while on study treatment, per schedule of events in Section 4.0.

11.2 Definitions of Measurable and Non-Measurable Disease

11.21 Measurable Disease

11.211 A non-nodal lesion is considered measurable if its longest diameter can be accurately measured as ≥2.0 cm with chest x-ray, or as ≥1.0 cm with CT scan, CT component of a PET/CT, or MRI.

11.212 A superficial non-nodal lesion is measurable if its longest diameter is ≥1.0 cm in diameter as assessed using calipers (e.g. skin nodules) or imaging. In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

11.213 A malignant lymph node is considered measurable if its short axis is >1.5 cm when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm).

NOTE: Tumor lesions in a previously irradiated area are not considered measurable disease.

NOTE: "Cystic lesions" thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions. In addition, lymph nodes that have a short axis <1.0 cm are considered non- pathological (i.e., normal) and should not be recorded or followed.

11.22 Non-Measurable Disease

All other lesions (or sites of disease) are considered non-measurable disease, including pathological nodes (those with a short axis ≥1.0 to <1.5 cm). Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable as well.

11.3 Guidelines for Evaluation of Measurable Disease

11.31 Measurement Methods:

- All measurements should be recorded in metric notation (i.e., decimal fractions of centimeters) using a ruler or calipers.

- The same method of assessment and the same technique must be used to characterize each identified and reported lesion at baseline and during follow-up. For patients having only lesions measuring at least 1 cm to less than 2 cm must use CT imaging for both pre- and post-treatment tumor assessments.

- Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used at the same evaluation to assess the antitumor effect of a treatment.

11.32 Acceptable Modalities for Measurable Disease:

- Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is ≤5 mm. If CT scans have slice thickness >5 mm, the minimum size for a measurable lesion should be twice the slice thickness.

    - As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. The lesions should be measured on the same pulse sequence. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

11.33 Measurement at Follow-up Evaluation

- In the case of stable disease (SD), follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 8 weeks (see Section 11.44).

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

- Cytologic and histologic techniques can be used to differentiate between PR and CR in rare cases (e.g., residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain.)

11.4 Measurement of Effect

11.41 Target Lesions & Target Lymph Nodes

- Measurable lesions (as defined in Section 11.21) up to a maximum of 5 lesions and representative of all involved organs should be identified as "Target Lesions" and recorded and measured at baseline. These lesions can be non-nodal or nodal (as defined in 11.21), where no more than 2 lesions are from the same organ and no more than 2 malignant nodal lesions are selected.

  NOTE: If fewer than 5 target lesions and target lymph nodes are identified, there is no reason to perform additional studies beyond those specified in the protocol to discover new lesions.

- Target lesions and target lymph nodes should be selected on the basis of their size, be representative of all involved sites of disease, and in addition should be those that lend themselves to reproducible, repeated measurements. It may be the case that, on occasion, the largest lesion (or malignant lymph node) does not lend itself to reproducible measurements, in which circumstance the next largest lesion (or malignant lymph node) which can be measured reproducibly should be selected.

- Baseline Sum of Dimensions (BSD): A sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes will be calculated and reported as the baseline sum of dimensions (BSD). The BSD will be used as reference to further characterize any objective tumor response in the measurable dimension of the disease.

- Post-Baseline Sum of the Dimensions (PBSD): A sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes will be calculated and reported as the post-baseline sum of dimensions (PBSD). If the radiologist is able to provide an actual measure for the target lesion (or target lymph node), that should be recorded, even if it is below 0.5 cm. If the target lesion (or target lymph node) is believed to be present and is faintly seen but too small to measure, a default value of 0.5 cm should be assigned. If it is the opinion of the radiologist that the target lesion or target lymph node has likely disappeared, the measurement should be recorded as 0 cm.

- The minimum sum of the dimensions (MSD) is the minimum of the BSD and the PBSD.

11.42 Non-Target Lesions & Non-Target Lymph Nodes

Non-measurable sites of disease (Section 11.22) are classified as non- target lesions or non-target lymph nodes and should also be recorded at baseline. These lesions and lymph nodes should be followed in accord with Section 11.43.

11.43 Response Criteria

All target lesions and target lymph nodes followed by CT/MRI/PET-CT/Chest X-ray/physical examination must be measured on re-evaluation at evaluation times specified in Section 11.1. Specifically, a change in objective status to either a PR or CR cannot be done without re-measuring target lesions and target lymph nodes.

NOTE: Non-target lesions and non-target lymph nodes should be evaluated at each assessment, especially in the case of first response or confirmation of response. In selected circumstances, certain non-target organs may be evaluated less frequently. For example, bone scans may need to be repeated only when complete response is identified in target disease or when progression in bone is suspected.

Evaluation of Target Lesions

- Complete Response (CR) - **All** of the following must be true:

    a. Disappearance of all target lesions.

    b. Each target lymph node must have reduction in short axis to <1.0 cm.

- Partial Response (PR) - At least a 30% decrease in PBSD (sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes at current evaluation) taking as reference the BSD (see Section 11.41).

- Progression (PD) - **At least one** of the following must be true:

    a. At least one new malignant lesion, which also includes any lymph node that was normal at baseline (< 1.0 cm short axis) and increased to ≥ 1.0 cm short axis during follow-up.

    b. At least a 20% increase in PBSD (sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes at current evaluation) taking as reference the MSD (Section 11.41). In addition, the PBSD must also demonstrate an absolute increase of at least 0.5 cm from the MSD.

    c. See Section 11.32 for details in regards to the requirements for PD via FDG-PET imaging.

- Stable Disease (SD) - Neither sufficient shrinkage to qualify for PR, nor sufficient increase to qualify for PD taking as reference the MSD.

Evaluation of Non-Target Lesions & Non-target Lymph Nodes

- Complete Response (CR) - **All** of the following must be true:

    a. Disappearance of all non-target lesions.

    b. Each non-target lymph node must have a reduction in short axis to <1.0 cm.

    c. Normalization of tumor biomarkers (i.e. CEA)

- Non-CR/Non-PD - **Persistence of one or more** non-target lesions or non-target lymph nodes and/or maintenance of tumor marker level above the normal limits.

- Progression (PD) - **At least one** of the following must be true:

    a. At least one new malignant lesion, which also includes any lymph node that was normal at baseline (<1.0 cm short axis) and increased to ≥1.0 cm short axis during follow-up.

    b. Unequivocal progression of existing non-target lesions and non-target lymph nodes. (**NOTE**: Unequivocal progression should not normally trump target lesion and target lymph node status. It must be representative of overall disease status change.)

    c. See Section 11.32 for details in regards to the requirements for PD via FDG-PET imaging.

11.44 Overall Objective Status

The overall objective status for an evaluation is determined by combining the patient's status on target lesions, target lymph nodes, non-target lesions, non-target lymph nodes, and new disease as defined in the following tables:

For Patients with Measurable Disease

Target Lesions & Target Lymph Nodes	Non-Target Lesions & Non-Target Lymph Nodes	New Sites of Disease	Overall Objective Status
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
PR	CR Non-CR/Non-PD	No	PR
CR/PR	Not All Evaluated*	No	PR**
SD	CR Non-CR/Non-PD Not All Evaluated*	No	SD
Not all Evaluated	CR Non-CR/Non-PD Not All Evaluated*	No	Not Evaluated (NE)
PD	Unequivocal PD CR Non-CR/Non-PD Not All Evaluated*	Yes or No	PD
CR/PR/SD/PD/Not all Evaluated	Unequivocal PD	Yes or No	PD
CR/PR/SD/PD/Not all Evaluated	CR Non-CR/Non-PD Not All Evaluated*	Yes	PD

* See Section 11.431

** **NOTE:** This study uses the protocol RECIST v1.1 template dated 2/16/2011. For data collection and analysis purposes the objective status changed from SD to PR in the ACCRU protocol RECIST v1.1 template as of 2/16/2011 and to match RECIST v1.1 requirements.

11.45 Symptomatic Deterioration

Patients with global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time, and not either related to study treatment or other medical conditions, should be reported as PD due to "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment due to symptomatic deterioration.

A patient is classified as having PD due to "symptomatic deterioration" if any of the following occur that are not either related to study treatment or other medical conditions:

- Weight loss >10% of body weight.
- Worsening of tumor-related symptoms.
- Decline in performance status of >1 level on ECOG scale.

12.0 Descriptive Factors

12.1 PIK3CA mutation: E542K vs. E545K vs. E545G vs. Q546K vs. Q546R vs. H1047R vs. Other.

12.2 Microsatellite instability: MSI-high vs. MSI-negative.

12.3 MSI instability identification method: PCR vs. IHC vs. next generation sequencing vs. multiple.

12.4 Safety run-in dose level: 1 - Palbociclib 100 mg vs. 2 - Palbociclib 75 mg.

13.0 Treatment/Follow–up Decision at Evaluation of Patient

13.1 Patients who are CR, PR, or SD will continue treatment per protocol for a maximum total of 24 cycles. Subsequent treatment is at the discretion of their attending physician.

13.2 Patients who develop PD at any time should go to event monitoring. These patients should be treated with alternative therapy if their clinical status is good enough to allow furthertherapy.

13.3 Observation Phase is part of the Active Monitoring Phase of a study and is defined as the time period following the active treatment phase when the participant continues to receive cycles of evaluation in compliance with the Test Schedule. Participants will be required to return to the consenting site for follow-up every 12 weeks (± 7 days) until disease progression, alternative therapy, death, or a maximum of 24 months from Registration/ Randomization. Note: Observation patients are those who go off treatment other than progressive disease, alternative therapy, or other (ineligible, major deviation, insurance coverage, etc.).

13.3 Event Monitoring is not part of the Active Monitoring phase of a study and is defined as the time period when the participant is no longer following the protocol test schedule. Patients need to follow Event Monitoring who progress on study. During Event Monitoring, the data collection schedule is dictated by the protocol, but the visit schedule is determined by clinical practice at each participating site. During the Event Monitoring Phase of the study, the participant is being monitored for key study events such as progression, new primaries, and death. Event monitoring should occur every 6 months ±30 days until death or a maximum of 24 months from Registration/ Randomization. Phone or email visits are permitted during Event Monitoring.

13.4 Follow-up Decisions during Active Treatment

Status During Treatment	Arms	Go To…
(cycles 1-24) Complete response (CR), partial response (PR), stable disease (SD)	Safety Run-In Arm A Arm B Crossover	Continue protocol treatment; maximum 24 cycles
(cycle >24) CR, PR, SD	Safety Run-In Arm A Arm B Crossover	Off treatment; no further follow-up
Off treatment for disease progression	Safety Run-In Arm A Arm B* Crossover	Event Monitoring every 6 months up to 24 months from Registration/ Randomization per Section 18.0
*Off treatment for disease progression	Arm B	Optional Crossover
Off treatment for alternative therapy or withdrawal/ refusal	Safety Run-In Arm A Arm B Crossover	Event Monitoring every 6 months up to 24 months from Registration/ Randomization per Section 18.0
Off treatment for adverse	Safety Run-In	Observation every 12 weeks up

Status During Treatment	Arms	Go To…
events/side effects/complications	Arm A Arm B	to 24 months from Registration/ Randomization
Off treatment for adverse events/side effects/complications	Crossover	Event Monitoring every 6 months up to 24 months from Registration/ Randomization per Section 18.0
Off treatment for other complicating disease	Safety Run-In Arm A Arm b	Observation every 12 weeks up to 24 months from Registration/ Randomization
Off treatment for other complicating disease	Crossover	Event Monitoring every 6 months up to 24 months from Registration/ Randomization per Section 18.0
Off treatment for any other reason	Safety Run-In Arm A Arm B Crossover	Event Monitoring every 6 months up to 24 months from Registration/ Randomization per Section 18.0

13.5 Follow-up Decision during Observation

Status During Observation	Arms	Go To…
Complete response (CR), partial response (PR), stable disease (SD)	Safety Run-In Arm A Arm B Crossover	Continue observation; maximum 24 months from Registration/ Randomization
Disease progression (PD) or alternative therapy	Safety Run-In Arm A Arm B Crossover	Event Monitoring every 6 months up to 24 months from Registration/ Randomization per Section 18.0
Death or withdrawal/refusal	Safety Run-In Arm A Arm B Crossover	No further follow-up

13.6 A patient is deemed *ineligible* if after registration, it is determined that at the time of registration, the patient did not satisfy each and every eligibility criteria for study entry. The patient may continue treatment off-protocol at the discretion of the physician as long as there are no safety concerns, and the patient was properly registered. The patient will go directly to the event-monitoring phase of the study (or off study, if applicable).

- If the patient received treatment, all data up until the point of confirmation of ineligibility must be submitted. Event monitoring will be required per Section 18.0 of the protocol.

13.7 A patient is deemed a *major violation*, if protocol requirements regarding treatment in cycle 1 of the initial therapy are severely violated that evaluability for primary end point is questionable. All data up until the point of confirmation of a major violation must be submitted. If the patient received treatment, the patient may continue treatment at the discretion of the physician as long as there are no safety concerns, and the patient was properly registered. The patient will continue in the Active Monitoring/Treatment phase of the study, as per Section 4.0 of the protocol. All data submission should continue per protocol. If the patient does not continue with treatment, the patient will go off treatment and be followed in survival follow-up.

13.8 A patient is deemed a *cancel* if he/she is removed from the study for any reason before any study treatment is given. On-study material and the End of Active Treatment/Cancel Notification Form must be submitted.

14.0 Body Fluid Biospecimens

14.1 Body Fluid Biospecimen Submission

14.11 Summary Table of Body Fluid Biospecimens for This Protocol

Type of biospecimen to submit	**Mandatory or optional**	**When to submit**	**Reason for submission (background/methodology section)**	**Where to find specific details for specimen submission**
Blood/blood products (STRECK whole blood)	Mandatory	Refer to kit instructions	Defined translational studies (Section 14.41)	Section 14.411
Blood/blood products (no additive whole blood)	Mandatory	Refer to kit instructions	Defined translational studies (Section 14.41)	Section 14.412
Blood/blood products (SST whole blood)	Mandatory	Refer to kit instructions	Defined translational studies (Section 14.41)	Section 14.411

14.2 Blood/Blood Products Handling

14.21 Kits are required for this study.

14.211 The kit contains supplies and instructions for collecting, processing, and shipping specimens.

14.212 Participating institutions may obtain kits by completing and faxing the Supply Order Form (found in the Forms Packet) to the number listed on the form. Fill out the site address to where the kits will be shipped on the Fax Supply form. Because we are now being charged for all outgoing kits, a small, but sufficient, supply of the specimen collection kits should be ordered prior to patient entry. Do not send the unused kits back to Biospecimen Accessioning and Processing (BAP) Receiving or the BAP Shared Resource. Note: Expired tubes may be replaced with site stock if available.

14.213 Kits will be sent via FedEx® Ground at no additional cost to the participating institutions. **Allow at least two weeks to receive the kits.** Kits will arrive inside the shipping boxes.

14.214 Kits will not be sent via rush delivery service unless the participating institution provides their own FedEx® account number or alternate billing number for express service. **ACCRU will <u>not</u> cover the cost for rush delivery of kits.**

14.22 All samples must be collected **Monday-Friday.**

14.23 Label specimen tube(s) with protocol number, ACCRU patient ID number, and time and date blood was drawn.

14.24 Collect and process all blood/blood products according to specific kit instructions and table below.

14.241 Summary Table of Research Blood/Blood Products to Be Collected for This Protocol

Applicable Arm	Mandatory or Optional	Collection tube description and/or additive	Volume to collect per tube (number of tubes to be collected)	Blood product being submitted	Cycle 1 Day 1 (+/- 3 days)	Cycle 1 Day 15 (+/- 3 days)	Cycles 2 Day 1 (+/- 3 days)	≤37 days after progression	Additional processing required at site after blood draw?	Storage /shipping conditions[1]
▪ Safety Run-In ▪ Arm A ▪ Crossover	Mandatory	Streck	10 ml (2)	Whole blood for Platelet Poor Plasma	X		X	X	No	Ambient/ room temperature
▪ Safety Run-In ▪ Arm A ▪ Crossover	Mandatory	Na Heparin	10 ml (1)	Whole blood for Peripheral blood mononuclear cells	X		X	X	No	Ambient
▪ Safety Run-In ▪ Arm A ▪ Crossover	Mandatory	SST	10 ml	Serum for TK assay	X	X	X	X	No	Refrigerated / cold pack

1. After all samples have been processed according to kit instructions, ship all specimens according to shipping instructions (see Section 14.3 for detailed shipping instructions.)

14.3 Shipping

14.31 Verify ALL sections of the Blood Specimen Submission Form (see Forms Packet), BAP Requisition Form (provided in kit) and specimen collection labels are completed and filled in correctly.

14.32 Specimens must be shipped the same day they are drawn.

14.33 Ship SST tubes via Priority Overnight service refrigerated/on cold packs.

Ship STRECK and Na Heparin tubes via Priority Overnight service ambient/room temperature.

14.34 Ship specimens via Priority Overnight service, **Monday – Friday,** to BAP Receiving according to kit instructions. **Do not send samples on weekends or just prior to federal holidays.**

14.35 The BAP kits will include a smart shipper label (3x5 white barcoded label) affixed to the shipping boxes. The smart shipper label is a pre-addressed return label, which replaces the need for an airbill. Shipping costs will be covered by ACCRU if the shipping box provided with the BAP kit is used for shipping specimens to BAP Receiving.

Ship samples to: [redacted]

At study completion, samples will be shipped by BAP to The University of Texas MD Anderson Cancer Center:

[redacted]

14.4 Study Methodology and Storage Information

14.41 Blood/blood product samples will be collected for the following research

14.411 A portion of the plasma will initially be analyzed for the presence of circulating free tumor DNA using standard laboratory protocols. We will utilize digital PCR or ultra-deep sequencing technology to assay patient serum for circulating free tumor DNA, which can be assayed for mutations longitudinally. This analysis will be useful in determining whether resistant clones harboring mutations undergo expansion over the course of treatment, as detected by increasing allele frequency of mutations predicted to contribute to resistance. The analysis will take place at the laboratory of [redacted] located at The University of Texas MD Anderson Cancer Center. According to patient consent information (see Section 6.14), remaining serum/plasma will be stored frozen at -70ºC at The University of Texas MD Anderson Cancer Center, until specific analyses are identified. As protocols are developed, they will be presented for ACCRU and IRB review and approval. This collection is part of a general strategy of investigation for the majority of ACCRU studies.

14.412 Peripheral blood mononuclear cells (PBMCs) will be analyzed to determine pharmacodynamic effects of palbociclib/binimetinib in PBMCs as a surrogate. PBMCs may also be analyzed for evaluation of immune response to therapy. The analysis will take place at the laboratory of [redacted] located at The University of Texas MD Anderson Cancer Center. According to patient consent information (see Section 6.14), remaining specimens will be stored frozen at -70ºC at The University of Texas MD Anderson Cancer Center, until specific analyses are identified. As protocols are developed, they will be presented for ACCRU and IRB review and approval. This collection is part of a general strategy of investigation for the majority of ACCRU studies.

14.5 Return of Genetic Testing Research Results

Because the results generated by the genetic testing included in this section are not currently

anticipated to have clinical relevance to the patient or their family members, the genetic results will not be disclosed to the patients or their physicians.

If at any time, genetic results are obtained that may have clinical relevance, IRB review and approval will be sought regarding the most appropriate manner of disclosure and whether or not validation in a CLIA-certified setting will be required. Sharing of research data with individual patients should only occur when data have been validated by multiple studies and testing has been done in CLIA-approved laboratories.

15.0 Drug Information

Refer to the package insert for complete, up-to-date information.

15.1 Binimetinib (MEK162, ARRY-438162, ONO-7703)

15.11 Background

Binimetinib is an orally bioavailable, selective and potent MEK1 and MEK 2 inhibitor. As a MEK inhibitor, this compound has the potential to benefit patients with advanced cancers by inhibiting the MAPK (mitogen-activated protein kinases) pathway.

15.12 Formulation: Binimetinib drug product is supplied as film-coated tablets in a dose strength of 15 mg. The film coated tablets consist of binimetinib, colloidal silicon dioxide/silica colloidal anhydrous; croscarmellose sodium; lactose monohydrate; magnesium stearate; microcrystalline cellulose/cellulose, microcrystalline; and a commercial film coating. The tablet is ovaloid biconvex (capsule shaped), yellow to dark yellow in color.

15.13 Preparation and storage: Binimetinib film-coated tablets should not be stored above 25°C and should be protected from light. Tablets are packaged in plastic bottles acceptable for pharmaceutical use.

Binimetinib oral suspension prepared from 15 mg binimetinib tablets should not be stored above 25°C and should not be refrigerated. The suspension should be used within 30 days after preparation.

15.14 Administration: Binimetinib is administered twice daily with water, approximately 12 hours apart with or without meals. Tablets should be swallowed whole and should not be chewed.

Binimetinib oral suspension is intended for oral administration as prepared.

15.15 Pharmacokinetic information:
Absorption: The pharmacokinetics of binimetinib are characterized by moderate to high variability, accumulation of approximately 1.5-fold, and steady state concentrations reached within 15 days. The human ADME study CMEK162A2102 indicated that approximately 50% of binimetinib dose was absorbed.

Distribution: Binimetinib is more distributed in plasma than blood. The blood-to-plasma concentration ratio of binimetinib in humans is 0.718. It is highly bound to plasma proteins (humans: 97.2%).

Metabolism: The primary metabolic pathways include glucuronidation (up to 61.2% via UGT1A1), N-dealkylation (up to 17.8% via CYP1A2 and CYP2C19) and amide hydrolysis.

Excretion: Results of a human ADME study indicated 62% of the dose was eliminated in feces, and 31% was eliminated in the urine. The $T_{1/2}$ range was 8.1-13.6 hours, median 8.66 hours.

Results from a hepatic impairment study indicate the exposure of binimetinib in mild hepatic impairment is similar compared to that of subjects with normal liver function; study results indicate exposures patients with moderate and severe hepatic impairment may be increased up to approximately 2-fold [Clinical Study CMEK162A2104].

Results from a renal impairment study indicate the exposure of binimetinib in subjects with severe renal impairment is 14-29% higher compared to that in healthy subjects [Clinical Study ARRAY-162-106].

15.16 Potential Drug Interactions:

Overall, the risk for binimetinib to be a cause of or be affected by significant drug-drug interactions is predicted to be low. However, given the predominant role of UGT1A1 in the metabolism of binimetinib, and because the effect of a UGT1A1 inhibitor or inducer has not been evaluated in a formal clinical study, special consideration should be taken for co-administration of drugs that are UGT1A1 inhibitors or inducers, and administration of binimetinib to patients with low UGT1A1 activity.

Binimetinib has been shown to be a substrate for P-gp and BCRP in vitro. The impact of P-gp/BCRP inhibitors on the PK of binimetinib in vivo is unknown; therefore, it is recommended that P-gp and BCRP inhibitors are dosed with caution.

15.17 Known potential toxicities:

Very Common (≥ 10%) - diarrhea, nausea, vomiting, fatigue, peripheral edema, increased AST, increased blood creatine phosphokinase, dermatitis acneiform, dry skin, pruritus, rash, decreased ejection fraction

Common (≥1% - <10%) - anemia, chorioretinopathy, dry eye, macular edema, retinal detachment, retinal vein occlusion, retinopathy, serous retinal damage, blurred vision, reduced visual acuity, visual impairment, abdominal pain, constipation, dry mouth, dyspepsia, gastroesophageal reflux disease, stomatitis, mouth ulceration, asthenia, facial edema, generalized edema, malaise, pyrexia, folliculitis, paronychia, pustular rash, increased ALT, increased amylase, increased blood alkaline phosphatase, increased blood creatinine, increased GGT, lipase increased, arthralgia, muscular weakness, myalgia, dizziness, dysgeusia, epistaxis, alopecia, xerosis, nail disorder, palmar- plantar erythrodysesthesia syndrome, eczema, erythema, erythematous rash, papular rash, macular rash, maculo-papular rash, skin fissures, hypertension, neutropenia pneumonitis

Uncommon (≥0.1 - <1%) – anemia, left ventricular dysfunction, eye edema, gastritis, upper gastrointestinal hemorrhage, general physical health deterioration, infection, skin infection, cellulitis, erysipelas, irregular heart rate, increased troponin I, hypoglycemia, musculoskeletal pain, myositis, rhabdomyolysis, dropped head syndrome, ageusia, renal failure, pneumonitis, pulmonary embolism, xeroderma, follicular rash, pruritic rash, deep vein thrombosis, hypertensive crisis, hypotension

15.18 Drug procurement

Pfizer will supply commercial supply of binimetinib (Mektovi) to RxCossroads by McKesson Clinical Research Services. Each participating ACCRU treating location will order the drug from RxCrossroads by McKesson Clinical Research Services. Submit the Drug Order Request Form (found on the ACCRU web site) to:

[redacted]

Each participating ACCRU treating location will be responsible for monitoring the supply of binimetinib and will use the Drug Order Request Form to order additional supplies as needed.

Outdated or remaining drug is to be destroyed on-site as per procedures in place at each institution.

15.181 Temperature excursions that occur at the site should be reported by the site to RxCrossroads by McKesson Clinical Research Services via email [redacted] Any shipment deviations (those not occurring at the site) should be reported to RxCrossroads by McKesson Clinical Research Services via email to: [redacted] RxCrossroads by McKesson Clinical Research Services will report any temperature and shipment deviations (those not occurring at the site) to Pfizer via email to: globalmedicalgrants@pfizer.com

15.1811 When reporting a temperature excursion to RxCrossroads by McKesson, please include the following information as required by Pfizer:

- Study/protocol number
- Name and contact information
- Site location and address
- Pfizer lot and kit numbers affected (if applicable)
- High/low temperature recorded for event
- Duration of the event
- All supporting data or charts (Temp Log, TempTale, etc.)
- Temperature deviation event form (if site has their own)

Following a temperature deviation, the affected material should be physically quarantined by the site until a response is received from Pfizer regarding the disposition of the affected materials.

15.19 Nursing Guidelines

15.191 Instruct patient to take binimetinib twice daily approximately 12 hours apart. Agent may be taken with or without food.

15.192 MEK inhibitors can have significant cardiac side effects including cardiac failure, tachycardia, myocarditis, and decreased ejection fraction. Instruct patients to report any side effects concerning for heart failure (SOB, peripheral edema, chest, pain, etc) to the study team immediately.

15.193 Warn patient of eye disorders, which can be severe and lead to permanent loss of eyesight. Instruct patient to report any eye pain, dryness, itching, etc. to study

team. Refer patient to ophthalmologist for treatment.

15.194 Binimetinib may cause gastrointestinal side effects (diarrhea, nausea, vomiting, GI bleeding, etc). Treat symptomatically and/or premedicate as necessary and monitor for effectiveness.

15.195 Monitor LFT's. Patients have experienced acute hepatic failure. Instruct patients to report any acute and or worsening RUQ pain and/or any jaundice to study team immediately.

15.196 Patients may experience pruritus and/or rash. Rash is generally acneiform in nature. Manage symptomatically and monitor for effectiveness.

15.197 Patients may experience generalized edema, including the face and the limbs. Instruct patient to report any edema and rule out any allergic and/or cardiac component.

15.198 Monitor creatinine levels.

15.199a Patients may experience myositis or rarely rhabdomyolysis.. Patients should be instructed to report generalized muscle pain to the study team.

15.199b Agent may cause pneumonitis. Instruct patients to report any cough, SOB, or chest pain to study team.

15.199c Monitor any new skin lesions. Patients may develop secondary skin cancer or cysts. Refer to dermatology as necessary.

15.199d Patients may experience palmar-plantar erythrodysaesthesia (hand-foot syndrome). Instruct patients to report any redness, pain, or skin changes of the hands or feet to the study team immediately. Encourage good hand and foot care and the use of moisturizers.

15.2 Palbociclib (Ibrance®, PD-0332991, NSC 772256) for Oral Administration

Refer to the package insert for complete, up-to-date information.

15.21 Background

Palbociclib, an orally active pyridopyrimidine, is a potent and highly selective reversible inhibitor of cyclin-dependent kinase (CDK) 4 and CDK6. The compound prevents cellular DNA synthesis by prohibiting progression of the cell cycle from G1 into the S phase, as demonstrated in laboratory models and early clinical trials.

15.22 Formulation

125 mg tablets: Oval, light purple, film-coated tablets debossed with "Pfizer" on one side and "PBC 125" on the other side.
100 mg tablets: Oval, green, film-coated tablets debossed with "Pfizer" on one side and "PBC 100" on the other side.
75 mg tablets: Round, light purple, film-coated tablets debossed with "Pfizer" on one side and "PBC 75" on the other side.

Capsule: PD-0332991-00 (free-base formulation) will be provided as the active ingredient with precedented excipients filled in hard gelatin capsules composed of gelatin and precedented colorants. Capsules contain 75 mg, 100 mg, or 125 mg equivalents of palbociclib free base.

15.23 Preparation and storage

Store at 20C to 25 C (68F to 77F); excursions permitted between 15C to 30C (59F to 86F). Store in the original blister pack.

Store capsules at controlled room temperature, 15-30°C, in their original containers.

15.24 Administration

Caution: Capsules containing the free base formulation of palbociclib should be given once daily with food. Palbociclib capsules must not be opened and/or emptied into any vehicle for oral ingestion; capsules must be swallowed whole.

Palbociclib tablet may be taken with or without food. Patients should be instructed to take the dose of palbociclib at approximately the same time each day. Palbociclib tablets should be swallowed whole (do not chew, crush, or split them prior to swallowing).

15.25 Pharmacokinetic information

Absorption: Median T_{max} values ranged between 4-12 hours after oral dosing
Bioavailability: Mean absolute oral bioavailability 46%
Distribution: Mean volume of distribution 2583 L
Metabolism: Extensively hepatically metabolized. The major primary metabolic pathways are comprised of oxidation and sulfonation, with glucuronidation and acylation contributing as minor pathways.
Half-life elimination: Mean $T_{½}$ 28.8 hours
Excretion: Median 17.5% recovered in urine, 74.1% recovered in feces

15.26 Potential Drug Interactions

The effect of multiple dosing of palbociclib on the single dose PK of midazolam showed that palbociclib is a weak time-dependent inhibitor of CYP3A.

Concomitant use of strong CYP3A inhibitors (e.g. boceprevir, clarithromycin, conivaptan, delavirdine, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole, and grapefruit or grapefruit juice) and inducers (e.g. carbamazepine, enzalutamide, felbamate, nevirapine, phenobarbital, phenytoin, primidone, rifabutin, rifampin, rifapentin, and St. John's wort) should be avoided.

Moderate CYP3A inducers (e.g. bosentan, efavirenz, etravirine, modafinil, and nafcillin) can be used concurrently with palbociclib if it cannot be avoided.

15.27 Known potential toxicities

See the current version of the palbociclib Investigator's Brochure for complete toxicity information.

Very Common (≥ 10%):
Infections, neutropenia, leukopenia, anemia, thrombocytopenia, decreased appetite, stomatitis, nausea, diarrhea, vomiting, rash, alopecia, fatigue, fever

Common: (≥1% - 10%)
Blurred vision, increased lacrimation, dry eyes, dysgeusia, epistaxis, dry skin, asthenia, pyrexia, increased ALT

Interstitial lung disease (ILD)/non-infectious pneumonitis has been reported as a potential known adverse reaction. This toxicity has been identified during post-approval use of palbociclib. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

15.28 Drug procurement

Pfizer will provide commercial formula of palbociclib to RxCrossroads by McKesson Clinical Research Services for investigational use in this study. The product will be labeled, "For Investigational Use." Each participating ACCRU treating location will order the drug from RxCrossroads by McKesson Clinical Research Services. It will take 1-business days to receive the palbociclib.

Fax the Drug Order Request Form (found on the ACCRU web site) to:

[redacted]

Each participating ACCRU treating location will be responsible for monitoring the supply of palbociclib and will use the appropriate Drug Order Request Form to order additional supplies as needed.

Outdated or remaining drug is to be destroyed on-site as per procedures in place at each institution.

15.281 Temperature excursions that occur at the site should be reported by the site to RxCrossroads by McKesson Clinical Research Services via email to: [redacted] Any shipment deviations (those not occurring at the site) should be reported to RxCrossroads by McKesson Clinical Research Services via email to: [redacted] RxCrossroads by McKesson Clinical Research Services will report any temperature and shipment deviations (those not occurring at the site) to Pfizer via email to: [redacted]

15.2811 When reporting a temperature excursion to RxCrossroads by McKesson, please use the Pfizer Site Temperature Excursion Report Form found on the ACCRU web site. RxCrossroads by McKesson will report all temperature excursions to Pfizer.

15.29 Nursing Guidelines

15.291 Please refer to section 15.24 for administration guidelines.

15.292 Monitor CBC w/diff as cytopenias are common and require dose reductions. Instruct patients to report signs or symptoms of infection and/or any unusual bruising or bleeding to the study team.

15.293 GI symptoms are common, including nausea/vomiting, stomatitis and diarrhea. Treat symptomatically and monitor for effectiveness. Some side effects may require dose reductions.

15.294 Patients should avoid grapefruit and grapefruit juice, due to possible increase in the serum concentration of palbociclib.

15.295 There are drug to drug interactions with CYP3A4 substrates. Obtain a complete list of patient medications including OTC and herbal products. Instruct patients to report any new medications to the study team immediately.

15.296 Warn patient of risk of thromboembolic events, specifically pulmonary

embolism.

15.297 Warn patients of possibility of alopecia.

15.298 Patients may experience upper respiratory infection. Instruct patients to report URI symptoms to study team.

15.299 Rarely patients may experience peripheral neuropathy. Monitor patients closely who may have preexisting CIPN from previous therapy.

15.3 Trifluridine (FTD)/Tipiracil (TPI) (TAS-102, Lonsurf®)

Refer to the package insert for complete, up-to-date information.

15.31 Background

FTD/TPI is an orally available combination drug of an antineoplastic thymidine-based nucleoside analogue, 1M trifluridine (FTD), and 0.5 M tipiracil hydrochloride (TPI). FTD is incorporated into deoxyribonucleic acid (DNA) of tumor cells following phosphorylation. TPI inhibits degradation of FTD by thymidine phosphorylase (TPase).

15.32 Formulation

FTD/TPI contains trifluridine (FTD) and tipiracil (TPI as active ingredients with a molar ratio of 1:0.5. TAS-102 drug products are immediate-released film coated tablets, with two strengths of 15 mg and 20 mg (expressed as FTD). The inactive ingredients of the FTD/TPI 15 mg and 20 mg tablets are lactose monohydrate, pregelatinized starch, stearic acid, hypromellose, polyethylene glycol, titanium dioxide, red ferric oxide (only 20 mg tablet), and magnesium stearate.

- FTD/TPI (TAS-102) tablet (15 mg) contains 15 mg trifluridine and 6.14 mg tipiracil as active ingredients. The appearance is white round tablet.
- FTD/TPI (TAS-102) tablet (20 mg) contains 20 mg trifluridine and 8.19 mg tipiracil as active ingredients. The appearance is pale red round tablet.

15.33 Preparation and storage

Store at 20°C to 25°C (68°F to 77°F); excursions are permitted from 15°C to 30°C (59°F to 86°F). If stored outside of original bottle, discard after 30 days.

15.34 Administration

Recommended to take within 1 hour after completion of the morning and evening meals.

15.35 Pharmacokinetic information

Protein Binding: Trifluridine: >96% (primarily to albumin); Tipiracil: <8%
Metabolism: Trifluridine and tipiracil are not metabolized by cytochrome P450 (CYP) enzymes. Trifluridine is mainly eliminated by metabolism via thymidine phosphorylase to form an inactive metabolite, 5-(trifluoromethyl) uracil (FTY)
Half-life elimination: Trifluridine: 2.1 hours (at steady state); Tipiracil: 2.4 hours (at steady state)
Time to peak, plasma: ~2 hours
Excretion: Trifluridine: Urine (<2% [as unchanged drug]; ~19% [as inactive metabolite FTY]); Tipiracil: Urine (~29% [as unchanged drug]

15.36 Potential Drug Interactions

Caution is required when using drugs that are human thymidine kinase substrates, e.g., zidovudine. Such drugs, if used concomitantly with FTD/TPI, may theoretically compete with the effector of FTD/TPI, i.e., FTD, for activation via thymidine kinases. Therefore, when using antiviral drugs that are human thymidine kinase substrates, monitor for possible decreased efficacy of the antiviral agent, and consider switching to an alternative antiviral agent that is not a human thymidine kinase substrate such as: lamivudine, zalcitabine, didanosine, abacavir, etc.

15.37 Known potential toxicities

Very common known potential toxicities, ≥ 10%:
Blood and lymphatic: Anemia, leukopenia, neutropenia, thrombocytopenia
Gastrointestinal: Diarrhea, nausea, vomiting
General: Fatigue
Metabolism and nutrition: Decreased appetite

Common known potential toxicities, ≥1% - <10%:
Blood and lymphatic: Febrile neutropenia, lymphopenia, monocytosis
Dermatologic: Alopecia, dry skin, Palmar-plantar erythrodysesthesia syndrome, pruritis, rash
Gastrointestinal: Abdominal pain, constipation, oral disorder, stomatitis
General: Malaise, mucosal inflammation, edema, pyrexia
Hepatobiliary: Hyperbilirubinemia
Infections: Lower respiratory tract infection, upper respiratory tract infection
Investigations: Blood alkaline phosphatase increased, hepatic enzyme increased, weight decreased
Metabolism and nutrition: Hypoalbuminemia
Nervous System: Dizziness, dysgeusia, headache, peripheral neuropathy
Psychiatric: Insomnia
Renal and urinary: Proteinuria
Respiratory: Cough, dyspnea
Vascular: Flushing

Uncommon known potential toxicities, <1% (Limited to important or life-threatening):
Blood and lymphatic: Pancytopenia
Gastrointestinal: Ascites, colitis, ileus, acute pancreatitis, subileus
General: General physical health deterioration
Infections: Bacterial infection, biliary tract infection, enteritis infection, urinary tract infection
Investigations: Blood lactate dehydrogenase increased
Metabolism and nutrition: Dehydration
Respiratory: Pulmonary embolism

15.38 Drug procurement

Each participating ACCRU treating location will be responsible for procuring the supply of TAS-102.

15.39 Nursing Guidelines:

15.391 Instruct patients that agent should be taken within 1 hour after completion of morning and evening meal.

15.392 Patients may experience fatigue. Instruct patients in energy conserving lifestyle.

15.393 GI side effects are common, including nausea, decreased appetite, diarrhea, vomiting, and abdominal pain.

15.394 Cytopenias are common. Monitor CBC w/diff and instruct patients to report any signs or symptoms of infection and/or unusual bruising or bleeding to the study team.

15.395 Rarely Pulmonary embolism has been reported with this agent. Instruct patient to report any shortness of breath or chest pain to study team and/or seek out emergency medical attention.

15.396 Although uncommon, warn patients of the possibility of alopecia.

16.0 Statistical Considerations and Methodology

16.1 Study Overview / Rationale

This randomized Phase II trial is designed to primarily compare the progression-free survival (PFS) between patients randomized to palbociclib/binimetinib and those randomized to TAS-102 in patients with refractory KRAS or NRAS mutant metastatic colorectal cancer. We will also conduct a safety run-in, which consists of a thorough review of adverse event data within the initial 6-12 patients enrolled on the experimental arm (palbo+bini) before randomization. (details see Section 16.62). Other endpoints of interest that will be evaluated are adverse events, overall survival, and overall response rate.

16.2 Statistical Design

16.21 Primary Endpoint

The primary endpoint for this study will compare PFS between palbociclib/binimetinib vs. TAS-102 in patients with refractory *KRAS* or *NRAS* mutant metastatic CRC. PFS is defined as the time from randomization date to either disease progression or death from any cause, whichever occurs first. Patients who are still alive and progression-free at the time of analysis will be censored at the time of their last disease assessment. Disease progression will be determined based on RECIST 1.1 and will be documented at each enrolling site with no central review planned.

16.211 Analysis Plan

PFS will be compared between treatment arms using the stratified log rank test at one-sided level 0.05. The stratification factors listed in Section 5.1 will be used for the analysis. The HR for PFS will be estimated using a stratified Cox proportional hazards model and the 95% CI for the HR will be provided. Results from an unstratified analysis will also be provided. Kaplan-Meier methodology will be used to estimate the median PFS for each treatment arm, and Kaplan-Meier curves will be produced.

16.22 Decision Rule

The primary goal is to compare PFS between those randomized to palbociclib/binimetinib and those randomized to TAS-102. The alternative hypothesis is that the combination of palbociclib and binimetinib has improvement in PFS compared to TAS-102.

16.221 Interim Analysis Decision Rule

One interim analysis for futility will be conducted when 37 events have occurred. PFS will be used as the endpoint for interim analysis. The interim futility boundary was selected using EAST v6.4 software. The trial will continue accrual while

interim analysis is being conducted. To reject the alternative hypothesis at the interim (i.e. reject palbociclib/binimetinib as effective), the HR will need to be ≥ 1.043 for palbociclib/binimetinib compared to TAS-102, which corresponds to a 1-sided p-value of 0.551 or larger. Otherwise, if the HR is < 1.043 (1-sided p-value <0.551), the study will continue to full accrual, and the final analysis will be conducted as discussed below.

16.222 Final Analysis Decision Rule

The primary efficacy analysis will be conducted when at least 73 patients across both arms combined have provided documentation of either disease progression or death without progression of disease, which will take place approximately 3 months after last patient enrollment. To reject the alternative hypothesis at the final analysis (i.e. reject palbociclib/binimetinib as effective), the HR will need to be ≥ 0.68 for palbociclib/binimetinib compared to TAS-102, which corresponds to a 1-sided p-value of 0.05 or larger. Otherwise, if the HR is < 0.68 (1-sided p-value < 0.05), the palbociclib/binimetinib treatment will be considered effective. All eligible patients who sign the consent form, are randomized, and receive any protocol treatment will be considered evaluable for this endpoint.

16.23 Power and Significance Level

If we enter 45 evaluable patients to each arm of the study using a 1:1 randomization scheme (90 evaluable patients in total), then with a total of 73 observed events, we have 90% power to detect an improvement in the median PFS from 2 to 4 months (hazard ratio (HR) = 0.5), assuming a 1-sided significance level of 0.05 and an accrual rate of 8 patients per month. The trial has a single interim analysis for futility, adopting Rho family (Rho = 3) beta spending function, for controlling the overall type II error rate.

The operating characteristics of current design are tabulated below. Probabilities reported in the table are calculated based on simulation study with 50,000 replicates.

Scenario	Median PFS in TAS-102 (months)	Median PFS in Palbo/ Binimetinib (month)	Hazard Ratio (HR)	Probability of declaring that Palbo/ Binimetinib warrants further studies is…	Probability of stopping at the interim analysis due to futility is…
1	2	1.5	1.333	0.0021	0.7686
2	2	2	1	0.0506	0.4478
3	2	2.5	0.8	0.2426	0.2152
4	2	3	0.667	0.5229	0.0909
5	2	3.5	0.571	0.7588	0.0368
6	2	4	0.5	0.8982	0.0143

16.24 Secondary Endpoints

16.241 Overall Response Rate

Assessment of response data will be performed on the basis of definitions of responses according to RECIST v1.1. For patients that elect to crossover, only responses that occur prior to crossover will be considered for this endpoint. Objective response is defined as a complete or partial response by RECIST v1.1. Subjects with missing or no response assessments will be classified as non-responders. This will be reported as a proportion with a 95% confidence interval for the true proportion.

16.242 Overall Survival

Overall survival is defined as the time from first dose of study treatment to death from any cause. Patients who are still alive at the time of analysis will be censored at the time of their last study assessment (if still actively on study) or at last known date alive (if on survival follow-up). Due to the crossover component of this trial, all analyses relating to OS will be descriptive in nature. No formal statistical tests will be performed. We will use Kaplan-Meier methods to evaluate time to event endpoints, and will report median OS and its 95% confidence interval.

16.243 Adverse Events

Adverse events (AEs) will be described by grade for Grade 1 and above with and without attribution considered.

All eligible patients that have initiated treatment will be considered evaluable for assessing adverse event rate(s). For patients that elect to crossover, only AEs that occur prior to crossover will be considered for this endpoint. AEs after crossover will be described independently. The maximum grade for each type of adverse event will be recorded for each patient, and described using frequency tables. The adverse events will be compared by arm to determine any differences. Additionally, the relationship of the adverse event(s) to the study treatment will be taken into consideration.

16.25 Exploratory analyses of correlative studies

As correlative studies will be performed as an exploratory analysis, we do not have formal statistical power testing. Analyses that are planned for correlative studies are described in Section 17.3.

16.3 Sample Size

The study design to be utilized is fully described in Section 16.2 and includes a planned interim analysis. There will be 45 evaluable patients randomized to each arm of this study (total of 90 patients). We anticipate accruing an additional 5 patients in each arm (10 total) to account for ineligibilities, cancellations, major violations, or other reasons. Including 6-12 patients for early adverse event assessment in the experimental arm, thus the maximum accrual is 112 patients in total.

16.4 Accrual Time and Study Duration

We conservatively estimated the accrual rate at about 8 patients per month, as enrollment of KRAS/NRAS mutant refractory metastatic CRC on clinical trials at each site is at least 1-2 per month. We make the same assumption for the accrual rate for the current study. Therefore, following the safety run-in we anticipate that the study will take approximately 14 months to accrue. Assuming an accrual period of 11.25 months, we anticipate that the study will take just over a year to complete.

16.5 Over Accrual

If more than the target number of patients are accrued, the additional patients will not be used to evaluate the stopping rule or used in any decision making processes; however, they will be

included in final point estimates, confidence intervals, and secondary endpoints.

16.6 Adverse Events Stopping Rule

16.61 Data Safety Monitoring Board

This study will be monitored by the Mayo Clinic Data Safety Monitoring Board (DSMB). Reports containing patient characteristics, toxicity and administrative information will be provided to the DSMB every six months, with the first report due at the first reporting period after study initiation.

16.62 Early Adverse Assessment in Experimental Arm (Safety Run-In)

To ensure safety before randomization, the first 6 patients entered onto this study will be only enrolled in the experimental arm. This phase of early adverse event assessment will be open throughout ACCRU. For this phase of the study, patients will be deemed evaluable for toxicity assessment if they initiate any protocol treatment. As mentioned previously in Section 7.12, a patient may only be replaced if the patient withdraws from the study for any reason other than study drug toxicity or adverse event prior to completing one cycle. For evaluation of the toxicity rule, we will consider AE data for all evaluable patients in the first cycle. When the last of these 6 patients is enrolled, accrual will be halted. When the last of these 6 patients becomes evaluable for toxicity (started protocol treatment and either: 1, completed one cycle of AE assessments or 2. went off treatment prior to one cycle), the data from these first 6 patients will be reviewed. If there are 0-1 excessive toxicities (as defined in Section 7.15) among the first 6 patients, we will consider start to randomize patients to both Arms A and B. If there are 2 or more excessive toxicities among the first 6 patients, we will pursue dose de-escalation as described in Section 7.11. We acknowledge that the final decision to open randomization will rest in the clinical judgment of the investigative team and that mitigating factors may impact the decision-making process.

Patients in Arm A enrolled before randomization for early toxicity assessment (Safety Run-In Cohort)

i. will not be used to evaluate the efficacy stopping rule or used in any decision making processes;
ii. will not be included in the primary and secondary efficacy comparison; will be included in the descriptive analysis of adverse events and analyses in translational study.

16.63 Adverse Events Stopping Rule

The monitoring rule specified below is based on the knowledge available at the time of study development. We note that the Adverse Event Monitoring Rule may be adjusted in the event of either (1) the study re-opening to accrual after any temporary suspension or (2) at any time during the conduct of the trial and in consideration of newly acquired information regarding the adverse event profile of the treatment(s) under investigation. The study team may also choose to suspend accrual because of unexpected adverse event profiles that have not crossed the specified rule below.

Accrual will be temporarily suspended to this study if at any time we observe events considered at least possibly related to study treatment (i.e., an adverse event with attribute specified as “possible,” “probable,” or “definite”) that satisfy any of the following criteria for each arm separately:

- If at any time 3 of the initial 10 treated patients or ≥30% of all patients on the experimental arm (i.e., when accrual is greater than 10 patients) have experienced at least one grade 4 adverse event at least possibly related to protocol treatment at any point during treatment, excluding lymphocytopenia, uncomplicated neutropenia <7 days, and uncomplicated leukopenia <7 days.
- If at any time 2 patients on the experimental arm have experienced a grade 5 adverse event at least possibly related to protocol treatment (not due to progressive disease).

NOTE: For evaluation of the AE Stopping Rule above, we will only consider patients that are included in the randomized portion of the trial.

17.0 Pathology Considerations/Tissue Biospecimens

17.1 Tissue Biospecimen Submission

NOTE: Patients must have consented to submission of the tissue(s) listed in the following table.

17.11 Summary Table of Tissue Biospecimens for This Protocol

Section	Type of tissue biospecimen to submit	Mandatory or optional	When to submit	Reason for submission (background/ methodology section)	Where to find specific details for biospecimen submission
17.111	Archival tissue: Formalin-fixed paraffin-embedded (FFPE) tissue blocks with corresponding H&E **from surgical resection or biopsy (primary or metastatic; in cases where both available primary preferred)** (OR at least 10 unstained slides with corresponding H&E)	Mandatory	≤60 days after registration/ randomization , shipped prior to C1d1	Correlative studies (Section 17.31)	Section 17.2

17.2 Archival Paraffin Embedded Tissue Blocks/Slides

17.21 Submit one formalin fixed paraffin-embedded (FFPE) tumor tissue block with largest amount of invasive tumor (at least 1 cm of tumor for cases of surgical resection) from original and/or recurrent surgery or biopsy. **A corresponding H&E slide for each submitted block must be provided** to permit quality assessment of each tissue block.

17.22 The FFPE tissue block is preferred; however, if an institution is unable to provide a tissue block, cut 11 five micron sections and mount on charged glass slides. Label the slides with ACCRU patient ID number, accession number, and order of sections. H&E stain every tenth slide (i.e., slides labeled 1, 11, 21, etc.). These H&E slides will be reviewed centrally under the research base's protocol for assessing tissue quality. The remaining unstained

slides will be processed as described in 17.51. For samples containing less than 7 square millimeters of tumor tissue, multiple sections should be mounted onto each slide to ensure that the appropriate amount of tumor tissue is available. Ideally, each slide must have a minimum of 75% tumor tissue on the slide to be deemed adequate for study. Do not bake or place covers slips on the slides. **Do not place sticky labels on the slides.**

17.23 The following materials below are mandatory (unless indicated otherwise) and required for shipment:

- Paraffin embedded tissue blocks with corresponding H&E slide (OR 10 unstained slides with corresponding H&E(s)).
- Specimen Submission: Tissue form
- Surgical Pathology Report
- Operative Report *(optional)*
- Note: Please include the ACCRU patient ID number on all materials listed above.

17.24 The block/slides must be appropriately packed to prevent damage (e.g., slides should be placed in appropriate slide container) and placed in an individual plastic bag. Label the bag with the protocol number, ACCRU patient ID number, and patient initials.

17.25 Tissue specimens must be shipped ≤ 60 days after registration/randomization and shipped before Cycle 1, Day 1.

17.26 Verify that the appropriate sections of the Specimen Submission: Tissue form are completed and filled in correctly. Enter information from the Specimen Submission: Tissue form into the remote data entry system on the same day the specimen is submitted (see Forms Packet).

17.27 Ship all block/slide tissue specimens and accompanying materials to the ACCRU Research Base:

[redacted]

17.28 If a corresponding H&E wasn't submitted with the block/slides, the ACCRU Operations Office will request a slide to be processed (i.e., cut and H&E stained) from the tumor tissue block at the IHC core facility at Mayo Clinic Rochester.

17.3 Study Methodology and Storage Information

Submitted tissue samples will be analyzed as follows:

17.31 Archival formalin-fixed paraffin-embedded tissue will be collected for the following research:

17.311 We will perform whole-exome or hotspot sequencing for a panel of relevant oncogenes and tumor suppressors to assay for mutations. This data will be utilized to determine whether specific mutations in *KRAS* or *NRAS* predict differential response to combination palbociclib/binimetinib. In addition, we will investigate whether alterations in the PI3K/AKT/MTOR pathway predict for differential

responses to combination palbociclib/binimetinib.

17.312 We will perform gene expression profiling to determine gene expression subtypes via the Consensus Molecular Subtypes (CMS subtypes). Distinct CMS subtypes are associated with distinct clinicopathologic characteristics, differential prognosis, and activation of distinct signaling pathways.[21] We will investigate whether CMS subtypes are associated with efficacy of therapy withpalbociclib/binimetinib.

17.313 We will perform immunohistochemistry to confirm staining withretinoblastoma protein is present at baseline. Additional immunohistochemical stains may be considered as well.

17.314 ACCRU will batch ship blocks/slides to The University of Texas MD Anderson Cancer Center at the end of the study.

17.32 At the completion of the study, any unused/remaining material will be stored at the The University of Texas MD Anderson Cancer Center for future research according to the patient consent permission (see Section 6.15). Potential future research may include immunohistochemistry (IHC) analyses to analyze predictive biomarkers, changes in expression pattern with therapy, and correlation with response and/or adverse events. When a protocol is developed, it will be presented for IRB review and approval.

17.33 The institutional pathologist will be notified by the Pathology Coordinator if the block may be depleted.

17.34 Blocks requested to accommodate individual patient management will be returned promptly upon request.

17.35 Return of Genetic Testing Research Results: No genetic specimens will be collected from tissue biospecimens for this study. If future genetic testing is being requested for stored tissue, patient reconsent is required.

18.0 Records and Data Collection Procedures

All data must be entered by Remote Date Entry (RDE) and completed by qualified and authorized personnel. Access the RAVE RDE system through the iMedidata portal at [redacted] All data on the CRF must reflect the corresponding source document. Please refer to the ACCRU website [redacted]) for instructions.

18.1 Submission Timetable

Initial Material(s)

CRF	**Active-Monitoring Phase** (Compliance with Test Schedule Section 4.0)
Institutional Contacts	≤ 2 weeks after registration
On-Study Form	
On-Study: Prior Surgery	
On-Study: Prior Radiation	
On-Study: Prior Systemic Therapy	
Adverse Events: Baseline	

CRF	Active-Monitoring Phase (Compliance with Test Schedule Section 4.0)
RECIST Measurements: Baseline	
Supporting Documentation: Baseline	
Laboratory Tests and Results: Baseline	
Specimen Submission: Tissue (Baseline)[2]	
Patient Status: Baseline	
OP and Path Reports (see Section 17.0)[3]	
Off Treatment	Submit ≤2 weeks after registration if withdrawal/refusal occurs prior to beginning protocol therapy
ACCRU Deviation Form[1]	Submit only if applicable during ***all*** **phases** of the study (initial, active and observation)

1. Submit only if applicable.
2. After registration/randomization, but prior to C1D1.
3. Attach an electronic copy in RAVE on the Supporting Documentation Form. This is in addition to the pathology material requirements for tissue submission (Section 17.0).

Test Schedule Material(s)

CRF	Active-Monitoring Phase (Compliance with Test Schedule Section 4.0)		
	At each evaluation during treatment	At end of treatment	Observation
Treatment (Intervention) Form	X[1]	X	
Treatment (Intervention):Dose modifications, Omissions, and Delays[2]	X	X	
Adverse Events: Solicited	X	X	
Adverse Events: Other[2]	X	X	
RECIST Measurements	X	X	X
RECIST Measurements: Crossover (Baseline)[3]	X		
RECIST Measurements: Crossover[3]	X	X	X
Supporting Documentation[2]	X	X[1]	
Specimen Submission: Blood	X	X	
Laboratory Tests and Results	X	X	X
Patient Status: Treatment (Intervention)	X	X	
Off Treatment		X	
End of Initial Treatment[3]		X	
Patient Status: Clinical Follow-up/Observation			X
Adverse Event: Late[2]			X
Notice of New Primary[2]	X	X	X
Consent Withdrawal[2]	X	X	X
Consent Withdrawal: Specimen Only[2]	X	X	X

CRF	Active-Monitoring Phase (Compliance with Test Schedule Section 4.0)		
	At each evaluation during treatment	At end of treatment	Observation
Consent Withdrawal: Clinical Follow-Up Only[2]	X	X	X
Consent Withdrawal: All Follow-Up[2]	X	X	X
ACCRU Deviation Form[2]	X	X	X

1. Attach a copy of documentation of response or progression in RAVE on the Supporting Documentation form if disease is evaluated. **NOTE: All reports must be de-identified, and labeled with study number, ACCRU patient ID number, and initials.**
2. Submit only if applicable.
3. For optional crossover only

Follow-up Material(s)

CRF	Event Monitoring Phase/Survival Follow-Up[1,4]				
	q. 6 months until PD[2]	At PD[2]	After PD q. 6 mos.	Death	At Each Event Occurrence
Patient Status: Survival and Disease Status Follow-up/Event Monitoring	X	X	X	X	
Supporting Documentation[2]		X			
Adverse Events: Late[3]	X		X		
Consent Withdrawal (choose appropriate form)[3] • Consent Withdrawal: Specimen Only • Consent Withdrawal: Clinical Follow-Up Only • Consent Withdrawal: All Follow-up	X		X		
ACCRU Deviation Form[3]					X
Notice of New Primary[3]					X

1. Patients are followed in Event Monitoring for a maximum of 3 years from registration.
2. Attach a copy in RAVE for documentation of progression on the Supporting Documentation Form.
3. Submit only if applicable.
4. Event monitoring evaluations may occur via telephone

19.0 Budget

19.1 Each site should review the test schedule (Section 4.0), taking into account local and regional coverage policies, to determine which items are standard of care and which are research at their site. Refer to the payment synopsis for funding provided per accrual for covering study costs, as

well as any additional invoiceables that may be allowed.

19.2 Tests to be research funded:

- Mandatory archival tumor tissue submission
- Mandatory blood sample

19.3 Other budget concerns:

19.31 Pfizer will provide palbociclib and binimetinib free of charge to patients while they are participating in this study.

20.0 References

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Appendix I: List of Medication to be used with Caution when Administered with Binimetinib

Version 4 – 19 August 2016

List of CYP2B6 substrates to be used with caution

CYP Enzyme	Substrates
CYP2B6	**Alkylating Agents (anticancer):** cyclophosphamide, ifosfamide, thiotepa **Others:** bupropion[1], efavirenz[1], methadone
This database of CYP substrates was compiled from the Indiana University School of Medicine's "Clinically Relevant" Table; from the FDA's "Guidance for Industry, Drug Interaction Studies" and from the University of Washington's Drug Interaction Database. [1] Sensitive substrates: Drugs that exhibit an AUC ratio (AUCi/AUC) of 5-fold or more when co-administered with a known potent inhibitor.	

List of UGT1A1 inhibitors and inducers to be used with caution

Inhibitors of UGT1A1	Inducers of UGT1A1
Atazanavir, erlotinib, flunitrazepam, gemfibrozil, indinavir, ketoconazole, nilotinib, pazopanib, propofol, regorafenib, sorafenib	Carbamazepine, nicotine, rifampicin, testosterone propionate

List of P-gp and BCRP inhibitors to be used with caution

Transporter	Inhibitor	Inducer
P-gp	Alogliptin, amiodarone, azithromycin, captopril, carvedilol, clarithromycin, conivaptan, cyclosporine, daclatasvir, diltiazem, dronedarone, eliglustat, erythromycin, felodipine, flibanserin, fluvoxamine, indinavir, indinavir and ritonavir, itraconazole, ivacaftor, ketoconazole, lapatinib, lopinavir and ritonavir, nelfinavir, paroxetine, propafenone, quercetin, quinidine, quinine, ranolazine, rifampin, ritonavir, rolapitant, saquinavir and ritonavir, simeprevir, St. John's Wort, suvorexant, telaprevir, ticagrelor, tipranavir and ritonavir, velpatasvir, verapamil, vorapaxar	Avasimibe, carbamazepine, danshen (Salvia miltiorrhiza), efavirenz, phenytoin, rifampin, St. John's wort, tipranavir/ritonavir
BCRP	Cyclosporine, elacridar (GF120918), eltrombopag, gefitinib	Not known

Based on University of Washington Database [redacted] and the FDA draft guidance for drug-drug interaction studies [redacted]

[1] Inhibitors listed for P-gp are those that showed > 25% increase in digoxin or fexofenadine area under the concentration-time curve (AUC).

[2] Inducers listed for P-gp are those that showed > 20% decrease in digoxin or fexofenadine AUC.

Appendix II: Patient Medication Diary: Binimetinib and Palbociclib

Patient Initials:_____ **Patient Study ID:**_____

MEDICATION DIARY

Patient Instructions

- Please use an ink pen when completing the Medication Diary as these will be retained in our research record. To correct an error or mistake, please make a single line through that entry and write your initials and date next to the error or mistake.
- Please record each dose as soon as you take it and fill in the date as directed.
- Please indicate on the calendar below every day that you take your study medication by placing the time the dose was taken on the line under the date.
- If you miss a dose, place a "**0**" under the date, but remember to take your prescribed dose at the next regularly scheduled time.
- Please bring your Medication Diary and ***all*** bottles and any unused study medication with you to every appointment.
- Please contact your physician and study coordinator any time you go into the hospital. Your physician can advise if you should stop taking your medication or continue it.
- Binimetinib is taken twice daily with water, approximately 12 hours apart.
- Binimetinib can be taken with our without food
- Palbociclib is taken once daily with food.
- Your study team should enter your dose of each drug in the table below.

Medication	Dose
Binimetinib **A.M.**	MG
Binimetinib **P.M.**	MG
Palbociclib	MG

Study Drug	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Date:							
Binimetinib A.M.							
Binimetinib P.M.							
Palbociclib							

Patient Initials:_____ **Patient Study ID:**_____

Study Drug	**Day 8**	**Day 9**	**Day 10**	**Day 11**	**Day 12**	**Day 13**	**Day 14**
Date:							
Binimetinib A.M.							
Binimetinib P.M.							
Palbociclib							

Study Drug	**Day 15**	**Day 16**	**Day 17**	**Day 18**	**Day 19**	**Day 20**	**Day 21**
Date:							
Binimetinib A.M.							
Binimetinib P.M.							
Palbociclib							

Study Drug	**Day 22**	**Day 23**	**Day 24**	**Day 25**	**Day 26**	**Day 27**	**Day 28**
Date:							
Binimetinib A.M.							
Binimetinib P.M.							
Palbociclib	**Do not take Palbociclib on days 22-28**						

Date:_____ Participant Signature_____

Appendix II: Patient Medication Diary: TAS-102

Patient Initials:_____ Patient Study ID:_____

MEDICATION DIARY

Patient Instructions

- Please use an ink pen when completing the Medication Diary as these will be retained in our research record. To correct an error or mistake, please make a single line through that entry and write your initials and date next to the error or mistake.
- Please record each dose as soon as you take it and fill in the date as directed.
- Please indicate on the calendar below every day that you take your study medication by placing the time the dose was taken on the line under the date.
- If you miss a dose, place a "**0**" under the date, but remember to take your prescribed dose at the next regularly scheduled time.
- Please bring your Medication Diary and ***all*** bottles and any unused study medication with you to every appointment.
- Please contact your physician and study coordinator any time you go into the hospital. Your physician can advise if you should stop taking your medication or continue it.
- TAS-102 dosage is calculated based on weight. Your study team should enter your dose in the table below.
- TAS-102 should be taken within 1 hour after completing your morning and evening meal.

Medication	Dose
TAS-102 **A.M.**	MG
TAS-102 **P.M.**	MG

Study Drug	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Date:							
TAS-102 A.M.							
Time of a.m. meal							
TAS-102 P.M.							
Time of p.m. meal							

Patient Initials:_____ Patient Study ID:_____

Study Drug	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14
Date:							
TAS-102 A.M.							
Time of a.m. meal							
TAS-102 P.M.							
Time of p.m. meal							

Study Drug	Day 15	Day 16	Day 17	Day 18	Day 19	Day 20	Day 21
Date:							
TAS-102 A.M.							
Time of a.m. meal							
TAS-102 P.M.							
Time of p.m. meal							

Study Drug	Day 22	Day 23	Day 24	Day 25	Day 26	Day 27	Day 28
Date:							
TAS-102 A.M.							
Time of a.m. meal							
TAS-102 P.M.							
Time of p.m. meal							

Date:_____ Participant Signature_____

Appendix III: Study Contraception Guidelines

Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, must agree to use highly effective methods of contraception throughout the study and for 12 weeks after study drug discontinuation.

Highly effective contraception methods include:

- Total abstinence when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are NOT acceptable methods of contraception
- Double barrier methods
  - Condom with spermicide in conjunction with use of an intrauterine device
  - Condom with spermicide in conjunction with use of a diaphragm
- Birth control patch or vaginal ring
- Oral, injectable, or implanted contraceptives
- Surgical sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up levels of luteinizing hormone (LH), follicle-stimulating hormone (FSH), and/or estradiol.
- Male sterilization (at least 6 months prior to registration). For female patients on the study, the vasectomized male partner should be the sole partner for that patient

NOTE: Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation ≥42 days of registration. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment is she considered not of child bearing potential.

Sexually active males must use highly effective methods of contraception throughout the study and for 12 weeks after study drug discontinuation and should not father a child in this period.

Highly effective contraception methods include:

- Total abstinence when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are NOT acceptable methods of contraception
- Double barrier methods
  - Condom with spermicide in conjunction with use of an intrauterine device
  - Condom with spermicide in conjunction with use of a diaphragm
- Surgical sterilization (vasectomy) at least 6 weeks prior to registration

Appendix IV: Patient Lifestyle Guidelines

Patients should not embark on a new, strenuous exercise regimen after first dose of study treatment.

NOTE: Muscular activities, such as strenuous exercise, that can result in significant increases in plasma CPK levels should be avoided while on binimetinib treatment.

Appendix V: Snellen Equivalence visual acuity conversion chart

Visual Acuity Conversion Chart*											
Distance			LogMAR Acuity Chart				Near				
Snellen Feet 20/	Equivalent Meter 6/	Decimal	Line Number	LogMAR†	Spatial Frequency (cyc/deg)	% Central Visual Efficiency	Jaeger Standard	Inches (14/)	Centimeters (35/)	Revised American Point-Type	"M" Notation
10	3.0	2.00	-3	-0.30	60.00	100	—	7.0	17.5	—	0.20
12.5	3.8	1.60	-2	-0.20	48.00	100	—	8.8	21.9	—	0.25
16	4.8	1.25	-1	-0.10	37.50	100	—	11.2	28.0	—	0.32
20	6.0	1.00	0	0.00	30.00	100	1	14.0	35.0	3	0.40
25	7.5	0.80	1	0.10	24.00	95	2	17.5	43.8	4	0.50
30	9.0	0.67	—	0.18	20.00	91	3	21.0	52.5	5	0.60
32	9.6	0.63	2	0.20	18.75	90	4	22.4	56.0	6	0.64
40	12.0	0.50	3	0.30	15.00	85	5	28.0	70.0	7	0.80
50	15.0	0.40	4	0.40	12.00	75	6	35.0	87.5	8	1.0
60	18.0	0.33	—	0.48	10.00	67	7	42.0	105.0	9	1.2
63	18.9	0.32	5	0.50	9.52	65	8	44.1	110.3	10	1.3
70	21.0	0.29	—	0.54	8.57	63	—	49.0	122.5	—	1.4
80	24.0	0.25	6	0.60	7.50	60	9	56.0	140.0	11	1.6
100	30.0	0.20	7	0.70	6.00	50	10	70.0	175.0	12	2.0
114	34.2	0.18	—	0.76	5.26	44	11	79.8	199.5	13	2.3
125	37.5	0.16	8	0.80	4.80	40	12	87.5	218.8	14	2.5
150	45.0	0.13	—	0.88	4.00	32	—	105.0	262.5	—	3.0
160	48.0	0.13	9	0.90	3.75	30	13	112.0	280.0	21	3.2
200	60.0	0.10	10	1.00	3.00	20	14	140.0	350.0	23	4.0

**Courtesy Jack Holladay, MD, modified from full Holladay table. For full table, visit www.journalofrefractivesurgery.com*
†Log minimum angle of resolution; bold values are standard logMAR progression.

Note: 20/2000 is equivalent to count fingers @ 2 feet; 20/20000 is equivalent to hand motion @ 2 feet

Resources
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5. *Newell FW. Ophthalmology: Principles and Concepts. 7th ed. St Louis, MO: CV Mosby Co; 1992.*
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Revised Visual Acuity Abbreviations*

UDVA	uncorrected distance visualacuity
UIVA	uncorrected intermediate visualacuity
UNVA	uncorrected near visual acuity
CDVA	corrected distance visualacuity
CIVA	corrected intermediate visualacuity
CNVA	corrected near visual acuity
DCNVA	distance-corrected near visualacuity

**Kohnen T. New abbreviations for visual acuity values (editorial). J Cataract Refract Surg. 2009;35:1145.*

REPORTABLE EVENT FAX COVER SHEET

Appendix VI
Internal Use Only by ACCRU

Use this fax cover sheet to fax a reportable event for investigator-initiated research studies

Include with this form the completed Pfizer investigator-initiated research (IIR) serious adverse event (SAE) form, MedWatch Form FDA 3500A-Mandatory Reporting, which can be obtained from the FDA website: [redacted] or other Pfizer agreed-upon form for SAE reporting. If you are using the MedWatch Form to report, the following information should be included in block 5 of the adverse events section:

The complete clinical course of the patient receiving Pfizer drug
The causality assessment for each reportable event
The action taken for each study drug and for each reportable event
The outcome for each reportable event

This cover sheet MUST be provided with each completed SAE form.
Do not substitute forms/reports or submit additional documentation (such as source documentation) other than what is required.

Do not fax these forms to any additional fax numbers other than the one listed below.

TO:	***Pfizer U.S. Clinical Trial Department***		
FAX:	[redacted]		
FROM:		DATE:	
TELEPHONE:		FAX:	
NUMBER OF PAGES (INCLUDING COVER SHEET):			
PRODUCT	Ibrance® (palbociclib)		
PFIZER REFERENCE NUMBER	WI220239	EXTERNAL REFERENCE NUMBER	ACCRU-GI-1618
STUDY TITLE	*Combination of MEK inhibitor Binimetinib and CDK4_6 inhibitor Palbociclib in KRAS and NRAS mutant metastatic colorectal cancers*		
PATIENT NUMBER			
INVESTIGATOR	[redacted]		

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