Title: Phase 2 trial of palbociclib and ganitumab in pa□ents with relapsed or refractory Ewing sarcoma

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TITLE: Phase 2 trial of palbociclib and ganitumab in patients with relapsed or refractory Ewing sarcoma or SDH-deficient gastrointestinal stromal tumor (GIST)

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Statistician:

Agent Supply: Palbociclib supplied by Pfizer / Ganitumab supplied by ImmunityBio

IND #: 146033
IND Sponsor:

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0 SCHEMA

This is a prospective, open-label, non-randomized, single arm two-cohort phase 2 clinical trial conducted at Dana-Farber/Harvard Cancer Center sites: Dana-Farber/Boston Children's Cancer and Blood Disorders Center; Dana-Farber/Brigham and Women's Hospital; and Massachusetts General Hospital.

In November of 2020, new pre-clinical evidence was made available indicating a potential vulnerability in SDH-deficient gastrointestinal stromal tumor (GIST) to the combination of CDK4/6 inhibition and IGF-1R inhibition. The study is amended to include one cohort for patients with relapsed or refractory Ewing sarcoma (Cohort A), and a second cohort for patients with SDH-deficient gastrointestinal stromal tumor (SDH-GIST, Cohort B). Participants will be treated with a CDK4/6 inhibitor (palbociclib) in combination with a monoclonal antibody inhibitor of IGF-1R (ganitumab). Participants in each of the two disease-based cohorts will be enrolled in a single-stage design to estimate the radiographic objective response rate as the primary endpoint. Once enrolled, patients will begin therapy in 28-day cycles with palbociclib orally once daily on days 1-21 and ganitumab 18 mg/kg IV days 1 and 15 (**Figure 1**). Cohort A will begin therapy with a palbociclib dose of 100 mg daily on days 1-21, while patients in Cohort B will begin therapy at a dose of 125 mg daily on days 1-21.

Disease will be evaluated at baseline, then after cycle 2, 4, 6, 8, 10 and 12 unless otherwise clinically indicated. In the absence of disease progression or unacceptable toxicity, patients may receive up to 12 cycles of therapy (approximately 12 months).

As palbociclib and ganitumab have not previously been studied in combination, stopping rules will be utilized to monitor for unexpected toxicity.

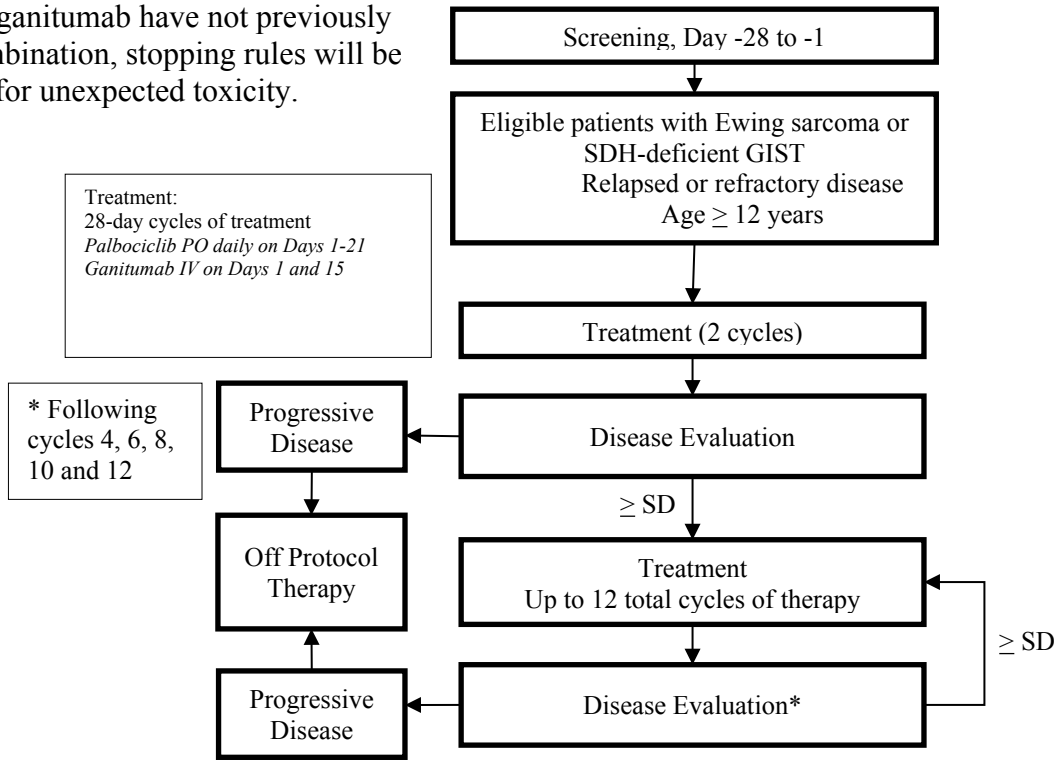

Figure 1: Study schema

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1 OBJECTIVES

1.1 Study Design

This is a prospective, open-label, non-randomized, single arm two cohort phase 2 clinical trial. Cohorts of patients with relapsed or refractory Ewing sarcoma (Cohort A) or SDH-deficient GIST (Cohort B) will be enrolled and treated with a combination of palbociclib and ganitumab.

The study will be conducted at Dana-Farber/Harvard Cancer Center sites: Dana-Farber/Boston Children's Cancer and Blood Disorders Center; Dana-Farber/Brigham and Women's Hospital; and Massachusetts General Hospital.

The primary study objective is to evaluate the potential efficacy of palbociclib and ganitumab in one cohort of patients with relapsed or refractory Ewing sarcoma or (based on preclinical rationale presented in 2020) a second cohort of patients with SDH-deficient GIST, using a single-stage design in each cohort to assess radiographic objective response as the endpoint for the primary objective.

To be evaluable for the assessment of response or toxicity, a patient on either cohort must receive at least one dose of either agent. Additionally, to be evaluable for assessment of response, patients must either have evidence of clinical progression or have had at least one follow-up disease evaluation of their RECIST measurable disease after initiation of protocol therapy.

Disease will be evaluated at baseline, after cycles 2, 4, 6, 8, 10 and 12. In the absence of disease progression or unacceptable toxicity, patients may receive up to 12 cycles of therapy (approximately 12 months).

As palbociclib and ganitumab have not previously been studied in combination, stopping rules will be utilized to monitor for unexpected toxicity. Given that toxicity profiles of patients with Ewing sarcoma and GIST may not overlap, there will be separate stopping rules for Cohort A and Cohort B.

1.2 Primary Objectives

1.2.1 To estimate the objective radiographic response rate to the combination of palbociclib and ganitumab in a cohort of patients with relapsed or refractory Ewing sarcoma or in a separate cohort of patients with SDH-deficient GIST.

1.2.2 To describe the toxicity of the combination of palbociclib and ganitumab in patients with relapsed or refractory Ewing sarcoma, as well as in a separate cohort of patients with SDH-deficient GIST.

1.3 Secondary Objective

1.3.1 To estimate progression-free survival and overall survival in patients with relapsed or refractory Ewing sarcoma as well as in the separate cohort of patients with SDH-deficient GIST treated with the combination of palbociclib and ganitumab.

1.4 Correlative Biology Objectives

1.4.1 To evaluate serial measurements of circulating tumor DNA burden as a surrogate marker of response to protocol therapy.

1.4.2 To evaluate serial measurements of IGF-1 related serum proteins as potential pharmacodynamic markers of IGF pathway inhibition.

1.4.3 To explore secondary somatic mutations and tumor protein and RNA markers as potential predictive markers of clinical benefit from the combination of palbociclib and ganitumab.

1.4.4 To bank tumor material, germline DNA, and peripheral blood for potential future research for participating subjects who provide additional consent.

2 BACKGROUND

2.1 Relapsed and Refractory Ewing sarcoma

Ewing sarcoma
Ewing sarcoma is a rare, aggressive malignancy of bone and soft tissue, most commonly affecting adolescents and young adults. Patients with localized Ewing sarcoma have a 70-75% overall survival with surgery, and/or radiation for local control, and compressed every two-week cycles of vincristine, doxorubicin and cyclophosphamide, alternating with ifosfamide/etoposide.[1–3] While serial cooperative group studies have gradually improved outcomes for patients with localized Ewing sarcoma, survivors carry a significant burden of late effects. Patients with metastatic Ewing sarcoma transiently respond to therapy, but only a small minority of patients will have long-term disease control.[4–7] Patients with relapsed Ewing sarcoma likewise fare poorly, with only few survivors.[8–11]

Ewing sarcoma is a classic translocation-associated malignancy, with nearly all cases carrying an identifiable *EWSR1* or *FUS* translocation (most commonly *EWRS1/FLI1*). The translocation leads to an aberrant fusion oncoprotein that is thought to function as a pathogenic transcription factor. Despite our understanding of the fundamental biology of this disease, targeting this transcription factor has been elusive and most strategies have focused on targeting downstream vulnerabilities.

2.2 Study Agents

2.2.1 Ganitumab: IGF-1R inhibitor

2.2.1.1 IGF-1R inhibitors demonstrate significant pre-clinical activity in EWS

Several lines of evidence indicate that targeting the insulin-like growth factor receptor-1 (IGF-1R) pathway will be an effective strategy in the treatment of Ewing sarcoma. All but one Ewing sarcoma cell line evaluated in two early studies demonstrated expression of both IGF-1 and IGF-IR.[12,13] Ewing sarcoma cell lines express higher IGF-1 levels compared to other pediatric sarcomas (osteosarcoma and rhabdomyosarcoma).[14] In contrast to wild-type fibroblasts, fibroblasts lacking the IGF-1R were not transformed after transfection with *EWSR1/FLI1*.[15] *EWSR1/FLI1* appears to repress expression of IGF binding protein-3 (IGF-BP3), an endogenous inhibitor of the IGF-1 pathway.[16] Several small molecule inhibitors of IGF-1R have demonstrated activity in preclinical models of Ewing sarcoma.[17–19] In one study, Ewing sarcoma was among the solid tumor histologies most sensitive to inhibition by one such inhibitor, GSK1904529A.[19]

Early studies demonstrated that a monoclonal antibody against the IGF-1R inhibited the growth of all tested Ewing sarcoma cell lines.[12,13,20] This effect was also observed in Ewing sarcoma mouse xenografts.[12] Compared to 43% of control-treated mice, no antibody-treated mice developed lung metastases. The Pediatric Preclinical Testing Program (PPTP) has evaluated two IGF-1R monoclonal antibodies (SCH 717454 and cixutumumab) in a panel of Ewing sarcoma cell lines and xenografts.[21,22] SCH 717454 demonstrated little *in vitro* activity. In contrast, 2 of 5 Ewing sarcoma xenografts demonstrated significant prolongation of time to event and significant inhibition of tumor growth after treatment with SCH 717454.[22] Cituxumumab demonstrated both *in vitro* and *in vivo* activity. Two of four Ewing sarcoma cell lines demonstrated more than 50% reduction in cell growth. Two of five Ewing sarcoma xenografts showed reductions in tumor size and three of five showed prolongation in time to event.[21]

2.2.1.2 Clinical experience with IGF pathway inhibitors in Ewing sarcoma

These preclinical results have translated into clinical activity for IGF-1R monoclonal antibodies in patients with relapsed or refractory Ewing sarcoma. A phase 2 study of ganitumab included 18 patients with Ewing sarcoma. One patient had a confirmed partial response (6% response rate).[23] Closer evaluation of the data demonstrated that 6/18 (33%) patients had tumor regression of at least 10%. In Children's Oncology Group (COG) protocol ADVL0712, one of 10 patients with Ewing sarcoma treated with cituxumumab at the 6 mg/kg dose level had a confirmed partial response and 4 additional patients had stable disease for at least 3 cycles. At the 9 mg/kg dose level, 2 of 20 patients had RECIST partial responses.[24] Of the 16 patients with Ewing sarcoma treated on a phase 1 study of figitumumab, one patient had a complete response, one patient had a partial response, and 6 patients had stable disease for more than 4 months (12.5% response rate).[25] A phase 2 study of figitumumab in 106 patients with relapsed or refractory Ewing sarcoma demonstrated a 14% response rate.[26] A phase 1 study of dalotuzumab included 6 patients with Ewing sarcoma, one of whom had a mixed response.[27] [redacted]

These studies indicate that IGF-1R monoclonal antibodies have single agent activity in patients with relapsed or refractory EWS, with objective response rates of approximately 10%. Moreover, this class of agents has been well tolerated. For example, an adult phase 1 trial of ganitumab did not identify a maximum tolerated dose up to 20 mg/kg every 2 weeks.[28] The most common adverse events were generally low grade and included fatigue, thrombocytopenia, fever, rash, chills and anorexia. Hyperglycemia was noted in <5% of patients and there were no grade 4+ related adverse events. In the phase 2 trial of ganitumab in patients with Ewing sarcoma and desmoplastic small round cell tumor, the most common related adverse events of any grade were fatigue (9%), thrombocytopenia (8%), infusion reaction (6%), nausea (6%), anemia (5%), and hyperglycemia (5%).[23] Ganitumab has also been evaluated in combination with gemcitabine in the context of a randomized trial for patients with metastatic pancreatic carcinoma.[29] Compared to patients treated with placebo + gemcitabine, patients treated with ganitumab + gemcitabine appear to have higher rates of hyperglycemia, thrombocytopenia, fatigue, vomiting and diarrhea.

[redacted]

2.2.2 Palbociclib: Small molecule CDK4/6 inhibitor

2.2.2.1 CDK4/6 activity has been implicated in Ewing sarcoma

[redacted]

2.2.2.2 Clinical experience with palbociclib

Palbociclib is an FDA-approved oral CDK4/6 inhibitor indicated for the treatment of adults with

hormone receptor-positive, HER2 negative advanced breast cancer. The approved dose is 125 mg by mouth daily for 21 days followed by 7 days of rest in 28-day cycles. This dose is tolerable when given in combination with fulvestrant or an aromatase inhibitor. The most common adverse events include neutropenia, infection, leukopenia, fatigue, nausea, stomatitis, anemia, alopecia, diarrhea, thrombocytopenia, rash, vomiting, decreased appetite, asthenia, and fever (FDA Package Insert). The most common grade 3 adverse events are neutropenia and infection.

Palbociclib has been studied in an unpublished Pediatric Brain Tumor Consortium trial, with a defined maximum tolerated dose of 75 mg/m^2/dose in that population. The ongoing Pediatric MATCH subprotocol investigating palbociclib utilizes a dose of 75 mg/m^2/dose to a maximum of 125 mg/dose. In this trial focused on adolescents and adults, flat dosing of 125 mg/dose was utilized initially, consistent with FDA draft guidance for adolescents > 40 kg. Given that two initial patients in Cohort A treated with palbociclib 125 mg dosing experienced first cycle DLTs, a contingency dosing strategy was enacted on 1/8/2020 and subsequent patients in Cohort A have started treatment with 100 mg dosing on days 1-21 of a 28-day cycle. Patients with SDH-deficient GIST do not receive upfront chemotherapy in most cases and never with the intensity given to patients with Ewing sarcoma. As such, hematologic toxicity is unlikely to be overlapping between Cohorts. Patients in Cohort B will thus start treatment at a palbociclib dose of 125 mg orally on days 1-21.

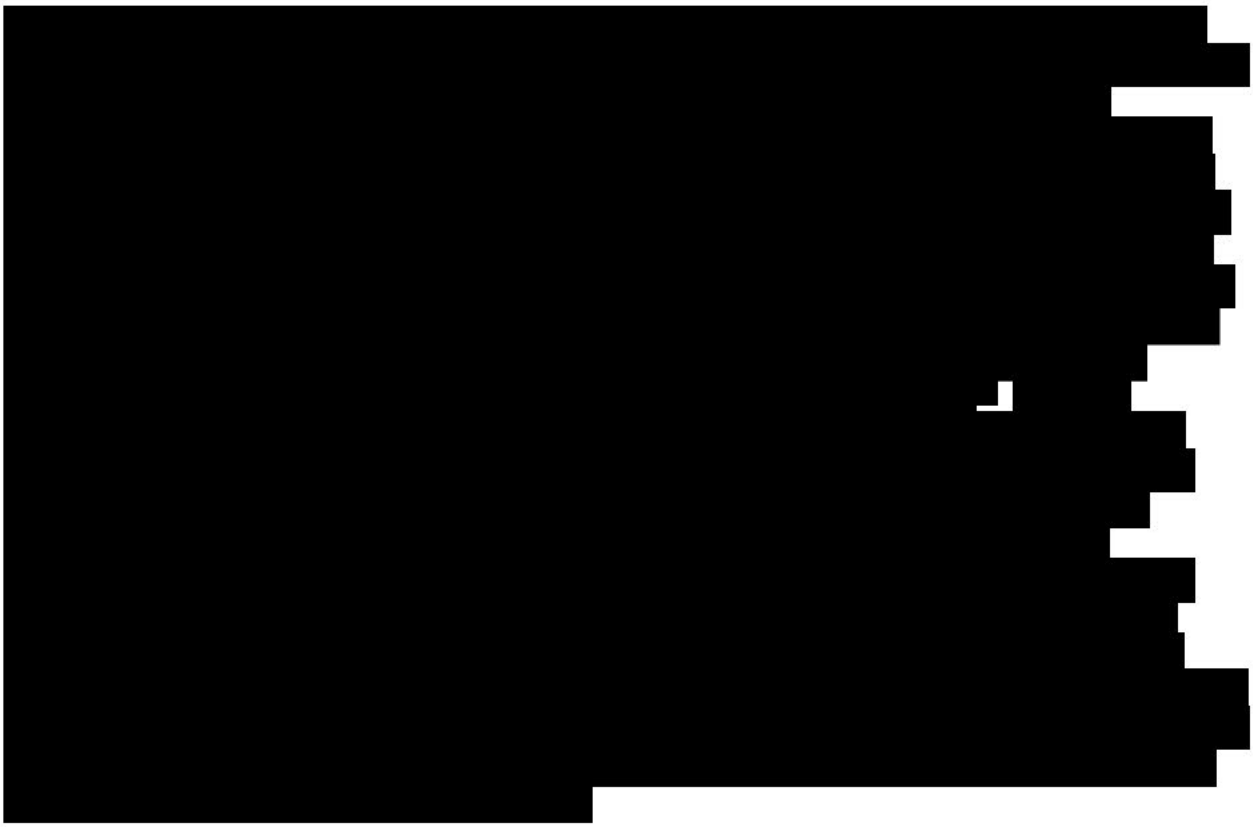
2.3 **Rationale for evaluation of palbociclib and ganitumab in combination**

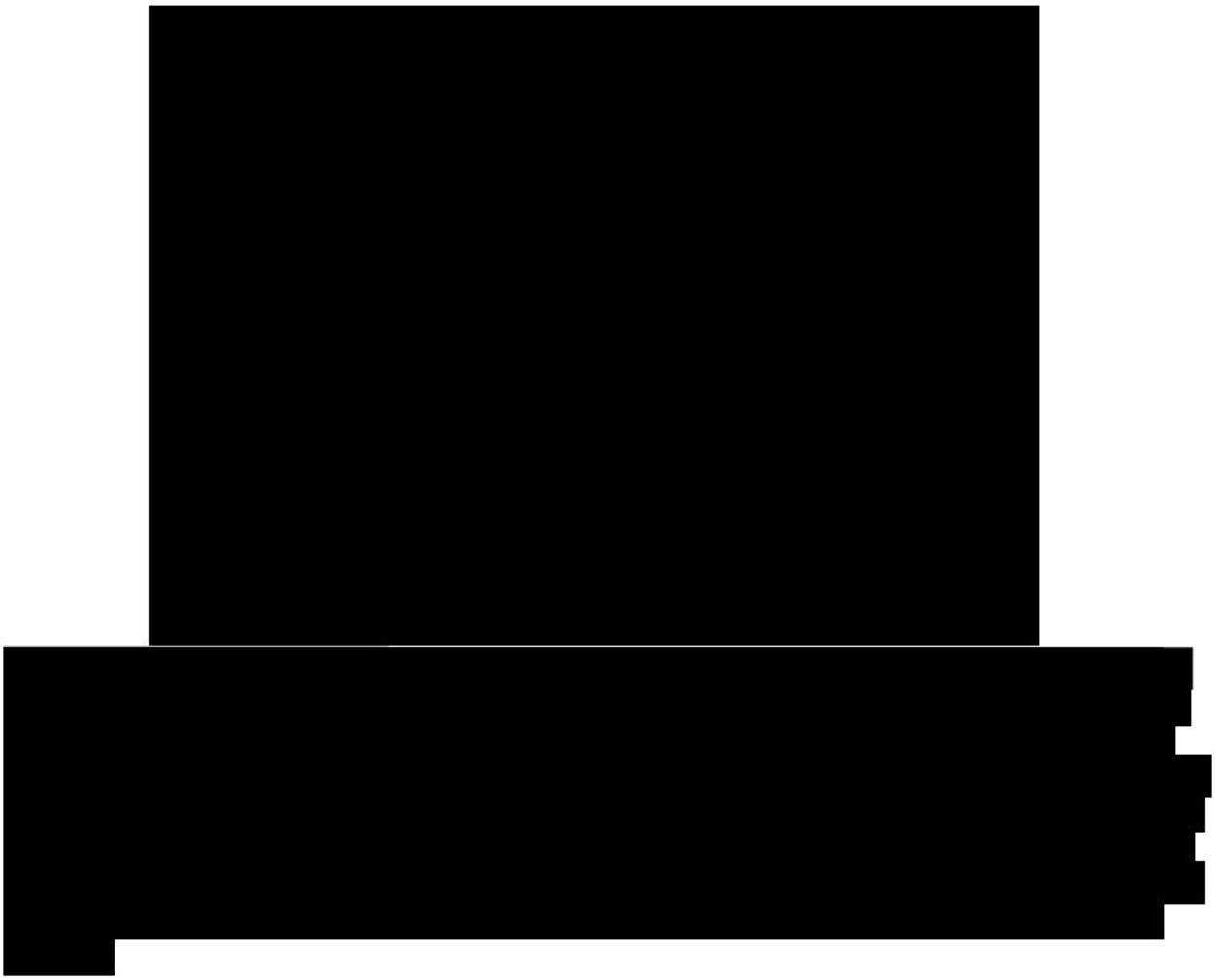
[redacted]

2.4 Rationale for evaluation of palbociclib and ganitumab in SDH-Deficient GIST

GIST is among the most common soft tissue sarcomas, with an estimated annual incidence in the US of 6,000 cases.[30] While activating mutations in the receptor tyrosine kinase *KIT* represent the most common oncogenic driver in this disease, 10-15% of cases are characterized by loss of the succinate dehydrogenase (SDH) complex, leading to altered metabolism and epigenetic dysregulation.[31,32] Patients with metastatic or unresectable SDH-deficient GIST are treated with tyrosine kinase inhibitors as standard therapy, though response rates are modest and more targeted therapies are urgently needed.[33]

Prospective trials studying effects of treatment in SDH-deficient GIST are limited. As compared to imatinib, sunitinib demonstrated activity in a cohort of 7 patients, with one patient achieving a partial response.[31] In a study of regorafenib which included 6 SDH-deficient GIST patients, two of these patients experienced a PR, with a median PFS of 10 months.[34] In a recent study of linsitinib in SDH-deficient GIST, no responses were seen, and median PFS was 10 months.[35]





2.5 **Rationale for planned correlative studies**

New technology has emerged that enables detection of circulating tumor DNA (ctDNA) collected from the plasma. This technology enables non-invasive detection and quantification of ctDNA as well as detection of a range of potential translocations of interest and other potential mutations of interest in Ewing sarcoma (eg. *STAG2* and *TP53*).[38,39] ctDNA has not been previously described in SDH-deficient GIST, and deletions or mutations in SDHx genes can be assessed using this investigational approach. This testing will be performed by the Crompton laboratory at Dana-Farber/Boston Children's. ctDNA will be assessed at the time of study enrollment and in response to therapy.

Data have emerged that support a potential association between serum IGF-1 levels and outcome after anti-IGF-1R therapy in patients with relapsed Ewing sarcoma. These studies demonstrated that elevated baseline and Week 6 total serum IGF-1 as well as a higher relative increase in serum IGF-1 correlated with outcomes in patients with relapsed Ewing sarcoma treated with

R1507.[40] Total and free serum IGF-1 levels also correlated with outcomes in patients with relapsed Ewing sarcoma treated with figitumumab.[26] Increases in growth hormone, insulin, and IGFBP3 have also been reported in patients with Ewing sarcoma treated with IGF-1R monoclonal antibodies, though the impact of these changes on outcomes have not yet been reported.[24,26] In preclinical studies, upregulation of IGF-2 expression has been described as a mechanism of resistance to IGF-1R inhibition in Ewing sarcoma, though not yet evaluated as a potential biomarker of resistance in clinical studies.[41] In SDH-deficient GIST patients treated with the small molecule IGF-1R inhibitor linsitinib, higher levels of IGF-1 and insulin were found in circulation while on study compared to baseline.[35]

The genetic landscape of Ewing sarcoma has recently been described by several groups and highlights the relative paucity of mutations in this disease. In addition to EWSR1/ETS translocations, a subset of these tumors harbor *STAG2*, *TP53*, and *CDKN2A* mutations. Similarly, SDH-deficient GIST has been described to have a paucity of secondary mutations, though this has not been formally examined using modern sequencing approaches. We will use next generation sequencing techniques to assess these and other mutations in archival tumor material to determine if the presence of these mutations impacts the likelihood of clinical benefit to protocol therapy. We will also have an opportunity to interrogate the ctDNA for these same mutations over time in response to protocol therapy.

2.6 **Overall summary of rationale**

Studies of IGF-1R monoclonal antibodies administered as a single agent to patients with relapsed Ewing sarcoma provide proof-of-concept that this strategy has activity in this context, though objective response rates are low. Compelling preclinical data demonstrate that combining IGF-1R inhibition with CDK4/6 inhibition leads to synergistic activity in Ewing sarcoma. We will now test this combination in a phase 2 clinical trial of palbociclib and ganitumab for patients with relapsed or refractory Ewing sarcoma.

Given the favorable toxicity profile of both agents and the dismal outcomes for this population, maximizing exposure to this combination is a priority. Dosing in this trial initially utilized the established combination therapy dose for palbociclib of 125 mg PO once daily for 21 days out of every 28-day cycle as well as the dose of ganitumab (18 mg/kg IV on days 1 and 15) that has been shown to be tolerable in combination with intensive multiagent chemotherapy (AEWS1221). Palbociclib is FDA approved as combination therapy with aromatase inhibitors or fulvestrant at a dose of 125 mg. A drug-drug interaction between this small molecule inhibitor and a monoclonal antibody is not anticipated. Nevertheless, as palbociclib and ganitumab have not previously been studied in combination, the protocol includes stopping rules to monitor for an unanticipated safety signal.

Given that two initial patients treated on the Ewing sarcoma cohort (Cohort A) with palbociclib 125 mg dosing experienced first cycle DLTs, a contingency dosing strategy was enacted on 1/8/2020 and subsequent patients have started treatment with 100 mg dosing on days 1-21 of a 28-day cycle.

In November of 2020, new pre-clinical evidence was made available indicating a potential vulnerability in SDH-deficient GIST to the combination of CDK4/6 inhibition and IGF-1R inhibition. Given the lack of effective options for this cohort of patients this study was amended to include a parallel single stage cohort (Cohort B) for patients with SDH-deficient GIST. Patients in this cohort will enroll to full dose palbociclib (125 mg daily on days 1-21 of a 28-day cycle; and ganitumab: 18 mg/kg IV on days 1 and 15). Unlike patients with Ewing sarcoma, patients with SDH-deficient GIST do not receive maximally intensive cytotoxic chemotherapy as frontline therapy and thus are not predicted to experience the same degree of hematologic toxicity with this combination. Given the toxicity profile of these agents may differ significantly in patients with GIST given the vast differences in upfront therapy, Cohort B will have a toxicity monitoring rule that is separate from Cohort A.

3 PARTICIPANT SELECTION

Prior to approaching a potential participant, treating investigators should reserve a treatment slot by contacting the Study Coordinator. Upon reserving a treatment slot, an investigator may begin the informed consent process for that participant. Once informed consent has been obtained, the investigator may begin screening studies to confirm eligibility. Once all eligibility criteria have been satisfied, the investigator may enroll the participant according to Section 4.0.

Baseline laboratory tests and ECG must be completed within 14 days prior to the date of enrollment. Laboratory tests used to meet eligibility requirements may be completed within 14 days prior to date of enrollment, but select tests must be repeated within 5 days prior to dosing on Cycle 1, Day 1 if obtained > 5 days prior to Cycle 1, Day 1 as described in Section 5.2. If repeat laboratory studies no longer meet eligibility requirements, the patient must not receive protocol therapy. In this case, required studies may be repeated again within 5 days. If these studies now meet eligibility requirements, the patient may proceed with protocol therapy, otherwise the patient will be removed from study and replaced.

Baseline disease assessments (such as MRIs, CT scans, bone marrow biopsies, and nuclear medicine studies) must be performed within 28 days prior to the date of enrollment.

3.1 **Eligibility Criteria**

3.1.1 Age ≥ 12 years at time of enrollment for patients with Ewing sarcoma.

3.1.2 Age ≥ 12 years at time of enrollment for patients with SDH-deficient GIST.

3.1.3 Karnofsky performance status ≥ 50% for patients ≥16 years of age and Lansky ≥ 50% for patients <16 years of age (see Appendix A)

3.1.4 Disease Requirement for Cohort A: Participants with Ewing sarcoma must have:

3.1.4.1 RECIST measurable disease at study entry, including at least one RECIST measurable site that has either not been previously radiated or that has had progression after prior radiotherapy;

3.1.4.2 Participants must have relapsed or refractory disease for which standard curative or palliative measures do not exist or are no longer effective.

3.1.4.3 Histologic diagnosis consistent with Ewing sarcoma or PNET; and

3.1.4.4 Molecular evidence of translocation involving *EWSR1* or *FUS* (also known as *TLS*), such as FISH, RT-PCR, or next generation sequencing. If the translocation partner is known it must be of the ETS family (i.e. FLI1 or ERG).

3.1.5 Disease Requirement for Cohort B: Participants with SDH-deficient GIST must have:

3.1.5.1 RECIST measurable disease at study entry, including at least one RECIST measurable site; and

3.1.5.2 Histologic diagnosis consistent with GIST; and

3.1.5.3 Evidence of SDH-deficiency by immunohistochemistry, or molecular evidence of SDHX mutation.

3.1.6 Patients must have fully recovered (Common Terminology Criteria for Adverse Events [CTCAE] version 5 Grade ≤1) from the acute toxic effects of all prior anti-cancer therapy except organ function as noted in Section 3.1.6. Patients must meet the following minimum washout periods prior to enrollment:

3.1.6.1 Myelosuppressive chemotherapy: At least 14 days after the last dose of myelosuppressive chemotherapy (42 days for nitrosourea or mitomycin C).

3.1.6.2 Radiotherapy:

- At least 14 days after local palliative XRT (small port);
- At least 90 days must have elapsed after craniospinal XRT or if >50% radiation of pelvis;
- At least 6-months must have elapsed following TBI or thoracic radiation involving the lungs;
- At least 42 days must have elapsed if other substantial bone marrow radiation;

3.1.6.3 Small molecule biologic therapy: At least 7 days following the last dose of a biologic agent. For agents with known adverse events occurring beyond 7 days, this duration must be extended beyond the time in which adverse events are known to occur. If extended duration is required, this should be discussed and approved by the study chair.

3.1.6.4 Monoclonal antibody: At least 21 days must have elapsed after the last dose of antibody.

3.1.6.5 Myeloid growth factors: At least 14 days following the last dose of long-acting growth factor (e.g. Neulasta®) or 7 days following short-acting growth factor.

3.1.6.6 Immunotherapy: At least 4 weeks since the completion of immunotherapy (e.g. tumor vaccines) aside from monoclonal antibodies with immune effects covered under Section 3.1.5.4.

3.1.6.7 Stem Cell Infusion or Cellular Therapies: The patient must have no evidence of graft versus host disease and at least 42 days must have elapsed after transplant, stem cell infusion, or cellular therapy.

3.1.6.8 Major Surgery: At least 2 weeks from prior major surgical procedure. Note: Biopsy and central line placement/removal are not considered major surgery.

3.1.6.9 CDK4/6 and IGF-1R inhibitors: The participant must not have received a prior CDK4/6 inhibitor. Prior therapy with IGF-1R inhibitor is allowed if the patient did not relapse while on IGF-1R therapy. Patients must not have received prior therapy with a combination of CDK4/6 inhibitor and IGF-1R inhibitor.

3.1.7 Participants must have normal organ function as defined below.

3.1.7.1 Hematologic Requirements for Subjects without Known Bone Marrow Involvement by Disease:

- Absolute neutrophil count >1000 /uL
- Hemoglobin ≥ 8 g/dL (transfusion allowed)
- Platelets ≥100,000 /uL and transfusion independent, defined as not receiving a platelet transfusion for at least 7 days prior to CBC documenting eligibility.

3.1.7.2 Hematologic Requirements for Subjects with Bone Marrow Involvement by Disease as Demonstrated on Clinically-Indicated Bone Marrow Biopsy:

- Absolute neutrophil count >750 /uL
- Hemoglobin ≥ 8 g/dL (transfusion allowed)
- Platelets ≥50,000 /uL and transfusion independent, defined as not receiving a platelet transfusion for at least 7 days prior to CBC documenting eligibility.
- Not known to be refractory to platelet or red cell transfusions.

3.1.7.3 Hepatic Function:

- Total bilirubin ≤ 1.5 x upper limit of normal for age
  Patients with Gilbert's syndrome with a total bilirubin < 2 x upper limit of normal for age and

a direct bilirubin within normal limits are permitted.

- ALT (SGPT) ≤ 135 U/L
  For the purpose of this study, the ULN for ALT is 45 U/L
- AST ≤ 90 U/L
  For the purpose of this study, the ULN for AST is 30 U/L
- Serum albumin ≥ 2 g/dL

3.1.7.4 Renal Function:

- A serum creatinine based on age/gender as follows:

Age	Maximum Serum Creatinine (mg/dL)	
	Male	Female
12 to < 13 years	1.2	1.2
13 to < 16 years	1.5	1.4
≥ 16 years	1.7	1.4

OR

- Creatinine clearance ≥ 70 mL/min/1.73 m^2 for participants with creatinine levels above institutional normal.

3.1.7.5 Adequate Cardiac Function: QTc ≤ 480 msec on ECG

3.1.7.6 Adequate GI Function: Diarrhea < grade 2 by CTCAE version 5

3.1.7.7 Adequate Metabolic Function: Fasting glucose ≤ 160 mg/dL (or ≤ 8.9 mmol/L) without the use of antihyperglycemic agents. If random glucose ≤ 160 mg/dL (or ≤ 8.9 mmol/L), fasting value does not need to be obtained.

3.1.8 Additional Agent-Specific Requirements

3.1.8.1 Patients must be able to swallow pills.

3.1.7.3 For patients with CNS metastatic disease, any baseline neurologic deficits (including seizure) must be stable for at least one week prior to study enrollment.

3.1.9 Ability to understand and/or the willingness of the patient (or parent or legally authorized representative, if minor) to provide informed consent, using an institutionally approved informed consent procedure.

3.2 **Exclusion Criteria**

3.2.1 Patients must not be receiving any of the following concomitant medications:

3.2.1.1 Pharmacologic doses of systemic corticosteroids unless for CNS metastatic disease. For patients with CNS metastatic disease receiving corticosteroids, they should be on a stable or decreasing dose over the 7 days prior to registration and meet criteria in Section 3.1.6.7.

For all patients, receipt of systemic physiologic replacement steroids, topical and/or inhaled corticosteroids is acceptable.

3.2.1.2 Patients receiving medications that are strong inhibitors or inducers of CYP3A4 within 7 days of enrollment (refer to Appendix B, **Table 10** for prohibited medications)

3.2.1.3 Patients receiving medications that cause significant QTc prolongation as outlined in **Table 12** of Appendix B.

3.2.2 Patients who have had tumor molecular testing with sequencing of the RB1 gene and were found to have RB1 mutation or loss will be excluded.

3.2.3 Patients with a history of pneumonitis will be excluded.

3.2.4 Pregnant participants will not be entered on this study given that the effects of palbociclib and ganitumab on the developing human fetus are unknown.

3.2.5 Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with palbociclib and ganitumab, breastfeeding mothers are not eligible.

3.2.6 Participants of child-bearing or child-fathering potential must agree to use adequate contraception (hormonal birth control; intrauterine device; double barrier method; or total abstinence) throughout their participation, including up until 30 days after last dose of palbociclib or ganitumab, whichever was administered last.

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

3.2.8 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.

3.2.9 Participants with a personal history of any of the following: syncope due to an intrinsic cardiac etiology (note that syncope due to vasovagal episodes or dehydration/orthostasis would NOT exclude a participant), pathologic ventricular arrhythmias (including, but not

limited to, ventricular tachycardia and ventricular fibrillation), or sudden cardiac arrest.

3.2.10 Patients with known HIV, hepatitis B, and/or hepatitis C (testing not required as part of screening).

3.2.11 Patients with a known history of type 1 or type 2 diabetes mellitus.

3.2.12 Patients with gastrointestinal disease or disorder that could interfere with absorption of palbociclib, such as bowel obstruction or inflammatory bowel disease.

3.2.13 Patients < 40 kg will be excluded given use of palbociclib at non-weight / non-BSA based flat dosing.

3.2.14 Patients with prior invasive malignancies within 5 years are excluded, with the exception of curatively-treated basal cell or squamous cell carcinoma of the skin or carcinoma *in situ* of the cervix.

3.3 Inclusion of Children and Minorities

Both male and female children and young adults of all races and ethnic groups are eligible for this trial.

4 REGISTRATION PROCEDURES

4.1 General Guidelines for All Sites

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

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

An investigator will confirm eligibility criteria and will complete and sign the protocol-specific eligibility checklist.

Following registration, participants may begin protocol therapy and should begin protocol therapy within 5 calendar days. Issues that would cause treatment delays should be discussed with the Overall Principal Investigator (PI). If a participant does not receive protocol therapy following registration, the participant's registration on the study must be canceled. Registration cancellations must be made in OnCore as soon as possible.

5 TREATMENT PLAN

5.1 **Treatment Regimen**

5.1.1 Overview of Treatment Regimen

Once enrolled, patients will begin therapy in 28-day cycles with palbociclib orally once daily on days 1-21 according to the below Cohort dosing, and ganitumab 18 mg/kg on days 1 and 15 as shown in **Figure 4**. Disease will be evaluated at baseline, after cycle 2, 4, 6, 8, 10 and 12.

Palobociclib dosing:

- Cohort A – Palbociclib 100 mg orally daily on days 1-21
- Cohort B – Palbociclib 125 mg orally daily on days 1-21

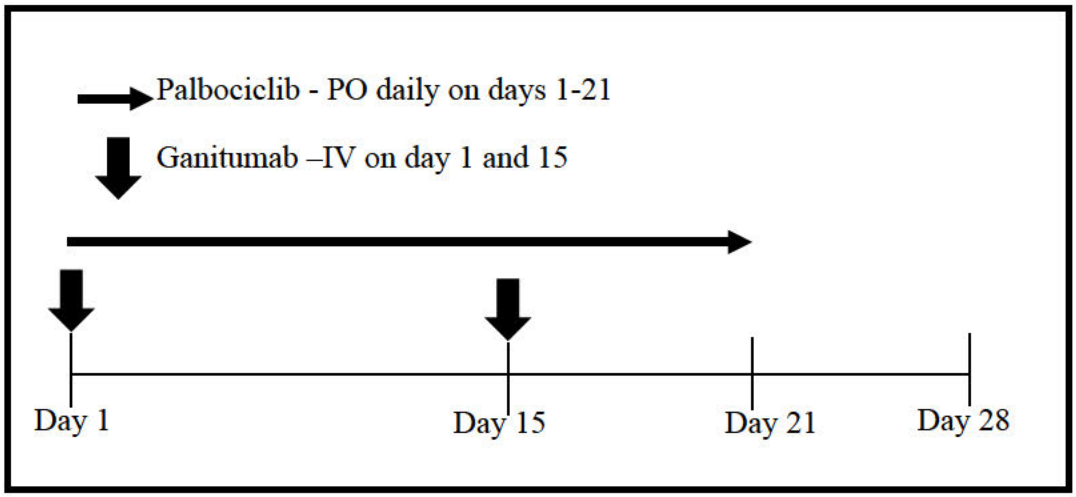


Figure 4: Treatment overview

Patients may begin therapy on any day of the week as an inpatient or as appropriate for the outpatient clinic schedule. A window of +/- 3 days around Day 1 cycle start dates and +/- 1 day around Day 15 ganitumab administration is allowable for logistical reasons.

Appropriate dose modifications are described in Section 6. Reported adverse events and potential risks are described in Section 7. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy.

In the absence of criteria for removal from protocol therapy (see Section 5.6), participants may continue to receive the study regimen for up to 12 cycles (approximately 12 months of therapy).

5.2 **Pre-Treatment Criteria**

5.2.1 Cycle 1, Day 1

If screening laboratory and diagnostic studies for registration were obtained > 5 days prior to Cycle 1, Day 1, then **the following studies must be repeated within 5 days of Cycle 1, Day 1 and prior to the Cycle 1, Day 1 palbociclib and ganitumab dose: CBC; creatinine or creatinine clearance; bilirubin; ALT; serum albumin; fasting or random glucose** (see Section 3.1.7.7).

If any of these repeat laboratory studies do not meet organ function requirements in Section 3.1.7, then the patient must not receive protocol therapy. In this case, laboratory studies may be repeated again within 5 days. If these laboratory studies now meet eligibility requirements, the patient may proceed with protocol therapy, otherwise the patient will be removed from study.

5.2.2 Subsequent Cycles

Prior to the start of each subsequent cycle of therapy, patients without bone marrow involvement must meet all of the following criteria:

- No clinical or radiographic evidence of disease progression;
- Meet hematologic, renal, hepatic, and metabolic organ function requirements listed in Section 3.1.7, with the following exception:
  - ANC ≥ 750/uL
  - Platelets ≥ 75,000/uL and transfusion independent, defined as not receiving a platelet transfusion for at least 5 days prior to CBC
- All other adverse events at baseline or ≤ grade 2, whichever is lower.

Prior to the start of each subsequent cycle of therapy, patients who enrolled with bone marrow involvement as demonstrated on a clinically indicated bone marrow must meet all of the following criteria:

- No clinical or radiographic evidence of disease progression;
- Meet hematologic, renal, hepatic, and metabolic organ function requirements listed in Section 3.1.7, with the following exception:
  - ANC ≥ 500/uL
  - Platelets ≥ 50,000/uL and transfusion independent, defined as not receiving a platelet transfusion for at least 5 days prior to CBC
- All other adverse events at baseline or ≤ grade 2, whichever is lower.

Laboratory studies to meet these requirements may be obtained within 3 days of Day 1 of each cycle.

5.3 **Agent Administration**

5.3.1 Palbociclib

Palbociclib will be administered at 100 mg daily orally on Days 1-21 of each cycle for patients in Cohort A and 125 mg daily orally on Days 1-21 of each cycle for Cohort B.

Palbociclib will be provided as 125 mg, 100 mg or 75 mg pills.

Palbociclib should be taken as follows:

- Patients should be instructed to take their dose at approximately the same time each day (+/- 4-hour window acceptable around each dose). On days when ganitumab is administered, the timing of palbociclib administration can proceed independently of the timing of ganitumab administration.
- Each dose of palbociclib should be taken with water (no required minimum volume).
- Pills should be swallowed whole and not chewed, crushed or split.
- Palbociclib may be provided as a tablet or capsule formulation. Instructions differ based on formulation. Tablets may be taken with or without food. Capsules must be taken within 1 hour of eating.
- If a patient vomits or misses (not taken within 6 hours of the intended time) a dose of palbociclib, the patient should take the next dose as scheduled and not redose.
- Patients should inform the investigational site staff of any missed or delayed doses.

Each dose of palbociclib will be recorded in a medication diary. The medication diary will be returned to clinic staff at the end of each cycle. Palbociclib blister packs (tablet formulation) or pill bottles (capsule formulation) should be returned to the clinic at the start of each subsequent cycle. The study team will perform pill counts.

In the absence of safety data in pregnant animals or humans, women who are pregnant or could be pregnant should use gloves when handling palbociclib. Caregivers should use caution when cleaning up emesis, with the use of gloves recommended.

5.3.2 Ganitumab

Ganitumab is administered via IV on days 1 and 15 of each cycle.

Ganitumab will be administered at a dose of 18 mg/kg.

Ganitumab should be administered as follows:

- The infusion line should be thoroughly flushed with saline before and after administration of ganitumab to avoid mixing with other drug products or IV solutions.
- The first dose should be administered over 60 minutes without premedication. If well tolerated over 60 minutes, subsequent infusions may be administered over 30 minutes, at the investigator's discretion. Infusion times can be extended to a maximum of 120 minutes for subjects unable to tolerate the 60-minute infusion.
- Doses over 2100 mg should be infused over 120 minutes. If well tolerated over 120 minutes, subsequent infusions may be administered over 60 minutes at the investigator's discretion.
- The dose of ganitumab is to be based upon the participant's weight in kg obtained within 7 days of the start of each cycle. There is no adjustment for obesity.

See section 8.1.2.5 for ganitumab preparation.

5.3.3 Allowed Local Control Measures

Patients may undergo surgery and/or radiotherapy to sites of disease according to the following rules:

- Only after confirmed response (meaning two consecutive disease evaluation scans showing at least a partial response);
- Hold both study drugs at least 1 week prior to surgery and for a minimum of 2 weeks following surgery;
- Hold both study drugs at least 24 hours prior to radiation, during radiation, and for a minimum of 1 week following radiation;
- Defer to institutional standard for surgical or radiation approaches;
- Thoracic radiation is forbidden while on therapy given potential risk of pneumonitis in patients treated with ganitumab.

5.4 **Dose-Limiting Toxicity (DLT)**

5.4.1 Definition of Dose-Limiting Toxicity

Toxicity will be graded using the CTCAE criteria, version 5. The CTCAE provides descriptive terminology and a grading scale for each adverse event listed. A copy of the CTCAE can be downloaded from the CTEP home page (**http://ctep.cancer.gov**). Any dose-limiting toxicity should be reported immediately via email to the overall Principal Investigator and to the Study Coordinator.

Definition of Dose-Limiting Toxicity

DLT is defined as any of the following events that are possibly, probably or definitely attributable to palbociclib or ganitumab. A DLT may occur in any cycle and will guide dose modifications, but only DLTs occurring in the first cycle will be used for implementation of the safety monitoring rule (Section 13.4).

Non-Hematological DLT:

- Any Grade 3 or higher non-hematological toxicity attributable to palbociclib or ganitumab with the specific exclusion of:
  - Grade 3 nausea and vomiting, anorexia, diarrhea or dehydration resolving to ≤ grade 2 within 72 hours (note that grade 3 diarrhea requiring hospitalization would constitute DLT).
  - Grade 3 AST or ALT liver enzyme elevation that return to < grade 2 within 7 days (except as below if bilirubin also elevated). If grade 3 liver enzyme elevation occurs, palbociclib and ganitumab should be held and liver enzymes rechecked within 4 days of initial date of grade 3 abnormality to determine if DLT criteria have been met. See also Section 6.4. **Recall:** For the purposes of this study the ULN for ALT is defined as 45 U/L and for AST is 30 U/L.

- Grade 3 hypophosphatemia, hypokalemia, hypocalcemia or hypomagnesemia responsive to oral supplementation within 72 hours.
- Grade 2 elevation of AST and/or ALT WITH total bilirubin > 2 x ULN, in the absence of cholestasis.
- Any Grade 2 non-hematological toxicity that persists for ≥ 7 days and is considered sufficiently medically significant or sufficiently intolerable by patients that it requires treatment interruption.
- Any non-hematologic toxicity that results in delay in start of subsequent cycle by > 14 days.

Hematological DLT:

- Hematological dose limiting toxicity is defined as:
  - Grade 4 thrombocytopenia or grade 4 neutropenia of any duration, in the absence of bone marrow disease; or
  - Grade 3 or higher febrile neutropenia with or without documentation of infection; or
  - Grade 3 thrombocytopenia in association with a grade 2 or higher bleeding episode; or
  - Delay in the start of subsequent cycle by > 14 days due to thrombocytopenia or neutropenia, in patients without known bone marrow disease.

Patients with bone marrow metastatic disease at study entry will not be evaluable for hematologic DLT for the purposes of evaluating the toxicity monitoring rule. Such patients will follow the dose modification criteria in Section 6.2.1 in the setting of defined hematologic DLT.

Any Grade 5 toxicity that is possibly, probably, or definitely attributable to palbociclib or ganitumab will be considered a DLT.

Management and dose modifications associated with the above adverse events are outlined in Section 6.

5.4.2 Dose de-escalation rules

If at any time, safety stopping rules are met as outlined in section 13.4, enrollment will be paused and one of two contingency dosing strategies for subsequent patients will be considered based upon the nature of the observed dose-limiting toxicities. The choice of contingency dose strategy will be made by the study committee in consultation with Pfizer and ImmunityBio.

Upon initial activation of this study, two of the first three enrolled patients in Cohort A experienced cycle 1 DLTs. This met stopping criteria for our interim monitoring rule and Contingency A was enacted on 1/8/2020. Should the new stopping rule as outlined in section 13.4 be met, Contingency B or C as outlined below will be considered for Cohort A. Cohort B has not yet met any stopping critiera.

- Contingency A: Palbociclib 100 mg daily on days 1-21 and ganitumab 18 mg/kg on days 1 and 15
- Contingency B: Palbociclib 75 mg daily on days 1-21 and ganitumab 18 mg/kg on days 1 and 15

- Contingency C: Palbociclib 75 mg daily on days 1-21 and ganitumab 12 mg/kg on days 1 and 15

If a contingency dosing strategy is implemented, the same monitoring rule will apply (starting anew with next enrollment). If criteria are met again for the toxicity monitoring rule, the protocol will be flagged for amendment. Any toxic death will be cause for review by the DSMB and the study committee for consideration of protocol amendment.

5.5 **General Concomitant Medication and Supportive Care Guidelines**

5.5.1 Concomitant Medications

5.5.1.1 No other cancer chemotherapy or anticancer therapies are allowed except local measures specified in section 5.3.3.

5.5.1.2 Appropriate antibiotics, blood products, anti-emetics, fluids, electrolytes and general supportive care are to be used as necessary (see Section 5.5.2).

5.5.1.3 Patients may not receive corticosteroids EXCEPT under the following conditions:

- Physiologic replacement for patients with adrenal insufficiency
- As needed to manage allergic reactions
- To prevent transfusion reactions
- Inhaled or topical administration
- In patients with metastatic CNS disease, use of doses that have been stable or tapering since enrollment.

5.5.1.4 Subjects must not receive any of the QT prolonging agents in Appendix B, Table 12. QT prolonging agents in Appendix B, Table 13 are to be used with caution.

5.5.1.5 Subjects must not receive strong CYP3A inducers or inhibitors (delineated in Appendix B, Table 10) within 7 days of enrollment and while on protocol therapy. Subjects receiving moderate CYP3A inhibitors should be monitored (see Appendix B, Table 11).

Subjects receiving concomitant medications metabolized by CYP3A enzymes should be monitored at the discretion of the investigator, particularly if the concomitant medication has a narrow therapeutic window and/or is known to rely strongly on one of these isoenzymes for its metabolism. Such medications may have an interaction with palbociclib.

Patients must avoid consumption of grapefruit products, and Seville oranges or products containing the juice of each while on protocol therapy, due to potential CYP3A4 interaction with the study medications. Orange juice is allowed.

Please refer to the palbociclib and ganitumab Investigator's Brochures for additional drug interaction information.

5.5.2 Supportive Care Guidelines

5.5.2.1 Use of Myeloid Growth Factors

Myeloid growth factors are only to be utilized in the setting of grade 3 or 4 neutropenia together with documented invasive fungal infection, bacteremia, or fever with sepsis physiology. The overall Principal Investigator should be notified in the event of myeloid growth factor use. Patients who receive myeloid growth factor for grade 3 neutropenia will be excluded from assessment of dose-limiting neutropenia in that cycle. If a patient receives myeloid growth factor, palbociclib and ganitumab must not be resumed until at least 48 hours following the last administered dose of short acting myeloid growth factor and until at least 7 days following the last administered dose of long-acting myeloid growth factor.

5.5.2.2 Antiemetics

Palbociclib may be emetogenic, but routine use of prophylactic antiemetics is not indicated. For patients who develop nausea, appropriate non-corticosteroid antiemetics should be utilized according to institutional guidelines (aprepitant is discouraged; see Appendix B).

5.6 **Criteria for Taking a Participant Off Protocol Therapy**

Duration of therapy will depend on individual response, evidence of disease progression, and tolerance. Treatment may continue for up to 12 cycles or until one of the following criteria applies:

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Dose-limiting or other toxicity that meets criteria for removal from protocol therapy (see Section 6)
- Participant demonstrates an inability or unwillingness to comply with the oral medication regimen and/or documentation requirements
- Participant decides to withdraw from the protocol therapy
- Pregnancy
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the judgment of the treating investigator

Participants will be removed from the protocol therapy when any of these criteria apply. The reason for removal from protocol therapy, and the date the participant was removed, must be

documented in the case report form (CRF). Alternative care options will be discussed with the participant.

When a participant is removed from protocol therapy and/or is off of the study, the participant's status must be updated in OnCore in accordance with REGIST-OP-1.

In the event of unusual or life-threatening complications, treating investigators must immediately notify the Overall PI, [redacted]

5.7 Duration of Follow Up

Participants will return to the study center for adverse event follow-up approximately 30 days from last dose of protocol therapy. This period may be extended until resolution of any ongoing adverse events. Participants removed from protocol therapy for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event. For participants unable to return to the study center for the planned 30-day follow-up visit, documentation of a clinic evaluation at their referring center is acceptable.

Patients will be followed for survival until 1 year from when the last dose of protocol therapy is given to the last enrolled participant. Return to the study center will not be required as part of survival follow-up.

5.8 Criteria for Taking a Participant Off Study

Participants will be removed from study when any of the following criteria apply:

- Completion of follow-up per section 5.7;
- Found to be ineligible, including participants who have repeat organ function laboratory studies obtained within 5 days of Cycle 1, Day 1 that do not meet entry eligibility requirements. Participants who are found to have a diagnosis other than Ewing sarcoma/PNET, or SDH-deficient GIST during the course of study therapy may continue on protocol therapy only if evidence of clinical benefit and only after discussion with the overall Principal Investigator. Such patients will be replaced for the purposes of evaluating the primary aim of the study.;
- Lost to follow-up;
- Withdrawal of consent for data submission;
- Death.

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

6 DOSING DELAYS/DOSE MODIFICATIONS

Dose delays and modifications will be made as indicated in the following text and table(s). The descriptions and grading scales found in the revised NCI Common Terminology Criteria for

Adverse Events (CTCAE) version 5.0 will be utilized for guiding dose delays and dose modifications.

6.1 Dose Modification for Dose-Limiting Toxicity

Patients with protocol-defined DLT (Section 5.4.1) will have palbociclib and ganitumab held. Except where noted below for specific target toxicities, palbociclib and ganitumab will be held until resolution of toxicity to ≤ Grade 1 (or baseline, whichever is higher grade), and then palbociclib and ganitumab will be resumed with dose reduction according to Sections 6.2 (palbociclib) and 6.3 (ganitumab). If a patient cannot resume therapy within 21 days of holding palbociclib and ganitumab, they will be removed from protocol therapy.

Patients with recurrent DLT (regardless of category of DLT) despite this dose reduction are eligible for up to one additional dose reduction of palbociclib. Patients with recurrent DLT despite two dose reductions of palbociclib will be removed from protocol therapy. If a second dose reduction is required for toxicity related to ganitumab, the patient will be removed from protocol therapy.

Patients who meet criteria for permanent discontinuation of one study agent (e.g., severe allergic reaction), will be removed from protocol therapy altogether rather than continuing with monotherapy.

6.2 Management of Palbociclib Dose Reductions

Dose reductions for palbociclib are outlined in **Table 1**.

Table 1: Palbociclib dose modifications for adverse reactions

Cohort A	
Dose Level	**Dose of Palbociclib**
Starting dose	100 mg daily
First dose reduction	75 mg daily
Cohort B	
Dose Level	**Dose of Palbociclib**
Starting dose	125 mg daily
First dose reduction	100 mg daily
Second dose reduction	75 mg daily

6.3 Management of Ganitumab Dose Reductions

Dose reductions for ganitumab are outlined in **Table 2**.

Table 2: Ganitumab dose modifications for adverse reactions

Dose Level	**Dose of Ganitumab**
Starting dose	18 mg/kg on days 1 and 15
First dose reduction	12 mg/kg on days 1 and 15

6.4 **Dose Modifications for Non-Hematologic Toxicity**

6.4.1 Management of QTc Prolongation

QTc prolongation is a potential risk of palbociclib. In the setting of QTc prolongation, treat reversible causes such as serum electrolyte abnormalities and/or reduce usage of concomitant QTc-prolonging medications. See **Table 3** for recommended dose modifications in the setting of QTc prolongation.

Table 3: Palbociclib dose modifications for prolonged QTc

	Grade 2 QTc prolongation	**Grade 3 QTc prolongation**	**Grade 4 QTc Prolongation**
Reversible cause identified	Treat reversible causes Initiate more frequent ECG monitoring according to investigator's best medical judgement until QTc < 480 msec Continue at the same dose level	Treat reversible causes Withhold treatment until QTc < 501 msec Resume treatment at same dose Initiate more frequent ECG monitoring according to investigator's best medical judgement until QTc < 480 msec	Remove from protocol therapy
No reversible cause identified	Initiate more frequent ECG monitoring according to investigator's best medical judgement until QTc < 480 msec Continue at the same dose level	Withhold treatment until QTc < 501 msec Resume treatment at one dose level below the current dose unless the patient has had two dose reductions of palbociclib in which case the patient must	Remove from protocol therapy

		be removed from protocol therapy Initiate more frequent ECG monitoring according to investigator's best medical judgement until QTc < 480 msec	

6.4.2 Management of Hyperglycemia

For patients who develop hyperglycemia (based on random, non-fasting glucose levels), discontinue use of corticosteroids before modifying ganitumab dose. If hyperglycemia occurs without use of corticosteroids, ganitumab therapy modifications should be as follows:

Hyperglycemia Grade (per CTCAE, under *Hyperglycemia*)	**Action**
Grade 1	Continue ganitumab.
Grade 2	Continue ganitumab. Consider consultation with Pediatric Endocrinologist.
Grade 3 **or** Urine glucose > 0.1 g/dL	• Initiate insulin therapy or oral diabetic agent* as indicated. • Hold ganitumab until resolves to ≤ Grade 2 without glycosuria. • Resume ganitumab at same dose IF patient is asymptomatic, AND serum glucose is consistently < 250 mg/dL (≤ Grade 2) without glycosuria AND resolution to ≤ Grade 2 has occurred within 2 weeks of interruption. The patient may continue to receive concomitant insulin or an oral diabetic agent for the management of hyperglycemia while receiving ganitumab. • If Grade 3 hyperglycemia recurs despite a stable dose of insulin or oral diabetic agent OR if resolution to consistent levels ≤ Grade 2 requires more than 2 weeks of interruption, subsequent doses should be administered with a reduced dose of 12 mg/kg/dose.
Grade 4	• Initiate insulin therapy as indicated. • If associated with diabetic ketoacidosis or hyperosmolar nonketotic syndrome, discontinue ganitumab permanently. Otherwise, use the following instructions. • Hold ganitumab until resolves to ≤ Grade 2.

	• Resume ganitumab with a reduced dose of 12 mg/kg/dose IF patient is asymptomatic, AND serum glucose is consistently < 250 mg/dL (≤ Grade 2) without glycosuria AND resolution to ≤ Grade 2 has occurred within 2 weeks of interruption. The patient may continue to receive concomitant insulin or an oral diabetic agent for the management of hyperglycemia while receiving ganitumab. • If resolution to consistent levels ≤ Grade 2 requires more than 2 weeks of interruption OR if Grade 4 toxicity recurs after re-challenge with 12 mg/kg, then discontinue ganitumab permanently.

*** Recommended guidelines for use of oral diabetic agents:**
Initiation of treatment for hyperglycemia should occur under the guidance of a pediatric endocrinologist at the local institution. Metformin may be used per local endocrinologist's recommendations.

Other oral anti-hyperglycemic agent may be used at the discretion of the local treating institution. Insulin therapy should be directed by specialists in pediatric diabetes with the goal of normal fasting blood sugars < 126 mg/dL **and HgbA1C < 8%.**

6.4.3 Management of ganitumab-related infusion reactions

For patients who have allergic or acute infusion reactions, therapy modifications based on grade should be as follows. Guidelines for emergency management of infusion reactions are recommendations and institutional standard practice may be used as an alternative.

Grade	Action
Grade 1 Transient flushing or rash, drug fever < 38°C (< 100.4° F)	• Slow infusion rate by 50% and monitor patient for worsening of condition. Maximum infusion duration is 120 minutes.
Grade 2 Rash, flushing, urticaria, dyspnea, drug fever ≥ 38° C (≥ 100.4° F)	• Stop infusion; symptom control (diphenhydramine hydrochloride **1 mg/kg** (max 50 mg) IV, acetaminophen 10-15 mg/kg (max 650 mg) PO or IV for fever, and oxygen if needed). • Resume infusion at 50% of the prior rate once the reaction has decreased to ≤ Grade 1. Monitor patient for worsening condition. Maximum infusion duration is 120 minutes. • For subsequent dose, premedicate with diphenhydramine hydrochloride **1 mg/kg** (max 50 mg) IV. • If Grade 1-2 infusion reactions reoccur with subsequent dose, add dexamethasone **0.2 mg/kg** (max 10 mg) IV or equivalent to premedications above. (Only dose interruption/discontinuation, but not dose reduction, is required for allergic/infusional reactions.)

Grade 3 Symptomatic bronchospasm with or without urticaria, allergy-related edema/ angioedema, hypotension	• Stop infusion immediately. • Administer diphenhydramine hydrochloride **1 mg/kg** (max: 50 mg) IV, dexamethasone **0.2 mg/kg** (max: 10 mg) IV (or equivalent), bronchodilators for bronchospasms, and other medications as medically indicated. Hospital admission should be considered. • Discontinue ganitumab treatment permanently.
Grade 4 Anaphylaxis	• Stop infusion immediately • Administer diphenhydramine hydrochloride **1 mg/kg** (max 50 mg) IV, dexamethasone **0.2 mg/kg** (max 10 mg) IV (or equivalent), and other anaphylaxis medications as indicated. Epinephrine or bronchodilators should be administered as indicated. Hospital admission for observation may be indicated. • Discontinue ganitumab treatment permanently.

6.5 **Dose Modifications for Hematologic Toxicity**

Hematologic toxicity is considered an adverse event with the use of palbociclib and has also been reported less commonly with IGF-1R monoclonal antibodies, including ganitumab. Palbociclib dose modifications are outlined in Sections 6.5.1. Ganitumab should be held if a patient meets criteria for hematologic DLT per Section 5.4.1. For a patient's first hematologic DLT, palbociclib will be dose reduced, but ganitumab may be resumed without dose modification once the patient meets criteria to resume palbociclib according to **Table 8 or 9**. For recurrent hematologic DLTs despite one palbociclib dose reduction, ganitumab should be resumed at a lower dose according to **Table 2** in addition to any additional required dose reductions for palbociclib.

6.5.1 Palbociclib Dose Modifications in the Setting of Hematologic Toxicity

Patients with dose-limiting hematologic toxicity should have their palbociclib dose modified according to **Table 8** or **9** depending on whether they have bone marrow involvement by disease.

Table 8: Palbociclib Dose Modification and Management of Hematologic Toxicities for Patients without Bone Marrow Involvement by Disease

CTCAE Grade	Palbociclib Dose Modifications
ANC < LLN to 750/uL, or platelet count < LLN to 75,000/uL	No dose modification is required.
ANC <750 to 500/uL, or platelet count <75,000/uL to 50,000	Continue current dosing. Dose reduction is only required if this definition of hematologic DLT is met: o Delay in the start of subsequent cycle by > 14 days due to thrombocytopenia or neutropenia, in the absence of bone marrow disease seen on clinically-indicated bone marrow biopsy.
Platelet count < 50,000 to 25,000/uL	Hold palbociclib until platelet count recovers to 75,000/uL. Resume at prior dose unless one or both of these definitions of hematologic DLT is met: o Grade 3 thrombocytopenia in association with a grade 2 or higher bleeding episode; or o Delay in the start of subsequent cycle by > 14 days due to thrombocytopenia, in the absence of bone marrow disease seen on clinically-indicated bone marrow biopsy.
Grade 4 neutrophil count	Suspend dose until ANC improves to ≥ 750 /uL. Once recovered, resume at next lower dose (as long as neutropenia not due to progressive bone marrow involvement, in which case patient must come off protocol therapy).
Grade 4 platelet count	Suspend dose until platelet count improves to ≥ 75,000/uL and transfusion independent, defined as not receiving a platelet transfusion for at least 5 days prior to CBC. Once recovered, resume at next lower dose (as long as thrombocytopenia not due to progressive bone marrow involvement, in which case patient off protocol therapy).
Patient requires administration of myeloid growth factor	Suspend palbociclib dose for at least 48 hours after the last dose of myeloid growth factor and until ANC improves to ≥ 750 /uL. If growth factor was given in the setting of grade 4 neutropenia, resume palbociclib at next lower dose unless the dose was already reduced for the toxicity that led to the use of the growth factor.

Table 9: Palbociclib Dose Modification and Management of Hematologic Toxicities for Patients Enrolling with Bone Marrow Involvement by Disease

Hematologic criteria	Palbociclib Dose Modifications
ANC < LLN - 500/uL, or platelet count < LLN - 50,000/uL	No dose modification is required.
ANC < 500/uL, or platelet count < 50,000/uL during Cycle 1	Continue current dosing unless: • Life threatening infection; or • Life threatening bleeding. Dose reduction is not required unless delay in the start of subsequent cycle by > 14 days due to thrombocytopenia or neutropenia, then reduce by one dose level.
ANC < 500/uL, or platelet count < 50,000/uL during subsequent cycles	Suspend dose until ANC improves to ≥ 500 /uL and platelet count to ≥ 50,000 /uL and transfusion independent, defined as not receiving a platelet transfusion for at least 5 days prior to CBC. Dose reduction is not required unless delay in the start of subsequent cycle by > 14 days due to thrombocytopenia or neutropenia, then reduce by one dose level.
Patient requires administration of a myeloid growth factor	Suspend palbociclib dose for at least 48 hours after the last dose of short-acting myeloid growth factor or 7 days after long-acting growth factor and until ANC improves to ≥ 500 /uL. Follow guidelines in preceding rows if ANC was < 500 /uL

LLN – Lower Limit of Normal

7 ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

7.1 Introduction to Adverse Event Reporting

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of reported and/or potential AEs (Sections 7.2 and 7.3) and the characteristics of an observed AE (Section 7.4) will determine whether the event requires expedited reporting **in addition** to routine reporting.

7.2 **Adverse Event List for Palbociclib**

The following adverse events have been reported in the phase I monotherapy studies of palbociclib in adults (see Investigator Brochure).

Greater than 20% Incidence
- Diarrhea
- Nausea
- Constipation
- Fatigue
- Neutropenia
- Anemia
- Anorexia
- Infection

10-20% Incidence
- Vomiting
- Abdominal Pain
- Leukopenia
- Thrombocytopenia
- Pyrexia
- Nervous System Disorders
- Arthralgia
- Peripheral Edema
- Pain
- Dyspnea
- Cough
- Back Pain
- Rash
- Insomnia

Rare but serious side effects reported
- Interstitial Lung Disease / pneumonitis

For the purposes of determining expectedness for expedited adverse event reporting, all of the above adverse events are to be considered expected.

7.3 **Adverse Event List for Ganitumab**

The following adverse events have been reported in the monotherapy studies of ganitumab (see Investigator Brochure).

Greater than 20% Incidence
- Fatigue

- Nausea
- Anorexia
- Thrombocytopenia
- Vomiting
- Pyrexia
- Anemia
- Dyspnea

10-20% Incidence
- Neutropenia
- Diarrhea
- Rash
- Back Pain
- Constipation
- Abdominal Pain
- Peripheral Edema
- Cough
- Infusion-related reaction
- Anxiety
- Arthralgia
- Chest Pain
- Chills
- Hyperglycemia
- Depression
- Pain

In the recent Phase 3 trial of ganitumab given combination with intensive multiagent chemotherapy (AEWS1221), pneumonitis was reported in 5 patients who had received prior thoracic radiation.

7.4 **Adverse Event Characteristics**

Investigators are to provide the following adverse event characteristics for all adverse events experienced from start of protocol therapy until 30 days after last dose of palbociclib or ganitumab, which ever came later:

- CTCAE term (AE description) and grade**:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site, https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.
- Attribution of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.

- Possible – The AE *may be related* to the study treatment.
- Unlikely – The AE *is doubtfully related* to the study treatment.
- Unrelated – The AE *is clearly NOT related* to the study treatment.

- Seriousness of the AE: An AE is to be classified as "serious" (SAE) if it meets any of the following criteria:

Death of Patient	An event that results in the death of a patient.
Life-Threatening	An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
Hospitalization	An event that results in an admission to the hospital for any length of time. This does not include an emergency room visit or admission to an outpatient facility.
Prolongation of Hospitalization	An event that occurs while the study patient is hospitalized and prolongs the patient's hospital stay.
Congenital Anomaly	An anomaly detected at or after birth or any anomaly that result in fetal loss.
Persistent or Significant Disability/ Incapacity	An event that results in a condition that substantially interferes with the activities of daily living of a study patient. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, or accidental trauma (*e.g.,* sprained ankle).
Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome	An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the patient and may require medical or surgical intervention to prevent any of the outcomes listed above (*i.e.,* death of patient, life-threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

An AE that meets none of the above criteria is considered "non-serious".

Note: Seriousness is independent of attribution or expectedness of the AE.

- Expectedness of the AE: In addition to term, grade, attribution, and seriousness, adverse events that have the potential to qualify for expedited reporting (see Section 7.6) are to be designated as "expected" or "unexpected". For the purposes of determining expectedness, all of the adverse events listed in Section 7.2 and 7.3 are to be considered expected.

7.5 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions to the Overall PI on the toxicity case report forms. **AEs that also meet criteria for expedited reporting (see Section 7.6) must also be reported in routine study data submissions.**

7.6 Expedited Adverse Event Reporting

7.6.1 Criteria for Expedited Adverse Event Reporting

Investigators **must** report to the Overall PI in an expedited manner any adverse events (AE) that occur after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment if they meet any of the following criteria and are not listed as adverse events exempt from expedited reporting in Section 7.6.2:

- Serious adverse events;
- Other adverse events (serious or not serious) that meet DFCI Institutional Review Board Adverse Event Reporting policy for expedited reporting:
  - Grade 2 or 3 unexpected adverse events that are attributed as at least possibly related to palbociclib or ganitumab;
  - All Grade 4 unexpected adverse events, regardless of attribution, unless listed as not reportable (see section 7.6.2).

Note: Grade 2 and Grade 3 laboratory abnormalities that are considered by the investigator to be clinically insignificant and do not require therapy, or adjustment in prior therapy, do not need to be reported to the Overall Principal Investigator or the DFCI IRB.

Regardless of treating institution, these expedited reports will be submitted to the Overall Principal Investigator using a DF/HCC AE Reporting form.

The treating institution must notify the Overall Principal Investigator by phone or email of any serious adverse event within 24 hours of learning of the event, with a formal written report within 3 business days.

For non-serious AE's that nevertheless meet the above DF/HCC definition for expedited reporting, the following timelines apply for submission of a DF/HCC AE Reporting form to the Overall Principal Investigator.

Attribution	DF/HCC Reportable AEs**				
	Gr. 2 & 3 AE Expected	**Gr. 2 & 3 AE Unexpected**	**Gr. 4 AE Expected**	**Gr. 4 AE Unexpected**	**Gr. 5 AE Expected or Unexpected**
Unrelated Unlikely	Not required	Not required	Not required	10 working days	24 hours*
Possible Probable Definite	Not required	10 working days	Not required	10 working days	24 hours*
* For participants enrolled and actively participating in the study ***or*** for AEs occurring within 30 days of the last intervention, the AE should be reported within 24 hours of learning of the event.					
**Please follow these reporting timelines only if the event qualifies as non-serious.					

7.6.2 Protocol-Specific Expedited Adverse Event Reporting Exclusions

Unless the adverse event meets the definition of serious, the following grade 2 adverse events do not require expedited reporting to the Overall PI or the DFCI OHRS: nausea; vomiting; fatigue; anemia; anorexia; headache; constipation; diarrhea; dry mouth.

Unless the adverse event meets the definition of serious, lymphopenia of any grade does not require expedited reporting to the Overall PI or the DFCI OHRS.

7.7 **Expedited Reporting to the Food and Drug Administration (FDA)**

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

Specifically, the IND holder will notify the FDA and all participating investigators in a written IND safety report of any adverse experience **associated with use of the drug** that is **both serious and unexpected.** Each written notification shall be made as soon as possible, and in no event later than **15 calendar** days after the sponsor's initial receipt of the information. Each written notification may be submitted on FDA Form 3500A (MedWatch) or in a narrative format and must bear prominent identification of its contents, i.e., "IND Safety Report". Follow-up information to a safety report should be submitted as soon as the relevant information is available.

The sponsor must also notify FDA of any **unexpected fatal or life-threatening experience associated with use of the drug** in the clinical studies conducted under the IND as soon as possible but in no event later than **7 calendar** days after initial receipt of the information. Notification may occur via telephone, facsimile, or other mode of transmission. In the event a 7-day report is required, the sponsor or designee will consult with the assigned FDA Project Manager and follow the preferred mode of communication for reporting the event.

The sponsor will determine whether any AE's reported in an expedited manner on an Expedited AE Reporting form meet criteria for submission as an expedited report to the FDA. The sponsor will prepare the FDA expedited report using information provided by the treating investigator on the Expedited AE Reporting form.

7.8 Expedited Reporting to Hospital Risk Management

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

7.9 Reporting to Pfizer

For the purposes of reporting to Pfizer, a serious adverse event is defined as an adverse event: (1) resulting in death; (2) that is life threatening (3) requiring in-patient hospitalization or prolonged hospitalization; (4) resulting in persistent or significant disability or incapacity; (5) resulting in congenital anomaly or birth defect; or (6) that is considered an important medical event.

In addition, episodes of elevated AST and/or ALT in combination with elevated bilirubin without other etiology for liver injury will be reported to Pfizer following the same procedure and timelines used to report SAEs.

The Overall Principal Investigator will report all serious AEs (SAEs), whether related or not related to study drug, to Pfizer Safety on the Pfizer CT SAE Report Form. SAEs that are fatal or life-threatening must be reported immediately to Pfizer upon the Principal Investigator becoming aware of them. All other SAEs must be reported within 24 hours of the Principal Investigator becoming aware of them. All pregnancy exposures to study drug, exposure via breastfeeding, or occupational exposures (regardless of whether associated with an AE) must be reported within 24 hours of the Principal Investigator becoming aware of the event via the Pfizer CT SAE Report Form. All reports should be submitted with a Pfizer Reportable Events Fax Cover Sheet.

If only limited information is initially available, reporting should not be delayed. Additional information once available may be submitted in a follow-up report as above.

7.10 **Reporting to ImmunityBio, Inc.**

The Overall Principal Investigator will report all serious AEs (SAEs), whether related or not related to study drug, and any pregnancies to ImmunityBio Drug Safety within 24 hours with regards to ImmunityBio drug use. SAEs should be recorded on the Generic Nant Investigator Sponsored Study SAE report form. in.

For the purposes of reporting to ImmunityBio, a serious adverse event is defined as: (1) death; (2) in-patient hospitalization or prolonged hospitalization; (3) life-threatening; (4) persistent or significant disability or incapacity; (5) congenital abnormality or birth defect; or (6) other serious events that may jeopardize the patient and may require medical or surgical intervention to prevent one of the other five listed outcomes.

All fields on the SAE report form should be completed prior to submitting the SAE report to NantBio. But at minimum, the Reporter information, Subject info, Event term (one per SAE report form please), Onset date, SAE criteria, Causality (Suspected or Not suspected for each/all Study medications being used) and Expectedness (Labeled or Not Labeled) for the Nant Drug being used in your study, according to the IB. (Only Expectedness for the Nant Drug being used in the study is required for our use)

If an SAE has been reported to any regulatory authority (the SAE meets expedited reporting criteria), please provide us a copy of the regulatory submission. In addition, please ensure the following is provided; the authority reported to, date reported and authority confirmation of report receipt.

[redacted]

[redacted]

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.) If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours to ImmunityBio using the same procedure used for transmitting the initial SAE report. All SAEs should be followed to resolution or stabilization. The Overall Principal Investigator will ensure that all SAEs in the clinical database are reported to ImmunityBio and any applicable health authority during the conduct of the study. This reconciliation will occur at least quarterly and be initiated by the sponsor/investigator.

The Overall Principal Investigator will request a reconciliation report from: [redacted] During reconciliation, any events found to not be reported previously to ImmunityBio must be sent to: [redacted]

The sponsor will be responsible for submitting all safety correspondence to the FDA. ImmunityBio will be provided with a simultaneous copy of all Serious Adverse Event submissions filed with the FDA or the local IRB.

All SAEs submitted to the FDA/IRB should simultaneously be faxed or e-mailed to ImmunityBio at:

[redacted]

8 PHARMACEUTICAL INFORMATION

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

9 BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

9.1 Laboratory Correlative Studies

9.1.1 Pharmacodynamics: IGF-1 serum levels – required

9.1.1.1 Sampling Strategy

For all patients, 5 mL of blood will be drawn into a serum separator tube tubes at the following timepoints:

- Cycle 1: Day 1 – prior to the first ganitumab dose
- Cycle 2: Day 1 – prior to ganitumab dose
- Cycle 4: Day 1 – prior to ganitumab dose

9.1.1.2 Sample Handling Instructions

Allow the blood to clot at 4°C (or in a bucket with ice) for at least 30 minutes but no longer than 3 hours. Centrifuge the blood at 1000g for 15 minutes at 4ºC (preferred) or room temperature to separate the serum (top, straw-colored layer) from the red blood cells (bottom, red layer). Dispense (aliquot) the serum into cryovials labeled according to the directions in 9.1.1.3. Aliquot serum into 0.5 – 1 mL aliquots. Cap the vials securely. Immediately **freeze the serum in an upright position** in a -70ºC to -80ºC freezer.

9.1.1.3 Sample Labeling Instructions

Cyrovials should be labeled with the patient's study ID number, the words "Pediatric palbo-ganitumab", "serum", and the date of blood draw, and one of the following indicators of the sample timing:

- Cycle 1
- Cycle 2
- Cycle 4

No other identifiers should be included on the label.

9.1.1.4 Sample Shipment

Cryovials from all draws for a patient should be batch shipped after the final sample has been obtained. These samples should be shipped frozen on dry ice. Ensure adequate dry ice to keep the samples frozen.

Sample shipment must include a copy of the Pharmacodynamic Worksheet (Appendix C). Please retain a copy of the worksheet at the site and also send a copy of the worksheet to the Study Coordinator at Dana-Farber.

Samples should be hand delivered (Dana-Farber sites) or couriered (MGH sites) to:

[redacted]

9.1.1.5 Description of Assay

Serum will be analyzed by the Boston Children's Hospital TransLab for a panel of IGF-related proteins, including but not limited to: IGF-1; IGF-2; growth hormone; IGFBP-3 and related proteins using ELISA assays.

9.1.2 Circulating Tumor DNA (ctDNA) – required

9.1.2.1 Sampling Strategy

Two 10 mL tubes of blood will be drawn into provided EDTA (1 tube) and CellSave Preservation Tubes (1tube) for Cohort A and one 10mL tube of blood will be drawn into a CellSave Preservation Tube for Cohort Bat the following time points:

- Cycle 1, Day 1, pre-dose
- Cycle 1, Day 15, pre-dose
- Cycle 2, Day 1, pre-dose
- Cycle 3, Day 1, pre-dose
- Cycle 5, Day 1, pre-dose
- Cycle 7, Day 1, pre-dose
- Cycle 9, Day 1, pre-dose
- Cycle 11, Day 1, pre-dose
- At time of disease progression or other reason off protocol therapy

All samples must be shipped or delivered same day unless drawn on a Friday, Saturday or Sunday, in which case they must be stored at room temperature and shipped same day the following Monday. EDTA tubes should only be drawn if they can be delivered to the [redacted] lab within two hours.

EDTA and CellSave tubes and the derivatives and data drawn under local banking studies (DFCI protocol: 17-104) may be used to supplement the timepoints stated above if any are omitted in error. The sample, data or derivatives will be transferred from the banking study after appropriate approvals and labeling.

9.1.2.2 Sample Handling Instructions

Blood should be drawn directly into CellSave Preservation Tubes (1 tube) and EDTA tubes (1 tube). Tubes should be completely inverted 8-10 times after sample collection. EDTA tubes should be refrigerated if not immediately delivered to the lab and must be delivered to the [redacted] Lab (address below) within two hours of the blood draw. For patients treated at Massachusetts General Hospital, EDTA tubes do not need to be obtained and instead a single CellSave Preservation Tube should be collected at the above time points. No other on-site processing is required. CellSave samples should be kept at room temperature until shipped. DO NOT REFRIGERATE CellSave tubes.

9.1.2.3 Sample Labeling Instructions

CellSave Preservation Tubes and EDTA tubes should be labeled with the patient's study ID number, the words "Pediatric palbo-ganitumab", the date of blood draw, and one of the following indicators of the sample timing:

- Cycle #, Day #
- Off protocol therapy

No other identifiers should be included on the label.

9.1.2.4 Sample Shipment

Each sample should be hand delivered (Dana-Farber sites) or couriered (MGH sites) on the day the sample was obtained, unless obtained on a Friday, Saturday or Sunday. EDTA tubes (Dana-Farber sites) should be hand delivered within 2 hours of the blood draw and should only be drawn if they can be delivered to the [redacted] laboratory within 2 hours. If EDTA tubes cannot be immediately delivered they should be refrigerated. If obtained on a Friday, Saturday or Sunday, CellSave samples should be STORED AT ROOM TEMPERATURE until shipment or delivery the following Monday. CellSave samples must be KEPT AT ROOM TEMPERATURE. Sample shipment must include a copy of the specimen transmittal sheet (Appendix C). Please retain a copy of the worksheet at the site and also send a copy of the worksheet to [redacted]

Samples should be hand delivered (Dana-Farber sites) or couriered (MGH sites) to:

[redacted]

9.1.2.5 Description of Assay

A next generation sequencing approach will be used to detect ctDNA extracted from approximately 2 milliliters of plasma for each patient using a commercial kit. After extraction, sequencing of cell free DNA will be performed utilizing oligonucleotides complementary to the genomic regions of interest. In an exploratory fashion, circulating tumor cells will be isolated and profiled from the cellular layer of blood samples obtained for detection of ctDNA using Cellsee or other technology. Sequencing and data analysis will be performed by the Center for Cancer Genome Discovery (CCGD) at Dana-Farber Cancer Institute and at the Broad Institute, with the work supervised by [redacted]

9.1.3 Tissue Biomarkers – required

9.1.3.1 Requested samples

Up to 20 unstained tumor slides (5 micron, positively charged) will be submitted (minimum of 10 unstained slides) at study entry. Material obtained from biopsy to diagnose or treat recurrent disease is preferred. If not available, material from biopsy/resection to obtain initial diagnosis will be submitted. If not available, material from resection of tumor after neoadjuvant chemotherapy will be submitted, taking care to submit material representing viable tumor. Material from primary tumor or metastatic deposits is acceptable. Materials obtained during bone marrow biopsy or fine needle aspirate procedure are not acceptable to support this evaluation.

For patients who undergo clinically-indicated biopsy or surgical resection while on therapy or within 30-days after last dose of palbociclib or ganitumab, whichever was last given, an additional set of 10-20 unstained tumor slides will be submitted.

For patients without available tumor material, the site investigator should notify the overall Principal Investigator.

9.1.3.2 Sample Handling
Slides should be placed in a slide box.

9.1.3.3 Sample Labeling
The slide box should be labeled with the patient's assigned study ID number, the word "palbo-ganitumab", and the date of biopsy/resection.

No other identifiers should be included on the label.

9.1.3.4 Sample Shipment
Slides should be hand delivered (Dana-Farber sites) or couriered (MGH sites) to:

Sample shipment must include a copy of the Tissue Biomarker Worksheet (Appendix C) and a redacted copy of the pathology report with patient's study ID number in place of identifiers. Please retain a copy of the worksheet at the site and also send a copy of the worksheet to the Study Coordinator at Dana-Farber.

9.1.3.5 Description of Assay
Next generation sequencing approaches to assess *CDKN2A, STAG2, TP53*, and other aberrations will be used. Immunohistochemistry for IGF-1R, insulin receptor, and ErbB3 will be performed. This work will be performed at Dana-Farber.

RNA-Seq will also be performed where applicable to evaluate gene expression. This work will be performed by NantOmics (ImmunityBio).

9.2 **Banking for Potential Future Research**

For patients who provide additional consent for banking, remaining tumor material, PBMCs, blood, extracted nucleic acids will be stored for up to 5 years after the completion of the trial for potential future correlative biology studies and correlation with clinical data. Future research may be performed at the Dana-Farber Cancer Institute or with outside collaborating Investigators. If samples and data are shared with outside collaborators the information will be processed in a deidentified manner.

9.3 **Summary of Blood Volumes for Research Blood Draws**

Cohort A:
The volume needed for the required correlative biology draws is 45 mL in Cycle 1, 25 mL in Cycle 2, 20 mL in Cycle 3, and 5 ml in Cycle 4. Subsequently, 20 ml of blood will be drawn at the start of cycle 5, 7, 9 and 11, and at time of progression or other reason for off protocol therapy. Assuming a 40 kg patient enrolls, 45 mL will represent 1.5% of that patient's estimated blood volume of 3000 mL.

Cohort B:
The volume needed for the required correlative biology draws is 35 mL in Cycle 1, 15 mL in Cycle 2, 10 mL in Cycle 3, and 5 ml in Cycle 4. Subsequently, 10 ml of blood will be drawn at the start of cycle 5, 7, 9 and 11, and at time of progression or other reason for off protocol therapy. Assuming a 40 kg patient enrolls, 35 mL will represent 1% of that patient's estimated blood volume of 3000 mL.

If a treating site or investigator has concerns about this volume of blood for a specific patient, prioritize the serum separator tube, followed by the CellSave tube then lastly the EDTA tube.

10 STUDY CALENDAR

Baseline laboratory tests and ECG must be completed within 14 days prior to the date of enrollment. Laboratory tests used to meet eligibility requirements may be completed within 14 days prior to date of enrollment, but select tests must be repeated prior to Cycle 1, Day 1 if obtained > 5 days prior to Cycle 1, Day 1 as described in section 5.2. Baseline disease assessments, such as MRIs, CT scans and nuclear medicine studies, must be performed within 28 days prior to the date of enrollment.

Once enrolled, required observations should be obtained within ± 3 days of the protocol-specified date, unless otherwise noted. Start of subsequent cycles may be +/- 3 days from day 29 of the previous cycle.

Observation	Screening	Cycle 1[1]	Cycle 2	Subsequent Cycles	End of Therapy[2]	Follow-up[3]
Physical Exam[4] (Includes Ht, Wt, BSA, Vital signs[4]; Performance status[5] only during screening)	X	Weekly	Start of cycle and day 15	Start of cycle and day 15	X	X[3]
CBC, Diff, Platelets[5]	X	Twice weekly[6]	Start of cycle and weekly[6]	Start of cycle and day 15[6]	X	X[3]
Electrolytes, Calcium, Magnesium, Phosphorus, BUN, Serum Creatinine, Glucose[5]	X	Weekly	Start of cycle and day 15[6]	Start of cycle and day 15[6]	X	X[3]
AST, ALT, Alk Phos, Total + Direct Bilirubin, Albumin[5]	X	Weekly	Start of cycle and day 15[6]	Start of cycle and day 15[6]	X	X[3]
Serum or urine pregnancy test[5,7]	X		Start of cycle	Start of cycle		
ECG	X					
Disease evaluation[8,9]	X		X[9]	X[9]	X[9]	X[10]
Blood for pharmacodynamic markers and ctDNA		See Section 9.1	See Section 9.1	See Section 9.1	See Section 9.1	
Tissue for biomarker studies	See Section 9.1				See Section 9.1	

OBTAIN OTHER STUDIES AS NEEDED FOR GOOD PATIENT CARE.

1. Laboratory studies obtained in screening do not need to be repeated on Cycle 1, Day 1, UNLESS obtained > 5 days prior to Cycle 1 Day 1. In that event repeat the following: CBC; creatinine or creatinine clearance; bilirubin; ALT; albumin; fasting glucose or random glucose.
2. End of therapy visit and observations should be performed within 7 days of decision to permanently discontinue palbociclib and ganitumab (± 7 days).
3. All participants will have a follow-up visit approximately 30-days following their last dose of study therapy. days or until all toxicity related to the study drug has resolved, whichever is longer. For participants who are unable to return to the study center, observations may be performed at referring center.
4. Vital signs include temperature, heart rate, blood pressure, respiratory rate, and oxygen saturation.

5. Required for verification of eligibility. Creatinine clearance may be required at screening if creatinine does not meet criteria in Section 3.1.6.3.
6. More frequent CBCs and chemistries may be needed as part of good patient care, particularly if adverse events noted during more frequent lab screenings during Cycles 1 and 2.
7. Obtain for females 12 years of age and older or post-pubertal.
8. Studies obtained as part of disease evaluation will depend upon underlying sites of disease and initial imaging modalities. Studies may include anatomic imaging, nuclear imaging, bone marrow biopsies. Baseline disease status tests must be performed ≤ 28 days prior to study registration and subsequent to any intervening therapy.
9. Perform disease re-staging during Week 3 or 4 of Cycles 2, 4, 6, 8, 10 and 12. Confirmatory scans will also be obtained 4 weeks following initial documentation of an objective response (partial response or better).
10. Once a participant is off protocol therapy, they will be followed for survival until one year after the last dose of protocol therapy is given to the last enrolled patient. Participants will undergo disease surveillance at the discretion of their local treating physician following completion of study therapy.

11 MEASUREMENT OF EFFECT

The primary endpoint of the study will be assessed by the below criteria. See Section 10 for required disease staging at study entry, after initiation of protocol therapy and during follow-up. Confirmatory scans will also be obtained a minimum of 4 weeks following initial documentation of an objective response.

11.1 **Key Definitions**

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started, or death due to any cause. Participants without events reported are censored at the last disease evaluation).

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

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

Progression-Free Survival: Progression-Free Survival (PFS) is defined as the time from registration to the earliest time of progression or death due to any cause. Participants alive without disease progression are censored at date of last disease evaluation.

Overall Survival: Overall Survival (OS) is defined as the time from registration to death. Participants alive are censored at date of last follow-up.

11.2 **Antitumor Effect**

Response and progression will be evaluated using Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1).[42] Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

11.2.1 Definitions

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

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

Non-measurable evaluable disease: All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are considered non-measurable disease. Leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pneumonitis, inflammatory breast disease, and cystic lesions are all considered non-measurable (except as described in Section 11.3.1.3). Bone lesions are considered non-measurable unless associated with a soft tissue lesion that itself meets criteria for measurable disease.

Important notes: Tumor lesions that are situated in a previously irradiated area are not considered measurable or evaluable unless that site meets criteria for progression after completion of radiation.

Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) unless biopsy proven since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases, particularly if biopsy proven, can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same participant, these are preferred for selection as target lesions.

11.2.2 Requirements for Disease Assessments

Investigators are to determine the optimal mode of disease assessment at baseline, including anatomic imaging studies, nuclear medicine studies, clinical measurements, tumor markers, and bone marrow biopsies. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

All measurements should be taken and recorded in metric notation using a ruler, calipers, or a digital measurement tool. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 28 days before enrollment.

11.2.3 Response Criteria

11.2.3.1 Evaluation of Target Lesions

Target lesions: All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should

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

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

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

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

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

11.2.3.2 Evaluation of Non-Target Lesions

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

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

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

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

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

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

11.2.3.3 Evaluation of New Lesions

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

11.2.3.4 Need for confirmatory testing

RECIST criteria specify the need for confirmation of response a minimum of 4 weeks from the disease evaluation that first demonstrated a response. Responses will be reported as confirmed or unconfirmed based upon the results of this restaging.

11.2.3.5 Evaluation of Best Overall Response

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

Overall Response Criteria

Target Lesions	Non-Target Lesions	New Lesions*	Overall Response	Best Overall Response when Confirmation is Required
CR	CR	No	CR	≥4 wks Confirmation
CR	Non-CR/Non-PD	No	PR	≥4 wks Confirmation
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks from baseline
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD**	Yes or No	PD	
Any	Any	Yes	PD	

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

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

11.3 **Response Review**

Patients with confirmed objective response (partial response or better) will have de-identified imaging studies submitted to the Study Coordinator for central confirmation of response. Imaging studies to be submitted include baseline scans, initial scans documenting response, and second set of scans confirming response. When relevant to the patient's response assessment, de-identified copies of bone marrow pathology reports and tumor marker lab reports will be submitted as well.

12 DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0.

12.1 **Data Reporting**

12.1.1 Method for Data Submission

All sites will submit data using the electronic data capture system, InForm.

The DFCI Office of Data Quality (ODQ) will perform quality checks on the data for this study.

12.1.2 Timelines for Data Submission

All investigative sites are expected to submit data in InForm according to the following timelines.

Form	**Submission Timeline**
Eligibility Checklist	Complete prior to registration
On Study Form	Within 14 days of registration
Toxicity Log (Baseline Adverse events)	Within 14 days of registration
Baseline Disease Assessment Form	Within 14 days of registration
Reporting Period Forms	Cycle 1: Within 5 business days of the last day of the cycle Other Cycles: Within 10 days of the last day of the cycle
Toxicity Log	Cycle 1: Within 5 business days of the last day of the cycle Other Cycles: Within 10 days of the last day of the cycle
Response Assessment Form	Within 14 days of the completion of disease evaluation
Off Protocol Therapy Form	Within 14 days of completing treatment
Follow-up Form	Within 14 days of the protocol defined follow up visit date and every 3 months once off therapy until 1 year after the last enrolled patient receives their final dose of protocol therapy
Off Study Form	Within 14 days of being taken off study for any reason
Outcome Form	Within 14 days of being taken off study for any reason

12.2 **Data Safety Monitoring**

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this study. The committee is composed of clinical specialists with experience in oncology and who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the Overall PI and study team.

The DSMC will review this protocol up to four times a year or more often if required to review toxicity and accrual data. Information to be provided to the committee may include: up-to-date participant accrual; current dose level information; DLT information; all grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring within 30 days of intervention; any response information; audit results; and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

13 STATISTICAL CONSIDERATIONS

This is a prospective, open-label, non-randomized, single arm two cohort Phase 2 study to test for preliminary evidence of efficacy of the combination of palbociclib and ganitumab. The study will be powered to evaluate the efficacy of this combination separately within two different cohorts:

A. Cohort A - relapsed or refractory Ewing sarcoma; and,
B. Cohort B - SDH-deficient GIST.

The cohort of patients with SDH-deficient GIST was added in an amendment developed in December 2020. The toxicity of this combination will be monitored with early stopping rules separately in each cohort.

13.1 **Study Design/Endpoints**

13.1.1 Study Design

The efficacy of the combination of palbociclib and ganitumab will be assessed separately within each cohort, using a one-stage design for Cohort A, and a two-stage design for Cohort B. The primary endpoint is a patient's objective overall response as defined in Section 11. A "responder" is defined as a patient having a confirmed overall response of ≥ PR.

13.2 **Sample Size, Accrual Rate and Study Duration**

A total of 15 response evaluable patients with Ewing sarcoma (Cohort A) and 12 response evaluable patients with SDH-deficient GIST (Cohort B) will be required to address the primary objective. Patients who are not eligible and/or evaluable for response will be replaced. Therefore, given potentially inevaluable patients a maximum of 33 patients with Ewing sarcoma or SDH-deficient GIST are expected to enroll.

Study Duration: We anticipate that 1-2 patients with Ewing sarcoma and 1-2 patient per GIST per month will be available for enrollment. Enrollment of the maximum sample size of 33 patients with Ewing sarcoma and GIST will require approximately 18-24 months.

13.3 **Analysis of Primary Endpoints**

13.3.1 Evaluability

To be evaluable for the analysis of the primary endpoint (objective response) patients must have received at least one dose of palbociclib or ganitumab. Additionally, patients must either have evidence of clinical progression or have had at least one follow-up disease evaluation of their RECIST measurable disease after initiation of protocol therapy to be evaluable for response. Patients who receive non-protocol anti-cancer therapy during the response evaluation period after the patient is first considered as having a partial response, but prior to confirmation of this status by repeat tumor imaging and before progressive disease is noted, will be considered evaluable. Should dose de-escalation rules be met as per section 5.4.2 for either cohort, all

patients prior to de-escalation and following de-escalation will be analyzed as a single cohort within either Cohort A or Cohort B for the primary efficacy endpoint.

13.3.2 Response endpoint

Each patient will be classified as a responder or non-responder. Responders are defined as evaluable patients with either a complete or partial objective response, according to RECIST version 1.1.

Cohort A: Among patients with Ewing sarcoma, the response rate will be reported as the proportion of responders, among response evaluable patients. The null hypothesis that the true response rate is 10% will be tested against a one-sided alternative. This design requires 15 evaluable patients to determine whether the proportion responding is less than or equal to 10% (the estimated null response rate with IGF-1R inhibition as monotherapy) or greater than or equal to 40%. If the number of responses is 4 or more, the hypothesis that the true response rate is less than or equal to 10% will be rejected with a type 1 error rate of 0.056, and we will conclude that the combination therapy is worthy of further study in this cohort. If the number of responses is 3 or fewer, then the hypothesis that the response rate is greater than or equal to 40% will be rejected with power of 91%. A two-sided exact 95% confidence interval will be placed on the proportion of responders.

Cohort B: Among patients with SDH-deficient GIST, the response rate will be reported as the proportion of patients with complete or partial response, among response evaluable patients. The null hypothesis that the true response rate is 4% will be tested against a one-sided alternative of a 32% response rate. This design will be conducted in two stages.

In stage 1, 7 evaluable patients will be enrolled. If 0 of 7 evaluable patients are responders, there is insufficient evidence of efficacy to continue enrollment to the cohort. If ≥1 patients are responders, continue to stage 2.

In stage 2, 5 additional evaluable patients will be enrolled for a total of 12. If ≥ 2 of 12 evaluable patients are responders, there is sufficient evidence for further study of the combination therapy in this cohort. If < 2 patients are responders, there is insufficient evidence to support further study of the combination therapy in this cohort.

The two-stage design has the following operating characteristics. If the number of responders is ≥ 2, the hypothesis that the true response rate is less than or equal to 4% will be rejected with a type 1 error rate of 0.07. If the number of responses is < 2, then the hypothesis that the response rate is greater than or equal to 32% will be rejected with power of 90%.

A two-sided 95% confidence interval will be placed on the proportion of responders.

13.3.3 Toxicity endpoint

All toxicities observed will be summarized in terms of type (organ affected or laboratory

determination), severity (by NCI CTCAE), and attribution. Tables will be created to summarize theses toxicities by cohort and by cycle.

13.4 **Interim Toxicity Monitoring Plan**

The primary endpoint for the interim toxicity monitoring rule of the study will be the occurrence of a Cycle 1 DLT that is attributable to palbociclib or ganitumab or the combination, as defined in Section 5.4.1. To be evaluable for the interim toxicity monitoring rule of Cycle 1 DLTs, a patient must receive at least one dose of either drug and have been followed for at least 30 days following the last dose of protocol therapy or to the start of Cycle 2, whichever occurs first. Additionally, any patient with Cycle 1 DLT will be considered evaluable for the interim toxicity monitoring rule. Cohorts A and B will have separate toxicity monitoring rules as the rate of DLTs is expected to differ by cohort due to differences in frontline therapy for patients in each cohort.

Toxicity as graded by CTCAE v5.0 will be recorded and monitored throughout all cycles of therapy. The number and proportion of toxicities will be tabulated by type, grade, and attribution. A given toxicity will be counted only once in a given patient, at the highest grade observed.

13.4.1 Cohort A toxicity monitoring plan

For Cohort A, the original two-stage toxicity monitoring rule was triggered with 2 DLTs out of the first 3 evaluable patients. A new one-stage design has been developed for the remaining 12 patients, all of whom will be treated at a lower dose level than the first 3 patients (contingency A, see Section 5.4.2).

Enroll up to 12 toxicity evaluable patients. If at any time 3 or more patients have a first cycle DLT, enrollment will be paused, the trial will be reviewed by the study committee and the DSMC, and a lower dose level will be considered as outlined in Section 5.4.2. If fewer than 3 of 12 patients have a first cycle DLT, the dose level will be considered sufficiently safe for further study. This rule has the following operating characteristics. The null hypothesis is that the proportion of patients with a Cycle 1 DLT is $\geq$39% versus the alternative that the proportion with a Cycle 1 DLT is $\leq$9%. The power is 91.3% and the type 1 error is 9.5%.

13.4.2 Cohort B toxicity monitoring plan

For Cohort B, we will utilize the following one-stage toxicity monitoring rule:

Enroll up to 12 toxicity evaluable patients. If at any time 3 or more patients have a first cycle DLT, enrollment will be paused, the trial will be reviewed by the study committee and the DSMC, and a lower dose level will be considered as outlined in Section 5.4.2. If fewer than 3 of 12 patients have a first cycle DLT, the dose level will be considered sufficiently safe for further study. This rule has the following operating characteristics. The null hypothesis is that the

proportion of patients with a Cycle 1 DLT is ≥ 39% versus the alternative that the proportion with a Cycle 1 DLT is ≤ 9%. The power is 91.3% and the type 1 error is 9.5%.

The number and proportion of toxicities will be tabulated within each cohort, by type, grade, and attribution. A given toxicity will be counted only once in a given patient, at the highest grade observed.

13.5 **Analysis of Secondary Efficacy Endpoints**

Progression-free survival (PFS) will be defined as the time from study enrollment to first episode of disease progression or death due to disease, with patients without event censored at last follow-up. Overall survival (OS) will be defined as the time from study enrollment to death, with surviving patients censored at last follow-up. PFS and OS will be estimated using Kaplan-Meier methods separately for each cohort, with standard errors according to Greenwood.

13.6 **Analysis of Exploratory Endpoints**

The pharmacodynamic, ctDNA, CTC and tissue biomarker studies (including but not limited to DNA sequencing, RNA-Seq and immunohistochemistry) are considered exploratory. Within the group of patients who begin treatment with palbociclib and ganitumab, the mean, standard deviation, and median relative change from baseline will be calculated for each marker. ctDNA positivity will be tested for association with PFS and OS using a log-rank test, and quantified with hazard ratios. Association between continuous measures of modulation of these markers versus a) occurrence of any DLT and b) clinical response of partial response or better will be tested using a Wilcoxon rank-sum test and presented descriptively using box and whisker plots. Secondary somatic mutations will be analyzed from tumor material and tested for association with objective response using Fisher's Exact test.

Graphical presentation of tumor marker data will be key to hypothesis development. Spaghetti plots will be used to display the serial measurements of ctDNA and IGF-1 related serum proteins.

14 PUBLICATION PLAN

The results are expected to be made public within 24 months of reaching the end of the study. The end of the study is the time point at which the last data items are to be reported. The initial release may be an abstract to be presented at a relevant scientific meeting. A full report of the outcomes should be made public no later than three (3) years after the end of the study.

15 REFERENCES

1. Womer RB, West DC, Krailo MD, et al. Randomized controlled trial of interval-compressed chemotherapy for the treatment of localized ewing sarcoma: A report from the children's oncology group. *J Clin Oncol*. 2012;30(33):4148-4154.

doi:10.1200/JCO.2011.41.5703
2. Grier HE, Krailo MD, Tarbell NJ, et al. Addition of ifosfamide and etoposide to standard chemotherapy for Ewing's sarcoma and primitive neuroectodermal tumor of bone. *N Engl J Med*. 2003;348(8):694-701. doi:10.1056/NEJMoa020890
3. DuBois SG, Krailo MD, Gebhardt MC, et al. Comparative evaluation of local control strategies in localized Ewing sarcoma of bone: A report from the Children's Oncology Group. *Cancer*. 2015;121(3):467-475. doi:10.1002/cncr.29065
4. Ladenstein R, Pötschger U, Le Deley MC, et al. Primary disseminated multifocal Ewing sarcoma: Results of the Euro-EWING 99 trial. *J Clin Oncol*. 2010;28(20):3284-3291. doi:10.1200/JCO.2009.22.9864
5. Bernstein ML, Devidas M, Lafreniere D, et al. Intensive therapy with growth factor support for patients with Ewing tumor metastatic at diagnosis: Pediatric Oncology Group/Children's Cancer Group Phase II Study 9457--a report from the Children's Oncology Group. *J Clin Oncol*. 2006;24(1):152-159. doi:10.1200/JCO.2005.02.1717
6. Miser JS, Krailo MD, Tarbell NJ, et al. Treatment of metastatic Ewing's sarcoma or primitive neuroectodermal tumor of bone: Evaluation of combination ifosfamide and etoposide - A children's cancer group and pediatric oncology group study. *J Clin Oncol*. 2004;22(14):2873-2876. doi:10.1200/JCO.2004.01.041
7. Cangir A, Vietti TJ, Gehan EA, et al. Ewing's sarcoma metastatic at diagnosis. Results and comparisons of two intergroup Ewing's sarcoma studies. *Cancer*. 1990;66(5):887-893.
8. Stahl M, Ranft A, Paulussen M, et al. Risk of recurrence and survival after relapse in patients with Ewing sarcoma. *Pediatr Blood Cancer*. 2011;57(4):549-553. doi:10.1002/pbc.23040
9. Barker LM, Pendergrass TW, Sanders JE, Hawkins DS. Survival after recurrence of Ewing's sarcoma family of tumors. *J Clin Oncol*. 2005;23(19):4354-4362. doi:10.1200/JCO.2005.05.105
10. Bacci G, Ferrari S, Longhi A, et al. Therapy and survival after recurrence of Ewing's tumors: The Rizzoli experience in 195 patients treated with adjuvant and neoadjuvant chemotherapy from 1979 to 1997. *Ann Oncol*. 2003;14(11):1654-1659. doi:10.1093/annonc/mdg457
11. Leavey PJ, Mascarenhas L, Marina N, et al. Prognostic factors for patients with Ewing sarcoma (EWS) at first recurrence following multi-modality therapy: A report from the Children's Oncology Group. *Pediatr Blood Cancer*. 2008;51(3):334-338. doi:10.1002/pbc.21618
12. Scotlandi K, Benini S, Sarti M, et al. Insulin-like growth factor I receptor-mediated circuit in Ewing's sarcoma/peripheral neuroectodermal tumor: a possible therapeutic target. *Cancer Res*. 1996;56(20):4570-4574. http://www.ncbi.nlm.nih.gov/pubmed/8840962.
13. Yee D, Favoni RE, Lebovic GS, et al. Insulin-like growth factor I expression by tumors of neuroectodermal origin with the t(11;22) chromosomal translocation. A potential autocrine growth factor. *J Clin Invest*. 1990;86(6):1806-1814. doi:10.1172/JCI114910
14. Zhong H, Fazenbaker C, Breen S, et al. MEDI-573, alone or in combination with mammalian target of rapamycin inhibitors, targets the insulin-like growth factor pathway in sarcomas. *Mol Cancer Ther*. 2014;13(11):2662-2673. doi:10.1158/1535-7163.MCT-14-0144

15. Toretsky JA, Kalebic T, Blakesley V, LeRoith D, Helman LJ. The Insulin-like Growth Factor-I Receptor Is Required for EWS/FLI-1 Transformation of Fibroblasts. *J Biol Chem*. 1997;272(49):30822-30827. doi:10.1074/jbc.272.49.30822
16. Prieur A, Tirode F, Cohen P, et al. EWS / FLI-1 Silencing and Gene Profiling of Ewing Cells Reveal Downstream Oncogenic Pathways and a Crucial Role for Repression of Insulin-Like Growth Factor Binding Protein 3 EWS / FLI-1 Silencing and Gene Profiling of Ewing Cells Reveal Downstream Oncoge. 2004;24(16):7275-7283. doi:10.1128/MCB.24.16.7275
17. Manara MC, Landuzzi L, Nanni P, et al. Preclinical in vivo study of new insulin-like growth factor-I receptor-specific inhibitor in Ewing's sarcoma. *Clin Cancer Res*. 2007;13(4):1322-1330. doi:10.1158/1078-0432.CCR-06-1518
18. Martins AS, Mackintosh C, Herrero Martín D, et al. Insulin-like growth factor I receptor pathway inhibition by ADW742, alone or in combination with imatinib, doxorubicin, or vincristine, is a novel therapeutic approach in Ewing tumor. *Clin Cancer Res*. 2006;12(11 I):3532-3540. doi:10.1158/1078-0432.CCR-05-1778
19. Sabbatini P, Korenchuk S, Rowand JL, et al. GSK1838705A inhibits the insulin-like growth factor-1 receptor and anaplastic lymphoma kinase and shows antitumor activity in experimental models of human cancers. *Mol Cancer Ther*. 2009;8(10):2811-2820. doi:10.1158/1535-7163.MCT-09-0423
20. van Valen F, Winkelmann W, Jürgens H. Type I and type II insulin-like growth factor receptors and their function in human Ewing's sarcoma cells. *J Cancer Res Clin Oncol*. 1992;118(4):269-275. http://www.ncbi.nlm.nih.gov/pubmed/1315779.
21. Houghton PJ, Morton CL, Gorlick R, et al. Initial testing of a monoclonal antibody (IMC-A12) against IGF-1R by the Pediatric Preclinical Testing Program. *Pediatr Blood Cancer*. 2010;54(7):921-926. doi:10.1002/pbc.22367
22. Kolb EA, Gorlick R, Houghton PJ, et al. Initial testing (stage 1) of a monoclonal antibody (SCH 717454) against the IGF-1 receptor by the pediatric preclinical testing program. *Pediatr Blood Cancer*. 2008;50(6):1190-1197. doi:10.1002/pbc.21450
23. Tap WD, Demetri G, Barnette P, et al. Phase II study of ganitumab, a fully human anti-type-1 insulin-like growth factor receptor antibody, in patients with metastatic ewing family tumors or desmoplastic small round cell tumors. *J Clin Oncol*. 2012;30(15):1849-1856. doi:10.1200/JCO.2011.37.2359
24. Malempati S, Weigel B, Ingle AM, et al. Phase I/II trial and pharmacokinetic study of cixutumumab in pediatric patients with refractory solid tumors and Ewing sarcoma: A report from the Children's Oncology Group. *J Clin Oncol*. 2012;30(3):256-262. doi:10.1200/JCO.2011.37.4355
25. Olmos D, Postel-Vinay S, Molife LR, et al. Safety, pharmacokinetics, and preliminary activity of the anti-IGF-1R antibody figitumumab (CP-751,871) in patients with sarcoma and Ewing's sarcoma: a phase 1 expansion cohort study. *Lancet Oncol*. 2010;11(2):129-135. doi:10.1016/S1470-2045(09)70354-7
26. Juergens H, Daw NC, Geoerger B, et al. Preliminary efficacy of the anti-insulin-like growth factor type 1 receptor antibody figitumumab in patients with refractory Ewing sarcoma. *J Clin Oncol*. 2011;29(34):4534-4540. doi:10.1200/JCO.2010.33.0670
27. Atzori F, Tabernero J, Cervantes A, et al. A phase I pharmacokinetic and pharmacodynamic study of dalotuzumab (MK-0646), an anti-insulin-like growth factor-1

receptor monoclonal antibody, in patients with advanced solid tumors. *Clin Cancer Res*. 2011;17(19):6304-6312. doi:10.1158/1078-0432.CCR-10-3336

28. Tolcher AW, Sarantopoulos J, Patnaik A, et al. Phase I, pharmacokinetic, and pharmacodynamic study of AMG 479, a fully human monoclonal antibody to insulin-like growth factor receptor 1. *J Clin Oncol*. 2009;27(34):5800-5807. doi:10.1200/JCO.2009.23.6745
29. Fuchs CS, Azevedo S, Okusaka T, et al. A phase 3 randomized, double-blind, placebo-controlled trial of ganitumab or placebo in combination with gemcitabine as first-line therapy for metastatic adenocarcinoma of the pancreas: the GAMMA trial. *Ann Oncol*. 2015;26(5):921-927. doi:10.1093/annonc/mdv027
30. Corless CL, Heinrich MC. Molecular pathobiology of gastrointestinal stromal sarcomas. *Annu Rev Pathol Mech Dis*. 2008;3:557-586. doi:10.1146/annurev.pathmechdis.3.121806.151538
31. Janeway KA, Kim SY, Lodish M, et al. Defects in succinate dehydrogenase in gastrointestinal stromal tumors lacking KIT and PDGFRA mutations. *Proc Natl Acad Sci U S A*. 2011;108(1):314-318. doi:10.1073/pnas.1009199108
32. Flavahan WA, Drier Y, Johnstone SE, et al. Altered chromosomal topology drives oncogenic programs in SDH-deficient GISTs. *Nature*. 2019;575(7781):229-233. doi:10.1038/s41586-019-1668-3
33. Janeway KA, Albritton KH, Van Den Abbeele AD, et al. Sunitinib treatment in pediatric patients with advanced GIST following failure of imatinib. *Pediatr Blood Cancer*. 2009;52(7):767-771. doi:10.1002/pbc.21909
34. Ben-Ami E, Barysauskas CM, von Mehren M, et al. Long-term follow-up results of the multicenter phase II trial of regorafenib in patients with metastatic and/or unresectable GI stromal tumor after failure of standard tyrosine kinase inhibitor therapy. *Ann Oncol*. 2016;27(9):1794-1799. doi:10.1093/annonc/mdw228
35. Von Mehren M, George S, Heinrich MC, et al. Linsitinib (OSI-906) for the treatment of adult and pediatric wild-type gastrointestinal stromal tumors, a SARC phase II study. *Clin Cancer Res*. 2020;26(8):1837-1845. doi:10.1158/1078-0432.CCR-19-1069
36. Franco J, Balaji U, Freinkman E, Witkiewicz AK, Knudsen ES. Metabolic Reprogramming of Pancreatic Cancer Mediated by CDK4/6 Inhibition Elicits Unique Vulnerabilities. *Cell Rep*. 2016;14(5):979-990. doi:10.1016/j.celrep.2015.12.094
37. Klein ME, Kovatcheva M, Davis LE, Tap WD, Koff A. CDK4/6 Inhibitors: The Mechanism of Action May Not Be as Simple as Once Thought. *Cancer Cell*. 2018;34(1):9-20. doi:10.1016/j.ccell.2018.03.023
38. Klega K, Imamovic-Tuco A, Ha G, et al. Detection of Somatic Structural Variants Enables Quantification and Characterization of Circulating Tumor DNA in Children With Solid Tumors. *JCO Precis Oncol*. 2018;2018(2):1-13. doi:10.1200/PO.17.00285
39. Shulman DS, Klega K, Imamovic-Tuco A, et al. Detection of circulating tumour DNA is associated with inferior outcomes in Ewing sarcoma and osteosarcoma: a report from the Children's Oncology Group. *Br J Cancer*. 2018;(July):1-7. doi:10.1038/s41416-018-0212-9
40. Pappo AS, Patel SR, Crowley J, et al. R1507, a monoclonal antibody to the insulin-like growth factor 1 receptor, in patients with recurrent or refractory Ewing sarcoma family of tumors: Results of a phase II Sarcoma Alliance for research through Collaboration study. *J*

Clin Oncol. 2011;29(34):4541-4547. doi:10.1200/JCO.2010.34.0000

41. Garofalo C, Manara MC, Nicoletti G, et al. Efficacy of and resistance to anti-IGF-1R therapies in Ewing's sarcoma is dependent on insulin receptor signaling. *Oncogene*. 2011;30(24):2730-2740. doi:10.1038/onc.2010.640
42. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45(2):228-247. doi:10.1016/j.ejca.2008.10.026

APPENDIX A: PERFORMANCE STATUS SCALES/SCORES

Performance Status Criteria
Karnofsky and Lansky performance scores are intended to be multiples of 10

ECOG (Zubrod)		Karnofsky		Lansky*	
Score	Description	Score	Description	Score	Description
0	Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease	100	Fully active, normal.
		90	Able to carry on normal activity, minor signs or symptoms of disease.	90	Minor restrictions in physically strenuous activity.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.	80	Normal activity with effort; some signs or symptoms of disease.	80	Active, but tires more quickly
		70	Cares for self, unable to carry on normal activity or do active work.	70	Both greater restriction of and less time spent in play activity.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours	60	Required occasional assistance, but is able to care for most of his/her needs.	60	Up and around, but minimal active play; keeps busy with quieter activities.
		50	Requires considerable assistance and frequent medical care.	50	Gets dressed, but lies around much of the day; no active play, able to participate in all quiet play and activities.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.	40	Mostly in bed; participates in quiet activities.
		30	Severely disabled, hospitalization indicated. Death not imminent.	30	In bed; needs assistance even for quiet play.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.	20	Often sleeping; play entirely limited to very passive activities.
		10	Moribund, fatal processes progressing rapidly.	10	No play; does not get out of bed.

*The conversion of the Lansky to ECOG scales is intended for NCI reporting purposes only.

APPENDIX B: DRUG EXCLUSIONS AND INTERACTIONS FOR PALBOCICLIB

Palbociclib is predominantly cleared by oxidative metabolism via CYP3A4. Clinical drug interaction studies with a CYP3A inhibitor and CYP3A inducer significantly altered the PK of palbociclib and its circulating major metabolites. Therefore, drugs that are strong and moderate inducers of CYP3A and/or strong inhibitors of CYP3A should be avoided or substituted if necessary.

The following medications in **Table 10** are prohibited. For medications known to be strong CYP3A inhibitors or inducers not listed use must be discussed with the Principal Investigator.

Table 10: List of prohibited medications with CYP3A interaction

Strong CYP3A Inhibitors	CYP3A Inducers
clarithromycin	carbamazepine
indinavir	efavirenz
itraconazole	nevirapine
ketoconazole	phenobarbital
lopinavir/ritonavir	phenytoin
nefazodone	rifabutin
nelfinavir	rifampin
posaconazole	rifapentine
ritonavir	St. John's wort
saquinavir	
telaprevir	
telithromycin	
voriconazole	

1. Glucocorticoids are allowed for patients with CNS metastatic disease. However, they should be on a stable or decreasing dose over the 7 days prior to registration and meet criteria in Section 3.1.6.7. Inhaled and topical corticosteroids are allowed.

The following medications outlined in **Table 11** are discouraged, but not prohibited.

Table 11: List of medications with CYP3A interactions to be used with caution

Moderate CYP3A Inhibitors	Weak CYP3A Inhibitors
aprepitant	alprazolam
conivaptan	amiodarone
crizotinib	amlodipine
diltiazem	atorvastatin
dronedarone	bicalutamide
erythromycin	cilostazol
fluconazole	cimetidine
fosamprenavir	ciprofloxacin
grapefruit[3]	cyclosporine
grapefruit juice[3]	fluvoxamine
imatinib	fosaprepitant
mifepristone	isoniazid
nilotinib	nicardipine
verapamil	propofol
	quinidine
	1.1.1.1.1.1.1 ranolazine

Palbociclib is associated with a risk of QTc prolongation.

The following medications in **Table 12** are prohibited.

Table 12: List of prohibited QTc prolonging medications

Drug Name	**Drug Class**
Amitriptyline, Desipramine, Imipramine	Antidepressants
Chloroquine	Antimalarials
Chlorpromazine, Mesoridazine, Risperidone	Antipsychotics
Itraconazole, Ketoconazole	Antifungals
Tacrolimus, Arsenic trioxide, Domperidone	Miscellaneous drugs

The following medications outlined in **Table 13** are discouraged, but not prohibited.

Table 13: List of medications causing QTc prolongation to be used with caution

Drug Name	**Drug Class**
Dolasetron, Ondansetron, Tropisetron	Anti-emetics
Doxepin, Maprotiline, Venlafaxine	Antidepressants
Gatifloxacin, Moxifloxacin, Sparfloxacin	Quinolone antibiotics
Halofantrine	Antimalarials
Pentamidine, Droperidol, Methadone, Bepridil	Miscellaneous drugs
Thioridazine, Ziprasidone	Antipsychotics

APPENDIX C: CORRELATIVE BIOLOGY WORKSHEETS

Form 1: IGF-1 PHARMACODYNAMIC WORKSHEET

Patient ID:			**Ganitumab Dose:** **Cohort A / Cohort B (circle one)**	
			5 mL of blood into serum separator tube (not provided)	
Cycle	**Day**	**Sample Time Points**	**# of aliquots included**	**Date and Time** **(use 24-hour clock for times; e.g. 1622 instead of 4:22)** Example: *12/30/16 @ 1622*
1	1	Pre-dose	5 mL __ aliquots	
		ganitumab dose administered: _____ mg		
2	1	Pre-dose	5 mL __ aliquots	
		ganitumab dose administered: _____ mg		
4	1	Pre-dose	5 mL __ aliquots	
		ganitumab dose administered: _____ mg		

Total blood volume for PD samples per cycle: 5 mL

Cycle 1: _____ _____
Signature of site staff responsible for sample collection **Date**

Cycle 2: _____ _____
Signature of site staff responsible for sample collection **Date**

Cycle 4: _____ _____
Signature of site staff responsible for sample collection **Date**

INCLUDE A COPY OF THIS WORKSHEET WITH EACH SAMPLE SHIPMENT AND RETAIN A COPY AT THE STUDY SITE.

Form 2: ctDNA WORKSHEET DFCI 19-373 – Cycles 1 and 2

Patient ID:			**Ganitumab Dose:** **Palbociclib Dose:** **Cohort A / Cohort B (circle one)**	
			10 mL in CellSave Preservation Tube (provided) AND 2x 5mL or 1x 10mL EDTA tube (provided, DFCI Only)	
Cycle	**Day**	**Sample Time Points**	**Volume**	**Date and Time** **(use 24-hour clock for times; e.g. 1622 instead of 4:22)** Example: *12/30/16 @ 1622*
1	1	Pre-dose	[ ] 10 mL CellSave [ ] 10 mL EDTA (Cohort A only)	
1	15	Pre-dose	[ ] 10 mL CellSave [ ] 10 mL EDTA (Cohort A only)	
2	1	Pre-dose	[ ] 10 mL CellSave [ ] 10 mL EDTA (Cohort A only)	

Total blood volume for ctDNA samples in this cycle: ___

Cycle 1 Day 1: _____ _____
Signature of site staff responsible for sample collection **Date**

Cycle 1 Day 15: _____ _____
Signature of site staff responsible for sample collection **Date**

Cycle 2 Day 1: _____ _____
Signature of site staff responsible for sample collection **Date**

INCLUDE A COPY OF THIS WORKSHEET WITH EACH SAMPLE SHIPMENT AND RETAIN A COPY AT THE STUDY SITE.

Form 3: ctDNA WORKSHEET DFCI 19-373 – Disease Evaluation Timepoint

Patient ID:			**Ganitumab Dose:** **Palbociclib Dose:** **Cohort A / Cohort B (circle one)**	
			10 mL in CellSave Preservation Tube (provided) AND 2x 5mL or 1x 10mL EDTA tube (not provided, DFCI Only)	
Cycle	**Day**	**Sample Time Points**	**Volume**	**Date and Time** **(use 24-hour clock for times; e.g. 1622 instead of 4:22)** Example: *12/30/16 @ 1622*
_____	____	Disease Evaluation	[ ] 10 mL CellSave [ ] 10 mL EDTA (Cohort A only)	

Total blood volume for ctDNA samples per timepoint: ____

_____ _____

Signature of site staff responsible for sample collection **Date**

INCLUDE A COPY OF THIS WORKSHEET WITH EACH SAMPLE SHIPMENT AND RETAIN A COPY AT THE STUDY SITE.

Form 4: ctDNA WORKSHEET DFCI 19-373 – End of Treatment

Patient ID:			**Ganitumab Dose:** **Palbociclib Dose:** **Cohort A / Cohort B (circle one)**	
			10 mL in CellSave Preservation Tube (provided) AND 2 5mL or 1 10mL EDTA tube (not provided, DFCI Only)	
Cycle	**Day**	**Sample Time Points**	**Volume**	**Date and Time** **(use 24-hour clock for times; e.g. 1622 instead of 4:22)** Example: *12/30/16 @ 1622*
_____	____	Off protocol therapy	[ ] 10 mL CellSave [ ] 10 mL EDTA (Cohort A only)	

Total blood volume for ctDNA samples per timepoint: _____

Off Protocol Therapy: _____ _____
Signature of site staff responsible for sample collection **Date**

INCLUDE A COPY OF THIS WORKSHEET WITH EACH SAMPLE SHIPMENT AND RETAIN A COPY AT THE STUDY SITE.

Form 5: TISSUE BIOMARKER WORKSHEET

Patient ID:	**Ganitumab Dose:** **Palbociclib Dose:** **Cohort A / Cohort B (circle one)**
Time point	[ ] Pre-enrollment [ ] Initial diagnosis [ ] Second look surgery [ ] Biopsy or surgery at time of relapse [ ] Post-enrollment [ ] Biopsy or surgery at time of progression [ ] Biopsy or surgery in setting of response
Source of material	[ ] Primary tumor [ ] Metastatic lesion
Date of biopsy/surgery	
Number of unstained slides submitted	

Signature of site staff responsible for sample collection **Date**

INCLUDE A COPY OF THIS WORKSHEET WITH EACH SAMPLE SHIPMENT ALONG WITH A REDACTED COPY OF THE PATHOLOGY REPORT. RETAIN A COPY OF THIS WORKSHEET AT THE STUDY SITE.