PHASE 1/2 STUDY TO EVALUATE PALBOCICLIB (IBRANCE®) IN COMBINATION WITH IRINOTECAN AND TEMOZOLOMIDE OR IN COMBINATION WITH TOPOTECAN AND CYCLOPHOSPHAMIDE IN PEDIATRIC PATIENTS WITH RECURRENT OR REFRACTORY SOLID TUMORS

Investigational Product Number:	PD-0332991
Investigational Product Name:	Palbociclib Irinotecan Temozolomide Topotecan Cyclophosphamide
United States (US) Investigational New Drug (IND) Number:	135,210
European Clinical Trials Database (EudraCT) Number:	2021-003444-25
ClinicalTrials.gov ID	NCT03709680
Protocol Number:	A5481092
Phase:	1/2
Sponsor Legal Address:	Pfizer Inc. 66 Hudson Boulevard East New York, NY 10001

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Protocol Amendment Summary of Changes Table

Amendment 7 (31 May 2023)

Overall Rationale for the Amendment:

The overall rationale for the amendment is to incorporate changes requested by Regulatory Authorities and to revise eligibility criteria to tumor specific cohort for patients with neuroblastoma.

Section # and Name	Description of Change	Brief Rationale
Substantial		
Section 4.1 Inclusion Criteria	**Inclusion # 4** (adequate bone marrow function) updated to Platelet count ≥75,000/mm^3 eligible.	Inclusion criterion revised following eligibility criteria revision for patients with bone marrow involvement and to align count criteria with on treatment criteria to start next cycle.
Section 4.1 Inclusion Criteria	**Inclusion # 7** updated so that patients with neuroblastoma with at least evaluable disease per INRC criteria are eligible to tumor specific cohort.	Inclusion criterion revised as the INRC criteria allow for objective tumor response assessment in patients with evaluable disease and bone marrow involvement only.
Section 4.2 Exclusion Criteria	**Exclusion # 3** : strong cytochrome P450 (CYP) 3A inhibitors or inducers are prohibited within 12 days of study entry.	Change to clarify wash out period for strong cytochrome P450 (CYP) 3A inhibitors or inducers.
Section 4.2 Exclusion Criteria	**Exclusion # 9** patients with hypersensitivity to dacarbazine are not eligible.	Change for clarity and on request of Regulatory Authority in France.
Section 4.2 Exclusion Criteria	**Exclusion # 16** added toexclude patients with serious active or uncontrolled bacterial, fungal or viral infection or known history of hepatitis, or HIV infection or acquired immunodeficiency syndrome-related illness. Screening for viral hepatitis	Change to clarify exclusionary infections and infectious conditionsd and to document country requirement of testing for viral hepatitis and HIV, on request of Czech Republic Regulatory Authority.

Section # and Name	Description of Change	Brief Rationale
	and HIV is under discretion of investigator unless required by local regulation.	
Section 4.3 Lifestyle Requirements	Updated document contraception requirements for patients receiving cyclophosphamide.	Section updated to align requirements for the duration of contraception with chemotherapy drugs SmPC and upon Regulatory Authority request.
Nonsubstantial		
Protocol Summary	Added wording of "since completion of 1st line treatment" in corresponding sentences.	Changes added for clarity of stratification factor definition.
Section 1.2.2.2.3 Palbociclib in Combination With Irinotecan and Temozolomide	Section updated add safety information on most common TEAE for palbociclib in combination with IRN and TMZ	To update safety information on most common TEAEs per the IB v 16.0 (cutoff 31 Aug 2022) to align with added Section 1.2.2.2.4.
Section 1.2.2.2.4 Palbociclib in Combination With Topotecan and Cyclophosphamide	Section added to list most common TAE for palbociclib in combination with TOPO and CTX TMZ	To add safety information on most common TEAEs for palbociclib with TOPO and CTX as became available in the IB v 16.0 (cutoff 31 Aug 2022).
Section 1.3.1.1.1 Preclinical Findings	Sentence added to document that differences in beta cell proliferation capacity appear to play a role in the sensitivity to development of altered glucose metabolism in rats. Deleted conclusion that the potential for palbociclib to cause pancreatic islet beta cell loss, subsequent dysregulation of glucose, and cataracts in humans is considered low.	Updated to clarify preclinical findings in rats in regards to sensitivity to development of altered glucose metabolism.
Section 1.3.1.5.1 Combination of	Clinical Risks and Precautions for palbociclib	To update safety information/risks for the

Section # and Name	Description of Change	Brief Rationale
Palbociclib With IRN and TMZ and Section 1.3.1.5.2 Combination of Palbociclib With TOPO and CTX	updated to add safety information for palbociclib in combination with IRN and TMZ and for palbociclib in combination with TOPO and CTX	combinations of palbociclib per the IB v 16.0(cutoff date 31 Aug 2022).
Section 4.3 Lifestyle Requirements	Updated to clarify condom with separate spermicide is not appropriate contraceptive method in Czech Republic.	Clarification added upon Czech Republic Regulatory Authority request. PACL (Czech Rep.) 29 Aug 2022.
Section 4.3 Lifestyle Requirements	Updated to add guidance for assessment of childbearing potential in pediatric population.	Clarification added to incorporate DIL16 Sep 2022.
Section 5.8 Known Toxicities of Temozolomide, Section 5.9 Known Toxicities of Irinotecan, Section 5.10 Known Toxicities of Topotecan, and Section 5.11 Known Toxicities of Cyclophosphamide	Updated tables that list known toxicities of TMZ, IRN, TOPO, CTX to align with the following categories: Very common (≥1/10); Common (≥1/100 to <1/10) and Uncommon (≥1/1,000 to <1/100).	Update to apply adverse events frequency groupings, as per regulatory requirements.
Schedule of Activities: Table 2 Footnote 5 & Table 3 Footnote 6	Footnote 5: Lansky for patients ≤ 16 years old; ECOG for > 16 years old. If a patient turns 17 years old while on study, ECOG should be used.	Clarification added on age appropriate tool to assess performance status.
Schedule of Activities: Table 2 and Footnote 7 & Table 3 and Footnote 8	Laboratory test of HbA1c: EoT sample for HbA1c should be collected if more then 12 weeks have passed since prior assessment.	To document HbA1c test is required at EoT visit if more then 12 weeks have passed since prior assessment.

Section # and Name	Description of Change	Brief Rationale
Schedule of Activities: Table 2 and Footnote 18	Activities of MRI/CT scan, MIBG scan/FDG-PET (Neuroblastoma patients only), Bilateral bone marrow aspirate and biopsy (Neuroblastoma patients only).	Clarification added on imaging and bone marrow assessments requirements in patients with neuroblastoma enrolled to TSC.
Schedule of Activities: Table 2 Footnote 33	Footnote 33: applicable during COVID-19 pandemic (and upon written notification from Pfizer during other public emergencies) in Dose Escalation, Dose Expansion Cohorts and Dose Determination Part and outside public emergencies in Tumor-Specific Cohorts.	Added clarification that alternative measures (Appendix 14) apply in TSC during COVID-19 pandemic AND outside public emergencies.
Schedule of Activities: Table 3 & Footnote 20 Tumor response assessment	Activities of MRI/CT scan, distant metastase staging, PET-CT or PET-MRI.	Clarification added on imaging assessments requirements in patients enrolled to Phase 2 portion of the study.
Schedule of Activities: Table 3 Footnote 17	Footnote 17: QoL questionnaire to be completed before patient/parents learn about results of tumor assessment.	Clarification added to ensure QoL assessment is not impacted by disease response assessment results.
Schedule of Activities: Table 3 Footnote 20	Footnote 20: Bone marrow assessment performed (as per standard of care) within 8 weeks of randomization is acceptable unless the last bone marrow assessment was positive and there is an intervening anti-cancer treatment.	Clarification added on bone marrow assessments requirements in patients enrolled to Phase 2 portion of the study.
Schedule of Activities: Table 3 Footnote 34	Footnote 34: Text that refered to COVID-19 pandemic (and upon written notification from Pfizer	Change so that the alternative measures (Appendix 14) apply in Phase 2 outside public

Section # and Name	Description of Change	Brief Rationale
	during other public emergencies) was deleted.	emergencies. PACL (Canada) dated 25 Aug 2022.
Schedule of Activities: Table 4 Footnote 2 & Table 5 Footnote 3	Footnote 2: The time window for palbociclib predose PK sample collection should be no more than 1 hr postdose on the day of PK collection.	Clarification added pre dose PK sample window.
Section 1.3.1.5.3 Pneumonitis/Interstitial lung disease (ILD)	Participants will be monitored for signs and symptoms of pneumonitis/ILD and disease will be managed, as described in Section 5.7.7.	Text added to document additional safety measures to monitor patients for pneumonitis/ILD.
Section 3.1 Study Overview Protocol Summary	The following text was removed: The Phase 1 portion of the study will be conducted in US.The Phase 2 portion of the study will be conducted in North America, South America, Europe, Asia and Australia.	Text removed as the Phase 1 tumor specific cohort and the Phase 2 will be conducted in North America (US and Canada) and other countries. PACL (Canada) 03 Mar 2023.
Section 3.2 DLT Definition for Both Combinations	DLT assessment is not required in the Phase 2 portion of the study and tumor specific cohorts. DLT definitions apply for dosing interruption (Section 5.4.9) and dose reductions (Section 5.4.11).	Text added to clarify DLT assessment requirements.
Section 5.4.9 Dosing Interruptions and Section 5.4.11 Dose Reductions	Clarification regarding drug supply in the event of dose reduction moved from Section 5.4.9 to Section 5.4.11	Change for clarity.
Table 13 & Table 14	Added dose modification guidance for ILD and DILI. Added definitions of dose-limiting neutropenia and	Dose modification guidance added for ILD and DILI cases.

Section # and Name	Description of Change	Brief Rationale
	dose-limiting thrombocytopenia.	Change to improve clarity of guidance for dose modifications for hematologic toxicities.
Table 15	Pregnancy Test For girls ≥8 years serum or urine.	Change to clarify pregnancy test age requirements.
Section 5.7.1 Prohibited Medications	Ciprofloxacin and norfloxacin added to the list of Strong/Moderate CYP3A inhibitors. Live vaccines added to prohibited concomitant treatments list.	Change to document fluorochinolones that are strong/moderate CYP3A inhibitors . Live vaccines added on Czech Regulatory request.
Section 5.7.2 Medications Not Recommended	Recommendations on chronic immunosuppressive therapies.	Change for clarity that recommendations apply to all steroids use (not only dexamethasone).
Section 5.7.5 Anti-Diarrheal, Anti-Emetic Therapy	Ciprofloxacin and norfloxacin are not permitted as antibiotic prophylaxis for IRN-induced diarrhoea andquinolones should be used with caution due to their class potential for QT prolongation.	Change for clarity to add guidance on fluoroquinolones use as alternative antibiotics for diarrhoea prophylaxis
Section 5.7.7 Interstitial Lung Disease Management	**Section on** Interstitial Lung Disease management added.	To provide guidance on ILD diagnosis and management.
Section 5.7.9 Corticosteroids	Systemic steroids given during radiotherapy are allowed.	Added for clarity to provide additional guidance on steroids use during on treatment radiotherapy.
Section 7.1.1 Pregnancy Testing	Pregnancy testing requirements in long term follow up.	Clarification added on request of France Regulatory, to document country requirement to perform pregnancy tests during follow up

Section # and Name	Description of Change	Brief Rationale
		for the duration of contraception period.
Section 7.1.5 Schedule of Activities Table 3 Footnote 21	DEXA scans and X-ray of hand will not be required per protocol in patients enrolled in Germany.	Change to incorporate PACL (Germany) 13 Mar 2023.
Section 7.5 Tumor Response Assessments	Tumor assessment imaging requirements CT/MRI and FDG-PET.	To provide guidance on interchangeable methods of tumor lesion assessment.
Section 7.6 Quality of Life	QoL timing and guidance to complete QoL assessment prior informing a patient of tumor assessment response results.	To provide additional guidance on adequate QoL assessment.
Section 7.9.1 Screening/Baseline Tumor Assessments and Section 7.9.2 Post-Baseline Tumor Assessments	Screening/Baseline and On Treatment Tumor imaging requirements and bone marrow assessment in patients enrolled to TSC and Phase 2.	Change to clarify response assessment requirements
Section 8.1.4.2 Recording Non-serious AEs and SAEs on the CRF	The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE or SAE.	Change to clarify adverse events/serious adverse events reporting requirements.
Section 8.4.3.1 Medication Errors	Medication error	Additional clarification provided on what events constitute medication error
Section 9.4.2 Analysis of Safety Endpoints (Phase 1, Tumor-Specific	Removed list of specific safety analyses and included additional languages of AE summaries.	Specific details of the safety analyses will be included in the SAP.

Section # and Name	Description of Change	Brief Rationale
Cohorts and Randomized Phase 2)		
Section 9.6.1	Analysis of Primary Endpoint. Phase 1 and Tumor-Specific Cohorts.	Change to add clarity so that Primary Endpoint Analyses described in Section 9.6 apply to TSC.
Section 9.6.2	Updated to specify Tumor-Specific Cohorts for the corresponding analyses.	Change to add clarity to the analyses that are associated with tumor-specific cohorts.
Section 9.6.2	Updated to specify Tumor-Specific Cohorts for the corresponding analyses. Removed the analysis of repeated measures mixed effects model to compare QoL scores and change from baseline between the treatment arms.	Analyses are not considered warranted due to limited sample size and by age group analysis. QoL analysis will be descriptive only with details specified in the SAP.
Section 11.1 Case Report Forms/Electronic Data Record Section 11.3 Data Protection Section 12.3 Patient Information and Consent Section 12.4 Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP Section 13.1 End of Trial in All Participating Countries	Minor edits and revisions. Deleted Section 12.4	Updated to align with current protocol template

Section # and Name	Description of Change	Brief Rationale
Section 15.1 Dissemination of Clinical Study Data		
Appendix 5	RECIST 1.1 Objective Response Status at Each Assessment for Patients with Non-Measurable Disease at Baseline.	Clarification provided for overall response assessment in patients with non-measurable disease. Edit to clarify requirements of baseline tumor asssessment in Phase 2 to be performed within 21 days of randomization.
Appendix 14	Alternative measures applicable outside public emergencies for patients enrolled in TSC and in Phase 2. Study Interventions – IMP administration requirements and alternative facility use.	Changes for clarity and to incorporate PACL (Canada) dated 25 Aug 2022.
Appendix 15	Summary of Changes documenting changes Amendment # 5 to Amendment # 6 (UK specific) moved to Appendix 15	As per Protocol template requirements.
Section 6.1 Screening Section 7 Assessments Section 7.1.4 Vital Signs and Physical Examination Section 7.1.5 (Assessments of Growth and Bone Metabolism Section 7.8 Survival Sections 8.1.3 Withdrawal From the	Minor edits and corrections for clarity	

Section # and Name	Description of Change	Brief Rationale
Study Due to Adverse Events (see also the Patient Withdrawal section) Section 8.1.4 Time Period for Collecting AE/SAE Information Section 8.2.4 Hospitalization		

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and institutional review boards (IRBs)/ethics committees (ECs)and any protocol administrative change letter(s).

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PROTOCOL SUMMARY

Indication:

Pediatric (children, adolescent and young adult) patients with recurrent or refractory solid tumors.

Background and Rationale:

Palbociclib (PD-0332991) is a highly selective, reversible, small molecule inhibitor of cyclin-dependent kinases (CDK) 4 and 6, administered orally. Cyclin D1 and CDK4/6 are downstream of multiple signaling pathways which lead to cellular proliferation. CDKs are important regulatory enzymes that mediate cell cycle control by regulating and promoting transition through the cell cycle. While a number of various CDK enzymes are recognized, in complex organisms the control over cell cycle entry is regulated at the level of CDK4 and CDK6. As cancer represents a process of uncontrolled cell division and proliferation, CDKs represent potential therapeutic targets.[2]

During cell proliferation, the G_1 to S transition of the cell cycle is under the control of CDKs which are activated through specific complex formation with regulatory cyclins. CDK4 and CDK6 are activated by binding to D-type cyclins in early G_1 phase.[3-6] The only known natural substrate for CDK4 and CDK6 activity is retinoblastoma susceptibility gene product (pRb), which mediates G_1 arrest through sequestration of transcriptional factors of the heterodimeric transcription factor (E2F-DP) family. Phosphorylation of pRb and other members of the pocket protein family (p107 and p130) by active cyclin-CDK complexes leads to release of E2F and DP transcription factors and transcription of requisite genes for S-phase entry.[6]

Palbociclib (IBRANCE®) is approved for the treatment of patients with hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced or metastatic breast cancer in combination with an aromatase inhibitor as initial endocrine-based therapy, or in combination with fulvestrant in patients with disease progression following endocrine therapy. Additional information is provided as per local approved labeling.

There is an increasing body of literature showing the dependency of pediatric tumor cells on CDK4/6 and cyclin D1 including Ewing sarcoma (EWS),myeloid and lymphoblastic leukemia to support the use of CDK4/6 inhibitors.[7] Palbociclib has shown synergy when administered with antiestrogen therapy in the treatment of estrogen receptor positive breast cancer and supports its use as a combination therapy.[8] The antitumor activity of palbociclib in combination with the chemotherapy regimen, temozolomide (TMZ) and irinotecan (IRN), has been investigated in 3 different patient-derived EWS models grown subcutaneously in immunocompromised mice to determine the extent of therapeutic benefit from the addition of palbociclib to the regimen. The IRN and TMZ combination resulted in significant tumor growth inhibition (TGI) in 2 models and non-significant decrease of tumor volume in 1 model. The addition of palbociclib to IRN and TMZ resulted in similar TGI to that with the IRN and TMZ alone for 2 models while in the third model the triple combination demonstrated significantly increased antitumor activity versus IRN and TMZ alone. In the

latter model, the superiority of the triple combination was sustained in the post-dosing period of several weeks. The addition of palbociclib to the chemotherapy regimen increased the number of responders from 1 partial response to 2 complete responses and 1 tumor free survivor, further supporting improved efficacy for the triple combination in this model.[9] These findings highlight the potential antitumor benefit of adding palbociclib, a CDK4/6 inhibitor, to a combination of a topoisomerase inhibitor (eg, IRN or topotecan) and an alkylating agent (eg, TMZ or cyclophosphamide).

Curative options for pediatric, adolescent or young adult patients with relapsed or refractory solid tumors are limited, and outcomes are poor. TMZ and IRN are used frequently in clinical practice for many recurrent pediatric cancers, including recurrent EWS.[10,11] In several pediatric case series and Phase 2 clinical trials, IRN, and TMZ given alone or in combination with other agents such as vincristine or temsirolimus have been associated with response rates of up to 68% in patients with recurrent EWS, with some patients maintaining a response for >14 cycles of therapy.[12,13,14] New agents have been combined with this backbone in pediatric clinical trials.[15]

Other therapies for relapsed solid tumors include topotecan (TOPO) and cyclophosphamide (CTX). This combination has been tested and shown responses in a variety of pediatric tumors including recurrent EWS, neuroblastoma, rhabdomyosarcoma (RMS), nephroblastoma and osteosarcoma.[16,17,18]

The multicenter, non-randomized open label, Phase 1 portion of the study of palbociclib in combination with a backbone chemotherapy consisting of either TMZ and IRN or TOPO and CTX will follow the approach outlined below:

The Phase 1 evaluation of palbociclib in combination with IRN and TMZ consists of a dose escalation part and a dose expansion cohort. The dose escalation part will estimate the maximum tolerable dose (MTD) for palbociclib in combination with IRN and TMZ based on the safety profile and the pharmacokinetics (PK) in children, adolescents, and young adults with recurrent or refractory solid tumors without a curative option as a standard therapy. The dose expansion cohort will further evaluate the safety and PK of the MTD in children, adolescents, and young adults with recurrent or refractory solid tumors without a curative option as a standard therapy. Following the dose expansion, tumor-specific cohorts other than EWS (eg, neuroblastoma, rhabdomyosarcoma, rhabdoid tumor or medulloblastoma) may be opened if 2 or more patients from the dose escalation or dose expansion show a confirmed objective response (OR) in the specific tumor type to further evaluate antitumor activity of palbociclib in combination with IRN and TMZ in that specific tumor type.

The Phase 1 evaluation of palbociclib in combination with TOPO and CTX consists of a dose determination part and a dose expansion cohort. The dose determination part will evaluate the safety and tolerability of the potential recommended Phase 2 dose (RP2D) of palbociclib in combination with TOPO and CTX in children, adolescents, and young adults with recurrent or refractory solid tumors without a curative option as a standard therapy. The starting dose of palbociclib in combination with TOPO and CTX will be the MTD for palbociclib in combination with IRN and TMZ, which is also considered the maximum

administered dose (MAD) of palbociclib in combination with TOPO and CTX. If the MAD is deemed safe and tolerable, it will be further confirmed in a dose expansion cohort as the RP2D for palbociclib in combination with TOPO and CTX. If excessive toxicity is observed, dose de-escalation to the next lower dose level of palbociclib will occur. In such case, if the next lower dose level is deemed safe and tolerable, it will be further confirmed in a dose expansion cohort as the RP2D. The dose expansion cohort will evaluate the safety and PK of palbociclib in combination with TOPO and CTX in children, adolescents, and young adults with recurrent or refractory solid tumors without a curative option as a standard therapy. If 2 or more patients from the dose determination part and/or dose expansion cohort show a confirmed objective response in a specific tumor type (eg, EWS, neuroblastoma, rhabdomyosarcoma, rhabdoid tumor or medulloblastoma), a tumor specific cohort may be opened to further evaluate antitumor activity of palbociclib in combination with TOPO and CTX in the specific tumor type.

The multicenter, open-label, randomized Phase 2 portion of the study will compare the efficacy of the combination of palbociclib with IRN and TMZ versus IRN and TMZ alone in the treatment of children, adolescents and young adults with recurrent or refractory EWS for whom no standard therapy is available.

Study Objectives and Endpoints

Phase 1 Portion of the Study and Tumor Specific Cohorts	
Dose Escalation/Dose Determination Parts	
Primary Objective(s):	**Primary Endpoint(s):**
• To estimate the MTD for the combination of palbociclib, TMZ, and IRN in children, adolescents, and young adults with recurrent or refractory solid tumors. • To determine the potential RP2D for palbociclib in combination with TOPO and CTX in children, adolescents, and young adults with recurrent or refractory solid tumors.	• First cycle dose-limiting toxicities (DLTs).
Secondary Objective(s):	**Secondary Endpoint(s):**
• To characterize the safety profile of palbociclib combined with TMZ and IRN. • To characterize the safety profile of palbociclib combined with TOPO and CTX.	• Adverse Events (AEs) as characterized by type, frequency, severity (as graded by National Cancer Institute [NCI] Common Terminology Criteria for Adverse events [CTCAE] version 4.03), timing, seriousness, and relationship to study therapy; laboratory test data including hemoglobin A1c (HbA1c) as characterized by type, frequency, severity (as graded by NCI CTCAE version 4.03), and timing; electrocardiogram (ECG) parameters, and vital signs.

• To describe the PK of palbociclib, TMZ, and IRN in children, adolescents, and young adults with recurrent or refractory solid tumors when given in combination. • To describe the PK of palbociclib, TOPO, and CTX in children, adolescents, and young adults with recurrent or refractory solid tumors when given in combination	• PK parameters of palbociclib, TMZ, IRN, TOPO, and CTX: • Palbociclib PK: Multiple Dose (MD; assuming steady-state is achieved)-$C_{ss,max}$, T_{max}, $AUC_{ss,\tau}$, $C_{ss,trough}$, and CL/F, as data permit. • TMZ PK: MD - $C_{ss,max}$, T_{max}, $AUC_{ss,\tau}$, $C_{ss,trough}$, and CL/F, as data permit. • IRN (and active metabolite, SN-38) PK: MD - $C_{ss,max}$, T_{max}, $AUC_{ss,\tau}$, $C_{ss,trough}$, and CL/F, as data permit. • CTX PK: MD - $C_{ss,max}$, T_{max}, $AUC_{ss,\tau}$, $C_{ss,trough}$, and CL/F, as data permit. • TOPO (and active metabolite) PK: MD - $C_{ss,max}$, T_{max}, $AUC_{ss,\tau}$, Css,trough, and CL/F, as data permit.
• To evaluate the preliminary antitumor activity of palbociclib combined with TMZ and IRN. • To evaluate the preliminary antitumor activity of palbociclib combined with TOPO and CTX.	• Objective response (OR), as assessed by investigator using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1/modified Response Assessment in Neuro-Oncology (RANO) for CNS malignancies/International Neuroblastoma Response Criteria (INRC) for neuroblastoma, duration of response (DOR).
Dose Expansion Cohorts and Tumor-Specific Cohorts	
Primary Objective(s):	**Primary Endpoint(s):**
• To evaluate the safety, and confirm the RP2D for the combination of palbociclib, TMZ, and IRN at the MTD in children, adolescents and young adults with recurrent or refractory solid tumors that are known to be sensitive to a CDK4/6 inhibitor. • To evaluate the safety, and confirm the RP2D for the combination of palbociclib, TOPO and CTX in children, adolescents and young adults with recurrent or refractory solid tumors that are known to be sensitive to a CDK4/6 inhibitor.	• AEs as characterized by type, frequency, severity (as graded by NCI CTCAE version 4.03), timing, seriousness, and relationship to study therapy; laboratory test data including HbA1c as characterized by type, frequency, severity (as graded by NCI CTCAE version 4.03), and timing; ECG parameters, and vital signs.
• To evaluate the preliminary antitumor activity of palbociclib combined with TMZ and IRN. • To evaluate the preliminary antitumor activity of palbociclib combined with TOPO and CTX.	• OR, as assessed by investigator using RECIST version 1.1/modified RANO for CNS malignancies/INRC for neuroblastoma.
Secondary Objective(s):	**Secondary Endpoint(s):**
• To evaluate other efficacy parameters of palbociclib combined with TMZ and IRN. • To evaluate other efficacy parameters of palbociclib combined with TOPO and CTX.	• DOR, PFS, and OS.

• To describe the PK of palbociclib, TMZ, and IRN in children, adolescents, and young adults with recurrent or refractory solid tumors when given in combination. • To describe the PK of palbociclib, TOPO and CTX in children, adolescents, and young adults with recurrent or refractory solid tumors when given in combination.	• PK parameters of palbociclib, TMZ, IRN, TOPO and CTX: • Palbociclib PK: MD (assuming steady state is achieved) - $C_{ss,max}$, T_{max}, $AUC_{ss,\tau}$, $C_{ss,trough}$, and CL/F, as data permit. • TMZ PK: MD - $C_{ss,max}$, T_{max}, $AUC_{ss,\tau}$, $C_{ss,trough}$, and CL/F, as data permit. • IRN (and active metabolite, SN-38) PK: MD - $C_{ss,max}$, T_{max}, $AUC_{ss,\tau}$, $C_{ss,trough}$, and CL/F, as data permit. • CTX PK: MD - $C_{ss,max}$, T_{max}, $AUC_{ss,\tau}$, $C_{ss,trough}$, and CL/F, as data permit. • TOPO (and active metabolite) PK: MD - $C_{ss,max}$, T_{max}, $AUC_{ss,\tau}$, Css,trough, and CL/F, as data permit.
Exploratory Objectives & Endpoints for Study	
• To characterize candidate biomarkers of sensitivity or resistance in pretreatment tumor tissue that may aid in the identification of patient subpopulations most likely to benefit from treatment.	• Identify,but not limited to, abnormalities in P16 and RB genes and effect on response.
• To explore pharmacodynamics modulation of thymidine kinase (TK)-1 activity in blood following palbociclib exposure.	• Palbociclib exposure and correlation with pharmacodynamics markers in blood (TK1 activity).
• Evaluate circulating nucleic acid (CNA) biomarkers in blood.	• DNA sequencing to evaluate gene mutations (genomic alterations) in patient blood.
• To evaluate preliminary information on the palatability of the oral solution formulation of palbociclib.	• Palatability of the palbociclib oral solution formulation, as assessed by a questionnaire.
• To explore the effect of treatment with palbociclib and parameters of bone metabolism and growth, including linear growth, bone age, bone mineral density , physical signs of pubertal maturation in patients who are pre or peripubertal (<Tanner 4).	• Analyze bone metabolism and growth, including linear growth, bone age, bone mineral density, physical signs of pubertal maturation (Tanner stage), and hormones associated with growth and pubertal development (insulin-like growth factor 1 [IGF1], luteinizing hormone [LH], follicle-stimulating hormone [FSH], estradiol for girls, testosterone for boys).
Randomized Phase 2	
Primary Objective(s):	**Primary Endpoint(s):**
• To compare the efficacy of palbociclib in combination with TMZ and IRN vs TMZ and IRN chemotherapy alone in the treatment of children, adolescents, and young adults with recurrent or refractory EWS.	• Event-free survival (EFS) based on investigator assessment.
Secondary Objective(s):	**Secondary Endpoint(s);**
• To further compare the efficacy of palbociclib in combination with TMZ and IRN vs TMZ and IRN chemotherapy alone.	• Event-free survival (EFS) assessed by an independent review committee. • Objective response (OR), as assessed by investigator using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.

	• PET-CT response after cycle 4 compared to objective response on MRI/CT. • Progression free survival (PFS) based on investigator assessment. • Overall survival (OS).
• To characterize the toxicity and safety of the combination of TMZ and IRN plus or minus palbociclib.	• Adverse Events (AEs) as graded by National Cancer Institute [NCI] Common Terminology Criteria for Adverse events [CTCAE] version 4.03).
• To describe the PK of palbociclib, TMZ, and IRN in children, adolescents, and young adults with recurrent or refractory EWS when given in combination.	• Pharmacokinetic parameters of palbociclib, TMZ, IRN: • • Palbociclib PK: MD (assuming steady state is achieved) - $C_{ss,max}$, T_{max}, $AUC_{ss,\tau}$, $C_{ss,trough}$, and CL/F, as data permit. • TMZ PK: MD - $C_{ss,max}$, T_{max}, $AUC_{ss,\tau}$, $C_{ss,trough}$, and CL/F, as data permit. • IRN (and active metabolite, SN-38) PK: MD - $C_{ss,max}$, T_{max}, $AUC_{ss,\tau}$, $C_{ss,trough}$, and CL/F, as data permit.
• To assess the impact of the combination of palbociclib with TMZ and IRN treatment on the quality of life (QoL) of patients with refractory or recurrent EWS.	• QoL reported by patient at baseline and after 2 and 4 cycles using age-appropriate tools. • Days of hospitalization.
Exploratory Objective	**Exploratory Endpoint**
• To characterize candidate biomarkers of sensitivity or resistance in pretreatment tumor tissue that may aid in the identification of patient subpopulations most likely to benefit from treatment.	• Identify, but not limited to, abnormalities in P16 and RB genes and effect on response.
• To explore pharmacodynamics modulation of thymidine kinase (TK)-1 activity in blood following palbociclib exposure.	• Palbociclib exposure and correlation with pharmacodynamics markers in blood (TK1 activity).
• Evaluate circulating nucleic acid (CNA) biomarkers in blood.	• DNA sequencing to evaluate gene mutations (genomic alterations) in patient blood.
• To evaluate preliminary information on the palatability of the oral solution formulation of palbociclib.	• Palatability of the palbociclib oral solution formulation, as assessed by a questionnaire.
• To explore the effect of treatment with palbociclib and parameters of bone metabolism and growth, including linear growth, bone age, bone mineral density, physical signs of pubertal maturation in patients who are pre or peripubertal (<Tanner 4).	• Analyze bone metabolism and growth, including linear growth, bone age, bone mineral density, physical signs of pubertal maturation (Tanner stage), and hormones associated with growth and pubertal development (insulin-like growth factor 1 [IGF 1], luteinizing hormone [LH], follicle-stimulating hormone [FSH], estradiol for girls, testosterone for boys) and a marker of bone formation and bone resorption (bone alkaline phosphatase and C-telopeptide cross-links).

Study Design

This is a Phase 1/2 multicenter, open-label study to evaluate palbociclib in combination with either IRN and TMZ or TOPO and CTX chemotherapy in children, adolescents and young adults with recurrent or refractory solid tumors. The study consists of a non- randomized Phase 1 portion for recurrent or refractory solid tumors followed by potential non-randomized tumor specific cohort(s) and a randomized Phase 2 portion for recurrent or refractory EWS.

Phase 1 Design

The Phase 1 portion of the study is to estimate the MTD and confirm the RP2D of palbociclib in combination with IRN and TMZ and palbociclib in combination with TOPO and CTX in patients with relapsed or refractory solid tumors for whom no standard therapy is available.

The combination of palbociclib with IRN and TMZ portion of the study consists of a dose escalation part using a rolling 6 dose escalation design to estimate the maximum tolerable dose (MTD) for palbociclib in combination with IRN and TMZ.). This part of the study will enroll up to approximately 24 patients. Once the MTD has been estimated, a dose expansion cohort will enroll a minimum of 12 patients with recurrent or refractory solid tumors to confirm the MTD as the RP2D. Following the dose expansion, tumor-specific cohorts other than EWS (eg, neuroblastoma, rhabdomyosarcoma, rhabdoid tumor or medulloblastoma) may be opened with a maximum of 21 patients per cohort, if 2 or more patients from the dose escalation or dose expansion show a confirmed objective response in a specific tumor type, to further evaluate antitumor activity in the specific tumor type using a modified Simon's 2-stage optimal design.

The combination of palbociclib with TOPO and CTX portion of the study consists of a dose determination part to evaluate the safety and tolerability of the potential RP2D of palbociclib in combination with TOPO and CTX in patients with relapsed or refractory solid tumors for whom no standard therapy is available. The palbociclib starting dose will be the same as the MTD determined for the combination of palbociclib with IRN and TMZ. This dose is considered the MAD for palbociclib in combination with TOPO and CTX and will not be exceeded. If the palbociclib MAD is deemed tolerable, this dose will be further confirmed in a dose expansion cohort as the RP2D. If excessive toxicity is observed, dose de-escalation to the next lower palbociclib dose level will be evaluated. In such case, if the next lower dose level is deemed tolerable, it will be further confirmed in a dose expansion cohort as the RP2D. The dose determination part of the TOPO and CTX combination will enroll approximately 12 patients. The dose expansion cohort will enroll a minimum of 12 patients with recurrent or refractory solid tumors to confirm the RP2D. If 2 or more patients from dose determination part and/or dose expansion cohort show a confirmed objective response in a specific tumor type (eg, EWS, neuroblastoma, rhabdomyosarcoma, rhabdoid tumor or medulloblastoma), a tumor-specific cohort with a maximum of 21 patients per cohort may be opened to further evaluate antitumor activity of palbociclib in combination with TOPO and CTX in each specific tumor type using a modified Simon's 2-stage optimal design.

If required, the study may continue to enroll patients until data from 6 PK-evaluable patients in each of the following age groups: ≤6 years old, >6 years and <12 years old, and ≥12 years and <18 years old for each combination. The expansion cohorts may remain open for targeted enrollment by age group and by combination. However, given the relatively limited patient population of pediatric cancer patients in some of the age groups particularly the ≤ 6 and the >6 and <12 subgroups the dose expansion cohorts may be closed if the available PK data is deemed sufficient per the Sponsor assessment.

Randomized Phase 2 Design

Once the RP2D is confirmed for the combination of palbociclib with IRN and TMZ in the Phase 1 portion of the study, the Phase 2 portion of the study will be initiated to compare the efficacy of palbociclib in combination with IRN and TMZ versus IRN and TMZ alone in children, adolescents, and young adults with recurrent or refractory EWS for whom no standard therapy is available. Approximately 75 patients will be randomized in a 2:1 ratio to receive either palbociclib in combination with IRN and TMZ (Arm A: approximately 50 patients) or IRN and TMZ chemotherapy alone (Arm B: approximately 25 patients). Randomization will be stratified using block randomization by type and time of current disease recurrence (primary refractory or 1st recurrence < 2 years versus 1st recurrence ≥2 years since completion of 1st line treatment or 2nd or greater recurrence).

Study Treatments

For the palbociclib combination with IRN and TMZ, for each 21-day treatment cycle, palbociclib will be administered orally once daily (QD) on Days 1 to 14 followed by 7 days off-treatment, with doses of TMZ administered orally QD at 100 mg/m^2 on Days 1 to 5 and doses of IRN administered intravenously (IV) at 50 mg/m^2 over 90 minutes on Days 1 to 5. TMZ can be given at the same time as palbociclib and will be administered at least 1 hour prior to administering IRN due to the fact that preclinical data suggests schedule-dependent effects.[19] For patients who cannot swallow the TMZ capsules, TMZ will be administered as an IV infusion over 90 minutes. IRN infusion will then be given at least 1 hour after completion of TMZ infusion. Palbociclib should be administered at the start of TMZ infusion.

For the palbociclib combination with TOPO and CTX, for each 21-day treatment cycle, palbociclib will be administered orally once daily (QD) on Days 1 to 14 followed by 7 days off -treatment, with doses of CTX administered IV at 250 mg/m^2 over 30-60 minutes on Days 1 to 5 and doses of TOPO administered IV at 0.75 mg/m^2 on Days 1 to 5 over 30 minutes. CTX is to be administered first followed by TOPO infusion. It is recommended to start TOPO infusion immediately after CTX, however, the investigator may follow the administration protocol standard for their institution. Palbociclib should be administered at the start of CTX infusion.

Palbociclib will be utilized either as an oral solution formulation or capsule.

Administration of Capsules

When palbociclib capsules are used, palbociclib must be administered with food around the same time of the day. The capsules must not be opened. Palbociclib capsules can be used in this study when the calculated dose falls within 15% of the available dose strengths of 75 mg, 100 mg, or 125 mg.

Administration of Oral Solution

The oral solution formulation (concentration 25 mg/ml) should be administered around the same time of the day. When palbociclib oral solution is used, palbociclib can be administered with or without food. If a patient's body surface area (BSA)-based dose is more than 15% below the 75-mg capsule strength, the oral solution must be used.

Please refer to the investigational brochure for additional information.

Statistical Methods

Phase 1

Palbociclib in Combination With TMZ and IRN

Dose escalation part of study to determine the MTD for palbociclib in combination with IRN and TMZ follows a rolling 6 design allowing for accrual of 2 to 6 patients with recurrent or refractory solid tumors concurrently into a dose level. Decisions as to whether to enroll a new patient onto the current, next highest, or next lowest dose level will be made based on available safety data at the time of new patient enrollment.

Decisions as to which dose level to enroll a patient will be based on the number of patients currently enrolled and evaluable, the number of patients experiencing dose-limiting toxicities (DLTs), and the number of patients still at risk of developing a DLT at the time of new patient entry.

Once the MTD has been estimated in the dose escalation part, a dose expansion cohort will enroll a minimum of 12 patients treated at the MTD to confirm this dose as the RP2D for palbociclib in combination with IRN and TMZ.

If a tumor-specific cohort is opened, a modified Simon's 2-stage optimal design with the following decisions rules (see below Table 1) will be used for each of the opened tumor-specific cohorts of up to 21 patients per cohort. Under the null hypothesis of a true ORR that does not exceed 33%, the 2-stage optimal design will control 1-sided type I error to be approximately 0.10. If the true ORR is at least 58%, type II error will be no more than 0.20 (ie, at least 80% power):

Table 1. Modified Simon's 2-Stage Optimal Design Decision Rules for Tumor Specific Cohorts

	Cumulative Number of Responses[a]	Decision
Stage 1: Enroll a total of 7 patients[b]	2	Terminate enrollment - agent ineffective
	3-5	Inconclusive - proceed to Stage 2
	6[c]	Terminate enrollment - agent effective
Stage 2: Enroll 14 additional patients	9 or less	Agent ineffective
	10 or more	Agent effective

a. Assumption based on an objective response rate of 33% for IRN/TMZ or TOPO/CTX and 58% for palbociclib/IRN/TMZ or palbociclib/TOPO/CTX, respectively.
b. Evaluated patients will include the 2 objective responses observed and any other patients with the same tumor type during the dose escalation part/dose determination part and dose expansion cohort of the study.
c. Lower bound of the Wilson's 2-sided 80% confidence interval is greater than 62%.

Palbociclib in Combination With TOPO and CTX

A dose determination part of study for palbociclib in combination with TOPO and CTX follows a modified rolling 6 design allowing for accrual of 2 to 6 patients with recurrent or refractory solid tumors concurrently into a dose level. Planned starting dose is the MTD for the combination of palbociclib with IRN and TMZ. This dose is considered the MAD for palbociclib in combination with TOPO and CTX and no dose escalation for this combination is planned. Dose expansion cohort will further evaluate the safety and confirm the RP2D for this combination in children, adolescents, and young adults with recurrent or refractory solid tumors.

If 2 or more patients from dose determination part and/or dose expansion cohort show a confirmed objective response in a specific tumor type, a tumor-specific cohort may be opened to evaluate the antitumor activity of palbociclib in combination with TOPO and CTX in the specific tumor type using a modified Simon's 2-stage optimal design with the decisions rules described in Table 1. Under the null hypothesis of a true objective response rate (ORR) that does not exceed 33%, the 2-stage optimal design will control 1-sided type I error to be approximately 0.10. If the true ORR is at least 58%, type II error will be no more than 0.20 (ie, at least 80% power).

Safety will be evaluated based on adverse events assessed using National Cancer Institute (NCI) common terminology criteria for adverse events (CTCAE) version 4.03. ORR is defined as the proportion of patients with a best overall response of either confirmed complete response or confirmed partial response based on the Investigator's assessment according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, modified Response Assessment in Neuro-Oncology (RANO) for CNS malignancies, or the revised International Neuroblastoma Response Criteria (INRC) for neuroblastoma. Within each tumor-specific cohort, ORR will be estimated with the corresponding 2-sided 80% confidence interval using Wilson's method.[1]

Randomized Phase 2

Once the RP2D is confirmed for the combination of palbociclib with IRN and TMZ, the Phase 2 portion of the study will be initiated to compare the event-free survival (EFS) of palbociclib in combination with IRN and TMZ versus IRN and TMZ alone in children, adolescents, and young adults with recurrent or refractory EWS. All primary and secondary endpoints based on radiological assessments of tumor burden (ie, EFS, OR, PFS) will be based on investigator assessment. A blinded independent review committee (BIRC) will perform retrospective independent review of radiographic images and clinical information collected on-study and the data will be used to verify the primary endpoint of investigator-assessed EFS through the secondary objective.

A total of approximately 50 EFS events based on investigator assessment are required in the 2 treatment arms of the study based on a 2:1 randomization to have at least 80% power to detect a hazard ratio of 0.58 in favor of palbociclib plus IRN and TMZ arm using a 1-sided log-rank test at a significance level of 0.20. A group sequential design with a Rho family (1.0) β-spending function is used to determine the futility boundary. Assuming a 5% and 10% dropout rates by 12 months on the palbociclib combination arm and chemotherapy alone arm, respectively, a non-uniform accrual accomplished over a 25-month period and follow-up for about 6 months after the last patient is enrolled, a total sample size of approximately 75 patients (approximately 50 patients in combination of palbociclib with IRN and TMZ arm and approximately 25 patients in IRN and TMZ alone arm) is required. Randomization will be stratified by type and time of current disease recurrence (primary refractory or 1st recurrence <2 years versus 1st recurrence ≥2 years since completion of 1st line treatment or 2nd or greater recurrence). It is expected approximately 75% of the patients will be pediatric patients (age ≥2 and <18 years old).

An interim futility analysis will be conducted to allow for early stopping of the study due to futility/no signal of activity based on the primary endpoint of EFS. The analysis will be performed after approximately 30 investigator-assessed EFS events (60% of total events expected) have been documented.

The primary analysis of EFS based on investigator assessment will be summarized in the full analysis set using the Kaplan-Meier method and displayed graphically where appropriate. The median EFS and corresponding 2-sided 95% CI will be provided. A stratified log-rank test will be used to compare EFS between the two treatment arms. The hazard ratio and associated 2-sided 95% CI will be estimated using the stratified Cox proportional hazards model.

SCHEDULE OF ACTIVITIES

The schedule of activities table provides an overview of the protocol visits and procedures. Refer to the ASSESSMENTS section of the protocol for detailed information on each assessment required for compliance with the protocol. Refer to Appendix 14 for detailed guidance on alternative measures during COVID-19 and other public emergencies.

The investigator may schedule visits (unplanned visits) in addition to those listed in the schedule of activities table in order to conduct evaluations or assessments required to protect the well-being of the patient.

Table 2. Dose Escalation Part, Dose Expansion Cohorts, Dose Determination Part, and Tumor-Specific Cohorts[32]

		Cycle 1				Cycle 2			Subsequent Cycles[27]	End of Treatment[28]	Follow-Up[29]
Visit Identifier	**Screening**	**Day 1**	**Day 5**	**Day 6[26]**	**Day 14**	**Day 1**	**Day 5**	**Day 14**	**Day 1**		
Frequency and Visit Window	**Between Day -21 and Cycle 1 Day 1**				**-2/+1 days**	**±2 days**		**-2/+1 days**	**±2 days**	**≥28 calendar days and <35 calendar days**	**±7 days**
Informed consent and pediatric assent[1]	X										
Baseline signs and symptoms, past medical history, prior medications[2]	X										
Physical examination[32]	X	X				X			X	X	
Tanner Stage[3]	X								Every 4 cycles (±1 week)	X	
Vital signs[4,32]	X	X	X[25]		X[25]	X[25]			X[25]	X	
ECOG or Lansky Performance Score[5,32]	X	X				X			X	X	
Menarchal status[32]	X	X				X			X	X	
Height[32]	X								Every odd cycle only	X	
Body Weight[32]	X	X				X			X	X	
BSA	X	X				X			X	X	

Table 2. Dose Escalation Part, Dose Expansion Cohorts, Dose Determination Part, and Tumor-Specific Cohorts[32]

		Cycle 1				Cycle 2			Subsequent Cycles[27]	End of Treatment[28]	Follow-Up[29]
Visit Identifier	**Screening**	**Day 1**	**Day 5**	**Day 6[26]**	**Day 14**	**Day 1**	**Day 5**	**Day 14**	**Day 1**		
Frequency and Visit Window	**Between Day -21 and Cycle 1 Day 1**				**-2/+1 days**	**±2 days**		**-2/+1 days**	**±2 days**	**≥28 calendar days and <35 calendar days**	**±7 days**
Laboratory											
Hematology[6,32]	X[32]	X	X[25]		X[25]	X[25]	X[25]	X[25]	X[25,]	X	
Blood Chemistry[7,32]	X	X	X[25]		X[25]	X[25]	X[25]	X[25]	X[25,]	X	
HbA1c[7]	X	X[25]							X[25] (repeat at Cycle 4 and then repeat every 4 cycles)	X[7]	
Pregnancy test and Contraception Check[8,32]	X	X				X[25]			X[25,]	X	
Urine analysis[9,32]	X	As clinically indicated								X	
PK levels[10]			X	X	X		X	X			
Thymidine kinase analysis[10]	X		X	X	X						
ECG[11,32]	X	X				X			Cycle 3 only	X	
Tumor tissue collection[12]	X										
Blood sample for biomarker[12]		X							Cycle 3 only	X	
Registration and Treatment											
Registration[13]	X										
Palbociclib (oral)[14,15]		Once daily Days 1 to 14				Once daily Days 1 to 14			Once daily Days 1 to 14		
Temozolomide (oral or IV) and Irinotecan (IV)[14], OR Cyclophosphamide (IV) and Topotecan (IV)[15]		Once daily Days 1 to 5				Once daily Days 1 to 5			Once daily Days 1 to 5		

Table 2. Dose Escalation Part, Dose Expansion Cohorts, Dose Determination Part, and Tumor-Specific Cohorts[32]

		Cycle 1				Cycle 2			Subsequent Cycles[27]	End of Treatment[28]	Follow-Up[29]
Visit Identifier	**Screening**	**Day 1**	**Day 5**	**Day 6[26]**	**Day 14**	**Day 1**	**Day 5**	**Day 14**	**Day 1**		
Frequency and Visit Window	**Between Day -21 and Cycle 1 Day 1**				**-2/+1 days**	**±2 days**		**-2/+1 days**	**±2 days**	**≥28 calendar days and <35 calendar days**	**±7 days**
Palbociclib Palatability Questionnaire[16,32]		X			X	X Cycle 2 only		X			
Oral medication compliance monitoring[17,32]					X			X	X	X	
Disease response assessment											
MRI/CT scan[18]	X								X Every 2 cycles X 4 (±7days) and then every 4 cycles (±7 days) from C1D1	X	X[30]
MIBG scan/FDG-PET[18] (Neuroblastoma patients only)	X								X Every 2 cycles X 4 (±7 days) and then every 4 cycles (±7 days) from C1D1	X	X[30]
Bilateral bone marrow aspirate and biopsy[18] (Neuroblastoma patients only)	X								X Every 2 cycles X 4 (±7 days) and then every 4 cycles (±7 days) from C1D1	X	X[30]
Assessments of growth and bone metabolism											
DEXA for bone mineral density[19]	X								Every 12 cycles (±3 weeks)	X[31]	
Bone age[20]	X								Every 12 cycles (±3 weeks)	X[31]	
LH, FSH, Estradiol for female patients or LH, FSH, Testosterone for male patients[21]	X								Every 4 cycles (±1 week)	X	
IGF-1; IGFBP-3; 25-hydroxyvitamin D;	X								Every 4 cycles (±1 week)	X	

Table 2. Dose Escalation Part, Dose Expansion Cohorts, Dose Determination Part, and Tumor-Specific Cohorts[32]

		Cycle 1				Cycle 2			Subsequent Cycles[27]	End of Treatment[28]	Follow-Up[29]
Visit Identifier	**Screening**	**Day 1**	**Day 5**	**Day 6[26]**	**Day 14**	**Day 1**	**Day 5**	**Day 14**	**Day 1**		
Frequency and Visit Window	**Between Day -21 and Cycle 1 Day 1**				**-2/+1 days**	**±2 days**		**-2/+1 days**	**±2 days**	**≥28 calendar days and <35 calendar days**	**±7 days**
1, 25-dihidroxyvitamin D; fasting cortisol[22]											
Other clinical assessments											
Serious and non-serious adverse event monitoring[23,32]	X	X	X[25]		X[25]	X	X[25]	X[25]	X[25]	X	
Concomitant treatments and non-drug supportive intervention[24,32]	X	X	X[25]		X[25]	X	X[25]	X[25]	X[25]	X	
Survival											X

Abbreviations: BSA = body surface area; CT = Computed tomography; ECG = electrocardiogram; DEXA = dual-energy X-ray absorptiometry; ECOG = Eastern Cooperative Oncology Group; IGF-1 = insulin-like growth factor 1; IGFBP-3 = insulin-like growth factor binding protein 3; FSH = follicle-stimulating hormone; HbA1c = hemoglobin A1c; IV = intravenous; LH = luteinising hormone; MRI = magnetic resonance imaging; PK = pharmacokinetic(s);.

1. **Informed Consent:** Must be obtained prior to undergoing any study-specific procedures.
2. **Baseline Signs & Symptoms:** Patients will be asked about any signs and symptoms experienced within the 21 days prior to study entry (defined as C1D1).
3. **Tanner Stage:** Assess in girls ≥8 years of age and boys ≥9 years of age, or if sexual development is present in children who are younger. If the patient is less than these ages, and no sexual development present, Tanner grade 1 should be used. Once a patient reaches Tanner Stage 5, assessment is no longer necessary. See Appendix 3 for Tanner Stage Definition.
4. **Vital Signs:** Blood pressure (BP) and pulse rate to be recorded in sitting position. Vital signs should be recorded on a day of drug administration unless window is allowed. See Footnote 25
5. **ECOG or Lansky Performance Status:** Lansky for patients ≤16 years old; ECOG for > 16 years old. If a patient turns 17 years old while on study, ECOG should be used.See Appendix 2.
6. **Hematology**: No need to repeat on Cycle 1 Day 1 (C1D1) if screening assessment performed within 7 days prior to that date. See ASSESSMENTS section for Laboratory Tests list.
7. **Blood Chemistry including HbA1c**: No need to repeat on C1D1 if screening assessment performed within 7 days prior to that date. Collection of 1 baseline blood sample on C1D1 will not constitute protocol deviation as long as sample is taken prior C1D1 dosing. See ASSESSMENTS section for Laboratory Tests list. . EoT sample for

Table 2. Dose Escalation Part, Dose Expansion Cohorts, Dose Determination Part, and Tumor-Specific Cohorts[32]

		Cycle 1				Cycle 2			Subsequent Cycles[27]	End of Treatment[28]	Follow-Up[29]
Visit Identifier	**Screening**	**Day 1**	**Day 5**	**Day 6[26]**	**Day 14**	**Day 1**	**Day 5**	**Day 14**	**Day 1**		
Frequency and Visit Window	**Between Day -21 and Cycle 1 Day 1**				**-2/+1 days**	**±2 days**		**-2/+1 days**	**±2 days**	**≥28 calendar days and <35 calendar days**	**±7 days**

HbA1c should be collected if more then 12 weeks have passed since prior assessment. Blood tests for HbA1c assessments will be analyzed by a central independent laboratory. For details of sample collection refer to the Laboratory manual.

8. **Pregnancy Test**: Described in the Pregnancy Testing section (Section 7.1.1).
9. **Urine analysis**: TOP and CTX combination only. On treatment, to be performed when clinically indicated. See ASSESSMENTS section for Laboratory Test list.
10. **See Table 4 for PK and thymidine kinase schedule**.
11. **Triplicate 12-Lead ECG**. At each time point, 3 consecutive 12-lead ECGs will be performed approximately 2 minutes apart. On C1D1 and C2D1, ECGs should be collected prior to palbociclib dosing, and 6 and 24 hours (±120 minutes) following palbociclib dosing. On C3D1 ECG should be collected prior to palbociclib dosing and 6 hours (±120 minutes) following palbociclib dosing. ECGs should also be obtained when medically necessary. If patient is receiving 5-HT3 antagonist for nausea/vomiting prophylaxis or treatment, the ECG should be performed prior to administration of the 5-HT3 antagonist. See Section 7.1.6.
12. **Tumor Tissue and Blood Biomarker Samples (Highly Recommended Biomarker Sample Collection)**: Patients will provide tumor sample if available. Most recent biopsy tumor tissue sample is preferred but archival tissue is acceptable if patient has not had recent surgery. 4 mL of whole blood for each biomarker sample will be collected. Details for handling of these samples including processing, storage, and shipment will be provided in the Laboratory Manual.
13. **Registration**: Patient number and dose level allocation assigned by Pfizer Inc. Registration will be performed prior to or on C1D1.
14. **Study Treatment (IRN and TMZ combination)**: Described in the STUDY TREATMENTS section. To prevent IRN-induced diarrhea, start antibiotics for diarrhea prophylaxis 1-2 days prior to administration of treatments on Day 1 of each cycle and continue until Day 7 of each cycle (see Section 5.7.5).
15. **Study Treatment (TOPO and CTX combination)**: Described in the STUDY TREATMENTS section. Subcutaneous granulocyte-colony stimulating factor (G-CSF) (5 µg/kg/dose daily) is mandatory starting Cycle 1. G-CSF should be initiated 24-48 hours after the administrations of TOPO and CTX are completed (ie, on Day 6 or Day 7 of a cycle (see Section 5.7.4).
16. **For patients taking palbociclib oral solution only**. See Table 13. C1D14 and C2D14 Palatability Questionnaire can be completed after any dose between Day 8 and Day14.
17. **Review of study diaries and perform drug accountability:** Palbociclib bottle(s) including any unused capsules or the amount of oral solution, will be returned to the clinic for drug accountability prior to the start of a new cycle and at the end of the trial.
18. **Tumor Assessments**: Tumor assessments will include all known or suspected disease sites. Imaging may include chest, abdomen, pelvis CT or MRI, and brain CT or MRI scans at screening (within 21 days of C1D1) then every 2 cycles (±7 days) for the first 4 assessments and then every 4 cycles (±7 days) from C1D1 (eg, at completion of Cycle 2, 4, 6, 8, 12,16, etc.) unless clinically indicated at additional time points. Bone scans will be performed at baseline if disease is suspected and on study as appropriate to follow disease. Baseline imaging central nervous system (CNS) for non-CNS tumors should be performed on symptomatic patients to rule out CNS metastases. CT/MRI is the preferred method of tumor evaluation and measurements. However, if the CT/MRI component of FDG-PET scan is identical to diagnostic CT/MRI, then this can be used for target/non-target tumor evaluation. If the CT/MRI component of the FDG-PET scan is for anatomical mapping/localization but does not

Table 2. Dose Escalation Part, Dose Expansion Cohorts, Dose Determination Part, and Tumor-Specific Cohorts[32]

		Cycle 1				Cycle 2			Subsequent Cycles[27]	End of Treatment[28]	Follow-Up[29]
Visit Identifier	**Screening**	**Day 1**	**Day 5**	**Day 6[26]**	**Day 14**	**Day 1**	**Day 5**	**Day 14**	**Day 1**		
Frequency and Visit Window	**Between Day -21 and Cycle 1 Day 1**				**-2/+1 days**	**±2 days**		**-2/+1 days**	**±2 days**	**≥28 calendar days and <35 calendar days**	**±7 days**

have diagnostic quality, then CT/MRI scan is needed for target/non-target tumor evaluation. Patients with neuroblastoma are required to have MIBG or FDG-PET scans (for those with MIBG non-avid tumor) as part of their tumor assessment per clinician determination and MIBG avidity. Imaging scans performed per standard of care prior to consent are acceptable as baseline scans as long as performed within 1) 21 days of C1D1, 2) there was no intervening anticancer therapy, 3) imaging parameters meet standard RECIST 1.1, RANO or INRC requirements, as applicable, and 4) same imaging modalities can be continued for on treatment tumor response assessment. Bilateral bone marrow aspirates and biopsies are mandatory at baseline for patients with neuroblastoma. If positive at baseline, repeat bone marrow aspirates and biopsies are required at tumor assessment time points. If negative at baseline, repeat bone marrow aspirates and biopsies are highly recommended but not required and should be done as clinically indicated. For patients with neuroblastoma, bone marrow assessments performed as per standard of care prior to consent are acceptable as baseline assessments as long as performed within 1) 21 days of C1D1, 2) there was no intervening anticancer therapy, 3) bilateral aspirates and biopsies from two anatomic locations (ie, left and right posterior iliac crests) were assessed. For other tumor types; bone marrow aspirates and biopsies are only needed as clinically indicated. Tumor assessment should be repeated at the end of treatment visit if more than 6 weeks have passed since the last evaluation if the patient has not completed at least 8 cycles and more than 12 weeks if the patient have completed 8 cycles. For patients with evidence of response (partial response or complete response), a confirmatory scan must be performed ≥4 weeks after the initial scan. Patients with no evidence of disease progression at the time of treatment discontinuation should continue to have tumor assessment performed as outlined in Section 7.9.2.

19. **DEXA (dual-energy X-ray absorptiometry) Scan for Bone Mineral Assessment:** Only for patients who have Tanner stage less than 4 (ie, Tanner 1-3). The total body, lumbar spine and/or femur bone density scan (as per local standard of care) should be performed at screening, every 12 cycles (±3 weeks) thereafter, and at the End of Treatment visit.
20. **Bone age:** Only for Tanner stage less than 4 (ie, Tanner 1-3). X-ray of hand for assessment of bone age should be performed at screening, every 12 cycles (±3 weeks) thereafter, and at the End of Treatment visit. Once the bone age assessment demonstrates that a patient has completed growth, additional assessments are not necessary.
21. Only for patients who have a Tanner stage less than 4 (1-3). **LH, FSH, Estradiol:** For girls, serum for measurement of LH, FSH and estradiol levels should be obtained at screening, every 4 cycles thereafter (±1 week), and at the End of Treatment visit. **LH, FSH, Testosterone:** For boys, serum for measurement of LH, FSH, and testosterone levels should be performed at screening, every 4 cycles (±1 week) thereafter, and at the End of Treatment visit. Blood tests for LH, FSH, Estradiol & Testosterone assessments will be analyzed by a central independent laboratory. For details of sample collection, refer to the Laboratory Manual.
22. **IGF-1; IGFBP-3; 25-hydroxyvitamin D; 1, 25-dihidroxyvitamin D; and fasting cortisol:** Only for patients who have a Tanner stage less than 4 (1-3). Blood tests for assessments of growth and bone metabolism will be analyzed by a central independent laboratory. For details of sample collection, refer to the Laboratory Manual.
23. **Serious and Non-Serious Adverse Event (AE) Monitoring**: AEs should be documented and recorded at each visit using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03. The time period for actively eliciting and collecting AEs and serious AEs (SAEs; "active collection period") for each patient begins from the time the patient provides informed consent through and including a minimum of 28 calendar days after the last investigational product administration. The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis rather than individual signs/symptoms should be reported as AE or SAE on the CRF. If the patient begins a new anticancer therapy, the period for recording

Table 2. Dose Escalation Part, Dose Expansion Cohorts, Dose Determination Part, and Tumor-Specific Cohorts[32]

		Cycle 1				Cycle 2			Subsequent Cycles[27]	End of Treatment[28]	Follow-Up[29]
Visit Identifier	**Screening**	**Day 1**	**Day 5**	**Day 6[26]**	**Day 14**	**Day 1**	**Day 5**	**Day 14**	**Day 1**		
Frequency and Visit Window	**Between Day -21 and Cycle 1 Day 1**				**-2/+1 days**	**±2 days**		**-2/+1 days**	**±2 days**	**≥28 calendar days and <35 calendar days**	**±7 days**

non-serious AEs on the case report form (CRF) ends at the time the new treatment is started. However, any SAEs occurring during the active collection period must still be reported to Pfizer Safety and recorded on the CRF, irrespective of any intervening treatment (Section 8).

24. **Concomitant Treatments**: all concomitant medications and non-drug supportive interventions should be recorded on the CRF (see Section 5.7).
25. Assessments for AEs, concomitant medications, vital signs, hematology, and blood chemistry can be performed within ±1 day from the Day 5 and -2/+1 day(s) from Day 14 visits during Cycle 1 and within ±2 days from Day 5 and -2/+1 day(s) from Day 14 visits during Cycle 2 and within -2 days from Day 1 for Cycle 2 and subsequent cycles. There is ±2 days window from Day 1 for HbA1c (starting Cycle 4 Day 1) and -2 days window from Day 1 for pregnancy tests (starting Cycle 2 Day 1). Results of hematology, blood chemistry and pregnancy test to confirm patient is eligible to continue study medication administration per dose modification requirements in Section 5.4.11 should be available and reviewed prior to dosing.
26. To accommodate investigative sites which are not open 7 days a week and thus not capable of implementing certain scheduled activities, missing the Cycle 1 Day 6 visit will not constitute a protocol deviation. Thus, the Cycle 1 Day 6 palbociclib PK sample collection is recommended but not required.
27. Laboratory tests after Day 1 can be done as clinically indicated.
28. **End of Treatment Visit (EoT):** At least 28 calendar days, and no more than 35 calendar days, after last dose of study treatment, patients will return to undergo review of concomitant treatments, vital signs, and assessment for resolution of any treatmentrelated toxicity and tumor assessments, if applicable. If patient initiates new anticancer therapy prior to 28 days after last dose of study treatment, then EoT visit should be performed prior to starting new anticancer therapy.
29. **Follow up:** Patients will be followed for overall survival after completion of treatment. Contact should be made every 2 months (±7 days) from EoT visit. If patient receives additional anticancer therapies, this should be noted. Contact can be via clinic visit, email or equivalent electronic communication or phone call to patient/caregiver for minimum of 2 years post last dose of study drug.
30. Patients without evidence of disease progression at the time of treatment discontinuation should continue to have tumor assessments performed as scheduled until documented progressive disease, initiation of new anticancer therapy, or discontinuation of patient from overall study participation.
31. If these studies have been done within 3 months when the patient is permanently discontinued from treatment, these studies do not need to be repeated.
32. Alternative measures: During COVID-19 pandemic (and upon written notification from Pfizer during other public emergencies) in Dose Escalation, Dose Expansion Cohorts and Dose Determination Part. Outside public emergencies in Tumor-Specific Cohorts: Screening, on treatment, and EoT, hematology, blood chemistry, pregnancy test and urine analysis tests may be conducted at a local laboratory. ECGs and routine safety assessments can be performed at a local facility. Selected assessments (serious/non-serious AE monitoring, concomitant treatment, oral medication compliance, contraceptive check can be performed via Telehealth visit if in-clinic study visit cannot be conducted (see Appendix 14 for detailed guidance).

Table 3. Phase 2 Portion of the Study[34]

		Cycle 1				Cycle 2			Subsequent Cycles[29]	End of Treatment[30]	Follow-Up[31]
Visit Identifier	**Screening**	**Day 1**	**Day 5**	**Day 6[28]**	**Day 14**	**Day 1**	**Day 5**	**Day 14**	**Day 1**		
Frequency and Visit Window	**Between Day -21 and Randomization**				**-2/+1 days**	**±2 days**		**-2/+1 days**	**±2 days**	**≥28 calendar days and <35 calendar days**	**±7 days**
Informed consent and pediatric assent[1]	X										
Confirmation of EWS[2] diagnosis.	X										
Baseline signs and symptoms, past medical history, prior medications[3]	X										
Physical examination[34]	X	X				X			X	X	
Tanner Stage[4]	X								Every 4 cycles (±1 week)	X	
Vital signs[5,34]	X	X	X[27]		X[27]	X[27]			X[27]	X	
ECOG or Lansky Performance Score[6,34]	X	X				X			X	X	
Menarchal status[34]	X	X				X			X	X	
Height[34]	X								Every odd cycle only	X	
Body Weight[34]	X	X				X			X	X	
BSA	X	X				X			X	X	
Laboratory											
Hematology[7,34]	X	X	X[27]		X[27]	X[27]	X[27]	X[27]	X[27,]	X	
Blood Chemistry[8,34]	X	X	X[27]		X[27]	X[27]	X[27]	X[27]	X[27,]	X	
HbA1c[8]	X	X[27]							X[26] (repeat at Cycle 4 and then repeat every 4 cycles)	X[8]	
Pregnancy test and Contraception Check[9,34]	X	X				X[27]			X[27]	X	
PK levels[10]			X	X	X		X	X			
Thymidine kinase analysis[10]		X	X	X	X						
ECG[11,34]	X	X				X			Cycle 3 only	X	

Table 3. Phase 2 Portion of the Study[34]

		Cycle 1				Cycle 2			Subsequent Cycles[29]	End of Treatment[30]	Follow-Up[31]
Visit Identifier	**Screening**	**Day 1**	**Day 5**	**Day 6[28]**	**Day 14**	**Day 1**	**Day 5**	**Day 14**	**Day 1**		
Frequency and Visit Window	**Between Day -21 and Randomization**				**-2/+1 days**	**±2 days**		**-2/+1 days**	**±2 days**	**≥28 calendar days and <35 calendar days**	**±7 days**
Tumor tissue collection[12]	X										
Blood sample for biomarker[12]		X							Cycle 3 only	X	
Registration and Treatment											
Randomization[13]	X										
Palbociclib (oral)[14]		Once daily Days 1 to 14				Once daily Days 1 to 14			Once daily Days 1 to 14		
Temozolomide (oral or IV) and Irinotecan (IV)[14]		Once daily Days 1 to 5				Once daily Days 1 to 5			Once daily Days 1 to 5		
Palbociclib Palatability Questionnaire[15,34]		X			X	X Cycle 2 only		X			
Oral medication compliance monitoring[16,34]					X			X	X	X	
Quality of Life assessment[17]	X								X (Cycle 3 & Cycle 5)		
Hospitalization[18]		X				X			X	X	
Tumor response assessment											
MRI/CT scan[19]	X								X Every 2 cycles/ 6 weeks X 4 (±7days) and then every 4 cycles/ 12 weeks (±7 days) from the date of randomization	X	X[32]
Distant metastases[20] staging	X								X Every 4 cycles/12 weeks (±7days)	X	X[32]
PET-CT or PET-MRI[20]	X								X (Cycle 4/Week 12)		

Table 3. Phase 2 Portion of the Study[34]

		Cycle 1				Cycle 2			Subsequent Cycles[29]	End of Treatment[30]	Follow-Up[31]
Visit Identifier	**Screening**	**Day 1**	**Day 5**	**Day 6[28]**	**Day 14**	**Day 1**	**Day 5**	**Day 14**	**Day 1**		
Frequency and Visit Window	**Between Day -21 and Randomization**				**-2/+1 days**	**±2 days**		**-2/+1 days**	**±2 days**	**≥28 calendar days and <35 calendar days**	**±7 days**
Assessments of growth and bone metabolism											
DEXA for bone mineral density[21]	X								Every 12 cycles (±3 weeks)	X[33]	
Bone age[22]	X								Every 12 cycles (±3 weeks)	X[33]	
LH, FSH, Estradiol for female patients or LH, FSH, Testosterone for male patients[23]	X								Every 4 cycles (±1 week)	X	
IGF-1; IGFBP-3; 25-hydroxyvitamin D; 1, 25-dihidroxyvitamin D; C-telopeptide, bone ALP, fasting cortisol[24]	X								Every 4 cycles (±1 week)	X	
Other clinical assessments											
Serious and non-serious adverse event monitoring[25,34]	X	X	X[26]		X[26]	X	X[26]	X[26]	X[26]	X	
Concomitant treatments and non-drug supportive intervention[26,34]	X	X	X[26]		X[26]	X	X[26]	X[26]	X[26]	X	
Survival											X

Abbreviations: BSA = body surface area; CT = Computed tomography; ECG = electrocardiogram; DEXA = dual-energy X-ray absorptiometry; ECOG = Eastern Cooperative Oncology Group; IGF-1 = insulin-like growth factor 1; IGFBP-3 = insulin-like growth factor binding protein 3; FSH = follicle-stimulating hormone; HbA1c = hemoglobin A1c; IV = intravenous; LH = luteinising hormone; MRI = magnetic resonance imaging; PK = pharmacokinetic(s); ALP = alkaline phosphatase.

1. **Informed Consent:** Must be obtained prior to undergoing any study-specific procedures.
2. **Ewing sarcoma** histopathological diagnosis must be confirmed by presence of EWSR1-ETS or FUS-ETS fusion genes. Please refer to Section 6.1.
3. **Baseline Signs & Symptoms:** Patients will be asked about any signs and symptoms experienced within 21 days of randomization.

Table 3. Phase 2 Portion of the Study[34]

		Cycle 1				Cycle 2			Subsequent Cycles[29]	End of Treatment[30]	Follow-Up[31]
Visit Identifier	**Screening**	**Day 1**	**Day 5**	**Day 6[28]**	**Day 14**	**Day 1**	**Day 5**	**Day 14**	**Day 1**		
Frequency and Visit Window	**Between Day -21 and Randomization**				**-2/+1 days**	**±2 days**		**-2/+1 days**	**±2 days**	**≥28 calendar days and <35 calendar days**	**±7 days**

4. **Tanner Stage:** Assess in girls ≥8 years of age and boys ≥9 years of age, or if sexual development is present in children who are younger. If the patient is less than these ages, and no sexual development present, Tanner grade 1 should be used. Once a patient reaches Tanner Stage 5, assessment is no longer necessary. See Appendix 3 for Tanner Stage Definition.
5. **Vital Signs:** Blood pressure (BP) and pulse rate to be recorded in sitting position. Vital signs should be recorded on a day of drug administration unless window is allowed. See Footnote 27
6. **ECOG or Lansky Performance Status:** Lansky for patients ≤ 16 years old; ECOG for > 16 years old. If a patient turns 17 years old while on study, ECOG should be used.See Appendix 2**.**
7. **Hematology**: No need to repeat on Cycle 1 Day 1 (C1D1) if screening assessment performed within 7 days prior to that date. See ASSESSMENTS section for Laboratory Tests list.
8. **Blood Chemistry including HbA1c**: No need to repeat on C1D1 if screening assessment performed within 7 days prior to that date. Collection of one baseline blood sample on C1D1 will not constitute protocol deviation as long as sample is taken prior C1D1 dosing.See ASSESSMENTS section for Laboratory Tests list. EoT sample for HbA1c should be collected if more then 12 weeks have passed since prior assessment. Blood tests for HbA1c assessments will be analyzed by a central independent laboratory. For details of sample collection refer to the Laboratory manual.
9. **Pregnancy Test**: Described in the Pregnancy Testing section (Section 7.1.1).
10. **See** Table 5 **for PK and thymidine kinase (TK) schedule.** PK and TK samples will be collected for patients randomized to palbociclib in combination with IRN and TMZ arm.
11. **Triplicate 12-Lead ECG**. At each time point, 3 consecutive 12-lead ECGs will be performed approximately 2 minutes apart. On treatment, for patients randomized to palbociclib with IRN and TMZ, ECG should be collected on C1D1 and C2D1, prior to palbociclib dosing and 24 hours (±120 minutes) following palbociclib dosing (C1D2 and C2D2 respectively); and on C3D1 prior to palbociclib dosing and at any time when medically necessary. On treatment for patients randomized to IRN and TMZ only arm, ECGs should be obtained prior to IRN infusion on C2D2 and when medically necessary. If patient is receiving 5-HT3 antagonist for nausea/vomiting prophylaxis or treatment (in either treatment arm), the required ECG should be performed prior to administration of the 5-HT3 antagonist. See Section 7.1.6.
12. **Tumor Tissue and Blood Biomarker Samples (Highly Recommended Biomarker Sample Collection):** Patients will provide tumor tissue sample if available. Most recent biopsy tumor tissue sample is preferred but archival tissue is acceptable if patient has not had recent surgery. 4 mL of whole blood for each biomarker sample will be collected. Details for handling of these samples including processing, storage, and shipment will be provided in the Laboratory Manual.
13. **Randomization**: Randomization will be performed using IRT system once all screening procedures have been completed and eligibility of a patient is confirmed. Patients should be dosed within 3 calendar days of randomization. For details please refer to the IRT Manual.
14. **Study Treatment (IRN and TMZ combination)**: Described in the STUDY TREATMENTS section. To prevent IRN-induced diarrhea, start antibiotics for diarrhea prophylaxis 1-2 days prior to administration of treatments on Day 1 of each cycle and continue until Day 7 of each cycle (see Section 5.7.5).

Table 3. Phase 2 Portion of the Study[34]

		Cycle 1				Cycle 2			Subsequent Cycles[29]	End of Treatment[30]	Follow-Up[31]
Visit Identifier	**Screening**	**Day 1**	**Day 5**	**Day 6[28]**	**Day 14**	**Day 1**	**Day 5**	**Day 14**	**Day 1**		
Frequency and Visit Window	**Between Day -21 and Randomization**				**-2/+1 days**	**±2 days**		**-2/+1 days**	**±2 days**	**≥28 calendar days and <35 calendar days**	**±7 days**

15. **For patients taking palbociclib oral solution only.** See Table 13. C1D14 and C2D14 Palatability Questionnaire can be completed after any dose between Day 8 and Day14.
16. **Review of study diaries and perform drug accountability:** Palbociclib bottle(s) including any unused capsules or the amount of oral solution, will be returned to the clinic for drug accountability prior to the start of a new cycle and at the end of the trial.
17. **Quality of Life** should be performed at baseline prior to dosing and subsequently after completion of Cycle 2 (preferably immediately before Cycle 3 Day 1 dosing) and after completion of Cycle 4 (preferably immediately before Cycle 5 Day 1 dosing). The QoL questionnaires should be completed before patient/parent learns about their tumor response assessment results. See Section 7.6 and Appendix 13.
18. **Hospitalization:** Planned and unplanned inpatient admissions, outpatient visits, attendance for transfusions, blood tests and study related procedures should be recorded on the CRF. (see Section 7.7)
19. **Tumor Assessments**: Tumor assessments will include all known or suspected disease sites. Depending on tumor location, i**maging should include CT chest and may include CT or MRI abdomen/pelvis/extremity and brain CT or MRI scans at screening (within 21 days of randomization) then every** 2 cycles **(±7days) for the first 4 assessments (eg, at** completion of Cycle 2, 4, 6, 8**) and then every** 4 cycles **(±7 days) from** C1D1 **(eg, at** completion of Cycle 12, 16, 20 **etc.) unless clinically indicated**. **Every effort should be made to perform tumor assessment in a fixed 6- week intervals (±7days) for the first 4 assessments (eg, end of week 6, 12, 18, 24 from the date of randomization and then in 12-week intervals (±7days) (eg, end of week 36, 48, 60) particularly in patients with treatment cycle delays.** CT/MRI is the preferred method of tumor evaluation and measurements. However, if the CT/MRI component of FDG-PET scan is identical to diagnostic CT/MRI, then this can be used for target/non-target tumor evaluation. If the CT/MRI component of the FDG-PET scan is for anatomical mapping/localization but does not have diagnostic quality, then CT/MRI scan is needed for target/non-target tumor evaluation. Baseline imaging of central nervous system (CNS) should be performed on symptomatic patients to assess for CNS metastases. Tumor assessment should be repeated at the EoT visit if more than 6 weeks have passed since the last evaluation if the patient is discontinued prior to Cycle 8 (week 24) tumor assessment timepoint and more than 12 weeks if patient is discontinued after Cycle 8 (week 24) tumor assessment timepoint. For patients with evidence of response (partial response or complete response), a confirmatory scan must be performed ≥4 weeks after the initial scan. Patients with no evidence of disease progression or secondary malignancy at the time of treatment discontinuation should continue to have tumor assessment performed regardless of initiation of anticancer therapy, and until disease progression is documented. See Section 7.9.2. Imaging scans performed per standard of care prior to consent are acceptable as baseline scans as long as: 1)performed within 21 days of randomization, 2) there was no intervening anticancer therapy, 3) imaging parameters meet standard RECIST 1.1 requirements, as documented in the Imaging manual and 4) same imaging modalities can be continued for on treatment tumor response assessment.
20. **Distant metastases staging** with bone scan,FDG-PET/PET-CT or PET-MRI will be performed at baseline and subsequently every 4 Cycles (±7days) [every 12-weeks (±7days)] or as clinically indicated. PET-CT or PET-MRI, if performed at baseline for distant metastases, repeat after Cycle 4 (not mandatory). Increased FDG uptake alone on PET-CT/PET-MRI without an associated increase in the size or number of lesions must not be used to define disease progression. Bone marrow aspirates and biopsies are required at baseline if bone marrow involvement is suspected and/or patient had bone marrow disease in the past (eg, at initial diagnosis or prior recurrence). Bone marrow assessment performed (as per standard of care) within 8 weeks of randomization is acceptable if the bone marrow assessment was positive and there was no

Table 3. Phase 2 Portion of the Study[34]

		Cycle 1				Cycle 2			Subsequent Cycles[29]	End of Treatment[30]	Follow-Up[31]
Visit Identifier	**Screening**	**Day 1**	**Day 5**	**Day 6[28]**	**Day 14**	**Day 1**	**Day 5**	**Day 14**	**Day 1**		
Frequency and Visit Window	**Between Day -21 and Randomization**				**-2/+1 days**	**±2 days**		**-2/+1 days**	**±2 days**	**≥28 calendar days and <35 calendar days**	**±7 days**

intervening anti-cancer treatment. For patients with bone marrow disease at study entry, on treatment bone marrow assessment will follow institutional standard; however, bone marrow aspirates and biopsies are required for patients who have evidence of complete response.

21. **DEXA (dual-energy X-ray absorptiometry) Scan for Bone Mineral Assessment:** Only for patients who have Tanner stage less than 4 (ie, Tanner 1-3). The total body, lumbar spine and/or femur bone density scan (as per local standard of care) should be performed at screening, every 12 cycles (±3 weeks) thereafter, and at the EOT visit. DEXA scans and X-ray of hand will not be required per protocol in patients enrolled in Germany.
22. **Bone age:** Only for Tanner stage less than 4 (ie, Tanner 1-3). X-ray of hand for assessment of bone age should be performed at screening, every 12 cycles (±3 weeks) thereafter, and at the End of Treatment visit. Once the bone age assessment demonstrates that a patient has completed growth, additional assessments are not necessary.
23. Only for patients who have a Tanner stage less than 4 (1-3). **LH, FSH, Estradiol:** For girls, serum for measurement of LH, FSH and estradiol levels should be obtained at screening, every 4 cycles thereafter (±1 week), and at the End of Treatment visit. **LH, FSH, Testosterone:** For boys, serum for measurement of LH, FSH, and testosterone levels should be performed at screening, every 4 cycles (±1 week) thereafter, and at the EoT visit. Blood tests for LH, FSH, Estradiol & Testosterone assessments will be analyzed by a central independent laboratory. For details of sample collection refer to the Laboratory Manual.
24. **IGF-1; IGFBP-3; 25-hydroxyvitamin D; 1, 25-dihidroxyvitamin D; C-telopeptide, bone alkaline phosphatase (bone ALP) and fasting cortisol:** Only for patients who have a Tanner stage less than 4 (1-3). IGF-1; IGFBP-3; 25-hydroxyvitamin D; 1, 25-dihidroxyvitamin D,fasting cortisol, C-telopeptide and bone alkaline phosphatase will be collected for all patients enrolled to phase 2 portion with Tanner stage 1-3. Blood tests for assessments of growth and bone metabolism will be analyzed by a central independent laboratory. For details of sample collection, refer to the Laboratory Manual.
25. **Serious and Non-Serious Adverse Event (AE) Monitoring**: AEs should be documented and recorded at each visit using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03. The time period for actively eliciting and collecting AEs and serious AEs (SAEs; "active collection period") for each patient begins from the time the patient provides informed consent through and including a minimum of 28 calendar days after the last investigational product administration. If the patient begins a new anticancer therapy, the period for recording nonserious AEs on the case report form (CRF) ends at the time the new treatment is started. However, any SAEs occurring during the active collection period must still be reported to Pfizer Safety and recorded on the CRF, irrespective of any intervening treatment (Section 8).
26. **Concomitant Treatments**: all concomitant medications and non-drug supportive interventions should be recorded on the CRF (see Section 5.7).
27. Assessments for AEs, concomitant medications, vital signs, hematology, and blood chemistry can be performed within ±1 day from the Day 5 and -2/+1 day(s) from Day 14 visits during Cycle 1 and within ±2 days from Day 5 and -2/+1 day(s) from Day 14 visits during Cycle 2 and within -2 days from Day 1 for Cycle 2 and subsequent cycles. There is ±2 days window from Day 1 for HbA1c (starting Cycle 4 Day 1) and -2 days window from Day 1 for pregnancy tests (starting Cycle 2 Day 1). Results of hematology, blood chemistry and pregnancy test to confirm patient is eligible to continue study medication administration per dose modification requirements in Section 5.4.11 should be available and reviewed prior to dosing.
28. To accommodate investigative sites which are not open 7 days a week and thus not capable of implementing certain scheduled activities, missing the Cycle 1 Day 6 visit will not constitute a protocol deviation. For details of PK sample schedule refer to Table 6.

Table 3. Phase 2 Portion of the Study[34]

		Cycle 1				Cycle 2			Subsequent Cycles[29]	End of Treatment[30]	Follow-Up[31]
Visit Identifier	**Screening**	**Day 1**	**Day 5**	**Day 6[28]**	**Day 14**	**Day 1**	**Day 5**	**Day 14**	**Day 1**		
Frequency and Visit Window	**Between Day -21 and Randomization**				**-2/+1 days**	**±2 days**		**-2/+1 days**	**±2 days**	**≥28 calendar days and <35 calendar days**	**±7 days**

29. Laboratory tests after Day 1 can be done as clinically indicated.
30. **End of Treatment Visit (EoT):** At least 28 calendar days, and no more than 35 calendar days, after last dose of study treatment, patients will return to undergo review of concomitant treatments, vital signs, and assessment for resolution of any treatment-related toxicity and tumor assessemnts, if applicable. If patient initiates new anticancer therapy prior to 28 days after last dose of study treatment, then EoT visit should be performed prior to starting new anticancer therapy.
31. **Follow up:** Patients will be followed for survival after completion of treatment. Contact should be made every 2 months (±7 days) from EoT visit. If patient receives additional treatments, this should be noted. Contact can be via clinic visit, email or equivalent electronic communication or phone call to patient/caregiver for minimum of 2 years post last dose of study drug.
32. Patients without evidence of disease progression at the time of treatment discontinuation should continue to have tumor assessments performed as scheduled until documented progressive disease or discontinuation of patient from overall study participation.
33. If these studies have been done within 3 months when the patient is permanently discontinued from treatment, these studies do not need to be repeated.
34. Alternative measures: Screening, on treatment and EoT, hematology, blood chemistry, pregnancy test and urine analysis tests may be conducted at a local laboratory. ECGs and routine safety assessments can be performed at a local facility. Selected assessments (serious/non-serious AE monitoring, concomitant treatment, oral medication compliance, contraceptive check can be performed via Telehealth visit if in-clinic study visit cannot be conducted (see Appendix 14 for detailed guidance).

Table 4. Pharmacokinetic and Pharmacodynamic Sampling for Dose Escalation Part, Dose Expansion Cohorts, Dose Determination Part and Tumor-Specific Cohorts

Study Visit	Screening	Cycle 1 Day 2	Cycle 1 Day 5							Cycle 1 Day 6	Cycle 1 Day 14 (-2/+1 days)	Cycle 2 Day 5			Cycle 2 Day 14 (-2/+1 days)
Hour (Post-Dose)[1]		**Pre-Dose[2]**	**Pre-Dose[2]**	**Post-Infusion[3]**	**1**	**2**	**4**	**6**	**8**	**24[4]**	**Pre-Dose**	**Pre-Dose[2]**	**Post-Infusion[3]**	**1**	**Pre-Dose[5]**
Whole blood collection[6,7]															
Palbociclib PK		X	X			X	X	X	X	X	X	X			X
Irinotecan (IV) PK		X	X	X			X		X[9]	X		X	X		
Temozolomide (Oral) PK			X		X		X		X			X		X	
Temozolomide (IV) PK			X	X			X		X			X	X		
Topotecan (IV) PK		X	X	X			X		X	X		X	X		
Cyclophosphamide (IV) PK		X	X	X			X		X	X		X	X		
Thymidine kinase analysis[8]	X						X		X	X	X				

Abbreviations: EDTA = ethylenediaminetetraacetic acid; IV = intravenous; PK = pharmacokinetic(s); TK = thymidine kinase; IRN = irinotecan; TMZ = temozolomide; TOPO = topetecan; CTX = cyclophosphamide.

1. For agents administered by IV infusion, the time post-dose represents the time elapsed since the start of the infusion.
2. Pre-dose and post-dose refers to each agent individually (ie, pre-dose PK sample for palbociclib would occur just prior to palbociclib administration). The time window for palbociclib predose PK sample collection should be no more than 1 hr postdose on the day of PK collection. Pre-dose PK sample for Irinotecan would occur shortly before irinotecan IV infusion. If not feasible, irinotecan pre-dose PK sample can be drawn at the same time as palbociclib and temozolomide.
3. Post-Infusion PK should refer to each agent individually and should be taken ±10% of the infusion duration length (ie, within ±9 minutes of the stop time of a 90 minute infusion).
4. 24 hours (±10%) after Day 5 dose of palbociclib, and just prior to Day 6 dosing administration for palbociclib. To accommodate investigative sites which are not open 7 days a week and thus not capable of implementing certain scheduled activities, missing the Cycle 1 Day 6 visit will not constitute a protocol deviation. Thus, the Cycle 1 Day 6 sample collection is recommended but not required.
5. Day 14 samples can be drawn 24 hours ±2 hours after the previous palbociclib dose.
6. 1.0 mL of whole blood for each palbociclib, TMZ,and IRN PK assays (for patients in the combination cohorts of palbociclib with IRN and TMZ) **OR** 1.0 mL of whole blood for each of palbociclib,TOPO, and CTX PK assays (for patients in the combination cohorts of palbociclib with TOPO and CTX) will be drawn into a tube(s) containing potassium (K2) EDTA at the specified time points (separate blood draw for each analyte should be collected). Preferably, avoid more than 10% deviations in collection time; however, samples obtained within 20% from the nominal time will not be captured as protocol deviation. It is essential to document the exact time of sample collection, exact time of oral drug administration, and exact start/stop time of IV drug infusion.

Table 4. Pharmacokinetic and Pharmacodynamic Sampling for Dose Escalation Part, Dose Expansion Cohorts, Dose Determination Part and Tumor-Specific Cohorts

Study Visit	Screening	Cycle 1 Day 2	Cycle 1 Day 5							Cycle 1 Day 6	Cycle 1 Day 14 (-2/+1 days)	Cycle 2 Day 5			Cycle 2 Day 14 (-2/+1 days)
Hour (Post-Dose)[1]		Pre-Dose[2]	Pre-Dose[2]	Post-Infusion[3]	1	2	4	6	8	24[4]	Pre-Dose	Pre-Dose[2]	Post-Infusion[3]	1	Pre-Dose[5]

7. If local regulations prohibit full sample collections (such as PD analysis or PK for IRN and TMZ or TOPO and CTX) for a given patient due to local blood volume collection restrictions in patients with small body size, please contact the study Sponsor for guidance in prioritizing the sampling scheme.
8. Thymidine kinase analysis: 1.0-mL blood specimens optimized for serum preparation for TK activity assessment will be collected. Collection times should be relative to palbociclib dose.
9. The 8-hour post-infusion PK collection for irinotecan can be collected within ±2 hours.

Table 5. Pharmacokinetic and Pharmacodynamic Sampling for Phase 2 Portion of the Study[1]

Study Visit	Screening	Cycle 1 Day 1	Cycle 1 Day 2	Cycle 1 Day 5							Cycle 1 Day 6	Cycle 1 Day 14 (-2/+1 days)	Cycle 2 Day 5			Cycle 2 Day 14 (-2/+1 days)
Hour (Post-Dose)[2]		**Pre-Dose**	**Pre-Dose[3]**	**Pre-Dose[3]**	**Post-Infusion[4]**	**1**	**2[5]**	**4[5]**	**6[5]**	**8[5]**	**24[5]**	**Pre-Dose[3]**	**Pre-Dose[3]**	**Post-Infusion[4]**	**1**	**Pre-Dose[5]**
Whole blood collection[7,8]																
Palbociclib PK			X	X			X	X	X	X	X	X	X			X
Irinotecan (IV) PK[1]			X	X	X			X		X[10]	X		X	X		
Temozolomide (Oral) PK[1]				X		X		X		X			X		X	
Temozolomide (IV) PK[1]				X	X			X		X			X	X		
Thymidine kinase analysis[9]		X						X		X	X	X				

Abbreviations: EDTA = ethylenediaminetetraacetic acid; IV = intravenous; PK = pharmacokinetic(s); TK = thymidine kinase; IRN = irinotecan; TMZ = temozolomide.

1. PK and TK samples will be collected from patients randomized to palbociclib in combination with IRN and TMZ treatment arm only. PK and TK samples are not required for patients randomized to IRN and TMZ chemotherapy alone arm.
2. For agents administered by IV infusion, the time post-dose represents the time elapsed since **the start of the infusion.**
3. Pre-dose and post-dose refers to each agent individually (ie, pre-dose PK sample for palbociclib would occur just prior to palbociclib administration). The time window for predose palbociclib PK sample collection should be no more than 1 hr postdose on the day of PK collection. Pre-dose PK sample for Irinotecan would occur shortly before irinotecan IV infusion. If not feasible, irinotecan pre-dose PK sample can be drawn at the same time as palbociclib and temozolomide.
4. Post-Infusion PK should refer to each agent individually and should be taken ±10% of the infusion duration length (ie, within ±9 minutes of the stop time of a 90 minute infusion).
5. Every effort should be made to follow the Cycle 1 Day 5 sampling schedule however missing any of the 2, 4, 6 or 8 hours Cycle 1 Day 5 post dosing sample collections will not constitute a protocol deviation. The Cycle 1 Day 6 sample should be drawn 24 hours (±10%) after Day 5 dose of palbociclib, and just prior to Day 6 dosing administration for palbociclib. To accommodate investigative sites which are not open 7 days a week and thus not capable of implementing certain scheduled activities, missing the Cycle 1 Day 6 visit will not constitute a protocol deviation. Thus, for the Phase 2 portion of the study the Cycle 1 Day 5 post dosing PK sample collections and the Cycle 1 Day 6 PK sample collections are recommended but not required.
6. Day 14 samples can be drawn 24 hours ±2 hours after the previous palbociclib dose.
7. 1.0 mL of whole blood for each palbociclib, TMZ,and IRN PK assays will be drawn into a tube(s) containing potassium (K2) EDTA at the specified time points (separate blood draw for each analyte should be collected). Preferably, avoid more than 10% deviations in collection time; however, samples obtained within 20% from the nominal time will not be captured as protocol deviation. It is essential to document the exact time of sample collection, exact time of oral drug administration, and exact start/stop time of IV drug infusion.
8. If local regulations prohibit full sample collections (such as PD analysis or PK for IRN and TMZ) for a given patient due to local blood volume collection restrictions in patients with small body size, please contact the study Sponsor for guidance in prioritizing the sampling scheme.

Table 5. Pharmacokinetic and Pharmacodynamic Sampling for Phase 2 Portion of the Study[1]

Study Visit	Screening	Cycle 1 Day 1	Cycle 1 Day 2	Cycle 1 Day 5							Cycle 1 Day 6	Cycle 1 Day 14 (-2/+1 days)	Cycle 2 Day 5			Cycle 2 Day 14 (-2/+1 days)
Hour (Post-Dose)[2]		Pre-Dose	Pre-Dose[3]	Pre-Dose[3]	Post-Infusion[4]	1	2[5]	4[5]	6[5]	8[5]	24[5]	Pre-Dose[3]	Pre-Dose[3]	Post-Infusion[4]	1	Pre-Dose[5]

9. Thymidine kinase analysis: 1.0-mL blood specimens optimized for serum preparation for TK activity assessment will be collected only for patients randomized to palbociclib in combination with IRN and TMZ arm. Collection times should be relative to palbociclib dose. TK samples are not required for patients randomized to IRN and TMZ chemotherapy alone arm.
10. The 8-hour post-infusion PK collection for irinotecan can be collected within ±2 hours.

1. INTRODUCTION

1.1. Mechanism of Action/Indication

Palbociclib (PD-0332991) is a highly selective, reversible, small molecule inhibitor of cyclin-dependent- kinases (CDK) 4 and 6, administered orally. Cyclin D1 and CDK4/6 are downstream of multiple signaling pathways which lead to cellular proliferation. CDKs are important regulatory enzymes that mediate cell cycle control by regulating and promoting transition through the cell cycle. While a number of various CDK enzymes are recognized, in complex organisms the control over cell cycle entry is regulated at the level of CDK4 and CDK6. As cancer represents a process of uncontrolled cell division and proliferation, CDKs represent potential therapeutic targets.[2]

During cell proliferation, the G_1 to S transition of the cell cycle is under the control of CDKs which are activated through specific complex formation with regulatory cyclins. CDK4 and CDK6 are activated by binding to D-type cyclins in early G_1 phase.[3-6] The only known natural substrate for CDK4 and CDK6 activity is retinoblastoma susceptibility gene product (pRb), which mediates G_1 arrest through sequestration of transcriptional factors of the heterodimeric transcription factor (E2F-DP) family. Phosphorylation of pRb and other members of the pocket protein family (p107 and p130) by active cyclin-CDK complexes leads to release of E2F and DP transcription factors and transcription of requisite genes for S-phase entry.[6]

1.2. Background and Rationale

1.2.1. Palbociclib

Palbociclib (IBRANCE®) is approved for the treatment of patients with hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced or metastatic breast cancer in combination with an aromatase inhibitor as initial endocrine-based therapy or in combination with fulvestrant in patients with disease progression following endocrine therapy. Additional information is provided as per local approved labeling.

There is an increasing body of literature showing the dependency of pediatric tumor cells on CDK4/6 and cyclin D1 including Ewing sarcoma (EWS) and myeloid and lymphoblastic leukemia to support the use of CDK4/6 inhibitors.[7] Palbociclib has shown synergy when administered with antiestrogen therapy in the treatment of estrogen receptor positive breast cancer and supports its use as a combination therapy.[8] The antitumor activity of palbociclib in combination with the chemotherapy regimen, temozolomide (TMZ) and irinotecan (IRN) has been investigated in 3 different patient-derived EWS models grown subcutaneously in immunocompromised mice to determine the extent of therapeutic benefit from the addition of palbociclib to the regimen. The IRN and TMZ combination resulted in significant tumor growth inhibition (TGI) in 2 models and non-significant decrease of tumor volume in 1 model. The addition of palbociclib to IRN and TMZ resulted in similar TGI to that with the IRN and TMZ alone for 2 models while in the third model the triple combination demonstrated significantly increased antitumor activity versus IRN and TMZ alone. In the latter model, the superiority of the triple combination was sustained in the post-dosing period of several weeks. The addition of palbociclib to the chemotherapy regimen increased the

number of responders from 1 partial response to 2 complete responses and 1 tumor free survivor, further supporting improved efficacy for the triple combination in this model.[9] These findings highlight the potential antitumor benefit of adding palbociclib, a CDK4/6 inhibitor, to a combination of a topoisomerase inhibitor (eg, IRN or topotecan) and an alkylating agent (eg, TMZ or cyclophosphamide).

1.2.1.1. Palbociclib Pharmacokinetics in Adult Clinical Trials

PK data from patients with advanced cancer indicate that the plasma PK of palbociclib are low to moderately variable with generally dose proportional exposures over the dose range evaluated (25 mg to 225 mg) following single and multiple doses. Palbociclib is slowly absorbed with a median time of maximum concentration (T_{max}) between 4 and 8 hours post-dose and is slowly eliminated with an elimination half-life ($t_{1/2}$) ranging from 23.2 hours to 28.8 hours. Palbociclib accumulates after repeated daily dosing (median accumulation ratio [R_{ac}] ranged from 1.9 to 2.4), which was consistent with its terminal $t_{1/2}$. The median R_{ss} (the predicted accumulation to estimate linearity) was approximately 1.1, indicating that palbociclib clearance does not change over time. Palbociclib was shown to achieve steady-state concentrations within 8 days of once daily (QD) dosing. The palbociclib geometric mean apparent volume of distribution (V_z/F) was 2583 L in women with advanced breast cancer (Study A5481003), which is significantly greater than total body water (42 L), indicating that palbociclib extensively distributes to peripheral tissues.

1.2.1.2. Single Agent Palbociclib Efficacy in Clinical Trials of Adults

A total of 74 adult patients with various types of solid tumors or lymphomas were enrolled in Study A5481001. The primary purpose of this study was to establish the safety and determine the RP2D of palbociclib in adults. Although efficacy was not the primary objective, patients were evaluated for response according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0. For patients who received palbociclib QD administered for 3 weeks with a 1 week rest period (Schedule 3/1), 37 patients were evaluable for response, 13 patients (35%) had an overall best response of stable disease for at least 2 cycles.

For the patients who received palbociclib administered daily for 2 weeks with a 1 week rest period (Schedule 2/1), 31 of the 33 patients completed at least 1 on-treatment tumor assessment and were considered to be evaluable for response. One patient with testicular cancer had a partial response (PR) to palbociclib 200 mg QD for 22 months and the PR was ongoing at the time of data cutoff.[20] An additional 9 patients (29%) experienced stable disease lasting ≥2 cycles. There were 11 first-cycle dose-limiting toxicities (DLTs) reported, 5 for patients on Schedule 3/1 and 6 for patients on Schedule 2/1. All DLTs consisted of neutropenia and/or thrombocytopenia and most were categorized as a DLT due to the need for a treatment interruption of longer than 7 days duration. Febrile neutropenia was not reported as a DLT, and no episodes of febrile neutropenia were observed during this study.

A total of 17 adult patients with relapsed or refractory mantle cell lymphoma were enrolled in completed Study A5481002. The dose evaluated in this study was 125 mg QD on Schedule 3/1. The objective response rate (ORR) for the 16 patients who were evaluable for

response was 18.8% (95% confidence interval [CI]: 4.0%, 45.6%) with 1 patient with a complete response (CR; 6.3%) 2 patients with a PR (12.5%). Seven patients (43.8%) had an overall best response of stable disease. Both median time to progression and median progression-free survival (PFS) were 5.5 months (95% CI: 2.0, 18.6 months). Due to the small number of patients who had a response, duration of response (DOR) was not calculated.

For the combined safety across Studies A5481001 and A5481002, the most frequently reported treatment-emergent adverse events (TEAEs; ≥20% of patients) of any grade, regardless of causality, were fatigue (52.7% of patients); neutropenia (48.4%); nausea (35.2%); diarrhea and anemia (30.8% each); constipation (26.4%); decreased appetite (22.0%); and vomiting and thrombocytopenia (20.9% each). The most frequently reported TEAEs ≥20% of patients) of any grade that were considered related to the study treatment were neutropenia (46.2% of patients); fatigue (45.1%); diarrhea and anemia (25.3% each); and nausea (24.2%). The most frequently reported Grade 3 TEAEs irrespective of causality were neutropenia (24.2%), anemia (8.8%), fatigue (6.6%), leukopenia, thrombocytopenia and dyspnea (5.5% each). The most frequently reported Grade 4 TEAEs were neutropenia (6.6% [6 patients]) and thrombocytopenia (3.3% [3 patients]), Grade 4 leukopenia was reported for 2 patients (2.2%) and Grade 4 anemia, pulmonary embolism, increased blood uric acid, decreased hemoglobin level and hyperglycemia for 1 patient each (1.1%). Grade 5 events were reported for 8 patients (8.8%) which included disease progression (5.5% [5 patients]), cardiac arrest (2.2% [2 patients]), and failure to thrive (1.1% [1 patient]). No Grade 5 event was considered to be related to palbociclib.

1.2.2. Rationale

Curative options for pediatric, adolescent or young adult patients with relapsed/refractory solid tumors are limited, and outcomes are poor. Multiple chemotherapy combinations have been used with some activity including irinotecan (IRN)/temozolomide (TMZ), cyclophosphamide/topotecan and gemcitabine/docetaxel.[21,22,23] Unfortunately outcomes remain poor and there has been minimal improvement in survival.[24-27] With molecular analysis providing new insights to mechanisms of growth of pediatric solid tumors, targeted agents are now being utilized in the treatment of these tumors and are being combined with chemotherapy backbones.

1.2.2.1. CDK4/6 as a Therapeutic Target in Pediatrics

There is a growing body of clinical data on CDK4/6 inhibitors in pediatric tumors. Data have shown that aberrations in the CDK4/6 pathway can drive the growth of a variety of pediatric tumors including neuroblastoma, rhabdoid tumor, Ewing sarcoma (EWS), and rhabdomyosarcoma.

1.2.2.1.1. Rhabdoid Tumor

Malignant rhabdoid tumors present mainly in the kidney or in the CNS. They are characterized by loss of SMARCB1 (INI1), a tumor suppressor that is part of the SWItch/Sucrose Non-Fermentable (SWI/SNF) complex. SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily B member 1 (SMARCB1) directly affects

the transcription of Cyclin D1 and upregulates direct suppressors of CDK4/6, p21, and p16.[28,29] Loss of SMARCBI will cause loss of cell cycle arrest in these subset of tumors.

1.2.2.1.2. Ewing Sarcoma

EWS is an aggressive bone and soft tissue tumor mediated by somatic chromosomal translocations resulting in the expression of chimeric fusions of EWS and E26 transformation-specific- (ETS) family transcription factors.[30] EWS/FLI1 fusions can suppress Rb function by deregulated Cyclin D1 gene (CCND1) and CDK4/6 activity. Characterization of the EWS/FLI1 fusion has shown both Cyclin D1 and CDK4 to be marked by super-enhancers aberrantly driving transcription so significantly that CCND1 expression is highest in EWS compared to other tumor types. Functional dependence of EWS cell lines and tumor xenografts on Cyclin D1/CDK4 via genetic knockdown has shown both Cyclin D1 and CDK4 as critical dependencies for EWS cell line proliferation.[31]

1.2.2.1.3. Neuroblastoma

Neuroblastoma is an aggressive soft tissue tumor that involves the sympathoadrenal lineage of the neural crest cell during development. In children over the age of 1, it is more aggressive and more likely to have metastasized. Neuroblastoma has defect in regulatory areas seen as essential for embryonic development and regulation of cellular differentiation. Involvement of cell cycle regulators such as CDK4/6 could be driving factors of tumorigenesis. Inhibition of neuroblastoma cell lines with palbociclib reduced the growth of neuroblastoma cell lines and induced cell cycle arrest at G1.[32]

1.2.2.1.4. Medulloblastoma

Medulloblastoma is the most common malignant brain tumor and is subdivided into 4 distinct molecular subtypes. Genomic studies showed CDK6 overexpression as an independent prognostic indicator for poor overall survival in patients.[33] Palbociclib was found to cause G1 arrest in patient derived xenografts of medulloblastoma in MYC (myelocytomatosis oncogene)-amplified medulloblastoma.[34]

1.2.2.1.5. Rhabdomyosarcoma

Rhabdomyosarcoma is an aggressive soft tissue tumor. It is classified into 2 major subtypes: alveolar and embryonal. In a large genetic analysis, the alveolar subtype had mutations and copy number alterations in cell cycle regulators such as CDK4 & CDK2NB.[35] In addition, in vitro and in vivo studies showed inhibition of growth in both embryonal and alveolar cell lines when exposed to palbociclib.[36]

1.2.2.2. Palbociclib in Pediatric Solid Tumors.

In a case report of a PPD year-old patient with growing teratoma syndrome, palbociclib, 75 mg (approximately 75 mg/m^2), daily dosing on Schedule 3/1, administered over 22 cycles was well tolerated with uncomplicated neutropenia and fatigue as the only adverse events (AEs) attributed to palbociclib.[37] Growing teratoma syndrome is characterized by growth of mature teratoma elements of a mixed germ cell tumor despite resolution of immature/malignant elements with administration of chemotherapy. Surgical resection is the only known cure for

growing teratoma syndrome but in the brain, complete resection may be impossible. In these instances, mature teratoma, although histologically benign, may be fatal.

A single-agent palbociclib Phase 1 study has been conducted by the United States (US) Pediatric Brain Tumor Consortium (PBTC) in children with retinoblastoma protein 1 (Rb1) positive recurrent, progressive or refractory central nervous system tumors. A total of 35 patients were enrolled and 30 were evaluable for DLT. There were no DLTs at 50 mg/m^2 dose level. Three of 19 patients enrolled at 75 mg/m^2 experienced DLT (Grade 3 dehydration, Grade 4 neutrophil count decrease and Grade 3 platelet count decrease). Grade 4 neutropenia was also reported as a DLT for 2 of 4 patients treated at 95 mg/m^2. Across the 3 dose levels (50 mg/m^2, 75 mg/m^2, and 95 mg/m^2), Grade 3 neutropenia was reported for 18 patients, Grade 3 lymphopenia was reported for 10 patients. One patient experienced Grade 4 thrombocytopenia and 1 patient experienced Grade 3 thrombocytopenia (events were not considered DLTs as both occurred after the DLT assessment period). The MTD was established at 75 mg/m^2 on Schedule 3/1.[38]

1.2.2.2.1. Irinotecan and Temozolomide in Pediatric Solid Tumors

There is no standard of care therapy for patients with relapsed solid tumors, but IRN and TMZ is used frequently in clinical practice for many recurrent pediatric cancers, including recurrent EWS.[9,11] In several case series and Phase 2 clinical trials, IRN and TMZ given alone or in combination with other agents such as vincristine or temsirolimus have been associated with response rates of up to 68% in patients with recurrent EWS, with some patients maintaining a response for >14 cycles (3 weeks/cycle) of therapy.[12,13,14,39] Combining this backbone with new agents in pediatric clinical trials has been done with different experimental combination partners.[15]

Compared to other cytotoxic chemotherapy, this regimen is less myelosuppressive. In a Phase 2 study of this combination, 39% of patients with measurable disease had Grade 3 or 4 myelosuppression with 25% having Grade 3 or 4 neutropenia and 7% having Grade 3 or 4 thrombocytopenia. Less than 10% of patients developed evidence of neutropenic infection.[40]

1.2.2.2.2. Topotecan and Cyclophosphamide in Pediatric Solid Tumors

The combination of TOPO and CTX has been proven superior over either agent alone. The combination has shown activity in a wide variety of pediatric solid tumors including recurrent EWS, neuroblastoma, RMS, nephroblastoma and osteosarcoma.[16-18,22] In a Phase 2 trial in pediatric patients with recurrent and refractory solid tumors, the highest response rates were seen in patients with RMS (67%), followed by patients with neuroblastoma (46%) and EWS (32%). The treatment schedule used was CTX (250 mg/m^2/dose) followed by TOPO (0.75mg/m^2/dose), each given as a 30-minute infusion daily for 5 days, followed by filgrastim beginning on Day 6.[22] The most common toxicities observed in this treatment were hematopoietic, ie, neutropenia, anemia and thrombocytopenia; 53% of TOPO and CTX courses were associated with Grade 3 or 4 neutropenia, 44% with Grade 3 or 4 thrombocytopenia and 27% with Grade 3 or 4 anemia. Majority of patients required RBC and/or platelet transfusion support. There were few non-hematopoetic- toxicities.[22] Mucositis and hemorrhagic cystitis were uncommon in this dosing of CTX.[22]

1.2.2.2.3. Palbociclib in Combination With Irinotecan and Temozolomide

In the Phase 1 and Phase 2 portion of the study (as of 31 Aug 2022 data cutoff) the most frequently reported (≥20%) TEAEs of any grade, regardless of causality were Neutropenia (77.5%), Diarrhoea and Nausea (65.0% each), Vomiting (60.0%), Anaemia (52.5%), Leukopenia (50.0%), Thrombocytopenia (45.0%), Lymphopenia (37.5%), Decreased appetite, and Fatigue (27.5% each),Cough, and Headache (25.0% each), Abdominal pain (22.5%), Weight decreased, Back pain and Constipation, (20.0% each). The most frequently reported TEAEs (≥20%) of any grade that were considered to be related to the study treatment were Neutropenia (66.7%), Nausea (53.3%), Vomiting (44.4%), Leukopenia (42.2%), Thrombocytopenia (40.0%), Diarrhoea (37.8%), Anemia (35.6%), Lymphopenia (33.3%).

The most frequently reported (≥10%) Grade 3 TEAEs irrespective of causality were Neutropenia (45.0%), Leukopenia (25.0%), Anaemia (22.5%), Lymphopenia, and Vomiting (10.0% each) . The most frequent (≥10%) Grade 3 TEAEs related to study treatment were Neutropenia (42.5%), Anaemia (17.5%), Leukopenia (25.0%), Lymphopenia and Vomiting (10% each). The most frequently reported (≥5%) Grade 4 TEAEs irrespective of causality were Neutropenia (27.5%), and Leukopenia (5.0%). The most frequent (≥5%) Grade 4 TEAE related to study treatment were Neutropenia (25.0%). No treatment related Grade 5 events were reported as of 31 August 2022.

1.2.2.2.4. Palbociclib in Combination With Topotecan and Cyclophosphamide

In the Phase 1 portion of the study (as of 31 Aug 2022 data cutoff) the most most frequently reported (≥20%) TEAEs of any grade, regardless of causality, were Thrombocytopenia (88.5%), Anemia, and Neutropenia (84.6% each), Leukopenia (80.8%), Lymphopenia (69.2%), Nausea (65.4%), Vomiting (50.0%), Fatigue (42.3%), Hypophosphataemia (34.6%), Febrile neutropenia and Headache (30.8% each), Hypocalcaemia and Hypokalaemia (26.9% each), and Pyrexia (23.1%). The most frequently reported TEAEs (≥20%) of any grade that were considered to be related to the study treatment were Thrombocytopenia (84.6%), Anemia, and Neutropenia (76.9% each), Leukopenia (69.2%), Lymphopenia (57.7%), Nausea (53.8%), Vomiting (34.6%), Fatigue (30.8%), and Febrile neutropenia (26.9%). The most frequently reported (≥10%) Grade 3 TEAEs irrespective of causality were Anemia (65.4%), Lymphopenia (30.8%), Febrile neutropenia, and Neutropenia (26.9% each), Leukopenia (19.2%). The most frequent (≥10%) Grade 3 TEAEs related to study treatment were Anemia (61.5%), Lymphopenia (30.8%), Febrile neutropenia, Neutropenia (23.1%), Leukopenia (19.2%). The most frequently reported (≥5%) Grade 4 TEAEs irrespective of causality were Thrombocytopenia (65.4%), Leukopenia (46.2%), Neutropenia, (42.3%), Lymphopenia (34.6%). The most frequently reported (≥5%) Grade 4 TEAEs related to study treatment were Thrombocytopenia (65.4%), Leukopenia (46.2%), Neutropenia, (42.3%), Lymphopenia (23.1%). No Grade 5 treatment related events were reported as of 31 August 2022.

1.2.2.3. Rationale for Starting Dose for the Combination of Palbociclib With Chemotherapy Agents

The Phase 1 portion of the study is the first pediatric study to evaluate palbociclib in combination with chemotherapy. Based on available data in pediatric monotherapy treatment scenarios, adjusting adult palbociclib doses based on patient body surface area (BSA) can be expected to provide similar safety and systemic exposure in pediatric patients. However, there is no prior clinical experience in adult patients combining palbociclib with TMZ plus IRN or TOPO plus CTX, so there is no previously established safe dosing regimen for the combinations that can be extrapolated to pediatric patients, and the tolerability of this combination regimens will be determined in the pediatric population in this study.

1.2.2.3.1. Combination of Palbociclib With IRN and TMZ

As palbociclib will be evaluated in combination with chemotherapeutic agents with overlapping toxicities, the palbociclib starting dose selected for the Phase 1 dose-escalation portion has been chosen that is sufficiently lower than the expected palbociclib monotherapy MTD in this pediatric patient population. As described in Section 1.2.2.2, the PBTC-042 Study established the MTD of palbociclib monotherapy in a pediatric population as 75 mg/m^2 QD on Schedule 3/1, and this dosing regimen represents the pediatric equivalent of the approved adult starting dose adjusted for BSA on the same dosing schedule (125 mg QD divided by a standard adult BSA of 1.72 m^2).[38] The MTD identified when palbociclib was administered as a single agent on Schedule 2/1 (2 weeks on treatment followed by 1 week off treatment) in adult cancer patients is 200 mg QD (ie, ~118 mg/m^2). Palbociclib will be administered on Schedule 2/1 to align with the backbone TMZ/IRN dosing schedule with a starting dose of 55 mg/m^2, which is ~50% of the monotherapy MTD on Schedule 2/1 in adults. The starting dose of TMZ will be 100 mg/m^2 along with a full dose of IRN (50 mg/m^2). The doses of IRN and TMZ used for this study are standard doses and commonly used in medical practice.

1.2.2.3.2. Combination of Palbociclib With TOPO and CTX

The palbociclib starting dose will be the same as the MTD determined in the IRN and TMZ combination. Given that palbociclib with TOPO and CTX combination is expected to be more myelosuppressive than the palbociclib with IRN and TMZ combination, this dose is considered the palbociclib MAD for this combination and will not be exceeded. Palbociclib will be administered on Schedule 2/1 as in IRN and TMZ combination of the study.

The MTD for palbociclib in combination with IRN and TMZ has been determined as 75 mg/m^2 which is the palbociclib starting dose for combination with TOPO and CTX. The dose of TOPO will be 0.75 mg/m^2 along with a dose of CTX (250 mg/m^2). The doses of TOPO and CTX used for this study are standard doses commonly used in medical practice.

1.2.2.3.3. Rationale for Administration of Granulocyte-Colony Stimulating Factor (G-CSF)

In a Phase 1 study of the TOPO and CTX combination in recurrent and refractory solid tumors, neutropenia has been the DLT at all dose levels. The addition of G-CSF (filgrastim)

allowed the re-escalation of TOPO dose to 0.75 mg/m^2 (RP2D) and resulted in reduction of incidence of neutropenic fevers (85% of treatment cycles at 0.75 mg/m^2 without filgrastim support were complicated by neutropenic fever versus 20% of cycles with filgrastim support).[18]

In order to maintain treatment intensity and avoid dose reductions, subcutaneous G-CSF (5 µg/kg/dose daily) will be mandatory in combination of palbociclib with TOPO and CTX starting Cycle 1. The G-CSF should be initiated 24-48 hours after the administrations of TOPO and CTX are completed and must be stopped 24 hours prior to the next treatment cycle. At the discretion of the investigator the daily G-CSF (filgrastim) can be substituted by PEG-filgrastim in a standard weight based dosing for pediatric patients. PEG-filgrastim should be initiated 24-48 hours after the administrations of TOPO and CTX are completed and must be stopped 14 days prior to the next treatment cycle.

1.3. Risk/Benefit Assessment

In the IRN and TMZ combination, G-CSF may be used at the investigator's discretion according to the institutional guidance for treatment of neutropenia, except for the Cycle 1 DLT evaluation period in the Phase 1 portion of the study (Section 5.7.4).

1.3.1. Risk Assessment

Juvenile toxicity studies have not been conducted with palbociclib. The nonclinical safety findings of particular interest to a pediatric population are related to the potential for palbociclib to cause glucose dysregulation and related effects on the pancreas, eyes, kidneys, and adipose tissue, as well as effects on male reproductive organs, bone, and actively growing teeth.

1.3.1.1. Dysregulation of Glucose Metabolism

1.3.1.1.1. Preclinical Findings

Pivotal toxicity studies in young male rats identified dysregulation of glucose metabolism (increased glycemia and/or glucosuria) in relationship to effects on the pancreas with secondary findings in the eye, kidney, and adipose tissue.

Investigatory work in aged rats (with similar beta cell proliferation rates to adult humans) did not identify alterations in glucose metabolism or pancreatic microscopic findings at exposures where effects were previously identified in young male rats, suggesting a susceptibility of young male rats to the development of endocrine/metabolic effects. Differences in beta cell proliferation capacity appear to play a role in the sensitivity to development of altered glucose metabolism in rats. Neither hyperglycemia nor cataracts were observed in dogs. More details can be found in the Palbociclib IB.

1.3.1.1.2. Clinical Data

The potential risk of hyperglycemia was evaluated in Clinical Study A5481027 including assessment of hemoglobin A1c (HbA1c), fasting glucose and fasting insulin levels at baseline, during treatment and at the end of treatment, AEs relevant to hyperglycemia and

ocular AEs in previously untreated Asian postmenopausal women with ER + HER2- advanced breast cancer treated with palbociclib plus letrozole versus placebo plus letrozole. The analysis showed comparable incidence and exposure-adjusted incidence of abnormal laboratory results, AEs relevant to hyperglycemia and ocular AEs between treatment groups. Overall, the results demonstrated that palbociclib plus endocrine therapy, when compared to placebo plus endocrine therapy, is not associated with increased risk of developing hyperglycemia or worsening of diabetes.

The potential risk of hyperglycemia in pediatric population will be examined in the A5481092 study. Patients enrolled in A5481092 will be monitored for their morning glucose levels and HbA1c levels. Blood glucose is required as a part of broad biochemistry panel to be performed at baseline and on Day 1 of each cycle (and additionally on Day 5 and Day 14 of the initial two cycles) and at End of Treatment visit and HbA1c is required at baseline and subsequently every 4 cycles. Any signs or symptoms of glucose dysregulation will be managed per clinical standard of care and will be reported as an adverse events. If required per protcocol guidance on dose modification palbociclib dose will be reduced for ≥Grade 3 toxicities. (Section 5.4.11.2)

1.3.1.2. Male Reproductive Organs

Effects on male reproductive organs (testis, epididymis, prostate, seminal vesicle) were observed in rats and dogs in pivotal repeat-dose toxicity studies ≥3 weeks in duration. Observed effects include seminiferous tubule degeneration (also described as testicular degeneration) , epididymal ductal atrophy, hypospermia, and/or intratubular cellular debris in the epididymides accompanied the degenerative changes in the testis. More details can be found in the Palbociclib IB.

Considering the above mentioned male reproductive organ effects in pre-clinical studies fertility preservation counseling should be offered to post pubertal male patients and sperm preservation should be a consideration prior to beginning therapy.

1.3.1.3. Effects on Bone

Effects on bone were observed in male rats in the pivotal 27-week toxicity study. The effect on bone consisted of a mild to moderate decrease in trabeculae identified in the femur of males, characterized by decreased thickness of the physis, decreased or segmental loss of primary and secondary spongiosa, and/or decreased trabeculae within the metaphysis. There were no palbociclib-related bone effects in female rats though palbociclib exposures were approximately 2-times higher than that in males. Bone effects were also not identified in dogs in studies up to 39 weeks duration at palbociclib exposures 3-times those associated with the human adult clinical dose of 125 mg QD. More details can be found in the Palbociclib IB.

The effect on bone is likely related to primary pharmacology, based on literature that suggests a role of CDK4/6 in osteoblast and osteoclast function and understanding of the balance between osteoblast and osteoclast function needed to maintain normal physiologic development and growth of bones.

We will perform analyses of bone metabolism and growth, including linear growth, bone age, bone mineral density, and hormones associated with growth and pubertal development (insulin-like growth factor 1 [IGF-1], insulin-like growth factor binding protein 3 [IGFBP-3], 25-hydroxyvitamin D; 1, 25-dihidroxyvitamin D, fasting cortisol luteinizing hormone [LH], follicle-stimulating hormone [FSH], estradiol for girls, and testosterone for boys in prepubertal and peripubertal children below Tanner Stage 4 at baseline to assess the effect of palbociclib treatment on bone, growth and sexual development. Any clinically significant abnormalities in the bone and growth tests and/or laboratory results should prompt further medical workout and should be recorded as adverse events in clinical database.

1.3.1.4. Effects on Actively Growing Incisors

Effects on actively growing incisors were observed in rats following 27 weeks of intermittent dosing. White (discolored) incisor teeth were noted during clinical observations in males and correlated histopathologically with minimal to moderate ameloblast degeneration/necrosis and/or minimal to mild pigmented mononuclear cell infiltrate. More details can be found in the Palbociclib IB.

Formal dental evaluation is not mandated by the study protcocol but if dental abnormalities are seen in screening any dental abnormalities noted on physical exam should be reported and the patient should be referred for a dental evaluation, treatment and follow-up (Section 7.1.4).

1.3.1.5. Clinical Risks and Precautions

1.3.1.5.1. Combination of Palbociclib With IRN and TMZ

Potential risks associated with palbociclib in combination with IRN and TMZ include gastrointestinal toxicities of nausea, vomiting, diarrhoea and myelotoxicity resulting in neutropenia, leukopenia, thrombocytopenia, anemia, and lymphopenia. In the Phase 1 and Phase 2 portion of the study (as of 31 Aug 2022 data cut off), these adverse events were the most frequently reported (≥20%) TEAEs of any grade that were considered related to the combination of palbociclib with IRN and TMZ (Section 1.2.2.2.3).

In the combination of palbociclib with IRN and TMZ, adverse drug reactions that met DLT criteria occurred at palbociclib dose level of 95 mg/m^2. Two patients enrolled at this dose level experienced hematopoietic toxicity. One patient experienced Grade 4 decreased neutrophil count and one patient experienced Grade 4 decreased platelet count . No DLT occurred in the Phase 1 portion among 18 patients treated with the RP2D of 75 mg/m^2 of palbociclib with IRN and TMZ.

In order to mitigate the risk of severe IRN- induced diarrhoea, the protocol mandates antibiotic prophylaxis with cefixime or an equivalent antibiotic. (Section 5.7.5) Detailed guidance for management of chemotherapy-induced nausea and vomiting should be followed, as described in Section 5.7.5. Myelotoxicities will be managed per standard of care and hematopoetic growth factors (G-CSF) may be used per Investigator’s discretion (Section 5.7.4).

1.3.1.5.2. Combination of Palbociclib With TOPO and CTX

Potential risks associated with palbociclib in combination with TOPO and CTX include myelotoxicity resulting in thrombocytopenia, anemia, neutropenia, leukopenia, lymphopenia; and febrile neutropenia, gastrointestinal toxicities of nausea and vomiting, and fatigue. In the Phase 1 portion of the study (as of 31 Aug 2022 data cut off), these adverse events were the most frequently reported (≥20%) TEAEs of any grade that were considered related to the combination of palbociclib with TOPO and CTX (Section 1.2.2.2.4).

Three of 18 patients were evaluable for DLT and 3 (16.7%) experienced toxicity that met DLT criteria in the Phase 1 portion of the study to establish the RP2D for the combination of palbociclib with TOPO and CTX. One patient experienced DLT due to Grade 4 decreased neutrophil count and Grade 3 decreased platelet count and 2 patients experienced DLT due to Grade 4 decreased platelet count and Grade 3 hypotension.

In order to mitigate the risk of severe myelotoxicity and optimize treatment intensity, G-CSF prophylaxis will be mandatory in the combination of palbociclib with TOPO and CTX starting in Cycle 1. Section 5.7.4 guidance must be followed. Failure to administer G-CSF support will be considered a potentially important protocol deviation. Detailed guidance for management of chemotherapy-induced nausea and vomiting should be followed, as described in Section 5.7.5.

1.3.1.5.3. Pneumonitis/Interstitial lung disease (ILD)

Pneumonitis/ILD has been reported in adult patients receiving palbociclib even if the causal association between palbociclib treatment and pneumonitis/ILD/could not be established.

Participants will be monitored for signs and symptoms of pneumonitis/ILD (eg, hypoxia, cough, dyspnea). In patients who have new or worsening respiratory symptoms and are suspected to have developed ILD/pneumonitis, study treatments will be immediately interrupted. Pneumonitis/ILD will be managed, as described in Section 5.7.7.

Additional information for the investigational products may be found in the Single Reference Safety Documents (SRSDs), which for palbociclib is the Investigator's Brochure (IB) for TMZ (oral and IV) is the Merck Temodar US Prescribing Information, for IRN (IV) is the Pfizer Camptosar® US Prescribing Information, for TOPO is Novartis Hycamtin US Prescribing Information, and for CTX is Baxter Cyclophosphamide US Prescribing Information.

1.3.2. Benefit Assessment

Phase 2 and Tumor Specific Cohort

All participants in the study will receive a chemotherapy combination (IRN and TMZ or TOPO and CTX) that is known to be active in EWS, neuroblastoma and other solid tumors and will be closely monitored for safety and response to therapy. Patients will be monitored beyond the standard of care with assessments of growth and development, bone health, and cardiac effects of medications. Patients will contribute valuable data to the development of

new therapies for recurrent/refractory solid tumors (ie, EWS and neuroblastoma), an area of high unmet need.

1.3.3. Overall Risk/Benefit Conclusion

The results of the nonclinical toxicity and safety pharmacology studies, together with the clinical experience obtained to date with palbociclib, support the evaluation of the safety, PK, pharmacodynamic, and antitumor activity of palbociclib in the combination with IRN and TMZ or TOPO and CTX for the treatment of children, adolescent and young adult patients with recurrent/refractory solid tumors for whom no standard therapy is available.

The toxicity profile observed in the Phase 1 and Phase 2 portion of the study for the combination of palbociclib with IRN and TMZ and for the combination of palbociclib with TOPO and CTX as described in Section 1.2.2.2.3 and Section 1.2.2.2.4, further supports the continued development of the combination for the treatment of recurrent/refractory EWS in children, adolescents and young adults.

Taking into account the measures taken to minimize risk to study participants, the potential risks identified in association with the combination of palbociclib with IRN and TMZ are justified by the anticipated benefits that may be afforded to participants with recurrent/refractory solid tumors including recurrent/refractory EWS.

2. STUDY OBJECTIVES AND ENDPOINTS

Phase 1 Portion of the Study and Tumor Specific Cohorts	
Dose Escalation/Dose Determination Parts	
Primary Objective(s):	**Primary Endpoint(s):**
• To estimate the MTD for the combination of Palbociclib, TMZ and IRN in children, adolescents, and young adults with recurrent or refractory solid tumors. • To determine the potential RP2D for palbociclib in combination with TOPO and CTX in children, adolescents, and young adults with recurrent or refractory solid tumors.	• First cycle DLTs.
Secondary Objective(s):	**Secondary Endpoint(s):**
• To characterize the safety profile of palbociclib combined with TMZ and IRN. • To characterize the safety profile of palbociclib combined with TOPO and CTX.	• Adverse Events (AEs) as characterized by type, frequency, severity (as graded by National Cancer Institute [NCI] Common Terminology Criteria for Adverse events [CTCAE] version 4.03), timing, seriousness, and relationship to study therapy; laboratory test data including hemoglobin A1c (HbA1c) as characterized by type, frequency, severity (as graded by NCI CTCAE version 4.03), and timing; electrocardiogram (ECG) parameters, and vital signs.
• To describe the PK of palbociclib, TMZ and IRN in children, adolescents, and young adults	• PK parameters of palbociclib, TMZ, IRN, TOPO, and CTX:

with recurrent or refractory solid tumors when given in combination. • To describe the PK of palbociclib, TOPO, and CTX in children, adolescents, and young adults with recurrent or refractory solid tumors when given in combination.	• Palbociclib PK: Multiple Dose (MD; assuming steady-state is achieved)- $C_{ss,max}$, T_{max}, $AUC_{ss,\tau}$, $C_{ss,trough}$, and CL/F, as data permit. • TMZ PK: MD - $C_{ss,max}$, T_{max}, $AUC_{ss,\tau}$, $C_{ss,trough}$, and CL/F, as data permit. • IRN (and active metabolite, SN-38) PK: MD - $C_{ss,max}$, T_{max}, $AUC_{ss,\tau}$, $C_{ss,trough}$, and CL/F, as data permit. • CTX PK: MD - Css,max, Tmax, $AUC_{ss,\tau}$, $C_{ss,trough}$, and CL/F, as data permit. • TOPO (and active metabolite) PK: MD - $C_{ss,max}$, T_{max}, $AUC_{ss,\tau}$, Css,trough, and CL/F, as data permit.
• To evaluate the preliminary antitumor activity of palbociclib combined with TMZ and IRN. • To evaluate the preliminary antitumor activity of palbociclib combined with TOPO and CTX.	• Objective response (OR), as assessed by investigator using RECIST version 1.1/modified Response Assessment in Neuro-Oncology (RANO) for CNS malignancies/International Neuroblastoma Response Criteria (INRC) for neuroblastoma, and DOR.
Dose Expansion Cohorts and Tumor-Specific Cohorts	
Primary Objective(s):	**Primary Endpoint(s):**
• To evaluate the safety, and confirm the RP2D for the combination of palbociclib, TMZ, and IRN at the MTD in children, adolescents and young adults with recurrent or refractory solid tumors that are known to be sensitive to a CDK4/6 inhibitor. • To evaluate the safety, and confirm the RP2D for the combination palbociclib, CTX, and TOPO in children, adolescents and young adults with recurrent or refractory solid tumors that are known to be sensitive to a CDK4/6 inhibitor.	• AEs as characterized by type, frequency, severity (as graded by NCI CTCAE version 4.03), timing, seriousness, and relationship to study therapy; laboratory test data including HbA1c as characterized by type, frequency, severity (as graded by NCI CTCAE version 4.03), and timing; ECG parameters, and vital signs.
• To evaluate the preliminary antitumor activity of palbociclib combined with TMZ and IRN. • To evaluate the preliminary antitumor activity of palbociclib combined with TOPO and CTX.	• OR, as assessed by investigator using RECIST version 1.1/modified RANO for CNS malignancies/INRC for neuroblastoma.
Secondary Objective(s):	**Secondary Endpoint(s):**
• To evaluate other efficacy parameters of palbociclib combined with TMZ and IRN. • To evaluate other efficacy parameters of palbociclib combined with TOPO and CTX.	• DOR, PFS, and OS.

• To describe the PK of palbociclib, TMZ, and IRN in children, adolescents, and young adults with recurrent or refractory solid tumors when given in combination. • To describe the PK of palbociclib, TOPO, and CTX in children, adolescents, and young adults with recurrent or refractory solid tumors when given in combination.	• Pharmacokinetic parameters of palbociclib, TMZ, IRN, TOPO and CTX: • Palbociclib PK: MD (assuming steady state is achieved) - $C_{ss,max}$, T_{max}, $AUC_{ss,\tau}$, $C_{ss,trough}$, and CL/F, as data permit. • TMZ PK: MD - $C_{ss,max}$, T_{max}, $AUC_{ss,\tau}$, $C_{ss,trough}$, and CL/F, as data permit. • IRN (and active metabolite, SN-38) PK: MD - $C_{ss,max}$, T_{max}, $AUC_{ss,\tau}$, $C_{ss,trough}$, and CL/F, as data permit. • CTX PK: MD - $C_{ss,max}$, T_{max}, $AUC_{ss,\tau}$, $C_{ss,trough}$, and CL/F, as data permit. • TOPO (and active metabolite) PK: MD - $C_{ss,max}$, T_{max}, $AUC_{ss,\tau}$, $C_{ss,trough}$, and CL/F, as data permit.
Exploratory Objectives & Endpoints for Study	
• To characterize candidate biomarkers of sensitivity or resistance in pretreatment tumor tissue that may aid in the identification of patient subpopulations most likely to benefit from treatment.	• Identify, but not limited to, abnormalities in P16 and RB genes and effect on response.
• To explore pharmacodynamics modulation of thymidine kinase (TK)-1 activity in blood following palbociclib exposure.	• Palbociclib exposure and correlation with pharmacodynamics markers in blood (TK1 activity).
• Evaluate circulating nucleic acid (CNA) biomarkers in blood.	• DNA sequencing to evaluate gene mutations (genomic alterations) in patient blood.
• To evaluate preliminary information on the palatability of the oral solution formulation of palbociclib.	• Palatability of the palbociclib oral solution formulation, as assessed by a questionnaire.
• To explore the effect of treatment with palbociclib and parameters of bone metabolism and growth, including linear growth, bone age, bone mineral density, physical signs of pubertal maturation in patients who are pre or peripubertal (<Tanner 4).	• Analyze bone metabolism and growth, including linear growth, bone age, bone mineral density, physical signs of pubertal maturation (Tanner stage), and hormones associated with growth and pubertal development (insulin-like growth factor 1 [IGF 1], luteinizing hormone [LH], follicle-stimulating hormone [FSH], estradiol for girls, testosterone for boys.).
Randomized Phase 2	
Primary Objective(s):	**Primary Endpoint(s):**
• To compare the efficacy of palbociclib in combination with TMZ and IRN vs TMZ and IRN chemotherapy alone in the treatment of children, adolescents, and young adults with recurrent or refractory EWS.	• Event-free survival (EFS) based on investigator assessment.

Secondary Objective(s):	**Secondary Endpoint(s):**
• To further compare the efficacy of palbociclib in combination with TMZ and IRN vs TMZ and IRN chemotherapy alone.	• Event-free survival (EFS) assessed by an independent review committee. • Objective response (OR), as assessed by investigator using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. • PET-CT response after cycle 4 compared to objective response on MRI/CT. • Progression free survival (PFS) based on investigator assessment. • Overall survival (OS).
• To characterize the toxicity and safety of the combination of TMZ and IRN plus or minus palbociclib.	• Adverse Events (AEs) as graded by National Cancer Institute (NCI) Common Terminology Criteria for Adverse events (CTCAE) version 4.03.

• To describe the PK of palbociclib, TMZ, and IRN in children, adolescents, and young adults with recurrent or refractory EWS when given in combination.	• Pharmacokinetic parameters of palbociclib, TMZ, IRN:
	  • Palbociclib PK: MD (assuming steady state is achieved) - $C_{ss,max}$, T_{max}, $AUC_{ss,\tau}$, $C_{ss,trough}$, and CL/F, as data permit.
	  • TMZ PK: MD - $C_{ss,max}$, T_{max}, $AUC_{ss,\tau}$, $C_{ss,trough}$, and CL/F, as data permit.
	  • IRN (and active metabolite, SN-38) PK: MD - $C_{ss,max}$, T_{max}, $AUC_{ss,\tau}$, $C_{ss,trough}$, and CL/F, as data permit.

• To assess the impact of the combination of palbociclib with TMZ and IRN treatment on the quality of life (QoL) of patients with refractory and recurrent EWS.	• QoL reported by patient at baseline and after 2 and 4 cycles using age-appropriate tools. • Days of hospitalization.
Exploratory Objective	**Exploratory Endpoint**
• To characterize candidate biomarkers of sensitivity or resistance in pretreatment tumor tissue that may aid in the identification of patient subpopulations most likely to benefit from treatment.	• Identify, but not limited to, abnormalities in P16 and RB genes and effect on response.
• To explore pharmacodynamics modulation of thymidine kinase (TK)-1 activity in blood following palbociclib exposure.	• Palbociclib exposure and correlation with pharmacodynamics markers in blood (TK1 activity).

• Evaluate circulating nucleic acid (CNA) biomarkers in blood.	• DNA sequencing to evaluate gene mutations (genomic alterations) in patient blood.
• To evaluate preliminary information on the palatability of the oral solution formulation of palbociclib.	• Palatability of the palbociclib oral solution formulation, as assessed by a questionnaire.
• To explore the effect of treatment with palbociclib and parameters of bone metabolism and growth, including linear growth, bone age, bone mineral density, physical signs of pubertal maturation in patients who are pre or peripubertal (<Tanner 4).	• Analyze bone metabolism and growth, including linear growth, bone age, bone mineral density, physical signs of pubertal maturation (Tanner stage), and hormones associated with growth and pubertal development (insulin-like growth factor 1 [IGF 1], luteinizing hormone [LH], follicle-stimulating hormone [FSH], estradiol for girls, testosterone for boys) and a marker of bone formation and bone resorption (bone alkaline phosphatase and C-telopeptide- cross-links).

3. STUDY DESIGN

3.1. Study Overview

The open-label, multicenter, non-randomized Phase 1 portion of the study will evaluate the safety, PK, pharmacodynamic, and antitumor activity of palbociclib in combination with chemotherapy consisting of either IRN and TMZ or TOPO and CTX in children, adolescent and young adult patients with recurrent/refractory solid tumors for whom no standard therapy is available. The open-label, randomized Phase 2 portion of the study will will compare the efficacy of the combination of palbociclib with IRN and TMZ versus IRN and TMZ alone in the treatment of children, adolescents and young adults with recurrent or refractory EWS for whom no standard therapy is available.

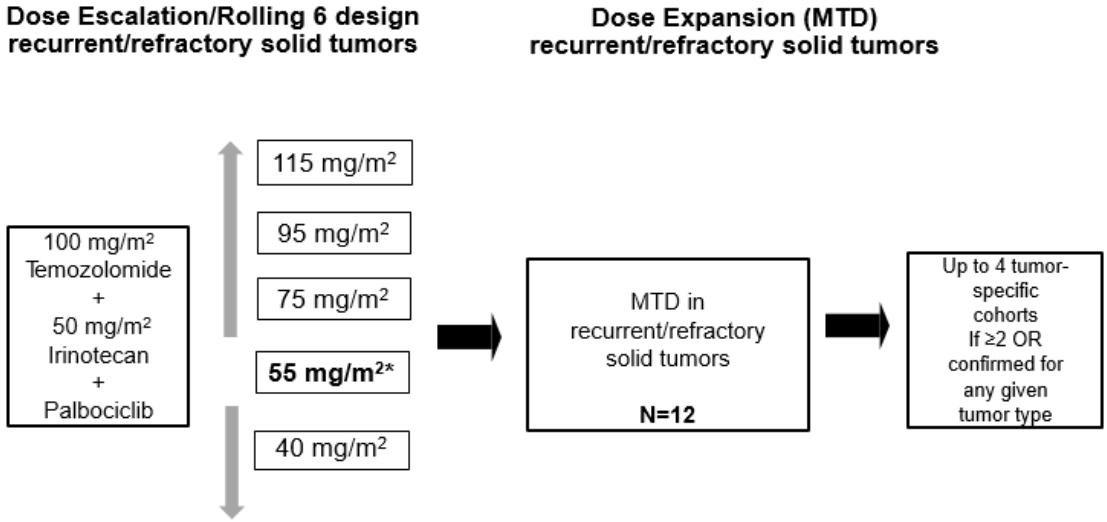
3.1.1. Combination of Palbociclib With IRN and TMZ

The Phase 1 portion of the study will evaluate the safety, PK, pharmacodynamic, and antitumor activity of palbociclib in combination with TMZ and IRN chemotherapy in children, adolescent and young adults patients with recurrent/refractory solid tumor for whom no standard therapy is available. Evaluation of palbociclib in combination with TMZ and IRN will be comprised of: dose escalation followed by a dose expansion cohort, (Figure 1), and if applicable, followed by tumor specific cohorts. In the dose escalation part, palbociclib will be administered orally QD on Days 1 to 14, with doses of TMZ administered at 100 mg/m^2 daily (IV/orally) on Days 1 to -5 and IRN administered daily at 50 mg/m^2 over 90 minutes IV on Days 1 to 5 (Table 6). Dose escalation or de-escalation will proceed according to decision rules outlined in following a rolling 6 design. TMZ can be given at the same time as palbociclib and will be administered at least 1 hour prior to administering IRN due to the fact that preclinical data suggests schedule-dependent- effects.[19] Patients who are unable to swallow the capsules should receive an IV formulation of TMZ, administered according to the product information. IRN infusion will then be given at least 1 hour after completion of TMZ infusion. Palbociclib should be administered at the start of TMZ infusion (Section 5.4.3). Palbociclib treatment will be on an outpatient basis starting from 55 mg/m^2

QD which is approximately 50% of the monotherapy MTD on Schedule 2/1 in adult patients (200 mg QD or ~118 mg/m^2 QD). A successive cohort of patients will receive escalating doses of palbociclib to a maximum of 115 mg/m^2 capped at 200 mg QD adult dose. The MTD is the highest dose level at which <33% of a minimum of 6 evaluable patients experience a DLT.

Once the MTD has been estimated in the dose escalation part, a minimum of 12 patients with recurrent or refractory solid tumors will be enrolled and treated at the MTD in a dose expansion cohort in order to confirm the MTD as the RP2D.

Figure 1. Study Schema - Phase 1 Palbociclib in Combination With IRN and TMZ

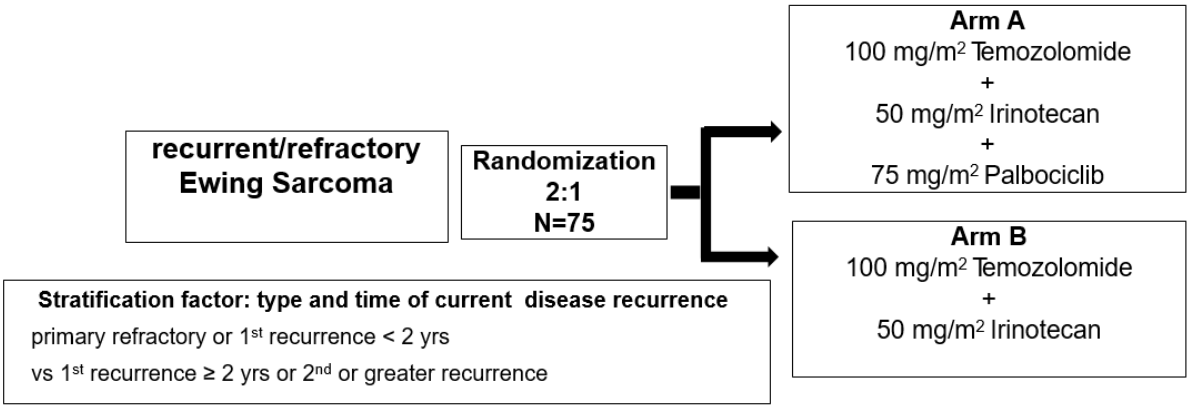


* palbociclib starting dose

Following the dose expansion, tumor-specific cohorts, other than EWS (eg, neuroblastoma, rhabdomyosarcoma, rhabdoid tumor or medulloblastoma) may be opened if 2 or more patients from the dose escalation part and/or dose expansion cohort show a confirmed objective response in a specific tumor type. The antitumor activity of palbociclib in combination with IRN and TMZ will be evaluated in each specific tumor type using a modified Simon's 2-stage optimal design (maximum of 21 patients per cohort).

The Phase 2 portion of the study will further evaluate efficacy, safety and PK of palbociclib in combination with IRN and TMZ in children, adolescent and young adult patients with recurrent/refractory EWS for whom no standard therapy is available. Patients will be randomized 2:1 to receive either palbociclib in combination with IRN and TMZ backbone chemotherapy or backbone chemotherapy alone. Randomization will be stratified as described in Section 5.1. Palbociclib at RP2D of 75 mg/m^2 will be administered orally QD on Days 1 to 14, with doses of TMZ administered at 100 mg/m^2 daily (IV/orally) on Days 1 to 5 and IRN administered daily at 50 mg/m^2 over 90 minutes IV on Days 1 to 5. (Section 5.4.1).

Figure 2. Study Schema - Phase 2 Palbociclib in Combination With IRN and TMZ



Treatment with the combination of IRN and TMZ with or without palbociclib will continue until disease progression, patient refusal, unacceptable toxicity occurs, or secondary malignancy is diagnosed or up to 24 months of treatment, whichever occurs first. Patients who complete 24 months on the combination regimen and demonstrate clinical benefit as determined by the investigator with manageable toxicity and/or are willing to continue receiving this regimen will be given the opportunity to continue treatment either on this study or as part of a separate treatment extension study, which will also capture long-term safety data.

As part of this study, several biomarkers will be evaluated to help understand the in vivo mechanism of action of the combination regimen as well as potential mechanisms of resistance. The results of the biomarker analyses may help in the future development of palbociclib in combination with other compounds.

3.1.1.1. Criteria for Dose Escalation

In the Phase 1 dose escalation part the starting dose of palbociclib in combination with IRN and TMZ will be 55 mg/m^2 administered once daily on Days 1 to 14 of each 21 day cycle Schedule 2/1. The doses of IRN and TMZ will be 50 mg/m^2 daily on Days 1 to 5 and 100 mg/m^2 daily on Days-1 to 5 respectively. All dosing will be in 21-day cycles.

The following dose levels will be evaluated in this study:

Table 6. Dose Levels for Palbociclib, TMZ and IRN

Dose Levels	Palbociclib Orally, once daily (mg/m^2) Day 1-14 in 21-Day Cycles	TMZ Orally (or IV if cannot swallow capsules), once daily (mg/m^2) Day 1-5 in 21-Day Cycles	IRN IV over 90 min, once daily, (mg/m^2) Day 1-5 in 21-Day Cycles
-1	40	100	50
1 (starting dose)	55	100	50
2	75	100	50
3	95	100	50
4	115	100	50

Abbreviations: IRN = irinotecan; IV = intravenous; TMZ = temozolomide.

Dose escalation follows a rolling 6 design allowing for accrual of 2 to 6 patients concurrently onto a dose level.[44] Table 7 provides the decision rules for enrolling a patient at the current dose level, at an escalated dose level, at a de-escalated dose level, or whether the study is suspended to accrual.

Table 7. Decision Rules in Rolling 6 Design for Palbociclib, TMZ and IRN

# of Patients	# of Patients with DLT	# of Patients with Data Pending	Decision for next patient
2	2		De-escalate*
	else		Same dose level
3	≥2		De-escalate*
	0	0	Escalate**
	else		Same dose level
4	≥2		De-escalate*
	0	0	Escalate**
	else		Same dose level
5	≥2		De-escalate*
	0	0	Escalate**
	else		Same dose level
6	≥2		De-escalate*
	≤1	0	Escalate**
	0	1	Escalate**
	else		Suspend

Note: In the event that the MTD is not reached, PK analysis will be used to define the RP2D or additional dose levels to be tested.
*If a minimum of 6 evaluable patients have been treated at next lower dose level, the MTD has been defined;
**If final dose level has been reached with <33% of minimum of 6 evaluable patients experiencing a DLT, the MTD will not have been reached and the highest dose will proceed to dose expansion.

Initially, up to 6 patients will be concurrently enrolled. Decisions as to whether to enroll a new patient onto the current, next highest, or next lowest dose level will be made based on available safety data at the time of new patient enrollment.

Decisions as to which dose level to enroll a patient will be based on the number of patients currently enrolled and evaluable, the number of patients experiencing DLTs, and the number of patients still at risk of developing a DLT at the time of new patient entry.

For example, when 3 patients are enrolled at a dose level in a cycle and all 3 patients have been evaluated for DLTs when the fourth patient is ready to enter and there are no DLTs among the first 3 patients, the dose is escalated, and the fourth patient is enrolled to the next higher dose level.

If DLT data are not yet available for 1 or more of the first 3 patients, or if 1 DLT has been observed, the new patient will enter at the same dose level.

If 2 or more DLTs are observed, the dose level will be de-escalated. The process will be repeated for patients 5 and 6. Accrual to the study will only be suspended when awaiting safety data from 6 patients. When patients are non-evaluable for DLTs, they will be replaced with the next available patient if escalation or de-escalation rules are not fulfilled at the time the next available patient is ready to enter onto the study.

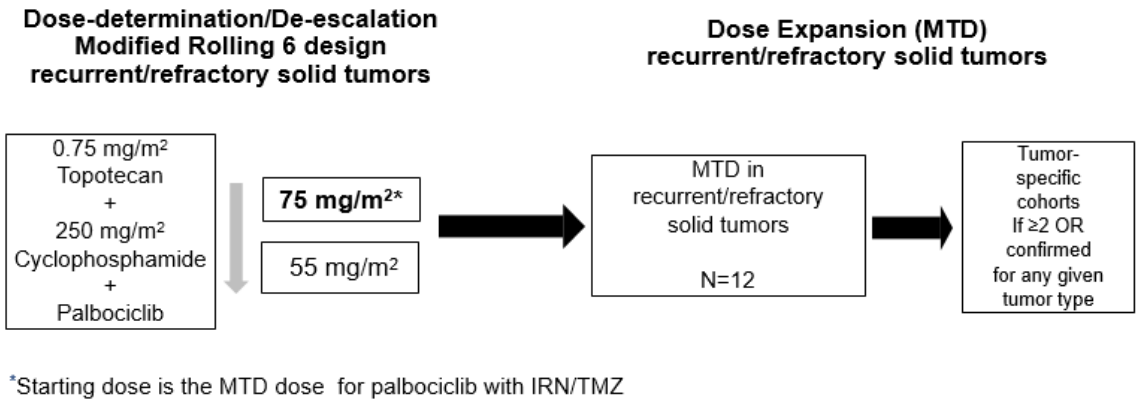
Dose re-escalation and intra-patient dose escalation are not permitted on this study.

3.1.2. Combination of Palbociclib With TOPO and CTX

This portion of the study will evaluate the safety, PK, pharmacodynamic, and antitumor activity of the combination of palbociclib with TOPO and CTX chemotherapy in children, adolescent and young adult patients with recurrent/refractory solid tumor for whom no standard therapy is available. Evaluation of palbociclib in the combination with TOPO and CTX will comprised of 3 parts: dose determination part followed by a dose expansion cohort, and if applicable, followed by tumor specific cohorts. In the dose determination part, palbociclib will be administered orally QD on Days 1 to 14, with doses of CTX administered at 250 mg/m^2 daily (IV) on Days 1 to 5 over 30-60 minutes and TOPO administered daily at 0.75 mg/m^2 over 30 minutes IV on Days 1 to 5 (see Table 8).

The starting dose of palbociclib in combination with TOPO and CTX will be the MTD determined in the IRN and TMZ combination. This dose is considered the MAD and no further dose escalation is planned. If <33% of a minimum of 6 evaluable patients experience a DLT at the MAD, the MAD will proceed to dose expansion to be confirmed as the RP2D. If ≥33% of evaluable patients experience a DLT, dose de-escalation to the next lower dose level will occur according to decision rules outlined in Table 9 following a modified rolling 6 design. For example, if 2 or more of the 6 evaluable patients treated at the MAD experience a DLT, the dose will be de-escalated to the next lower dose level. If less than 2 of 6 evaluable patients experienced DLTs, this dose level will proceed to dose expansion to be confirmed as the RP2D. Accrual to the study will only be suspended when awaiting safety data from the 6 patients. The dose determination part will enroll up to 12 DLT-evaluable patients and will be followed by dose expansion cohort to enroll a minimum of 12 patients with recurrent or refractory solid tumors to confirm the RP2D.

Figure 3. Study Schema - Phase 1 Palbociclib in Combination with TOPO and CTX



If 2 or more patients from the dose determination part and/or dose expansion cohort show a confirmed objective response in a specific tumor type (eg, EWS, neuroblastoma, rhabdomyosarcoma, rhabdoid tumor or medulloblastoma), a tumor-specific cohort with a maximum of 21 patients per cohort may be opened to further evaluate antitumor activity of the palbociclib in combination with TOPO and CTX in the specific tumor type using a modified Simon's 2-stage optimal design.

Treatment with this combination regimen will continue until disease progression, patient and/or legal guardian refusal, or unacceptable toxicity occurs, or up to 24 months of treatment, whichever occurs first. Patients who complete 24 months on the combination regimen and demonstrate clinical benefit with manageable toxicity and are willing to continue receiving this regimen will be given the opportunity to continue treatment either on this study or as part of a separate treatment extension study, which will also capture long-term safety data.

The proposed doses, schedule(s), and PK time points may be amended during the study based on the emerging safety and PK data.

As part of this study, several biomarkers will be evaluated to help understand the in vivo mechanism of action of the combination regimen as well as potential mechanisms of resistance. The results of the biomarker analyses may help in the future development of palbociclib in combination with other compounds.

3.1.2.1. Starting Dose

In the Phase 1 dose determination part the starting dose of palbociclib in the combination with TOPO and CTX will be the MTD for palbociclib in combination with IRN and TMZ administered once daily on Days 1 to 14 of each 21-day cycle Schedule 2/1.

Based on the dose escalation cohort of the combination of palbociclib with IRN and TMZ, the MTD for palbociclib has been determined as 75 mg/m^2 as 2 hematopoietic DLTs were observed at the 95 mg/m^2 dose level (ie, MTD had been exceeded) while no DLTs were observed at the 75 mg/m^2. The enrollment to dose expansion phase to confirm the 75 mg/m^2 palbociclib dose in combination with IRN and TMZ has been completed at the time of finalizing the current protocol amendment.

The 75 mg/m^2 dose will be the palbociclib starting dose level in the combination with TOPO and CTX and is the palbociclib MAD for this combination.

The doses of TOPO and CTX will be 0.75 mg/m^2 daily on Days 1 to 5 and 250 mg/m^2 daily on Days 1 to 5 respectively. All dosing will be in 21-day cycles. Subcutaneous G-CSF (5 µg/kg/dose daily) is mandatory starting in Cycle 1. The G-CSF should be initiated 24 to 48 hours after the administrations of TOPO and CTX are completed and should be continued until the expected neutrophil nadir is passed and the neutrophil count has recovered to a minimum of ANC ≥1000/mm^3. G-CSF must be stopped 24 hours prior to the next treatment cycle. At the discretion of the investigator the daily G-CSF (filgrastim) can be substituted by PEG-filgrastim in a standard weight-based dosing for pediatric patients. PEG-filgrastim should be initiated 24 to 48 hours after the administrations of TOPO and CTX are completed and must be stopped 14 days prior to the next treatment cycle.

The dose of CTX used in this schedule will not normally require the use of hydration and/or Mesna urothelial protection. Use of these supportive measures is at the discretion of the investigator based on patient experience and toxicity associated with first-line treatment.

3.1.2.2. Criteria for Dose De-Escalation

The following dose levels (see Table 8) will be evaluated in this study:

Table 8. Dose Levels for Palbociclib, TOPO and CTX

Dose Levels	Palbociclib Orally, once daily (mg/m^2) Days 1 to 14 in 21-Day Cycles	CTX (IV), over 30-60 min, once daily (mg/m^2) Days 1 to 5 in 21-Day Cycles	TOPO (IV), over 30 min, once daily, (mg/m^2) Days 1 to 5 in 21-Day Cycles
-1	55	250	0.75
1 (Starting Dose)	75	250	0.75

Abbreviations: TOPO = topotecan; IV = intravenous; CTX = cyclophosphamide.

Dose de-escalation follows a modified rolling 6 design allowing for accrual of 2 to 6 patients concurrently onto a dose level. Table 9 provides the decision rules for enrolling a patient at the current dose level and at a de-escalated dose level, or whether the study is suspended to accrual.

Table 9. Decision Rules in Modified Rolling 6 Design for Palbociclib, TOPO and CTX

# of Patients	# of Patients with DLT	# of Patients with Data Pending	Decision for next patient
2	2		De-escalate*
	else		Same dose level
3	≥2		De-escalate*
	else		Same dose level
4	≥2		De-escalate*
	else		Same dose level
5	≥2		De-escalate*
	else		Same dose level
6	≥2		De-escalate*
	≤1	0	Proceed**
	0	1	Proceed**
	else		Suspend

*If a minimum of 6 evaluable patients have been treated at the next lower dose level, the dose will proceed to dose expansion.
**If <33% of minimum of 6 evaluable patients treated at the MAD experiencing a DLT, the MAD will proceed to dose expansion.

Approximately 109 patients are expected to be enrolled in Phase 1 portion of the study, assuming 4 tumor specific cohorts are opened. Approximately 75 patients will be enrolled in the randomized Phase 2 portion of the study. Overall the study may enroll approximately 184 patients. The final number of enrolled patients may vary depending upon the number of tumor-specific cohorts.

The study will aim to enroll 6 PK-evaluable patients per treatment combination in each of the following age groups: ≤6 years old, >6 years and <12 years old, and ≥12 years and <18 years old for each combination. The expansion cohorts may remain open for targeted enrollment by age group and by combination. However, given the relatively limited patient population of pediatric cancer patients in some of the age groups, particularly the ≤6 and the >6 to<12 subgroups, the dose expansion cohorts may be closed if the available PK data is deemed sufficient per the Sponsor assessment.

3.2. DLT Definition for Both Combinations

Severity of AEs will be graded according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. For the purpose of dose escalation, any of the following AEs occurring in the first cycle of treatment (until the start of Cycle 2) which are attributable to at least one of the agents in the combination will be classified as a DLT in order to establish the MTD:

Hematologic AEs:

- Grade 4 neutropenia lasting >7 days;
- Grade 4 thrombocytopenia lasting >7 days or need for platelet transfusion for a platelet count of less than 20,000/mm^3 twice within a 7-day period;

- Greater than 14-day delay in the start of a subsequent course because of neutropenia or thrombocytopenia. (Section 5.7.4; next cycle not started by Day 35);

- Grade 3 or 4 febrile neutropenia will not be considered a DLT.

Non-hematologic AEs:

- Grade ≥3 toxicities despite optimal treatment (eg, Grade ≥3 nausea or vomiting despite the optimal use of anti-emetics and/or diarrhea lasting for more than 3 days despite optimal use of anti-diarrheals, or any Grade 4 diarrhea);

- Any Grade ≥2 toxicity requiring discontinuation/interruption of palbociclib for ≥7 (eg, pneumonitis) consecutive days during the first cycle of treatment or any grade toxicity that delays the start of Cycle 2 by more than 14 days;

- Clinically significant laboratory test abnormality Grade ≥3 not resolving to Grade ≤1 or baseline within 7 days;

- Note that hypersensitivity reactions will not be considered DLTs.

Any AE that meets the above DLT definitions must be reported within 24 hours of site personnel becoming aware of the event to the Pfizer/Syneos shared mailbox A5481092@syneoshealth.com with CRA in copy.

DLT assessment is not required in the Phase 2 portion of the study and tumor specific cohorts. DLT definitions apply for dosing interruption (Section 5.4.9) and dose reductions (Section 5.4.11).

3.3. MTD Definition for IRN and TMZ

The MTD is defined as the highest dose level at which <33% of a minimum of 6 evaluable patients experience a DLT during Cycle 1 of treatment. If 6 or more patients have been treated at the highest dose level studied and <33% experience a DLT, then the MTD is not reached and the highest dose will proceed to dose expansion.

3.4. MAD Definition for TOPO and CTX

The MTD determined in the IRN and TMZ combination will be the MAD for palbociclib with TOPO and CTX combination. Given that TOPO and CTX chemotherapy combination is expected to be more myelosuppressive than IRN and TMZ combination, this dose will be the starting dose of palbociclib in combination with TOPO and CTX and no further dose escalation is allowed.

3.5. Tumor-Specific Cohorts

Tumor-specific cohorts (eg, EWS, neuroblastoma, rhabdomyosarcoma, rhabdoid tumor or medulloblastoma) for palbociclib in combination with IRN and TMZ and/or TOPO and CTX may be opened if 2 or more patients from the dose escalation/dose determination part and/or dose expansion cohort show a confirmed objective response to the respective combination in

a specific tumor type to further evaluate antitumor activity in the specific tumor type using a modified Simon's 2-stage optimal design (maximum of 21 patients per cohort). Palbociclib in combination with IRN and TMZ will be assessed in Phase 2 portion of the study, and therefore, a EWS tumor specific cohort in the Phase 1 portion of the study for this combination is not planned.

3.6. Recommended Phase 2 Dose (RP2D) Definition for IRN and TMZ

The RP2D is the dose chosen for further investigation based on the results of the Phase 1 portion of this study. If the MTD proves to be clinically feasible for long-term administration in a reasonable number of patients, then this dose usually becomes the RP2D. Further experience with the MTD may result in a RP2D dose lower than the MTD. In the event that MTD is not reached, PK analysis will be used to define the RP2D or additional dose levels to be tested based on comparison to exposures reported in historical trials in adults at equivalent doses and at the MTD dose for the 2/1 schedule.

3.7. Recommended Phase 2 Dose (RP2D) Definition for TOPO and CTX

The RP2D dose for combination of palbociclib with TOPO and CTX will not be determined via a standard Phase 1 dose-escalation design. Given that TOPO and CTX chemotherapy combination is expected to be more myelosuppressive than IRN and TMZ combination, the palbociclib starting dose in the TOPO and CTX combination is considered the MAD and no further dose escalation is planned. If <33% of a minimum of 6 evaluable patients experience a DLT at the MAD, the MAD will proceed to dose expansion to further confirm the RP2D. If ≥33% of evaluable patients at the MAD experience a DLT, the dose will be de-escalated to the next lower dose level and additional patients will be enrolled at this dose level. If <33% of a minimum of 6 evaluable patients experience a DLT, this dose level will proceed to dose expansion to be confirmed as the RP2D.

4. PATIENT ELIGIBILITY CRITERIA

This study can fulfill its objectives only if appropriate patients are enrolled. The following eligibility criteria are designed to select patients for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular patient is suitable for this protocol.

4.1. Inclusion Criteria

Patients must meet all the following inclusion criteria to be eligible for enrollment in the study:

1. Histologically confirmed relapsed or refractory solid tumor as follows:

    - **For dose escalation and dose determination parts:** Histologically confirmed relapsed or refractory solid tumor (including CNS tumors but not lymphomas). Patients with Diffuse Intrinsic Pontine Glioma do not require histological only radiographic confirmed relapse to enroll.

- **For dose expansion cohorts:** Histologically confirmed relapsed or refractory solid tumor including but not limited to EWS, rhabdoid tumor, rhabdomyosarcoma, neuroblastoma, and medulloblastoma. Patients with Diffuse Intrinsic Pontine Glioma do not require histological only radiographic confirmed relapse to enroll.

- **For tumor-specific cohorts:** Histologically confirmed relapsed or refractory solid tumor including but not limited to EWS, rhabdoid tumor, rhabdomyosarcoma, neuroblastoma, and medulloblastoma. Patients with Diffuse Intrinsic Pontine Glioma do not require histological only radiographic confirmed relapse to enroll. .

- **For randomized Phase 2 part:** Histologically confirmed Ewing sarcoma at diagnosis or at relapse, with presence of EWSR1-ETS or FUS-ETS rearrangement. Histopathology confirmation of both EWSR1-ETS or FUS-ETS rearrangement partners is required OR availability of formalin fixed paraffin embedded (FFPE) tumor tissue sample for central testing. Patient must have relapsed or have refractory disease and at least evaluable disease in at least one site other than bone marrow that can be followed by imaging.

2. Age ≥2 and <21 years at the time of study entry. Refer to Section 4.3 for reproductive criteria for male and female participants.

3. Lansky performance status ≥50% for patients ≤16 years of age, or Eastern Cooperative Oncology Group (ECOG) 0, 1 or 2 for patients >16 years of age.

4. Adequate bone marrow function.

   - Absolute neutrophil count ≥1000/mm^3;

   - Platelet count ≥75,000/mm^3 (transfusion independent, no platelet transfusion in past 7 days prior study entry);

   - Hemoglobin ≥8.5 g/dL (transfusion allowed).

5. Adequate renal function: Serum creatinine level based on age/gender must be less than or equal to the following maximum upper limits as shown in Table 10:

Table 10. Maximum Allowed Creatinine Levels

Age	Maximum Serum Creatinine (mg/dL)	
	Male	Female
2 to <6 years	0.8	0.8
6 to <10 years	1.0	1.0
10 to <13 years	1.2	1.2
13 to <16 years	1.5	1.4
16 to <21 years	1.7	1.4

The threshold creatinine values in this table were derived from the Schwartz formula for estimating glomerular filtration rate utilizing child length and stature data published by the CDC.[45]

6. Adequate liver function, including:

   - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5 × upper limit of normal (ULN) or ≤5 × ULN for age, if attributable to disease involvement of the liver;

   - Total bilirubin ≤1.5 × ULN for age unless the patient has documented Gilbert's syndrome. Patients with documented Gilbert's syndrome are eligible if direct bilirubin is within normal ranges (≤ULN).

7. Patients enrolled to Phase 1 portion of the study and tumor specific cohorts must have measurable disease as defined by RECIST version 1.1 or modified RANO criteria for CNS disease or at least evaluable disease by INRC for neuroblastoma.

   The eligible patients with neuroblastoma must have at least one of the following at the time of study entry:

   - Measurable tumor by CT or MRI that is avid on MIBG scan or demonstrates increased FDG uptake on PET scan;

   - Avid lesion on MIBG scan with positive uptake at a minimum of one site;

   - For disease that is not avid by MIBG-scan, at least one lesion that demonstrates increased FDG uptake on PET scan AND viable neuroblastoma confirmed by current or prior biopsy;

   - bone marrow involvement with more than 5% neuroblastoma cells in at least one sample from bilateral bone marrow biopsies;

   - In non MIBG-avid refractory soft tissue disease that does not demonstrate increased FDG uptake; lesion biopsy is required to document the presence of

viable neuroblastoma, unless patient has a new soft tissue lesion (radiographic evidence of disease progression).

Patients with EWS enrolled to Phase 2 portion of the study are eligible with at least evaluable disease (eg, bone only disease with no soft tissue component).

8. Recovered to CTCAE Grade ≤1, or to baseline, from any non-hematological acute toxicities of prior surgery, chemotherapy, immunotherapy, radiotherapy, differentiation therapy or biologic therapy, with the exception of alopecia.

9. Serum/urine pregnancy test (for all girls ≥8 years of age) negative at screening and at the baseline visit.

4.2. Exclusion Criteria

Patients with any of the following characteristics/conditions will not be included in the study:

1. Phase 1 portion and tumor specific cohorts: For palbociclib with IRN and TMZ combination, prior treatment with a CDK4/6 inhibitor or progression while on treatment with an IRN-containing regimen that includes TMZ. Patients who have received the combination of IRN and TMZ and did not progress while on these medications are eligible. For patients enrolling in the palbociclib with TOPO and CTX combination, prior treatment with a CDK4/6 inhibitor or progression while on treatment with a TOPO-containing regimen that includes CTX. Patients who have received the combination of TOPO and CTX and did not progress while on these medications are eligible. Phase 2 portion: prior treatment with a CDK4/6 inhibitor or progression while on treatment with an IRN-containing or TMZ-containing regimen. Patients who have received IRN and/or TMZ and did not progress while on these medications are eligible.

2. Prior intolerability to IRN and/or TMZ for IRN and TMZ plus/minus palbociclib combinations and prior intolerability to TOPO and/or CTX for TOPO and CTX combination. For patients enrolled in the UK, any contraindication for IRN and/or TMZ treatment, as per the local SmPC.

3. Use of strong cytochrome P450 (CYP) 3A inhibitors or inducers within 12 days of study entry. Patients who are receiving strong uridine diphosphate-glucuronosyl transferase 1A1 (UGT1A1) inhibitors within 12 days of C1D1 are not eligible for the palbociclib with IRN and TMZ combination. Patients who are receiving strong UGT1A1 inhibitors within 12 days of C1D1 are eligible for the palbociclib with TOPO and CTX combination (see Section 5.7.1 for list of products).

4. Systemic anticancer therapy within 2 weeks prior to study entry and 6 weeks for nitrosoureas.

5. Prior irradiation to >50% of the bone marrow (see Appendix 9).

6. Participation in other studies involving investigational drug(s) within 2 weeks or 5 halflives, whichever is longer, prior to study entry.

7. Major surgery within 4 weeks prior to study entry. Surgical biopsies or central line placement are not considered major surgeries.

8. For IRN and TMZ with/without palbociclib combinations: known or suspected hypersensitivity to palbociclib, dacarbazine, IRN and/or TMZ. For combination of palbociclib with TOPO and CTX: known or suspected hypersensitivity to palbociclib, TOPO and/or CTX.

9. Patients with known symptomatic brain tumors or brain metastases and require steroids, unless they have been on a stable or on a decreasing steroid dose for >14 days.

10. Patients with previously diagnosed brain metastases are eligible if they have completed their prior treatment and have recovered from the acute effects of radiation therapy or surgery prior to study entry for these metastases for at least 14 days postradiation and 4 weeks post-surgery and are neurologically stable.

11. Hereditary bone marrow failure disorder.

12. QTc >470 msec.

13. History of clinically significant or uncontrolled cardiac disease, including:

    - History of or active congestive heart failure; if patient had congestive heart failure resolve and >1 year from resolution, patient will be considered eligible;
    - Clinically significant ventricular arrhythmia (such as ventricular tachycardia, ventricular fibrillation or Torsades de Pointes);
    - Diagnosed or suspected congenital or acquired prolonged QT syndrome;
    - Need for medications known to prolong the QT interval;
    - Uncorrected hypomagnesemia or hypokalemia because of potential effects on the QT interval;
    - Left ventricular ejection fraction <50% or shortening fraction <28%.

14. Recent or ongoing clinically significant gastrointestinal disorder that may interfere with absorption of orally administered drugs (eg, gastrectomy).

15. Evidence of serious active or uncontrolled bacterial, fungal or viral infection or known history of hepatitis B virus, hepatitis C virus, or human immunodeficiency virus infection or acquired immunodeficiency syndrome-related illness. Screening for viral

hepatitis and HIV is under discretion of investigator unless required by local regulation.

16. Severe acute or chronic medical or laboratory test abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results, and in the judgment of the Investigator, would make the patient inappropriate for entry into this study.

17. Investigator site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or patients who are Pfizer employees, including their family members, directly involved in the conduct of the study.

18. Fertile male patients or female patients of childbearing potential who are unwilling or unable to follow contraceptive requirements as detailed in Section 4.3.

19. Pregnant or breastfeeding women.

4.3. Lifestyle Requirements

All fertile male patients and female patients who are of childbearing potential, as applicable to the study who are, in the opinion of the investigator, sexually active and at risk for pregnancy with their partner(s), must agree to use a highly effective method of contraception consistently and correctly for the duration of the active treatment period and continue after the last dose of study treatment. A highly effective method of contraception should be used as follows: for female patients receiving IRN and TMZ – for at least 180 days after the last dose of investigational product; for female patients receiving TOPO and CTX - for 12 months after the last dose of CTX. For male patients receiving IRN and TMZ - for at least 90 days after the last dose of investigational product and for male patients receiving TOPO and CTX- for at least 120 days after the last dose of CTX.

A woman is considered of childbearing potential (WOCBP), ie, fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. However, the assessment of childbearing potential is the responsibility of an investigator and in the pediatric patient's population should include the combination of key components of the assessment ie, patient's age (≥8 years old), Tanner stage and menarchal status. The childbearing potential is not exactly defined solely by menarche, nor solely by Tanner stage; however all girls following menarche and/or girls of pubertal development at stage Tanner ≥3 should be considered fertile and able to become pregnant. The investigator or his or her designee will confirm that the patient has selected an appropriate method of contraception from the list of permitted contraception methods (see below). At time points indicated in the Schedule of Activities, the investigator or designee will instruct the patient of the need to use highly effective contraception consistently and correctly and document the conversation, and the patient's affirmation, in the patient's chart. In addition, the investigator or designee will instruct the patient to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the patient or partner.

Highly effective methods of contraception are those that, alone or in combination, result in a failure rate of less than 1% per year when used consistently and correctly (ie, perfect use) and include the following:

1. Established use of hormonal methods of contraception associated with inhibition of ovulation (eg, oral, inserted, injected, implanted, transdermal), provided the patient plans to remain on the same treatment throughout the entire study and has been using that hormonal contraceptive for an adequate period of time to ensure effectiveness.

2. Correctly placed copper-containing intrauterine device (IUD).

3. Male condom or female condom used WITH a separate spermicide product (ie, foam, gel, film, cream, or suppository). For countries where spermicide is not available or condom plus spermicide is not accepted as highly effective contraception, this option is not appropriate (eg, condom plus spermicide is not accepted as highly effective contraception method in the UK and Czech Republic and should not be used by patients enrolled in these countries).

NOTE: Sexual abstinence, defined as completely and persistently refraining from all heterosexual intercourse (including during the entire period of risk associated with the study treatments) may obviate the need for contraception ONLY if this is the preferred and usual lifestyle of the patient.

All sexually active male patients must agree to prevent potential transfer to and exposure of partner(s) to drug through ejaculate by using a condom consistently and correctly, beginning with the first dose of investigational product and continuing for at least 90 days after the last dose of investigational product.

4.4. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the Study Manual.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, patients are provided with a contact card. The contact card contains, at a minimum, protocol and investigational product identifiers, patient study numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the patient's participation in the study. The contact number can also be used by investigator staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigator site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the patient directly, and if a patient calls that number, he or she will be directed back to the investigator site.

5. STUDY TREATMENTS

Per International Conference on Harmonisation (ICH) guidelines, investigational product is defined as a pharmaceutical form of an active ingredient or placebo being tested or used as a reference/comparator in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use (ICH E6 1.33).

For this study, the investigational products are palbociclib, irinotecan, temozolomide, topotecan, and cyclophosphamide.

5.1. Allocation to Treatment

Phase 1 Portion of the Study and Tumor Specific Cohorts

The Phase 1 portion of the study and tumor specific cohorts are open-label, non-randomized portions of the study. Patients will be enrolled into dose levels in accordance with the dose escalation (palbociclib in combination with IRN and TMZ) and the dose determination (palbociclib in combination with TOPO and CTX) scheme (see Section 3) followed by the respective dose expansion cohorts at the MTD or potential RP2D. Patients in tumor specific cohorts will be assigned to palbociclib RP2D level.

Dose level allocation will be performed by the sponsor after patient or patient's legally acceptable representative has given their written informed consent, the patient, if indicated, has provided assent, and the patient has completed the necessary baseline assessments. The site staff will submit a complete Registration Form to the designated sponsor study team member or designee. The sponsor will assign a patient identification number which will be used on all case report forms (CRFs) and supply this number to the site. The patient identification number will be used on all study-related documentation or correspondence (including fax and/or email) referencing that patient to the site.

No patient will receive investigational product until the investigator or designee has received the following information in writing from the sponsor:

- Confirmation of the patient's enrollment;
- Specification of the dose level for that patient and;
- Permission to proceed with dosing the patient.

The sponsor or designee will notify the other sites of the inclusion of a new patient, and will inform study sites about the next possible enrollment date.

Phase 2 Portion of the Study

The Phase 2 portion of the study is an open-label, randomized study. Patients will be randomized 2:1 to receive either palbociclib in combination with IRN and TMZ or IRN and TMZ alone. Randomization will be stratified using block randomization by type and time of

current disease recurrence (primary refractory or 1st recurrence <2 years versus 1st recurrence ≥2 years since completion of 1st line treatment or 2nd or greater recurrence).

Definition of Refractory Disease

Refractory disease is defined as disease progression during 1st line treatment or within 12 weeks of treatment completion. Disease progression at or after 12 weeks of completion of 1st line treatment is defined as recurrent disease.

The specific study intervention dispensed to the participant will be assigned using an interactive randomization technology (IRT). The site will contact the IRT prior to the start of study intervention administration for each participant. The site will record the study intervention assignment on the applicable CRF, if required. Potential bias will be reduced by the central randomization.

Randomization Criteria

Patients will be randomized into the Phase 2 portion of the study provided they have satisfied all patient selection criteria.

- The investigators or their pre-specified designee will randomize eligible patients by IRT as described in the Study Reference Manual.
- At the time of randomization, information about the stratification factor (ie, type and time of current disease recurrence) will be requested.
- The central computerized system will provide the randomization number and treatment assignment.

Considering this is an open-label study the investigator's knowledge of the treatment should not influence the decision to enroll a particular participant or affect the order in which participants are enrolled.

Patient will be dosed within 3 days of randomization. Study intervention will be dispensed at the study visits summarized in the SoA Table 3.

Returned study intervention must not be redispensed to the participants.

The study-specific IRT reference manual and investigational product manual will provide further details on the use of the IRT system.

It is possible that multiple cohorts could be opened concurrently to patients with EWS. These cohorts include: randomized Phase 2 portion of the study, tumor specific cohort, targeted enrollment to dose expansion PK cohort. Allocation of patients will follow Investigator's choice and will require consultation with the sponsor prior to informed consent.

5.2. Patient Compliance

All IV doses (IRN, TMZ, TOPO and CTX) and oral TMZ will be administered by the appropriately designated study staff at the investigational site. Palbociclib can also be administered by designated study staff on Days 1 to 5 with oral TMZ.

Patients will be required to return all unused palbociclib prior to beginning each cycle. The number of capsules or the amount of oral solution returned by the patient will be counted/measured, documented, and recorded. Please refer to investigational product manual for instructions to assess patient compliance.

A patient diary will be provided to the patients and/or patient's legally acceptable representative, to aid in patient compliance with the dosing instructions. The diary will be maintained by the patient or patient representative, to include missed or changed palbociclib doses. Patients will be required to return all bottles of palbociclib prior to the start of the next cycle. The number of palbociclib capsules or amount of oral solution remaining will be documented and recorded prior to the start of each cycle. The patient diary may also be used at the end of each cycle and prior to starting the next cycle to support this part of the palbociclib accountability process.

5.3. Investigational Product Supplies

5.3.1. Dosage Form(s) and Packaging

5.3.1.1. Palbociclib Capsules

Palbociclib will be supplied as capsules containing 75 mg, 100 mg, or 125 mg equivalents of palbociclib free base. The sponsor will supply the oral drug formulation to sites in high-density-polyethylene (HDPE) bottles containing 75 mg, 100 mg, or 125 mg capsules. The capsules can be differentiated by their size and color, as shown in Table 11. Labeling will occur according to local regulatory requirements.

Table 11. Palbociclib Capsule Characteristics

Strength	Capsule color
75 mg	Sunset Yellow
100 mg	Caramel/Sunset Yellow
125 mg	Caramel

5.3.1.2. Palbociclib Oral Solution

Palbociclib, 25 mg/mL, oral solution will be supplied in HDPE packaged bottles with a push-in bottle adapter and a reusable oral syringe for dosing. Labeling will occur according to local regulatory requirements.

5.3.1.3. Irinotecan

IRN, 20 mg/mL concentrate for solution for infusion, will be supplied in single-use vials for preparation and dosing. Labeling will occur according to local regulatory requirements.

5.3.1.4. Temozolomide

TMZ, for oral use, will be supplied as capsules that vary in size, color, and imprint according to strength, and packaged in bottles, blisters, or sachets depending on the market in which they are sourced. For patients who cannot swallow capsules, TMZ, 2.5 mg/mL powder for solution for infusion, will be supplied in single-use vials for preparation and dosing Labeling will occur according to local regulatory requirements.

5.3.1.5. Topotecan

TOPO, 1 mg/mL concentrate or powder for solution for infusion, will be supplied in single-use vials for preparation and dosing Labeling will occur according to local regulatory requirements.

5.3.1.6. Cyclophosphamide

CTX, 20 mg/mL powder for solution for infusion, will be supplied in single-use vials for preparation and dosing Labeling will occur according to local regulatory requirements.

5.3.2. Preparation and Dispensing

Palbociclib will be dispensed at each visit per the treatment schedule. A qualified staff member will dispense the investigational product in the bottles provided, in quantities appropriate for the study visit schedule. The formulation provided and the route of administration for TMZ and palbociclib need to be documented in the medical record and CRF. Times dose given for IRN, TMZ, TOPO and CTX (IV), dosage start and stop times should be recorded and placed in the CRF. The dates and times of most recent doses given for palbociclib and oral TMZ (both before and after PK sample collection) should be recorded and placed in the CRF on days that PK levels are done.

The patient/caregiver should be instructed to maintain the investigational product in the bottle provided throughout the course of dosing, keep the investigational product away from children, and return the bottle along with the drug diaries, to the study site at the next study visit.

IRN and TMZ, or TOPO and CTX are to be given by qualified staff members only in a clinic or hospital setting.

Only qualified personnel who are familiar with procedures that minimize undue exposure to themselves and to the environment should undertake the preparation, handling, and safe disposal of study medication.

A cycle is defined as 21 days and Day 1 of each cycle is the day when the next course of palbociclib is started.

5.4. Administration

5.4.1. Palbociclib Capsules

Patients should be instructed to swallow palbociclib capsule daily, whole, and not to chew them prior to swallowing. No capsule should be ingested if it is broken, cracked, or otherwise not intact. Patients should contact site personnel if capsules are not intact for replacement capsules. Patients should be encouraged to take their dose at approximately the same time each day. Patients should be instructed to record daily administration of the palbociclib investigational product in a patient diary.

Patients must be instructed to withhold their daily dose of palbociclib on PK sampling days until the pre-dose PK sample and safety assessments (ie, hematology, blood chemistry, and electrocardiograms [ECGs]) have been completed. On days the patient is in the clinic, palbociclib will be taken when instructed by the investigator.

Patients should take palbociclib capsules with food around the same time of the day.

Palbociclib capsules will be administered QD, orally, for 14 days followed by 7 days off treatment in 21-day cycles.

Patients who miss a day's dose entirely must be instructed NOT to "make it up" the next day.

Patients who vomit any time after taking a dose must be instructed NOT to "make it up," and to resume treatment the next day as prescribed.

Patients who inadvertently take 1 extra dose during a day must be instructed to skip the next day's dose. Also refer to Section 8.4.3 for further details on medication errors and overdose.

Patients experiencing investigational product related toxicity may have their dose modified according to Section 5.4.9.

5.4.2. Palbociclib Oral Solution

For patients who are unable to swallow capsules or when a patient's BSA-based dose is more than 15% below the 75-mg capsule strength, a palbociclib oral solution should be used. Patients should contact site personnel if bottle seals are not intact or if bottle leaks for replacements.

For patients who develop inability to swallow capsules during the study, it is allowed to switch to the palbociclib oral solution.

The palbociclib 25 mg/mL oral solution will be administered using an oral syringe at volumes corresponding to the dose prescribed by the investigator. Detailed instructions for administration of the oral solution can be found in the dosage and administration instruction.

Palbociclib oral solution will be administered once a day, orally or via feeding tube (nasogastric or gastrostomy tube), for 14 days followed by 7 days off treatment in 21-day

cycles. The route of administration of the oral solution (oral vs via feeding tube) will be recorded in the CRF.

Patients can take palbociclib oral solution with or without food.

Patients should be encouraged to take their dose at approximately the same time each day. Patients and/or caregivers should be instructed to record daily administration of the palbociclib investigational product in a patient diary.

Patients and/or caregivers must be instructed to withhold their daily dose of palbociclib on PK sampling days until the pre-dose PK sample and safety assessments (ie, hematology, blood chemistry, and ECGs) have been completed. On days the patient is in the clinic, palbociclib will be taken when instructed by the investigator.

Patients who miss a day's dose must be instructed NOT to "make it up" the next day.

Patients who vomit any time after taking a dose must be instructed NOT to "make it up," and to resume treatment the next day as prescribed.

Patients who inadvertently take 1 extra dose during a day must be instructed to skip the next day's dose. Also refer to Section 8.4.3 for further details on medication errors and overdose.

Patients experiencing study treatment related toxicity may have their dose modified according to Section 5.4.8.

The dose of palbociclib will depend on the dose level that the patient is assigned to and will be adjusted for the patient's BSA measured during a scheduled clinic visit. If the patient can swallow capsules, the dose can be rounded to meet the available capsule strength if within ±15% of the capsule strength. When a patient's BSA-based dose is more than 15% below the 75-mg capsule strength or when patients cannot swallow capsules, oral solution must be used (see Appendix 10). Table 12 provides the dosing information for palbociclib based on BSA for capsule dosing.

Table 12. Palbociclib Oral Capsule Dosing Table

Body Surface Area (m^2)*	Actual Daily Dose (mg)				
	40 mg/m^2	55 mg/m^2	75 mg/m^2	95 mg/m^2	115 mg/m^2
0.3	Oral Solution needed**	Oral Solution needed	Oral Solution needed	Oral Solution needed	Oral Solution needed
0.4	Oral Solution needed	Oral Solution needed	Oral Solution needed	Oral Solution needed	Oral Solution needed
0.5	Oral Solution needed	Oral Solution needed	Oral Solution needed	Oral Solution needed	Oral Solution needed
0.6	Oral Solution needed	Oral Solution needed	Oral Solution needed	Oral Solution needed	75
0.7	Oral Solution needed	Oral Solution needed	Oral Solution needed	Oral Solution needed	75
0.8	Oral Solution needed	Oral Solution needed	Oral Solution needed	75	100

Table 12. Palbociclib Oral Capsule Dosing Table

Body Surface Area (m^2)*	Actual Daily Dose (mg)				
	40 mg/m^2	55 mg/m^2	75 mg/m^2	95 mg/m^2	115 mg/m^2
0.9	Oral Solution needed	Oral Solution needed	75	Oral Solution needed***	100
1.0	Oral Solution needed	Oral Solution needed	75	100	125
1.1	Oral Solution needed	Oral Solution needed	75	100	125
1.2	Oral Solution needed	75	100	125	150
1.3	Oral Solution needed	75	100	125	150
1.4	Oral Solution needed	75	100	125	150
1.5	Oral Solution needed	75	100	125	175
1.6	75	100	125	150	200
1.7	75	100	125	150	200
1.8	75	100	125	175	200
1.9	75	100	125	175	200
2.0	75	100	150	200	200
2.1	75	125	150	200	200
2.2	100	125	150	200	200
2.3	100	125	150	200	200
2.4	100	125	200	200	200

Note: Highest dose is capped at 200 mg, the palbociclib monotherapy MTD in adults on the Schedule 2/1 (dosing for 14 days, followed by 7 days off treatment).
*The BSA should be rounded to nearest tenth m^2 for dose determination.
**Oral solution must be used when a patient's BSA-based dose is more than 15% below the 75-mg capsule strength.
*** Oral solution needed due to overlap in capsule strength.

5.4.3. Temozolomide

On the basis of the calculated BSA, 5-mg, 20-mg, 100-mg capsules of TMZ may be used to generate the treatment dose of 100 mg/m^2 orally Days 1 to 5 of each 21-day cycle (Appendix 12). Every effort should be made to administer a treatment dose as close to the target dose without exceeding, using a combination of capsules as necessary. Capsules will be administered in whole doses only (will not be split or divided). TMZ can be given at the same time as palbociclib and will be administered at least 1 hour prior to administering IRN due to the fact that preclinical data suggests schedule-dependent effects.[19] Patients who are unable to swallow the capsules should receive an IV formulation of TMZ, administered according to the product information. IRN infusion will then be given at least 1 hour after completion of TMZ infusion. Palbociclib should be administered at the start of TMZ infusion.

5.4.4. Irinotecan

IRN will be dosed at 50 mg/m^2 IV over 90 minutes (±10%) on Days 1 to 5 of each 21-day cycle. IRN will be administered at least 1 hour after administration of TMZ and palbociclib.

5.4.5. Topotecan

TOPO will be dosed at 0.75 mg/m^2 IV over 30 minutes (±10%) on Days 1 to 5 of each 21-day cycle. It is recommended to start TOPO infusion immediately after CTX infusion however sites may follow their local standard of care.

5.4.6. Cyclophosphamide

CTX will be dosed at 250 mg/m^2 IV over 30-60 minutes (±10%) on Days 1 to 5 of each 21-day cycle. Palbociclib should be administered at the start of CTX infusion

5.4.7. Criteria for Starting Subsequent Cycles

After Cycle 1, a cycle may be repeated every 21 days if the patient has at least stable disease and has met all laboratory test criteria to continue study medication administration per the dose modification requirements in Section 5.4.10.

5.4.8. Recommended Dose Modifications

Every effort should be made to administer palbociclib plus TMZ and IRN or palbociclib plus TOPO and CTX on the planned dose and schedule. In the Phase 2 portion, every effort should be made to administer TMZ and IRN with or without palbociclib at the planned dose and on schedule.

In the event of significant toxicity, dosing may be delayed and/or reduced as described below. In the event of multiple toxicities, dose modification should be based on the worst toxicity observed. Patients/caregivers are to be instructed to notify investigators at the first occurrence of any adverse symptom.

Depending on the nature of the toxicity observed, dose modifications may be required for palbociclib. If palbociclib is delayed, the chemotherapy backbone therapy may be continued as scheduled. Dose modifications are allowed for IRN-induced diarrhea and CTX induced hematuria.

Dose modifications may occur in one of 3 ways:

- Within a cycle: dosing interruption until adequate recovery and dose reduction, if required, during a given treatment cycle;
- Between cycles: next cycle administration may be delayed due to persisting toxicity when a new cycle is due to start;
- In the next cycle: dose reduction may be required in a subsequent cycle based on toxicity experienced in the previous cycle.

5.4.9. Dosing Interruptions

Patients experiencing a DLT as defined in Section 3.2 should have their treatment interrupted.

Appropriate follow-up assessments should be done until adequate recovery occurs as assessed by the investigator. Criteria required before treatment can resume are described in Section 5.4.10.

Doses may be held as needed until toxicity resolution. Depending on when the AE resolved, a treatment interruption may lead to the patient missing all subsequent planned doses within that same cycle or even to delay the initiation of the subsequent cycle.

If the AE that led to the treatment interruption recovers within the same cycle, then redosing in that cycle is allowed. Doses omitted for toxicity are not replaced within the same cycle. The need for a dose reduction for palbociclib at the time of treatment resumption should be based on the criteria defined in the Table 13, Table 14, and Section 5.4.11. In the event of a treatment interruption for reasons other than treatment-related toxicity (eg, elective surgery) lasting >4 weeks, treatment resumption will be decided in consultation with the sponsor.

5.4.10. Dose Delays

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

- ANC ≥1,000/mm^3;
- Platelets count ≥75,000/mm^3;
- Non-hematologic toxicities have returned to baseline or Grade ≤1 severity (or, at the investigator's discretion, Grade ≤2 if not considered a safety risk for the patient).

If a treatment delay results from worsening of hematologic or clinical chemistry parameters, the frequency of relevant blood tests should be increased as clinically indicated.

If these conditions are met within 2 weeks of treatment interruption or cycle delay, study treatment may be resumed. Refer to Section 5.4.11 for AEs requiring dose reduction at the time of treatment resumption.

If these conditions are not met, treatment resumption must be delayed up to a maximum of 2 weeks, unless the investigator's benefit/risk assessment suggests otherwise after discussion with the Sponsor's medical monitor. If patients require discontinuation of palbociclib for more than 14 days at any time during the study, then study treatment should be permanently discontinued, unless the investigator's benefit/risk assessment suggests otherwise after discussion with the Sponsor's medical monitor.

If a treatment interruption continues beyond Day 21 of the current cycle, then the day when treatment is restarted will be counted as Day 1 of the next cycle.

5.4.11. Dose Reductions

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

Step-wise dose reductions of IRN, TMZ or TOPO, CTX or palbociclib according to Table 13 and Table 14 will be allowed depending on the type and severity of toxicity encountered. Once a dose has been reduced for a given patient, all subsequent cycles should be

administered at that dose level, unless further dose reduction is required. Intra-patient dose re-escalation is not allowed. Patients can have up to 3 dose reductions. If the toxicity persists, they will be discontinued from the treatment and entered into the follow-up phase, unless otherwise agreed between the investigator and the sponsor. All dose modifications/adjustments must be clearly documented in the patient's source notes and CRF.

Unless agreed otherwise following documented discussion between the investigator and the sponsor, if a dose reduction is applied in the same cycle, the patient will need to return to the clinic to receive a new drug supply.

5.4.11.1. Dose Modifications for Hematological Toxicity Combination of IRN and TMZ With or Without Palbociclib

Patients who have dose-limiting hematological toxicity (see Section 3.2) may continue on protocol therapy upon meeting laboratory test dosing criteria as defined in Section 5.4.10.

No dose reduction is required for the first episode of dose limiting neutropenia (Grade 4 neutropenia of >7 days duration or delay in the start of the next cycle for >14 days due to neutropenia) with no other DLT. Patients who have dose-limiting neutropenia should receive the same doses of study medication in the next cycle with myeloid growth factor support 24 to 48 hours after completion of IRN and TMZ dosing. Reoccurrence of dose-limiting neutropenia requires dose reductions starting with TMZ. Reoccurrence of dose-limiting neutropenia despite TMZ dose reduction should result in palbociclib followed by IRN dose reduction (palbociclib with IRN and TMZ treatment arm) or IRN followed by second TMZ dose reduction (chemotherapy only treatment arm).

For dose-limiting thrombocytopenia (Grade 4 thrombocytopenia lasting >7 days or need for platelet transfusion for a platelet count of less than 20,000/mm^3 twice within a 7-day period or delay in the start of the next cycle for >14 days due to neutropenia), after counts recover, the next cycle should be started with a decrease in TMZ to 75% of the original dose (75 mg/m^2/dose) on Days 1 to 5. Recurrence of dose-limiting thrombocytopenia requires palbociclib dose reduction followed by reduction of IRN dose (palbociclib with IRN and TMZ treatment arm) or IRN dose reduction followed by second reduction of TMZ dose (IRN and TMZ alone treatment arm).

Maximum 3 dose reductions are allowed. If dose-limiting hematological toxicity recurs after use of myeloid growth factor and dose reductions of TMZ, IRN and palbociclib, the patient should be permanently discontinued from protocol therapy.

Recommended dose modifications for hematological toxicities of the IRN and TMZ with or without palbociclib combination are detailed in Table 13.

Patients who have a dose-limiting hematological toxicity that does not resolve to dosing criteria defined in Section 5.4.10 within 21 days after the planned start of the next treatment cycle must be permanently discontinued from protocol therapy.

5.4.11.2. Dose Modifications for Non-Hematological Toxicity Combination of IRN and TMZ With or Without Palbociclib

Combination of Palbociclib with IRN and TMZ

Patients who have any non-hematological toxicity that meets dose limiting-criteria may continue on protocol therapy upon meeting laboratory test dosing criteria as defined in Section 5.4.10 or baseline but subsequent doses of palbociclib should be decreased by 30% (rounded down to the nearest capsule strength) except as detailed in Table 13. If needed, patient can change to oral solution. IRN and TMZ should be continued at the same dose, except in the case of dose-limiting mucositis or diarrhea in which case the irinotecan dose should also be reduced to 75% of the original dose and palbociclib should be continued at the same dose.

If the same non-hematological DLT recurs after 1 dose reduction, the patient must be permanently discontinued from protocol therapy.

Combination of IRN and TMZ only

Patients who have any non-hematological toxicity that meets dose limiting-criteria may continue on protocol therapy upon meeting laboratory test dosing criteria as defined in Section 5.4.10 or baseline but TMZ dose must be reduced to 75% of the original dose (75 mg/m^2/dose), except dose-limiting toxicity that could be clearly attributed to IRN, eg, mucositis or diarrhea in which case the irinotecan dose should be reduced to 75% of the original dose while TMZ should be continued at the same dose as detailed in Table 13.

If the same non-hematological DLT recurs after 1 dose reduction, the patient must be permanently discontinued from protocol therapy.

Patients who have a dose-limiting non-hematological toxicity that does not resolve to baseline or meets laboratory test dosing criteria as defined in Section 5.4.10 within 21 days after the planned start of the next treatment cycle must be permanently discontinued from protocol therapy.

Table 13. Recommended Dose Modifications for Specific Adverse Events for Combination of IRN and TMZ With or Without Palbociclib

Toxicity (Grading as in NCI CTCAE version 4.03)	Proposed Action for:		
	Palbociclib	TMZ	IRN
Hematologic			
Dose-limiting neutropenia (Grade 4 neutropenia of >7 days duration or delay in the start of the next cycle for >14 days due to neutropenia)	Withhold all study medication, delay start of the next cycle until absolute neutrophil count recovers and repeat complete blood count monitoring at least weekly. Patients should receive the same doses of study medication in the next cycle with myeloid growth factor support 24-48 hours after completion of IRN and TMZ. In Phase 1 growth factor should not be given during the Cycle 1 DLT evaluation period except in the case of documented bacterial or fungal infection. The sponsor should be notified if this occurs as it will be considered a DLT.		

Table 13. Recommended Dose Modifications for Specific Adverse Events for Combination of IRN and TMZ With or Without Palbociclib

Toxicity (Grading as in NCI CTCAE version 4.03)	Proposed Action for:		
	Palbociclib	TMZ	IRN
	If dose-limiting neutropenia recurs after myeloid growth factor is added, the next cycle should be started with a decrease in TMZ dose to 75% of the original dose (75 mg/m^2/dose) on Days 1 to 5. IRN/TMZ+palbociclib treatment arm If hematologic dose-limiting toxicity occurs at 75% of the original dose of TMZ, then palbociclib dose should be decreased by 30% (rounded down to the nearest capsule strength). If needed, patient can change to oral solution. If dose-limiting neutropenia occurs after reducing TMZ and palbociclib have been reduced, reduce IRN to 75% (37.5 mg/m^2/dose) of the original dose on Days 1 to 5. IRN/TMZ treatment arm If hematologic dose-limiting toxicity occurs at 75% of the original dose of TMZ, then IRN dose should be reduced to 75% (37.5 mg/m^2/dose) of the original dose on Days 1 to 5. If dose-limiting neutropenia occurs after reducing TMZ and IRN, then further reduce TMZ to 50% of the original dose (50 mg/m^2/dose) on Days 1 to 5. If dose-limiting neutropenia recurs after use of growth factor and dose reductions of TMZ, IRN and palbociclib, the patient should be permanently discontinued from protocol therapy.		
Dose-limiting thrombocytopenia (Grade 4 thrombocytopenia lasting >7 days or need for platelet transfusion for a platelet count of less than 20,000/mm^3 twice within a 7-day period or delay in the start of the next cycle for >14 days due to neutropenia)	Withhold all study medication, delay start of the next cycle until platelet counts recover and repeat complete blood count monitoring at least weekly. The temozolomide dose should be decreased to 75% of the original dose (75 mg/m^2/dose) on Days 1 to 5. IRN/TMZ+palbociclib treatment arm If hematologic dose-limiting toxicity occurs at 75% of the original dose of TMZ, then palbociclib dose should be decreased by 30% (rounded down to the nearest capsule strength). If needed, patient can change to oral solution.The IRN should be given at full dose. If dose-limiting thrombocytopenia occurs after reducing TMZ and palbociclib have been reduced, reduce IRN to 75% (37.5 mg/m^2/dose) of the original dose on Days 1 to 5. IRN/TMZ treatment arm If hematologic dose-limiting toxicity occurs at 75% of the original dose of TMZ, then IRN dose should be reduced to 75% (37.5 mg/m^2/dose) of the original dose on Days 1 to 5. If dose-limiting neutropenia occurs after reducing TMZ and IRN, then further reduce TMZ to 50% of the original dose (50 mg/m^2/dose) on Days 1 to 5.		

Table 13. Recommended Dose Modifications for Specific Adverse Events for Combination of IRN and TMZ With or Without Palbociclib

Toxicity (Grading as in NCI CTCAE version 4.03)	Proposed Action for:		
	Palbociclib	TMZ	IRN
	If dose-limiting thrombocytopenia recurs after dose reductions of TMZ, IRN and palbociclib, then the patient should be permanently discontinued from protocol therapy.		
Any type of Grade 3 hematologic toxicity >7 days except lymphopenia (unless associated with clinical events, eg, opportunistic infections) and except Grade 3 anemia.	Day 1 of cycle: Withhold all study medication, repeat complete blood count monitoring within 1 week. When recovered to Grade ≤2, start the next cycle at the same dose. Day 15 of cycle: Repeat complete blood count on Day 1 of next cycle. In IRN/TMZ+palbociclib treatment arm first consider dose reduction for palbociclib by 30% (rounded down to the nearest capsule strength) in cases of prolonged (>1 week) recovery from Grade 3 neutropenia and/or thrombocytopenia or recurrent Grade 3 neutropenia and/or thrombocytopenia in subsequent cycles. If needed, patient can change to oral solution. If after dose reduction of palbociclib, patient has recurrent myelosuppression, reduce TMZ to 75% of the original dose and then to 50% of the original dose for continued prolonged myelosuppression. In TMZ/IRN treatment arm, start with TMZ dose reduction to 75% of the original dose, followed by IRN dose reduction to 75% of the original dose, then further reduction of TMZ to 50% of the original dose.		
Grade ≥3 Neutropenia with a single temperature ≥38.3ºC or sustained temperature of ≥38ºC for more >1 hour.	Withhold all study medication, delay start of the next cycle until absolute neutrophil count recovers and repeat complete blood count monitoring at least weekly. Patients should receive the same doses of study medication in the next cycle with myeloid growth factor support 24-48 hours after completion of IRN and TMZ. In phase 1 growth factor should not be given during the Cycle 1 DLT evaluation period except in the case of documented bacterial or fungal infection. Please notify the sponsor if this occurs as it will be considered a DLT. If Grade 4 febrile neutropenia and/or dose-limiting neutropenia occurs after myeloid growth factor is added, the next cycle should be started with a decrease in TMZ dose to 75% of the original dose (75 mg/m^2/dose) on Days 1 to 5. If Grade 4 febrile neutropenia and/or hematologic DLT occurs at 75% of the original dose of TMZ, in the IRN/TMZ + palbociclib treatment arm, then palbociclib dose should be decreased by 30% (rounded down to the nearest capsule strength). If needed, patient can change to oral solution. Patients on IRN/TMZ treatment arm should have further reduction of TMZ dose to 50% of the original dose. If Grade 4 febrile neutropenia and/or dose-limiting neutropenia recurs after use of growth factor and dose reductions of TMZ and/or palbociclib, the patient should be permanently discontinued from protocol therapy.		

Table 13. Recommended Dose Modifications for Specific Adverse Events for Combination of IRN and TMZ With or Without Palbociclib

Toxicity (Grading as in NCI CTCAE version 4.03)	Proposed Action for:		
	Palbociclib	TMZ	IRN
Grade 4 hematologic toxicity >7 days except lymphopenia (unless associated with clinical events, eg, opportunistic infections) and Grade 4 anemia.	Withhold all study medication until recovery to Grade ≤2. IRN/TMZ+palbociclib treatment arm: Resume palbociclib at a 30% reduction (rounded down to the nearest capsule strength). If needed, patient can change to oral solution. If after dose reduction of palbociclib, patient has recurrent myelosuppression, reduce TMZ to 75% of the original dose and then to 50% of the original dose for continued prolonged myelosuppression on subsequent cycles. IRN/TMZ treatment arm: Resume TMZ at 75% of the original dose and full dose of IRN. If after TMZ dose reduction, patient has recurrent myelosuppression, reduce TMZ to 50% of the original dose for continued prolonged myelosuppression on subsequent cycles.		
Grade 3 or 4 anemia.	Transfuse, do not dose modify.		
Cardiovascular			
QTc prolongation.	Monitor patient carefully; refer to Section 7.1.6if Grade ≥3.		
Gastrointestinal			
Diarrhea any grade	Onset <24 hours from IRN: Consider 0.25-1 mg atropine IV or S.C. Onset >24 hours from IRN: Monitor and replace fluid and electrolytes as needed. Treat with loperamide. Use antibiotic support as needed for ileus and fever. See Appendix 4.		
Grade ≥3 mucositis or diarrhea, lasting for over 3 days despite maximum supportive care measures with prophylactic antibiotics and anti-diarrheals.	Withhold IRN, TMZ, and palbociclib until symptoms resolve to Grade ≤1. IRN should be reduced to 75% of the original dose. Palbociclib and TMZ should be continued at the same dose.		
Mucositis or Diarrhea, Grade 4.	Permanently discontinue all study medication if symptoms uncontrollable by supportive care.		
Nausea or Vomiting, Grade 3 lasting for over 2 days, despite optimal supportive care.	Withhold until symptoms resolve to Grade ≤1 or to Grade ≤2 (if not considered a safety risk); In IRN/TMZ+palbociclib treatment arm, resume palbociclib at a 30% dose reduction (rounded down to the nearest capsule strength). If needed, patient can change to oral solution. Continue TMZ and IRN at same dose level. In IRN/TMZ treatment arm, resume TMZ at 75% of the original dose. Continue IRN at same dose level.		
Nausea or Vomiting, Grade 4, despite optimal supportive care.	Permanently discontinue all study medication if symptoms uncontrollable by supportive care.		

Table 13. Recommended Dose Modifications for Specific Adverse Events for Combination of IRN and TMZ With or Without Palbociclib

Toxicity (Grading as in NCI CTCAE version 4.03)	Proposed Action for:		
	Palbociclib	TMZ	IRN
Hepatic			
AST and/or ALT >10 × ULN	Withhold all study medication until recovery to baseline or ≤ Grade 1, then resume palbociclib at a 30% dose reduction (rounded down to the nearest capsule strength). If needed, patient can change to oral solution. Continue TMZ and IRN at same dose level or permanently discontinue all study medication as per investigator judgment. In IRN/TMZ treatment arm, consider dose reduction of TMZ at 75% of the original dose. Continue IRN at same dose level or permanently discontinue all study medication as per investigator judgment.		
Potential DILI laboratory abnormalities (as defined in Section 8.4.1).	Withhold all study medication until recovery to baseline or ≤Grade 1, and contact study medical monitor for further guidance. Confirmed DILI cases should result in permanent treatment discontinuation.		
Infection			
Sepsis (with or without neutropenia).	Withhold all study medication until resolution and ANC ≥1000/mm^3; resume palbociclib at a 30% dose reduction with TMZ and IRN at same dose level (palbociclib + IRN/ TMZ treatment arm) OR resume with TMZ at 75% of the original dose with IRN at the same dose level (IRN/TMZ treatment arm).		
Lung			
Pneumonitis/ILD.	Permanently discontinue all study medication if ≥Grade 2.		
Nervous System			
Treatment emergent peripheral neuropathy Grade 3 or 4.	Withhold until improves to ≤Grade 1; resume palbociclib, TMZ and IRN at the same dose. If there is a second recurrence, permanently discontinue all study medication.		
Immune System			
Hypersensitivity reactions Grade 3 or 4.	Permanently discontinue all study medication for Grade 4; premedication is permitted for Grade 3 per institutional guidelines.		
Other			
Any other Grade ≥3 non-hematologic toxicity.	Palbociclib +IRN/TMZ treatment arm: withhold palbociclib and/or TMZ/IRN treatment until Grade 1 or Grade 2 (if not considered a safety risk), then resume palbociclib at a 30% dose reduction (rounded down to the nearest capsule strength). If needed, patient can change to oral solution. Continue TMZ and IRN at same dose level or permanently discontinue all study medication as per investigator judgment. If toxicity clearly attributable to IRN or TMZ, dose reduce the responsible agent first (eg, 75% of IRN or TMZ). IRN/TMZ treatment arm: withhold TMZ/IRN treatment until Grade 1 or Grade 2 (if not considered a safety risk), then resume TMZ at 75% of original dose. Continue IRN at same dose level or permanently discontinue all study medication as per investigator judgment. If toxicity clearly attributable to IRN or TMZ, dose reduce the responsible agent first (eg, 75% of IRN or TMZ).		

Table 13. Recommended Dose Modifications for Specific Adverse Events for Combination of IRN and TMZ With or Without Palbociclib

Toxicity (Grading as in NCI CTCAE version 4.03)	Proposed Action for:		
	Palbociclib	TMZ	IRN

Abbreviations: ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; IRN = irinotecan; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; TMZ = temozolomide; ULN = upper limit of normal.

Patients experiencing a DLT may resume dosing at the reduced dose levels defined above (if applicable) once adequate recovery is achieved. Patients experiencing recurrent and intolerable Grade 2 toxicity may resume dosing at the reduced dose levels defined above (if applicable) once recovery to Grade≤1 or baseline is achieved.

5.4.11.3. Dose Modifications for Hematological Toxicity Combination of Palbociclib With TOPO and CTX

Patients who have dose-limiting hematological toxicity may continue on protocol therapy upon meeting laboratory test dosing criteria as defined in Section 5.4.10.

For dose-limiting thrombocytopenia (Grade 4 thrombocytopenia lasting >7 days or need for platelet transfusion for a platelet count of less than 20,000/mm^3 twice within a 7-day period or delay in the start of the next cycle for >14 days due to neutropenia), and/or dose-limiting neutropenia despite the use of G-CSF (Grade 4 neutropenia of >7 days duration or delay in the start of the next cycle for >14 days due to neutropenia), after counts recover, the next cycle should be started with a decrease in the TOPO dose to 75% of the original dose (0.56 mg/m^2/dose) on Days 1 to 5. Recurrence of dose-limiting thrombocytopenia and/or neutropenia requires palbociclib dose reduction followed by further reduction of TOPO dose.

Maximum 3 dose reductions are allowed. If dose-limiting hematological toxicity recurs despite use of G-CSF and 2 dose reductions of TOPO and palbociclib dose reduction, the patient should be permanently discontinued from protocol therapy.

Recommended dose modifications for hematological toxicities of palbociclib with TOPO and CTX are detailed in Table 14.

Patients who have a dose-limiting hematological toxicity that does not resolve to dosing criteria defined in Section 5.4.10 within 21 days after the planned start of the next treatment cycle must be permanently discontinued from protocol therapy.

5.4.11.4. Dose Modifications for Non-Hematological Toxicity Combination of Palbociclib With TOPO and CTX

Patients who have any dose-limiting non-hematological toxicity may continue on protocol therapy upon meeting laboratory test dosing criteria as defined in Section 5.4.10 or baseline but subsequent doses of palbociclib should be decreased by 30% (rounded down to the nearest capsule strength) except as detailed in Table 14.

If needed, patient can change to palbociclib oral solution. TOPO and CTX should be continued at the same dose, except in the case of dose limiting mucositis or hematuria in which case the CTX dose should also be reduced by 25% of the original dose and palbociclib continued at the same dose.

If the same non-hematological DLT recurs after 1 dose reduction, the patient must be permanently discontinued from protocol therapy.

Patients who have a dose-limiting non-hematological toxicity that does not resolve to baseline or meets laboratory test dosing criteria as defined in Section 5.4.10 within 21 days after the planned start of the next treatment cycle must be permanently discontinued from protocol therapy.

Table 14. Recommended Dose Modifications for Specific Adverse Events for Palbociclib in Combination With TOPO and CTX

Toxicity (Grading as in NCI CTCAE version 4.03)	Proposed Action for:		
	Palbociclib	TOPO	CTX
Hematologic			
Dose-limiting neutropenia (Grade 4 neutropenia of >7 days duration or delay in the start of the next cycle for >14 days due to neutropenia),	Withhold all study medication, delay start of the next cycle until ANC recovers and repeat complete blood count monitoring at least weekly. If dose-limiting neutropenia occurs despite the use of G-CSF, the next cycle should be started with a decrease in TOPO dose to 75% of the original dose (0.56 mg/m^2/dose) on Days 1 to 5. If hematologic dose-limiting toxicity occurs at 75% of the original dose of TOPO, then palbociclib dose should be decreased by 30% (rounded down to the nearest capsule strength). If needed, patient can change to oral solution. If dose-limiting neutropenia occurs after TOPO and palbociclib have been reduced, further reduce TOPO by 20% (0.45 mg/m^2/dose) of the original dose on Days 1 to 5. If dose-limiting neutropenia recurs despite use of G-CSF and dose reductions of TOPO and palbociclib the patient should be permanently discontinued from protocol therapy.		
Dose-limiting thrombocytopenia (Grade 4 thrombocytopenia lasting >7 days or need for platelet transfusion for a platelet count of less than 20,000/mm^3 twice within a 7-day period or delay in the start of the next cycle for >14 days due to neutropenia),	Withhold all study medication, delay start of the next cycle until platelet counts recover and repeat complete blood count monitoring at least weekly. The TOPO dose should be decreased to 75% of the original dose (0.56 mg/m^2/dose) on Days 1 to 5. Patients should continue to receive the full doses of palbociclib and CTX. If hematologic dose-limiting toxicity occurs at 75% of the original dose of TOPO, then palbociclib dose should be decreased by 30% (rounded down to the nearest capsule strength). If needed, patient can change to oral solution. The CTX should be given at full dose. If dose-limiting thrombocytopenia occurs after TOPO and palbociclib have been reduced, further reduce TOPO by 20% (0.45 mg/m^2/dose) of the original dose on Days 1 to 5.		

Table 14. Recommended Dose Modifications for Specific Adverse Events for Palbociclib in Combination With TOPO and CTX

Toxicity (Grading as in NCI CTCAE version 4.03)	Proposed Action for:		
	Palbociclib	TOPO	CTX
	If dose-limiting thrombocytopenia recurs after dose reductions of TOPO and palbociclib, then the patient should be permanently discontinued from protocol therapy.		
Any type of Grade 3 hematologic toxicity >7 days except lymphopenia (unless associated with clinical events, eg, opportunistic infections) and except Grade 3 anemia.	Day 1 of cycle: Withhold all study medication, repeat complete blood count monitoring within 1 week. When recovered to Grade ≤2, start the next cycle at the same dose. Day 15 of cycle: Repeat complete blood count on Day 1 of next cycle. First consider dose reduction for palbociclib by 30% (rounded down to the nearest capsule strength) in cases of prolonged (>1 week) recovery from Grade 3 neutropenia and/or thrombocytopenia or recurrent Grade 3 neutropenia and/or thrombocytopenia in subsequent cycles. If needed, patient can change to oral solution. If after dose reduction of palbociclib, patient has recurrent myelosuppression, reduce dose of TOPO by 25% and then to 50% for continued prolonged myelosuppression.		
Grade ≥3 neutropenia with a single temperature ≥38.3ºC or sustained temperature of ≥38ºC for more than 1 hour	Withhold all study medication, delay start of the next cycle until absolute neutrophil count recovers and repeat complete blood count monitoring at least weekly. If Grade 4 febrile neutropenia and/or dose-limiting neutropenia occurs, the next cycle should be started with a decrease in TOPO dose to 75% of the original dose (0.56 mg/m^2/dose) on Days 1 to 5. If Grade 4 febrile neutropenia and/or hematologic DLT occurs at 75% of the original dose of TOPO, then palbociclib dose should be decreased by 30% (rounded down to the nearest capsule strength). If needed, patient can change to oral solution. If Grade 4 febrile and/or dose-limiting neutropenia occurs after TOPO and palbociclib have been reduced, further reduce TOPO by 20% (0.45 mg/m^2/dose) of the original dose on Days 1 to 5. If Grade 4 febrile and/or dose-limiting neutropenia recurs again, despite G-CSF use and dose reductions of TOPO and palbociclib the patient should be permanently discontinued from protocol therapy.		
Grade 4 hematologic toxicity >7 days except lymphopenia (unless associated with clinical events, eg, opportunistic infections) and Grade 4 anemia	Withhold all study medication until recovery to Grade ≤2. Resume palbociclib at a 30% reduction (rounded down to the nearest capsule strength). If needed, patient can change to oral solution. If after dose reduction of palbociclib, patient has recurrent myelosuppression, dose reduce TOPO by 20% and then to 50% for continued prolonged myelosuppression on subsequent cycles.		
Grades 3 or 4 anemia	Transfuse, do not dose modify.		
Cardiovascular			
QTc prolongation.	Monitor patient carefully; refer to Section 7.1.6 if Grade ≥3.		

Table 14. Recommended Dose Modifications for Specific Adverse Events for Palbociclib in Combination With TOPO and CTX

Toxicity (Grading as in NCI CTCAE version 4.03)	Proposed Action for:		
	Palbociclib	TOPO	CTX
Gastrointestinal			
Grade 3 mucositis, lasting for over 3 days despite maximum supportive care measures	Withhold TOPO, CTX, and palbociclib until symptoms resolve to Grade ≤1. CTX should be reduced to 75% of the original dose. Palbociclib and TOPO should be continued at the same dose.		
Mucositis, Grade 4	Permanently discontinue all study medication if symptoms uncontrollable by supportive care.		
Nausea or Vomiting, Grade 3 lasting for over 2 days, despite optimal supportive care	Withhold until symptoms resolve to Grade ≤1 or to Grade ≤2 (if not considered a safety risk); resume palbociclib at a 30% dose reduction (rounded down to the nearest capsule strength). If needed, patient can change to oral solution. Continue TOPO and CTX at same dose level.		
Nausea or Vomiting, Grade 4, despite optimal supportive care	Permanently discontinue all study medication if symptoms uncontrollable by supportive care.		
Renal			
Hematuria any grade Hemorrhagic cystitis	Treatment is at the discretion of the investigator. The following suggestions may be followed or adapted as appropriate. Microscopic hematuria during CTX infusion: Commence an infusion of the locally preferred fluid at a rate of at least 83 ml/m^2/hour (2L/m^2/24 hours). If this initial infusion rate establishes clinical evidence of hydration, the rate of infusion may be increased up to double the initial rate and adjusted as clinically indicated. If MESNA is not currently being administered, consider whether it is necessary to do so. If MESNA is required treatment may be given as IV boluses or added to the infusion fluid at a dose equivalent to 100 mg/m^2 every 8 hours (120% of CTX dose in 24 hours). If MESNA is currently being given, consider the need to increase the dose and/or frequency of administration. ≥Grade 2 hematuria: Discontinue CTX infusion. The advice provided for Grade 1 hematuria above may be followed or adapted as clinically appropriate. Ensure that hydration and MESNA are prescribed for subsequent treatment cycles.		

Table 14. Recommended Dose Modifications for Specific Adverse Events for Palbociclib in Combination With TOPO and CTX

Toxicity (Grading as in NCI CTCAE version 4.03)	Proposed Action for:		
	Palbociclib	TOPO	CTX
Hepatic			
AST and/or ALT >10 × ULN	Withhold all study medication until recovery to baseline or ≤Grade 1, then resume palbociclib at a 30% dose reduction (rounded down to the nearest capsule strength). If needed, patient can change to oral solution. Continue TOPO and CTX at same dose level or permanently discontinue all study medication as per investigator judgment.		
Potential DILI laboratory abnormalities (as defined in Section 8.4.1).	Withhold all study medication until recovery to baseline or ≤Grade 1, and contact study medical monitor for further guidance. Confirmed DILI cases should result in permanent treatment discontinuation.		
Infection			
Sepsis (with or without neutropenia)	Withhold all study medication until resolution and ANC ≥1000/mm^3; resume palbociclib at a 30% dose reduction with TOPO and CTX at same dose level.		
Lung			
Pneumonitis/ILD	Permanently discontinue all study medication if ≥Grade 2.		
Nervous system			
Treatment emergent peripheral neuropathy Grade 3 or 4	Withhold until improves to ≤Grade 1; resume palbociclib, TOPO and CTX at the same dose. If there is a second recurrence, permanently discontinue all study medication.		
Immune system			
Hypersensitivity reactions Grade 3 or 4	Permanently discontinue all study medication for Grade 4; premedication is permitted for Grade 3 per institutional guidelines.		
Other			
Any other Grade ≥3 non-hematologic toxicity	Withhold palbociclib and/or TOPO and CTX treatment until Grade 1 or Grade 2 (if not considered a safety risk), then resume palbociclib at a 30% dose reduction (rounded down to the nearest capsule strength). If needed, patient can change to oral solution. Continue TOPO and CTX at same dose level or permanently discontinue all study medication as per investigator judgment. If toxicity clearly attributable to TOPO or CTX, dose reduce the responsible agent first (eg, 75% of TOPO or CTX).		

Patients experiencing a DLT may resume dosing at the reduced dose levels defined above (if applicable) once adequate recovery is achieved. Patients experiencing recurrent and intolerable Grade 2 toxicity may resume dosing at the reduced dose levels defined above (if applicable) once recovery to Grade ≤1 or baseline is achieved.

5.5. Investigational Product Storage

The investigator, or an approved representative, eg, pharmacist, will ensure that the investigational products palbociclib, TMZ, IRN, TOPO and CTX are stored in a secured area with controlled access under required storage conditions and in accordance with applicable regulatory requirements.

Palbociclib capsules should be stored in their original containers and in accordance with the label.

Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the product label.

Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations (as applicable, including frozen, refrigerated, and/or room temperature products). This should be captured from the time of investigational product receipt throughout the study. Even for continuous monitoring systems, a log or site procedure that ensures active evaluation for excursions should be available. The intent is to ensure that the minimum and maximum temperature is checked each business day to confirm that no excursion occurred since the last evaluation and to provide the site with the capability to store or view the minimum/maximum temperature for all nonworking days upon return to normal operations. The operation of the temperature monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure they are maintained in working order.

Any excursions from the product label storage conditions should be reported to Pfizer upon discovery. The site should actively pursue options for returning the product to the storage conditions described in the labeling, as soon as possible. Deviations from the storage requirements, including any actions taken, must be documented and reported to Pfizer.

Once an excursion is identified, the investigational product must be quarantined and not used until the Pfizer provides permission to use the investigational product. It will not be considered a protocol deviation if Pfizer approves the use of the investigational product after the temperature excursion. Use of the investigational product prior to Pfizer approval will be considered a protocol deviation.

Specific details regarding information the site should report for each excursion will be provided to the site.

Receipt of materials, door opening and closing, and other routine handling operations where the products are briefly out of the temperature range described in the labeling are not considered excursions.

Site staff will instruct patients on the proper storage requirements when the investigational product is taken home.

Please refer to IP manual for additional guidance on storage conditions and actions to be taken when conditions are outside specified range.

5.6. Investigational Product Accountability

The investigator site must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product. Palbociclib, TMZ, IRN, TOPO, and CTX will be accounted for using a drug accountability form/record.

All bottles of palbociclib (capsules or oral solution) must be returned to the investigator/site by the patient/guardian, with the diaries, prior to the start of a new cycle and at the end of the trial.

5.6.1. Destruction of Investigational Product Supplies

The sponsor or designee will provide guidance on the destruction of unused investigational product (eg, at the site). If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer, and all destruction must be adequately documented.

For all oral medication (bottles) returned to the investigator by the patient, the investigator will maintain the returned supply until destruction is authorized. Pfizer will provide instructions as to the disposition of any unused investigational product.

5.7. Concomitant Treatment(s)

Patients must be instructed not to take any additional medications (over-the-counter or other products) during the study without prior consultation with the investigator, or treating physician. Any medications including herbal supplements, vitamins, or treatment taken by the patient from 21 days prior the first dose of study medication (Phase 1 portion and tumor-specific cohorts) or the date of randomization (Phase 2 portion) and up to EoT visit following the last dose of investigational product and the reason for their administration must be recorded on the CRF, which includes antibiotics prior to IRN administration. If a patient begins a new therapy before the 28-day time period is complete, concomitant medication information will not be recorded (from the start of the new therapy).

Routine postoperative care, such as dressing changes, suture removal, drain removal, or venous access (central or peripheral), does not need to be recorded. Anesthetics used for any surgical procedures performed during the patient’s participation in the study can be recorded as “unspecified anesthesia” on the concomitant treatment records; it is not necessary to list the specific anesthetics. Palliative and supportive care for cancer-related symptoms will be provided to all patients in this study.

5.7.1. Prohibited Medications

The following treatments are prohibited throughout the duration of the active treatment phase:

- **Anticancer agents:** No additional investigational or commercial anticancer agents such as chemotherapy, targeted therapy, or biological response modifiers, will be permitted during the active treatment phase.

- **Strong/Moderate CYP3A inhibitors/inducers:** Palbociclib is metabolized to multiple metabolites in a qualitatively similar manner in rat, dog and human liver microsomes. In vitro, palbociclib is primarily metabolized by CYP3A4 enzymes. Coadministration with drugs that are strong CYP3A inhibitors or inducers in vivo has been shown to change the plasma concentrations of palbociclib in humans. Data from a drug-drug interaction (DDI) study in healthy subjects indicate that coadministration of multiple 200 mg doses of the strong CYP3A inhibitor itraconazole with a single 125 mg palbociclib dose increased palbociclib total exposure (AUC_{inf}) and the peak exposure (C_{max}) by approximately 87% and 34%, respectively, relative to a single 125 mg palbociclib dose given alone. Data from a DDI study in healthy subjects indicate that coadministration of multiple 600 mg doses of the strong CYP3A inducer rifampin with a single 125 mg palbociclib dose decreased palbociclib AUC_{inf} and C_{max} by 85% and 70%, respectively, relative to a single 125 mg palbociclib dose given alone.

- IRN and its active metabolite, SN-38, are metabolized via CYP3A4 and UGT1A1, respectively. Patients receiving concomitant ketoconazole, a CYP3A4 and UGT1A1 inhibitor, have increased exposure to IRN and its active metabolite SN-38. Exposure to IRN or its active metabolite SN-38 is substantially reduced in adult and pediatric patients concomitantly receiving the CYP3A4 enzyme-inducing anticonvulsants phenytoin, phenobarbital, carbamazepine, or St. John's wort.

- The concurrent use of the compounds listed below is not allowed in the study:

    - Strong/Moderate CYP3A inhibitors, including but not limited to amprenavir, atazanavir, boceprevir, ciprofloxacin, norfloxacin, clarithromycin, conivaptan, delavirdine, diltiazem, erythromycin, fosamprenavir, indinavir, itraconazole, ketoconazole, lopinavir, mibefradil, miconazole, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, suboxone, telaprevir, telithromycin, verapamil, voriconazole, and grapefruit, grapefruit juice or any product containing grapefruit.

    - Strong/Moderate CYP3A inducers, including but not limited to carbamazepine, felbamate, nevirapine, phenobarbital, phenytoin, primidone, rifampin, rifabutin, rifapentin, and St. John's wort.

    - Strong UGT1A1 inhibitors (only for patients receiving palbociclib in combination with IRN and TMZ or IRN and TMZ alone), including but not limited to

atazanavir, erlotinib, gemfibrozil, indinavir, ketoconazole, lopinavir-ritonavir, nilotinib, and zafirlukast.

- **Drugs known to cause QT interval prolongation** with a known associated risk of Torsades de Pointes are prohibited during the active treatment phase, except when administered for CINV prophylaxis or treatment within the defined limitations described in Section 5.7.5. Refer to Appendix 11 for a list of drugs known to predispose to Torsade de Pointes.

- **Live vaccines** are prohibited at least 30 days before the start of the study treatment, during the study treatment, and for at least 90 days after the last dose of the study medications.

5.7.2. Medications Not Recommended

The following treatments are not recommended throughout the duration of the active treatment phase. Alternative therapies should be considered whenever possible. If usage of the following treatments is deemed necessary, consultation and agreement with the sponsor is required prior to treatment initiation.

- **Chronic immunosuppressive therapies** should be avoided, including systemic corticosteroids. The concurrent use of systemic steroids is not recommended unless the patient is on a stable dose or decreasing dose for >14 days prior to starting therapy or if steroids are administered for CINV prophylaxis or treatment within the defined limitations described in Section 5.7.5. Topical steroids are permitted. Short course of oral steroids are allowed. Patients may continue on inhaled/topical steroids as indicated.

- The use of **herbal medicine** is not recommended during the active treatment phase.

5.7.3. Supportive Care

Palliative and supportive care for disease related symptoms may be administered at the investigator's discretion.

5.7.4. Hematopoietic Growth Factors

G-CSF may be used at investigator's discretion for the IRN and TMZ combination according to the institutional guidance for treatment of neutropenia. In the Phase 1 portion of the study, G-CSF should not be given during the Cycle 1 DLT evaluation period except in the case of documented bacterial or fungal infection. Please notify the sponsor if this occurs as it will be considered a DLT.

For the TOPO and CTX combination, subcutaneous G-CSF (5 µg/kg/dose daily) is mandatory starting Cycle 1. It should be initiated 24 to 48 hours after the administrations of TOPO and CTX are completed and should be continued until the expected neutrophil nadir is passed and the neutrophil counts has recovered to minimum of ANC ≥1000/mm^3. It should be discontinued 24 hours prior to the start of the next treatment cycle. At the discretion of the

investigator the daily G-CSF (filgrastim) can be substituted by PEG-filgrastim in a standard weight-based dosing for pediatric patients. PEG-filgrastim should be initiated 24 to 48 hours after the administrations of TOPO and CTX are completed and must be stopped 14 days prior to the next treatment cycle. Failure to administer G-CSF support will be considered a potentially important protocol deviation.

5.7.5. Anti-Diarrheal, Anti-Emetic Therapy

Each proposed treatment combination for this study contains at least 1 agent classified in ASCO's guidelines for antiemetic treatment to carry moderate emetic risk in pediatric patients.[54] Primary prophylaxis of nausea and vomiting is recommended in the first cycle. Continuation of primary prophylaxis in subsequent cycles is at the investigator's discretion.

Primary prophylaxis of nausea and vomiting for patients receiving palbociclib should be administered on Days 1 to 5 of a cycle and should consist of a 5-HT3 antagonist of either ondansetron or palonosetron with or without dexamethasone. Dexamethasone can be administered at doses up to 8-mg QD for primary CINV prophylaxis. Ondansetron should be administered orally prior to administration of chemotherapy at doses up to 8-mg for patients 12 years of age or greater and at doses up to 4 mg for patients 11 years of age or younger. A second dose may be given approximately 8 hours after the first. For patients who are acutely nauseous, ondansetron may be administered by IV infusion provided that the infusion be administered over a minimum of 15 minutes (ie, IV bolus dosing is prohibited due to increased risk for QTc prolongation) and at maximum doses that are half of the aforementioned maximum oral doses. Palonosetron should be administered prior to chemotherapy by IV infusion over a minimum of 15 minutes and at a maximum dose of 20 μg/kg (capped at 1.5 mg). Administration of other 5-HT3 antagonist than ondansetron or palonosetron (as described above) requires consultation with the study sponsor. Aprepitant and fosaprepitant are not allowed for primary CINV prophylaxis but may be administered for secondary prophylaxis or treatment beginning in Cycle 3.

Patients receiving palbociclib in combination with IRN and TMZ or IRN and TMZ alone

To prevent IRN-induced diarrhea, cefixime or an available equivalent antibiotic will be used as diarrheal prophylaxis during all cycles. Cefixime (8 mg/kg/day as a single daily dose; maximum daily dose 400 mg) or cefpodoxime (10 mg/kg/day, divided in 2 oral doses; maximum daily dose is 400 mg for patients <12 years and maximum daily dose is 800 mg for patients ≥12 years) beginning 1–2 days prior to the start of IRN therapy and continuing until Day 7 of each cycle is mandatory. Ciprofloxacin and norfloxacin are not permitted as antibiotic prophylaxis for IRN-induced diarrhoea and other quinolones should be used with caution due to their class potential for QT prolongation. Patients and guardians are to be educated regarding the potential for IRN-associated diarrhea and advised to maintain hydration and start loperamide if symptoms developed (see Appendix 4).

Per the UK requirement, the anti-diarrheal treatments and anti-emetic treatments should follow institutional guidance and final doses used should be as approved in the local SmPC based on patient's age, weight or BSA.

5.7.6. Pneumocystis Prophylaxis

Prophylaxis for pneumocystis can be prescribed as per institutional guidelines.

5.7.7. Interstitial Lung Disease Management

Suspected cases of pneumonitis/ILD will be identified with radiographic imaging, and if appropriate, participants will receive corticosteroids, supportive care, and antibiotics as applicable.

All study medications should be permanently discontinued in case of ≥Grade 2 pneumonitis/ILD as outlined in in Table 13 and Table 14.

5.7.8. Anti-Inflammatory Therapy

Anti-inflammatory or narcotic analgesic may be offered as needed if there is no known or expected DDI.

5.7.9. Corticosteroids

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

5.7.10. Surgery or Palliative Radiation

Concurrent radiotherapy or surgery for local control is at the discretion of the treating physician. However, local control measures for target lesions must be delayed until after the disease response assessment following Cycle 4. If after Cycle 4, the disease response assessment shows a response better than after Cycle 2 (eg, response after Cycle 2 is SD and response after Cycle 4 is PR), then it is required that the patient have a repeat disease response assessment ≥28 days later to determine best response prior to local control.

Palliative radiotherapy to specific sites of disease can be permitted during the active treatment phase if considered medically necessary by the treating physician. All attempts are to be made to rule out PD in the event of increased localized pain. If surgery or palliative radiation is going to be used, please contact the study team prior to planned treatment.

Caution is advised on theoretical grounds for any surgical procedures during the study. The appropriate interval of time between surgery and palbociclib required to minimize the risk of impaired wound healing and bleeding has not been determined. Based on the available pharmacokinetic data, stopping palbociclib is recommended at least 7 days prior to elective

surgery. Postoperatively, the decision to reinitiate palbociclib treatment should be based on a clinical assessment of satisfactory wound healing and recovery from surgery.

5.8. Known Toxicities of Temozolomide

Incidence	Toxicities*
Very Common (≥1/10 patients)	• Nausea • Vomiting • Constipation • Diarrhea • Headache • Fatigue • Fever • Alopecia • Nervous system disorders: seizure, hemiparesis, dizziness, coordination abnormal, amnesia • Edema peripheral
Common (≥1/100 to <1/10 patients)	• Anorexia • Abdominal pain • Alanine aminotransferase increased • Aspartate aminotransferase increased • Dysphagia • Mucositis oral • Anxiety • Depression • Insomnia • Ataxia • Edema/Localized edema • Rash maculopapular • Anemia • Platelet count decreased • White blood cell count decreased • Lymphocyte count decrease • Febrile neutropenia • Urinary frequency • Cough • Upper respiratory infection • Sinusitis

Incidence	Toxicities*
	• Lower gastrointestinal hemorrhage • Upper gastrointestinal hemorrhage
Uncommon (≥1/1,000 to <1/100 patients)	• Blood bilirubin increased • Aplastic anemia • Stevens-Johnson syndrome • Toxic epidermal necrolysis • Erythema multiforme • Cholecystitis • Alkaline phosphatase increased • Myelodysplastic syndrome • Leukemia secondary to oncology chemotherapy • Infections and infestations – other: Pneumocystis pneumonia, pulmonary fibrosis, anaphylaxis, allergic reaction, hepatic failure
Pregnancy & Lactation	**Pregnancy Category D** Adequate, well-controlled studies have not been conducted in humans. Women of childbearing potential should be advised against becoming pregnant while taking temozolomide and for at least 6 months following the end of therapy. Temozolomide administration to rats and rabbits at 3/8 and 3/4 the human dose resulted in the development of malformations of the external organs, soft tissues, and skeleton. These animal studies also demonstrated embryolethality (increased resorptions) at similar doses. There is no information available regarding the transmission of temozolomide during lactation; women should avoid breastfeeding while receiving temozolomide and for at least 1 week after the final dose.

* for more information on warnings, precautions and adverse reactions refer to TMZ USPI/SmPC.

5.9. Known Toxicities of Irinotecan

Incidence	Toxicities*
Very Common (≥1/10 patients)	• Nausea • Vomiting • Diarrhoea • Abdominal pain • Constipation • Anemia • Neutrophil count decreased • White blood cell count decreased • Thrombocytopenia • Cholinergic symptoms: (rhinitis, increased salivation, miosis, lacrimation, diaphoresis, flushing, and intestinal hyperperistalsis that can cause abdominal cramping and early diarrhea) • Anorexia • Fever • Asthenia • Alopecia • Mucositis • Dyspnea • Cough • Weight loss • Pain • Dizziness • Headache • Infection
Common (≥1/100 to <1/10 patients)	• Abdominal fullness • Flatulence • Vasodilation • Hypotension • Dehydration • Edema • AST increased • Alkaline phosphatase increased • Ascites • Jaundice/bilirubin increased • Febrile neutropenia • Chills • Insomnia • Rash • Dyspepsia • Somnolence

Incidence	Toxicities*
	• Disorientation/confusion • Thromboembolic events • Pneumonia
Uncommon (≥1/1,000 to <1/100 patients)	• Anaphylaxis • Bradycardia • Colitis • Renal failure (secondary to severe dehydration) • Ileus • Pancreatitis • Pneumonitis/Interstitial Lung Disease
Pregnancy & Lactation	Fetal toxicities and teratogenic effects of irinotecan have been noted in animals at doses similar or less than those used in humans. Toxicities include: decreased skeletal ossification, multiple anomalies, low birth weight and increased fetal mortality. Advise female patients of reproductive potential to avoid becoming pregnant and to use highly effective contraception during treatment with CAMPTOSAR and for 6 months after the final dose. Irinotecan and its metabolites are present in human milk. There is no information regarding the effects of irinotecan on the breastfed infant, or on milk production; women should not breastfeed during treatment and for 7 days after the final dose.

* for more information on warnings, precautions and adverse reactions refer to IRN USPI/SmPC.

5.10. Known Toxicities of Topotecan

Incidence	Toxicities*
Very Common (≥1/10 patients)	• Anemia • Neutropenia • Thrombocytopenia • Constipation • Diarrhea • Nausea • Vomiting • Fever • Pain: abdominal, skeletal, back pain • Mucositis • Bruising, bleeding, especially when platelet count is low • Febrile neutropenia • Astenia/Fatigue • Alopecia • Anorexia
Common (≥1/100 to <1/10 patients)	• Pain • Headache • Cough • Scarring of the lungs • Rash • Sepsis • Dyspnea • Hyperbilirubinemia • Alanine aminotransferase increased • Aspartate aminotransferase increased

Incidence	Toxicities*
Uncommon (≥1/1,000 to <1/100 patients)	• Extravasation and Tissue Injury • Hypersensitivity reactions • Interstitial Lung Disease
Pregnancy & Lactation	Fetal toxicities, embryolethality and teratogenic effects of topotecan have been noted in animals at doses similar to those used in humans. Toxicities include: fetal resorption, pre-implant loss and fetal malformations. The most frequent malformations were of the eye (microphthalmia, anophthalmia, rosette formation of the retina, coloboma of the retina, ectopic orbit), brain (dilated lateral and third ventricles), skull, and vertebrae. Advise women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment and for 6 months after the last dose of topotecan. It is not known if topotecan is excreted into breast milk but it is excreted into rat milk. Advise women not to breastfeed during treatment with and for 1 week after the last dose.

* for more information on warnings, precautions and adverse reactions refer to TOPO USPI/SmPC.

5.11. Known Toxicities of Cyclophosphamide

Incidence	Toxicities*
Very Common (≥1/10 patients)	• Mylosuppression • Leukopenia • Neutropenia • Immunosuppression • Alopecia • Nausea, vomiting, loss of appetite • Cystitis • Microhematuria • Fever • Gonadal dysfunction (azoospermia or oligospermia)
Common (≥1/100 to <1/10 patients)	• Infections • Febrile neutropenia • Mucosal inflammation Hepatic function abnormal Hemorrhagic cystitis, macrohematuria • Chills • Asthenia, malaise • Amenorrhea,Gonadal dysfunction ovarian • Diarrhea • Abdominal pain

Incidence	Toxicities*
Uncommon (≥1/1,000 to <1/100 patients)	• Pneumonia • Sepsis • Thrombocytopenia • Anemia • Anaphylactic/anaphylactoid and hypersensitivity reactions • Peripheral neuropathy, polyneuropathy, neuralgia • Stevens-Johnson disease • Cardiomyopathy • Myocarditis • Heart failure • Tachycardia • Secondary malignancies • Dizziness, confusion • Veno-occlusive liver disease • SIADH
Pregnancy & Lactation	Based on human data, exposure to cyclophosphamide during pregnancy may cause fetal malformations, miscarriage, fetal growth retardation, and toxic effects in the newborn. Cyclophosphamide is present in breast milk (human data). Female patients of reproductive potential should use highly effective contraception during and for up to 1 year after. Completion of treatment.

* for more information on warnings, precautions and adverse reactions refer to CTX USPI/SmPC.

6. STUDY PROCEDURES

Refer to the Schedule of Activities (Table 2 or Table 3) and Schedule of PK (Table 4 or Table 5) for the complete list of procedures to be performed and associated time points. All on-study procedures are permitted within the time windows indicated in the Schedule of Activities. Refer to Appendix 14 for guidance on alternative measures during COVID-19 and other public emergencies.

Prior to undergoing any study-specific procedure, legal guardians must read and sign the current Institutional Review Board (IRB)/Ethics Committee (EC) approved informed consent form and patients capable of providing written assent must sign approved assent form or provide verbal assent as per local guidelines.

6.1. Screening

For screening procedures see the Schedule of Activities and ASSESSMENTS sections.

All screening assessments must be completed over 1 or multiple visits within 21 days prior to the first dose of the investigational product (Phase 1 portion and tumor-specific cohorts) or the date of randomization (Phase 2 portion) unless otherwise specified. Date of enrollment is defined as the day the patient has satisfied all inclusion and exclusion criteria and is considered eligible for the study. For procedures during Screening, see Schedule of Activities (Table 2 or Table 3 and Table 4, and Assessments Section 7). Date of study entry is defined as C1D1.

Prior cancer history will be collected. All anti-cancer treatments (including hematopoietic stem cell transplantation) received by the patient, including dates of administration, dose(s), best response, DOR, and tolerability (including specific intolerance(s) to each therapy) of therapy will be collected from the time of original diagnosis.

Any other diagnosed malignancies, and any relevant treatments, will also be recorded at screening.

All relevant medical history and treatment received by the patient within 21 days before the first dose of study medication (Phase 1 portion and tumor-specific cohorts) or the date of randomization (Phase 2 portion) will be recorded on the patient's CRF, including the name of the procedure or drug and other related information.

Pathology confirmation of solid tumor diagnosis and disease staging must be done at screening. Acceptable documentation includes results from primary diagnosis or results following discontinuation/failure of prior therapy.

Pathology confirmation of EWS diagnosis in the Phase 2 portion of the study requires presence of EWSR1-ETS or FUS-ETS fusion genes.

If both rearrangement partners (EWSR1-ETS or FUS-ETS) are not confirmed by pathology report, then available formalin-fixed paraffin-embedded (FFPE) tumor tissue sample for central testing is required for patient to be considered eligible.

If acceptable by local law and regulations, after signing an informed consent, submission of blinded pathology report from initial diagnosis or a relapse sample is required for Sponsor review to confirm whether tumor tissue sample for central testing for EWSR1-ETS or FUS-ETS fusion genes is required.

Imaging must be performed within 21 days prior to the first dose of investigational product (Phase 1 portion and tumor-specific cohorts) or the date of randomization (Phase 2 portion) unless otherwise specified and measurable lesion(s) size documented in the CRF. Any non-measurable disease must be listed in the CRF. Radiographic tumor assessments that were performed before the signing of the informed consent as routine evaluation (but within 21 days prior to the start of study treatment or randomization) do not need to be repeated and may be used as baseline assessments.

Patients with r/r EWS with non-measurable disease at study entry (eg, bone only disease with no soft tissue component) are considered eligible for the Phase 2 portion of the study. All sites of disease for these patients should be listed in the CRF as non-measurable lesions.

Documentation of dentition should be done, a formal evaluation is not required unless the study physician notes any concerns. Evaluation can be done per institutional standards.

6.2. Study Period

For the treatment period procedures, see the Schedule of Activities in Table 2 or Table 3 and ASSESSMENTS sections.

6.3. Follow-up

For follow-up procedures see the Schedule of Activities in Table 2 or Table 3 and ASSESSMENTS sections.

Phase 1 portion and Tumor-specific Cohort

Patients without evidence of disease progression at the time of treatment discontinuation should continue to have tumor assessment performed until radiographically and/or clinically documented progressive disease (Section 7.9.2), initiation of new anticancer therapy, or discontinuation of patient from overall study participation (eg, death, patient's request, lost to follow-up).

Phase 2 portion

Patients without evidence of disease progression or secondary malignancy at the time of treatment discontinuation should continue to have tumor assessment performed as outlined in Section 7.9.2 until radiographically and/or clinically documented progressive disease (regardless initiation of new anticancer therapy), diagnosis of secondary malignancy or discontinuation of patient from overall study participation (eg, death, patient's request, lost to follow-up).

6.4. Patient Withdrawal

Withdrawal of consent:

Patients who request to discontinue receipt of study treatment will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a patient/guardian specifically withdraws consent for any further contact with him or her or persons previously authorized by the patient to provide this information. Patients should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of investigational product or also from study procedures and/or post-treatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the patient is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

Lost to follow-up:

All reasonable efforts must be made to locate patients to determine and report their ongoing status. This includes follow-up with persons authorized by the patient as noted above. Lost to follow-up is defined by the inability to reach the patient after a minimum of 2 documented phone calls, faxes, or e-mails as well as lack of response by the patient to 1 registered mail letter. All attempts should be documented in the patient's medical records. If it is determined that the patient has died, the site will use locally permissible methods to obtain the date and cause of death. If the investigator's use of a third-party representative to assist in the follow-up portion of the study has been included in the patient's informed consent, then the investigator may use a sponsor-retained third-party representative to assist site staff with obtaining the patient's contact information or other public vital status data necessary to complete the follow-up portion of the study. The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If, after all attempts, the patient remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the patient's medical records.

Patients may withdraw from treatment at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety (see also the Withdrawal From the Study Due to Adverse Events (see also the Patient Withdrawal section)) or behavioral reasons, or the inability of the patient to comply with the protocol-required schedule of study visits or procedures at a given investigator site.

Reasons for withdrawal of study treatment may include:

- Objective disease progression;
- Global deterioration of health status requiring discontinuation;

- Unacceptable toxicity;
- Secondary malignancy
- Pregnancy;
- Significant protocol violation;
- Lost to follow-up;
- Patient refused further treatment;
- Study terminated by sponsor;
- Death.

Reasons for withdrawal from study follow-up may include:

- Completed study follow-up;
- Study terminated by sponsor;
- Lost to follow-up;
- Refused further follow-up;
- Death.

If a patient does not return for a scheduled visit, every effort should be made to contact the patient. All attempts to contact the patient and information received during contact attempts must be documented in the patient's medical record. In any circumstance, every effort should be made to document patient outcome, if possible. The investigator should inquire about the reason for withdrawal, request that the patient return all unused investigational product(s), request that the patient return for a final visit, if applicable, and follow up with the patient regarding any unresolved AEs.

If the patient refuses further visits, the patient should continue to be followed for survival unless the patient withdraws consent for disclosure of future information or for any further contact. In this case, no further study-specific evaluations should be performed and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

7. ASSESSMENTS

All study procedures are detailed in the Schedule of Activities in Table 2 or Table 3 and Schedule of PK and PD in Table 4 and Table 5. Refer to Appendix 14 for guidance on

alternative measures (eg, during COVID-19 and other public emergencies or to limit travel burden).

Every effort should be made to ensure that the protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside of the control of the investigator that may make it unfeasible to perform the test. In these cases, the investigator will take all steps necessary to ensure the safety and wellbeing of the patient. When a protocol-required test cannot be performed, the investigator will document the reason for this and any corrective and preventive actions that he or she has taken to ensure that normal processes are adhered to as soon as possible. The study team will be informed of these incidents in a timely manner.

Blood volume limits have been set for pediatric patient populations according to those described in the Bulletin of the World Health Organization[53]. In accordance with these recommendations, blood sampling should not exceed 5% based on an estimated total blood volume of 75-80 mL/kg within a 24-hour period, or 10% of this volume within an 8-week period.

If, according to above mentioned recommendations and/or due to local regulations, completing the full planned sample collections for a given patient for his/her small body size is prohibited, please contact the study Sponsor for guidance in prioritizing the sampling scheme.

For samples being collected and shipped, detailed collection, processing, storage, shipment instructions and contact information will be provided to the investigator site prior to initiation of the study.

7.1. Safety Assessment

Safety assessments will include collection of AEs, serious AEs (SAEs), vital signs and physical examination, ECG (12-lead), laboratory assessments, including pregnancy tests and verification of concomitant treatments. All AEs regardless of severity and all SAEs will be recorded on the CRF for patients in Phase 1 portion of the study and Tumor specific cohorts. (see Section 8)

At minimum the following AEs/SAEs will be recorded on the CRF for patients in the Phase 2 portion of the study: all non-serious AEs Grade ≥3, all SAEs, any AEs leading to study treatment interruptions, any AEs requiring dose reduction and events leading to permanent discontinuation of study treatment.

7.1.1. Pregnancy Testing

For all girls ≥8 years of age , a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed at screening, Day 1 of each cycle, and at end of treatment.

A negative pregnancy test result is required before the patient may receive the study treatment(s). Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected). Pregnancy

tests may also be repeated and continue to be performed during long term follow up until the end of mandatory contraception time as defined in Section 4.3, if requested by institutional review boards (IRBs)/ethics committees (ECs) or if required by local regulations. The frequency of pregnancy tests in long term follow up is recommended to be monthly.

In the case of a positive confirmed pregnancy, the patient will be withdrawn from administration of investigational product but may remain in the study for follow-up and survival.

7.1.2. Adverse Events

Assessment of adverse events will include the type, incidence, severity (graded by the National Cancer Institute [NCI] CTCAE version 4.03) timing, seriousness, and relatedness.

7.1.3. Laboratory Safety Assessment

Hematology and blood chemistry will be drawn at the time points described in the Schedule of Activities and analyzed at local laboratories. Additional laboratory tests are required and can be found in the schedule of events.

Table 15. Safety Laboratory Tests

Hematology	Chemistry	Coagulation	Urine analysis	Pregnancy Test	Other
Hemoglobin	ALT	PT or INR when clinically indicated	Protein Glucose Blood	For girls ≥8 years serum or urine.	HbA1c**
Platelets	AST				
WBC	Alkaline Phosphatase				
Absolute Neutrophils	Sodium				
Absolute Lymphocytes	Potassium				
Absolute Monocytes	Magnesium				
Absolute Eosinophils	Chloride				
Absolute Basophils	Total calcium				
	Total bilirubin***				
	BUN/Urea				
	Creatinine				
	Glucose (nonfasted)				
	Albumin				
	Phosphorous or Phosphate				

Table 15. Safety Laboratory Tests

Hematology	Chemistry	Coagulation	Urine analysis	Pregnancy Test	Other

*** For potential Hy's Law cases (see Section 8.4.1), in addition to repeating AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, prothrombin time (PT)/INR, and alkaline phosphatase. Total bile acids., acetaminophen/paracetamol drug and/or protein adduct levels should be assessed, if available.
** Blood test for HbA1c assessment will be analyzed by a central independent laboratory.

7.1.4. Vital Signs and Physical Examination

Patients will have a physical examination to include weight, vital signs, assessment of Lansky or ECOG performance status (Appendix 2), and height at the time points described in the Schedule of Activities (Table 2 or Table 3). Except for findings during the screening visit, clinically meaningful abnormalities will be recorded on the Adverse Events CRF page.

On C1D1, patients will be asked about any signs and symptoms experienced within the 21 days prior to first dose of study medication (Phase 1 portion and tumor-specific cohorts) or the date of randomization (Phase 2 portion), and these will be recorded on the Adverse Events CRF page.

When possible, blood pressure and pulse rate should be recorded in the sitting position after patient has been in the supine position for approximately 2 minutes.

In patients 3 years of age or greater, height should be measured using a wall-mounted stadiometer by appropriately trained personnel. Length should be measured in patients <3 years of age. If possible, the same person should perform height measurement at each study visit.

Tanner stage should be assessed in girls ≥8 years of age and boys ≥9 years of age, or if any sexual development is present in children who are younger (See Appendix 3). Patients with no sexual development who are younger than these respective ages by gender should be graded as Tanner 1. Once a patient reaches Tanner Stage 5, this assessment will no longer be necessary.

Dental abnormalities have been seen in pre-clinical testing. Formal testing is not required but if any dental abnormalities are noted on physical exam, a formal dental evaluation should be obtained.

Calculation of patient BSA will occur following individual investigator site standards for each patient given their demographic characteristics.

7.1.5. Assessments of Growth and Bone Metabolism

For patients less than Tanner 4 (ie, Tanner 1-3), dual-energy X-ray absorptiometry (DEXA) scans, bone age assessment, and blood tests (IGF-1, IGFBP-3, 25-hydroxyvitamin D, 1, 25-dihidroxyvitamin D, C-telopeptide, bone ALP, fasting cortisol, luteinizing hormone (LH), follicle stimulating hormone (FSH), estradiol, and testosterone will be performed at the

time points described in the Schedule of Activities (Table 2 or Table 3). C-telopeptide and bone ALP will be collected only in Phase 2 portion of the study. DEXA scans and X-ray bone age assessments should be performed in accordance with relevant and applicable competent authorities requirements. DEXA scans and X-ray of hand will not be required per protocol in patients enrolled in Germany.

For female patients who are less than Tanner 4 (ie, Tanner 1-3), serum for measurement of LH, FSH, and estradiol levels should be performed at screening, every 4 cycles thereafter, and at the End of Treatment visit. For male patients who are less than Tanner 4 (ie, Tanner 1-3), serum for measurement of LH, FSH, and testosterone levels should be performed at screening, every 4 cycles thereafter, and at the End of Treatment visit.

Of note, once the bone age assessment demonstrates that a patient has completed growth, additional assessments are not necessary.

IGF-1, IGFBP-3, 25-hydroxyvitamin D, and 1, 25-dihidroxyvitamin D levels, C-telopeptide, bone ALP and hormonal assessments will be analyzed by a central independent laboratory.

7.1.6. (12-Lead) Electrocardiogram

Triplicate 12-lead (with a 10-second rhythm strip) tracing will be used for all ECGs. It is preferable that the machine used has a capacity to calculate the standard intervals automatically. At each time point (see Table 2 or Table 3), 3 consecutive ECGs will be performed at approximately 2 minutes apart to determine the mean QT interval corrected for heart rate using Fridericia's formula (QTcF). If patient receives 5-HT3 antagonist for nausea/vomiting prophylaxis or treatment the required ECGs should be taken prior to administration of the 5-HT3 antagonist. If the mean QTcF is prolonged (>500 msec, ie, Grade ≥3), then the ECGs should be re--evaluated by a qualified person at the site for confirmation as soon as the finding is made, including verification that the machine reading is accurate. If manual reading verifies a QTcF of >500 msec, immediate correction for reversible causes (including electrolyte abnormalities, hypoxia and concomitant medications for drugs with the potential to prolong the QTcF) should be performed. In addition, repeat ECGs should be immediately performed hourly for at least 3 hours until the QTcF falls below 500 msec. If the QTcF does not fall below 500 msec, hold study medication and refer for cardiology evaluation. If QTcF reverts to less than 500 msec, and in the judgment of the investigator(s) and sponsor is determined to be due to cause(s) other than study medication, study medication may be continued with regular ECG monitoring. If in that timeframe the QTcF intervals rise above 500 msec, the study medication will be held until the QTcF decreases to 500 msec. Patients will then restart the palbociclib at next lower dose level with TMZ and IRN OR TOPO and CTX at same dose level. If the QTcF has still not decreased to 500 msec after 2 weeks, or the patient becomes symptomatic, the patient will be removed from the study. Additional triplicate ECGs may be performed as clinically indicated.

If a patient experiences a cardiac or neurologic AE (specifically syncope, dizziness, seizures, or stroke), an ECG (triplicate) should be obtained as close to time of the event, as best possible.

7.2. Pharmacokinetics Assessments

7.2.1. Palbociclib PK Assessments

Plasma PK samples for palbociclib determination will be collected according to the Schedule described in Table 4 for patients enrolled in Phase 1 and in for patients enrolled in Phase 2 (note: patients randomized to the IRN and TMZ alone arm in Phase 2 will not undergo PK sampling). Patients must be instructed to withhold their daily dose of palbociclib on PK sampling days until the predose PK sample and safety assessments (ie, hematology, blood chemistry, etc.) have been completed. The actual date and time of the PK sample collection and the actual date and time of the most recent doses (both before and after PK sample collection) will be recorded on the CRF. The date of any missed dose(s) within the treatment cycle prior to the PK sample collection should also be recorded in the CRF.

The actual times may change but the number of samples will remain the same. All efforts will be made to obtain the PK samples at the exact nominal time relative to palbociclib dosing. However, PK samples drawn within ±20% of the nominal time will not be captured as protocol deviations, as long as the exact time of the sample collection and the exact dosing time are noted on the source document and data collection tool (eg, CRF). To accommodate investigator sites which are not open 7 days/week and thus not capable of implementing certain scheduled activities, missing the Cycle 1 Day 6 visit will not constitute a protocol deviation. Thus, the Cycle 1 Day 6 palbociclib PK sample collection is recommended but not required. The same applies to the Cycle 1 Day 5 post-dose sample collections at 2, 4, 6 or 8 hours post dosing in Phase 2 portion of the study. Every effort should be made to follow the Cycle 1 Day 5 sampling schedule; however, missing any of the 2, 4, 6 or 8 hours Cycle 1 Day 5 post dosing sample collections will not constitute a protocol deviation.

One 1 mL sample of venous blood will be collected in appropriately labeled K_2EDTA collection tubes at the protocol-specified times to obtain a minimum of 0.5 mL plasma. Samples will be analyzed using validated analytical methods in compliance with Pfizer standard operating procedures.

Blood samples will be collected from all participating patients for PK assessments of palbociclib according to the schedule described in Table 4 for patients enrolled Phase 1 and in Table 5 for patients enrolled in Phase 2. The investigator site should contact the Sponsor in the event that a blood sampling volume for PK assessments exceeds the maximum allowable limit for a patient. In the event that PK sample(s) cannot be/are not collected on Days 5 or 14 of Cycle 1 or Cycle 2 as scheduled, every effort should be made to collect makeup sample(s) in subsequent treatment cycles following discussion with the Sponsor. When the serial palbociclib PK samples scheduled for Cycle 1 Days 5 and 6 are not collected in Cycle 1 but are made up on Days 5 and 6 of a later cycle, the make-up samples should be collected using the “Make-up PK” visit kit and the collection details should be documented in the CRF using the “Make-up Visit” entries in the PK log. When the pre-dose PK samples scheduled for Cycle 1 Day 14 and/or Cycle 2 Day 14 are not collected as planned and are made up in a later cycle or collected outside of the allowed collection window (-2/+1 day[s]), the make-up sample should be collected using the “Unplanned” visit kit and the sample collection details should be documented in the CRF using the “Unplanned” entries in the PK log. When

collections are scheduled on the same visit, samples for thymidine kinase activity analysis should be obtained at the same time as palbociclib PK samples (±30 minutes) whenever possible. Documented rationale is needed in the database for any missing and delayed PK sampling.

Additional blood samples may be requested from patients experiencing unexpected or serious adverse events, or adverse events that lead to discontinuation and the date and time of blood sample collection and of last dosing prior to PK collection documented on the CRF.

As part of understanding the PK of palbociclib, blood samples may be used for metabolite identification and/or evaluation of the bioanalytical method. These data will be used for internal exploratory purposes and will not be included in the Clinical Study Report. Refer to the Laboratory Manual for detailed collection, processing and shipping procedures. The PK samples must be processed and shipped as indicated in the instructions provided to the investigator site to maintain sample integrity. Any deviations from the PK sample handling procedure (eg, sample collection and processing steps, interim storage or shipping conditions), including any actions taken, must be documented and reported to the sponsor. On a case-by-case basis, the sponsor may make a determination as to whether sample integrity has been compromised. Any deviation from the specified sample handling procedure resulting in compromised sample integrity will be considered a protocol deviation.

Palbociclib in Combination With TMZ and IRN

7.2.2. Irinotecan PK Assessments

Plasma PK samples for IRN and 7-Ethyl-10-hydroxycamptothecin (SN-38) determination will be collected according to the Schedule described in Table 4 for patients enrolled Phase 1 and in Table 5 for patients enrolled in Phase 2 (note: patients randomized to the IRN and TMZ alone arm in Phase 2 will not undergo PK sampling). The actual date and time of the PK sample collection and the actual date and the start and stop time of the most recent IV infusion will be recorded on the CRF. The date of any missed dose(s) within the treatment cycle prior to the PK sample collection should also be recorded in the CRF.

The actual times may change but the number of samples will remain the same. All efforts will be made to obtain the PK samples at the exact nominal time relative to the start of the IRN infusion. However, post-infusion PK samples drawn within ±20% of the nominal time (except for the 8-hour PK sample on Cycle 1 Day 5 which allows for ±25%) will not be captured as protocol deviations, as long as the exact time of the sample collection and the exact start and stop times for the IV infusion are noted on the source document and data collection tool (eg, CRF). IRN pre-infusion PK sample collections may be collected within 3 hours prior to the start of the IRN IV infusion to allow for the alignment of the sample collection with the palbociclib and TMZ pre-dose PK sample collections on the same visit. To accommodate investigator sites which are not open 7 days/week and thus, not capable of implementing certain scheduled activities, missing the Cycle 1 Day 6 visit will not constitute a protocol deviation. Thus, the Cycle 1 Day 6 IRN PK sample collection is recommended, but not required. The same applies to the Cycle 1 Day 5 post-dose sample collections at 4 and 8 hours post dosing in Phase 2 portion of the study. Every effort should be made to follow

the Cycle 1 Day 5 sampling schedule; however, missing the 4 and/or 8 hours Cycle 1 Day 5 post dosing sample collections will not constitute a protocol deviation.

One 1 mL sample of venous blood will be collected in appropriately labeled K_2EDTA collection tubes at the protocol-specified times to obtain a minimum of 0.5 mL plasma. Blood samples for post-infusion PK assessments of IRN should not be collected from the same arm that the IRN IV infusion was administered. Samples will be analyzed using validated analytical methods in compliance with Pfizer standard operating procedures.

Blood samples will be collected from all participating patients for PK assessments of IRN and SN-38 according to the schedule described in Table 4 for patients enrolled in Phase 1 and in Table 5 for patients enrolled in Phase 2. The investigator site should contact the Sponsor in the event that a blood sampling volume for PK assessments exceeds the maximum allowable limit for a patient. In the event that PK sample(s) cannot be/are not collected on Day 5 of Cycles 1 or 2 as scheduled, every effort should be made to collect makeup sample(s) in subsequent treatment cycles following discussion with the Sponsor. When the serial IRN PK samples scheduled for Cycle 1 Days 5 and 6 are not collected in Cycle 1 but are made up on Days 5 and 6 of a later cycle, the make-up samples should be collected using the "Make-up PK" visit kit and the collection details should be documented in the CRF using the "Make-up Visit" entries in the PK log. Documented rationale is needed in the database for any missing and delayed PK sampling.

Additional blood samples may be requested from patients experiencing unexpected or serious adverse events, or adverse events that lead to discontinuation and the date and time of blood sample collection and of last infusion prior to PK collection documented on the CRF.

As part of understanding the PK of the IRN and SN-38, blood samples may be used for metabolite identification and/or evaluation of the bioanalytical method. These data will be used for internal exploratory purposes and will not be included in the Clinical Study Report.

Refer to the Laboratory Manual for detailed collection, processing and shipping procedures. The PK samples must be processed and shipped as indicated in the instructions provided to the investigator site to maintain sample integrity. Any deviations from the PK sample handling procedure (eg, sample collection and processing steps, interim storage or shipping conditions), including any actions taken, must be documented and reported to the sponsor. On a case-by-case basis, the sponsor may make a determination as to whether sample integrity has been compromised. Any deviation from the specified sample handling procedure resulting in compromised sample integrity will be considered a protocol deviation.

7.2.3. Temozolomide PK Assessments

Plasma PK samples for TMZ determination will be collected according to the Schedule described in Table 4 for patients enrolled in Phase 1 and in Table 5 for patients enrolled in Phase 2 (note: patients randomized to the IRN and TMZ alone arm in Phase 2 will not undergo PK sampling). The actual date and time of the PK sample collection and the actual date and time of the most recent doses (or the start and stop time of the most recent IV

infusion, as applicable) will be recorded on the CRF. The date of any missed dose(s) within the treatment cycle prior to the PK sample collection should also be recorded in the CRF.

The actual times may change but the number of samples will remain the same. All efforts will be made to obtain the PK samples at the exact nominal time relative to (or the start of the TMZ infusion, as applicable). However, PK samples drawn within ±20% of the nominal time will not be captured as protocol deviations, as long as the exact time of the sample collection and the exact dosing time (or the exact start and stop times for the IV infusion, as applicable) are noted on the source document and data collection tool (eg, CRF).

Every effort should be made to follow the Cycle 1 Day 5 sampling schedule; however, missing the 4 and/or 8 hours Cycle 1 Day 5 post dosing sample collections will not constitute a protocol deviation. This exception refers to Phase 2 portion of the study only.

One 1 mL sample of venous blood will be collected in appropriately labeled K_2EDTA collection tubes at the protocol-specified times to obtain a minimum of 0.5 mL plasma. When TMZ is administered via an IV infusion, blood samples for post-infusion PK assessments of TMZ should not be collected from the same arm that the TMZ IV infusion was administered. Samples will be analyzed using validated analytical methods in compliance with Pfizer standard operating procedures.

Blood samples will be collected from all participating patients for PK assessments of TMZ according to the schedule described in Table 4 for patients enrolled in Phase 1 and in Table 5 for patients enrolled in Phase 2. The investigator site should contact the Sponsor in the event that a blood sampling volume for PK assessments exceeds the maximum allowable limit for a patient. In the event that PK sample(s) cannot be/are not collected on Day 5 of Cycles 1 or 2 as scheduled, every effort should be made to collect makeup sample(s) in subsequent treatment cycles following discussion with the Sponsor. When the serial TMZ PK samples scheduled for Cycle 1 Day 5 are not collected in Cycle 1 but are made up on Day 5 of a later cycle, the make-up samples should be collected using the “Make-up PK” visit kit and the collection details should be documented in the CRF using the “Make-up Visit” entries in the PK log. Documented rationale is needed in the database for any missing and delayed PK sampling.

Additional blood samples may be requested from patients experiencing unexpected or serious adverse events, or adverse events that lead to discontinuation and the date and time of blood sample collection and of last infusion prior to PK collection documented on the CRF.

As part of understanding the PK of the TMZ, blood samples may be used for metabolite identification and/or evaluation of the bioanalytical method. These data will be used for internal exploratory purposes and will not be included in the Clinical Study Report.

Refer to the Laboratory Manual for detailed collection, processing and shipping procedures. The PK samples must be processed and shipped as indicated in the instructions provided to the investigator site to maintain sample integrity. Any deviations from the PK sample handling procedure (eg, sample collection and processing steps, interim storage or shipping conditions), including any actions taken, must be documented and reported to the sponsor.

On a case-by-case basis, the sponsor may make a determination as to whether sample integrity has been compromised. Any deviation from the specified sample handling procedure resulting in compromised sample integrity will be considered a protocol deviation.

Palbociclib in Combination With TOPO and CTX

7.2.4. Topotecan PK Assessments

Plasma PK samples for TOPO determination will be collected according to the schedule described in Table 4. The actual date and time of the PK sample collection and the actual start and stop time of the most recent IV infusion will be recorded on the CRF. The date of any missed dose(s) within the treatment cycle prior to the PK sample collection should also be recorded in the CRF.

The actual times may change but the number of samples will remain the same. All efforts will be made to obtain the PK samples at the exact nominal time relative to the start of the TOPO infusion. However, PK samples drawn within ±20% of the nominal time will not be captured as protocol deviations, as long as the exact time of the sample collection and the exact start and stop times for the IV infusion, as applicable are noted on the source document and data collection tool (eg, CRF). To accommodate investigator sites which are not open 7 days/week and thus not capable of implementing certain scheduled activities, missing the Cycle 1 Day 6 visit will not constitute a protocol deviation. Thus, the Cycle 1 Day 6 palbociclib PK sample collection is recommended but not required.

One 1 mL sample of venous blood will be collected in appropriately labeled K_2EDTA collection tubes at the protocol-specified times to obtain a minimum of 0.5 mL plasma. Blood samples for post-infusion PK assessments of TOPO should not be collected from the same arm that the CTX IV infusion was administered. Samples will be analyzed using validated analytical methods in compliance with Pfizer standard operating procedures.

Blood samples will be collected from all participating patients for PK assessments of TOPO according to the schedule described in Table 4. The investigator site should contact the Sponsor in the event that a blood sampling volume for PK assessments exceeds the maximum allowable limit for a patient. In the event that PK sample(s) cannot be/are not collected on Day 5 of Cycles 1 or 2 as scheduled, every effort should be made to collect makeup sample(s) in subsequent treatment cycles following discussion with the Sponsor. When the serial TOPO PK samples scheduled for Cycle 1 Day 5 are not collected in Cycle 1 but are made up on Day 5 of a later cycle, the make-up samples should be collected using the "Make-up PK" visit kit and the collection details should be documented in the CRF using the "Make-up Visit" entries in the PK log. Documented rationale is needed in the database for any missing and delayed PK sampling.

Additional blood samples may be requested from patients experiencing unexpected or serious adverse events, or adverse events that lead to discontinuation and the date and time of blood sample collection and of last infusion prior to PK collection documented on the CRF.

As part of understanding the PK of the TOPO, blood samples may be used for metabolite identification and/or evaluation of the bioanalytical method. These data will be used for internal exploratory purposes and will not be included in the Clinical Study Report.

Refer to the Laboratory Manual for detailed collection, processing and shipping procedures. The PK samples must be processed and shipped as indicated in the instructions provided to the investigator site to maintain sample integrity. Any deviations from the PK sample handling procedure (eg, sample collection and processing steps, interim storage or shipping conditions), including any actions taken, must be documented and reported to the sponsor. On a case-by-case basis, the sponsor may make a determination as to whether sample integrity has been compromised. Any deviation from the specified sample handling procedure resulting in compromised sample integrity will be considered a protocol deviation.

7.2.5. Cyclophosphamide PK Assessments

Plasma PK samples for CTX determination will be collected according to the schedule described in Table 4. The actual date and time of the PK sample collection and the actual start and stop time of the most recent IV infusion will be recorded on the CRF. The date of any missed dose(s) within the treatment cycle prior to the PK sample collection should also be recorded in the CRF.

The actual times may change but the number of samples will remain the same. All efforts will be made to obtain the PK samples at the exact nominal time relative to the start of the CTX infusion. However, PK samples drawn within ±20% of the nominal time will not be captured as protocol deviations, as long as the exact time of the sample collection and the exact start and stop times for the IV infusion, as applicable are noted on the source document and data collection tool (eg, CRF). To accommodate investigator sites which are not open 7 days/week and thus, not capable of implementing certain scheduled activities, missing the Cycle 1 Day 6 visit will not constitute a protocol deviation. Thus, the Cycle 1 Day 6 CTX PK sample collection is recommended, but not required.

One 1 mL sample of venous blood will be collected in appropriately labeled K2 EDTA collection tubes at the protocol-specified times to obtain a minimum of 0.5 mL plasma. Blood samples for post-infusion PK assessments of CTX should not be collected from the same arm that the CTX IV infusion was administered. Samples will be analyzed using validated analytical methods in compliance with Pfizer standard operating procedures.

Blood samples will be collected from all participating patients for PK assessments of CTX according to the schedule described in Table 4. The investigator site should contact the Sponsor in the event that a blood sampling volume for PK assessments exceeds the maximum allowable limit for a patient. In the event that PK sample(s) cannot be/are not collected on Day 5 of Cycles 1 or 2 as scheduled, every effort should be made to collect makeup sample(s) in subsequent treatment cycles following discussion with the Sponsor. When the serial CTX PK samples scheduled for Cycle 1 Day 5 are not collected in Cycle 1 but are made up on Day 5 of a later cycle, the make-up samples should be collected using the "Make-up PK" visit kit and the collection details should be documented in the CRF using the

"Make-up Visit" entries in the PK log. Documented rationale is needed in the database for any missing and delayed PK sampling.

Additional blood samples may be requested from patients experiencing unexpected or serious adverse events, or adverse events that lead to discontinuation and the date and time of blood sample collection and of last infusion prior to PK collection documented on the CRF.

As part of understanding the PK of the CTX, blood samples may be used for metabolite identification and/or evaluation of the bioanalytical method. These data will be used for internal exploratory purposes and will not be included in the Clinical Study Report.

Refer to the Laboratory Manual for detailed collection, processing and shipping procedures. The PK samples must be processed and shipped as indicated in the instructions provided to the investigator site to maintain sample integrity. Any deviations from the PK sample handling procedure (eg, sample collection and processing steps, interim storage or shipping conditions), including any actions taken, must be documented and reported to the sponsor. On a case-by-case basis, the sponsor may make a determination as to whether sample integrity has been compromised. Any deviation from the specified sample handling procedure resulting in compromised sample integrity will be considered a protocol deviation.

7.3. Palatability Questionnaire

The palatability questionnaire (see Appendix 8) will be administered to all patients receiving oral palbociclib solution at the time of the first dose on Days 1 and 14 of Cycle 1, and Days 1 and 14 of Cycle 2.

7.4. Biomarker and Pharmacodynamic Assessments

Tumor tissues and/or blood (plasma and/or serum) samples will be collected from patients (or legal guardian of patients) who provide written consent. These biospecimens (tumor tissue samples and blood samples) will be processed and shipped to Pfizer dedicated central laboratory.

Most recent biopsy tumor tissue is preferred, but archival tumor tissue material (eg, obtained at initial diagnosis) is acceptable. Tumor tissue will be collected at screening. Biomarker analyses include, but not limited to, deoxyribonucleic acid (DNA), ribonucleic acid (RNA), and protein to explore the potential genomic and biological mechanisms of sensitivity and resistance of palbociclib plus chemotherapy treatment in this patient population.

Patient blood samples (serum/plasma) will be collected to study PD effect of treatment by using TK1 (a surrogate PD marker) activity assay and its association to the PK exposure. TK1 is an enzyme playing a critical role in the synthesis of DNA and in cell proliferation. TK1 expression is E2Fdependent and peaks in the S-phase of the cell cycle. CDK4/6 inhibition suppresses E2Fdependent transcription of TK1. Therefore, TK1 levels could be used as a potential surrogate PD marker for CDK4/6 inhibition since it is impractical to repeat on-treatment biopsies.

Patient blood samples (plasma) will be collected to test both somatic genetic mutations and /or germline genetic alterations. In addition, the potential association between the genomic alterations and patient treatment response will be evaluated.

Analysis will be only conducted when sufficient (both quantitatively and qualitatively) samples are collected for conducting such analysis.

Table 16 summarizes representative assays to be used and the source of the samples. Refer to the Schedule of Activities for details pertaining to specific days of sample collection and to the Laboratory Manual for details of sample preparation.

To accommodate investigator sites which are not open 7 days/week and thus, not capable of implementing certain scheduled activities, missing the Cycle 1 Day 6 visit will not constitute a protocol deviation. Thus, the Cycle 1 Day 6 TK sample collection is recommended, but not required. The same applies to the Cycle 1 Day 5 post-dose TK sample collections at 4 and/or 8 hours post dosing in Phase 2 portion of the study. Every effort should be made to follow the Cycle 1 Day 5 sampling schedule; however, missing the 4 and/or 8 hours Cycle 1 Day 5 post-dosing sample collections will not constitute a protocol deviation.

Table 16. Biomarker Assessments

Assay	Source
Thymidine kinase activity testing, circulating tumor DNA analysis by using Next generation sequencing (NGS)	Peripheral Blood
IHC, gene expression, and NGS	Tumor Tissue

7.5. Tumor Response Assessments

Tumor assessments will include all known or suspected disease sites. Imaging may include chest, abdomen, pelvis and extremity computed tomography (CT), magnetic resonance imaging (MRI), metaiodobenzylguanidine (MIBG), or PET scans (as appropriate); brain CT or MRI scan for patients with known or suspected brain metastases; bone scan and/or bone X-rays for patients with known or suspected bone metastases (Phase 1 portion of the study). Distant metastases staging with bone scan or PET scan is required for all patients in Phase 2 portion of the study.

In the Phase 2 portion of the study PET-CT or PET-MRI, if performed at baseline (eg, for distant metastases staging), should be repeated after Cycle 4 (not mandatory). Increased FDG uptake alone on PET-CT or PET-MRI without an associated increase in the size or number of lesions must not be used to define disease progression.

The same imaging technique used to characterize each identified and reported lesion at baseline will be employed in the following tumor assessments. CT/MRI is the preferred method of tumor evaluation and measuremnts. However, if the CT/MRI component of

FDG-PET scan is identical to diagnostic CT/MRI, then this can be used for target/non-target tumor evaluation. If the CT/MRI component of the FDG-PET scan is for anatomical mapping/localization, but does not have diagnostic quality, then CT/MRI scan is needed for target/non-target tumor evaluation.

Antitumor activity will be assessed through radiological tumor assessments conducted at baseline, during treatment as specified in the Schedule of Activities, whenever disease progression is suspected (eg, symptomatic deterioration), and at the time of withdrawal from treatment if not done in the previous 6 weeks if the patient has not completed at least 8 cycles and more than 12 weeks if they have completed 8 cycles or more.

For all patients with evidence of response (PR or CR), confirmatory imaging must be performed ≥4 weeks after the initial scan. For patients with EWS with bone marrow disease at study entry and with evidence of CR, bone marrow aspirates and biopsies are required to confirm CR.

Assessment of response will be made using RECIST version 1.1, modified RANO for CNS malignancies, or INRC for neuroblastoma (see Appendix 5, Appendix 6, and Appendix 7, respectively).

Tumor response for patients with non-measurable EWS disease (eg, bone only disease with no soft tissue component enrolled to Phase 2 portion of the study, should be evaluated per RECIST 1.1. criteria for non-measurable disease assessment. (Appendix 5)

For the Phase 2 portion of the study, blinded independent review committee (BIRC) will review all radiological images related to response assessment. All radiographic images will be collected and objectively verified by an independent third-party core imaging vendor as described in the Study Manual.

7.6. Quality of Life

All patients enrolled to Phase 2 portion of the study will be eligible for participation in the QoL assessment.

The study patient and/or parent(s)/legal guardian/legally acceptable representative (as applicable) will be given the QoL Questionnaire to complete at the following time points:

- Baseline: Prior to starting study treatment.
- After completion of Cycle 2 and preferably immediately before Cycle 3 Day 1.
- After completion of Cycle 4 and preferably immediately before Cycle 5 Day 1.

QoL Questionnaires should be completed prior to any Day 1 procedure and preferably prior to informing a patient of tumor assessment response results. The relevant age appropriate questionnaires will be given at baseline to the patient and/or patient's parent(s)/legal guardian/legally acceptable representative (as applicable) as detailed in Appendix 13, based on patient age at randomization. The same age questionnaires will then be used throughout the trial regardless of patient birthdays. Patients who are not able to understand the QoL questionnaires

in any of the languages for which there are validated copies should not complete the QoL assessments.

An explanation of how to complete the questionnaires should be given to patient and/or parent/legal guardian at the baseline assessment. Questions can be read to a child or teenager who is unable to complete the QoL questionnaire without assistance. The patient and parent(s)/legal guardian should complete the questionnaire independently of one another. Questionnaires should be completed at the beginning of the visit before any medical procedures or interactions with the medical staff (as much as practically possible) take place. On average it takes less than 10 minutes to complete the questionnaire.

Every effort should be made to ensure completeness of the questionnaires. The site staff is required to confirm that all questions are completed at the time the participant returns the questionnaire. Additional details regarding the process of administration of the questionnaires will be provided in a study-specific user manual supplied by the Sponsor. All questionnaires will be implemented using paper forms and once completed will be considered the source document for the QoL data that will be subsequently captured in the CRF.

7.7. Hospitalizations

In Phase 2 portion of the study, all planned and unplanned inpatient admissions, regardless of the reason; outpatient visits, attendance for transfusions, blood tests and study related procedures etc. must be captured on the CRF. The reporting period for hospital attendance starts with Cycle 1 Day 1 and continues throughout the study treatment period. The last study visit to report hospitalization is the EoT visit.

7.8. Survival

Patients will be followed for overall survival after discontinuation of study treatment. Follow up should be every 2 months (±7 days) from EoT visit and can be by phone contact, e-mail or equivalent electronic communication or clinic visit for minimum of 2 years post last dose of study drug. If patient receives additional anticancer therapies, this should be noted in the CRF.

7.9. Imaging Assessments

See the Table 2 and Table 3 for the schedule of tumor evaluations.

Disease assessments will be performed as per the Schedule of Activities. Failure to perform any of the required disease assessments will result in the inability to determine disease status for that time point. A series of incomplete disease assessments will result in censoring of the time to event endpoints based on tumor assessments (eg, EFS, PFS) back to the time of the last full assessment that did not show progression. Frequent off schedule or incomplete disease assessments have the potential to weaken the conclusion of this clinical trial.

7.9.1. Screening/Baseline Tumor Assessments

Screening/baseline tumor assessment should be carried out within 21 days before the first dose of study medication (Phase 1 portion and tumor-specific cohorts) or the date of randomization (Phase 2 portion). Imaging scans performed per standard of care, prior to consent are acceptable as baseline scans as long as performed within 1) 21 days of C1D1 (Phase 1 and tumor specific cohorts) or randomization (Phase 2), 2) there was no intervening anticancer therapy, 3) imaging parameters meet standard RECIST 1.1, RANO or INRC requirements, as applicable and 4) same imaging modalities can be continued for on-treatment tumor response assessment.

Disease assessment for all patients at baseline will include CT, MRI, MIBG (for neuroblastoma), PET or bone scans of all sites of disease as clinically indicated. CT/MRI is the preferred method of tumor evaluation and measurements. However, if the CT/MRI component of FDG-PET scan is identical to diagnostic CT/MRI, then this can be used for target/non-target tumor evaluation. If the CT/MRI component of the FDG-PET scan is for anatomical mapping/localization, but does not have diagnostic quality, then CT/MRI scan is needed for target/non-target tumor evaluation.

Bone marrow assessment neuroblastoma patients

Bilateral bone marrow aspirates and biopsies are required for patients with neuroblastoma at baseline. Bone marrow assessment performed, as per standard of care, prior to consent are acceptable as baseline assessments as long as performed within 1) 21 days of C1D1, 2) there was no intervening anticancer therapy, 3) bilateral aspirates and biopsies from 2 anatomic locations (ie, left and right posterior iliac crests) were assessed. If positive at baseline, repeat bone marrow aspirates and biopsies are required at tumor assessment time points. If negative at baseline, repeat bone marrow aspirates and biopsies should be done as clinically indicated.

Bone marrow assessment EWS patients

Bone marrow aspirates and biopsies are required for patients with EWS, if bone marrow involvement is suspected and/or patient had bone marrow disease in the past (eg, at initial diagnosis or prior recurrence). If negative at baseline, repeat bone marrow aspirates and biopsies should be done as clinically indicated. Bone marrow assessment performed, as per standard of care, within 8 weeks of randomization is acceptable if the bone marrow assessment was positive and there was no intervening anti-cancer treatment.

Bone marrow assessment other tumor types

For other tumor types; bone marrow aspirates and biopsies are only needed as clinically indicated.

7.9.2. Post-Baseline Tumor Assessments

Phase 1 Portion and Tumor Specific Cohorts

Post-baseline tumor assessments while on treatment will be performed every 2 cycles (±7 days) for the first 4 assessments and then every 4 cycles (±7 days) after start of study medication until radiographically and/or clinically documented disease progression as per RECIST version 1.1, modified RANO for CNS malignancies, or INRC for neuroblastoma, initiation of new anticancer therapy, or discontinuation of patient from overall study participation (eg, death, patient's request, lost to follow-up).

For patients with evidence of partial response or complete response, a confirmatory tumor response assessment must be performed ≥4 weeks after the initial assessment which showed the response.

Patients who permanently discontinue study medication for reasons other than radiographically and/or clinically (ie, for photographed or palpable lesions) documented disease progression as per RECIST, modified RANO, or INRC definitions will continue to have tumor assessment performed during the follow-up visits every 6 weeks (±7 days) from last on-treatment tumor assessment for the first 6 months since start of study treatment, then every 12 weeks (±7 days) thereafter until documented disease progression, initiation of new anticancer therapy or discontinuation of patient from overall study participation (eg, death, patient's request, lost to follow-up), whichever occurs first. Every effort should be made to perform a last tumor assessment before starting a new anticancer therapy. Additional unscheduled tumor assessments may be performed as clinically indicated at any time. Post-baseline tumor assessments will include clinical assessment of tumor sites identified at baseline. All lesion measurements must be recorded in the CRF.

CTs should be performed with contrast agents unless contraindicated for medical reasons. If IV contrast is medically contraindicated, the imaging modality to be used to follow the disease (either CT without contrast or MRI) should be the modality which best evaluates the disease, and the choice should be determined by the investigator in conjunction with the local radiologist. Diagnostic imaging should remain consistent throughout the study. The same method and technique should be used to characterize each lesion identified and reported at baseline, during the study treatment period and at follow-up. The use of plain-film X-rays is not recommended. If MRI is used to follow up bone lesion(s), it should be performed a few days before any treatment that may affect bone marrow cellularity (eg, G-CSF).

Response and progression will be evaluated in this study using RECIST guideline version 1.1, modified RANO for CNS malignancies, or INRC for neuroblastoma (Appendix 5, Appendix 6, and Appendix 7 respectively).

Phase 2 Portion

Post-baseline tumor assessments while on treatment will be performed every 2 cycles (±7 days) for the first 4 assessments (eg, at completion of Cycle 2, 4, 6, 8) and then every 4 cycles (±7 days) (eg, at completion of Cycle 12, 16, 20, etc.), from the date of randomization until radiographically and/or clinically documented disease progression as per

RECIST version 1.1 or discontinuation of patient from overall study participation (eg, death, patient's request, lost to -follow-up). At minimum, all sites of disease identified at screening must be assessed for response and results must be recorded in the CRF.

Every effort should be made to perform tumor assessment in a fixed 6-week (±7 days) interval for the first 4 assessments (eg, end of week 6, 12, 18, 24) from randomization and then in a 12-week (±7 days) interval (eg, week 36, 48, 60, etc) particularly in patients with treatment cycle delays.

For patients with evidence of response (partial response or complete response), a confirmatory scan must be performed ≥4 weeks after the initial scan showing the response. For patients with bone marrow disease at study entry and with evidence of CR, bone marrow aspirates and biopsies are required to confirm CR.

Patients who permanently discontinue study medication for reasons other than radiographically and/or clinically (ie, for photographed or palpable lesions) documented disease progression as per RECIST 1.1 or secondary malignancy will continue to have tumor assessment performed during the follow-up visits every 6 weeks (±7 days) for the first 6 months since the date of randomization, and then every 12 weeks (±7 days) thereafter until documented disease progression, diagnosis of secondary malignancy or discontinuation of patient from overall study participation (eg, death, patient's request, lost to follow-up), whichever occurs first. Every effort should be made to continue tumor assessments regardless of initiation of new anticancer therapy until progressive disease is documented. Additional unscheduled tumor assessments may be performed as clinically indicated at any time. All tumor assessments data including unscheduled tumor assessments must be reported in the study CRF. The imaging modality to be used to follow the disease (CT with or without contrast and/or MRI) should be the modality which best evaluates the disease, and the choice should be determined by the investigator in conjunction with the local radiologist. Diagnostic imaging should remain consistent throughout the study. The same method and technique should be used to characterize each lesion identified and reported at baseline, during the study treatment period and at follow-up. The use of plain-film X-rays is not recommended. FDG-PET/PET-CT or PET-MRI may be used for baseline and subsequent staging of distant metastatic disease as long as the quality of the CT/MRI component is sufficient to allow disease assessment according to RECIST 1.1 criteria. If MRI is used to follow up bone lesion(s) it should be performed a few days before any treatment that may affect bone marrow cellularity (eg, G-CSF).

The FDG-PET/PET-CT/PET-MRI if performed at baseline (not mandatory) to identify distant metastases should be repeated at completion of Cycle 4 (at week 12 ±7 days tumor assessment timepoint).

Response and progression will be evaluated in this study using RECIST guideline version 1.1 (Appendix 5).

8. ADVERSE EVENT REPORTING

8.1. Requirements

The table below summarizes the requirements for recording safety events on the CRF and for reporting safety events on the Clinical Trial (CT) Serious Adverse Event (SAE) Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) non-serious adverse events (AEs); and (3) exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure.

Safety Event	**Recorded on the CRF**	**Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness**
SAE	All	All
Non-serious AE	All*	None
Exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure.	All (regardless of whether associated with an AE), **except occupational exposure.**	Exposure during pregnancy, exposure via breastfeeding, occupational exposure (regardless of whether associated with an AE).

*In the Phase 2 portion of the study all AEs ≥Grade 3, any AEs leading to cycles delays, study treatment interruptions, any AEs requiring dose reduction and events leading to permanent discontinuation of study treatment will be recorded on the CRF.

All observed or volunteered events regardless of treatment group or suspected causal relationship to the investigational product(s) will be reported as described in the following paragraphs. Events listed in the table above that require reporting to Pfizer Safety on the CT SAE Report Form within 24 hours of awareness of the event by the investigator **are to be reported regardless of whether the event is determined by the investigator to be related to an investigational product under study**. In particular, if the SAE is fatal or life-threatening, notification to Pfizer Safety must be made immediately, irrespective of the extent of available event information. This timeframe also applies to additional new (follow-up) information on previously forwarded reports. In the rare situation that the investigator does not become immediately aware of the occurrence of an event, the investigator must report the event within 24 hours after learning of it and document the time of his/her first awareness of the event. For each event, the investigator must pursue and obtain adequate information both to determine the outcome and to assess whether it meets the criteria for classification as an SAE (see Section 8.2.3). In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion. This information is more detailed than that recorded on the CRF. In general, this will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a patient death, a summary of available autopsy findings must be submitted as soon as possible

to Pfizer Safety. Any pertinent additional information must be reported on the CT SAE Report Form; additional source documents (eg, medical records, CRF, laboratory data) are to be sent to Pfizer Safety **ONLY** upon request.

As part of ongoing safety reviews conducted by the sponsor, any non-serious AE that is determined by the sponsor to be serious will be reported by the sponsor as an SAE. To assist in the determination of case seriousness, further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

8.1.1. Additional Details On Recording Adverse Events on the CRF

All events detailed in the table above will be recorded on the AE page(s) of the CRF. It should be noted that the CT SAE Report Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the CT SAE Report Form for reporting of SAE information.

8.1.2. Eliciting Adverse Event Information

The investigator is to record on the CRF all directly observed AEs and all AEs spontaneously reported by the study patient/parent(s)/legal guardian/legally acceptable representative. In addition, each study patient/parent(s)/legal guardian/legally acceptable representative will be questioned about the occurrence of AEs in a non-leading manner.

8.1.3. Withdrawal From the Study Due to Adverse Events (see also the Patient Withdrawal section)

Withdrawal due to AEs should be distinguished from withdrawal due to other causes, according to the definition of AE noted below, and recorded on the CRF.

When a patient withdraws from the study because of a SAE, the SAE must be recorded on the CRF and reported, as appropriate, on the CT SAE Report Form, in accordance with the Requirements section above.

8.1.4. Time Period for Collecting AE/SAE Information

The time period for actively eliciting and collecting AEs and SAEs (“active collection period”) for each patient begins from the time the patient provides informed consent, which is obtained before the patient’s participation in the study (ie, before undergoing any study-related procedure and/or receiving investigational product), through and including a minimum of 28 calendar days after the last administration of the investigational product.

For patients who are screen failures, the active collection period ends when screen failure status is determined.

8.1.4.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a patient during the active collection period are reported to Pfizer Safety on the CT SAE Report Form.

SAEs occurring in a patient after the active collection period has ended are reported to Pfizer Safety if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to investigational product must be reported to Pfizer Safety.

Follow up by the investigator continues throughout and after the active collection period and until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

If a patient begins a new anticancer therapy, SAEs occurring during the above indicated active collection period must still be reported to Pfizer Safety irrespective of any intervening treatment.

8.1.4.2. Recording Non-serious AEs and SAEs on the CRF

During the active collection period, both nonserious AEs and SAEs are recorded on the CRF.

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE or SAE.

Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

If a patient begins a new anticancer therapy, the recording period for nonserious AEs ends at the time the new treatment is started; however, SAEs must continue to be recorded on the CRF during the above indicated active collection period.

8.1.5. Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and non-serious); the investigator must record the causal relationship on the CRF, and report such an assessment in accordance with the SAE reporting requirements, if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the sponsor. If the investigator's causality assessment is "unknown but not related" to investigational product, this should be clearly documented on study records.

In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and

report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

8.1.6. Sponsor's Reporting Requirements to Regulatory Authorities

AE reporting, including suspected unexpected serious adverse reactions, will be carried out in accordance with applicable local regulations.

8.2. Definitions

8.2.1. Adverse Events

An AE is any untoward medical occurrence in a study patient administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of AEs include, but are not limited to:

- Abnormal test findings;
- Clinically significant signs and symptoms;
- Changes in physical examination findings;
- Hypersensitivity;
- Drug abuse;
- Drug dependency.

Additionally, AEs may include signs and symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy (EDP);
- Exposure via breastfeeding;
- Medication error;
- Occupational exposure.

Worsening of signs and symptoms of the malignancy under study should be recorded as AEs in the appropriate section of the CRF. Disease progression assessed by measurement of malignant lesions on radiographs or other methods should not be reported as AEs.

8.2.2. Abnormal Test Findings

Abnormal objective test findings should be recorded as AEs when any of the following conditions are met:

- Test result is associated with accompanying symptoms; and/or
- Test result requires additional diagnostic testing or medical/surgical intervention; and/or
- Test result leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy; and/or
- Test result is considered to be an AE by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require recording as an AE.

8.2.3. Serious Adverse Events

A serious adverse event is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect.

Or that is considered to be:

- An important medical event.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the patient or may require intervention to prevent one of the other AE outcomes, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Progression of the malignancy under study (including signs and symptoms of progression) should not be reported as an SAE unless the outcome is fatal within the active collection period. Hospitalization due to signs and symptoms of disease progression should not be reported as an SAE. If the malignancy has a fatal outcome during the study or within the active collection period, then the event leading to death must be recorded as an AE on the CRF, and as an SAE with Common Terminology Criteria for Adverse Events (CTCAE) Grade 5 (see the Severity Assessment section).

8.2.4. Hospitalization

Hospitalization is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility, or any prolongation of an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, , or an inpatient rehabilitation floor to the oncology unit). An emergency room visit does not necessarily constitute a hospitalization; however, the event leading to the emergency room visit is assessed for medical importance.

Hospitalization does not include the following:

- Outpatient rehabilitation facilities;
- Hospice facilities;
- Respite care (eg, caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Same-day surgeries (as outpatient/same-day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for workup of a persistent pretreatment laboratory abnormality);
- Social admission (eg, patient has no place to sleep);
- Administrative admission (eg, for yearly physical examination);
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery);

- Hospitalization for observation without a medical AE;
- Preplanned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual patient;
- Admission exclusively for the administration of blood products.

Diagnostic and therapeutic noninvasive and invasive procedures, such as surgery, should not be reported as SAEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an SAE. For example, an acute appendicitis that begins during the reporting period should be reported if the SAE requirements are met, and the resulting appendectomy should be recorded as treatment of the AE.

8.3. Severity Assessment

GRADE	Clinical Description of Severity
1	MILD adverse event
2	MODERATE adverse event
3	SEVERE adverse event
4	LIFE-THREATENING consequences; urgent intervention indicated
5	DEATH RELATED TO adverse event

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example, a headache may be severe (interferes significantly with the patient's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above.

8.4. Special Situations

8.4.1. Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed "tolerators", while those who show transient liver injury, but adapt are termed "adaptors". In some patients, transaminase elevations are a harbinger of a more serious potential outcome. These patients fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as drug-induced liver injury (DILI). Patients who experience a transaminase elevation above 3 times the upper limit of normal (3 × ULN) should be monitored more frequently to determine if they are an "adaptor" or are "susceptible".

In the majority of DILI cases, elevations in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) precede total bilirubin (TBili) elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated

above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same lab sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy's Law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the patient's individual baseline values and underlying conditions. Patients who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy's Law) cases to definitively determine the etiology of the abnormal laboratory values:

- Patients with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values >3 × ULN AND a TBili value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available;

- For patients with baseline AST **OR** ALT **OR** TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

    - Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND >3 × ULN; or >8 × ULN (whichever is smaller).

    - Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least 1 × ULN **or** if the value reaches >3 × ULN (whichever is smaller).

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's Law case should be reviewed with the sponsor.

The patient should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment. For oncology studies, the possibility of hepatic neoplasia (primary or secondary) should be considered.

In addition to repeating measurements of AST and ALT and TBili, laboratory tests should include albumin, creatine kinase (CK), direct and indirect bilirubin, gamma-glutamyl transferase (GGT), prothrombin time (PT)/international normalized ratio (INR), alkaline phosphatase. Total bile acids, acetaminophen drug and/or protein adduct levels should be performed, if available. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine

etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's Law) cases if no other reason for the liver function test (LFT) abnormalities has yet been found. **Such potential DILI (Hy's Law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's Law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

8.4.2. Exposure to the Investigational Product During Pregnancy or Breastfeeding, and Occupational Exposure

Exposure to the investigational product under study during pregnancy or breastfeeding and occupational exposure are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.4.2.1. Exposure During Pregnancy

For both unapproved/unlicensed products and for marketed products, an EDP occurs if:

- A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, because of treatment or environmental exposure) to the investigational product; or the female becomes or is found to be pregnant after discontinuing and/or being exposed to the investigational product;
    - An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).
- A male has been exposed (eg, because of treatment or environmental exposure) to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy.

If a patient or patient's partner becomes or is found to be pregnant during the patient's treatment with the investigational product, the investigator must report this information to Pfizer Safety on the CT SAE Report Form and an EDP supplemental form, regardless of whether an SAE has occurred. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a patient reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or

spillage) to Pfizer Safety using the EDP supplemental form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP supplemental form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the investigational product.

Additional information regarding the EDP may be requested by the sponsor. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the patient with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the patient was given the Pregnant Partner Release of Information Form to provide to his partner.

8.4.2.2. Exposure During Breastfeeding

Scenarios of exposure during breastfeeding must be reported, irrespective of the presence of an associated SAE, to Pfizer Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form. An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug's administration, the SAE is reported together with the exposure during breastfeeding.

8.4.2.3. Occupational Exposure

An occupational exposure occurs when, during the performance of job duties, a person (whether a healthcare professional or otherwise) gets in unplanned direct contact with the product, which may or may not lead to the occurrence of an AE.

An occupational exposure is reported to Pfizer Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form, regardless of whether there is an associated SAE. Since the information does not pertain to a patient enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

8.4.3. Medication Errors

Other exposures to the investigational product under study may occur in clinical trial settings, such as medication errors.

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
Medication errors	All (regardless of whether associated with an AE)	Only if associated with an SAE

8.4.3.1. Medication Errors

Medication errors may result from the administration or consumption of the investigational product by the wrong patient, or at the wrong time, or at the wrong dosage strength. Unintentional palbociclib doses differing from the prescribed dose by >15% should be reported as medication errors.

Medication errors include:

- Medication errors involving patient exposure to the investigational product;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating patient.
- The administration of expired investigational product or an investigational product that has undergone temperature excursion from the specified storage range, unless it is determined by the sponsor that the investigational product under question is acceptable for use.

Such medication errors occurring to a study participant are to be captured on the medication error page of the CRF, which is a specific version of the AE page.

In the event of medication dosing error, the sponsor should be notified immediately.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is recorded on the medication error page of the CRF and, if applicable, any associated AE(s), serious and non-serious, are recorded on an AE page of the CRF.

Medication errors should be reported to Pfizer Safety within 24 hours on a CT SAE Report Form **only when associated with an SAE**.

9. DATA ANALYSIS/STATISTICAL METHODS

Detailed methodology for summary and statistical analyses of the data collected in this study is outlined here and further detailed in a statistical analysis plan (SAP), which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

9.1. Analysis Sets

9.1.1. Full Analysis Set

For the Phase 1 portion of the study, the full analysis set is same as the safety analysis set which includes all enrolled patients who receive at least 1 dose of study drug (ie, palbociclib, TMZ or IRN for palbociclib in combination with TMZ or IRN; palbociclib, TOPO or CTX for palbociclib in combination with TOPO and CTX). This will be the primary analysis set for all safety and efficacy endpoints in the dose escalation part/dose determination part, dose expansion cohort, and tumor-specific cohorts.

For the randomized Phase 2 portion of the study, the full analysis set will include all randomized patients. Patients will be analyzed according to the treatment they have been randomized to receive. The full analysis set will be the primary population for evaluating all efficacy endpoints and patient characteristics.

9.1.2. Safety Analysis Set

For the Phase 1 portion of the study, the safety analysis set will include all enrolled patients who receive at least 1 dose of study drug (ie, palbociclib, TMZ or IRN for palbociclib in combination with TMZ or IRN; palbociclib, TOPO or CTX for palbociclib in combination with TOPO and CTX). The full analysis set and the safety analysis set are identical.

For the randomized Phase 2 portion of the study, the safety analysis set will include all randomized patients who receive at least 1 dose of study drug (ie, palbociclib, TMZ or IRN for palbociclib in combination with TMZ or IRN). Patients will be analyzed according to the treatment actually received. The safety analysis set will be the primary population for evaluating safety and treatment administration/compliance.

9.1.3. Per protocol Analysis Set (Evaluable for DLT)

9.1.3.1. Per-Protocol Analysis Set for Palbociclib in Combination With IRN and TMZ

The per protocol analysis set includes all enrolled patients who receive at least 1 dose of investigational products (ie, palbociclib, TMZ or IRN) and who do not have major treatment deviations during the first cycle of treatment. Patients with major treatment deviations in the first cycle are not evaluable for the MTD assessment, unless the treatment deviation is due to a DLT or other treatment-related toxicity and will be replaced to permit MTD estimation. Major treatment deviations include:

- Administration of less than 80% of the planned dose of palbociclib, IRN, and/or TMZ in Cycle 1 for reasons other than treatment-related toxicity; ie, patients who receive less than 12 doses, 4 doses, and/or 4 doses of prescribed palbociclib, IRN, and/or TMZ, respectively, in Cycle 1 for reasons other than treatment-related toxicity (eg, disease progression, withdrawal of consent) will be considered inevaluable for estimating the MTD and will be replaced;

- Administration of more than 120% of the planned dose of palbociclib, IRN, and/or TMZ in Cycle 1; ie, patients who receive more than 16 doses, 6 doses, and/or 6 doses of prescribed palbociclib, IRN, and/or TMZ, respectively, in Cycle 1 will be considered inevaluable for estimating the MTD and will be replaced;

- Protocol-mandated prophylaxis in Cycle 1 is not administered. Note that patients who did not receive mandated antidiarrheal prophylaxis but did not experience diarrhea that meets DLT criteria will be considered DLT evaluable.

9.1.3.2. Per-Protocol Analysis Set for Palbociclib in Combination With TOPO and CTX

The per protocol analysis set includes all enrolled patients who receive at least 1 dose of investigational products (ie, palbociclib, TOPO or CTX) and who do not have major treatment deviations during the first cycle of treatment. Patients with major treatment deviations in the first cycle are not evaluable for the decision of dose determination, unless the treatment deviation is due to a DLT or other treatment-related toxicity and will be replaced. Major treatment deviations include:

- Administration of less than 80% of the planned dose of palbociclib, TOPO, and/or CTX in Cycle 1 for reasons other than treatment-related toxicity; ie, patients who receive less than 12 doses, 4 doses, and/or 4 doses of prescribed palbociclib, TOPO, and/or CTX, respectively, in Cycle 1 for reasons other than treatment-related toxicity (eg, disease progression, withdrawal of consent) will be considered inevaluable for the decision of dose determination and will be replaced;

- Administration of more than 120% of the planned dose of palbociclib, TOPO, and/or CTX in Cycle 1; ie, patients who receive more than 16 doses, 6 doses, and/or 6 doses of prescribed palbociclib, TOPO, and/or CTX, respectively, in Cycle 1 will be considered inevaluable for estimating the MTD and will be replaced;

- Protocol-mandated G-CSF in Cycle 1 is not administered. Note that patients who did not receive mandated G-CSF prophylaxis but did not experience neutropenia that meets DLT criteria will be considered DLT evaluable.

9.1.4. PK Analysis Set

The PK parameter analysis set is defined as all patients who are in the Safety Analysis Set and have sufficient information to estimate at least 1 of the PK parameters of interest.

The PK concentration analysis set is defined as all patients who are in the Safety Analysis Set and and have at least 1 reported analyte concentration.

9.1.5. Biomarker Analysis Set

The biomarker analysis set is defined as all randomized patients who have received at least 1 dose of investigational products (ie, palbociclib, TMZ or IRN for palbociclib in combination with TMZ or IRN; palbociclib, TOPO or CTX for palbociclib in combination with TOPO and CTX) and who have at least 1 baseline biomarker assessment. Analysis sets will be defined separately for serum, plasma, archival tumor tissue, and de novo tumor biopsies, as appropriate.

9.1.6. Patient Reported Outcome (PRO) Evaluable Analysis Set

For the randomized Phase 2 portion of the study, the PRO evaluable analysis set is defined as a subset of the full analysis set who have both baseline and at least 1 post-baseline PRO assessment. The PRO evaluable analysis set will be the primary population for the analysis of change from baseline.

9.2. Statistical Methods and Properties

9.2.1. Dose Escalation Part and Dose Expansion Cohort for Combination of Palbociclib With TMZ and IRN (Phase 1)

Due to the exploratory nature of the study, no confirmatory inferential analyses are planned since the primary objectives of the dose escalation part and dose expansion cohort are to assess the safety and tolerability of palbociclib in combination with TMZ and IRN in children, adolescents, and young adults with recurrent or refractory solid tumors in order to determine the MTD and confirm the RP2D.

The dose escalation part of the study employs a rolling 6 design[44] to guide dose escalation and to determine the MTD. The rolling 6 design for this pediatric Phase 1 study is considered to be advantageous over other conventional methods. This design leads to significant decrease in the overall duration of study conduct without increasing the risk of toxicity when compared to the standard “3+3” design. Given a narrow range of doses evaluated (3 dose levels including dose level -1), other model based designs (eg, Continual Reassessment Method) may not be suitable since very little data would be available to fit the model.

9.2.1.1. Statistical Methods for Dose Escalation/De-Escalation for Combination of Palbociclib With TMZ and IRN (Phase 1)

Decisions as to whether to enroll a new patient onto the current, next highest, or next lowest dose level will be made based on available data at the time of new patient enrollment. The rolling 6 design provides a way to shorten the timeline of pediatric Phase 1 trials by reducing the number of times a study is suspended to accrual, allowing accrual of 2 to 6 patients concurrently onto a dose level based on the number of patients currently enrolled and evaluable, the number of DLTs observed, and the number of patients at risk of developing a DLT.

Decision rules for dose escalation/de-escalation are described in Section 3.1.1.1. For example, when 3 patients are enrolled onto a dose cohort and all 3 patients have been evaluated for DLTs when the 4th patient enters and there are no DLTs among the first 3 patients, the dose is escalated and the 4th patient is enrolled to the next higher dose level. If DLT data is not yet available for 1 or more of the first 3 patients, or if 1 DLT has been observed, the new patient will enter at the same dose level. Lastly, if 2 or more DLTs have been observed, the dose level will be de-escalated. The process will be repeated for patients 5 and 6. Accrual to the study will only be suspended when awaiting data from 6 patients. When patients are not evaluable for toxicity, they will be replaced with the next available patient if escalation or de-escalation rules have not been fulfilled at the time the next available patient enrolls onto the study.

The dose escalation part of the study is terminated when 6 DLT evaluable patients have been treated at the highest dose with DLT rate <33%.

9.2.1.2. Statistical Method for Estimating the MTD (Phase 1)

The MTD is defined as the highest dose level at which <33% of a minimum of 6 evaluable patients experience a DLT during Cycle 1 of treatment. Specifically, a dose level will be defined as exceeding the MTD if 33% or more patients experience a DLT. If the MTD has been exceeded, the next lower dose will be defined as the MTD as long as 6 patients have been evaluated on that level. In the event that the MTD is not reached, PK analysis will be used to define the RP2D or additional dose levels to be tested and the highest dose will proceed to dose expansion.

9.2.2. Dose Determination Part and Dose Expansion Cohort for Combination of Palbociclib With TOPO and CTX (Phase 1)

The dose determination part of the study will evaluate the safety and tolerability of the potential RP2D for palbociclib in combination with TOPO and CTX. The starting dose of palbociclib is considered the MAD and no further dose escalation exceeding the MAD is planned. No inferential analyses are planned due to the nature of the study. The dose determination part of the study employs a modified rolling 6 design (Table 9) to guide dose de-escalation and to determine the dose proceeding to dose expansion to confirm the RP2D.

9.2.2.1. Statistical Methods for Dose Determination for Combination of Palbociclib With TOPO and CTX (Phase 1)

The starting dose of palbociclib in combination with TOPO and CTX is the MTD determined in the IRN and TMZ combination. This dose is considered the MAD and no further dose escalation is planned. If <33% of a minimum of 6 evaluable patients experience a DLT at the MAD, the dose will proceed to dose expansion to be confirmed as the RP2D. If ≥33% of evaluable patients experience a DLT, dose de-escalation to the next lower dose level will occur according to decision rules outlined in Table 9 following a modified rolling 6 design. For example, if 2 or more of the 6 evaluable patients treated at the MAD experience a DLT, the dose will be de-escalated to the next lower dose level. If a minimum of 6 evaluable patients have been treated at this dose level and <33% experience a DLT, the dose will proceed to dose expansion to further confirm the RP2D. Accrual to the study will only be suspended when awaiting safety data from 6 patients.

9.2.3. Tumor-Specific Cohorts

Once a tumor-specific cohort is opened, a modified Simon's 2-stage optimal design will be employed in order to evaluate the preliminary antitumor activity of palbociclib in combination with TMZ and IRN and/or palbociclib with TOPO and CTX within each specific tumor type treated at the respective RP2D. ORR is defined as the proportion of patients with best overall response of either confirmed CR or confirmed PR per RECIST v.1.1, modified RANO for CNS malignancies, or INRC for neuroblastoma.

9.2.4. Randomized Phase 2

Once the RP2D is confirmed for the combination of palbociclib with IRN and TMZ in the Phase 1 portion of the study, the Phase 2 portion of the study will be initiated to compare the efficacy of palbociclib in combination with IRN and TMZ versus IRN and TMZ alone in patients with recurrent or refractory EWS. Approximately 75 patients will be randomized in a 2:1 ratio to receive either palbociclib in combination with IRN and TMZ (Arm A: approximately 50 patients) or IRN and TMZ chemotherapy alone (Arm B: approximately 25 patients). Randomization will be stratified using block randomization by type and time of current disease recurrence (primary refractory or 1st recurrence <2 years versus 1st recurrence ≥2 years since completion of 1st line treatment or 2nd or greater recurrence).

9.3. Sample Size Determination

9.3.1. Dose Escalation/Dose Determination Parts (Phase 1)

Palbociclib in Combination With TMZ and IRN

The exact sample size of the rolling 6 design in the dose escalation part of the study cannot be determined in advance because of the dynamic feature of the design. The number of patients to be enrolled in the study will depend upon the number of DLTs observed which will in turn determine the number of patients at each dose level and the number of dose levels explored.

The maximum sample size for the dose escalation part for combination of palbociclib with IRN and TMZ is 24 patients, assuming that all the 4 dose levels are evaluated and require 6 patients each before the MTD is defined.

The probability of detecting at least 1 patient with a DLT in 6 evaluable patients is 0.469, 0.738, 0.882, 0.953, and 0.984, when the true underlying DLT rates are 10%, 20%, 30%, 40%, and 50%, respectively. A sample size of 24 patients (at any dose) enables detection of at least 1 AE with a probability of 0.214, 0.708, and 0.920, when the true underlying risk is 1%, 5%, and 10%, respectively.

Palbociclib in Combination With TOPO and CTX

The maximum sample size for the dose determination part for combination of palbociclib with TOPO and CTX is 12 patients, assuming that 6 patients are evaluated at the MAD and dose de-escalation proceeds to the next lower dose level with 6 evaluable patients.

9.3.2. Dose Expansion Cohort (Phase 1)

Palbociclib in combination With TMZ and IRN

Once the MTD has been estimated in the dose escalation part, a minimum of 12 patients with recurrent or refractory solid tumors will be enrolled and treated at the MTD in a dose expansion cohort.

Based on probability theory, a sample size of 12 patients at the MTD will allow for estimates of any binary variable (eg, ORR) with the width of the 95% CI no wider than 0.58. A sample size of 12 patients (at any dose) enables detection of at least 1 AE with a probability of 0.114, 0.460, and 0.718, when the true underlying risk is 1%, 5%, and 10%, respectively.

Palbociclib in combination With TOPO and CTX

For combination of palbociclib with TOPO and CTX, a sample size of 12 patients at the dose that proceeds to dose expansion is justified in a similar manner as described above.

Both Treatment Regimens

To adequately describe palbociclib PK, the study will aim to enroll a minimum of 6 PK-evaluable patients for each treatment combination in each of the following age groups: ≤6 years old, >6 years and <12 years old, and ≥12 years and <18 years old for each combination. The expansion cohorts may remain open for targeted enrollment by age group and by combination. However, given the relatively limited patient population of pediatric cancer patients in some of the age groups particularly the ≤ 6 and the >6-<12 subgroups the dose expansion cohorts may be closed if the available PK data is deemed sufficient per the Sponsor assessment.

9.3.3. Tumor-Specific Cohort

Tumor-specific cohorts of up to 21 patients for each treatment combination may be opened depending on observations of antitumor activity, ie, if 2 or more patients from the dose

escalation part and/or dose expansion cohort of the combination of palbociclib with TMZ and IRN or in the dose determination part and/or dose expansion cohort of the combination of palbociclib with TOPO and CTX show a confirmed objective response in the specific tumor type. Given the limited data and heterogeneity of the response rates with IRN and TMZ as well as TOPO and CTX in various pediatric tumor types, a total sample size of 21 patients was driven by the current hypothesis (a null hypothesis of 33% in ORR below which further investigation for the combination would not be warranted vs. an alternative hypothesis of 58% in ORR) based on the most likely tumor cohorts to open (neuroblastoma, rhabdomyosarcoma, rhabdoid tumor, medulloblastoma) to satisfy the error constraints (power and type I error). A modified Simon's 2-stage optimal design described below (Table 17) will be used for each of the opened tumor-specific cohorts. Under the null hypothesis of a true ORR that does not exceed 33%, the 2-stage optimal design will control 1sided type I error to be approximately 0.10. If the true response rate is at least 58%, type II error will be no more than 0.20 (ie, at least 80% power). In the first stage, 7 patients will be enrolled in each tumor-specific cohort. Patients with confirmed objective responses (responders) along with any other patients (non-responders) with the same tumor type from the dose escalation part/dose determination part and/or dose expansion cohort of the study will count towards the 7 patients in the first stage. If there are only 2 confirmed objective responses in these 7 patients, the cohort will be stopped for ineffectiveness, (ie, none of the additional enrolled patients had a confirmed objective response). If there are 6 or more confirmed objective responses in these 7 patients, the study will be stopped for effectiveness. Otherwise, 14 additional patients will be enrolled in the second stage for a total of 21 patients in each tumor-specific cohort. The null hypothesis will be rejected if 10 or more confirmed objective responses are observed in the 21 patients.

Table 17. Modified Simon's 2-Stage Optimal Design Decision Rules for Tumor-Specific Cohorts

	Cumulative Number of Responses[a]	Decision
Stage 1: Enroll a total of 7 patients[b]	2	Terminate enrollment - agent ineffective
	3-5	Inconclusive - proceed to Stage 2
	6[c]	Terminate enrollment - agent effective
Stage 2: Enroll 14 additional patients	9 or less	Agent ineffective
	10 or more	Agent effective

a. Assumption based on an objective response rate of 33% for IRN/TMZ or TOPO/CTX and 58% for palbociclib/IRN/TMZ or palbociclib/TOPO/CTX, respectively.
b. Evaluated patients will include the 2 objective responses observed and any other patients with the same tumor type during the dose escalation part/dose determination part and dose expansion cohort of the study.
c. Lower bound of the Wilson's 2-sided 80% confidence interval is greater than 62%.

9.3.4. Randomized Phase 2

The sample size for the Phase 2 portion of the study is determined based on the assumptions that median EFS for patients receiving IRN and TMZ chemotherapy alone in the treatment of recurrent and refractory EWS is 4.7 months[46] and an improvement to median EFS of

8.1 months (corresponding to a HR = 0.58) for palbociclib in combination with IRN and TMZ is considered clinically significant. A total of approximately 50 EFS events by investigator assessment are required in the 2 treatment arms of the study based on a 2:1 randomization to have at least 80% power to detect a hazard ratio of 0.58 in favor of palbociclib plus IRN and TMZ arm using a 1-sided log-rank test at a significance level of 0.20. A group sequential design with a Rho family (1.0) β-spending function is used to determine the futility boundary. Assuming a 5% and 10% dropout rates by 12 months on the palbociclib combination arm and chemotherapy alone arm, respectively, a non-uniform accrual accomplished over a 25-month period and follow-up for about 6 months after the last patient is randomized, a total sample size of approximately 75 patients (approximately 50 patients in the palbociclib in combination with IRN and TMZ arm and approximately 25 patients in the IRN and TMZ chemotherapy alone arm) is required. It is expected approximately 75% of the patients will be pediatric patients (age ≥2 and <18 years old).

9.4. Safety Analysis

The safety analysis set will be the primary population for safety evaluation. For the Phase 1 portion of the study, safety data will be summarized for each treatment combination by dose level using appropriate tabulations and descriptive statistics, including pooling together patients treated at the MTD/potential RP2D from the dose escalation/dose determination part of the study and the dose expansion cohort for the respective treatment combination (palbociclib with TMZ and IRN or palbociclib with TOPO and CTX). For the Phase 2 portion of the study, safety data will be summarized by treatment arm.

9.4.1. Analysis of the Primary Endpoint (Phase 1)

For combination of palbociclib with TMZ and IRN, first cycle DLT is the primary endpoint of the dose escalation part of the study. The occurrence of DLTs observed in the dosing cohorts is used to estimate the MTD as described in Section 3. AEs constituting DLTs will be listed per dose level.

For combination of palbociclib with TOPO and CTX, first cycle DLT is the primary endpoint of the dose determination part of the study. The occurrence of DLTs observed in the dosing cohorts is used to determine the dose that proceeds to dose expansion to confirm the RP2D.

Summaries and analyses of the primary safety endpoint (ie, first cycle DLT) will be based on the per protocol analysis set (evaluable for DLT) for combination of palbociclib with TMZ and IRN and for combination of palbociclib with TOPO and CTX , respectively.

9.4.2. Analysis of Safety Endpoints (Phase 1, Tumor-Specific Cohorts and Randomized Phase 2)

Adverse Events

AEs will be graded by the investigator according to the CTCAE version 4.03 and classified using the Medical Dictionary for Regulatory Activities (MedDRA). The focus of AE summaries will be on treatment emergent adverse events (TEAEs).

Summaries of AEs by MedDRA terms, toxicity grade, seriousness and relationship to study treatment will be presented, as well as summaries of AEs leading to death, dose modifications and permanent discontinuation from study treatment. The number and percentage of patients who experienced any AE, SAE, treatment-related AE, and treatment related SAE will be summarized according to worst toxicity grades.

For the Phase 1 portion of the study, the summaries will present AEs for all cycles and Cycle 1, respectively. For tumor-specific cohorts and Phase 2 portion of the study, the summaries will present AEs for all cycles.

Laboratory Test Abnormalities

The laboratory results will be graded according to the CTCAE version 4.03 severity grade, whenever applicable. The number and percentage of patients who experienced laboratory test abnormalities will be summarized according to worst toxicity grade observed for each laboratory test. The analyses will summarize laboratory tests for all cycles and Cycle 1. Shift tables will be provided to examine the distribution of laboratory toxicities.

For laboratory tests without CTCAE grade definitions, results may be categorized as normal, abnormal, or not done.

9.4.3. Electrocardiogram

The analysis of ECG results will be based on patients in the safety analysis set with baseline and on-treatment ECG data.

ECG measurements (an average of the triplicate measurements) will be used for the statistical analysis and all data presentations. Any data obtained from ECGs repeated for safety reasons after the nominal time-points will not be averaged along with the preceding triplicates. Interval measurements from repeated ECGs will be included in the outlier analysis (categorical analysis) as individual values obtained at unscheduled time points.

QT intervals will be corrected for heart rate (QTc) using standard correction factors (ie, Fridericia's [default correction], and Bazett's). Data will be summarized and listed for QT, heart rate, RR interval, PR interval, QRS complex, QTcF (and other correction factors, eg, QT interval corrected for heart rate using Bazett's formula, as appropriate). The most appropriate correction factor will be selected and used for the following analyses of central tendency and outliers and used for the study conclusions. Descriptive statistics (n, mean, median, standard deviation, minimum, and maximum) will be used to summarize the absolute corrected QT interval and changes from baseline in corrected QT after treatment by dose and time point. For each patient and by treatment, the maximum change from baseline will be calculated as well as the maximum post-baseline interval across time-points. Categorical analysis will be conducted for the maximum change from baseline in corrected QT and the maximum post-baseline QT interval.

Patients experiencing clinically relevant morphological ECG changes will be summarized (including frequency and percentage) if applicable.

9.5. Analysis of Pharmacokinetics and Pharmacodynamics

9.5.1. Analysis of Pharmacokinetics

In general, PK data in the dose escalation/dose determination, dose expansion, tumor-specific cohorts, and Phase 2 portion of the study will be summarized using descriptive statistics by dose level, and in patients treated at the RP2D. The PK data will also be reported by prespecified age groups (≤6 years old, >6 years and <12 years old, ≥12 years and <18 years old, and ≥18 years old).

9.5.1.1. Pharmacokinetic Analysis of Palbociclib, IRN, TMZ, TOPO and CTX

Plasma PK parameters including the maximum plasma concentration (C_{max}), time to maximum plasma concentration (T_{max}), and predose concentration (C_{trough}) will be estimated for all measured analytes using noncompartmental analysis as data permit. If data permit or if considered appropriate, area under the plasma concentration versus time curve (AUCt), apparent oral plasma clearance (CL/F) or CL for IV dosing will also be estimated. The single-dose and multiple-dose PK parameters will be summarized descriptively (n, mean, standard deviation, coefficient of variation (CV), median, minimum, maximum, geometric mean and its associated CV) by analyte, dose level, cycle and day of assessment.

Analyte concentrations will be summarized descriptively (n, mean, standard deviation, CV, median, minimum, maximum, geometric mean and its associated CV) by analyte, dose, cycle, day, and nominal time.

Palbociclib PK parameters and concentrations will be summarized separately by each treatment combination. In addition, palbociclib PK parameters and concentrations may be pooled across the 2 combinations and summarized.

The relationship between analyte concentrations and/or PK parameters with response, biomarkers and/or safety findings after accounting for potential covariates may be evaluated. The results of any exploratory correlational and/or population PK/PD analysis may be reported separately from the clinical study report.

9.5.2. Analysis of Biomarker Endpoints

Biomarkers will be assessed separately for serum, plasma, archival tumor tissue, and de novo tumor biopsies. In each case, summary statistics (eg, the mean and standard deviation, median, and minimum/maximum levels of continuous, and frequencies and percentages of categorical biomarker measures) will be determined at baseline and Post treatment. For each pair of specimens, the percent change from baseline of these same parameters will also be calculated.

Data from biomarker assays may be analyzed using graphical methods and descriptive statistics such as linear regression, t-test, and analysis of variance. The statistical approach will examine correlations of biomarker results with PK parameters and measures of antitumor efficacy.

Regarding exploratory biomarkers, data analyses will be conducted with the goal of identifying biomarkers with the strongest association with clinical outcome, encompassing both safety and efficacy. Candidate biomarkers will be validated in subsequent trials.

The extent of analyses of biomarker endpoints will depend on availability of samples collected from patients in this study.

The exploratory biomarker endpoints may be reported only if data allow and may not be included in the clinical study report. Results of exploratory research may be shared through presentation(s) to conferences and/or manuscript(s).

9.5.3. Population PK Analysis or PK/PD Modeling

PK and PD data from this study may be analyzed using modeling approaches to investigate any association between palbociclib exposure and PD endpoints (eg, TK1 activity) or significant safety and/or efficacy endpoints. The results of these analyses, if performed, may be reported separately.

9.6. Efficacy Analysis

For the Phase 1 portion of the study and tumor-specific cohorts, the full analysis set which is same as the safety analysis set will be used for all efficacy analyses. Efficacy endpoints related to disease assessments will be based on the investigator assessments.

For the Phase 2 portion of the study, the full analysis set that includes all randomized patients will be used for all efficacy analyses.

9.6.1. Analysis of Primary Endpoint

Phase 1 and Tumor-Specific Cohorts

Confirmed objective response is the primary endpoint for dose expansion cohorts and tumor-specific cohorts.

The best overall response is the best response recorded from the date of first dose of study treatment until disease progression or death from any cause. Confirmed objective response is defined as the best overall response of confirmed CR or PR per RECIST v.1.1 or, modified RANO for CNS malignancies, or confirmed CR, PR or MR per INRC for neuroblastoma (Appendix 5, Appendix 6 and Appendix 7, respectively). ORR will be calculated as the proportion of patients with a best overall response of confirmed CR, PR or MR, as applicable. ORR will be estimated with the corresponding 2-sided 95% CI using Wilson's method by dose level and across all dose levels.[1] For each tumor-specific cohort, if opened, ORR will be estimated with the corresponding 2-sided 80% CI using Wilson's method. A 2-sided Wilson's 95% CI will also be reported.

Randomized Phase 2

EFS based on investigator assessment is the primary efficacy endpoint for the Phase 2 randomized portion of the study. EFS is defined as the time from randomization until first event (ie, progression, recurrence following response, second malignancy or death without progression or recurrence). Patients last known to be event-free will be censored at the date of the last objective disease assessment that verified lack of disease progression, recurrence or second malignancy.

EFS will be summarized in the full analysis set using the Kaplan-Meier method and displayed graphically where appropriate. The median EFS and corresponding 2-sided 95% CI will be provided. A stratified log-rank test will be used to compare EFS between the two treatment arms. EFS rates at specific time points will be provided based on the Kaplan-Meier method with the corresponding 2-sided 95% CIs. The hazard ratio and associated 2-sided 95% CI will be estimated using the stratified Cox proportional hazards model. A 2-sided 60% CI of the hazard ratio will also be reported.

9.6.2. Analysis of Secondary Endpoints

For the Phase 1 portion of the study and tumor-specific cohorts, DOR, PFS, and OS will be described using the Kaplan-Meier method and displayed graphically where applicable. The median event time and 2-sided 95% CI for the median will be provided for each endpoint. PFS and OS rates at specific time points may be provided based on the Kaplan-Meier method with the corresponding 2-sided 95% CIs.

For the Phase 2 portion of the study, an additional analysis for EFS, using the same methodology as the primary analysis, will be performed based on the BIRC results. Other tumor-related secondary efficacy endpoints (eg. OR, PFS) will be performed based on investigator assessment and similar analyses based on the BIRC assessment may also be provided.

Best overall response will be summarized by treatment arm. OR is defined as a best overall response of confirmed CR or PR per RECIST v.1.1. ORR will be estimated as the proportion of patients with a best overall response of confirmed CR or PR with corresponding 2-sided 95% CI. Response rate comparisons between the two treatment arms as randomized will be assessed using Cochran-Mantel-Haenszel (CMH) test with the same stratification factors as for the EFS analysis.

PFS and OS will be summarized by treatment arm using Kaplan-Meier method. The median estimates and corresponding 95% CIs will be provided for each treatment arm. A stratified log-rank test will be used to compare PFS and OS between the 2 treatment arms. The hazard ratio and associated 2-sided 95% CI will be estimated using the stratified Cox proportional hazards model.

QoL will be reported by patients at baseline and after 2 and 4 cycles using age-appropriate tools. Descriptive statistics (mean, standard deviation, median, range and 95% CI) of absolute scores and change of absolute scores from baseline will be reported for the 2

treatment arms at each assessment time point for all of the subscales of the age-appropriate questionnaires. Summary of the absolute scores and change from baseline may be calculated within appropriate age groups.

9.7. Analysis of Other Endpoints

Descriptive statistics will be used to summarize all patient demographics and other baseline characteristics, treatment administration/compliance, other safety parameters, and biomarkers. Data will also be displayed graphically where appropriate.

9.8. Interim Analysis

No formal interim analysis will be conducted for the dose escalation, dose determination part and dose expansion cohorts of the study. However, as this is an open-label study, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, facilitating dose-escalation decisions, facilitating PK/pharmacodynamic modeling, and/or supporting clinical development.

For the tumor-specific cohort(s) with a modified Simon's 2-stage design, there will be 1 formal interim analysis for futility and efficacy after the first stage of accrual is complete and have been fully evaluated for response. Unless criteria for continuation have already been met, accrual will be temporarily suspended for assessment of the primary endpoint (OR) after the first stage of accrual. If continuation criteria are not met or pre-defined efficacy criteria are met (Table 17) after assessments are complete, the corresponding tumor-specific cohort will be permanently closed.

For the Phase 2 randomized portion on the study, there will be 1 formal interim analysis for futility to allow for early stopping of the study due to futility/no signal of activity based on the primary endpoint of investigator-assessed EFS. The analysis will be performed after approximately 30 EFS events (approximately 60% of total events expected) have been documented. If the 1-sided p-value is >0.4287 (Z >-0.1796) at the interim analysis, the Phase 2 portion of the study will be terminated early for lack of efficacy.

9.9. Data Monitoring Committee

The Phase 1 portion of the study (dose escalation, dose determination and dose expansion cohorts) and tumor specific cohorts will not use an external Data Monitoring Committee (E-DMC). For the purpose of this protocol, Pfizer procedures for periodic safety review will be applied by an internal safety review team with medical and statistical capabilities to review individual and summary data collected in the safety and clinical databases. Procedures include:

- Surveillance for SAEs according to regulatory guidelines;
- Discussions between the investigators and the sponsor of AEs and laboratory tests alterations seen at each dose level in an ongoing manner at regular teleconferences and/or meetings to determine the safety profile and risk/benefit assessment and decide if further enrollment is appropriate.

- The randomized Phase 2 portion of the study will use an E-DMC. The E-DMC is independent of the study team and includes only external members. The E-DMC charter describes the role of the E-DMC in more detail. E-DMC will be responsible for ongoing monitoring of the safety and efficacy of participants in the study according to the charter. The E-DMC will make recommendations as to whether or not the trial should continue based on ongoing reviews of safety data, as well as to evaluate the planned interim efficacy data and make a recommendation regarding study continuation based on observed results of the study. The recommendations made by the E-DMC will be forwarded to the appropriate authorized Pfizer personnel for review and final decision. Pfizer will communicate such decisions, which may include summaries of aggregate analyses of endpoint events of efficacy and safety data, to regulatory authorities and investigators, as appropriate. The sponsor will designate a biostatistician not affiliated with the project to prepare data for E-DMC review.

10. QUALITY CONTROL AND QUALITY ASSURANCE

Pfizer or its agent will conduct periodic monitoring visits during study conduct to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The monitors may review source documents to confirm that the data recorded on CRFs are accurate. The investigator and institution will allow Pfizer monitors/auditors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification. This verification may also occur after study completion.

During study conduct and/or after study completion, the investigator site may be subject to review by the IRB/EC, and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

The investigator(s) will notify Pfizer or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with Pfizer or its agents to prepare the investigator site for the inspection and will allow Pfizer or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the patient's medical records. The investigator will promptly provide copies of the inspection findings to Pfizer or its agent. Before response submission to the regulatory authorities, the investigator will provide Pfizer or its agents with an opportunity to review and comment on responses to any such findings.

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included patient. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer. The investigator shall ensure that the CRFs/DCTs are securely stored at the study site in encrypted electronic and/or paper] form and will be password protected or secured in a locked room to prevent access by unauthorized third parties. When participant data are to be deleted, the investigator will ensure that all copies of such data are promptly and irrevocably deleted from all systems.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs are true. Any corrections to entries made in the CRFs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

In most cases, the source documents are the hospital or the physician's chart. In these cases, data collected on the CRFs must match the data in those charts.

In some cases, the CRF may also serve as the source document. In these cases, a document should be available at the investigator site and at Pfizer that clearly identifies those data that will be recorded on the CRF, and for which the CRF will stand as the source document. When participant data are to be deleted, the investigator will ensure that all copies of such data are promptly and irrevocably deleted from all systems.

11.2. Record Retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent/assent documents, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, and telephone call reports). The records should be retained by the investigator according to ICH guidelines, according to local regulations, or as specified in the clinical study agreement (CSA), whichever is longer. The investigator must ensure that the records continue to be stored securely for so long as they are retained.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer.

Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

11.3. Data Protection

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant data.

Participants' personal data will be stored at the study site in encrypted electronic and/or paper form and will be password-protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site will be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of participants with regard to the processing of personal data, participants will be assigned a single, participant-specific numerical code. Any participant records or data sets that are transferred to the sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, participant-specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to their actual identity and medical record ID. In case of data transfer, the sponsor will protect the confidentiality of participants' personal data consistent with the clinical study agreement and applicable privacy laws.

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

The sponsor maintains SOPs on how to respond in the event of unauthorized access, use, or disclosure of sponsor information or systems.

12. ETHICS

12.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and CIOMS International Ethical Guidelines;
- Applicable ICH GCP guidelines;
- Applicable laws and regulations, including applicable privacy laws.

The protocol, protocol amendments, ICD, SRSD(s), and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor, submitted to an IRB/EC by the investigator, and reviewed and approved by the IRB/EC before the study is initiated.

Any amendments to the protocol will require IRB/EC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC.
- Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC procedures.
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH GCP guidelines, the IRB/EC, European regulation 536/2014 for clinical studies, European Medical Device Regulation 2017/745 for clinical device research, and all other applicable local regulations.

12.2. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the study intervention, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study participants against any immediate hazard, and

of any serious breaches of this protocol or of the ICH GCP that the investigator becomes aware of.

12.3. Informed Consent/Assent Process

12.3.1. Adult participants

The investigator or the investigator's representative will explain the nature of the study, including the risks and benefits, to the participant or their legally authorized representative and answer all questions regarding the study. The participant or their legally authorized representative should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial.

Participants must be informed that their participation is voluntary. Participants or their legally authorized representative (if allowed by local regulations) will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH GCP guidelines, privacy and data protection requirements, where applicable, and the IRB/EC or study center.

The investigator must ensure that each study participant or their legally authorized representative is fully informed about the nature and objectives of the study, the sharing of data related to the study, and possible risks associated with participation, including the risks associated with the processing of the participant's personal data.

The participant or their legally authorized representative must be informed that their personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant or their legally authorized representative.

The participant or their legally authorized representative must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities.

The investigator further must ensure that each study participant or their legally authorized representative is fully informed about his or her right to access and correct their personal data and to withdraw consent for the processing of his or her personal data.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date on which the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICD.

Participants or their legally authorized representative must be reconsented to the most current IRB/EC version of the IRB/EC-approved ICD(s) during their participation in the study as required per local regulations.

A copy of the ICD(s) must be provided to the participant or their legally authorized representative (if allowed by local regulations).

Participants who are rescreened are required to sign a new ICD.

12.3.2. Pediatric participants

The investigator or their representative will explain the nature of the study to the participant and their parent(s)/legal guardian and answer all questions regarding the study. The participant and their parent(s)/legal guardian should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial.

When consent is obtained from a participant's parent(s)/legal guardian, the participant's assent (affirmative agreement) must be subsequently obtained when the participant has the capacity to provide assent, as determined by the IRB/EC. If the investigator determines that a participant's decisional capacity is so limited they cannot reasonably be consulted, then, as permitted by the IRB/EC and consistent with local regulatory and legal requirements, the participant's assent may be waived with source documentation of the reason assent was not obtained. If the study participant does not provide their own assent, the source documents must record why the participant did not provide assent (for example, the child is not of assenting age per local regulations or policies), how the investigator determined that the person signing the consent was the participant's parent(s)/legal guardian, the consent signer's relationship to the study participant, and that the participant's assent was obtained or waived. If assent is obtained verbally, it must be documented in the source documents.

If study participants are minors who reach the age of majority or if a child reaches the age of assent (per local IRB/EC requirements) during the study, as recognized under local law, the child or adolescent must then provide the appropriate assent or consent to document their willingness to continue in the study. For an adolescent, who reaches the age of consent, parental consent would no longer be valid. If the enrollment of emancipated minors is permitted by the IRB/EC and local law, the participant must provide documentation of legal status to give consent without the permission of a legally authorized representative.

Participants and their parent(s)/legal guardian must be informed that their participation is voluntary. The participant's parent(s)/legal guardian will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, where applicable, and the IRB/EC or study center.

The investigator must ensure that each study participant's parent(s)/legal guardian and the study participant as applicable are fully informed about the nature and objectives of the study, the sharing of data related to the study, and possible risks associated with participation, including the risks associated with the processing of the participant's personal data.

The participant's parent(s)/legal guardian must be informed that the participant's personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant's parent(s)/legal guardian.

The participant's parent(s)/legal guardian must be informed that the participant's medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities.

The investigator further must ensure that each study participant's parent(s)/legal guardian is fully informed about their right to access and correct their child's personal data and to withdraw consent for the processing of their child's personal data, keeping in mind the privacy rights that may restrict access of older adolescents' medical records by their parent(s)/legal guardian in certain regions.

The source documentation must include a statement that written informed consent, and as applicable assent, was obtained before the participant was enrolled in the study and the date the written consent/assent was obtained. The authorized person obtaining the informed consent must also sign the ICD.

Parent(s)/legal guardian and the participant must be reconsented to the most current version of the ICD(s)/assent during their participation in the study as required per local regulations.

A copy of the ICD(s) and assent, if written, must be provided to the parent(s)/legal guardian and the participant.

Participants who are rescreened are required to sign a new ICD.

13. DEFINITION OF END OF TRIAL

13.1. End of Trial in All Participating Countries

End of trial in all participating countries is defined as the last patient last visit (LPLV). Since patients in this clinical trial will be followed for survival, the LPLV is anticipated to be the last survival follow-up for the last patient in the follow-up phase (ie, date last known alive or of death, withdrawal of consent or lost to follow-up).

14. STUDY AND SITE START AND CLOSURE

The study start date is the date of the first participant's first visit.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor, including (but not limited to) regulatory authority decision, change in opinion of the IRB/EC, or change in benefit-risk assessment. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time upon notification to the Sponsor if requested to do so by the responsible IRB/EC or if such termination is required to protect the health of study participants.

Reasons for the early closure of a study site by the sponsor may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the sponsor's procedures, or the ICH GCP guidelines;
- Inadequate recruitment of participants by the investigator;
- Discontinuation of further study intervention development;
- Sites may be closed early if they are unable to continue to enroll participants.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the ECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

If the sponsor decides to terminate the study for a reason unrelated to the safety of study intervention(s), participants may continue to receive study intervention(s) per the investigator's judgment and protocol-specified safety assessments will continue to be performed for these participants until the end of the study as defined in Section 13.1. The following nonsafety-related study procedures and assessments may be stopped upon written notification from the sponsor:

- PK, HbA1c, Thymidine kinase, Biomarkers,
- Bone metabolism and growth assessments (DEXA scans, bone age X-rays),
- Physical signs of pubertal maturation (Tanner stage), and hormones associated with growth and pubertal development (IGF-1; IGFBP-3; 25-hydroxyvitamin D;

1, 25-dihidroxyvitamin D; C-telopeptide, bone ALP, fasting cortisol, LH, FSH, and Estradiol for female patients or Testosterone for male patients.

- Tumor assessment schedule may follow institutional standard of care.

Study termination is also provided for in the clinical study agreement. If there is any conflict between the contract and this protocol, the contract will control as to termination rights.

15. PUBLICATION OF STUDY RESULTS

15.1. Dissemination of Clinical Study Data

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the EudraCT/CTIS, and/or www.pfizer.com, and other public registries and websites in accordance with applicable local laws/regulations. In addition, Pfizer reports study results outside of the requirements of local laws/regulations pursuant to its SOPs.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a product, regardless of the geographical location in which the study is conducted. These results are submitted for posting in accordance with the format and timelines set forth by US law.

EudraCT/CTIS

Pfizer posts clinical trial results on EudraCT/CTIS for Pfizer-sponsored interventional studies in accordance with the format and timelines set forth by EU requirements.

www.pfizer.com

Pfizer posts CSR synopses and plain-language study results summaries on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the corresponding study results are posted to www.clinicaltrials.gov. CSR synopses will have personally identifiable information anonymized.

Documents within marketing applications

Pfizer complies with applicable local laws/regulations to publish clinical documents included in marketing applications. Clinical documents include summary documents and CSRs including the protocol and protocol amendments, sample CRFs, and SAPs. Clinical documents will have personally identifiable information anonymized.

Data sharing

Pfizer provides researchers secure access to participant-level data or full CSRs for the purposes of "bona-fide scientific research" that contributes to the scientific understanding of the disease, target, or compound class. Pfizer will make data from these trials available 18 months after study completion. Participant-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information anonymized.

Data requests are considered from qualified researchers with the appropriate competencies to perform the proposed analyses. Research teams must include a biostatistician. Data will not be provided to applicants with significant conflicts of interest, including individuals requesting access for commercial/competitive or legal purposes.

15.2. Publications by Investigators

For multicenter trials, the primary publication will be a joint publication developed by the investigator and Pfizer reporting the primary endpoint(s) of the study covering all study sites. The investigator agrees to refer to the primary publication in any subsequent publications. Pfizer will not provide any financial compensation for the investigator's participation in the preparation of the primary congress abstract, poster, presentation, or primary manuscript for the study.

Investigators are free to publish individual center results that they deem to be clinically meaningful after publication of the overall results of the study or 12 months after primary completion date or study completion at all sites, whichever occurs first, subject to the other requirements described in this section.

The investigator will provide Pfizer an opportunity to review any proposed publication or any other type of disclosure of the study results (collectively, "publication") before it is submitted or otherwise disclosed and will submit all publications to Pfizer 30 days before submission. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days upon request from Pfizer. This allows Pfizer to protect proprietary information and to provide comments, and the investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study-intervention or Pfizer-related information necessary for the appropriate scientific presentation or understanding of the study results. For joint publications, should there be disagreement regarding interpretation and/or presentation of specific analysis results, resolution of, and responsibility for, such disagreements will be the collective responsibility of all authors of the publication.

For all publications relating to the study, the investigator and Pfizer will comply with recognized ethical standards concerning publications and authorship, including those established by the International Committee of Medical Journal Editors. The investigator will disclose any relationship with Pfizer and any relevant potential conflicts of interest, including any financial or personal relationship with Pfizer, in any publications. All authors will have access to the relevant statistical tables, figures, and reports (in their original format) required

to develop the publication. The results of this study may be published or presented at scientific meetings by the investigator after publication of the overall study results or 1 year after the end of the study (or study termination), whichever comes first.

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Appendix 1. Abbreviations

The following is a list of abbreviations that may be used in the protocol.

Abbreviation	Term
5-HT3-receptor	5-hydroxtryptamine type 3A receptor
AE	adverse event
AIC	4-amino-5-imidazole-carboxamide
ALP	alkaline phosphatase
ALT	alanine aminotranferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC_{inf}	area under the concentration-time curve from time zero to infinity
$AUC_{ss,t}$	area under the concentration-time curve during a dosing interval at steady state
AUCτ	area under the concentration-time curve at steady state over the dosing interval t
BIRC	Blinded Independent Review Committee
BP	blood pressure
BSA	body surface area
BUN	blood urea nitrogen
C1D1	Cycle 1 Day 1
CCND1	cyclin D1 gene
CDC	Centers for Disease Control and Prevention
CDK	cyclin-dependent kinase
CFR	Code of Federal Regulations
CI	confidence interval
CINV	chemotherapy induced nausea and vomiting
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CL/F	oral plasma clearance
C_{max}	maximum concentration
CNA	circulating nucleic acid
CNS	central nervous system
COVID-19	coronavirus disease
CR	complete response
CRF	case report form
CRO	contract research organization
CSA	clinical study agreement
CSF	cerebrospinal fluid
CSR	clinical study report
$C_{ss,\ max}$	maximum observed plasma concentration during a dosing interval at steady state

Abbreviation	Term
$C_{ss,trough}$	measured concentration at the end of a dosing interval at steady state (taken directly before next administration)
CT	clinical trial
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTIS	Clinical Trials Information System
C_{trough}	predose concentration
CTX	cyclophosphamide
CV	coefficient of variation
CYP	cytochrome P450
DCT	data collection tool
DDI	drug-drug interaction
DEXA	dual-energy X-ray absorptiometry
DILI	drug-induced liver injury
DLT	dose-limiting toxicity
DOR	duration of response
EC	Ethics Committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDP	exposure during pregnancy
EFS	Event-free survival
EoT	End of Treatment
ER	estrogen receptor
ETS	E26 transformation-specific
EU	European Union
EudraCT	European Clinical Trials Database
EWS	Ewing sarcoma
EWSR1-ETS	EWS RNA binding protein 1 fusion gene
FDG	fluorodeoxyglucose
FFPE	formalin-fixed paraffin-embedded
FSH	follicle-stimulating hormone
FUS-ETS	FUS RNA binding protein fusion gene
GCP	Good Clinical Practice
G-CSF	granulocyte-colony stimulating factor
GGT	gamma-glutamyl transferase
HbA1c	hemoglobin A1c
HDPE	high-density polyethylene
HER-2	Human Epidermal Growth Factor Receptor -2
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICD	informed consent document
ICH	International Council for Harmonisation Technical Requirements for Pharmaceuticals for Human Use

Abbreviation	Term
ID	identity
IGF-1	insulin-like growth factor 1
IGFBP-3	insulin-like growth factor binding protein 3
IHC	immunohistochemistry
ILD	interstitial lung disease
IMP	investigational medicinal product
IND	investigational new drug
INR	international normalized ratio
INRC	international neuroblastoma response criteria
IR	incomplete response
IRB	institutional review board
IRN	irinotecan
IRT	interactive randomization technology
IUD	intrauterine device
IV	intravenous(ly)
K	potassium
K_2EDTA	dipotassium ethylenediaminetetraacetic acid
LD	longest diameter
LFT	liver function test
LH	luteinising hormone
LPLV	last patient last visit
MAD	maximum administered dose
MD	multiple dose
MD	minimal disease
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
MIBG	metaiodobenzylguanidine
MR	minor response
MRI	magnetic resonance imaging
MTD	maximum tolerable dose
MTIC	5-(3-dimethyl-1-triazenyl) imidazole-4-carboxamide
MYC	myelocytomatosis oncogene
N/A	not applicable
NCI	National Cancer Institute
NE	not evaluable
NGS	Next Generation Sequencing
NI	not involved
OR	objective response
ORR	objective response rate
OS	overall survival
PACL	Protocol Administrative Clarification Letter
PBTC	Pediatric Brain Tumour Consortium
PCD	primary completion date

Abbreviation	Term
PD	pharmacodynamic(s)
PD	progressive disease
PEG	polyethylene glycol
PET	positron emission tomography
PFS	progression-free survival
PI	principal investigator
PK	pharmacokinetic(s)
PR	partial response
pRb	retinoblastoma susceptibility gene product
PT	prothrombin time
QD	once daily
QoL	quality of life
QTc	corrected QT interval
QTcF	QTc corrected using Fridericia's formula
r/r	recurrent/refractory
R_{ac}	accumulation ratio
RANO	Revised Assessment for Neuro-Oncology
Rb1	retinoblastoma protein 1
RBC	red blood cell(s)
RECIST	Response Evaluation Criteria in Solid Tumours
RMS	rhabdomyosarcoma
RNA	ribonucleic acid
RP2D	recommended Phase 2 Dose
R_{ss}	linearity ratio
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV2	severe acute respiratory syndrome coronavirus 2
SC	subcutaneous(ly)
SD	stable disease
SMARCB1	SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily B member 1
SmPC	Summary of Product Characteristics
SN-38	7-Ethyl-10-hydroxycamptothecin
SOP	Standard operating procedure
SPECT	single-photon emission computerized tomography
SRSD	single reference safety document
SWI/SNF	SWItch/Sucrose Non-Fermentable
T	transverse
$t_{1/2}$	elimination half-life
TBili	total bilirubin
TEAE	treatment-emergent adverse event
TGI	tumor growth inhibition
TK	thymidine kinase

Abbreviation	Term
T_{max}	maximum plasma concentration time
TMZ	temozolomide
TOPO	topotecan
TSC	Tumor Specific Cohort
UGT1A1	uridine-diphosphate glucuronosyltransferase 1A1
UK	United Kingdom
ULN	upper limit of normal
US	United States
USPI	US Prescribing Information
V_z/F	apparent volume of distribution (capsule)
W	width
WBC	white blood cell(s)
WOCBP	Women of childbearing potential

Appendix 2. Lansky Play Scale and Eastern Cooperative Oncology Group Scale

Lansky play-performance scale for pediatric patients

This scale may be used for children in this study for ages 1-16 who have any type of malignancy. It may be used for both inpatients & outpatients, and for patients undergoing active treatment as well as long-term follow-up. It is rated by parents based on their child's activity over the past week.

An excerpt of the relevant directions for parents is as follows:

"Think about your child's play and activity over the past week. Think about both good days and bad days. Average out this period. Now read the descriptions and pick the one that best describes your child's play during the past week."

Rating	Description
100	fully active, normal
90	minor restrictions with strenuous physical activity
80	active, but gets tired more quickly
70	both greater restriction of, and less time spent in, active play
60	up and around, but minimal active play; keeps busy with quieter activities
50	lying around much of the day, but gets dressed; no active play; participates in all quiet play and activities
40	mostly in bed; participates in quiet activities
30	stuck in bed; needs help even for quiet play
20	often sleeping; play is entirely limited to very passive activities
10	does not play nor get out of bed
0	unresponsive

ECOG Performance Status

These scales and criteria are used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis.

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

Appendix 3. Tanner Staging

Pubic Hair: Male and Female

- **Pubic Hair Stage 1**
  Prepubertal. The vellus over the pubis is similar to that on the abdomen. This hair has not yet developed the characteristics of pubic hair.

- **Pubic Hair Stage 2**
  There is sparse growth of long, slightly pigmented downy hair, straight or only slightly curled, mainly at the base of the penis (in males).

- **Pubic Hair Stage 3**
  The hair is considerably darker, coarser, and more curled. It is spread sparsely over the pubis.

- **Pubic Hair Stage 4**
  The hair is adult in type, but the area over which it is present is smaller than in most adults. It has not yet spread to the medial thighs or along the linea alba (in males).

- **Pubic Hair Stage 5**
  The hair is adult in quality and quantity and has the classical triangular distribution in females. It may spread to the medial surface of the thighs.

Breasts: Females

- **Breast Stage 1**
  There is no development. Only the nipple is elevated.

- **Breast Stage 2**
  The “breast bud” stage, the areola widens, slightly darkens, and elevates from the rest of the breast. A bud of glandular tissue is palpable below the nipple.

- **Breast Stage 3**
  The breast and areola further enlarge, presenting a rounded contour. There is no change of contour between the nipple and areola and the rest of the breast. The diameter of breast tissue is still smaller than in a mature breast.

- **Breast Stage 4**
  The breast continues to grow. The papilla and areola project to form a secondary mound above the rest of the breast.

- **Breast Stage 5**
  The mature adult stage. The secondary mound disappears. Some females never progress to Stage 5.

Genitals: Males

- **Genital Stage 1**
  Prepubertal. Penis, testes, and scrotum are about the same size and proportions as in early childhood. It is important to take into account whether the penis is uncircumsized when assessing penile growth, as the uncircumsized penis may appear larger than it really is.

- **Genital Stage 2**
  Only the testes and scrotum have begun to enlarge from the early childhood size. The penis is still prepubertal in appearance. The texture of the scrotal skin is beginning to become thinner and the skin appears redder due to increased vascularization.

- **Genital Stage 3**
  There is further growth of the testes and scrotum. The penis is also beginning to grow, mainly in length with some increase in breadth. It can be difficult to distinguish between Stages 2 and 3.

- **Genital Stage 4**
  The penis enlarges further in length and breadth and the glans becomes more prominent. The testes and scrotum are larger. There is further darkening of the scrotal skin.

- **Genital Stage 5**
  The penis, testes, and scrotum are adult in size and shape.

Appendix 4. Diarrhea Treatment

Guidelines for the Treatment of Irinotecan-induced Diarrhea

Institutional practice may be used in place of these guidelines.

You should purchase or will be given a prescription for loperamide to have available to begin treatment at the first episode of poorly formed or loose stools or the earliest onset of bowel movements more frequent than normally expected for the patient. Patients will also be instructed to contact their physician if any diarrhea occurs. Patients will be given loperamide based on body weight.

Be aware of your child's bowel movements. At the first sign they become softer than usual or if your child has any notable increase in the number of bowel movements over what is normal for him/her, begin taking loperamide.

Please follow these directions carefully, using dosing guidelines below:

- Take_____at the first sign of diarrhea.
- Continue taking_____every hours until the diarrhea slows or the normal pattern of bowel movements returns. Repeat the same doses and frequency if the diarrhea returns.
- Do not exceed_____in a 24 hour period.
- Please call your doctor if you have any questions about taking loperamide, if your child's diarrhea is not under control after two days, or if he/she is feeling extremely weak, lightheaded, or dizzy.
- Make an extra effort to give your child lots of fluids (several glasses of pedialyte, fruit juices, soda, soup, etc.) while your child is participating in this study.
- Side effects may include tiredness, drowsiness or dizziness. If your child experiences these side effects, or if your child is urinating less frequently than usual, please contact your child's physician.
- Do not give your child any laxatives without consulting with his/her physician.

LOPERAMIDE DOSING RECOMMENDATIONS[1] (NOTE: maximum dose of loperamide for adults is 16 mg/day) *ALL patients: discontinue loperamide when the patient is no longer experiencing significant diarrhea.*
Weight (kg)
<13 kg
≥13 kg to <20 kg
≥20 kg to <30 kg
≥30 kg to <43 kg
Over 43 kg

1. In the UK loperamide dosing should follow the local SmPC based on patient's age and weight.

Appendix 5. RECIST 1.1 Criteria

Adapted from E.A. Eisenhauer, et al: New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). European Journal of Cancer 45 (2009) 228–247.[47]

CATEGORIZING LESIONS AT BASELINE

Measurable Lesions

Lesions that can be accurately measured in at least one dimension.

- Lesions with longest diameter twice the slice thickness and at least 10 mm or greater when assessed by CT or MRI (slice thickness 5-8 mm);
- Lesions with longest diameter at least 20 mm when assessed by Chest X-ray;
- Superficial lesions with longest diameter 10 mm or greater when assessed by caliper;
- Malignant lymph nodes with the short axis 15 mm or greater when assessed by CT.

NOTE: The shortest axis is used as the diameter for malignant lymph nodes, longest axis for all other measurable lesions.

Non-measurable disease

Non-measurable disease includes lesions too small to be considered measurable (including nodes with short axis between 10 and <15 mm) and truly non-measurable disease such as pleural or pericardial effusions, ascites, inflammatory breast disease, leptomeningeal disease, lymphangitic involvement of skin or lung, clinical lesions that cannot be accurately measured with calipers, abdominal masses identified by physical exam that are not measurable by reproducible imaging techniques.

- Bone disease**:** Bone disease is non-measurable with the exception of soft tissue components that can be evaluated by CT or MRI and meet the definition of measurability at baseline.
- Previous local treatment: A previously irradiated lesion (or lesion subjected to other local treatment) is non-measurable unless it has progressed since completion of treatment.

Normal sites

- Cystic lesions**:** Simple cysts should not be considered as malignant lesions and should not be recorded either as target or non-target disease. Cystic lesions thought to represent cystic metastases can be measurable lesions, if they meet the specific definition above. If non-cystic lesions are also present, these are preferred as target lesions.
- Normal nodes**:** Nodes with short axis <10 mm are considered normal and should not be recorded or followed either as measurable or non-measurable disease.

RECORDING TUMOR ASSESSMENTS

All sites of disease must be assessed at baseline. Baseline assessments should be done as close as possible prior to study start. For an adequate baseline assessment, all required scans must be done within 21 days prior to to the first dose of study medication (Phase 1 portion and tumor-specific cohorts) or the date of randomization (Phase 2 portion) unless otherwise specified and all disease must be documented appropriately. If baseline assessment is inadequate, subsequent statuses generally should be indeterminate.

Target lesions

- All measurable lesions up to a maximum of 2 lesions per organ, 5 lesions in total, representative of all involved organs, should be identified as target lesions at baseline. Target lesions should be selected on the basis of size (longest lesions) and suitability for accurate repeated measurements. Record the longest diameter for each lesion, except in the case of pathological lymph nodes for which the short axis should be recorded. The sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions at baseline will be the basis for comparison to assessments performed post-baseline.

- If two target lesions coalesce the measurement of the coalesced mass is used. If a large target lesion splits, the sum of the parts is used.
- Measurements for target lesions that become small should continue to be recorded. If the lesion is considered to have disappeared, 0 mm should be recorded; otherwise if a lesion is determined to be present but too small to measure, the lesion status will indicate “too small to measure and judged to be less than 10 mm” and 5 mm will be used in the calculation of the sum of the diameters.

NOTE: When nodal lesions decrease to <10 mm (normal), the actual measurement should still be recorded.

Non-target disease

- All non-measurable disease is non-target. All measurable lesions not identified as target lesions are also included as non-target disease. Measurements are not required but rather assessments will be expressed as ABSENT, INDETERMINATE, PRESENT/NOT INCREASED, INCREASED. Multiple non-target lesions in one organ may be recorded as a single item on the case report form (eg, ‘multiple enlarged pelvic lymph nodes’ or ‘multiple liver metastases’).

OBJECTIVE RESPONSE STATUS AT EACH EVALUATION.

Disease sites must be assessed using the same technique as baseline, including consistent administration of contrast and timing of scanning. If a change needs to be made the case must be discussed with the radiologist and the Sponsor to determine if substitution is possible. If not, subsequent objective statuses are not evaluable.

Target disease

- Complete Response (CR): Complete disappearance of all target lesions with the exception of nodal disease. All target nodes must decrease to normal size (short axis <10 mm). All target lesions must be assessed.
- Partial Response (PR): Greater than or equal to 30% decrease under baseline of the sum of diameters of all target measurable lesions. All target lesions must be assessed.
- Stable Disease (SD): Does not qualify for CR, PR or Progression. All target lesions must be assessed. Stable can follow PR only in the rare case that the sum increases by less than 20% from the nadir (smallest sum of diameters consider baseline and all assessments prior to the time point under evaluation), but enough that a previously documented 30% decrease no longer holds.
- Objective Progression (PD): 20% increase in the sum of diameters of target measurable lesions above the smallest sum observed (over baseline if no decrease in the sum is observed during therapy), with a minimum absolute increase of 5 mm.
- Not evaluable (NE): Progression has not been documented, and:
  - one or more target lesions have not been assessed; or
  - assessment methods used were inconsistent with those used at baseline; or
  - one or more target lesions cannot be measured accurately (eg, poorly visible unless due to being too small to measure); or
  - one or more target lesions were excised or irradiated and have not reappeared or increased.

Non-target disease

- CR: Disappearance of all non-target lesions and normalization of tumor marker levels (if being followed). All lymph nodes must be 'normal' in size (<10 mm short axis).
- Non-CR/Non-PD: Persistence of any non-target lesions and/or tumor marker level (if being followed) above the normal limits.
- PD: Unequivocal progression of pre-existing lesions. Generally the overall tumor burden must increase sufficiently to merit discontinuation of therapy. In the presence of SD or PR in target disease, progression due to unequivocal increase in non-target disease should be rare.
- Not evaluable (NE): Progression has not been determined and:
  - one or more non-target lesion sites have not been assessed; or
  - assessment methods used were inconsistent with those used at baseline; or

- one or more non-target lesions cannot be assessed (eg, poorly visible or unclear images); or

- one or more non-target lesions were excised or irradiated and have not reappeared or increased.

New Lesions

The appearance of any new unequivocal malignant lesion indicates PD. If a new lesion is equivocal, for example due to its small size, continued assessment will clarify the etiology. If repeat assessments confirm the lesion, then progression should be recorded on the date of the initial assessment. A lesion identified in an area not previously scanned will be considered a new lesion.

Supplemental Investigations

- If CR determination depends on a residual lesion that decreased in size but did not disappear completely, it is recommended the residual lesion be investigated with biopsy or fine needle aspirate. If no disease is identified, objective status is CR.
- If progression determination depends on a lesion with an increase possibly due to necrosis, the lesion may be investigated with biopsy or fine needle aspirate to clarify status.

Subjective progression

Patients requiring discontinuation of treatment without objective evidence of disease progression should not be reported as PD on tumor assessment CRFs. This should be indicated on the end of treatment CRF as off treatment due to Global Deterioration of Health Status. Every effort should be made to document PD even after discontinuation of study treatment.

NON- MEASURABLE DISEASE ONLY

The non-target leasion(s) assessment criteria apply when assessing non-measurable disease response. When assessing patients for an unequivocal progression, a useful test to apply is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare progressive disease for measurable disease: ie,an increase in tumour burden representing an additional 73% increase in ‘volume’ (which is equivalent to a 20% increase diameter in a measurable lesion). In general, increase in tumor burden must be sufficient to require a change in therapy.

Determination of Tumor Response by RECIST

When both target and non-target lesions are present, individual assessments will be recorded separately. New lesions will also be recorded separately. Determination of tumor response at each assessment based on target, non-target and new lesions is summarized in the following table.

Objective Response Status at Each Assessment for Patients with Measurable Disease at Baseline

Target Lesions	Non-target Lesions	New Lesions	Objective status
CR	CR	No	CR
CR	Non-CR/Non-PD or not all evaluated	No	PR
PR	Non-PD* or not all evaluated	No	PR
SD	Non-PD* or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes**	PD

*Non-PD includes CR and Non-CR/Non-PD
** New lesions must be unequivocal

Objective Response Status at Each Assessment for Patients with Non-Measurable Disease at Baseline

Target Lesions	Non-target Lesions	New Lesions	Objective status
Not present	CR	No	CR
	Not all evaluated	No	NE
	Non-CR/Non-PD	No	Non-CR/Non-PD
	PD	Yes or No	PD
	Any	Yes**	PD

** New lesions must be unequivocal

Appendix 6. Modified RANO Criteria for Patients with CNS Malignancies

Adapted from P Wen, et al: Response Assessment in Neuro-Oncology Clinical Trials. Journal of Clinical Oncology 35 (2017) 2439-49.[48]

Methodology to Determine Tumor Measurement in CNS Tumors

Tumor dimensions are determined by measurement of the longest tumor dimension and its perpendicular for each target lesion. Regarding MRI imaging, the radiologist may select whatever sequence best highlights the tumor (T1 enhanced or T2 weighted or FLAIR images) and the same sequence should be used for serial measurements. Response determination will be based on a comparison of an area (W × T) between the baseline assessment and the study date designated in the follow-up Report Form. Reports for the follow-up exams should reiterate the measurements obtained at baseline for each target lesion. Non-target lesions or newly occurring lesions should also be enumerated in these reports, and changes in non-target lesions should be described.

Tumor response criteria are determined by changes in size using the longest tumor dimension, and its perpendicular. Either T1 or T2 weighted images are used - which ever gives the best estimate of tumor size. The following section describes the methodology. Longest diameter of target lesion(s) should be selected in the axial plane only for CT. For MRI imaging, the longest diameter can be measured from the axial plane or the plane in which the tumor is best seen or measured, provided the same plane is used in follow ups. This longest measurement of the tumor is referred to as the width (W).

The perpendicular measurements should be determined - transverse (T) measurement, perpendicular to the width in the selected plane. The cystic or necrotic components of a tumor are not considered in tumor measurements. Therefore only the solid component of cystic/necrotic tumors should be measured. If cysts/necrosis compose the majority of the lesion, the lesion may not be “measurable”.

Options:

- If the cyst/necrosis is eccentric, the W and T of the solid portion should be measured, the cyst/necrosis excluded from measurement.
- If the cyst/necrosis is central but represents a small portion of the tumor (<25%), disregard and measure the whole lesion.
- If the cyst/necrosis is central but represents a large portion of the tumor, identify a solid aspect of the mass that can be reproducibly measured.

Leptomeningeal tumor spread is usually not a target lesion, and usually cannot be measured accurately. Presence and location of leptomeningeal tumor spread should be noted and change in extent/thickness assessed on follow up studies.

Selection of Target and Non-Target Lesions

For most CNS tumors, only one lesion/mass is present and therefore is considered a "target" for measurement/follow up to assess for tumor progression/response.

If multiple measurable lesions are present, up to 3 should be selected as "target" lesions. Target lesions should be selected on the basis of size and suitability for accurate repeated measurements.

All other lesions will be followed as non-target lesions (including CSF positive for tumor cells). The lower size limit of the target lesion(s) should be at least twice the thickness of the slices showing the tumor to decrease the partial volume effect (eg, 8 mm lesion for a 4 mm slice).

Any change in size of non-target lesions should be noted, though does not need to be measured.

Evaluation of Target Lesions

Response criteria are assessed in 2 dimensions – the product of W × T

To assess response/progression, the ratio is calculated:

W × T (current scan)
W × T (reference scan)

Development of new disease or progression in any established lesions is considered progressive disease, regardless of response in other lesions – eg, when multiple lesions show opposite responses, the progressive disease takes precedence.

Complete Response (CR): Disappearance of all target lesions.

Partial response (PR): ≥50% decrease in the sum of the products of the two perpendicular diameters of target lesions, compared to baseline measurement.

Stable Disease (SD): Neither sufficient decrease in the sum of the products of the two perpendicular diameters of all target lesions to qualify for PR (taking as reference the initial baseline measurements), nor sufficient increase in a single target lesion to qualify for PD, (taking as reference the smallest disease measurement since the treatment started).

Progressive Disease (PD): ≥25% increase in the product of perpendicular diameters of ANY target lesion, taking as reference the smallest product observed since the start of treatment (see exception below); OR the appearance of one or more new lesions, OR worsening neurologic status not explained by causes unrelated to tumor progression (eg, anticonvulsant or corticosteroid toxicity, electrolyte disturbances, sepsis, hyperglycemia, presumed posttherapy swelling etc) PLUS any increase in tumor cross-sectional area (or tumor volume).

However, because radiotherapy may be associated with transient, reversible swelling during or within the first 3 months after completion of radiotherapy, there may be a lag time between the initiation of therapy and maximal antitumor effect. Removing a patient from protocol therapy as soon as the tumor area increases by 25%, may result in the treatment being terminated prematurely. It is quite possible that if these patients were maintained on protocol therapy, their disease might eventually stabilize and even regress.

Local progression is defined as progression of known residual tumor or the appearance of tumor at known prior sites of disease that were at some point without evidence of disease. Distant progression is defined as the appearance of tumor at sites other than known prior sites of disease. Distant progression most often occurs in the subarachnoid space and may occur at any point within the neuraxis. Although rare, extra-CNS metastasis represents distant failure. Combined local and distant progression is defined when evaluation of the entire neuraxis reveals local and distant progression.

Evaluation of Non-target Lesions

Complete Response (CR): Disappearance of all non-target lesions.

Incomplete Response/Stable Disease (IR/SD): The persistence of one or more non-target lesions.

Progressive Disease (PD): The appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.

Overall Response Assessment

The overall response assessment takes into account response in both target and non-target lesion, and the appearance of new lesions, where applicable, according to the criteria described in the table below. The overall response assessment is shown in the last column, and depends on the assessments of target, non-target, and new lesions in the preceding columns.

Overall Response Assessment for CNS Tumors

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	IR/SD	No	PR
PR	CR, IR/SD	No	PR
SD	CR, IR/SD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Abbreviations: CR = complete response; IR = incomplete response; PD = progressive disease; PR = partial response; SD = stable disease.

Appendix 7. Response Criteria for Neuroblastoma

Adapted from J.R. Park, et al: Revisions to the international neuroblastoma response criteria: A consensus statement from the National Cancer Institute clinical trials planning meeting. Journal of Clinical Oncology 35:2580-2587.[49]

This study will use the revised International Neuroblastoma Response Criteria for disease assessment. The updated response criteria incorporate current approaches to imaging of neuroblastoma, including functional imaging. Furthermore, a standardized approach to assessment of bone marrow involvement is included. The current INRC do not include methods of disease assessment that are less sensitive and/or specific for neuroblastoma (99Tc bone scan and catecholamine levels).

Key sites and terms

Primary site: The primary site will be identified as a measurable lesion ≥10 mm in diameter as assessed by cross sectional imaging (CT or MRI scan). Primary site measurements must be recorded in millimeters (or decimal fractions of centimeters). The longest diameter of the primary tumor will be recorded at baseline. Serial measurements of the primary tumor will include assessment of tumor size in the same orthogonal plane at the time of each evaluation. In patients with bilateral adrenal lesions, response will be based on the sum of the longest dimensions of both adrenal lesions unless biopsy proves one to be ganglioneuroma rather than neuroblastoma/ganglioneuroblastoma. In patients with multi-focal non-adrenal disease, the largest tumor will be considered the primary tumor. Response in additional lesions will be assessed as described below for metastatic lesions.

Tracer avidity (123I-MIBG or FDG-PET) in the primary site will be recorded at baseline. The scan appropriate for serial disease assessments should be used at each disease re-evaluation timepoint (eg, 123I-MIBG avid primary lesions should be followed using 123I- MIBG scans during therapy).

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a metastatic lymph node must be ≥15 mm in short axis when assessed by CT or MRI scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis of a discreet lymph node will be measured and followed as per RECIST criteria. Patients with neuroblastoma may have conglomerate masses of non discrete lymph nodes (ie, multiple contiguous retroperitoneal nodes). When a short axis of a discreet node cannot be identified, a lymph node conglomerate can be measured using the longest diameter of the composite lesion. Tracer avidity of metastatic nodes will be recorded at baseline and during disease evaluations.

For the purposes of response assessment, target lesions are disease sites that are measurable (non-nodal soft tissue mass ≥10 mm in longest dimension or lymph node ≥15 mm in short axis) and tracer avid OR are biopsy positive for neuroblastoma or ganglioneuroblastoma. The sum of diameters of target lesions is defined as the sum of the short axis of discrete lymph nodes (ie, cervical, axillary nodes) added to the sum of the longest diameters of nonlymph node soft tissue metastases.

Non-measurable disease: All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions are considered non-measurable.

Bone lesions: Osteomedullary disease will be assessed using 123I-MIBG scans or FDG-PET scans. Technitium bone scans are no longer used as part of the revised INRC and are not included as part of disease reassessments during this trial. The extent of tracer avid disease will be evaluated using the Curie scoring system (see worksheet within this appendix). Single-photon emission computer tomography (SPECT) may be used to confirm the presence or absence of lesions in a given segment of the body. The absolute Curie score should be reported at baseline. A relative score (Curie score at the time of disease assessment divided by baseline Curie score) should be recorded at the time of each disease evaluation.

Bone marrow disease: Bilateral bone marrow aspirates and trephine biopsies are required at disease assessment timepoints. The extent of marrow involvement in all 4 samples should be recorded. Use of immunohistochemical staining for evaluation of trephine biopsies is strongly encouraged. The percentage of tumor infiltration of bone marrow space assessed by histologic evaluation of trephine/biopsies or counting the number of tumor cells in aspirates by cytology or immunocytology (recommended if available) divided by the number of hematopoietic/mononuclear cells evaluated to obtain a percentage involvement (methodology described by Burchill et al.).[50]

The bone marrow sample with the highest percentage of tumor infiltration is used for response assessment. If >0% to ≤ 5% tumor infiltration is the highest percentage seen among samples obtained, the result should be recorded as minimal marrow disease.

Response Criteria

PRIMARY (SOFT TISSUE) TUMOR RESPONSE[1]

RESPONSE	ANATOMICAL IMAGING + MIBG (FDG-PET[2]) IMAGING
Complete Response (CR)	• <10 mm residual soft tissue at primary site, AND • complete resolution of MIBG or FDG-PET uptake (for MIBG non-avid tumors) at primary site.
• **Partial Response (PR)**	• ≥30% decrease in longest diameter (LD) of primary site. • MIBG or FDG-PET uptake at primary site stable, improved or resolved.
• **Progressive Disease (PD)**	• >20% increase in longest diameter taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study), AND • a minimum absolute increase of 5 mm in longest dimension[3]
Stable Disease (SD)	Neither sufficient shrinkage for PR nor sufficient increase for PD at the primary site.

1. Not for use in assessment of metastatic sites.
2. For 123I-MIBG non-avid tumors.
3. A mass that has not met PD measurement criteria but has fluctuating 123I-MIBG avidity will not be considered progressive disease.

RESPONSE AT METASTATIC SOFT TISSUE AND BONE SITES

RESPONSE	ANATOMICAL IMAGING + MIBG (FDG-PET[1]) IMAGING
Complete Response (CR)	• Resolution of all sites of disease defined as: • Non-primary target and non-target lesions measure <10 mm AND • Lymph nodes identified as target lesions decrease to a short axis. • <15 mm, AND • MIBG uptake or FDG-PET uptake (for MIBG non-avid tumors) of non-primary lesions resolves completely.
Partial Response (PR)	• ≥30% decrease in sum of diameters[2] of non-primary target lesions compared to baseline, AND all of the following: • Non-target lesions may be stable or smaller in size, AND • No new lesions, AND • ≥50% reduction in MIBG absolute bone score (Relative MIBG bone score ≥0.1 to ≤0.5) or ≥50% reduction in number of FDG-PET avid bone lesions.[3,4].
Progressive Disease (PD)	Any of the following:[5] • Any new soft tissue lesion detected by CT or MRI that is also MIBG avid or FDG-PET avid; • Any new soft tissue lesion seen on anatomic imaging that is biopsied and confirmed to be a neuroblastoma or ganglioneuroblastoma; • Any new bone site that is MIBG avid; • A new bone site that is FDG-PET avid (for MIBG non-avid tumors) AND has CT or MRI findings consistent with tumor OR has been confirmed histologically to be neuroblastoma or ganglioneuroblastoma; • >20% increase in longest diameter taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study), AND a minimum absolute increase of 5 mm in sum of diameters of target soft tissue lesions; • Relative MIBG score ≥1.2.[4]
Stable Disease (SD)	Neither sufficient shrinkage for PR nor sufficient increase for PD of non-primary lesions.

1. Used for MIBG non-avid tumors.
2. Sum of diameters is defined as the sum of the short axis of discrete lymph nodes (ie, cervical, axillary nodes) added to the sum of the longest diameters of non-lymph node soft tissue metastases. Masses of conglomerate non-discrete lymph nodes will be measured using longest diameter.
3. For patients with soft tissue metastatic disease, resolution of MIBG and/or FDG-PET uptake at the soft tissue sites is not required; all size reduction criteria must be fulfilled.
4. Relative Curie score is the absolute score for bone lesions at time of response assessment divided by the absolute score for bone lesions at entry onto a clinical trial. MIBG-SPECT or MIBG-SPECT/CT may be used for scoring purposes but the same imaging methodology should be used for all evaluations.
5. The post-infusion MIBG scan is not considered a diagnostic study for the purposes of response assessment. Progressive disease should NOT be designated on the basis of this scan.

BONE MARROW RESPONSE

RESPONSE	BONE MARROW STATUS[1]
Complete response (CR)	Bone marrow with no tumor infiltration upon reassessment, independent of baseline tumor involvement.
Progressive disease (PD)	Any of the following: • Bone marrow without tumor infiltration that becomes >5% tumor infiltration upon reassessment; or • Bone marrow with tumor infiltration that increases by >2 fold and has >20% tumor infiltration upon reassessment.
Minimal disease (MD)	Any of the following: • Bone marrow with ≤5% tumor infiltration and remains >0 ≤5% tumor infiltration upon reassessment; or • Bone marrow with no tumor infiltration that becomes ≤5%. • tumor infiltration upon reassessment; or • Bone marrow with >20% tumor infiltration that has >0 - ≤5% tumor infiltration upon reassessment.
Stable disease (SD)	Bone marrow with tumor infiltration that remains positive with >5% tumor infiltration upon reassessment but does not meet CR, MD, or PD criteria.

1. Immunohistochemistry strongly encouraged.

DETERMINATION OF OVERALL RESPONSE

RESPONSE	CRITERIA
Complete Response (CR)	All components meet criteria for CR.
Partial Response (PR)	PR in at least 1 component and all other components are either CR, MD (Bone marrow), PR (Soft tissue or Bone) or Not involved (NI); no component with PD.
Minor Response (MR)	PR or CR in at least one component but at least one other component with SD; no component with PD.
Stable Disease (SD)	SD in one component with no better than SD or NI in any other component; no component with PD.
Progressive Disease (PD)	Any component with PD.

NI = Not involved, site not involved at study entry and remains not involved; MD = Minimal Disease, for bone marrow assessment only.

OVERALL BEST RESPONSE ASSESSMENT

Each patient will be classified according to his "best response" for the purposes of analysis of treatment effect.

Primary Tumor	Soft Tissue and Bone Metastatic Disease (MIBG or FDG-PET)	Bone Marrow Metastatic Disease	Overall
CR	CR	CR	CR
CR for one response component with either CR or NI for other components			CR
CR	CR	MD	PR
CR	PR	CR	PR
CR	PR	MD	PR
CR	PR	NI	PR
CR	NI	MD	PR
PR	CR	CR	PR
PR	CR	NI	PR
PR	CR	MD	PR
PR	PR	CR	PR
PR	PR	NI	PR
PR	PR	MD	PR
PR	NI	CR	PR
PR	NI	NI	PR
PR	NI	MD	PR
NI	CR	MD	PR
NI	PR	CR	PR
NI	PR	MD	PR
CR	CR	SD	MR
CR	PR	SD	MR
CR	SD	CR	MR
CR	SD	MD	MR
CR	SD	SD	MR
CR	SD	NI	MR

Primary Tumor	Soft Tissue and Bone Metastatic Disease (MIBG or FDG-PET)	Bone Marrow Metastatic Disease	Overall
CR	NI	SD	MR
PR	CR	SD	MR
PR	PR	SD	MR
PR	SD	CR	MR
PR	SD	MD	MR
PR	SD	SD	MR
PR	SD	NI	MR
PR	NI	SD	MR
SD	CR	CR	MR
SD	CR	MD	MR
SD	CR	SD	MR
SD	CR	NI	MR
SD	PR	CR	MR
SD	PR	MD	MR
SD	PR	SD	MR
SD	PR	NI	MR
SD	SD	CR	MR
SD	NI	CR	MR
NI	CR	SD	MR
NI	PR	SD	MR
NI	SD	CR	MR
SD	SD	MD	SD
NI	SD	MD	SD
SD	NI	MD	SD
NI	NI	MD	SD
SD	SD	SD	SD
SD	NI	SD	SD
SD	NI	SD	SD
NI	SD	SD	SD
NI	SD	NI	SD
NI	NI	SD	SD
PD in any one component			PD
Response of Not Evaluable for any one of the 3 components that had measurable/evaluable tumor at study enrollment and no PD for any component			Not Evaluable
No response evaluation performed for any of the 3 components			Not Done

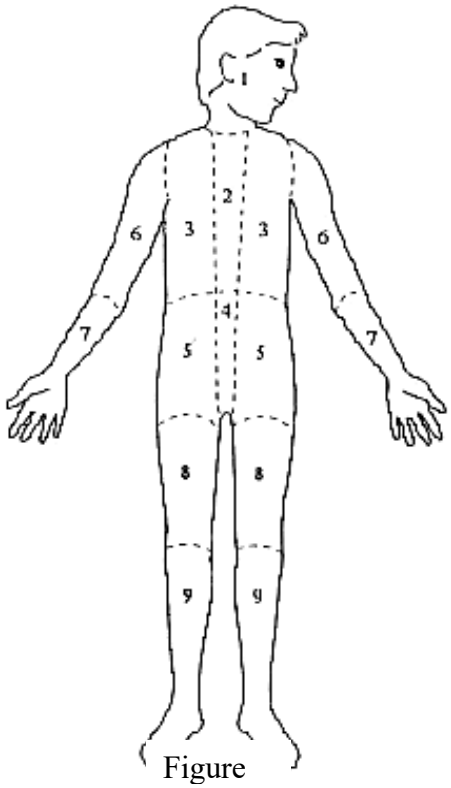
CR = Complete Response; MD = Minimal Disease; PR: Partial Response; MR = Minor Response; SD = Stable Disease; PD = Progressive disease; NI = not involved; site not involved at study entry and remains not involved.

Date of scan **Type of Scan** (check 1): □ I-123 MIBG □ I-131 MIBG (DD/MM/YYYY)

Scan time point (circle 1): Baseline On study tumor assessment Cycle #

Scoring (MIBG uptake)	Skeletal Site	Primary Soft Tissue Site
0	No skeletal lesion	No soft tissue uptake
1	1 distinct lesion	1 focal soft tissue site
2	2 or more distinct lesions	>1 focal soft tissue site
3	≥50% of a segment	≥50% of a region (chest/abdomen)

Region	Site	Curie score
1	Head/Neck	
2	Cervico-Thoracic spine	
3	Ribs/Sternum/Clavicles/Chest	
4	Lumbar Sacral spine	
5	Abdomen/Pelvis	
6	Upper Extremity (Proximal)	
7	Upper Extremity (Distal)	
8	Lower Extremity (Proximal)	
9	Lower Extremity (Distal)	
10	Soft Tissue	
TOTAL	Total scores from Regions 1 - 10	



Figure

Appendix 8. Palatability Questionnaire

Palbociclib Oral Solution Taste Feedback Questionnaire

1. Questionnaire should be administered to children or adults, preferably by the clinician or the nurse at the time of the first dose. After that, the questionnaire should be completed on Day 14 of Cycle 1 and Day 1 and 14 of Cycle 2.

2. Questions need to be answered shortly after dose administration (ideally within 10 minutes) so the data is collected within attention span of young children.

3. Please gather the following background information:

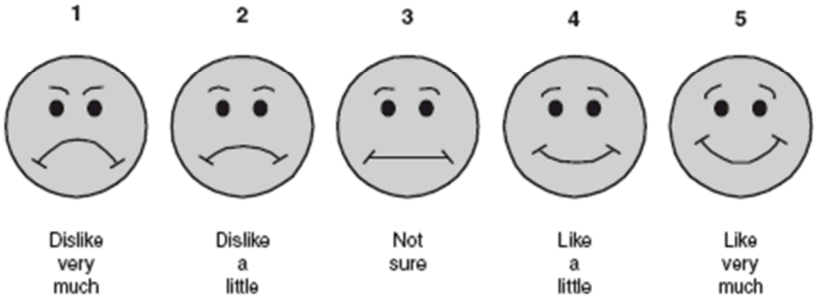
Background information

Study/Study Site	
Patient ID	
Patient age	
Treatment Cycle Number and Day of Cycle	
Date/Time of administration of medicine	
Questionnaire completed by (circle one)	Patient Nurse Caregiver such as parent or guardian
What volume of oral solution is taken daily?	

Questionnaire

1. Did you drink (or eat) water (or something else) after you took the medicine before answering these questions? If you did what was it?

1a. How much do you like this medicine overall?

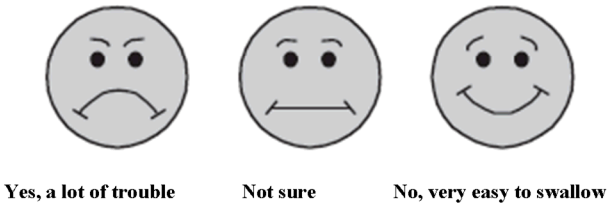


2. Was dosing successful (entire dose administered and swallowed)? Please circle one

YES

NO

2a) If the answer to question 2 is "YES" , then based on the overall taste - did you have trouble swallowing the medicine?



2b) If the answer to question 2 is "NO" please indicate the reason for unsuccessful dosing/not being able to swallow all of the medicine?

Appendix 9. Bone Marrow Reserve

***Adapted from R.E. ELLIS**: The Distribution of Active Bone Marrow in the Adult, Phy. Med. Biol. 5, 255-258, 1961*[51]

Marrow Distribution of the Adult

SITE		MARROW wt. (g)	FRACTION RED MARROW AGE 40	RED MARROW wt. (g) AGE 40	%TOTAL RED MARROW	
CRANIUM	Head:			136.6		
AND	Cranium	165.8	0.75	124.3	13.1	**13.1**
MANDIBLE	Mandible	16.4	0.75	12.3		
	Upper Limb Girdle :			86.7		
HUMERI, SCAPULAE,	2 Humerus, head & neck	26.5	0.75	20.0	8.3	8.3
CLAVICLES	2 Scapulae	67.4	0.75	50.5		
	2 Clavicles	21.6	0.75	16.2		
	Sternum	39.0	0.6	23.4	2.3	
	Ribs:			82.6		
	1 pair	10.2	All 0.4	4.1		
	2	12.6		5.0		
	3	16.0		6.4		
STERNUM	4	18.6		7.4		
AND	5	23.8		9.5	7.9	**10.2**
RIBS	6	23.6		9.4		
	7	25.0		10.0		
	8	24.0		9.6		
	9	21.2		8.5		
	10	16.0		6.4		
	11	11.2		4.5		
	12	4.6		1.8		
	Sacrum	194.0	0.75	145.6	13.9	
PELVIC BONES	2 os coxae	310.6	0.75	233.0	22.3	**36.2**
FEMUR	2 Femoral head and neck	53.0	0.75	40.0		**3.8**

MARROW DISTRIBUTION OF THE ADULT (CONT'D)

SITE		MARROW wt. (g)	FRACTION RED MARROW AGE 40	RED MARROW wt. (g) AGE 40	%TOTAL RED MARROW	
	Vertebrae (Cervical):			35.8		
	1	6.6	All 0.75	5.0		
	2	8.4		6.3		
	3	5.4		4.1	3.4	
	4	5.7		4.3		
	5	5.8		4.4		
	6	7.0		5.3		
	7	8.5		6.4		
	Vertebrae (Thoracic):			147.9		
	1 pair	10.8	All 0.75	8.1		
	2	11.7		8.8		
	3	11.4		8.5		
	4	12.2		9.1		
VERTEBRAE	5	13.4		10.1	14.1	**28.4**
	6	15.3		11.5		
	7	16.1		12.1		
	8	18.5		13.9		
	9	19.7		14.8		
	10	21.2		15.9		
	11	21.7		16.3		
	12	25.0		18.8		
	Vertebrae (Lumbar):			114.1		
	1 pair	27.8	All 0.75	20.8		
	2	29.1		21.8	10.9	
	3	31.8		23.8		
	4	32.1		24.1		
	5	31.4		23.6		
TOTAL		1497.7		1045.7	100.0	**100.0**

Appendix 10. Volume of Palbociclib Oral Solution to be Administered by Dose and BSA

Palbociclib Oral Solution Administration Table

Body Surface Area (m^2)	Dose Level - 40 mg/m^2		Dose Level – 55 mg/m^2		Dose Level – 75 mg/m^2		Dose Level – 95 mg/m^2		Dose Level – 115 mg/m^2	
	Daily Dose Delivered (mg)	Oral Solution Volume Delivered (mL)	Daily Dose Delivered (mg)	Oral Solution Volume Delivered (mL)	Daily Dose Delivered (mg)	Oral Solution Volume Delivered (mL)	Daily Dose Delivered (mg)	Oral Solution Volume Delivered (mL)	Daily Dose Delivered (mg)	Oral Solution Volume Delivered (mL)
0.3	12.5	0.5	17.5	0.7	22.5	0.9	30	1.2	35	1.4
0.4	15	0.6	22.5	0.9	30	1.2	40	1.6	45	1.8
0.5	20	0.8	30	1.2	40	1.6	50	2	60	2.4
0.6	25	1	35	1.4	45	1.8	55	2.2	70	2.8
0.7	25	1	40	1.6	55	2.2	65	2.6	80	3.2
0.8	30	1.2	45	1.8	60	2.4	75	3	90	3.6
0.9	35	1.4	50	2	70	2.8	85	3.4	105	4.2
1	40	1.6	55	2.2	75	3	95	3.8	115	4.6
1.1	45	1.8	60	2.4	85	3.4	105	4.2	125	5
1.2	50	2	65	2.6	90	3.6	115	4.6	140	5.6
1.3	50	2	70	2.8	100	4	125	5	150	6
1.4	55	2.2	75	3	105	4.2	135	5.4	160	6.4
1.5	60	2.4	85	3.4	115	4.6	145	5.8	175	7
1.6	65	2.6	90	3.6	120	4.8	150	6	185	7.4
1.7	70	2.8	95	3.8	130	5.2	160	6.4	195	7.8
1.8	70	2.8	100	4	135	5.4	170	6.8	200	8
1.9	75	3	105	4.2	145	5.8	180	7.2	200	8
2	80	3.2	110	4.4	150	6	190	7.6	200	8
2.1	85	3.4	115	4.6	160	6.4	200	8	200	8
2.2	90	3.6	120	4.8	165	6.6	200	8	200	8
2.3	90	3.6	125	5	175	7	200	8	200	8
2.4	95	3.8	130	5.2	180	7.2	200	8	200	8

Palbociclib Oral Solution Administration Table

Body Surface Area (m^2)	Dose Level - 40 mg/m^2		Dose Level – 55 mg/m^2		Dose Level – 75 mg/m^2		Dose Level – 95 mg/m^2		Dose Level – 115 mg/m^2	
	Daily Dose Delivered (mg)	Oral Solution Volume Delivered (mL)	Daily Dose Delivered (mg)	Oral Solution Volume Delivered (mL)	Daily Dose Delivered (mg)	Oral Solution Volume Delivered (mL)	Daily Dose Delivered (mg)	Oral Solution Volume Delivered (mL)	Daily Dose Delivered (mg)	Oral Solution Volume Delivered (mL)

Note: Highest dose is capped at 200 mg, the palbociclib monotherapy MTD in adults on the 2/1 Schedule (dosing for 2 weeks, followed by 1 week off treatment). Palbociclib oral solution will be administered using 1 mL or 5 mL oral syringes. Volumes >1 mL will be administered using a 5 mL syringe (marked increments of 0.2 mL), while volumes ≤1 mL will be administered using a 1 mL oral syringe (marked increments of 0.1 mL).

Appendix 11. List of Drugs Known to Predispose to Torsade de Pointes

Generic Name	Brand Name(s)
Amiodarone	Cordarone®, Pacerone®
Arsenic trioxide	Trisenox®
Astemizole	Hismanal®
Azithromycin	Zithromax®
Bepridil	Vascor®
Chloroquine	Aralen®
Chlorpromazine	Thorazine®
Cisapride	Propulsid®
Citalopram	Celexa®
Clarithromycin	Biaxin®
Disopyramide	Norpace®
Dofetilide	Tikosyn®
Domperidone	Motilium®
Droperidol	Inapsine®
Erythromycin	Erythrocin®, E.E.S.®
Flecainide	Tambocor®
Halofantrine	Halfan®
Haloperidol	Haldol®
Ibutilide	Corvert®
Levomethadyl	Orlaam®
Mesoridazine	Serentil®
Methadone	Dolophine®, Methadose®
Moxifloxacin	Avelox®
Ondansetron*	Zofran®
Pentamidine	Pentam®, NebuPent®
Pimozide	Orap®
Probucol	Lorelco®
Procainamide	Pronestyl®, Procan®
Quinidine	Cardioquin®, Quinaglute®
Sotalol	Betapace®
Sparfloxacin	Zagam®
Terfenadine	Seldane®
Thioridazine	Mellaril®
Vandetanib	Caprelsa®

*when administered intravenously at high dose (32 mg).
Adapted from the University of Arizona Cancer Center for Education and Research on Therapeutics: "Torsades List: Drugs with a Risk of Torsades de Pointes," drugs that are generally accepted by the QTdrugs.org Advisory Board to carry a risk of Torsades de Pointes on the University of Arizona CERT website: http://www.crediblemeds.org/. This list is not meant to be considered all inclusive. See website for current list.

Appendix 12. Dosing Nomogram for Oral Temozolomide

Body Surface Area (m^2)	Actual Daily Dose	
	100 mg/m^{2*}	75 mg/m^{2**}
0.3	30	20
0.4	40	30
0.5	50	35
0.6	60	45
0.7	70	50
0.8	80	60
0.9	90	65
1.0	100	75
1.1	110	80
1.2	120	90
1.3	130	95
1.4	140	105
1.5	150	110
1.6	160	120
1.7	170	125
1.8	180	135
1.9	190	140
2.0	200	150
2.1	210	155
2.2	220	165
2.3	230	170
2.4	240	180

Use combination of capsules (5 mg, 20 mg, 100 mg) for actual daily dose.
*Starting dose
**Dose reduction per Section 5.4.11.

Appendix 13. Quality of Life

The QoL Sub-study will utilize PROMIS® Pediatric and Parent Profile questionnaires.[52] The following questionnaires will be used in the Phase 2 portion of the study:

PROMIS® Early Childhood Parent Report Scale v1.0 – Global Health 8a -Parent-Report Scale
PROMIS® Early Childhood Parent Report Scale v1.0 – Global Health 8a instrument is completed by parents for children ages 1 to 5 years old and assesses a child's overall physical, mental, and social health. It consists of 8 items that produce one global health score. The measure is generic, not disease-specific.

PROMIS® Parent Proxy Profile v2.0 – Profile-25 & PROMIS® Pediatric Profile v2.0 – Profile-25
PROMIS® Parent Proxy Profile v2.0 – Profile-25 instrument is intended for parents serving as proxy reporters for their child (youth ages 5-17) while PROMIS® Pediatric Profile v2.0 – Profile-25 instrument is intended for pediatric self-report (ages 8-17). The Profile-25 is a collection of short forms containing 4 items from six PROMIS domains (Depressive Symptoms, Anxiety, Physical Function-Mobility, Pain Interference, Fatigue, and Peer Relationships) along with a single item on Pain Intensity. The Profile-25 is generic rather than disease-specific and assesses all domains over the past seven days.

PROMIS–29 Profile v2.1
PROMIS–29 Profile v2.1 instrument is intended for adults (ages 18+). The Profile-29 is a collection of short forms containing 4 items from seven PROMIS domains (Depression, Anxiety, Physical Function, Pain Interference, Fatigue, Sleep Disturbance, and Ability to Participate in Social Roles and Activities) along with pain intensity 0-10 numeric rating scale (NRS). The Profile-29 is generic rather than disease-specific and assesses all domains over the past seven days except for Physical Function which has no timeframe specified.

The relevant questionnaires will be given to the patient and/or their parent/legal guardian/legally acceptable representative (as applicable) at baseline based on patient age at randomization, as detailed below:

- No self-report questionnaires are available for patients under the 8 years of age
- PROMIS® Early Childhood Parent Report Scale v1.0 – Global Health 8a will be given to a parent/legal guardian of eligible patients ≥2 to <5 years of age;
- PROMIS® Parent Proxy Profile v2.0 will be given to a parent/legal guardian of eligible patients ≥5 to ≤17 years of age;
- PROMIS® Pediatric Profile v2.0 will be given to patients ≥ 8 to ≤ 17 years of age;
- PROMIS–29 Profile v2.1 will be given to adult patients (≥18 years of age).

Appendix 14. Alternative Measures

The alternative study measures described in this section are to be followed during public emergencies, including the COVID-19 pandemic. This appendix applies for the duration of the COVID-19 pandemic and will become effective for other public emergencies only upon written notification from Pfizer. In Phase 1 (Dose Escalation, Dose Expansion cohorts and Dose Determination part) use of these alternative study measures are expected to cease upon the return of business as usual circumstances (including the lifting of any quarantines and travel bans/advisories).

In Phase 2 and Tumor-Specific cohorts the alternative study measures described in this section can be also applied outside public emergencies in order to limit study participation burden (ie, travel burden).

1. Eligibility

While SARS-CoV2 testing is not mandated for this study, local clinical practice standards for testing should be followed. A patient should be excluded if he/she has a positive test result for SARS-CoV2 infection, is known to have asymptomatic infection, or is suspected of having SARS-CoV2. When the infection resolves, the patient may be considered for re-screening.

2. Telehealth Visits

In the event that in-clinic study visits cannot be conducted, every effort should be made to follow up on the safety of study participants at scheduled visits per the Schedule of Activities or unscheduled visits. Telehealth visits may be used to continue to assess participant safety and collect data points. Telehealth includes the exchange of healthcare information and services via telecommunication technologies (eg, audio, video, video-conferencing software) remotely, allowing the participant and the investigator to communicate on aspects of clinical care, including medical advice, reminders, education, and safety monitoring. The following assessments must be performed during a telehealth visit:

- Review and record study intervention(s), including compliance and missed doses.
- Review and record any AEs and SAEs since the last contact. Refer to Section 8.
- Review and record any new concomitant medications or changes in concomitant medications since the last contact.
- Review and record contraceptive method and results of pregnancy testing. Confirm that the participant is adhering to the contraception method(s) required in the protocol. Refer to Protocol Section 7.1. and Section 3.1 of this appendix regarding pregnancy tests.
- Application and review of palatability questionnaire.

Study participants must be reminded to promptly notify site staff about any change in their health status.

3. Alternative Facilities for Safety Assessments

An alternative facility to perform safety assessments may be appropriate for study procedures that are standard safety assessments and are routinely performed by the alternative facility (eg, vital signs, physical examination, performance status, weight/height measurements and menarchal status).

3.1. Laboratory Testing

If a study participant is unable to visit the site for protocol-specified safety laboratory evaluations, testing may be conducted at a local laboratory if permitted by local regulations. The local laboratory may be a standalone institution or within a hospital. The following safety laboratory evaluations may be performed at a local laboratory:

- Screening hematology, blood chemistry, urine analysis and pregnancy test;
- On treatment hematology, blood biochemistry, urine analysis and pregnancy test;
- End of Treatment visit hematology, blood biochemistry, urine analysis and pregnancy test.

If a local laboratory is used, qualified study site personnel must order, receive, and review results. Site staff must collect the local laboratory reference ranges and certifications/accreditations for filing at the site. Laboratory test results are to be provided to the site staff as soon as possible. The local laboratory reports should be filed in the participant's source documents/medical records. Relevant data from the local laboratory report should be recorded on the CRF. It is recommended to use the same local laboratory each time to ensure consistency.

If a participant requiring pregnancy testing cannot visit a local laboratory for pregnancy testing, a home urine pregnancy testing kit with a sensitivity of at least 25 IU/mL may be used by the participant to perform the test at home, if compliant with local regulatory requirements. The pregnancy test outcome should be documented in the participant's source documents/medical records and relevant data recorded on the CRF. Confirm that the participant is adhering to the contraception method(s) required in the protocol.

3.2. Electrocardiograms

If the participant is unable to visit the study site for screening, on treatment or End of Treatment visit (EoT) ECGs, the participant may visit an alternative facility to have the ECGs performed. Qualified study site personnel must order, receive, and review results.

4. Study Intervention

If the safety of a trial participant is at risk because they cannot complete required evaluations or adhere to critical mitigation steps, then discontinuing that participant from study intervention must be considered.

Study drugs should be administered on Days 1 to Day 5 at the study site/facilities. In circumstances where this is not possible, the study sponsor should be notified.

If the site has established capacity, the site may provide alternative arrangements for administration of the study drugs for the participants who would not be able to come to the site, if acceptable by local law and regulation. The study drugs must be administered in a health care setting where safety measures can be taken and complete study requirements can be performed. In case an alternative facility is used for drug infusion, site has to maintain the required study drug storage and reconstitution conditions specified in the IP Manual. Administration of study treatments at an alternative facility must be approved by IRB/EC, as applicable and may only occur after documented Pfizer approval.

The following is recommended for the administration of investigational product for participants who have active [confirmed (positive by regulatory authority-approved test) or presumed (test pending/clinical suspicion)] SARS-CoV2 infection:

- For symptomatic participants with active SARS-CoV2 infection, investigational product should be delayed for at least 14 days from the start of symptoms. This delay is intended to allow the resolution of symptoms of SARS-CoV2 infection.

- Prior to restarting treatment, the participant should be afebrile for 72 hours, and SARS-CoV2-related symptoms should have recovered to ≤Grade 1 for a minimum of 72 hours. Notify the study team when treatment is restarted.

- Continue to consider potential drug-drug interactions as described in Sections 5.7.1 and 5.7.2 for any concomitant medication administered for treatment of SARS-CoV2 infection.

5. Adverse Events and Serious Adverse Events

If a participant has COVID-19 during the study, this should be reported as an adverse event (AE) or serious adverse events (SAE) and appropriate medical intervention provided. Investigational product should be temporarily discontinued until the participant has recovered from COVID-19. It is recommended that the investigator discuss temporary or permanent discontinuation of study intervention with the study medical monitor.

6. Efficacy Assessments

Tumor assessments are to be performed at the study site/facilities. In circumstances where this is not possible, the study sponsor should be notified.

Appendix 15. Protocol Amendment History

The protocol amendment summary of changes table for the current amendment is located directly before the Table of Contents. The protocol amendment summary of changes tables for past amendment(s) can be found below:

Amendment 6 (23 December 2022)

Section # and Name	Description of Change	Brief Rationale
Substantial		
Section 4.1 Inclusion Criteria	**Inclusion # 6** (adequate liver function) updated to add upper limit for direct bilirubin for patients with documented Gilbert's syndrome**.**	Inclusion criterion revised upon UK Regulatory Authority (MHRA)'s request.
Section 4.2 Exclusion Criteria	**UK Specific: Exclusion # 2** updated to exclude patients with any contraindication to IRN and/or TMZ as per local SmPC.	Exlusion criterion updated upon UK Regulatory Authority (MHRA)'s request. Applicable to the UK only.
Section 4.2 Exclusion Criteria	**Exclusion # 17** added to exclude patients who are unwilling or unable to use contraception; **Exclusion # 18** added to exclude pregnant and breastfeeding women.	Exlusion criteria added upon upon UK Regulatory Authority (MHRA)'s request.
Nonsubstantial		
Section 4.3 Lifestyle Requirements	Updated to add definition of WOCBP.	Section updated upon UK Regulatory Authority (MHRA)'s request.
Section 4.3 Lifestyle Requirements	**UK Specific:** Updated to clarify condom with separate spermicide is not appropriate contraceptive method in the UK.	Clarification added upon UK Regulatory Authority (MHRA)'s request. Applicable to the UK only.
Section 5.7.5 Anti-Diarrheal, Anti-Emetic Therapy	**UK Specific:** Updated to clarify the anti-diarrheal treatments and anti-emetic treatments administration should follow institutional guidance and local SmPC in the UK .	Clarification added upon UK Regulatory Authority (MHRA)'s request. Applicable to the UK only.

Section # and Name	Description of Change	Brief Rationale
Appendix 4 Diarrhea Treatment	**UK Specific:** Loperamide dosing Table Footnote added to clarify dosing should follow local SmPC in the UK.	Clarification added upon UK Regulatory Authority

Document	Version Date	Summary of Changes and Rationale
Amendment 5	26 April 2022	The primary purpose of the amendment is to add the Phase 2 secondary efficacy endpoint of EFS based on independent review. The change is reflected in the appropriate protocol sections. The high-level summary of the additional changes made to the protocol, by section, is as follows: • **Schedule of Activities and Corresponding Sections:** • Tables 2 and 3 height measurement schedule updated; • Table 2 Footnote 12 edited to clarify tumor tissue collection requirements; • Table 2 Footnote 21 and 22 corrected to clarify all hormonal, growth and bone metabolism tests are performed at central laboratory; • Table 3 and Section 7.1.6 updated to clarify required ECG should be taken prior to 5-HT3 dosing; • Table 3 and Sections 7.5 and 7.9.2 updated to add PET-MRI modality for distant disease staging; • Table 3- QoL updated to be collected preferably prior to dosing on Cycle 3 Day 1 and Cycle 5 Day 1;

Document	Version Date	Summary of Changes and Rationale
		• Table 3 Footnote 23 and 24 corrected to clarify all hormonal, growth and bone metabolism tests are performed at central laboratory; • Table 3 screening duration corrected to -21 days prior randomization; • Table 3. Footnote 10 corrected to clarify TK samples in Phase 2 should be drawn on C1D1 and only from patients randomized to Palbociclib arm; • Table 3 Footnote 12 edited to clarify tumor tissue collection requirements; • Table 3 and Footnote 18 – details added to clarify hospitalization data collection; • Table 3 Footnote 19 detailes on requirements for bone marrow aspirates and biopsies removed and Footnote 20 updated to describe modified requirements for bone marrow aspirates and biopsies; • Section 1.2.2.2 updated with final data from PBTC study; • Section 1.2.2.2.3 added safety information from Phase 1 of A5481092 study (corresponding to IB version 14.0 March 2021; • Added Section 1.3 Risk/benefit Assessment; • **Section 2** added secondary endpoint EFS by BIRC; • **Section 3.1.1** • added Figure 1 – Schema of Phase 1 combination with IRN and TMZ; • added Figure 2 -Schema of Phase 2;

Document	Version Date	Summary of Changes and Rationale
		• Section 3.1.2 added Figure 3 Schema of Phase 1 Combination of palbociclib with TOPO and CTX; • Section 4.1 and 4.2 eligibility criteria modified; • Section 4.3 Lifestyle requirements modified for female patients; • Section 5.4.11 andTable 13 updated to clarify dose reductions in IRN/TMZ only treatment arm; • Section 5.4.11 Tables 13and14: added clarification regarding requirements for dose reduction for Grade 3 neutropenia with fever (febrile neutropenia); • **Section 5.7.9** requirements for concurrent surgery and radiotherapy modified to allow for local control measures; • **Section 7.1.3** Table 15 & Section 8.4.1 modified to clarify Hy's Law additional tests requirements; • **Section 7.1.5** edited to clarify DEXA scans and X-rays should be performed if acceptable by applicable competent authority requirements; • **Section 7.5** edited to add details on bone marrow assessment in Phase 2; • **Section 7.7** added to define hospitalization for Phase 2 secondary endpoint; • **Section 7.9** edited to provide details on bone marrow assessment; • Section 9.6 updated to reflect secondary endpoint of central tumor data review; • **Sections 11, 12, and 15** updated to align with current protocol template;

Document	Version Date	Summary of Changes and Rationale
		• **Appendix 5** added determination of tumor response by RECIST v 1.1; • **Appendix 14** clarification added Alternative Measures During Public Emergencies is applicable to all countries; PACL dated 07 Oct 2021 to clarify requirement of TK sample collection (SoA Table 3 and Table 5). Other editorial changes were made throughout the protocol amendment to improve text clarity and/or correct typos.
Amendment 4	18 June 2021	The primary purpose of the amendment is to add a randomized Phase 2 portion to compare the safety and efficacy of palbociclib in combination with IRN and TMZ vs. IRN and TMZ alone in children, adolescents, and young adults patients with recurrent or refractory Ewing sarcoma (EWS). These changes are reflected in the appropriate protocol sections. The high level summary of the additional changes made to the protocol, by section, is as follows: • **Study Title:** • Updated to "Phase 1/2 Study to Evaluate The Safety and Pharmacokinetics of Palbociclib (Ibrance®) in Combination With Irinotecan And Temozolomide or in Combination With Topotecan and Cyclophosphamide in Pediatric Patients With Recurrent or Refractory Solid Tumors" • **Schedule of Activities and Corresponding Sections:** • **Table 2 updated & Footnote 3** Tanner stage assessment schedule updated to match the hormonal assessments schedule; • **Table 2 Laboratory assessment of HbA1c** updated to be done on Day 1 of Subsequent

Document	Version Date	Summary of Changes and Rationale
		Cycles (repeat at Cycle 4 and then repeat every 4 cycles); • **Table 2 Laboratory assessment of Thymidine kinase analysis** was added and **Footnote 10** was revised; • **Table 2 Footnote 7** updated a wording: Collection of 1 baseline blood sample on C1D1 will not constitute protocol deviation as long as sample is taken prior C1D1 dosing; • **Table 2 Footnote 11** updated to correct typo and clarify that ECG Cycle 3 Day 1 is required and add wordings: If patient is receiving 5-HT3 antagonist for nausea/vomiting prophylaxis or treatment, the ECG should be performed prior to administration of the 5-HT3 antagonist. See Section 7.1.6; • **Table 2 Footnote 12** updated to document biomarker sample volume and clarify sample is required for all patients; • **Table 2 Footnote 18 & Section 7.5 & 7.8** updated to clarify post baseline, EoT and follow up tumor assessment requirements; • **Table 2 Footnote 28** updated to clarify EoT; • **Table 2 Footnote 29 & Section 7.7** updated to clarify survival follow up schedule starts from EoT visit; • **Table 4 Footnote 6** updated to clarify PK requirements for backbone chemotherapy agents per combination; • **Tables 3 and 5** were added for the Phase 2 portion of the study. **Other Sections:**

Document	Version Date	Summary of Changes and Rationale
		• **Section 3.1.2.2 & Section 9.3.2 & Section 9.3.4** updated to clarify enrollment duration for PK-evaluable patients per age groups; • **Section 4.1** added criterion for histologically confirmed relapsed or refractory solid tumor and updated the 7th criterion;**Section 5.1** updated to claritfy allocation to treatment of Phase 1 and Phase 2 portions; • **Sections 5.3.1.3-5.3.1.6** updated to clarify dosage forms and packaging of irinotecan, temozolomide, topotecan and cyclophosphamide; • **Section 5.3.2** updated to clarify requirements for recording and reporting of times of oral TMZ and palbociclib dosing; • **Section 5.4.8** updated to add a wording about Phase 2 portion; • **Subsections of Section 5.7 updated** and aligned to provide consistent guidance for recommended CINV prophylaxis regimens; • **Section 6.1** updated to clarify the screening of Phase 2 portion; • **Section 6.3** updated to clarify the follow-up of Phase 1 and Phase 2 portions; • **Section 7** updated to revise the wording of assessment; • **Section 7.1** updated to clarify the safety assessment; • **Table 13 & Table 14** updated to clarify dose reduction requirement for Grade 4 myelotoxicity;

Document	Version Date	Summary of Changes and Rationale
		• **Section 7.1.6** updated to clarify dose reduction of TOPO/CTX is not required for prolonged QTc; • **Section 7.2** updated to add content of pharmacokinetic assessment for Phase 2 portion; • **Section 7.4** updated to add content of biomarker and pharmacodynamic assessments for Phase 2 portion; • **Section 7.5** updated to clarfy the tumor response assessments of Phase 1 and Phase 2 portions; • **Section 7.6** updated to clarity the quality of life assessment for Phase 2 portion; • **Section 7.7** updated to clarify survival follow up visits; • Section 7.8.2 updated to add information of post-baseline tumor assessments for Phase 1 and Phase 2 portions; • Sections 9.1.1 and 9.1.2 updated to add information for Phase 1 and Phase 2 portions; • **Section 9.1.3** updated to clarify DLT evaluability definition; • **Section 9.1.6** was added to clarify patient reported outcome (PRO) evaluable analysis set; • **Section 9.2.4** was added to clarify the statistical methods and properties of randomized Phase 2; • **Sections 9.3.2, 9.3.3 and 9.3.4** updated to clarify the sample size determination of Phase 1 dose expansion cohort, Phase 1 tumor-specific cohort and randomized Phase 2. • **Section 9.4.1** updated to clarify safety analysis;

Document	Version Date	Summary of Changes and Rationale
		• **Sections 9.4.2, 9.6.1 and 9.6.2** updated to clarify planned safety and efficacy analyses; • **Section 9.8** updated to clarify interim analysis of Phase 2 potion; • **Section 9.9** updated to clarify the data monitoring committee of Phase 2 portion. **References:** • Added 4 references. **Appendices:** • **Appendix 5** updated to clarify the content of non- measurable disease only; • **Appendix 13** was added to clarify quality of life. Other editorial changes were made throughout the protocol amendment.
Amendment 3	06 Jul 2020	The primary purpose of the amendment is to include additional combination of palbociclib with topotecan and cyclophosphamide chemotherapy to evaluate the safety, pharmacokinetics (PK), and antitumor activity of the combination in pediatric patients with refractory or recurrent solid tumors. A cohort to evaluate the antitumor activity, safety, and PK of palbociclib in combination with irinotecan (IRN) and temozolomide (TMZ) in patients with Ewing sarcoma (EWS) will also be added. These changes will be reflected in the appropriate protocol sections. The high level summary of additional changes made to the protocol, by section, is as follows: **SoA updated & Footnote 9** added for Urine analysis; **SoA Footnote 11** updated to allow for ±120 minutes window for post dosing ECG and to remove requirement of 24 hours post dose ECG on Cycle 1 Day 3 (C1D3);

Document	Version Date	Summary of Changes and Rationale
		SoA Footnote 18 and Section 7.7 updated to clarify tumor assessments to be conducted every 2 cycles for the first 8 cycles; **SoA Footnote 25** updated to add requirement to review results of hematology and blood chemistry prior to dosing to confirm eligibility to continue study medication; **Section 1.2.1** updated to include nonclinical in vivo data for antitumor activity in a mouse model of EWS; **Section 2** updated to remove progression-free survival (PFS) and overall survival (OS) as secondary endpoints for dose escalation; **Sections 5.3.1.3-4** updated to modify potency and packaging information on IRN and TMZ; **Section 5.4.10** updated to change platelets count criterion required to restart treatment to $\geq$75,000/mm^3; **Section 5.4.11.1** updated to remove details on dose modifications with palbociclib in combination with TMZ and IRN for specific adverse events (AEs) as information is included in Table 12; **Section 7.1.3** updated to add urine analysis in Table 14; **Appendix 13** added on alternative measures during public emergencies.
Amendment 2	08 January 2020	The primary purpose of the amendment is to add additional dose levels with palbociclib doses of 95 mg/m^2 and 115 mg/m^2 due to no dose-limiting toxicities (DLTs) and observed palbociclib PK lower than reported at single agent MTD on Schedule 2/1. The high level summary of changes made to the protocol, by section, is as follows:

Document	Version Date	Summary of Changes and Rationale
		• **Section 1.2.2.3** updated to specify Single Reference Safety Document (SRSD) for irinotecan and temozolomide; • **SoA Footnotes 3 & 23** updated to clarify windows for safety laboratory, pregnancy and vital signs assessments; • **SoA Footnote 8** updated to add reference to Protocol Section 7.1.1; • **SoA Footnote 10** updated to allow for 60 minutes window for ECG assessment; • **SoA Footnote 12** updated to specify requirements for patient registration; • **SoA Footnotes 16 & 17** updated to provide details on tumor assessment and DEXA scan; • **SoA Footnotes 5, 18, 19, 20** updated to clarify Tanner stage assessment, bone age & hormonal assessment requirements in prepubertal children; • **SoA Footnotes: 7, 19 & 20** updated to identify lab samples to be sent to Central Laboratory; • **SoA Footnote 27** updated to add visit window; • **Section 3.3** MTD Definition & **Section 9.2.1.2** Statistical Method for Estimating MTD updated MTD definition; • **Section 9.3** Sample Size Determination updated for the 2 additional dose levels; • **Section 3 and Table 3** updated to add 2 additional palbociclib dose levels; • **Section 5** updated to document irinotecan and temozolomide are considered investigational products;

Document	Version Date	Summary of Changes and Rationale
		• **Section 5.4.1** Palbociclib Oral Solution, Table 7 updated to add details on palbociclib dosing for new dose levels; • **Section 5.4.9 & Table 8** Dose reduction updated to change the palbociclib dose reduction guideline; • **Section 5.6 Investigational Product Accountability** updated to add details on the requirements of data reporting for site sourced investigational medicinal products (IMPs) (TMZ and IRN); • **Sections 7.1.4 & 7.1.5** updated to clarify Tanner staging for prepubertal children and bone age/hormonal assessment requirements; • **Section 9.1 Analysis Set** updated to include TMZ and IRN as investigational products; • **Appendix 10** Volume of palbociclib – updated provide details on palbociclib dosing for new dose levels.
Amendment 1	30 July 2019	Section 7.5 and New Appendix 7: Added International Neuroblastoma Response Criteria (INRC). Added language to Section 7.5, Tumor Response Assessment describing INRC and added Appendix 7 with detail of INRC. Also corresponding changes made in protocol summary and objectives. Schedule of Activities: ^{123}MIBG or fluorodeoxyglucose (FDG)-positron emission tomography (PET) (only for patients whose tumor is MIBG non-avid) now mandatory for patients with neuroblastoma. Bilateral Bone Marrow Aspirates and Biopsies mandatory at baseline for all patients with neuroblastoma and during follow-up only if bone marrow disease is present at baseline.

Document	Version Date	Summary of Changes and Rationale
		Follow up response imaging will now include an early assessment after completion of Cycle 2 and Cycle 4 and then every 4 cycles. Moved bone growth evaluations to subsequent cycles column to clarify that these were not needed to be performed in Cycle 2. Clarified language on what day lab tests need to be performed for subsequent cycles and what endocrine tests need to be done. Exploratory Objectives: Removed language regarding labs for bone alkaline phosphatase and C-telopeptide as these are not needed for this study. Removed TMZ active metabolites from PK objectives. Section 3.2 DLT reporting Clarified reporting structure for patients with DLTs. Section 5.3.1.4 TMZ administration: Added that Pfizer will supply IV TMZ to patients that cannot swallow TMZ capsules. Section 7.2 PK assessments: Added language to clarify make up PK schedule and kits to use if patients miss PK draws in Cycle 1 or 2. Removed TMZ active metabolites MTIC and AIC from PK assessments. Section 7.5 Tumor Assessment: Confirmation of response change from 6-week time limit to >4 weeks after prior scan showing response. Section 7.7-Clarified time points for tumor assessments. Section 9: Data Analysis. Section 9.1.1 – Modified definition of safety analysis set. Section 9.1.2-Clarified definition of non-evaluable patients.

Document	Version Date	Summary of Changes and Rationale
		Added section 9.8 to define interim analysis within the study. Removed redundant language from section 9.
Original protocol	03 January 2019	Not applicable (N/A)