Protocol I3Y-MC-JPCS (f)

A Phase 1b/2 Study of Abemaciclib in Combination With Irinotecan and Temozolomide (Part A) and Abemaciclib in Combination With Temozolomide (Part B) in Pediatric and Young Adult Patients With Relapsed/Refractory Solid Tumors and Abemaciclib in Combination With Dinutuximab, GM-CSF, Irinotecan, and Temozolomide in Pediatric and Young Adult Patients With Relapsed/Refractory Neuroblastoma (Part C)

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Approval Date: 18 JUL 2023

Title Page

Protocol Title: A Phase 1b/2 Study of Abemaciclib in Combination with Irinotecan and Temozolomide (Part A) and Abemaciclib in Combination with Temozolomide (Part B) in Pediatric and Young Adult Patients with Relapsed/Refractory Solid Tumors and Abemaciclib in Combination with Dinutuximab, GM-CSF, Irinotecan, and Temozolomide in Pediatric and Young Adult Patients with Relapsed/Refractory Neuroblastoma (Part C).

Protocol Number: I3Y-MC-JPCS

Amendment Number: (f)

Compound Number: LY2835219

Study Phase: Phase 1b/2

Short Title: A Phase 1b/2 Study of Abemaciclib Plus Chemotherapy and/or Chemoimmunotherapy in Pediatric and Young Adult Patients with Relapsed/Refractory Solid Tumors

Acronym: JPCS

Sponsor Name: Eli Lilly and Company

Legal Registered Address: Indianapolis, Indiana, USA 46285

Regulatory Agency Identifier Number(s):

IND: 138024
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EU trial number: 2023-506778-11-00

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Approval Date: Protocol Amendment (f) Electronically Signed and Approved by Lilly on date provided below.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Amendment (e)	*11-Jul-2022*
Amendment (d)	*04-Mar-2021*
Amendment (c)	*15-Jan-2021*
Amendment (b)	*08-Jul-2020*
Amendment (a)	*17-Apr-2020*
Original Protocol	*14-Dec-2019*

Amendment (f)

This amendment is considered to be substantial

The amendment is considered to be substantial because it is likely to have a significant impact on the safety or the rights of the study participants.

Overall Rationale for the Amendment:

The overall rationale for this protocol amendment is to modify the inclusion criteria to allow flexibility related to retinoid use, to allow IV temozolomide (site sourced only) in Part C, and to align the protocol for transition to EU Clinical Trial Regulation (EU CTR) 536/2014. Additional changes in the protocol are summarized in the table below. Minor typographical or formatting changes are not listed.

Section # and Name	Description of Change	Brief Rationale
1.1. Synopsis	Added regulatory agency identifier numbers	To align with EU CTR
1.1. Synopsis	Added footnote "a" to objectives/endpoints table: "In Part C, PK is a primary endpoint for Stage 1 only"	Clarification
1.1. Synopsis	Added essential description of study population	To align with EU CTR
1.1. Synopsis	Added subsection for ethical considerations of risk benefit	To align with EU CTR
1.2. Schema	Updated study schema to include Cohort B5 and minor formatting changes	Error correction
1.3.1. Schedule of Activities for Parts A	In text above SoA table for Schedule of On-Study Treatment Activities for Parts A and B,	Clarification

Section # and Name	Description of Change	Brief Rationale
and B	"(pregnancy results are not required to be recorded in the eCRF)" added in the second to last sentence	
1.3.1. Schedule of Activities for Parts A and B	In On-Study Treatment Activities for Parts A and B, CCI [redacted]	Clarification
1.3.1. Schedule of Activities for Parts A and B	In On-Study Treatment Activities for Parts A and B, Hematology line-item comments modified and added: Current comment edited to: "≤7 days prior to C1D1. For C2 and beyond, ≤3 days before Day 1 and ±3 days for Days 8 and 15" Added: "If irinotecan has been discontinued (Part A) or not part of the regimen (Part B), and clinically significant cytopenia is not observed after 3 cycles, CBC may be reduced to Day 1 (can eliminate Days 8 and/or 15)."	To reduce participant burden
1.3.1. Schedule of Activities for Parts A and B	In On-Study Treatment Activities for Parts A and B, Clinical Chemistry line-item comments modified and added: Current comment edited to: ≤7 days prior to C1D1. For C2 and beyond, ≤3 days before Day 1 and ±3 days for Days 8 and 15 Added: "If on study >3 cycles and clinically significant chemistry adverse event is not observed, frequency may be reduced to Day 1 (can eliminate Days 8 and/or 15)."	To reduce participant burden
1.3.1. Schedule of Activities for Parts A and B	In On-Study Treatment Activities for Parts A and B, Cystatin C line-item comment modified: "≤7 days prior to C1D1. For C2 and beyond, ≤3 days before Day 1, unless more frequent assessment is clinically indicated. See Section 10.2, Appendix 2.	To reduce participant burden
1.3.1. Schedule of Activities for Parts A	In Posttreatment Follow-Up Schedule of Activities for Parts A and B, CCI [redacted]	To reduce participant burden

Section # and Name	Description of Change	Brief Rationale
and B	CCI [redacted]	
1.3.2. Schedule of Activities for Part C	In text for Section 1.3.2, "(pregnancy results are not required to be recorded in the eCRF)" added in the second to last sentence	Clarification
1.3.2. Schedule of Activities for Part C	In Schedule of Baseline and Screening Activities for Part C, line item for CCI [redacted]	To reduce participant burden
1.3.2. Schedule of Activities for Part C	In Schedule of Baseline and Screening Activities for Part C, line item for serum or urine pregnancy test, removed "X" from ≤14 column and added "X" to ≤7 column	Clarification
1.3.2. Schedule of Activities for Part C	In Schedule of On-Study Treatment Activities for Part C, deleted the first paragraph regarding remote visits	Error correction
1.3.2. Schedule of Activities for Part C	In Schedule of On-Study Treatment Activities for Part C, CCI [redacted]	Clarification
1.3.2. Schedule of Activities for Part C	In Schedule of On-Study Treatment Activities for Part C, CCI [redacted]	Clarification
1.3.2. Schedule of Activities for Part C	In Schedule of On-Study Treatment Activities for Part C, Hematology line-item comment, deleted "If patients remain on study for >4 cycles and clinically significant cytopenia is not observed, CBC frequency may be reduced to the start of subsequent cycles and as clinically indicated"	Clarification
1.3.2. Schedule of Activities for Part C	In Schedule of On-Study Treatment Activities for Part C, Biomarkers – plasma line-item, reduced participant weight threshold for sampling from CCI kg to CCI kg	Update

Section # and Name	Description of Change	Brief Rationale
1.3.2. Schedule of Activities for Part C	In Schedule of On-Study Treatment Activities for Part C, Biomarkers-whole blood line-item, reduced participant weight threshold for sampling from CCI kg to CCI kg for whole blood dried blood spot, and from CCI kg to CCI kg for whole blood sample	Update
1.3.2. Schedule of Activities for Part C	In Posttreatment Follow-Up Schedule of Activities for Part C, line item for CCI	To reduce participant burden
1.3.2. Schedule of Activities for Part C	In Posttreatment Follow-Up Schedule of Activities for Part C, CCI	To reduce participant burden
1.3.2. Schedule of Activities for Part C	In Posttreatment Follow-Up Schedule of Activities for Part C, Plasma biomarker sample line-item, added comments for • participants CCI kg, whole blood sample • initiation of subsequent therapy, and • only if not already obtained at visit when participant discontinued study.	Update
1.3.2. Schedule of Activities for Part C	In Posttreatment Follow-Up Schedule of Activities for Part C, Tissue submission from tumor biopsy obtained after progression line-item, edited to: "Only for patients on study treatment at least 6 months"	Update
1.3.2. Schedule of Activities for Part C	In Posttreatment Follow-Up Schedule of Activities for Part C, Collection of poststudy anticancer treatment line item, edited comment	Clarification
2.2.6. Preclinical and Clinical Rationale	Added "(KELLY and IR-32)" in the third paragraph	Clarification
2.3. Benefit/Risk Assessment	Changed "strategic" to "effective" in the first sentence	Clarification
2.3.2. Overall Benefit Risk Conclusion	Added subsection for overall benefit risk conclusion	To align with EU CTR

Section # and Name	Description of Change	Brief Rationale
3. Objectives and Endpoints	Added footnote "a" to objectives/endpoints table: "In Part C, PK is a primary endpoint for Stage 1 only"	Clarification
4.1.2. Two-stage Design for Part C	Stage 1 subsection • deleted "the trial" from Rules A and B • added "completing" to Rule B • replaced "minimum" with "minor" in Rule C	 Clarification Clarification Correction
4.1.2. Two-stage Design for Part C	In De-escalation during cohort expansion subsection, replaced "and" with "but" in the first sentence	Correction
5.1. Inclusion Criteria	Inclusion criterion #3, for Part C only, definition of the first relapse was edited to include "with or without retinoids"	To allow flexibility
5.1. Inclusion Criteria	Inclusion criterion #3, for Parts A, B and C, item ii, changed "cannot" to "can"	Correction
5.1. Inclusion Criteria	Inclusion criterion #5, added "and/or have a gastric/nasogastric tube. Refer to Section 6.1.2 for alternative administration methods"	Clarification
5.1. Inclusion Criteria	Inclusion criterion #6, text of the first sentence, added "deemed clinically insignificant at the investigator's discretion", and deleted "otherwise noted (Grade ≤2 for alopecia, decreased tendon reflex, and residual peripheral sensory neuropathy are acceptable)"	For flexibility
5.2. Exclusion Criteria	Exclusion criterion #20 edited, now reads "The patient has active systemic infections (e.g. bacterial, fungal, or viral infection requiring IV therapy). Individuals with stable HIV, Hepatitis B, or C for whom exposure to the investigational treatment is not expected to exacerbate their current disease may be considered eligible. Screening is not required for enrollment."	Clarification
5.2. Exclusion Criteria	Exclusion criterion #31, edited the first sentence to replace "or" with "and" and added "neurological"	Clarification
5.2. Exclusion	Exclusion criterion #32 was added: "Part C	For additional

Section # and Name	Description of Change	Brief Rationale
Criteria	only, have received prior anti-GD2 therapy during induction phase"	clarification
6.1. Study Intervention(s) Administered	Changed Cycle "4" to Cycle "3" in the first sentence of the fourth paragraph	Correction
6.1. Study Intervention(s) Administered	Treatment text was edited in subsections for abemaciclib, temozolomide, irinotecan, dinutuximab and GM-CSF	Clarification
6.1. Study Intervention(s) Administered	Added EU authorization-related text for each study intervention	To align with EU CTR
6.1. Study Intervention(s) Administered	Added subsection for packaging and labeling	To align with EU CTR
6.1.3. Criteria to Begin Subsequent Cycles of Treatment	CCI [redacted]	Clarification
6.1.3. Criteria to Begin Subsequent Cycles of Treatment	Added "unless deemed clinically insignificant by the investigator" at end of final bullet point and deleted "(except alopecia, anorexia, asthenia, and decreased tendon reflex)"	Clarification
6.5.1. Palliative, Medicine and Supportive Care	In Supportive Care subsection Third bullet: Deleted the first portion of the sentence and added "thrombopoietic growth factors" Fifth bullet: Deleted the second sentence	Clarification
6.5.2. Supportive Management for Diarrhea	Edited the first, second, and fourth paragraphs	Clarification
6.6.1.1. Dose Modification Guidance due to Toxicities Considered to be Attributed to Abemaciclib	In the Parts A and B table for abemaciclib dose adjustments and suspensions due to nonhematologic toxicity considered to be attributed to abemaciclib, added "unless deemed clinically insignificant by the investigator" to the line for Nonhematologic Toxicity (except diarrhea, ALT/AST increased, and ILD/pneumonitis)	Clarification
6.6.1.1. Dose Modification	In the Parts A and B table for abemaciclib dose adjustments and suspensions due to	Correction

Section # and Name	Description of Change	Brief Rationale
Guidance due to Toxicities Considered to be Attributed to Abemaciclib	nonhematologic toxicity considered to be attributed to abemaciclib, added superscript "b" footnote reference to lines for • Diarrhea Grade 2 that persists, and • ILD / pneumonitis.	
6.6.1.3. Part C-Specific Dose Modifications	In the table for Part C Dose Modifications for Diarrhea, added • superscript "a" footnote reference to line for Grade 2 Does not Resolve to ≤Grade 1 Within 24 hours, 1st Event column: "Persists or recurs[a] despite maximal supportive measures" • new footnote "[a] Determination of persistent events will be at the discretion of the investigator. Recurrent toxicity refers to the same event occurring within the next 8 weeks (as measured from the stop date of the preceding event)."	Clarification
6.6.1.3. Part C-Specific Dose Modifications	In the table for Part C Dose Modifications for Hepatotoxicity • added superscript "a" footnote reference to line title: "Persistent or Recurrent[a] Grade 2 AST/ALT Increase" • edited and reordered existing superscript footnote references • added new footnote "[a] Determination of persistent events will be at the discretion of the investigator. Recurrent toxicity refers to the same event occurring within the next 8 weeks (as measured from the stop date of the preceding event). • Changed footnote c from "36" days to "35"	Clarification
6.6.1.3. Part C-Specific Dose Modifications	In the table for Part C Dose Modifications for Miscellaneous Toxicity • added superscript "a" and footnote reference to Persistent or recurrent:	Clarification

Section # and Name	Description of Change	Brief Rationale
	"Persistent or recurrent[a] Grade 2 despite maximal supportive care[b]" • added superscript "b" footnote reference to line for Nonhematologic Toxicity not Otherwise Described Above: "Grade 2 Persistent or recurrent[a, b]" • added new footnote "[a] Determination of persistent events will be at the discretion of the investigator. Recurrent toxicity refers to the same event occurring within the next 8 weeks (as measured from the stop date of the preceding event). • edited former footnote "a" to "b" and modified text: "[b] Does not resolve with maximal supportive measures within 7 days to baseline or Grade 1 unless deemed clinically insignificant the investigator.	
8.3. Adverse Events and Serious Adverse Events	Added sections and content for "Definition of AE" and "Events meeting the AE definition"	To align with EU CTR
8.3. Adverse Events and Serious Adverse Events	Added "clinically relevant" in the second sentence of the eighth paragraph	Clarification
8.3.3. Regulatory Reporting Requirements for SAEs	Edited the second bullet and deleted the third bullet	To align with EU CTR
8.8.1. Biomarkers for Part C	Added "for instance to understand the role of various co-occurring alterations" to the last sentence of the second paragraph	Clarification
8.8.1. Biomarkers for Part C	Deleted the first sentence in the third paragraph	Correction
8.8.1. Biomarkers for Part C	In the fourth paragraph, revised timeframe for storage or retention of biomarker samples from CCI	Updated
8.8.1.1. Tissue Samples for Biomarker Research	Deleted the fourth and fifth paragraphs	Update

Section # and Name	Description of Change	Brief Rationale
8.8.1.2. Plasma Samples for Biomarker Research	Deleted the second paragraph	Update
9.4.6.2.1. 2017 INRC	Deleted footnote "a" for FDG-PET in the subsection, Primary tumor (soft tissue) response	Clarification
9.4.6.2.1. 2017 INRC	Deleted footnote "a" for SUV collection and renumbered other footnotes in the Soft tissue and bone metastatic disease tumor response subsection	Clarification
9.4.6.2.1. 2017 INRC	Deleted "SUV will be collected for FDG PET avid sites" from footnote b	
9.5. Interim Analyses	Modified the second and third bullets by adding "treatment-related" (treatment-related AE..) and replacing "minimal" with "minor" (minor response), respectively	Clarification
9.5. Interim Analyses	Added "If 55 mg/m^2 is declared the MTD, but either Rule A or B is triggered during cohort expansion, the DMC may recommend that subsequent patients be treated at 30 mg/m^2. See Section 4.1.2."	Clarification
10.1.1. Regulatory and Ethical Considerations	Added new fourth bullet point	Update
10.1.1. Regulatory and Ethical Considerations	Minor edit related to EU CTR in the final sub bullet of the fifth main bullet	To align with EU CTR
10.1.3. Data Protection	Replaced section text with updated EU CTR text	To align with EU CTR
10.1.5. Dissemination of Clinical Study Data	Deleted the first sentence and replaced the section text for "Data" with updated EU CTR text	To align with EU CTR
10.2. Appendix 2: Clinical Laboratory Tests	In clinical lab test tables for Parts A, B, and C, "Blood urea nitrogen" was edited to "Blood urea nitrogen (BUN) or blood urea"	Clarification
10.6. Appendix 6: Inducers and Strong Inhibitors of CYP3A4	Changed "CYP3A" to "CYP3A4" in section title and table headers	Clarification

Section # and Name	Description of Change	Brief Rationale
10.6. Appendix 6: Inducers and Strong Inhibitors of CYP3A4	Updated the table	Update
10.9. Appendix 9: Country-Specific Requirements	Country-Specific Addendum has been added as an appendix to the protocol. Only specific for JPCS sites in the EU.	Consolidation of Protocol as required by the EU CTR for Transition
10.10. Appendix 10: Abbreviations	Updated with items that align with EU CTR	To align with EU CTR

Table of Contents

1. Protocol Summary

1.1. Synopsis

Protocol Title: A Phase 1b/2 Study of Abemaciclib in Combination with Irinotecan and Temozolomide (Part A) and Abemaciclib in Combination with Temozolomide (Part B) in Pediatric and Young Adult Patients with Relapsed/Refractory Solid Tumors and Abemaciclib in Combination with Dinutuximab, GM-CSF, Irinotecan, and Temozolomide in Pediatric and Young Adult Patients with Relapsed/Refractory Neuroblastoma (Part C).

Short Title: A Phase 1b/2 Study of Abemaciclib Plus Chemotherapy and/or Chemoimmunotherapy in Pediatric and Young Adult Patients with Relapsed/Refractory Solid Tumors

Regulatory Agency Identifier Number(s):

IND: 138024

EudraCT: 2019-002931-27

EU trial number: 2023-506778-11-00

Rationale: Despite advances in the treatment of pediatric cancers, there is still an unmet need for efficacious and tolerable regimens for relapsed/refractory solid tumors. Study I3Y-MC-JPCS (JPCS) is designed to assess the pharmacokinetics (PK), safety, and tolerability of abemaciclib added to currently utilized chemotherapy and chemoimmunotherapy backbone regimens for pediatric solid tumors. JPCS consists of 3 parts: A, B, and C. All parts are intended to determine the recommended Phase 2 dose (RP2D) for their respective abemaciclib combinations, and the second stage of Part C is intended to evaluate objective response rate (ORR) of the abemaciclib combination with RP2D determined in the first stage.

Parts A and B will enroll pediatric and young adult patients with relapsed/refractory solid tumors. Part C will exclusively enroll pediatric and young adult patients with relapsed/refractory neuroblastoma. Part A will combine abemaciclib with irinotecan and temozolomide and will influence the doses in Parts B and C. Part B will combine abemaciclib and temozolomide. Part C will combine abemaciclib with dinutuximab, GM-CSF, irinotecan, and temozolomide.

Objectives and Endpoints

Objectives	Endpoints
Primary	
To determine the optimal RP2D for abemaciclib in patients with relapsed/refractory solid tumors: • Part A: in combination with irinotecan and temozolomide • Part B: in combination with temozolomide	• DLTs • MTD • PK (concentrations of abemaciclib, irinotecan, and temozolomide)
Part C: To determine the optimal RP2D, and anti-tumor activity of abemaciclib in combination with dinutuximab, GM-CSF, irinotecan, and temozolomide in patients with relapsed/refractory neuroblastoma per INRC	• DLTs • PK (concentrations of abemaciclib, irinotecan, and temozolomide)[a] • ORR determined by investigator assessment
Secondary	
To characterize the safety profile of the combination therapies	• Safety (including but not limited to): TEAEs, SAEs, deaths • Clinical laboratory abnormalities per CTCAE (version 5.0), vital signs, and physical examinations • Dose modifications of all study drugs
To document the preliminary anti-tumor activity of the combination therapy per RECIST v1.1 or RANO (for CNS tumors) for Parts A and B, and per INRC for part C.	• DoR • CBR • DCR • ORR (Parts A & B only) • PFS determined by investigator assessment (Part C only)
To assess the acceptability and palatability of the tablet and/or granule abemaciclib, including dispersed tablets and/or granules	Assessment of tablet, granule, or dispersed abemaciclib presentation, including acceptability and palatability

Abbreviations: CBR = clinical benefit rate; CTCAE = Common Terminology Criteria for Adverse Events; DCR = disease control rate; DoR = duration of response; DLT= dose-limiting toxicity; INRC = International Neuroblastoma Response Criteria; MTD = maximum tolerated dose; ORR = overall response rate; PFS = progression-free survival; PK = pharmacokinetics; RANO = Response Assessment in Neuro-Oncology; RECIST = Response Evaluation Criteria in Solid Tumors; RP2D = recommended Phase 2 dose; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

[a] In Part C, PK is a primary endpoint for Stage 1 only.

Overall Design:

Study JPCS is a multicenter, non-randomized, open-label, Phase 1b/2 study that will be comprised of 3 parts to evaluate:

- **Part A:** abemaciclib in combination with irinotecan and temozolomide
- **Part B:** abemaciclib in combination with temozolomide
- **Part C:** abemaciclib in combination with dinutuximab, GM-CSF, irinotecan, and temozolomide

in patients with relapsed/refractory solid tumors (Part C: relapsed/refractory neuroblastoma only) that have progressed on standard treatments and for whom the study drug combinations are deemed appropriate.

Disclosure Statement:

This is an open-label, single-arm dose finding study with no masking.

Study Population:

In general, an individual may take part in this study if they meet the following criteria:

Age and Weight

- **Parts A and B only:**
  a. Patients must be ≤18 years of age at the time of study enrollment, and
  b. Body weight ≥10 kg and BSA ≥0.5 m^2.

- **Part C only:**
  a. Patients must be <21 years of age at the time of study enrollment.
  b. For patients with a starting abemaciclib dose of 30 mg/m^2 BID, BSA must be ≥0.3 m^2.

Type of Participant and Disease Characteristics

- **Parts A and B only:** patients with any relapsed/refractory malignant solid tumors (excluding lymphoma), including CNS tumors, that have progressed on standard therapies. For sites that are actively enrolling Parts B and C, patients with neuroblastoma who are eligible for Part C will be excluded from Part B unless approved by Lilly CRP/CRS.

- **Part C only:** patients with first relapse/refractory neuroblastoma. Refractory is defined as either less than partial response (PR) by INRC at the conclusion of at least 4 cycles of standard front-line induction chemotherapy or progressive disease (PD) during front-line therapy. First relapse is defined as disease recurrence following completion of aggressive multi-drug chemotherapy, surgery, autologous stem cell transplant and radiation, with or without retinoids.

  NOTE: For Part C, front-line chemotherapy must have comprised 2 or more agents, including an alkylating agent and a platinum-containing compound.

- **For Parts A, B, and C:** Patients must have at least one measurable or evaluable lesion as defined by RECIST v1.1 or RANO for CNS tumors.

i. Measurable is defined as a nonlymphoid soft tissue mass ≥1 cm (longest dimension) or lymph node ≥1.5 cm (short axis) on a MRI or CT scan
ii. Evaluable disease is defined as the presence of at least one lesion, with no lesion that can be accurately measured in at least one dimension. Such lesions may be evaluable by nuclear medicine techniques, immunocytochemistry techniques, tumor markers or other reliable measures.
iii. For CNS tumors: Isolated leptomeningeal disease in relapsed/refractory CNS tumors that is evaluable may be eligible for inclusion after consultation with the Lilly CRP/CRS.

For Part C: A tumor (either measurable or evaluable) that is either

- MIBG-avid or that demonstrates increased FDG uptake on PET scan (for MIBG-nonavid tumor), or
- viable neuroblastoma confirmed by biopsy (submission of pathology report is required)

Patients with involvement of bone marrow only, without a measurable or evaluable lesion, are not eligible.

AND

Patients must have had histologic verification of malignancy at original diagnosis or relapse, except:

a. patients with CNS germ cell tumors or extra-cranial germ-cell tumors and who have elevations of serum tumor markers including alpha-fetoprotein or beta-HCG, and
b. patients with intrinsic brain stem tumors

In the judgment of the investigator, the patient is an appropriate candidate for the experimental therapy combination in the study part that is currently enrolling.

Neurologic deficits in patients with CNS tumors must have been stable for at least 7 days prior to study enrollment.

A Lansky score ≥50 for patients <16 years of age or a Karnofsky score ≥50 for patients ≥16 years of age

- Patients who are unable to walk because of paralysis, but are up in a wheelchair, will be considered ambulatory for the purpose of assessing the performance score.

Number of Participants:

Approximately 30 to 117 patients will be enrolled in this study. To ensure comprehensive PK sampling in a pediatric population, Parts A and B are designed to evaluate at least CCI years of age and at least CCI years of age. Additionally, in Part C, CCI should be in the age group of CCI years of age, with a CCI years of age and at least CCI years of age.

Intervention Groups and Duration:

In Parts A and B, patients will be sequentially assigned to one dose level of abemaciclib, beginning with the abemaciclib starting dose of Part A. No patients will be assigned to the next higher abemaciclib dose level before the previous dose level has been cleared. Once the maximum tolerated dose (MTD) in Part A has been determined, Parts B and C will open. Part B will start at one dose level above the MTD of abemaciclib determined in Part A. Part C will use the Part A MTD and will not escalate dosing for any study drug.

A cycle is defined as 21 days. Patients will be treated for at least 1 cycle. The duration of follow-up will be at least 30 days. Patients will continue study treatment until progressive disease, unacceptable toxicity, or investigator/patient decision. Continuation on chemotherapy beyond Cycle 12 will be up to the investigator's discretion and the individual patient's situation. Prior to continuing the patient on chemotherapy beyond Cycle 12, the investigator should discuss with the Lilly clinical research physician/clinical research scientist.

Part A: Triplet Combination Dosing

Dose-Level Cohort	Patients	Abemaciclib Dosing	Irinotecan Dosing	Temozolomide Dosing
A-1	3-6	55 mg/m^2 BID, PO	50 mg/m^2/day IV on Days 1-5 of a 21-day cycle	100 mg/m^2/day PO on Days 1-5 of a 21-day cycle
A1 (starting dose)	3-6	70 mg/m^2 BID, PO		
A2	3-6	90 mg/m^2 BID, PO		
A3	3-6	115 mg/m^2 BID, PO		
Part A Dose Expansion	6-12[a]	MTD_A		

Abbreviations: BID = twice daily; DLT = dose-limiting toxicity; IV = intravenous; MTD_A = Part A maximum tolerated dose; PO = orally.

[a] Expansion cohorts will enroll 6 patients initially. Additional patients can be enrolled if necessary to confirm safety. Examples may include testing a lower dose in 6 additional patients if DLTs are experienced by at least 2 of 6 patients in the initial expansion cohort or to further confirm tolerability of prolonged treatment.

Part B: Doublet Combination Dosing

Dose-Level Cohort	Patients	Abemaciclib Dosing	Temozolomide Dosing
B-1 (or below)[a]	3-6	Dose will be de-escalated according to the dose levels outlined in Part A, BID, PO	100 mg/m^2/day PO on Days 1-5 of a 21-day cycle
B1 (starting dose)[b]	3-6	One dose level above MTD_A, BID, PO	
B2 - B4[a]	3-6	Dose will be escalated according to the dose levels outlined in Part A	
B5[c]	3-6	115 mg/m^2 BID, PO	150 mg/m^2/day PO on Days 1-5 of a 21-day cycle
Part B Dose Expansion	6-12[d]	MTD_B	temozolomide RP2D (100 mg/m^2 or 150 mg/m^2)

Abbreviations: BID = twice daily; DLT = dose-limiting toxicity; MTD = maximum tolerated dose; MTD_A = Part A maximum tolerated dose; MTD_B = Part B maximum tolerated dose; PO = orally; RP2D = recommended Phase 2 dose.

[a] Dose will be escalated (Cohorts B1, B2, B3, B4, B5) or de-escalated (Cohorts B-1, B-2, B-3, B-4) following dose levels as outlined in Part A as needed. It is possible that not all dose levels will be enrolled.

[b] One dose level higher than the MTD of abemaciclib in Part A (or 115 mg/m^2 if this was the MTD_A) will serve as the starting dose of abemaciclib in Part B.

[c] Cohort B5 will only take place if the following occur:

1) The MTD of abemaciclib is **not** reached when dosed at 115 mg/m^2 BID in combination with 100 mg/m^2/day temozolomide in Part B; **OR**

2) If abemaciclib 115 mg/m^2 BID is the MTD for Part A. In this case, Part B will directly start with Cohort B5 using abemaciclib 115 mg/m^2 BID and temozolomide 150 mg/m^2/day.

[d] Expansion cohorts will enroll 6 patients initially. Additional patients can be enrolled if necessary to confirm safety. Examples may include testing a lower dose in 6 additional patients if DLTs are experienced by at least 2 of 6 patients in the initial expansion cohort or to further confirm tolerability of prolonged treatment.

Part C: Combination Dosing

Each Cycle	Part C
Abemaciclib PO BID	55 mg/m^2 (Days 1 to 21)[a, b]
Dinutuximab IV Daily × 4 days	17.5 mg/m^2/day × 4 days (Days 2 to 5)
GM-CSF SubQ Daily × 7 days	250 µg/m^2 × 7 days (Days 6 to 12)
Irinotecan IV Daily × 5 days	50 mg/m^2/day × 5 days (Days 1 to 5)
Temozolomide PO Daily × 5 days	100 mg/m^2/day × 5 days (Days 1 to 5)

Abbreviations: BID = twice daily; GM-CSF = granulocyte macrophage colony-stimulating factor; IV = intravenous; PO = orally; SubQ = subcutaneous.

[a] 30 mg/m^2 may be evaluated due to excessive toxicities, if necessary, as described in Section 4.1.2

[b] An intermediate dose level (ie: between 55 mg/m^2 and 30 mg/m^2) may be explored based on emerging data

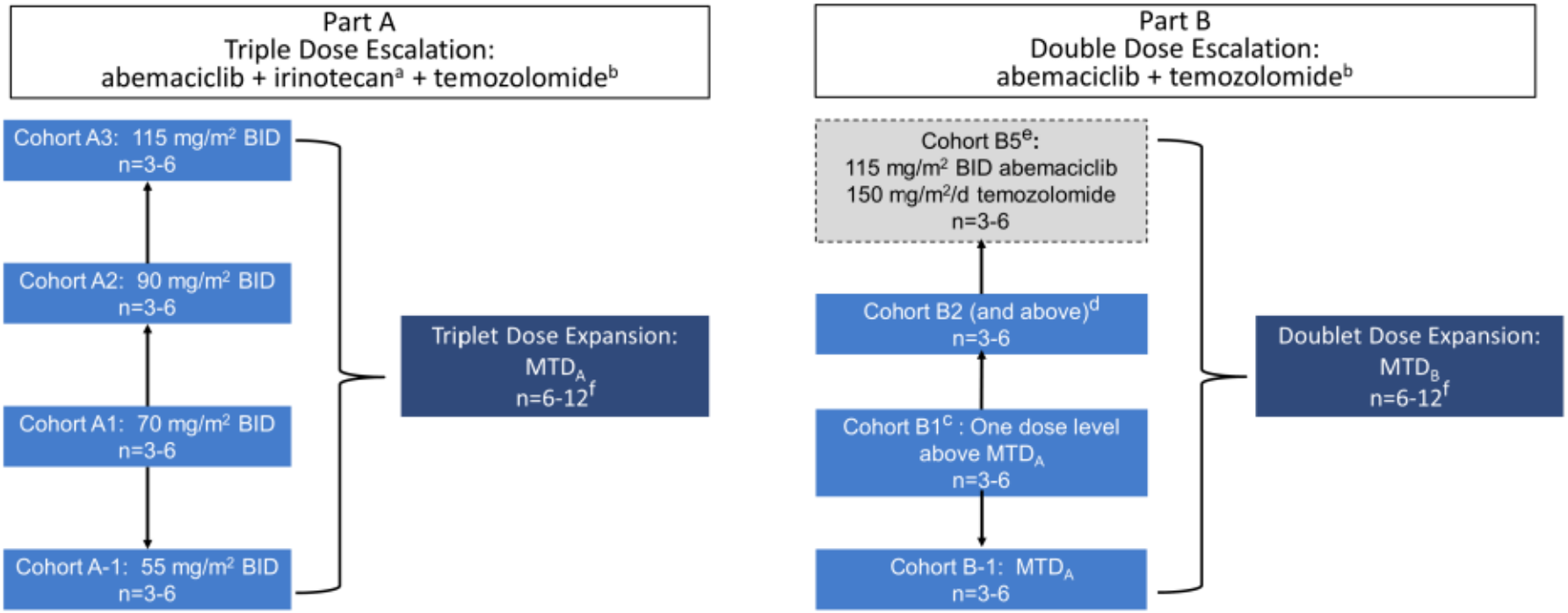
Ethical considerations of benefit/risk:

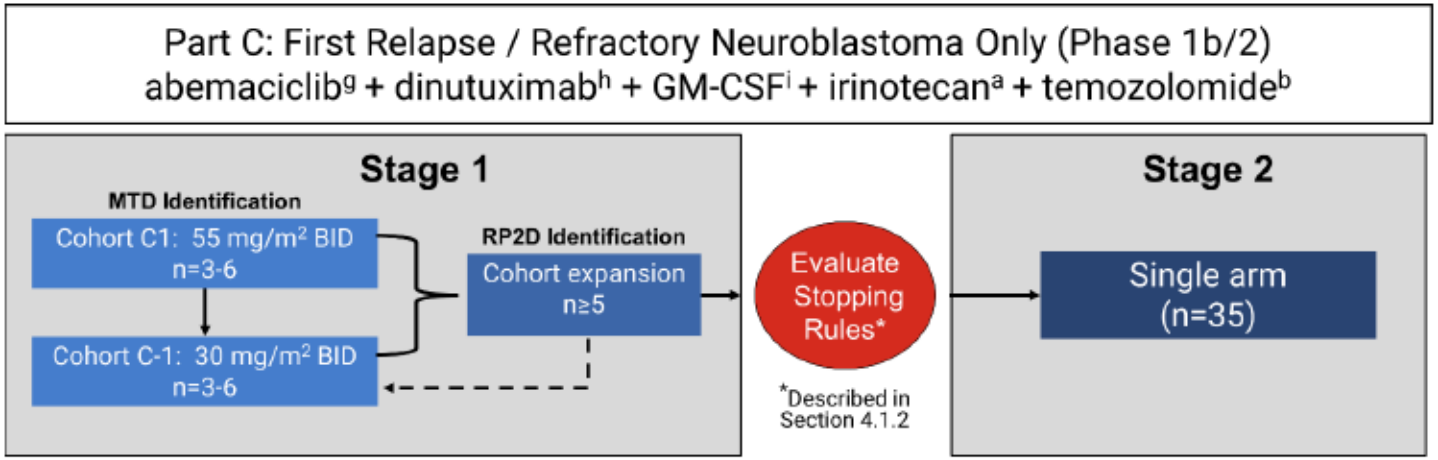
Given the observed safety profile of abemaciclib in adults and the known risk profiles of dinutuximab, GM-CSF, irinotecan, and temozolomide, the risk for the combinations in the proposed study are expected to be manageable. Additionally, considering the measures taken to ensure participant safety, the potential risks are justified by the potential benefits for individuals with relapsed malignancies.

Data Monitoring Committee:

- Parts A and B: No
- Part C: Yes

1.2. Schema





Abbreviations: BID = twice daily; DLT = dose-limiting toxicity; GM-CSF = granulocyte macrophage colony-stimulating factor; IV = intravenous; MTD = maximum tolerated dose; MTD_A = Part A maximum tolerated dose; MTD_B = Part B maximum tolerated dose; n = number of participants; PO = orally.

[a] Irinotecan administered via IV 50 mg/m²/day, Days 1-5 of Cycle. See Section 6.1.

[b] Temozolomide administered PO 100 mg/m²/day, Days 1-5 of Cycle. See Section 6.1.

[c] One dose level higher than the MTD of abemaciclib in Part A (or 115 mg/m² if this was the MTD_A) will serve as the starting dose of abemaciclib in Part B.

[d] Dose will be escalated (Cohorts B1, B2, B3, B4, B5) or de-escalated (Cohorts B-1, B-2, B-3, B-4) following dose levels as outlined in Part A as needed. It is possible that not all dose levels will be enrolled.

[e] Cohort B5 will only take place if the following occur:

- the MTD of abemaciclib is **not** reached when dosed at 115 mg/m² BID in combination with 100 mg/m²/day temozolomide in Part B; **OR**
- if abemaciclib 115 mg/m² BID is the MTD for Part A. In this case, Part B will start directly with Cohort B5 using abemaciclib 115 mg/m² BID and temozolomide 150 mg/m²/day.

[f] Expansion cohorts will enroll 6 patients initially. Additional patients can be enrolled if necessary to confirm safety. Examples may include testing a lower dose in 6 additional patients if DLTs are experienced by at least 2 of 6 patients in the initial expansion cohort or to further confirm tolerability of prolonged treatment.

[g] Abemaciclib administered at 55 mg/m² BID × 21 days, and if needed, 30 mg/m² BID × 21 days to determine the MTD for Part C. Sponsor may elect to explore an intermediate dose level (ie: between DL1 and DL-1) based on emerging data. See Section 6.1.

[h] Dinutuximab administered via IV 17.5 mg/m^2 × 4 days, Days 2-5 of Cycle. See Section 6.1.

[i] GM-CSF administered subcutaneously 250 µg/m^2 × 7 days, Days 6-12 of Cycle. See Section 6.1.

1.3. Schedule of Activities (SoA)

In this section, the study activities for Parts A and B are presented together for each study period (Section 1.3.1), while the activities for Part C are presented separately (see Section 1.3.2).

1.3.1. Schedule of Activities for Parts A and B

Schedule of Screening Activities for Parts A and B

Screening interactions and assessments must be performed at the clinical trial site, with the exception of laboratory assessments (hematology, clinical chemistry, cystatin c, and pregnancy test), which may be collected at a local clinic in accordance with local laws and regulations and when deemed appropriate by the investigator. Any screening procedures that fall outside of the required windows per the Schedule of Screening Activities must be repeated so that they fall within the required window.

Parts A and B				
Relative Day Prior to Cycle 1 Day 1	**≤28**	**≤14**	**≤7**	**Instructions**
Procedure				
Informed consent/assent		X		Must be signed prior to conducting any protocol-specific tests/procedures.
Inclusion/Exclusion evaluation			X	
Demographics			X	Include race, gender, ethnicity, and birth date per local regulations.
Prior and current medication			X	Include prior cancer treatments.
Medical and oncology history			X	Including assessment of preexisting conditions, historical illnesses, known somatic alterations, and habits.
Physical examination			X	Includes height, weight, and BSA.
CCI			[redacted]	CCI
CCI			[redacted]	
Vital signs			X	Includes blood pressure, pulse rate, oxygen saturation, and temperature.
Lansky/Karnofsky performance status			X	• Lansky for age <16 years • Karnofsky for age ≥16 years ○ For patients who turn 16 years old while on study, Karnofsky should be used after the 16th birthday
Hematology			X	See Section 10.2, Appendix 2.

Parts A and B				
Relative Day Prior to Cycle 1 Day 1	**≤28**	**≤14**	**≤7**	**Instructions**
Procedure				
Clinical chemistry		X		Include liver function tests. See Section 10.2, Appendix 2.
Cystatin C		X		See Section 10.2, Appendix 2.
Serum or urine pregnancy test			X	Applies to women of childbearing potential only. See Section 10.2, Appendix 2.
ECG	X			Local ECG.
Anatomic radiologic imaging according to RECIST v1.1 or RANO	X			Baseline disease assessment per RECIST v1.1 for non-CNS tumors; RANO criteria should be used for CNS tumors. If performed as part of routine clinical care, a 7-day window beyond 28 days is acceptable without being considered as a protocol deviation or screen fail. For patients with non-CNS tumors, perform CT scans of the chest, abdomen, pelvis, and the site of the known lesion if located elsewhere. For CNS tumors, perform MRI of the primary lesion including the entire brain or spine as applicable. For brain lesions, also include MRI of the spine if previous drop metastases were present. Imaging facility, image acquisition protocol, and imaging modality should be consistent for all visits for a given patient. See Section 8.1.
Lumbar puncture	X			Perform if clinically indicated and feasible to assess CSF cytology and tumor markers (alpha-fetoprotein and beta-HCG).
Adverse events collection/CTCAE grading	X			CTCAE Version 5.0.
Concomitant medication notation	X			

Abbreviations: BSA = body surface area; C1D1 = Cycle 1 Day 1; CSF = cerebrospinal fluid; CTCAE = Common Terminology Criteria for Adverse Events; CNS = central nervous system; ECG = electrocardiogram; CCI RANO = Response Assessment in Neuro-Oncology; RECIST = Response Evaluation Criteria in Solid Tumors.

Schedule of On-Study Treatment Activities for Parts A and B

If there is a concern during a remote visit that suggests on-site visit is necessary, the participant should have an on-site follow-up visit as soon as possible, at the investigator's discretion. For applicable patients, lumbar punctures must occur at the investigative site. For all patients at any time in the study, laboratory and pregnancy tests may be collected at a local clinic in accordance with local laws and regulations if deemed appropriate by the investigator. All results should be reviewed and recorded in the eCRF (pregnancy results are not required to be recorded in the eCRF). A virtual visit with the study investigator is not required for a local lab draw or pregnancy test.

Part A

All visits in Cycles 1 and 2, and Days 1–5 of all cycles thereafter should occur at the investigative site. In exceptional circumstances, procedures on Days 8 and 15 of Cycles 1 and 2 may be conducted remotely (see Section 10.7, Appendix 7). Remote visits should include a virtual visit with the study investigator (including video) and could also include mobile healthcare in accordance with local regulations if written approval is provided by the sponsor and according to the preferences of the participant and study site:

On Days 8 and 15 of Cycle 3 and beyond, the following procedures may be conducted remotely by a combination of virtual visit and mobile healthcare:

- Physical exam and weight
- Vital signs
- Questionnaires (when applicable)
- AE collection
- Concomitant medication notation

Part B

All visits in Cycles 1 and 2, along with Day 1 visits of cycles with radiologic imaging, should occur at the investigative site unless there are exceptional circumstances (see Section 10.7, Appendix 7). For Cycle 3 and beyond, some procedures may be conducted remotely (see guidance below) by a combination of virtual visit (including video) and could also include mobile healthcare in accordance with local regulations if written approval is provided by the sponsor and according to the preferences of the participant and study site:

For Cycles with radiologic imaging (Cycle 3, 5, 8, 11, and every third cycle afterwards):

On Days 8 and 15, the following procedures may be conducted remotely by a combination of virtual visit and mobile healthcare:

- Physical exam and weight
- Vital signs
- Questionnaires (when applicable)
- AE collection
- Concomitant medication notation

For Cycles where radiologic imaging does not occur (Cycles 4, 6, 7, 9, 10, 12, etc.):

- All procedures may be conducted remotely

Even under exceptional circumstances, patients should never go more than 3 cycles without having an onsite visit.

Parts A and B																
Procedure	**All Treatment Periods (Cycle = 21 Days)**															**Notes**
	Cycle 1			**Cycle 2**			**Cycle 3**			**Cycle 4**			**Cycle 5-n**			
Relative Day within Dosing Cycle	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	
Physical exam and weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X		Includes height (only Day 1 of each cycle), weight, and BSA. Perform weekly for first 4 cycles. From Cycle 5 onward, perform on Days 1 and 8 only. Perform on same day before starting a new cycle of therapy (i.e. Day 1). If not starting a new cycle of therapy (i.e. Days 8 and 15), a window ±3 days is acceptable. Further evaluations for any clinical concerns, such as bone pain, limp, and others should be conducted at the investigator's discretion.
CCI																

Parts A and B																
Procedure	**All Treatment Periods (Cycle = 21 Days)**															**Notes**
	Cycle 1			**Cycle 2**			**Cycle 3**			**Cycle 4**			**Cycle 5-n**			
Relative Day within Dosing Cycle	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	
Vital signs	See Notes		X	See Notes		X	See Notes		X	See Notes		X	See Notes			Includes blood pressure, pulse rate, oxygen saturation, and temperature. Perform on same day before starting a new cycle of therapy (i.e. Day 1). If not starting a new cycle of therapy (i.e. Days 8 and 15), a window ±3 days is acceptable. • For the first 4 cycles, perform on Days 1, 8 & 15. • For Cycle 5 and onwards, perform on Days 1 & 8. • **For all cycles, if receiving study treatment by infusion**, perform **prior** to every infusion (i.e. Days 1, 2, 3, 4, and 5 of any cycle) and within 1 hour **after** completion of infusion.
Lansky/ Karnofsky performance status	X			X			X			X			X			Complete before treatment initiation. • Lansky for age <16 years • Karnofsky for age ≥16 years o For patients who turn 16 years old while on study, Karnofsky should be used after the 16th birthday

Parts A and B																
Procedure	**All Treatment Periods (Cycle = 21 Days)**															**Notes**
	Cycle 1			**Cycle 2**			**Cycle 3**			**Cycle 4**			**Cycle 5-n**			
Relative Day within Dosing Cycle	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	
Drug product acceptability and palatability questionnaire	X		X	X	See Notes											• For patients ≤5 years old, only the caregiver will complete the questionnaires. • For patients ≥6 years old to <12 years old, both patient and caregiver will complete the questionnaires. • For patients ≥12 years old, only the patient will complete the questionnaires. Note: For Cycle 1 Days 1 and 15 and Cycle 2 Day 1, perform at time of dosing or within approximately 30 minutes after dose. If a patient changes the method of abemaciclib administration at any point during the trial, the appropriate questionnaire corresponding to the new administration method should be completed at the next clinic visit following the method change.
Review Patient Diary	X	X	X	X	X	X	X									Provide patient diary at Day 1 of each cycle. Patient/caregiver should complete daily until Cycle 3 Day 1. A window of ±3 days is acceptable. Review patient diary at each study visit for completion of date and time for each dose.
PK sampling	See Section 1.3.3 for time points															

Parts A and B																
Procedure	**All Treatment Periods (Cycle = 21 Days)**															**Notes**
	Cycle 1			**Cycle 2**			**Cycle 3**			**Cycle 4**			**Cycle 5-n**			
Relative Day within Dosing Cycle	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	≤7 days prior to C1D1. For C2 and beyond, ≤3 days before Day 1 and ±3 days for Days 8 and 15. May collect more frequently if clinically indicated. If irinotecan has been discontinued (Part A) or not part of the regimen (Part B), and clinically significant cytopenia is not observed after 3 cycles, CBC may be reduced to Day 1 (can eliminate Days 8 and/or 15). See Section 10.2, Appendix 2.
Clinical Chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	≤7 days prior to C1D1. For C2 and beyond, ≤3 days before Day 1 and ±3 days for Days 8 and 15. May collect more frequently if clinically indicated. Include liver function tests. If on study >3 cycles and clinically significant chemistry adverse event is not observed, frequency may be reduced to Day 1 (can eliminate Days 8 and/or 15). See Section 10.2, Appendix 2.
Cystatin C	X			X			X			X			X			≤7 days prior to C1D1. For C2 and beyond, ≤3 days before Day 1, unless more frequent assessment is clinically indicated. See Section 10.2, Appendix 2.
Serum or urine pregnancy test	X			X			X			X			X			For women of childbearing potential only. See Section 8.3.4 and Section 10.2, Appendix 2. **Note**: during study treatment, perform at start of each cycle (≤3 days) or as required per local regulations and/or institutional guidelines.

Parts A and B																
Procedure	**All Treatment Periods (Cycle = 21 Days)**															**Notes**
	Cycle 1			**Cycle 2**			**Cycle 3**			**Cycle 4**			**Cycle 5-n**			
Relative Day within Dosing Cycle	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	
Radiologic imaging	See Notes															Scans will be performed and reviewed locally; • Scan after Cycle 2 (prior to administering study drug for C3D1) • after Cycle 4 (prior to administering study drug for C5D1) • the end of every third cycle thereafter (after Cycle 7 [prior to administering study drug for C8D1], after Cycle 10 [prior to administering study drug for C11D1], etc.) Completion up to 7 days before Day 1 of each cycle with imaging is acceptable. RECIST v1.1 should be used for all non-CNS tumors; RANO criteria should be used for CNS tumors. For patients with non-CNS tumors, perform a CT scan of the known lesion(s) and of the chest. For CNS tumors, perform MRI of the primary lesion including the entire brain or spine as applicable. For brain lesions, also include MRI of the spine if history of drop metastases or if new drop metastases were present at baseline scan. If images of bones are present in the above scans, bones should be assessed for gross bone abnormalities. For patients unable to adhere to this schedule due to exceptional circumstances, the investigator should consult with the Lilly CRP/CRS. Imaging facility, image acquisition protocol, and imaging modality should be consistent for all visits for a given patient.

Parts A and B																
Procedure	**All Treatment Periods (Cycle = 21 Days)**															**Notes**
	Cycle 1			**Cycle 2**			**Cycle 3**			**Cycle 4**			**Cycle 5-n**			
Relative Day within Dosing Cycle	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	
Lumbar puncture	See Notes															Assess CSF cytology and tumor markers (alpha-fetoprotein and beta-HCG) according to institutional/standard guidelines for applicable patients who had positive tumor markers or cytology at baseline.
AE Collection / CTCAE Grading	See Notes															AEs collected continuously throughout study (any time there is an AE to report). CTCAE Version 5.0.
Concomitant Medication Notation	See Notes															Collected continuously throughout study (any time there is a concomitant medication to report). Refer to Section 6.5 for more information about concomitant medications.
Part A Patients: Administer irinotecan	See Notes															Administer Days 1-5 of each cycle. Continuation on chemotherapy beyond Cycle 12 will be up to the investigator's discretion and the individual patient's situation. See Section 6.1.
Administer temozolomide	See Notes															Administer Days 1-5 of each cycle. Continuation on chemotherapy beyond Cycle 12 will be up to the investigator's discretion and the individual patient's situation. See Section 6.1.
Administer abemaciclib	See Notes															Administer BID per Section 6.1.
Participant returns study drugs				X			X			X			X			Return at Day 1 (±5 days) of each cycle starting in Cycle 2 to assess compliance.

Abbreviations: AE = adverse event; BID = twice daily; BSA = body surface area; CNS = central nervous system; CRP/CRS = clinical research physician/clinical research scientist; CTCAE = Common Terminology Criteria for Adverse Events; CCI [redacted] PK = pharmacokinetic; RANO = Response Assessment in Neuro-Oncology; RECIST = Response Evaluation Criteria in Solid Tumors.

Posttreatment Follow-Up Schedule of Activities for Parts A and B

Posttreatment Follow-Up interactions and assessments should be conducted at the site, except in exceptional circumstances (see Section 10.7, Appendix 7). CCI and lumbar puncture are not permitted to be performed remotely even in exceptional circumstances.

Parts A and B		
	Short-Term Follow-Up (30±7 Days)[a]	**Comments**
Visit	**801**	
Physical examination	X	Includes height, weight, and BSA.
CCI		
Vital signs	X	Includes blood pressure, pulse rate, oxygen saturation, and temperature.
Lansky/Karnofsky performance status	X	• Lansky for age <16 years • Karnofsky for age ≥16 years For patients who turn 16 years old while on study or in follow-up, Karnofsky should be used after the 16th birthday
Adverse events collection/CTCAE grading	X	CTCAE Version 5.0. After Visit 801, only study treatment-related serious events are reported.
Concomitant medication	X	

Parts A and B		
	Short-Term Follow-Up (30±7 Days)[a]	**Comments**
Visit	**801**	
Radiologic imaging	X	RECIST v1.1 should be used for all non-CNS tumors; RANO should be used for CNS tumors. For patients with non-CNS tumors, perform a CT scan of the known lesion(s) and of the chest. For CNS tumors, perform MRI of the primary lesion including the entire brain or spine as applicable. For brain lesions, also include MRI of the spine if history of drop metastases or if new drop metastases were present at baseline scan. Imaging is not required if participant has discontinued due to progressive disease. For patients who discontinued for any reason other than progressive disease, scans should continue per the on-treatment schedule for radiologic imaging. Imaging facility, image acquisition protocol, and imaging modality should be consistent for all visits for a given patient.
Lumbar puncture	X	Assess CSF cytology and tumor markers (alpha-fetoprotein and beta-HCG) according to institutional/standard guidelines for applicable patients who had positive tumor markers or cytology at baseline **and** who are off study treatment for reasons other than disease progression.
Hematology	X	See Section 10.2, Appendix 2.
Clinical chemistry	X	Include liver function tests. See Section 10.2, Appendix 2.
Collection of poststudy anticancer treatment	X	Telephone assessment is acceptable. For all patients, details on subsequent anticancer treatment (start/stop dates and treatments administered).

Abbreviations: BSA = body surface area; CTCAE = Common Terminology Criteria for Adverse Events; CCI [redacted] RANO = Response Assessment in Neuro-Oncology; RECIST = Response Evaluation Criteria in Solid Tumors.

[a] Short-term follow-up begins when the patient and investigator agree that the patient will no longer continue study treatment and lasts approximately 30 days from the last administration of study drugs.

Continued Access Schedule of Activities for Parts A and B

Parts A and B			
Visit	**Study Treatment 501-5XX**	**Follow-Up 901**	**Notes**
Procedure			
AE collection/CTCAE grading	X	X	Per CTCAE Version 5.0. Collect all AEs/SAEs. Per standard of care, monitor vital signs and perform standard laboratory tests (hematology, chemistry, and pregnancy testing). See Sections 6.7.1.1 and Section 10.2, Appendix 2.
Administer abemaciclib	X		See Section 6.1.
Administer temozolomide (if applicable)	X		Administer Days 1-5 of each cycle. Continuation on chemotherapy beyond Cycle 12 will be up to the investigator's discretion and the individual patient's situation. See Section 6.1.
Part A Patients: Administer irinotecan (if applicable)	X		Administer Days 1-5 of each cycle. Continuation on chemotherapy beyond Cycle 12 will be up to the investigator's discretion and the individual patient's situation. See Section 6.1.

Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; SAE = serious adverse event.

1.3.2. Schedule of Activities for Part C

At any time in the study, laboratory and pregnancy tests may be collected at a local clinic in accordance with local laws and regulations if deemed appropriate by the investigator. All results should be reviewed and recorded in the eCRF (pregnancy results are not required to be recorded). A virtual visit with the study investigator is not required for a local lab draw or pregnancy test. All other screening interactions and assessments must be performed at the clinical trial site.

Schedule of Baseline and Screening Activities for Part C

Any screening procedures that fall outside of the required windows per the Schedule of Screening Activities must be repeated so that they fall within the required window.

Part C				
Relative Day Prior to Cycle 1 Day 1	**≤28**	**≤14**	**≤7**	**Instructions**
Procedure				
Informed consent/assent	X			Must be signed prior to conducting any protocol-specific tests/procedures.
Inclusion/exclusion evaluation		X		
Demographics		X		Include race, gender, ethnicity, and birth date per local regulations.
Prior cancer treatments		X		
Medical and oncology history		X		Including assessment of preexisting conditions, historical illnesses, known somatic alterations, and habits.
Physical examination		X		Includes height, weight, and BSA.
CCI				
Vital signs		X		Includes blood pressure, pulse rate, oxygen saturation, and temperature.
Lansky/Karnofsky performance status		X		• Lansky for age <16 years • Karnofsky for age ≥16 years For patients who turn 16 years old while on study, Karnofsky should be used after the 16th birthday
Hematology		X		• See Section 10.2, Appendix 2.
Clinical chemistry		X		• See Section 10.2, Appendix 2.

Part C				
Relative Day Prior to Cycle 1 Day 1	**≤28**	**≤14**	**≤7**	**Instructions**
Procedure				
Serum or urine pregnancy test			X	• Women of childbearing potential only. • See Section 10.2, Appendix 2.
Prothrombin time		X		
Echocardiogram or MUGA		X		
Tumor assessment CT or MRI		X		• If performed as part of routine clinical care, a 7-day window beyond 28 days is acceptable without being considered as a protocol deviation or screen fail. • CT scans of the chest, abdomen, pelvis, and the site of the known lesion if located elsewhere. • The CT portion of a PET-CT may be used for response assessment if the site can document that the CT is of identical quality to a diagnostic CT. • Imaging facility, image acquisition protocol, and imaging modality should be consistent for all visits for a given patient. • See Section 8.1.
Tumor assessment MIBG or PET CT		X		• If performed as part of routine clinical care, a 7-day window beyond 28 days is acceptable without being considered as a protocol deviation or screen fail. • MIBG scans for all patients with MIBG avid disease, including those with disease also detectable by CT or MRI. • FDG-PET may be used in patients whose tumors are MIBG non-avid.
Bone marrow assessment		X		• Bilateral bone marrow aspirates and biopsies. • If performed as part of routine clinical care, a 7-day window beyond 28 days is acceptable without being considered as a protocol deviation or screen fail.
Biomarkers – Tumor Tissue		X		• Archival or fresh tumor samples will be collected, when available. • CCI or CCI sample, when available, is preferred. • The most recent sample is desired. • Tumor samples in the form of a formalin-fixed, paraffin-embedded block are preferred. If this is not possible, CCI slides of freshly prepared, unstained, 5-micron sections may be provided. • Samples can be sent at any time during study if not submitted at screening.

Part C				
Relative Day Prior to Cycle 1 Day 1	**≤28**	**≤14**	**≤7**	**Instructions**
Procedure				
Adverse events collection and CTCAE grading		X		CTCAE Version 5.0.
Concomitant medication		X		

Abbreviations: BSA = body surface area; CTCAE = Common Terminology Criteria for Adverse Events; CT = computed tomography; FDG = fluorodeoxyglucose; CCI MIBG = metaiodobenzylguanidine; MRI = magnetic resonance imaging; MUGA = multigated acquisition; PET = positron emission tomography.

Schedule of On-Study Treatment Activities for Part C

The start of a cycle (Day 1) is defined as the first day that the combination of irinotecan, temozolomide, and abemaciclib are administered for that cycle.

All visits in Cycle 1 and Days 1 through 6 of all cycles thereafter should occur at the investigative site. GM-CSF may be administered in an out-patient setting per local standards of care. All visits that include radiologic imaging should occur at the investigative site (see Section 10.7).

Part C			
Procedures	**During Cycle 1**	**Cycle 2 onward**	**Instructions**
Physical assessment including vital signs	X	X	• Up to 3 days before Day 1 of each cycle • Daily prior to each dinutuximab infusion. See Section 6.1.1.1 • Only Day 1 values of each cycle must be recorded in the EDC system
Height, weight, BSA, and CCI	X	X	• Up to 3 days before Day 1 of each cycle • Daily weight prior to each dinutuximab infusion • Only the Day 1 values of each cycle must be recorded in the EDC system • CCI
CCI			
Performance status		X	• Up to 3 days before Day 1 of each cycle • Lansky for age <16 years • Karnofsky for age ≥16 years o For patients who turn 16 years old while on study, Karnofsky should be used after the 16th birthday
Hematology	Weekly	Weekly	• See Section 10.2, Appendix 2 • Up to 3 days before Day 1 of each cycle • Weekly = Days 1, 8, and 15

Part C			
Procedures	**During Cycle 1**	**Cycle 2 onward**	**Instructions**
Clinical chemistry	Weekly	X	• See Section 10.2, Appendix 2. Note the addition of $PO4^{-}$ and Mg^{++} • Up to 3 days prior to Day 1 of each cycle • Weekly = Days 1, 8, and 15
Abbreviated chemistry panel (electrolytes and creatinine)	Daily during dinutuximab administration	Daily during dinutuximab administration	• See Section 10.2, Appendix 2 • Days 2, 3, 4, and 5 of each cycle during dinutuximab administration • If dinutuximab is not administered, daily labs are not required
Serum or urine pregnancy test	X	X	• Applies to women of childbearing potential only • Up to 3 days prior to Day 1 of each cycle or as required per local regulations and/or institutional guidelines
Tumor evaluation: CT or MRI		End of Cycles 2, 4, and 6, then at the end every 4th cycle	• Up to 1 week prior to the start of the next planned cycle of therapy • Repeat assessment ≥4 weeks after initial response for patients with complete response, partial response, and minor response • Use same modality throughout the study • Scans will be performed and reviewed locally
Tumor evaluation: MIBG or PET CT		End of Cycles 2, 4, and 6, then at the end every 4th cycle	• Up to 1 week prior to the start of the next planned cycle of therapy • PET CT only for patients with non-MIBG avid lesions • Repeat assessment ≥4 weeks after initial response for patients with complete response, partial response, and minor response • Scans will be performed and reviewed locally
Bilateral bone marrow aspirates/biopsies		End of Cycles 2, 4, 6 and then after every 4th cycle - only for patients with marrow disease and all patients (even if no marrow disease) following Cycle 6	Up to 1 week prior to the start of the next planned cycle of therapy
Biomarkers – plasma	X	X	• Collect pre-dose at C1D1 on participants CCI only • Collect at disease progression and/or study discontinuation on participants CCI
Biomarkers - whole blood	X		• For participants CCI whole blood dried blood spot • For participants CCI whole blood sample • If not collected during screening/baseline, then obtain at C1D1 • If blood volume restrictions prevent collection during screening/baseline and C1D1, then sample can be collected at a subsequent timepoint

Part C			
Procedures	**During Cycle 1**	**Cycle 2 onward**	**Instructions**
			• Only one sample is needed per patient • See Section 8.8
Drug product acceptability and palatability questionnaire	Days 1 and 15	Cycle 2 Day 1 only	• For patients ≤5 years old, only the caregiver will complete • For patients ≥6 to <12 years old, patient and caregiver will complete • For patients ≥12 years old, only the patient will complete • Perform at time of dosing or within approximately 30 minutes after dose • If method of abemaciclib administration or formulation (tablets to granules or vice versa) changes, the appropriate questionnaire corresponding to the new administration method and formulation should be completed at the clinic visit following this change
Review Patient Diary	See Notes		• Provide patient diary at Day 1 of each cycle. Patient/caregiver should complete daily until Cycle 3 Day 1. A window of ±3 days is acceptable. • Review patient diary at each study visit for completion of date and time for each dose.
PK sampling	See Notes		See Section 1.3.3
AE collection and CTCAE grading	See Notes		AEs collected continuously throughout study (any time there is an AE to report) per CTCAE Version 5.0. Collect all AEs/SAEs
Dispense abemaciclib	See Notes		PO BID per detailed administration guidelines, see Section 6.1.
Administer temozolomide	See Notes		For detailed administration guidelines, see Sections 6.1, and 6.4.
Administer irinotecan	See Notes		For detailed administration guidelines, see Sections 6.1, and 6.4.
Administer dinutuximab	See Notes		• For detailed administration guidelines, see Sections 6.1, and 6.4. • **Important Note**: Monitor patients per guidelines in Section 6.1.1.1.
Dispense/administer GM-CSF	See Notes		• For detailed administration guidelines, see Sections 6.1 and 6.4
Participants return study drugs	See Notes		• Return at Day 1 (±5 days) of each cycle starting in Cycle 2 to assess compliance. Refer to section 6.4.

Part C			
Procedures	**During Cycle 1**	**Cycle 2 onward**	**Instructions**
Concomitant medication notation	See Notes		• Collected continuously throughout study (any time there is a concomitant medication to report). Refer to Section 6.5 for more information about concomitant medications

Abbreviations: AE = adverse event; BID = twice daily; BSA = body surface area; C1D1 = Cycle 1 Day 1; CBC = complete blood count; CTCAE = Common Terminology Criteria for Adverse Events; CT = computed tomography; EDC = electronic data capture system; CCI GM-CSF = granulocyte macrophage colony-stimulating factor; CCI Mg++ = magnesium; MIBG = metaiodobenzylguanidine; MRI = magnetic resonance imaging; CCI PET = positron emission tomography; PK = pharmacokinetic; PO = orally; PO4- = phosphorus; SAE = serious adverse event; VMA = vanillylmandelic acid.

Posttreatment Follow-Up Schedule of Activities for Part C

Part C			
	Short-Term Follow-Up (30±7 Days)	**Long-Term Follow-Up (90±14 Days)**	**Comments**
Visit	**801**	**802-X**	
Relative Day within Cycle	Begins when the patient and the investigator agree that the patient will no longer continue study treatment and lasts approximately 30 days.	Begins when short-term follow-up period is complete and continues until death, study withdrawal, or the patient is lost to follow-up. In all cases, no follow-up procedures will be performed for a patient who withdraws consent/assent unless he or she has explicitly provided permission and consent/assent.	
Clinically directed physical examination	X		Evaluations per examiner's discretion and patients' symptoms
Vital signs	X		Includes height, weight, blood pressure, pulse, temperature, and respiratory rate
Performance status	X		• Lansky for age <16 years • Karnofsky for age ≥16 years For patients who turn 16 years old while on study, Karnofsky should be used after the 16th birthday
CCI			

Part C			
	Short-Term Follow-Up (30±7 Days)	**Long-Term Follow-Up (90±14 Days)**	**Comments**
Visit	**801**	**802-X**	
Relative Day within Cycle	Begins when the patient and the investigator agree that the patient will no longer continue study treatment and lasts approximately 30 days.	Begins when short-term follow-up period is complete and continues until death, study withdrawal, or the patient is lost to follow-up. In all cases, no follow-up procedures will be performed for a patient who withdraws consent/assent unless he or she has explicitly provided permission and consent/assent.	
Tumor restaging evaluation CT or MRI and MIBG or PET CT	X	X	• Use same modality throughout the study • PET CT only for patients with non-MIBG avid lesions • Not required if PD is documented while on treatment, or if staging has been performed within the past 3 weeks • Perform during every long-term follow-up visit if PD has not occurred • Scans will be performed and reviewed locally
Adverse events collection/CTCAE grading	X	X	• CTCAE Version 5.0 • After Visit 801, only study treatment-related serious events are reported
Concomitant medication	X		
Hematology	X		• Local testing • See Section 10.2, Appendix 2
Clinical chemistry	X		• Local testing • See Section 10.2, Appendix 2
Plasma biomarker sample	X		• For participants CCI whole blood sample • Before initiation of subsequent therapy • Only if not already obtained at visit when participant discontinued study

Part C			
	Short-Term Follow-Up (30±7 Days)	**Long-Term Follow-Up (90±14 Days)**	**Comments**
Visit	**801**	**802-X**	
Relative Day within Cycle	Begins when the patient and the investigator agree that the patient will no longer continue study treatment and lasts approximately 30 days.	Begins when short-term follow-up period is complete and continues until death, study withdrawal, or the patient is lost to follow-up. In all cases, no follow-up procedures will be performed for a patient who withdraws consent/assent unless he or she has explicitly provided permission and consent/assent.	
Tissue submission from tumor biopsy obtained after progression	X		Optional Only for patients on study treatment at least 6 months
Collection of poststudy anticancer treatment	X	X	Telephone assessment is acceptable. Details of subsequent anticancer treatment (including radiotherapy, surgeries, systemic, and locoregional therapies including start/stop dates)
Survival assessment	X	X	Telephone assessment is acceptable

Abbreviations: CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; MIBG = metaiodobenzylguanidine; MRI = magnetic resonance imaging; PET = positron emission tomography.

Continued Access Schedule of Activities for Part C

Part C			
Visit	**Study Treatment**	**Follow-Up**	**Notes**
	501-5XX	**901**	
Procedure			
AE collection/CTCAE grading	X	X	• Per CTCAE Version 5.0 • Collect all AEs/SAEs • Per standard of care, monitor vital signs and perform standard laboratory tests (hematology, chemistry, and pregnancy testing) • See Section 6.7.1.1 and Section 10.2, Appendix 2
Administer abemaciclib	X		See Section 6.1 **Continuation on chemotherapy** beyond Cycle 12 will be up to the investigator's discretion and the individual patient's situation
Administer temozolomide	X		
Administer irinotecan	X		
Administer dinutuximab	X		
Administer GM-CSF	X		

Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; GM-CSF = granulocyte macrophage colony-stimulating factor; SAE = serious adverse event.

1.3.3. Pharmacokinetic Sampling and Study Drug Dosing Schedule

The daily dosing schedule for each study drug and the pharmacokinetic (PK) sampling schedule is summarized in the table and figures below.

Abemaciclib dosing dates and times are required to be collected 3 days prior to the PK samples. Irinotecan and temozolomide dosing dates and times should also be recorded. The date and exact time of collection of each venous blood sample must be recorded on the laboratory requisition. Beyond the first dose, PK samples may be aligned to coincide with standard laboratories when applicable, with the following collection dates/times to be used as a guide.

There will be no PK analysis of dinutuximab or GM-CSF.

For patients in Part A and Part B, and patients in Part C who weigh CCI at enrolment, all planned PK samples will be taken by venous blood draw and processed into plasma.

For patients in Part C who weigh CCI at enrolment, planned PK samples will be taken for abemaciclib (and its metabolites) only by a volumetric absorptive microsampling device. No PK samples for irinotecan (and SN-38) or temozolomide will be drawn.

Day	PK Schedule[a,c]		
	Cycle 1	Cycle 2	Cycle 3
1	See PK Timecourse and Dosing Schedule Figures	See PK Timecourse and Dosing Schedule Figures	Pre-dose[b]: Abemaciclib PK sample only
2		Pre-dose[b]: PK sample for each study drug (except dinutuximab and GM-CSF)	
15	Pre-dose[b]: Abemaciclib PK sample only		

Abbreviations: GM-CSF = granulocyte macrophage colony-stimulating factor; PK = pharmacokinetic.

[a] PK sampling will include abemaciclib, M2 and M20 (active metabolites of abemaciclib), irinotecan, SN-38 (active metabolite of irinotecan), and temozolomide. No PK samples will be collected for dinutuximab or GM-CSF.

[b] Pre-dose PK samples should be drawn prior to taking study drugs.

[c] For patients in Part C who weigh CCI at enrolment, abemaciclib PK samples should be taken by volumetric absorptive microsampling rather than venous blood draw. No temozolomide or irinotecan samples should be taken from these patients.

Abbreviations: hr = hour; IV = intravenous; PK = pharmacokinetic.

[a] Draw PK sample prior to administering any study drugs.

[b] Draw PK samples prior to irinotecan infusion. At least 1 hour should separate the temozolomide dose and the start of the irinotecan infusion.

[c] Refer to local label and/or standard of care for infusion duration.

[d] Draw PK samples immediately after irinotecan infusion.

[e] Second abemaciclib dose should not be administered until after last PK sample has been drawn.

[f] For patients in Part C who weigh CCI at enrolment, abemaciclib PK samples should be taken by volumetric absorptive microsampling rather than venous blood draw. No temozolomide or irinotecan samples should be taken from these patients.

Abbreviations: hr = hour; PK = pharmacokinetic.

[a] Draw PK sample prior to administering any study drugs.

[b] Second abemaciclib dose should not be administered until after last PK sample has been drawn.

2. Introduction

2.1. Study Rationale

Despite advances in the treatment of pediatric cancers, there is still an unmet need for efficacious and tolerable regimens for relapsed/refractory solid tumors. Abemaciclib is a selective and potent small-molecule cyclin-dependent kinase 4 and cyclin-dependent kinase 6 (CDK4 & 6) inhibitor, favoring CDK4 inhibition 14-fold over CDK6 inhibition in enzymatic assays (Torres-Guzmán et al. 2017). Based upon preclinical data and the role of CDK4 & 6 in multiple pediatric tumor types, Eli Lilly and Company (Lilly) hypothesizes that abemaciclib administered in combination with temozolomide, in combination with irinotecan and temozolomide, and/or in combination with dinutuximab, GM-CSF, irinotecan, and temozolomide will be sufficiently tolerable with evidence of clinical activity to support further development.

Study JPCS is designed to evaluate:

- the recommended Phase 2 dose (RP2D) for abemaciclib in pediatric patients with relapsed/refractory solid tumors
  - in combination with irinotecan and temozolomide (Part A),
  - in combination with temozolomide (Part B), and
  - in combination with dinutuximab, GM-CSF, irinotecan, and temozolomide in patients with relapsed/refractory neuroblastoma (Part C).
- the anti-tumor activity of abemaciclib in combination with dinutuximab, GM-CSF, irinotecan, and temozolomide in patients with relapsed/refractory neuroblastoma (Part C).

2.2. Background

Pediatric cancer represents a spectrum of rare malignancies with approximately 15,000 patients aged 0 to 19 years diagnosed in the United States in 2018 (NCI 2018). Pediatric patients with relapsed/refractory solid tumors typically have a poor prognosis. Treatment in this setting typically results in only minimal improvements in efficacy, with 5-year post-relapse survival rates often less than 30% for pediatric solid tumors, such as Ewing's sarcoma, neuroblastoma, central nervous system (CNS), osteosarcoma, and rhabdomyosarcoma (Ceschel et al. 2006; Dantonello et al. 2008; London et al. 2011; Stahl et al. 2011; Leary et al. 2013). In the relapsed/refractory disease setting, few treatment options exist and frequently consist of multiple rounds of cytotoxic chemotherapies, such as irinotecan and temozolomide.

New therapeutic strategies are needed to synergize with chemotherapy to effectively induce cancer cell death. Cell cycle inhibition with abemaciclib, a potent and selective CDK4 & 6 inhibitor, is one such strategy to potentiate the effects chemotherapy. Genetic aberrations in the Cyclin D/CDK4 & 6 pathway have been observed in pediatric tumors, potentially making them sensitive to CDK4 & 6 inhibition (Saab et al. 2006; Molenaar et al. 2012; Rader et al. 2013; Zhu et al. 2016; Cook Sangar et al. 2017; Geoerger et al. 2017; Sturm et al. 2017; Dowless et al. 2018). Preclinical evidence has demonstrated additive activity of abemaciclib in combination with temozolomide with and without irinotecan (see Section 2.2.6).

More specifically, neuroblastoma accounts for 12% of childhood cancer deaths. Despite aggressive multimodal therapy, over 50% of patients with high-risk disease will suffer disease relapse. Survival after relapse of high-risk neuroblastoma in children over 18 months of age remains poor (Lau and London 2012). Additionally, another 5% to 20% of newly diagnosed low-, intermediate-, and high-risk patients will be refractory to initial therapy (Zhou et al. 2015; Twist et al. 2019; Liu et al. 2020). These patients with either relapsed or refractory neuroblastoma warrant additional investigations.

Treatment of relapsed/refractory neuroblastoma has evolved to target the disialoganglioside GD2 that is expressed on neuroblastoma cells. Dinutuximab, the first anti-GD2 monoclonal antibody, was added to GM-CSF in a maintenance setting after intensive chemotherapy, radiation therapy, surgical resection, myeloablative chemotherapy, and autologous stem-cell rescue based on the ANBL0032 study results demonstrating a 20% EFS and 11% OS improvement when compared to standard therapies without dinutuximab (Yu et al. 2010). Subsequent development of dinutuximab-beta, a similar anti-GD2 monoclonal antibody, followed dinutuximab.

Additional research has provided evidence of the role of dinutuximab, GM-CSF, irinotecan, and temozolomide in patients with initial neuroblastoma relapse. In study ANBL1221, the combination of dinutuximab, GM-CSF, irinotecan, and temozolomide demonstrated significant anti-tumor activity and achieved an overall response rate of 41.5%, a one-year PFS of 67.9% and one-year OS of 84.9%. Despite these advances, there remains a significant unmet need for children with released and refractory neuroblastoma (Mody et al. 2020).

2.2.1. Temozolomide

Temozolomide is a DNA-alkylating agent with adult indications for glioblastoma and refractory anaplastic astrocytoma. In pediatric patients, it is commonly used in CNS tumors such as high-grade gliomas (World Health Organization Grades III/IV) in the front-line setting and in medulloblastoma/primitive neuroectodermal tumors in the recurrent setting (De Sio et al. 2006; Cohen et al. 2011; Cefalo et al. 2014; Guerra-García et al. 2020; Le Teuff et al. 2020). Temozolomide is also widely used in combination with irinotecan in pediatric solid tumors (see Section 2.2.2). The safety profile of temozolomide is well established and predictable and is known to cause myelosuppression and hepatotoxicity (Temozolomide US Package Insert 2017).

2.2.2. Irinotecan

Irinotecan is a topoisomerase I inhibitor that is indicated for metastatic colon cancer in adults, but is frequently used in combination with temozolomide for treatment of pediatric relapsed/refractory solid tumors, including but not limited to neuroblastoma, Ewing's sarcoma, osteosarcoma, rhabdomyosarcoma, and others due to the non-overlapping toxicity profile and the activity that has been observed in preclinical and clinical studies (Houghton et al. 2000; Wagner et al. 2004; Kushner et al. 2006; Casey et al. 2009; Wagner et al. 2009; Bagatell et al. 2011, 2014; Kurucu et al. 2015; Palmerini et al. 2018). The irinotecan adverse event (AE) profile is well documented and predictable. Notably, irinotecan can cause myelosuppression and early and late forms of diarrhea; early diarrhea may be accompanied by cholinergic symptoms (Irinotecan US Package Insert 2020).

2.2.3. Abemaciclib

Abemaciclib is an orally administered, potent, and selective inhibitor of CDK4 & 6 that is currently approved for the treatment of hormone receptor positive (HR+) / human epidermal growth factor receptor 2 negative (HER2-) advanced breast cancer as monotherapy and in combination with endocrine therapies (Dickler et al. 2017; Goetz et al. 2017; Sledge et al. 2017; Johnston et al. 2019). From a therapeutic standpoint, the goal of inhibiting CDK4 & 6 is to prevent cell cycle progression through the G1 restriction point, thus arresting tumor growth. Cyclin-dependent kinases 4 & 6 participate in a complex with D-type cyclins to initiate the transition through the G1 restriction point, which controls entry into S phase and is essential for maintaining control of cell division (Sherr 1996; Ortega et al. 2002) through phosphorylation of the retinoblastoma (RB) tumor suppressor protein. Alterations in this pathway occur frequently in human cancers and involve:

- loss of endogenous cyclin-dependent kinase (CDK) inhibitors by mutation or epigenetic silencing,
- mutation/overexpression of either CDK4 & 6 or Cyclin D, or
- inactivation of RB.

These alterations render cells less dependent on mitogenic signaling for proliferation. With the possible exception of those tumors with complete inactivation of RB, which functions downstream of the Cyclin D/CDK4 & 6 complex, cancers that involve CDK mutations or over-expression are potentially sensitive to pharmacologic inhibition of CDK4 & 6.

2.2.4. Dinutuximab

In humans, GD2 expression is almost exclusively limited to neuroblastoma cells and neurons, making GD2 a suitable target for immunotherapy (Yu et al. 2010). Anti-GD2 monoclonal antibodies, including dinutuximab and dinutuximab-beta, rely on immune effector functions like complement-dependent cytotoxicity and ADCC, which are enhanced when combined with GM-CSF. Anti-GD2 therapies have dramatically improved neuroblastoma treatment outcomes.

The anti-GD2 antibody dinutuximab was first approved in 2015 by the FDA for initial treatment of neuroblastoma following intensive multimodal therapy. Approval was granted based on the results from the prospective, randomized ANBL032 study in which dinutuximab was combined with GM-CSF, interleukin 2 (IL-2), and cis-retinoic acid (isotretinoin) for the treatment of pediatric patients with high-risk neuroblastoma who achieve at least a partial response to initial multimodality therapy. In Europe, dinutuximab-beta is the approved anti-GD2 monoclonal antibody. IL-2 has been removed from the standard combination based on the risk-benefit profile as demonstrated by Ladenstein et al. (2018, 2019).

After showing dramatic improvements when added to the maintenance setting in first-line treatment, anti-GD2 therapy has since been shown to add benefit in patients with relapsed or refractory disease, including in patients who experienced disease relapse after previous exposure to dinutuximab in the front-line maintenance setting. Dinutuximab with GM-CSF, irinotecan, and temozolomide showed an ORR of 41.5% (95% CI: 28.2%, 54.8%) in the ANBL1221 trial leading to adoption of this regimen as standard of care for first relapse within the US and prompting trials of dinutuximab-beta as relapsed/refractory therapy in Europe (Mody et al. 2020).

JPCS Part C aims to improve the outcomes of dinutuximab, GM-CSF, irinotecan, and temozolomide in the first relapsed/refractory setting.

2.2.5. GM-CSF

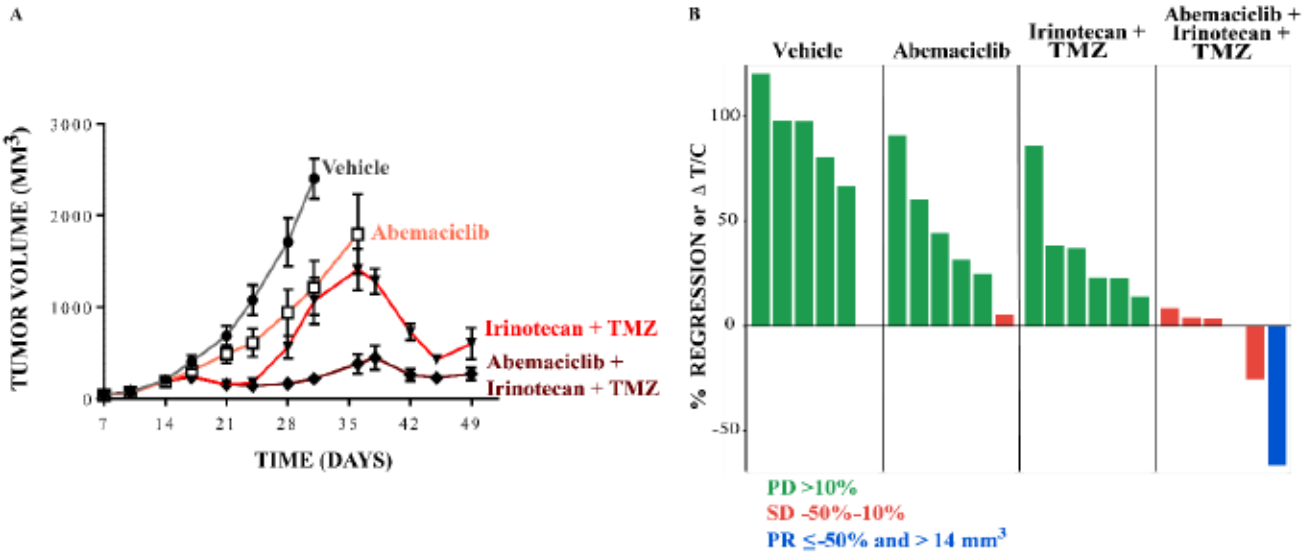
The cytokine GM-CSF is an important component of chemoimmunotherapy in neuroblastoma. GM-CSF amplifies the ADCC effects of anti-GD2 antibodies via activation and stimulation of granulocytes and macrophages to function as antigen-presenting cells to promote a host anti-tumor response (Yu et al. 2010). The addition of GM-CSF with dinutuximab to chemotherapy has been demonstrated to be efficacious in multiple studies (Mody et al. 2020; Yu et al. 2010), and the combination of anti-GD2 antibodies with GM-CSF now serves as part of the standard of care.

2.2.6. Preclinical and Clinical Rationale

Pediatric cancers often harbor genetic aberrations in the Cyclin D/CDK4 & 6 pathway, making them logical candidates for sensitivity to abemaciclib. In a panel of 39 cell lines derived from patients aged ≤21 years and encompassing a wide spectrum of histologies, the absolute IC_{50} of abemaciclib was within a clinically relevant range (<2 µM; within 2-fold of average patient concentrations [Gong et al. 2017; Dowless et al. 2018]) in approximately half of the cell lines, which warranted additional studies of abemaciclib in pediatric models.

Ewing's sarcoma has been reported to have deletion of *CDKN2A* (encodes the $p16^{INK4a}$ tumor suppressor that binds to CDK4 & 6) in approximately 10 to 30% of primary tumors and nearly 50% of Ewing's sarcoma cell lines (Dowless et al 2018). In the cell-derived xenograft Ewing's sarcoma model A673 (derived from a 15-year-old patient), of the 6 animals treated with the triplet combination of abemaciclib, irinotecan, and temozolomide, 1 had a partial regression and 5 had stable disease, while the 6 animals treated with irinotecan and temozolomide experienced progressive disease (Dowless et al. 2018). In addition, durable responses with abemaciclib in combination with irinotecan and temozolomide have been reported in other Ewing's sarcoma models (Dowless et al. 2018).

A673 Ewing's sarcoma CDX model in mice treated with vehicle, abemaciclib (daily for 28 days), irinotecan and temozolomide (daily for 5 days, rest for 16 days, then daily for 5 days), or abemaciclib, irinotecan, and temozolomide, (same schedules for each drug as above). Treatment started on approximately Day 15. (A) Tumor volume over time (B) Tumor response assessment at Day 31 (Modified from Dowless et al. [2018]).



Abbreviations: CDX = cell-derived xenograft; PD = progressive disease; PR = partial response; SD = stable disease; T/C = treated tumor size divided by control tumor size; TMZ = temozolomide.

Additionally, neuroblastoma has been reported to have deregulation of the CDK pathway through amplification of *CDK4* and *CCND1* (Cyclin D1) and deletion of *CDKN2A* (Molenaar et al. 2012; Rader et al. 2013). In a panel of 9 neuroblastoma cell lines, all 9 were sensitive to abemaciclib at clinically relevant concentrations. Abemaciclib (50 mg/kg/oral/once daily [QD]) was also evaluated as a single agent in 2 cell-derived xenograft models (KELLY and IR-32) of pediatric neuroblastoma. In both models, abemaciclib had a statistically significant tumor growth reduction when compared to the vehicle, resulting in a Response Evaluation Criteria in Solid Tumors (RECIST) of stable disease for KELLY and partial regression for IMR-32. IMR-32 is known to have a *FBX031* loss of function, a feature linked to Cyclin D1 activation, and therefore may be a the more sensitive model (Rihani et al. 2015; Gong et al. 2017). There were no significant concerns for tolerability as assessed by twice-weekly measurements of body weight and daily observation of general appearance.

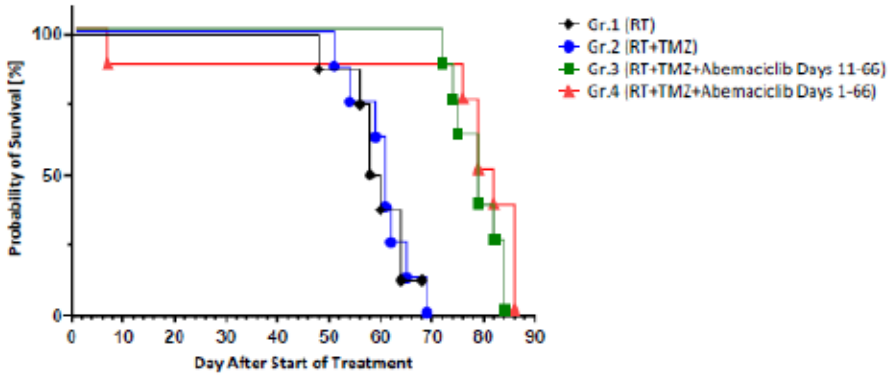
Evaluation of Abemaciclib in Cell-Derived Neuroblastoma Xenograft Models

Model	n	%T/C or Regression	P-value	RECIST	% change bodyweight from baseline	P -value
IMR-32	6	-69.5	<0.001	partial regression	-6.9	0.013
KELLY	5	13.5	<0.001	stable disease	-6.8	<0.001

Abbreviations: RECIST = Response Evaluation Criteria in Solid Tumors; T/C = treated tumor size divided by control tumor size.

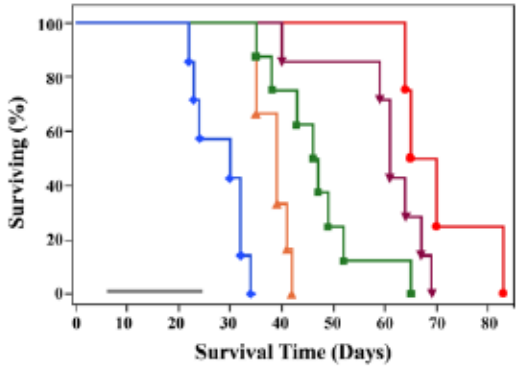
Pediatric high-grade glioma can also harbor genetic aberrations such as CCND/CDK amplification and *CDKN2A/B* deletion (Sturm et al. 2017). In a patient-derived xenograft model of pediatric high-grade glioma, radiotherapy, adjuvant temozolomide and abemaciclib significantly extended survival compared to both radiotherapy alone and to radiotherapy plus temozolomide in the model shown below. Three other models did not show consistent results.

CNXF 4204 pediatric high-grade glioma patient-derived xenograft model (n=8 per group). Mice were treated with 1 Gy x 1 day radiotherapy, temozolomide daily (approximately 5 days per cycle x 2 cycles depending on tolerability), and abemaciclib daily on days 1-66 or 11-66 as indicated.



Additionally, abemaciclib monotherapy and abemaciclib combined with temozolomide have been evaluated in an adult glioblastoma models. Using a rat orthotopic U87MG xenograft model, abemaciclib monotherapy resulted in a significantly improved survival compared to the control (vehicle-treated) (Raub et al. 2015). Furthermore, in rats with intracranial U87MG tumors, abemaciclib combined with temozolomide was, at minimum, additive compared to either as monotherapy (Raub et al. 2015). These and other studies indicated that abemaciclib can cross the blood-brain barrier with unbound brain levels expected to inhibit CDK4 & 6 (Raub et al. 2015).

U87MG orthotopic glioma model (n=8 per group). Rats were treated starting on day 6 at the indicated schedule in table (grey horizontal bar above x-axis indicates treatment period) (Modified from Raub et al. [2015]).



Treatment (mg/kg)	Schedule	Median Survival (days)	p-value
● Abemaciclib (40) + TMZ (3)	Q2Dx20 Days: 6, 13	67.5	0.0032
▼ Abemaciclib (40) + TMZ (3)	QDx20 Days: 6, 13	61	0.0002
■ TMZ (3)	Days: 6, 13	46.5	<0.0001
▲ Abemaciclib (40)	QDx20	39	0.0004
♦ Vehicle	-	30	-

Abbreviations: QD = once daily; Q2D = twice daily; TMZ = temozolomide.

Abemaciclib was also investigated in a glioblastoma cohort of adult patients in the Phase 1 Study I3Y-MC-JPBA. Of 17 enrolled, 3 patients exhibited stable disease at the time of the primary endpoint (Patnaik et al. 2016). Two patients continued to receive abemaciclib without disease progression for 19 and 23 cycles, and they remained on treatment at the time of data cutoff. In the Phase 2 Study I3Y-MC-JPBO of abemaciclib in patients with brain metastases there was evidence to support that abemaciclib achieved therapeutic concentrations in brain metastases (Tolaney et al. 2020).

Other pediatric solid tumors, such as osteosarcoma, malignant rhabdoid tumors, medulloblastoma, and rhabdomyosarcoma, have been reported to contain genetic aberrations that may confer sensitivity to abemaciclib, although sufficient studies have not been performed to validate activity (Saab et al. 2006; Zhu et al. 2016; Geoerger et al. 2017; Cook Sangar et al. 2017). Other CDK4 & 6 inhibitors (palbociclib and ribociclib) have been evaluated in preclinical or clinical studies with several of these tumor types, but results are limited based on small numbers and a lack of confirmatory studies (Hashizume et al. 2016; Cook Sangar et al. 2017; Geoerger et al. 2017).

Importantly, although Study JPCS is the first Lilly-sponsored pediatric clinical trial of abemaciclib, an exploratory investigator-sponsored Phase 1 clinical trial evaluating the single-agent activity of abemaciclib in children and young adults is currently ongoing in the United States (Cash et al. 2019). The 130 mg/m^2 BID dose level (equivalent to approximately 200 mg BID for an adult), is reported to be well tolerated in pediatric patients with recurrent/refractory solid tumors, including malignant brain tumors (Cash et al. 2019).

Together, the mechanism of action of abemaciclib, the nonclinical data supporting involvement of the Cyclin D/CDK4 & 6 pathway in pediatric cancers, as well as the great unmet medical need have prompted Study JPCS.

2.3. Benefit/Risk Assessment

There is an urgent need for new effective combinations of targeted therapies to treat relapsed malignancies. The addition of abemaciclib will build upon standard backbone chemotherapy to evaluate safety and tolerability and will inform efficacy assessments in future appropriately powered tumor-specific studies. The study design ensures that the commonly used disease-specific therapies (temozolomide ± irinotecan for many solid tumors and anti-GD2 antibodies with GM-CSF, temozolomide, and irinotecan for neuroblastoma) will not be withheld. Given the observed safety profile of abemaciclib in adults and the known risk profile of dinutuximab, GM-CSF, irinotecan, and temozolomide, the risk for the combinations in the proposed study population is expected to be manageable.

Extrapolating from adult clinical safety data with abemaciclib, diarrhea, neutropenia, and alanine aminotransferase (ALT) increased, all of which have demonstrated reversibility with reduction or discontinuation of abemaciclib, are considered potential areas of overlapping toxicity when given in combination with irinotecan and temozolomide and with dinutuximab. These events are readily monitored and manageable.

Additional details on the management of diarrhea are in Section 6.5.2; additional details on dose modifications for diarrhea, hematologic toxicity, hepatotoxicity, and other toxicities are in Section 6.6; and additional details of hepatic monitoring are in Section 8.2.1.1.

The molecular pathophysiology that promotes growth in many pediatric malignancies and the existing preclinical data support the evaluation of abemaciclib in relapsed/refractory pediatric solid tumors in combination with cytotoxic therapy (i.e. temozolomide, irinotecan). Importantly, the CDK4 & 6 pathway can also be deregulated in neuroblastoma, and the addition of abemaciclib to chemoimmunotherapy provides a novel strategy to potentially improve outcomes for patients with relapsed/refractory neuroblastoma.

More information about the known and expected benefits, risks, serious adverse events (SAEs), and reasonably anticipated AEs of abemaciclib are to be found in the Investigator's Brochure (IB).

More detailed information about the known and expected benefits and risks of dinutuximab, GM-CSF, irinotecan, and temozolomide, may be found in the Patient Information Leaflet, Package Insert, and/or Summary of Product Characteristics.

2.3.1. Benefit/Risk Assessment of COVID-19

Ensuring the health and safety of research participants, reducing the burden on the healthcare system, and upholding the integrity of clinical trial data are of the utmost importance. Based on the poor survival and lack of therapeutic options for pediatric patients with relapsed/refractory solid tumors, the potential benefits study patients may receive outweigh the risks they may encounter by being on-site at the facility to receive treatment during the COVID-19 pandemic. Whether these patients seek treatment in a clinical trial setting or in a standard healthcare setting, the risk of COVID-19 infection will be present. Activities in this trial were designed to reflect the standard of care activities for this patient population. However, there are some additional visits (such as on days with PK assessments) to ensure patient safety and to meet the trial objectives. These additional visits are not considered to pose a significant increase in risk, since standard local hospital/clinic procedures to prevent the spread of COVID-19 will be in place.

In order to maintain regular visits and treatment administration, flexibility measures, such as allowing remote visits, have been integrated into this clinical trial protocol as outlined in Section 10.7, Appendix 7, thus minimizing interpersonal contact. These flexibility measures will allow for compliance with this protocol, thereby ensuring patient safety and data reliability.

With the flexibility measures in place and the high unmet need of the patients participating in Study JPCS, the potential benefits of Study JPCS outweigh the potential risks of starting the trial during the COVID-19 pandemic.

2.3.2. Overall Benefit Risk Conclusion:

Given the observed safety profile of abemaciclib in adults and the known risk profiles of dinutuximab, GM-CSF, irinotecan, and temozolomide, the risk for the combinations in the proposed study are expected to be manageable. Additionally, considering the measures taken to ensure participant safety, the potential risks are justified by the potential benefits for individuals with relapsed malignancies.

3. Objectives and Endpoints

Objectives	Endpoints
Primary	
To determine the optimal RP2D for abemaciclib in patients with relapsed/refractory solid tumors: • Part A: in combination with irinotecan and temozolomide • Part B: in combination with temozolomide	• DLTs • MTD • PK (concentrations of abemaciclib, irinotecan, and temozolomide)
Part C: To determine the optimal RP2D, and anti-tumor activity of abemaciclib in combination with dinutuximab, GM-CSF, irinotecan, and temozolomide in patients with relapsed/refractory neuroblastoma per INRC	• DLTs • PK (concentrations of abemaciclib, irinotecan, and temozolomide)[a] • ORR determined by investigator assessment
Secondary	
To characterize the safety profile of the combination therapies	• Safety (including but not limited to): TEAEs, SAEs, deaths • Clinical laboratory abnormalities per CTCAE (version 5.0), vital signs, and physical examinations • Dose modifications of all study drugs
To document the preliminary anti-tumor activity of the combination therapy per RECIST v1.1 or RANO (for CNS tumors) for Parts A and B, and per INRC for part C.	• DoR • CBR • DCR • ORR (Parts A & B only) • PFS determined by investigator assessment (Part C only)
To assess the acceptability and palatability of the tablet and/or granule abemaciclib, including dispersed tablets and/or granules	Assessment of tablet, granule, or dispersed abemaciclib presentation, including acceptability and palatability
Tertiary/Exploratory	
CCI	

Abbreviations: CBR = clinical benefit rate; CTCAE = Common Terminology Criteria for Adverse Events; DCR = disease control rate; DoR = duration of response; DLT= dose-limiting toxicity; GM-CSF = granulocyte macrophage colony-stimulating factor; CCI MTD = maximum tolerated dose; ORR = overall response rate; CCI PFS = progression-free survival; PK = pharmacokinetics; RANO = Response Assessment in Neuro-Oncology; RECIST = Response Evaluation Criteria in Solid Tumors; RP2D = recommended Phase 2 dose; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

[a] In Part C, PK is a primary endpoint for Stage 1 only.

4. Study Design

4.1. Overall Design

Section 1.2 illustrates the study schema.

Study JPCS is a multicenter Phase 1b/2 study with 3 parts. Parts A and B are in patients with any relapsed/refractory solid tumor that has progressed on standard treatments and for whom experimental therapy with abemaciclib in combination with temozolomide or in combination with temozolomide and irinotecan is deemed medically appropriate by the investigator. Part C will exclusively enroll participants with relapsed/refractory neuroblastoma and for whom experimental therapy with abemaciclib in combination with dinutuximab, GM-CSF, irinotecan, and temozolomide is deemed medically appropriate by the investigator. Due to global differences in the standard of care for this population, the trial will enroll patients to Part C only in North America and Australia.

The total sample size for the study is dependent on the incidence of DLTs in all parts and responses in Part C. The study will enroll approximately 30 to 117 patients (see Section 9.2). Patients in Parts A and B must be ≤18 years of age and weigh ≥10 kg (with body surface area [BSA] ≥0.5 m^2). Patients in Part C must be <21 years of age (for patients with a starting abemaciclib dose of 30 mg/m^2 BID, BSA must be ≥0.3 m^2). The trial will be conducted following a 3+3 dose escalation scheme for Parts A and B and Simon's two-stage design (Simon 1989) with a dose finding component for Part C:

- Part A: abemaciclib in combination with irinotecan and temozolomide
- Part B: abemaciclib in combination with temozolomide
- Part C: abemaciclib in combination with dinutuximab, GM-CSF, irinotecan, and temozolomide.

Part A will be executed first to confirm the MTD of abemaciclib in combination with irinotecan and temozolomide. The MTD is defined as the highest dose level at which less than 33% of patients experience a DLT during Cycle 1. After the MTD of abemaciclib in Part A has been determined, Parts B and C will open. As Part B reduces cumulative exposure to myelosuppressive agents, it will enroll at a starting dose one level higher than the abemaciclib MTD in Part A (not to exceed 115 mg/m^2). Since Part B will not start at the lowest dose level (unless the lowest dose level of Part A is not tolerated), this sequential design has potential to minimize the number of patients necessary to complete Part B. The dose escalation/de-escalation method for abemaciclib in Parts A and B is described in detail in Section 4.1.1. Part C will utilize the MTD for the combination of abemaciclib, irinotecan, and temozolomide identified in Part A and the standard dosing of dinutuximab and GM-CSF (Mody et al. 2020) as the starting dose. Part C consists of two stages that will evaluate (1) safety and tolerability and (2) anti-tumor activity of the combination (details in Section 4.1.2).

Dose-limiting toxicities will be evaluated during the 21 days of treatment in Cycle 1. After the MTD has been identified, an expansion cohort for each part will be enrolled to further inform safety and PK and to confirm the tolerability in additional patients.

The cycle length is 21 days. Patients will continue study treatment until at least one of the discontinuation criteria is met (Section 7). Continuation on chemotherapy beyond Cycle 12 will be up to the investigator's discretion and the individual patient's situation. Prior to continuing the patient on chemotherapy beyond Cycle 12, the investigator should discuss with the Lilly clinical research physician/clinical research scientist (CRP/CRS).

The primary objective in Parts A and B is to determine the RP2D of abemaciclib in combination with irinotecan and temozolomide (Part A), and abemaciclib in combination with temozolomide (Part B) in patients with relapsed/refractory solid tumors. The secondary objectives include the assessment of the safety profile, preliminary anti-tumor activity, and abemaciclib acceptability and palatability. CCI

The co-primary objectives in Part C are to evaluate the safety, tolerability, and anti-tumor activity of abemaciclib in combination with dinutuximab, GM-CSF, irinotecan, and temozolomide in patients with relapsed/refractory neuroblastoma. The secondary objectives include the assessment of DoR, CBR, DCR, and PFS by investigator assessment, and evaluation of drug product acceptability and palatability. CCI

4.1.1. Dose Escalation Design for Parts A and B

The dose will be escalated following assessment of toxicity using the standard scoring system, Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0, established by the National Cancer Institute (NCI).

In Part A, patients will begin abemaciclib at Dose Level 1 (70 mg/m^2). After the dose escalation of Part A is completed, one dose level higher than the MTD of abemaciclib in Part A will be used as the starting dose in the dose escalation of Part B, but will not exceed 115 mg/m^2 BID. Three patients are planned for treatment at each dose level; however, the exact number of patients treated at a specific dose level depends on the number of patients within the cohort who experienced a DLT.

Patients will be considered DLT-evaluable if they have either completed the DLT-observation period and received at least 75% of planned doses of each study drug in Cycle 1 or have discontinued study treatment or study participation before completing Cycle 1 due to a DLT or received less than 75% of planned Cycle 1 doses due to drug-related toxicity. Non-evaluable patients may be replaced to ensure that enough patients complete 1 cycle unless accrual to that cohort has stopped due to a DLT.

Following the 3+3 dose escalation scheme, if 0 of 3 patients at a given dose level experience first cycle DLT, the subsequent cohort will enroll at the next higher dose level.

- If 0 of 3 evaluable patients experience a DLT, but safety concerns are present, 3 additional patients may be added to the same dose level cohort to provide additional data following discussion between the investigators and the sponsor.

If 1 of 3 evaluable patients in a cohort experience a DLT, the cohort will be expanded to include 6 patients.

- The dose escalation can proceed if <2 out of 6 evaluable patients experience a DLT.

- If a DLT is observed in ≥2 out of a maximum of 6 evaluable patients at any given dose, a safety review will be triggered, dose escalation will cease, and the next lower dose will be considered the MTD.

If the starting dose level of abemaciclib 70 mg/m^2 BID is not tolerated in Part A, the A−1 dose level of 55 mg/m^2 BID of abemaciclib will be explored. If 55 mg/m^2 of abemaciclib is not tolerated in Part A, a thorough safety review will be conducted in collaboration with investigators to weigh the benefits and risks of starting Part B. If the combination is deemed to be not tolerable due to overlapping toxicity of abemaciclib plus temozolomide or abemaciclib alone, the study will not proceed to Parts B or C. However, if the combination was not tolerable due to overlapping toxicity of abemaciclib plus irinotecan (e.g. DLTs of diarrhea), Part B using 55 mg/m^2 of abemaciclib as the starting dose may proceed.

In this study, intrapatient dose escalation is not permitted.

The RP2D of abemaciclib will be defined based on the totality of safety, tolerability, and PK results. Dose-limiting toxicities and dose selection decisions will be made after discussion between the investigators and the sponsor.

The RP2D from each part will be confirmed in expansion cohorts for each combination. Expansion cohorts will enroll 6 patients. In both study parts, upon completion of a thorough safety review, additional patients can be enrolled if necessary to confirm safety. Examples may include testing a lower dose in 6 additional patients if DLTs are experienced by at least 2 of 6 patients in the initial expansion cohort to further confirm tolerability of prolonged treatment.

4.1.2. Two-stage Design for Part C

Part C consists of two stages to first evaluate the safety and tolerability and then the anti-tumor activity of abemaciclib in combination with chemoimmunotherapy. The design is briefly described below with a figure immediately following.

Stage 1

Stage 1 starts with a dose optimization to identify MTD. Specifically, it will initially enroll 3 patients at 55 mg/m^2 (i.e., the MTD for abemaciclib in combination with irinotecan and temozolomide in Part A plus dinutuximab and GM-CSF) and use 3+3 rules to guide dose decision. During MTD identification, if 55mg/m^2 is deemed intolerable, then a lower abemaciclib dose of 30mg/m^2 (keeping the other drugs the same) will be explored. If this lower dose level is deemed intolerable, Arm C will be terminated due to intolerability.

In addition to the safety assessment, the anti-tumor activity will be measured by objective tumor response. If MTD is declared, an expansion cohort will enroll at the MTD to confirm the tolerability while evaluating the preliminary anti-tumor activity. In the expansion cohort, up to [redacted] patients may be simultaneously enrolled. Stage 1 will enroll up to [redacted] DLT-evaluable patients at the identified MTD. If none of the following stopping rules are triggered, the MTD will be confirmed as RP2D and Part C will move to Stage 2.

- Rule A: stop for toxicity if [redacted] of the DLT-evaluable patients experience DLT.
- Rule B: stop for intolerability if [redacted] patients discontinue due to treatment-related AE before completing [redacted] cycles.

- Rule C: stop for insufficient evidence of anti-tumor activity if < [redacted] of [redacted] patients are responders (i.e., have objective tumor response, including a best overall response of complete response [CR], partial response [PR] or minor response [MR] per INRC).

De-escalation during cohort expansion: If 55mg/m^2 is declared the MTD, but either stopping Rule A or B is triggered in the cohort expansion, subsequent patients will be treated at 30mg/m^2 and those at the 55 mg/m^2 dose may be dropped to 30 mg/m^2 upon investigator's discretion. Part C will continue to enroll until there are [redacted] total patients treated at 30 mg/m^2 with a minimum of [redacted] newly enrolled DLT-evaluable 30mg/m^2 patients. If no stopping rules are triggered, the dose combination with abemaciclib at 30 mg/m^2 is the RP2D and Part C will move to Stage 2.

Stage 2

An additional [redacted] patients will be enrolled at the RP2D in Stage 2. Among the [redacted] evaluable patients treated in Stages 1 and 2 at the RP2D, if there are [redacted] responders, then there is insufficient evidence of anti-tumor activity. If [redacted] of the patients are responders, then it is reasonable to conclude that the drug combination has promising anti-tumor activity that could warrant further study.

The figure below illustrates the Part C design.

Statistical details for the two-stage design are provided in Section 9.

4.1.3. Dose-Limiting Toxicity Determination and Maximum Tolerated Dose Definition

A DLT is defined as any of the events according to the NCI CTCAE version 5.0 below if both the following criteria are met:

- The event occurs during the DLT observation period of Cycle 1, between Days 1 and 21,

and,

- The event is clinically significant and either definitely, probably, or possibly related to abemaciclib or the combination treatment following discussion between the investigator and Lilly CRP/CRS.

Investigators, together with the Lilly CRP/CRS, can declare a DLT if a patient experiences a significant toxicity deemed to be dose-limiting.

In the event of any Grade 5 AE, enrollment will be suspended, and a thorough safety review will be performed prior to resuming enrollment.

If a patient receives <75% of any planned Cycle 1 study drug doses due to drug-related toxicity, the toxicity will be declared a DLT.

Nonhematological events:

With the exceptions listed below, all Grade ≥3 nonhematological AEs will be considered a DLT.

Exceptions:

- Grade 3 diarrhea controlled with supportive care and lasting <72 hours;
- Acute irinotecan-associated diarrhea lasting <7 days and controlled with supportive care;
- Grade ≥3 nausea, vomiting, or constipation that is manageable with supportive care and lasts <72 hours;
- Grade 3 mucositis/stomatitis of <72 hours duration;
- Grade 3 fever or infection;
- Grade ≥3 electrolyte abnormality that lasts <72 hours, is not clinically complicated, and resolves spontaneously or responds to conventional medical interventions;
- Grade ≥3 amylase or lipase that is not associated with symptoms or clinical manifestations of pancreatitis; or
- Aspartate aminotransferase (AST)/ALT elevation resolving to eligibility criteria within 7 days;

Hematological events:

- Cycle Delay: a >14-day delay in the start of a subsequent cycle because of neutropenia or thrombocytopenia in the absence of bone marrow disease progression seen on clinically indicated bone marrow biopsy (if performed).

  Note: Patients who experience dose-limiting neutropenia and/or thrombocytopenia will have these events reviewed by the sponsor to discuss attribution (bone marrow disease [baseline and subsequent, if performed and clinically indicated] versus study drugs). Patients with bone marrow disease progression will not be considered to have dose-limiting hematological toxicities.
- Grade ≥3 thrombocytopenia with clinically significant bleeding; or
- Grade ≥4 neutropenic fever.

Note: lymphopenia is not considered a DLT unless clinically significant.

Aggregate data will be reviewed and taken into consideration for determining the RP2Ds.

The I3Y-MC-JPCS Toxicity Documentation Form must be completed and sent to Lilly for **each patient** during the DLT period in order for timely evaluation of DLTs.

- If a DLT is experienced during the DLT evaluation period, the I3Y-MC-JPCS Toxicity Documentation Form should be completed and sent to Lilly within 3 days of becoming aware of the DLT.

- If no DLT is experienced, the form should be completed and sent 3 days after the DLT evaluation period has ended.

4.2. Scientific Rationale for Study Design

The overall rationale for the study design is described in the Introduction section under Study Rationale (Section 2.1) and in Statistical Considerations (Section 9). Dose selection details can be found in Section 4.3.

4.3. Justification for Dose

4.3.1. Abemaciclib

Abemaciclib has demonstrated efficacy with a tolerable safety profile in advanced breast cancer at a monotherapy dose of 200 mg BID, and in combination with fulvestrant or aromatase inhibitors at a dose of 150 mg BID (Dickler et al. 2017; Goetz et al. 2017; Sledge et al. 2017; Johnston et al. 2019). Across all pivotal registration trials for abemaciclib in adult patients with cancer, no clinically meaningful effect of age, body weight, sex, or race/ethnicity on the PK of abemaciclib has been identified. Therefore, in adults, abemaciclib is dosed without adjustment for body size.

In pediatric patients, the enzyme largely responsible for the clearance of abemaciclib (CYP3A4) reaches maturity after the first year of life (Bartelink et al. 2006). Between the age of 1 to 12 years, CYP-mediated metabolism is largely dependent on liver volume, which is better correlated with body surface area (BSA) rather than body weight (Bartelink et al. 2006). As such, in pediatrics, doses will be scaled linearly according to the patient's BSA (mg/m^2). Until additional PK and safety data become available for the drug combination across a wide range of pediatric ages and body sizes, the BSA adjustment will be applied to all pediatric patients <18 years of age. For participants aged 18 years and older, based on the known PK in adults and lack of required body size adjustment, an equivalent non-BSA-based dose will be used based on the planned starting dose adjusted for an assumed adult BSA of 1.73 m^2.

For patients aged between 6 months and 1 year, the activity of CYP3A4 is reduced by 50% compared to the typical adult population (Blake et al. 2005). Given the high variability and wide range of safe and efficacious exposures of abemaciclib in the adult population, an increase in exposures of 2-fold in patients aged 6 months to 1 year is expected to be well tolerated by the pediatric patient population. The Inclusion Criteria [1] and [2] in Study JPCS Parts A and B for body weight (at least 10 kg) and BSA (at least 0.5 m^2), and the Inclusion Criteria [3] for the disease characteristics of patients enrolled in Part C (relapsed/refractory neuroblastoma) will most likely exclude patients who are younger than 6 months of age.

Part A

The abemaciclib starting dose of 70 mg/m^2 BID for Part A in pediatric patients was selected based on 80% of the BSA-adjusted adult dose used for abemaciclib combination studies (that is, 150 mg BID÷1.73 m^2×0.8=70 mg/m^2 BID). Given the potential for patients with larger BSA to receive doses in excess of the approved adult dose, the maximum dose of abemaciclib will be capped at 150 mg BID (maximum adult combination dose).

Part B

Since Part B uses 1 less study drug, it will likely be more tolerable than the triplet combination due to fewer expected adverse events. Therefore, in Part B, one dose level higher than the MTD of abemaciclib (not to exceed 115 mg/m^2 BID) in Part A will be used as the starting dose in combination with temozolomide 100 mg/m^2/day on Days 1 through 5 of a 21-day cycle (see Section 6.1). Starting at a higher dose level in Part B may allow the MTD to be established with fewer patients since fewer dose levels may have to be tested in the doublet escalation. Given the potential for patients with larger BSA to receive doses in excess of the approved adult dose, as with Part A, the maximum dose of abemaciclib will be capped at 150 mg BID (maximum adult combination dose).

Part C

In Part C, the MTD_A of abemaciclib of 55mg/m^2 in combination with irinotecan and temozolomide (determined in Part A) will be used in combination with dinutuximab and GM-CSF. If this dose level is not tolerated, a lower dose of 30 mg/m^2 will also be explored. This 30mg/m^2 dose corresponds to an adult 50 mg dose, adjusting for a typical adult BSA of 1.73 m^2. In adult malignancies, 50 mg abemaciclib is the lowest dose with existing clinical efficacy data.

Given the addition of dinutuximab and GM-GSF to the Part A triplet combination, the maximum dose of abemaciclib will be capped at 100 mg BID in Part C to avoid excessive exposures in the largest patients.

4.3.2. Temozolomide

In Parts A and C of this study, a temozolomide dose of 100 mg/m^2/day will be used on Days 1 through 5 of a 21-day cycle, which has been reported to be safe and tolerable in combination studies in pediatric patients (Casey et al. 2009; Bagatell et al. 2011; Mody et al. 2017; Palmerini et al. 2018).

In Part B, the temozolomide dose may be escalated to 150 mg/m^2/day to further increase temozolomide exposure, if either

1. the MTD of abemaciclib is not reached when dosed at 115 mg/m^2 BID in Part B, or
2. abemaciclib 115 mg/m^2 is the RP2D for Part A.

Temozolomide 150 mg/m^2/day has been reported as tolerable in other combination studies (Geoerger et al. 2005; Kushner et al. 2006; Rubie et al. 2010; Ruggiero et al. 2010; Wagner et al. 2010; Hummel et al. 2013; Ruggiero et al. 2013; Di Giannatale et al. 2014; Setty et al. 2018), including in combination with dinutuximab and temozolomide (Mody et al. 2017).

4.3.3. Irinotecan

In Parts A and C of this study, irinotecan 50 mg/m^2/day (intravenous [IV]) will be administered on Days 1 through 5 of a 21-day cycle, which is cited in the pediatric section of the prescribing information (Irinotecan US Package Insert 2020) and has been used in other pediatric trials (Kushner et al. 2006; Raciborska et al. 2013; DuBois et al. 2016), including in combination with dinutuximab and temozolomide (Mody et al. 2017).

4.3.4. Dinutuximab and GM-CSF

In Part C, dinutuximab will be administered at a dose of 17.5 mg/m^2/day × 4 days of each cycle, as cited in the prescribing information (Dinutuximab package insert, 2015). This dose was previously administered to pediatric patients with relapsed/refractory neuroblastoma on Days 2 through 5 in combination with irinotecan (50 mg/m^2/day on Days 1 through 5), temozolomide (100 mg/m^2/day on Days 1 through 5), and GM-CSF (250 µg/m^2 per dose) subcutaneously on Days 6–12 in Study ANBL1221 (Mody et al. 2020). GM-CSF is added to dinutuximab to augment ADCC based on the ANBL0032 and ANBL1221 studies (Mody et al 2020, Yu et al 2010). This combination of dinutuximab, GM-CSF, irinotecan, and temozolomide, demonstrated a manageable toxicity profile and substantial activity with 22 of 53 patients exhibiting objective responses (Mody et al. 2020). Patients in Part C will receive the same dinutuximab, GM-CSF, irinotecan, and temozolomide doses and administration schedule as in Study ANBL1221.

Given that dinutuximab is a monoclonal antibody, it is highly unlikely that it would affect the clearance pathways of abemaciclib, irinotecan, or temozolomide, nor that these combination drugs would affect the clearance of dinutuximab. Therefore, it is not expected that the doses of any of the planned combination study drugs would need to be altered based on an anticipated PK interaction with dinutuximab.

4.4. End of Study Definition

The end of the study is defined as the date of last scheduled procedure shown in the Schedule of Activities (SoA; Section 1.3) for the last participant in the trial.

In the EU, study completion is the date of the last visit or last scheduled procedure shown in the SoA (Section 1.3) associated with Part B.

In the US, study completion is the date of the last visit or last scheduled procedure shown in the SoA (Section 1.3) associated with Part C.

5. Study Population

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age and Weight

1. **Parts A and B only:**
   a. Patients must be ≤18 years of age at the time of study enrollment, and
   b. Body weight ≥10 kg and BSA ≥0.5 m^2.

   Part C only:
   a. Patients must be <21 years of age at the time of study enrollment.
   b. For patients with a starting abemaciclib dose of 30 mg/m^2 BID, BSA must be ≥0.3 m^2

   All Parts: the Mosteller formula should be used to calculate BSA.

2. Inclusion Criterion 2 has been deleted.

Type of Participant and Disease Characteristics

3. **Parts A and B only:** patients with any relapsed/refractory malignant solid tumors (excluding lymphoma), including CNS tumors, that have progressed on standard therapies. For sites that are actively enrolling Parts B and C, patients with neuroblastoma who are eligible for Part C will be excluded from Part B unless approved by Lilly CRP/CRS.

   Part C only: patients with first relapse/refractory neuroblastoma. Refractory is defined as either less than partial response (PR) by INRC at the conclusion of at least 4 cycles of standard front-line induction chemotherapy or progressive disease (PD) during front-line therapy. First relapse is defined as disease recurrence following completion of aggressive multi-drug chemotherapy, surgery, autologous stem cell transplant and radiation, with or without retinoids.

   NOTE: For Part C, front-line chemotherapy must have comprised 2 or more agents, including an alkylating agent and a platinum-containing compound.

   For Parts A, B, and C: Patients must have at least one measurable or evaluable lesion as defined by RECIST v1.1 (Eisenhauer et al. 2009) or RANO for CNS tumors (Wen et al. 2010).

i. Measurable is defined as a nonlymphoid soft tissue mass ≥1 cm (longest dimension) or lymph node ≥1.5 cm (short axis) on a MRI or CT scan
ii. Evaluable disease is defined as the presence of at least one lesion, with no lesion that can be accurately measured in at least one dimension. Such lesions may be evaluable by nuclear medicine techniques, immunocytochemistry techniques, tumor markers or other reliable measures.
iii. For CNS tumors: Isolated leptomeningeal disease in relapsed/refractory CNS tumors that is evaluable may be eligible for inclusion after consultation with the Lilly CRP/CRS.

For Part C: A tumor (either measurable or evaluable) that is either

- MIBG-avid or that demonstrates increased FDG uptake on PET scan (for MIBG-nonavid tumor), or
- viable neuroblastoma confirmed by biopsy (submission of pathology report is required)

Patients with involvement of bone marrow only, without a measurable or evaluable lesion, are not eligible.

AND

Patients must have had histologic verification of malignancy at original diagnosis or relapse, except:

a. patients with CNS germ cell tumors or extra-cranial germ-cell tumors and who have elevations of serum tumor markers including alpha-fetoprotein or beta-HCG, and
b. patients with intrinsic brain stem tumors

In the judgment of the investigator, the patient is an appropriate candidate for the experimental therapy combination in the study part that is currently enrolling.

Neurologic deficits in patients with CNS tumors must have been stable for at least 7 days prior to study enrollment.

4. A Lansky score ≥50 for patients <16 years of age or a Karnofsky score ≥50 for patients ≥16 years of age
   - Patients who are unable to walk because of paralysis, but are up in a wheelchair, will be considered ambulatory for the purpose of assessing the performance score.

5. Patients must be able to swallow and/or have a gastric/nasogastric tube. Refer to Section 6.1.2 for alternative administration methods.

6. Patients must have discontinued all previous treatments for cancer or investigational agents as shown below and must have recovered from the acute effects to Grade ≤1 at the time of enrollment, unless deemed clinically insignificant by the investigator. For agents with known AEs occurring beyond the required wait period outlined in the table, this period must be extended until after the time during which the AE is known to occur. Consult with the Lilly CRP/CRS for the appropriate length of time prior to the first dose of study treatment on additional therapies not mentioned.

Previous Treatment	Length of Time Prior to First Dose of Study Treatment
Cytotoxic and myelosuppressive chemotherapy	≥21 days after the last dose of cytotoxic or myelosuppressive chemotherapy (or ≥42 days if prior nitrosourea)
Hematopoietic growth factors	≥14 days after the last dose of a long-acting growth factor (e.g. pegfilgrastim) ≥7 days for short-acting growth factor
Cellular therapy	≥42 days after the completion of any type of cellular therapy (e.g. modified T cells, NK cells, dendritic cells) agent
Interleukins, interferons, and cytokines (other than hematopoietic growth factors)	≥21 days after the completion of interleukins, interferon, or cytokines, including IL-2
Antibody therapy	≥21 days after the last infusion of antibody therapy, including anti-GD2 monoclonal antibody
Non-myelosuppressive biologic agent or retinoid (Part C only)	≥7 days after last dose
Radiotherapy	≥14 days since small port radiation therapy (i.e. local palliative); ≥84 days since large-field radiation therapy (i.e. TBI, craniospinal, whole abdominal, total lung, ≥50% or greater pelvic radiation, ≥50% marrow space); ≥42 days for other substantial bone marrow radiation or ^{131}I-MIBG therapy. For Part C only: No minimum interval between radiation and study entry is required for non-target lesions. However, target lesions must not have received radiation within 4 weeks of study entry. Previously radiated lesions cannot be used as target lesions unless there is radiographic evidence of progression following radiation or a post-radiation biopsy confirms viable neuroblastoma.
Radiopharmaceutical therapy (e.g. radiolabeled antibody, ^{131}I-MIBG)	≥42 days after radiopharmaceutical therapy
Stem cell infusion without TBI	≥84 days since transplant or stem cell infusion
Corticosteroids	≥14 days for patients who have received a course of systemic corticosteroids (≥5 days) to modify immune AEs related to prior therapy. Note: Patients who are on steroid inhalers for asthma, chronic replacement for endocrine disorders, or are on a stable or decreasing dose for at least 7 days for CNS lesions may still be eligible (consult Lilly CRP/CRS)
Surgery	≥28 days after a major surgical procedure, laparoscopic procedure, or significant traumatic injury. Surgical or other wounds must be

Previous Treatment	Length of Time Prior to First Dose of Study Treatment
	adequately healed prior to treatment. • Central line placement or subcutaneous port placement is not considered major surgery • Core biopsy, fine needle aspirate, and bone marrow biopsy/aspirate are not considered major surgeries.

Abbreviations: AE = adverse event; CNS = central nervous system; CRP/CRS = clinical research physician/clinical research scientist; IND = investigational new drug; ^{131}I-MIBG = ^{131}I-metaiodobenzylguanidine; NK = natural killer; TBI =total body irradiation; XRT = photon radiation therapy.

7. The patient has adequate hematologic and organ function ≤2 weeks (14 days) prior to first dose of study drug:

System	Laboratory Value
Hematologic	
ANC	Parts A and B: ≥1000/µL Part C: ≥750/µL G-CSF cannot be administered ≤1 week (7 days) prior to first dose of study drug. Pegfilgrastim cannot be administered ≤2 weeks (14 days) prior to first dose of study drug.
Platelets	≥75,000/mm^3 Platelet transfusion to meet this enrollment criterion is not allowed within the preceding 5 days of first dose of study drug.
Hemoglobin	≥8 g/dL (≥80 g/L) Transfusions to increase the patient's hemoglobin level to at least 8 g/dL are permitted; however, study treatment must not begin until 7 days after the transfusion and CBC criteria for eligibility are confirmed ≤ 24 hours before C1D1
Hepatic	
Total bilirubin	≤1.5×ULN Except patients with documented history of Gilbert Syndrome who must have a total bilirubin level of <3.0×ULN
ALT and AST	≤3×ULN **OR** ≤5.0×ULN if the liver has tumor involvement
Coagulation	
Prothrombin Time	Part C: ≤1.2× ULN

Abbreviations: ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; C1D1 = Cycle 1 Day 1; CBC = complete blood count; CRP/CRS = clinical research physician/clinical research scientist; G-CSF = granulocyte-colony stimulating factor; ULN = upper limit of normal.

- Creatinine clearance or calculated glomerular filtration rate (GFR) ≥60 mL/min/m^2
  OR

  Serum creatinine based on age/gender as follows:

Age	Maximum serum creatinine (mg/dL)	
	Male	**Female**
1-<2 years	0.6	0.6
2-<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 years	1.7	1.4

The threshold creatinine values in this table were derived from the Schwartz formula (see Section 10.5, Appendix 5) for estimating GFR_{99} (Schwartz and Gauthier 1985) utilizing child length and stature data published by the Centers for Disease Control and Prevention.

28. For Part C only: no dyspnea at rest and oxygen saturation of ≥94% on room air.
29. For Part C only: Adequate cardiac function with a shortening fraction of >30% or ejection fraction ≥50% on cardiac echo or gated radionucleotide study.
8. Female patients of childbearing potential must have a negative urine or serum pregnancy test within 7 days prior to Cycle 1 Day 1.
9. Female patients of reproductive potential must agree to use highly effective contraceptive precautions during the trial. For abemaciclib, females should use contraception for at least 3 weeks following the last abemaciclib dose. For other study drugs, highly effective contraceptive precautions (and avoiding sperm donation) must be used according to their label.
10. The patient has a life expectancy of at least 8 weeks and able to complete at least 1 cycle of treatment.
11. Patients/caregivers are able and willing to make themselves available for the duration of the study and are willing to follow study procedures, including adherence to the PK sampling schedule.

Informed Consent/Assent

12. The investigator, or a person designated by the investigator, will obtain written informed consent/assent from each study participant or the participant's legally acceptable representative, parent(s), or legal guardian and the participant's assent, when applicable, before any study-specific activity is performed unless a waiver of informed consent/assent has been granted by an Institutional Review Board (IRB)/ Independent Ethics Committee (IEC). The investigator will retain the original copy of each participant's signed consent/assent document.

5.2. Exclusion Criteria

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

Medical Conditions

13. Have had an allogeneic bone marrow or solid organ transplant.
14. Have received recent (within 4 weeks prior to Cycle 1 Day 1) live vaccination. Seasonal flu and COVID vaccines that do not contain a live virus are permitted.
15. Patients with psychiatric illness/social situation that, in the opinion of the investigator, could cause unacceptable safety risks or compromise compliance with the protocol.
16. Exclusion Criterion 16 has been deleted.
17. Have a known intolerability or hypersensitivity (such as urticaria, allergic reaction including anaphylaxis, toxic necrolysis, and Stevens-Johnson syndrome) to any of the study treatments or its components relevant to the study part that is currently enrolling or a known hypersensitivity to dacarbazine
18. Diagnosed and/or treated additional malignancy within 3 years prior to enrollment that, in the judgment of the investigator and Lilly, may affect the interpretation of results, with the exception of curatively treated basal cell carcinoma of the skin, squamous cell carcinoma of the skin, and/or curatively resected in situ cervical and/or breast cancers.
19. Are pregnant or breastfeeding.
20. The patient has active systemic infections (e.g. bacterial, fungal, or viral infection requiring IV therapy). Individuals with stable HIV, Hepatitis B, or C for whom exposure to the investigational treatment is not expected to exacerbate their current disease may be considered eligible. Screening is not required for enrollment.
21. The patient has serious and/or uncontrolled preexisting medical condition(s) that, in the judgment of the investigator, would preclude participation in this study (such as interstitial lung disease, severe dyspnea at rest or requiring oxygen therapy, history of major surgical resection involving the stomach or small bowel, or preexisting Crohn's disease or ulcerative colitis or a preexisting chronic condition resulting in clinically significant diarrhea).
26. Patients with a bowel obstruction will be excluded from Parts A and C of this study.

Prior/Concomitant Therapy

22. Patients treated with drugs known to be strong inhibitors or inducers of isoenzyme cytochrome P450 (CYP)3A or strong inhibitors of uridine diphosphate-glucuronosyl

transferase 1A1 (UGT1A1) if the treatment cannot be discontinued or switched to a different medication at least 5 half-lives prior to starting study drug.

23. Have received any prior CDK4 & 6 inhibitor.
30. Part C only, have received prior systemic therapy for relapsed/refractory neuroblastoma.
31. Patients with CNS disease are eligible if seizures and other neurological symptoms have been stable for 7 days. However, patients must not have received enzyme-inducing anticonvulsants, such as phenytoin, phenobarbital, valproic acid, or carbamazepine for at least 7 days prior to starting study drug. Non-enzyme-inducing anticonvulsants, such as gabapentin or levetiracetam, are acceptable.
32. Part C only, have received prior anti-GD2 therapy during induction phase

Prior/Concurrent Clinical Study Experience

24. Are currently enrolled in any other clinical study involving an investigational product or non-approved use of a drug or device (other than the study drug used in this study) or any other type of medical research judged not to be scientifically or medically compatible with this study
25. Have participated, within the last 30 days, in a clinical study involving an investigational product. If the previous product has a long half-life, 5 half-lives or 30 days, whichever is longer, should have passed. Exceptions will be considered on a case-by-case basis by the Lilly CRP/CRS.

Genetic Alterations

27. Exclusion Criterion 27 has been deleted.

5.3. Lifestyle Considerations

Patients should refrain from consuming grapefruit, grapefruit juice, and grapefruit-containing products while on study due to the effect on CYP3A4. See Section 6.5 for additional information on concomitant medications.

5.4. Screen Failures

Screen failures are defined as participants who consent/assent to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Individuals may be rescreened 1 time. The interval between rescreening should be ≥2 weeks. Each time rescreening is performed, the individual and/or the individual's legally acceptable representative, parent(s), or legal guardian (when applicable) must sign a new informed consent form (ICF) and assent (if applicable) and will be assigned a new identification number. Repeating of laboratory tests during the screening period or repeating screening tests to comply with the protocol-designated screening period does not constitute rescreening. Screening

must occur within 28 days of Cycle 1 Day 1, but a 7-day window beyond 28 days is acceptable without being considered as a protocol deviation or screen fail.

6. Study Intervention

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1. Study Intervention(s) Administered

The investigator or his/her designee is responsible for the following:

- explaining the correct use of the drugs and planned duration of each individual's treatment to the patient/study site personnel/legal representative
- verifying that instructions are followed properly
- maintaining accurate records of study treatment dispensing and collection
- recording all concomitant medications, including premedication, on the case report form (CRF)
- at the end of the study, returning all unused medication to Lilly, or its designee, unless Lilly and sites have agreed all unused medication is to be destroyed by the site, as allowed by local law

Abemaciclib will be provided by the sponsor as 25-mg and 50-mg tablets for oral administration. Additionally, in Part C, 2.5 mg oral granules may be used. In Parts A and B, the minimum dose is 25 mg BID due to the BSA requirement of at least 0.5 m^2. In Part C, the minimum dose is [redacted] or Section 10.8, Appendix 8). [redacted]
Refer to the Abemaciclib Dosing Charts in Section 10.8 (Appendix 8) for the dose rounding rules based on a patient's BSA for each dose level and if using granules, the number of granules required for each dose.

Participants taking oral granules should follow the provided instructions for the dispensing device and administration.

Until PK samples are completed on Cycle 3 Day 1, participants may only switch abemaciclib formulations (tablets to granules or vice versa) if necessary for a dose adjustment or BSA change. Following the last PK sample, participants may switch formulations as necessary (for reasons other than dose adjustment or BSA change). Oral granules and tablets can never be combined to make up a single dose.

If instructions have been provided to prepare abemaciclib in food/liquid, no other medications should be added to the food/liquid with abemaciclib.

For each cycle, the actual dose administered for all study drugs must be within 10% of the planned dose; any total cycle dose exceeding ±10% from the planned dose for the cycle will result in a protocol deviation. Please contact the Lilly CRP/CRS to discuss any questions for individual situations.

Investigational drugs (including abemaciclib, dinutuximab, GM-CSF, irinotecan, and temozolomide) will be supplied per local laws and regulation and country requirements.

Abemaciclib doses will be administered at approximately the same times on each day. Please see Section 10.8, Appendix 8 (Abemaciclib Dosing Chart) to determine if a change in BSA necessitates a change in abemaciclib dosing.

The planned duration of treatment is not fixed; participants will remain on study until disease progression, unacceptable toxicity, or patient withdrawal (see Section 7.1). Continuation beyond Cycle 12 will be up to the investigator's discretion and should be discussed with the Lilly.

The following treatments will be administered in 21-day cycles. Refer to Sections 1.3.1 and 1.3.2 for the daily schedule.

- **Abemaciclib** BID orally on Days 1 through 21 according to the dosing tables below. Doses should be separated by at least 6 hours. Abemaciclib should be swallowed whole (refer to Section 6.1.2 for patients with swallowing difficulties). Participants taking oral granules should follow the provided instructions for the dispensing device and administration. If a dose is missed, the patient should take the next dose at its scheduled time. If a participant spits out or vomits abemaciclib within 15 minutes of ingestion, repeat the dose. If vomiting occurs a second time, the dose should not be repeated.

  Abemaciclib is authorized in the EU as defined by the EU clinical trial regulation and is not used according to EU authorization in this study.

- **Temozolomide** once daily orally on Days 1 through 5 according to the dosing tables below. For Parts A and C, take temozolomide approximately 1 hour prior to irinotecan. Temozolomide can be taken at the same time as the abemaciclib dose. Temozolomide should be taken on an empty stomach. Temozolomide should be taken according to local standard of care (refer to Section 6.1.2 for patients with swallowing difficulties). If a participant spits out or vomits temozolomide capsule(s) within 15 minutes of ingestion, repeat the dose. If participant vomits temozolomide capsule(s) a second time, the dose should not be repeated. In Part C, IV temozolomide may be allowed if locally sourced and approved by the Lilly CRP/CRS. IV temozolomide should be administered over approximately 90 minutes or per institutional standards. A minimum of 20 hours between temozolomide doses is recommended.

  Temozolomide is authorized in the EU as defined by the EU clinical trial regulation and is not used according to EU authorization in this study.

- **Irinotecan (Parts A and C Only)** once daily as IV infusion on Days 1 through 5 according to the dosing table below. A minimum of 20 hours between irinotecan doses is recommended.

  Irinotecan is authorized in the EU as defined by the EU clinical trial regulation and is not used according to EU authorization in this study.

- **Dinutuximab (Part C Only)** once daily as an IV infusion over 10 hours on Days 2 through 5. Infusions may be extended to a maximum of 20 hours. The dinutuximab infusion should follow irinotecan. Held doses of dinutuximab are not made up. See Section 6.1.1 for detailed administration guidelines.

  Dinutuximab is not authorized in the EU.

- **GM-CSF (Part C only)** 250 µg/m^2/day subQ on Days 6-12 (may be administered at home per local standard of care). IV administration (2 hour duration or per institutional standard) may be approved by Lilly CRP/CRS. Held doses of GM-CSF are not made up.

  GM-CSF is not authorized in the EU.

Packaging and labeling

Study interventions will be supplied by the sponsor or its designee in accordance with current Good Manufacturing Practice. Study interventions will be labeled as appropriate for country requirements.

Part A: Triplet Combination Dosing

Dose-Level Cohort	Patients	Abemaciclib Dosing	Irinotecan Dosing	Temozolomide Dosing
A-1	3-6	55 mg/m^2 BID, PO	50 mg/m^2/day IV on Days 1-5 of a 21-day cycle	100 mg/m^2/day PO on Days 1-5 of a 21-day cycle
A1 (starting dose)	3-6	70 mg/m^2 BID, PO		
A2	3-6	90 mg/m^2 BID, PO		
A3	3-6	115 mg/m^2 BID, PO		
Part A Dose Expansion	6-12[a]	MTD_A		

Abbreviations: BID = twice daily; DLT = dose-limiting toxicity; IV = intravenous; MTD_A = Part A maximum tolerated dose; PO = orally.

[a] Expansion cohorts will enroll 6 patients initially. Additional patients can be enrolled if necessary to confirm safety. Examples may include testing a lower dose in 6 additional patients if DLTs are experienced by at least 2 of 6 patients in the initial expansion cohort or to further confirm tolerability of prolonged treatment.

Part B: Doublet Combination Dosing

Dose-Level Cohort	Patients	Abemaciclib Dosing	Temozolomide Dosing
B-1 (or below)[a]	3-6	Dose will be de-escalated according to the dose levels outlined in Part A, BID, PO	100 mg/m^2/day PO on Days 1-5 of a 21-day cycle
B1 (starting dose)[b]	3-6	One dose level above MTD_A, BID, PO	
B2 - B4[a]	3-6	Dose will be escalated according to the dose levels outlined in Part A	
B5[c]	3-6	115 mg/m^2 BID, PO	150 mg/m^2/day PO on Days 1-5 of a 21-day cycle

Dose-Level Cohort	Patients	Abemaciclib Dosing	Temozolomide Dosing
Part B Dose Expansion	6-12[d]	MTD_B	temozolomide RP2D (100 mg/m^2 or 150 mg/m^2)

Abbreviations: BID = twice daily; IV = intravenous; MTD = maximum tolerated dose; MTD_A = Part A maximum tolerated dose; MTD_B = Part B maximum tolerated dose; PO = orally; RP2D = recommended Phase 2 dose.

[a] Dose will be escalated (Cohorts B1, B2, B3, B4, B5) or de-escalated (Cohorts B-1, B-2, B-3, B-4) following dose levels as outlined in Part A as needed. It is possible that not all dose levels will be enrolled.

[b] One dose level higher than the MTD of abemaciclib in Part A (or 115 mg/m^2 if this was the MTD_A) will serve as the starting dose of abemaciclib in Part B.

[c] Cohort B5 will only take place if the following occur:

1) The MTD of abemaciclib is **not** reached when dosed at 115 mg/m^2 BID in combination with 100 mg/m^2/day temozolomide in Part B; **OR**

2) If abemaciclib 115 mg/m^2 BID is the MTD for Part A. In this case, Part B will directly start with Cohort B5 using abemaciclib 115 mg/m^2 BID and temozolomide 150 mg/m^2/day.

[d] Expansion cohorts will enroll 6 patients initially. Additional patients can be enrolled if necessary to confirm safety. Examples may include testing a lower dose in 6 additional patients if DLTs are experienced by at least 2 of 6 patients in the initial expansion cohort or to further confirm tolerability of prolonged treatment.

Part C: Combination Dosing

Part C Dosing Schedule							
	Day 1	Day 2	Day 3	Day 4	Day 5	Days 6-12	Days 13-21
Abemaciclib PO 55 mg/m^2 BID x 21 days [a, b]	X	X	X	X	X	X	X
Temozolomide PO 100 mg/m^2/day x 5 days	X	X	X	X	X		
Irinotecan IV 50 mg/m^2/day x 5 days	X	X	X	X	X		
Dinutuximab IV 17.5 mg/m^2/day x 4 days		X	X	X	X		
GM-CSF SubQ 250 µg/m^2/day x 7 days						X	

Abbreviations: BID = twice daily; GM-CSF = granulocyte-macrophage colony-stimulating factor; IV = intravenous; PO = orally; MTD_A = Part A maximum tolerated dose; SubQ = subcutaneous.

[a] 30 mg/m^2 may be evaluated due to excessive toxicities, if necessary, as described in Section 4.1.2.

[b] An intermediate dose level (ie: between 55 mg/m^2 and 30 mg/m^2) may be explored based on emerging data.

6.1.1. Detailed Administration Guidelines (Part C Only)

Side effects should be anticipated with dinutuximab administration and may occur even with use of pretreatment medications. The need to slow, pause, or even discontinue infusion should be anticipated and is not unexpected. See Section 6.5.3 for guidance for supportive management of anticipated dinutuximab-associated toxicities.

Days 2-5

Administer premedications as outlined in Sections 6.1.4 and 6.5.3.

Hour 0: Administer abemaciclib and temozolomide.

Hour 1: Administer irinotecan over 90 minutes and simultaneously begin normal saline bolus of 10-20 mL/kg.

Hour 2.5: Begin dinutuximab infusion. Start infusion rate at 0.88 mg/m^2/hour for the first 30 minutes.

Hour 3: If starting rate is tolerated, increase dinutuximab infusion rate to 1.75 mg/m^2/hour. If not tolerated, see Section 6.5.3 for management guidelines

Note: The infusion should be completed at Hour 10, but may be extended for anticipated toxicities, such as uncontrolled pain, fever, hypotension, and tachypnea. The maximum infusion duration is 20 hours; the infusion MUST be stopped at 20 hours even if total planned dose has not completed. The infusion duration and dose delivered must be recorded.

Important Note: Monitoring guidelines should be followed **DURING** dinutuximab infusion (see Section 6.1.1.1 immediately below).

6.1.1.1. Monitoring Guidelines During Dinutuximab Infusion (Days 2-5)

Vital signs should be assessed every15 minutes for the first hour of infusion, then hourly if stable. More frequent assessment may be required based on the patient's clinical condition. Between dinutuximab infusions, vital signs should be measured every 4 hours at a minimum.

Strict measurement of intake and output is required on Days 2-5.

Daily physical exams, including pupillary reflexes and extraocular movement evaluation, are required before each daily infusion.

Weigh patients daily to assess fluid status. Use diuretics with extreme caution.

See Section 6.5.3 for guidance for supportive management of anticipated dinutuximab-associated toxicities.

6.1.2. Patients with Difficulty Swallowing After Initiating Treatment

If a patient has difficulty swallowing after initiating study treatment, the following should be considered. In all cases, the method of administration should be documented on the CRF.

- For abemaciclib, the Medication Alternative Administration Guide provides instructions for dispersing tablets for oral administration as well as dispersing tablets/granules for NG/G-tube administration. Patients unable to swallow tablets may also switch to oral granules (Part C only) (refer to Oral Granule Dispensing Device and Administration Training Video and Oral Granules IFU).
- For temozolomide, follow standard of care for alternative administration (Trissel et al. 2006; CCLG 2016).

6.1.3. Criteria to Begin Subsequent Cycles of Treatment

To begin dosing at each cycle, the following criteria must be fulfilled. If a patient has not met the criteria to start the next cycle, and the toxicity does not warrant an abemaciclib dose hold per Section 6.6.1.1 (Parts A and B) or Section 6.6.1.3 (Part C), the investigator may use his/her discretion to hold abemaciclib while waiting for the toxicity to resolve. The dose hold should be recorded in the eCRF. A cycle may begin 1 day early (i.e. Day 21) if needed for logistical reasons if all Day 1 criteria are satisfied.

- Absolute neutrophil count $\geq 750/mm^3$
  - Parts A and B: G-CSF is not permitted within the past 48 hours
  - Part C: G-CSF is not permitted
- Platelets $\geq 75,000/mm^3$ (platelet transfusion is not permitted within the past 72 hours)
- Total bilirubin $\leq 1.5 \times$ upper limit of normal (ULN), except patients with documented history of Gilbert Syndrome who must have a total bilirubin level of $<3.0 \times ULN$
- AST and ALT $\leq 3.0 \times ULN$, or $\leq 5 \times ULN$ if the transaminase elevation is due to liver metastases
- For parts A and B, patients must weigh ≥ 10 kg and have BSA ≥ 0.5 m^2
- For part C, patients with a starting abemaciclib dose of 30 mg/m^2 BID, BSA must be ≥ 0.3 m^2
- Any nonhematologic toxicity deemed related to study treatment must be NCI-CTCAE, v5.0 Grade ≤ 1 or equivalent severity to baseline unless deemed clinically insignificant by the investigator.

6.1.4. Premedication

Irinotecan and temozolomide should be administered following institutional-approved standard-of-care premedication guidelines. Additional premedication and supportive management for dinutuximab can be found in Section 6.5.3.

6.1.4.1. Nausea

A prophylactic treatment with anti-emetics is recommended before each treatment with irinotecan and/or temozolomide.

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate storage conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention and only authorized study personnel may supply, prepare, or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized study personnel.
3. The investigator or authorized study personnel is responsible for study intervention accountability, reconciliation, and record maintenance (i.e. receipt, reconciliation, and final disposition records).

4. Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy Manual.
5. Investigators should consult the study drug information provided in the label for the specific administration information (including warnings, precautions, contraindications, adverse reactions, and dose modifications).

6.3. Measures to Minimize Bias: Randomization and Blinding

This is an open-label study.

6.4. Study Intervention Compliance

Study intervention will be administered under medical supervision by the investigator or designee. The dose of study intervention and study participant identification will be confirmed prior to the time of dosing. The date and time of each dose administered will be recorded in the source documents and will be provided to the sponsor as requested.

When participants self-administer study intervention(s) at home, compliance with study intervention will be assessed at Day 1 (±5 days) of each Cycle starting at Cycle 2. Compliance will be assessed by direct questioning, counting returned tablets/capsules, or by weighing returned granules. Compliance assessments will be documented in the source documents and CRF. When assessing compliance of granules, refer to the "Abemaciclib Oral Granules Compliance Form". Deviation(s) from the prescribed dosage regimen should be recorded in the electronic case report form (eCRF).

A record of the quantity of self-administered study intervention(s) dispensed to and returned by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions, will also be recorded in the CRF.

The patient must take ≥75% of the planned doses for study treatment in a cycle to be deemed compliant unless dose holds are necessitated by AE. As outlined in Section 6.6, dose suspensions or cycle delays may occur and will not result in a patient being considered as noncompliant. A patient may be considered noncompliant if he/she is judged by the investigator to have intentionally or repeatedly taken ≥125% of the planned doses of study treatment in a cycle. Potential discontinuation of a patient due to study drug noncompliance will be discussed between the investigator and the Lilly CRP/CRS before any determination is made to discontinue the patient.

6.5. Concomitant Therapy

With the exceptions listed in the sections below, no other chemotherapy, investigational medications, other anticancer therapy, immunotherapy, hormonal cancer therapy, herbal supplements and/or herbal drugs intended to treat cancer, radiation, or surgery for cancer will be permitted while patients are on study treatment. Palliative radiation therapy will be permitted as detailed in Section 6.5.1.

Because of a potential impact on antibody-dependent cellular cytotoxicity, any treatment with immunosuppressive activity and immunoglobulins should not be administered within 21 days

prior to Cycle 1 and for 1 week after final dinutuximab infusion. However, these medications may be allowed if medically needed to treat acute, potentially life-threatening events.

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates

Abemaciclib is extensively metabolized through oxidation by CYP3A. In clinical drug interaction studies, coadministration of clarithromycin, a strong CYP3A inhibitor, increased exposure (area under the curve [AUC]) to abemaciclib by 3.4-fold (Study I3Y-MC-JPBE) and coadministration of rifampin, a strong CYP3A inducer, decreased exposure to abemaciclib by 95% (Study I3Y-MC-JPBF). Therefore, grapefruit or grapefruit juice, cannabis, cannabis products, and other strong inhibitors of CYP3A (see Section 10.6, Appendix 6) should not be taken during Cycle 1. Beyond Cycle 1, grapefruit or grapefruit juice, cannabis, cannabis products, as well as inducers and strong or moderate inhibitors of CYP3A should be substituted or avoided if possible (see Section 10.6, Appendix 6). The information in Appendix 6 is provided for guidance to investigators and does not preclude the use of these medications if clinically indicated.

All patients may receive supportive therapy with dexamethasone, preferably ≤7 days, if clinically indicated. Patients requiring more than 7 days of dexamethasone therapy will not incur a protocol deviation.

Abemaciclib can be coadministered with drugs that are substrates of CYP enzymes.

Abemaciclib and/or its major metabolites inhibit the efflux transporters P-glycoprotein and breast cancer resistance protein and renal transporters organic cation transporter 2, multidrug and toxin extrusion protein (MATE) 1 and MATE2-K at clinically relevant concentrations. Therefore, substrates of these transporters such as metformin and those with a narrow therapeutic index such as digoxin and dofetilide should be substituted or avoided if possible.

The active metabolite of irinotecan, SN-38, is metabolized via UGT1A1. Patients receiving concomitant ketoconazole, a strong CYP3A4 and UGT1A1 inhibitor, exhibited increased exposures of irinotecan and SN-38 (Irinotecan US Package Insert 2020). Therefore, strong inhibitors of UGT1A1 (e.g. gemfibrozil, atazanavir, indinavir) should not be taken during Cycle 1. Beyond Cycle 1, strong inhibitors of UGT1A1 should be substituted or avoided if possible.

For further information regarding concomitant medications with dinutuximab, GM-CSF, irinotecan, and temozolomide refer to the guidance in each of the product labels.

Live vaccines are not permitted while on treatment and for at least 3 months after the last dose of abemaciclib. Vaccines that do not contain a live virus are permitted. Live vaccines following treatment with other study drugs should be administered according to label.

All concomitant medication administered to treat an AE or SAE must be recorded until resolution, or if events are no longer drug-related, the patient dies or is lost to follow-up, or a

new treatment is initiated. While on study, patients may be administered medications at the discretion of the investigator to treat AEs or as supportive care (e.g. anti-emetics, antibiotics).

The Lilly CRP/CRS should be contacted if there are any questions regarding concomitant or prior therapy.

6.5.1. Palliative Medicine and Supportive Care

All concomitant medications should be recorded throughout the patient's participation in the study.

Palliative Medicine

- Palliative radiation therapy of ≤14 days is permitted after Cycle 6 and after discussion with and agreement of the Lilly CRP/CRS for irradiating small areas of painful metastases that cannot be managed adequately using systemic or local analgesics. Such areas must not be an identified target lesion and must not constitute progressive disease or meet RECIST criteria for progressive disease. Abemaciclib should be suspended during the palliative radiotherapy period and until complete recovery from acute reactions and potential gastrointestinal toxicities. Any symptomatic deterioration or clinical disease progression requiring, in the opinion of the investigator, other forms of specific anti-tumor systemic therapy, will be cause for discontinuation of study therapy.

Supportive Care

Patients should receive full supportive care.

- The use of anti-diarrheal (i.e. loperamide) medication is strongly recommended. See Section 6.5.2 for details.
- In Parts A and B, the use of G-CSF is permitted for all cycles, including Cycle 1, at the discretion of the investigator based on American Society of Clinical Oncology (ASCO) (Smith et al. 2015) and European Society for Medical Oncology (Crawford et al. 2010) guidelines. Administration of G-CSF should be considered alongside study treatment for those patients at high risk of severe neutropenia (e.g. previously treated with chemotherapy or radiation). G-CSF is not allowed in Part C.
- Erythropoietin, thrombopoietic growth factors, packed red blood cell transfusions, and other blood products may be used according to ASCO guidelines (Rizzo et al. 2008) at the investigator's discretion.
- Prophylactic antibiotic treatment should be consistent with ASCO guidelines (Lehrnbecher et al. 2017).
- *Pneumocystis jirovecii* pneumonia may occur in participants receiving irinotecan and temozolomide. PCP prophylaxis is encouraged.
- Refer to temozolomide and irinotecan labels for recommendations on prophylactic supportive care.

6.5.2. Supportive Management for Diarrhea

Diarrhea is an overlapping toxicity of abemaciclib, irinotecan, and dinutuximab. It may be difficult to discern the difference between causes of diarrhea. Investigators should attempt to

determine to which study drug the diarrhea is likely attributed using the descriptions below. Patients should receive diarrhea management instructions and maximal supportive care. Loperamide is recommended.

See Section 6.6.1.1 for diarrhea-related dose modifications. For patients in Part C, see Section 6.5.3.2 for suggested premedication to prevent diarrhea.

Guidance for diarrhea attributed to irinotecan:
Early diarrhea (onset during or shortly after infusion) is usually transient and infrequently severe. It may be accompanied by cholinergic symptoms of rhinitis, increased salivation, miosis, lacrimation, diaphoresis, flushing, and intestinal hyperperistalsis that can cause abdominal cramping. Bradycardia may occur. Early diarrhea and other cholinergic symptoms may be prevented and treated. Consider prophylactic or therapeutic administration of atropine (according to label or institutional practice) unless clinically contraindicated.

Late diarrhea (onset more than 24 hours after administration) can be life-threatening since it may be prolonged, lead to dehydration, electrolyte imbalance, or sepsis, and can be complicated by colitis, ulceration, bleeding, ileus, obstruction, and infection. Cases of megacolon and intestinal perforation have been reported. Patients should have loperamide available prior to first irinotecan infusion. Begin loperamide at the first episode of poorly formed, loose, or increased frequency of stool. Monitor and replace fluid and electrolytes. Patients should be followed closely.

Prophylactic or concomitant use of antibiotics, such as cefixime, can be used at the investigator's discretion (Wagner et al. 2008).

Refer to prescribing information for additional management of diarrhea attributed to irinotecan.

Guidance for diarrhea attributed to abemaciclib:
Diarrhea was the most frequently reported treatment-emergent adverse event (TEAE) with abemaciclib in adult Phase 3 registration studies (MONARCH 2 [Sledge et al. 2017]; MONARCH 3 [Goetz et al. 2017; Johnston et al. 2019]). Characteristics of abemaciclib diarrhea from these studies include:

- Predominantly of low severity (Grade 1 or 2) with no Grade 4 or 5 diarrhea observed.
- Incidence was greatest during the first month of abemaciclib treatment.
- The median time to onset of the first diarrhea event was 6 to 8 days, and the median duration of diarrhea for Grade 2 was 9 to 11 days and Grade 3 was 6 to 8 days (Abemaciclib US Package Insert 2019).
- Generally manageable with standard anti-diarrheal agents and dose adjustment.

Initiate supportive measures as early as possible. Supportive measures include:

- Anti-diarrheal medication (e.g. loperamide) initiation at the first sign of loose stools.
- Patient/caregiver should notify the investigator for further instructions.
- Patients should be encouraged to drink sufficient fluids.
- Site personnel should assess response within 24 hours.
- Modify treatment as outlined in Section 6.6 (Dose Modification).
- Adjust doses as outlined in Section 6.6.1.1.

If severe, measure absolute neutrophil counts, body temperature, and monitor for signs of bacterial infection. If associated with fever or severe neutropenia, begin broad-spectrum antibiotics per institutional guidelines.

Patients with severe diarrhea or any diarrhea associated with nausea or vomiting should be carefully monitored and given IV hydration and electrolyte replacement. Hospitalization should be considered.

6.5.3. Supportive Management of Anticipated Dinutuximab-Associated Toxicities (Part C Only)

Side effects during dinutuximab infusion should be anticipated and will frequently occur even with use of pretreatment medications. The need to slow, pause, or discontinue infusion should be anticipated and is not unexpected. Refer to Section 6.6.1.3 for dose modifications of dinutuximab.

6.5.3.1. Hypotension (Without Evidence of Allergic Reaction)

Severe Hypotension is defined as:

- Symptomatic decrease in blood pressure and/or
- Age 1-12 years: SBP <70 mmHg
- Age >12 years: SBP <80 mmHg
- Either SBP or DBP decrease by more than 15% from baseline.

If severe, accompanied by poor perfusion, end organ dysfunction, or acidemia, stop infusion and initiate resuscitation efforts.

Moderate Hypotension is defined as hypotension with normal perfusion, absence of end organ dysfunction, and without acidemia

For moderate hypotension:

- Pause dinutuximab infusion
- Give 20 mL/kg normal saline bolus
- Stop or adjust narcotic and sedating H1 blocker infusions
- Consider Trendelenberg position.

For moderate hypotension that persists despite the measures above:

- Reassess perfusion and end organ function and initiate standard resuscitation efforts
- Repeat normal saline bolus
- Consider albumin infusion if albumin level is <3 gm/dL
- Consider PRBC transfusion if Hgb is <10 gm/dL
- Consider transfer to intensive care unit.

If hypotension persists following 2 fluid boluses, give additional boluses and initiate pressors. Note that epinephrine is preferred over dopamine based on its desired vasoconstrictive properties.

Resumption of dinutuximab infusion after hypotension

For hypotension that resolves promptly and completely with limited resuscitation, dinutuximab may be resumed at 50% infusion rate. If >20 hours have elapsed since initiation of dinutuximab infusion, then do not resume that day's dose.

If same-day infusion is resumed and if blood pressures are stable for 2 hours, the infusion rate may be increased to the maximum rate for remainder of that day and subsequent days.

If hypotension recurs at a reduced same-day infusion rate, stop the infusion and repeat the supportive care measures described above. Do not administer any additional dinutuximab on that day. The following day, ensure that the patient is volume replete and begin infusion at 50% rate.

If blood pressure is stable for 2 hours at a reduced rate, the infusion can be increased to maximum rate and, if tolerated, subsequent infusion days may begin at maximum starting rate.

If blood pressure only remains stable at the 50% infusion rate, then all subsequent infusions should be initiated at the 50% infusion rate without attempts to increase.

If >60 mL/kg fluid boluses were required at maximal dinutuximab rate, but the 50% infusion rate was tolerated, then all remaining days should be administered at the 50% reduced infusion rate without attempts to increase.

If pressors were required but then were able to be discontinued and the patient's blood pressure remained stable for ≥6 hours following discontinuation, the next day's dinutuximab infusion may resume at 50%.

Patients who require pressor support for ≥24 hours or more than once must permanently discontinue all study drugs.

6.5.3.2. Diarrhea Management

Due to irinotecan-induced diarrhea, consider using cefixime (8 mg/kg/day) or an available equivalent of oral cephalosporin (i.e., cefpodoxime 10 mg/kg/day divided BID; maximum dose 400 mg/day) starting 2 days prior to first irinotecan dose and continued until 3 days after the last irinotecan dose per cycle. For patients receiving 5 days of irinotecan, the total course of diarrhea prevention is 10 days.

6.5.3.3. Allergic Reaction due to Dinutuximab

Prophylactic Antihistamine

- Consider administration of an antihistamine, such as diphenhydramine (0.5 to 1 mg/kg; maximum dose 50 mg) 20 minutes prior to dinutuximab and every 4 to 6 hours as tolerated during the dinutuximab infusion.

Mild Allergic Reactions: limited to Grade 1-2 rash, flushing, urticaria, and/or dyspnea

Suggested management of mild allergic reactions includes

- Decrease dinutuximab infusion rate to 50%
- Administer an H1 blocker, such as diphenhydramine or cetirizine
- Administer H2 blocker
- When symptoms resolve, resume original infusion rate

- If symptoms recur, again decrease infusion rate to 50%
- Infusion MUST be stopped after 20 hours even if full dose has not been administered; document total amount of dinutuximab infused.

Moderate to Severe Allergic Reactions: includes any of the following: symptomatic bronchospasm, allergy-related angioedema, generalized edema, hypotension, or anaphylaxis (Grade 3 or 4)

Suggested management of moderate to severe allergic reactions includes

- Immediately stop dinutuximab infusion
- Evaluate airway, breathing, and circulation
- Follow institutional guidelines for rapid response or critical care response team
- For airway concerns:
  - Administer oxygen and albuterol for bronchospasm
  - Administer IV diphenhydramine
  - Administer epinephrine (1:1000 IM recommended) for upper airway involvement or if accompanied by circulatory collapse
  - Administer IV hydrocortisone (1-2 mg/kg) for anaphylaxis with cardiovascular collapse, if ≥2 doses epinephrine are required, or for moderate to severe symptoms that recur upon dinutuximab rechallenge.
- For hypotension in the setting of allergic reaction
  - Give 20 mL/kg normal saline bolus
  - Stop or adjust narcotics and sedating H1 blockers
  - Consider use of Trendelenburg position
  - See previous section for hypotension management.
- For mild bronchospasm or angioedema without impact on breathing and that completely resolves without epinephrine or hydrocortisone, dinutuximab infusion may resume at 50% rate
- For hypotension that resolves following fluid bolus, dinutuximab infusion may resume at 50% rate on the same day of the reaction
- If symptomatic angioedema or bronchospasm recurs after dinutuximab infusion resumes, then discontinue infusion for that day
- If symptoms resolved completely on the day dinutuximab was discontinued, then resume the following day with hydrocortisone 1-2 mg/kg IV premedication. This rechallenge should be in the intensive care unit
- If bronchospasm or angioedema requires epinephrine, permanently discontinue dinutuximab
- For bronchospasm or angioedema with hypotension requiring volume resuscitation, refer to hypotension guidance in Section 6.5.3.1.

6.5.3.4. Capillary Leak Syndrome (≥Grade 3)

Management of capillary leak syndrome:

- Stop dinutuximab infusion

- Administer oxygen and fluids as appropriate
- Diuretics should be used with caution and hypotension should be avoided
- If symptoms persist on the same day or recur on subsequent days within the same cycle, discontinue dinutuximab for that cycle
- Only resume when capillary leak symptoms are ≤Grade 2
- If resolves, resume dinutuximab at 50% rate the same day and for remaining doses within the same cycle. For subsequent cycles, the dinutuximab may be given at the full rate
- If therapy-related capillary leak syndrome requires pressors for ≥24 hours or any duration of mechanical ventilation, the patient must discontinue all study drugs.

6.5.3.5. Renal Insufficiency

- For borderline hypotension, consider the possibility of renal hypoperfusion and administer volume as appropriate
- If creatinine is ≥2× ULN and elevation persists despite optimized fluid management, hold dinutuximab infusion
- Modify concomitant medications that may contribute to or be affected by renal insufficiency
- If urine output normalizes and creatinine returns to <2× ULN, the dinutuximab infusion may resume at 50% rate. If renal function returns to normal by the next day, dinutuximab infusion may resume at the full rate
- If urine output has not normalized and/or creatinine remains ≥2× ULN by Day 7, no further dinutuximab should be given in the cycle. If renal function has normalized by planned start date of next cycle, then retreatment is permitted.

6.5.3.6. Hyponatremia (≥Grade 3; Na <130 mEq/L)

- Switch hypotonic fluids to isotonic fluids as compatibilities allow
- Do not administer oral free water
- Correct fluid losses caused by diarrhea
- Use 3% saline only if:
  - Hyponatremia leads to seizure
  - Sodium level decreases by >10 points in ≤6 hours
  - Sodium level <117 mEq/L
- If Grade 4 hyponatremia persists despite optimal fluid management, do not administer dinutuximab during the rest of the cycle. Monitor sodium levels closely in the subsequent cycle
- If Grade 4 hyponatremia recurs in the subsequent cycle despite optimal fluid management, permanently discontinue all study drugs.

6.5.3.7. Fever in the Absence of Hypotension

- Administer antipyretics
- If fever is persistent, adjust fluids to account for insensible losses
- Obtain blood culture and then administer empiric antibiotics per institutional policy.

6.5.3.8. Treatment-Related Pain

- For patients who experience pain that is uncontrolled by narcotics, no further dinutuximab should be given during a given cycle
- For recurrent uncontrolled pain in a subsequent cycle, discontinue all study drugs
- For patients requiring intravenous narcotics for ≥48 hours after completion of dinutuximab infusion, gabapentin or similar agent should be initiated (if not already being administered)
- If pain requiring intravenous narcotics for ≥48 hours after completion of dinutuximab infusion recurs in a subsequent cycle, discontinue all study drugs.

Pain Management

- Non-opioid analgesics (i.e., acetaminophen and ibuprofen): before each dinutuximab infusion and every 4-6 hours as needed for pain and/or fever
- Gabapentin:
  - 10 mg/kg/day 3 days before dinutuximab infusion
  - 2 × 10 mg/kg/day 2 days before dinutuximab infusion
  - 3 × 10 mg/kg/day 1 day before dinutuximab infusion; can be paused between cycles or continuous during cycles
  - Taper dose at discontinuation of dinutuximab
- Morphine:
  - 0.02-0.05 mg/kg/hour continuous infusion prior to dinutuximab infusion and
  - 0.02-0.05 mg/kg/hour or as required for adequate pain control during dinutuximab infusion and for 2 hours after infusion is complete
  - Discontinue or reduce infusion rate (e.g., 0.01 mg/kg/hour) 2 hours after infusion each day, as tolerated
- If morphine is contraindicated, consider fentanyl or hydromorphone per investigator discretion
- Lidocaine and/or ketamine can be considered for pain that is not manageable using the above medications
- Refer to Section 6.1.1 for infusion rate adjustments of dinutuximab.

6.5.3.9. Visual Changes

- Discontinue current course of dinutuximab for patients who develop dilated pupils with sluggish light reflexes
- If papillary abnormalities remain stable or improve before the next course, resume dinutuximab at 50% of prior dose
- If there is no worsening of ocular toxicity at the reduced dose, then full dose may be given in subsequent courses
- If ocular toxicity worsens or recurs after resuming the full dose, permanently discontinue all study drugs
- Isolated changes in accommodation do not require dose reductions.

6.5.3.10. Serum Sickness

- Identification of serum sickness is important. Signs and symptoms include arthralgias/arthritis, splenomegaly, lymphadenopathy, glomerulonephritis in the presence of persistent fevers, and cutaneous eruptions
- Serum sickness typically develops 1 to 3 weeks after administration of the causative agent but can develop within 12-36 hours in sensitized patients
- Patients with Grade 2 serum sickness should receive antihistamines
- Patients with ≥ Grade 3 serum sickness should permanently discontinue all study drugs.

6.5.3.11. Neurotoxicity

- For Grade 3 sensory or motor neuropathy, discontinue dinutuximab for the remainder of the current cycle
- If neuropathy resolves by start of next cycle, reduce dinutuximab dose to 50%
- If neuropathy symptoms do not resolve, or if they recur, then permanently discontinue all study drugs
- Grade 4 neurotoxicity requires permanent dinutuximab discontinuation.

6.6. Dose Modification

In the event of a cycle delay due to logistical reasons (e.g. due to patient availability), the patient should continue on abemaciclib if the patient has adequate drug supply. If a patient's treatment is interrupted as a result of not having sufficient drug supply, the cycle may be delayed up to 7 days (and not be considered a protocol violation). In exceptional circumstances, a delay >7 days is permitted upon agreement between the investigator and the Lilly CRP/CRS. In exceptional cases, for planned delays (including but not limited to vacation or holidays), additional study treatment may be dispensed upon consultation with Lilly CRP/CRS.

For patients undergoing surgery, refer to the following guidelines for abemaciclib dose modifications:

- For minor surgeries and procedures (e.g. ambulatory), investigators should treat as clinically indicated and closely monitor any signs of infection or healing complications.
- For major surgeries, the recommendation is to suspend dosing of abemaciclib for at least 7 days before and may be resumed as clinically indicated.
- Consider monitoring neutrophils and platelets before surgery and before resuming abemaciclib. The scars should be aseptic and the healing process should be reasonable before resuming abemaciclib.
- Dose suspensions ≥21 days must be discussed with Lilly CRP/CRS.

Parts A and B:

Patients may discontinue chemotherapy while continuing abemaciclib monotherapy (i.e. due to minor chemotherapy-associated toxicities) upon discussion with the Lilly CRP/CRS. In the event that abemaciclib must be discontinued, patients may continue to receive chemotherapy. For each study drug, if further dose reductions are required beyond the allowable dose reductions outlined below, the drug should be discontinued.

Part C:

For each study drug, if further dose reductions are required beyond the allowable dose reductions outlined below, the drug should be discontinued. If any study drug must be discontinued, the patient must discontinue all protocol therapy. Discontinuation of chemotherapy after Cycle 12 is permitted at the investigator's discretion without having to discontinue abemaciclib, dinutuximab, and GM-CSF (refer to Section 4.1). For dose modification guidance specific to Part C, see Section 6.6.1.3. For dose modifications of GM-CSF, refer to Section 6.6.1.4.

Parts A and B: Starting Dose and Adjustments for Abemaciclib-Related Toxicities[a]

Dose at Enrollment	First Reduction	Second Reduction
150 mg	100 mg	50 mg
125 mg	75 mg	50 mg
100 mg	75 mg	50 mg
75 mg	50 mg	25 mg
50 mg	25 mg	Not permitted; must discontinue
25 mg	Not permitted; must discontinue	

[a] Reduced doses of abemaciclib should still be taken twice daily.

Part C: Starting Dose and Adjustments for Abemaciclib-Related Toxicities[a]

Dose at Enrollment	First Reduction	Second Reduction
100 mg	75 mg	50 mg
75 mg	50 mg	25 mg
50 mg	25 mg	17.5 mg
25 mg	17.5 mg	10 mg
22.5 mg	15 mg	10 mg
20 mg	15 mg	10 mg
17.5 mg	12.5 mg	Not permitted; must discontinue
15 mg	10 mg	
12.5 mg	Not permitted; must discontinue	
10 mg		

[a] Reduced doses of abemaciclib should still be taken twice daily.

Dose Levels and Adjustments for Irinotecan-related Toxicities

Dose at Enrollment	First Reduction	Second Reduction
50 mg/m^2	-25%	-50%

Dose Levels and Adjustments for Temozolomide-related Toxicities

Dose at Enrollment	First Reduction	Second Reduction
150 mg/m^2	100 mg/m^2	75 mg/m^2
100 mg/m^2	75 mg/m^2	

6.6.1. Dose Modification Guidance due to Toxicity

- Treatment will be suspended for DLT and may be resumed after resolution. The abemaciclib dose must be reduced. If no further dose reductions are available (refer to Section 6.6), the patient must discontinue abemaciclib. For toxicities that are not dose-limiting, see Section 6.6.1.1.
- Investigators will document whether or not an AE has a reasonable possibility of being related to each of the study drugs, taking into account the disease, concomitant treatments, or pathologies, in order to individually adjust study drug doses.
- Treatment may be suspended for a maximum of 21 days to allow sufficient time for recovery. Cycle delays >21 days due to an AE require discontinuation of all study treatments.
- Any additional questions related to dose adjustments may be discussed with the Lilly CRP/CRS.
- For Parts A and B only.
    - if the AE is, in the opinion of the investigator, more likely due to 1 drug than another, adjustment drug causing the toxicity should be adjusted, and the dosing and schedule of the other study drugs may be maintained.
    - if the roles of each agent are impossible to separate, all involved therapies should have dose adjustments and/or suspensions.
    - refer to irinotecan and temozolomide prescribing information for additional dose modification guidelines.

See Section 6.6.1.3 dose modification tables for guidance specific to Part C.

6.6.1.1. Dose Modification Guidance due to Toxicities Considered to be Attributed to Abemaciclib

Abemaciclib hematological toxicities may overlap with those of chemotherapy. To aid in appropriately attributing hematological toxicities to abemaciclib, below is a description based on adult Phase 3 registration studies (MONARCH 2 [Sledge et al. 2017]; MONARCH 3 [Goetz et al. 2017; Johnston et al. 2019]):

- The TEAE of neutropenia was the most frequent hematological toxicity reported and was predominantly of low-grade severity and not associated with severe infection. Febrile neutropenia was infrequent.
- Neutropenia was observed early in the treatment course, within the first 2 months, and maintained over the course of treatment.
- On central laboratory analysis, neutrophil count decrease from the baseline visit was observed; mean neutrophil counts generally remained stable at the later visits and were reversible once patients discontinued from treatment.
- Anemia and thrombocytopenia were reported but were less frequent than neutropenia and mostly of low-grade severity.

See Section 6.6.1.3 dose modification tables for guidance specific to Part C.

Parts A and B: Dose modification guidance is outlined below for **hematologic toxicities considered to be attributed to abemaciclib**:

Toxicity Type	Toxicity Profile and Severity	Abemaciclib Dose Suspension	Abemaciclib Dose Reduction
Neutropenia Grade 4 (ANC <500/mm^3)	Initial incidence	Dose **MUST** be suspended until ANC ≥750/mm^3	Dose **MAY** be reduced at the investigator's discretion Consider addition of G-CSF at the investigator's discretion according to ASCO/ESMO guidelines (Crawford et al. 2010; Smith et al. 2015)
	If lasting >7 days or causing cycle delay of >14 days	Suspend abemaciclib until ANC ≥750/mm^3	Dose **MUST** be reduced by 1 dose level.
	Subsequent incidences	Suspend abemaciclib until ANC ≥750/mm^3	Dose **MUST** be reduced by 1 dose level.
Thrombocytopenia Grade 4 (platelets<25,000/mm^3)	Initial incidence	Dose **MUST** be suspended until platelets ≥75,000/mm^3	Dose **MAY** be reduced at the investigator's discretion.
	If lasting >7 days or causing cycle delay of >14 days	Dose **MUST** be suspended until platelets ≥75,000/mm^3	Dose **MUST** be reduced by 1 dose level.
	Subsequent incidences	Dose **MUST** be suspended until platelets ≥75,000/mm^3	Dose **MUST** be reduced by 1 dose level.

Toxicity Type	Toxicity Profile and Severity	Abemaciclib Dose Suspension	Abemaciclib Dose Reduction
Febrile neutropenia	Grade 3	Dose **MUST** be suspended until toxicity resolves.	Dose **MAY** be reduced by 1 dose level at the investigator's discretion.
	Recurrent Grade 3[a]	Dose **MUST** be suspended until toxicity resolves.	Dose **MUST** be reduced by 1 dose level.
	Grade 4	Dose **MUST** be suspended until toxicity resolves.	Dose **MUST** be reduced by 1 dose level.

Abbreviations: ANC = absolute neutrophil count; ASCO = American Society of Clinical Oncology; CRP/CRS = clinical research physician/clinical research scientist; ESMO = European Society for Medical Oncology; G-CSF = granulocyte-colony stimulating factor.

[a] Recurrent toxicity refers to the same event occurring within the next 8 weeks (as measured from the stop date of the preceding event).

Parts A and B: The table below presents guidance for abemaciclib dose adjustments and suspensions due to **nonhematologic toxicity considered to be attributed to abemaciclib.**

Toxicity Type	Toxicity Profile and Severity	Abemaciclib Dose Suspension	Abemaciclib Dose Reduction
Nonhematologic Toxicity[a] (except diarrhea, ALT/AST increased, and ILD/pneumonitis)	Persistent or recurrent[b] Grade 2 that does not resolve with maximal supportive measures within 7 days to baseline or Grade 1 unless deemed clinically insignificant by the investigator	Dose **MUST** be suspended until toxicity resolves to either baseline or ≤Grade 1.	Dose **MUST** be reduced by 1 dose level.
	Grade 3 or 4	Dose **MUST** be suspended until toxicity resolves to either baseline or ≤Grade 1.	Dose **MUST** be reduced by 1 dose level.
Diarrhea[c]	Grade 2 that does not resolve within 24 hours to ≤Grade 1	Dose **MUST** be suspended until toxicity resolves to ≤Grade 1.	Dose **MAY** be reduced by 1 dose level.
	Grade 2 that persists or recurs[b] after resuming the same dose despite maximal supportive measures	Dose **MUST** be suspended until toxicity resolves to ≤Grade 1.	Dose **MUST** be reduced by 1 dose level.

Toxicity Type	Toxicity Profile and Severity	Abemaciclib Dose Suspension	Abemaciclib Dose Reduction
	Grade 3 or 4	Dose **MUST** be suspended until toxicity resolves to ≤Grade 1.	Dose **MUST** be reduced by 1 dose level.
	Any grade that requires hospitalization	Dose **MUST** be suspended until toxicity resolves to ≤Grade 1.	Dose **MUST** be reduced by 1 dose level.
ALT/AST Increased	Persistent or recurrent[b] Grade 2 (>3.0-5.0×ULN), or Grade 3 (>5.0-20.0×ULN)[d]	Dose **MUST** be suspended until toxicity resolves to baseline or Grade 1.	Dose **MUST** be reduced by 1 dose level.
	Grade 4 (>20.0×ULN)	Abemaciclib treatment **MUST** be discontinued	Abemaciclib treatment **MUST** be discontinued
ALT/AST Increased with increased total bilirubin, in the absence of cholestasis	ALT/AST >3.0×ULN with total bilirubin >2×ULN	Abemaciclib treatment **MUST** be discontinued.	Abemaciclib treatment **MUST** be discontinued.
ILD / pneumonitis	Grade 2 that persists[b] or recurs despite maximal supportive measures and does not return to baseline or Grade 1 within 7 days	Dose **MUST** be suspended until toxicity resolves to either baseline or ≤Grade 1.	Dose **MUST** be reduced by 1 dose level.
	Grade 3 or 4 (severe ILD/pneumonitis)	Abemaciclib treatment **MUST** be discontinued.	Abemaciclib treatment **MUST** be discontinued.

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; ILD = interstitial lung disease; ULN = upper limit of normal.

[a] Additional guidance for hepatic and renal monitoring is in Section 8.2.1.1 and Section 8.2.1.2.

[b] Determination of persistent events will be at the discretion of the investigator. Recurrent toxicity refers to the same event occurring within the next 8 weeks (as measured from the stop date of the preceding event).

[c] Diarrhea is a known overlapping toxicity of abemaciclib and irinotecan. This guidance is for diarrhea attributed to abemaciclib. Irinotecan has been reported to cause acute/cholinergic diarrhea and late diarrhea (>24 hours post-infusion). Refer to the label and institutional practice for dose modifications for diarrhea attributed to irinotecan. See Section 6.5.2 for descriptions of descriptions of irinotecan-induced and abemaciclib-induced diarrhea and supportive management.

[d] Grade ≥3 ALT increased is a trigger for additional assessments and possibly hepatic monitoring. See Section 8.2.1.1 for additional guidance for hepatic monitoring.

6.6.1.2. Dose Modification Guidance due to Toxicities Considered to be Attributed to Irinotecan

For individuals receiving irinotecan who experience elevated bilirubin or impaired glucuronidation, the following guidance is suggested for all study Parts:

- Elevated bilirubin: For patients with bilirubin ranging from 1.5 to 3 times the ULN, a reduced dose of irinotecan should be considered. For patients with bilirubin beyond 3 times the ULN, irinotecan should not be used.
- Impaired glucuronidation: Patients known to have reduced UGT1A1 activity (whether preexistent substance-induced, disease-induced, due to an inherited disorder [e.g. Gilbert syndrome, Crigler-Najjar syndrome], or induced by trial therapy) may have increased risk of hematological toxicity and/or diarrhea. These participants should be carefully monitored for hematologic toxicities and diarrhea. A reduced irinotecan starting dose should be considered for patients who have experienced prior hematologic toxicity or significant diarrhea with previous treatment.
- For Grade 4 therapy-related diarrhea that develops despite maximal anti-diarrhea medications and prophylactic antibiotics, reduce irinotecan by 25% (i.e., 37.5 mg/m^2/dose) in subsequent cycles.

See Section 6.6.1.3 dose modification tables for guidance specific to Part C.

6.6.1.3. Part C-Specific Dose Modifications

- For any toxicity attributed to abemaciclib that is not listed in the tables below, refer to tables in Section 6.6.1.1 for dose modifications of abemaciclib.
- For any toxicity attributed to irinotecan that is not listed in the tables below, refer to Section 6.6.1.2 for dose modifications of irinotecan.
- All dose reductions should be calculated from the starting dose level.

Part C Dose Modifications for Hematological Toxicities *See Section 6.6.1.4 for GM-CSF dose modifications*					
Patients known to have bone marrow involvement are not evaluable for hematological toxicity, and dose modification decisions will be investigator's discretion.					
		Abemaciclib	**Irinotecan**	**Temozolomide**	**Dinutuximab**
Grade 4 Neutropenia	1st Event	Hold until ANC ≥750/mm^3, may reduce dose	No change	No change	No change
	Lasting >7 days or cycle delay >14 days	Hold until ANC ≥750/mm^3, must reduce dose	Reduce 25%	Reduce 25%	Reduce 25%
	Recurrent Grade 4	Hold until ANC ≥750/mm^3, must reduce dose	Reduce 25%	Reduce 25%	Reduce 25%
	Recurrent cycle delay >14 days despite dose reduction[a]	Discontinue all study drugs			
Febrile Neutropenia	Grade 3 1st Event	Hold until ANC ≥750/mm^3, may reduce dose	No change	No change	No change
	Recurrent Grade 3	Hold until ANC ≥750/mm^3, must reduce dose	No change	No change	No change
	Grade 4	Hold until ANC ≥750/mm^3, must reduce dose	Reduce 25%	Reduce 25%	No change
	Recurrent Grade 4	Hold until ANC ≥750/mm^3, further reduce dose	Reduce 50%	Reduce 50%	No change
Grade 4 Thrombocytopenia	1st Event	Hold until platelets ≥75,000/mm^3 may reduce dose	No change	Reduce 25%	No change
	Recurs despite dose reduction	Discontinue all study drugs			
Thrombocytopenia (Any Grade) Associated Cycle Delay >14 Days[a]	1st Event	Hold until platelets ≥75,000/mm^3 then reduce dose	Reduce 25%	Reduce 25%	No change
	Recurs despite dose reduction	Discontinue all study drugs			

Abbreviation: ANC = absolute neutrophil count.

[a] Delay of >14 days indicates more than 36 days from Day 1 of previous cycle.

Part C Dose Modifications for Diarrhea					
		Abemaciclib	**Irinotecan**	**Temozolomide**	**Dinutuximab**
Grade 2 Does not Resolve to ≤Grade 1 Within 24 hours	1st Event	Hold until ≤Grade 1, may reduce dose	Hold until ≤Grade 1, may reduce 25%	No change	No change
	Persists or recurs[a] despite maximal supportive measures	Hold until ≤Grade 1, then must reduce dose	Hold until ≤Grade 1, may reduce 25%	No change	No change
Grade 3 Diarrhea		Hold until ≤Grade 1, then reduce dose	Hold until ≤Grade 1, may reduce 25%	No change	No change
Grade 4 Diarrhea	1st Event	Hold until ≤Grade 1, then reduce dose	Hold until ≤Grade 1, reduce 25%	No change	No change
	Recurs despite abemaciclib reduction	Hold until ≤Grade 1, then reduce dose	Hold until ≤Grade 1, reduce 50%	No change	No change
	Recurs despite abemaciclib and irinotecan reduction	Hold until ≤Grade 1, then resume reduced dose	Hold until ≤Grade 1, then resume reduced dose	No change	Reduce to 13.13 mg/m^2/dose
	Recurs despite maximum dose reductions	Discontinue all study drugs			

[a] Determination of persistent events will be at the discretion of the investigator. Recurrent toxicity refers to the same event occurring within the next 8 weeks (as measured from the stop date of the preceding event).

Part C Dose Modifications for Vomiting and Dehydration					
		Abemaciclib	**Irinotecan**	**Temozolomide**	**Dinutuximab**
Vomiting Despite Maximum Supportive Care	Persistent or recurrent[a] Grade 2 that does not resolve within 7 days to baseline or Grade 1	Hold until ≤Grade 1, then reduce dose	No change	No change	No change
	Grade 3	Hold until ≤Grade 1, then reduce dose	No change	No change	No change
	Grade 4: 1st Event	Hold until ≤Grade 1, then reduce dose	Reduce 25%	Reduce 25%	No change
	Grade 4: Recurs despite supportive care and dose reductions	Discontinue all study drugs			
≥ Grade 3 Dehydration Persisting > 3 Days Not Associated with Vomiting or Diarrhea	1st Event	No change	Reduce 25%	Reduce 25%	No change
	Recurs despite dose reductions	Discontinue all study drugs			

[a] Determination of persistent events will be at the discretion of the investigator. Recurrent toxicity refers to the same event occurring within the next 8 weeks (as measured from the stop date of the preceding event).

Part C Dose Modifications for Hepatotoxicity					
		Abemaciclib	**Irinotecan**	**Temozolomide**	**Dinutuximab**
Elevated Bilirubin	1.5-3x ULN	No change	Hold until ≤Grade 1, may reduce	No change	No change
	>3x ULN	Discontinue all study drugs			
Persistent or Recurrent[a] Grade 2 AST/ALT Increase	Persistent or recurrent	Hold until ≤Grade 1, then reduce dose	No change	No change	No change
Grade 3 AST or ALT Increase[a]	≤7 days	Hold until ≤Grade 1, then reduce dose	No change	No change	No change
	Persists > 7 days	Hold until ≤Grade 1, then reduce dose	No change	No change	Reduce to 13.13 mg/m^2/dose
	Recurrent despite reductions	Hold until ≤Grade 1, then reduce dose	No change	No change	Reduce to 8.75 mg/m^2/dose
Grade 4 (>20x ULN AST or ALT) Any Duration[b]	1st Event	Discontinue all study drugs			
ALT Increase (Any Grade) Causing Cycle Delay >14 days[b,c]	1st Event	Modify per Section 6.6.1.1	No change	No change	Reduce to 13.13 mg/m^2/dose
	Recurs despite dinutuximab dose reduction	Discontinue all study drugs			

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of normal.

[a] Determination of persistent events will be at the discretion of the investigator. Recurrent toxicity refers to the same event occurring within the next 8 weeks (as measured from the stop date of the preceding event).

[b] Grade ≥3 ALT increased is a trigger for additional assessments and possibly hepatic monitoring. See Section 8.2.1.1 for additional guidance for hepatic monitoring.

[c] Delay of >14 days indicates more than 35 days from Day 1 of previous cycle.

Part C Dose Modifications for Miscellaneous Toxicity					
		Abemaciclib	**Irinotecan**	**Temozolomide**	**Dinutuximab**
ILD or Pneumonitis	Persistent or recurrent[a] Grade 2 despite maximal supportive care[b]	Hold until ≤Grade 1 then reduce dose	Hold until ≤Grade 1 then reduce dose	No change	No change
	Grade 3 or 4	Discontinue all study drugs			
Nonhematologic Toxicity not Otherwise Described Above	Grade 2 Persistent or recurrent[a, b]	Hold until ≤Grade 1 then reduce dose	No change	No change	No change
	Grade 3 or 4	Hold until ≤Grade 1 then reduce dose	Hold until ≤Grade 1 then reduce dose	Hold until ≤Grade 1 then reduce dose	No change
Any AE-Associated Cycle Delay of >21 Days[c]	1st Event	Discontinue all study drugs			

Abbreviations: AE = adverse event; ILD = interstitial lung disease.

[a] Determination of persistent events will be at the discretion of the investigator. Recurrent toxicity refers to the same event occurring within the next 8 weeks (as measured from the stop date of the preceding event).

[b] Does not resolve with maximal supportive measures within 7 days to baseline or Grade 1 unless deemed clinically insignificant by the investigator.

[c] Delay of >21 days indicates more than 42 days from Day 1 of previous cycle. Exceptional circumstances may be allowed upon approval by CRP/CRS.

6.6.1.4. Part C-Specific Dose Modification Guidance due to Toxicity Attributed to GM-CSF

White blood cell (WBC) count elevation

- If total WBC count is >50,000/uL, hold GM-CSF.
- When WBC count returns to <20,000/uL, resume GM-CSF at 50% of dose.
- In subsequent cycles, use full dose of GM-CSF, but adjust dose again if the WBC count >50,000/uL.

Localized skin reaction

- GM-CSF can be continued when skin reactions are localized and mild.
- Rotation of injection sites is recommended.
- Use of IV infusion, insuflon, or other subcutaneous injection port is not recommended.
- If ≥Grade 3 injection site reaction occurs, permanently discontinue GM-CSF.

First-dose reaction

A syndrome characterized by respiratory distress, hypoxia, flushing, hypotension, syncope, and/or tachycardia has been reported following the administration of the first dose of GM-CSF within a cycle. This generally resolves with symptomatic treatment and does not recur in the same cycle.

- If "first dose reaction" occurs, reduce the next GM-CSF dose to 50%.
- If a similar reaction occurs at the 50% dose, permanently discontinue GM-CSF.
- If the 50% does not cause recurrent symptoms, escalate subsequent doses to 100%.
    - If there are recurrent severe symptoms, then all future doses will be reduced to 50% without any further attempts to escalate.
    - If 50% is tolerated, that dose should be administered for all subsequent protocol treatment for that patient.

6.7. Intervention after the End of the Study

The end of study definition is provided in Section 4.4. Investigators will continue to follow the SoA (Section 1.3) until notified by Lilly that the end of study has occurred.

6.7.1. Treatment after Study Completion

Study completion will occur following the final analysis of primary and secondary objectives, as determined by Lilly. Investigators will continue to follow the SoA (Section 1.3) for all patients until notified by Lilly that study completion has occurred.

6.7.1.1. Continued Access

Participants who are still on study intervention at the time of study completion may continue to receive study intervention if they are experiencing clinical benefit and no undue risks. The continued access period will apply to this study only if at least 1 participant is still on study intervention when study completion occurs. Lilly will notify investigators when the continued access period begins. Lilly may allow patients to enroll in a "rollover" protocol to provide long-term continued access for patients enrolled in this study.

Participants or their legal representatives are not required to sign a new ICF/assent (as applicable) before treatment is provided during the continued access period; the initial ICF/assent (as applicable) for this study includes continued access under this protocol.

The participant's continued access to study intervention will end when a criterion for discontinuation is met (Section 7). Continued access follow-up will begin when the participant or legal representative, if applicable, and the investigator agree to discontinue study intervention and lasts approximately 30 days. Follow-up procedures will be performed as shown in the Continued Access Schedule of Activities (Section 1.3).

During the continued access period, all AEs and SAEs will be reported on the CRF. Serious adverse events will also be reported to Lilly Global Patient Safety (see Section 8.3). In the event that an SAE occurs, Lilly may request additional information (such as local laboratory results, concomitant medications, and hospitalizations) in order to evaluate the reported SAE. Investigators will perform any other standard procedures and tests needed to treat and evaluate patients; however, the choice and timing of the tests will be at the investigator's discretion. Lilly will not routinely collect the results of these assessments.

Participants who are in short-term follow-up when the continued access period begins will continue in short-term follow-up until the 30-day short-term follow-up visit is completed.

In all cases, no follow-up procedures will be performed for a participant who withdraws informed consent/assent unless he or she has explicitly provided permission and consent/assent.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1. Discontinuation of Study Intervention

If a clinically significant finding is identified after enrollment, the investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed. Any new clinically relevant finding should be reported as an AE.

Possible reasons leading to permanent discontinuation of investigational product:

- the participant or the participant's designee, for example, parents or legal guardian, requests to discontinue investigational product.
- progressive disease
- cycle delay >21 days due to study drug-related AEs, unless an exception has been granted upon consultation with the Lilly CRP/CRS for an exceptional circumstance
- the patient becomes pregnant during the study
- the patient is significantly noncompliant with study procedures and/or treatment
- enrollment in any other clinical trial involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- sponsor or investigator decision
- the patient, for any reason, requires treatment from another therapeutic agent that has been demonstrated to be effective for treatment of the study indication. Discontinuation from abemaciclib will occur prior to introduction of the new agent
- the patient experiences unacceptable toxicity

Participants discontinuing from the investigational product prematurely for any reason should complete AE and other follow-up procedures per Section 1.3 (SoA), Section 8.3 (Adverse Events and Serious Adverse Events), and Section 8.2 (Safety Assessments) of the protocol.

7.2. Participant Discontinuation/Withdrawal from the Study

Participants will be discontinued in the following circumstances:

- enrollment in any other clinical study involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- participation in the study needs to be stopped for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP)
- participant decision
    - the participant or the patient's designee, for example, parents or legal guardian requests to be withdrawn from the study

Participants discontinuing from the study prematurely for any reason should complete AE and other safety follow-up per Section 1.3 (SoA), Section 8.3 (Adverse Events and Serious Adverse Events), and Section 8.2 (Safety Assessments) of this protocol.

7.3. Lost to Follow up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. Site personnel or designee are expected to make diligent attempts to contact participants who fail to return for a scheduled visit or were otherwise unable to be followed up by the site.

8. Study Assessments and Procedures

- Unless otherwise stated in the subsections below, all samples collected for specified laboratory tests will be destroyed within 60 days of receipt of confirmed test results. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.
- Study procedures and their timing are summarized in the SoA (Section 1.3).
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA (Section 1.3), is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (e.g. blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA (Section 1.3).
- Repeat or unscheduled samples may be taken for safety reasons for technical issues with the samples.

8.1. Efficacy Assessments

Tumor assessments will be performed for each patient at the times shown in the SoA (Section 1.3).

Response Evaluation Criteria in Solid Tumors v1.1 (Eisenhauer et al. 2009) and RANO for CNS tumors (Wen et al. 2010) will be applied as the primary criteria in Parts A and B, and INRC (Park et al. 2017) in Part C for assessment of tumor response and date of tumor progression. For patients with evaluable disease only, response assessments should be made according to RECIST v1.1. for non-target disease only.

The method of tumor assessment used at baseline must be used consistently throughout the study. Local tumor imaging (investigator assessment with site radiological reading) will be used.

Computed tomography (CT) scans, including spiral CT, are the preferred methods of measurement (CT scan thickness recommended to be ≤5 mm); however, magnetic resonance imaging is also acceptable in certain situations, such as when body scans are indicated or if there is a concern about radiation exposure associated with CT, primary CNS tumors, primary bone tumors, or others. Intravenous contrast is required unless medically contraindicated or unavailable due to shortage (oral contrast is optional).

The CT portion of a PET-CT may be used for response assessment if the site can document that the CT is of identical quality to a diagnostic CT.

If images of bones are present in the above scheduled scans, bones should be assessed for gross bone abnormalities.

Refer to the SoA (Section 1.3) for additional details on imaging.

In Part C only, histologic evaluation for bone marrow involvement is required for all patients at baseline. For patients with known bone marrow involvement, marrow evaluation is also required at the end of Cycles 2, 4, and 6 and then after every fourth cycle thereafter. Bone Marrow evaluations should include cytology, histology, immunohistochemistry, immunocytology and RT-PCR as available and per institutional standards. For patients without marrow involvement, reexamination should occur following Cycle 6. Note: If PD is documented by RECIST criteria using tumor measurements, or by MIBG scan, then a repeat bone marrow evaluation is not needed to confirm PD.

In Part C only, patients will undergo a ^{123}I-MIBG scan for the presence or absence of MIBG avid lesions at the start of therapy and according to the SoA (Section 1.3.2). Those with MIBG avid lesions will be evaluable for MIBG response. For all patients with MIBG-avid lesions, including those with disease also detectable by CT/MRI, serial MIBG evaluations are required per the SoA. PET-CT may replace MIBG only for patients without MIBG avid lesions.

In Part C only, response confirmation is required based on a repeat assessment completed at least 4 weeks after initial response for patients with complete response, partial response, and minor response.

See Section 9.4.6 for definitions of the efficacy endpoints.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

Results from any clinical safety laboratory test analyzed by a central laboratory (see Section 10.2, Appendix 2) will be provided to investigative sites by Lilly or its designee.

Refer to Section 8.3 for details on the recording of AEs.

Lilly will periodically review evolving aggregate safety data within the study by appropriate methods.

- All enrolled patients will be continuously monitored for AEs. Dose escalation or the opening of new dosing/expansion cohorts can occur after prior review and discussion of safety data between the investigator and Lilly. The decision will be documented in writing.
- Safety data of patients enrolled in the expansion cohorts will be reviewed and discussed between the investigators and Lilly after every third patient has completed the DLT period.

8.2.1. Clinical Safety Laboratory Assessments

- Lilly or its designee will provide the investigator with the results of safety laboratory tests analyzed by a central vendor, if a central vendor is used for the clinical trial.

- See Section 10.2, Appendix 2 for the list of clinical laboratory tests to be performed and the SoA (Section 1.3) for the timing and frequency.
- The investigator must review the laboratory results, document this review, and report any clinically relevant changes occurring during the study as an AE. The laboratory reports must be retained with source documents unless a Source Document Agreement or comparable document cites an electronic location that accommodates the expected retention duration. Clinically significant abnormal laboratory findings are those that are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or until Visit 801 after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.
    - If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the sponsor notified.
    - All protocol-required laboratory assessments, as defined in Section 10.2, Appendix 2, must be conducted in accordance with the SoA (Section 1.3), standard collection requirements, and laboratory manual.
    - If laboratory values from non-protocol specified laboratory assessments performed at an investigator-designated local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g. SAE or AE or dose modification), then report the information as an AE.

8.2.1.1. Hepatic Safety Monitoring

In the randomized Phase 3 studies (MONARCH 2 and MONARCH 3), there was a higher incidence of increased ALT and AST, both as TEAEs and on central laboratory analysis, in the abemaciclib plus endocrine therapy arms than in the placebo plus endocrine therapy arms. These were predominantly of Grade 1 or Grade 2 severity, and a concurrent increase in blood bilirubin was infrequent. Generally, ALT and AST increases were manageable by dose adjustment or dose suspension and resolved upon discontinuation of study treatment. Several patients had isolated episodes of elevated ALT and AST that resolved without dose adjustment.

Liver testing (Section 10.4, Appendix 4), including ALT, AST, alkaline phosphatase, total bilirubin (TBL), direct bilirubin, gamma-glutamyl transferase, and creatine phosphokinase, should be repeated within 2 to 4 days to confirm the abnormality and to determine if it is increasing or decreasing, if one or more of these conditions occur:

If a participant with baseline results of…	develops the following elevations:
ALT or AST <1.5× ULN	ALT or AST ≥5× ULN or ALT or AST ≥3× ULN concurrent with TBL ≥2× ULN
ALT or AST ≥1.5×ULN	ALT or AST ≥3× baseline or ALT or AST ≥2× baseline or concurrent with TBL ≥2× ULN

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; TBL = total bilirubin; ULN = upper limit of normal.

If the abnormality persists or worsens, clinical and laboratory monitoring and evaluation for possible causes of abnormal liver tests, should be initiated by the investigator in consultation with the Lilly-designated medical monitor. At a minimum, this evaluation should include physical examination and a thorough medical history, including symptoms, recent illnesses (for example, heart failure, systemic infection, hypotension, or seizures), history of concomitant medications (including over-the-counter, herbal and dietary supplements, history of alcohol drinking and other substance abuse). In addition, the evaluation should include a blood test for prothrombin time-international normalized ratio; serological tests for viral hepatitis A, B, C, E, autoimmune hepatitis; and an abdominal imaging study (for example, ultrasound or CT scan).

Based on the patient's history and initial evaluation results, further testing should be considered, in consultation with the Lilly designated medical monitor, including tests for hepatitis D virus, cytomegalovirus, Epstein-Barr virus, acetaminophen levels, acetaminophen protein adducts, urine toxicology screen, Wilson's disease, blood alcohol levels, urinary ethyl glucuronide, and serum phosphatidylethanol. Based on the circumstances and the investigator's assessment of the participant's clinical condition, the investigator should consider referring the participant for a hepatologist or gastroenterologist consultation, magnetic resonance cholangiopancreatography, endoscopic retrograde cholangiopancreatography, cardiac echocardiogram, and/or a liver biopsy.

Additional Hepatic Safety Collection

Additional safety data should be collected via the CRF if 1 or more of the following conditions occur:

In participants with baseline ALT or AST <1.5 ULN

- Elevation of serum ALT or AST to ≥5× ULN on 2 or more consecutive blood tests
- The combination of elevated ALT or AST ≥3× ULN and elevated TBL ≥2× ULN

In participants enrolled with baseline ALT or AST ≥1.5× ULN

- Elevated ALT or AST ≥3× baseline on 2 or more consecutive tests
- The combination of elevated ALT or AST ≥2× baseline and elevated TBL ≥2× ULN

In all study participants

- discontinuation from study treatment due to a hepatic event or abnormality of liver tests

- occurrence of a hepatic event considered to be an SAE

8.2.1.2. Guidance for Monitoring Renal Function

Abemaciclib has been shown to increase serum creatinine due to inhibition of renal tubular transporters without affecting glomerular function (as measured by iohexol clearance). Increases in serum creatinine occurred within the first month of abemaciclib treatment, remained stable through the treatment period, and were reversible upon treatment discontinuation. If deterioration of renal function is suspected, serum creatinine should not be the only measurement used to assess a patient's renal function.

Dose adjustments (omission, reduction, or discontinuation) should not be solely based on interpretation of serum creatinine values because these may not reflect renal function. Other measures of renal function such as cystatin C or calculated GFR should be used as an alternative to creatinine as creatinine is not an accurate method to assess renal function in this scenario. If deterioration of renal function is suspected per the investigator's clinical assessment, dose adjustment should follow the protocol guidance for nonhematological toxicities.

8.2.1.3. Guidance for Venous Thromboembolic Events

In the randomized Phase 3 studies in breast cancer patients who received abemaciclib in combination with endocrine therapy, there was a greater number of patients who experienced venous thromboembolic events (VTEs) in the abemaciclib plus endocrine therapy arms than in the placebo plus endocrine therapy arms. The majority of the events were non-serious and were treated with low-molecular-weight heparin. Generally, these events did not result in discontinuation of the study treatment. At this time, the mechanism underlying the association between abemaciclib and the occurrence of VTEs is not known. For suspected or confirmed VTE (e.g. deep vein thrombosis or pulmonary embolism), treatment should occur according to usual clinical practice.

8.2.1.4. Guidance for Interstitial Lung Disease/Pneumonitis

Interstitial lung disease/pneumonitis has been identified as an adverse drug reaction for abemaciclib. The majority of events observed in clinical trials were Grade 1 or Grade 2 with serious cases and fatal events reported. Additional information is available in the IB.

Ask your patients to report any new or worsening pulmonary symptoms such as cough, dyspnea, fever, and investigate and treat as per your local clinical practice, including corticosteroids as appropriate. If interstitial lung disease/pneumonitis is suspected, investigations may include imaging, such as high-resolution CT scans, bronchoalveolar lavage, and biopsy as clinically indicated.

Refer to Section 6.6 for guidance on dose adjustments of abemaciclib for patients with interstitial lung disease/pneumonitis. Discontinue abemaciclib in cases of severe interstitial lung disease/pneumonitis.

8.3. Adverse Events and Serious Adverse Events

Investigators are responsible for monitoring the safety of participants who have entered this study and for alerting Lilly or its designee to any event that seems unusual, even if this event may be considered an unanticipated benefit to the participant.

The investigator is responsible for the appropriate medical care of participants during the study.

Investigators must document their review of each laboratory safety report.

Definition of AE

An AE is any untoward medical occurrence in a participant administered a pharmaceutical product and which does not necessarily have a causal relationship with the study intervention. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal (investigational) product, or investigational combination product, whether or not related to the medicinal (investigational) product or investigational combination product.

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments, for example, ECG, radiological scans, and vital signs measurements, including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator, that is, not related to progression of underlying disease.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Medication error, misuse, or abuse of IMP, including signs, symptoms, or clinical sequelae.

The investigator remains responsible for following, through an appropriate health care option, AEs that are serious or otherwise medically important, considered related to the investigational product or the study, or that caused the participant to discontinue the investigational product before completing the study. The participant should be followed until the event resolves, stabilizes with appropriate diagnostic evaluation, or is otherwise explained. The frequency of follow-up evaluations of the AE is left to the discretion of the investigator.

Lack of drug effect is not an AE in clinical studies, because the purpose of the clinical study is to establish treatment effect.

After the ICF is signed (and assent, if applicable), study site personnel will record via CRF the occurrence and nature of each participant's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study. In addition, site personnel will record any change in the condition(s) and any new clinically relevant conditions as AEs. Investigators should record their assessment of the potential relatedness of each AE to protocol procedure and investigational product, via CRF.

The investigator will interpret and document whether or not an AE has a reasonable possibility of being related to study treatment, study device, or a study procedure, taking into account the disease, concomitant treatment, or pathologies.

A "reasonable possibility" means that there is a cause and effect relationship between the investigational product, study device and/or study procedure and the AE.

The investigator answers yes/no when making this assessment.

Planned surgeries and nonsurgical interventions should not be reported as AEs unless the underlying medical condition has worsened during the course of the study.

If a participant's investigational product is discontinued as a result of an AE, study site personnel must report this to Lilly or its designee via CRF, clarifying if possible the circumstances leading to any dosage modifications, or discontinuations of treatment.

Serious Adverse Events

An SAE is any AE from this study that results in one of the following outcomes:

- death
- initial or prolonged inpatient hospitalization
- a life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

All AEs occurring after signing the ICF are recorded in the CRF and assessed for serious criteria. The SAE reporting to the sponsor begins after the participant has signed the ICF and has received investigational product. However, if an SAE occurs after signing the ICF, but prior to receiving investigational product, the SAE should be reported to the sponsor as per SAE reporting requirements and timelines (see Section 8.3.1) if it is considered reasonably possibly related to study procedure.

Study site personnel must alert Lilly or its designee of any SAE within 24 hours of investigator awareness of the event via a sponsor-approved method. If alerts are issued via telephone, they are to be immediately followed with official notification on study-specific SAE forms. This 24-hour notification requirement refers to the initial SAE information and all follow-up SAE information. Participants with a serious hepatic AE should have additional data collected using the CRF.

Pregnancy (during maternal or paternal exposure to investigational product) does not meet the definition of an AE. However, to fulfill regulatory requirements any pregnancy should be reported following the SAE process to collect data on the outcome for both mother and fetus.

Investigators are not obligated to actively seek AEs or SAEs in subjects once they have discontinued and/or completed the study (the participant disposition CRF has been completed). However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably possibly related to the study treatment or study participation, the investigator must promptly notify Lilly.

Serious adverse events, including death, caused by disease progression should not be reported unless the investigator deems them to be possibly related to study treatment.

Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the IB and that the investigator identifies as related to investigational product or procedure. United States 21 CFR 312.32 and European Union Clinical Trial Directive 2001/20/EC and the associated detailed guidances or national regulatory requirements in participating countries require the reporting of SUSARs. Lilly has procedures that will be followed for the identification, recording, and expedited reporting of SUSARs that are consistent with global regulations and the associated detailed guidances.

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

Although all AEs after signing the ICF are recorded by the site in the CRF, SAE reporting to Lilly begins after the patient has signed the ICF and has received study drug. However, if an SAE occurs after signing the ICF, but prior to receiving abemaciclib, it needs to be reported ONLY if it is considered reasonably possibly related to study procedures.

Medical occurrences that begin before the start of study intervention but after obtaining informed consent/assent will be recorded on the AE CRF.

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available. Serious adverse events, including death, caused by disease progression should not be reported unless the investigator deems them to be possibly related to study treatment.

Investigators are not obligated to actively seek AE or SAE after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant and/or legal guardian is the preferred method to inquire about AE occurrences.

8.3.2. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

8.3.3. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will evaluate the reported SAEs, including confirmation of relatedness and assessment of expectedness. The sponsor has processes for safety reports for identification, recording, and expedited reporting of SUSARs according to local regulatory requirements. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.
-
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g. summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.4. Pregnancy

- Details of all pregnancies and exposure during breastfeeding, from the time of treatment through 120 days following cessation of study treatment, or 30 days following cessation of study treatment if the participant initiates new anticancer therapy.
- If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Section 10.3, Appendix 3.
- Abnormal pregnancy outcomes (e.g. spontaneous abortion, fetal death, stillbirth, congenital anomalies, and ectopic pregnancy) are considered SAEs.
- Additional requirements for pregnancy testing during and after study intervention are located in Section 10.3, Appendix 3.
- The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a female with an early undetected pregnancy.

8.3.5. Cardiovascular and Death Events

Not applicable.

8.3.6. Complaint Handling

Lilly collects product complaints on investigational products and drug delivery systems used in clinical studies in order to ensure the safety of study participants, monitor quality, and facilitate process and product improvements.

Participants will be instructed to contact the investigator as soon as possible if he or she has a complaint or problem with the investigational product so that the situation can be assessed.

8.4. Treatment of Overdose

Refer to the IB and/or Product Label for abemaciclib for available information on the signs, symptoms, and treatment of overdose.

For dinutuximab, GM-CSF, irinotecan, and temozolomide, refer to the respective Product Label for available information on the signs, symptoms, and treatment of overdose.

8.5. Pharmacokinetics

At the visits and times specified in the SoA (Section 1.3), PK samples will be collected to determine the concentrations of:

- abemaciclib and its metabolites M2 and M20
- irinotecan and its metabolite SN-38
- temozolomide

The PK of dinutuximab and GM-CSF will not be assessed.

To ensure comprehensive PK sampling in a pediatric population, Parts A and B are designed to evaluate at least CCI including at least CCI and at least 2 CCI If no patients CCI and evaluable in the above groups, then CCI will be evaluated. The number of patients 18 years of age will be capped at [redacted] until patient numbers in the above age groups are enrolled.

Additionally, in Part C, at least CCI should be in the age group CCI of age, with at least CCI and at least CCI [redacted]

Abemaciclib dosing dates and times are required to be collected 3 days prior to the PK samples. The date and exact time of collection of each PK sample must be recorded on the laboratory requisition. Beyond the first dose, PK samples may be aligned to coincide with standard laboratories when applicable, with the collection dates/times specified in the SoA (Section 1.3.3) to be used as a guide.

For patients receiving chemotherapy infusions, the PK samples should be drawn from a separate line at a peripheral access site.

A maximum of 5 samples may be collected at additional time points during the study if warranted and agreed upon between both the investigator and sponsor. Instructions for the collection and handling of blood samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sampling will be recorded.

The PK sampling schedule is designed to comply with blood volume limitations in pediatric patients. If the collection of PK samples will exceed maximum blood draw volumes for any patient, blood samples for safety will be prioritized over PK after discussion between the sponsor and the investigator.

Bioanalytical samples collected to measure investigational product concentration will be retained for a maximum of 1 year following last participant visit for the study. During this time, samples remaining after the bioanalyses may be used for exploratory analyses (such as quantification of circulating metabolites and/or protein binding work).

8.5.1. Patient Diary

A diary will be provided to patients/caregivers in order to help track date and time of each dose during cycles in which PK samples are collected. Patient diary evaluations will occur through Cycle 3 Day 1. The diary is not intended for compliance monitoring. Refer to Section 1.3 for additional information.

8.6. Pharmacodynamics

Pharmacodynamics will not be evaluated in this study.

8.7. Genetics

8.7.1. Whole Blood and/or Saliva Samples for Pharmacogenetic Research

Whole blood and/or saliva samples will not be collected for Parts A and B. Only whole blood will be collected for Part C in this study. Genetic research will not be performed.

8.8. Biomarkers

If available, participants' somatic alterations may be obtained at baseline as part of their medical oncology history (see Section 1.3). This study may analyze somatic alterations relevant to study intervention, mechanism of action, the variable response to study drug(s), cell cycle, and pathways associated with cancer.

See Section 9.4.10 for biomarker analyses.

8.8.1. Biomarkers for Part C

This study will analyze biomarkers relevant to study intervention, mechanism of action, the variable response to study drug(s) (including evaluation of AEs or differences in efficacy), cell cycle, immune function, or pathways associated with neuroblastoma. Samples collected will enable examination of these questions through the measurement of biomolecules, including DNA, RNA, proteins, lipids, and other circulating or cellular elements. Derivatives of samples, for example, tumor images, can also be used to identify biomarkers of participant response or resistance. Except for the cases detailed in Section 8.8.1.1 (tumor DNA sequencing without patient-matched germline subtraction) and Section 8.8.1.2 ([circulating tumor DNA] ctDNA sequencing without patient-matched germline subtraction), biomarker analyses will not produce interpretable results on germline DNA and therefore will not lead to the identification of genetic findings. Biomarker analyses using RNA as substrate will avoid the identification of genetic

variants and will focus on quantifying gene expression and reporting tumor somatic gene fusions and other tumor somatic rearrangements. Biomarker analysis results may occur after the clinical study report (CSR) is written and therefore a separate biomarker Data Analysis Plan will be developed.

Samples for biomarker research will be collected as specified in the Schedule of Activities (Section 1.3), where local regulations allow. It is possible that biomarker data for participants in the study have already been generated from samples that were collected and analyzed prior to enrolling in this trial. This may include data generated from genetic analyses. If available, these data may be requested from medical records for use in the research described in Sections 8.8.1.1 and 8.8.1.2, for instance to understand the role of various co-occurring alterations

Samples may be used to develop related research methods or to validate diagnostic tools or assays, but only within the specific research scope described in this protocol. The samples may be analyzed as part of a multi-study assessment of non-genetic factors involved in the response to study intervention or study interventions of this class, and/or to understand study disease or related conditions, within the scope described in this protocol.

All samples will be coded with the participant number. These samples and any data generated can be linked back to the participant only by the study site personnel. Samples will be retained for a maximum of CCI after the last participant visit for the study, or for a shorter period if local regulations and/or ERBs/IRBs impose shorter time limits, at a facility selected by the Sponsor or its designee. This retention period enables use of new technologies, response to questions from regulatory agencies, and investigation of variable response that may not be observed until later in the development of study treatment or after study treatment becomes commercially available. Technologies are expected to improve during the CCI storage period, and therefore, cannot be specifically named. Regardless of the technology utilized, data generated will be used only for the specific biomarker research scope described in this section, and within the limits of this protocol.

8.8.1.1. Tissue Samples for Biomarker Research

Tissue samples for biomarker research will be collected for the purposes described in Section 8.8.1. The following samples for biomarker research will be collected according to the sampling schedule in the Schedule of Activities (Section 1.3), where local regulations allow.

Submission of tumor sample, archival or fresh, obtained prior to initiation of study treatment, will be collected, when available. The most recent sample is desired. Relapse or metastatic sample where available is preferred. The tumor samples will preferably be in the form of a CCI. If this is not possible, approximately CCI slides of freshly prepared unstained 5-micron sections may be provided. Due diligence should be used to make sure that tumor sample, not a normal adjacent or a tumor margin sample, is provided. Samples can be sent at any time during study if not submitted at screening.

Pathology report accompanying tumor tissue will be requested. Pathology reports must be coded with the participant number. Personal identifiers, including the participant's name and initials, must be removed from the institutional pathology report prior to submission. Archival blocks will be sectioned. Sponsor has a right to retain a portion of the submitted tissue, and archival

blocks may be returned to the study site, upon request. Tissue blocks from biopsies collected at baseline or disease progression may be returned to sites if there is available tissue left over, upon request.

Tumor DNA analysis (whole exome or panel DNA sequencing) may be performed with patient-matched germline DNA subtraction. Germline DNA for each patient will originate from DNA extracted from whole blood as described in Section 8.8.1.3. Review of germline DNA sequencing results may be conducted, but only for data quality control purposes. At no point in this process will germline DNA variants be analyzed and interpreted by the research personnel. As such, tumor DNA analysis with germline DNA subtraction will not produce interpretable results on germline DNA, is not considered genetic research, and therefore, will not lead to the identification of genetic incidental findings. Genetic incidental findings are variations present in germline DNA that are discovered unintentionally.

Tumor DNA analysis (whole exome or panel DNA sequencing) may be performed without germline DNA subtraction. When analyzed this way, it may be considered genetic research and the identification of genetic incidental findings is possible. However, the methods used in this study for biomarker analyses are not clinically validated to detect germline variants, and therefore, no clinical conclusions can be derived from them. As such, no genetic findings will be reported to the patients participating in biomarker research, subject to local regulations.

Tumor RNA sequencing analyses quantitate tissue mRNA expression levels, report gene fusions, splice variants, and other somatic rearrangements and do not detect germline variants. Therefore, these analyses are not considered genetic research, and no genetic findings will be identified.

8.8.1.2. Plasma Samples for Biomarker Research

Plasma samples for biomarker research will be collected from participants as specified in the Schedule of Activities (Section 1.3), where local regulations allow.

Plasma samples may also be used for ctDNA analyses. ctDNA analysis may be performed with patient-matched germline DNA subtraction. Germline DNA for each patient will originate from DNA extracted from whole blood as described in Section 8.8.1.3. Review of germline DNA sequencing results may be conducted, but only for data quality control purposes. At no point in this process will germline DNA variants be analyzed and interpreted by the research personnel. As such, ctDNA analysis with germline DNA subtraction will not produce interpretable results on germline DNA, is not considered genetic research, and therefore, will not lead to the identification of genetic incidental findings.

ctDNA analysis may be performed without germline DNA subtraction. In this case, it may be considered genetic research, and the identification of genetic incidental findings is possible. Regardless of whether participant-matched germline DNA subtraction is used or not during the ctDNA analysis, the methods used in this study for biomarker analyses are not clinically validated to detect germline variants, and therefore, no clinical conclusions can be derived from them. As such, no genetics findings will be reported to the patients participating in biomarker research, subject to local regulations.

8.8.1.3. Whole Blood Samples for Biomarker Research

A whole-blood sample for biomarker research will be collected from all participants as specified in the Schedule of Activities (Section 1.3), where local regulations allow. This sample may be used for the extraction of DNA that allows patient-matched germline DNA subtraction during tumor DNA analysis from tissue (Section 8.8.1.1) and ctDNA (Section 8.8.1.2).

8.9. Medical Resource Utilization and Health Economics

Health economics and medical resource utilization parameters will not be evaluated in this study.

8.10. Product Acceptability and Palatability Assessments

The patient and/or caregiver will be asked to provide responses to questions designed to assess the acceptability and palatability of the tablet swallowed whole, dispersed in food or liquid, or dispersed and administered through a nasogastric or gastrostomy tube (Kozarewicz 2014). If the patient is using abemaciclib oral granules, the patient and/or caregiver will be asked to provide responses to questions designed to assess the acceptability and palatability of the oral granules swallowed whole, placed in food or liquid, or dispersed and administered through a nasogastric or gastrostomy tube. The questionnaire for tablet or oral granule acceptability will assess the subject's ability to swallow the drug product as designed. The questionnaire for acceptability and palatability of the tablet or oral granules dispersed in food or liquid will assess the subject's experience relating to the taste, appearance, smell, mouthfeel, and aftertaste of the dispersion and ease of preparing and taking the dispersion. The questionnaire for acceptability of the tablet or oral granules dispersed and administered through a nasogastric or gastrostomy tube will assess the ease of preparation and administration of the dispersion. The appropriate questionnaire will be administered at the time of dosing or within approximately 30 minutes after dosing at Cycle 1 Day 1, Cycle 1 Day 15, and Cycle 2 Day 1. If a patient changes the method of abemaciclib administration or formulation (tablets to granules or vice versa) at any point during the trial, the appropriate questionnaire corresponding to the new administration method or formulation should be completed at the next clinic visit following the method change. The questionnaire will be completed by caregivers (proxy) for patients aged ≤5 years. For patients ≥6 years old to <12 years old, both patient and caregiver will complete the questionnaires. For patients ≥12 years old, the questionnaire will be self-completed.

9. Statistical Considerations

9.1. Statistical Hypotheses

Parts A and B

Parts A and B of Study JPCS is designed to evaluate

- the PK, safety, and tolerability of abemaciclib in combination with irinotecan and temozolomide (Part A) and abemaciclib in combination with temozolomide (Part B) in pediatric patients with relapsed/refractory solid tumors that have progressed on standard treatment,
- the RP2D, and
- preliminary efficacy.

Lilly hypothesizes that abemaciclib in combination with temozolomide and irinotecan (Part A), abemaciclib in combination with temozolomide (Part B) will be sufficiently tolerable with evidence of clinical activity to support further development.

Part C

Lilly hypothesizes that abemaciclib in combination with dinutuximab, GM-CSF, irinotecan, and temozolomide (Part C) will be sufficiently tolerable and have sufficient anti-tumor activity. The drug combination will be assessed by evaluating the PK, safety, and tolerability of the drug combination in pediatric and young adult patients with relapsed/refractory neuroblastoma.

At the same time, the anti-tumor activity is assessed using Simon's optimal two-stage design (Simon 1989), where the null hypothesis is that the objective response rate (ORR) [redacted] CCI and the alternative hypothesis is that the ORR CCI

9.2. Sample Size Determination

Approximately 30 to 117 patients will be enrolled in this Phase1b/2 study, with 24 to 60 in Parts A and B and 6 to 57 in Part C. The sample size for Parts A and B is primarily determined by DLTs (up to 6 evaluable patients at a dose level before establishing the MTD), while the sample size for Part C depends on both DLTs and responses. The maximum sample size of 57 in Part C is determined by considering dose finding and ensuring that CCI patients are treated on the RP2D. The sample size of CCI is determined using Simon's optimal two-stage design with a power of 80% and a one-sided type I error rate of 0.025, given a null ORR of CCI against an alternative ORR of CCI assumed at the RP2D.

9.3. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Entered	All participants who sign informed consent/assent (if applicable)
Treated Patients (safety population)	Patients who have been assigned to study treatment and have received at least 1 dose of any study treatment.
Screen Failures	Patients or legal guardian (if applicable) who have signed informed

	consent/assent, do not meet eligibility criteria or due to AEs, physician's decision, etc. and are not enrolled.

Patients who withdraw from the study before receiving study drug(s) will be replaced and will not be included in the safety or efficacy assessments. Safety analyses will be conducted on all patients who have been exposed to study drug, regardless of whether they are deemed evaluable for other assessments. In Parts A, B, and Stage 1 of Part C, any patient who is discontinued from the study before completing 1 cycle will be deemed DLT non-evaluable for assessment of the combination unless the patient experiences a DLT prior to withdrawal. If a patient is noncompliant during Cycle 1 or receives <75% of doses due to reasons other than drug-related toxicity, he or she will be considered DLT non-evaluable for assessment of the combination and may be replaced. DLT non-evaluable patients may be replaced to ensure that enough patients complete 1 cycle unless accrual to that cohort has stopped due to a DLT.

9.4. Statistical Analyses

9.4.1. General Statistical Considerations

Statistical analysis of this study will be the responsibility of Lilly or its designee. The analyses for this study will be descriptive, except for possible exploratory analysis as deemed appropriate. Data analyses will be provided by study part, dose group, and for all study patients combined wherever appropriate. For continuous variables, summary statistics will include number of patients, mean, median, standard deviation, minimum, and maximum. Categorical variables will be summarized using number of patients, frequency, and percentages. Missing data will not be imputed, except for missing date of birth for analysis purpose. If birth year and month is available and date is not available or missing, date will be imputed to the 15th of that month. Refer to the statistical analysis plan for this study for further detail.

The interpretation of the study results will be the responsibility of the investigator with the Lilly CRP/CRS, pharmacokineticist, and statistician. The Lilly CRP/CRS and statistician will also be responsible for the appropriate conduct of an internal review for both the final study report and any study-related material to be authorized by Lilly for publication.

Any change to the data analysis methods described in the protocol will require an amendment ONLY if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the CSR. Additional exploratory analyses of the data will be conducted as deemed appropriate.

9.4.2. Analysis Population

All entered patients will be used in summarizing patient disposition. All treated patients (safety population) will be used in analyzing patient characteristics and safety and efficacy data.

9.4.3. Participant Disposition

A detailed description of participant disposition will be provided. It will include a summary of the number and percentage of patients entering the study, treated, reasons for discontinuation from study treatment, and reasons for discontinuation from study. Reasons of discontinuation from study treatment and study will be listed.

All clinically relevant protocol deviations will be listed by pre-determined categories (e.g. inclusion/exclusion criteria, non-compliance with protocol procedures, drug dosage/intervention, use of excluded treatments, informed consent/assent process, continuing after meeting withdrawal criteria, or other).

9.4.4. Patient Characteristics

Patient characteristics will include a summary of the following:

- Patient demographics
- Baseline disease characteristics
- Prior disease-related therapies
- Concomitant medications

Other patient characteristics will be summarized as deemed appropriate.

9.4.5. Safety Analyses

All patients who have received at least 1 dose of any study treatment will be evaluated for safety and toxicity.

Safety analyses will include summaries of the following:

- Adverse events, including severity and possible relationship to study drug
- Dose adjustments
- Vital signs
- Dose-limiting toxicities
- Laboratory values

9.4.6. Efficacy Analyses

The study was not designed to make an efficacy assessment in Parts A and B, CCI [redacted] The following efficacy measures will be listed and summarized where appropriate.

9.4.6.1. Parts A and B Efficacy Analyses

Parts A and B will not have a formal efficacy assessment. The following efficacy measures are important secondary endpoints measured using RECIST v1.1 or RANO criteria.

Objective Response Rate (ORR): The ORR is the percentage of patients with a best response of complete response [CR] or partial response [PR]

Duration of Response (DoR): The DoR is defined only for responders (patients with a CR or PR). It is measured from the date of first evidence of a CR or PR to the date of objective progression or the date of death due to any cause, whichever is earlier.

Disease Control Rate (DCR): The DCR is the percentage of patients with a best response of CR, PR, or stable disease (SD).

Clinical Benefit Rate (CBR): The CBR is the percentage of patients with a best response of CR or PR, or SD for at least 6 months.

Progression-free survival (PFS): Progression-free survival is measured as the time from first dose of any study drug to progressive disease or death, whichever occurs first. The PFS rate will be calculated at appropriate time intervals (e.g. at 3 and 6 months).

9.4.6.2. Part C Efficacy Analyses

In Part C, the primary efficacy measure is investigator-assessed tumor response as defined by INRC. The primary endpoint ORR will be based on the 2017 INRC (Park et al. 2017) as described in Section 9.4.6.2.1. The primary analysis of ORR will occur 6 cycles after last patient has entered treatment, in order to ensure adequate response and durability of response data is available at the time of analysis. The point estimate of ORR with a two-side exact 95% confidence interval will be provided, and one-sided exact p-value will be reported.

9.4.6.2.1. 2017 INRC

For Part C, efficacy will be evaluated using the 2017 INRC (Park et al. 2017).

A responder is defined as any patient who exhibits a CR, PR, or MR.

The response criteria integrate the response of all lesions using CT/MRI and/or MIBG/FDG-PET lesions, and assessment of bone marrow disease.

Primary tumor (soft tissue) response is as follows:

- Complete Response (CR):
  - <10 mm residual soft tissue at primary site AND
  - complete resolution of MIBG-avid tumors or FDG-PET uptake (for MIBG-nonavid tumors) at primary site
- Partial Response (PR):
  - ≥30% decrease in longest diameter of primary site AND
  - MIBG-avid tumors or FDG-PET uptake (for MIBG-nonavid tumors) at primary site is stable, improved, or resolved
- Stable Disease (SD): Neither PR nor PD at the primary site
- Progressive Disease (PD):
  - >20% increase in longest diameter taking as reference the smallest sum while on study, including baseline sum if that is the smallest, AND
  - minimum absolute increase of 5mm in longest dimension
  - Note: a lesion that does not meet PD measurement criteria but has fluctuating MIBG avidity will not be considered PD

Soft tissue and bone metastatic disease tumor response is as follows:

- Complete Response (CR): Complete resolution of all disease sites defined as:
  - nonprimary target and nontarget lesions <10 mm AND
  - lymph nodes identified as target lesions decrease to a short axis <10 mm AND
  - MIBG-avid update or FDG-PET uptake (for MIBG-nonavid tumors) of nonprimary lesions resolves completely
- Partial Response (PR): ≥30% decrease in sum of diameters[a] of nonprimary target lesions compared with baseline AND all of the following:

- Nontarget lesions may be stable or smaller in size 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[b, c] AND
- No new lesions

- Progressive Disease (PD): Any of the following:
  - Any new soft tissue lesion detected by CT/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 neuroblastoma or ganglioneuroblastoma
  - Any new bone site that is MIBG-avid
  - A new bone site that is FDG-PET avid (for MIBG-nonavid tumors) AND has CT/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 minimum absolute increase of 5 mm in sum of diameters of target soft tissue lesions
  - Relative MIBG score ≥ 1.2[c]
- Stable disease (SD): Neither PR nor PD of nonprimary lesions

[a] 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 nondiscrete lymph nodes will be measured using longest diameter.

[b] 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.

[c] MIBG scoring of bone lesions will consist of 9 sectors (cranio-facial, cervical and thoracic spine, ribs/sternum/clavicles/scapula, lumbar and sacral spine, pelvis, upper arms, lower arms and hands, femurs, and lower legs and feet). Each sector will be scored from 0-3 (0=no sites; 1=1 site; 2= more than 1 site; 3=massive involvement [>50% of segment]) using the Curie scoring method (maximum absolute score of 27). The score of each sector will be collected in the CRF. Relative MIBG score is the absolute score for bone lesions at time of response assessment divided by the absolute score for bone lesions at baseline before therapeutic interventions. The same scoring method (eg, Curie) must be used at all assessment time points. MIBG single-photon emission computed tomography (SPECT) or MIBG-SPECT/CT may be used for scoring purposes, but the same imaging methodology should be used for all evaluations.

Bone marrow response is determined by cytology (recommended to be accompanied by immunocytology)/histology (accompanied by immunohistochemistry [Burchill et al. 2017]). Use the bone marrow sample with the highest percentage of tumor infiltration to assess response. Grading is as follows:

- Complete Marrow Response: No tumor infiltration on reassessment, independent of baseline tumor involvement
- Progressive Marrow Disease: either
  - bone marrow without tumor infiltration that becomes > 5% tumor infiltration on reassessment, or

  - bone marrow with tumor infiltration that increases by >2 times and has >20% tumor infiltration on reassessment
- Minimal Disease (MD): any of the following:
  - ≤5% tumor infiltration at baseline and remains > 0 to ≤5% tumor infiltration on reassessment, or
  - no tumor infiltration at baseline and ≤5% tumor infiltration on reassessment, or
  - >20% tumor infiltration at baseline and >0 to ≤5% tumor infiltration on reassessment
- Stable Marrow Disease: Persistence of >5% tumor infiltration on reassessment that does not meet the criteria for CR, MD, or PD.

Overall response is as follows:

- Complete Response (CR): All components meet criteria for CR
- Partial Response (PR):
  - PR in ≥1 component AND
  - ALL other components are either CR, MD (bone marrow only), PR (soft tissue or bone), or NI (site not involved at study entry remain uninvolved) AND
  - No component with PD
- Minor Response (MR):
  - PR or CR in ≥1 component AND
  - SD in ≥1 component AND
  - No component with PD
- Stable disease (SD):
  - SD in ≥1 component AND
  - No better than SD or NI (site not involved at study entry and remains uninvolved) AND
  - No component with PD
- Progressive Disease (PD): Any component with PD

The overall response based on the combined evaluations is summarized in the table below. The best response observed at any time point for each individual patient will be considered that patient's best overall response on this study.

Primary tumor	Soft tissue or bone metastatic disease	Bone marrow metastatic disease	Overall response
CR	CR	CR	**CR**
CR for one category and CR or NI for remaining categories			**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**

Primary tumor	Soft tissue or bone metastatic disease	Bone marrow metastatic disease	Overall response
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
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

Primary tumor	Soft tissue or bone metastatic disease	Bone marrow metastatic disease	Overall response
SD	NI	SD	**SD**
NI	SD	SD	**SD**
NI	SD	NI	**SD**
NI	NI	SD	**SD**
PD in any single category			**PD**
Response that is not evaluable for any single category that had measurable or evaluable tumor at baseline and no PD for any category			**Not evaluable**
Response evaluation not done for one or more category			**Not done**

Abbreviations: CR = complete response; MD = minimal disease; MR = minor response; NI = not involved (site not involved at baseline and remains not involved); PD = progressive disease; PR = partial response; SD = stable disease.

9.4.7. Pharmacokinetic/Pharmacodynamic Analyses

All patients who have received at least 1 dose of study treatment and at least 1 post baseline evaluable PK sample will be included in the PK analysis population.

Abemaciclib, irinotecan, and temozolomide concentrations will be summarized by analyte using descriptive statistics. Additional analyses utilizing the population PK approach may also be conducted if deemed appropriate. Relationships between exposure and measures of efficacy and safety may be explored.

9.4.8. Subgroup Analyses

Subgroup analyses for PK, efficacy, and safety will be performed by method of administration (whole administration and alternative administration) of study drug when applicable.

9.4.9. Product Acceptability and Palatability

Responses from the drug product acceptability and palatability questionnaires for tablet and oral granules swallowed whole, dispersed in food or liquid, or dispersed and administered through a nasogastric or gastrostomy tube will be summarized categorically (frequency and percentage) by age group, for each visit separately and in aggregate. In addition, general trends in acceptability and palatability from Cycle 1 Day 1 (baseline), Cycle 1 Day 15, and Cycle 2 Day 1 will be analyzed.

9.4.10. Biomarker Analyses

Somatic alterations related to treatment, treatment mechanism, and/or cancer may be collected and reported. In addition, the relationship between somatic alterations and clinical outcome may be assessed.

9.5. Interim Analyses

Data will be reviewed on a cohort-by-cohort basis during the study, until the MTDs (not to exceed 115 mg/m^2 BID) are determined for Parts A and B or CCI [redacted] The purpose of these reviews is to evaluate the safety data at each dose level and determine if a DLT has been

observed that would suggest the MTD for each cohort has been met or exceeded in the dose finding portion. The investigators and Lilly study team will make the determination regarding dose escalation based upon the review of the safety and tolerability data as described in this protocol.

During the dose-expansion portion of each study part, interim analyses may be conducted to review available safety, PK, and efficacy data.

CCI [redacted] DMC will conduct the first interim analysis approximately 2 months (or earlier if deemed appropriate) after Stage 1's last patient begins Cycle 1. If any of the following stopping rules are met or a significant safety signal is identified, the DMC may recommend termination of enrollment, and/or termination of study treatment.

- Rule A: stop for toxicity if [redacted] CCI of the DLT-evaluable patients experience DLT.
- Rule B: stop for intolerability if CCI patients discontinue due to a treatment-related AE before completing [redacted] cycles.
- Rule C: stop for insufficient evidence of anti-tumor activity if [redacted] of the CCI patients are responders (i.e., have objective tumor response, including a best overall response of complete response [CR], partial response [PR] or minor response [MR] per INRC).

If 55 mg/m^2 is declared the MTD, but either Rule A or B is triggered during cohort expansion, the DMC may recommend that subsequent patients be treated at 30 mg/m^2. See Section 4.1.2.

The DMC will meet and review the overall safety and efficacy data approximately every 6 months thereafter while patients remain in the study. At the recommendation of the DMC, the frequency of safety interim analyses may be modified. See Section 10.1.4 for further details.

Other interim analysis may be added as deemed appropriate by the sponsor.

10. Supporting Documentation and Operational Considerations

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. 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 Council for International Organizations of Medical Sciences International Ethical Guidelines
  - Applicable International Council for Harmonisation (ICH) GCP Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g. advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC 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/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of study conduct for participants under their responsibility and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations
  - Reporting to the sponsor or designee significant issues related to participant safety, participant rights, or data integrity.

After reading the protocol, each principal investigator will sign the protocol signature page and send a copy of the signed page to a Lilly representative.

The CSR coordinating investigator will sign the final CSR for this study, indicating agreement that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

10.1.2. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative (defined as the participant's parent, guardian, or legal representative) will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that legally authorized representative (parent/guardian) consent and child/adolescent assent (if deemed appropriate by local ethics review) was obtained before the participant was enrolled in the study and the date the written consent was obtained. The medical record should also describe how the clinical investigator determined that the person signing the ICF was the participant's legally authorized representative (parent/guardian). The authorized person obtaining the informed consent must also sign the ICF.
- Participants and, when applicable, their legally authorized representative (parent/guardian) must be re-consented to the most current version of the ICF(s) during their participation in the study.
- Minor participants must be re-consented if they reach the age of majority during the course of the study, in order to continue participating.
- A copy of the ICF(s) must be provided to the participant, the participant's legally authorized representative, or the participant's parent/guardian when applicable.

Participants who are rescreened and/or their legally authorized representative are required to sign a new ICF and assent, if applicable.

10.1.3. Data Protection

- Participants will be assigned a unique identifier by the sponsor to protect the participant's personal data. Any participant information, such as records, datasets or tissue samples that are transferred to the sponsor will contain the identifier only. Participant names or any information which would make the participant identifiable will not be transferred.
- The participant 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 who will be required to give consent for their data to be used as described in the informed consent. This is done by the site personnel through the informed consent process.
- The participant must be informed through the informed consent by the site personnel that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

- The sponsor has processes in place to ensure information security, data integrity, and data protection. These processes address management of data transfer, and prevention and management of unauthorized access, disclosure, dissemination, alteration or loss of information or personal data. These processes include appropriate contingency plan(s) for appropriate and timely response in the event of a data security breach.
- The transfer of personal data is subject to appropriate safeguards through contractual agreements and processes. The sponsor's processes are compliant with local privacy laws and relevant legislations including the General Data Protection Regulation (GDPR).

10.1.4. Committee Structure

In Part C, after the safety lead-in, interim analyses for safety and efficacy will be conducted under the guidance of an independent DMC. The DMC will consist of at least 3 members, including a chair, a physician, and a statistician. The DMC will communicate any recommendations based on interim analysis to the Sponsor. Further details on the members, activities, and responsibilities of the DMC can be found in the DMC charter.

10.1.5. Dissemination of Clinical Study Data

Reports

On completion of the research, a report or summary shall be submitted to regulatory bodies according to local law. The sponsor will disclose a summary of study information, including tabular study results, on publicly available websites where required by local law or regulation.

Data

The sponsor provides access to all individual participant data collected during the trial, after anonymization, except for pharmacokinetic and genetic data.

Data are available to request 6 months after the indication studied has been approved in the US and EU and after primary publication acceptance, whichever is later. No expiration date of data requests is currently set once data are made available.

Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data-sharing agreement.

Data and documents, including the study protocol, statistical analysis plan, clinical study report, and blank or annotated case report forms, will be provided in a secure data-sharing environment for up to 2 years per proposal.

For details on submitting a request, see the instructions provided at www.vivli.org.

10.1.6. Data Quality Assurance

To ensure accurate, complete, and reliable data, Lilly or its representative will do the following:

- provide instructional material to the study sites, as appropriate

- provide sponsor start-up training to instruct the investigators and study coordinators. This training will give instruction on the protocol, the completion of the CRFs, and study procedures.
- make periodic visits to the study site
- be available for consultation and stay in contact with the study site personnel by mail, telephone, and/or fax
- review and verify data reported to detect potential errors.

In addition, Lilly or its representative will periodically check a sample of the participant data recorded against source documents at the study site. The study may be audited by Lilly or its representative and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

The investigator will keep records of all original source data. This might include laboratory tests, medical records, and clinical notes. If requested, the investigator will provide Lilly, applicable regulatory agencies, and applicable ethical review boards (ERBs) with direct access to original source documents.

Data Capture System

The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor.

An electronic data capture (EDC) system will be used in this study for the collection of CRF data. The investigator maintains a separate source for the data entered by the investigator or designee into the sponsor-provided EDC system. The investigator is responsible for the identification of any data to be considered source and for the confirmation that data reported are accurate and complete by signing the CRF.

Additionally, clinical outcome assessment (COA) data (e.g. scales, self-reported diary data, rating scales, taste and palatability questionnaire) will be collected by the participant/authorized study personnel, via a paper source document and will be transcribed by the authorized study personnel site into the EDC system/via direct data captured in the EDC system and will serve as the source documentation.

Data collected via the sponsor-provided data capture system(s) will be stored at third-party organizations. The investigator will have continuous access to the data during the study and until decommissioning of the data capture system(s). Prior to decommissioning, the investigator will receive an archival copy of pertinent data for retention.

Data managed by a central vendor, such as laboratory test data, will be stored electronically in the central vendor's database system and results will be provided to the investigator for review and retention. Data will subsequently be transferred from the central vendor to the Lilly data warehouse.

Data from complaint forms submitted to Lilly will be encoded and stored in the global product complaint management system.

10.1.7. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

10.1.8. Study and Site Closure

10.1.8.1. Discontinuation of the Study

The study will be discontinued if Lilly or its designee judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

10.1.8.2. Discontinuation of Study Sites

Study site participation may be discontinued if Lilly or its designee, the investigator, or the ERB of the study site judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

10.1.9. Publication Policy

In accordance with Lilly's publication policy, the results of this study will be submitted for publication by a peer-reviewed journal if the results are deemed to be of significant medical importance.

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed below will be performed as indicated in the tables below. Tests to be performed for study Parts A and B are presented in one table, and the tests to be performed in Part C in a second, separate table.
- If there is an abnormal laboratory value or abnormal value for any other diagnostic or screening test (e.g. blood pressure increased, neutrophils decreased), this should be entered into the CRF. Do not enter the test abnormality, enter the diagnosis or categorical term.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- Local laboratories must be qualified in accordance with applicable local regulations.

Investigators must document their review of the laboratory safety results.

Clinical Laboratory Tests for Parts A and B

Hematology: local or investigator-designated laboratory

Hemoglobin	Lymphocytes
Hematocrit	Monocytes
Erythrocyte count	Eosinophils
Leukocytes	Basophils
Neutrophils, segmented and banded	Platelets

Clinical Chemistry: local or investigator-designated laboratory

Serum Concentrations of:	
Sodium	Alkaline phosphatase
Potassium	Creatinine
Chloride	Calcium
Bicarbonate	Glucose
Total bilirubin	Albumin
Direct bilirubin	Total Protein
Alanine aminotransferase	Blood urea nitrogen (BUN) or blood urea
Aspartate aminotransferase	Cystatin C
Beta-HCG*	Alpha-fetoprotein*
CSF Concentrations of:	
Beta-HCG*	Alpha-fetoprotein*

Pregnancy Test (for female patients of childbearing potential): local or investigator-designated laboratory

Serum pregnancy test

Urine pregnancy test

CCI [redacted]

CCI [redacted] CCI [redacted]

CCI [redacted]

CSF cytology*

*If applicable for patients who may have positive tumor markers or cytology (done if clinically indicated and feasible at baseline) for tumor response. See Section 1.3 for more details.

Clinical Laboratory Tests for Part C

Hematology: local or investigator-designated laboratory	
Hemoglobin	Lymphocytes
Leukocytes	Platelets
Neutrophils, absolute neutrophil count	
Clinical Chemistry: local or investigator-designated laboratory	
Serum Concentrations of:	
Sodium	Alkaline phosphatase
Potassium	Creatinine
Chloride	Calcium
Bicarbonate	Glucose
Total bilirubin	Albumin
Direct bilirubin	Total Protein
Alanine aminotransferase	Blood urea nitrogen (BUN) or blood urea
Aspartate aminotransferase	Cystatin C[a]
Phosphorus	Magnesium
Abbreviated Chemistry Panel (electrolytes and creatinine): local or investigator-designated laboratory	
Serum Concentrations of:	
Sodium	Bicarbonate
Potassium	Creatinine
Chloride	
Pregnancy Test (for female patients of childbearing potential): local or investigator-designated laboratory	
Serum pregnancy test	
Urine pregnancy test	
CCI	
CCI	CCI
CCI	
Prothrombin time	

a Cystatin C is optional.

10.3. Appendix 3: Contraceptive Guidance and Collection of Pregnancy Information

Definitions:

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

If fertility is unclear (e.g. amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

1. Premenarchal
2. Female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

   For individuals with permanent infertility due to an alternate medical cause other than the above (e.g. Mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

   Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.

Contraception Guidance:

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods[b] That Have Low User Dependency
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
• Intrauterine device
• Intrauterine hormone-releasing system[c]
• Bilateral tubal occlusion
• Vasectomized partner • *(Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.)*
Highly Effective Methods[b] That Are User Dependent
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c] o oral o intravaginal o transdermal o injectable
• Progestogen-only hormone contraception associated with inhibition of ovulation[c] o oral o injectable
• Sexual abstinence *(Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)*
a) Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies. b) Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly. c) Male condoms must be used in addition to hormonal contraception. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action. Note: Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception for this study. Male condom and female condom should not be used together (due to risk of failure with friction)

Collection of Pregnancy Information

Male participants with partners who become pregnant

- The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive abemaciclib.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female Participants who become pregnant

- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a participant's pregnancy.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any post-study pregnancy related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.3.2. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention and be withdrawn from the study.

10.4. Appendix 4: Liver Safety: Suggested Actions and Follow-up Assessments

Selected tests may be obtained in the event of a treatment-emergent hepatic abnormality and may be required in follow-up with participants in consultation with the Lilly CRP/CRS or Lilly's designee. Labs will be assessed by local or investigator-designated laboratory.

Hematology	**Clinical Chemistry**
Hemoglobin	Total bilirubin
Hematocrit	Direct bilirubin
Erythrocytes (RBCs - red blood cells)	Alkaline phosphatase (ALP)
Leukocytes (WBCs - white blood cells)	Alanine aminotransferase (ALT)
Differential:	Aspartate aminotransferase (AST)
Neutrophils, segmented	Gamma-glutamyl transferase (GGT)
Lymphocytes	Creatine kinase (CK)
Monocytes	**Other Chemistry**
Basophils	Acetaminophen
Eosinophils	Acetaminophen protein adducts
Platelets	Alkaline phosphatase isoenzymes
Cell morphology (RBC and WBC)	Ceruloplasmin
	Copper
Coagulation	Ethyl alcohol (EtOH)
Prothrombin time, INR (PT-INR)	Haptoglobin
Serology	Immunoglobulin IgA (quantitative)
Hepatitis A virus (HAV) testing:	Immunoglobulin IgG (quantitative)
HAV total antibody	Immunoglobulin IgM (quantitative)
HAV IgM antibody	Phosphatidylethanol (PEth)
Hepatis B virus (HBV) testing:	**Urine Chemistry**
Hepatitis B surface antigen (HBsAg)	Drug screen
Hepatitis B surface antibody (anti-HBs)	Ethyl glucuronide (EtG)
Hepatitis B core total antibody (anti-HBc)	**Other Serology**
Hepatitis B core IgM antibody	Anti-nuclear antibody (ANA)
Hepatitis B core IgG antibody	Anti-smooth muscle antibody (ASMA) [a]
HBV DNA [c]	Anti-actin antibody [b]
Hepatis C virus (HCV) testing:	Epstein-Barr virus (EBV) testing:
HCV antibody	EBV antibody

HCV RNA [c]	EBV DNA [c]
Hepatitis D virus (HDV) testing:	Cytomegalovirus (CMV) testing:
HDV antibody	CMV antibody
Hepatitis E virus (HEV) testing:	CMV DNA [c]
HEV IgG antibody	Herpes simplex virus (HSV) testing:
HEV IgM antibody	HSV (Type 1 and 2) antibody
HEV RNA [c]	HSV (Type 1 and 2) DNA [c]
Microbiology	Liver kidney microsomal type 1 (LKM-1) antibody
Culture:	
Blood	
Urine	

[a] Not required if anti-actin antibody is tested.

[b] Not required if anti-smooth muscle antibody (ASMA) is tested.

[c] Reflex/confirmation dependent on regulatory requirements, testing availability, or both.

10.5. Appendix 5: Creatinine Clearance Formula

Note: This formula is to be used for calculating creatinine clearance (CrCl) from **local laboratory results only.**

Patients ≥18 years old

Cockcroft-Gault prediction of CrCl from serum creatinine (1976)

For serum creatinine concentration in mg/dL:

$$\text{CrCl (mL/min)} = \frac{(140 - \text{age}^{a}) \times (\text{wt}) \times 0.85 \text{ (if female), or} \times 1.0 \text{ (if male)}}{72 \times \text{serum creatinine (mg/dL)}}$$

For serum creatinine concentration in µmol/L:

$$\text{CrCl (mL/min)} = \frac{(140 - \text{age}^{a}) \times (\text{wt}) \times 0.85 \text{ (if female), or} \times 1.0 \text{ (if male)}}{0.81 \times \text{serum creatinine (µmol/L)}}$$

[a] Age in years, weight (wt) in kilograms.

Source: Cockcroft and Gault 1976.

-OR-

Patients <18 years old.

All Females and Pre-adolescent Males:

C_{cr} (mL/min/1.73 m^2) = 0.55 x Height (cm)/S_{cr} (mg/dL)

Adolescent Males:

C_{cr} (mL/min/1.73 m^2) = 0.70 x Height (cm)/S_{cr} (mg/dL)

Note: C_{cr} = creatinine clearance and S_{cr} = serum creatinine

Sources: Schwartz et al. 1976; Schwartz and Gauthier 1985.

10.6. Appendix 6: Inducers and Strong Inhibitors of CYP3A4

Note: The information in this table is provided for guidance to investigators. This list is not intended to be exhaustive, but with available information continually evolving, the status of every relevant drug cannot be guaranteed. Please consult with the medical monitor in case of any doubt about a potential drug-drug interaction.

Strong Inducers of CYP3A4	Special Status
Aminoglutethimide	Very limited use. Possibly available in Egypt, Lithuania
Apalutamide	
Carbamazepine (daily dose exceeding 600 mg)	
Enzalutamide	
Fosphenytoin (see also phenytoin)	
Ivosidenib	
Lumacaftor	
Mitotane	
Phenobarbital	
Phenytoin	
Rifabutin	
Rifampicin (rifampin)	
Rifapentine	
St John's wort	Supplement or food/drink
Moderate Inducers of CYP3A4	
Bosentan	
Carbamazepine (daily dose 600 mg or lower)	
Cenobamate	
Dabrafenib	
Danshen (*Salvia miltiorrhiza*)	Supplement or food/drink
Efavirenz	
Elagolix	
Encorafenib	Probable moderate inducer based on observed autoinduction
Etravirine	
Genistein	Supplement or food/drink
Lopinavir (alone)	
Lorlatinib	
Modafinil	
Nafcillin (intravenous)	Very limited use; Available in US
Pentobarbital	Very limited use
Primidone	
Sotorasib	
Thioridazine	Very limited use; available in US; importable into UK
Tocilizumab (atlizumab)	Non-traditional mechanism: reverses the IL-6 mediated suppression of CYP3A activity in patients with rheumatoid arthritis
Strong Inhibitors of CYP3A4	
Atazanavir and cobicistat	
Boceprevir	
Ceritinib	

Clarithromycin	
Cobicistat (see atazanavir and cobicistat)	
Conivaptan	
Danoprevir and ritonavir	
Elvitegravir and ritonavir	
Fosamprenavir and ritonavir	
Grapefruit juice	Supplement or food/drink
Idelalisib	
Indinavir and ritonavir	
Itraconazole	
Josamycin	Outside US
Ketoconazole	Very limited use
Lonafarnib	
Lopinavir and ritonavir	
Mifepristone	Very limited use; Cushing's disease in US
Nefazodone	Very limited use; Available in US
Nelfinavir	
Nirmatrelvir and ritonavir	
Posaconazole	
Ribociclib	
Ritonavir	
Saquinavir and ritonavir	
Telithromycin	
Tipranavir and ritonavir	
Tucatinib	
Viekirax (paritaprevir and ritonavir and ombitasvir and/or dasabuvir)	Outside of US
Voriconazole	

10.7. Appendix 7: Provisions for Changes in Study Conduct During Exceptional Circumstances

Implementation of this appendix

The changes to procedures described in this appendix are temporary measures intended to be used only during specific time periods as directed by the sponsor in partnership with the investigator.

Exceptional circumstances

Exceptional circumstances are rare events that may cause disruptions to the conduct of the study. Examples include pandemics or natural disasters. These disruptions may limit the ability of the investigators, participants, or both to attend on-site visits or to conduct planned study procedures.

Implementing changes under exceptional circumstances

In an exceptional circumstance, after receiving the sponsor's written approval, sites may implement changes if permitted by local regulations.

Ethical Review Boards (ERBs), regulatory bodies and any other relevant local authorities, as required, will be notified as early as possible to communicate implementation of changes in study conduct due to exceptional circumstances. To protect the safety of study participants, urgent changes may be implemented before such communications are made, but all changes will be reported as soon as possible following implementation. If approval of ERBs, regulatory bodies, or both is required per local regulations, confirmation of this approval will be retained in the study records.

In the event written approval is granted by the sponsor for changes in study conduct, additional written guidance, if needed, will be provided by the sponsor.

In exceptional circumstances, the flexibility measures outlined in the SoA (Section 1.3) and this appendix may be considered for the following visits after consultation with and prior approval by the sponsor:

- **Part A:** Visits 8 and 15 of Cycles 1 and 2, short-term follow-up
- **Part B:** All visits in Cycles 1 and 2, and Day 1 of cycles with imaging procedures, short-term follow-up

10.7.1. Informed Consent

Additional consent/assent from the participant will be obtained, as required by ERB's and local regulations. Assent will also be obtained to the same parameters, with consent for participants reaching the legal age for consent during the trial for continued participation, for:

- participation in remote visits, as defined below in Section 10.7.2.1,
- alternate delivery of study intervention and ancillary supplies, and
- provision of their personal or medical information required prior to implementation of these activities.

10.7.2. Changes in Study Conduct

Changes in study conduct not described in this appendix, or not consistent with applicable local regulations, are not allowed.

The following changes in how study conduct will be performed (e.g. virtual vs at the investigative site) will not be considered protocol deviations. Every effort should be made for the participant to return to on-site visits as soon as reasonably possible, while ensuring the safety of the participant and investigational site staff.

10.7.2.1. Remote Visits

In source documents and the CRF, the study site should capture the method, with a specific explanation for any data missing because of missed in-person site visits. Remote visits will include a combination of telemedicine and mobile healthcare as appropriate, according to the investigator's discretion and written approval by the sponsor.

Assessments may be completed by a combination of video conference (telemedicine) and may also include mobile healthcare for the following visits:

- **Part A:** Visits 8 and 15 of Cycles 1 and 2, short-term follow-up
- **Part B:** All visits in Cycles 1 and 2, and Day 1 of cycles with imaging procedures, short-term follow-up.

Applicable assessments include physical exam and weight, vital signs, CCI [redacted] performance status, questionnaires, review of patient diary, imaging (see heading below), PK (see heading below), AE collection and grading, and concomitant medication recording. Other assessments (such as applicable blood draws and pregnancy tests) may be completed remotely according to local regulations by a mobile healthcare service or at a local clinic without video conference at the investigator's discretion. If there is a concern during the remote visit, the participant should have an on-site follow-up visit as soon as possible.

Telemedicine: Technology-assisted virtual visits, including video, to complete appropriate study assessments are acceptable.

Mobile healthcare: Healthcare visits may be performed at locations other than the study site (for example, participant's home) when participants cannot travel to the site due to an exceptional circumstance. Such visits will be performed by a mobile healthcare provider trained on the study.

Local Imaging: In exceptional circumstances, imaging procedures required during screening, on-study treatment, or follow up may be performed locally at an alternate location than the study site or designated facility. Imaging facility, image acquisition protocol, and imaging modality should be consistent for all visits for a given patient. A different facility may be utilized after receiving approval from the sponsor. The same image acquisition protocol and imaging modality must remain the same across facilities.

Regardless of the type of remote visits implemented, the protocol requirements for reporting of adverse events (AEs), serious adverse events (SAEs), and product complaints as outlined in Protocol JPCS remain unchanged. Furthermore, every effort should be made to enable

participants to return to on-site visits as soon as reasonably possible, while ensuring the safety of both the participants and the site staff.

Pharmacokinetics

If in exceptional circumstances a patient is unable to be on-site for temozolomide or irinotecan PK sampling, only abemaciclib PK samples should be collected remotely and the temozolomide/irinotecan samples should be recorded as not collected on the requisition form by the nurse.

10.7.2.2. Study Intervention and Ancillary Supplies (Including Participant Diaries)

When a participant is unable to go to the site to receive study supplies during normal on-site visits, the site should work with the sponsor to determine appropriate actions. These actions may include:

- asking the participant or designee to go to the site and receive study supplies from site staff without completion of a full study visit,
- arranging delivery of study supplies, and
- working with the sponsor to determine how study intervention that is typically administered on site will be administered to the participant; for example, during a mobile healthcare visit.

These requirements must be met before action is taken:

- Alternate delivery of abemaciclib and temozolomide should be performed in a manner that does not compromise product integrity. The existing protocol requirements for product accountability remain unchanged, including verification of participant's receipt of study supplies.
- When delivering supplies to a location other than the study site (for example, participant's home), the investigator, sponsor, or both should ensure oversight of the shipping process to ensure accountability and product quality (that is, storage conditions maintained and intact packaging upon receipt).
- Instructions may be provided to the participant or designee on the final disposition of any unused or completed study supplies.

In addition, if study intervention will be administered to the participant during a mobile healthcare visit or at an alternate location, this additional requirement must be met:

Only authorized personnel may supply study intervention. See Section 6.2.

10.7.2.3. Screening Period Guidance

If the screening period lasts for more than 35 days due to exceptional circumstances, the participant must be discontinued because of screening interruption due to an exceptional circumstance. This is documented as a screen fail in the CRF. This screen fail due to an exceptional circumstance is allowed in addition to the main protocol screen fail. The participant can reconsent and be rescreened as a new participant with a new participant number.

Any screening procedures that fall outside of the required windows per the JPCS Protocol Schedule of Screening Activities (Protocol Section 1.3) must be repeated.

10.7.3. Documentation

10.7.3.1. Documentation of Changes in Study Conduct

Changes to study conduct will be documented:

- Sites will identify and document the details of how participants, visit types, and conducted activities were affected by exceptional circumstances. Dispensing/shipment records of study intervention and relevant communications, including delegation, should be filed with site study records.
- Source documents generated at a location other than the study site should be part of the investigator's source documentation and should be transferred to the site in a secure and timely manner.

10.8. Appendix 8: Abemaciclib Dosing Charts

Parts A and B:

	BSA Ranges (m^2) for each Dose Level			
Dose (BID)	**55 mg/m^2**	**70 mg/m^2**	**90 mg/m^2**	**115 mg/m^2**
25 mg	0.50-0.68	0.50-0.53		
50 mg	0.69-1.13	0.54-0.89	0.50-0.69	0.50-0.54
75 mg	1.14-1.59	0.90-1.24	0.70-0.97	0.55-0.76
100 mg	1.60-2.04	1.25-1.60	0.98-1.24	0.77-0.97
125 mg	2.05-2.49	1.61-1.96	1.25-1.52	0.98-1.19
150 mg	2.50+	1.97+	1.53+	1.20+

Abbreviations: BID = twice daily; BSA = body surface area.

Part C:

	BSA Ranges (m^2) for each Dose Level	
Dose (BID)	**30mg/m^2**	**55mg/m^2**
10mg	0.30-0.37[a]	0.20
12.5mg	0.38-0.45	0.21-0.24
15mg	0.46-0.54	0.25-0.29
17.5mg	0.55-0.62	0.30-0.34
20mg	0.63-0.70	0.35-0.38
22.5mg	0.71-0.79	0.39-0.43
25mg	0.80-1.24	0.44-0.68
50mg	1.25-2.08	0.69-1.13
75mg	2.09-2.91	1.14-1.59
100mg	2.92+	1.60+

Abbreviations: BID = twice daily; BSA = body surface area.

a At the 30mg/m^2 dose, patients must be ≥0.3m^2 as a smaller BSA would require a dose that exceeds their calculated dose by >10%.

Abemaciclib Oral Granules Dosing Chart			
Dose (mg)	**Device Setting**	**# Times to Dispense**	**# Granules per dose**
10	4	1	4
12.5	5	1	5
15	6	1	6
17.5	7	1	7
20	8	1	8
22.5	9	1	9
25	10	1	10
50	20	1	20
75	15	**2**	30
100	20	**2**	40

10.9. Appendix 9: Country-Specific Requirements

The country-specific addendum presented in this appendix must be performed in addition to all procedures required by the current version of Protocol JPCS where applicable. The consolidation of this country-specific addendum in the JPCS protocol appendix is to facilitate transition of this trial to the Clinical Trial Information System (CTIS) under the new clinical trial regulation in the EU.

10.9.1. Addendum 2.3 (Country-Specific Content for the European Union)

This addendum addresses the additional requirements for Study JPCS sites in the EU. The purpose of this addendum is to incorporate feedback from the competent authorities within the EU.

The following table describes the changes being made to Protocol JPCS for participants in the EU.

Main Protocol Section # and Name	Description of Change
1.3. Schedule of Activities	Added text indicating the investigators will provide age-appropriate explanations
5.1. Inclusion Criteria	Inclusion criterion 5 was modified to specify "intact capsules"
6.1 Study Intervention(s) Administered	Removed the allowance of other presentations of temozolomide
6.1.2. Patients with Difficulty Swallowing After Initiating Treatment	Removed bullet for temozolomide
10.1.5. Dissemination of Clinical Study Data	Added qualifying text to "reports" content
10.2.1. Blood Volumes	Added blood volume details for Parts A and B

Protocol Revisions

For JPCS Protocol Addendum, additions have been identified by the use of underscore and deletions have been identified by ~~strikethrough~~.

Protocol Section 1.3 Schedule of Activities

Investigators will provide age-appropriate explanations to all children prior to any assessment or procedure. Investigators should assess and monitor physical pain and distress at each visit.

Protocol Section 5.1 Inclusion Criteria

[5] Patients must be able to swallow intact capsules.

Protocol Section 6.1 Study Intervention(s) Administered

…

Temozolomide once daily orally on Days 1 through 5 at the dose specified in the dosing tables below. For Part A, take temozolomide approximately 1 hour prior to irinotecan infusion. Temozolomide can be taken at the same time as the first abemaciclib dose. Temozolomide should be taken on an empty stomach. Temozolomide should be taken by oral administration according to label ~~standard of care (refer to Section 6.1.1. for patients will swallowing difficulties). Other presentations (e.g. IV) of temozolomide may be allowed upon discussion with the Lilly CRP/CRS. The method of administration should be documented on the CRF~~.

…

Protocol Section 6.1.2. Patients with Difficulty Swallowing After Initiating Treatment

If a patient has difficulty swallowing after initiating study treatment, the following should be considered. In all cases, the method of administration should be documented on the CRF.

- For abemaciclib, refer to the Medication Alternative Administration guide.
- ~~For temozolomide, follow standard of care for alternative administration (Trissel et al. 2006; CCLG 2016).~~

Protocol Section 10.1.5 Dissemination of Clinical Study Data

Dissemination of study data will be performed according to all applicable Lilly and international policies.

Reports

On completion of the research, regardless of whether the trial is terminated prematurely or there are unfavourable results, a report or summary shall be submitted to regulatory bodies and ethics committees according to local law within 6 months. In addition, ~~T~~the sponsor will disclose a summary of study information, including tabular study results, on publicly available websites where required by local law or regulation within 6 months.

Protocol Section 10.2.1. Blood Volumes

The highest volume of blood planned to be drawn from patients for pharmacokinetics (PK) and safety labs in one day is CCI [redacted] Additionally, the highest volume of blood planned to be drawn from patients for PK and safety labs in CCI [redacted] Therefore, these volumes are less than the maximum limits calculated using the safe weight-based limit formula for a 10kg patient, which is the smallest patient allowed to enroll on this study.

Blood Draw Volumes Per Visit (mL) – Part A

Baseline[a]	Cycle 1 Day 1	Cycle 1 Day 8	Cycle 1 Day 15	Cycle 2 Day 1
CCI	CCI	CCI	CCI	CCI
Cycle 2 Day 2	**Cycle 2 Day 8**	**Cycle 2 Day 15**	**Cycle 3 Day 1**	**Cycle 3 Day 8**
4	3	CCI	CCI	CCI
Cycle 3 Day 15	**Cycle 4 and onward Day 1**	**Cycle 4 and onward Day 8**	**Cycle 4 and onward Day 15**	**Visit 801**
CCI	CCI	CCI	CCI	CCI
Renal Monitoring		**Hepatic Monitoring**	**Tumor Markers[a]**	CCI
CCI		CCI	CCI	CCI

[a] If applicable, some patients may have additional blood draws for tumor markers (alpha-fetoprotein and beta-HCG).

[b] CCI

Blood Draw Volumes Per Visit (mL) – Part B

Baseline[a]	Cycle 1 Day 1	Cycle 1 Day 8	Cycle 1 Day 15	Cycle 2 Day 1
CCI	CCI	CCI	CCI	CCI
Cycle 2 Day 2	**Cycle 2 Day 8**	**Cycle 2 Day 15**	**Cycle 3 Day 1**	**Cycle 3 Day 8**
CCI	CCI	CCI	CCI	CCI
Cycle 3 Day 15	**Cycle 4 and onward Day 1**	**Cycle 4 and onward Day 8**	**Cycle 4 and onward Day 15**	**Visit 801**
CCI	CCI	CCI	CCI	CCI
Renal Monitoring		**Hepatic Monitoring**	**Tumor Markers[a]**	CCI
CCI		CCI	CCI	CCI

[a] If applicable, some patients may have additional blood draws for tumor markers (alpha-fetoprotein and beta-HCG).

[b] CCI

10.10. Appendix 10: Abbreviations and Definitions

Term	Definition
abuse	Use of a study intervention for recreational purposes or to maintain an addiction or dependence
ADCC	antibody dependent cellular cytotoxicity
AE	adverse event: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
ALT	alanine aminotransferase
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
authorized IMP	*Applicable to the EU only*: a medicinal product authorized in accordance with Regulation (EC) No 726/2004 or in any Member State concerned in accordance with Directive 2001/83/EC, irrespective of changes to the labelling of the medicinal product, which is used as an investigational medicinal product
AUC	area under the curve
BID	twice daily
BSA	body surface area
CBC	complete blood count
CBR	clinical benefit rate
CDK	cyclin-dependent kinase
CDK4	cyclin-dependent kinase 4
CDK6	cyclin-dependent kinase 6
CNS	central nervous system
COA	clinical outcome assessment
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.

compliance	Adherence to all study-related, good clinical practice (GCP), and applicable regulatory requirements.
CR	complete response
CrCl	creatinine clearance
CRF	case report form
CRP/CRS	clinical research physician/clinical research scientist: Individual responsible for the medical conduct of the study. Responsibilities of the CRP/CRS may be performed by a physician, clinical research scientist, global safety physician or other medical officer.
CSF	cerebrospinal fluid
CSR	clinical study report
CT	computed tomography
ctDNA	circulating tumor DNA
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DBP	diastolic blood pressure
DCR	disease control rate
DLT	dose-limiting toxicity
DoR	duration of response
EDC	electronic data capture
enroll	The act of assigning a participant to a treatment. Participants who are enrolled in the study are those who have been assigned to a treatment.
enter	Participants entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
ERB	ethical review board
FDG	fluorodeoxyglucose
GCP	good clinical practice
G-CSF	granulocyte-colony stimulating factor
GD2	disialoganglioside belonging to b-series ganglioside
GDPR	EU General Data Protection Regulation
GFR	glomerular filtration rate

GM-CSF	granulocyte macrophage colony stimulating factor
H1	H1 histamine receptor
H&E	hematoxylin-eosin stain
HCG	human chorionic gonadotropin
HER2-	human epidermal growth factor receptor 2 negative
Hgb	hemoglobin
HR+	hormone receptor-positive
HVA	homovanillic acid
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IHC	immunohistochemistry
ILD	interstitial lung disease
IM	intramuscular
IMP	Investigational Medicinal Product (see also "investigational product") A medicinal product which is being tested or used as a reference, including as a placebo, in a clinical trial.
Informed consent	A process by which a participant voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the participant's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
INRC	International Neuroblastoma Response Criteria
interim analysis	An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked.
investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
IRB	Institutional Review Board
IV	Intravenous

MATE	multidrug and toxin extrusion protein
medication error	Errors in the prescribing, dispensing, or administration of a study intervention, regardless of whether or not the medication is administered to the participant or the error leads to an AE. Medication error generally involve a failure to uphold one or more of the five "rights" of medication use: the right participant, the right drug, the right dose, right route, at the right time. In addition to the core five rights, the following may also represent medication errors: • dose omission associated with an AE or a product complaint • dispensing or use of expired medication • use of medication past the recommended in-use date • dispensing or use of an improperly stored medication • use of an adulterated dosage form or administration technique inconsistent with the medication's labeling (for example, Summary of Product Characteristics, IB, local label, protocol), or • shared use of cartridges, prefilled pens, or both.
MIBG	metaiodobenzylguanidine
misuse	Use of a study intervention for self-treatment that either is inconsistent with the prescribed dosing regimen, indication, or both, or is obtained without a prescription
mRNA	messenger RNA
MTD	maximum tolerated dose
MTD_A	Part A maximum tolerated dose
NCI	National Cancer Institute
NIMP	Non-investigational Medicinal Product. A medicinal product used for the needs of a clinical trial as described in the protocol, but not as an investigational medicinal product. Examples include rescue medication, challenge agents, agents to assess endpoints in the clinical trial, or background treatment.
CCI	[redacted]
ORR	objective response rate
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic(s)
PO	orally

PR	partial response
PRBC	packed red blood cell
PRO/ePRO	patient-reported outcomes/electronic patient-reported outcomes
QD	daily
RANO	Response Assessment in Neuro-Oncology
RB	retinoblastoma
RECIST	Response Criteria in Solid Tumors
RP2D	recommended phase 2 dose
SAE	serious adverse event
SBP	systolic blood pressure
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
SD	stable disease
SoA	Schedule of Activities
SUSAR	suspected unexpected serious adverse reaction Refers to an adverse event that occurs in a clinical trial participant, which is assessed by the sponsor and or study investigator as being unexpected, serious and as having a reasonable possibility of a causal relationship with the study intervention.
TBL	total bilirubin
TEAE	Treatment-emergent adverse event: An untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment.
UGT1A1	uridine diphosphate-glucuronosyl transferase 1A1
ULN	upper limit of normal
VGPR	very good partial response
VMA	vanillylmandelic acid
VTE	venous thromboembolic event
WBC	white blood cell
WOCBP	woman/women of childbearing potential

10.11. Appendix 11: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

Amendment (e): 11-Jul-2022

This amendment is considered to be substantial.

The amendment is considered to be substantial because it is likely to have a significant impact on the

- safety or the rights of the study participants, and
- the quality or safety of any investigational medicinal product used in the study.

Overall Rationale for the Amendment:

The primary reason for amending the JPCS protocol is to add study Part C. Part C will evaluate abemaciclib in combination with dinutuximab, granulocyte macrophage colony-stimulating factor (GM-CSF; sargramostim), irinotecan, and temozolomide in pediatric patients with relapsed/refractory neuroblastoma.

Section # and Name	Description of Change	Brief Rationale
1.1. Synopsis; 1.2. Schema; 1.3.2. Schedule of Activities for Part C; 4.1. Overall Design; 4.1.1. Dose Escalation Method for Parts A and B; 4.1.2. Two-stage Design for Part C; 6.1. Study Intervention(s) Administered; 6.5. Concomitant Therapy; 8.1. Efficacy Assessments; 8.8.1. Biomarkers for Part C; 8.8.1.1. Tissue Samples for Biomarker Research; 8.8.1.2. Plasma Samples for Biomarker Research; 8.8.1.3. Whole Blood Samples for Biomarker Research; 9.1. Statistical Hypotheses; 9.3. Populations for Analysis; 9.4.6. Efficacy Analyses; 9.4.6.2. Part C Efficacy Analyses; 10.2. Appendix 2: Clinical Laboratory Tests	Addition of Part C to Study Design	See Overall Rationale for Amendment
1.1. Synopsis; 3. Objectives and Endpoints	Updated objectives for Part C; specified abemaciclib for acceptability/palatability objective and endpoint; removed plasma from PK endpoint	Updated for Part C; clarifications
1.1. Synopsis; 4.1. Overall Design; 9.2. Sample Size Determination	Updated total number of patients to be enrolled	Updated for Part C
1.3.1. Schedule of Activities for Parts A and B	Added pregnancy test to list of laboratory assessments at screening that do not have to be performed at the clinical trial site	Flexibility for patients
1.3.1. Schedule of Activities for Parts	For anatomic radiologic imaging, edited text regarding performance of imaging as	Clarification

Section # and Name	Description of Change	Brief Rationale
A and B	part of routine clinical care	
1.3.1. Schedule of Activities for Parts A and B; 8.10. Product Acceptability and Palatability Assessments	Added clarifications for when questionnaires are needed	Clarification
1.3.1. Schedule of Activities for Parts A and B	Added age specifications for Lansky/Karnofsky performance status	Clarification
1.3.1. Schedule of Activities for Parts A and B	Added line for participant returns study drugs	Clarification for compliance assessment
1.3.1. Schedule of Activities for Parts A and B	Removed ECG and Cystatin C from posttreatment follow-up procedures	Not necessary
1.3.1. Schedule of Activities for Parts A and B	Added option for laboratory and pregnancy tests to be collected locally for all patients at any time in the study; removed notes requiring patient to go to local laboratory close to patient's home if not performed at the investigative site	Flexibility for patients
1.3.3. Pharmacokinetic Sampling and Study Drug Dosing Schedule	Reformatted table; added details for Part C	Clarification; update for Part C
2.1. Study Rationale; 2.2. Background; 2.2.4. Dinutuximab; 2.2.5. GM-CSF	Updated to include content for Part C	Update for Part C
2.2.1. Temozolomide; 2.2.2. Irinotecan; 4.3.2. Temozolomide; 4.3.3. Irinotecan	Moved temozolomide and irinotecan content to subsections under Dose Justification	Moved to improve readability
2.2.6. Preclinical and Clinical Rationale	Section number changed and updated figure caption for A673 Ewing's sarcoma CDX model in mice	Clarification
2.3. Benefit/Risk Assessment	Added content for Part C	Update for Part C
4.1.1. Dose Escalation Design for Parts A and B	Modified DLT-evaluable definition; Removed MTD definition from section	Update for Part C / readability
4.1.1. Dose Escalation Design for Parts A and B	Reworded details of intrapatient dose escalation not being permitted	Clarification
4.1.1. Dose Escalation Design for Parts A and B; 4.1.3. Dose-Limiting Toxicity Determination and Maximum Tolerated Dose Definition	Moved statement of enrollment being suspended in the event of Grade 5 AE to Section 4.1.3; Moved statement DLT declaration in the event of significant toxicities	Clarification / readability
4.1.2. Two-stage Design for Part C	Added details of design for Part C	Update for Part C
4.1.3. Dose-Limiting Toxicity Determination and Maximum Tolerated Dose Definition	Revised statement that investigators and Lilly CRP/CRS can declare a DLT if patient experiences dose-limiting toxicity; Added statement that if a patient receives <75% of any planned Cycle 1 study drug doses due to drug-related toxicity, the toxicity will be declared a DLT	Reworded for clarity; added to broaden DLT definition
4.1.3. Dose-Limiting Toxicity	Added statement that all Grade ≥3	Reworded for clarity

Section # and Name	Description of Change	Brief Rationale
Determination and Maximum Tolerated Dose Definition	nonhematological AEs outside of listed exceptions will be considered a DLT	
4.1.3. Dose-Limiting Toxicity Determination and Maximum Tolerated Dose Definition	Changed "subsequent course" to "subsequent cycle" under hematological events	Clarification
4.1.3. Dose-Limiting Toxicity Determination and Maximum Tolerated Dose Definition	Reworded acute irinotecan-associated diarrhea definition	Clarification
4.1.3. Dose-Limiting Toxicity Determination and Maximum Tolerated Dose Definition	Added "Cycle Delay" to first Hematological events bullet	Clarification
4.1.3. Dose-Limiting Toxicity Determination and Maximum Tolerated Dose Definition	Updated language regarding the Toxicity Documentation Form	Operational
4.3.1. Abemaciclib	Revised abemaciclib dose justification	Improved readability; Update for Part C
4.3.2. Temozolomide; 4.3.3. Irinotecan; 4.3.4. Dinutuximab and GM-CSF	Added sections	Added to provide justification for doses in respective study parts
4.4. End of Study Definition	Added text describing study completion in the EU and US for Parts B and C, respectively	Update for Part C
5.1. Inclusion Criteria	Added Part-specific requirements in Criteria 1 and 3	Update for Part C
5.1. Inclusion Criteria	Removed Inclusion 2	Combined age/weight requirements in Inclusion Criterion 1
5.1. Inclusion Criteria	Inclusion 6: Modified table of previous treatments and added clarifications	Update for Part C
5.1. Inclusion Criteria	Inclusion 7: Added specifications for Parts A, B, and C where applicable	Update for Part C
5.1. Inclusion Criteria	Inclusion 9: Updated contraceptive requirements	Update with most recent abemaciclib guidance
5.1. Inclusion Criteria	Added Inclusion 28 and 29	Update for Part C
5.2. Exclusion Criteria	Exclusion 14: specified that COVID vaccines that do not contain a live virus are permitted	Clarification
5.2. Exclusion Criteria	Removed Exclusion 16	Alignment with safety guidance
5.2. Exclusion Criteria	Exclusion 21: Removed "severe renal impairment"	Redundant with Inclusion 7
5.2. Exclusion Criteria	Added Exclusion 26, 30, 31	Update for Part C
5.2. Exclusion Criteria	Removed Exclusion 27	Sponsor strategy decision

Section # and Name	Description of Change	Brief Rationale
6.1. Study Intervention(s) Administered	Added dosing instruction specifications for Parts A, B, C as applicable	Update for Part C
6.1. Study Intervention(s) Administered	Added clarification for participants taking oral granules should follow provided instructions	Clarification
6.1.1. Detailed Administration Guidelines (Part C Only); 6.1.1.1. Monitoring Guidelines During Dinutuximab Infusion (Days 2-5)	Added Sections	Update for Part C
6.1.2. Patients with Difficulty Swallowing After Initiating Treatment	Added details for oral granule administration/dispersion	Update for Part C
6.1.3. Criteria to Begin Subsequent Cycles of Treatment	Edited first bullet to clarify G-CSF use in Parts A and B; specified G-CSF is not permitted in Part C; clarified "any nonhematologic toxicity deemed related to study treatment"	Update for Part C; clarification
6.1.4. Premedication; 6.1.4.1. Nausea; Section 6.5.2. Supportive Management for Diarrhea	Moved text from 6.1.4 to 6.1.4.1; Moved text regarding vomiting associated with diarrhea to Section 6.5.2	Clarification / readability
6.2. Preparation/Handling/Storage/Accountability	Removed reference to Pharmacy Manual	Operational
6.4. Study Intervention Compliance	Replaced compliance text with content addressing study intervention administration and compliance assessment	Modified for timing
6.4. Study Intervention Compliance	Added text for oral granules	Update for Part C
6.4. Study Intervention Compliance	Added "unless dose holds are necessitated by AE." to statement regarding percentage of doses needed for compliance	Clarification
6.5. Concomitant Therapy	Deleted "Seasonal flu" vaccines, and made it general "Vaccines"	Clarification
6.5.1. Palliative Medicine and Supportive Care	Added text in second bullet in Supportive Care subsection clarifying that G-CSF use is permitted in Parts A and B; however, G-CSF is not permitted in Part C	Update for Part C
6.5.1. Palliative Medicine and Supportive Care	Added bullet regarding risk of PCP in participants receiving irinotecan and temozolomide, and that PCP prophylaxis is encouraged	Alignment with current safety
6.5.2. Supportive Management for Diarrhea	Specified that loperamide should be readily available to begin treatment of late diarrhea prior to first irinotecan infusion	Clarification
6.5.3. Supportive Management of Anticipated Dinutuximab-Associated Toxicities (Part C Only)	Added section and subsequent subsections 6.5.3.1 through 6.5.3.11	Update for Part C

Section # and Name	Description of Change	Brief Rationale
6.6. Dose Modification	Changed "study treatment" to "abemaciclib"; Modified title and table values in "Starting Dose and Adjustments for Abemaciclib-Related Toxicities". Changed dosing units from mg/m^2 to mg; added language and subsections for Part C	Clarifications; update for Part C
6.6.1. Dose Modification Guidance due to Toxicity	Updated section to align with DLT guidance and provide additional clarifications / better readability	Alignment with DLT guidance / clarifications
6.6.1.1. Dose Modification Guidance due to Toxicities Considered to be Attributed to Abemaciclib	Deleted all but the first sentence of footnote "a" below the dose modification guidance table for hematologic toxicities considered to be attributed to abemaciclib	Deleted because Grade 3 hematological toxicity is not listed in this table except febrile neutropenia
6.6.1.2. Dose Modification Guidance due to Toxicities Considered to be Attributed to Irinotecan	Updated section to align with safety guidance and provide additional clarifications	Clarification / update with irinotecan safety information
6.6.1.3. Part C-Specific Dose Modifications; 6.6.1.4. Dose Modification Guidance due to Toxicity Attributed to GM-CSF	Added sections	Update for Part C
7.1. Discontinuation of Study Intervention	Deleted portion of final bullet point "…or a DLT at the lowest dose level under investigation."	Due to new options to dose reduce based on strength (mg) rather that dose level (mg/m^2)
7.2.1. Discontinuation of Inadvertently Enrolled Patients	Removed section	Operational
8.2.1.2. Guidance for Monitoring Renal Function	Edited wording regarding measures of renal function	For clarity
8.4. Treatment of Overdose	Added overdose text for interventions other than abemaciclib	Update for Part C / clarification
8.5. Pharmacokinetics	Added details for Part C	Update for Part C
8.5.1. Patient Diary	Added statement that the patient diary is not intended for compliance monitoring	Clarification
8.7.1. Whole Blood and/or Saliva Samples for Pharmacogenetic Research	Added text clarifying that whole blood and/or saliva samples will not be collected in Parts A and B, but that whole blood but not saliva will be collected in Part C. Also added text stating that genetic research would not be performed	Update for Part C
8.10. Product Acceptability and Palatability Assessments	Moved text from under Section 8.1 to new Section 8.10; added text for acceptability and palatability of abemaciclib oral granules	Clarification; update for Part C
9.3. Populations for Analysis	Deleted sentence at end of section regarding replacement of patients to ensure adequate PK	Remove redundancy

Section # and Name	Description of Change	Brief Rationale
9.4.6.1. Parts A and B Efficacy Analyses	Specified that Parts A and B will not have a formal efficacy assessment	Clarification
9.4.6.2.1. 2017 INRC	Added description of INRC response grading and summarization used in Part C	Update for Part C
9.4.7. Pharmacokinetic / Pharmacodynamic Analyses	Clarified that abemaciclib, irinotecan, and temozolomide concentrations will be summarized by analyte	Clarification
9.4.8. Subgroup Analyses	Added "when applicable" at the end of the sentence.	Clarification
9.4.9. Product Acceptability and Palatability	Added "oral granules" to first sentence.	Update for Part C
9.5. Interim Analyses	Added text to clarify interim analyses and MTD in Parts A and B and confirming safety in Part C; added details of DMC in Part C	Update for Part C
10.1.1. Regulatory and Ethical Considerations	Added final bullet: "Reporting significant issues related to participant safety, participant rights, or data integrity"	Per new EMA guidance related to EU CTR 536/2014
10.1.4. Committee Structure	Added details of DMC for Part C	Update for Part C
10.6. Appendix 6: Inducers and Strong Inhibitors of CYP3A	Edited table of inducers and strong inhibitors of CYP3A	Update for current abemaciclib guidance
10.7. Appendix 7: Provisions for Changes in Study Conduct During Exceptional Circumstances	Added short-term follow-up to the Part A and Part B bullets	Indicates the visits for which flexibility would apply
10.8. Appendix 8: Abemaciclib Dosing Charts	Updated table for Parts A and B, added table for Part C	Updated rounding for consistency; update for Part C
Throughout the protocol	Minor formatting and editorial changes	Minor, therefore not detailed

Amendment d: 04 March 2021

This amendment is considered to be nonsubstantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

Overall Rationale for the Amendment

The purpose of this amendment is to incorporate regulatory agency feedback and make minor clarifications for consistency within the document.

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities; Appendix 2:	Specified lumbar puncture at baseline should be performed if clinically indicated	Regulatory agency

Section # and Name	Description of Change	Brief Rationale
Clinical Laboratory Tests	and feasible	feedback
1.3 Schedule of Activities	Removed blank footnote	Editorial
5.1 Inclusion Criteria	Specified contraceptive guidance for study drugs must follow label, removed typographical error	Regulatory agency feedback, editorial correction
8.3 Adverse Events and Serious Adverse Events	Clarified that SAE statement applies to study treatment	Clarification
10.7.2.1 Remote Visits	Added short-term follow-up to list of visits allowing remote visits to match text in Section 1.3	Consistency with SoA

Amendment c: 15 January 2021

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

The purpose of this amendment is to provide additional operational flexibility for sites and participants.

Section # and Name	Description of Change	Brief Rationale
1.1. Synopsis; 1.3. Schedule of Activities; 3. Objectives and Endpoints; 8.1. Efficacy Assessments; 9.4.6. Efficacy Analyses	Added RANO criteria for CNS tumors to secondary objective; updated imaging guidance and analysis language throughout document	RANO added to provide more accurate response assessment of CNS tumors
1.3. Schedule of Activities; Appendix 7: Provisions for Changes in Study Conduct During Exceptional Circumstances	Added appendix and guidance for exceptional circumstances and eligibility for remote visits	Site and patient flexibility
1.3 Schedule of Activities; 8.8. Biomarkers; 9.4.10. Biomarker Analyses	Added language for potential analyses if available	Addition of analysis
1.3. Schedule of Activities	Added/modified collection time and visit windows for physical exam and weight, CCI [redacted] vital signs, Lansky/Karnofsky performance status, patient diary review, and lab assessments	Site and patient flexibility; alignment with required on-site visits
1.3. Schedule of Activities	Added lumbar puncture to schedule for applicable patients	Alignment with potential analysis for applicable patients
1.3. Schedule of Activities	Clarified that short-term follow-up lasts for 30 days from the last administration of study drugs	Clarification
2.2.1. Temozolomide	Clarified temozolomide doses in Part A and Part B of study	Clarification
2.3.1. Benefit/Risk Assessment of COVID-19	Added language describing benefit/risk assessment of trial activities during the COVID-19 pandemic	Provided rationale for conducting study during COVID-19 pandemic
4.1.2. Dose-Limiting Toxicity Determination and Maximum Tolerated Dose Definition	Modified hematological events; added guidance for completion of Toxicity Documentation Form	Modified to provide more clarity for hematological events and to allow G-CSF; guidance added to provide clarity to investigators
5.1. Inclusion Criteria	Added language outlining requirements for evaluable lesions, CNS tumors, and histological verification of malignancy	Provided clarity to ensure patient population is accurately enrolled
5.2. Exclusion Criteria	Added specification of somatic or germline RB mutation to criterion 27	Clarification
6.1. Study Intervention(s)	Added new appendix and	Guidance added for determining if a

Section # and Name	Description of Change	Brief Rationale
Administered; Appendix 8: Abemaciclib Dosing Chart	guidance in 6.1; added guidance for missed or vomited doses of abemaciclib and temozolomide	change in BSA necessitates a change in abemaciclib dosing; added instructions in case of missed or vomited dose
6.1.2. Criteria to Begin Subsequent Cycles of Treatment	Removed hemoglobin ≥8 g/dL	Correction
6.2. Preparation/Handling/Storage/ Accountability	Modified requirement for storage condition confirmation; added supply, preparation, and administration flexibility for authorized study personnel	Administrative
6.5. Concomitant Therapy	Clarified that live vaccines following treatment with other study drugs should be administered according to label	Clarification
6.5.1. Palliative Medicine and Supportive Care	Updated guidance for G-CSF	Allowance of G-CSF in order to increase supportive care measures
6.5.2. Supportive Management for Diarrhea	Changed "after each loose stool" to "at the first sign of loose stools"	Revised guidance to align with Investigator's Brochure
6.6.1.1. Dose Modification Guidance due to Toxicities Considered to be Attributed to Abemaciclib	Updated abemaciclib dose modification instructions	Updated to align with Investigator's Brochure and to make dose adjustments for hematological toxicity
7.3. Lost to Follow up	Added "or designee" to follow up instructions	Administrative
8. Study Assessments and Procedures	Removed "Protocol waivers or exemptions are not allowed"	Administrative
8.2.1. Clinical Safety Laboratory Assessments	Revised laboratory report and source document language	Administrative
10.1.1. Regulatory and Ethical Considerations	Clarification on investigator oversight	Administrative
10.1.5. Data Quality Assurance	Revised COA data collection requirements	Administrative
Appendix 2: Clinical Laboratory Tests	Added language specifying local laboratory must meet qualifications according to local regulations; changed "each laboratory safety report" to "the laboratory safety results"; added beta-HCG, alpha-fetoprotein, and CSF cytology testing for applicable patients	Administrative; beta-HCG, alpha-fetoprotein, and CSF cytology added to assess tumor response for applicable patients

Section # and Name	Description of Change	Brief Rationale
Appendix 4: Liver Safety: Suggested Actions and Follow-up Assessments	Updated table of tests	Updated to align with safety guidance
Throughout	Minor editorial and formatting changes	Minor, therefore not detailed

Amendment b: 08 July 2020

This amendment is considered to be nonsubstantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

Overall Rationale for the Amendment:

This amendment incorporates changes according to regulatory agency feedback in addition to edits made to provide improved clarity for sites.

Section # and Name	Description of Change	Brief Rationale
Title Page	Added regulatory agency identifier numbers	Per regulatory agency feedback
Section 1.3 Schedule of Activities	Removed vital signs evaluation on Cycle 5-n Day 15	Editorial error, Day 15 evaluation did not align with instructional text
Section 1.3 Schedule of Activities	Update to physical exam details	Per regulatory agency feedback
Section 1.3 Schedule of Activities	Update to radiologic imaging notes	Per regulatory agency feedback
Section 2.3 Benefit/Risk Assessment	Correction to focus the benefit on the primary objective	Per regulatory agency feedback
Section 4.3 Justification for Dose	Added CYP3A maturation on abemaciclib PK exposure background	Per regulatory agency feedback
Section 6.1 Study Interventions	Added drug sourcing information	Per regulatory agency feedback
Section 8.1 Efficacy Assessments	Added details on assessing for gross bone abnormalities	Per regulatory agency feedback
Section 8.2.1.2	Update to renal function monitoring guidance	Consistency with Investigator's Brochure
Section 10.1.3 Data Protection	Added clarification that sponsor will verify that participants have consented, in writing, to direct access to their medical records for trial-related monitoring, audit, IRB/ERB review, and regulatory inspection	Per regulatory agency feedback
Section 10.1.4. Dissemination of Clinical Study Data	Added language regarding the submission of a report or summary of research to regulatory bodies	Per regulatory agency feedback
Section 10.1.8 Publication Policy	Added description of publication policy	Per regulatory agency feedback

Section # and Name	Description of Change	Brief Rationale
Throughout	Minor editorial and formatting changes	Minor, therefore not detailed

Amendment a: 17 April 2020

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

This amendment incorporates changes according to regulatory agency feedback in addition to edits made to provide improved clarity for sites.

Section # and Name	Description of Change	Brief Rationale
Section 1.1. Synopsis (Intervention Groups and Duration), Section 1.2. Schema, Section 6.1. Study Intervention(s) Administered	Updated cohort labels and descriptions	Added clarity to dosing cohorts
Section 1.3. Schedule of Activities, Appendix 2: Clinical Laboratory Tests	CCI [redacted]	Per regulatory feedback
Section 1.3. Schedule of Activities	Split vital signs from physical exam row; provided additional collection guidance	Created new row and detailed instructions for clarity
Section 1.3. Schedule of Activities	Added visit windows to physical exams, Lansky/Karnofsky performance status, pregnancy tests, and lab assessments	Windows added to provide flexibility
Section 1.3. Schedule of Activities	Revised notes for adverse event collection/CTCAE grading in the Continued Access Period	Clarification of when vital signs and laboratory tests should be performed
Section 1.3. Schedule of Activities	Added timepoint to collect questionnaire if method of abemaciclib administration is changed at any point during the trial	Additional timepoint for more robust data set
Section 1.3. Schedule of Activities	Revised notes for diary completion	Clarification that caregivers can complete the diary if needed
Section 1.3. Schedule of Activities	Amended instructions for hematology, clinical chemistry, cystatin C, and serum or urine pregnancy test	Clarification on timing of samples
Section 2.2. Background	Added a sentence about the 5-year postrelapse survival rate for pediatric solid tumors to emphasize unmet need for this study	Clarification

Section # and Name	Description of Change	Brief Rationale
Section 2.2.1. Temozolomide	Amended a tumor type targeted by temozolomide in pediatric patients	Correction and clarification
Section 2.2.4. Preclinical and Clinical Rationale	Added clarification of clinically relevant range for abemaciclib	Per regulatory feedback
Section 2.3. Benefit/Risk Assessment	Added language clarifying additional potential benefit of combination targeted therapies	Clarification
Section 4.1.1. Dose Escalation Method	Revised DLT-evaluable description	Description revised for consistency
Section 4.1.1. Dose Escalation Method	Added details of safety reviews within dose escalation and expansion cohorts in the event of Grade 5 AEs. Also added considerations for starting Part B at a dose of 55 mg/m^2.	Per regulatory feedback
Section 4.1.1. Dose Escalation Method	Added statement regarding enrollment suspension in the event of any Grade 5 adverse event	Per regulatory feedback
Section 4.1.2. Dose-Limiting Toxicity Determination	Removal of clinically nonsignificant, treatable, or reversible laboratory abnormalities; removal of electrolyte abnormalities responsive to supplementation within 7 days; revised Grade 3 diarrhea event; revised electrolyte abnormalities event; added clarification for Grade ≥3 amylase or lipase event; removed platelet count; added Grade ≥3 thrombocytopenia with clinically significant bleeding; added Grade ≥4 neutropenic fever	Per regulatory feedback
Section 4.3. Justification for Dose	Provided additional justification for dose levels in Part B of study	Per regulatory feedback
Section 5.1. Inclusion Criteria	Modified Inclusion Criterion 3 to specify that the criterion applies to the study part currently enrolling	Modified for clarity
Section 5.1. Inclusion Criteria	Added residual peripheral sensory neuropathy as an exception to Inclusion Criterion 6	Clarification of eligible population
Section 5.2. Exclusion Criteria	Removed reference to randomization and replaced with Cycle 1 Day 1 from Exclusion Criterion 14	Clarification

Section # and Name	Description of Change	Brief Rationale
Section 5.2. Exclusion Criteria	Added Exclusion Criterion 26 related to bowel obstruction	Per regulatory feedback
Section 5.2. Exclusion Criteria	Added "or strong inhibitors of UGT1A1" to Exclusion Criterion 22	Per regulatory feedback
Section 5.2. Exclusion Criteria	Removal of "(4 months for studies conducted in Japan)" from Exclusion Criterion 25	Clarification of eligible population
Section 5.2. Exclusion Criteria	Added Exclusion Criterion 27	Exclude patients with known retinoblastoma mutation
Section 6.1. Study Intervention(s) Administered	Added statement directing reader to an abemaciclib dosing chart based on patient's BSA level	Study tool provides assigned dose
Section 6.1. Study Intervention(s) Administered	Removed statements regarding sourcing of study drugs	Sourcing covered in other documents outside protocol
Section 6.1.1. Patients with Difficulty Swallowing After Initiating Treatment	Added new section to provide guidance for patients having difficulty with swallowing	Per regulatory feedback
Section 6.1.2. Criteria to Begin Subsequent Cycles of Treatment	Added criterion related to weight and BSA	Ensures patients are still within size required in eligibility criteria
Section 6.5. Concomitant Therapy	Revised cannabis and cannabis product use language; language regarding CYP enzyme substrates and dexamethasone therapy added	Clarification of acceptable concomitant therapy
Section 6.5. Concomitant Therapy	Added cautionary language regarding use of strong inhibitors of UGT1A1	Per regulatory feedback
Section 6.6.1.2. Dose Modification Guidance due to Toxicities Considered to be Attributed to Irinotecan	Dose modification guidance for irinotecan added	Per regulatory feedback
Section 8.1.1. Product Acceptability and Palatability Assessments	Added language if patient changes method of abemaciclib administration at any point during the trial	Additional timepoint for more robust data set
Section 8.2. Safety Assessments	Provided additional details regarding monitoring and review of safety data	Per regulatory feedback

Section # and Name	Description of Change	Brief Rationale
Section 8.5.1. Patient Diary	Added reference to caregiver	Clarification
Appendix 2: Clinical Laboratory Tests	Removed reference to reconciling local and central labs and CCI [redacted]	Clarification and regulatory feedback, respectively
Appendix 6: Inducers and Strong Inhibitors of CYP3A	Added footnote a and updated Moderate Inducers of CYP3A	Clarification and removal of item from list to align with most recent guidance
Throughout	Minor editorial and formatting changes	Minor, therefore not summarized

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