Statistical Analysis Plan I3Y-MC-JPCS (Version 2)

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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1. Statistical Analysis Plan: I3Y-MC-JPCS: 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)

Abemaciclib (LY2835219)

Study I3Y-MC-JPCS is a multicenter, non-randomized, open-label, Phase 1b dose-escalation study comprised of 2 parts of 3+3 dose escalation of abemaciclib in pediatric patients with relapsed/refractory solid tumors. Part A will test abemaciclib in combination with irinotecan and temozolomide. Part B will test abemaciclib in combination with temozolomide. Part C will test abemaciclib in combination with dinutuximab, GM-CSF, irinotecan, and temozolomide.

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Protocol I3Y-MC-JPCS
Phase 1b/2

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3. Abbreviations and Definitions

Term	Definition
AE	adverse event
BID	twice-daily
BOR	best overall response
BSA	body surface area
CBR	clinical benefit rate
CI	confidence interval
CR	complete response
CRP	clinical research physician
CRS	clinical research scientist
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CTR	Clinical Trial Registry
DCR	disease control rate
DLT	dose-limiting toxicity
DoR	duration of response
ECG	electrocardiogram
GM-CSF	granulocyte macrophage colony-stimulating factor
LLT	Lowest Level Term
MedDRA	Medical Dictionary for Regulatory Activities
MIBG	meta-iodobenzylguanidine
MTD	maximum tolerated dose
MR	minor response
NCI	National Cancer Institute
ORR	objective response rate
OS	overall survival

Term	Definition
PFS	progression-free survival
PK	pharmacokinetic
PR	partial response
PT	Preferred Term
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
TEAE	treatment-emergent adverse event

4. Revision History

SAP version 1 was approved (23 October 2020) prior to the first visit when a subject receives study treatment or any other protocol intervention.

SAP version 2 was made based on the Protocol Amendment (e) which added Part C to the study. SAP version 2 was approved before the enrollment of Part C began, but after the MTD was established in Part A and enrollment to Part B was ongoing. Specific changes in this version include:

- changes to maintain consistency with Protocol Amendment (e),
- planned analyses for Part C, and
- re-organization of efficacy analysis to accommodate the addition of Part C and updates of study objectives.

5. Study Objectives

Table JPCS.5.1. Study 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) • 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 [redacted]	CCI [redacted]

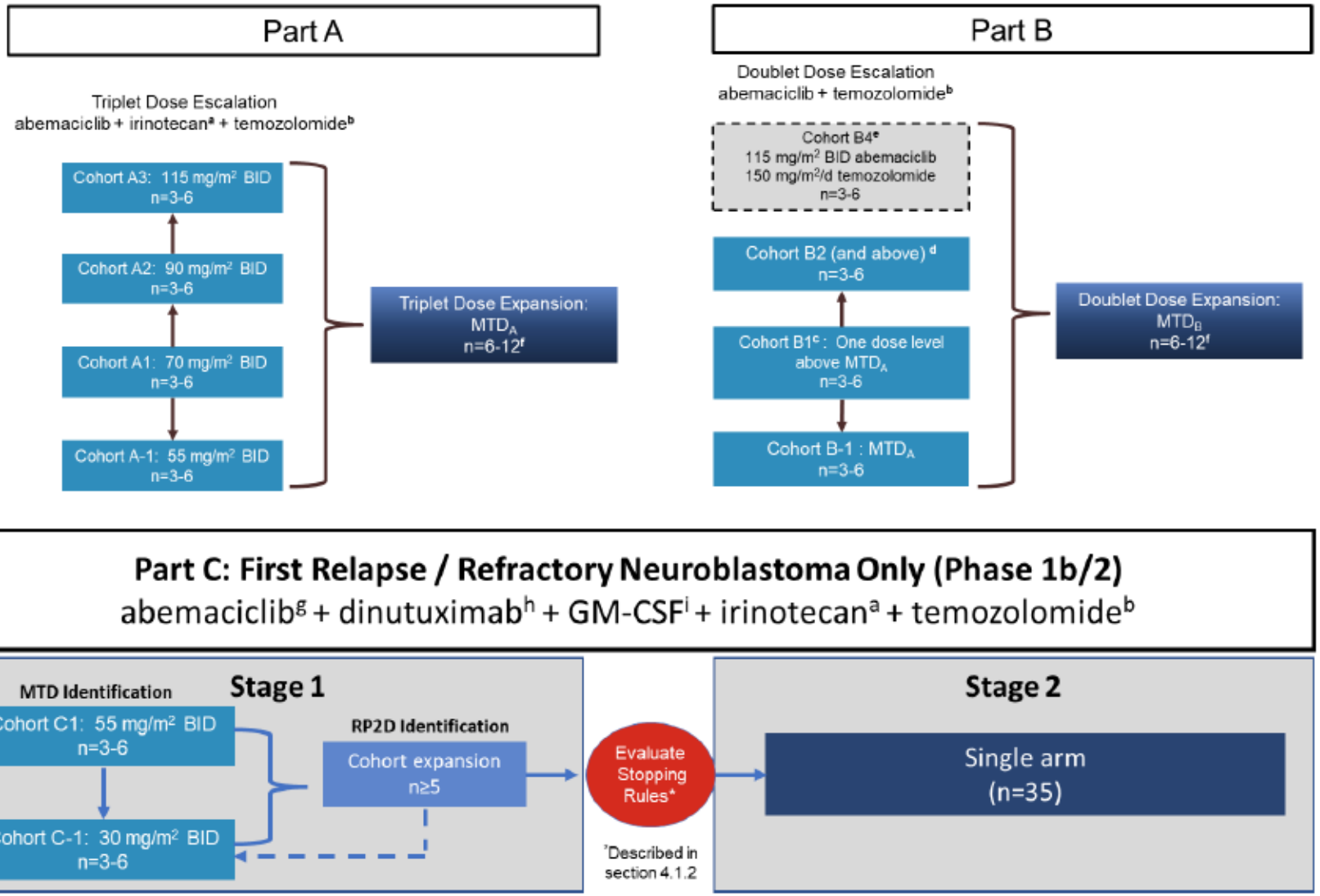
Objectives	Endpoints
CCI	CCI
CCI	CCI
CCI	CCI

Abbreviations: CBR = clinical benefit rate; CNS = central nervous system; CTCAE = Common Terminology Criteria for Adverse Events; DCR = disease control rate; DLT = dose-limiting toxicity; DoR = duration of response; GM-CSF = granulocyte macrophage colony-stimulating factor; INRC = International Neuroblastoma Response Criteria; 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.

6. Study Design

6.1. Summary of Study Design

Figure 6.1 illustrates the study 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/m^2/day, Days 1-5 of Cycle. See Protocol Section 6.1.
[b] Temozolomide administered PO 100 mg/m^2/day, Days 1-5 of Cycle. See Protocol Section 6.1.
[c] 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.
[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/m^2 BID in combination with 100 mg/m^2/day temozolomide in Part B; **OR**
- if abemaciclib 115 mg/m^2 BID is the MTD for Part A. In this case, Part B will start directly with Cohort B5 using abemaciclib 115 mg/m^2 BID and temozolomide 150 mg/m^2/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/m^2 BID × 21 days, and if needed, 30 mg/m^2 BID × 21 days to determine the MTD for Part C. Sponsor may elect to explore an intermediate dose level (that is: between DL1 and DL-1) based on emerging data. See Protocol Section 6.1.
[h] Dinutuximab administered via IV 17.5 mg/m^2 × 4 days, Days 2-5 of Cycle. See Protocol Section 6.1.
[i] GM-CSF administered subcutaneously 250 µg/m^2 × 7 days, Days 6-12 of Cycle. See Protocol Section 6.1.

Figure 6.1. 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 and irinotecan or in combination with temozolomide 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 dose-limiting toxicities (DLTs) in all parts and responses in Part C. The study will enroll approximately 30 to 117 patients (see Protocol Section 9.2). Patients in Parts A and B must be ≤18 years of age and weigh ≥10 kg (with 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 2-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 6.1.1. 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 2 stages that will evaluate (1) safety and tolerability and (2) anti-tumor activity of the combination (details in Section 6.1.2).

DLTs 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 (Protocol 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 [redacted]

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 [redacted]

6.1.1. Dose Escalation Design for Parts A and B

The dose will be escalated following assessment of toxicity using the standard scoring system, CTCAE version 5.0, established by the 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, 1 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 (for example, 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. DLTs 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.

6.1.2. Two-Stage Design for Part C

Part C consists of 2 stages to first evaluate the safety and tolerability and then the anti-tumor activity of abemaciclib in combination with chemoimmunotherapy.

Stage 1

Stage 1 starts with a dose optimization to identify MTD. Specifically, it will initially enroll 3 patients at 55 mg/m^2 (that is, the MTD for abemaciclib in combination with irinotecan and temozolomide in Part A plus dinutuximab and GM-CSF) and uses 3+3 rules to guide dose decision. During MTD identification, if 55mg/m^2 is deemed intolerable due to DLT, then a lower dose of 30mg/m^2 (that is, reduce abemaciclib to 30mg/m^2 while 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 be enrolled at the MTD to further confirm the tolerability while evaluating the preliminary anti-tumor activity. In the expansion cohort, up to 5 patients may be simultaneously enrolled. Stage 1 will enroll up to CCI 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 the trial for toxicity if CCI of the DLT-evaluable patients experience DLT.

- Rule B: stop the trial for intolerability if [redacted] patients discontinue due to treatment-related AE before [redacted] cycles.
- Rule C: stop for insufficient evidence of anti-tumor activity if < [redacted] of the [redacted] patients are responders (that is, have objective tumor response, including a BOR of CR, PR, or MR per INRC).

De-escalation during cohort expansion: If 55mg/m^2 is declared as the MTD, and any stopping rule is triggered during cohort expansion on this dose level, subsequent patients will be treated at 30mg/m^2. Patients in the cohort expansion for 55 mg/m^2 may be moved to 30 mg/m^2 upon investigator's discretion. Part C will continue to enroll patients until there are [redacted] patients treated on 30 mg/m^2, including newly enrolled patients and those moved from the 55 mg/m^2. For the new patients, a minimum of [redacted] DLT-evaluable patients are required. If none of the 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

When Part C moves to Stage 2, an additional [redacted] patients will be enrolled at the RP2D. 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.

6.1.3. 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 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:

Any Grade ≥3 nonhematological toxicity **except**:

- Grade 3 diarrhea that can be controlled with appropriate supportive care and lasting <72 hours
- Acute diarrhea lasting <7 days, secondary to irinotecan infusion, that is consistent with infusion-related cholinergic diarrhea and can be controlled with maximal supportive care
- Grade ≥3 nausea, vomiting, constipation that is manageable with maximal 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/alanine transaminase 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.

6.2. 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 2-stage design (Simon 1989), where the null hypothesis is that ORR CCI, and the alternative hypothesis is that ORR CCI.

6.3. 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 46 patients are treated on the RP2D. The sample size of CCI is determined using Simon's optimal 2-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.

7. A Priori Statistical Methods

7.1. General 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.

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.

7.1.1. Populations

For purposes of analysis, the following populations are defined in Table JPCS.7.1.

Table JPCS.7.1. Analysis Populations

Population	Description
Entered	All participants who sign informed consent/assent
Treated Patients	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.

Abbreviations: AE = adverse event; DLT = dose-limiting toxicity.

Patients who withdraw from the study before receiving study treatment 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 treatment, 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 due to reasons other than drug-related toxicity, he or she will be considered non-evaluable for assessment of the combination and may be replaced. 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.

7.1.2. Definitions and Conventions

Study drug refers to abemaciclib.

Study treatment refers to abemaciclib plus irinotecan and temozolomide for patients in Part A, abemaciclib plus temozolomide for patients in Part B, and abemaciclib plus dinutuximab, GM-CSF, irinotecan, and temozolomide in Part C.

Date of first dose is the date of the first dose of study drug, irinotecan, temozolomide, dinutuximab, or GM-CSF.

Study day will be calculated as the difference between the date of the event or assessment and:

- The date of first dose plus 1 for all events or assessments occurring on or after the day of first dose. For example, if an event occurs on 08 November 2020 and the date of first dose was 06 November 2020, the study day of the event is 3.
- The date of first dose for all events or assessments occurring before the day of first dose. For example, if an event occurs on 05 November 020 and the date of first dose was 06 November 2020, the study day of the event is -1.

One **month** is defined as 365/12 days.

Unless otherwise noted, **summaries of continuous variables** will include a mean, median, standard deviation, minimum, and maximum.

Unless otherwise noted, **summaries of categorical variables** will include the frequency and percentage (relative to the population being analyzed) of each category.

The assumptions for each statistical method will be evaluated. If there is violation of assumptions, alternative statistical methods may be used. Additional exploratory analyses of the data will be conducted as deemed appropriate. Unless otherwise stated, all tests of treatment effects will be conducted at a 1-sided alpha level of .025, and all CIs will be given at a 2-sided 95% level.

7.1.3. Handling of Dropouts of Missing Data

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.

7.2. Safety Analyses

Safety analyses will be completed as specified below, unless COVID-19 impact creates a situation requiring a change to an existing analysis or a need for additional analyses as outlined by Nilsson et al. (2020).

Safety analyses will be based on the safety population, unless otherwise stated, and summarized by cohort corresponding to the actual regimen received at first dose. Additionally, all patients assigned to the RP2D (for example, the applicable cohort from dose escalation and the dose expansion cohort) within each study part may be aggregated and summarized together.

7.2.1. Extent of Exposure

Drug exposure, dose intensity, and drug adjustments (dose omissions and reductions) will be summarized for abemaciclib, for temozolomide, for irinotecan, for dinutuximab, and for GM-CSF where applicable. Drug exposure will include summaries of cycles received per patient, duration on therapy, and cumulative dose. Dose intensity will be calculated as the actual cumulative amount of drug taken divided by the duration of treatment. Relative dose intensity will be calculated as

$$\frac{the\ amount\ of\ actual\ drug\ taken}{(the\ amount\ of\ drug\ prescribed)}\ x\ 100\%$$

(expressed as a percentage). The summary of dose adjustments and omissions will include the reason for adjustment or omission.

Extent of exposure for abemaciclib will be measured by pill counts. Dose intensity will be expressed in mg/day. The assigned cumulative dose while on study is 2 doses per day × planned amount of drug dose (dependent on dose level and patient BSA at the beginning of each cycle) × number of days on treatment.

7.2.2. Adverse Events

MedDRA version 22.0 (or higher) will be used to map reported AEs to MedDRA terms. The MedDRA LLT will be used in the treatment-emergent computation. PTs identified as clinically identical or synonymous may be grouped together under a single consolidated PT. For example, 'Neutropenia' and 'Neutrophil count decreased' may be aggregated and reported as 'Neutropenia.' The NCI CTCAE version 5.0 will serve as the reference document for grading the severity of all AEs and other symptoms.

Preexisting conditions are defined as AEs that begin prior to the first dose of study treatment.

A TEAE is defined as any AE that begins between the day of first dose and 30 days after treatment discontinuation (or up to any time if serious and related to study treatment), or any preexisting condition that increases in CTCAE grade between the day of first dose and 30 days after treatment discontinuation (or up to any time if serious and related to study treatment). Comparisons of preexisting conditions to on-treatment events at the LLT level will be used in the treatment-emergent computation.

An SAE is any AE during 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, or considered significant by the investigator for any other reason. Additionally, important medical events that may not result in death, be life-threatening, or require hospitalization may be

considered SAEs when, based on appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition.

The following summaries and listings will be produced:

- overview of AEs
- summary of TEAEs by PT (any grade and Grade ≥3)*
- summary of TEAEs by System Organ Class and PT (any grade and Grade ≥3)*
- summary of TEAEs by PT and maximum grade (1 through 5)*
- summary of SAEs by PT (any grade and Grade ≥3)*
- summary of TEAEs as reason for study treatment discontinuation by PT (overall and for each study treatment)
- summary of TEAEs leading to dose adjustments by PT (overall and for each study treatment)
- listing of SAEs, and
- listing of DLTs.

Summaries marked with an (*) will be produced both using all TEAEs/SAEs and using only TEAEs/SAEs related to study treatment, as assessed by the investigator (yes or no).

7.2.3. Deaths

A summary table of all deaths, including reasons for deaths, will be provided. For deaths due to AE, the PT will be provided. In addition to the tabular summary, a by-patient listing of all deaths on study not attributed to study disease by the investigator will be provided.

7.2.4. Clinical Laboratory Evaluation

All relevant hematology and chemistry laboratory values will be graded according to CTCAE version 5.0. These calculated grades will be summarized by cycle and maximum postbaseline grade over the entire study for each treatment arm/cohort. Treatment-emergent changes will be summarized by the maximum postbaseline grade, and a shift table of baseline grade by maximum postbaseline grade will be produced.

7.2.5. Vital Signs and Other Physical Findings

Temperature, blood pressure, pulse rate, weight, BSA, and Lansky/Karnofsky Performance Status will be summarized by cycle, including a summary of treatment-emergent abnormal changes.

7.2.6. Electrocardiograms

ECGs are scheduled to be performed. A listing of ECG findings at baseline and unscheduled postbaseline visits that are considered to be a medical history condition or an AE will be provided. Other analyses may also be done as appropriate.

7.3. Efficacy Analyses

Unless otherwise noted, all efficacy analyses will be performed on the treated population and summarized by cohort where appropriate. Additionally, all patients assigned to the RP2D (for example, the applicable cohort from dose escalation and the dose expansion cohort) within each study part may be aggregated and summarized together.

7.3.1. Primary Efficacy Endpoints

The study was not designed to make an efficacy assessment in Parts A and B, while ORR will be assessed as co-primary endpoint in Part C if a RP2D is achieved. In Part C, ORR is the percentage of patients with a BOR ≥ PR (CR, PR, and MR) per INRC (Park et al. 2017). The response criteria integrate the responses of all lesions using computed tomography/magnetic resonance imaging and/or MIBG/fluorodeoxyglucose-positron emission tomography lesions, and assessment of bone marrow disease. Details are provided in Protocol Section 9.4.6.2.1. All time point responses observed while on study treatment and during short-term follow-up, but before the initiation of post-discontinuation therapy, will be included in the derivation. The primary analysis of response will be based on confirmed responses as defined in Table JPCS.7.2. However, summaries including unconfirmed responses will also be provided. For the interim analysis for Part C, unconfirmed responses may be used.

Table JPCS.7.2. Best Overall Response When Confirmation of Responses Required for Part C

Overall Response First Time Point (1)	Overall Response Subsequent Time Period	Confirmed Best Overall Response
CR	CR (≥28 days from 1)	CR
CR	CR (<28 days from 1)	SD
CR	PR	SD
CR	MR	SD
PR	≥PR (≥28 days from 1)	PR
PR	≥PR (<28 days from 1)	SD
PR	MR	SD
MR	≥MR (≥28 days from 1)	MR
MR	≥MR (<28 days from 1)	SD
CR/PR/MR	SD	SD
CR/PR/MR	PD	SD if minimum duration of stable disease is met[a], otherwise PD

Overall Response First Time Point (1)	Overall Response Subsequent Time Period	Confirmed Best Overall Response
CR/PR/MR	NE/Missing	SD if minimum duration of stable disease is met[a], otherwise NE

Abbreviations: CR = complete response; MR = minor response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

[a] CR/PR/MR occurs at study day >35.

7.3.2. Secondary Efficacy Endpoints

7.3.2.1. Parts A and B

The study was not designed to make an efficacy assessment in Parts A and B, the following are the key secondary endpoints to consider for the 2 parts.

BOR: BOR is defined per RECIST version 1.1 using investigator-assessed time point responses. All time point responses observed while on study treatment and during short-term follow-up, but before the initiation of post-discontinuation therapy, will be included in the derivation. Responses will require confirmation (based on RECIST version 1.1), but where appropriate **BOR** and endpoints using **BOR** may also consider unconfirmed responses.

ORR: The ORR is the percentage of patients with a best response of CR or PR.

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.

DCR: The DCR is the percentage of patients with a best response of CR, PR, or SD.

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

7.3.2.2. Part C

BOR: defined per INRC (Park et al. 2017). Details are provided in Protocol Section 9.4.6.2.1. All time point responses observed while on study treatment and during short-term follow-up, but before the initiation of post-discontinuation therapy, will be included in the derivation. Responses will require confirmation (Table JPCS.7.2), but where appropriate **BOR** and endpoints using **BOR** may also consider unconfirmed responses (for example, interim analysis).

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

DCR: the percentage of patients with a BOR of CR, MR, PR, or SD.

CBR: the percentage of patients with a BOR of CR, MR, PR, or SD for at least 6 months.

Investigator assessed PFS: the time from first dose of any drug in study treatment to documented disease progression per INRC or death, whichever occurs first. The Kaplan-Meier method (Kaplan and Meier 1958) will be used to estimate the PFS curves as well as PFS rates at appropriate time intervals (for example, at 3 and 6 months). Detailed censoring rules are provided in Table JPCS.7.3.

Table JPCS.7.3. JPCS PFS Censoring Scheme

Situation[a]	Event/Censor	Date of Event or Censor
Tumor progression or death	Event	Earliest date of PD or death
No tumor progression and no death	Censored	Date of last adequate assessment or date of first dose (whichever is later)[b]
Unless		
No adequate baseline tumor assessment available	Censored	Date of first dose
No adequate postbaseline tumor assessment available and death reported after 2 scan intervals after first dose	Censored	Date of first dose
New anticancer treatment started and no tumor progression or death within 14 days	Censored	Date of adequate assessment prior to (start of new therapy +14 days) or date of first dose (whichever is later)
Tumor progression or death documented immediately after 2 or more scan intervals after last adequate tumor assessment or first dose (whichever is later)[b]	Censored	Date of last adequate assessment or date of first dose (whichever is later)[b]

Abbreviations: CR = complete response; MR = minimal response; PD = progressive disease; PFS = progression-free survival; PR = partial response; SD = stable disease.

[a] Symptomatic deterioration (that is, symptomatic progression that is not radiologically confirmed) will not be considered as tumor progression.

[b] Adequate tumor assessment refers to an assessment with one of the following responses: CR, PR, MR, SD, or PD.

7.3.3. *Exploratory Efficacy Endpoints*

CCI
CCI

CCI
CCI

CCI [redacted]

7.4. Other Statistical Analyses

7.4.1. Patient Disposition

The number and percentage of patients entered into the study and treated, as well as reasons for discontinuation from study treatment and reasons for discontinuation from study, will be summarized by treatment arm or cohort. The numbers and percentages of patients completing the study (completed at least 1 cycle of treatment) will also be summarized. A listing of patient disposition will be provided.

7.4.2. Patient Characteristics

Summaries will be presented by cohort, unless otherwise noted.

7.4.2.1. Demographics

Patient demographics will be summarized and listed for all treated patients. Patient demographics will include sex, race, ethnicity, country, age, height, weight, and BSA.

7.4.2.2. Baseline Disease Characteristics

Disease characteristics will be summarized. Disease characteristics will include, but not be limited to, the following:

- initial pathological diagnosis
- tumor type and stage at diagnosis
- stage of disease at enrollment, and
- Lansky/Karnofsky performance status at enrollment.

7.4.2.3. Historical Illnesses

Historical illnesses are clinically relevant events in the past that ended before the screening visit. Historical illnesses (using PTs from the most current version of the MedDRA, version 22.0 or higher) will be summarized.

7.4.2.4. Prior Therapies

Prior radiotherapy, surgery, and systemic therapy will be summarized. Prior radiotherapy and surgery will be categorized by reason for regimen. Prior systemic therapies will be categorized by treatment intent and setting.

7.4.2.5. Therapies After Study Treatment Discontinuation

The numbers and percentages of patients receiving anticancer therapies following study treatment discontinuation will be summarized. As appropriate, therapies will be summarized overall and by category.

7.4.3. Treatment Compliance

Treatment compliance for abemaciclib will be derived from the difference between the total number of pills dispensed and returned over the course of the patient's treatment. The number of cycles received, dose omissions, dose reductions, dose delays, and dose intensity will be summarized for all treated patients by cohort. Compliance will be assessed as the proportion of treatment that is actually taken, relative to what is expected, after accounting for protocol-defined dose adjustments. The proportion of patients who are <75% compliant with abemaciclib will be reported.

7.4.4. Concomitant Therapy

All medications will be coded to the generic preferred name according to the current World Health Organization drug dictionary. All concomitant medications will be summarized for the safety population using the preferred name by treatment arm/cohort and overall.

7.4.5. Pharmacokinetic/Pharmacodynamic Analyses

Plasma concentrations will be summarized for each drug (and metabolite) 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.

As necessary, PK and pharmacodynamic analyses will be described in a separate PK analysis plan.

7.5. Subgroup Analyses

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

In Part C, subgroup analyses for objective response will be performed by disease status (relapsed vs refractory), bone marrow status (present vs absent), tumor avidity for target tumors (MIBG/positron emission tomography avid vs non-avid).

If results are suggestive of isolated efficacy or toxicity, other subgroup analyses may be performed to identify hypotheses requiring further research.

7.6. Protocol Violations

Significant protocol violations that potentially compromise the data integrity and patients' safety will be summarized by treatment arm and overall. These violations will include deviations which can be identified programmatically and those which can only be identified by the clinical research associate during monitoring. Significant protocol deviations are described in another document within the electronic study Trial Master File.

7.7. Interim Analyses

7.7.1. Parts A and B

Since Parts A and B are dose-finding only, 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 the 2 parts. 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. 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. Other interim analyses may be added as deemed appropriate by the sponsor.

7.7.2. Part C

In addition to regular cohort-by-cohort analyses for the dose escalation/de-escalation, an interim analysis for both safety and efficacy is planned for Part C, given that MTD is declared in Stage 1. Specifically, after the MTD is established, an expansion cohort will be enrolled at the MTD to further confirm the tolerability while evaluating the preliminary antitumor 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. The interim analyses will be triggered with data cutoff approximately 1 month (or earlier if deemed appropriate) after the last DLT-evaluable patient begins Cycle 2. 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 the trial for toxicity if ≥[redacted] of the DLT-evaluable patients experience DLT.
- Rule B: stop the trial for intolerability if ≥[redacted] patients discontinue due to treatment-related AE before [redacted] cycles.
- Rule C: stop for insufficient evidence of anti-tumor activity if <[redacted] of the [redacted] patients are responders (that is, have objective tumor response, including a BOR of CR, PR or MR per INRC).

7.8. Annual Report Analyses

Annual report analyses, including Developmental Safety Update Report and Investigator's Brochure analyses, are described in the LY2835219 Program SAP.

7.9. Clinical Trial Registry Analyses

Additional analyses will be performed for the purpose of fulfilling the CTR requirements.

Analyses provided for the CTR requirements include the following:

- Summary of AEs, provided as a dataset which will be converted to an XML file. Both SAEs and 'Other' AEs will be summarized by: treatment group, MedDRA PT.

- An AE is considered 'Serious' whether or not it is a TEAE.
- An AE is considered in the 'Other' category if it is both a TEAE and is not serious. For each SAE and 'Other' AE, for each term and treatment group, the following are provided:
    - the number of participants at risk of an event
    - the number of participants who experienced each event term
    - the number of events experienced.
- Consistent with www.ClinicalTrials.gov requirements, 'Other' AEs that occur in fewer than 5% of patients/subjects in every treatment group may not be included if a 5% threshold is chosen (5% is the minimum threshold).
- AE reporting is consistent with other document disclosures for example, the CSR, manuscripts, and so forth.

In addition, a participant flow will be created that will describe how many treated patients completed the study, and for those who did not, the frequency of each reason for not completing. This analysis will be based on study discontinuation, not treatment discontinuation. A patient will be identified as having completed the study if the patient dies while on the study or the patient had discontinued study treatment and is in follow up at the time of the final analysis. Patients who withdraw consent before the final analysis or who are still on treatment at the time of the final analysis will be identified as not completing the study.

8. References

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