27 June 2024
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Committee for Medicinal Products for Human Use (CHMP)

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

IBRANCE

Palbociclib

Procedure no: EMEA/H/C/003853/P46/006

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Status of this report and steps taken for the assessment				
Current step	**Description**	**Planned date**	**Actual Date**	**Need for discussion**
☐	Start of procedure	29/04/2024	29/04/2024	☐
☐	CHMP Rapporteur Assessment Report	03/06/2024	03/06/2024	☐
☐	CHMP members comments	17/06/2024	17/06/2024	☐
☐	Updated CHMP Rapporteur Assessment Report	20/06/2024	N/A	☐
☒	CHMP adoption of conclusions:	27/06/2024	27/06/2024	☐

Administrative information

Procedure resources	
Rapporteur:	**Name:** Filip Josephson
Contact person Rapporteur **Assessor Rapporteur**	**Name: Elina Jonasson** Email: elina.jonasson@lakemedelsverket.se **Name:** Helena Fridborg Email: Helena.Fridborg@lakemedelsverket.se **Name:** David Khan Email: david.Khan@lakemedelsverket.se
EMA Product Lead **Procedure Assistant**	**Name: Margaux Philippe** Email: Margaux.Philippe@ema.europa.eu **Name: Giulia Di Passio** Email: giulia.dipassio@ext.ema.europa.eu

Declarations

☒ The assessor confirms that this assessment does **not** include non-public information, including commercially confidential information (e.g. ASMF, information shared by other competent authorities or organisations, reference to on-going assessments or development plans etc), irrespective from which entity was received*.

If the entity from which non-public information originates has consented to its further disclosure, the box should be ticked and there** would **be no need to add details below.

Whenever the above box is un-ticked please indicate section and page where confidential information is located here:

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1. Introduction

On 28 March 2024, the MAH submitted a completed paediatric study (Study A5481092: Ewing sarcoma cohort) for palbociclib, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that study A5481092 is the clinical measure of the agreed palbociclib paediatric investigational plan (PIP) in the treatment of Ewing sarcoma (EWS).

The MAH does not consider that a change in the palbociclib Product Information is warranted at this stage.

2.2. Information on the pharmaceutical formulation used in the study

Palbociclib was administered either as capsule or oral solution (concentration 25 mg/ml).

2.3. Clinical Pharmacology aspects

Study A5481092 is a Phase 1/2 multicentre, open-label study to evaluate palbociclib in combination with either Irinotecan (IRN) and Temozolomide (TMZ) or Topotecan (TOPO) and Cyclophosphamide (CTX) chemotherapy in children, adolescents and young adults (aged ≥2 and <21 years at the time of study entry) with r/r solid tumours. The study consists of a non-randomized Phase 1 portion for participants with r/r solid tumours followed by potential non-randomized tumour specific cohort(s) (TSC) and a randomized Phase 2 portion for participants with r/r Ewing sarcoma (EWS).'

The following palbociclib, IRN, SN-38 (active metabolite of IRN), TMZ, TOPO, and CTXPK parameters were calculated for each participant and treatment, as appropriate, using noncompartmental analysis of plasma concentration-time data. Samples below the lower LLOQ were set to zero for the PK analysis. Actual sample collection times were used for the PK analysis. Samples for all analyte concentrations were analyzed using their respective validated analytical assays in compliance with Pfizer SOPs. For the purpose of this report, only Palbociclib PK will be reported. The PK parameters determined are listen in the below table.

Table 1 PK Parameters Determined in Protocol A5481092

Parameter	Definition	Method of Determination
AUC_{τ}	Area under the plasma concentration-time curve from time zero to time tau (τ), the dosing interval, where tau = 24 hours (QD dosing)	Linear/Log trapezoidal method
C_{max}	Maximum plasma concentration	Observed directly from data
T_{max}	Time for C_{max}	Observed directly from data as time of first occurrence
C_{trough}	Predose plasma concentration	Observed directly from data
CL/F (extravascular dosing) or CL (intravenous dosing)	Clearance	Dose/ AUC_{τ}
AUC_{τ} (dn)[a]	Dose normalized AUC_{τ}	AUC_{τ} /Dose
C_{max}(dn)[a]	Dose normalized C_{max}	C_{max}/Dose
C_{trough}(dn)[a]	Dose normalized C_{trough}	C_{trough}/Dose

PK parameters were calculated using a Pfizer validated oNCA version 2.7.8
[a] Only calculated for palbociclib in the pooled presentations.

The PK is described for the specific dose regimens below:

Drug	Phase	Dose	Schedule	Route
Palbociclib	1	55 mg/m^2	QD, Days 1-14/Cycle	Oral or Nasogastric
Palbociclib	1, 2	75 mg/m^2	QD, Days 1-14/Cycle	Oral or Nasogastric
Palbociclib	1	95 mg/m^2	QD, Days 1-14/Cycle	Oral or Nasogastric
IRN	1, 2	50 mg/m^2	QD, Days 1-5/Cycle	Intravenous Infusions (90-minute)
TMZ	1, 2	100 mg/m^2	QD, Days 1-5/Cycle	Intravenous Infusions (90-minute) or Oral[a]
TOPO	1	0.75 mg/m^2	QD, Days 1-5/Cycle	Intravenous Infusions (30-minute)
CTX	1	250 mg/m^2	QD, Days 1-5/Cycle	Intravenous Infusions (30-minute)

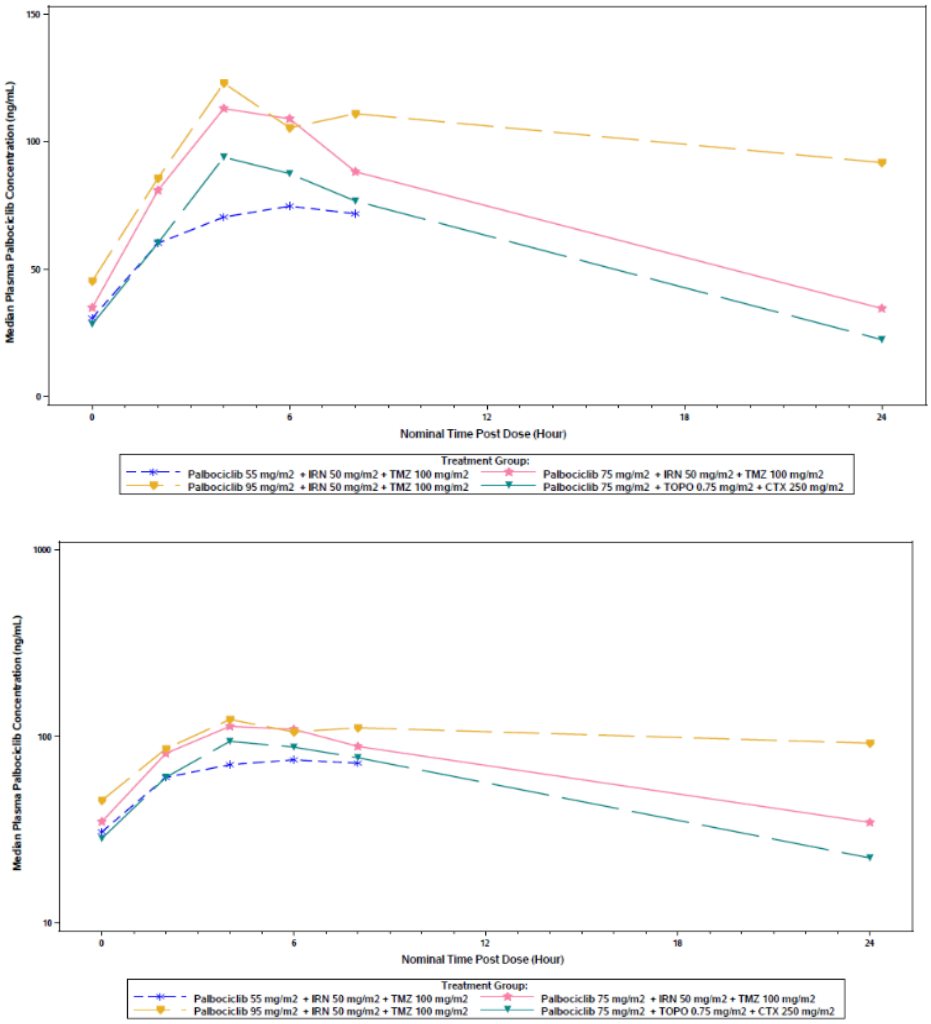
a. Intravenous and oral administration routes are bioequivalent (TMZ label (TEMODAR)).

Pharmacokinetic results – Phase 1 part

Median plasma steady-state palbociclib concentration-time profiles on C1D5 or make-up visit after palbociclib administration at 55, 75, or 95 mg/m2 in combination with IRN + TMZ or TOPO + CTX are presented in the below figure. Palbociclib plasma steady-state PK parameters are summarized in the below table. Box plots of geometric mean Ctrough by visit are presented also below.

Median Tmax of palbociclib ranged from 4.05 to 6.03 hours across treatment groups. In general, palbociclib exposure on C1D5 based on AUCτ, Cmax, and Ctrough increased dose-proportionally from 55 to 95 mg/m2 when palbociclib was co-administered with IRN + TMZ. Palbociclib exposure on C1D5 based on AUCτ and Cmax were comparable after 75 mg/m2 when palbociclib was co-administered with IRN + TMZ or TOPO + CTX, whereas Ctrough was slightly higher after co-administered with IRN + TMZ than when co-administered with TOPO + CTX; however, variability was higher when palbociclib was co-administered with TOPO + CTX. Ctrough palbociclib levels were comparable between visits C1D5, C1D14, C2D5, and C2D14 across the treatment groups, suggesting C1D5 to be approximately at steady-state.

Figure 1 Median Plasma Steady-State Palbociclib Concentrations-Time Profiles by Treatment, Phase 1, Upper Panel: Linear Scale; Lower Panel: Semi-log Scale; Protocol A5481092



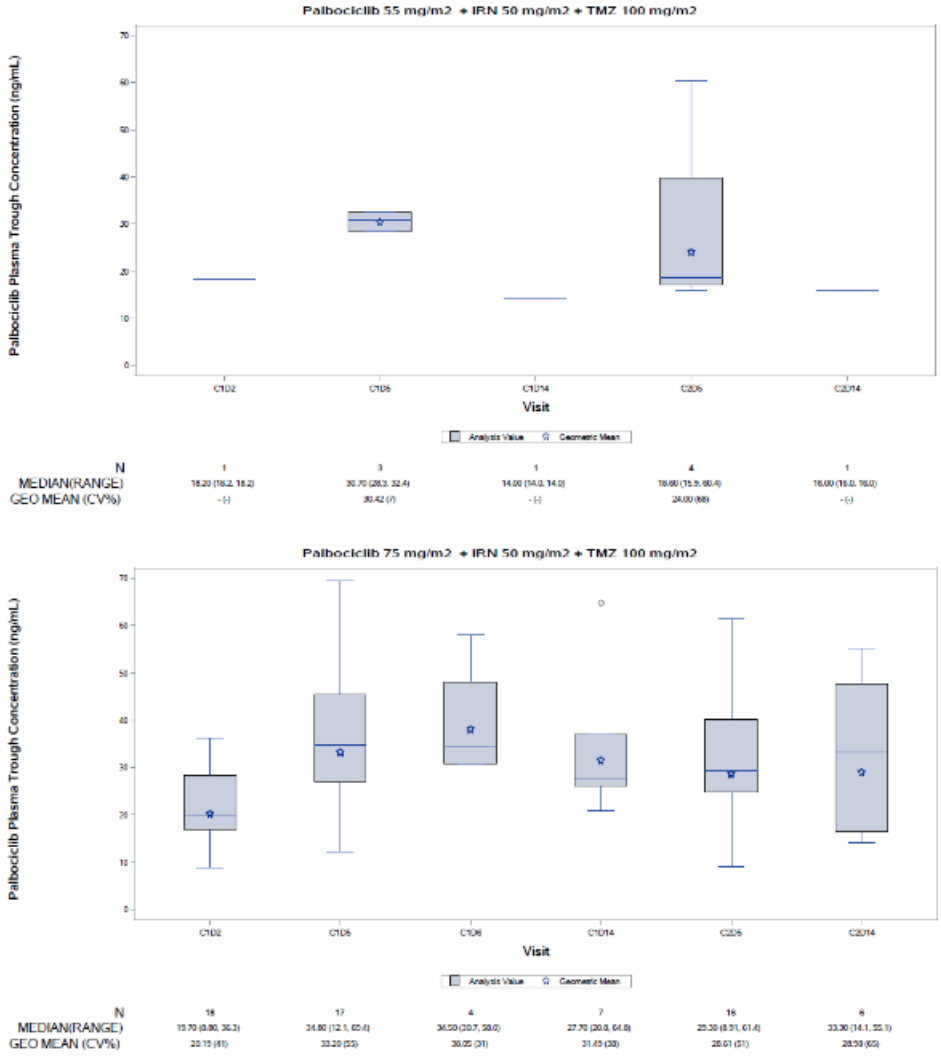
The lower limit of quantification is 1.00ng/mL.
Summary statistics have been calculated by setting concentration values below the lower limit of quantification to zero.
Summaries include concentrations that meet steady state criteria.
Samples with more than 30 mins time deviation when nominal TPD=0H are excluded.
Profiles with vomit comments from Dosing CRF page are excluded.
Samples from make-up visit are excluded.
PK concentrations with sampling deviation time of greater than 20% are excluded.
PFIZER CONFIDENTIAL SDTM Creation: 15FEB2024 (19:05) Source Data: adpc Table Generation: 22FEB2024 (05:01)
(Data cutoff date : 31JUL2023 Database snapshot date : 21NOV2023) Output File: ./A5481092/a5481092_pk_ph1/adpc_f101_2

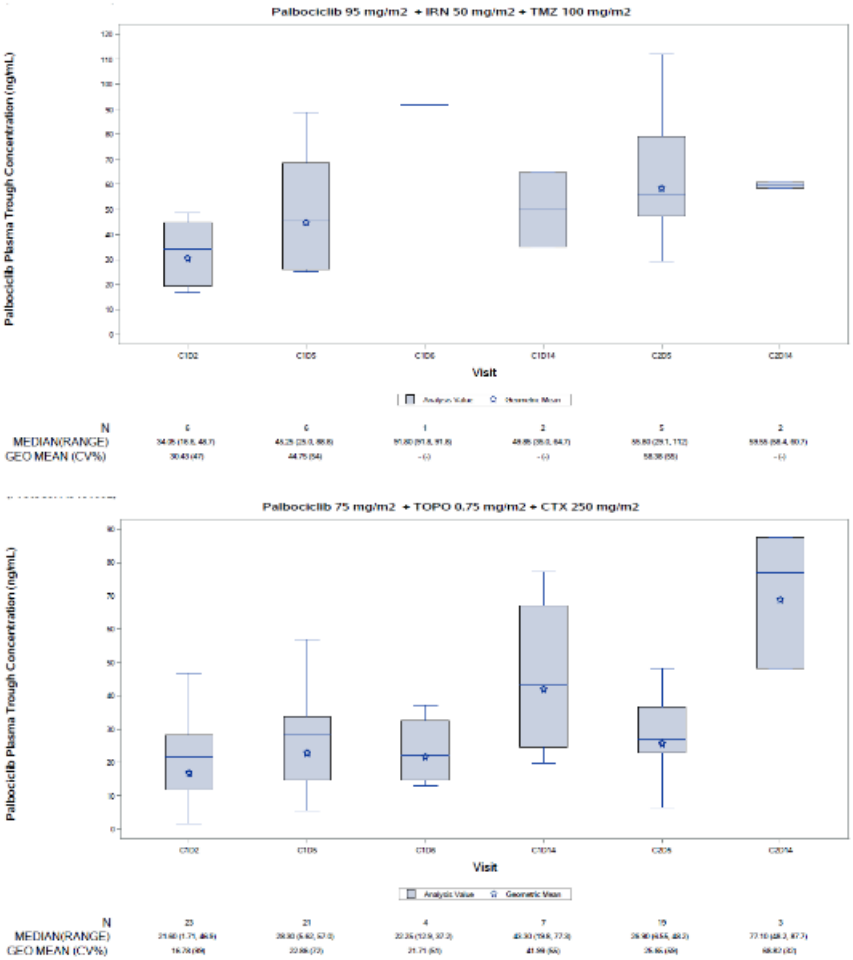
Table 2 Descriptive Summary of Steady-State Palbociclib Plasma PK Parameters (Phase 1) – PK Parameter Analysis Set (Protocol A5481092)

Parameter (Units)[a]	Palbociclib 55 mg/m2 + IRN 50 mg/m2 + TMZ 100 mg/m2 (N=4) n	Statistics	Palbociclib 75 mg/m2 + IRN 50 mg/m2 + TMZ 100 mg/m2 (N=20) n	Statistics	Palbociclib 95 mg/m2 + IRN 50 mg/m2 + TMZ 100 mg/m2 (N=6) n	Statistics	Palbociclib 75 mg/m2 + TOPO 0.75 mg/m2 + CTX 250 mg/m2 (N=26) n	Statistics
AUCTAU (h*ng/mL)	3	1161 (7)	14	1538 (49)	6	2082 (38)	20	1290 (59)
CL/F (L/h/m2)	3	47.31 (8)	14	48.75 (49)	6	45.61 (39)	20	58.12 (59)
CL/F (L/h)	3	62.07 (44)	14	59.87 (88)	6	63.47 (56)	20	72.41 (59)
CMAX (ng/mL)	3	80.44 (21)	15	113.2 (49)	6	127.9 (44)	23	91.45 (58)
CTROUGH (ng/mL)	3	30.42 (7)	15	36.01 (50)	6	44.75 (54)	23	23.98 (81)
TMAX (h)	3	6.03 (2.02-6.08)	15	4.17 (1.85-6.47)	6	5.02 (2.07-8.05)	23	4.05 (1.97-24.0)

Source: Table 14.4.5.1.2.1.1
N = Total number of participants in the treatment group in the indicated population.
n = number of participants contributing to the summary statistics.
a. Geometric mean (geometric %coefficient of variation) for all except median (range) for Tmax.
Individual values are listed when there are less than 3 evaluable measurements.
Summaries include parameters derived from profiles that meet steady state criteria.
Samples with more than 30 mins time deviation when nominal TPD=0H are excluded from CTROUGH summaries.
Profiles with vomit comments from Dosing CRF page are excluded.
Make-up visits are included only if Cycle 1 Day 5 is not available/reportable.
PFIZER CONFIDENTIAL SDTM Creation: 15FEB2024 (19:06) Source Data: adpp Table Generation: 22FEB2024 (11:38)
(Data cutoff date : 31JUL2023 Database snapshot date : 21NOV2023) Output File: ./A5481092/a5481092_pk_ph1/adpp_s101_1i
Table 14.4.5.1.3.1.1 Palbociclib (PD-0332991) is for Pfizer internal use.

Figure 2 Geometric Mean Steady-State Palbociclib C_{trough} Values by Visit (Linear Scale), Phase 1, Protocol A5481092

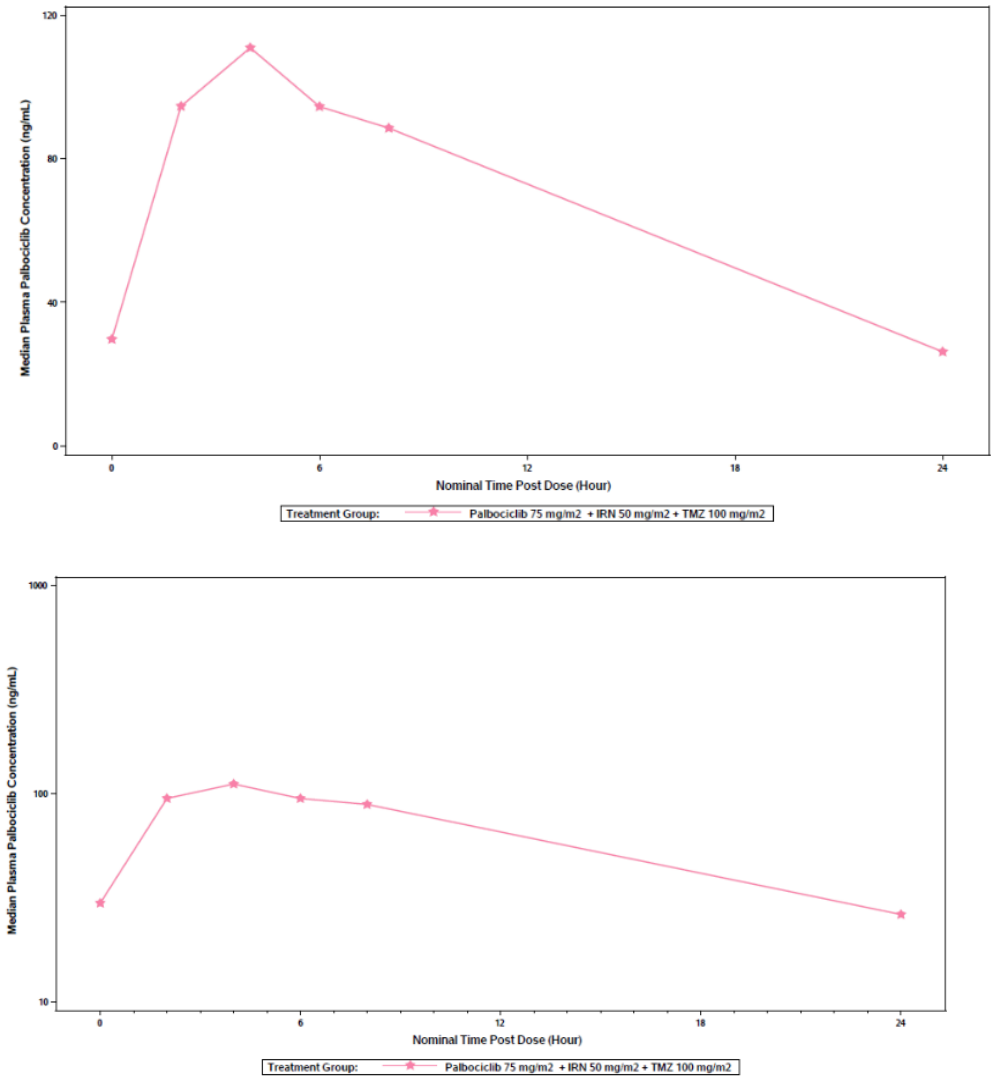




Pharmacokinetic results - phase 2 part

Median plasma steady-state palbociclib concentration-time profiles on C1D5 in EWS participants following 75 mg/m2 doses (administered orally QD), in combination with IRN + TMZ are presented below. Plasma steady-state PK parameters for palbociclib are summarized in Table 68. Box plots of individual and geometric mean Ctrough by visit are presented also below.

Figure 3 Median Plasma Steady-State Palbociclib Concentration-Time Profiles, Phase 2, Upper Panel: Linear Scale; Lower Panel: Semi-Log Scale; Protocol A5481092



The lower limit of quantification is 1.00ng/mL.
Summary statistics have been calculated by setting concentration values below the lower limit of quantification to zero.
Summaries include concentrations that meet steady state criteria.
Samples with more than 30 mins time deviation when nominal TPD=0H are excluded.
Profiles with vomit comments from Dosing CRF page are excluded.
Samples from make-up visit are excluded.
PK concentrations with sampling deviation time of greater than 20% are excluded.
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(Data cutoff date : 31JUL2023 Database snapshot date : 21NOV2023) Output File: /A5481092/a5481092_pk_ph2/adpc_f101_2

Figure 4 Individual and Geometric Mean Steady-State Palbociclib C_{trough} Values by Visit (Linear Scale), Phase 2, Protocol A5481092

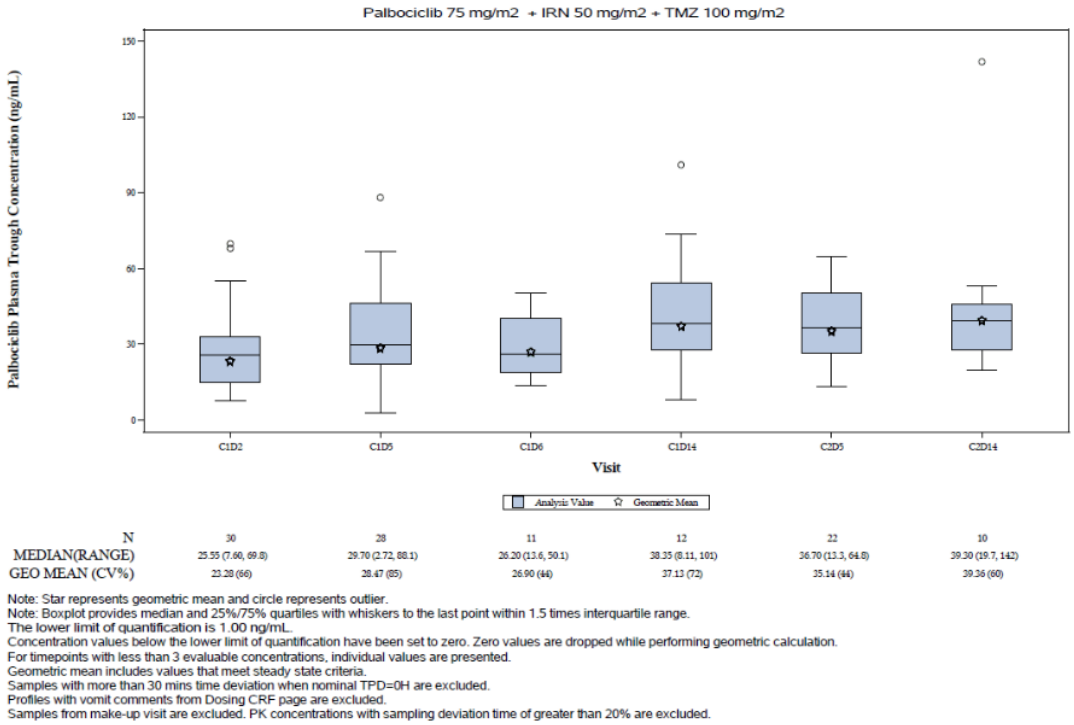


Table 3 Descriptive Summary of Steady-State Palbociclib Plasm PK Parameters (Phase 2) – PK Parameter Analysis Set (Protocol A5481092)

Parameter (Units)[a]	Palbociclib 75 mg/m2 + IRN 50 mg/m2 + TMZ 100 mg/m2 (N=31)	
	n	Statistics
AUCTAU (h*ng/mL)	20	1578 (41)
CL/F (L/h/m2)	20	47.52 (41)
CL/F (L/h)	20	60.54 (56)
CMAX (ng/mL)	22	121.1 (48)
CTROUGH (ng/mL)	23	26.19 (90)
TMAX (h)	22	4.00 (1.68-8.00)

Source: Table 14.4.5.1.2.1.2
N = Total number of participants in the treatment group in the indicated population.
n = number of participants contributing to the summary statistics.
a. Geometric mean (geometric %coefficient of variation) for all except median (range) for Tmax.
Individual values are listed when there are less than 3 evaluable measurements.
Summaries include parameters derived from profiles that meet steady state criteria.
Samples with more than 30 mins time deviation when nominal TPD=0H are excluded from CTROUGH summaries.
Profiles with vomit comments from Dosing CRF page are excluded.
Make-up visits are included only if Cycle 1 Day 5 is not available/reportable.
PFIZER CONFIDENTIAL SDTM Creation: 15FEB2024 (19:10) Source Data: adpp Table Generation: 22FEB2024 (11:40)
(Data cutoff date : 31JUL2023 Database snapshot date : 21NOV2023) Output

2.3.1. Discussion on clinical pharmacology aspects

Plasma steady-state PK exposure (75mg/m2 palbociclib dose) and PK parameters for palbociclib were similar between phase 1 and phase 2.

2.4. Clinical aspects

2.4.1. Introduction

Palbociclib (IBRANCE) is a small molecule inhibitor of cyclin-dependent kinases (CDK) 4 and 6, administered orally. It is approved in the EU for the treatment of patients with hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced or metastatic breast cancer in combination with an aromatase inhibitor as initial endocrine-based therapy or in combination with fulvestrant in patients with disease progression following endocrine therapy.

Paediatric Ewing sarcoma (EWS) is an aggressive bone and soft tissue tumour mediated by somatic chromosomal translocations resulting in the expression of chimeric fusions of EWS and ETS family transcription factors. There is an increasing body of literature showing the dependency of paediatric tumour cells on CDK4/6 and cyclin D1 including EWS and myeloid and lymphoblastic leukaemia to support the use of CDK4/6 inhibitors.

The antitumor activity of palbociclib in combination with the chemotherapy regimen, temozolomide (TMZ) and irinotecan (IRN) has been investigated in 3 different patient-derived EWS models grown subcutaneously in immunocompromised mice. The IRN and TMZ combination resulted in significant tumour growth inhibition (TGI) in 2 models and non-significant decrease of tumour volume in 1 model. The addition of palbociclib to IRN and TMZ resulted in similar TGI to that with the IRN and TMZ alone for 2 models while in the third model the triple combination demonstrated significantly increased antitumor activity versus IRN and TMZ alone. In the latter model, the superiority of the triple combination was sustained in the post-dosing period of several weeks. The addition of palbociclib to the chemotherapy regimen increased the number of responders from 1 partial response to 2 complete responses and 1 tumour free survivor, further supporting improved efficacy for the triple combination in this model (Pfizer, 2020). These findings highlighted the potential antitumor benefit of adding palbociclib, a CDK4/6 inhibitor, to a combination of a topoisomerase inhibitor (e.g. IRN or topotecan (TOPO) and an alkylating agent (e.g. TMZ or cyclophosphamide [CTX]).

Study A5481092 is a Phase 1/2 multicenter, open-label study to evaluate palbociclib in combination with either irinotecan and temozolomide or in combination with topotecan and cyclophosphamide in paediatric patients with recurrent or refractory (r/r) solid tumours. The study consists of a non-randomized Phase 1 portion for r/r solid tumours followed by potential non-randomized Tumour Specific Cohort (TSC) and a randomized Phase 2 portion for r/r EWS.

The randomized Phase 2 portion of the study crossed the pre-specified futility boundary at the pre-planned interim analysis (IA) and therefore did not meet its primary endpoint of EFS based on investigator assessment. The external Data Monitoring Committee (eDMC) recommended that enrolment to the Phase 2 portion of the study be stopped for lack of efficacy.

The MAH is therefore submitting this study within 6 months following acceptance of eDMC recommendation, in accordance with Article 46 of the Paediatric Regulation (European Commission [EC]) No 1901/2006, even though the TSC cohort for neuroblastoma is ongoing, since the interim clinical study report (CSR) fulfils the clinical measure of the agreed PIP in the treatment of EWS.

2.4.2. Clinical study -Study A5481092

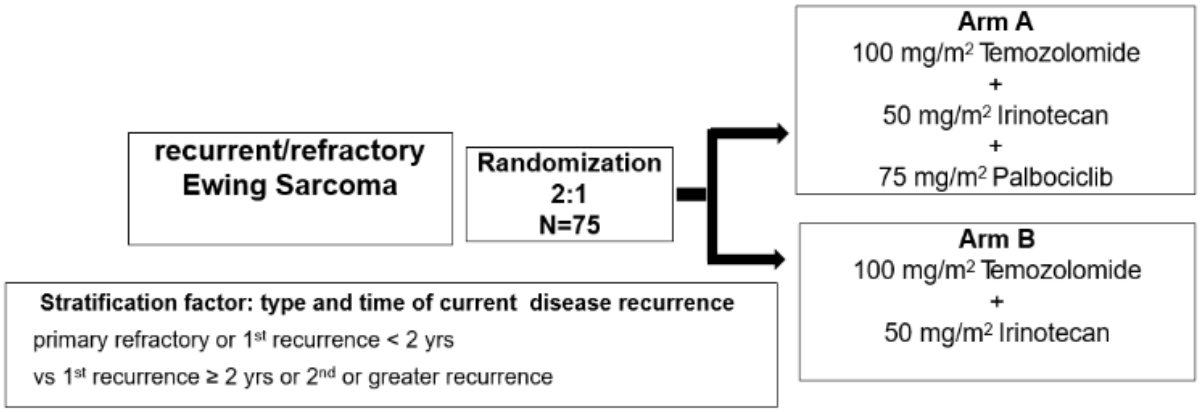
2.4.2.1. Description

Study A5481092 is a Phase 1/2 multicenter, open-label study to evaluate palbociclib in combination with either Irinotecan (IRN) and Temozolomide (TMZ) or Topotecan (TOPO) and Cyclophosphamide (CTX) chemotherapy in children, adolescents and young adults with r/r solid tumours. The study consists of a non-randomized Phase 1 portion for participants with r/r solid tumours followed by potential non-randomized tumor specific cohort(s) (TSC) and a randomized Phase 2 portion for participants with r/r Ewing sarcoma (EWS). The Phase 2 portion is part of the agreed PIP for palbociclib in the treatment of EFS.

The Phase 1 portion of the study was to estimate the MTD/potential RP2D and to confirm the RP2D of palbociclib in combination with IRN and TMZ and palbociclib in combination with TOPO and CTX in participants with r/r solid tumours for whom no standard therapy was available.

Once the RP2D was confirmed for the combination of palbociclib with IRN and TMZ in the Phase 1 portion of the study, the Phase 2 portion of the study was initiated to compare the efficacy of palbociclib in combination with IRN and TMZ versus IRN and TMZ alone in children, adolescents, and young adults with r/r EWS for whom no standard therapy was available. Approximately 75 participants were to be randomized in a 2:1 ratio to receive either palbociclib in combination with IRN and TMZ (Arm A: approximately 50 participants) or IRN and TMZ chemotherapy alone (Arm B: approximately 25 participants). Randomization was stratified using block randomization by type and time of current disease recurrence (primary refractory or 1st recurrence <2 years versus 1st recurrence ≥2 years since completion of 1st line treatment or 2nd or greater recurrence). The schema is shown in **Error! Reference source not found.**.

Figure 5 Study Schema – Phase 2 Palbociclib in Combination With IRN and TMZ in Ewing sarcoma (EWS)



2.4.2.2. Objective(s) and endpoints

	Primary objectives	**Endpoints**
Dose escalation/dose determination parts	To estimate the MTD for the combination of palbociclib, TMZ and IRN in children, adolescents, and young adults with r/r solid tumours. To determine the potential RP2D for palbociclib in combination with TOPO and CTX in children, adolescents, and young adults with r/r solid tumours	First cycle DLTs
Dose expansion cohort	To evaluate the safety, and confirm the RP2D for the combination of palbociclib, TMZ, and IRN at the MTD in children, adolescents and young adults with r/r solid tumours that are known to be sensitive to a CDK4/6 inhibitor. To evaluate the safety, and confirm the RP2D for the combination palbociclib CTX, and TOPO in children, adolescents and young adults with r/r solid tumours that are known to be sensitive to a CDK4/6 inhibitor.	AEs as characterized by type, frequency, severity, timing, seriousness, and relationship to study therapy; laboratory test data including HbA1c as characterized by type, frequency, severity, and timing; ECG parameters, and vital signs
	To evaluate the preliminary antitumor activity of palbociclib combined with TMZ and IRN. To evaluate the preliminary antitumor activity of palbociclib combined with TOPO and CTX	OR, as assessed by investigator using RECIST version 1.1/modified RANO for CNS malignancies/INRC for neuroblastoma
Randomised Phase 2	To compare the efficacy of palbociclib in combination with TMZ and IRN vs TMZ and IRN chemotherapy alone in the treatment of children, adolescents, and young adults with r/r EWS	EFS based on investigator assessment

Abbreviations: AEs, adverse events; DLT, dose limiting toxicity, EFS, event-free survival; OR, objective response

2.4.2.3. Participant flow

A total of 114 participants (aged ≥2 and <21 years at the time of study entry) with r/r solid tumours were enrolled at 110 centers in 19 countries.

Phase 1

As of the cut-off date, a total of 70 participants were screened, of which 60 participants were enrolled and 59 participants were treated.

- 34 participants were enrolled for treatment with the combination of palbociclib + IRN + TMZ, of which 33 participants were treated. All the treated participants discontinued the study intervention with the most common reason being progressive disease (78.8%). A total of 27 (81.8%) participants entered the follow-up period, of which 22 (66.7%) participants discontinued with the most common reason being death (60.6%). There were 2 (6.1%) participants who completed the follow-up and 3 (9.1%) ongoing participants.
- 26 participants were enrolled and treated with the combination of palbociclib + TOPO + CTX. A total of 25 (96.2%) participants discontinued the study intervention with the most common

reason being progressive disease (61.5%). A total 23 (88.5%) participants entered the follow-up period, of which 15 (57.7%) participants discontinued with the most common reason being death (53.8%). There were 7 (26.9%) ongoing participants. There was 1 (3.8%) participant who completed follow-up.

Phase 2

As of the cutoff date, a total of 70 participants were screened, of which 54 participants were randomized (35 to the palbociclib + IRN + TMZ arm and 19 to the IRN + TMZ arm) and 53 participants were treated (34 in the palbociclib + IRN + TMZ arm and 19 in the IRN + TMZ arm)

- A total of 35 (100%) and 19 (100%) in the palbociclib + IRN +TMZ arm and the IRN + TMZ arm, respectively, were entered in the treatment phase. Of these participants, 1 (2.9%) in the palbociclib + IRN + TMZ arm was not dosed; 6 (17.1%) and 7 (36.8%) participants were still receiving study treatment; 29 (82.9%) and 12 (63.2%) participants discontinued treatment, respectively.
    - The most common reason for discontinuation was progressive disease (60.0% and 42.1%, respectively).
    - No participant completed the treatment phase in either arm.
- A total of 25 (71.4%) and 12 (63.2%) participants in the palbociclib + IRN + TMZ arm and the IRN + TMZ arm, respectively, entered the follow-up period. Of these participants, 11 (31.4%) and 5 (26.3%) participants discontinued with the most common reason being death (28.6% and 21.1%, respectively); 14 (40.0%) and 7 (36.8%) participants were under follow-up. No participants in either arm completed the follow-up period.

2.4.2.4. Demographics

Phase 1

Treatment combination of palbociclib + IRN +TMZ

- Most participants were male (21, 63.6%); the median age was 14 years (range: 2, 20), with most participants (16, 48.5%) between the age of 12-17 (inclusive) years old; most of the participants (21, 63.6%) were White.
- For participants >16 years, most participants had a baseline ECOG PS of 0 (3 participants) or 1 (5 participants). For participants ≤16 years, most participants had a baseline of 90-100% Lansky Performance Status (15 participants) or 70-80% Lansky Performance Status (7 participants).

Treatment combination of palbociclib + TOPO + CTX

- Most participants were female (14, 53.8%); the median age was 11 years (range: 2, 20), with most participants (8, 30.8%, each) between the age of 7-11, and 12-17 years old; most of the participants (19, 73.1%) were White.
- For participants >16 years, 1 participant had a baseline ECOG PS of 0, 3 participants had a baseline ECOG PS of 1, and 3 participants had a baseline ECOG PS of 2. For participants ≤16 years, all participants had a baseline of 70-80% (5 participants) or 90-100% Lansky Performance Status (15 participants).

Phase 2

Demographic and baseline characteristics of the 54 participants randomized are shown below:

- The median age (range) was 13.0 (5, 19) years in the palbociclib + IRN + TMZ arm and 15.0 (9, 20) years in the IRN + TMZ arm, with most participants aged <18 years old in both arms (30 [85.7%] in the palbociclib + IRN + TMZ arm and 16 [84.2%] in the IRN + TMZ arm).
- Most of the participants were male (27 [77.1%] in the palbociclib + IRN + TMZ arm and 11 [57.9%] in the IRN + TMZ arm).
- ECOG PS was examined for participants >16 years. Comparing the palbociclib + IRN + TMZ arm to the IRN + TMZ arm, 8.6% versus 15.8% of participants had a baseline ECOG PS of 0, 11.4% versus 15.8% of participants had a baseline ECOG PS of 1, and 2.9% of participants versus none had a baseline ECOG PS of 2.
- Type and time of current disease recurrence was generally balanced between the two arms (71.4% and 68.4% had primary refractory or first recurrence <2 years; 28.6% and 31.6% had first recurrence ≥ 2 years or second or greater recurrence in the palbociclib + IRN + TMZ arm and the IRN + TMZ arm, respectively).
- The majority of participants had metastatic recurrence in both arms (80.0% in the palbociclib + IRN + TMZ arm and 84.2% in the IRN+TMZ arm)

2.4.2.5. Efficacy results

Phase 1

Palbociclib + IRN + TMZ: The confirmed OR rates based on investigator assessment were 8.7% (95% CI: 2.4%, 26.8%) in the pooled DL2 and expansion cohort.

Palbociclib +TOPO + CTX: The confirmed OR rates based on investigator assessment were 11.5% (95% CI: 4.0%, 29.0%) in the pooled DL1 and expansion cohort.

For the combination of palbociclib + IRN + TMZ, the MTD and the confirmed RP2D was determined to be palbociclib 75 mg/m2.

Phase 2

Primary endpoint

The prespecified interim analysis was performed per protocol based on 33 EFS events (61.1% of 54 participants) with the data cutoff date of 31 July 2023.

The study did not meet its primary objective of improving EFS with palbociclib + IRN + TMZ when compared to IRN + TMZ alone in the indicated participant population. The observed HR was 2.03 (95% CI: 0.902, 4.572; stratified 1-sided p-value=0.9621). The median EFS was 1.5 months (95% CI: 1.4, 4.2) for the palbociclib + IRN + TMZ arm and 4.4 months (95% CI: 2.6, NE) for the IRN + TMZ arm (**Table *4***).

The Kaplan-Meier plot of EFS based on investigator assessment is presented in **Figure *6***.

The median duration of follow-up for EFS was 4.5 months (95% CI: 3.6, NE) in the palbociclib + IRN + TMZ arm and 5.5 months (95% CI: 3.2, 9.1) in the IRN + TMZ arm.

Table 4. Summary of Event-Free Survival Based on Investigator Assessment (Phase 2) - Full Analysis Set

	Palbociclib+IRN+TMZ (N=35)	IRN+TMZ (N=19)
Participants with event, n (%)	23 (65.7)	10 (52.6)
Type of event, n (%)		
Progressive disease	22 (62.9)	10 (52.6)
Secondary malignancy	0	0
Death	1 (2.9)	0
Participants censored, n (%)	12 (34.3)	9 (47.4)
Reason for censoring, n (%)		
No adequate baseline assessment	2 (5.7)	0
Event after ≥ 2 missing or inadequate post-baseline assessments	1 (2.9)	0
Withdrawal of consent	1 (2.9)	0
Lost to follow-up	0	0
No adequate post-baseline tumor assessment	0	0
Ongoing without an event	8 (22.9)	9 (47.4)
EFS (%) (95% CI) [a]		
at 3 months	34.6 (18.3, 51.6)	66.0 (36.5, 84.3)
at 6 months	18.2 (5.4, 36.8)	29.7 (7.8, 56.0)
at 12 months	NE (NE, NE)	29.7 (7.8, 56.0)
at 18 months	NE (NE, NE)	NE (NE, NE)
Kaplan-Meier estimates of Time to Event (months) Quartiles (95% CI) [b]		
Q1	1.35 (1.25, 1.51)	1.31 (1.31, 5.49)
Median	1.54 (1.41, 4.24)	4.40 (2.60, NE)
Q3	4.90 (1.64, 6.01)	12.78 (4.40, NE)
Stratified analysis [c] Comparison vs IRN+TMZ		
Hazard Ratio [d]	2.03	
60% CI [d]	1.433, 2.877	
95% CI [d]	0.902, 4.572	
1-sided p-value [e]	0.9621	

The denominator to calculate percentages is N, the number of participants in the full analysis set within each treatment.
[a] Estimated from the Kaplan-Meier curve. CIs are derived using the log-log transformation with back transformation to untransformed scale.
[b] Based on the Brookmeyer and Crowley method.
[c] Stratified by type and time of current disease recurrence (primary refractory or 1st recurrence < 2 years versus 1st recurrence≥2 years or 2nd or greater recurrence) at randomization from IRT stratification values.
[d] Hazard ratio based on Cox proportional hazards model. Naïve CIs are presented.
[e] p-value based on stratified log-rank test.
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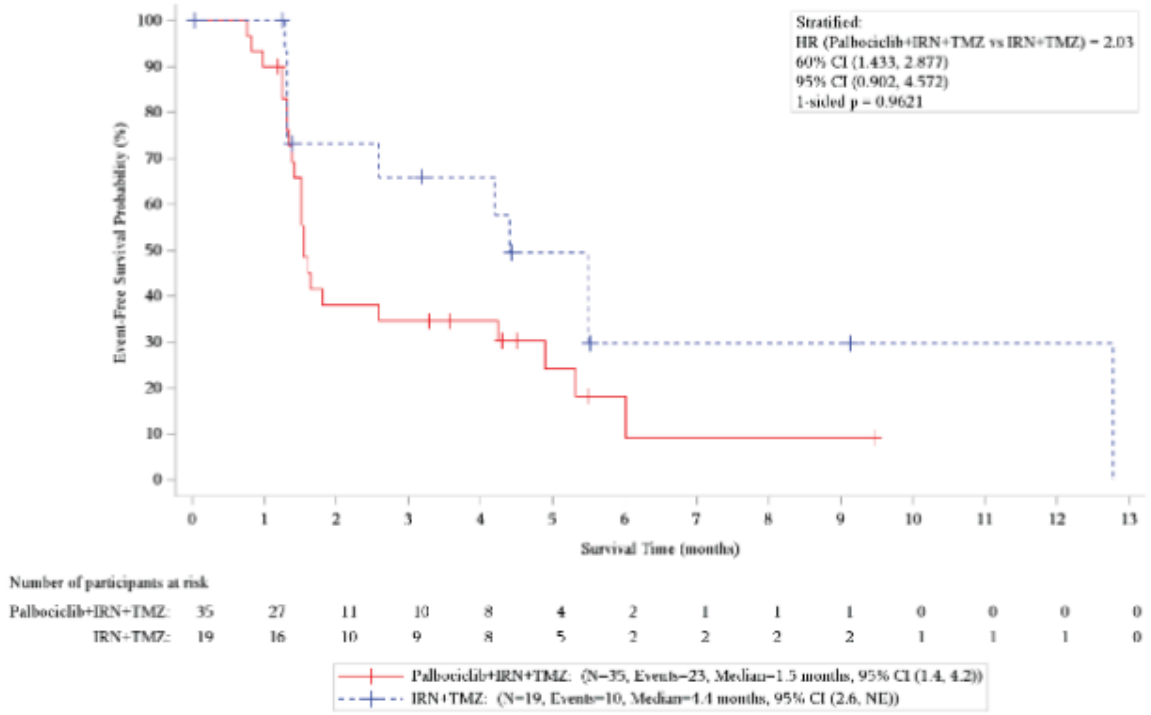
Figure 6. Kaplan-Meier Plot of Event-Free Survival Based on Investigator Assessment (Phase 2)



The performed sensitivity analyses were consistent with the primary EFS results described above, supporting the robustness of the primary EFS analysis.

Results for investigator assessed EFS in the pre-specified subgroups, including type and time of current disease recurrence, age, race, prior treatment combination of IRN and/or TMZ, were consistent with the primary EFS analysis. These subgroup analyses were exploratory in nature and results should be interpreted with caution due to small sample sizes of the subgroups.

Secondary Efficacy Endpoint: Event-Free Survival Assessed by BIRC Assessment

The HR for EFS by BIRC assessment was 1.54 (95% CI: 0.743, 3.201; stratified 1-sided p-value=0.8768). The median EFS was 1.5 months (95% CI: 1.3, 3.2) for the palbociclib + IRN + TMZ arm and 4.1 months (95% CI: 1.4, 9.1) for the IRN + TMZ arm.

Secondary Efficacy Endpoint: Objective Response

The confirmed OR rates for the full analysis set (FAS) based on investigator assessment were 14.3% (95% CI: 6.3%, 29.4%) for the palbociclib + IRN + TMZ arm and 15.8% (95% CI: 5.5%, 37.6%) for the IRN + TMZ arm.

2.4.2.6. Safety results

Exposure

Phase 1

For the combination of palbociclib + IRN + TMZ, the median duration of treatments for all participants was 1.6 months (range: 0.4, 22.5). The median relative dose intensity was 93.9% (range: 72.3%, 114.3%) for palbociclib, 92.9% (range: 73.7%, 102.4%) for IRN, and 94.3% (range: 73.9%, 102.4%) for TMZ.

For the combination of palbociclib + TOPO + CTX, the median duration of treatments for all participants was 1.4 months (range: 0.5, 24.0), the median relative dose intensity was 95.2% (range: 69.3%, 100.5%) for palbociclib, 97.3% (range: 85.6%, 100.0%) for TOPO, and 97.3% (range: 85.6%, 100.0%) for CTX.

Phase 2

In the palbociclib + IRN + TMZ arm, the median duration of treatments is 1.4 months (range: 0.3, 7.9). The median relative dose intensity was 94.1% (range: 65.0%, 107.7%) for palbociclib, 95.2% (range: 75.4%, 100.0%) for IRN, and 95.2% (range: 75.4%, 100.0%) for TMZ. In the IRN + TMZ arm, the median duration of treatment is 1.5 months (range: 0.2, 8.4). The median relative dose intensity was 100.0% (range: 73.3%, 102.4%) for IRN and 100.0% (range: 73.3%, 102.4%) for TMZ.

Summary of adverse events

Phase 1

Treatment Combination of Palbociclib + IRN+TMZ

- All treated 33 participants were evaluable for TEAEs and they all had at least 1 all-causality TEAE and at least 1 treatment-related TEAE.
- All-causality SAEs were reported in 14 (42.4%) participants, and 7 (21.2%) participants had treatment-related SAEs.
- A total of 28 (84.8%) had all-causality maximum Grade 3 or 4 TEAEs, all of which were treatment-related. Two (6.1%) participants had all-causality Grade 5 AEs, both of which were not related to study treatment.

Treatment Combination of Palbociclib + TOPO + CTX

- All treated 26 participants were evaluable for TEAEs and they all had at least 1 all-causality TEAE and at least 1 treatment-related TEAE.
- All-causality SAEs were reported in 12 (46.2%) participants, and 10 (38.5%) participants had treatment-related SAEs.
- A total of 25 (96.2%) and 24 (92.3%) participants had all-causality and treatment- related maximum Grade 3 or 4 TEAEs, respectively. No participants had Grade 5 AEs.

Phase 2

An overall summary of AEs in Phase 2 is presented in the table below.

Table 5. Treatment-Emergent Adverse Events (Phase 2)

Number (%) of Participants	Palbociclib+IRN+TMZ (N=34) n (%)	IRN+TMZ (N=19) n (%)	Total (N=53) n (%)
TEAEs			
Number of TEAEs	151	69	220
Participants with:			
TEAEs	30 (88.2)	18 (94.7)	48 (90.6)
Treatment-emergent SAEs	13 (38.2)	4 (21.1)	17 (32.1)
Maximum Grade 3 or 4 TEAEs	27 (79.4)	14 (73.7)	41 (77.4)
Maximum Grade 5 TEAEs	1 (2.9)	0	1 (1.9)
TEAEs leading to permanent discontinuation of all study drugs	2 (5.9)	1 (5.3)	3 (5.7)
TEAEs leading to dose reduction of any study drug	1 (2.9)	4 (21.1)	5 (9.4)
TEAEs leading to dose reduction of palbociclib	1 (2.9)	NA	1 (1.9)
TEAEs leading to dose interruption of any study drug	24 (70.6)	8 (42.1)	32 (60.4)
TEAEs leading to dose interruption of palbociclib	24 (70.6)	NA	24 (45.3)
Treatment-related TEAEs			
Number of TEAEs	108	46	154
Participants with:			
TEAEs	29 (85.3)	17 (89.5)	46 (86.8)
Treatment-emergent SAEs	7 (20.6)	3 (15.8)	10 (18.9)
Maximum Grade 3 or 4 TEAEs	26 (76.5)	13 (68.4)	39 (73.6)
Maximum Grade 5 TEAEs	0	0	0
TEAEs leading to permanent discontinuation of all study drugs	1 (2.9)	1 (5.3)	2 (3.8)
TEAEs leading to dose reduction of any study drug	1 (2.9)	4 (21.1)	5 (9.4)
TEAEs leading to dose reduction of palbociclib	1 (2.9)	NA	1 (1.9)
TEAEs leading to dose interruption of any study drug	22 (64.7)	8 (42.1)	30 (56.6)
TEAEs leading to dose interruption of palbociclib	21 (61.8)	NA	21 (39.6)

Includes all data collected since the first dose of study drug up to 35 days after last dose of study treatment.
Except for the number of adverse events participants are counted only once per treatment in each row.
Serious Adverse Events - according to the investigator's assessment.
Drug interrupted per AE CRF page which includes dose interruption or cycle delay.
MedDRA v26.1 coding dictionary applied.
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Common adverse events

Phase 1

Treatment Combination of Palbociclib + IRN+TMZ

- Among all-causality TEAEs, the most common (reported in ≥60% participants) TEAEs (by either cluster or PT) were Neutropenia (81.8%), Diarrhoea (78.8%), Nausea (72.7%), Vomiting (66.7%), Anemia (63.6%), and leukopenia (60.6%). Three (9.1%) participants had TEAEs of COVID-19.

- Among treatment-related TEAEs, the most common (reported in ≥60% participants) TEAEs (by either cluster or PT) were Neutropenia (78.8%), Diarrhoea (75.8%), Nausea (72.7%), and Vomiting (63.6%).

Treatment Combination of Palbociclib + TOPO + CTX

- Among all-causality TEAEs, the most common (reported in ≥60% participants) TEAEs (by either CLUSTER or PT) were thrombocytopenia (92.3%), anemia (88.5%), neutropenia (84.6%), leukopenia (80.8%), Lymphocyte count decreased (69.2%), and Nausea (69.2%) (Table 33). One (3.8%) participant had TEAE of COVID-19.
- Among treatment-related TEAEs, the most common (reported in ≥60% participants) TEAEs (by either CLUSTER or PT) were thrombocytopenia (92.3%), anemia (84.6%), neutropenia (80.8%), leukopenia (76.9%), Lymphocyte count decreased (69.2%), and Nausea (65.4%).

Phase 2

The incidence of all-causality and treatment-related TEAEs were generally similar across the two arms, except that the incidence of NEUTROPENIA (cluster term) was reported more in the palbociclib + IRN + TMZ arm than in the IRN + TMZ arm (Table 6).

Table 6. TEAEs by Descending Frequency MedDRA PT (including Clusters of PTs) (All Causalities, >=25% of Participants in Either Arm, All Cycles) (Phase 2)

Number (%) of Participants: by Preferred Term	Palbociclib+IRN+TMZ (N=34) n (%)	IRN+TMZ (N=19) n (%)	Total (N=53) n (%)
With Any Adverse Event	30 (88.2)	18 (94.7)	48 (90.6)
NEUTROPENIA	23 (67.6)	8 (42.1)	31 (58.5)
LEUKOPENIA	13 (38.2)	5 (26.3)	18 (34.0)
Diarrhoea	11 (32.4)	6 (31.6)	17 (32.1)
ANEMIA	10 (29.4)	6 (31.6)	16 (30.2)
Vomiting	10 (29.4)	4 (21.1)	14 (26.4)
Nausea	9 (26.5)	4 (21.1)	13 (24.5)
THROMBOCYTOPENIA	9 (26.5)	4 (21.1)	13 (24.5)

Participants are only counted once per treatment per event.
Includes all data collected since the first dose of study drug up to 35 days after last dose of study treatment.
MedDRA v26.1 coding dictionary applied.
PFIZER CONFIDENTIAL SDTM Creation: 30NOV2023 (14:03) Source Data: adae Table Generation: 14FEB2024 (04:44)
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Serious adverse events

Phase 1

Treatment Combination of Palbociclib + IRN+TMZ

- 14/33 participant (42.4%) had at least 1 all-causality SAE and 7 (21.2%) had at least 1 treatment-related SAE.

- Among all-causality SAEs, the most common (reported in ≥5% participants) SAEs (by either CLUSTER or PT) were Febrile neutropenia, INFECTIONS, and Vomiting (6.1% each).
- Among treatment-related SAEs, the most common (reported in ≥5% participants) SAEs (by either CLUSTER or PT) were Febrile neutropenia and Vomiting (6.1% each).

Treatment Combination of Palbociclib + TOPO + CTX

- 12/26 participants (46.2%) had at least 1 all-causality SAE and 10 (38.5%) had at least 1 treatment-related SAE
- Among all-causality SAEs, the most common (reported in ≥5% participants) SAEs (by either CLUSTER or PT) were Febrile neutropenia (26.9%) and INFECTIONS (11.5%)
- Among treatment-related SAEs, the most common (reported in ≥5% participants) SAEs (by either CLUSTER or PT) were Febrile neutropenia (23.1%) and INFECTIONS (11.5%)

Phase 2

The incidence of participants with all-causality SAEs in the palbociclib + IRN + TMZ arm (13 [38.2%] participants) was higher than the IRN + TMZ arm (4 [21.1%] participants). Treatment-related SAEs occurred in 7 (20.6%) participants in the palbociclib + IRN + TMZ arm and 3 (15.8%) participants in the IRN + TMZ arm, and all treatment-related SAEs were Maximum Grade 3 or 4.

Among all-causality SAEs, the most common (reported in ≥5% participants) SAEs (by either CLUSTER or PT) were Febrile neutropenia and INFECTIONS (both were 7.5%) (all were in the palbociclib + IRN + TMZ arm).

Among treatment-related SAEs, the most common (reported in ≥5% participants) SAE (by either CLUSTER or PT) was Febrile neutropenia (7.5%) (all were in the palbociclib + IRN + TMZ arm).

Deaths

Phase 1

Treatment Combination of Palbociclib + IRN+TMZ

As of the data cutoff date (31 July 2023), 22 (66.7%) deaths were reported. Most of the deaths (19/22) occurred during the follow-up period (greater than 35 days after last dose) due to "Disease under study". Three deaths were reported within 35 days after last dose of study treatment due to "disease under study". Of which, 2 (6.1%) deaths were associated with AEs, which were Malignant neoplasm progression and Respiratory failure, respectively, 1 death was after safety reporting period (within 28 days after the last dose). No deaths were associated with study treatments.

Treatment Combination of Palbociclib + TOPO + CTX

As of the data cutoff date (31 July 2023), 15 (57.7%) deaths were reported during the follow-up period (greater than 35 days after last dose). All deaths were due to "Disease under study" (Table 48). No deaths were associated with AEs.

Phase 2

As of the data cutoff date (31 July 2023), 1 (2.9%) death in the palbociclib + IRN + TMZ arm was reported within 35 days after last dose of study treatments due to disease under study (Neoplasm progression) and was not treatment-related. No deaths were observed in the IRN + TMZ arm.

During the follow-up period (greater than 35 days after last dose), a total of 13 (24.5%) deaths occurred including 9 deaths in the palbociclib + IRN + TMZ arm and 4 deaths in the IRN + TMZ arm). The primary cause of death was disease under study (12/13).

Dose modifications and treatment discontinuations

Phase 1

There was a total of 4 permanent discontinuations in the two treatment groups. In three of the cases, treatment was discontinued due to events that were considered treatment related (including thrombocytopenia, febrile neutropenia and infection).

There were a total of 8 participants who had a dose reduction of any study treatment. The most common reasons were thrombocytopenia and neutropenia.

In the palbociclib + IRN + TMZ group, there were 22 (66.7%) participants who had dose interruption of any study treatment due to all-causality TEAEs, and all of them had dose interruption of palbociclib. The most common ones (in ≥15% participants) were NEUTROPENIA (48.5%) and THROMBOCYTOPENIA (18.2%).

In the palbociclib + TOPO + CTX group there were 14 (53.8%) participants who had dose interruption of any study treatment due to all-causality TEAEs, and all of them had dose interruption of palbociclib. The most common ones (in ≥15% participants) were THROMBOCYTOPENIA (38.5%), Febrile neutropenia (19.2%), and NEUTROPENIA (19.2%).

Phase 2

There were 3 (5.7%) participants who had TEAEs leading to permanent discontinuation (2 [5.9%] participants in the palbociclib + IRN + TMZ arm and 1 [5.3%] participant in the IRN + TMZ arm), of which 2 (3.8%) were considered treatment-related (Grade 3 Alanine aminotransferase increased and Grade 3 Aspartate aminotransferase increased in the palbociclib arm and Grade 3 Diarrhoea in the IRN+TMZ arm).

In the palbociclib + IRN + TMZ arm, there was 1 (2.9%) participant who had dose reduction of palbociclib and TMZ due to TEAEs of Diarrhoea, Nausea, and Vomiting, all of which were considered treatment-related. In the IRN + TMZ arm, there were 4 (21.1%) who had dose reduction of either IRN or TMZ due to TEAEs of THROMBOCYTOPENIA and Diarrhoea, all of which were considered treatment-related.

There were 24 (70.6%) participants in the palbociclib + IRN + TMZ arm who experienced all-causality TEAEs leading to dose interruption of any study treatments with the majority of them (22 [64.7%] participants) having treatment-related TEAEs. All cases led to dose interruption of palbociclib. Among them, 21 (61.8%) participants had treatment-related TEAEs. The most common all-causality and treatment-related TEAEs (in ≥10% participants) were NEUTROPENIA (both were 47.1%) and THROMBOCYTOPENIA (both were 14.7%).

There were 8 (42.1%) participants in the IRN + TMZ arm who experienced all-causality TEAEs leading to dose interruption of any study treatments with all of these participants having treatment-related TEAEs. The most common all-causality and treatment-related TEAEs (in ≥10% participants) in the IRN + TMZ were the same to the palbociclib + IRN + TMZ arm, which were NEUTROPENIA (both were 31.6%) and THROMBOCYTOPENIA (both were 21.1%).

2.4.3. Discussion on clinical aspects

Non-clinical data have indicated that the addition of a CDK4/6 inhibitor to a combination of a topoisomerase inhibitor and an alkylating agent may improve tumour growth inhibition in Ewing sarcoma (EWS) tumour models. The agreed PIP for palbociclib therefore includes evaluation of palbociclib in the treatment of paediatric EWS.

The MAH submitted an interim report for Study A5481092, which is a Phase 1/2 multicentre, open-label study to evaluate palbociclib in combination with either Irinotecan (IRN) and Temozolomide (TMZ) or Topotecan (TOPO) and Cyclophosphamide (CTX) chemotherapy in children, adolescents and young adults with r/r solid tumours. The finalised, randomised Phase 2 portion of the study in patients with r/r EWS is part of the agreed PIP for palbociclib in the treatment of EWS. A non-randomised tumour specific cohort in neuroblastoma is still ongoing, and is not part of the current submission.

The results of the randomised Phase 2 part of study A5481092 did not show an improved EFS by adding palbociclib to the combination of IRN and TMZ in the treatment of paediatric r/r EWS. On the contrary, palbociclib appeared to have a detrimental effect on EFS as compared with IRN+TMZ alone in this patient population. Thus, the study crossed the pre-specified futility boundary at the pre-planned interim analysis. The MAH's decision to stop enrolment to the Phase 2 portion of the study is supported.

The safety profile for the combination of palbociclib and IRN+TMZ in the paediatric EWS population was as expected from the known safety profiles of palbociclib, IRN and TMZ, respectively. Although the combination appeared poorly tolerated, with a high rate of dose interruptions for palbociclib, no new safety signals were identified.

Currently, the SmPC contains the following information concerning paediatrics:

> Section 4.2
>
> *Paediatric population*
>
> *The safety and efficacy of IBRANCE in children and adolescents < 18 years of age have not been established. No data are available.*
>
> Section 5.1
>
> *The European Medicines Agency has waived the obligation to submit the results of studies with IBRANCE in all subsets of the paediatric population in the treatment of breast carcinoma (see section 4.2 for information on paediatric use).*

The approved adult indication (breast cancer) is not relevant for paediatric patients. Thus, although data from paediatric patients with EWS are now available, the results do not warrant an immediate update of the SmPC.

3. Rapporteur's overall conclusion and recommendation

☒ Fulfilled:

No further action required, however further data are expected in the context of a variation before any conclusion on product information amendments is made.