Plain Language Clinical Study
Summary

This summary reports the results of only one study. Researchers must look at the results of many types of studies to understand if a study medicine works, how it works, and if it is safe to prescribe to patients. The results of this study might be different than the results of other studies that the researchers review.

Sponsor: Pfizer Inc.

Medicine(s) Studied: Ibrance® (palbociclib)

Protocol Number: A5481092

Dates of Study: 24 May 2019 to ongoing

Title of this Study: Study of Palbociclib Combined With Chemotherapy in Pediatric Patients With Recurrent/Refractory Solid Tumors

[Phase 1/2 Study to Evaluate Palbociclib (Ibrance®) in Combination With Irinotecan and Temozolomide or in Combination With Topotecan and Cyclophosphamide in Pediatric Patients With Recurrent or Refractory Solid Tumors]

Date(s) of this Report: 14 August 2025

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– Thank You –

If you or your child participated in this study, Pfizer, the Sponsor, would like to thank you for your participation.

This summary will describe the study results. Do you have any questions about the study or the results? If so, please contact the doctor or staff at your study site.

Why was this study done?

What is a recurrent or refractory malignant solid tumor?

Cancer occurs when cells in the body divide without control. Sometimes these cells form masses called “tumors”. Tumors are called solid when they are entirely made up of cells and don’t have any liquid areas in them. A tumor is called “malignant” when it grows uncontrollably and spreads to other parts of the body. A recurrent tumor is one that comes back after treatment. A refractory tumor is one that did not respond to treatment, or that got worse during treatment.

What is Ewing sarcoma?

Ewing sarcoma is a type of cancer that grows and spreads to form solid tumors in bones or the soft tissues that surround bones. Symptoms of Ewing sarcoma may include pain and swelling near the tumor site. Ewing sarcoma is most common in children, adolescents, and young adults.

What is Neuroblastoma?

Neuroblastoma is a type of cancer that grows and spreads in developing nerve cells to form a solid tumor. Neuroblastoma is one of the most common types of cancer in children after brain cancer.

What is Ibrance® (palbociclib)?

Ibrance® (EYE-brans), also known as palbociclib, is a medicine that is approved to treat adults with some types of breast cancer that is advanced or has spread from where it started.

Palbociclib targets specific proteins or enzymes called cyclin-dependent kinases CDK4 and CDK6. These enzymes are important for normal cell division. They may cause cancer cells to grow and spread. Certain cancers are more likely to have disturbances in CDK4 and CDK6. Palbociclib prevents CDK4 and CDK6 enzymes

from functioning, which stops the cells from dividing and stops cancer growth. In this study, palbociclib was taken by mouth, as a capsule or liquid.

What are irinotecan, temozolomide, topotecan, and cyclophosphamide?

Topotecan (toh-poh-TEE-kan) and cyclophosphamide (SY-kloh-FOS-fuh-mide) are chemotherapy medicines used together in this study. In this report they are referred to as TOPO and CTX. They are given as infusions, through a needle into a vein.

Irinotecan (ir-in-oh-TEE-kan) and temozolomide (teh-moh-ZOH-loh-mide) are chemotherapy medicines used together in this study. In this report they are referred to as IRN and TMZ. IRN is given as an infusion, through a needle into a vein. TMZ is taken as a capsule by mouth or given as an infusion, through a needle into a vein.

Both of these medicine combinations have been used before to treat patients with recurrent or refractory solid tumors. This study looked at the use of different doses of palbociclib in combination with IRN + TMZ. The researchers also tested a single dose of palbociclib in combination with TOPO + CTX.

What was the purpose of this study?

The purpose of this study was to learn about the safety of combining palbociclib with chemotherapy (either IRN + TMZ or TOPO + CTX). The researchers also wanted to know if the study treatment had an effect on the cancer in children, adolescents, and young adults with recurrent or refractory solid tumors, including Ewing sarcoma and neuroblastoma.

This study had 3 parts: a Phase 1 part, a tumor specific group (cohort) part, and a Phase 2 part. The purpose of each part is shown below.

Phase 1

- In this part of the study, researchers wanted to find the highest dose of palbociclib that could be used safely with IRN + TMZ. This is also called the maximum tolerated dose or MTD. They also wanted to confirm that this dose was well-tolerated with TOPO + CTX. To do this, the researchers looked at "dose-limiting toxicities" (DLTs). A DLT is an unacceptable medical problem that usually prevents further increases in the dose of the study medication.
- Researchers also looked at the effect of treatment with palbociclib + IRN + TMZ or palbociclib + TOPO + CTX on participant's cancer. This effect was measured using the number of participants with an "objective response". Having an objective response meant that their cancer completely or partly responded to treatment.
- If 2 or more participants in Phase 1 with a specific type of tumor responded to treatment, a tumor specific cohort was to be initiated. This was to further evaluate the effectiveness of this treatment for the specific tumor type. Because 2 participants with neuroblastoma showed a response to palbociclib + TOPO + CTX, a tumor specific cohort was initiated as described below.

Tumor specific cohort

- This part of the study looked at the effect of palbociclib + TOPO + CTX on participants' cancer for participants with neuroblastoma. This effect was measured using the number of participants with an objective response. The safety of this treatment was also evaluated.

Phase 2

- This part of the study compared the effectiveness of palbociclib + IRN + TMZ to treatment with IRN + TMZ alone, in participants

with Ewing sarcoma. Researchers looked at participants' "event-free survival", or EFS. This was the length of time from the start of the study until a participant had an "event". An event could have been their cancer getting worse, being diagnosed with a second malignant cancer, or if the participant died from any cause, including their cancer or some other reason, whichever occurred first.

Researchers wanted to know:

Phase 1:

- **What was the MTD of palbociclib that could be used in combination with IRN + TMZ and was it also well-tolerated with TOPO + CTX?**

- **Did any participants who took palbociclib in combination with IRN + TMZ or with TOPO + CTX have an objective response to treatment in the dose expansion phase?**

Tumor specific cohort:

- **How many participants with neuroblastoma had an objective response to treatment with palbociclib + TOPO + CTX?**

Phase 2:

- **How long was the event-free length of time for participants with Ewing sarcoma treated with palbociclib + IRN + TMZ, compared to participants treated with IRN + TMZ alone?**

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What happened during the study?

How was the study done?

First, a study doctor checked each participant to make sure they were able to join the study. This is known as screening. What treatment they were then given depended on what group and part of the study they were in. The groups and parts are described later in this section.

Study treatments were given in continuous blocks of 21 days, called "cycles". Doses were given in milligrams per square meter of body surface area, or mg/m^2. This was because study treatment doses were calculated for each participant based on the participant's weight and height.

- Participants took palbociclib from Day 1 to Day 14 of each cycle.
- Participants took either IRN 50 mg/m^2 and TMZ 100 mg/m^2, or TOPO 0.75 mg/m^2 and CTX 250 mg/m^2, from Day 1 to Day 5 of each cycle. Which treatment they took depended on which part of the study they took part in. This is explained further below.

Participants and researchers knew which treatment and dose they were assigned to. This is called an "open-label" study.

Participants were treated until their cancer got worse, they didn't want to continue taking treatment, they had unacceptable medical problems, they were diagnosed with cancer in another place in their body, or they completed up to 24 months of treatment.

Participants' health was monitored during the study, including blood tests, physical examination, blood pressure and heart rate, and tests of the electrical activity of their heart (called an electrocardiogram or ECG). The participants' cancer was monitored with scans.

Participants had a check-up visit at least 28 days and no more than 35 days after they stopped taking their study treatment. This visit was sooner if the participant started a new non-study therapy after they stopped their study treatment. After their check-up visit, participants were then contacted about every 2 months to see how they were doing. These checks were continued for up to 2 years after the participant's last dose of study treatment.

Phase 1

Palbociclib + IRN + TMZ

Dose increase: researchers looked for the highest dose level where fewer than 2 in 6 participants (less than 33%) had a DLT, to find the MTD.

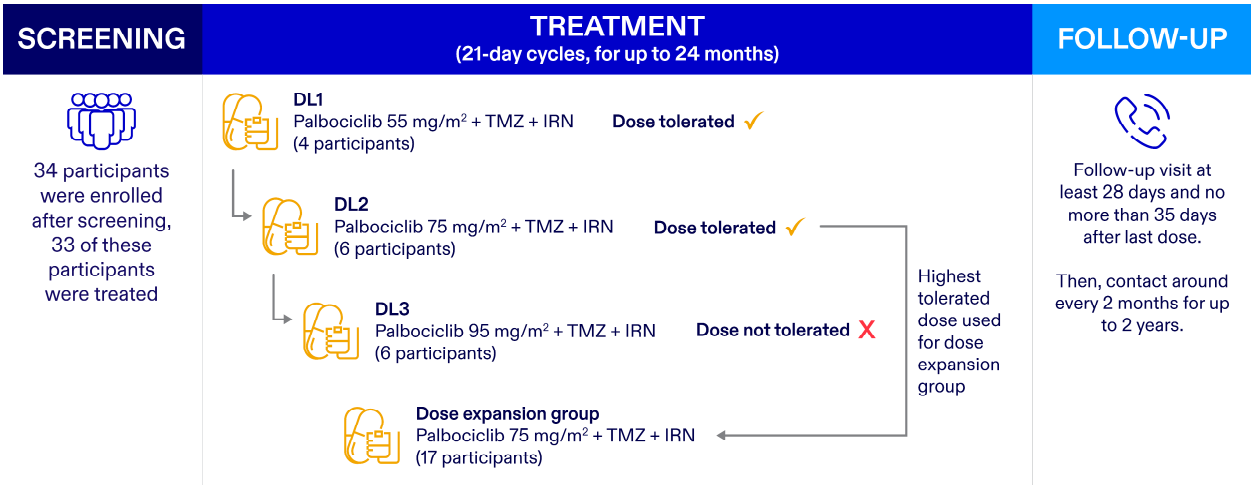
Four (4) participants were enrolled at first and took 55 mg/m^2 palbociclib with IRN and TMZ as "dose level 1" or "DL1". Once researchers found participants could tolerate this dose level, another 6 participants were enrolled to test DL2 at 75 mg/m^2 palbociclib with IRN and TMZ. Once researchers found these participants could tolerate DL2, another 6 participants were enrolled to test DL3 at 95 mg/m^2 palbociclib with IRN and TMZ. Researchers found that DL3 was not well-tolerated and palbociclib dose was not increased further.

DL2 at 75 mg/m^2 was found to be the MTD and was tested in the dose expansion as described below.

Dose expansion: seventeen (17) participants were then enrolled to confirm the MTD.

A summary is shown in Figure 1 below.

Figure 1. Study plan for Phase 1 palbociclib + IRN + TMZ



Palbociclib + TOPO + CTX

Dose determination: six (6) participants were enrolled to take 75 mg/m^2 palbociclib with TOPO + CTX. This dose was the palbociclib MTD that had been identified for use with IRN + TMZ.

Researchers looked to see if fewer than 2 in 6 participants (less than 33%) had DLTs, to confirm the 75 mg/m^2 palbociclib dose. All participants who took palbociclib + TOPO + CTX also took a medicine called "granulocyte colony stimulating factor (G-CSF)", to help them maintain their blood cell count.

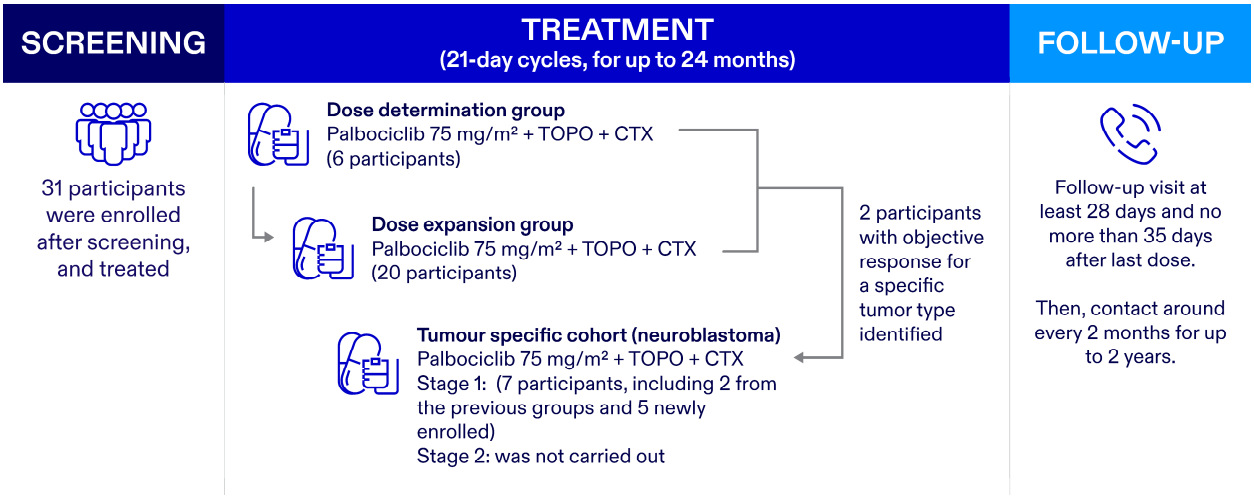
Dose expansion: twenty (20) participants were then enrolled to confirm the 75 mg/m^2 dose of palbociclib with TOPO + CTX.

Tumor specific cohort

Participants with neuroblastoma took palbociclib 75 mg/m^2 + TOPO + CTX. This was Stage 1 of what was intended to be a 2-stage evaluation. Not enough treatment response was seen at Stage 1 so evaluation of this treatment was stopped. Because of this a Stage 2 evaluation was not carried out.

What happened during the study for participants treated with palbociclib + TOPO + CTX for the Phase 1 part and the tumor specific cohort part is shown in Figure 2 below.

Figure 2. Study plan for Phase 1 and the tumor specific cohort palbociclib + TOPO + CTX

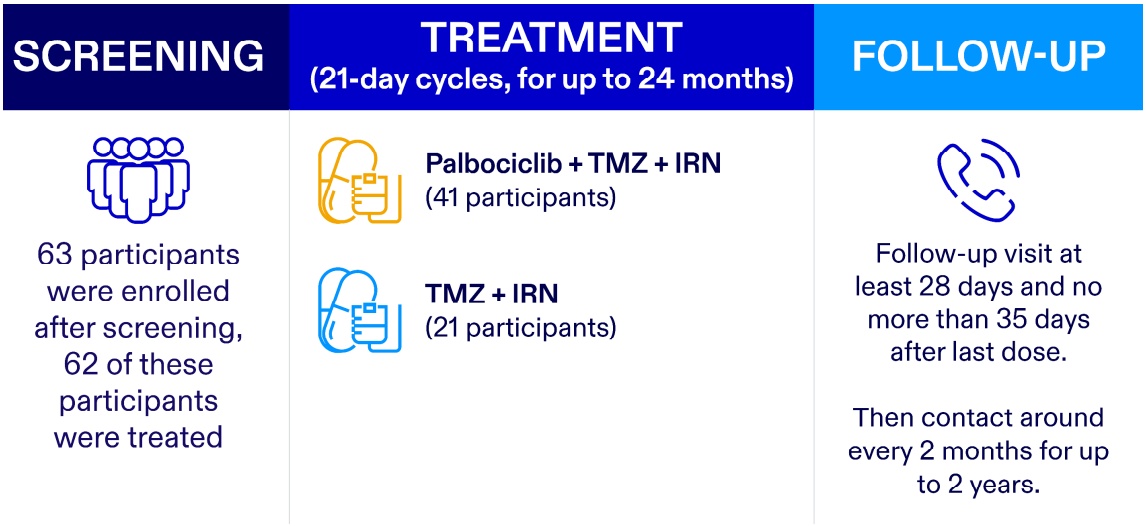


Phase 2

Participants were assigned by chance (like flipping a coin) to take either palbociclib + IRN + TMZ, or IRN + TMZ alone. There were twice as many participants randomly assigned to the palbociclib + IRN + TMZ group as to the IRN + TMZ group.

A summary is shown in Figure 3 below.

Figure 3. Study plan for Phase 2



Where did this study take place?

The Sponsor ran this study at 58 locations in 12 countries in East Asia, Europe, the Middle East, North America, South America, and South Asia.

When did this study take place?

It began 24 May 2019 and is ongoing.

Who participated in this study?

Phase 1

This part of the study included children, adolescents, and young adults who had recurrent or refractory solid tumors, including Ewing sarcoma or neuroblastoma, for whom no standard therapy was available. The results for this part of the study were recorded up to July 2023. A summary of who participated in the Phase 1 part of the study is shown in Figure 4 and Figure 5.

Figure 4. Who participated in the Phase 1 palbociclib + IRN + TMZ part of the study?

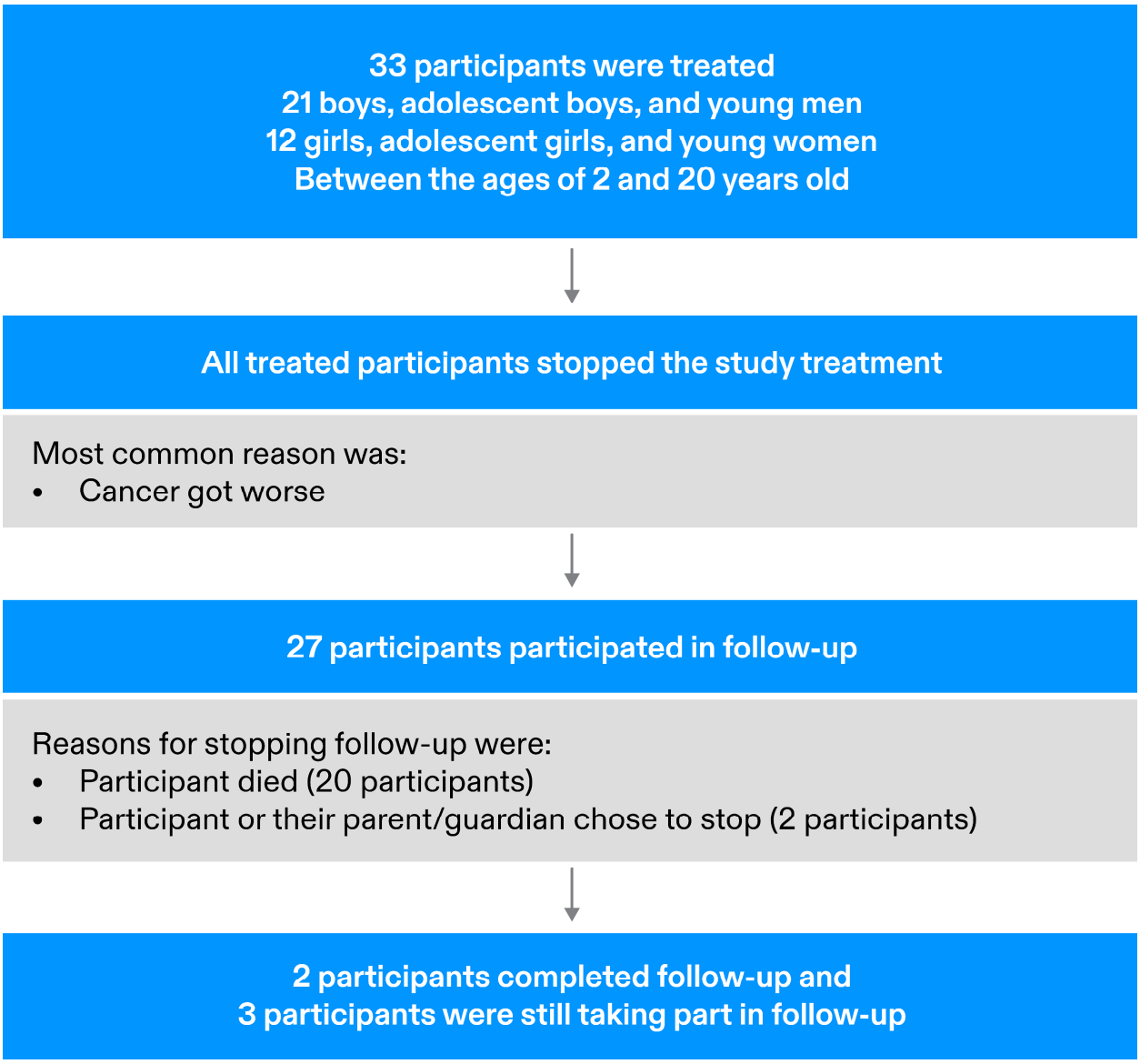
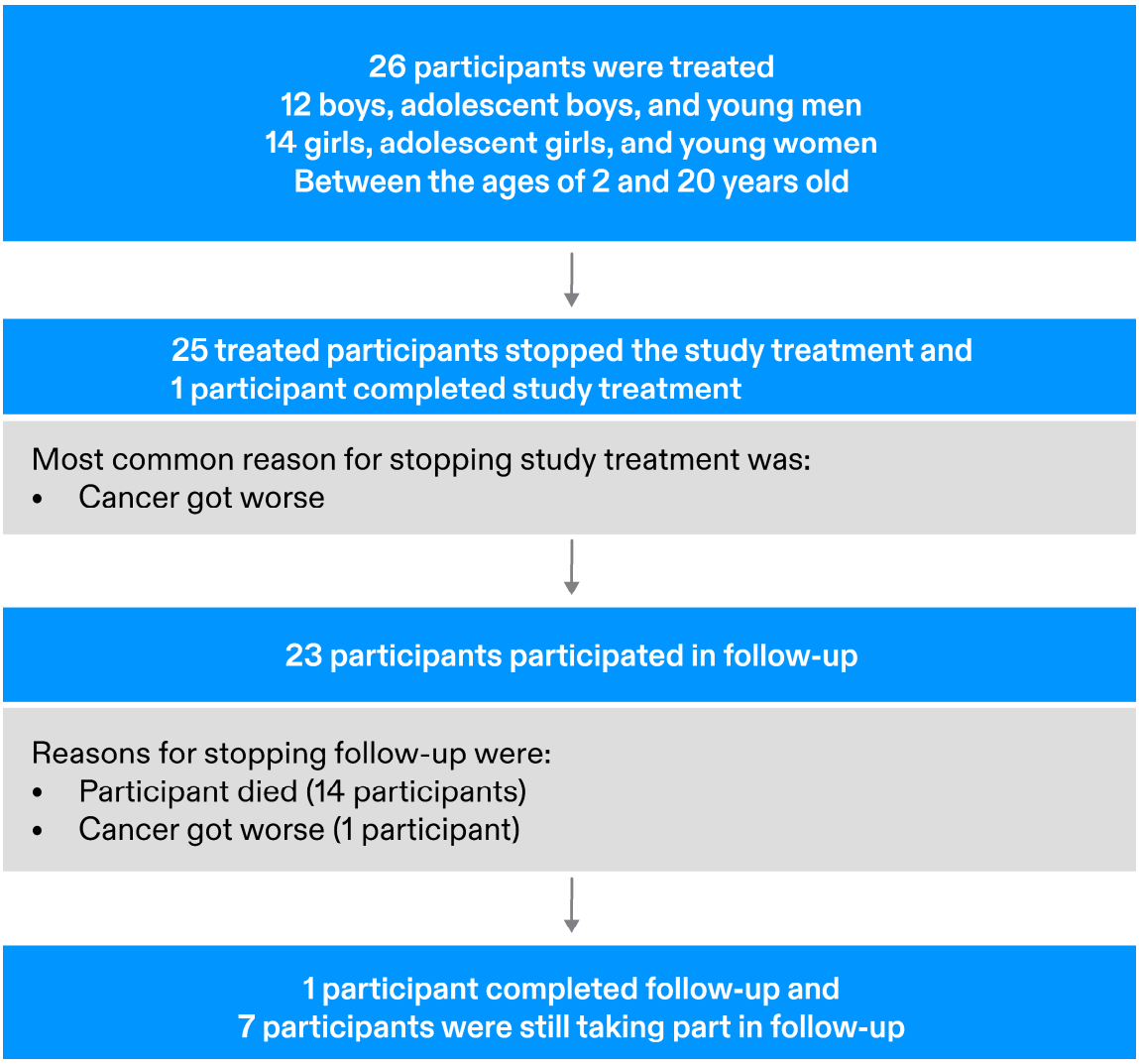


Figure 5. Who participated in the Phase 1 palbociclib + TOPO + CTX part of the study?

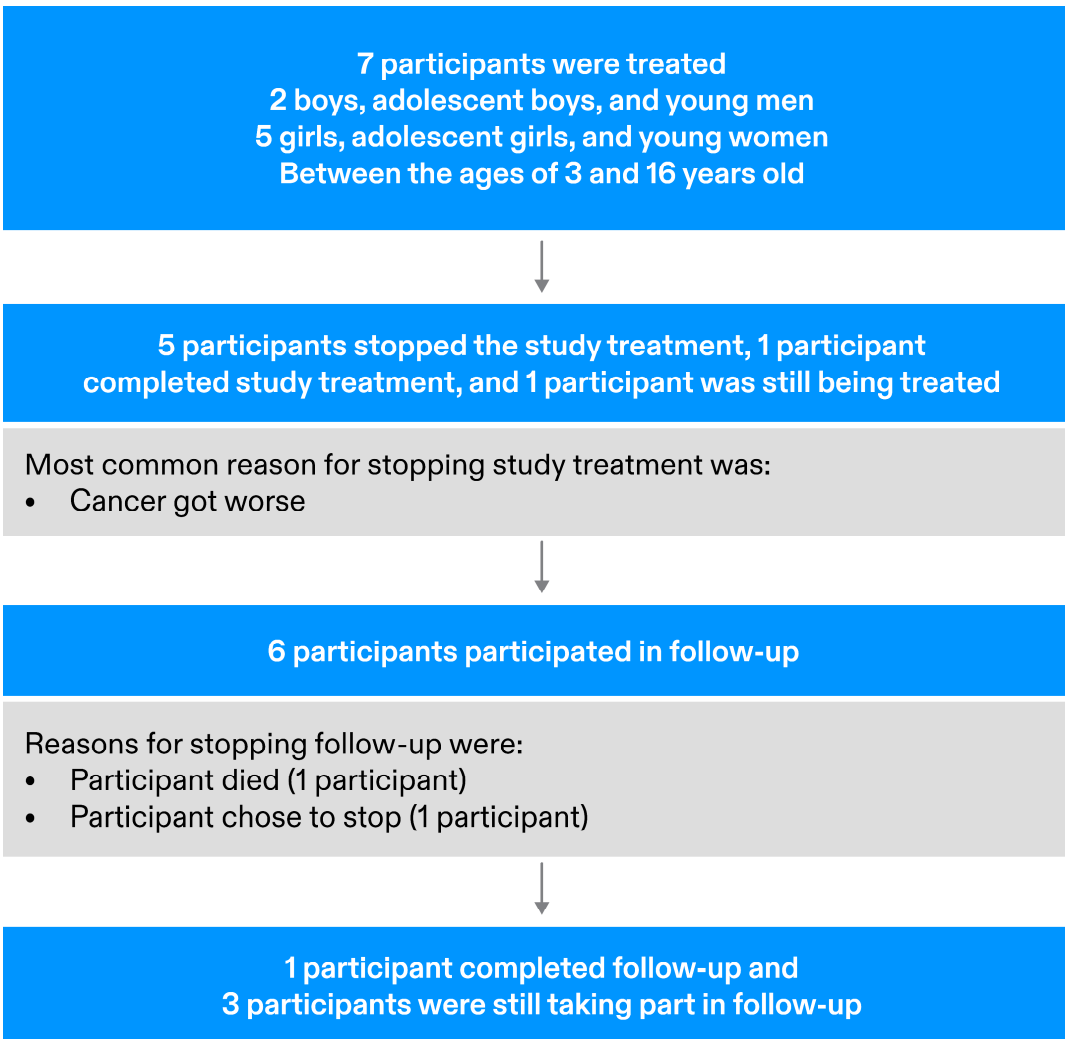


From this part of the study, 2 participants with relapsed or refractory neuroblastoma were included in Stage 1 of the tumor specific cohort part of the study.

Tumor specific cohort

This part of the study included children, adolescents, and young adults with recurrent or refractory neuroblastoma, for whom no standard therapy was available. The results for this part of the study were recorded up to August 2024 for this report. Two (2) of these participants had previously taken part in the dose finding part of the study. A summary of who participated in the tumor specific part of the study in shown in Figure 6.

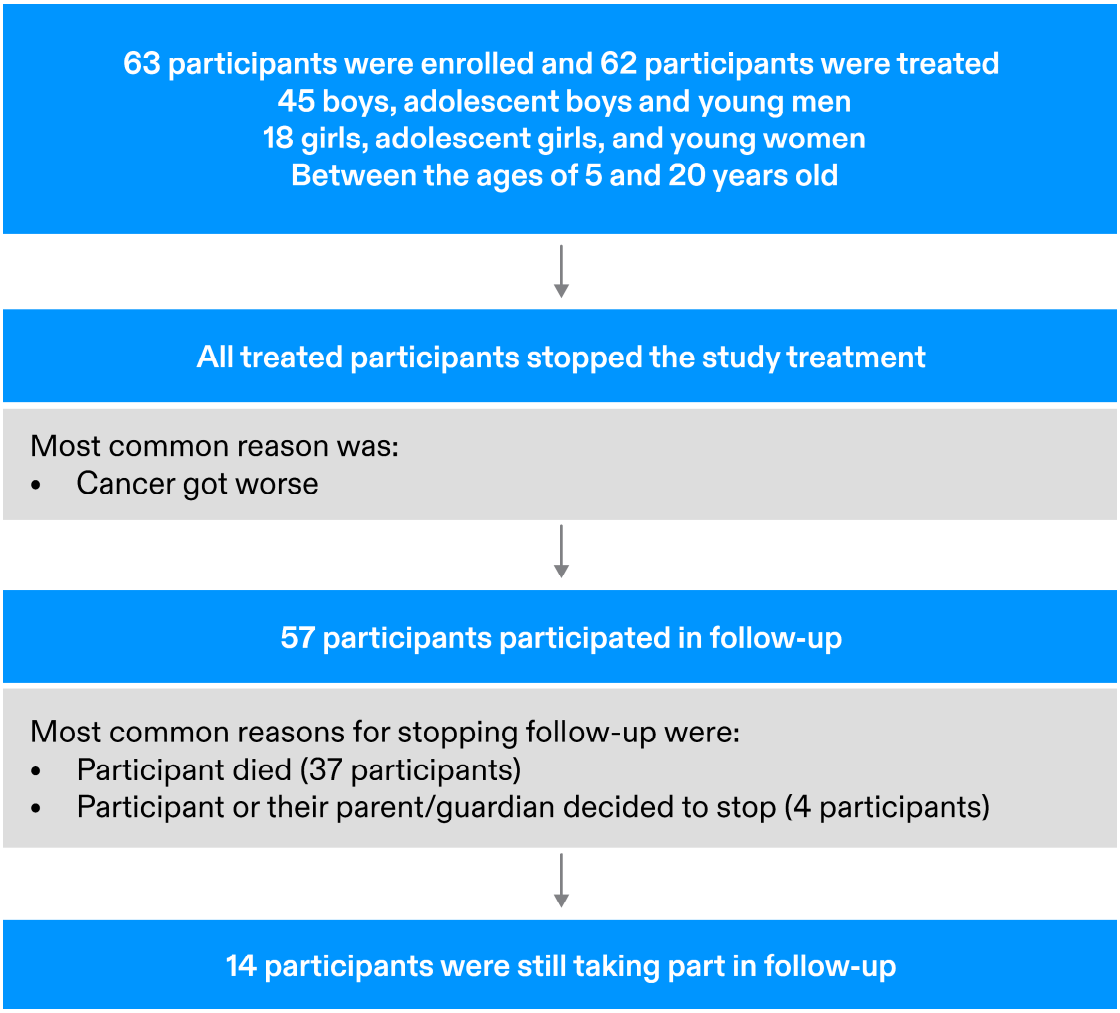
Figure 6. Who participated in the tumor specific cohort Stage 1 part of the study?



Phase 2

This part of the study included children, adolescents, and young adults with recurrent or refractory Ewing sarcoma, for whom no standard therapy was available. The results for this part of the study were recorded up to August 2024 for this report, with the EFS results recorded up to July 2023. A summary of who participated in Phase 2 of the study is shown in Figure 7.

Figure 7. Who participated in the Phase 2 palbociclib + IRN + TMZ or IRN + TMZ part of the study?



How long did the study last?

Study participants were in the study for variable lengths of time. The entire study had been running for around 5 years and 3 months as of August 2024. The study is ongoing.

In July 2023, and then in August 2024, the Sponsor reviewed the information that was available at those times. In August 2024, the Sponsor created reports of the results. This is a summary of those reports.

What were the results of the study?

Phase 1:

What was the MTD of palbociclib that could be used in combination with IRN + TMZ and was it also well-tolerated with TOPO + CTX?

To answer this question, researchers counted the number of participants who had DLTs in the dose increase/dose determination parts of the study:

- For palbociclib + IRN + TMZ, no participants who took 55 mg/m^2 palbociclib (DL1) or 75 mg/m^2 palbociclib (DL2) had DLTs. Two (2) out of 6 participants (33.3%) who took 95 mg/m^2 palbociclib had DLTs. This was over the threshold the researchers had set, of fewer than 2 in 6 participants.
- For palbociclib + TOPO + CTX, 1 out of 6 participants (16.7%) who took 75 mg/m^2 palbociclib had DLTs. This was under the threshold the researchers had set, of fewer than 2 in 6 participants. A higher palbociclib dose level was not tested because 75 mg/m^2 was the MTD identified for the palbociclib + IRN + TMZ combination.

Researchers also looked at all medical problems that participants had during the dose increase and dose expansion parts of the study. The medical problems results are shown in the next section of this report.

Based on the results to all these dose-finding questions, researchers decided that 75 mg/m^2 was the dose of palbociclib to be used with IRN + TMZ, and with TOPO + CTX.

Did any participants who took palbociclib in combination with IRN + TMZ or with TOPO + CTX have an objective response to treatment in the dose expansion phase?

To answer this question, researchers counted the number of participants who had an objective response to treatment in the dose expansion phases (Figure 8).

Figure 8. Number of participants who had an objective response to treatment with palbociclib + IRN + TMZ or palbociclib + TOPO + CTX in the dose expansion phase

Two (2) out of 17 participants (11.8%) had an objective response to treatment with palbociclib + IRN + TMZ.

Two (2) out of 20 participants (10.0%) had an objective response to treatment with palbociclib + TOPO + CTX.

Tumor specific cohort:

How many participants with neuroblastoma had an objective response to treatment with palbociclib + TOPO + CTX?

To answer this question, researchers counted the number of participants who had an objective response to their treatment in the tumor specific cohort.

This part of the study was done because 2 participants with neuroblastoma who had been given palbociclib + TOPO + CTX in the previous part of the study had an objective response to treatment, as shown above. Another 5 participants who had this type of cancer were enrolled in the study and the results from all 7 participants were analysed (Figure 9).

Figure 9. Number of participants with neuroblastoma who had an objective response to treatment with palbociclib + TOPO + CTX

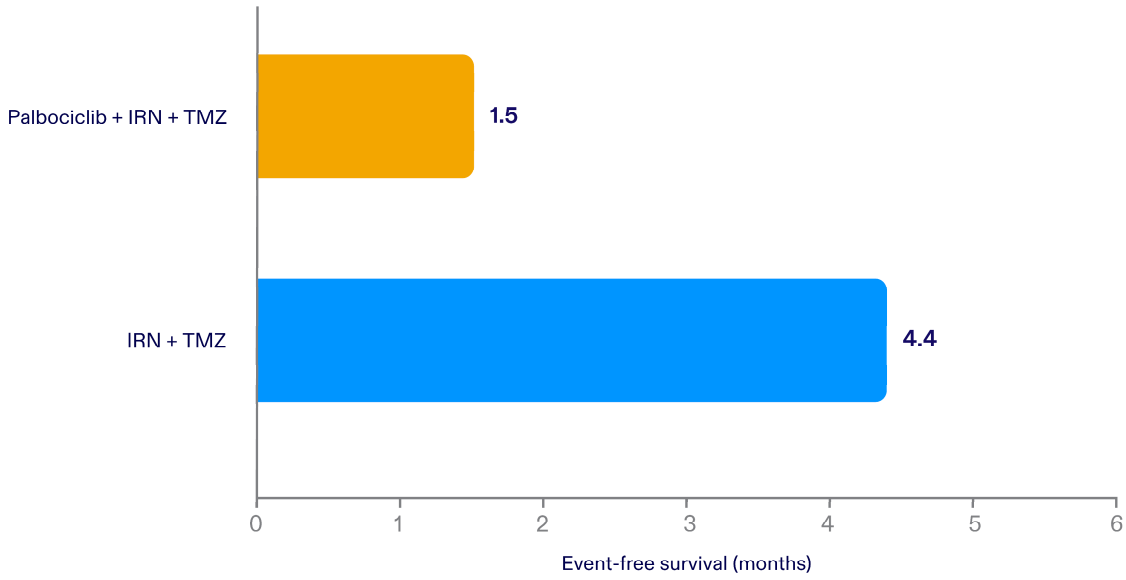
Two (2) out of 7 participants (28.6%) had an objective response.

Phase 2:

How long was the event-free length of time for participants with Ewing sarcoma treated with palbociclib + IRN + TMZ, compared to participants treated with IRN + TMZ alone?

The median number of months without an event was 1.5 months for the palbociclib + IRN + TMZ group and 4.4 months for the IRN + TMZ group (Figure 10). For these results, the median was the length of time before an event for half the participants in the study.

Figure 10. Median event-free survival in participants with Ewing sarcoma



Based on these results, the researchers think that the results are not likely the result of chance. The study medicine is not likely to help lengthen the time participants with Ewing sarcoma have without their condition worsening.

This does not mean that everyone in this study had these results. This is a summary of just some of the main results of this study. Other studies may have different results.

What medical problems did participants have during the study?

The researchers recorded any medical problems the participants had during the study. Participants could have had medical problems for reasons not related to the study (for example, caused by an underlying disease or by chance). Or, medical problems could also have been caused by a study treatment or by

another medicine the participant was taking. Sometimes the cause of a medical problem is unknown. By comparing medical problems across many treatment groups in many studies, doctors try to understand what effects a study medicine might have on a participant.

Phase 1

The results for this part of the study were recorded up to July 2023.

Palbociclib + IRN + TMZ

All 33 treated participants (100%) in this part of the study had at least 1 medical problem. A total of 2 participants stopped taking all study treatments because of medical problems.

The most common medical problems – those reported by at least 60% of all participants – are described in Table 1 below.

Below are instructions on how to read Table 1.

Instructions for Understanding Table 1.

- The **1st** row of the table shows the groups in the study and the number of participants in each group.
- The grey and white rows in Table 1 show individual medical problems that were commonly reported by at least 60% of all participants. Some medical problems were grouped together because they were the same type of problem but reported differently. For example, all the problems that meant low levels of neutrophils were grouped together under the term "low count of white blood cells called neutrophils". Groups like this are known as clustered medical problems. They are marked with a star (*) in this report.

- The **1st** column of Table 1 tells how many of the 4 participants at DL1 reported each medical problem. Below the number is the percentage of the 4 participants at DL1 who reported the medical problem.
- The **2nd** column of Table 1 tells how many of the 6 participants at DL2 reported each medical problem. Below the number is the percentage of the 6 participants at DL2 who reported the medical problem.
- The **3rd** column of Table 1 tells how many of the 6 participants at DL3 reported each medical problem. Below the number is the percentage of the 6 participants at DL3 who reported the medical problem.
- The **4th** column of Table 1 tells how many of the 17 participants in the Expansion group reported each medical problem. Below the number is the percentage of the 17 participants from the Expansion group who reported the medical problem.
- The **5th** column of Table 1 tells how many of the 23 participants at DL2 or in the Expansion group reported each medical problem. This is the number in the 2nd column and the 4th column added together. Below the number is the percentage of the 23 participants at DL2 or in the Expansion group who reported the medical problem.
- Using these instructions, you can see that 2 out of the 4 participants (50.0%) at DL1 reported low count of white blood cells called “neutrophils”*.

Table 1. Commonly reported medical problems by study participants – Phase 1 palbociclib + IRN + TMZ

DL1 Palbociclib 55 mg/m^2 + IRN + TMZ (4 Participants)	DL2 Palbociclib 75 mg/m^2 + IRN + TMZ (6 Participants)	DL3 Palbociclib 95 mg/m^2 + IRN + TMZ (6 Participants)	Expansion Palbociclib 75 mg/m^2 + IRN + TMZ (17 Participants)	DL2 + Expansion Palbociclib 75 mg/m^2 + IRN + TMZ (23 Participants)
Low count of white blood cells called "neutrophils"*				
2 out of 4 participants (50.0%)	4 out of 6 participants (66.7%)	5 out of 6 participants (83.3%)	16 out of 17 participants (94.1%)	20 out of 23 participants (87.0%)
Loose stools (diarrhea)				
4 out of 4 participants (100.0%)	5 out of 6 participants (83.3%)	4 out of 6 participants (66.7%)	13 out of 17 participants (76.5%)	18 out of 23 participants (78.3%)
Nausea				
3 out of 4 participants (75.0%)	4 out of 6 participants (66.7%)	4 out of 6 participants (66.7%)	13 out of 17 participants (76.5%)	17 out of 23 participants (73.9%)
Vomiting				
4 out of 4 participants (100.0%)	3 out of 6 participants (50.0%)	3 out of 6 participants (50.0%)	12 out of 17 participants (70.6%)	15 out of 23 participants (65.2%)

Table 1. Commonly reported medical problems by study participants – Phase 1 palbociclib + IRN + TMZ				
DL1 Palbociclib 55 mg/m^2 + IRN + TMZ (4 Participants)	DL2 Palbociclib 75 mg/m^2 + IRN + TMZ (6 Participants)	DL3 Palbociclib 95 mg/m^2 + IRN + TMZ (6 Participants)	Expansion Palbociclib 75 mg/m^2 + IRN + TMZ (17 Participants)	DL2 + Expansion Palbociclib 75 mg/m^2 + IRN + TMZ (23 Participants)
Low red blood cell count*				
2 out of 4 participants (50.0%)	1 out of 6 participants (16.7%)	4 out of 6 participants (66.7%)	14 out of 17 participants (82.4%)	15 out of 23 participants (65.2%)
Low white blood cell count*				
2 out of 4 participants (50.0%)	1 out of 6 participants (16.7%)	4 out of 6 participants (66.7%)	13 out of 17 participants (76.5%)	14 out of 23 participants (60.9%)

*Clustered (grouped) term

For this part of the study, one of the main purposes involved looking at the medical problems in more detail. The results were as follows.

All 33 treated participants (100%) in this part of the study had at least 1 medical problem that researchers believed was related to study treatments. Most of the medical problems shown in Table 1 above were believed to be related to study treatments.

The severity of medical problems can be described by grade.

- Grade 1: mild or no symptoms.
- Grade 2: moderate symptoms.

- Grade 3: severe or medically important, needs hospital care.
- Grade 4: life-threatening, urgent intervention needed.
- Grade 5: causes death.

A total of 28 out of 33 treated participants (84.8%) had Grade 3 or Grade 4 medical problems, which were all believed to be related to the study treatment. These were mostly problems with levels of blood cells. Two (2) out of 33 treated participants (6.1%) had Grade 5 medical problems, which were not believed to be related to the study treatment.

Palbociclib + TOPO + CTX

All 26 treated participants (100%) in this part of the study had at least 1 medical problem. A total of 2 participants stopped taking all study treatments because of medical problems.

The most common medical problems – those reported by at least 60% of all participants – are described in Table 2 below.

Below are instructions on how to read Table 2. Table 5 can be read in a similar way.

Instructions for Understanding Table 2.

- The **1st** column of Table 2 lists medical problems that were commonly reported during the study. All medical problems reported by at least 60% of all participants are listed.
- The **2nd** column tells how many of the 6 participants in the Determination group reported each medical problem. Next to this number is the percentage of the 6 participants in the Determination group who reported the medical problem.

- The **3rd** column tells how many of the 20 participants in the Expansion group reported each medical problem. Next to this number is the percentage of the 20 participants in the Expansion group who reported the medical problem.
- Using these instructions, you can see that all 6 out of the 6 participants (100%) in the Determination group reported a decreased amount of platelets, that help blood to clot*. A total of 18 out of the 20 participants (90.0%) in the Expansion group reported a decreased amount of platelets, that help blood to clot*.

Table 2. Commonly reported medical problems by study participants – Phase 1 palbociclib + TOPO + CTX

Medical Problem	Determination Palbociclib 75 mg/m^2 + TOPO + CTX (6 Participants)	Expansion Palbociclib 75 mg/m^2 + TOPO + CTX (20 Participants)
Decreased amount of platelets, that help blood to clot*	6 out of 6 participants (100.0%)	18 out of 20 participants (90.0%)
Low red blood cell count*	4 out of 6 participants (66.7%)	19 out of 20 participants (95.0%)
Low count of white blood cells called "neutrophils"*	6 out of 6 participants (100.0%)	16 out of 20 participants (80.0%)
Low white blood cell count*	5 out of 6 participants (83.3%)	16 out of 20 participants (80.0%)

Table 2. Commonly reported medical problems by study participants – Phase 1 palbociclib + TOPO + CTX		
Medical Problem	**Determination Palbociclib 75 mg/m^2 + TOPO + CTX (6 Participants)**	**Expansion Palbociclib 75 mg/m^2 + TOPO + CTX (20 Participants)**
Low count of white blood cells called "lymphocytes"	4 out of 6 participants (66.7%)	14 out of 20 participants (70.0%)
Nausea	4 out of 6 participants (66.7%)	14 out of 20 participants (70.0%)

*Clustered (grouped) term

For this part of the study, one of the main purposes involved looking at the medical problems in more detail. The results were as follows.

All 26 treated participants (100%) in this part of the study had at least 1 medical problem that researchers believed was related to study treatments.

A total of 25 out of 26 participants (96.2%) had a Grade 3 or Grade 4 medical problem. A total of 24 out of 26 participants (92.3%) had a Grade 3 or Grade 4 medical problem that was believed to be related to the study treatment. These were mostly problems with levels of blood cells. No participants had Grade 5 medical problems.

Tumor specific cohort

All 7 treated participants (100%) in this part of the study had at least 1 medical problem. No participants stopped taking study treatments because of medical problems.

The most common medical problems – those reported by at least 50% of participants – are described in Table 3 below.

Below are instructions on how to read Table 3. Table 4 can be read in a similar way.

Instructions for Understanding Table 3.

- The **1st** column of Table 3 lists medical problems that were commonly reported during the study. All medical problems reported by at least 50% of participants are listed.
- The **2nd** column tells how many of the 7 participants who took the study medicine reported each medical problem. Next to this number is the percentage of the 7 participants who took the study medicine and reported the medical problem.
- Using these instructions, you can see that 7 out of the 7 participants (100%) who took the study medicine reported low red blood cell count*.

Table 3. Commonly reported medical problems by study participants – tumor specific cohort

Medical Problem	Palbociclib 75 mg/m^2 + TOPO + CTX (7 Participants)
Low red blood cell count*	7 out of 7 participants (100.0%)
Decreased amount of platelets, that help blood to clot*	7 out of 7 participants (100.0%)

Table 3. Commonly reported medical problems by study participants – tumor specific cohort	
Medical Problem	**Palbociclib 75 mg/m^2 + TOPO + CTX (7 Participants)**
Low count of white blood cells called "neutrophils"*	6 out of 7 participants (85.7%)
Infections*	5 out of 7 participants (71.4%)
Nausea	5 out of 7 participants (71.4%)
Increased level of a liver protein (enzyme) called "AST" in the blood	4 out of 7 participants (57.1%)
Loose stools (diarrhea)	4 out of 7 participants (57.1%)
Low white blood cell count*	4 out of 7 participants (57.1%)
Vomiting	4 out of 7 participants (57.1%)

*Clustered (grouped) term

For this part of the study, one of the main purposes was also to look at the medical problems in detail. The results were as follows.

All 7 treated participants in this part of the study had at least 1 medical problem that researchers believed was related to study treatments. The most common treatment-related medical problems – those reported by at least 50% of participants – are shown in Table 4 below.

Table 4. Commonly reported treatment-related medical problems by study participants – tumor specific cohort	
Medical Problem	**Palbociclib 75 mg/m^2 + TOPO + CTX (7 Participants)**
Low red blood cell count*	7 out of 7 participants (100.0%)
Decreased amount of platelets, that help blood to clot*	7 out of 7 participants (100.0%)
Low count of white blood cells called "neutrophils"*	6 out of 7 participants (85.7%)
Nausea	4 out of 7 participants (57.1%)
Loose stools (diarrhea)	4 out of 7 participants (57.1%)
Low white blood cell count*	4 out of 7 participants (57.1%)

*Clustered (grouped) term

All 7 participants (100%) in this part of the study had at least 1 Grade 3 or Grade 4 medical problem. All were believed to be related to the study treatment. These were mostly problems with levels of blood cells. No Grade 5 medical problems were reported.

The researchers looked at participant's laboratory test results. Abnormal blood test results that were reported as medical problems are included in Table 3 and Table 4 above. All participants had some abnormal blood cell count results that were between Grade 1 and Grade 4. Other types of abnormal laboratory test results were between Grade 1 and Grade 3.

During Phase 1 and the tumor specific cohort parts of the study, the researchers also looked particularly at participant's blood sugar levels, the electrical

functioning of their hearts, and their "vital signs" such as heart rate and blood pressure. The researchers found that none of these results showed any concerning change for participants.

Phase 2

A total of 58 out of 62 treated participants (93.5%) in this part of the study had at least 1 medical problem. Four (4) participants stopped taking all study treatment because of medical problems.

The most common medical problems – those reported by at least 25% of participants in any group – are shown in Table 5 below.

Table 5. Commonly reported medical problems by study participants – Phase 2

Medical Problem	Palbociclib + IRN + TMZ (41 Participants)	IRN + TMZ (21 Participants)
Low count of white blood cells called "neutrophils"*	27 out of 41 participants (65.9%)	9 out of 21 participants (42.9%)
Loose stools (diarrhea)	13 out of 41 participants (31.7%)	9 out of 21 participants (42.9%)
Vomiting	15 out of 41 participants (36.6%)	5 out of 21 participants (23.8%)
Low white blood cell count*	13 out of 41 participants (31.7%)	6 out of 21 participants (28.6%)

Table 5. Commonly reported medical problems by study participants – Phase 2		
Medical Problem	**Palbociclib + IRN + TMZ (41 Participants)**	**IRN + TMZ (21 Participants)**
Low red blood cell count*	12 out of 41 participants (29.3%)	6 out of 21 participants (28.6%)
Decreased amount of platelets, that help blood to clot*	10 out of 41 participants (24.4%)	6 out of 21 participants (28.6%)
Nausea	11 out of 41 participants (26.8%)	4 out of 21 participants (19.0%)

*Clustered (grouped) term

Did study participants have any serious medical problems?

A medical problem is considered “serious” when it is life-threatening, needs hospital care, or causes lasting problems.

Phase 1

The results for this part of the study were recorded up to July 2023.

Palbociclib + IRN + TMZ

A total of 14 out of 33 treated participants (42.4%) had at least 1 serious medical problem.

- Two (2) out of 4 participants (50.0%) at DL1 had at least 1 serious medical problem. Of these, 1 out of 4 participants (25.0%) had at least 1 serious medical problem that researchers believed was related to the study treatment.
- Two (2) out of 6 participants (33.3%) at DL2 had at least 1 serious medical problem. Of these, 1 out of 6 participants (16.7%) had at least 1 serious medical problem that researchers believed was related to the study treatment.
- Two (2) out of 6 participants (33.3%) at DL3 had at least 1 serious medical problem and at least 1 serious medical problem that researchers believed was related to the study treatment.
- Eight (8) out of 17 participants (47.1%) in the Expansion group had at least 1 serious medical problem. Of these, 3 out of 17 participants (17.6%) had

at least 1 serious medical problem that researchers believed was related to the study treatment.

- Combining the DL2 and Expansion group results showed that 10 out of 23 participants (43.5%) at this dose level had at least 1 serious medical problem. Of these, 4 out of 23 participants (17.4%) had at least 1 serious medical problem that researchers believed was related to the study treatment.

The most frequently reported serious medical problems were a low level of white blood cells called neutrophils (with fever), infections*, and vomiting. These serious medical problems were reported for 2 participants each.

As of July 2023, 22 out of 33 participants (66.7%) died during this part of the study. For 19 of these participants, this happened more than 35 days after their last dose of study medication. For 3 of these participants, this happened within 35 days of their last dose of study medication. All of the deaths were believed to be due to the participant's cancer. The deaths were not believed to be related to study treatment.

Palbociclib + TOPO + CTX

A total of 12 out of 26 participants (46.2%) had serious medical problems.

- Two (2) out of 6 participants (33.3%) in the Determination group had at least 1 serious medical problem and at least 1 serious medical problem that researchers believed was related to the study treatment.
- Ten (10) out of 20 participants (50.0%) in the Expansion group had at least 1 serious medical problem. Of these, 8 out of 20 participants (40.0%) had at least 1 serious medical problem that researchers believed was related to the study treatment.

The most frequently reported serious medical problem was a low level of white blood cells called neutrophils, with fever. This was reported for

7 participants (1 participant in the Determination group and 6 participants in the Expansion group).

As of July 2023, 15 out of 26 participants (57.7%) died during this part of the study. These deaths all happened more than 35 days after the last dose of study treatment. The deaths were believed to be due to the participants' cancer and not related to study treatment.

Tumor specific cohort

A total of 4 out of 7 participants (57.1%) had at least 1 serious medical problem. Of these, 2 out of 7 participants (28.6%) had at least 1 serious medical problem that researchers believed was related to the study medication. All the serious medical problems were different and were reported once.

As of August 2024, 1 out of 7 participants (14.3%) had died in this part of the study. This death was in the follow-up period and was more than 35 days after the participant's last dose of study treatment. The death was due to the participant's cancer.

Phase 2

A total of 19 out of 62 treated participants (30.6%) had serious medical problems.

- Fifteen (15) out of 41 participants (36.6%) who took palbociclib + IRN + TMZ had serious medical problems. Of these, 7 out of 41 participants (17.1%) had at least 1 serious medical problem that researchers believed was related to the study treatment.
- Four (4) out of 21 participants (19.0%) who took IRN + TMZ had serious medical problems. Of these, 3 out of 21 participants (14.3%) had at least 1 serious medical problem that researchers believed was related to the study treatment.

The most frequently reported serious medical problem was infections*. This was reported for 7 participants (6 participants who took palbociclib + IRN + TMZ and 1 participant who took IRN + TMZ).

As of August 2024, 37 out of 62 participants (59.7%) had died during this part of the study.

- One (1) out of 41 participants (2.4%) died within 35 days of their last dose of study treatment in the palbociclib + IRN + TMZ group. The death was believed to be due to the participants' cancer and not related to the study treatment. There were no deaths in the IRN + TMZ group within 35 days of the last dose of study treatment.
- Twenty-three (23) out of 41 participants (56.1%) in the palbociclib + IRN + TMZ group and 13 out of 21 participants (61.9%) in the IRN + TMZ group died more than 35 days after their last dose of study treatment. These deaths were believed to be due to the participant's cancer and not related to the study treatment, and for 1 participant in the palbociclib + IRN + TMZ the cause of death was unknown.

Where can I learn more about this study?

If you or your child have questions about the results of your study, please speak with the doctor or staff at your study site.

For more details on your study protocol, please visit:

www.pfizer.com/research/research_clinical_trials/trial_results	Use the protocol number **A5481092**

The full scientific report of this study is available online at:

www.clinicaltrials.gov	Use the study identifier **NCT03709680**
https://euclinicaltrials.eu	Use the study identifier **2021-003444-25**

Please remember that researchers look at the results of many studies to find out which medicines can work and are safe for patients.

Again, if you or your child participated in this study, **thank you** for volunteering. We do research to try to find the best ways to help patients, and you helped us to do that!

Pfizer