A PHASE I/II DOSE SCHEDULE FINDING STUDY OF CH14.18/CHO CONTINUOUS INFUSION COMBINED WITH SUBCUTANEOUS ALDESLEUKIN (IL-2) IN PATIENTS WITH PRIMARY REFRACTORY OR RELAPSED NEUROBLASTOMA

A SIOPEN Study

EudraCT No: 2009-018077-31

End of Trial Study Report Summary

Layperson Version

END OF TRIAL LAYPERSON SUMMARY

Administrative Information

Title of trial:	**A PHASE I/II DOSE SCHEDULE FINDING STUDY OF ch14.18/CHO CONTINUOUS INFUSION COMBINED WITH SUBCUTANEOUS ALDESLEUKIN (IL-2) IN PATIENTS WITH PRIMARY REFRACTORY OR RELAPSED NEUROBLASTOMA. A SIOPEN STUDY**
Short title:	**Long term continuous infusion ch14.18/CHO plus s.c. aldesleukin (IL-2)**
EudraCT. no.:	2009-018077-31
ClinicalTrials.gov no	NCT01701479
Date of first authorization of trial:	25.11.2010 (International Birth Date)
Sponsor name and Adress:	St. Anna Kinderkrebsforschung GmbH Zimmermannplatz 10 1090 Wien
Chief Investigator	Prof. Holger Lode, MD University Children's Hospital Greifswald, Germany Paediatrics and Pediatric Haematology/Oncology Sauerbruchstrasse 1 17475 Greifswald, Germany Phone: +49 3834 866301/6300 lode@uni-greifswald.de
Senior Investigator and Sponsor Delegate	Prof. Ruth Ladenstein, MD, MBA, cPM St. Anna Kinderkrebsforschung GmbH Zimmermannplatz 10, 1090 Wien Tel.: +431404070 4750 E-Mail: ruth.ladenstein@ccri.at
No. of patients recruited:	288 patients

Approved:

Prof. Holger Lode; MD
Chief Investigator

09-02-2026 _____
(date, signature)

Prof. Dr. Ruth Ladenstein, MBA, cPM
Sponsor delegate, Senior investigator

09-02-2026 _____
(date, signature)

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1 GENERAL INFORMATION

1.1 Why was this clinical trial done?

Neuroblastoma is a type of cancer that mainly affects children. It is one of the most difficult childhood cancers to treat, especially if it comes back after treatment or does not get better with usual treatments. Most neuroblastoma cancer cells have a molecule (a marker) called GD2 on their surface. The study medicine tested in this study, dinutuximab beta, is an antibody made to attach to GD2. This helps the body's immune system (the defensive system of the body) to recognise and attack the cancer cells. Dinutuximab beta is usually given over a short time each day, which can be very painful. Doctors found that giving this medicine slowly over a longer time helped reduce the pain. This study was done to find out whether giving dinutuximab beta continuously over several days could:

- Make treatment less painful, and
- Still work well to treat patients with high-risk neuroblastoma.

The study also wanted to see if adding another medicine called interleukin-2 (IL-2) , which helps boost the immune system, made the treatment work better.

1.2 What treatments were studied?

All patients received **dinutuximab beta** as a slow, continuous infusion (i.e. giving medicine slowly into the body, usually through a vein) over several days.

Some patients also received:

- **Interleukin-2 (IL-2)**, given as injections under the skin to stimulate the immune system
- **Isotretinoin (vitamin A)**, taken by mouth after each treatment cycle

In the later part of the study, patients were randomly assigned to:

- Dinutuximab beta **with** interleukin-2, or
- Dinutuximab beta **without** interleukin-2

This allowed researchers to compare the two approaches fairly.

1.3 Who took part in the clinical trial?

A total of **288 patients** took part. Most patients were aged **1 to 21 years and** had **high-risk neuroblastoma** that had either returned after treatment or not responded to at least two previous standard treatments.
Patients aged **over 21 and up to 45 years** were allowed to be included. However, no patients of this age group entered on this trial.

1.4 How was the clinical trial carried out?

This was a forward-looking (prospective), **open-label study**, meaning patients and doctors knew which treatments were given. The study was carried out in several stages:

a) An **early phase** to find a dose and schedule that reduced pain while remaining effective
b) A **confirmation phase** to check tolerability and outcomes in more patients
c) A **randomised phase** to compare treatment with and without interleukin-2

Patients received up to **five treatment cycles**, each lasting **35 days**, followed by long-term follow-up.

1.5 Study Timeline

- The **first patient** joined the study on **25 January 2012**.
- The **last patient** started treatment on **5 July 2017**.
- The **last patient completed treatment** on **30 November 2017**.
- The study officially **closed on 31 January 2025** after long-term follow-up.

In total, **288 patients** took part in the study:

- 24 patients in an **exploratory group**
- 100 patients in a **confirmation group**
- 164 patients in a **randomised group** (4 of these patients chose not to be randomised)

The study was carried out in several phases using updated versions of the study protocol:

- **Version 1 (2012):** 44 patients
- **Version 2 (2012–2014):** 80 additional patients (100 in total)
- **Version 3 (2014–2017):** 164 patients

1.6 Who Could Take Part (Eligibility)

The study included patients aged **1 to 21 years** with **high-risk neuroblastoma** that had either come back after treatment, or not responded to at least **two previous standard (usual) treatments**

1.7 Study Goals and Treatment Plan

1.7.1 Early Phase (Protocol Version 1)

The main goal was to find a treatment dose and schedule that:

- Reduced **pain caused by dinutuximab beta**, and
- Still supported the immune system to fight cancer

Different daily doses of dinutuximab beta were tested, all given as a **slow, continuous infusion over several days**. The dose that best balanced tolerability and effectiveness was selected.

Patients also received:

- **Interleukin-2 (IL-2)** given by injection under the skin, to stimulate the immune system
- **Isotretinoin (High-dose vitamin A)** taken by mouth for two weeks after each treatment cycle

1.7.2 Confirmation Phase (Protocol Version 2)

The main goal was to confirm, in a larger group of patients, that the selected treatment schedule:

- Was well tolerated, and
- Showed acceptable treatment outcomes

Patients received **five treatment cycles**, each lasting **35 days**, using the same continuous infusion schedule identified in the earlier phase.

1.7.3 Randomised Phase (Protocol Version 3)

The main goal was to find out whether adding **interleukin-2** to dinutuximab beta improved how long patients stayed free from cancer worsening.

Patients were randomly assigned to one of two groups:

- Dinutuximab beta **with** interleukin-2
- Dinutuximab beta **without** interleukin-2

All patients continued to receive vitamin A. Additional outcomes studied included safety, overall survival, and immune system responses.

1.7.4 Planned but Not Activated Amendment

A later change to the study was planned to lower the dose of interleukin-2 because many patients experienced side effects and stopped treatment early. Although this change was approved by regulators, new evidence showed that interleukin-2 did **not provide additional benefit**. Therefore, this change (amendment) was never started.

1.7.5 Concomitant (Supportive) Medication

Because dinutuximab beta can cause pain, all patients received **preventive pain treatment**, including:

- Gabapentin by mouth
- Morphine given through a vein before and during treatment, with the dose reduced over time if pain improved

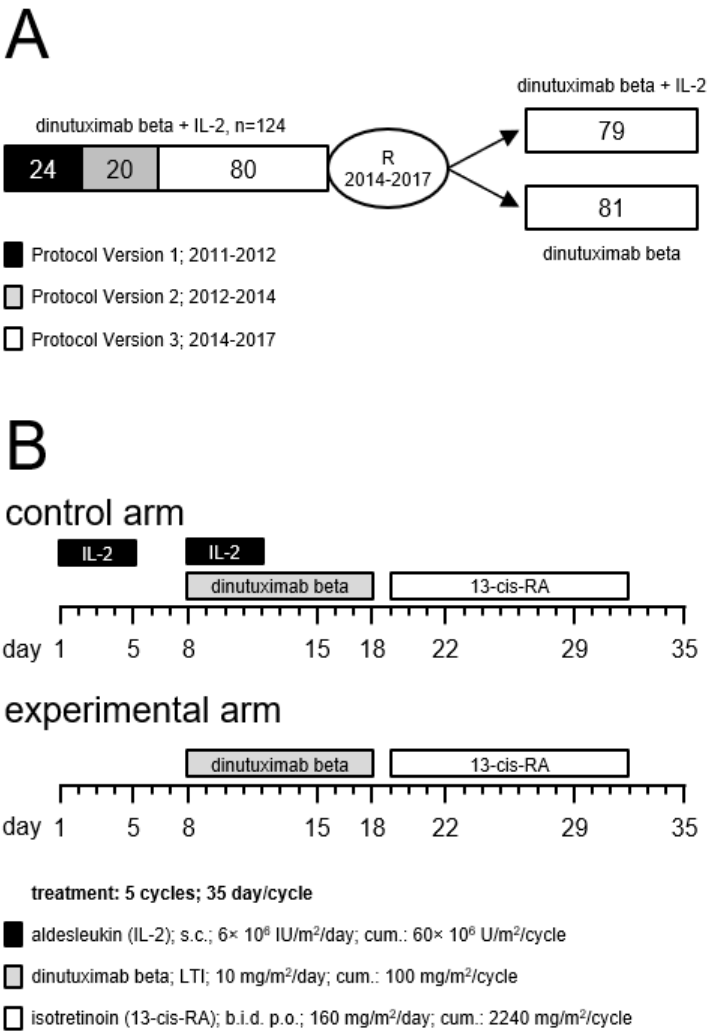
Additional pain medicine was allowed if needed. Medicines to prevent or treat fever were also given according to local hospital practice.

Other cancer treatments were **not allowed** during the study. Medicines that suppress the immune system, such as steroids, were not permitted shortly before or during the study.

2 TRIAL POPULATION

2.1 Trial design

Total population oversight and randomisation arms



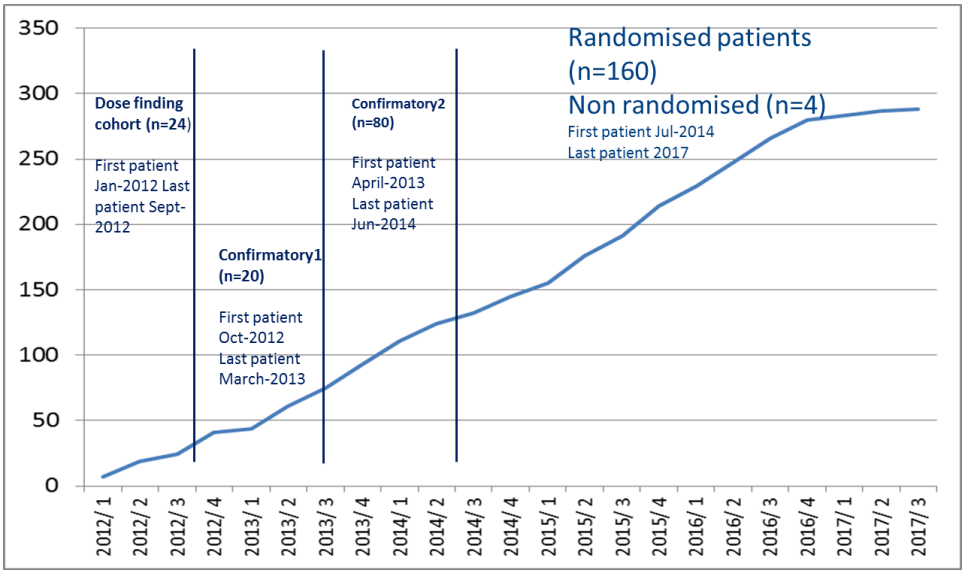
2.2 How many people took part in the clinical trial?

A total of 288 patients took part in this clinical trial.

Patients were included in different parts of the study:

- 24 patients took part in the early phase of the study, which focused on finding a suitable dose and treatment schedule.
- 100 patients took part in the confirmation phase, which checked how well the selected treatment schedule was tolerated in a larger group.
- 164 patients were included in the later phase of the study after a protocol update.
    - Of these, 160 patients were randomly assigned to one of the two treatment groups (with or without interleukin-2).

Total patient recruitment on the LTI trial



Recruitment according to country and treatment arm

Country	Total	Dose finding + Confirmatory cohort		Amendment-Randomised cohort				
				Total		With IL-2	Without IL-2	No random
	288	**124**		**164**		**79**	**81**	**4**
IT	64	22	18%	42	26%	20	21	1
FR	53	25	20%	28	17%	14	14	
GE	52	33	27%	19	12%	9	8	2
UK	50	17	14%	33	20%	17	16	
ES	30	18	15%	12	7%	5	6	1
IL	13	7	6%	6	4%	3	3	
PL	8	0	0%	8	5%	4	4	
AT	7	1	1%	6	4%	3	3	
IE	6	1	1%	5	3%	2	3	
BE	5	0	0%	5	3%	2	3	

2.3 Trial Locations

2.3.1 For the V1/V2 population:

Country and Hospital	Eligible patients (N=123) n
Germany	**33**
University Children's Hospital Greifswald	27
Universitätsklinik Frankfurt	5
Universitätsklinikum Jena	1
France	**25**
Institute Gustave Roussy	16
Institute Curie	9
Italy	**21**
Gaslini Children 's Hospital	20
Fondazione IRCCS Istituto Nazionale dei Tumori	1
Spain	**18**
Hospital Universitario La Fe	18
United Kingdom	**17**
Great Ormond Street Hospital for Children London	5
Alder Hey Children's NHS Foundation Trust	4
Leeds Teaching Hospital Leeds General Infirmary	3
Royal Hospital for Sick Children Glasgow	3
Southampton General Hospital	1
University Hospitals Bristol	1
Israel	**7**
Schneider Children's Medical Centre of Israel	7
Austria	**1**
St. Anna Children's Hospital	1
Ireland	**1**
Our Lady's Children's Hospital Crumlin	1

2.3.2 For the V3 population:

Country and Hospital	total patients	randomization result		
		ch14.18/CHO with IL2	ch14.18/CHO without IL2	not random.
Total patients	164	79	81	4
Germany				
University Childrens Hospital Greifswald	18	9	7	2
Universitätsklinikum Tübingen	1	.	1	.
Italy				
Gaslini Children's Hospital	34	15	18	1
Ospedale Bambino Gesù, Rome	5	3	2	.
Fondazione IRCCS Istituto Nazionale dei Tumori	3	2	1	.
France				
Institut Gustave Roussy	13	7	6	.
Hôpital des Enfants, Toulouse	8	4	4	.
Centre Léon Bérard Lyon	5	2	3	.
Institut Curie	2	1	1	.
United Kingdom				
Great Ormond Street Hospital for Children London	10	6	4	.
Our Lady s Children s Hospital Crumlin	7	3	4	.
Southampton General Hospital	5	2	3	.
The Newcastle upon Tyne Hospitals Royal Victoria Infirmary	4	1	3	.
Leeds Teaching Hospital Leeds General Infirmary	4	3	1	.
University Hospitals Bristol	3	.	3	.
Royal Hospital for Sick Children Glasgow	3	2	1	.
Alder Hey Children s NHS Foundation Trust	2	2	.	.
Spain				
Hospital Universitario Nino Jesus Madrid	7	3	4	.
Hospital Universitario La Fe	5	2	2	1
Poland				
University Children's Hospital Krakow	8	4	4	.
Austria				
St. Anna Children s Hospital	5	3	2	.
Medizinische Universität Innsbruck	1	.	1	.
Israel				
Schneider Children s Medical Centre of Israel	6	3	3	.
Belgium				
UZ Leuven Belgium	2	.	2	.
University Hospital Ghent	2	1	1	.
Cliniques Universitaires Saint-Luc (UCL)	1	1	.	.

3 WHAT MEDICINE WAS STUDIED?

3.1 What is dinutuximab beta and how was it developed?

The study medicine, **dinutuximab beta**, is a type of antibody treatment. Antibodies are proteins that help the immune system recognise and attack harmful cells.

Dinutuximab beta is designed to attach to **GD2**, a marker found on the surface of most neuroblastoma cancer cells. By attaching to GD2, the medicine helps the body's immune system find and destroy these cancer cells.

The development of this antibody started in the **1980s**. Early versions were made entirely from mouse proteins. Later, researchers developed a **mouse–human "chimeric" antibody**, which combines parts of mouse and human antibodies. This reduced side effects while keeping the anti-cancer effect.

The version used in this study is produced in **Chinese hamster ovary (CHO) cells**, which is a modern and widely used method for producing antibody medicines. This version is called **ch14.18/CHO**, also known as **dinutuximab beta**.

The antibody consists mostly of human protein parts, with a smaller mouse-derived part that allows it to recognise GD2. Laboratory and animal studies showed that this version works in the same way as earlier versions, with at least the same ability to kill cancer cells.

3.2 What was already known about this medicine before the study?

Before this study, dinutuximab beta had already been tested in children with neuroblastoma. Early clinical studies showed that the medicine could be given safely, and the medicine showed signs of effectiveness against neuroblastoma.
The most common side effect was **pain**, especially when the medicine was given quickly over a few hours.In earlier trials, dinutuximab beta was usually given as a **short daily infusion** over several days. This required strong pain medication, such as morphine.

3.3 Why was this study needed?

Doctors observed that giving dinutuximab beta **more slowly over a longer time** caused less pain. In some patients, pain medication could even be reduced or stopped.

Before this study, more than **50 patients** with neuroblastoma, that had returned or did not respond to treatment, received dinutuximab beta as a **continuous infusion over 10 days**, together with:

- **Interleukin-2 (IL-2)** to stimulate the immune system, and
- **Isotretinoin (Vitamin A)**

These patients generally needed less pain medication, and some showed improvement of their disease. Based on these encouraging results, this clinical trial was started to:

- Confirm whether long-term continuous infusion is better tolerated
- Study the effectiveness of this treatment approach
- Evaluate whether adding interleukin-2 to treatment improves patients' outcomes

3.4 Why was interleukin-2 studied?

Interleukin-2 (IL-2) is a medicine that activates parts of the immune system. Earlier laboratory and clinical studies suggested that IL-2 might increase the anti-cancer effect of antibody treatments like dinutuximab beta.

However, results from a large study in newly diagnosed (front-line) neuroblastoma patients later showed that adding IL-2 **did not improve patients survival outcomes,** that IL-2 caused **significant side effects** and that many patients could not complete treatment because of IL-2-related toxicity. These findings supported the need to:

- Test improved treatment schedules (the plan for when and how often treatment happens)
- Reduce treatment-related side effects
- Focus on maintaining benefits while improving tolerability

3.5 How did this lead to the current study?

The results from earlier studies showed that Dinutuximab beta is effective against neuroblastoma; pain is the main treatment-limiting side effect; slower, continuous infusion reduces pain and improves tolerability and Interleukin-2 may not add benefit and can increase side effects.

This study was therefore designed to test a **long-term continuous infusion schedule** of dinutuximab beta in patients with neuroblastoma that had come back or did not respond to previous treatments, with the goal of reducing pain and side effects; maintaining or improving treatment effectiveness and clarifying the role of interleukin-2 in this setting.

3.6 Has the study medicine been approved for use?

Yes. The study medicine **Qarziba® (dinutuximab beta)** has been approved for use in the European Union. On **8 May 2017**, the **European Commission** granted **marketing authorisation** for Qarziba® as an **orphan medicine**. Orphan medicines are treatments developed for rare diseases, such as high-risk neuroblastoma. Qarziba® is approved for the treatment of **high-risk neuroblastoma** in patients who have already received standard treatments.

3.7 Who is responsible for Qarziba® today?

Qarziba® was originally developed by **APEIRON Biologics**.
In **2016**, the medicine was licensed from **APEIRON Biologics** to **EUSA Pharma** for further development and commercial use.
2017: Qarziba® received European Union marketing authorisation for high-risk neuroblastoma.
In **2022**, **Recordati S.p.A.** acquired EUSA Pharma. As a result:

- Recordati became the **Marketing Authorisation Holder** for Qarziba®
- Recordati assumed full responsibility for:
    - Regulatory compliance
    - Safety monitoring (pharmacovigilance)
    - Commercial distribution of the medicine

Since **2023**, Recordati has been fully responsible for Qarziba® for all regulatory and legal purposes.

3.8 Side effects in the early and confirmation phases (V1 and V2)

This section describes the side effects seen in the early and confirmation phases of the study (Versions 1 and 2).
Most patients experienced **side effects related to the antibody treatment**, which were already known from previous studies of dinutuximab beta.

3.8.1 Most common side effects

The most frequently reported side effects were:

- **Pain**, especially nerve-related pain
- **Fever**
- **Low blood pressure**

- **Skin reactions**, such as rash
- **Swelling caused by fluid leakage from blood vessels**
- **Gastrointestinal symptoms**, such as nausea or vomiting

Pain was the **most important side effect**, but it was generally **less severe** than with shorter infusion schedules used in earlier studies.

3.8.2 Pain and pain management

All patients received **preventive pain treatment** before and during dinutuximab beta infusion.

Because the medicine was given as a **slow, continuous infusion**, many patients:

- Needed **lower doses of strong pain medication**, such as morphine
- Were able to **reduce or stop intravenous pain medication** during treatment

This confirmed that the long-term infusion schedule improved treatment tolerability.

3.8.3 Side effects related to interleukin-2 (IL-2)

Patients who also received **interleukin-2 (IL-2)** experienced additional side effects more often, including:

- Fever and flu-like symptoms
- Fatigue
- Low blood pressure
- Increased inflammation

Some patients found these side effects difficult to tolerate, which sometimes led to:

- Treatment interruptions
- Early discontinuation of IL-2

3.8.4 Serious side effects

Serious side effects did occur but were **expected and manageable** with standard medical care.

Importantly:

- **No deaths related to the study treatment** were reported in these study phases
- Most side effects were **temporary** and improved after treatment stopped

3.8.5 Overall safety conclusion for V1 and V2

The early and confirmation phases of the study showed that:

- Dinutuximab beta given as a **long-term continuous infusion** was **better tolerated** than shorter infusions
- Side effects were **consistent with previous experience** with this medicine
- Adding interleukin-2 increased side effects without clear additional benefit

These results led the researchers to focus later on making the treatment easier to tolerate and studying better how interleukin-2 should be used.

3.9 Side effects in the randomised part of the study (V3)

This section describes side effects seen in the **randomised phase of the study (Version 3)**.

In this part of the study:
- **80 patients** received **dinutuximab beta alone**
- **78 patients** received **dinutuximab beta together with interleukin-2 (IL-2)**

Side effects were recorded across **all treatment cycles (Cycles 1 to 5)**. For each patient, the **most severe side effect experienced** during treatment was counted. Side effects were grouped as Mild to moderate, or Severe.

3.9.1 Overall comparison between treatment groups

Almost all patients experienced at least one side effect. However, severe side effects were much more common in patients who received dinutuximab beta plus IL-2. Patients treated with dinutuximab beta alone experienced fewer severe side effects overall.

This difference between the two treatment groups was statistically significant, meaning it was very unlikely to be due to chance.

3.9.2 Most common side effects

Pain
- Pain was common in **both treatment groups**
- The **frequency and severity of pain were similar**, regardless of whether IL-2 was given

This shows that pain was mainly related to dinutuximab beta itself and not increased by IL-2.

Fever and flu-like symptoms
- **Fever** occurred much more often in patients who received **IL-2**
- Severe fever was **significantly more common** in the IL-2 group
- Flu-like symptoms (such as chills and body aches) were also frequent, especially with IL-2

Allergic and immune reactions
Patients receiving **dinutuximab beta plus IL-2** more often experienced:

- **Allergic reactions**
- **Capillary leak syndrome** (fluid leaking from blood vessels into tissues)
- **Cytokine release symptoms** (strong immune reactions)

These reactions were less frequent and less severe in patients treated with dinutuximab beta alone.

3.9.3 Effects on blood and laboratory tests

Changes in blood test results were common in both groups, but:

- **Severe blood-related side effects** (such as low red blood cells or low platelets) were **more frequent with IL-2**
- Low haemoglobin and low platelet counts were notably more common in the IL-2 group

Most of these changes were detected through routine blood tests; temporary and managed with standard medical care.

3.9.4 Effects on organs and body systems

Nervous system

- Side effects affecting the **nervous system** were more common in the IL-2 group
- These included symptoms affecting both the **central nervous system** and **peripheral nerves**
- Severe nerve-related side effects were rare in patients treated with dinutuximab beta alone

Lungs and breathing

- Lung-related side effects occurred more often and were more severe in patients receiving IL-2

Kidneys and urinary system

- Kidney and urinary side effects were **more frequent** in the IL-2 group
- Severe kidney-related problems were uncommon overall

Liver

- Changes in liver blood tests were seen in both groups
- Severe liver-related side effects occurred **more often with IL-2**, but were still manageable

Skin and swelling

- Skin reactions (such as rash) were common in both groups
- Swelling and weight gain related to fluid retention were observed, especially with IL-2

3.9.5 Serious side effects and safety conclusions

- Serious side effects occurred **more frequently** when **IL-2 was added**
- Many of these side effects led to:
    - Treatment interruptions
    - Dose reductions
    - Stopping IL-2 early

Importantly:

- **No new or unexpected safety problems** were identified
- The side effects matched what was already known about these medicines
- Side effects were generally **manageable with appropriate medical care**

3.9.6 Overall safety conclusion for the randomised phase (V3)

The randomised phase of the study showed that:

- **Dinutuximab beta alone** had a **more favourable safety profile**
- Adding **interleukin-2 increased the number and severity of side effects**
- IL-2 did **not provide sufficient benefit** to outweigh the increased side effects

These findings supported later decisions to:

- Focus on dinutuximab beta without IL-2
- Optimise treatment schedules to reduce side effects while maintaining effectiveness.

4 WHAT ARE THE BENEFITS AND RISKS OF THE STUDY TREATMENT?

This section summarises the possible benefits and risks of the treatments studied. It is based on the results of this clinical trial and on what was already known about the study medicines.

4.1 What were the possible benefits?

The study showed several potential benefits for patients with high-risk neuroblastoma that had come back or did not respond to previous treatments:

- **Improved tolerability**:
  Giving dinutuximab beta as a slow, continuous infusion caused less severe pain compared with shorter infusion schedules used in earlier studies.
- **Reduced need for strong pain medication**:
  Many patients needed lower doses of morphine, and some were able to stop intravenous pain medication during treatment.
- **Maintained anti-cancer activity**:
  The continuous infusion schedule allowed patients to receive effective doses of dinutuximab beta without reducing its ability to target cancer cells.
- **Better treatment completion**:
  Fewer severe side effects made it easier for patients to complete planned treatment cycles.
- **Improved treatment approach**:
  The study helped define a treatment schedule that balances effectiveness with improved quality of life during therapy.

4.2 What were the risks and side effects?

As with all cancer treatments, side effects were common.

Risks related to dinutuximab beta: the most frequent side effects included:

- Pain, especially nerve-related pain
- Fever and flu-like symptoms
- Low blood pressure
- Skin reactions
- Temporary changes in blood test results

These side effects were expected, usually temporary, and could be managed with standard medical care.

Additional risks related to interleukin-2 (IL-2): patients who received interleukin-2 in addition to dinutuximab beta experienced:

- More frequent and more severe side effects
- Increased immune-related reactions, such as:
  - Fever
  - Allergic reactions
  - Capillary leak syndrome
  - Inflammation affecting organs

These side effects often led to treatment interruptions; dose reductions and early stopping of IL-2.

4.3 Did the benefits outweigh the risks?

For dinutuximab beta given as a continuous infusion, the study showed that benefits such as improved tolerability and reduced pain outweighed the risks. Side effects were manageable and consistent with previous experience.

For dinutuximab beta plus interleukin-2, the addition of IL-2 increased side effects with no clear additional benefit. In this case, the risks outweighed the benefits.

5 WHAT DID THE EARLY ANALYSIS OF THE STUDY SHOW? (EXPLORATORY PHASE – V1)

This section describes the results from the **exploratory phase** of the study. This early analysis helped researchers decide which treatment schedule should be used in the later parts of the study.

The exploratory phase included **24 patients** and was completed on **14 May 2012**. Only the **first treatment cycle** for each patient was used for this analysis.

5.1 What was the purpose of this early analysis?

The goal was to find a treatment schedule that caused less pain, still showing signs that the treatment was working, and able to be given safely to most patients.

A treatment schedule was considered suitable if at least 80% of patients had completed the treatment; Pain was acceptable and manageable; the treatment showed immune system activity, suggesting potential effectiveness

5.2 What was measured?

The following measurements were taken at the start of treatment and during the first two weeks:

- How much **strong pain medicine (morphine)** patients needed after starting treatment
- Changes in **natural killer (NK) cells**, which are immune cells involved in fighting cancer
- The amount of **dinutuximab beta** in the blood over time

5.3 What were the main findings?

Pain control: 81% of patients were able to receive dinutuximab beta without needing intravenous morphine after the first 5 days of treatment. This showed that giving the medicine slowly over time significantly reduced pain

Immune system response: it has been evaluated by the number of natural killer (NK) cells in the blood increased during treatment; by the most active NK cells increased 3 to 6 times compared with levels before treatment. This finding suggested that the treatment was stimulating the immune system, which is important for fighting cancer.

Medicine levels in the blood: Dinutuximab beta reached stable and measurable levels in the blood by day 15, confirming that the continuous infusion schedule delivered the medicine effectively

5.4 How were these results used?

An independent **Data Monitoring Committee** reviewed the results from the 24 patients.

Based on this review, the treatment schedule of **dinutuximab beta given over 10 days** met all requirements; more than 80% of patients tolerated the treatment with acceptable pain levels and signs of immune activity observed. As a result, the long term infusion treatment schedule was selected for the **next phase of the study**. The same dose of **interleukin-2** and **isotretinoin (vitamin A)** was continued in later patients.

5.5 What does this mean?

This early analysis showed that a **long-term continuous infusion** of dinutuximab beta can reduce pain; the immune system still responds to the treatment and the chosen treatment schedule was suitable for further testing in more patients. These findings laid the foundation for the later confirmation and randomised phases of the study.

6 WHAT WERE THE RESULTS FOR PATIENTS IN THE EARLY AND CONFIRMATION PHASES (V1 AND V2)?

This section summarises the results from patients treated in the **exploratory (V1)** and **confirmation (V2)** phases of the study. In total, **122 patients** received dinutuximab beta using the long-term continuous infusion schedule.

6.1 Pain control and treatment completion:

most patients received dinutuximab beta at a dose given slowly over 10 days. 95% of patients were able to complete treatment with acceptable pain levels. By day 5 of the first treatment cycle, at least 80% of patients no longer needed intravenous morphine. This confirmed that the treatment schedule met the study's main goal of reducing pain while continuing treatment

6.2 How well did the treatment work against the cancer?

Among patients whose response to treatment could be assessed, 45% showed a reduction in their cancer by the end of treatment. This includes patients whose tumours shrank or disappeared.

Survival outcomes:
two years after starting treatment, 56% of patients were alive without their cancer getting worse and 73% of patients were still alive overall. In patients whose cancer had returned or did not respond to earlier treatments, 45% were alive without cancer worsening after two years and 65% were alive after two years. These results showed that the treatment was **effective** in a group of patients with very difficult-to-treat disease.

6.3 What did the immune system results show?

Dinutuximab beta works by helping the immune system kill cancer cells. In particular, it activates natural killer (NK) cells, which are immune cells that destroy cancer cells. The study found that patients with higher numbers of NK cells had better outcomes; patients with certain inherited immune system features that allow antibodies to work more effectively also had better outcomes.

Two years after treatment, patients with strong immune responses had higher survival rates and patients with weaker immune responses had lower survival rates. This suggests that the immune system plays an important role in how well dinutuximab beta works.

6.4 Factors linked to poorer outcomes:

some patient characteristics were associated with less favourable results:

- Age older than 5 years
- Cancer that had returned or not responded to previous treatments
- Weaker immune system features linked to antibody activity

These factors were identified as increasing the risk of poorer outcomes, regardless of treatment.

6.5 Overall conclusion from V1 and V2

The results from the exploratory and confirmation phases showed that Dinutuximab beta given as a long-term continuous infusion was well tolerated showing meaningful anti-cancer activity. Pain was significantly reduced compared with earlier treatment schedules. I addition the results showed that certain immune system markers may help predict which patients benefit most. These findings supported continuing the study and helped improve understanding of how this treatment works in children with high-risk neuroblastoma.

7 . WHAT WERE THE RESULTS FOR PATIENTS IN THE RANDOMISED PART OF THE STUDY (V3)?

This section describes the results from the **randomised phase of the study (Version 3)**. In this part of the study, patients were randomly assigned to one of two treatment groups to allow a fair comparison. Almost all patients who entered the randomised phase could be evaluated for treatment tolerance.

What did long-term follow-up show for all patients in the study?

7.1 Event-free survival over the long term

Patients in this study were followed for many years after treatment to understand how long they lived **without their cancer getting worse or coming back**. This is called **event-free survival**.

The long-term results for all patients who took part in this study were **very encouraging**. After **5 years**, only **a small number of patients** experienced a return or worsening of their cancer. This result shows that many patients benefited from immunotherapy over the long term.

7.2 How do these results compare with earlier outcomes?

Before immunotherapy treatments like dinutuximab beta were available, outcomes for patients whose neuroblastoma came back or worsened were much poorer. Earlier large international analyses of similar patients showed that only about **20% of patients** were still alive **5 years after their first relapse or progression.** In comparison:

- Patients in this study showed **substantially better long-term outcomes**
- Far fewer cancer-related events occurred after the first few years following treatment

7.3 What does this mean for patients?

These long-term follow-up results suggest that immunotherapy with dinutuximab beta can provide **lasting benefit** for patients with high-risk neuroblastoma. The risk of cancer returning appears to **decrease over time** after successful treatment and outcomes for patients treated with immunotherapy are **better than those reported in the past**, before such treatments were available.

7.4 Overall conclusion from long-term follow-up

The long-term results of this study support the role of **dinutuximab beta immunotherapy** as an important treatment option for patients with high-risk neuroblastoma, including those whose disease has returned or not responded to earlier treatments.

These findings add to the evidence that immunotherapy can lead to **meaningful and durable improvements** in patient outcomes.

8 WHAT ARE THE OVERALL CONCLUSIONS OF THE STUDY AND WHAT HAPPENS NEXT?

8.1 What did this study show overall?

This study showed that **dinutuximab beta** can be given safely and effectively as a **long-term continuous infusion**. The results showed that:

- The **best tolerated dose** was **10 mg per square metre of body surface per day**
- Giving the medicine **more slowly over a longer time** clearly reduced pain
- Patients experienced **fewer and less severe side effects** compared with shorter infusion schedules
- The treatment still worked as intended by:
    - Activating the immune system
    - Increasing natural killer (NK) cells
    - Maintaining effective antibody levels in the blood

This means that the long-term infusion schedule improved **treatment tolerance without reducing effectiveness**.

8.2 What was learned about interleukin-2 (IL-2)?

Across this study and other related clinical trials, it was discovered that adding subcutaneous interleukin-2 (IL-2) did not improve treatment results. Actually, IL-2 caused more side effects and so, patients receiving IL-2 were less likely to complete treatment. These findings were consistent in this long-term infusion study, and also in a separate randomised frontline neuroblastoma study that also used a long-term infusion schedule

Overall, the evidence showed that **IL-2 does not add benefit** and increases risks.

8.3 How did these results influence other studies?

Because the long-term infusion schedule was better tolerated, the same approach was adopted in later neuroblastoma studies that confirmed that the long term infusion schedule improved tolerability and that there was no added benefit from IL-2

This shows that the findings from this trial helped **improve treatment strategies beyond this study**.

8.4 Why was the study closed from a regulatory perspective?

With the introduction of the new EU Clinical Trial Regulation and the Clinical Trials Information System (CTIS), that is EU online system that manages, reviews, and publishes information about clinical trials, making the process simpler, more transparent, and centralized across Europe, new regulatory procedures became mandatory and older trials that had already completed treatment and follow-up were reviewed.

As this study had completed all patient treatment and long-term follow-up, and had already generated clear and clinically relevant results, a decision was made to officially close the trial on 31 January 2025 from a regulatory perspective.

For this reason, the study was not transferred into CTIS, however, all the relevant results are reported through this final summary and scientific publications

8.5 Key messages for parents and caregivers

- This study looked at a treatment called **dinutuximab beta** for children and young people with **high-risk neuroblastoma** when the cancer had come back or did not respond to earlier treatments.
- The study showed that giving this medicine **slowly over several days** causes **less pain and fewer side effects** than giving it over a short time.
- Because of this, many children needed **less strong pain medicine**, and more children were able to complete their treatment.
- The treatment was still **effective at fighting the cancer**, and many children had **long-term benefit**.
- Adding another medicine called **interleukin-2** did **not improve results** and caused **more side effects**, so it is no longer recommended with this treatment.
- The findings from this study have helped doctors improve how this treatment is given, making it **safer and easier for children to tolerate**.

8.6 Key messages for children and young people

- This study tested a medicine called **dinutuximab beta**, which helps the body fight cancer.
- Doctors found that giving the medicine **slowly over time** made it **hurt less** and caused **fewer bad side effects**.
- Many children did not need as much strong pain medicine during treatment.
- The medicine still worked well to help fight the cancer.
- Another medicine that was tested did **not help** and made some children feel worse, so doctors stopped using it.
- Because of this study, doctors now know a **better and gentler way** to give this treatment.

9 PUBLICATIONS RELATED TO CH14.18/CHO

1. ***Anti-neuroblastoma effect of ch14.18 antibody produced in CHO cells is mediated by NK-cells in mice.*** *Zeng Y, Fest S, Kunert R, Katinger H, Pistoia V, Michon J, Lewis G, Ladenstein R, Lode HN. Mol Immunol. 2005 Jul;42(11):1311-9.*

2. ***Validated detection of anti-GD2 antibody ch14.18/CHO in serum of neuroblastoma patients using anti-idiotype antibody ganglidiomab****. Siebert N, Seidel D, Eger C, Brackrock D, Reker D, Schmidt M, Lode HN.* **J Immunol Methods. 2013 Dec 15;398-399:51-9.**

3. ***Ch14.18 antibody produced in CHO cells in relapsed or refractory Stage 4 neuroblastoma patients: a SIOPEN Phase 1 Study.*** *Ladenstein R, Weixler S, Baykan B, Bleeke M, Kunert R, Katinger D, Pribill I, Glander P, Bauer S, Pistoia V, Michon J, Garaventa A, Lode HN.*
    a. ***MAbs. 2013 Sep-Oct;5(5):801-9. doi: 10.4161/mabs.25215. Epub 2013 May 31.***

4. ***Functional bioassays for immune monitoring of high-risk neuroblastoma patients treated with ch14.18/CHO anti-GD2 antibody****. Siebert N, Seidel D, Eger C, Jüttner M, Lode HN.* ***PloS One. 2014 Sep 16;9(9).***

5. ***Validated detection of human anti-chimeric immune responses in serum of neuroblastoma patients treated with ch14.18/CHO.*** *Siebert N, Eger C, Seidel D, Jüttner M, Lode HN.* ***J Immunol Methods. 2014 May;407:108-15.***

6. ***Neuroblastoma patients with high-affinity FCGR2A, -3A and stimulatory KIR 2DS2 treated by long-term infusion of anti-GD₂ antibody ch14.18/CHO show higher ADCC levels and improved event-free survival****. Siebert N, Jensen C, Troschke-Meurer S, Zumpe M, Jüttner M, Ehlert K, Kietz S, Müller I, Lode HN.* ***Oncoimmunology. 2016 Sep 26;5(11).***

7. ***Pharmacokinetics and pharmacodynamics of ch14.18/CHO in relapsed/refractory high-risk neuroblastoma patients treated by long-term infusion in combination with IL-2.*** *Siebert N, Eger C, Seidel D, Jüttner M, Zumpe M, Wegner D, Kietz S, Ehlert K, Veal GJ, Siegmund W, Weiss M, Loibner H, Ladenstein R, Lode HN.* ***Mabs. 2016;8(3):604-16.***

8. ***Neuroblastoma patients with high-affinity FCGR2A, -3A and stimulatory KIR 2DS2 treated by long-term infusion of anti-GD(2) antibody ch14.18/CHO show higher ADCC levels and improved event-free survival.*** *Siebert N, Jensen C, Troschke-Meurer S, Zumpe M, Jüttner M, Ehlert K, Kietz S, Müller I, Lode HN.* ***Oncoimmunology. 2016 Sep 26;5(11).***

9. ***Tolerability, response and outcome of high-risk neuroblastoma patients treated with long-term infusion of anti-GD2 antibody ch14.18/CHO****. Mueller I, Ehlert K, Endres S, Pill L, Siebert N, Kietz S, Brock P, Garaventa A, Valteau-Couanet D, Janzek E, Hosten N, Zinke A, Barthlen W, Varol E, Loibner H, Ladenstein R, Lode HN.* ***MAbs. 2018 Jan;10(1):55-61.***

10. ***Interleukin 2 with anti-GD2 antibody ch14.18/CHO (dinutuximab beta) in patients with high-risk neuroblastoma (HR-NBL1/SIOPEN): a multicentre, randomised, phase 3 trial.*** *Ladenstein R, Pötschger U, Valteau-Couanet D, Luksch R, Castel V, Yaniv I, Laureys G, Brock P, Michon JM, Owens C, Trahair T, Chan GCF, Ruud E, Schroeder H, Beck Popovic M, Schreier G, Loibner H, Ambros P, Holmes K, Castellani MR, Gaze MN, Garaventa A, Pearson ADJ, Lode HN.* ***Lancet Oncol. 2018 Dec;19(12):1617-1629.***

11. ***Tolerability, response and outcome of high-risk neuroblastoma patients treated with long-term infusion of anti-GD(2) antibody ch14.18/CHO****. Mueller I, Ehlert K, Endres S, Pill L, Siebert N, Kietz S, Brock P, Garaventa A, Valteau-Couanet D, Janzek E, Hosten N, Zinke A, Barthlen W, Varol E, Loibner H, Ladenstein R, Lode HN.* ***MAbs. 2018 Jan;10(1):55-61.***

12. ***Impact of HACA on Immunomodulation and Treatment Toxicity Following ch14.18/CHO Long-Term Infusion with Interleukin-2: Results from a SIOPEN Phase 2 Trial.*** *Siebert N, Troschke-Meurer S, Marx*

M, Zumpe M, Ehlert K, Gray J, Garaventa A, Manzitti C, Ash S, Klingebiel T, Beck J, Castel V, Valteau-Couanet D, Loibner H, Ladenstein R, Lode HN. ***Cancers (Basel). 2018 Oct 17;10(10).***

13. ***Inflammatory response and treatment tolerance of long-term infusion of the anti-GD(2) antibody ch14.18/CHO in combination with interleukin-2 in patients with high-risk neuroblastoma.*** *Ceylan K, Jahns LJ, Lode BN, Ehlert K, Kietz S, Troschke-Meurer S, Siebert N, Lode HN.* ***Pediatr Blood Cancer. 2018 Jun;65(6):e26967.***

14. ***Low CD4$^+$/CD25$^+$/CD127$^-$ regulatory T cell- and high INF-γ levels are associated with improved survival of neuroblastoma patients treated with long-term infusion of ch14.18/CHO combined with interleukin-2.*** *Troschke-Meurer S, Siebert N, Marx M, Zumpe M, Ehlert K, Mutschlechner O, Loibner H, Ladenstein R, Lode HN.* ***Oncoimmunology. 2019 Sep 8;8(12):1661194.***

15. ***Investigation of the Role of Dinutuximab Beta-Based Immunotherapy in the SIOPEN High-Risk Neuroblastoma 1 Trial (HR-NBL1)*** *Ladenstein R, Pötschger U, Valteau-Couanet D, Luksch R, Castel V, Ash S, Laureys G, Brock P, Michon JM, Owens C, Trahair T, Chi Fung Chan G, Ruud E, Schroeder H, Beck-Popovic M, Schreier G, Loibner H, Ambros P, Holmes K, Castellani MR,* ***Gaze MN, Garaventa A, Pearson ADJ, Lode HN. Cancers (Basel). 2020 Jan 28;12(2):309.***

16. ***Clinical Phenotype and Management of Severe Neurotoxicity Observed in Patients with Neuroblastoma Treated with Dinutuximab Beta in Clinical Trials.*** *A. Manzitti C, Garaventa A, Gray J, Papadakis V, Valteau-Couanet D, Zachwieja K, Poetschger U, Pribill I, Fiedler S, Ladenstein R, Lode HN* ***Cancers (Basel), 2022 Apr 10;14(8):1919.***

17. ***Clinical Phenotype and Management of Severe Neurotoxicity Observed in Patients with Neuroblastoma Treated with Dinutuximab Beta in Clinical Trials*** *Wieczorek A., Manzitti C., Garaventa A., Gray J., Papadakis V., Valteau-Couanet D., Zachwieja K., Pötschger U., Pribill I., Fiedler S., Ladenstein R., Lode HN.* ***Cancers 2022, 14(8), 1919****; https://doi.org/10.3390/cancers14081919, 2022 April 10.*

18. ***Effect and Tolerance of N5 and N6 Chemotherapy Cycles in Combination with Dinutuximab Beta in Relapsed High-Risk Neuroblastoma Patients Who Failed at Least One Second-Line Therapy.*** *Lode HN, Ladenstein R, Troschke-Meurer S, Struppe L, Siebert N, Zumpe M, Ehlert K, Huber S, Glogova E, Hundsdoerfer P, Eggert A, Zaniewska-Tekieli A, Balwierz W, Wieczorek A.* ***Cancers (Basel). 2023*** *Jun 27;15(13):3364*

19. ***Multimodal Therapy with Consolidating Haploidentical Stem Cell Transplantation and Dinutuximab Beta for Patients with High-Risk Neuroblastoma and Central Nervous System Relapse.*** *Flaadt, T., Ebinger, M., Schreiber, M., Ladenstein, R.L., Simon, T., Lode, H.N., Hero, B., Schuhmann, M.U., Schäfer, J., Paulsen, F., Timmermann G., Eggert A. and Lang P.* ***J Clin Med. 2023 Sep 25;12(19):6196.***

20. ***Immunotherapy of high-risk neuroblastoma patients with long term infusion of dinutuximab beta is associated with a survival advantage over short term infusion. Results from the HR-NBL1/SIOPEN trial.*** *Ruth Ladenstein (1), Ulrike Pötschger (2), Dominique Valteau-Couanet (3), Juliet Gray (4), Roberto Luksch (5), Aleksandra Wieczorek (6), Adela Canete (7), Shifra Ash (8), Maja Beck Popovic (9), Genevieve Laureys (10), Godfrey Chi Fung Chan (11), Ellen Ruud (12), Kim Vettenranta (13), Cormac Owens (14), Henrik Schroeder (15), Hans Loibner (16), Sabine Taschner-Mandl (2), Sabine Sarnacki (17), Holger N. Lode (18).* ***ASCO publication, J Clin Oncol 43, 10000(2025)*** *Volume 43, Number 16_suppl;*

21. ***High Risk Neuroblastoma (HR-NB) with MycN Amplification and Age < 18 months: Results from the HR-NBL1/SIOPEN trial.*** *Ruth Ladenstein1*, MD, Ulrike Pötschger2* MSc, Dominique Valteau-Couanet3 MD, Shifra Ash4 MD, Maja Beck Popovic5 MD, Walentyna Balwierz 6, Pavel Bician 7, Tom Boterberg 8, Sue Burchill9, Penelope Brock10 MD, Godfrey Chi Fung Chan11 MD, Maja Cesen12 MD, Martin Elliot13 MD, Mikolas Garami 14 MD, Alberto Garaventa15 MD, Mark Gaze MD16, Per Kogner17MD, Ana Forjaz de Lacerda 18MD, Genevieve Laureys19 MD, Prof. Holger N. Lode20 MD, Hans Loibner21 PhD, Roberto Luksch22 MD, Josef Malis 23MD, Jean Marie Michon24 MD, Cormac Owens25 MD, Vassilios Papadakis 26 MD, Prof. Andrew DJ Pearson27 MD, Ellen Ruud28 MD, Sabine Sarnacki 29MD, Prof. Henrik Schroeder30 MD, Toby Trahair31 MD, Kim Vettenranta 32MD, Dragana*

Vujic33 MD, Sabine Taschner-Mandl34, PhD, Gudrun Gudrun Schleiermacher35, MD , Adela Canete36 ***MDJ Clin Oncol 41, 10000(2023), Volume 41, Number 16_suppl***

22. ***Long-Term Outcomes and Quality of Life of High-Risk Neuroblastoma Patients Treated with a Multimodal Treatment Including Anti-GD2 Immunotherapy: A Retrospective Cohort Study*** *Tim Flaadt, Jonas Rehm, Thorsten Simon, Barbara Hero, Ruth L. Ladenstein, Holger N. Lode, Desiree Grabow, Sandra Nolte, Roman Crazzolara, Johann Greil, Martin Ebinger, Michael Abele, Ursula Holzer, Michaela Döring, Johannes H. Schulte, Peter Bader, Paul-Gerhardt Schlegel, Matthias Eyrich, Peter Lang, Thomas Klingebiel, and Rupert Handgretinger****.. Cancers 2025, 17, 149.***

23. ***Fcγ Receptor Polymorphism in Patients with Relapsed/Refractory High-Risk Neuroblastoma Correlates with Outcomes in the SIOPEN Dinutuximab Beta Long-Term Infusion Trial.*** *Holger N. Lode, Nikolai Siebert, Dominique Valteau-Couanet, Alberto Garaventa, Adela Canete, John Anderson, Isaac Yaniv, Shifra Ash, Juliet Gray, Thomas Klingebiel, Hans Loibner, Roberto Luksch, Carla Manzitti, Jean Marie Michon, Cormac Owens, Ulrike Potschger, Sascha Troschke-Meurer, Evgenia Glogova and Ruth Ladenstein; for the SIOP Europe Neuroblastoma Group (SIOPEN).* ***Clin Cancer Res 2025;31:3692–701;****(V1&V2 cohort).*

24. ***Dinutuximab Beta Versus Naxitamab in the Treatment of Relapsed/Refractory Neuroblastoma in Patients with Stable Disease, Minor Response or Partial Response and Disease in Bone or Bone Marrow: Systematic Review and Matching-Adjusted Indirect Comparison*** *Holger N. Lode, Przemysław Holko, Aleksandra Wieczorek, Nikolai Siebert, Dominique Valteau-Couanet, Alberto Garaventa, Adela Cañete, John Anderson, Isaac Yaniv, Shifra Ash, Juliet Gray, Roberto Luksch, Carla Manzitti, Sascha Troschke-Meurer Torsten Ebeling, Paweł Kawalec, Katarzyna Sladowska and Ruth L. Ladenstein..* ***Cancers 2025, 17, 2723.***

25. ***Long-term Infusion dinutuximab beta alone or with subcutaneous IL-2 for high-risk neuroblastoma patients with unfavorable disease course: results from an open-label, randomized, SIOPEN Phase II trial.*** *Holger N. Lode1*; Sascha Troschke-Meurer1*; Alberto Garaventa2; Carla Manzitti2; Roberto Luksch3; Dominique Valteau-Couanet4,5; Marion Gambart6; John Anderson7; Juliet Gray8; Adela Canete9; Lucas Moreno10; Aleksandra Wieczorek11; Cormac Owens12; Shifra Ash13; Isaac Yaniv14; Genevieve Laureys15; Hans Loibner16; Ulrike Pötschger17; Evgenia Glogova17**; and Ruth Ladenstein17,18** for the SIOP Europe Neuroblastoma Group (SIOPEN). In submission (V3- cohort*

26. ***Pharmacokinetics and pharmacodynamics of dinutuximab beta in pediatric neuroblastoma patients: non-compartmental analyses, population PK modeling, and PK/PD correlations*** *Holger N. Lode1, Ted Parton4, Peter Buchan, Ignacio Alvarez Rojo, Claudio Giuliano3, Hans Baumeister, Scott Van Wart, Andrew R Santulli and Ruth Ladenstein2..In submission*

ABBREVIATIONS

13-cis-RA	13-cis retinoic acid, Isotretinoin
ADCC	Antibody dependent cellular cytotoxicity
AE	Adverse Event
ALT, ALAT	Alanine aminotransferase
AR	Adverse reaction
AST, ASAT	Aspartate aminotransferase
CCRI	Children's Cancer Research Institute
CDC	Complement dependent cellular cytotoxicity
ch14.18/CHO	Chimeric 14.18 anti-GD_2 monoclonal antibody produced in Chinese hamster ovary cells
CHO	Chinese hamster ovary
CNS	Central nervous system
CR	Complete response
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DB	dinutuximab beta (DB)
DLT	Dose limiting toxicity
DMC	Data monitoring committee
eCRF	Electronic Case Report Form
EFS	Event free survival
GCP	Good clinical practice
GD2	Ganglioside
HR-NBL-1	SIOPEN high risk neuroblastoma 1 clinical trial
IB	Investigator's Brochure
IBD	International Birth Date
IL-2	Interleukin-2, aldesleukin, Proleukin®
i.v.	intravenous
LTI	Long Term Infusion; acronym for the study
mAb	Monoclonal antibody
MIBG	Metaiodbenzylguanidine
MRI	Magnetic Resonance Imaging
NK cells	Natural killer cells
PI	Principal investigator
PR	Partial Response
RSI	Reference Safety Information
S^2IRP	Studies and statistics integrated research & projects
SAE	Serious Adverse Event

SAR	Serious Adverse Reaction
s.c.	subcutaneous
SIOPEN	SIOP (Société Internationale d'Oncologie Pédiatrique) Europe Neuroblastoma
SmPC	Summary of Product Characteristics
SP2/0	Mouse myeloma cell line SP2/0
SUSAR	Suspected Unexpected Serious Adverse Reaction