HR-NBL1 / SIOPEN Clinical Trial

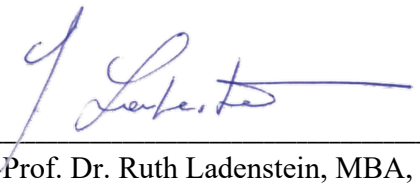
Public Lay Summary of Results

This document is a public summary of the results prepared in accordance with the European Clinical Trial Regulation requirements for lay summaries.

The goal is to explain the purpose of the trial, what treatments were tested, and what the results mean for patients and families.

Additional explanatory information is provided to ensure the results of the trial are understandable for patients and the public while maintaining scientific accuracy.

DATE: March 30th, 2026

SIGNATURE: 

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HR-NBL1 / SIOPEN Trial

Summary of Results for Patients and Families

What is the Study About?

High-Risk Neuroblastoma:

A cancer in young children.

Who Participated?

3,577 Patients

Over **20** Countries

High-risk neuroblastoma is an aggressive cancer that mainly affects infans and young children. The HR-NBL1 study tested different treatment strategies to identify the *most effective and safest therapies.*

Main Findings

Best High-Dose Chemo

BuMel Better Than CEM

Preferred Induction Chemo

Rapid **COJEC**

Role of IL-2

No Benefit, More Side Effects

Optimal Immunotherapy

Dinutuximab Beta Infusion

Future Impact

Guides Neuroblastoma Research

Why It Matters

Improved Survival & Safer Treatment

Impact on Future Research

- Design improved neuroblastoma treatments
- Develop safer immunotherapy approaches
- Guide future international clinical trials

Thank You to Patients and Families

More than **3,500 patients** and their families participated in the HR-NBL1 / SIOPEN study.

Their contribution has helped improve treatment strategies for children diagnosed with neuroblastoma around the world.

Contents

1. Key Findings of the HR-NBL1 Study – Patient Summary Box

1.1. What Was the Purpose of the Study?

The HR-NBL1/SIOPEN clinical trial studied **different treatment strategies for children with high-risk neuroblastoma** to determine which treatments provide the best survival outcomes while reducing unnecessary side effects.

More than **3,500 patients from over 20 countries** participated in the study.

Main Results of the Study:

Key Question	What the Study Found	What This Means for Patients
Which induction chemotherapy should be used?	Rapid COJEC and Modified N7 had similar survival results. However, Modified N7 caused more side effects.	Rapid COJEC became the **recommended induction chemotherapy regimen**
Which high-dose chemotherapy works best?	Busulfan + Melphalan (BuMel) improved survival compared with Carboplatin + Etoposide + Melphalan (CEM).	BuMel became the **preferred high-dose chemotherapy treatment** before stem-cell transplant.
Does adding IL-2 improve immunotherapy?	Adding IL-2 to anti-GD2 antibody therapy **did not improve survival** but increased side effects.	Immunotherapy is now usually given **without IL-2**.
How should anti-GD2 immunotherapy be given?	Continuous infusion of dinutuximab beta improved tolerability.	This approach became the **recommended immunotherapy strategy**.

1.2. What Do These Findings Mean?

The HR-NBL1 study helped doctors determine the **most effective treatment combination for high-risk neuroblastoma**.

The results showed that:

- Some treatments **significantly improve survival**.
- Other treatments **increase toxicity without improving outcomes**.
- Adjusting treatment strategies can **improve safety while maintaining effectiveness**.

These findings helped establish the **current standard treatment approach used by many paediatric oncology centres worldwide**.

2. Background

Neuroblastoma is a cancer that develops from immature nerve cells. It mainly affects infants and young children. The tumour most commonly begins in the adrenal glands or in nerve tissues along the spine. Neuroblastoma can behave very differently from patient

to patient. Some tumours respond well to treatment, while others are aggressive and difficult to cure.

Patients classified as having high-risk neuroblastoma typically have cancer that has spread to other parts of the body or tumours with specific genetic features such as MYCN amplification.

Historically, survival rates for children with high-risk neuroblastoma were low. Even with intensive treatment, fewer than one-third of patients survived long-term. Researchers therefore designed the HR-NBL1 trial to test different treatment strategies in order to improve outcomes.

3. Trial Information

Trial title: High Risk Neuroblastoma Study 1 of the SIOP Europe Neuroblastoma Group (HR-NBL1/SIOPEN).

Clinical trial phase: Phase III randomised clinical trial.

Disease studied: High-risk neuroblastoma in children and adolescents.

Trial duration: February 2002 – July 2023 (regulatory closure January 2025).

Sponsor: St. Anna Children's Cancer Research Institute (CCRI), Zimmermannplatz 10, Vienna 1090, Austria.

Coordinating investigator: Prof. Ruth Ladenstein, MD, MBA cPM.

3.1. Country-Level Patient Participation

International collaboration was essential for several reasons:

- **Rare disease** – high-risk neuroblastoma affects a relatively small number of children each year.
- **Specialised treatment centres** – patients require care in hospitals with expertise in paediatric oncology.
- **Large patient population** – combining patients from multiple countries allowed researchers to compare treatments using a sufficiently large study population.

By pooling expertise and patient participation across many countries, the HR-NBL1/ SIOPEN study became **one of the largest neuroblastoma trials ever conducted worldwide**.

The HR-NBL1/SIOPEN trial was conducted as a large international collaboration involving specialist paediatric oncology centres across Europe and several additional countries worldwide. Participating countries were in Europe, Australia, Israel, Hong Kong and other international centres.

Hospitals participating in the trial were responsible for:

- diagnosing patients with high-risk neuroblastoma
- providing treatment according to the study protocol
- collecting clinical data and reporting results to the central study database
- monitoring patient safety throughout the trial

All participating centres followed **international ethical standards and Good Clinical Practice (GCP) guidelines**.

Hospitals participating in the study were located in the following countries:

Australia, Austria, Belgium, Czech Republic, Denmark, Finland, France, Greece, Hong Kong, Hungary, Ireland, Israel, Italy, Norway, Poland, Portugal, Serbia, Slovakia, Slovenia, Spain, Sweden (including Iceland), Switzerland, United Kingdom.

These centres are members or collaborators of the SIOP Europe Neuroblastoma Group (SIOPEN), a network of hospitals and researchers working together to improve treatment for children with neuroblastoma.

3.2. Participant Protection and Ethical Oversight

3.2.1. Ethical Approval

Before the HR-NBL1/SIOPEN trial began, the study protocol was reviewed and approved by **independent Ethics Committees and Regulatory Authorities** in each participating country. These committees ensure that clinical trials are conducted ethically and that the rights, safety, and well-being of participants are protected.

The study was conducted according to:

- **International ethical guidelines**
- **Good Clinical Practice (GCP) standards**
- **National and European clinical trial regulations**

These rules require that clinical trials are carefully monitored and that patient safety remains the highest priority throughout the study.

3.2.2. Informed Consent

Participation in the HR-NBL1 study was entirely voluntary.
Before enrolling in the study:

- parents or legal guardians received detailed information about the trial,
- the potential benefits and risks of participation were explained,
- families were given time to ask questions and consider their decision.

3.2.3. Only patients whose parents or guardians provided **written Informed Consent** were included in the study. For older children and adolescents, information about the study was also provided in a way appropriate for their age so they could understand the treatment they were receiving.

3.2.4. Safety Monitoring

Patient safety was closely monitored throughout the trial.
Several mechanisms were used to ensure that treatments remained safe:

Clinical Monitoring
Doctors and study staff carefully monitored patients during treatment for side effects and complications.

Data Monitoring Committee
An independent **Data Monitoring Committee (DMC)** regularly reviewed safety data and treatment results during the study. The committee could recommend changes to the study if safety concerns arose or if important results became clear before the planned completion of the trial.

Adverse Event Reporting
All side effects experienced by patients during the trial were recorded and evaluated. Serious or unexpected side effects were reported promptly to regulatory authorities. These safety monitoring procedures helped ensure that the study was conducted responsibly and that patients received appropriate care.

4. Purpose of the Trial

The HR-NBL1 study was designed to determine which treatment strategies provide the best balance between effectiveness and safety.

To optimize treatment strategies for children with high-risk neuroblastoma the main objectives were:

- to compare different induction chemotherapy regimens,
- to determine the most effective high-dose chemotherapy before stem-cell transplantation,
- to evaluate immunotherapy approaches using an anti-GD2 antibody (Dinutuximab beta),
- to assess whether adding the immune-stimulating drug interleukin-2 improves outcomes.

5. Who Participated

A total of 3,577 patients were enrolled in the HR-NBL1 study. Because neuroblastoma is a rare disease, recruiting patients from many countries was necessary to ensure that the study could answer the research questions reliably.

Most patients were diagnosed during early childhood. The average age at diagnosis was about three years. Participants included infants, toddlers, children and adolescents.
Approximately 58 percent of patients were male and 42 percent were female.
Patients were treated in hospitals across more than twenty participating countries.

6. Study Design

The HR-NBL1 trial was an international open-label randomised study conducted at multiple hospitals.
More than 3,500 patients were registered in the study. Because high-risk neuroblastoma is rare, international collaboration was essential to recruit a large enough number of patients to answer the research questions.

6.1. Timeline of the HR-NBL1 Treatment Pathway

6.1.1. Treatment components

Treatment for high-risk neuroblastoma consists of several phases.

- **Induction therapy** is the first phase. It uses intensive chemotherapy to shrink the tumour and treat disease that has spread to other parts of the body.
- After induction therapy, **surgery** is performed whenever possible to remove the primary tumour.
- Patients then receive **high-dose chemotherapy followed by autologous stem-cell transplantation.** This step aims to eliminate remaining cancer cells while restoring bone marrow function.
- **Radiotherapy** is given to the site of the original tumour.
- Finally, patients receive **maintenance therapy**, more recently including immuno-therapy to reduce the risk of relapse.

6.1.2. Timelines in the HR-NBL1 Trial

Treatment usually takes **about 12–18 months**, followed by several years of follow-up.

Step 1 – Diagnosis and Study Enrolment

Timeframe: At diagnosis
Doctors first confirm the diagnosis of **high-risk neuroblastoma** using several tests:

- imaging scans (MRI or CT)
- MIBG scans to detect tumour spread
- bone marrow tests
- tumour biopsy and genetic testing

If the child meets the study criteria, the family is informed about the clinical trial and asked to provide **written Informed Consent** for participation.

Step 2 – Induction Chemotherapy

Timeframe: First 4–6 months
The goal of induction chemotherapy is to **shrink the tumour and treat cancer that has spread to other parts of the body**.

Patients receive several cycles of chemotherapy. In the HR-NBL1 trial, the main induction regimen used was **Rapid COJEC chemotherapy**.
During this phase:

- doctors monitor tumour response
- stem cells are collected from the patient's blood for later transplantation
- supportive care helps manage side effects such as infection risk

Step 3 – Surgery to Remove the Tumour

Once the tumour has shrunk, surgeons attempt to **remove the primary tumour**. The goal is to remove as much of the tumour as possible while protecting nearby organs and nerves.
Timeframe: If resectable after induction chemotherapy, alternatively after high-dose therapy.

Step 4 – High-Dose Chemotherapy and Stem-Cell Transplant

Timeframe: Several weeks
Patients receive **very high doses of chemotherapy** to destroy remaining cancer cells. In the HR-NBL1 study, the preferred regimen became:
Busulfan + Melphalan (BuMel)
Because high-dose chemotherapy damages the bone marrow, the patients previously collected **stem cells are returned to the body** to help the blood system recover.
During this phase:

- patients usually stay in hospital
- doctors monitor blood counts and organ function closely

Step 5 – Radiotherapy

Timeframe: After recovery from transplant
Radiotherapy is given to the **original tumour site**.
The goal is to eliminate any remaining cancer cells in that area and reduce the risk of relapse.

Step 6 – Maintenance Therapy / Immunotherapy

Timeframe: About 6 months
The final phase of treatment aims to eliminate **minimal residual disease**.
Patients receive:

- **Isotretinoin (13-cis retinoic acid)** to help cancer cells mature and stop growing
- **Anti-GD2 immunotherapy (dinutuximab beta)** to help the immune system attack neuroblastoma cells

The HR-NBL1 study showed that adding **interleukin-2 (IL-2)** increased side effects without improving outcomes, so immunotherapy is usually given **without IL-2**.

Step 7 – Long-Term Follow-Up

Timeframe: Several years

After treatment is completed, patients continue to attend regular follow-up visits.
Doctors monitor:

- recovery from treatment
- possible long-term side effects
- signs that the cancer may return

Follow-up is an important part of care and helps researchers understand the **long-term outcomes of treatment**.

6.1.3. Overview of the Treatment Timeline

Treatment Phase	Main Goal	Approximate Timing
Diagnosis and enrolment	Confirm disease and enter study	At diagnosis
Induction chemotherapy	Shrink tumour and treat metastases	Months 0–4
Surgery	Remove primary tumour	Around month 4–6
High-dose chemotherapy + transplant	Destroy remaining cancer cells	Month 6–7
Radiotherapy	Control disease at tumour site	Month 7–8
Immunotherapy / maintenance	Prevent relapse	Months 8–14
Follow-up monitoring	Check long-term outcomes	Several years

7. The 5 Randomisations

The study included several randomised comparisons labelled R0 through R4. Each randomisation evaluated a specific treatment question during a different phase of therapy.

7.1. R0 Randomized use of prophylactic granulocyte colony-stimulating factor during rapid COJEC induction

This **randomization evaluated within the HR-NBL1/SIOPEN trial**, the role of **prophylactic granulocyte colony-stimulating factor (G-CSF)** during induction chemotherapy with the Rapid COJEC regimen in children with high-risk neuroblastoma.

The study demonstrated that the use of prophylactic G-CSF:

- **r**educed the incidence of febrile neutropenia
- shortened hospitalisation time
- improved delivery of planned chemotherapy cycles

Importantly, the use of G-CSF did **not compromise treatment efficacy**, supporting its role as a **supportive care measure to improve treatment tolerability and protocol adherence** during intensive induction therapy.

Within the context of the HR-NBL1/SIOPEN program, this study provided evidence that **optimised supportive care can enhance feasibility and safety of dose-intensive induction chemotherapy**, contributing to the overall treatment strategy for high-risk neuroblastoma.

Ladenstein R, Valteau-Couanet D, Brock P, et al. Randomized trial of prophylactic granulocyte colony-stimulating factor during rapid COJEC induction in pediatric patients with high-risk neuroblastoma: the European HR-NBL1/SIOPEN study. J Clin Oncol. 2010;28(21):3516-3524. doi:10.1200/JCO.2009.27.3524.

7.2.R1 Randomisation Results – High-Dose Chemotherapy

The R1 randomisation compared two high-dose chemotherapy regimens before stem-cell transplantation.

Table 1. R1 Randomisation – High-Dose Chemotherapy Before Stem-Cell Transplant

Treatment Compared	Number of Patients	Key Result	What This Means for Patients
Busulfan + Melphalan (BuMel)	296	5-year event-free survival: **46%**	More patients remained alive without relapse
Carboplatin + Etoposide + Melphalan (CEM)	302	5-year event-free survival: **33%**	Fewer patients remained free of relapse

Interpretation (Lay Explanation)
Patients treated with **BuMel had a lower risk of relapse or death** than those treated with CEM.

- Hazard ratio for relapse or death: **0.71**
- This means the **risk was about 29% lower** with BuMel.

Conclusion:
BuMel became the **preferred high-dose chemotherapy regimen** in SIOPEN treatment strategies.

Ladenstein R, Pötschger U, Pearson ADJ, et al. Busulfan and melphalan versus carboplatin, etoposide, and melphalan as high-dose chemotherapy for high-risk neuroblastoma (HR-NBL1/SIOPEN): an international, randomised, multi-arm, open-label, phase 3 trial. Lancet Oncol. 2017;18(4):500-514. doi:10.1016/S1470-2045(17) 30070-0.

7.3.R2 Randomisation Results – Immunotherapy ± IL-2

The R2 comparison examined whether adding interleukin-2 to anti-GD2 antibody (Dinutuximab beta) therapy improved outcomes. Anti-GD2 antibodies help the immune system recognise and attack neuroblastoma cells. Patients received either antibody therapy alone or antibody therapy combined with interleukin-2.

Table 2. R2 Randomisation – Immunotherapy with or without IL-2

Treatment Compared	Number of Patients	Key Result	What This Means
Anti-GD2 antibody (ch14.18/CHO)	200	5-year event-free survival: **53%**	Effective immunotherapy
Anti-GD2 antibody + IL-2	206	5-year event-free survival: **58%**	Similar survival outcome

Interpretation

Survival was **similar between both groups**, but the group receiving **IL-2 experienced more side effects**.
However, adding interleukin-2 increased side effects, including fever, inflammation fatigue and diarrhoea.

Conclusion: Results showed that survival outcomes were similar between the two groups IL-2 **did not improve survival** but increased toxicity, so routine use with Dinutuximab beta therapy was not recommended.

Ladenstein R, Pötschger U, Valteau-Couanet D, et al. 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. Lancet Oncol. *2018;19(12): 1617-1629. doi:10.1016/S1470-2045(18)30578-3.*

7.4.R3 Randomisation Results – Induction Chemotherapy

The R3 randomisation compared two induction chemotherapy regimens, namely Rapid COJEC and the Modified N7 regimen.

Table 3. R3 Randomisation – Induction Chemotherapy

Treatment Compared	Number of Patients	Key Result	What This Means
Rapid COJEC chemotherapy	313	3-year overall survival: **62%**	Effective induction therapy
Modified N7 chemotherapy	317	3-year overall survival: **67%**	Similar survival outcome

Interpretation

Both treatments achieved **similar survival outcomes**.
However, **Modified N7 caused more treatment-related side effects**.
Examples of increased toxicity including higher rates of infections and more days in hospital.

Conclusion: Rapid COJEC became the **preferred induction chemotherapy regimen** because it was **better tolerated while providing similar survival results**.

Garaventa A, Pötschger U, Valteau-Couanet D, et al. Randomized Trial of Two Induction Therapy Regimens for High-Risk Neuroblastoma: HR-NBL1.5 International Society of Pediatric Oncology European Neuroblastoma Group Study. J Clin Oncol. *2021; 39(23):2552-2563. doi:10.1200/JCO.20.03144.*

7.5.R4 Randomisation Results – Immunotherapy Schedule

The R4 randomisation evaluated whether changing the infusion schedule of the anti-GD2 antibody dinutuximab beta and adding reduced-dose interleukin-2 improved outcomes.

Table 4. R4 Randomisation – Immunotherapy Schedule

Treatment Compared	Number of Patients	Key Result	What This Means
Dinutuximab beta (continuous infusion)	~200	Effective immunotherapy with manageable toxicity	Standard approach
Dinutuximab beta + reduced-dose IL-2	~200	Similar survival outcome	More treatment-related side effects

Interpretation

Continuous infusion of dinutuximab beta maintained **strong anti-tumour activity and** produced **better tolerability.** Adding IL-2 **did not improve survival outcomes**.

Conclusion: The recommended immunotherapy approach became **Dinutuximab beta without IL-2.**

Ladenstein RL, Pötschger U, Valteau-Couanet D, et al. Association of immunotherapy of high-risk neuroblastoma with dinutuximab beta long-term infusion and survival in the HR-NBL1/SIOPEN trial. J Clin Oncol. *2025;43(16_suppl):10000.*

Ladenstein R, Pötschger U, Valteau-Couanet D, et al. Investigation of the role of dinutuximab beta-based immunotherapy in the SIOPEN High-Risk Neuroblastoma 1 Trial (HR-NBL1). Cancers (Basel). *2020;12(2):309. Doi:10.3390/cancers12020309.*

7.6.Overall Findings from the Trial

Study Question	Final Recommendation
Best high-dose chemotherapy	**Busulfan + Melphalan (BuMel)**
Best induction chemotherapy	**Rapid COJEC**
Role of IL-2 in immunotherapy	**Not recommended due to increased toxicity**
Best antibody therapy approach	**Dinutuximab beta continuous infusion without IL-2**

8. Role of Local Therapy in the HR-NBL1/SIOPEN Treatment Strategy

Local therapy plays an important role in the treatment of children with high-risk neuroblastoma. In the HR-NBL1/SIOPEN trial, local therapy consisted of **surgical resection of the primary tumour and radiotherapy to the primary tumour site**. These treatments were administered after completion of induction chemotherapy and before or after consolidation therapy, depending on the individual treatment schedule.

The goal of local therapy is to **achieve maximum control of the primary tumour site**, thereby reducing the risk of local relapse while complementing systemic treatments that target metastatic disease.

8.1. Surgical Resection of the Primary Tumour

Surgical removal of the primary tumour was planned after completion of induction chemotherapy when feasible. Induction chemotherapy aims to reduce tumour size and improve the safety and success of surgical resection.

The objectives of surgery were:

- removal of as much of the primary tumour as safely possible
- preservation of surrounding organs and critical structures
- reduction of residual tumour burden

Complete resection was not always achievable due to the location of neuroblastoma tumours, which often involve major blood vessels or other vital structures.

8.2. Impact of Surgical Resection on Outcome

Analyses from the HR-NBL1/SIOPEN study showed that the **extent of surgical tumour resection was associated with improved survival outcomes** in patients with stage 4 high-risk neuroblastoma.

Patients who underwent more extensive tumour removal generally showed an improved event-free survival and improved overall survival. These findings support the role of surgery as an important component of multimodal therapy for high-risk neuroblastoma.

However, complete resection must be balanced against the potential risk of surgical complications, and the decision to pursue extensive surgery is based on individual patient factors and surgical feasibility.

Holmes K, Pötschger U, Pearson ADJ, et al. Influence of Surgical Excision on the Survival of Patients With Stage 4 High-Risk Neuroblastoma: A Report From the HR-NBL1/SIOPEN Study. J Clin Oncol. 2020;38(25):2902-2915. doi:10.1200/JCO.19.03117.

8.3. Purpose of Radiotherapy

Radiotherapy was used to treat the **primary tumour site after high-dose chemotherapy and stem-cell transplantation**.

The purpose of radiotherapy is to:

- eliminate any remaining tumour cells at the primary site
- reduce the risk of local relapse
- improve long-term disease control

Radiotherapy was delivered according to the HR-NBL1 protocol guidelines using standard paediatric oncology radiotherapy techniques.

8.4. Radiotherapy Quality Assurance

Because the HR-NBL1/SIOPEN trial involved many participating centres across different countries, **radiotherapy quality assurance procedures** were implemented to ensure consistent treatment delivery.

These procedures included:

- central review of radiotherapy plans
- verification of radiation dose and treatment fields
- adherence to protocol-specified radiotherapy guidelines

Quality assurance analyses demonstrated that protocol compliance for radiotherapy was generally high across participating centres, supporting the reliability of the treatment approach used in the trial.

Gaze MN, Boterberg T, Dieckmann K, et al. Results of a quality assurance review of external beam radiation therapy in the International Society of Paediatric Oncology (Europe) Neuroblastoma Group's High-risk Neuroblastoma Trial: a SIOPEN study. Int J Radiat Oncol Biol Phys. 2013;85(1):170-174. doi:10.1016/j.ijrobp.2012.05.004.

8.5. Integration of Local and Systemic Therapy

In the HR-NBL1 treatment strategy, local therapy was integrated with systemic treatments including:

- induction chemotherapy
- high-dose chemotherapy with stem-cell transplantation
- maintenance therapy with isotretinoin and Dinutuximab beta immunotherapy

This **multimodal treatment approach** aims to address both:

- **local tumour control**, through surgery and radiotherapy
- **systemic disease control**, through chemotherapy and immunotherapy

The combination of systemic and local treatments is essential for improving outcomes in children with high-risk neuroblastoma.

8.6. Summary on Local Therapy

In the HR-NBL1/SIOPEN trial, local therapy consisting of surgery and radiotherapy formed an integral part of the overall treatment strategy.

Key findings include:

- surgical resection of the primary tumour contributes to improved survival outcomes
- radiotherapy helps reduce the risk of local tumour recurrence
- quality assurance procedures ensured consistent radiotherapy delivery across participating centres

Together with systemic therapy, these local treatment approaches contributed to the comprehensive multimodal treatment strategy evaluated in the HR-NBL1/SIOPEN trial.

9. Lay Explanation of Survival Curves

9.1. What Are Survival Curves?

In clinical trials, researchers often use **survival curves** to show how patients do over time during and after treatment.

A survival curve is a graph that shows the **percentage of patients who remain alive or free of disease events over time**.

The horizontal axis (X-axis) usually represents **time after treatment**, often measured in months or years. The vertical axis (Y-axis) shows the **percentage of patients who have not experienced the event being studied**. Each treatment group in the study is represented by a separate line on the graph.

9.2. What is a Hazard Ratio

Hazard ratio – statistical measure comparing risk between treatment groups.

9.3. What Event-Free Survival Means

Event-free survival (EFS) measures the length of time after treatment during which a patient:

- remains alive **and**
- has **no relapse, disease progression, or other defined event** related to the cancer.

An "event" in this type of study usually includes:

- cancer returning (relapse)
- cancer getting worse (progression)
- development of a second cancer
- death from any cause

Therefore, event-free survival describes **how many patients remain alive without these events occurring**.

9.4. How to Read an Event-Free Survival Curve

At the start of the trial, **all patients are alive and event-free**, so the curve begins at **100%**. Over time, if patients experience relapse, progression, or death, the curve **moves**

downward. A **higher curve indicates better outcomes**, meaning more patients remain free from relapse or progression.
For example: if the curve shows **50% at 5 years**, this means that **half of the patients were alive without relapse five years after treatment**.

9.5. Example from the HR-NBL1 Trial

In the HR-NBL1 study, event-free survival was compared between two high-dose chemotherapy treatments.
At five years after treatment:

- **Busulfan + Melphalan (BuMel)**
  About **46% of patients** remained alive without relapse or disease progression.
- **Carboplatin + Etoposide + Melphalan (CEM)**
  About **33% of patients** remained alive without relapse or disease progression.

This means that more patients treated with BuMel remained event-free, which indicates better treatment effectiveness.

9.6. What Overall Survival Means

Overall survival (OS) measures how long patients remain alive after starting treatment. Unlike event-free survival, overall survival **does not consider relapse or disease progression**.
It only measures **whether the patient is alive**.
This means that even if a patient experiences relapse but continues to live, they are still counted in overall survival statistics.

9.7. How to Read an Overall Survival Curve

Overall survival curves are interpreted in a similar way to event-free survival curves.
At the beginning of the study:

- all patients are alive
- the curve starts at **100%**

Over time, if patients die, the curve gradually moves downward.
A **higher curve indicates better survival outcomes**.

9.8. Example from the HR-NBL1 Trial

In the HR-NBL1 study:
At five years after treatment:

- **BuMel:** approximately **54% of patients were alive**
- **CEM:** approximately **42% of patients were alive**

This indicates that **overall survival was higher for patients treated with BuMel**.

9.9. Why Survival Curves Are Important

Survival curves help researchers and doctors understand:

- how effective treatments are over time
- whether one treatment provides better long-term outcomes than another
- when differences between treatments begin to appear

They are also important for identifying whether treatments improve **short-term or long-term survival**.

9.10. What the HR-NBL1 Survival Curves Show

The survival curves from the HR-NBL1 study demonstrated that:

- **BuMel improved event-free survival and overall survival compared with CEM**
- **Rapid COJEC and Modified N7 had similar survival outcomes**
- **Adding IL-2 to immunotherapy did not improve survival**

These results helped establish the **current standard treatment strategy for high-risk neuroblastoma**.

10. Summary of Side Effects Observed in the Study

The treatments used in the HR-NBL1 study were intensive because high-risk neuroblastoma is a life-threatening disease. Most patients experienced side effects related to chemotherapy, stem-cell transplantation, or immunotherapy.

10.1. Major Side Effects

The table below summarises the **most common or clinically important side effects reported during the study.**

Table: Major Side Effects Observed During the Study

Type of Treatment	Common Side Effects	How Often They Occurred	What This Means for Patients
Induction Chemotherapy (Rapid COJEC / N7)	Infections, low blood counts, fatigue, nausea and vomiting	Very common	These side effects occur because chemotherapy temporarily weakens the immune system and bone marrow.
High-Dose Chemotherapy (BuMel or CEM)	Severe low blood counts, infections, organ stress (liver, kidneys)	Very common	These treatments require stem-cell transplantation to help the bone marrow recover.
Stem-Cell Transplantation	Fever, infection risk, weakness, need for hospital monitoring	Common	Patients usually remain in hospital during recovery while blood cells regenerate.
Radiotherapy	Fatigue, skin irritation, local tissue effects	Common	Side effects usually occur near the treated area of the body.
Anti-GD2 Immunotherapy (Dinutuximab beta)	Pain during infusion, fever, allergic reactions	Common	These effects occur because the immune system is being activated to attack tumour cells.

Type of Treatment	Common Side Effects	How Often They Occurred	What This Means for Patients
Interleukin-2 (IL-2)	Fever, diarrhoea, inflammation, capillary leak syndrome	More frequent when IL-2 was used	IL-2 increased immune activity but also caused more treatment-related side effects.

10.2. Important Safety Findings from the Trial

The HR-NBL1 trial found that adding **interleukin-2 (IL-2)** to anti-GD2 immunotherapy caused **more side effects** without improving survival outcomes.

Common IL-2 related side effects included fever, diarrhoea, fatigue, inflammation and fluid leakage from blood vessels (capillary leak syndrome).

Because IL-2 did **not improve survival but increased toxicity**, it is **not routinely recommended in current treatment protocols**.

10.3. Rare but Important Side Effects

Although uncommon, some patients experienced more serious complications, including:

Rare Side Effect	Description
Severe allergic reactions	Immune responses to antibody therapy
Neurological symptoms	Temporary vision or nerve effects
Organ toxicity	Effects on liver or kidneys after high-dose chemotherapy
Secondary cancers	Rare long-term complication after intensive treatment

Doctors carefully monitored patients for these complications throughout the study.

10.4. Overall Safety Conclusion

The treatments used in the HR-NBL1 study were associated with significant side effects because they are designed to treat a very aggressive form of cancer.

However, the study showed that some treatments **improve survival significantly**, while other treatments **increase toxicity without improving outcomes**.

Despite these risks, the treatments were considered acceptable because high-risk neuroblastoma is a life-threatening disease. By identifying these differences, the HR-NBL1 study helped doctors **optimise treatment strategies to improve survival while reducing unnecessary side effects**.

10.5. Benefit-Risk Evaluation

Overall, the benefits of the treatments evaluated in the HR-NBL1 study were considered greater than the risks. The study demonstrated that certain treatment strategies improve survival while others add toxicity without improving outcomes. Removing unnecessary treatments helps reduce treatment burden while maintaining effectiveness.

Benefits of Participation

Participation in the trial allowed patients to receive treatment within a carefully monitored clinical study designed to improve therapy for high-risk neuroblastoma.

11. Impact on Clinical Practice

The knowledge gained from patients and families who took part in this trial has helped improve treatment strategies for children diagnosed with neuroblastoma around the world. The HR-NBL1 trial significantly influenced international treatment guidelines for high-risk neuroblastoma. Key outcomes included the adoption of BuMel as standard high-dose chemotherapy, confirmation of Rapid COJEC as the preferred induction regimen, and the use of dinutuximab beta immunotherapy without interleukin-2.

11.1. What the Results Mean for Patients

For children diagnosed with high-risk neuroblastoma, the HR-NBL1 trial helped identify treatment strategies that improve survival while reducing unnecessary toxicity. Although treatment remains intensive, outcomes have improved compared with historical results.

- Stem-cell transplantation – procedure used to restore bone marrow after high-dose chemotherapy.
- Immunotherapy – treatment that helps the immune system attack cancer cells.

11.2. Contribution of Patients and Families

11.2.1. Importance of Patient Participation

Clinical trials depend on the willingness of patients and families to participate in research studies.

The HR-NBL1/SIOPEN trial involved **more than 3,500 patients**, making it one of the largest clinical trials ever conducted for high-risk neuroblastoma. The participation of these patients and their families made it possible to answer important questions about treatment strategies.

11.2.2. How Participation Helped Improve Treatment

Because patients and families agreed to take part in the study, researchers were able to determine:

- which chemotherapy regimens provide the best outcomes,
- which treatments improve survival,
- which therapies add unnecessary toxicity without improving results.

These findings have directly influenced international treatment guidelines for children with high-risk neuroblastoma.

Patient privacy and confidentiality are protected in accordance with applicable data protection laws. Personal information identifying individual patients is not shared publicly. All research data used for analysis are anonymised or coded so that individual participants cannot be identified.

12. Long-Term Impact

The results of the HR-NBL1 trial continue to benefit patients today. The knowledge gained from this study has helped establish the **current standard treatment strategy** used by many paediatric oncology centres worldwide.
Participation in clinical trials like HR-NBL1 contributes to improving treatments for future patients diagnosed with neuroblastoma.
The contribution of patients and families is therefore essential for advancing medical knowledge and improving outcomes for children with cancer.

13. How the Results Will Be Shared with Participants

13.1. Communication of Study Results

The results of the HR-NBL1/SIOPEN clinical trial are made publicly available so that patients, families, healthcare professionals, and researchers can learn from the findings.
This lay summary has been prepared to explain the study results in language that can be understood by the general public. The summary is intended to help participants and their families understand the outcomes of the trial in which they took part.

13.2. Public Availability of the Results

The results of the HR-NBL1 study are shared through several channels, including:

- **Public clinical trial registries**, such as the European Clinical Trials Information System (CTIS)
- **Scientific publications** in peer-reviewed medical journals
- **Presentations at international medical conferences**
- **Information provided by participating hospitals and clinical research networks**

These dissemination methods ensure that the knowledge gained from the study can benefit the wider medical community and improve future treatment strategies.

13.3. Communication Through Treating Hospitals

Participating hospitals and clinicians may also inform patients and families about the results of the study during follow-up visits or through institutional communication channels. Healthcare professionals involved in the trial can help explain the results and their implications for future treatment approaches.

13.4. Importance of Transparency

Sharing the results of clinical trials is an important part of responsible research. Making trial findings publicly available helps ensure transparency, supports scientific progress, and allows other researchers to build on the knowledge gained from the study.

14. Data Sharing and Future Research Use of Trial Data

14.1. Use of Data in Future Research

The data collected during the HR-NBL1/SIOPEN trial provide valuable information about the treatment of high-risk neuroblastoma.

Researchers may continue to analyse the data collected in the study to better understand:

- long-term outcomes of patients,
- treatment-related side effects,
- biological factors that influence response to therapy,
- and international collaborative research efforts to explore ways to improve treatment strategies in the future,

These analyses can help guide the development of new therapies and improve survival outcomes for children with neuroblastoma. With appropriate ethical approvals, anonym-ised study data may be used in future scientific research projects related to neuro-blastoma. The knowledge gained from this study will help researchers and clinicians improve treatments for children diagnosed with neuroblastoma in the future.

14.2. Contribution to Future Advances

By allowing study data to be used responsibly in future research, the contributions of patients and families participating in the HR-NBL1 trial will continue to support medical progress. Researchers continue to study ways to further improve treatment for neuroblastoma. Future research focuses on targeted therapies, precision medicine approaches and methods to reduce treatment-related side effects while maintaining high cure rates. These future research activities help maximize the scientific value of the information collected during the HR-NBL1 trial.

14.3. Confidentiality of Participant Information

The HR-NBL1/SIOPEN clinical trial was conducted in accordance with international ethical standards and applicable data protection regulations to ensure the privacy and confidentiality of all participating patients.

Personal information collected during the study was handled in a manner designed to protect the identity of participants. Patients were identified in study records using **unique study identification numbers**, and no directly identifying information (such as names or addresses) was included in the research dataset used for analysis.

14.4. Data Handling and Storage

Clinical data collected during the study included information on diagnosis, treatment, response to therapy, side effects, and long-term outcomes. These data were recorded in secure clinical trial databases and were accessible only to authorised study personnel.
Appropriate safeguards were implemented to protect patient information, including:

- restricted access to study databases
- secure storage of electronic and paper records
- controlled transfer of study data between participating centres and the central study database

These measures ensured that patient data were managed in compliance with **Good Clinical Practice (GCP) standards** and applicable national and international data protection laws.

14.5. Use of Anonymised Data

For the purposes of scientific analysis and reporting, patient data were **coded or anonymised** so that individual participants could not be identified.
When study results are published in scientific journals or shared with regulatory authorities, only **aggregated data** are reported. Individual patient identities are not disclosed. This approach allows researchers to analyse and share important scientific findings while maintaining strict protection of patient privacy.

14.6. Compliance with Data Protection Regulations

The HR-NBL1/SIOPEN trial was conducted in accordance with relevant data protection frameworks, including:

- **International Council for Harmonisation and Good Clinical Practice guidelines (ICH-GCP)**
- **European Union data protection regulations**
- national data protection laws applicable in participating countries

These regulations require that patient data be collected, stored, and used only for legitimate scientific and medical purposes.

14.7. Long-Term Data Retention and Future Research

Clinical trial data may be stored for an extended period after completion of the study to allow further scientific analysis or regulatory review.
Any future use of the data for research purposes will continue to respect patient confidentiality. Data used in such analyses will remain **coded or anonymised**, and researchers will not have access to information that could identify individual patients.

14.8. Summary

The HR-NBL1/SIOPEN study implemented strict procedures to ensure the protection of patient privacy throughout the study. Personal data were handled securely, coded for analysis, and reported only in aggregated form. These measures ensured that the scientific

value of the study could be realised while maintaining the confidentiality and dignity of all participating patients.

15. Conclusion

The HR-NBL1/SIOPEN trial represents a major international effort to improve treatment for children with high-risk neuroblastoma.

The study identified treatment strategies that significantly improved outcomes and helped to establish the current standard of care.

16. References

A. Pivotal and core HR-NBL1/SIOPEN publications:

1. **Ladenstein R, Valteau-Couanet D, Brock P, et al.** Randomized trial of prophylactic granulocyte colony-stimulating factor during rapid COJEC induction in pediatric patients with high-risk neuroblastoma: the European HR-NBL1/ SIOPEN study. *J Clin Oncol.* 2010;28(21):3516-3524. doi:10.1200/JCO. 2009.27.3524.
   Why it matters: This is the published R0 randomization and documents the induction-supportive-care question that was built into the trial from the start. It showed fewer febrile neutropenic episodes, fewer hospital days, and better protocol delivery with prophylactic G-CSF.
2. **Ladenstein R, Pötschger U, Pearson ADJ, et al.** Busulfan and melphalan versus carboplatin, etoposide, and melphalan as high-dose chemotherapy for high-risk neuroblastoma (HR-NBL1/SIOPEN): an international, randomised, multi-arm, open-label, phase 3 trial. *Lancet Oncol.* 2017;18(4):500-514. doi:10.1016/S1470-2045(17)30070-0.
   Why it matters: This is the pivotal R1 paper and one of the key efficacy anchors for any regulatory report. It established BuMel as the preferred myeloablative regimen by showing superior event-free survival versus CEM, with fewer severe adverse events overall.
3. **Ladenstein R, Pötschger U, Valteau-Couanet D, et al.** 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. *Lancet Oncol.* 2018;19(12):1617-1629. doi:10.1016/S1470-2045(18)30578-3.
   Why it matters: This is the randomized R2 publication and the clearest frontline evidence within HR-NBL1 that adding IL-2 increased toxicity without improving outcome. It is a mandatory citation for benefit–risk discussion around IL-2.
4. **Garaventa A, Pötschger U, Valteau-Couanet D, et al.** Randomized Trial of Two Induction Therapy Regimens for High-Risk Neuroblastoma: HR-NBL1.5 International Society of Pediatric Oncology European Neuroblastoma Group Study. *J Clin Oncol.* 2021;39(23):2552-2563. doi:10.1200/JCO.20.03144.
   Why it matters: This is the definitive R3 publication comparing Rapid COJEC with modified N7/MSKCC-N5. For regulatory summaries, it supports the conclusion that Rapid COJEC remained preferred because outcomes were similar while toxicity favored COJEC.
5. **Ladenstein R, Pötschger U, Valteau-Couanet D, et al.** Investigation of the role of dinutuximab beta-based immunotherapy in the SIOPEN High-Risk Neuroblastoma 1 Trial (HR-NBL1). *Cancers (Basel).* 2020;12(2):309. doi:10. 3390/cancers12020309.
   Why it matters: This is a key HR-NBL1 immunotherapy paper linking dinutuximab beta-based maintenance to improved outcomes in the trial program and is highly relevant for the maintenance-treatment narrative in the CSR and lay summary.

B. Key HR-NBL1 companion analyses that strengthen regulatory reporting:

6. **Holmes K, Pötschger U, Pearson ADJ, et al.** Influence of Surgical Excision on the Survival of Patients with Stage 4 High-Risk Neuroblastoma: A Report From the HR-NBL1/SIOPEN Study. *J Clin Oncol.* 2020;38(25):2902-2915. doi:10.1200/JCO.19.03117.
   Why it matters: Important for the local-therapy section. It provides trial-based evidence on the role of surgical resection within multimodal therapy.
7. **Gaze MN, Boterberg T, Dieckmann K, et al.** Results of a quality assurance review of external beam radiation therapy in the International Society of Paediatric Oncology (Europe) Neuroblastoma Group's High-risk Neuroblastoma Trial: a SIOPEN study. *Int J Radiat Oncol Biol Phys.* 2013;85(1):170-174. doi:10.1016/j.ijrobp.2012.05.004.
   Why it matters: Useful for radiotherapy quality assurance and protocol compliance. This is one of the best sources to support the RT methods and local-control sections in a regulatory report.
8. **Viprey VF, Gregory WM, Corrias MV, et al.** Neuroblastoma mRNAs predict outcome in children with stage 4 neuroblastoma: a European HR-NBL1/SIOPEN study. *J Clin Oncol.* 2014;32(10):1074-1083. doi:10.1200/JCO.2013.53.3604.
   Why it matters: Strong translational companion paper from HR-NBL1 showing that baseline blood and marrow mRNA markers identified an ultrahigh-risk subgroup. This is useful for biomarker and stratification discussion.
9. **Ladenstein R, Lambert B, Pötschger U, et al.** Validation of the mIBG skeletal SIOPEN scoring method in two independent high-risk neuroblastoma populations: the SIOPEN/HR-NBL1 and COG-A3973 trials. *Eur J Nucl Med Mol Imaging.* 2018;45(2):292-305.doi:10.1007/s00259-017-3829-7.
   Why it matters: This is the key imaging/response-methodology reference for SIOPEN scoring and highly relevant when explaining response criteria, prognostic imaging, and trial assessment methods.
10. **Corrias MV, Parodi S, Tchirkov A, et al.** Event-free survival of infants and toddlers enrolled in the HR-NBL-1/SIOPEN trial is associated with the level of neuroblastoma mRNAs at diagnosis. *Pediatr Blood Cancer.* 2018;65(7):e27052. doi:10.1002/pbc.27052.
    Why it matters: Supports the infant/toddler subgroup narrative and provides additional translational evidence from HR-NBL1.
11. **Morgenstern DA, Baruchel S, Irwin MS, et al.** Risk stratification of high-risk metastatic neuroblastoma: A report from the HR-NBL-1/SIOPEN study. *Pediatr Blood Cancer.* 2019;66(1):e27363. doi:10.1002/pbc.27363.
    Why it matters: Useful for baseline prognostic stratification in patients aged ≥18 months with metastatic disease. The report derived a simple risk score using age, LDH, and metastatic burden.
12. **Bellini A, Pötschger U, Bernard V, et al.** Frequency and Prognostic Impact of ALK Amplifications and Mutations in the European Neuroblastoma Study Group (SIOPEN) High-Risk Neuroblastoma Trial (HR-NBL1). *J Clin Oncol.* 2021; 39(30):3377-3390.doi:10.1200/JCO.21.00086.
    Why it matters: Important molecular-biology companion paper from the HR-NBL1 cohort. It documents the frequency and prognostic impact of ALK alterations and strengthens the biology section of a regulatory dossier.

13. **Berlanga P, Pasqualini C, Pötschger U, et al.** Central nervous system relapse in high-risk stage 4 neuroblastoma: The HR-NBL1/SIOPEN trial experience. *European Journal of Cancer.* 2021;144:1-8. doi:10.1016/j.ejca.2020.10.020.
    Why it matters: Useful for relapse pattern discussion and late-event characterization in the CSR.
14. **Wieczorek A, Manzitti C, Garaventa A, et al.** Clinical Phenotype and Management of Severe Neurotoxicity Observed in Patients with Neuroblastoma Treated with Dinutuximab Beta in Clinical Trials. *Cancers (Basel).* 2022;14(8):1919.doi:10.3390/cancers14081919.
    Why it matters: This is one of the best safety-focused references for dinutuximab beta in the HR-NBL1 context, especially for neurological adverse reactions and their management.

C. Conference abstracts and interim/bridging references worth citing in a regulatory bibliography:

15. **Garaventa A, Valteau-Couanet D, Castel V, et al.** The randomised induction for high-risk neuroblastoma comparing COJEC and N5-MSKCC regimens: Early results from the HR-NBL1.5/SIOPEN trial. *J Clin Oncol.* 2018;36(15_suppl): 10507.doi:10.1200/JCO.2018.36.15_suppl.10507.
    Why it matters: Interim/early R3 presentation. In a bibliography I would keep it as a historical abstract but cross-reference it to the full 2021 JCO paper as the authoritative source.
16. **Ladenstein RL, Pötschger U, Valteau-Couanet D, et al.** Randomization of dose-reduced subcutaneous interleukin-2 in maintenance immunotherapy with anti-GD2 antibody dinutuximab beta long-term infusion in frontline high-risk neuroblastoma patients: Early results from the HR-NBL1/SIOPEN trial. *J Clin Oncol.* 2019;37(15_suppl):10013.doi:10.1200/JCO.2019.37.15_suppl.10013.
    Why it matters: Early R4 abstract. I would include it if you wanted a complete development trail, but I label it clearly as conference evidence rather than final peer-reviewed evidence.
17. **Ladenstein RL, Pötschger U, Valteau-Couanet D, et al.** Association of immunotherapy of high-risk neuroblastoma with dinutuximab beta long-term infusion and survival in the HR-NBL1/SIOPEN trial. *J Clin Oncol.* 2025; 43(16_suppl):10000.
    Why it matters: Recent abstract-level update tying long-term infusion immunotherapy to outcome. It is useful as a "latest presentation" citation, but I would not rely on it as the primary source over the 2018 and 2020 full papers until a full manuscript appears.
18. **Maris JM, Healy J, Park J, Ladenstein R, Pötschger U.** G-CSF Is a Cancer Stem Cell-Specific Growth Factor—Letter. *Cancer Res.* 2015;75(18):3991. doi:10.1158/0008-5472.CAN-15-1445.
    Why it matters: This is not a core trial efficacy paper, but it is useful when discussing later concerns about G-CSF biology versus the lack of adverse long-term signal seen in HR-NBL1 follow-up context.

D. Trial-registration and regulatory sources to cite alongside the publications:

19. **Clinical trial identifiers used in the core HR-NBL1 publications:** ClinicalTrials.gov **NCT01704716** and EudraCT **2006-001489-17** are explicitly stated in the pivotal randomized paper.
20. **SIOPEN official trial page:** *High Risk Neuroblastoma Study 1 (HR-NBL1).* The SIOPEN site lists HR-NBL1 as a follow-up trial and summarizes the current overall objective now that the randomization questions are closed.
Why it matters: Good official organizational source for study status language in public-facing documents.
21. **EMA EPAR:** *Qarziba (dinutuximab beta).* The EMA product page and product information remain the authoritative EU regulatory references for indication wording and current authorized use of dinutuximab beta.
Why it matters: For EMA-facing writing, this is the regulatory anchor for current product status and label language, distinct from the HR-NBL1 clinical evidence itself.
22. **EMA orphan-designation background for dinutuximab beta:** EU/3/12/1062.
Why it matters: Helpful if your document needs a short regulatory-development timeline for the product rather than only a clinical bibliography.