Refractory Neuroblastoma

F.Malek M.D

COG Phase 2 Trial

Randomised Phase II Trial of Irinotecan/Temozolomide (I/T) With Temsirolimus (TEM) or Dinutuximab (DIN) in Children With Relapsed or Refractory Neuroblastoma (COG ANBL1221)” by Mody et al., published in 2017.

Why was this study done?

Children with **relapsed or refractory neuroblastoma** have poor outcomes and no universally accepted salvage regimen.

The investigators used a common chemotherapy backbone:

- Irinotecan
- Temozolomide

and added one of two targeted approaches:

1. **Temsirolimus** (mTOR inhibitor)
2. **Dinutuximab** (anti-GD2 monoclonal antibody)

The goal was to determine which combination showed greater antitumor activity.

Study design

- Children’s Oncology Group (COG)

COG Phase 2 Trial

- open-label
- Randomized Phase II
- Patients: relapsed/refractory neuroblastoma

- Infusion reactions

Temsirolimus arm

- Mucositis
- Cytopenias
- Metabolic toxicities

Overall toxicities were considered manageable.

Why is this paper important?

This trial established that:

Irinotecan + Temozolomide + Dinutuximab became one of the most active salvage regimens for relapsed neuroblastoma.

The study significantly influenced subsequent Children's Oncology Group approaches and helped support broader use of anti-GD2 immunotherapy in relapse.

- Treatment arms:

Arm A

Irinotecan + Temozolomide + Temsirolimus

Arm B

Irinotecan + Temozolomide + Dinutuximab

Patients were assessed for objective tumor response.

Main results

The dinutuximab arm clearly outperformed the temsirolimus arm.

Objective response rate (ORR)

Approximate reported response rates:

- Dinutuximab arm: ~53%
- Temsirolimus arm: ~6%–12%

depending on analysis cohort.

This difference was large enough that the study favored further development of the dinutuximab-containing regimen.

Toxicity

Expected toxicities were observed:

Dinutuximab arm

- Neuropathic pain
- Fever
- Capillary leak

Temsirolimus arm

- Mucositis
- Cytopenias
- Metabolic toxicities

Overall toxicities were considered manageable.

PDQ Cancer Information Summaries

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Neuroblastoma Treatment (PDQ®)

Health Professional Version

PDQ Pediatric Treatment Editorial Board.

Published online: April 28, 2025.

This PDQ cancer information summary for health professionals provides comprehensive, peer-reviewed, evidence-based information about the treatment of neuroblastoma. It is intended as a resource to inform and assist clinicians in the care of their patients. It does not provide formal guidelines or recommendations for making health care decisions.

This summary is reviewed regularly and updated as necessary by the PDQ Pediatric Treatment Editorial Board, which is editorially independent of the National Cancer Institute (NCI). The summary reflects an independent review of the literature and does not represent a policy statement of NCI or the National Institutes of Health (NIH).

General Information About Neuroblastoma

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Dramatic improvements in survival have been achieved for children and adolescents with cancer.[1,2] Between 1975 and 2020, childhood cancer mortality decreased by more than 50%.[1-5] Between 1975 and 2020, the 5-year survival rate for patients with neuroblastoma increased, from 86% to 93% for children younger than 1 year and from 34% to 83% for children aged 1 to 14 years.[2,3]

Childhood and adolescent cancer survivors require close monitoring because cancer therapy side effects may persist or develop months or years after treatment. For specific information about the incidence, type, and monitoring of late effects in childhood and adolescent cancer survivors, see Late Effects of Treatment for Childhood Cancer.

Incidence and Epidemiology

Neuroblastoma is the most common extracranial solid tumor in childhood. More than 650 cases are diagnosed each year in the United States.[2,6-8] The prevalence is about 1 case per 7,000 live births. The incidence is 8.3 cases per 1 million per year in children younger than 15 years. The overall incidence of neuroblastoma cases in the United States has remained stable.[9] About 37% of patients are diagnosed as infants, and 90% are younger than 5 years at diagnosis, with a median age at diagnosis of 17 months.[8,10] The data on age at diagnosis show that this is a disease of infancy, with the highest rate of diagnosis in the first month of life.[6,10,11]

Population-based studies (of screening for infants with neuroblastoma) have demonstrated that spontaneous regression of neuroblastoma without clinical detection in the first year of life is at least as prevalent as clinically detected neuroblastoma.[12-14]

The United States Cancer Statistics database and the National Program of Cancer Registries survival database were used to describe epidemiological trends in incidence and outcomes in patients with neuroblastoma between 2003 and 2019. Non-Hispanic White patients have a higher risk of developing neuroblastoma than all other race and ethnicity groups. Compared with non-Hispanic White patients, the relative risks were 0.54 for Hispanic patients, 0.64 for non-Hispanic Asian or Pacific Islander patients, 0.69 for non-Hispanic American Indian and Alaska Native patients, and 0.73 for non-Hispanic Black patients.[9] The 5-year relative survival rates

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randomised, phase 2 trial.

Mody R [1], Naranjo A [2], Van Ryn C [2], Yu AL [3], London WB [4], Shulkin BL [5], Parisi MT [6], Servaes SE [7], Diccianni MB [8], Sondel PM [9], Bender JG [10], Maris JM [7], Park JR [6], Bagatell R [7]

Author information

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10.1200/JCO.20.00203

Irinotecan, Temozolomide, and Dinutuximab With GM-CSF in Children With Refractory or Relapsed Neuroblastoma: A Report From the Children's Oncology Group

Rajen Mody [1], Alice L Yu [2,3], Arlene Naranjo [4], Fan F Zhang [5], Wendy B London [6], Barry L Shulkin [7], Marguerite T Parisi [8],

Key Points

1. Neuroblastoma Overview

- Most common extracranial solid tumor of childhood.
- Median age at diagnosis ≈ 17 months.
- About 90% of patients are diagnosed before age 5 years.
- Clinical behavior is highly heterogeneous: spontaneous regression in some infants versus aggressive metastatic disease

2. Major Prognostic Factors

Risk stratification depends on:

- Age at diagnosis
- Stage (INRG/INSS)
- Histology
- MYCN amplification
- Chromosomal abnormalities (e.g., 1p, 11q loss)
- Tumor ploidy
- Molecular/genomic features
- Response to therapy

High risk

High-Risk

Multimodal therapy:

1. Induction chemotherapy
2. Surgical resection
3. Consolidation with high-dose chemotherapy and autologous stem-cell rescue
4. Radiation therapy
5. Maintenance/post-consolidation immunotherapy

Common maintenance approaches:

- Anti-GD2 immunotherapy
- Isotretinoin (13-cis-retinoic acid)

Outcome:

- Survival has improved substantially but relapse remains a major challenge.

Refractory NB

Recurrent/Refractory Neuroblastoma

The PDQ emphasizes that there is **no universally accepted standard salvage regimen**.

Commonly used approaches include:

- Irinotecan + temozolomide
- Cyclophosphamide + topotecan
- ICE (ifosfamide, carboplatin, etoposide)
- High-dose chemotherapy approaches
- MIBG therapy (when available)
- Anti-GD2–based strategies
- Targeted therapy for actionable mutations (e.g., ALK inhibitors)
- Enrollment in clinical trials whenever feasible.

Molecular Genetics in Neuroblastoma Prognosis

by **Margherita Lerone** [1], **Marzia Ognibene** [1], **Annalisa Pezzolo** [2], **Giuseppe Martucciello** [3,4], **Federico Zara** [1,4], **Martina Morini** [5,*,†] and **Katia Mazzocco** [6,†]

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2024 — Five-year survival ra
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2025 — Generally, treatmer
blastoma is based on whethe

High-risk neuroblastoma

This remains the major therapeutic challenge.

Standard modern therapy includes:

Induction

- Intensive multi-agent chemotherapy

Local control

- Surgical resection
- Radiotherapy

Consolidation

- High-dose chemotherapy
- Autologous stem-cell transplantation (often tandem transplant in COG protocols)

Post-consolidation

- Isotretinoin (13-cis-retinoic acid)
- Anti-GD2 immunotherapy (dinutuximab-based)

Despite advances:

- Long-term survival remains approximately 50–60%.

JNCCN

Neuroblastoma, Version 2.2024, NC Clinical Practice ...

1 Aug 2024 — Five-year survival rate are >95% for patients with low-risk r

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Neuroblastoma Treatment (PDQ®) ·

28 Apr 2025 — Generally, treatment neuroblastoma is based on whether

r a **true refractory neuroblastoma**, the current PDQ highlights:

- Re-biopsy and molecular characterization when feasible.
- Evaluation for targetable alterations (ALK, ATRX, TERT, RAS/MAPK pathway, etc.).
- MIBG avidity assessment.
- Consideration of immunotherapy-based salvage approaches.
- Enrollment in clinical trials whenever available.

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Topic	High-Yield Point
Best prognostic marker	Risk group, not stage alone
Most important adverse biology	MYCN amplification
Standard maintenance after high-risk therapy	Isotretinoin + anti-GD2 immunotherapy

Thank you