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című program

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SURVIVOR AND SURVIVAL IN PEDIATRIC ONCOLOGY

Ph.D. Thesis

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Budapest

2026

“Do not go gentle into that good night.

Rage, rage against the dying of the light.”

Dylan Thomas

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1 LIST OF ABBREVATIONS

ADCC	antibody-dependent cellular cytotoxicity
AE	adverse event
ALK	anaplastic lymphoma kinase
ASCT	autologous stem cell transplantation
ATRX	alpha-thalassemia/mental retardation (gene)
CCS	childhood cancer survivor
CDC	complement-dependent cytotoxicity
CENTRAL	Cochrane Central Register of Controlled Trials
CI	confidence interval
CNS	central nervous system
COG	Children's Oncology Group
EFS	event-free survival
EMA	European Medicines Agency
FDA	Food and Drug Administration
GD2	disialoganglioside 2
HR-NBL	high-risk neuroblastoma
HuPON	Hungarian Pediatric Oncology Network
IDRF	image-defined risk factor
INRC	International Neuroblastoma Response Criteria
INRG	International Neuroblastoma Risk Group
INRGSS	International Neuroblastoma Risk Group Staging System
INSS	International Neuroblastoma Staging System
MD	mean difference
NBL	neuroblastoma

Non-CNS	non-central nervous system
OR	odds ratio
ORR	objective response rate
OS	overall survival
PedsQL	Pediatric Quality of Life Inventory
PHOX2B	paired-like homeobox 2B (gene)
PR	partial response
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analyses
PROSPERO	International Prospective Register of Systematic Reviews
QoL	quality of life
QUIPS	Quality in Prognostic Studies (risk of bias assessment tool)
RCT	randomized clinical trial
RoB	risk of bias
RWD	real-world data
RWE	real-world evidence
SF-36	36-Item Short Form Health Survey
SIOP	International Society of Pediatric Oncology
SIOPEN	International Society of Pediatric Oncology European Neuroblastoma (workgroup)
SMD	standardized mean difference
TERT	telomerase reverse transcriptase (gene)
WHO	World Health Organization

2 STUDENT PROFILE

2.1 Vision and mission statement, specific goals

Vision statement: Cure all children with cancer and help them grow into adulthood to live a full life.

Mission statement: To advance pediatric oncology beyond survival by generating rigorous, real-world and population-level evidence that improves long-term psychosocial reintegration and optimizes therapeutic outcomes for children with cancer.

2.2 Scientometrics

Number of all publications:	11
Cumulative IF:	46.9
Av IF/publication:	4.26
Ranking (SCImago): Q4:-	D1:8, Q1:3, Q2:-, Q3:-,
Number of publications related to the subject of the thesis:	2
Cumulative IF:	20.9
Av IF/publication:	10.45
Ranking (Sci Mago): Q4:-	D1:1, Q1:1, Q2:-, Q3:-,
Number of citations on Google Scholar:	85
Number of citations on MTMT (independent):	53
H-index:	5

The detailed bibliography of the student can be found on pages 77-79.

2.3 Future plans

I plan to complete my residency in pediatrics while continuing my academic development in pediatric oncology. My future work will focus on clinical and translational research aimed at improving both survival and long-term quality of life for children with cancer, with particular emphasis on survivorship, treatment-related late effects, and evidence-based optimization of oncological care.

3 SUMMARY OF THE THESIS

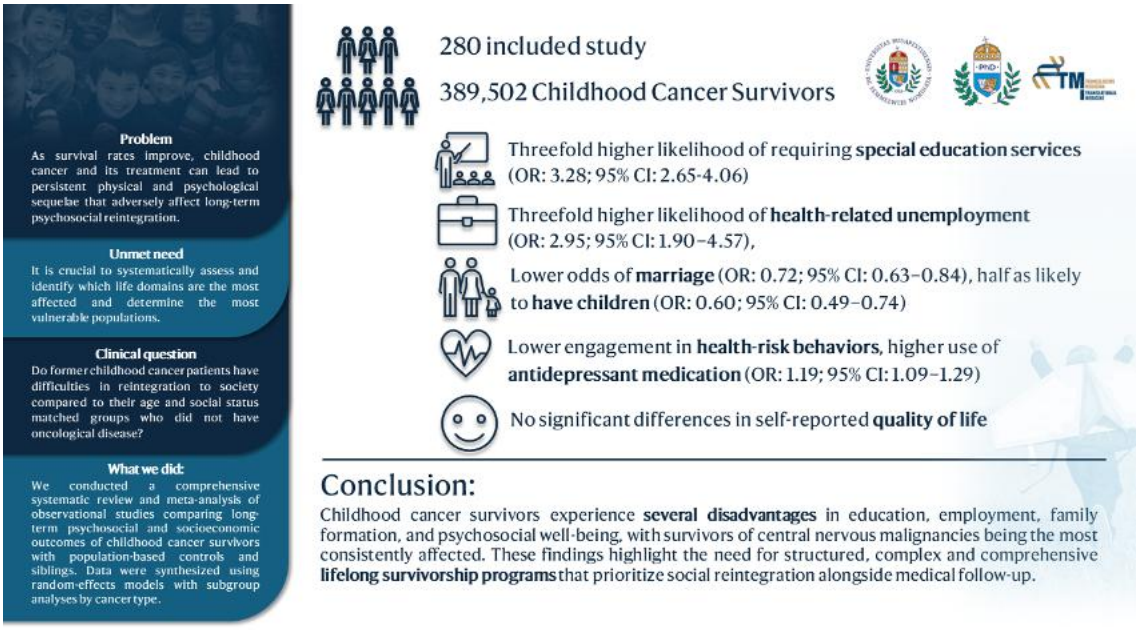
Survival rates in pediatric oncology have improved significantly in recent decades. However, survival alone does not guarantee full recovery, as cancer and its treatment during childhood can have long-lasting medical, psychological, and socioeconomic consequences. Understanding both long-term survivorship outcomes and treatment effectiveness in high-risk disease is therefore essential in pediatric oncology.

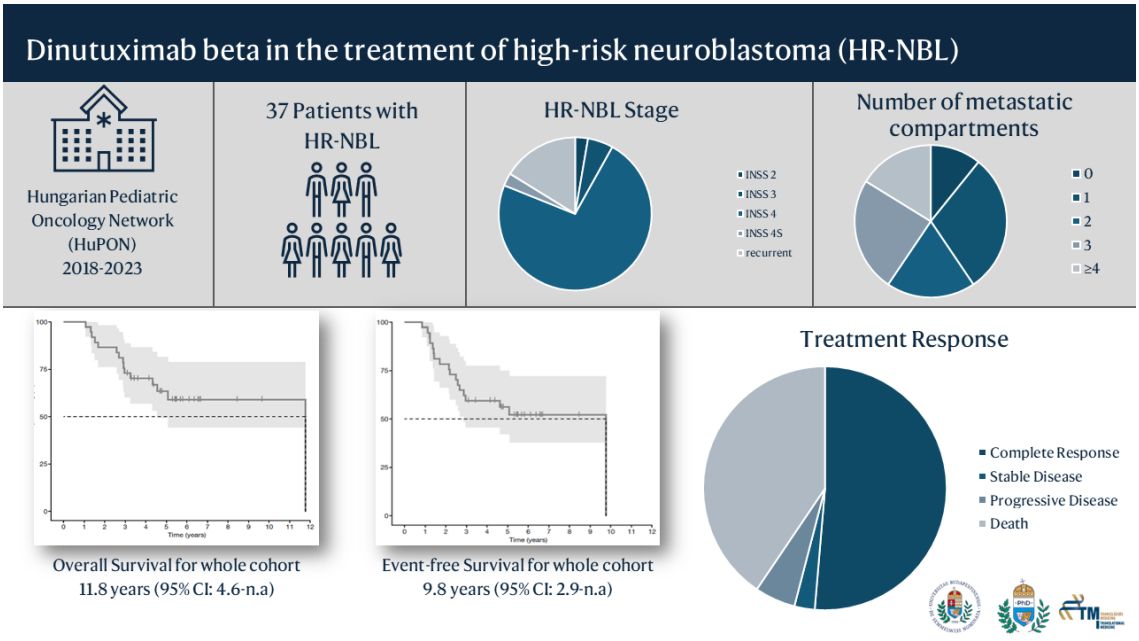
In this thesis, we investigate survivorship and survival from two complementary perspectives. First, systematically evaluate the long-term psychosocial and socioeconomic reintegration of childhood cancer survivors, focusing on education, employment, family formation, health-related behaviors, and quality of life. Second, we assess the real-world effectiveness and safety of dinutuximab beta in children with high-risk neuroblastoma, including its use in both first-line and relapsed settings.

Our results demonstrate that childhood cancer survivors experience several disadvantages across multiple domains of adult life, with the greatest burden observed among survivors of central nervous system malignancies. In parallel, dinutuximab beta achieved substantial disease control and long-term survival with a manageable safety profile in a national cohort in real-world clinical practice settings.

We conclude that pediatric oncology must aim for more than survival alone. Our work, Survivor and Survival in Pediatric Oncology, captures the dual responsibility of modern care: to deliver effective, life-saving treatments while ensuring that children cured of cancer can grow into adults who live full, independent and meaningful lives. Achieving this goal requires not only continued therapeutic innovation, but also the systematic development of lifelong survivorship care that addresses the enduring medical, psychological, and socioeconomic consequences of childhood cancer.

4 GRAPHICAL ABSTRACT





5 INTRODUCTION

5.1 Overview of the topic

5.1.1 What is the topic?

Cancer is the leading disease-related cause of death in childhood, with common types including leukemias, lymphomas, central nervous system (CNS) tumors, and other non-central nervous system (non-CNS) solid tumors. In the United States alone, approximately 15,000 children are diagnosed with cancer each year, corresponding to about 1 in every 285 children.(1)

On one hand, thanks to substantial recent advances in diagnostic and therapeutic strategies in pediatric oncology, 5-year survival rate improved to 85% in recent years, meaning that 1 in 530 adults is a long-term survivor of childhood cancer.(1, 2) On the other hand, there are still numerous cases in which therapeutic success falls significantly short of the desired outcome. In the case of neuroblastoma, which is the most common extracranial solid tumor in children, the 5-year overall survival rate for patients with high-risk disease remains around 50-62%.(3, 4)

Therefore, our aim was to investigate two topics:

- The Socioeconomic and Psychosocial Reintegration of Childhood Cancer Survivors (CCSs) – Study 1
- Treatment Results of High-Risk Neuroblastoma (HR-NBL) Based on Real-World Data from the Hungarian Pediatric Oncology Network (HuPON) – Study 2

5.1.2 What is the problem to solve?

As survival rates in pediatric oncology continue to improve, a new challenge has emerged, shifting the focus towards the long-term fate and well-being of survivors. The World Health Organization (WHO) defines health as a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity. Therefore, the ultimate goal of pediatric oncology is not only to cure cancer, but also to provide successful long-term socioeconomic and psychosocial reintegration for patients. Several studies suggest that CCSs may face various short-, medium-, and long-term hardships, including difficulties with education, employment and family formation.(5-8) The long-term consequences of childhood cancer for socioeconomic reintegration and psychosocial

adjustment appear substantially heterogeneous, while available evidence is limited and often conflicting, highlighting the crucial need for comprehensive analytic studies.(9)

High-risk neuroblastoma is one of the most lethal pediatric malignancies, accounting for 15% of all childhood cancer deaths despite multimodal therapy.(4, 10) The introduction of anti-GD2 monoclonal antibody-based immunotherapy (dinutuximab beta) provided the first major improvement in survival for patients with HR-NBL in recent decades.(11) While the majority of efficacy and safety data originate from controlled clinical trial settings (e.g. SIOPEN, COG), real-world patient populations and treatment environments can differ significantly in terms of refractory and relapsed cases, comorbidities, toxicity management, access to supportive care, and therapeutic adherence. Real-world data (RWD) are increasingly recognized by the Food and Drug Administration (FDA) and European Medicines Agency (EMA) as essential complements to randomized controlled trials (RCTs), especially in case of rare diseases such as HR-NBL, where large, randomized cohorts are often infeasible. Furthermore, while RCTs can reduce bias through randomization, they frequently lack the genetic, socioeconomic and geographic diversity required for generalizable conclusions.(12) Consequently, there is a critical need to determine whether the efficacy and safety observed in randomized clinical trials (RCTs) translate into effectiveness under routine national practice conditions.

5.1.3 What is the importance of the topic?

Comparing CCSs with individuals not affected by malignant diseases during childhood allows the long-term socioeconomic and psychosocial consequences of childhood cancer to be assessed. Identifying the most vulnerable subpopulations of survivors and areas of life most affected by cancer is inevitable for targeted interventions. Understanding the burden of childhood cancer is essential for designing, implementing and executing supportive lifelong survivorship programs which provide adequate aid for survivors based on their primary needs. Cure is merely the first step, the true success of pediatric oncology is to achieve complete reintegration and to preserve an undiminished quality of life for every survivor.

Despite substantial improvements in survival for patients with HR-NBL, the optimal treatment protocol is still being refined, and one in two patients continues to die within five years of diagnosis.(13) Furthermore, even with recent therapeutic advances,

approximately 50% of patients with HR-NBL experience relapse, and about 15% of patients do not respond to first-line therapy.(14, 15) Providing real-world data on the safety and effectiveness of HR-NBL treatment contributes to a clearer understanding of the clinical role of dinutuximab beta, while also supporting the generalizability of trial results and the equity of care, which is especially important for patients with relapsed and refractory diseases.

5.1.4 What would be the impact of our research results?

Performing a complex and comprehensive analysis of the long-term consequences of childhood cancer focusing primarily on education, employment, family formation, health-risk behaviors, and quality of life (QoL) can identify the most affected domains and highlight areas where survivors require additional support. Investigating the subpopulations of CCSs (i.e. based on their primary tumor types) and comparing them to unaffected peers can reveal the most vulnerable populations. Altogether, this research can contribute to uncovering the obstacles faced by survivors, and act as substantial foundation for a targeted, complex, and lifelong survivorship program. The development of such program would facilitate the complete and successful socioeconomic and psychosocial reintegration of CCSs, thus ensuring the achievement of Health as defined by the WHO.

The analysis of RWD on dinutuximab beta use in HR-NBL treatment can provide evidence of its effectiveness and safety in routine clinical settings, while also generating valuable insights for hard-to-treat relapsed and refractory cases, thereby supporting clinicians in selecting the best therapy for their patients.

5.2 Childhood Cancer Survivors

5.2.1 Late effects of Childhood Cancer

Besides the evident short-, and medium-term adverse effects of cancer and its treatment, including therapy-related acute toxicity, psychological distress and social isolation from school and peers, childhood cancer also leads to long-lasting physical, psychological and psychosocial consequences, commonly referred to as late effects. These late effects cause significantly elevated risk for morbidity and mortality, with 60% to over 90% of survivors developing one or more chronic health conditions, and having an eight-fold higher risk of severe or life-threatening conditions.(16-18)

5.2.2 Childhood Cancer – Shield or Scar?

The long-term psychological and behavioral consequences of the "cancer experience" in childhood is still a debated topic.(19) There are two main ongoing narratives attempting to explain these effects. One perspective conceptualizes the childhood cancer experience as a formative process associated with enhanced resilience, determination and as a source of strength and motivation, fostering a more positive outlook on life and accelerated maturation. In such cases children might experience post-traumatic growth, manifesting as beneficial psychological changes and as a protective long-term effect.(20, 21)

On the other hand, the diagnosis and treatment of cancer, together with its short-, and long-term effects are profound traumatic experiences not only for the affected child, but for the entire family.(9, 22) It is known that childhood cancer patients suffer not only from the physical consequences of cancer and its treatment, but also face major psychological challenges, which adversely influence their perceived quality of life.(23, 24)

In conclusion, the childhood cancer experience may function both as a foundation for post-traumatic growth, and as a source of post-traumatic stress symptoms.

5.2.3 Population-based versus Sibling controls

As mentioned above, childhood cancer affects the entire family, including the siblings of patients. Furthermore, familial support, shared environment, and coping strategies may act as important confounders and substantially influence long-term socioeconomic outcomes of CCSs. Sibling-comparison study designs inherently control for confounding factors shared within families, however, they may be more susceptible to bias arising from non-shared confounders.(25) Moreover, siblings of children with cancer may also experience post-traumatic stress symptoms, emotional distress, somatic problems, academic difficulties, increased risk for mental health disorders, among other adverse outcomes.(26-30) Therefore, to provide comprehensive evaluation, such studies focusing on long-term attainment of CCSs should include both population-based and sibling controls, with results analyzed and interpreted separately.

5.3 Neuroblastoma

5.3.1 Prognostic factors and Risk stratification of Neuroblastoma

Neuroblastoma (NBL) is a pediatric malignancy originating from neural crest-derived cells of the peripheral sympathetic nervous system. It can occur at any final site of neural crest cell migration, most frequently in the adrenal medulla or paraspinal sympathetic ganglia. With approximately 3-15 cases per million children (0-14 years of age), being the most common extracranial solid tumor in children, NBL accounts for about 10% of all pediatric cancers.(31)

NBL typically affects children in the first five years of life and may present as either localized or metastatic disease at diagnosis. Risk stratification is based on several prognostic factors, including age at diagnosis, disease stage, histopathological features, and underlying molecular alterations, especially in MYCN and anaplastic lymphoma kinase (ALK).(31, 32)

One of the most important prognostic factors of NBL is the amplification of MYCN oncogene, which plays a substantial role in the tumor pathogenesis, and associated with an aggressive subset of tumors. MYCN amplification is present in approximately 20% of NBL cases, conferring a poor prognosis. Furthermore, activating mutations of ALK, found in 6-10% of NBL cases, also have an essential role in tumorigenesis, and responsible for unfavorable prognosis. Other prognostic factors may include mutations in the Paired-like Homeobox 2B (PHOX2B), Alpha-Thalassemia/Mental Retardation, X-linked gene (ATRX), p53 tumor suppressor gene, and Telomerase Reverse Transcriptase (TERT) among others.(33, 34)

Due to the clinical and biological heterogeneity of NBL, multiple classification systems have been developed. The historically used, first comprehensive, postsurgical International Neuroblastoma Staging System (INSS) was recently updated by the International Neuroblastoma Risk Group (INRG), through the incorporation of additional prognostic factors, resulting in the INRG Staging System (INRGSS), sometimes informally referred to as the “Toronto staging”. The INRGSS defines four stages, namely L1, L2, M, MS, corresponding to localized disease without image-defined risk factors (IDRFs), locoregional disease with IDRFs, metastatic disease, and a special metastatic category in children under 18 months with favorable prognosis, respectively. Building on

this staging framework, pretreatment risk stratification incorporates the most significant and clinically relevant prognostic factors, including INRG stage, age at diagnosis, histologic category, grade of tumor differentiation, MYCN amplification, 11q aberration and tumor cell ploidy to classify patients into distinct pretreatment risk groups, namely very low-, low-, intermediate-, and high-risk disease categories.

There are substantial differences in treatment approach and survival across NBL risk groups. Asymptomatic patients with low-risk disease, who have an estimated survival of >98%, are frequently managed with observation or surgical resection alone, whereas patients with intermediate-risk disease, with an estimated survival of >90%, require moderate doses of response-adjusted chemotherapy in combination with surgical resection. Detailed, evidence-based risk stratification in NBL has enabled the intensification of therapy for patients with the highest-risk disease while allowing safe treatment de-escalation in low-risk patients.(35-37)

5.3.2 High-risk Neuroblastoma (HR-NBL)

Approximately half of all patients with neuroblastoma have high-risk disease, which is associated with a poor prognosis and a 5-year overall survival (OS) of 40-50%.(38, 39) Among patients with HR-NBL, around 20% are refractory to frontline therapy, and relapse occurs in more than half of responders.(40) High-risk neuroblastoma is defined according to the INRG classification system and includes patients with metastatic disease aged ≥18 month, tumors with MYCN amplification regardless of stage or age, and a distinct group of metastatic young patients with unfavorable biological features (i.e. 11q aberrations).(36)

In case of patients with HR-NBL, first-line therapy typically includes multi-agent induction chemotherapy, surgical resection, consolidation myeloablative chemotherapy followed by autologous stem cell transplantation (ASCT) and radiation, in accordance with the SIOPEN group recommendations and other European treatment protocols.(41) Results from a multicenter, randomized phase 3 trial conducted by the SIOPEN group and published in 2018 demonstrated that the addition of the anti-GD2 monoclonal antibody (dinutuximab beta) as maintenance therapy significantly improved survival outcomes, achieving a 5-year OS exceeding 60% for the first time in patients with HR-NBL.(11)

5.3.3 Dinutuximab beta the anti-GD2 monoclonal antibody

GD2 is a complex disialoganglioside located on the outer cell membrane that is widely present during fetal development on neural and mesenchymal stem cells, while postnatal expression is restricted to peripheral neurons, the central nervous system, and skin melanocytes. Furthermore, neuroblastoma cells present very high levels of GD2 expression, with estimates ranging from 5 to 10 million molecules per cell. Although the biological function of GD2 is not yet fully understood, it is thought to play a role in normal neural differentiation and repair and may also function as a receptor for microbial toxins and mediate cell adhesion. In contrast, its tumorigenic roles have been implicated in oncogenic signaling through the phosphorylation of tyrosine kinases, enhanced cellular invasion and motility, and immunosuppressive effects.(42)

Dinutuximab was the first chimeric anti-GD2 IgG1 monoclonal antibody to receive regulatory approval from the FDA and EMA for the treatment of patients with HR-NBL, who are ≥12 months of age and who have achieved at least a partial response (PR) to induction chemotherapy, and received myeloablative chemotherapy and stem cell transplant. Moreover, dinutuximab was subsequently approved for the treatment of patients with relapsed or refractory HR-NBL with or without residual disease based on evidence from a consecutive study undertaken by the SIOPEN group.(43, 44) Dinutuximab exerts its antitumor effect by binding to the GD2 antigen on tumor cells and inducing antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC). In addition to immune-mediated mechanisms, anti-GD2 monoclonal antibodies may also show direct antitumor effects including survival signal blockade and anoikis, a specific form of apoptosis initiated upon detachment from the extracellular matrix.(42)

Besides the significant survival benefits, dinutuximab has demonstrated an overall manageable safety profile, with most common grade 3-4 adverse events being hypersensitivity, fever, pain, infection, capillary leak and impaired general condition.(11, 35)

5.3.4 Real-world data and evidence in Pediatric Oncology

While the abovementioned SIOPEN trials were conducted within rigorously designed, high-quality clinical trial frameworks and included patients from multiple countries,

population-based registry and health policy data continue to demonstrate persistent east-west inequalities (e.g. higher proportion of undiagnosed patients, diagnostic delays, and variable access to novel therapies in Southern/Eastern Europe compared to Western Europe), which may result in different real-world populations that differ substantially from those enrolled in predominantly Western European trial settings. Furthermore, existing real-world studies and data from Eastern European countries remain limited in number and in sample size. Consequently, analyses based on national registry data may help to address this regional evidence gap and improve the representativeness of results.(10)

Moreover, both the FDA and EMA have issued position papers highlighting the growing importance of real-world data (RWD) and evidence (RWE) in regulatory decision-making. RCTs are primarily designed to investigate efficacy under controlled conditions, whereas observational studies and population-based RWD are more suitable to assess effectiveness, implementation and external validity in routine clinical practice. Integrating evidence from both sources can help to fill the efficacy-effectiveness gap.(45, 46)

In addition, real-world evidence (RWE) is particularly valuable for evaluating treatment effects across heterogeneous clinical settings and patient populations that are underrepresented in traditional randomized clinical trials, including patients with comorbidities, variable adherence, and differing health system characteristics. However, the interpretation of real-world data requires careful attention to data quality, completeness, and potential confounding as observational analyses are inherently more susceptible to bias than randomized trials. Consequently, robust methodology and transparent analytic approaches are essential to ensure that RWE provides reliable and clinically meaningful evidence that complements trial data and informs real-world decision-making.(47-49)

5.3.5 The Hungarian Pediatric Oncology Network (HuPON)

The Hungarian Pediatric Oncology Network (HuPON) is a professional organization dedicated to advancing the care of children with cancer and to oncology research in Hungary. The HuPON was established in 1971, over 50 years ago, as the third national

pediatric oncology network founded in Europe. It currently comprises eight centers across the country, namely:

- Pediatric Center, Semmelweis University, Budapest
- Heim Pál National Pediatric Institute, Budapest
- Department of Pediatric Bone Marrow and Stem Cell Transplant, South-Pest Hospital Centre-National Institute for Infectology and Haematology, Budapest
- Department of Pediatrics, University of Pécs, Pécs
- Department of Pediatrics, University of Debrecen, Debrecen
- Department of Pediatrics and Pediatric Health Center, University of Szeged, Szeged
- Velkey László Children's Health Center, B.A.Z. County Central Hospital and University Teaching Hospital, Miskolc
- Department of Pediatrics, Vas County Markusovszky University Teaching Hospital, Szombathely

The registry collects data on patients' diagnoses, timing of diagnosis, anatomical site of the disease, follow-up data and relevant clinical records. These data are particularly important, since they enable monitoring of annual changes in patient numbers and geographical distribution along with therapeutic outcomes, which may contribute to identifying disease patterns, evaluating treatment success and facilitate planning of medical care and pharmaceutical provision. Due to its nationwide coverage and long-standing, standardized data collection, HuPON provides a comprehensive and representative real-world dataset that is particularly well suited for evaluating long-term outcomes and treatment effectiveness in pediatric oncology.(50)

5.4 From Survival to Survivorship in Pediatric Oncology

In light of the above, the present thesis addresses two interrelated and clinically meaningful gaps in pediatric oncology. First, it investigates the long-term socioeconomic and psychosocial consequences of childhood cancer survivorship using comprehensive population-based and sibling-comparison approaches, with the aim of characterizing vulnerable survivor subgroups and identifying the most affected domains of life. Second, it evaluates real-world treatment outcomes in high-risk neuroblastoma using data derived

from the national pediatric oncology network, with particular emphasis on the effectiveness and safety of anti-GD2 immunotherapy under routine clinical conditions.

By integrating epidemiological, psychosocial and real-world clinical data, this work seeks to complement evidence from randomized clinical trials to enhance the external validity and generalizability of existing knowledge. Taken together, these investigations embody the central concept of *Survivor and Survival in Pediatric Oncology*, underscoring that meaningful progress in the field depends not only on improving cure rates, but also on understanding and optimizing the long-term fates of survivors.

6 OBJECTIVES

6.1 Study I. – Burden of Childhood Cancer and the Social and Economic Challenges in Adulthood

Our aim was to comprehensively assess the long-term psychosocial and socioeconomic reintegration of Childhood Cancer Survivors (CCSs) by comparing their educational attainment, employment outcomes, family formation, quality of life (QoL) and health-risk behaviors with those of unaffected peers. To account for the potential influence of shared familial, environmental, and socioeconomic characteristics, both population-based and sibling comparison designs were applied. Furthermore, subgroup analyses were performed according to primary malignancy type to explore heterogeneity and identify the most vulnerable groups of survivors. These objectives were addressed through a systematic review and meta-analysis of the available scientific literature.

6.2 Study II. – Dinutuximab beta for the Treatment of High-Risk Neuroblastoma

Our aim was to evaluate the real-world safety and effectiveness of dinutuximab beta for the treatment of patients with high-risk neuroblastoma (HR-NBL) in routine clinical practice. Patient data were obtained from the Hungarian Childhood Cancer Registry and the participating centers of the Hungarian Pediatric Oncology Network. Clinical outcomes were assessed using overall survival and event-free survival. In addition, we examined the safety profile of dinutuximab treatment according to the Common Terminology Criteria of Adverse Events (CTC-AE).

7 METHODS

7.1 Study I.

7.1.1 Study Design and Protocol

This study was conducted in accordance with the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions and is reported following the current Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.(51, 52) Prestudy protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO Identifier: CRD42021283792). The only deviations from the prespecified protocol were the inclusion of additional outcomes related to quality of life and health-risk behaviors.

7.1.2 Information Sources and Search Strategy

The systematic search was conducted in three major electronic databases, namely MEDLINE (via PubMed), Embase, and CENTRAL (Cochrane Central Register of Controlled Trials) on October 23, 2021, and subsequently updated to include studies published up to July 31, 2023. Due to the large number of records retrieved, title-abstract based search filter was applied, however, no further restrictions related to language, publication date, or study design were applied during the search in order to maximize sensitivity and ensure comprehensive retrieval of eligible studies. Database-specific adaptations of the search strategy were applied where required.

The following search key was used:

((pediatric* OR paediatric* OR adolescent OR adolescence OR child* OR "young adult" OR "young adults" OR kids OR youth OR juvenile OR infant* OR infancy OR preschooler* OR teen OR teens OR teenager*) AND (cancer* OR cancer OR carcinom* OR tumor* OR tumour* OR malignan* OR oncolog* OR neoplasm OR neoplas* OR metasta* OR "posterior fossa syndrome" OR neuroblastoma OR astrocytoma OR glioblastoma OR DIPG OR HGG OR LGG OR ATRT OR PNET OR sarcoma OR osteosarcoma OR ewing OR ewings OR rhabdomyosarcoma OR wilms OR nephroblastoma OR retinoblastoma OR medulloblastoma OR teratoma OR germinoma OR dysgerminoma OR seminoma OR gonadoblastoma OR glioma OR carcinoma OR leukem* OR leukaem* OR leukemia OR leukaemia OR lymphoma* OR leucocythaemia

OR CML OR ALL OR AML OR JMML OR "myelodysplastic syndrome" OR "myelodysplastic syndromes" OR myeloproliferative OR "hodgkin disease" OR "hodgkins disease") AND (survivor OR survivors OR survivorship OR surviv* OR defeated OR healed OR "former pediatric cancer" OR "former paediatric cancer" OR divorce OR separation) AND (income OR occupat* OR employment OR job OR employed OR vocation* OR unemployed OR unemployment OR "return to work" OR "highest level of education" OR "education attainment" OR "academic attainment" OR "educational status" OR (family AND (function* OR dysfunction* OR relations OR relationship* OR conflict*)) OR divorce* OR "parental separation" OR romantic OR family OR friend* OR peers OR peer OR "independent living" OR marital OR marriage OR unmarried OR (social AND support) OR "sociological factors" OR "social behavior" OR "social skills" OR relationship* OR social OR reintegration OR "economic status" OR "economic hardship*" OR "economic well-being" OR "economic well being" OR "economic wellbeing" OR socioeconomic OR "socio-economic" OR attainment OR smok* OR tobacco OR "illegal drug use" OR "drug abuse" OR "substance use" OR marijuana OR antidepress* OR suicid* OR depression OR depressive OR alcohol* OR "quality of life" OR qol))

7.1.3 Eligibility Criteria

Eligible studies reported on educational attainment, employment, family formation, quality of life, or health-risk behavior-related outcomes among CCSs and included comparisons with unaffected peers, defined as either population-based or healthy siblings. Studies focusing on survivors diagnosed at >21 years of age or on patients undergoing active cancer treatment were excluded from our analysis to ensure that only childhood-onset malignancies were considered.

7.1.4 Study Selection and Data Collection Process

Study selection was performed in duplicate by four blinded, independent reviewers initially based on titles and abstracts and subsequently on full-text assessment, according to predefined eligibility criteria. Disagreements were resolved through consultation with an independent fifth reviewer. Interrater agreement was quantified using Cohen’s kappa coefficient.

Data extraction was performed by five independent reviewers using a standardized data collection table, while disagreements were resolved through discussion with a specialist. The following data were extracted: (1) basic study characteristics (first author, year of publication, study site and data source – countries, national registers, institutes, study design, study period), (2) participant characteristics (demographic characteristics, follow-up period, number of survivors, number of unaffected controls, and type of comparison group (matched controls, population norms, siblings)), (3) clinical characteristics, including type of survived malignancy (all cancer types, central nervous system (CNS) tumors, hematological malignancies including lymphomas, solid tumors, and non-CNS tumors), (4) outcome data, including event rates and odds ratios (ORs) for dichotomous outcomes and means with standard deviations for continuous outcomes. Outcomes of interest were educational attainment, special education needs, employment-related outcomes (employment status, income, job rejection), family formation (independent living, marriage, divorce, parenthood), QoL, health-risk behaviors (including alcohol consumption, smoking, substance use, etc.), depression, antidepressant use, suicidal risk.

7.1.5 Study Risk of Bias Assessment

Risk of bias (RoB) assessment was performed by two independent reviewers using the Quality in Prognostic Studies (QUIPS) tool, in accordance with the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions.(51, 53) Interrater differences were resolved through consultation with a third reviewer. Results of the RoB assessment were summarized and presented in the published study.

7.1.6 Data Synthesis and Statistical Analysis

Statistical analyses were performed using the R statistical software version 4.1.2 (R Project for Statistical Computing). Meta-analyses were conducted for outcomes for which at least three studies provided data suitable for pooling. Effect size estimates were calculated using random-effects models to account for between-study heterogeneity. For dichotomous outcomes, pooled odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. For continuous outcomes, pooled mean differences (MDs) or standardized mean differences (SMDs) with 95% CIs were estimated. Population-based control studies and sibling-comparison studies were analyzed separately to account for differing sources of confounding. Statistical heterogeneity was assessed using the I^2

statistic. Results were presented using forest plots with corresponding CIs and prediction intervals where applicable. Publication bias was explored using funnel plots and Egger's test.

All statistical tests were two-sided, and a p value <0.05 was considered statistically significant. In addition to statistical significance, clinically and socially meaningful differences were interpreted with particular consideration, given the nature of survivorship outcomes.

7.2 Study II.

7.2.1 Study design

This study was designed as a multicenter, retrospective, observational cohort study using real-world data. The primary objective was to evaluate the effectiveness and safety of dinutuximab beta immunotherapy in the treatment of HR-NBL under routine clinical practice conditions.

7.2.2 Study population

The study population consisted of pediatric patients (<18 years of age) diagnosed with HR-NBL who received dinutuximab beta immunotherapy either as part of the first-line treatment or for relapsed or refractory disease. Eligible patients were treated between October 2018 and February 2023 at one of the five participating centers of the HuPON. HR-NBL was defined using the INSS classification system and established SIOPEN high-risk criteria. This included patients ≥12 months of age with INSS stage 4 NBL; patients with INSS stage 3, 4 or 4S NBL and MYCN amplification; and patients with INSS stage 2 NBL with MYCN amplification and unfavorable histology.(54, 55) Furthermore, patients aged 12-18 months were included when they met SIOPEN high-risk criteria, i.e. metastatic (M) NBL diagnosed >365 days of age, irrespective of MYCN status, or MYCN-amplified disease at any stage or age. Patients with relapsed or refractory NBL were also eligible for inclusion. All patients were required to have measurable or evaluable disease at the initiation of dinutuximab beta therapy. First-line treatment followed the HR-NBL-1.8/SIOPEN version, with full therapeutic details reported previously.

7.2.3 Data sources and Data collection

Data were collected from the five participating institutes of HuPON, namely the Pediatric Center, Semmelweis University, Budapest; the Heim Pál National Pediatrics Institute, Budapest; the Department of Pediatric Bone Marrow & Stem Cell Transplant, South-Pest Hospital Centre–National Institute for Infectology and Hematology, Budapest; the Department of Pediatrics, University of Pécs, Pécs; and the Velkey László Children's Health Center, B.A.Z. County Central Hospital and University Teaching Hospital, Miskolc.

Patient-level data were obtained through the Hungarian Childhood Cancer Registry and directly from the participating centers via a standardized data collection sheet.

7.2.4 Assessments and Outcomes

Tumor responses were evaluated locally by a multidisciplinary team comprising oncologists, surgeons, and radiologists using the International Neuroblastoma Response Criteria for metastatic lesions.(56) Assessments were performed at baseline, after five cycles of dinutuximab beta and every two cycles thereafter in patients who received more than five cycles, and at any time when disease progression or relapse was suspected by the treating physician.

OS was defined as the time from diagnosis until death from any cause, while EFS was defined as the time from diagnosis until the occurrence of a disease-related event, including progression of disease.

Data on occurrence and severity of adverse events (AE) were also registered and graded using the CTC-AE version 5.0 coding system.

7.2.5 Data synthesis and analysis

OS and EFS were analyzed with a data cutoff of 9 April 2025. Patients were censored at the date of last follow-up if no event had occurred. Survival analyses were stratified according to clinically relevant predictors, including MYCN amplification status and use of dinutuximab beta as first-line therapy.

Survival probabilities for OS and EFS were estimated using the Kaplan-Meier method and compared across subgroups. Median survival times with 95% confidence intervals were derived from Kaplan-Meier estimates. The impact of MYCN amplification and

treatment line (first-line vs. relapsed/refractory) on survival outcomes was assessed using Cox proportional hazards regression model. Right-censoring occurred only in patients who had not reached the endpoint by the end of the study period and no patients were lost to follow-up. All analyses were performed using R statistical software (version 4.4.1), applying standard survival analysis packages.

7.2.6 Ethical considerations

The parents/legal guardians of the patient or the patients themselves provided informed consent for treatment and for the collection and use of clinical data within the Hungarian Childhood Cancer Registry.

The study was conducted in accordance with the Declaration of Helsinki and was approved by the appropriate institutional ethics committee (approval number: 14258/2019/EKU).

8 RESULTS

8.1 Study I

8.1.1 Results of the Systematic Search

Our systematic search identified 43,913 records, of which 280 studies met the predefined eligibility criteria after automatic and manual duplicate removal and study selection. The included studies were published between 1986 and 2023 and reported data on a total of 389,502 childhood cancer survivors, and compared them with matched controls, population-based norms, or siblings without a history of childhood cancer. The detailed selection process is presented in Figure 1.

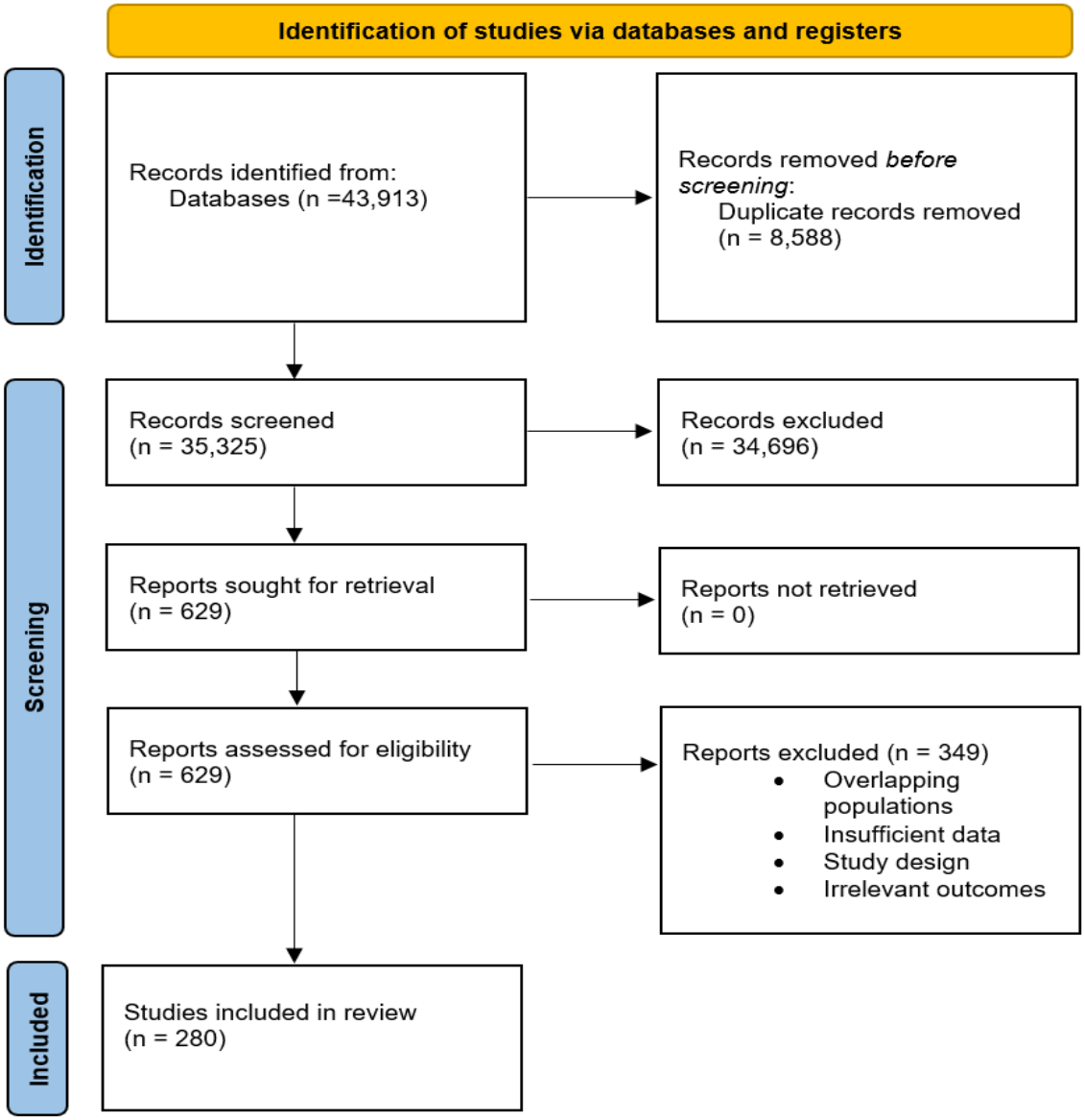


Figure 1. PRISMA Flowchart of systematic search and study selection process

8.1.2 Basic characteristics of studies included in the meta-analysis

The basic characteristics of the included studies are summarized in Appendix Table 1. (57-282) All included studies applied retrospective cohort or cross-sectional study designs.

Appendix Table 1. Basic characteristics of studies included in the meta analysis. (ALL=acute lymphoblastic leukemia; AML=acute myeloid leukemia; BT=bone tumor; CCSS=Childhood Cancer Survivor Study; CML=chronic myeloid leukemia; CNS=central nervous system; Edu=education-related outcomes; Emp=employment-related outcomes; Fam=family formation; HL=Hodgkin lymphoma; HR= health-risk behaviors; HSCT=hematopoietic stem cell transplantation; IA=infratentorial astrocytoma; LGG=low-grade glioma; MBL=medulloblastoma; n.a.=not available; NHL=non-hodgkin lymphoma; OS=osteosarcoma; QoL=quality of life; RBL=retinoblastoma; RMS=rhabdomyosarcoma; WT= Wilms tumor; y=year;)

8.1.3 Results of Educational Attainment

First, educational attainment outcomes were assessed across multiple levels and compared with population-based and sibling control groups. CCSs demonstrated similar odds of achieving at least high school graduation/matriculation examination compared with population-based controls (OR: 1.00; 95% CI: 0.74-1.37) and lower odds when compared with their siblings (OR: 0.33; 95% CI: 0.10-1.12), however, this estimate did not reach statistical significance.

At the tertiary level, CCSs had lower odds of completing at least lower-level tertiary education (i.e. college or bachelor's degree) compared with both population-based controls (OR: 0.85; 95% CI: 0.68-1.06) and siblings (OR: 0.54; 95% CI: 0.42-0.69), with only the latter comparison reaching statistical significance. Similar patterns were observed for higher-level tertiary attainment (i.e. advanced level, master's degree or postgraduate studies), with reduced odds among CCSs compared with population-based controls (OR: 0.69; 95% CI: 0.40-1.18) and siblings (OR: 0.41; 95% CI: 0.06-2.83), although these results did not reach the level of statistical significance.

Furthermore, CCSs showed significantly higher odds of requiring special education services during their studies (OR: 3.28; 95% CI: 2.65-4.06).

Subgroup analysis based on cancer type showed that **survivors of CNS tumors** had significantly lower odds of achieving at least high school graduation (OR: 0.48; 95% CI: 0.39-0.58) and lower-level tertiary education (OR: 0.53; 95% CI: 0.44-0.63) compared with population-based controls. In contrast, no significant difference was observed for attainment of higher-level tertiary education (OR: 0.77; 95% CI: 0.32-1.85). When compared with their siblings, survivors of CNS tumors also demonstrated reduced odds of completing at least high school (OR: 0.38; 95% CI: 0.11-1.26) and lower-level tertiary education (OR: 0.31; 95% CI: 0.13-0.72), with statistical significance reached only for the latter outcome.

Survivors of hematological malignancies had odds of educational attainment comparable to population-based controls, including the achievement of at least high school graduation (OR: 1.05; 95% CI: 0.67-1.66), college graduation (OR: 0.86; 95% CI: 0.47-1.57), and higher-level tertiary education (OR: 0.88; 95% CI: 0.09-8.62). When compared with their siblings, survivors of hematological malignancies showed lower

chances of completing high school education (OR: 0.72; 95% CI: 0.48-1.08), lower-level tertiary education (OR: 0.62; 95% CI: 0.31-1.21), or higher-level tertiary education (OR: 0.63; 95% CI: 0.29-1.39), however these results did not reach statistical significance.

In contrast, **survivors of solid tumors** had elevated odds of completing at least high school (OR: 1.31; 95% CI: 0.78-2.19) and at least lower-level tertiary education (OR: 1.57; 95% CI: 0.92-2.66) when compared with population-based controls. In comparison with their siblings, the odds of completing high school for survivors of solid tumors decreased (OR: 0.44; 95% CI: 0.03-6.92), however, the wide confidence interval indicates substantial uncertainty around this result.

Survivors of non-CNS tumors showed slightly lower, but not statistically significant chances of graduating from high school (OR: 0.87; 95% CI: 0.57-1.31) and similar chances of completing at least lower-level tertiary education (OR: 1.11; 95% CI: 0.67-1.85) compared with population-based controls.

Summarized results of educational attainment are shown in Figure 2.

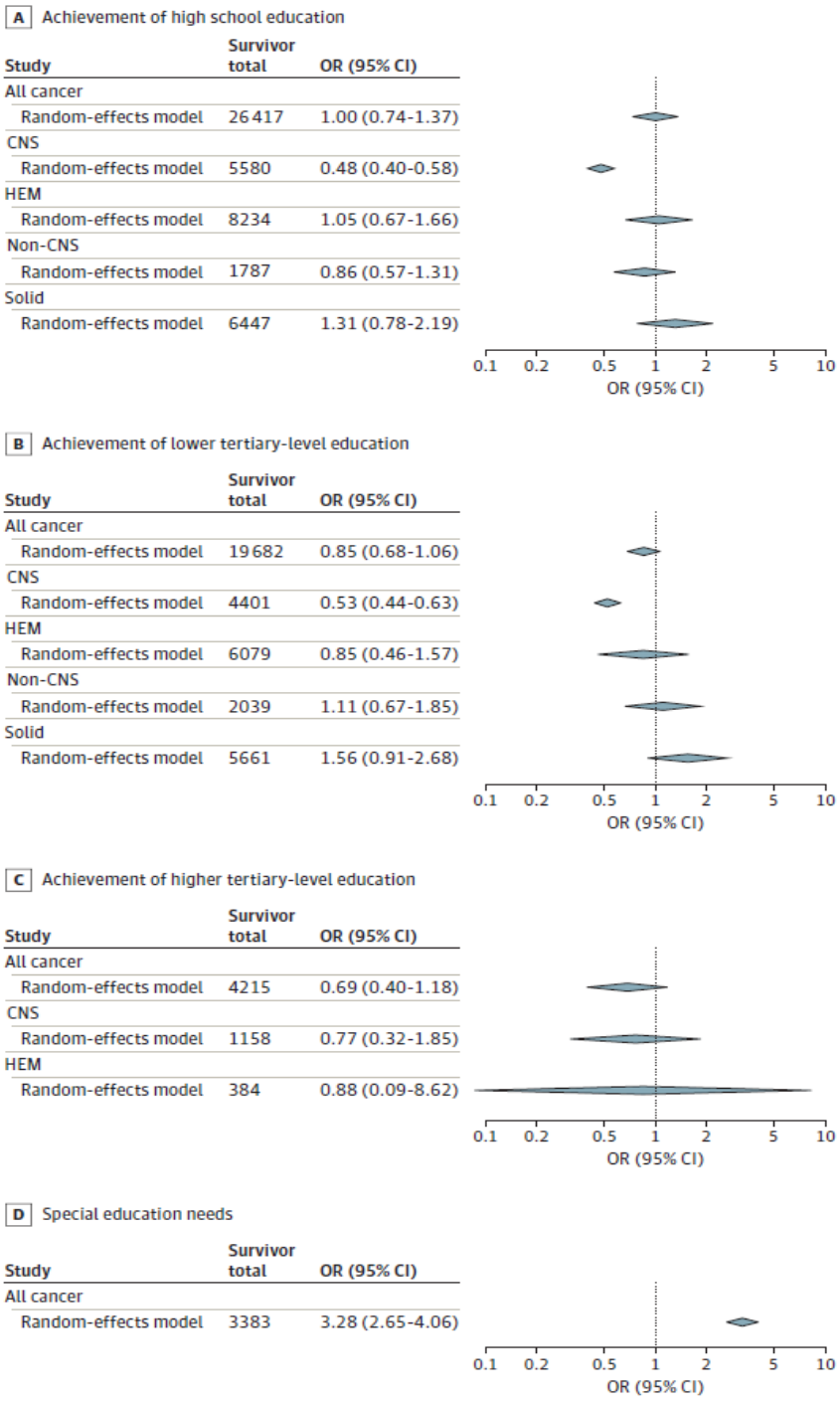


Figure 2. Summary forest plots of educational attainment odds ratios (ORs) with 95% confidence intervals (CI) of childhood cancer survivors and survivors of central nervous system (CNS), hematological (HEM), solid, and non-CNS malignancies compared with population-based controls. A: achievement of high school education; B: achievement of lower-level tertiary education; C: achievement of higher-level tertiary education; D: special education needs;

8.1.4 Results of Employment

Following the assessment of educational performance, employment-related outcomes were analyzed to further evaluate social reintegration. In comparison with population-based controls CCSs had similar rates of employment (OR: 1.03; 95% CI: 0.80-1.34), whereas significantly worse rates were observed when compared with siblings (OR: 0.58; 95% CI: 0.40-0.83).

Further analysis and **comparison with population-based controls** demonstrated that survivors of CNS tumors had significantly lower odds of being employed (OR: 0.44; 95% CI: 0.26-0.76), however the lower chance of employment for survivors of hematological malignancies (OR: 0.75; 95% CI: 0.53-1.05), solid tumors (OR: 0.75; 95% CI: 0.50-1.13), and those who received hematopoietic stem cell transplantation as part of their treatment (OR: 0.68; 95% CI: 0.43-1.07) did not reach statistical significance. Survivors of non-CNS malignancies had increased odds of being employed (OR: 1.56; 95% CI: 1.23-1.98).

In **comparison with their siblings**, CCSs showed lower rates of employment, while this difference was statistically significant in case of survivors of hematological malignancies (OR: 0.78; 95% CI: 0.62-0.99). Lower rates of employment were found in the cases of survivors of CNS and solid tumors without statistical significance (OR: 0.31; 95% CI: 0.07-1.40 and OR: 0.63; 95% CI: 0.36-1.09; respectively).

Across both comparison groups, CCSs were less likely to belong in the middle- or high-income category versus the **low-income category**. This difference was significant when compared with siblings (OR: 0.61; 95% CI: 0.48-0.79) and in the overall pooled analysis (OR: 0.76; 95% CI: 0.61-0.94).

Higher chances of **job rejection** were found when we compared CCSs with population-based controls (OR: 1.96; 95% CI: 0.43-8.99) although this association did not reach statistical significance. Rejection from military service was significantly more common among CCSs (OR: 7.95; 95% CI: 1.98-31.97). In addition, CCSs had significantly higher odds of **health-related unemployment** than population-based controls (OR: 2.95; 95% CI: 1.90-4.57), however there were substantial differences between survivors of CNS tumors (OR: 8.96; 95% CI: 5.62-14.01), hematological malignancies (OR: 2.02; 95% CI: 1.35-3.01) and solid tumors (OR: 2.16; 95% CI: 1.08-3.27).

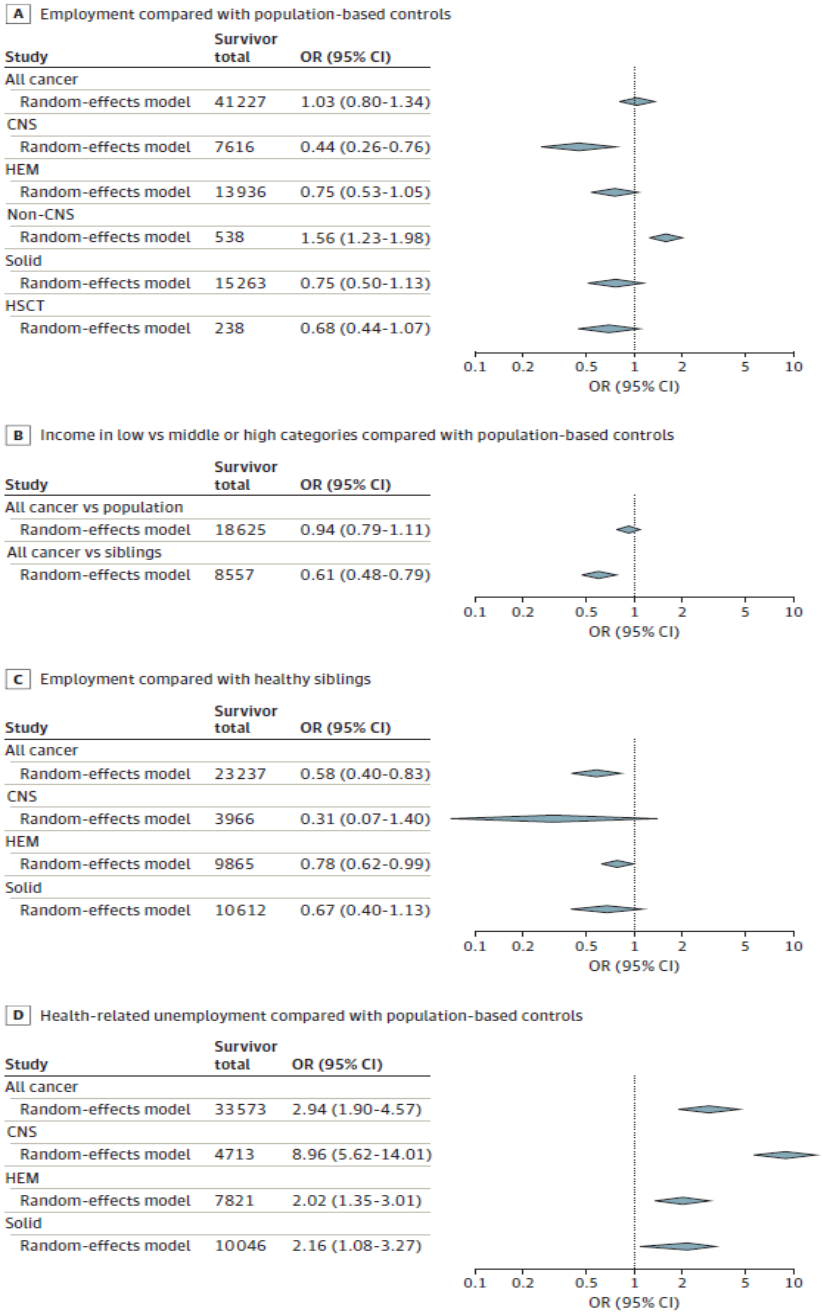


Figure 3. Summary forest plots of employment-related odds ratios (ORs) with 95% confidence intervals (CI) of childhood cancer survivors, survivors of central nervous system (CNS), hematological (HEM), solid, non-CNS malignancies, and hematopoietic stem cell transplant (HSCT)-treated survivors compared with population-based controls and siblings. A: employment compared with population-based controls; B: income in low vs middle or high categories compared with population based controls and siblings; C: employment compared with siblings; D: health-related unemployment compared with population-based controls

8.1.5 Results of Family Formation

Alongside the evaluation of educational and employment-related outcomes as indicators of individual achievement, family formation, including marriage, parenthood, and independent living were analyzed as key markers of social reintegration.

CCSs demonstrated significantly lower odds of **being married** compared with population-based controls (OR: 0.72; 95% CI: 0.63-0.84) and siblings (OR: 0.63; 95% CI: 0.55-0.72). Subgroup analyses stratified by cancer type revealed significant reductions among survivors of CNS tumors (OR: 0.32 95% CI: 0.21-0.47), while lower, but non-significant odds were observed among survivors of hematological malignancies (OR: 0.64; 95% CI: 0.39-1.06) and solid tumors (OR: 0.53; 95% CI: 0.20-1.09) when compared with population-based controls. Several studies reported whether the survivors and controls had ever been married, therefore this outcome was analyzed separately. CCSs were significantly less likely to have ever been married as population-based controls (OR: 0.66; 95% CI: 0.48-0.90) or siblings (OR: 0.56; 95% CI: 0.46-0.68). Survivors of CNS tumors had the lowest odds of having ever been married compared with their siblings (OR: 0.25; 95% CI: 0.12-0.52).

In addition, CCSs had significantly lower odds of **having children** of their own in comparison with population-based controls (OR: 0.60; 95% CI: 0.49-0.74) or their siblings (OR: 0.43; 95% CI: 0.40-0.46). CCSs also had lower mean number of children than population-based controls (MD: -0.44; 95% CI: -1.27 to -0.40).

CCSs had similar odds of **divorce** when compared with population-based controls (OR: 0.83; 95% CI: 0.54-1.27) and their siblings (OR: 0.94; 95% CI: 0.74-1.18). Further subgroup analysis showed comparable odds of divorce in case of survivors of CNS tumors (OR: 0.82; 95% CI: 0.64-1.03), hematological malignancies (OR: 0.76; 95% CI: 0.27-2.16), or solid tumors (OR: 0.91; 95% CI: 0.78-1.07).

CCSs demonstrated lower odds of living independently or leaving the parental home compared with population-based controls (OR: 0.80; 95% CI: 0.61-1.03). Based on cancer type stratification, survivors of CNS tumors (OR: 0.67; 95% CI: 0.43-1.03), hematological malignancies (OR: 0.77; 95% CI: 0.31-1.93) and solid tumors (OR: 0.83; 95% CI: 0.40-1.68) all showed lower odds of independent living, however, none of these associations were statistically significant.

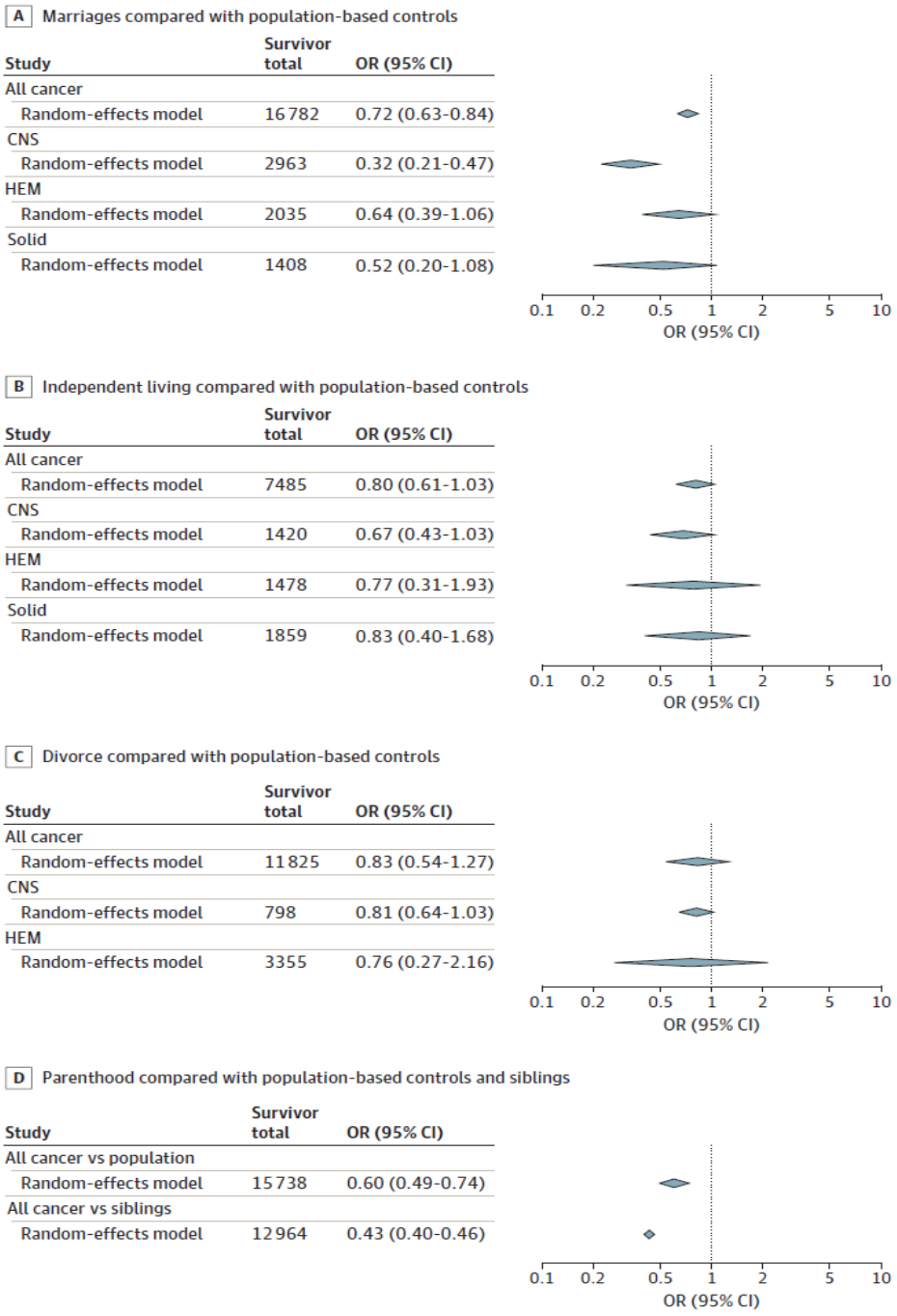


Figure 4. Summary forest plots of family formation-related odds ratios (ORs) with 95% confidence intervals (CI) of childhood cancer survivors, survivors of central nervous system (CNS), hematological (HEM), solid tumors compared with population-based controls and siblings. A: marriages compared with population-based controls; B: independent living compared with population-based controls; C: divorce compared with population-based controls; D: parenthood compared with population-based controls and siblings;

8.1.6 Results of Health-risk Behaviors

Potential lifestyle-related risk behaviors and psychological vulnerabilities were also examined. CCSs had lower chances of alcohol consumption compared with population-based controls (OR: 0.66; 95% CI: 0.41-1.07) and siblings (OR: 0.63; 95% CI: 0.31-1.28), although these differences did not reach statistical significance. Similar non-significant tendencies were found in case of problematic drinking (OR: 0.74; 95% CI: 0.45-1.22) and binge drinking (OR: 0.78; 95% CI: 0.48-1.24).

CCSs were less likely to be current smokers compared with population-based controls (OR: 0.72; 95% CI: 0.54-0.96), while a similar, but non-significant reduction was observed in comparison with siblings (OR: 0.85; 95% CI: 0.71-1.01). In subgroup analysis stratified by cancer type, survivors of CNS tumors had significantly lower odds of current smoking compared with population-based controls (OR: 0.43; 95% CI: 0.19-0.99). Survivors of hematological malignancies showed comparable odds (OR: 0.84; 95% CI: 0.41-1.71), while survivors of solid tumors demonstrated reduced, but non-significant odds of current smoking (OR: 0.72; 95% CI: 0.38-1.38).

Survivors had similar odds of using illegal drugs as population-based controls (OR: 0.94; 95% CI: 0.48-1.83). However, marijuana use was less frequent in survivors compared with population-based controls (OR: 0.66; 95% CI: 0.42-1.02), although this difference did not reach statistical significance.

In comparison with population-based controls CCSs showed elevated, but non-significant odds of depression (OR: 1.47; 95% CI: 0.85-2.54) and comparable risk of suicidal behavior (OR: 1.12; 95% CI: 0.78-1.61). In contrast, antidepressant use was significantly more common among CCSs than population-based controls (OR: 1.19; 95% CI: 1.09-1.29). Antidepressant use had also higher chances among survivors of CNS tumors (OR: 1.27; 95% CI: 1.19-1.35), whereas no significant differences were observed among survivors of hematological malignancies (OR: 1.14; 95% CI: 0.97-1.34) and solid tumors (OR: 1.19; 95% CI: 0.98-1.44).

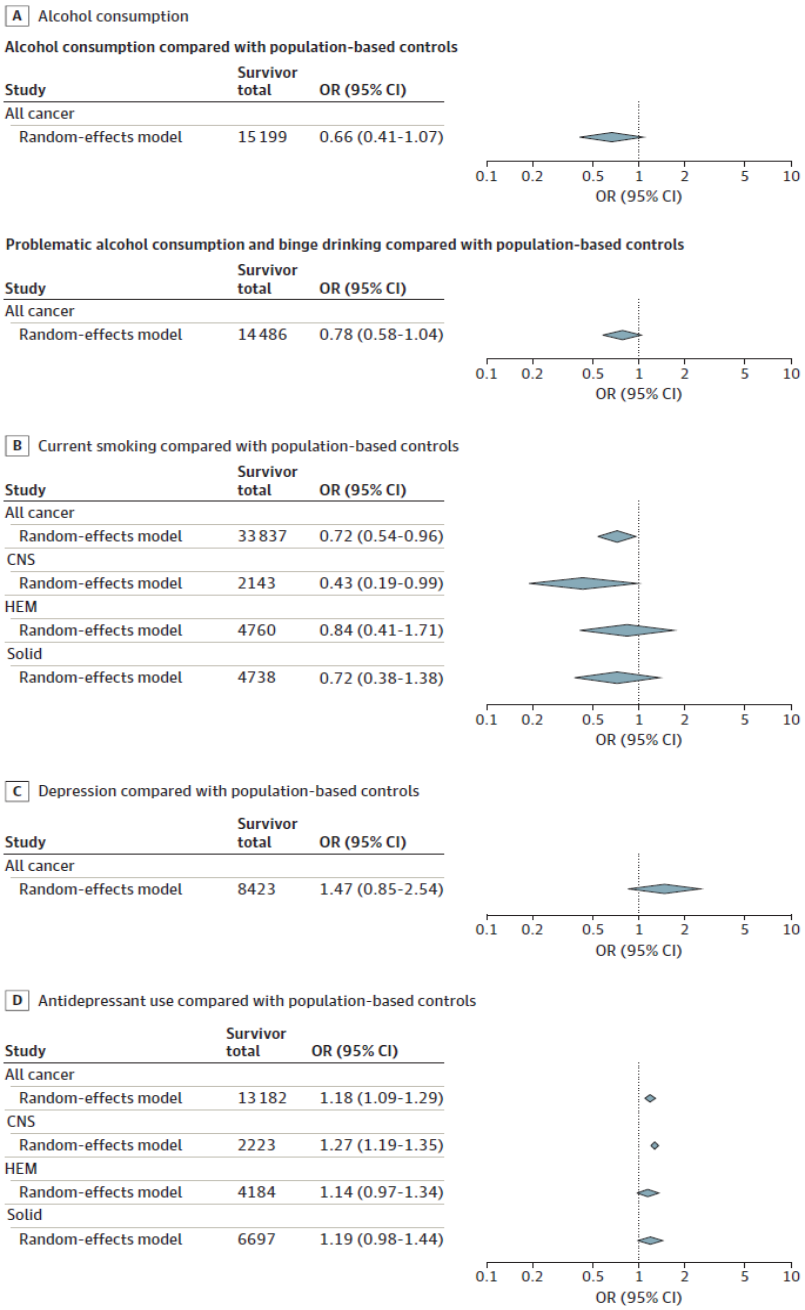


Figure 5. Summary forest plots of health-risk behavior and mental health condition-related odds ratios (ORs) with 95% confidence intervals (CI) of childhood cancer survivors, survivors of central nervous system (CNS), hematological (HEM), solid tumors compared with population-based controls. A: alcohol consumption, problematic alcohol consumption and binge drinking compared with population-based controls; B: current smoking compared with population-based controls; C: depression compared with population-based controls; D: antidepressant use compared with population-based controls;

8.1.7 Results of Quality of Life

Quality of life outcomes were analyzed separately for studies using the Pediatric Quality of Life Inventory (PedsQL 4.0) and the 36-Item Short Form Survey (SF-36). Standardized mean differences (SMDs) were applied to enable comparison across conceptually similar domains assessed by different QoL instruments.

Overall, CCSs reported QoL levels comparable to those of their controls. In contrast, survivors of CNS tumors demonstrated lower QoL scores, with the lowest scores reported in parent-proxy assessments.

8.1.8 Results of Risk of Bias Assessment

Risk of bias assessment was performed using the QUIPS tool for the included studies. The risk of bias was low and moderate in most cases, while high risk was found in case of conference abstracts or insufficient reporting of confounders.

8.2 Study II

8.2.1 Patient Characteristics

A total of 37 patients with HR-NBL received dinutuximab beta at one of five participating HuPON centers in Hungary between October 2018 and February 2023. Dinutuximab beta was administered as part of first-line treatment in 31 patients (83.8%), while six patients (16.2%) received treatment for relapsed disease, of whom four presented with distant metastases at relapse. Patients were followed for overall survival for maximum duration of 11.8 years.

At initiation of dinutuximab beta therapy, all included patients had measurable or evaluable disease by study design. Baseline disease status was assessed using the International Neuroblastoma Response Criteria (INRC), incorporating soft tissue, bone and bone marrow components.

The majority of patients were male (n=26, 70.3%), and the median age at treatment initiation was 39.2 months (range: 22 days – 12.4 years). MYCN amplification was present in 15 patients (40.5%), including 11 of the 27 patients with INSS stage 4 disease and one patient with INSS stage 2 disease and unfavorable histopathology. Three patients were diagnosed before 12 months of age: one with stage 3 disease who received dinutuximab beta as second-line therapy, one with stage 4S disease, and one with stage 2 disease.

Primary tumors were most frequently located in the adrenal glands (n=34, 91.9%), with two tumors (5.4%) originating from the abdomen and one (2.7%) from lymph nodes. At diagnosis, four patients (10.8%) had localized disease without metastases. The majority of patients (59.5%) presented with metastatic involvement of two or more compartments, most commonly affecting the bone marrow, bone, and lymph nodes.

Detailed patient and disease characteristics are shown on Table 1.

Table 1. Baseline patient and disease characteristics. [a] Refractory disease (misdiagnosis): due to initial misdiagnosis, two patients were incorrectly treated for Wilms tumor and one patient for non-Hodgkin lymphoma, to which there was no response. [b] recurrent: patients received dinutuximab beta as second-line treatment. [c] MYCN status was not evaluable in one patient with INSS stage 3 disease; this patient received dinutuximab beta in the relapse setting. [d] Histopathology was "not otherwise specified" in one patient. CNS: central nervous system; HR-NBL: high-risk neuroblastoma; INSS: International Neuroblastoma Staging System.

Number of Patients, n	**37**
Patients with HR-NBL who received dinutuximab beta, n (%)[a]	**37 (100)**
First line treatment, n (%)	31 (83.8)
Relapsed disease, n (%)	6 (16.2)
Distant relapse, n (%)	4 (10.8)
Male, n (%)	**26 (70.3)**
INSS stage at diagnosis, n (%)	
2	1 (2.7)
3	2 (5.4)
4	27 (73.0)
4S	1 (2.7)
recurrent[b]	6 (16.2)
MYCN amplified[c], n (%)	**15 (40.5)**
INSS Stage 2	1 (2.7)
INSS Stage 3	1 (2.7)
INSS Stage 4	11 (29.7)
INSS Stage 4S	1 (2.7)
recurrent[b]	1 (2.7)
Unfavorable histopathology[d], n (%)	30 (81.1)

Table 1. Continued

Primary tumor major location, n (%)	
Adrenal glands, n (%)	34 (91.9)
Abdomen, n (%)	2 (5.4)
Lymph nodes, n (%)	1 (2.7)
Number of metastatic compartments at diagnosis, n (%)	
0	4 (10.8)
1	11 (29.7)
2	7 (18.9)
3	9 (24.3)
≥4	6 (16.2)

8.2.2 Treatment Characteristics

Five cycles of dinutuximab beta were administered to 23 patients (62.2%), whereas twelve patients (32.4%) received fewer than five cycles. One patient (2.7%) received a total of six cycles, comprising five cycles as first-line therapy and one additional cycle administered for relapsed disease. This patient subsequently received multiple salvage treatments, including RIST therapy (rapamycin, and dasatinib in combination with irinotecan and temozolomide), MIBG treatment and haploidentical hematopoietic stem cell transplantation (haplo-SCT), before treatment was discontinued due to death. One additional patient (2.7%) received nine cycles of dinutuximab beta in total, including five cycles as first-line treatment and four additional cycles for relapsed disease, followed by MIBG therapy and haplo-SCT.

Overall, 11 patients (29.7%) received additional anticancer therapies following dinutuximab beta treatment. These post-dinutuximab regimens were heterogeneous in composition and intensity with RIST treatment being the only regimen administered to more than one patient in exactly six cases (16.2%).

8.2.3 Results of Response and Survival analysis

At the data cutoff, the objective response rate (ORR) was 51.4% (19/37), with all responses being complete responses (CRs), and no partial responses were observed. One additional patient (2.7%) achieved stable disease (SD), resulting in a disease control rate of 54.1% (20/37). Progressive disease (PD) was observed in two patients (5.4%), and 15 patients (40.5%) had died at the data cutoff.

The median overall survival (OS) was 11.8 years (95% CI: 4.6-n.a.) for the entire cohort, and the median event-free survival (EFS) was 9.8 years (95% CI: 2.9-n.a.). The upper confidence limits could not be determined due to the low number of patients reaching endpoint. The 5-year OS and EFS rates were 63.3% (95% CI: 49.1-81.7%) and 56.2% (95% CI: 42.1-75.0%), respectively.

Among patients receiving dinutuximab beta as **first-line therapy**, the median OS was not reached, therefore could not be determined. The EFS was 5.1 years (95% CI: 2.5-n.a.), with 5-year OS rate and EFS rate of 59% (95% CI: 43-80%) and 55% (95% CI: 40-75%), respectively. For the cohort receiving dinutuximab beta as **second-line treatment**, neither median OS nor EFS was reached, the 5-year OS and EFS rates were 83% (95% CI: 58-100%) and 67% (95% CI: 38-100%), respectively. No statistically significant differences were observed between first-line and second-line treatment groups (p=0.55 and p=0.73, respectively).

In the MYCN amplification negative cohort, the median OS was 11.8 years (95% CI: 4.6-n.a.) and the median EFS was 5.1 years (95% CI: 2.7-n.a.), with a 5-year OS rate of 67% (95% CI: 48-93%) and a 5-year EFS of 56% (95% CI: 38-83%). In contrast, median OS and EFS were not reached in the MYCN amplification positive cohort, with the 5-year OS and EFS rates being 53% (95% CI: 33-86%) and 53% (95% CI: 33-86%), respectively. OS and EFS outcomes did not differ significantly between MYCN amplification negative and positive cohorts (p=0.33 and p=0.84, respectively).

Cox proportional hazards regression analyses revealed no statistically significant associations between OS or EFS and treatment setting (first-line vs second-line), MYCN amplification status (positive vs negative), or the interaction between these factors. Overall, the models as a whole did not explain a significant amount of survival variability, possibly due to small sample size.

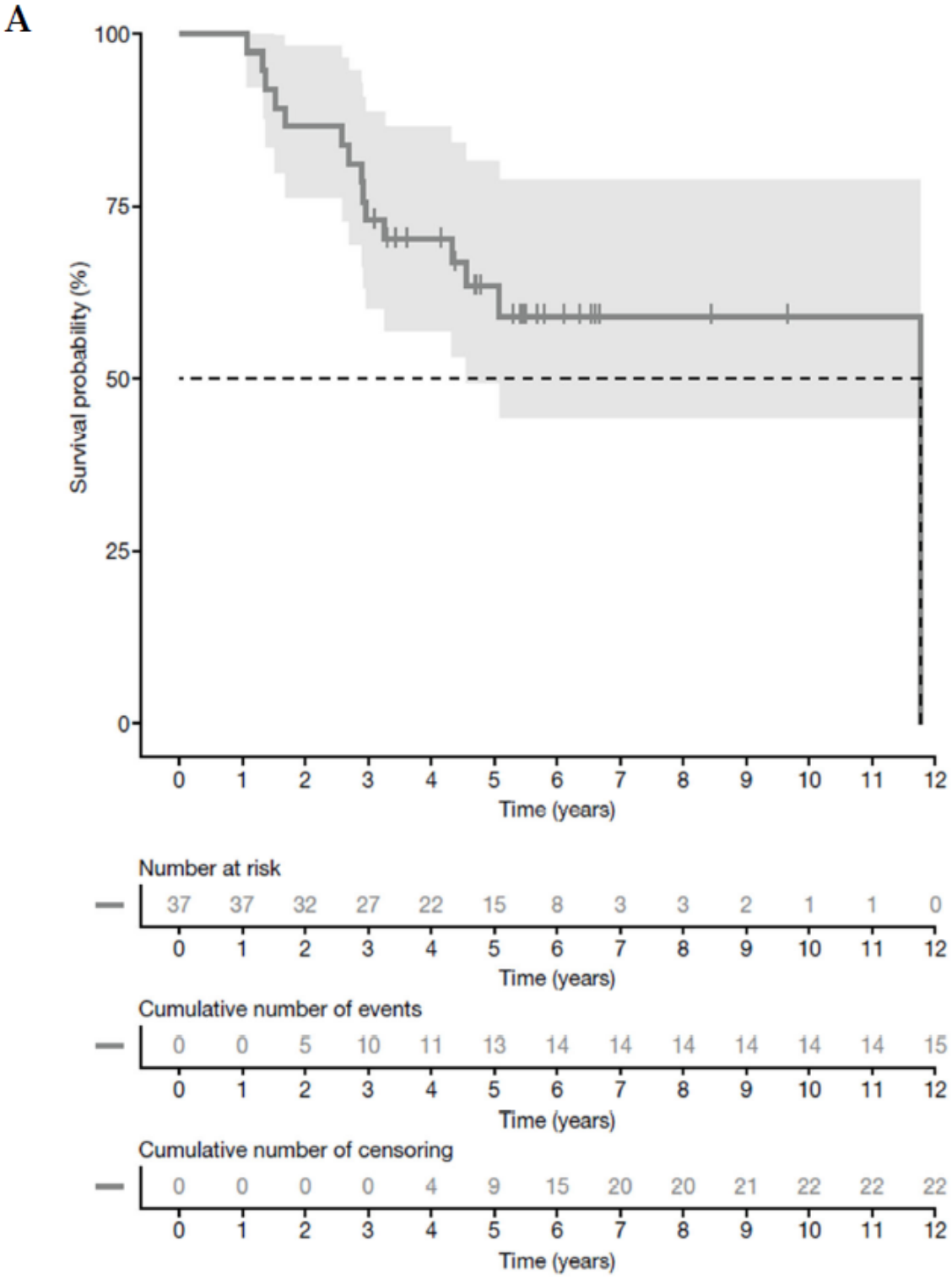


Figure 6. Kaplan-Meier curves for overall survival (OS) for the whole cohort. Event timelines were calculated from initial diagnosis.

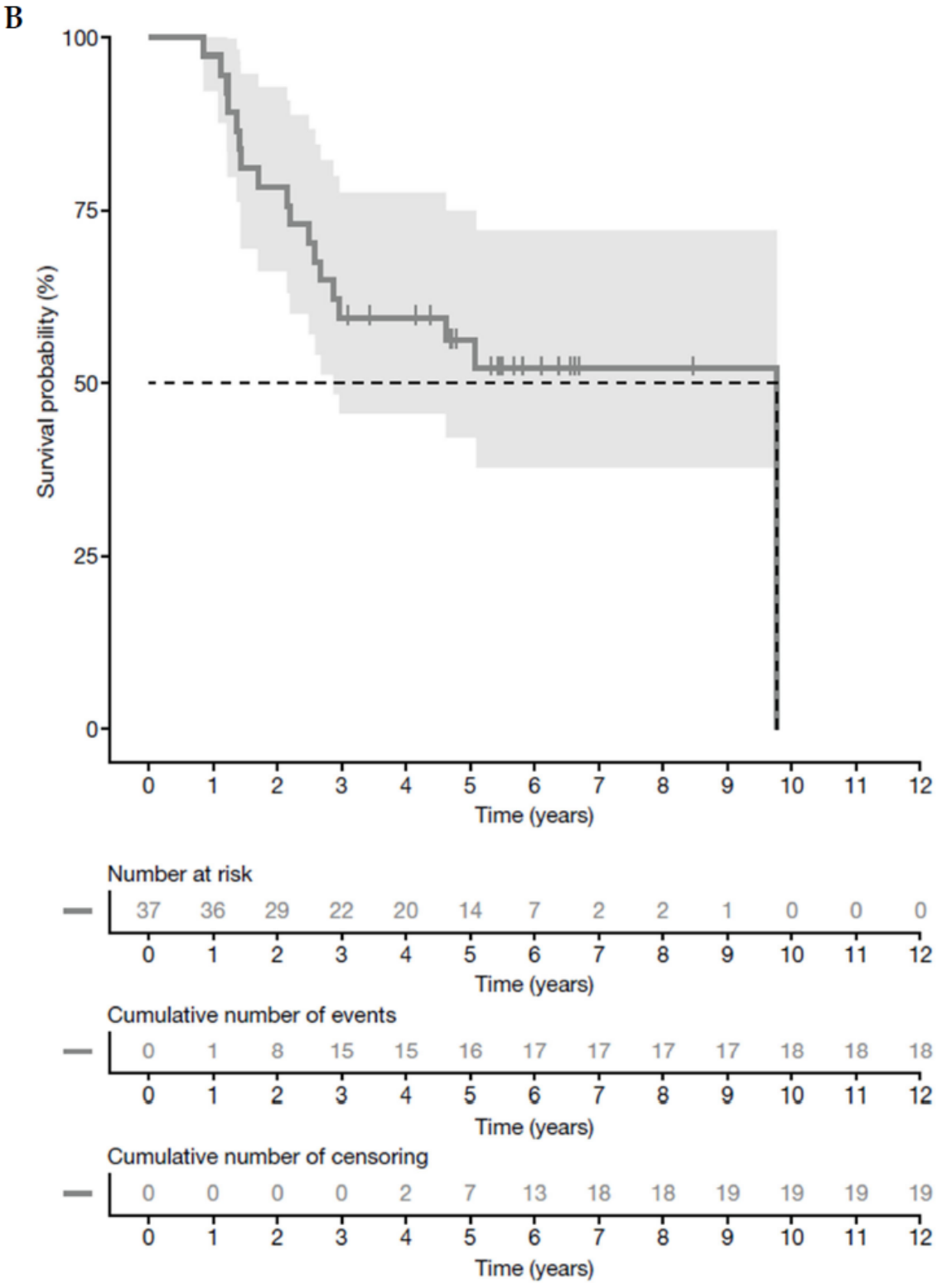


Figure 7. Kaplan-Meier curves for event-free survival (EFS) for the whole cohort. Event timelines were calculated from initial diagnosis.

8.2.4 Results of Safety Assessment

Therapy-related adverse events were categorized and graded using the CTC-AE v5.0. The most common grade 3 or 4 adverse events (AEs), affecting at least 5% of patients, were blood and lymphatic system disorders-other (37.8%), hypoxia (37.8%), hepatobiliary disorders-other (29.2%), hypotension (27.0%), capillary leak syndrome (13.5%), diarrhea (8.1%), generalized edema (5.4%), and urinary tract infection (5.4%). A small number of isolated grade 3-4 AEs were reported (n=1, 2.7% each), including Epstein-Barr virus reactivation, pulmonary edema, and typhlitis. Only five patients (13.5%) experienced grade 4 AEs, namely hepatobiliary disorders-other (n=2, 5.4%), capillary leak syndrome (n=1, 2.7%), acute respiratory distress syndrome (n=1, 2.7%), typhlitis (n=1, 2.7%).

9 DISCUSSION

9.1 Summary of findings, international comparisons (including all studies)

Our aim in Study I was to evaluate long-term psychosocial and socioeconomic reintegration of CCSs in adulthood. Our results in pooled analysis showed that survivors experience several disadvantages in almost all investigated aspects of life. These differences were most consistently observed among survivors of CNS malignancies. Overall, our findings support the premise that childhood cancer survivorship can be associated with long-term challenges extending into adult life.

CCSs demonstrated a decreasing trend in the educational attainment as progressively higher levels of education were analyzed. In contrast to previously published meta-analysis, we observed no relevant difference between CCSs and population-based controls in achieving at least high school graduation, however, this result was substantially worse when compared with siblings. (283) This disparity became more pronounced at the tertiary level, where CCSs showed reduced chances of completing both lower- and higher-level tertiary education, in line with previously reported patterns in the literature. (283) Notably, a distinct pattern was observed among survivors of CNS tumors. These survivors were significantly less likely to achieve at least high school graduation, however, the educational gap appeared to narrow at higher levels of attainment. This pattern is consistent with prior research by Schulte et al. and partially align with the results of Saatci et al. (5, 8) Sibling-based comparisons further underscore the persistent educational challenges faced by CCSs even within comparable family and socioeconomic environments. The particularly unfavorable educational outcomes observed among survivors of CNS tumors are likely related to the significant neurocognitive impact of both the disease itself and its treatment.

Our findings indicate that, when all cancer survivors were taken into consideration, CCSs exhibited employment rates comparable to population-based controls, however comparison with siblings revealed significantly lower employment rates, mirroring the patterns observed for educational outcomes. Subgroup analyses demonstrated that survivors of hematological malignancies, solid tumors, and those who underwent HSCT as part of their treatment were more likely to be unemployed, with survivors of CNS tumors showing the most unfavorable outcomes. In this subgroup the likelihood of

unemployment was nearly threefold higher than that of controls. These findings are broadly consistent with previous research. (6, 7, 284)

Importantly, our analysis also identified employment-related vulnerabilities that had not been studied in prior studies. The odds of health-related unemployment were two- to nine-fold higher among CCSs, depending on cancer type, with CNS tumor survivors again being the most affected. Moreover, even among survivors who were employed, CCSs were more likely to have lower income than their peers.

Reduced employment rates among CCSs may be partially explained by the long-term somatic and psychological sequelae of childhood cancer and its treatment. This interpretation is supported by the particularly adverse outcomes observed among CNS tumor survivors, who showed the highest odds of health-related unemployment. Additionally, income disparities may be indirectly influenced by the lower rates of tertiary educational attainment previously observed in this population.

Family is the cornerstone and smallest functional unit of society therefore leaving the parental home and forming a family are key milestones of social reintegration. To our knowledge, no prior comprehensive synthesis has examined these outcomes in detail among CCSs. Our findings suggest that survivors of childhood cancer are less likely to leave the family home and achieve independent living and are significantly less likely to marry, particularly survivors of CNS tumors, which corroborates previous findings reported by Schulte et al. (8)

One of the most frequently expressed concerns among survivors relates to future parenthood. (285, 286) Our results validate these concerns, demonstrating that CCSs are approximately half as likely to have children compared with their peers. However, once married, CCSs appear to have lower likelihood of divorce than controls.

Despite substantial progress in mitigating acute treatment-related toxicities through comprehensive medical and supportive care, considerably less attention has been directed toward addressing long-term challenges in family formation. Given the significant improvements in survival rates achieved in pediatric oncology, increasing emphasis should be placed on outcomes such as the ability to form long-term partnerships and become a parent which represent meaningful aspects of survivorship. Long-term effects of cancer and its treatment can lead to lower self-esteem and impaired fertility,

highlighting the importance and need for structured psychosocial support, fertility counseling, and fertility preservation strategies. (287, 288)

In terms of QoL, this study is, to our knowledge, the first to synthesize available evidence on this topic using a meta-analytic approach. Analyses of overall QoL scores indicated that CCSs report self-perceived QoL comparable to that of their control groups. These findings may reflect mechanisms of posttraumatic growth, potentially facilitated by social support, educational opportunities, structured interventions and peer or survivor group activities. (289) In contrast, self-reported QoL among survivors of CNS malignancies was consistently lower than that of their peers, in line with previously published studies. (290, 291) Notably, parent-proxy assessments of CNS survivors' QoL were even lower than their self-reports, suggesting a discrepancy between survivor and caregiver perceptions and highlighting the substantial long-term burden perceived by families.

The reported and analyzed data suggest that CCSs are less likely to engage in health-damaging patterns of alcohol, tobacco, and marijuana consumption, indicating a more health-conscious lifestyle compared with their peers. However, despite lower rates of substance use, survivors appear to carry a substantial psychological burden, which may contribute to the higher prevalence of antidepressant use observed in this population. Our findings are consistent with those reported by Marjerrison et al., who described similar or lower rates of risk-taking behaviors among survivors, and with a systematic review by Kosir et al., which highlighted an increased risk of anxiety and depressive symptoms among adolescent cancer survivors. (292, 293)

One general and key finding of our study concerns the use of two distinct control groups. Across multiple outcome domains, CCSs consistently performed worse when compared with their siblings than when compared with population-based controls. Although siblings of CCSs are considered a vulnerable population, this comparison offers important insights, as it accounts more effectively for shared familial, social, and socioeconomic environments. Consequently, sibling comparisons provide valuable insights, due to the strong influence of family microenvironment on the fulfilment of social potential. (294, 295)

In our Study II we aimed to assess the performance of dinutuximab beta for the treatment of HR-NBL based on real-world data collected from clinical practice settings. To achieve

our goal, we conducted a retrospective analysis of patients with HR-NBL who received dinutuximab beta treatment either as first-line maintenance therapy or in the relapsed/refractory setting at one of the five participating centers of HuPON. All patients were treated according to the HR-NBL Study 1/SIOPEN protocol, without the addition of interleukin-2, reflecting contemporary European clinical practice.

The observed overall disease control rate was 54.1%, with 51.4% of patients achieving complete response, while partial responses were not observed. Patients treated with dinutuximab beta in the first-line setting demonstrated a 5-year OS rate of 58% and a 5-year EFS rate of 56%, while corresponding values for patients who received dinutuximab beta for relapsed/refractory disease were 71% and 54%, respectively. These findings suggest that dinutuximab beta is capable of inducing durable responses in a substantial proportion of patients in real-world settings.

Grade 3 or 4 adverse events (AEs) were consistent with the established safety profile of dinutuximab beta. (43) The most frequently reported severe AEs included blood and lymphatic system disorders, hypoxia, hypotension, capillary leak syndrome, diarrhea, generalized edema, and urinary tract infections. Hepatobiliary disorders were also relatively common, affecting nearly one-third of patients. In addition, some rare grade 3-4 events were also documented, each occurring in a single patient, including acute respiratory distress syndrome, allergic disorders, anaphylaxis, depressed level of consciousness, Epstein-Barr virus reactivation, pulmonary edema, and typhlitis. Importantly, only a minority (n=5) of patients experienced grade 4 toxicity, and no unexpected safety signals emerged. Overall, the emerging AEs were manageable with supportive care and their occurrence decreased with successive treatment cycles. These findings underscore the acceptable tolerability of dinutuximab beta in routine practice and highlight the importance of vigilant monitoring and proactive management of treatment-related toxicity, particularly during early treatment cycles.

Approximately, one third of patients (29.7%) received additional anticancer therapy following dinutuximab beta treatment. These post-dinutuximab interventions were heterogeneous and reflected individualized treatment decisions based on disease course and response. RIST-based regimens were the most frequently applied approach, while other multimodal salvage strategies were used sporadically. Notably, the majority of

patients (70.3%) did not require any further anticancer treatment after the completion of dinutuximab beta therapy.

Several real-world studies have evaluated the effectiveness and tolerability of dinutuximab beta in patients with HR-NBL. (296-298) Retrospective cohorts from Poland, Croatia and Bratislava consistently reported high complete response rates in both first-line and relapsed/refractory settings, along with favorable short- to mid-term survival outcomes and manageable toxicity profiles. Across these studies, dinutuximab beta was generally well tolerated, with adverse events largely consistent with its known safety profile and typically manageable with supportive care. Compared with these reports, the complete response rate observed in our first-line cohort was lower (40.5% vs 75.7-85.5%), and overall mortality was higher (35.1% vs 22.2%). These differences may reflect the fact that higher proportion of patients presented with metastatic disease at treatment initiation in our cohort. In contrast, survival outcomes among patients treated in the second-line setting were unexpectedly favorable, with high 5-year OS and EFS rates (71% and 54%, respectively. Although these findings must be interpreted cautiously due to the small sample size and wide confidence intervals, they are consistent with previously reported real-world data demonstrating durable responses in relapsed/refractory patients. Results of the safety assessment of the current study were generally consistent with previously published data.

Overall, the effectiveness and safety outcomes observed in our study align with existing real-world evidence supporting dinutuximab beta as an effective and tolerable component of HR-NBL treatment.

Taken together, the findings of Study I (*Burden of Childhood Cancer and the Social and Economic Challenges in Adulthood*) and Study II (*Dinutuximab beta for the Treatment of High-Risk Neuroblastoma*) demonstrate the evolving landscape of pediatric oncology and childhood cancer survivorship. While contemporary multimodal therapies, including dinutuximab beta, contribute to substantial long-term survival in diseases such as high-risk neuroblastoma, survivors frequently face persistent psychosocial and socioeconomic challenges extending into adulthood. Collectively, our results highlight the importance of evaluating cancer outcomes across the entire survivorship trajectory, from diagnosis and acute treatment response to long-term quality of life and social functioning.

9.2 Strengths

9.2.1 Study I

The strengths of this study include that it was conducted according to a prospectively developed and rigorously predefined protocol, aligned with international recommendations, ensuring transparency and accountability. Furthermore, in contrast to previous studies we placed particular emphasis on excluding overlapping populations and on analyzing appropriately matched control groups, including both population-based controls and siblings, to improve accuracy and interpretability of pooled estimates.

Importantly, this work represents one of the most comprehensive quantitative evaluations of long-term psychosocial and socioeconomic outcomes among CCSs to date. Several domains, including family formation, health-related unemployment, quality of life, and health-risk behaviors have not previously been examined in a systematic meta-analytic framework.

Overall, our results provide a holistic overview of adult survivorship, offering robust evidence base to inform future research, survivorship care strategies, and policy development.

9.2.2 Study II

Our study provides nationwide real-world data from the Hungarian Childhood Cancer Registry, and from five HuPON centers across the country. This multicenter design enhances the representativeness and external validity of the findings within a national healthcare setting. The study includes both first-line and relapsed/refractory treatment settings, allowing comprehensive assessment of dinutuximab beta effectiveness and safety across clinically relevant scenarios that are often underrepresented in clinical trials. Treatment response, survival, and safety outcomes were assessed using standardized and internationally accepted criteria (i.e. INRC, CTC-AE v5.0), ensuring methodological consistency and comparability with other published studies.

Finally, our study adds valuable real-world evidence from Central and Eastern Europe, a region that is often underrepresented in scientific literature. It complements to existing trial and registry data and contributes to a more globally balanced understanding of dinutuximab beta treatment.

9.3 Limitations

9.3.1 Study I

This study has several limitations that should be acknowledged. First, many of the investigated outcomes were socioeconomic and psychological in nature, which are inherently complex and difficult to measure. The lack of standardized, long-term follow-up frameworks and reporting systems for the abovementioned outcomes in childhood cancer survivorship may have introduced variability across studies.

Second, the analysis captured a broad, but time-limited segment of adulthood. As a result, outcomes that evolve over the course of life, including employment, income trajectories, family formation, parenthood, etc. may not be fully represented, potentially leading to underestimation or delayed manifestation of certain long-term effects.

Finally, some pooled estimates were characterized by moderate to high statistical heterogeneity, which likely reflects differences in study designs, populations, outcome definitions, healthcare systems, and should be considered when interpreting the results.

9.3.2 Study II

A number of limitations should be considered when interpreting the findings of this study. The retrospective design inherently carries a risk of selection bias and limits control over confounding variables. In addition, the absence of a comparator group excludes the possibility of direct comparison with alternative treatment strategies. Furthermore, the study cohort was relatively small, particularly in case of subgroup analyses, resulting in high levels of uncertainty and limited statistical power. Consequently, survival estimates, especially in the relapsed/refractory setting should be interpreted as exploratory. Moreover, the relatively low number of survival events limited the explanatory potential of multivariable survival models.

Finally, there was significant heterogeneity in subsequent and salvage therapies administered after dinutuximab beta, reflecting the real-world clinical practice, but complicating attribution of long-term outcomes exclusively to dinutuximab beta. This treatment variability may have influenced survival and response outcomes independently of immunotherapy.

10 CONCLUSIONS

10.1 Study I

The results of this systematic review and meta-analysis indicate that childhood cancer survivors face substantial long-term socioeconomic challenges, especially in educational attainment, employment, and family formation, compared with their peers. These disparities are most pronounced among survivors of central nervous system tumors. Our findings highlight the urgent need for structured, lifelong follow-up strategies with a dedicated focus on psychosocial support and successful social reintegration. We firmly believe that our work has the potential to provide foundation for the development of such protocol, highlighting the most affected areas and the most vulnerable populations. Addressing these long-term consequences is essential to ensure the sustained psychosocial well-being and life fulfillment of current and future generations of childhood cancer survivors.

10.2 Study II

This retrospective analysis suggests that dinutuximab beta is an effective and well-tolerated treatment for high-risk neuroblastoma. The observed safety profile was consistent with known toxicities and generally manageable, and survival outcomes were favorable in both first-line and relapsed/refractory settings. Together, these findings provide real-world evidence supporting the use of dinutuximab beta in routine clinical practice and offer practical insights for optimizing treatment strategies in pediatric oncology.

11 IMPLEMENTATIONS FOR PRACTICE

11.1 Study I

Our recommendation based on the results of this study is to develop a disease-, and treatment-specific standardized data collection and follow-up system adapted to CCSs and to implement it in bedside use and during long-term follow-up. Based on the acquired and regularly updated data, a personalized nationally and culturally considerate, complex and comprehensive protocol should be developed and implemented as a life-long follow-up survivorship program.

11.2 Study II

Real-world data from this study support the use of dinutuximab beta as an effective and manageable treatment option for children with HR-NBL in both first-line maintenance and relapsed/refractory settings. These findings reinforce its integration into routine clinical practice and highlight the importance of structured toxicity monitoring and supportive care during treatment.

12 IMPLEMENTATION FOR RESEARCH

12.1 Study I

Future research should prioritize the development of standardized data systems and outcome measures, particularly for psychosocial and socioeconomic domains. Prospective, longitudinal studies are needed to better understand survivorship trajectories and identify modifiable factors that influence long-term outcomes. Studies should also focus on the disease course and treatment-related factors to identify potential determinants of adverse long-term challenges.

12.2 Study II

Prospective, multicenter studies with large patient populations and appropriate comparator groups are needed to better define the survival benefit of dinutuximab beta and to identify clinical and biological factors influencing treatment response and long-term outcomes. Future research should also aim to clarify the impact of subsequent therapies on survival to refine treatment sequencing strategies.

13 IMPLEMENTATION FOR POLICYMAKERS

13.1 Study I

The significant long-term psychosocial and socioeconomic disadvantages identified among CCSs highlight the need for national survivorship policies that extend beyond medical follow-up and explicitly address education, employment, and family support. Policymakers should prioritize the development and funding of structured, lifelong survivorship programs, with particular attention to high-risk groups, especially survivors of CNS malignancies.

13.2 Study II

The real-world evidence on the effectiveness and safety of dinutuximab beta treatment supports its sustained inclusion in international pediatric oncology treatment protocols and reimbursement frameworks. Policymakers should ensure equitable access to immunotherapy and invest in registry-based outcome monitoring to inform evidence-based updates of treatment strategies.

14 FUTURE PERSPECTIVES

Future efforts should prioritize the development and implementation of structured, lifelong survivorship programs integrating medical, psychosocial, educational, vocational and family support services, based on standardized registry-based data collection to enable personalized follow-up. Advances in risk stratification, digital health tools, early intervention and multidisciplinary survivorship care models may further improve long-term outcomes for childhood cancer survivors.

The development and prospective evaluation of standardized relapsed/refractory treatment protocols incorporating dinutuximab beta in high-risk neuroblastoma is necessary to optimize therapeutic strategies and long-term effectiveness. In addition, the target of dinutuximab beta (GD2) is expressed in several other pediatric tumors, therefore expanding research into GD-2 directed immunotherapy beyond neuroblastoma represents a promising area for translational and clinical investigation.

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"Happiness is only real when shared."

Alexander Supertramp

Thank you,

for sharing.

APPENDIX

Appendix Table 1. Basic characteristics of studies included in the meta-analysis (Study I).

(ALL=acute lymphoblastic leukemia; AML=acute myeloid leukemia; BT=bone tumor; CCSS=Childhood Cancer Survivor Study; CML=chronic myeloid leukemia; CNS=central nervous system; Edu=education-related outcomes; Emp=employment-related outcomes; Fam=family formation; HL=Hodgkin lymphoma; HR= health-risk behaviors; HSCT=hematopoietic stem cell transplantation; IA=infratentorial astrocytoma; LGG=low-grade glioma; MBL=medulloblastoma; n.a.=not available; NHL=non-hodgkin lymphoma; OS=osteosarcoma; QoL=quality of life; RBL=retinoblastoma; RMS=rhabdomyosarcoma; WT= Wilms tumor; y=year;)

	Author, y	**Country**	**Cancer type (without subgroups)**	**Time period of diagnosis**	**No. of survivors**	**Age at study mean [range], y**	**Mean age at diagnosis, y**	**Control group**	**Outcomes measured**
1	Abadie, 2020 (57)	France	All cancer (except leukemia)	1987-1999	247	26.8 (median) [18.6-38.6]	n.a	Population sample	HR
2	Ahomaki, 2016 (58)	Finland	CNS	1964-2009	3243	n.a [17-50]	n.a	Population sample	Edu, Emp
3	Aili, 2021 (59)	Sweden	Hematological (ALL)	1985-1997	227	28 [23-41]	n.a	Siblings	Emp, Fam, HR, QoL
4	Alias, 2020 (60)	Malaysia	CNS	n.a	38	12.5 [6-18.9]	7.2 ± 3.6	Matched controls	Edu, HR, QoL
5	Asfar, 2016 (61)	USA	All cancer	1997-2010	1438	n.a	n.a	Population sample	Edu, Emp, HR

6	Aukema, 2013 (62)	Netherlands	CNS	1990-2006	34	14.1-15.3	6.6-6.9	Population sample	QoL
7	Badr, 2013 (63)	USA	All cancer	1992-2007	170	17.7	n.a	Population sample	QoL
8	Barbati, 2022 (64)	Belgium, France	Hematological (ALL)	1971-1998	507	25 (median) (18.53)	n.a	Population sample, matched controls	Edu, Emp, Fam
9	Barrera, 2005 (65)	Canada	All cancer	1981-1990	800	n.a [6-16]	n.a	Matched controls	Edu
10	Barrera, 2011 (66)	Canada	Solid (BT)	n.a	28	25.1	11.6 ± 3.3	Population sample	QoL
11	Batra, 2016 (67)	India	Solid (RBL)	2012-2014	122	9.3 [5.08-20.67]	n.a	Siblings	QoL
12	Baughan, 2023 (68)	Scotland	All cancer	n.a	1313	n.a	n.a	Population sample	Edu, Emp
13	Bauld, 2005 (69)	Australia	All cancer	1976-1987	153	18.2 [13-24]	6.2 ± 4.1	Population sample	HR
14	Baytan, 2016 (70)	Turkey	Hematological (ALL)	n.a	50	15.8 [13-18]	n.a	Siblings	HR, QoL
15	Beal, 2018 (71)	USA	All cancer	n.a	88	24.8	9.4 ± 6.1	Matched controls	Fam
16	Becktell, 2020 (72)	USA	All cancer	n.a	155	n.a	n.a	Population sample	QoL

17	Belson, 2022 (73)	USA	Solid (RBL)	n.a	101	17 (median) (IQR: 15-19)	1.25 (median) (IQR: 0.67-1.92)	Matched controls	QoL
18	Berbis, 2016 (74)	France	Hematological (leukemia)	1980-2011	845	22.3	7.9 ± 4.6	Population sample	Emp
19	Bhatt, 2021 (75)	USA	All cancer	n.a	9837	33 [25-54]	9 (median)	Population sample	Emp
20	Blaauwbroek, 2007 (76)	Netherlands	All cancer	2004-2005	123	33 (median) [19-50]	6 (median)	Population sample	QoL
21	Boman, 2004 (77)	Sweden	All cancer	n.a	30	21.6 [18-29]	8.3 ± 3.9	Matched controls	Edu, Emp, Fam
22	Boman, 2010 (78)	Sweden	All cancer	n.a	1716	31.6	n.a	Population sample	Edu, Emp
23	Bougas, 2021 (79)	France	All cancer	1945-2000	2887	n.a	n.a	Population sample	HR
24	Bouwman, 2022 (80)	Netherlands	All cancer	1963-2001	2677	n.a	n.a	Siblings	HR
25	Bradley-Eilertsen, 2012 (81)	Norway	All cancer	1993-2003	50	12.5 (median)	n.a	Matched controls	QoL
26	Brown, 2023 (82)	USA	CNS	n.a	187	11.29 [8-15]	n.a	Matched controls	QoL

27	Burghardt, 2018 (83)	Germany	All cancer	n.a	951	n.a [24-49]	34.2 (median)	Matched controls	Edu, Emp, Fam, HR
28	Byrne, 1989 (84)	USA	All cancer	n.a	2170	n.a	n.a	Siblings	Fam
29	Byrne, 2004 (85)	USA	Hematological (ALL female)	1970-1987	182	22.6	10.7	Siblings	Fam
30	Calaminus, 2014 (86)	Germany	Hematological (HL)	1978-2002	725	28.4	13.63 ± 3.09	Matched controls	Edu, Emp, Fam
31	Cantrell, 2014 (87)	USA	All cancer (females)	n.a	66	28.6	n.a	Population sample	QoL
32	Cantrell, 2016 (88)	USA	All cancer	n.a	90	28.8	n.a	Matched controls	HR
33	Carceles-Alvarez, 2020 (89)	Spain	All cancer	n.a	117	13.23	3.63	Population sample	QoL
34	Carswell, 2008 (90)	Canada	All cancer	1981-1990	1263	n.a [16-37]	n.a	Matched controls	Edu, HR
35	Castellano-Tejedor, 2014 (91)	Spain	All cancer	n.a	393	16.74 [14-19]	n.a	Population sample	QoL
36	Cetingül, 1999 (92)	Turkey	Hematological (ALL)	n.a	19	n.a	5.7 ± 2.8	Siblings	QoL
37	Chan, 2014 (93)	China	All cancer	n.a	614	21.9 (16-39)	n.a	Siblings	Emp, QoL

38	Chan, 2020 (94)	China	All cancer	n.a	614	21.9	n.a	Siblings	Edu, Emp, Fam, HR
39	Chantziara, 2022 (95)	Belgium, France	Hematological (ALL)	1971-1998	186	27.6 [18.1-52.8]	5.62 ± 3.30	Matched controls	QoL
40	Chiou, 2010 (96)	Taiwan	Hematological	1992-2005	32	13.17	4.43 ± 2.21	Matched controls, siblings	QoL
41	Clarke, 2011 (97)	UK	Hematological (ALL)	n.a	54	13.00-13.79	5.23-5.34	Population sample	QoL
42	Claessens, 2023 (98)	Netherlands	All cancer (males)	1963-2001	1317	n.a	n.a	Siblings	Edu, Emp, Fam
43	Crom, 2007 (99)	USA	All cancer	1962-1992	1437	29.7 (median) [18.2-55.3]	7 (median)	Population sample	Emp, Fam
44	Dama, 2009 (100)	Italy	All cancer	1960-2000	1237	28.5 [18.1-51.7]	n.a	Population sample	Fam
45	Deleemans, 2021 (101)	Canada	All cancer	n.a	60	25.3 [18-39]	15.6 ± 1.6	Population sample	HR
46	Deyell, 2013 (102)	Canada	All cancer	1970-1995	2389	28.8	6.3 ± 4.6	Population sample	HR
47	Dhingra, 2021 (103)	India	Solid (RBL)	2018-2019	98	5.7	4.8	Siblings	QoL
48	Dieluweit, 2010 (104)	Germany	All cancer	n.a	820	30.4 [20-46]	15.8 ± 0.9	Matched controls, population sample	Fam

49	Dieluweit, 2011 (105)	Germany	All cancer	n.a	820	30.4 [20-46]	15.8 ± 0.9	Matched controls	Edu, Emp, Fam
50	Dolgin, 1999 (106)	Israel	All cancer	n.a	64	23.54 [18-35]	11.52 ± 4.69	Matched controls	Edu, Emp, Fam
51	Dowling, 2010 (107)	USA	All cancer	1997-2006	410	n.a	n.a	Population sample	Emp, Fam
52	Dumas, 2016 (108)	France	All cancer	1948-2000	2066	36 [25-64]	6	Population sample	Edu, Emp
53	Eaton, 2020 (109)	USA	All cancer	2004-2011	40	9.1 (median)	n.a	Population sample	QoL
54	Effinger, 2019 (110)	USA	CNS (astrocytoma)	1970-1986	1182	n.a	n.a	Siblings	Edu, Fam
55	Ehrhardt, 2018 (111)	USA	Hematological (NHL)	n.a	187	35.1 (median) (19.3-58.3)	10.4 (median)	Population sample	Emp, Fam
56	Eiser, 2005 (112)	UK	Hematological+CNS	n.a	77	n.a [8-18]	n.a	Population sample	QoL
57	Ellenberg, 2009 (113)	USA	CNS, nonCNS	1970-1986	802 + 5937	31.5 [17.4-51.8]	n.a	Siblings	Emp
58	Ernst, 2023 (114)	Germany	All cancer	1980-1990	633	34.92	6.34 ± 4.38	Population sample	QoL
59	Eroglu, 2023 (115)	Turkey	All cancer	1998-2008	56	n.a [8-18]	n.a	Matched controls	QoL

60	Felder-Puig, 1998 (116)	Austria	BT	n.a	60	23.53	15.27 ± 5	Population sample	Edu, Fam
61	Fernandez-Pineda, 2017 (117)	USA	Solid (sarcoma)	1962-2004	206	34.7-38.0	11.4-13.1	Matched controls	Emp, Fam, QoL
62	Fidler, 2015 (118)	UK	Solid (sarcoma)	1940-1991	411	43.3 [22.4-76.8]	10.8	Population sample	Fam, HR
63	Fluchel, 2008 (119)	Uruguay	All cancer	1992-1994	95	13.6	n.a	Matched controls	QoL
64	Font-Gonzalez, 2015 (120)	Netherlands	All cancer	1966-2001	1283	n.a	n.a	Population sample	Fam
65	Foster, 2021 (121)	USA	Solid (Wilms tumor)	1970-1999	666	15.3 [12-18]	2.8 ± 1.8	Siblings	QoL
66	Frederiksen, 2022 (122)	Denmark, Finland, Sweden	All cancer	1971-2006	10 461	41.0 (median) [31-66]	n.a	Population sample, siblings	Emp
67	Freycon, 2013 (123)	France	Hematological	1988-2011	59	n.a [18-38.2]	9.1 (median)	Population sample	Edu, Emp
68	Frobisher, 2008 (124)	UK	All cancer	1940-1991	14 836	n.a	n.a	Population sample	HR
69	Frobisher, 2010 (125)	UK	All cancer	1940-1991	10 389	n.a	n.a	Population sample	HR
70	Frobisher, 2010 (126)	UK	All cancer	1940-1991	8155	n.a	n.a	Population sample	Fam

71	Frobisher, 2017 (127)	UK	All cancer	1940-1991	10 257	28.9 (median) [16.0-74.2]	n.a (0-14)	Population sample	Edu, Emp
72	Fukushima, 2023 (128)	Japan	All cancer	1984-2020	151	16.1 (median) [7.0-43.2]	7.0 (median) [0.0-15.9]	Population sample	QoL
73	Gerhardt, 2007 (129)	USA	nonCNS	n.a	56	18.65	n.a	Matched controls	Edu, Emp
74	Ghaderi, 2016 (130)	Norway	All cancer	1965-1985	2213	n.a	n.a	Population sample	Education
75	Gibson, 2015 (131)	USA	All cancer	1970-1986	9397	28	n.a	Population sample, siblings	HR
76	Gordijn, 2012 (132)	Netherlands	Hematological (ALL)	1997-2008	62	n.a [5-17]	n.a	Population sample	QoL
77	Gunn, 2013 (133)	Finland	Hematological (ALL males)	n.a	52	29 (median) [25-38]	n.a	Matched controls	QoL
78	Gunnes, 2017 (134)	Norway	All cancer	n.a	5440	n.a	n.a [0-24]	Population sample	HR
79	Gunnes, 2016 (135)	Norway	All cancer	1985-2007	2687	n.a	n.a	Population sample	Emp, Fam
80	Guy, 2016 (136)	USA	All cancer	n.a	239	n.a	n.a	Population sample	Fam
81	Haavisto, 2016 (137)	Finland	Hematological (ALL males)	1970-1995	52	28.5 [25-38]	4.5 ± 5.8	Matched controls	Fam

82	Halvorsen, 2017 (138)	Norway	All cancer	1991-2007	91	24.7	15.3 ± 3.83	Matched controls	Employment
83	Harila, 2010 (139)	Finland	Hematological (ALL)	1971-1994	74	24 [17-37]	5 [0-15]	Matched controls	QoL
84	Harila, 2011 (140)	Finland	Hematological (ALL)	1971-1994	73	24 [17-37]	5 [0-15]	Matched controls	QoL
85	Haupt, 1992 (141)	USA	All cancer	1945-1974	1289	31.5	12.6	Siblings	HR
86	Hays, 1992 (142)	USA	All cancer	1945-1975	219	n.a	n.a	Matched controls	Edu, Emp, Fam
87	Hjern, 2007 (143)	Sweden	All cancer	n.a	2503	28.9	n.a	Population sample	Fam
88	Hollen, 2007 (144)	USA	nonCNS	n.a	76	16.1 [14-19]		Population sample	HR
89	Holmqvist, 2010 (145)	Sweden	Hematological (ALL)	1970-1999	167	n.a	6	Matched controls	Edu, Fam
90	Horan, 2023 (146)	USA	All cancer	1962-2012	4294	30.7	n.a	Population sample	HR
91	Hörnquist, 2014 (147)	Sweden	CNS	1982-2001	528	26.3 [19-40]	n.a	Matched controls	Edu, Emp, Fam
92	Hsu, 2023 (148)	Taiwan	All cancer	2000-2011	5121	n.a [0-17]	9.08	Population sample	HR

93	Hu, 2021 (149)	China	Hematological (NHL)	n.a	23	26.2 [16.9-55.8]	10.4	Population sample	QoL
94	Huang, 2017 (150)	USA, CCSS	All cancer	1970-1986	7103	31.8	n.a	Siblings	QoL
95	Huang, 2022 (151)	Taiwan	nonCNS	n.a	90	10.10-15.86	3.9-8.2	Siblings	QoL
96	Ishida, 2011 (152)	Japan	All cancer	n.a	189	23.1	8.3 ± 4.8	Siblings	Edu, Emp, Fam
97	Janson, 2009 (153)	USA	All cancer	1970-1986	9230	n.a	n.a	Siblings, population sample	Fam
98	Jeong, 2013 (154)	South Korea	Hematological (ALL)	n.a	53	[5-17]	n.a	Population sample	QoL
99	Jervaeus, 2014 (155)	Sweden	All cancer	2004-2006	63	17 (median) [12-22]	n.a	Matched controls	QoL
100	Ji, 2021 (156)	USA	All cancer	n.a	832	n.a [12-34]	n.a	Population sample	HR
101	Johannesen, 2007 (157)	Norway	CNS, Hematological	1970-1997	1144	n.a	n.a	Population sample	Employment
102	Jóhannsdóttir, 2010 (158)	Denmark, Finland, Iceland, Norway, Sweden	Mixed (AML, WT, IA)	1985-2001	247	23 [19-34]	8 ± 4.1	Matched controls	Fam
103	Jóhannsdóttir, 2016 (159)	Norway	All cancer	1965-2000	5341	n.a	n.a	Matched controls	HR

104	Kamibeppu, 2010 (160)	Japan	All cancer	n.a	185	23.1-23.2	n.a	Population sample, siblings	QoL
105	Kanellopoulos, 2013 (161)	Norway	Hematological (ALL)	1970-2000	285	31.0	n.a	Population sample	QoL
106	Kasteler, 2018 (162)	Switzerland	All cancer	1976-2010	511	n.a [16-19]	5 (median)	Population sample, siblings	HR
107	Keating, 2023 (163)	Ireland	CNS	n.a	34	12.21	9.09 ± 4.27	Population sample	QoL
108	Kelaghan, 1988 (164)	USA	All cancer	1945-1974	2283	31.3 [21-55]	n.a	Siblings	Education
109	Kenney, 2009 (165)	USA	All cancer	n.a	55	55 (median)	8.8	Matched controls	Edu, Fam, HR, QoL
110	King, 2017 (166)	USA	CNS (MBL)	1970-1986	380	30 (median)	n.a	Siblings	Education
111	Kirchhoff, 2010 (167)	USA	All cancer	1970-1986	6339	n.a [25-54]	n.a	Siblings	Emp, Fam
112	Kizmazoglou, 2019 (168)	Turkey	Hematological (ALL)	n.a	70	12.7	4.8 ± 2.4	Siblings	QoL
113	Klosky, 2012 (169)	USA	All cancer	1970-1986	307	18.1 [15.4-20.4]	n.a	Siblings	HR
114	Koch, 2004 (170)	Denmark	All cancer	1960-1996	2384	n.a [13-39]	n.a	Population sample	Education

115	Koch, 2006 (171)	Denmark	All cancer	1980-1997	1597	n.a	n.a	Population sample	Emp, Fam
116	Koch, 2011 (172)	Denmark	All cancer	1965-1996	1877	n.a	n.a	Population sample	Fam
117	Korhonen, 2019 (173)	Denmark, Finland, Sweden	All cancer	1971-2009	29 285	n.a	n.a	Matched controls	HR
118	Kumar, 2023 (174)	UK	CNS (benign intracranial tumors)	2000-2015	23	21 (median) [17-26]	13 (median)	Population sample	QoL
119	Kunin-Batson, 2011 (175)	USA	All cancer	1970-1986	6047	n.a	n.a	Siblings	Fam
120	Kyrönlahti, 2023 (176)	Denmark, Finland, Sweden	All cancer	1971-2009	17 392	33 (median)	n.a	Population sample	Emp
121	Lahteenmaki, 1998 (177)	Finland	All cancer (males)	n.a	207	n.a	10.0	Population sample	Emp
122	Lancashire, 2010 (178)	UK	All cancer	1940-1991	10 183	n.a	n.a	Population sample	Education
123	Langeveld, 2003 (179)	Netherlands	All cancer	n.a	500	24 [16-49]	8 ± 4.7	Matched controls	Edu, Emp, Fam
124	Larcombe, 2002 (180)	UK	All cancer	n.a	178	25.2 [18-30]	8.2	Matched controls, siblings	HR
125	Lehmann, 2015 (181)	USA	All cancer	n.a	87	27.8 [20-40]	12.1 ± 3.8	Matched controls	Edu, Emp

126	Ljungman, 2022 (182)	Finland	CNS	1970-2008	60	28.1	8.5 ± 4.3	Matched controls	Emp, Fam, QoL
127	Lorenzi, 2009 (183)	Canada	All cancer	1975-1995	782	n.a	n.a	Population sample	Edu
128	Löf, 2011 (184)	Sweden	All cancer with HSCT	1978-2001	51	21 [19-24]	10 ± 4.7	Population sample	Emp
129	Lönnerblad, 2022 (185)	Sweden	CNS	n.a	452	n.a	n.a	Matched controls	Emp
130	Lown, 2013 (186)	USA, CCSS	All cancer	1970-1986	10 398	n.a [18-56]	n.a	Population sample, siblings	HR
131	Lubas, 2020 (187)	USA	All cancer	n.a	7312	n.a	8.3	Matched controls	HR
132	Lund, 2015 (188)	Denmark	All cancer	1975-2009	5452	n.a	n.a	Population sample	HR
133	Maas, 2023 (189)	Netherlands	All cancer	1963-2001	1797	35.4 [18-71]	6.75 ± 4.71	Population sample	QoL
134	Mader, 2017 (190)	Switzerland	All cancer	n.a	160	33.5	21.1 ± 2.9	Population sample	Fam
135	Martens, 2014 (191)	Germany	CNS (intracranial germinoma)	1984-2007	33	18 (median [18-38]	n.a	Population sample	QoL
136	Maule, 2017 (192)	Italy	All cancer	1971-2000	637	n.a	n.a	Population sample	Edu

137	Maurice-Stam, 2022 (193)	Netherlands	All cancer	1963-2001	558	25.78 [18.10-30.97]	4.25 ± 3.12	Population sample	Emp
138	Meadows, 1989 (194)	USA	All cancer	1948-1975	95	23.6 [18-35]	6.1	Siblings	Fam
139	Milam, 2018 (195)	USA	All cancer	2000-2007	100	19.9	n.a	Matched controls	HR
140	Mitby, 2003 (196)	USA	All cancer	1970-1986	12 430	n.a [6-59]	n.a	Siblings	Education
141	Mody, 2008 (197)	USA	Hematological (ALL)	1970-1986	4151	21.2	4 (median)	Siblings	Fam
142	Moe, 1997 (198)	Norway	Hematological (ALL)	n.a	94	22	n.a	Matched controls	Edu, Emp
143	Molnar, 2019 (199)	Hungary	All cancer	2007-2010	21	16.22	n.a	Matched controls	QoL
144	Morse, 2022 (200)	USA	Solid (RBL)	n.a	69	10.89	0.3-5.94	Population sample	QoL
145	Mört, 2011 (201)	Finland	nonCNS	n.a	203	14.4	3.9 ± 2.97	Matched controls	QoL
146	Mostow, 1991 (202)	USA	CNS	n.a	342	32	11.3	Siblings	Emp, Fam
147	Mulrooney, 2008 (203)	USA	Hematological (AML)	1970-1986	272	28 [10-49]	7	Siblings, population sample	Emp

148	Musiol 2019 (204)	Poland	CNS	n.a	46	n.a	n.a	Matched controls	QoL
149	Nagarajan, 2003 (205)	USA	OS	1970-1986	733	35.3 [13-51]	13.7	Siblings	Emp, Fam
150	Nayiager, 2017 (206)	Canada	Hematological (ALL)	n.a	75	21.5 (median) [13.5-38]	n.a	Population sample	QoL
151	Nazari, 2014 (207)	Iran	Hematological (ALL)	2010-2011	100	8.97	n.a	Matched controls	QoL
152	Norris, 2010 (208)	Canada	All cancer	1990-2007	17	13.5	n.a	Siblings	QoL
153	Nugent, 2018 (209)	USA	All cancer	n.a	23	23.8 [18-39]	17.4	Matched controls	Emp, Fam
1545	Overbeek, 2010 (210)	Netherlands	All cancer	n.a	107	24 (median)	7 (median)	Siblings	Fam
155	Pang, 2008 (211)	USA	All cancer	1970-1986	10 399	n.a [18-48]	n.a	Siblings	Emp, Fam
156	Park, 2005 (212)	USA	All cancer	1970-1986	12 358	n.a	n.a	Siblings	Fam
157	Pastore, 2001 (213)	Italy	All cancer	n.a	485	24.3 [15.9-41.4]	n.a	Population sample	Edu, Emp
158	Pemberger, 2005 (214)	Austria	All cancer	1975-1995	78	22.6	8.0 ± 5.0	Population sample	QoL

159	Peng, 2021 (215)	China	Hematological (ALL)	n.a	152	23.5	n.a	Population sample	QoL
160	Phillips-Salimi, 2012 (216)	USA	All cancer	n.a	651	33.49 [18-50]	n.a	Population sample	Edu, Emp, Fam, HR
161	Pickering, 2023 (217)	Denmark	CNS	1980-2015	2283	n.a	9.42 ± 5.58	Matched controls	Edu, Emp, Mar
162	Pillon, 2013 (218)	Italy	Hematological (ALL)	1961-1990	141	33 (median)	4.8 (median)	Population sample	Edu, Emp, Fam
163	Plotka, 2021 (219)	Poland	Hematological, CNS	2003-2015	57	20.8 [15-39]	11.9 ± 3.6	Matched controls	Edu, Emp, HR
164	Poretti, 2004 (220)	Switzerland	CNS (craniopharyngeoma)	1980-2002	25	n.a	9.17 ± 4.25	Population sample	QoL
165	Poretti, 2007 (221)	Switzerland	CNS (intraspinal tumor)	1975-2005	28	n.a	n.a	Population sample	QoL
166	Portwine, 2016 (222)	Canada	Solid (neuroblastoma)	1991-2010	99	n.a	3.56 ± 2.37	Population sample	QoL
167	Puhr, 2021 (223)	Norway	CNS	n.a	114	23.4 (18-30)	n.a	Matched controls	Edu, Emp, Fam
168	Pui, 2003 (224)	USA	Hematological (ALL)	1962-1992	584	27 (median) [18-50]	4.5 (median)	Population sample	Emp, Fam
169	Punyko, 2006 (225)	USA	Solid (RMS)	1970-1986	417	26 (median [18-45]	n.a	Siblings	Emp, Fam

170	Radunic, 2022 (226)	Croatia	All cancer	n.a	40	n.a	n.a	Siblings	Edu, Emp, Fam
171	Rebholz, 2011 (227)	Switzerland	All cancer	1976-2003	1049	n.a [20-40]	n.a	Population sample	Edu, Emp, HR
1672	Rebholz, 2012 (228)	Switzerland	All cancer	1976-2003	835	26.1 [20-35]	7.9 ± 4.7	Matched controls	Fam, HR
173	Recklitis, 2010 (229)	USA	All cancer	1970-1986	9126	n.a [18-48]	n.a	Siblings	HR
174	Ribi, 2005 (230)	Switzerland	CNS (MBL)	1980-2000	18	18.9 [8.5-31.9]	6.8	Population sample	QoL
175	Ris, 2019 (231)	USA	CNS (LGG)	1970-1986	181	n.a [27-58]	7.0-8.0	Siblings	Education
176	Rossi, 2021 (232)	Belgium, France	Hematological (ALL)	1971-1998	507	25.2-25.4 [18.1-52.8]	n.a	Matched controls	Fam
177	Sajko, 2012 (233)	Slovenia	All cancer	1978-2008	1647	22.3 [5-66]	8.2 ± 4.9	Population sample	HR
178	Sato, 2018 (234)	Japan	CNS	n.a	38	23.5	12.7 ± 3.6	Population sample	Edu, Emp, Fam
179	Schleicher, 2022 (235)	Germany	Hematological (CML treated with HSCT)	1985-2016	37	29 (median) [18-43]	11 (median)	Population sample	QoL
180	Scholtes, 2019 (236)	Germany	CNS	n.a	270	n.a [25-45]	n.a	Population sample	Edu, Emp

181	Schwartz, 2006 (237)	USA	All cancer	n.a	57	21.7 [18-28]	11.35 ± 3.91	Matched controls	Emp, Fam
182	Seitz, 2010 (238)	Germany	All cancer	n.a	820	30.4	15.78 ± 0.89	Matched controls	QoL
183	Servitzoglou, 2008 (239)	Greece	All cancer	n.a	103	19.8 [15-29]	8.8	Matched controls	Edu, Emp, Fam
184	Souza, 2015 (240)	Brazil	Hematological (ALL), solid (WT)	n.a	60	n.a	n.a	Matched controls	Emp, Fam, QoL
185	Speechley, 2006 (241)	Canada	All cancer	1981-1990	800	n.a	2.2	Matched controls	QoL
186	Stam, 2004 (242)	Netherlands	All cancer	n.a	353	24.3 [17.7-31.1]	7.3 ± 4.7	Matched controls	Edu, Fam, HR, QoL
187	Stefanski, 2021 (243)	USA	Hematological (AML)	1970-1999	482	30 (median) [18-49]	8 (median)	Siblings	Fam
188	Stolley, 2015 (244)	USA	nonCNS	n.a	452	n.a	n.a	Matched controls	Edu, HR
189	Stuber, 2010 (245)	USA	All cancer	1970-1986	6542	31.9 [18-53]	8.2 ± 5.9	Siblings	Emp
190	Sundberg, 2011 (246)	Sweden	All cancer	1985-1999	246	24	9	Matched controls	Edu, Emp, Fam
191	Sylvest, 2021 (247)	Denmark	All cancer (childhood and young adult male survivors)	1978-2016	9353	n.a	n.a	Population sample	Fam

192	Sylvest, 2022 (248)	Denmark	All cancer (childhood and young adult male survivors)	1978-2016	4222	n.a	n.a	Population sample	Fam
193	Tacyildiz, 2021 (249)	Turkey	Solid (OS)	2002-2018	39	17.4	n.a	Siblings	Emp, Fam
194	Tacyildiz, 2022 (250)	Turkey	HEM (NHL)	2003-2019	50	19.09	n.a	Siblings	Edu, Emp, Fam, HR
195	Tao, 1998 (251)	USA	Hematological (ALL)	1970-1987	592	21.8 (median) [18.0-33.2]	n.a	Matched controls	HR
196	Tardy, 2022 (252)	France	Solid (bone tumor)	1987-1999	25	31.3	11.3 ± 3.8	Population sample	QoL
197	Tebbi, 1989 (253)	USA	All cancer	n.a	40	26.4 [18-35]	n.a	Matched controls	Emp, Fam
198	Teckle, 2018 (254)	Canada	All cancer	1970-1999	3958	38.9	14.4 ± 3.7	Population sample	Fam
199	Teeter, 1987 (255)	USA	All cancer	1945-1975	263	32.8 [23-54]	n.a	Siblings	Fam
200	Teta, 1986 (256)	USA	All cancer	1945-1974	450	n.a	n.a	Siblings	Emp, HR
201	Tillery, 2022 (257)	USA	All cancer	n.a	171	17.15 [12-23]	n.a	Matched controls	HR
202	Tonning Olsson,	USA	Solid (WT)	1963-2005	158	33	3.6 ± 2.6	Matched controls	Edu, Fam

	2019 (258)								
203	Tremolada, 2016 (259)	Italy	All cancer	n.a	205	18.96	7.09 ± 4.38	Matched controls	Edu, Emp, Fam, QoL
204	Tremolada, 2022 (260)	Italy	All cancer	n.a	205	18.96	7.09 ± 4.38	Matched controls	Edu, Emp, Mar
205	Uderzo, 2011 (261)	Italy	Hematological with HSCT	1985-1998	55	25 (median) [18-40]	5.2(median) ±0.8	Matched controls	Edu, Emp
206	Vaarwerk, 2018 (262)	Netherlands, UK	Solid (RMS)	1990-2010	65	16.0-19.6 (median)	5.1-6.4 (median)	Population sample	QoL
207	Van der Plas, 2021 (263)	Canada	Hematological (ALL)	n.a	71	11.9	3.8	Matched controls	QoL
208	Van Dijk, 2007 (264)	Netherlands	All cancer	n.a	60	24.6 [17-39]	8.3 ± 4.5	Population sample	QoL
209	Van Dijk, 2018 (265)	Netherlands	All cancer (females)	1963-2002	1106	24 (median)	7 (median)	Matched controls	Fam
210	Van Erp, 2021 (266)	Netherlands	All cancer	n.a	151	24.1	10.5 ± 4.5	Population sample	QoL
211	Van Litsenburg, 2013 (267)	Netherlands	Hematological (ALL)	n.a	33	9.3	5.5 ± 3.2	Population sample	QoL
212	Verril, 2000 (268)	USA	All cancer	n.a	26	n.a	n.a	Matched controls	HR

213	Wasilewski-Masker, 2014 (269)	USA	All cancer (males)	1970-1986	6497	37.9	7.6-9.0	Siblings	Fam
214	Weintraub, 2010 (270)	Israel	Solid (RBL)	n.a	46	8.5	n.a	Population sample	QoL
215	Weintraub, 2019 (271)	Israel	Solid (RBL)	n.a	27	8.28	2.26 ± 1.6	Matched cointrols	QoL
216	Wengenroth, 2014 (272)	Switzerland	All cancer	1976-2005	1096	26.6	7.8 ± 4.8	Population sample	Edu, Fam
217	Wengenroth, 2016 (273)	Switzerland	All cancer	1976-2005	1506	29.3 [18-55]	n.a	Siblings	Edu, Emp, Fam
218	Winterling, 2015 (274)	Sweden	All cancer	n.a	48	16 [12-21]	11	Matched controls	Fam
219	Winterling, 2018 (275)	Sweden	Hematological with HSCT	1978-2008	59	28	11 ± 4.7	Population sample	Edu, Emp, Fam
220	Wong, 2016 (276)	UK	Solid (WT)	1940-1991	947	28.3	3.3 ± 2.9	Population sample	Fam, HR, QoL
221	Yagci-Küpeli, 2012 (277)	Turkey	All cancer	n.a	302	13 (median) [8-18]	6 (median)	Matched controls	QoL
222	Yagci-Küpeli, 2013 (278)	Turkey	Solid	n.a	201	23 [18-39]	10	Population sample	Emp, Fam, HR

223	Yen, 2020 (279)	USA	Hematological	1982-2005	1228	28.4-29.2	n.a	Matched controls	QoL
224	Yilmaz, 2014 (280)	Turkey	All cancer	n.a	56	n.a [7-18]	n.a	Matched controls	QoL
225	Zeltzer, 1997 (281)	USA	Hematological (ALL)	n.a	580	22.6 [18.0-33.3]	n.a	Siblings	Emp, Fam
226	Zeltzer, 2008 (282)	USA	All cancer	1970-1986	7147	32 (median) [18-58]	7 (median)	Siblings	QoL