CONTROLLO DI MALATTIA NEI NEUROBLASTOMA (NB) REFRATTARI E RECIDIVATI (RR): UNA QUESTIONE APERTA

FAD SINCRONA 10 Luglio 2026

Neuroblastoma Refrattario: quali opzioni

Dr.ssa Stefania Sorrentino

Disclosures STEFANIA SORRENTINO

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
RECORDATI Rare Disease			X				

...NB Refrattari ... *chi sono* ???

Cancer. 2022 November 01; 128(21): 3775–3783. doi:10.1002/cncr.34445.

Early Phase Clinical Trial Eligibility and Response Evaluation Criteria for Refractory, Relapsed or Progressive Neuroblastoma: A Consensus Statement from the National Cancer Institute-Clinical Trials Planning Meeting

Julie R. Park, MD[1], Judith G. Villablanca, MD[2], Barbara Hero, MD[3], Brian H. Kushner, MD[4], Keith Wheatley, DPhil[5], Klaus H. Beiske, MD, PhD[6] [Prof.], Ruth L. Ladenstein, MD[7] [Prof.], Sylvain Baruchel, MD[8], Margaret E. Macy, MD[9], Lucas Moreno, MD, PhD[10], Nita L. Seibel,

Disease Characteristics Required for Eligibility Criteria (Table 2)

Based on data suggesting differences in prognosis,[4, 12, 49–51] patients will be classified into distinct groups (Table 2). The Progressive Disease Group includes patients that develop INRC defined PD[9] during any phase of treatment for newly diagnosed NB, and those patients who develop PD or recurrence of disease after completion of therapy. The Refractory Disease Group encompasses patients with incomplete responses of high-risk NB to all treatments but who never developed PD. This group is subdivided into two

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RESEARCH ARTICLE

Management and outcome of children with high-risk neuroblastoma: insights from the Spanish Society of Pediatric Hematology and Oncology (SEHOP) neuroblastoma group on refractory and relapse/progressive disease

Blanca Martínez de las Heras[1,7] · Pedro M Rubio-Aparicio[2] · Alba Rubio-San-Simón[3] · Lucas Moreno[4] · Paula Mazorra[4] · Ricardo López Almaraz[5] · Mercedes Llempén López[6] · Julia Balaguer Guill[1,7] · Vanessa Segura[7] · Mar Bermúdez[8] · Irene Jiménez[8] · Désirée Ramal[7] · Adela Cañete[1,7]

sus proposal from the National Cancer Institute (NCI) [14].
Refractory disease was defined as incomplete response of HR-NB to front-line treatment (at least 4 cycles of induction), without new lesions nor increase of disease burden. Progression was considered, per INRC definition [15], as appearance of new lesions, or objective increase of known lesions. Subsequent events in the same patient were considered as relapses/progressions during the study period.

Journal of *Clinical Medicine*

MDPI

Systematic Review

Assessment of Chemo-Immunotherapy Regimens in Patients with Refractory or Relapsed Neuroblastoma: A Systematic Review with Meta-Analysis of Critical Oncological Outcomes

Nur Olgun [1,2,*], Mehmet Emin Arayici [3,4], Deniz Kızmazoglu [1] and Refik Emre Cecen [1]

in relevant biomarkers, as described in prior consensus guidelines [14,15]. Refractory neuroblastoma was defined as the failure to achieve complete or partial response after at least one line of standard treatment, including chemotherapy, as outlined by previous studies and clinical criteria [14,15]. Only studies explicitly reporting on these patient populations

ELSEVIER

European Journal of Cancer

journal homepage: www.ejcancer.com

Review

Current treatment strategies for first relapse of high-risk neuroblastoma

Sveva Castelli [a,1], Franziska Schulze [a,1], Theresa M. Thole-Kliesch [a,1], Kathy Astrahantseff [a], Giuseppe Barone [b], Maja Beck-Popovic [c], Pablo Berlanga [d], Selim Corbacioglu [e], Matthias Fischer [f,g], Marion Gambart [h], Sally L. George [i,j], Louis Chesler [i,j], Juliet C. Gray [k], Barbara Hero [l], Annette Künkele [a,m,n], Tim Flaadt [o], Peter Lang [o], Holger N. Lode [p], Jan J. Molenaar [q,r], Gudrun Schleiermacher [s], Carolina Rosswog [f,g,l], Lucas Moreno [t], Cormac Owens [u], Alba Rubio-San-Simón [v], Johannes H. Schulte [n,o], Thorsten Simon [l], Deborah A. Tweddle [w], Hedwig E. Deubzer [a,m,n,x,2,*], Angelika Eggert [a,m,n,y,2], on behalf of the SIOPEN New Drug Development, Immunotherapy and Relapse Groups

relapse trials, creating a heterogeneous patient population with (1) progressive disease during first-line induction therapy, (2) refractory disease (up to 20 % of cases) with insufficient metastatic response to first-line induction therapy, (3) first HRNB relapse, (4) first metastatic relapse of initially localized disease and (5) second or subsequent HRNB

Received: 22 February 2016 | Revised: 14 June 2016 | Accepted: 5 July 2016 | Published on: 24 August 2016

DOI: 10.1002/pbc.26192

RESEARCH ARTICLE

WILEY Pediatric Blood & Cancer

Outcome of children with relapsed or refractory neuroblastoma: A meta-analysis of ITCC/SIOPEN European phase II clinical trials

Lucas Moreno[1] | Herve Rubie[2] | Amalia Varo[1] | Marie Cecile Le Deley[3] | Loredana Amoroso[4] | Aurelie Chevance[4] | Alberto Garaventa[5] | Marion Gambart[2] | Francisco Bautista[1] | Dominique Valteau-Couanet[6] | Birgit Geoerger[6] | Gilles Vassal[6] | Xavier Paoletti[4] | Andrew D. J. Pearson[7]

Most trials include two populations of children: (i) those experiencing relapse/progression after a complete or partial response and (ii) those with disease that is refractory to frontline therapy (e.g., no response [NR], mixed response [MR], or insufficient partial response [PR] but without relapse/progression).

Quindi…

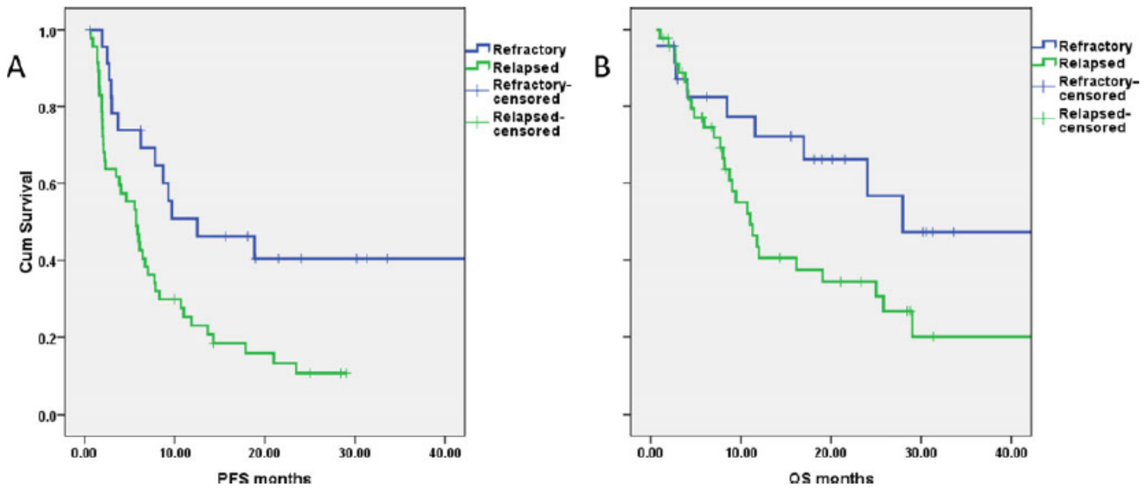
Stato di malattia	Definizione usata in letteratura
Refrattario	Risposta incompleta dopo terapia di induzione (dopo ≥4 cicli di induzione), senza nuove lesioni o progressione delle lesioni note
Recidivato	Ricomparsa della malattia dopo una precedente risposta al trattamento
Progressione	Nuove lesioni o aumento obiettivo di lesioni già note

→ 20% dei NB HR

→ 50% dei NB HR

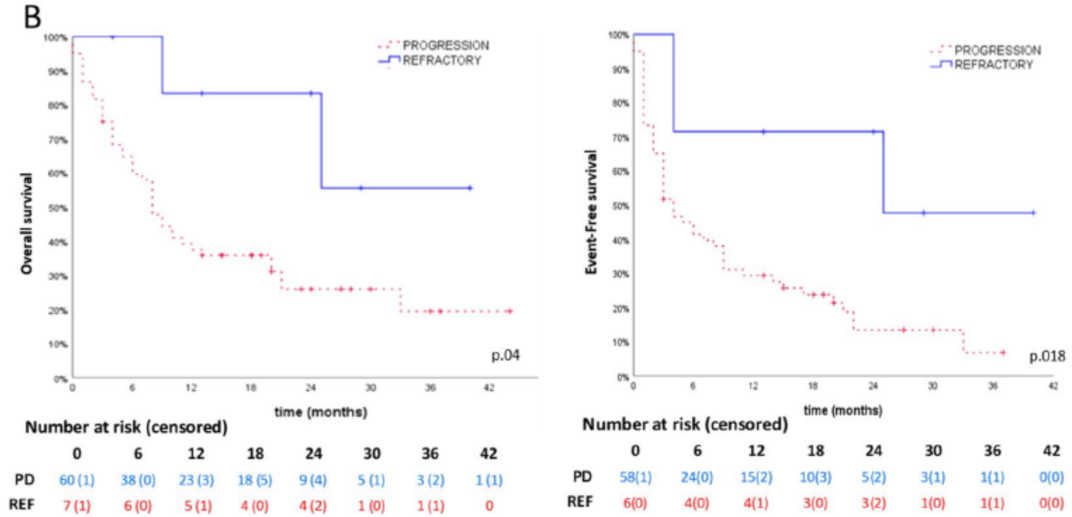
Outcome

Moreno 2017



- PFS: 12,5 mesi nel refrattario vs 5,7 mesi nel relapsed
- OS mediana:27,9 mesi vs 11,0 mesi

de las Heras 2025



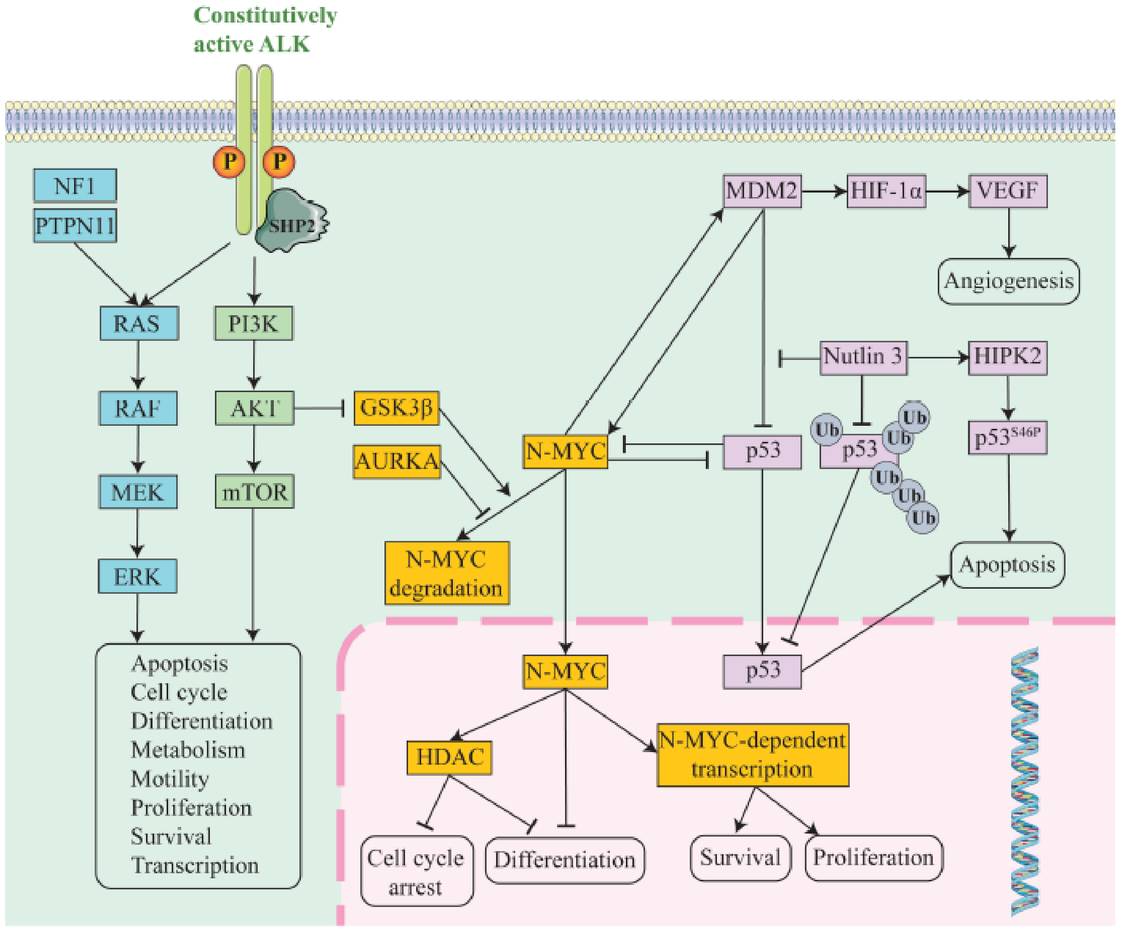
- OS 71.4% vs. 28.3%
- EFS 51.7% vs. 16.7%

Perché ci sono NB refrattari

La refrattarietà non dipende da un singolo driver, ma da un sistema adattativo in cui cellule tumorali e stroma cooperano per mantenere sopravvivenza, evasione immunitaria e ricrescita dopo terapia

- **MYCN/ ALK / TERT / p53 / instabilità cromosomica** → dedifferenziazione e proliferazione
- **Aberrazioni cromosomiche e pathway di resistenza** come RAS/MAPK, PI3K/AKT/mTOR e MDM2
- **difetti di differenziazione** delle cellule derivate dalla cresta neurale
- **rimodellamento del microambiente**
- **rewiring metabolico**

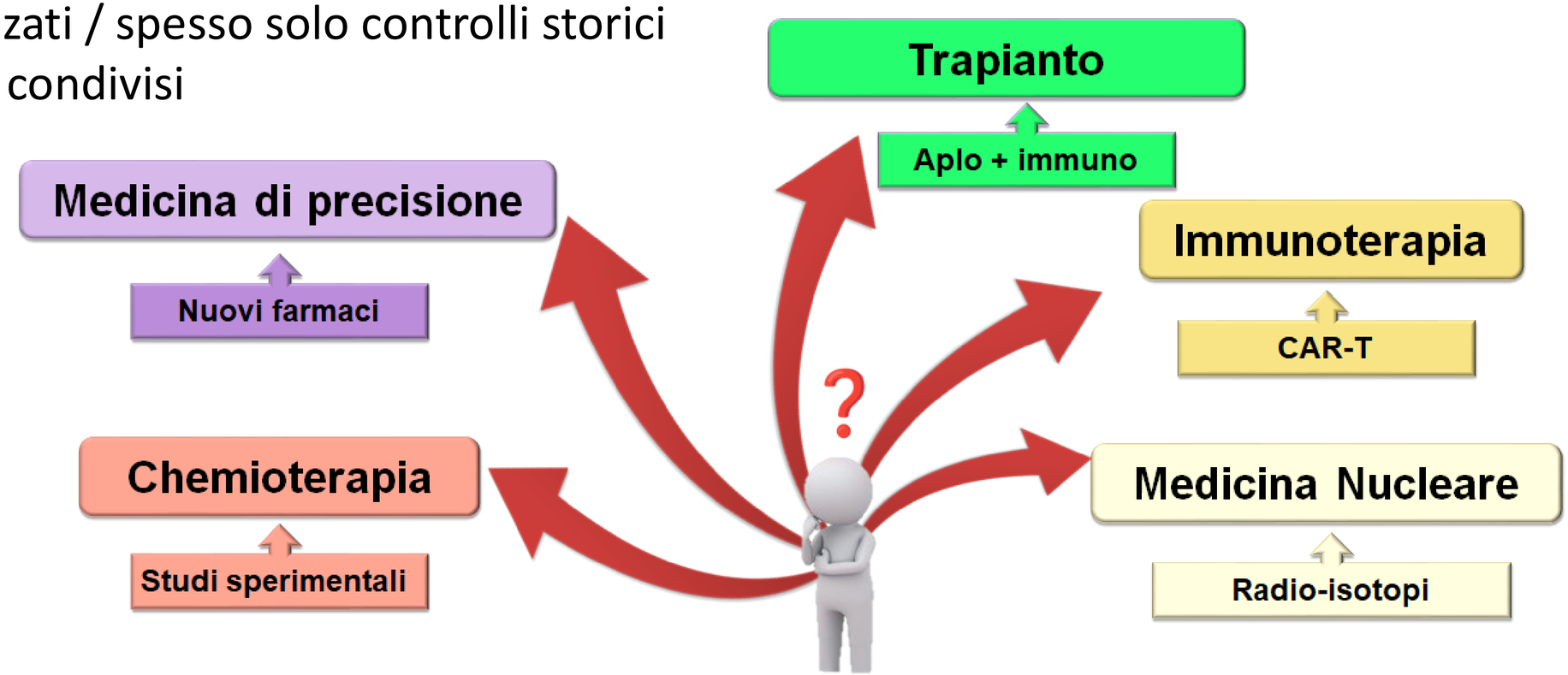
approcci combinati
profilazione molecolare per target terapeutici



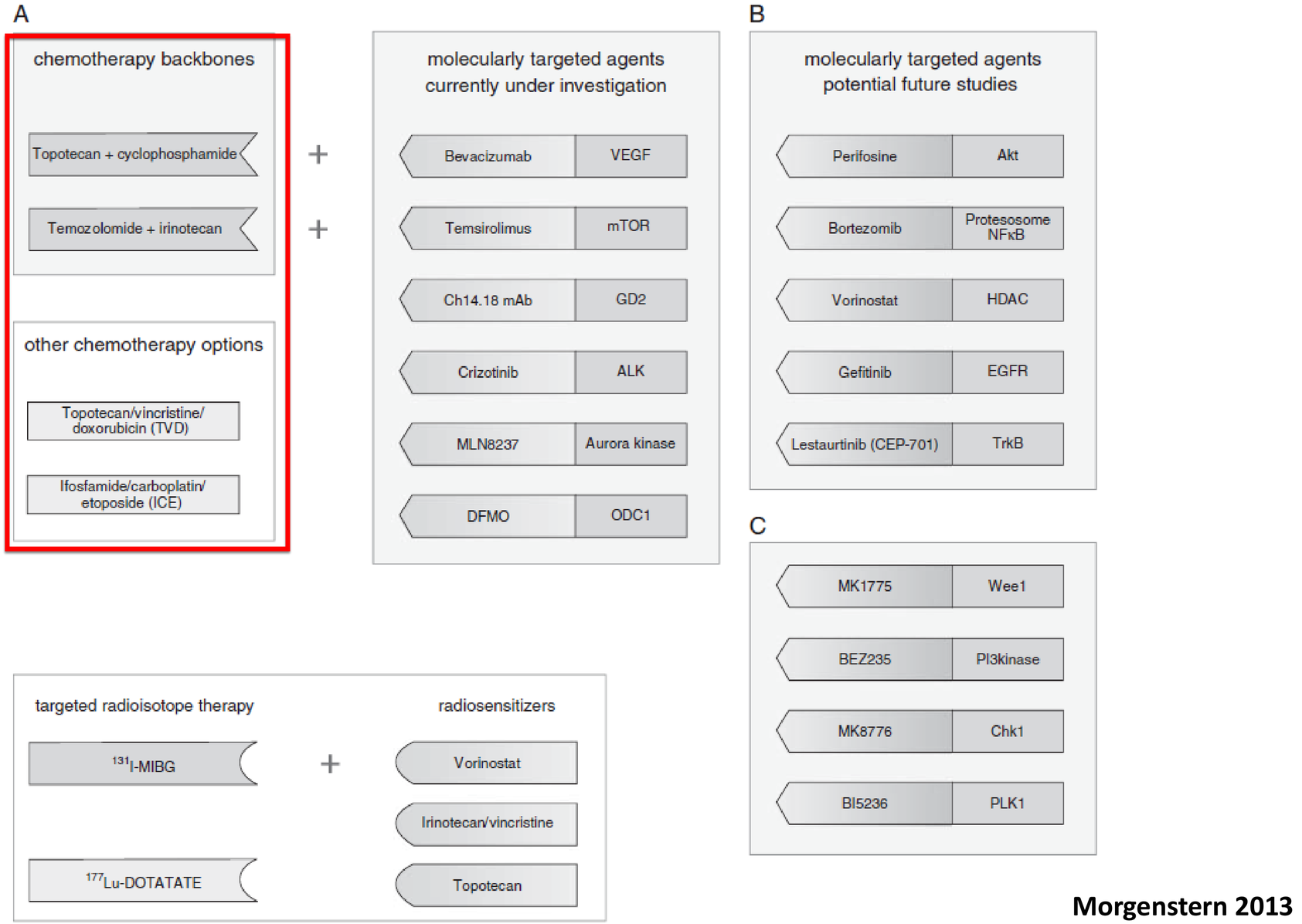
Chen2025

Perché è difficile trattare un NB refrattario

- Recidivati / Refrattari / PM trattati allo stesso modo
- Pochi farmaci a disposizione
- Pochi studi randomizzati / spesso solo controlli storici
- Assenza di protocolli condivisi



Chemioterapia

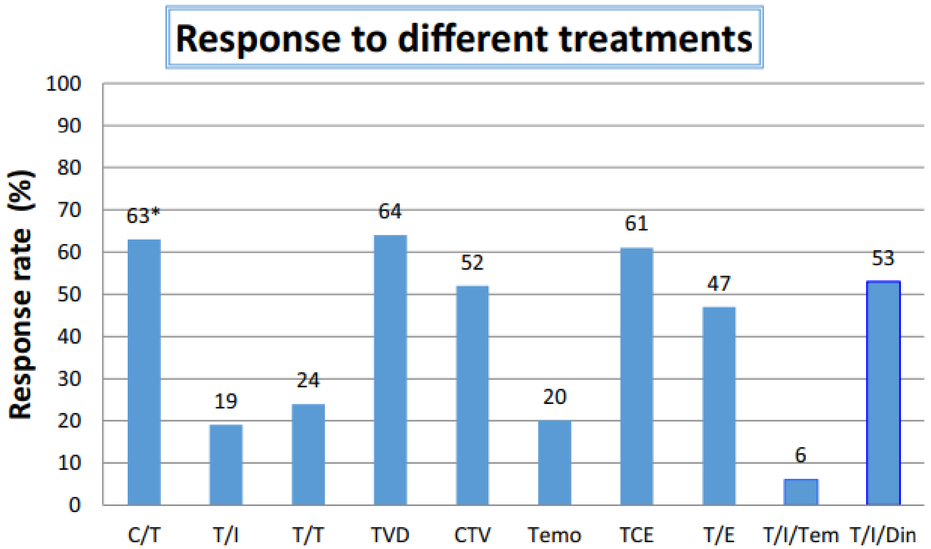


Morgenstern 2013

Summary of response assessment in each study.

Study	Drug	Timing of response assessment	Response rate (%)
Ashraf 2013 [16]	Topotecan/cyclophosphamide	Best	63[a]
Bagatell 2011 [17]	Temozolomide/irinotecan	After 3 cycles	19
Di Giannatale 2014 [18]	Temozolomide/topotecan	Best	24
Garaventa 2003 [19]	Topotecan/vincristine/doxorubicin	Best	64
Kushner 2010 [20]	Cyclophosphamide/topotecan/vincristine	Best	52
Rubie 2006 [21]	Temozolomide	Best	20
Simon 2007 [22]	Topotecan/etoposide	Best	47
Simon 2007 [23]	Topotecan/cyclophosphamide/etoposide	Best	61
Mody 2017 [24]	Temozolomide/irinotecan	Best	6
	+ temsirolimus		53
	+ dinutuximab		

[a] Denotes that the response includes mixed response.



European Journal of Cancer 111 (2019) 50–58

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Available online at www.sciencedirect.com

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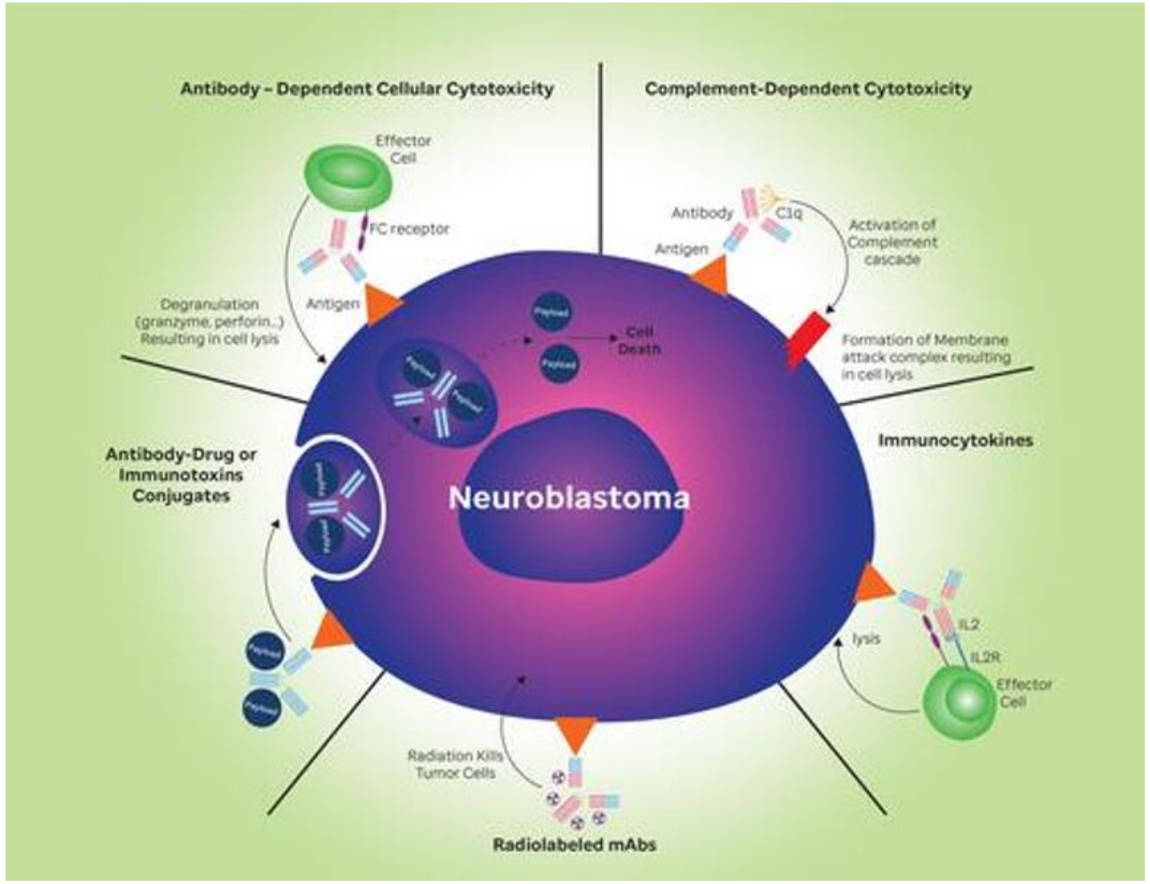
journal homepage: www.ejcancer.com

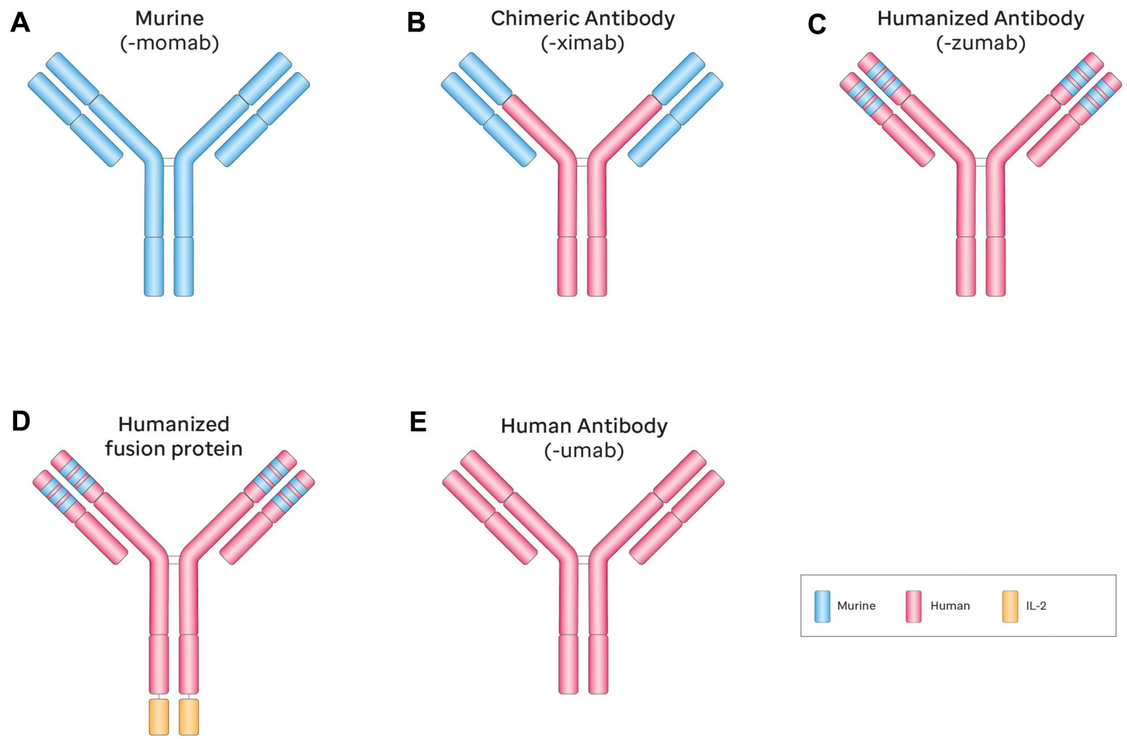
Review

A systematic review of re-induction chemotherapy for children with relapsed high-risk neuroblastoma

Fiona Herd [a], Nermine O. Basta [b], Richard J.Q. McNally [b], Deborah A. Tweddle [a,c,*]

Immunoterapia





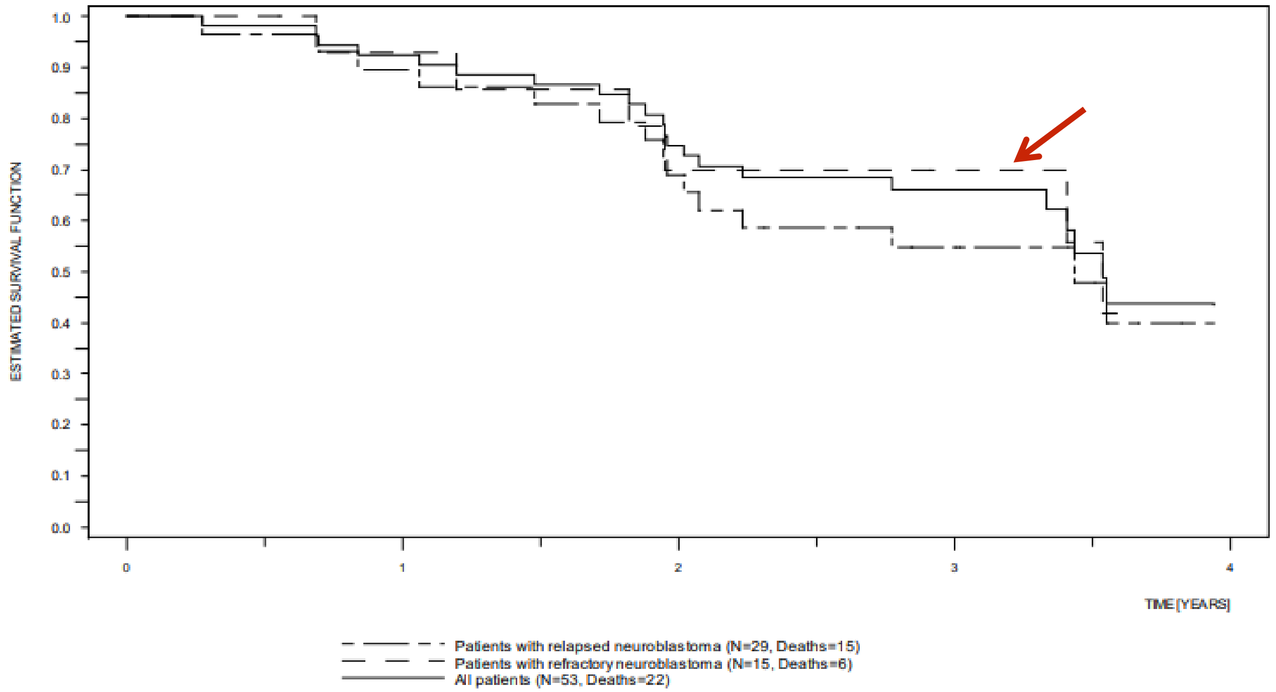
Furman 2021

Study APN311-202

A Phase I/II Dose Schedule Finding Study of ch14.18/CHO Continuous Infusion Combined with Subcutaneous Aldesleukin (IL-2) in Patients with Primary Refractory or Relapsed Neuroblastoma

Study APN311-303

Retrospective analysis of data collected during the administration of ch14.18/CHO continuous infusion combined with subcutaneous aldesleukin (IL-2) in patients with high risk neuroblastoma under a compassionate use program



Analysis Populations			APN311-303 N=29	APN311-202 N=19	APN311-303 N=15	APN311-202 N=25
			Relapsed patients		Refractory patients	
	EFS	1 year	44.8%	42.1%	58.2%	60.0%
		2 years	31.0%	36.8%	29.1%	55.7%
		3 years	24.1%	36.8%	29.1%	44.6%
	OS	1 year	89.7%	73.7%	92.9%	100.0%
		2 years	69.0%	42.1%	69.8%	78.3%
		3 years	54.7%	42.1%	69.8%	62.5%

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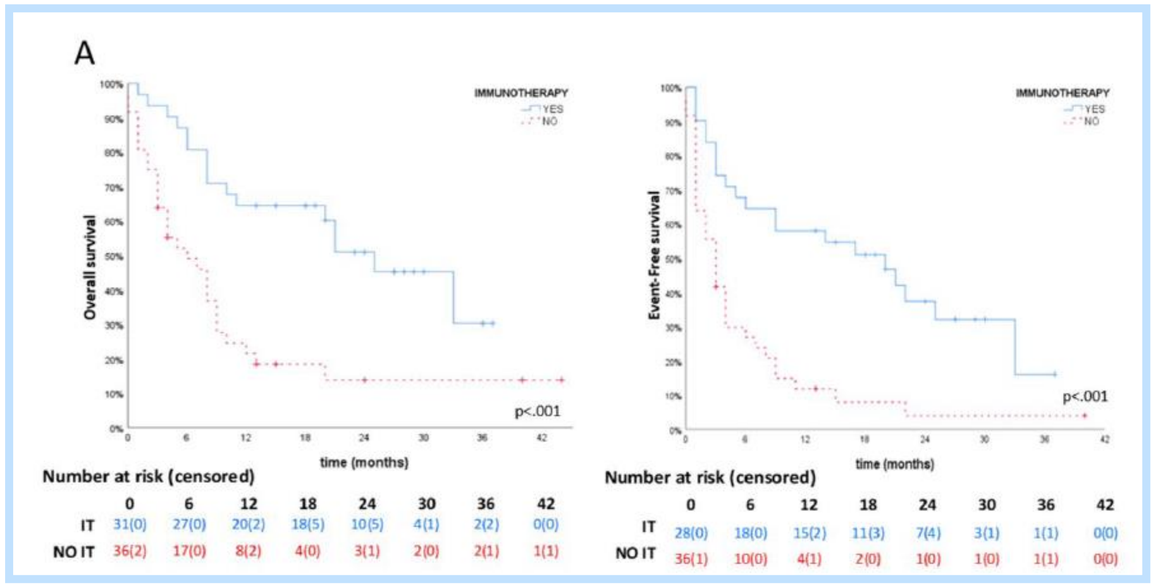
https://doi.org/10.1007/s12094-025-03853-w

RESEARCH ARTICLE

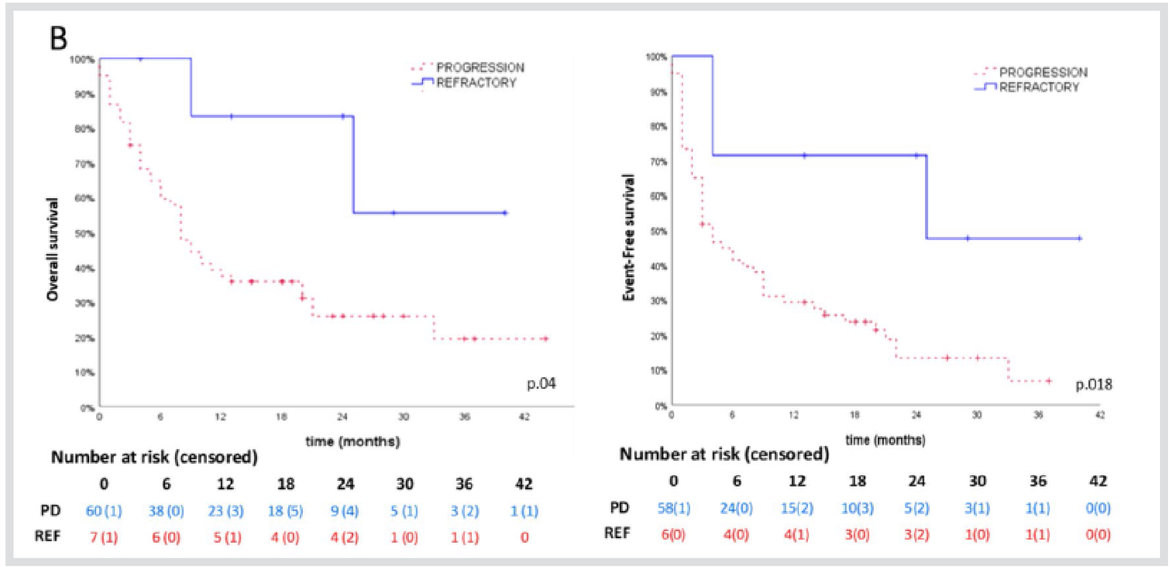
Management and outcome of children with high-risk neuroblastoma: insights from the Spanish Society of Pediatric Hematology and Oncology (SEHOP) neuroblastoma group on refractory and relapse/progressive disease

Blanca Martínez de las Heras[1,7] · Pedro M Rubio-Aparicio[2] · Alba Rubio-San-Simón[3] · Lucas Moreno[4] · Paula Mazorra[4] · Ricardo López Almaraz[5] · Mercedes Llempén López[6] · Julia Balaguer Guill[1,7] · Vanessa Segura[7] · Mar Bermúdez[8] · Irene Jiménez[8] · Désirée Ramal[7] · Adela Cañete[1,7]



l'uso di anti-GD2 si associava a OS 48,4% vs 19,4% ed EFS 35,5% vs 8,3%

7 refrattari



refractory vs progressive
OS 71.4% vs. 28.3%, P = 0.034
EFS 51.7% vs. 16.7%, P = 0.034

Journal of *Clinical Medicine* 2023 MDPI

Article

Dinutuximab Beta Maintenance Therapy in Patients with High-Risk Neuroblastoma in First-Line and Refractory/Relapsed Settings—Real-World Data

Aleksandra Wieczorek [1,2,*], Urszula Żebrowska [2], Marek Ussowicz [3], Agnieszka Sokół [3], Marzena Stypińska [4], Bożenna Dembowska-Bagińska [4], Katarzyna Pawińska-Wąsikowska [1,2] and Walentyna Balwierz [1,2]

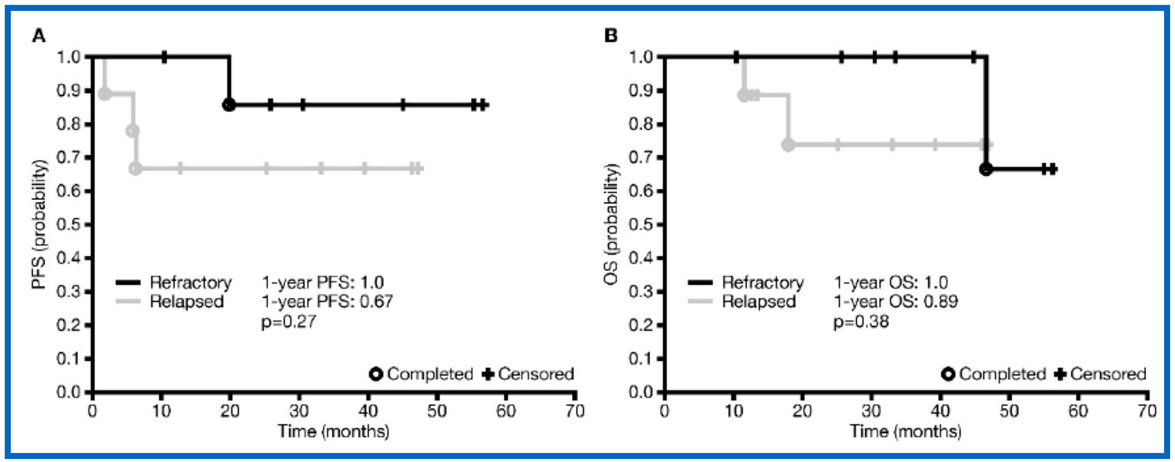
Dinutuximab beta combined with chemotherapy in patients with relapsed or refractory neuroblastoma

Aleksandra Wieczorek [1,2*], Anna Zaniewska-Tekieli [2], Karoline Ehlert [3], Katarzyna Pawinska-Wasikowska [1,2], Walentyna Balwierz [1,2†] and Holger Lode [3†]

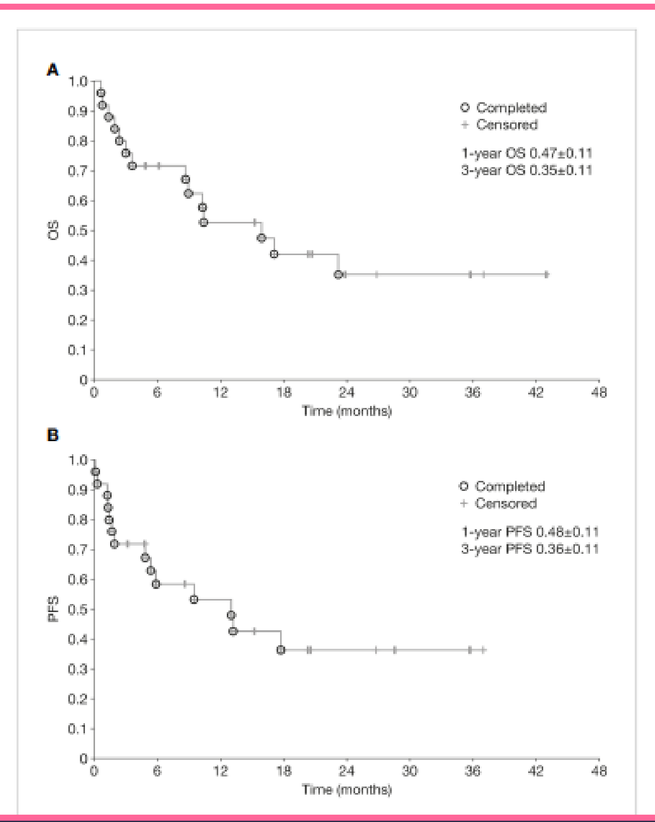
frontiers | Frontiers in Oncology

TYPE Original Research
PUBLISHED 03 February 2023
DOI 10.3389/fonc.2023.1082771

	Relapsed *n* (%)	Refractory *n* (%)
Total number of patients	8	9



Per dinutuximab beta per relapsed/refractory, i best response rates erano 28,6–54,8% e l'OS a 3 anni 54–86%, con risultati migliori nei refrattari rispetto ai relapsed **WIECZOREK 2025**.



2020

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

Rajen Mody, MS, MD[1]; Alice L. Yu, MD, PhD[2,3]; Arlene Naranjo, PhD[4]; Fan F. Zhang, MS[5]; We
Barry L. Shulkin, MBA, MD[7]; Marguerite T. Parisi, MS, MD[8]; Sabah-E-Noor Servaes, MD[9]; Mitc
Jacquelyn A. Hank, PhD[10]; Mildred Felder, BS[10]; Jennifer Birstler, MS[10]; Paul M. Sondel, MD,
Julia Glade-Bender, MD[12]; Howard Katzenstein, MD[13]; John M. Maris, MD[9]; Julie R. Park, MD[8]

Disease status at enrollment		
Relapsed	22	41.5
Refractory/PD	31	58.5

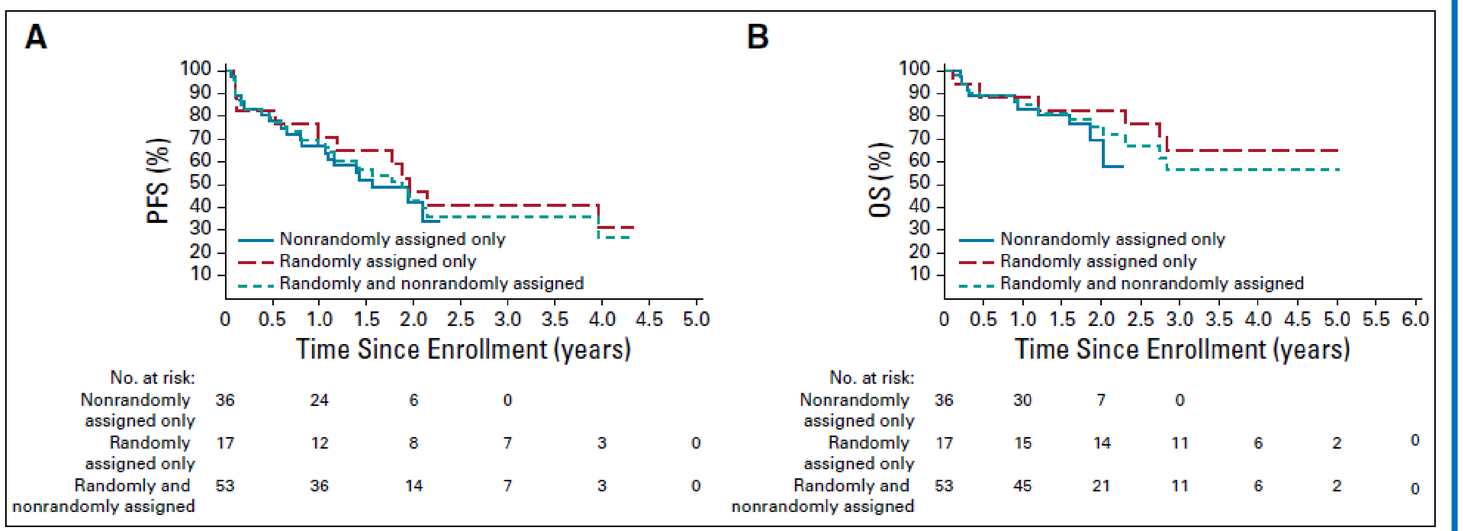


FIG 2. Survival by ANBL1221 cohort. (A) Progression-free survival (PFS) and (B) overall survival (OS) for patients treated in the initial (randomly assigned) cohort, expansion (nonrandomly assigned) cohort, and combined cohort.

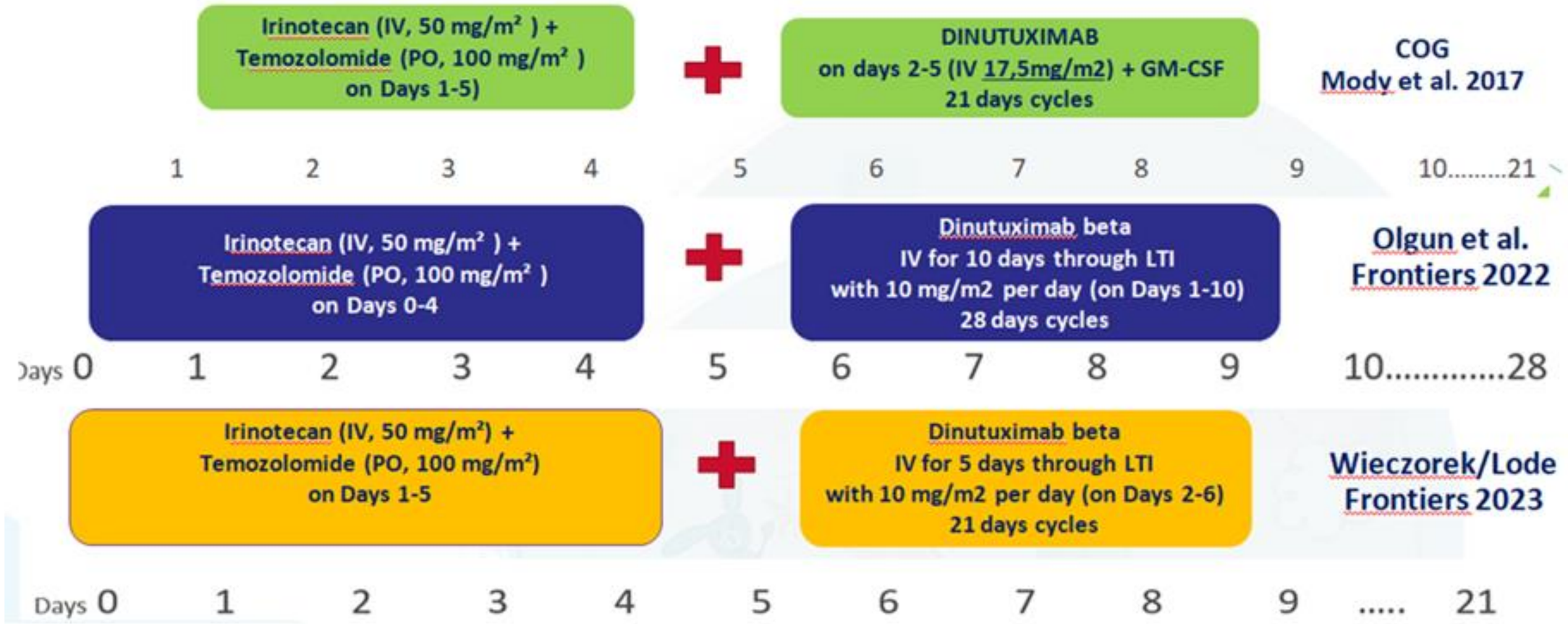
frontiers | Frontiers in Oncology 2022

Dinutuximab beta plus conventional chemotherapy for relapsed/refractory high-risk neuroblastoma: A single-center experience

Nur Olgun[1*], Emre Cecen[1], Dilek Ince[1], Deniz Kizmazoglu
Birsen Baysal[1], Ayse Onal[1], Ozhan Ozdogan[2],
Handan Guleryuz[3], Riza Cetingoz[4], Ayse Demiral[4],
Mustafa Olguner[5], Ahmet Celik[6], Serra Kamer[7],
Erdener Ozer[8], Zekiye Altun[9] and Safiye Aktas[9]

treatments, hence concealing real antitumor activity [11].

Recently, other European centers have reported retrospective data from patients treated with dB and chemotherapy [12–14]. Olgun et al. report retrospective data from 19 patients with relapsed ($n = 10$) or refractory ($n = 9$) high-risk neuroblastoma, treated in a single institution with dB combined with various chemotherapy backbones with a 63% reported ORR. Nonetheless, it seems most patients had controlled disease at the time chemo-immunotherapy was started, thus potentially


Irinotecan (IV, 50 mg/m²) +
Temozolomide (PO, 100 mg/m²)
on Days 1-5)
DINUTUXIMAB
on days 2-5 (IV 17,5mg/m2) + GM-CSF
21 days cycles
COG
Mody et al. 2017
1 2 3 4 5 6 7 8 9 10.....21
Irinotecan (IV, 50 mg/m²) +
Temozolomide (PO, 100 mg/m²)
on Days 0-4
Dinutuximab beta
IV for 10 days through LTI
with 10 mg/m2 per day (on Days 1-10)
28 days cycles
Olgun et al.
Frontiers 2022
Days 0 1 2 3 4 5 6 7 8 9 10.....28
Irinotecan (IV, 50 mg/m²) +
Temozolomide (PO, 100 mg/m²)
on Days 1-5
Dinutuximab beta
IV for 5 days through LTI
with 10 mg/m2 per day (on Days 2-6)
21 days cycles
Wieczorek/Lode
Frontiers 2023
Days 0 1 2 3 4 5 6 7 8 9 21

cancers 2023

MDPI

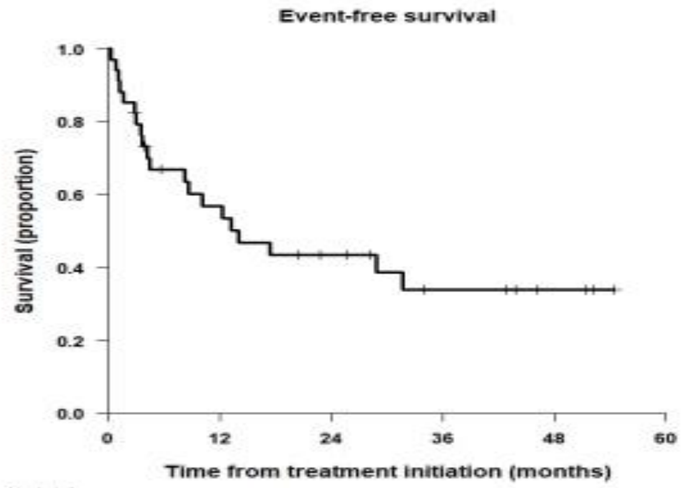
Article

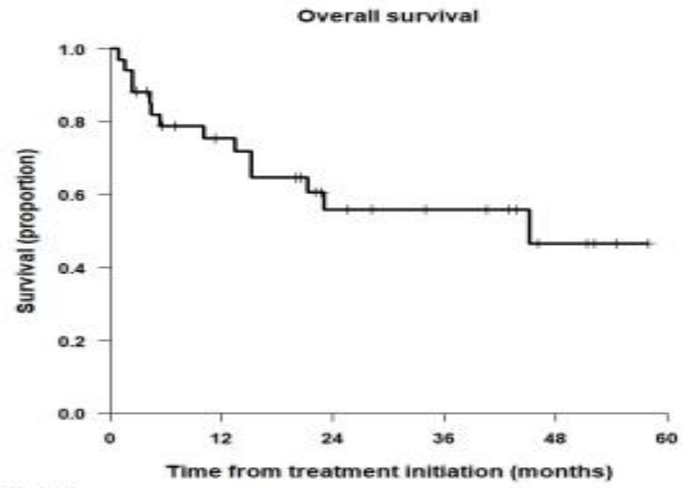
Early Salvage Chemo-Immunotherapy with Irinotecan, Temozolomide and Naxitamab Plus GM-CSF (HITS) for Patients with Primary Refractory High-Risk Neuroblastoma Provide the Best Chance for Long-Term Outcomes

Juan Pablo Muñoz, Cristina Larrosa, Saray Chamorro, Sara Perez-Jaume, Margarida Simao, Nazaret Sanchez-Sierra, Amalia Varo, Maite Gorostegui, Alicia Castañeda, Moira Garraus, Sandra Lopez-Miralles and Jaume Mora *

34 pazienti

Naxitamab è un **anticorpo monoclonale umanizzato diretto contro GD2**, approvato dalla **Food and Drug Administration (FDA)** per l'impiego in associazione con **GM-CSF** nei pazienti che abbiano ottenuto una risposta parziale o una risposta minore ai trattamenti precedenti, oppure che presentino una malattia recidivata o refrattaria stabile limitata all'osso o al midollo osseo.





Immunoterapia

ORR was :
58% in patients with refractory disease
42% in patients with relapsed disease

Article

https://doi.org/10.1038/s41467-025-56619-x

The anti-GD2 monoclonal antibody naxitamab plus GM-CSF for relapsed or refractory high-risk neuroblastoma: a phase 2 clinical trial

Received: 19 January 2024

Accepted: 20 January 2025

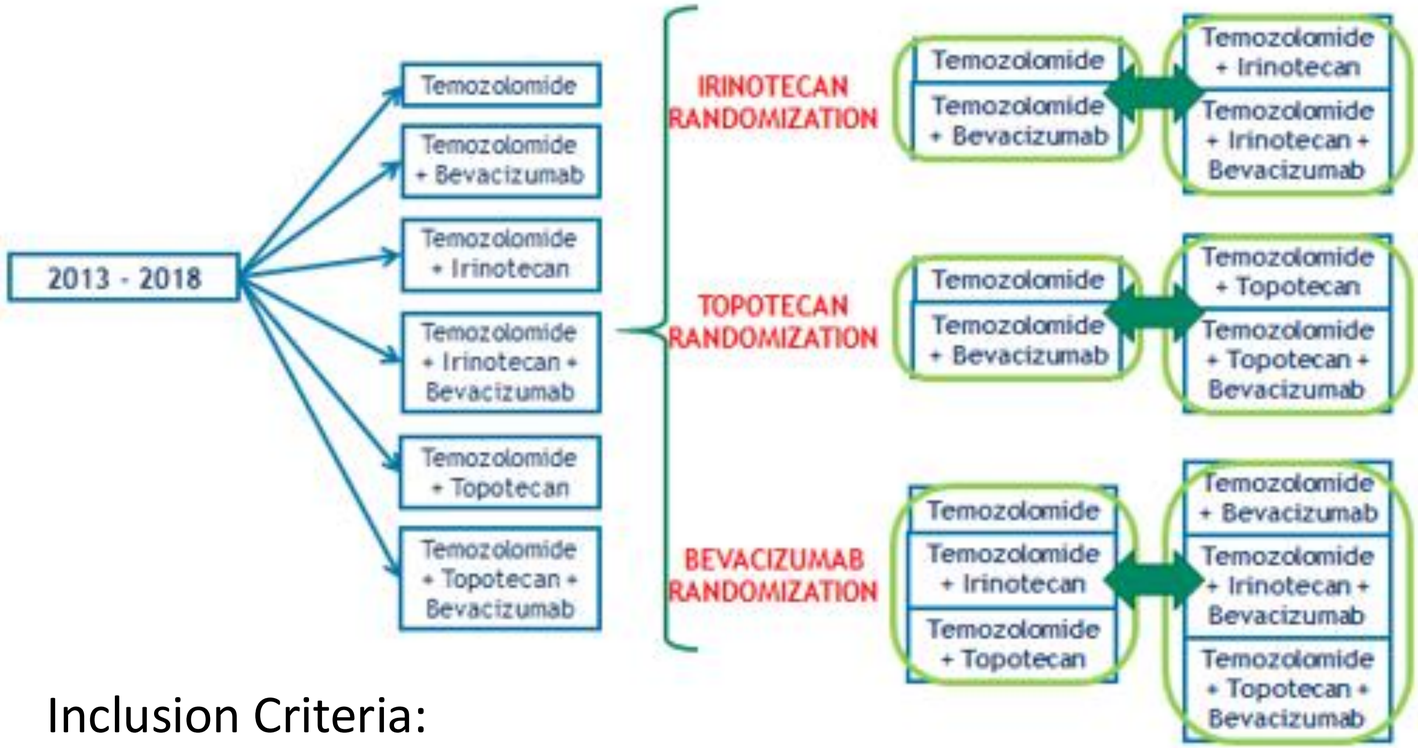
Published online: 14 February 2025

Jaume Mora[1], Godfrey C. F. Chan[2,3], Daniel A. Morgenstern[4], Loredana Amoroso[5,6], Karsten Nysom[7], Jörg Faber[8], Arthur Wingerter[8], Melissa K. Bear[9], Alba Rubio-San-Simon[10], Blanca Martínez de Las Heras[11], Karen Tornøe[12], Maria Düring[12] & Brian H. Kushner[13]

Table 2 | Best responses overall and by disease status in 52 patients treated with naxitamab plus GM-CSF

Patient population	Endpoint	Patients	
		n (%)	95% CI, %
Overall (*N* = 52)	CR	20 (39)	25–53
	PR	6 (12)	4–23
	MR	5 (10)	3–21
	SD	10 (19)	10–33
	PD	8 (15)	7–28
	NE	3 (6)	–
ORR	CR + PR	26 (50)	36–64
Disease status			
Refractory neuroblastoma (*n* = 26)	CR	12 (46)	27–67
	PR	3 (12)	2–30
	MR	3 (12)	2–30
	SD	3 (12)	2–30
	PD	4 (15)	4–35
	NE	1 (4)	–
ORR	CR + PR	15 (58)	37–77
Relapsed neuroblastoma (*n* = 26)	CR	8 (31)	14–52
	PR	3 (12)	2–30
	MR	2 (8)	1–25
	SD	7 (27)	11–48
	PD	4 (15)	4–35
	NE	2 (8)	–
ORR	CR + PR	11 (42)	23–63

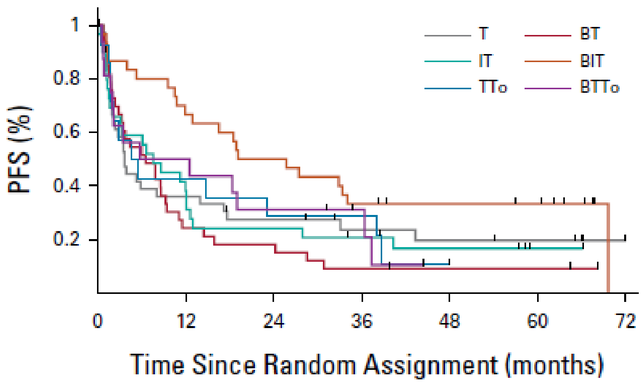
Beacon trial (2013-2018)



BEACON-Neuroblastoma

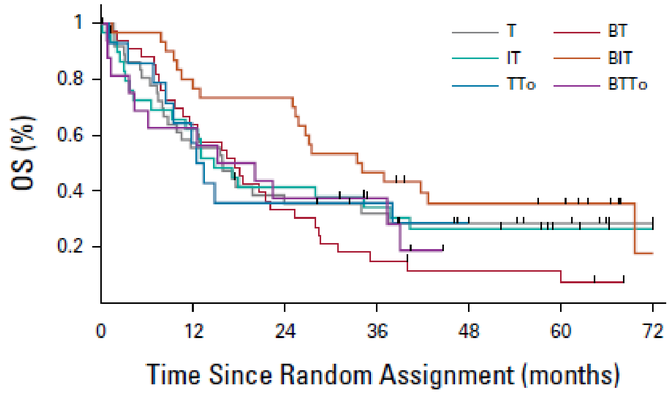
Inclusion Criteria:
High-risk neuroblastoma, 1–21 years
Relapsed or refractory to first-line therapy
No prior treatment with temozolomide, irinotecan, bevacizumab

Beacon trial (2013-2018)



No. at risk:

T	36	(23)	13	(3)	9	(1)	6	(1)	5	(0)	4	(0)	1
BT	34	(25)	8	(2)	6	(3)	3	(0)	2	(0)	2	(0)	0
IT	30	(18)	11	(4)	7	(1)	5	(1)	4	(0)	1	(0)	0
BIT	30	(10)	20	(5)	15	(5)	10	(0)	8	(0)	7	(1)	0
TTo	14	(8)	6	(2)	4	(0)	4	(2)	0	(0)	0	(0)	0
BTTo	16	(8)	8	(3)	5	(0)	3	(2)	0	(0)	0	(0)	0



No. at risk:

T	36	(16)	20	(7)	12	(1)	9	(1)	7	(0)	5	(0)	1
BT	34	(12)	21	(10)	11	(6)	5	(1)	3	(1)	2	(0)	0
IT	30	(11)	18	(6)	12	(2)	9	(2)	7	(0)	3	(0)	1
BIT	30	(7)	23	(1)	22	(8)	14	(3)	9	(0)	8	(1)	1
TTo	14	(6)	8	(3)	5	(0)	5	(1)	0	(0)	0	(0)	0
BTTo	16	(6)	10	(4)	6	(0)	4	(2)	0	(0)	0	(0)	0

Moreno et al, JCO 2024

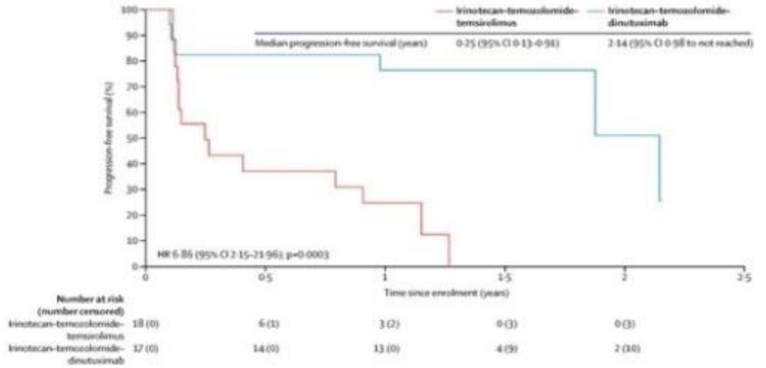
Bevacizumab, Irinotecan, or Topotecan Added to Temozolomide for Children With Relapsed and Refractory Neuroblastoma: Results of the ITCC-SIOPEN BEACON-Neuroblastoma Trial

Lucas Moreno, MD, PhD[1]; Rebekah Weston, MSc[2]; Cormac Owens, MD[3]; Dominique Valteau-Couanet, MD[4]; Marion Gambart, MD[5]; Victoria Castel, MD, PhD[6]; C. Michel Zwaan, MD, PhD[7]; Karsten Nysom, MD, PhD[8]; Nicolas Gerber, MD[9]; Aurora Castellano, MD[10]; Genevieve Laureys, MD, PhD[11]; Ruth Ladenstein, MD, PhD[12]; Jochen Rössler, MD[13]; Guy Makin, MD[14]; Dermot Murphy, MD[15]; Bruce Morland, MD[16]; Sucheta Vaidya, MD[17]; Estelle Thebaud, MD[18]; Natasha van Eijkelenburg, MD, PhD[7]; Deborah A. Tweddle, MD, PhD[19]; Giuseppe Barone, MD, PhD[20]; Julie Tandonnet, MD[21]; Nadege Corradini, MD[22]; Pascal Chastagner, MD, PhD[23]; Catherine Paillard, MD[24]; Francisco J. Bautista, MD, PhD[7]; Soledad Gallego Melcon, MD, PhD[1]; Bram De Wilde, MD, PhD[11]; Lynley Marshall, PhD, MB, BCH[17]; Juliet Gray, MD, PhD[25]; Susan A. Burchill, PhD[26]; Gudrun Schleiermacher, MD, PhD[27]; Louis Chesler, MD, PhD[17]; Andrew Peet, MD, PhD[16]; Martin O. Leach, PhD[17]; Kieran McHugh, MD[20]; Roisin Hayes, MD[3]; Neil Jerome, PhD[17]; Hubert Caron, MD, PhD[28]; Jennifer Laidler, BSc[2]; Nicola Fenwick, BSc[2]; Grace Holt, MsC[2]; Veronica Moroz, MsC[2]; Pamela Kearns, MD, PhD[2]; Simon Gates, PhD[2]; Andrew D.J. Pearson, MD[17]; and Keith Wheatley, DPhil[2]; on behalf of Innovative Therapies for Children with Cancer (ITCC) and European Association for Neuroblastoma Research (SIOPEN)

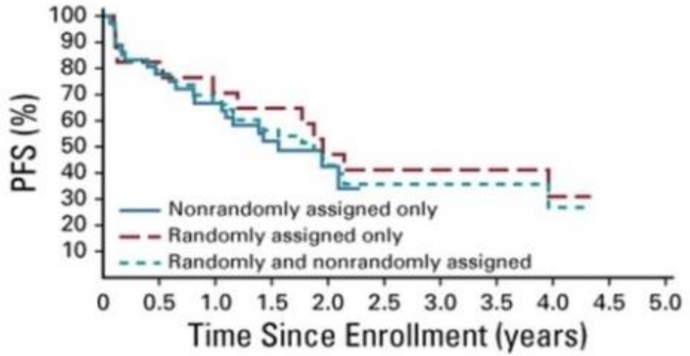
TEMIRI/TOTEM > temozolomide
TEMIRI = TOTEM
TOTEM + Bevacizumab = TOTEM
TEMIRI + Bevacizumab > TEMIRI **TEMIRI + Bevacizumab (BIT) = BEACON winner**

Rationale for BEACON Immuno (anti-GD2) amendment in 2019

- Emerging evidence of benefit of chemo-immunotherapy
- ANBL1221; Tem-Iri-Dinutuximab-GM-CSF. n= 34 randomised (17 with chemo-antibody) plus expansion cohort n=36. *(Mody, Lancet Oncol 2017, JCO 2020)*
- St Jude: Hu14.18K322A-GM-CSF-IL2 + chemo (Topo-cyclo, Tem-Iri and ICE). n=13. *(Federico, CCR 2017)*
- HITS protocol: Hu3F8 + irinotecan, temozolomide, and GM-CSF. n=46 *(Mora, ASCO 2019)*

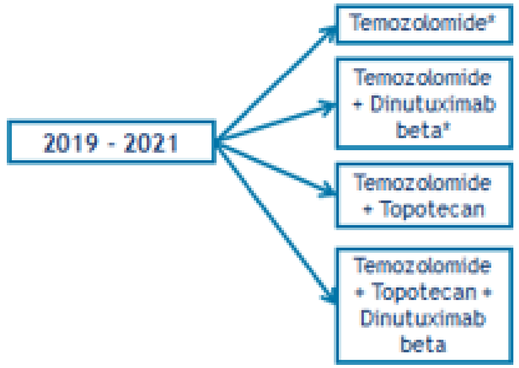


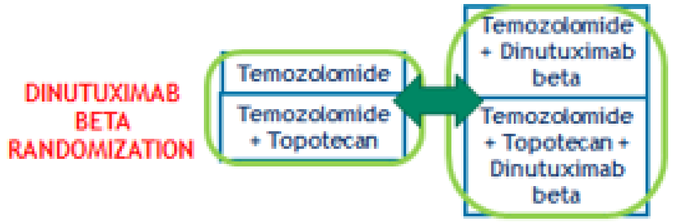
Mody Lanc.Oncology 2017



Mody JCO 2020

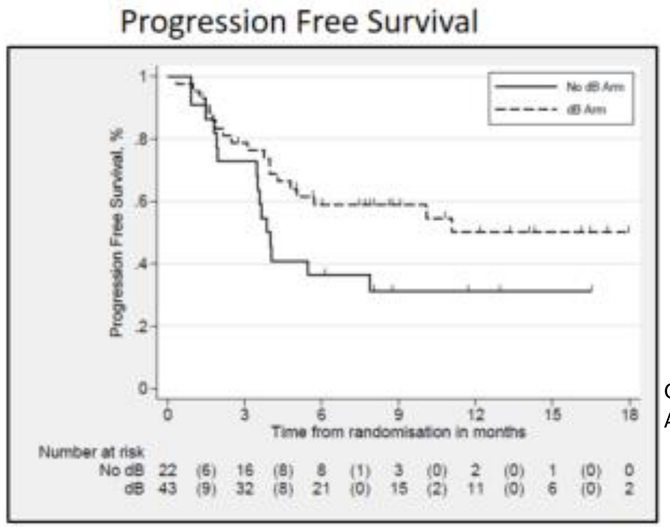
Beacon-immuno (2019-2021)





BEACON-Neuroblastoma

	No dB (22)	+ dB (43)
Complete response	2 (9.1%)	5 (11.6%)
Partial response	2 (9.1%)	10 (23.3%)
Stable disease	12 (54.5%)	16 (37.2%)
Progressive disease	6 (27.3%)	10 (23.2%)
Withdrawn early because of toxicity	0	2 (4.6%)
Overall response rate (PR + CR)	**4 (18.2%)**	**15 (34.8%)**



Gray et al, ASCO 2022

1 year PFS 27% (no dB) and 57% (+dB)

Unadjusted HR 0.56 (p=0.09)

Adjusted HR (topo/strat. factors) 0.63 p=0.19

Chemiotherapy + dinutuximab beta (dbIT) = BEACON-Immuno winner

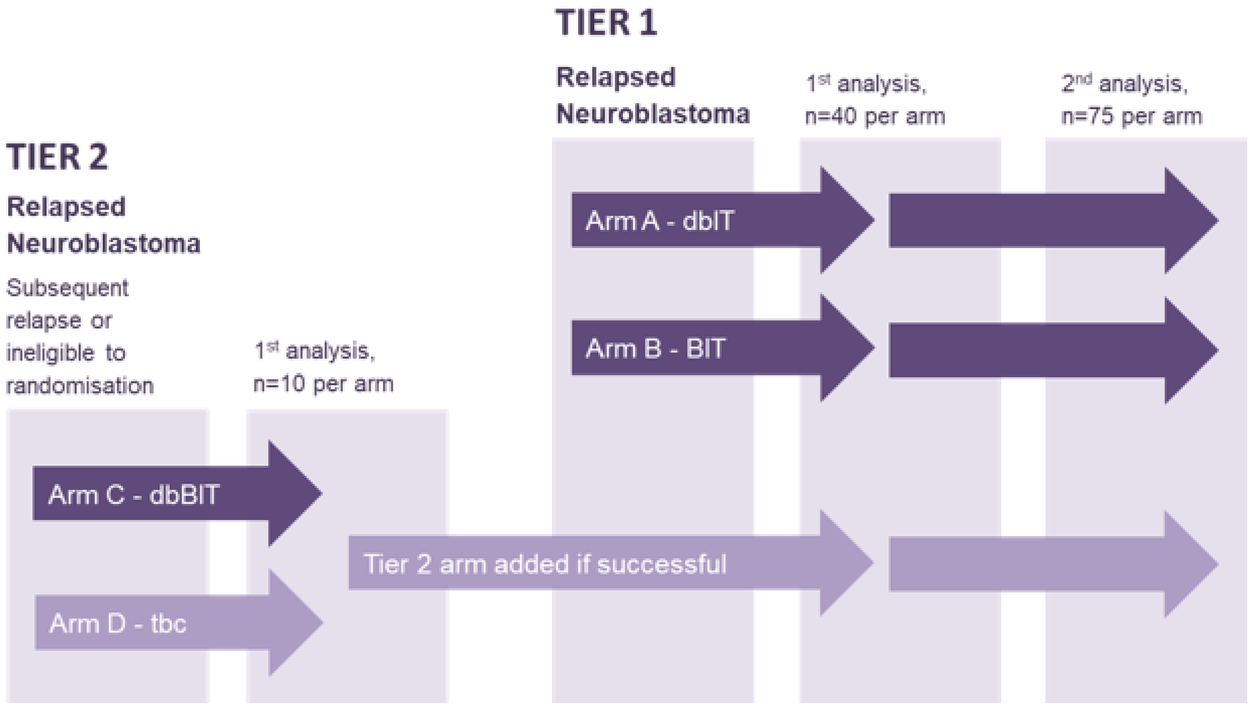
Beacon 2

BEACON2

A Multi-Arm, Multi-Stage Platform Trial For Relapsed Neuroblastoma

CANCER RESEARCH UK | BIRMINGHAM CANCER RESEARCH UK CLINICAL TRIALS UNIT | UNIVERSITY OF BIRMINGHAM

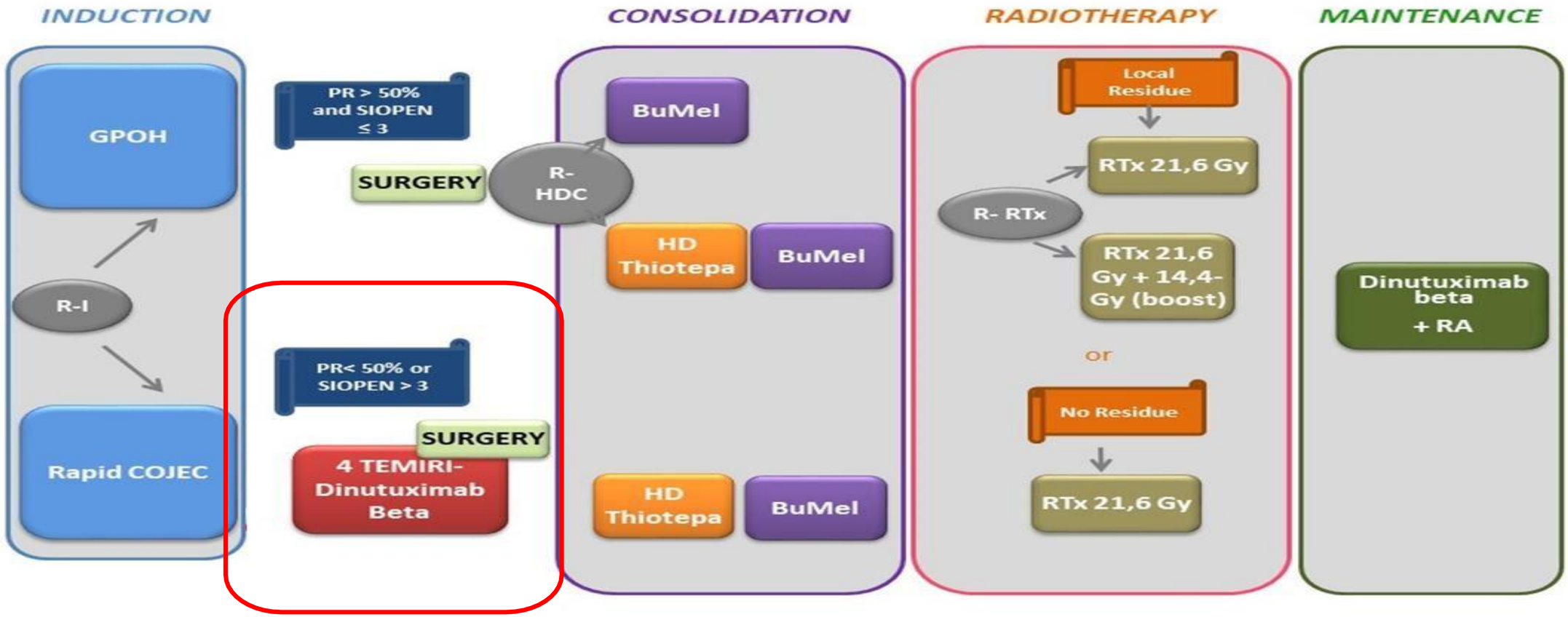
PI: Lucas Moreno, Juliet Gray



Tier 1
cbIT: TEMIRI + dinutuximab beta = BEACON-immune winner
BIT: TEMIRI + Bevacizumab = BEACON trial winner
TIER 2
new combinations to be tested (second relapse/progression)

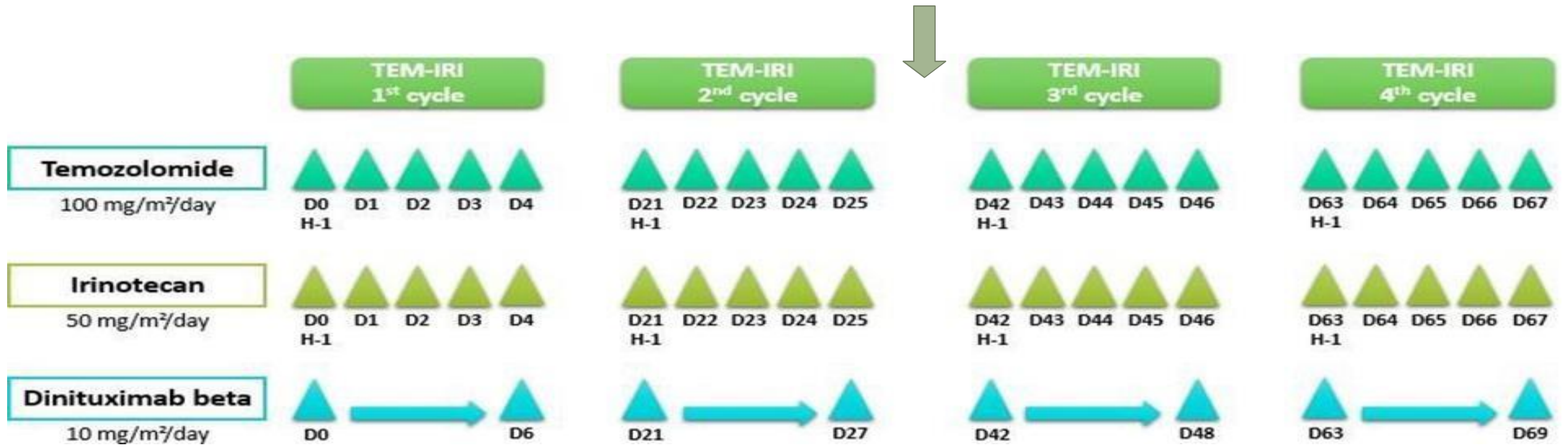
SIOPEN
NEUROBLASTOMA
RESEARCH NETWORK

NBL-HR 02



if INsufficient metastatic response after induction

CHEMO-IMMUNOTHERAPY ARM



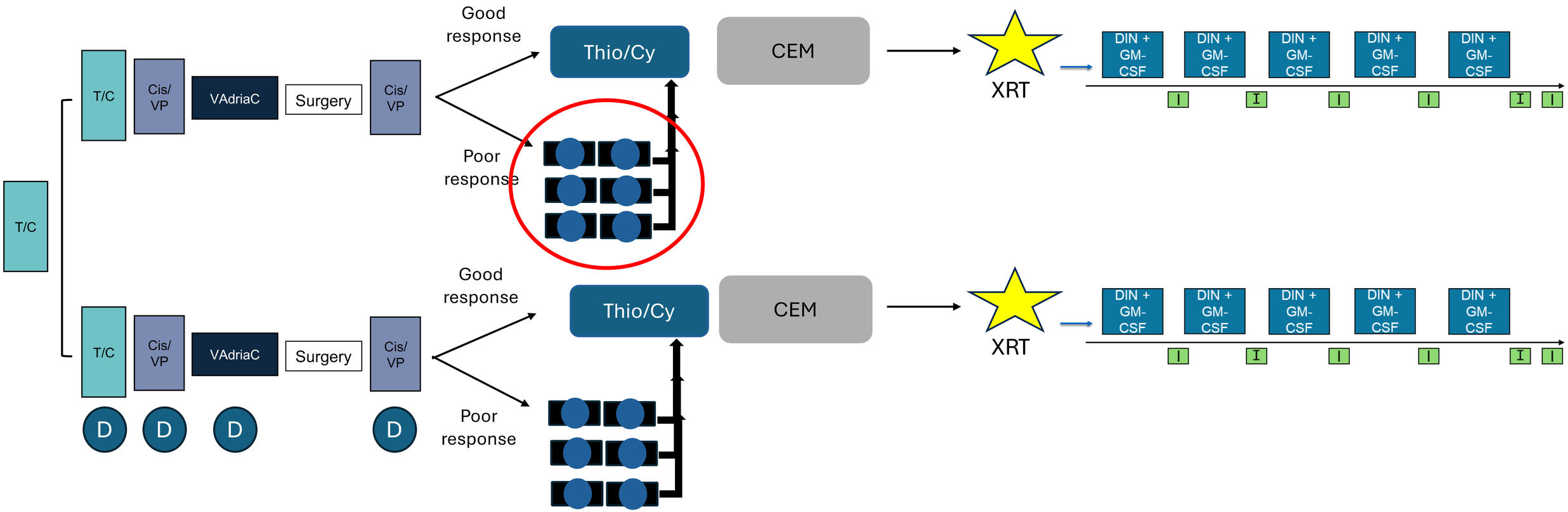
Tandem HDC

Thio 900

Bu-Mel

N = 93 patients All patients will receive the 4 TEMIRI + dinutuximab beta and tandem HDC, unless progression. Metastatic response rate (mRR) after Cycle 4 as primary endpoint

ANBL2131



= irino/tem/dinutuximab as in ANBL1221

Radioisotopi

- **revisione sistematica** della letteratura sul ruolo della **terapia con 131I-mIBG** nel trattamento del **neuroblastoma recidivato o refrattario (R/R)**
- le percentuali di risposta sono risultate molto variabili (circa **0–66%** negli studi iniziali in monoterapia)
- Il principale effetto collaterale è la mielosoppressione
- 131I-mIBG **riduce il carico tumorale** ("bridging therapy"), verso anticorpi anti-GD2, trapianto aploidentico, chemioterapia ad alte dosi, CAR-T.

ELSEVIER

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journal homepage: www.elsevier.com/locate/critrevonc

^{131}I-mIBG therapy in relapsed/refractory neuroblastoma: A weapon from the future past

Francesco Fabozzi [a,1], Maria Felicia Villani [b,1], Francesca Del Bufalo [a], Claudio Altini [b], Vittorio Cannatà [c], Ciucci Davide [c], Milena Pizzoferro [b], Margherita Drago [a], Federica D'Antonio [a], Elizabeth Katherine Anna Triumbari [b], Angela Di Giannatale [a], Sabina Vennarini [d], Angela Mastronuzzi [a], Maria Antonietta De Ioris [a,*,1], Maria Carmen Garganese [b,1]

VOLUME 25 · NUMBER 9 · MARCH 20 2007

JOURNAL OF CLINICAL ONCOLOGY

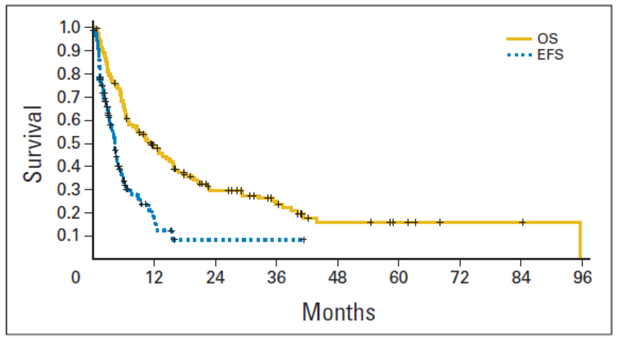
ORIGINAL REPORT

Phase II Study on the Effect of Disease Sites, Age, and Prior Therapy on Response to Iodine-131-Metaiodobenzylguanidine Therapy in Refractory Neuroblastoma

Katherine K. Matthay, Gregory Yanik, Julia Messina, Alekist Quach, John Huberty, Su-Chun Cheng, Janet Veatch, Robert Goldsby, Patricia Brophy, Leslie S. Kersun, Randall A. Hawkins, and John M. Maris

Patients

Characteristics of the 164 eligible patients are shown in Table 1. Twenty-six patients had either refractory disease or progression during induction before any myeloablative therapy. The remainder had relapsed disease, either with (N = 128) or without (N = 10) prior to transplantation. Most patients (n = 148) had stem cell product and



Conclusion

The high response rate and low nonhematologic toxicity with ^{131}I-MIBG suggest incorporation of this agent into initial multimodal therapy of neuroblastoma.

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ESMO OPEN SCIENCE FOR OPTIMAL CANCER CARE

- ORR 48%
- SIOPEN (mediano) score da 10 a 6
- il 65% dei pazienti ha poi potuto ricevere una terapia con cellule CAR-T dirette contro GD2
- 50% è stato sottoposto a chemioterapia ad alte dosi con busulfano e melphalan.
- 3yOS 55% (IC 95%: 33%-73%)
- 3yEFSv 42% (IC 95%: 23%-60%)

ORIGINAL ARTICLE

^{131}I-mIBG therapy in relapsed/refractory neuroblastoma: an old bridge to the future

M. A. De Ioris[1*], M. F. Villani[2], F. Fabozzi[1], F. Del Bufalo[1], C. Altini[2], M. G. Cefalo[2], V. Cannata[3,4], G. Del Baldo[1], M. Pizzoferro[2], I. Alessi[2], F. Lanzaro[5], C. Davide[3], P. Tomà[3], M. L. D'Andrea[3], A. Di Giannatale[1], A. Serra[3], A. Mastronuzzi[1], M. C. Garganese[2] & F. Locatelli[1,6]

[1]Paediatric Haematology and Oncology, Cell and Gene Therapy, Bambino Gesù Children's Hospital, IRCCS, Rome; [2]Nuclear Medicine Unit, Bambino Gesù Children's Hospital, IRCCS, Rome; [3]Medical Physics Unit, Bambino Gesù Children's Hospital, IRCCS, Rome; [4]Radiology, Bambino Gesù Children's Hospital, IRCCS, Rome; [5]Department of Woman, Child and General and Specialized Surgery, University of Campania 'Luigi Vanvitelli', Naples; [6]Departr Catholic University of the Sacred Heart, Rome, Italy

Available online 4 April 2025

Table 1. Patient characteristics

Patients, *n*	26
Median age, years (range)	5.9 (2.5-17.2)
Sex ratio (male/female)	14/12
Disease status at mIBG treatment, *n* (%)	
- Refractory	10 (38)
o PD	2 (8)
o SD	7 (27)
o MR	0
o PR	1 (4)
- Relapsed	16 (62)
o PD	5 (19)
o SD	5 (19)
o MR	1 (4)
o PR	4 (15)

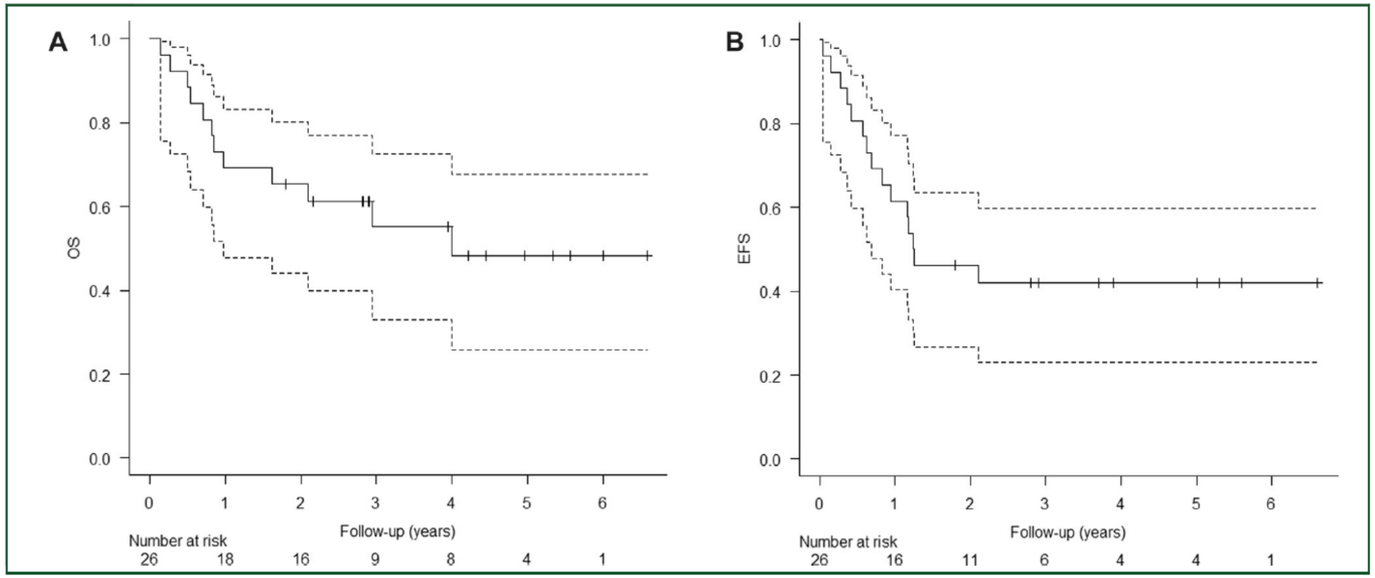


Figure 1. Kaplan–Meier curves for 3-year OS (A) and 5-year EFS (B). Dashed lines enclose the 95% confidence interval. EFS, event-free survival; OS, overall survival.

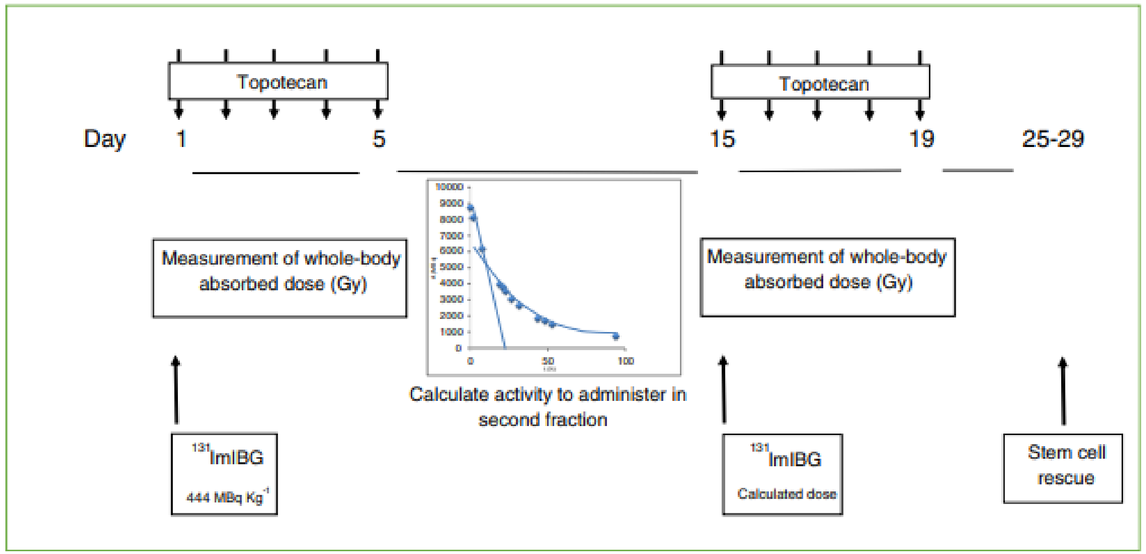
CONTROLLO DI MALATTIA NEI NEUROBLASTOMA (NB) REFRATTARI E RECIDIVATI (RR): UNA QUESTIONE APERTA

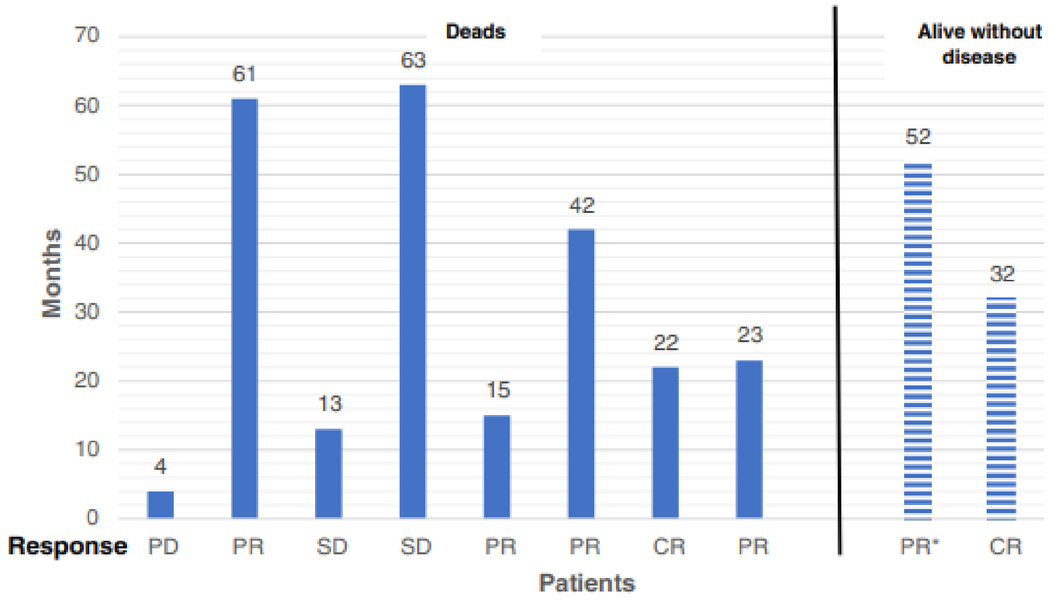
European Journal of Nuclear Medicine and Molecular Imaging (2019) 46:1567–1575
https://doi.org/10.1007/s00259-019-04291-x

ORIGINAL ARTICLE

Dosimetry-based high-activity therapy with ^{131}I-metaiodobenzylguanidine (^{131}I-mIBG) and topotecan for the treatment of high-risk refractory neuroblastoma

Jose Genolla[1] · Trinidad Rodriguez[1] · Pablo Minguez[2] · Ricardo Lopez-Almaraz[3] · Veronica Llorens[1] · Aizpea Echebarria[3]





Received: 3 May 2023 | Revised: 5 July 2023 | Accepted: 21 July 2023
DOI: 10.1002/pbc.30615

RESEARCH ARTICLE

Pediatric Blood & Cancer
aspho
WILEY

Phase II study of ^{131}I-metaiodobenzylguanidine with 5 days of topotecan for refractory or relapsed neuroblastoma: Results of the French study MIITOP

François Sevrin[1] | Hélène Kolesnikov-Gauthier[2] | Olivier Cougnenc[3] | Emilie Bogart[4] | Gudrun Schleiermacher[5] | Frederic Courbon[6] | Marion Gambart[7] | Anne-Laure Giraudet[8] | Nadège Corradini[9] | Jean-Noël Badel[8] | Erwann Rault[10] | Aurore Oudoux[2] | Marie Cécile Le Deley[4] | Dominique Valteau-Couanet[11] | Anne-Sophie Defachelles[1]

Randomized Phase II Trial of MIBG Versus MIBG, Vincristine, and Irinotecan Versus MIBG and Vorinostat for Patients With Relapsed or Refractory Neuroblastoma: A Report From NANT Consortium

Steven G. DuBois, MD[1]; M. Meaghan Granger, MD[2]; Susan Groshen, PhD[3]; Denice Tsao-Wei, MS[3]; Lingyun Ji, PhD[3]; Anasheh Shamirian, BA[4]; Scarlett Czarnecki, BSN[5]; Fariba Goodarzian, MD[6]; Rachel Berkovich, MD[6]; Hiroyuki Shimada, MD[7]; Judith G. Villablanca, MD[4]; Kieuhoa T. Vo, MD[8]; Navin Pinto, MD[9]; Yael P. Mosse, MD[10]; John M. Maris, MD[10]; Suzanne Shusterman, MD[1]; Susan L. Cohn, MD[11]; Kelly C. Goldsmith, MD[12]; Brian Weiss, MD[13]; Gregory A. Yanik, MD[14]; Clare J. Twist, MD[15]; Meredith S. Irwin, MD[16]; Daphne A. Haas-Kogan, MD[17]; Julie R. Park, MD[9]; Araz Marachelian, MD[4]; and Katherine K. Matthay, MD[8]

J Clin Oncol 39:3506-3514. © 2021 by American Society of Clinical Oncology

TABLE 2. Overall Response to One Course of Therapy According to Randomized Arm

Arm	CR	CR-MRD	PR	MR	SD	PD	Response Rate,[a] No. (%)
Arm A (n = 36)	1	1	3	5	17	9	5 (14)
Arm B (n = 35)	0	0	5	5	17	8	5 (14)
Arm C (n = 34)	2	0	9	4	10	9	11 (32)

MIBG alone

VRC + irinotecan

Vorinostat

TABLE 1. Baseline Characteristics of 105 Eligible and Evaluable Patients in Total and According to Randomized Arm

Characteristic	All Arms (N = 105)	Arm A (n = 36)	Arm B (n = 35)	Arm C (n = 34)
Median age at study entry (range), years	6.5 (1.8-28.1)	6.3 (1.8-26.2)	6.7 (1.8-28.1)	5.9 (1.8-21.8)
Sex, female, No. (%)	50 (48)	18 (50)	17 (49)	15 (44)
MYCN status, No. (%)				
Amplified	16 (15)	3 (8)	6 (17)	7 (21)
Nonamplified	73 (70)	29 (81)	23 (66)	21 (62)
Unknown or not done	16 (15)	4 (11)	6 (17)	6 (18)
Disease status, No. (%)				
Relapse	68 (65)	21 (58)	23 (66)	24 (71)
Refractory	29 (28)	11 (31)	10 (29)	8 (24)
Persistent	8 (8)	4 (11)	2 (6)	2 (6)
Median Curie score at baseline (range)	8 (1-26)	7 (1-25)	8 (1-22)	7 (1-26)
Baseline soft tissue target lesion(s) present, No. (%)	61 (58)	22 (61)	22 (63)	17 (50)
Marrow involved at baseline, No. (%)	47 (45)	16 (44)	17 (49)	14 (41)
High-dose chemotherapy with stem-cell rescue in the past 6 months, No. (%)	15 (14)	4 (11)	5 (14)	6 (18)
Previous anti-GD2 therapy, No. (%)	63 (60)	22 (61)	23 (66)	18 (53)
Previous MIBG, No. (%)	9 (9)	3 (8)	3 (9)	3 (9)
Previous irinotecan, No. (%)	65 (62)	27 (75)	22 (63)	16 (47)
Previous vorinostat, No. (%)	7 (7)	1 (3)	3 (9)	3 (9)

CONCLUSION Vorinostat and MIBG is likely the arm with the highest true response rate, with manageable toxicity. Vincristine and irinotecan do not appear to improve the response rate to MIBG and are associated with increased toxicity.

miniVAN

Initial toxicity and response data from MINIVAN, a Phase 1 trial of 131-I mIBG, Nivolumab and Dinutuximab Beta in relapsed/refractory neuroblastoma

- Studio di escalation della dose con disegno Rolling 6
- sono stati arruolati 43 pazienti tra luglio 2018 e ottobre 2024 (7 nella Coorte 1, 6 nella Coorte 2 e 30 nella Coorte 3).
- La tossicità osservata nelle Coorti 1 e 2 è risultata accettabile.
- Nella Coorte 3, su 30 pazienti, 4 hanno interrotto il trattamento per tossicità (3 epatotossicità, 1 infezione), 6 per progressione di malattia e 5 sono tuttora in trattamento.

MINIVAN; Trial design

- **Non-myeloablative dose ^{131}-mIBG (2 Gy)** – fixed
- **3 mg/Kg Nivolumab (anti-PD-1) every 2 weeks** – fixed
- **Dose escalation of dinutuximab beta** (Rolling 6 design):
  - *Cohort 1:* No dinutuximab beta (3-6 patients)
  - *Cohort 2:* 50% *LTI dose of dinutuximab beta (50mg/m^2 over 10 days) (3-6 patients)
  - *Cohort 3:* 100% LTI dose of dinutuximab beta (100 mg/m^2 over 10 days) (initial 18 patients, extended to 30 patients)
- **4 sites**
  - Southampton, UCLH (UK)
  - Madison (US)
  - Greifswald (Germany)

** Long Term Infusion schedule*

MINT
mIBG therapy in neuroblastoma combined with talazoparib

A biomarker enriched phase I/II clinical trial of ^{131}I-mIBG therapy in combination with talazoparib for children with relapsed/refractory neuroblastoma

Group A: Genetic alterations in HRR/DSB genes

Group B: Absence of genetic alterations in HRR/DSB genes

Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Talazoparib	x	x	x	x	x	x	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)			
^{131}I-mIBG			x														
PBSC rescue																	x

21 patients per group

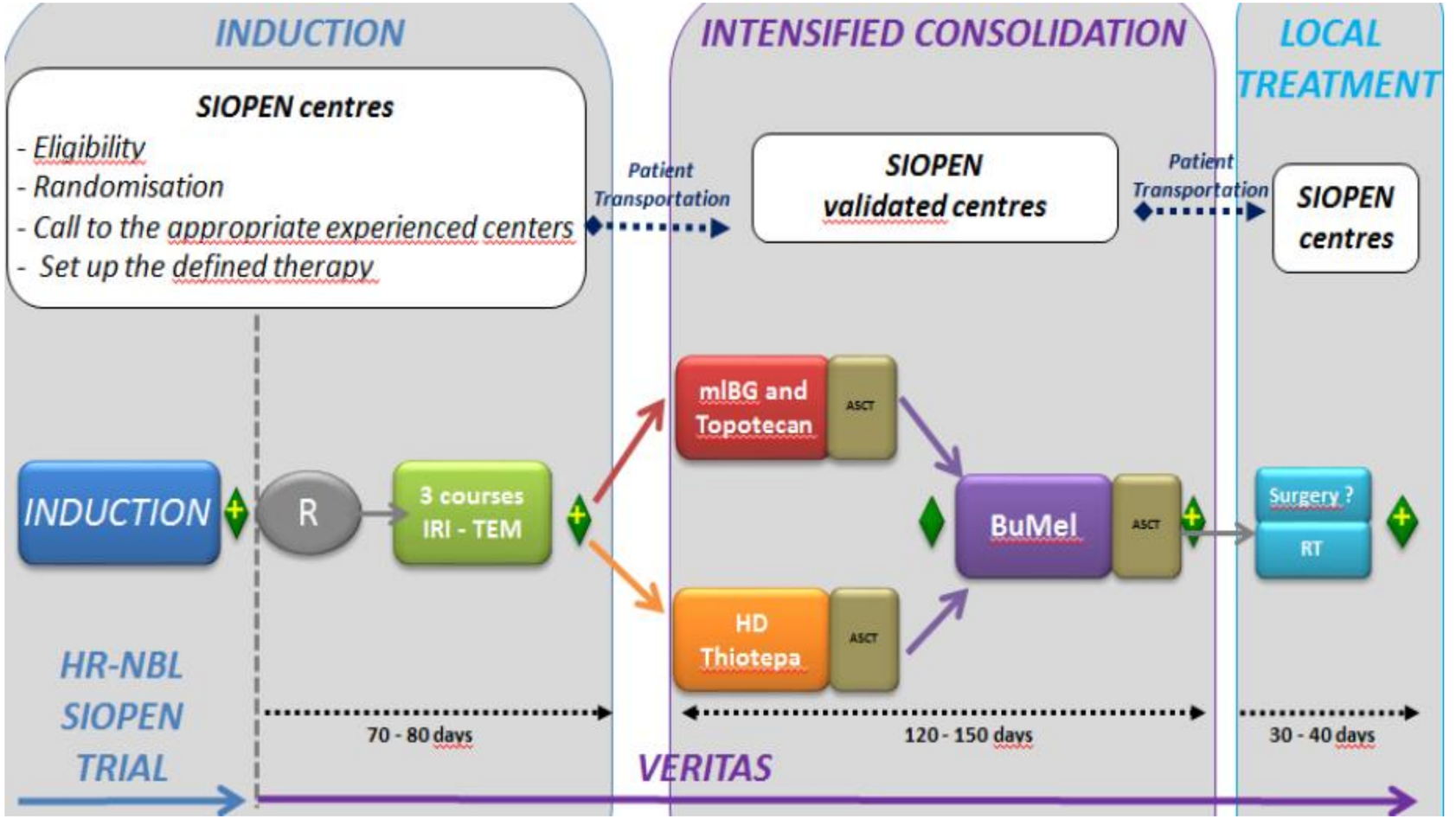
**ATRX, ATM, ATR, BARD1, BRCA1, BRCA2, BRIP1, CHEK2, PALB2, PTEN, RAD50, RAD51B, RAD51C, RAD51D*

- Fase I/II dedicata a bambini e giovani adulti con NB R/R.
- Obiettivo: valutare efficacia e sicurezza della **131I-MIBG therapy** combinata con **talazoparib (PARP inhibitor)**
- Il talazoparib blocca la riparazione del DNA nelle cellule tumorali, rendendole molto più vulnerabili ai danni causati dalla radioterapia mirata con MIBG.
- I ricercatori mirano a identificare se specifiche mutazioni genetiche (come nel gene BARD1) indichino quali pazienti rispondono meglio a questo approccio combinato.

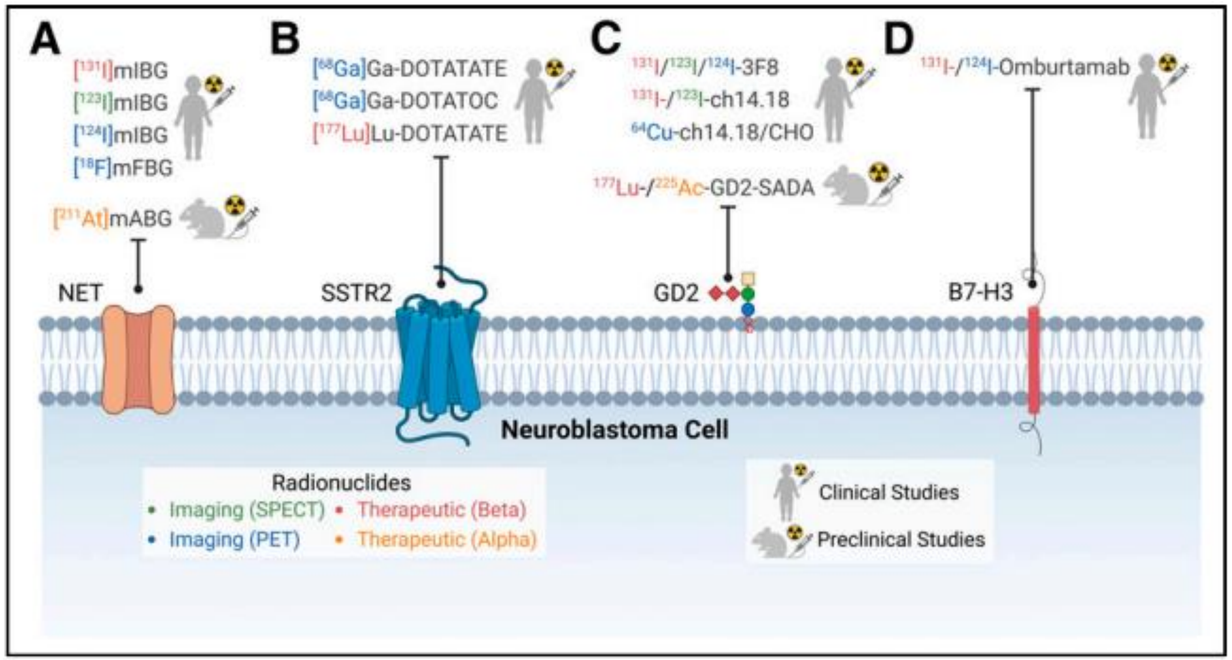
SIOPEN R NET

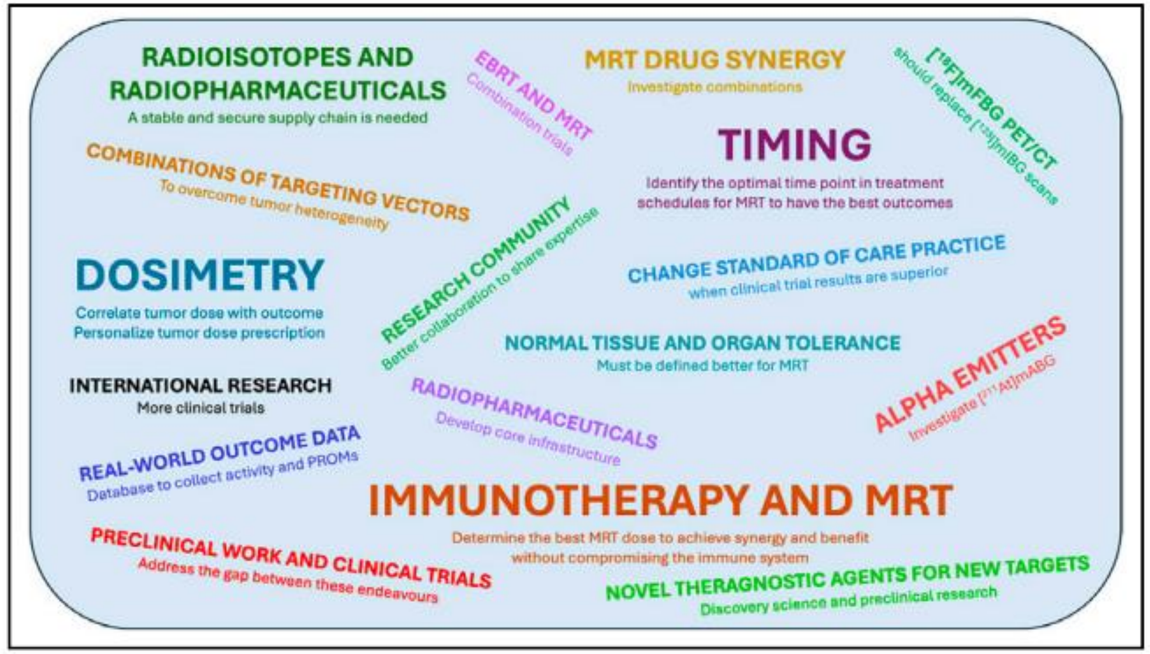
VERITAS

A randomised trial of two treatment strategies for metastatic neuroblastoma responding poorly to induction chemotherapy:



Radioisotopi Nuovi





THERANOSTICS FOR NEUROBLASTOMA Gawne et al. 2025

Radioisotopi Nuovi

European Journal of Nuclear Medicine and Molecular Imaging
https://doi.org/10.1007/s00259-020-04741-x

ORIGINAL ARTICLE

A phase IIa trial of molecular radiotherapy with 177-lutetium DOTATATE in children with primary refractory or relapsed high-risk neuroblastoma

Jennifer E. Gains[1] · Veronica Moroz[2] · Matthew D. Aldridge[1,3] · Simon Wan[3] · Keith Wheatley[2] · Jennifer Laidler[2] · Connie Peet[1] · Jamshed B. Bomanji[3] · Mark N. Gaze[1]

International Neuroblastoma Response Criteria (primary outcome), progression-free survival (PFS), and overall survival (OS).
Results The trial recruited 21 patients; eight received the planned four courses. There was dose-limiting haematologic toxicity in one case, but no other significant haematologic or renal toxicities. None of 14 evaluable patients had an objective response at 1 month after completion of treatment (Wilson 90% CI 0.0, 0.16; and 95% CI is 0.0, 0.22). The trial did not therefore proceed to the second stage. The median PFS was 2.96 months (95% CI 1.71, 7.66), and the median OS was 13.0 months (95% CI 2.99, 21.52).
Conclusion In the absence of any objective responses, the use of LuDO as a single agent at the dose schedule used in this study is not recommended for the treatment of neuroblastoma. There are several reasons why this treatment schedule may not have resulted in objective responses, and as other studies do show benefit, the treatment should not be regarded as being of no value. Further trials designed to overcome this schedule's limitations are required.

PFS mediana 2.96 mesi e OS mediana 13 mesi;

A Phase II Trial of a Personalized, Dose-Intense Administration Schedule of ^{177}Lutetium-DOTATATE in Children With Primary Refractory or Relapsed High-Risk Neuroblastoma–LuDO-N

Fredrik Sundquist[1], Kleopatra Georgantzi[1,2], Kirsten Brunsvig Jarvis[3], Jesper Brok[4], Minna Koskenvuo[5], Jelena Rascon[6], Max van Noesel[7], Per Grybäck[8], Joachim Nilsson[8], Arthur Braat[9], Mikael Sundin[10], Sandra Wessman[11], Nikolas Herold[1,2], Lars Hjorth[12], Per Kogner[1], Dan Granberg[13], Mark Gaze[14] and Jakob Stenman[1,15]

(*J Pediatr Hematol Oncol* 2016;38:87–96)

Initial Experience With Gallium-68 DOTA-Octreotate PET/CT and Peptide Receptor Radionuclide Therapy for Pediatric Patients With Refractory Metastatic Neuroblastoma

*Grace Kong, MBBS (Hons), FRACP, FAANMS,**
Michael S. Hofman, MBBS (Hons), FRACP, FAANMS,†*
William K. Murray, MBBS, FRCPA, FRCPath,‡
Sharyn Wilson, BAppSc, MHlthSc,‡
Paul Wood, MBBS, BPharm, MSc, FRACP,§‖¶
Peter Downie, MBBS, FRACP,§¶# Leanne Super, MBBS, FRACP,§#
*Annette Hogg, BAppSc, PhD,**
*Peter Eu, BSc (Pharmacy), MSc (Radiopharmacy),**
and Rodney J. Hicks, MBBS (Hons), MD, FRACP‖***

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Theranostics

2024; 14(3): 1212-1223. doi: 10.7150/thno.92481

Research Paper

A novel approach to guide GD2-targeted therapy in pediatric tumors by PET and [^{64}Cu]Cu-NOTA-ch14.18/CHO

Nils Florian Trautwein[1,2], Johannes Schwenck[1,2,3], Christian Seitz[3,4], Ferdinand Seith[5], Eduardo Calderón[1], Sebastian von Beschwitz[1], Stephan Singer[6], Gerald Reischl[2,3], Rupert Handgretinger[4], Jürgen Schäfer[5], Peter Lang[4], Bernd J. Pichler[2,3,7], Johannes H. Schulte[4], Christian la Fougère[1,3,7]✉ and Helmut Dittmann[1]

Medicina di Precisione

cancers 2023 MDPI

Review

Neuroblastoma in the Era of Precision Medicine: A Clinical Review

Andrew Wahba, Russ Wolters and Jennifer H. Foster *

Table 2. FDA-approved drugs that are used in the treatment of relapsed high-risk neuroblastoma.

Molecular Target	Drug	Year Approved
ALK	Crizotinib	2011
	Lorlatinib	2018
	Alectinib	2015
	Ceritinib	2019
TRK/ROS1/ALK	Entrectinib	2019
GD2	Naxitimab	2020
	Dinutuximab	2015
	Dinutuximab beta *	2017
RAS-MAPK	Selumetinib	2020
	Binimetinib	2018
mTOR	Sirolimus	1999
	Temsirolimus	2007
CDK4/6	Palbociclib	2015
	Abemaciclib	2017
	Ribociclib	2017

* European Medical Association approval.

Molecular Target	Agent	Active Clinical Trial
ALK	Crizotinib	NCT01121588
	Lorlatinib	NCT03107988, NCT03126916
	Alectinib	NCT05770037
	Ceritinib	NCT05489887, NCT02559778
	Ensartinib	NCT03213652
TRK/ROS1/ALK	Entrectinib	NCT02650401, NCT04589845
	Reprotrectinib	NCT04094610, NCT03093116, NCT03093116
Aurora kinase A	Erbumine	NCT04106219
MDM2	ALRN-6924	NCT03654716
	APG-115	NCT03611868
GD2	GD2-CART01	NCT03373097
	iC9-GD2 T	NCT01822652
	C7R-GD2.CART	NCT03635632
	BCD-245	NCT05782959
	iC9.GD2.CAR.IL-15 T	NCT03721068
	GINAKIT	NCT03294954
	Ex Vivo Expanded Allogeneic γδ T Cells	NCT05400603
	Naxitimab	NCT05489887, NCT03363373, NCT02650648, NCT01419834
	Dinutuximab beta	NCT02914405, NCT01704716NCT05272371, NCT04221035, NCT05754684
	Dinutuximab	NCT03332667, NCT03794349, NCT04211675, NCT03126916, NCT02573896
GPC2	GPC2 CAR T	NCT05650749
B7H3	131I-Omburtamab	NCT04022213
	B7H3 CAR T	NCT04483778
RAS-MAPK	Selumetinib	NCT03213691
	Binimetinib	NCT05564377
	Ulixertinib	NCT03698994
mTOR	Samotolisib	NCT03213678
	Sirolimus	NCT02574728
	Temsirolimus	NCT02389309
	ABI-009	NCT02975882
CDK4/6	Palbociclib	NCT03709680
	Abemaciclib	NCT04238819, NCT02644460
	Ribociclib	NCT05429502

nature medicine

2023

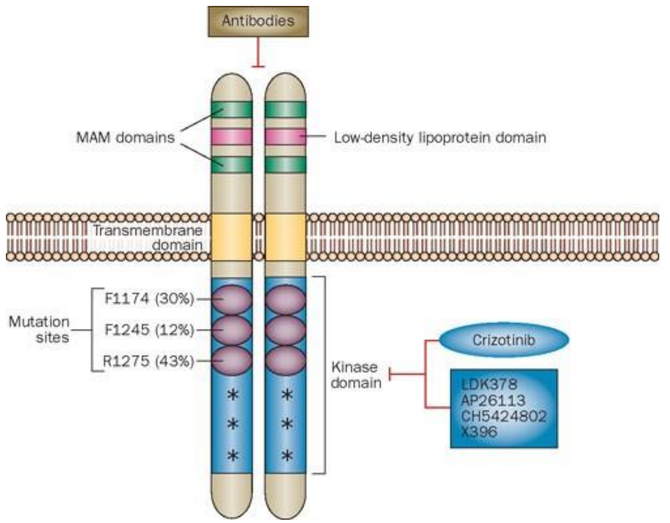
Article

https://doi.org/10.1038/s41591-023-02297-5

Lorlatinib with or without chemotherapy in ALK-driven refractory/relapsed neuroblastoma: phase 1 trial results

Kelly C. Goldsmith[1,2], Julie R. Park[3,4], Kimberly Kayser[5], Jemily Malvar[6], Yueh-Yun Chi[6,7], Susan G. Groshen[7], Judith G. Villablanca[6,7], Kateryna Krytska[8], Lillian M. Lai[9], Patricia T. Acharya[7,10], Fariba Goodarzian[7,10], Bruce Pawel[7,11], Hiroyuki Shimada[12], Susan Ghazarian[6], Lisa States[13], Lynley Marshall[14,15], Louis Chesler[14,15], Meaghan Granger[16], Ami V. Desai[17], Rajen Mody[18], Daniel A. Morgenstern[19,20], Suzanne Shusterman[21], Margaret E. Macy[22,23], Navin Pinto[3,4], Gudrun Schleiermacher[24,25], Kieuhoa Vo[26], Holger C. Thurm[27], Joseph Chen[27], Marlon Liyanage[27], Gerson Peltz[27], Katherine K. Matthay[26], Esther R. Berko[8,28,29], John M. Maris[8,13], Araz Marachelian[6,7] & Yael P. Mossé[8,13]

49 pazienti (9 refrattari) Lornatinib + Topo/Ex RR 63%



Lancet Oncol 2024; 25: 922–32

Irinotecan and temozolomide in combination with dasatinib and rapamycin versus irinotecan and temozolomide for patients with relapsed or refractory neuroblastoma (RIST-rNB-2011): a multicentre, open-label, randomised, controlled, phase 2 trial

Selim Corbacioglu, Holger Lode, Susanne Ellinger, Florian Zeman, Meinolf Suttorp, Gabriele Escherich, Konrad Bochennek, Bernd Gruhn, Peter Lang, Marius Rohde, Klaus Michael Debatin, Daniel Steinbach, Andreas Beilken, Ruth Ladenstein, Rainer Spachtholz, Peter Heiss, Dirk Hellwig, Anja Tröger, Michael Koller, Karin Menhart, Markus J Riemenschneider, Saida Zoubaa, Silke Kietz, Marcus Jakob, Gunhild Sommer, Tilman Heise, Patrick Hundsdörfer, Ingrid Kühnle, Dagmar Dilloo, Stefan Schönberger, Georg Schwabe, Irene von Luettichau, Norbert Graf, Paul-Gerhardt Schlegel, Michael Frühwald, Norbert Jorch, Michael Paulussen, Dominik T Schneider, Markus Metzler, Alfred Leipold, Michaela Nathrath, Thomas Imschweiler, Holger Christiansen, Irene Schmid, Roman Crazzolara, Naghmeh Niktoreh, Gunnar Cario, Joerg Faber, Martin Demmert, Florian Babor, Birgit Fröhlich, Stefan Bielack, Toralf Bernig, Johann Greil, Angelika Eggert, Thorsten Simon, Juergen Foell

	Control group (n=63)	RIST group (n=61)
Sex		
Female	25 (40%)	21 (34%)
Male	38 (60%)	40 (66%)
Disease status at enrolment		
Refractory	14 (22%)	10 (16%)
Relapse	49 (78%)	50 (82%)
First relapse	43 (88%)	41 (82%)
Second relapse	4 (8%)	8 (16%)
Third relapse	2 (4%)	1 (2%)
Unknown	0	1 (2%)

(Table 1 continues in next column)

results of the RIST trial.

In conclusion, to our knowledge, the trial shows for the first time that the addition of rapamycin–dasatinib to irinotecan–temozolomide can improve long-term progression-free survival and overall survival, exclusively in patients with *MYCN*-amplified relapsed or refractory neuroblastoma, demonstrating that *MYCN* amplification is a clinically relevant molecular target. The ubiquitous availability of the drugs used in the study, most in oral liquid formulation, the outpatient applicability, and the acceptable adverse event profile suggests that RIST could be a potential treatment option for even of the most fragile patients with neuroblastoma.

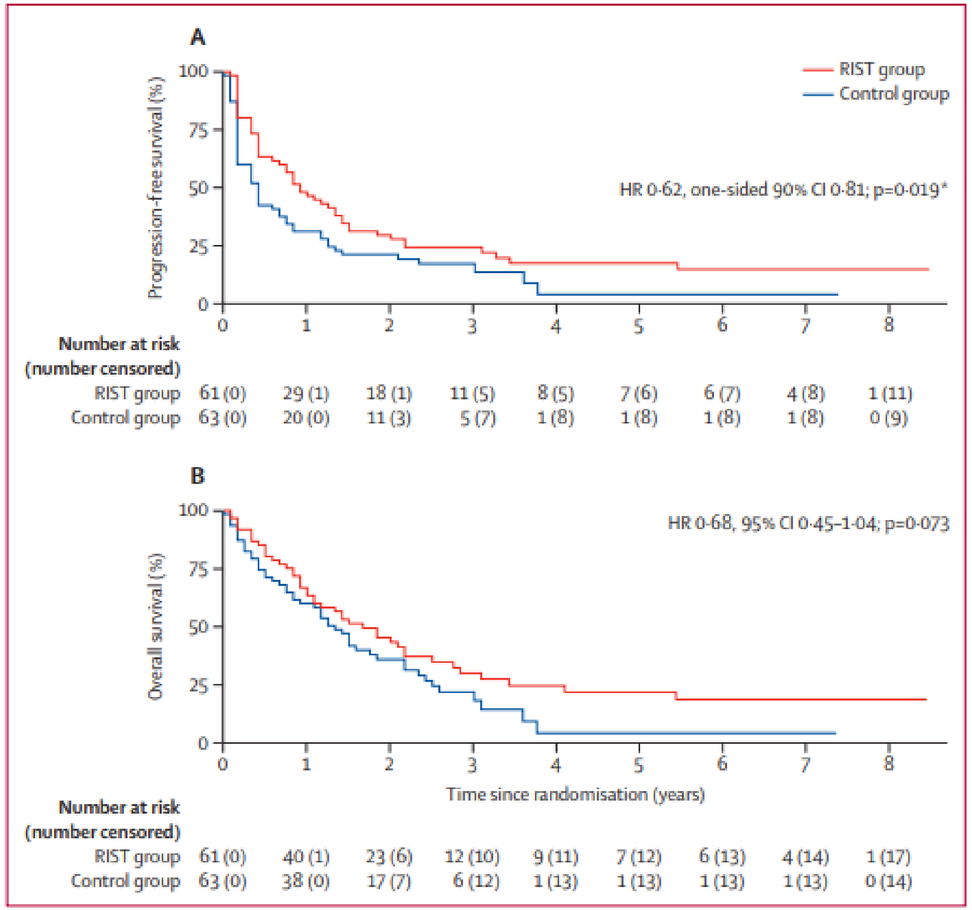


Figure 2: **Progression-free survival (A) and overall survival (B) in intention-to-treat population**
RIST=irinotecan–temozolomide and dasatinib–rapamycin. *Post-hoc two-sided 95% CI 0·42–0·92.

CONTROLLO DI MALATTIA NEI NEUROBLASTOMA (NB) REFRATTARI E RECIDIVATI (RR): UNA QUESTIONE APERTA

PREME

Capasso et al.
Journal of Translational Medicine (2024) 22:151
https://doi.org/10.1186/s12967-024-04954-w

Journal of Translational Medicine

RESEARCH Open Access

From the identification of actionable molecular targets to the generation of faithful neuroblastoma patient-derived preclinical models

Mario Capasso[1,3†], Chiara Brignole[2†], Vito A. Lasorsa[3†], Veronica Bensa[2], Sueva Cantalupo[1,3], Enrico Sebastiani[4], Alessandro Quattrone[4], Eleonora Ciampi[2], Marianna Avitabile[1,3], Angela R. Sementa[5], Katia Mazzocco[5], Barbara Cafferata[5], Gabriele Gaggero[5], Valerio G. Vellone[5], Michele Cilli[6], Enzo Calarco[2], Elena Giusto[2], Patrizia Perri[2], Sanja Aveic[7], Doria
Marco Rabusin[12], Francesco De L
Maria V. Corrias[2], Massimo Conte
Fabio Pastorino[2†]

International Journal of Molecular Sciences

cancers

MDPI

Article

Therapeutic Targeting of ALK in Neuroblastoma: Experience of Italian Precision Medicine in Pediatric Oncology

Fabio Pastorino [1,†], Mario Capasso [2,3,†], Chiara Brignole [1], Vito A. Lasorsa [3], Veronica Bensa [1], Patrizia Perri [1], Sueva Cantalupo [2,3], Serena Giglio [4], Massimo Provenzi [5], Marco Rabusin [6], Elvira Pota [7], Monica Cellini [8], Annalisa Tondo [9], Maria A. De Ioris [10], Angela R. Sementa [11], Alberto Garaventa [12], Mirco Ponzoni [1,*,‡] and Loredana Amoroso [12,‡]

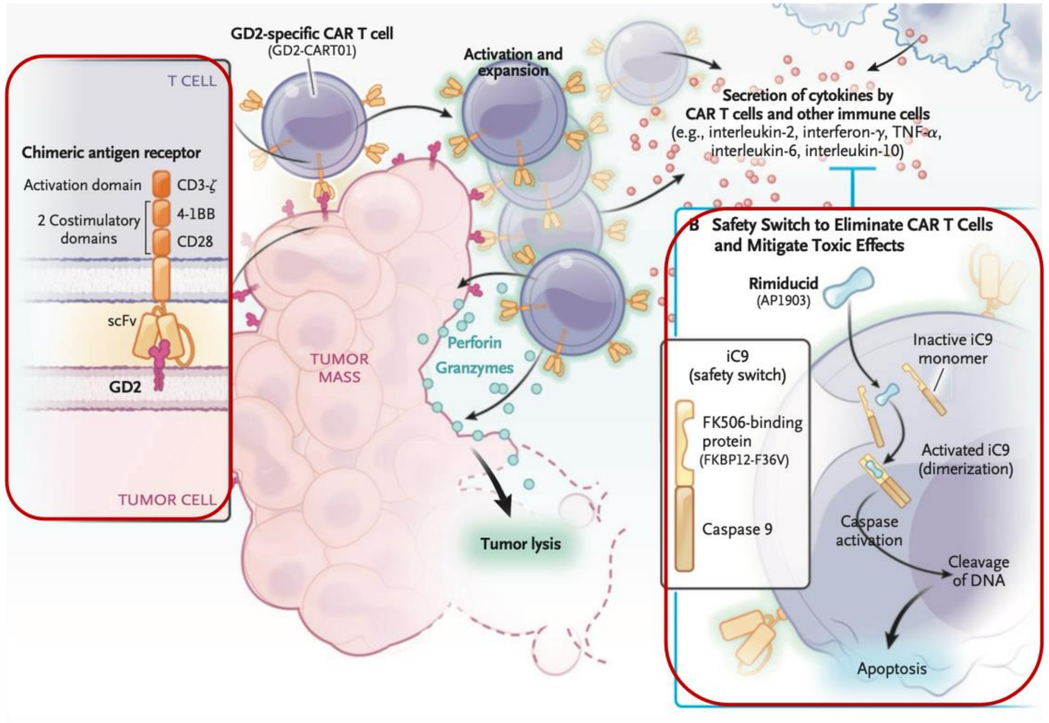
Case Report

Italian Precision Medicine in Pediatric Oncology: Moving beyond Actionable Alterations

Fabio Pastorino [1,†], Mario Capasso [2,3,†], Chiara Brignole [1], Serena Giglio [4], Veronica Bensa [1], Sueva Cantalupo [2,3], Vito Alessandro Lasorsa [3], Annalisa Tondo [5], Rossella Mura [6], Angela Rita Sementa [7], Alberto Garaventa [4], Mirco Ponzoni [1,*,‡] and Loredana Amoroso [4,‡]

INFANTES·SUMMIS·CARITATIS·ET·SCIENTIAE·BENEFICIIS·SUUM
GASLINI

Third Generation CAR Targeting GD2



Yeko

The NEW ENGLAND JOURNAL of MEDICINE

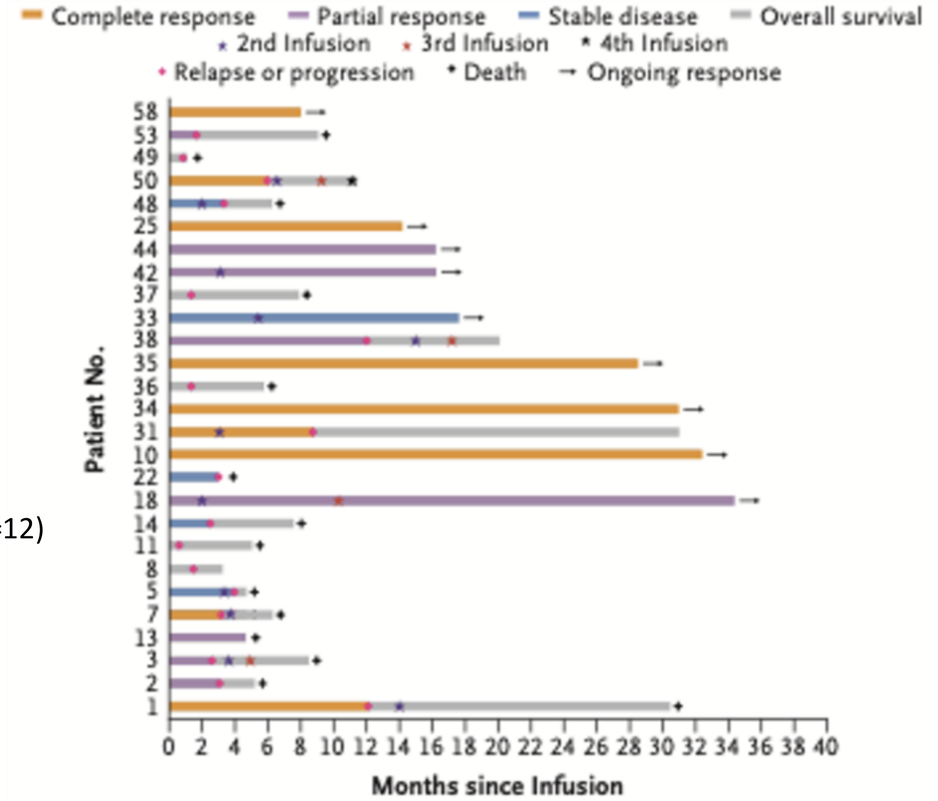
ORIGINAL ARTICLE

GD2-CART01 for Relapsed or Refractory High-Risk Neuroblastoma

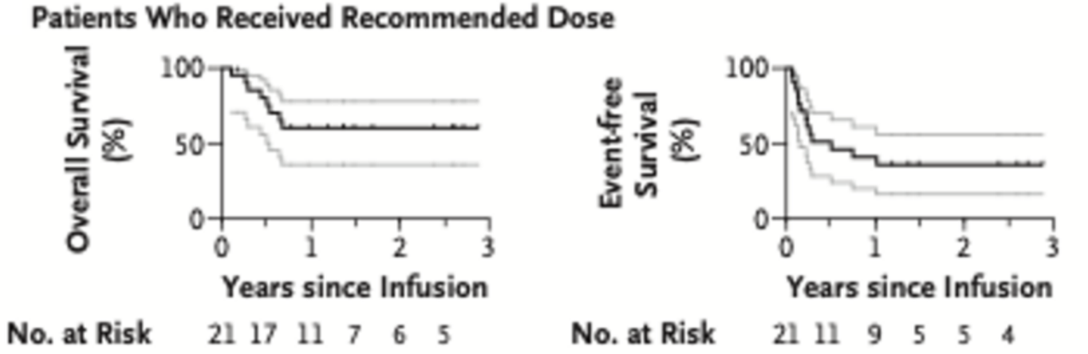
F. Del Bufalo, B. De Angelis, I. Caruana, G. Del Baldo, M.A. De Ioris, A. Serra, A. Mastronuzzi, M.G. Cefalo, D. Pagliara, M. Amicucci, G. Li Pira, G. Leone, V. Bertaina, M. Sinibaldi, S. Di Cecca, M. Guercio, Z. Abbaszadeh, L. Iaffaldano, M. Gunetti, S. Iacovelli, R. Bugianesi, S. Macchia, M. Algeri, P. Merli, F. Galaverna, R. Abbas, M.C. Garganese, M.F. Villani, G.S. Colafati, F. Bonetti, M. Rabusin, K. Perruccio, V. Folsi, C. Quintarelli, and F. Locatelli, for the Precision Medicine Team–IRCCS Ospedale Pediatrico Bambino Gesù*

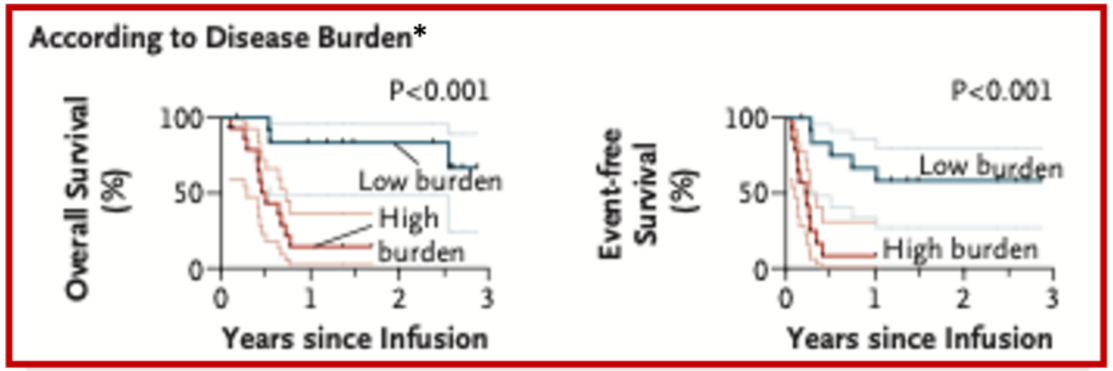
Clinical response and outcome

HRNB refrattario (n=12)



ORR: 63%





*Low disease burden:
- SIOPEN skeletal score ≤7
- Tumor mass with longest diameter <5cm
- BM infiltration ≤50%

Del Bufalo F, [...] Locatelli F. NEJM 2023

EU-GD2-CAR01

- Allocation: Randomized
- Endpoint Classification: Feasibility/Efficacy
- Study Intervention Model: single arm
- Masking: Open Label
- Primary Purpose: Treatment
- **International sponsor: Ospedale Pediatrico Bambino Gesù**
- **International multicenter study**

Bambino Gesù
OSPEDALE PEDIATRICO

EU-GD2-CAR01: study design

Phase II

Patients with NB relapsed/progressing during/after first line

↓

Reinduction treatment to reduce tumor burden
(choice of each treating center, preferably according to Beacon2)

↓

Achievement of low tumor burden

↓

Manufacturing of GD2-CAR01

Bridging therapy ↓

GD2-CART01 infusion

Bambino Gesù
OSPEDALE PEDIATRICO

Trapianto aploidentico di cellule staminali ematopoietiche con deplezione TCRαβ⁺CD19⁺ *seguito da* immunoterapia (mAb antiGD2 + donor-derived NK cells) in pazienti con HR NB refrattario o recidivato

- EudraCTnumber: 2022-000488-27
- Sponsor: ISTITUTO G.GASLINI di GENOA
- Principal Investigator: Stefano Giardino

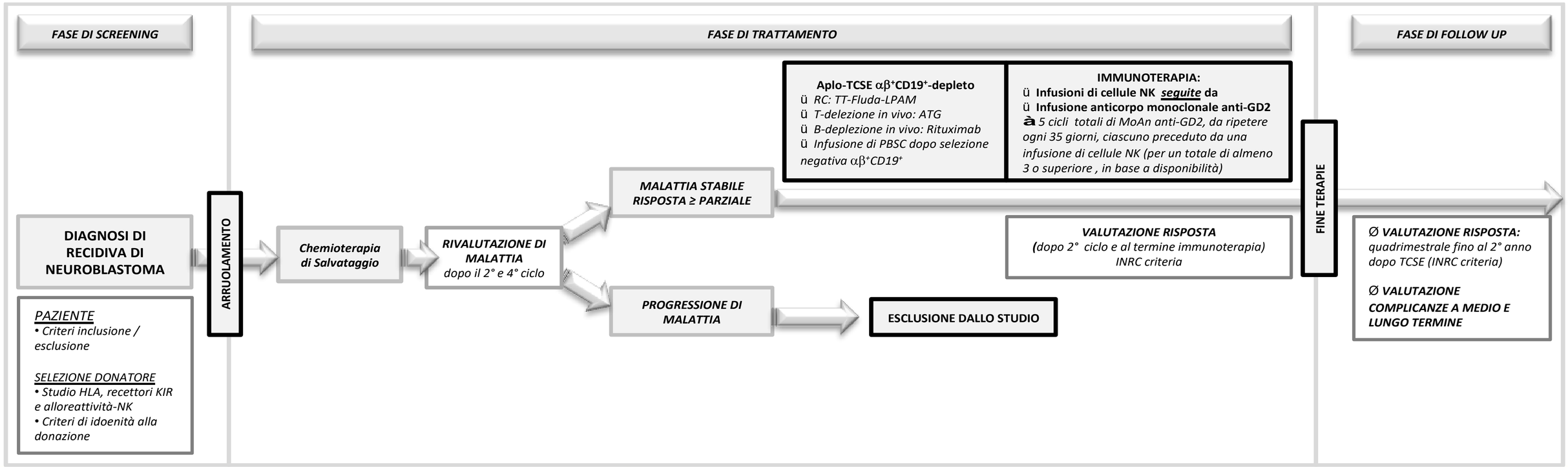
Study design

- ✓ prospective interventional **phase II**
- ✓ single-arm
- ✓ single-center

Primary objective

To evaluate the safety and activity in high-risk relapsed NB of:

- Haplo TCRαβ⁺CD19⁺ depleted SCT
- ImmunoCELL-therapy with
  1. *donor-derived NK-cells CD3⁻56⁺*
  2. *anti-GD2 mAb*



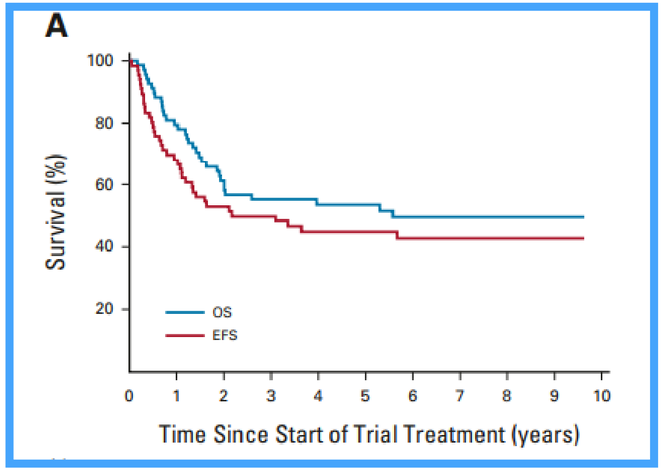
5 yrs EFS and OS rates of 43% and 53% respectively
aGvHD rates 7.5%

68 pazienti

Journal of Clinical Oncology 2023

Anti-GD2 Antibody Dinutuximab Beta and Low-Dose Interleukin 2 After Haploidentical Stem-Cell Transplantation in Patients With Relapsed Neuroblastoma: A Multicenter, Phase I/II Trial

Tim Flaadt, MD[1]; Ruth L. Ladenstein, MD, PhD[2,3]; Martin Ebinger, MD[1]; Holger N. Lode, MD[4]; Helga Björk Arnardóttir, MSc[5]; Ulrike Poetschger, PhD[5]; Wolfgang Schwinger, MD[6]; Roland Meisel, MD[7]; Friedhelm R. Schuster, MD[7]; Michaela Döring, MD[1]; Peter F. Ambros, PhD[8]; Manon Queudeville, MD[1]; Jörg Fuchs, MD[9]; Steven W. Warmann, MD[9]; Jürgen Schäfer, MD[10]; Christian Seitz, MD[1,11]; Patrick Schlegel, MD[12]; Ines B. Brecht, MD[1]; Ursula Holzer, MD[1]; Tobias Feuchtinger, MD[13]; Thorsten Simon, MD[14]; Johannes H. Schulte, MD[15]; Angelika Eggert, MD[15]; Heiko-Manuel Teltschik, MD[16]; Toni Illhardt, MD[1]; Rupert Handgretinger, MD[1]; and Peter Lang, MD[1,11]

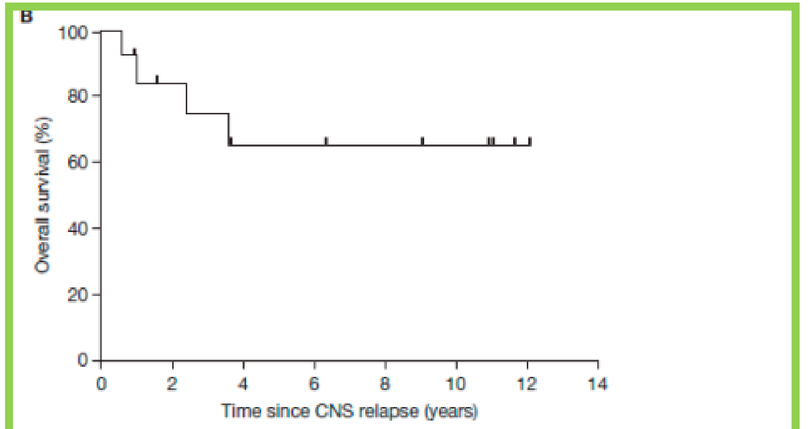


Journal of Clinical Medicine 2023
MDPI

Article

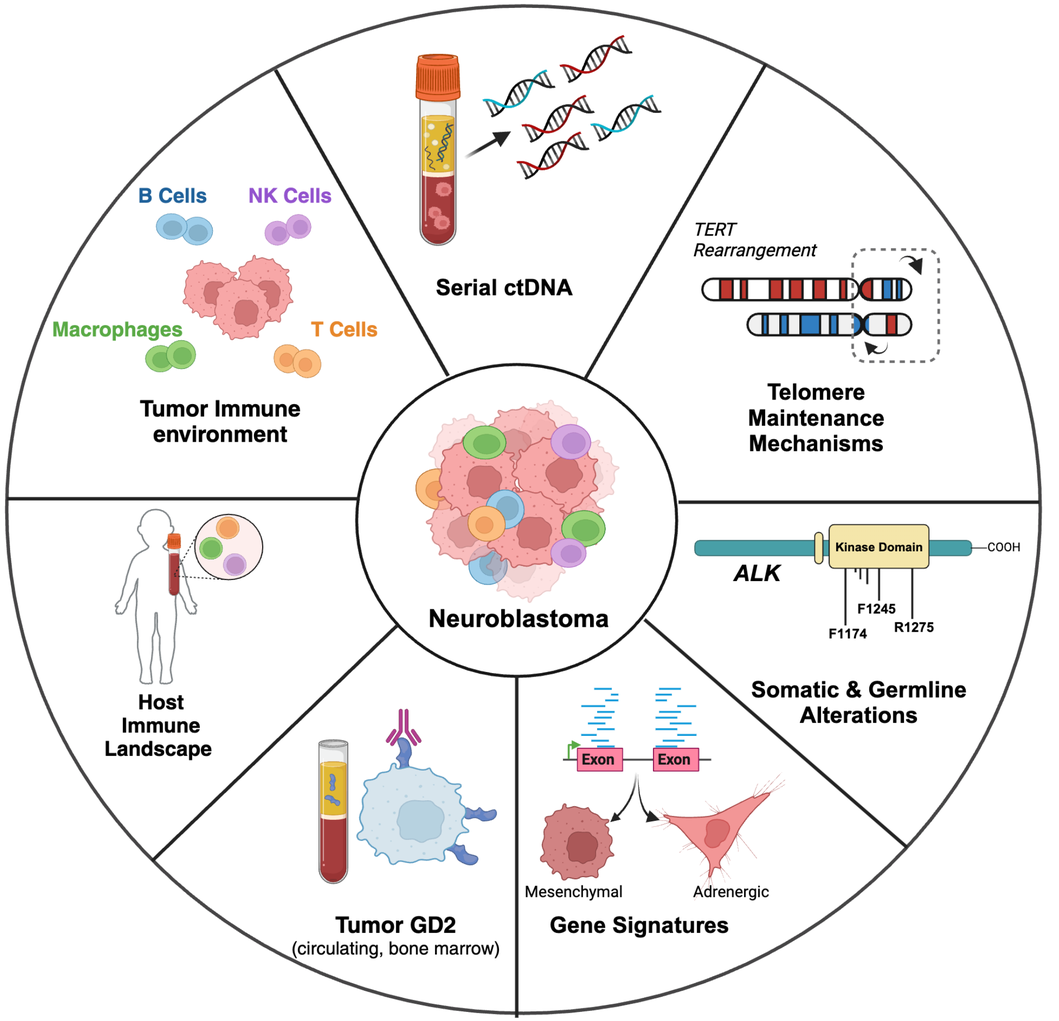
Multimodal Therapy with Consolidating Haploidentical Stem Cell Transplantation and Dinutuximab Beta for Patients with High-Risk Neuroblastoma and Central Nervous System Relapse

Tim Flaadt [1,*], Martin Ebinger [1], Malin Schreiber [1], Ruth L. Ladenstein [2,3], Thorsten Simon [4], Holger N. Lode [5], Barbara Hero [4], Martin U. Schuhmann [6], Jürgen Schäfer [7], Frank Paulsen [8], Beate Timmermann [9], Angelika Eggert [10] and Peter Lang [1]



Take-home messages

- ✓ NB refrattario è distinto da recidivato e tende ad avere outcome relativamente migliori, ma la prognosi resta severa
- ✓ Non esiste ancora uno standard di seconda linea; la gestione è multimodale e molto eterogenea
- ✓ Le strategie più promettenti sono chemo-immunoterapia anti-GD2, 131I-mIBG, approcci targeted guidati da profilo molecolare e terapie cellulari
- ✓ Per migliorare la prognosi saranno necessari:
  - studi clinici multicentrici per valutare nuove immunoterapie, radiofarmaci e terapie cellulari
  - una migliore comprensione dei meccanismi di resistenza ai trattamenti
  - una gestione più efficace delle tossicità acute e degli effetti collaterali a lungo termine
  - un accesso più equo alle terapie innovative



SCAN ME