



**XLIX**  
CONGRESSO  
NAZIONALE  
**AIEOP**

# Neuroblastoma

**Malattia recidivata dopo prima linea di trattamento**

Massimo CONTE

UOC Oncologia IRCSS G.Gaslini GE

Bologna, 1 ottobre 2024



***Il sottoscritto Massimo CONTE***

*ai sensi dell'art. 3.3 sul Conflitto di Interessi, pag. 17 del Reg. Applicativo dell'Accordo Stato-Regione del 5 novembre 2009,*

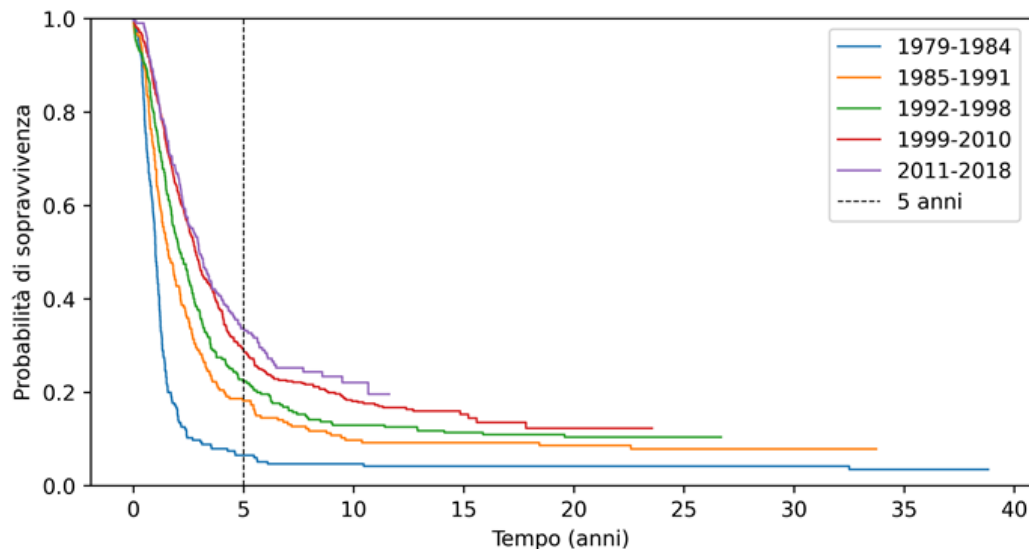
dichiara

- ☐ *che negli ultimi due anni NON ha avuto rapporti diretti di finanziamento con soggetti portatori di interessi commerciali in campo sanitario*
- ☒ **X** *che negli ultimi due anni ha avuto rapporti diretti di finanziamento con i seguenti soggetti portatori di interessi commerciali in campo sanitario:*
  - ***Recordati Rare Diseases***
  - ***Norgine Italia***



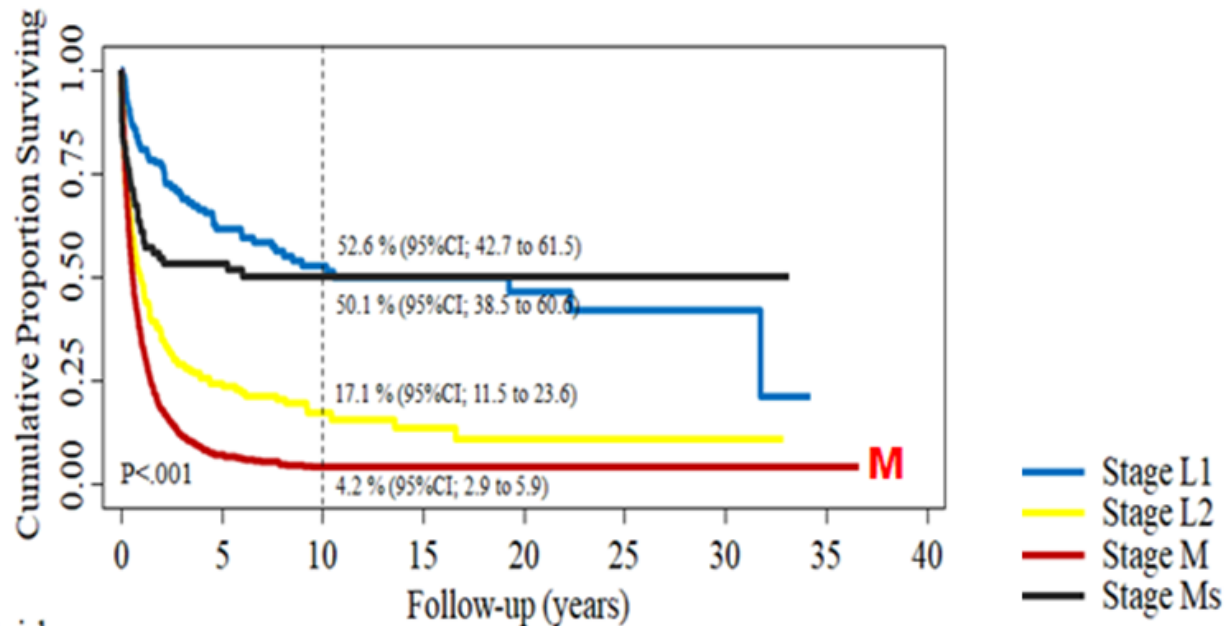
**RINB. Sopravvivenza dopo recidiva / PM per anni di arruolamento. 1374 casi**

	Enrollment period					Total N (%)
	1979-1984 N (%)	1985-1991 N (%)	1992-1998 N (%)	1999-2010 N (%)	2011-2018 N (%)	
<b>Total</b>	337 (100)	497 (100)	617 (100)	1216 (100)	612 (100)	3279 (100)
<b>Relapse/PM</b>						
No	122 (36.2)	277 (55.7)	362 (58.7)	746 (61.3)	398 (65.0)	1905 (58.1)
Yes	215 (63.8)	220 (44.3)	255 (41.3)	470 (38.7)	214 (35.0)	1374 (41.9)



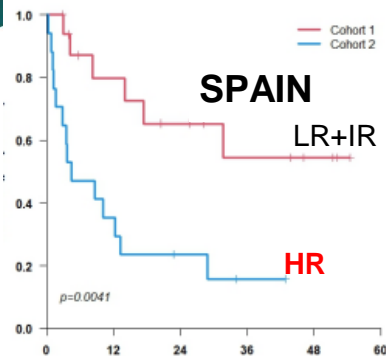


**RINB. Sopravvivenza per stadio dopo recidiva. 1374 casi**

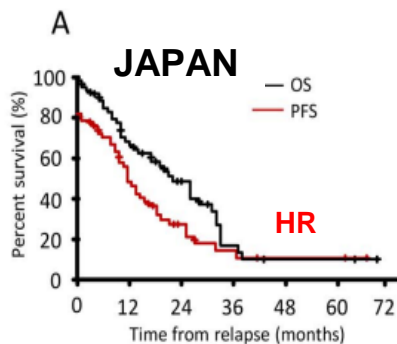




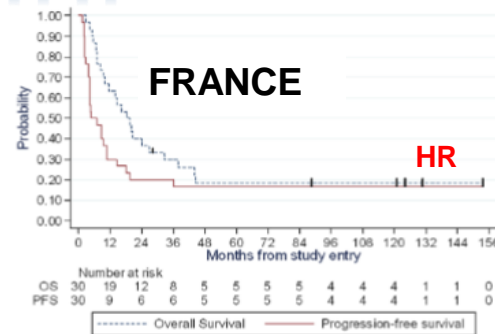
# UN PROBLEMA DI TUTTI ...



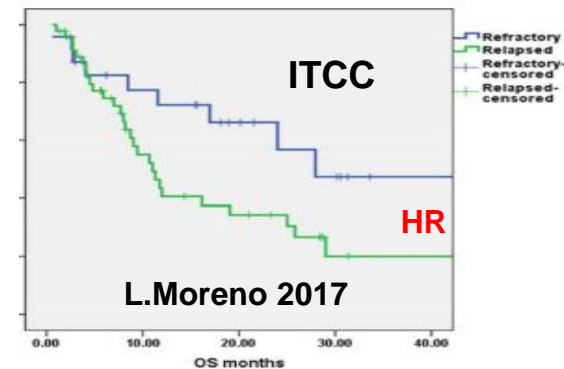
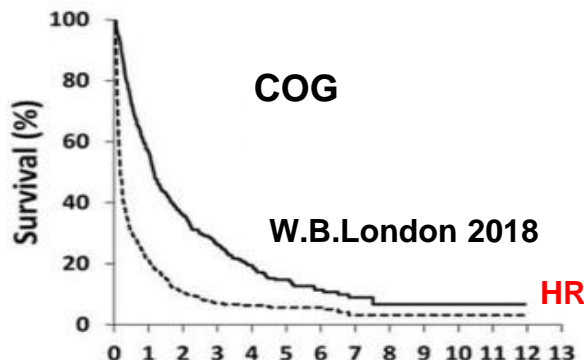
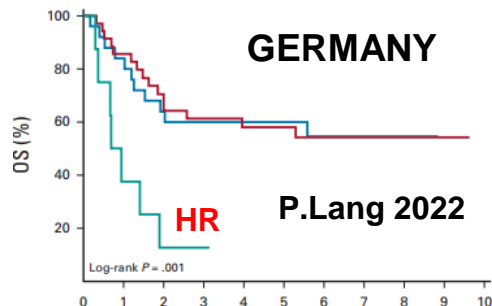
J.B. Munoz 2023



J.Hara 2022



F.Servin 2023





## **Perché è difficile recuperare una recidiva di NB-HR ???**

1. Pochi farmaci a disposizione
2. Pochi studi randomizzati / Spesso solo controlli storici
3. Criteri di inclusione e risposta differenti
4. Recidivati / Refrattari / PM trattati allo stesso modo
5. Endpoints diversi (ORR-PFS-EFS-OS)
6. Assenza di protocolli condivisi
7. Necessità di revisione centralizzata delle risposte







## ...Recidivati – Refrattari – PM ... **chi sono ???**

2022



### HHS Public Access

Author manuscript

*Cancer*. Author manuscript; available in PMC 2023 November 01.

Published in final edited form as:

*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<sup>1</sup>, Judith G. Villablanca, MD<sup>2</sup>, Barbara Hero, MD<sup>3</sup>, Brian H. Kushner, MD<sup>4</sup>, Keith Wheatley, DPhil<sup>5</sup>, Klaus H. Beiske, MD, PhD<sup>6</sup> [Prof.], Ruth L. Ladenstein, MD<sup>7</sup> [Prof.], Sylvain Baruchel, MD<sup>8</sup>, Margaret E. Macy, MD<sup>9</sup>, Lucas Moreno, MD, PhD<sup>10</sup>, Nita L. Seibel, MD<sup>11</sup>, Andrew D. Pearson, MD<sup>12</sup>, Katherine K. Matthay, MD<sup>13</sup>, Dominique Valteau-Couanet, MD, PhD<sup>14</sup>

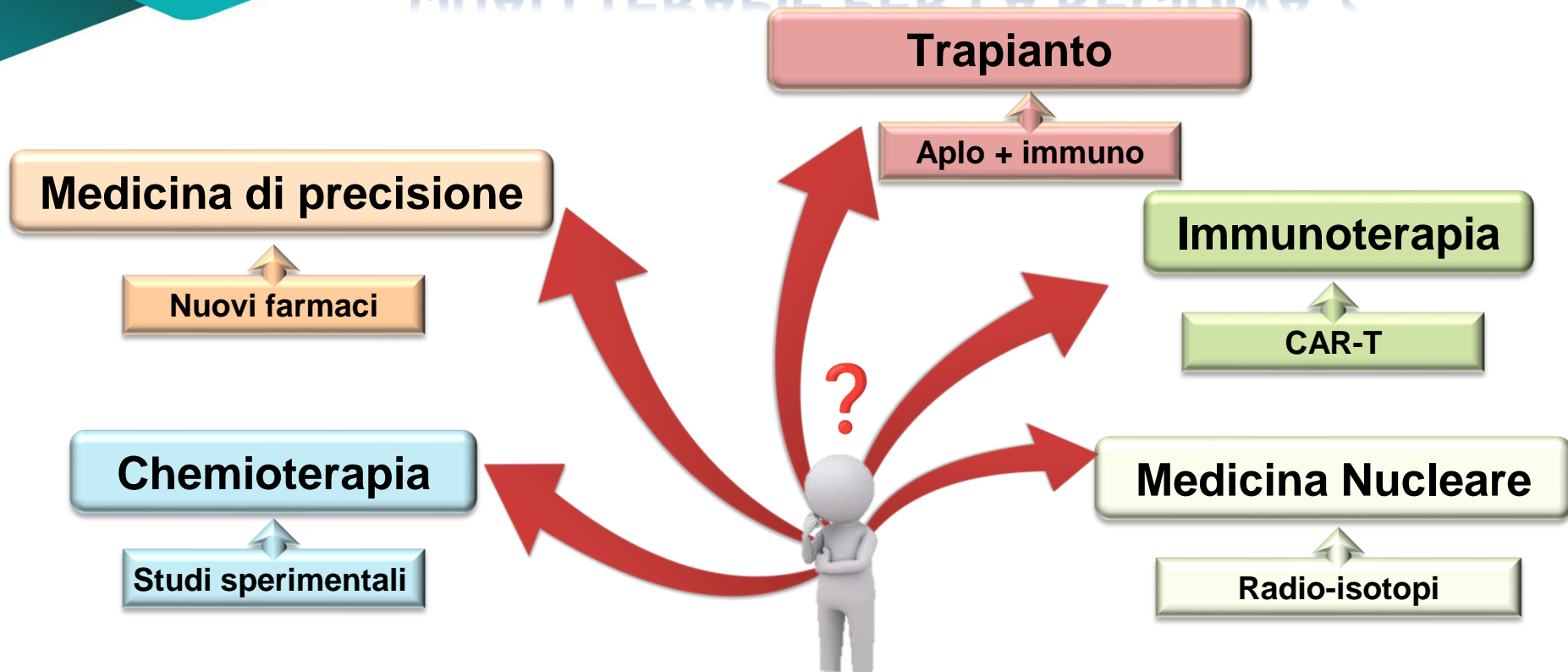


**Conclusions:** The use of international consensus eligibility, evaluability and response criteria for early phase clinical studies will facilitate collection of comparable data across international trials and promote more rapid identification of effective treatment regimens for high-risk neuroblastoma.





## QUALI TERAPIE PER LA RECIDIVA ?





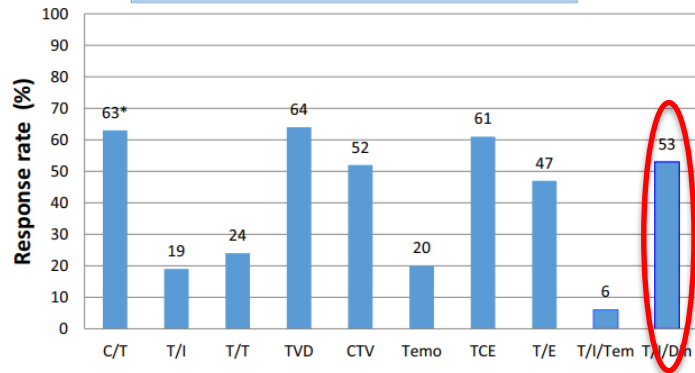
Summary of response assessment in each study.

Study	Drug	Timing of response assessment	Response rate (%)
Ashraf 2013 [16]	Topotecan/cyclophosphamide	Best	63 <sup>a</sup>
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 + temsirolimus + dinutuximab	Best	6 53

<sup>a</sup> Denotes that the response includes mixed response.

# CHEMIOTERAPIA

## Response to different treatments



2019

European Journal of Cancer 111 (2019) 50–58



Available online at [www.sciencedirect.com](http://www.sciencedirect.com)

**ScienceDirect**

journal homepage: [www.ejancer.com](http://www.ejancer.com)



## Review

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

Fiona Herd <sup>a</sup>, Nermine O. Basta <sup>b</sup>, Richard J.Q. McNally <sup>b</sup>, Deborah A. Tweddle <sup>b,c,\*</sup>

**UK**

<sup>a</sup> Department of Paediatric Oncology, Great North Children's Hospital, Royal Victoria Infirmary, Newcastle, NE1 4LP, UK  
<sup>b</sup> Institute of Health & Society, Newcastle University, Sir James Spence Institute, Royal Victoria Infirmary, Queen Victoria Road, Newcastle upon Tyne, NE1 4LP, United Kingdom  
<sup>c</sup> Wolfson Childhood Cancer Research Centre, Northern Institute for Cancer Research, Newcastle University, Level 6 Herschel Building, Brewery Lane, Newcastle upon Tyne, NE1 7RU, UK

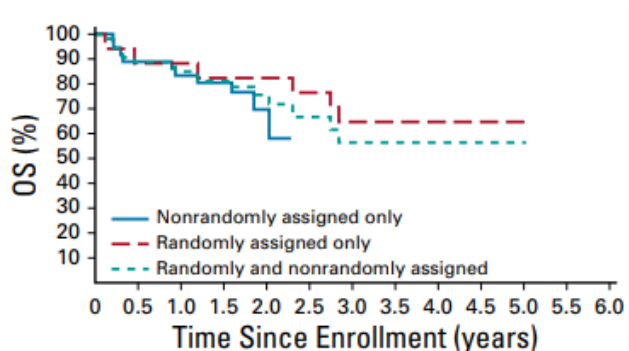
**TEMIRI + anti GD2**



**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<sup>1</sup>; Alice L. Yu, MD, PhD<sup>2,3</sup>; Arlene Naranjo, PhD<sup>4</sup>; Fan F. Zhang, MS<sup>5</sup>; Wendy B. London, PhD<sup>6</sup>; Barry L. Shulkin, MBA, MD<sup>7</sup>; Marguerite T. Parisi, MS, MD<sup>8</sup>; Sabah-E-Noor Servaes, MD<sup>9</sup>; Mitchell B. Diccianni, PhD<sup>2</sup>; Jacquelyn A. Hank, PhD<sup>10</sup>; Mildred Felder, BS<sup>10</sup>; Jennifer Birstler, MS<sup>10</sup>; Paul M. Sondel, MD, PhD<sup>10</sup>; Shahab Asgharzadeh, MD<sup>11</sup>; Julia Glade-Bender, MD<sup>12</sup>; Howard Katzenstein, MD<sup>13</sup>; John M. Maris, MD<sup>9</sup>; Julie R. Park, MD<sup>8</sup>; and Rochelle Bagatell, MD<sup>9</sup>



**Casi 53**

**2022**

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

Nur Olgun<sup>1\*</sup>, Emre Cecen<sup>1</sup>, Dilek Ince<sup>1</sup>, Deniz Kizmazoglu<sup>1</sup>, Birsan Baysal<sup>1</sup>, Ayse Onal<sup>1</sup>, Ozhan Ozdogan<sup>2</sup>, Handan Guleryuz<sup>3</sup>, Riza Cetingoç<sup>4</sup>, Ayse Demiral<sup>4</sup>, Mustafa Olguner<sup>5</sup>, Ahmet Celik<sup>6</sup>, Serra Kamer<sup>7</sup>, Erdener Ozer<sup>8</sup>, Zekiye Altun<sup>9</sup> and Safiye Aktas<sup>9</sup>

**Casi 19**

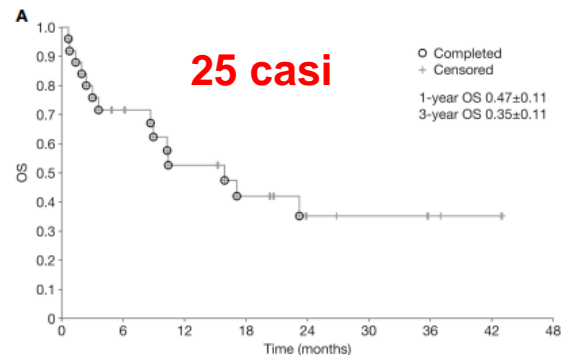
2023

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

Aleksandra Wieczorek <sup>1,2\*</sup>, Anna Zaniewska-Tekieli <sup>2</sup>, Karoline Ehlert <sup>3</sup>, Katarzyna Pawinska-Wasikowska <sup>1,2</sup>, Walentyna Balwierz <sup>1,2†</sup> and Holger Lode <sup>1,2,3†</sup>

frontiers | Frontiers in Oncology

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



2024

39 casi



ELSEVIER

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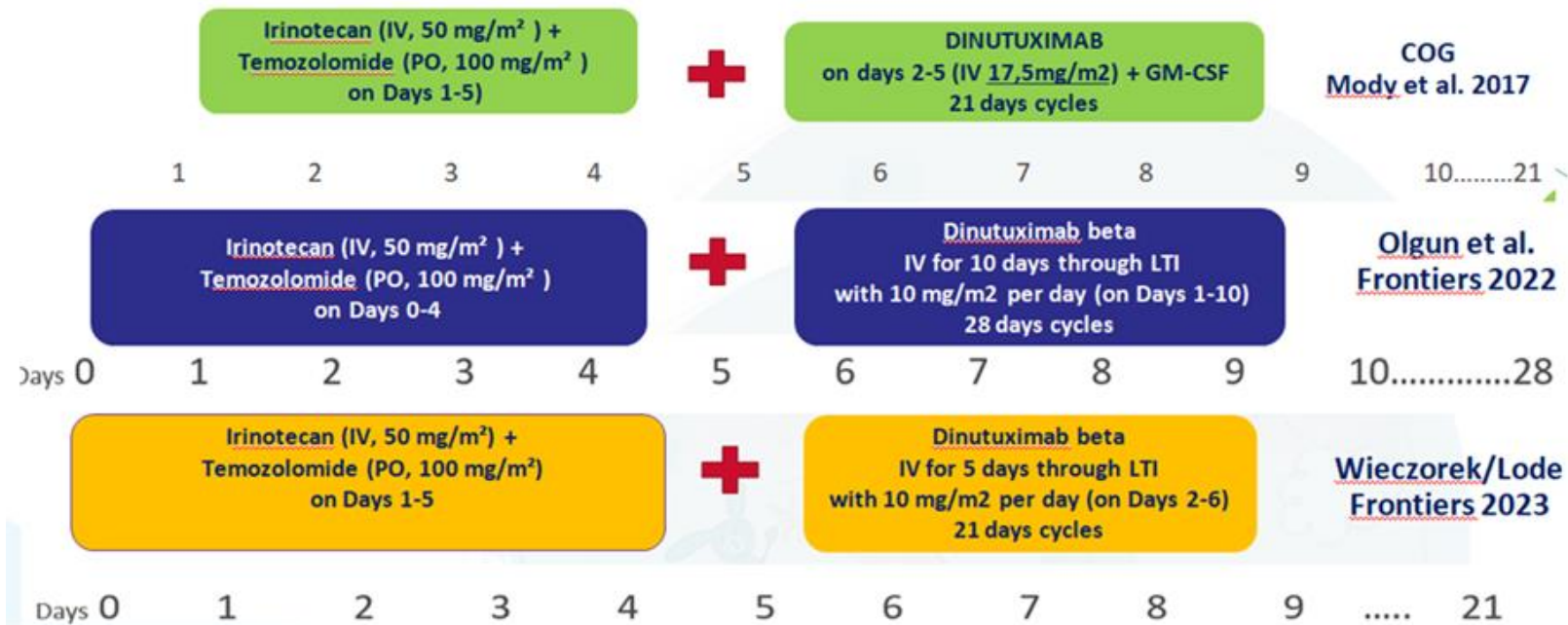


Original research

Chemo-immunotherapy with dinutuximab beta in patients with relapsed/progressive high-risk neuroblastoma: does chemotherapy backbone matter?

Patricia Raiser <sup>a</sup>, Gudrun Schleiermacher <sup>b,c</sup>, Marion Gambart <sup>d</sup>, Benoit Dumont <sup>e</sup>, Anne-Sophie Defachelles <sup>f</sup>, Estelle Thebaud <sup>g</sup>, Julie Tandonnet <sup>h</sup>, Claudia Pasqualini <sup>a</sup>, Stéphanie Proust <sup>i</sup>, Natacha Entz-Werle <sup>j</sup>, Isabelle Aerts <sup>b,c</sup>, Lee A. Ndounga-Diakou <sup>k</sup>, Arnaud Petit <sup>l</sup>, Chloe Puiseux <sup>m</sup>, Camille Khanfar <sup>n</sup>, Jeremie Rouger <sup>o</sup>, Ludovic Mansuy <sup>p</sup>, Joy Benadiba <sup>q</sup>, Frédéric Millot <sup>r</sup>, Claire Pluchart <sup>s</sup>, Salim Laghouati <sup>k</sup>, Birgit Geoerger <sup>a,t</sup>, Gilles Vassal <sup>a</sup>, Dominique Valteau-Couanet <sup>a</sup>, Pablo Berlanga <sup>a,\*</sup>







## Marzo 24 Survey italiana: chemio + immuno in pazienti recidivi/refrattari

Centro/ casi	Recidiva	Refrat/Resisten ti	Risposta SI / NO	Outcome Vivi/Dec
Trieste / 0				
Catanzaro /1	1		1/0	1/0
Roma BG/10	5	5	5/5	9/1
Verona/0				
Bologna/1		1	1/0	1/0
Pisa/1	1		1/0	1/0
Genova/2	2		2/0	2/0
Brescia/2		2	2/0	2/0
Bergamo/1	1		1/0	1/0
Ancona/1	1		Too early	1/0
Napoli/0				
Gemelli RO/0				
Palermo/1	1		0/1	0/1
Sassari/0				
Padova/2	2		1/1	1/1
Bari/3	1	2	1/2	1/2
MI/1		1	1/0	1/0
FI/3	1	2	3/0	2/1
Pescara/0				
Catania/1	1		1/0	1/0
Torino/0				
Cagliari/0				
Modena/0				
Perugia/3	1	2	2/1	3/0
Pavia/2	2		0/2	1/1
<b>25 Centri / 35</b>	<b>20</b>	<b>15</b>	<b>22/12 1 too early</b>	<b>28/7</b>



**25 centri AIEOP**  
**35 casi**  
**Rec/Res-Ref 20/15**

**Risposte**  
**SI 22 (63%)**  
**NO 12**  
**Too early 1**



**Promotore IRCSS Ospedale Pediatrico Bambino Gesù Roma: Chemoimmunotherapy in Relapsed/Refractory Neuroblastoma: a real-world retrospective observational study**



# BEACON 1

2024

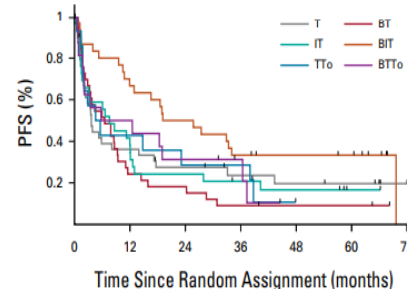
Original Reports | Pediatric Oncology

**casi 160**

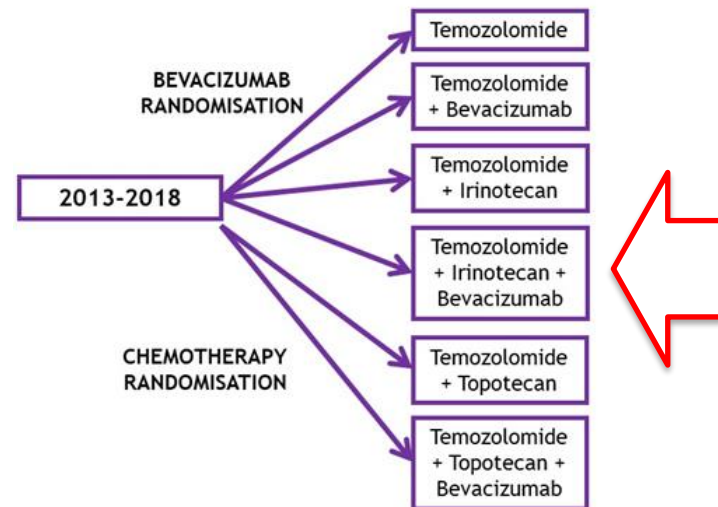
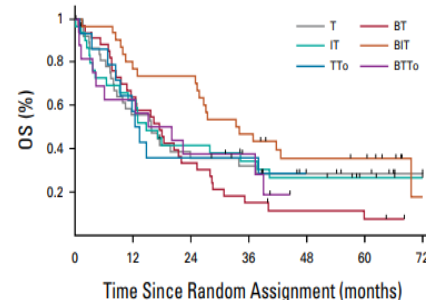
## Bevacizumab, Irinotecan, or Topotecan Added to Temozolomide for Children With Relapsed and Refractory Neuroblastoma: Results of the ITCC-SIOPEN BEACON-Neuroblastoma Trial

Lucas Moreno, MD, PhD<sup>1</sup>; Rebekah Weston, MSc<sup>2</sup>; Cormac Owens, MD<sup>3</sup>; Dominique Valteau-Couanet, MD<sup>4</sup>; Marion Gambart, MD<sup>5</sup>; Victoria Castel, MD, PhD<sup>6</sup>; C. Michel Zwaan, MD, PhD<sup>7</sup>; Karsten Nysom, MD, PhD<sup>8</sup>; Nicolas Gerber, MD<sup>9</sup>; Aurora Castellano, MD<sup>10</sup>; Genevieve Laureys, MD, PhD<sup>11</sup>; Ruth Ladenstein, MD, PhD<sup>12</sup>; Jochen Rössler, MD<sup>13</sup>; Guy Makin, MD<sup>14</sup>; Dermot Murphy, MD<sup>15</sup>; Bruce Morland, MD<sup>16</sup>; Sucheta Vaidya, MD<sup>17</sup>; Estelle Thebaud, MD<sup>18</sup>; Natasha van Eijkelenburg, MD, PhD<sup>19</sup>; Deborah A. Tweddle, MD, PhD<sup>19</sup>; Giuseppe Barone, MD, PhD<sup>20</sup>; Julie Tandonnet, MD<sup>21</sup>; Nadege Corradini, MD<sup>22</sup>; Pascal Chastagner, MD, PhD<sup>23</sup>; Catherine Paillard, MD<sup>24</sup>; Francisco J. Bautista, MD, PhD<sup>25</sup>; Soledad Gallego Melcon, MD, PhD<sup>26</sup>; Bram De Wilde, MD, PhD<sup>27</sup>; Lynley Marshall, PhD, MB, BCH<sup>28</sup>; Juliet Gray, MD, PhD<sup>29</sup>; Susan A. Burchill, PhD<sup>30</sup>; Gudrun Schleiermacher, MD, PhD<sup>31</sup>; Louis Chesler, MD, PhD<sup>32</sup>; Andrew Peet, MD, PhD<sup>33</sup>; Martin O. Leach, PhD<sup>34</sup>; Kieran McHugh, MD<sup>35</sup>; Roisin Hayes, MD<sup>36</sup>; Neil Jerome, PhD<sup>37</sup>; Hubert Caron, MD, PhD<sup>38</sup>; Jennifer Laidler, BSc<sup>39</sup>; Nicola Fenwick, BSc<sup>40</sup>; Grace Holt, MSc<sup>41</sup>; Veronica Moroz, MSc<sup>42</sup>; Pamela Kearns, MD, PhD<sup>43</sup>; Simon Gates, PhD<sup>44</sup>; Andrew D.J. Pearson, MD<sup>45</sup>; and Keith Wheatley, DPhil<sup>46</sup>; on behalf of Innovative Therapies for Children with Cancer (ITCC) and European Association for Neuroblastoma Research (SIOPEN)

G



H



**ARM BIT THE BEST !!**



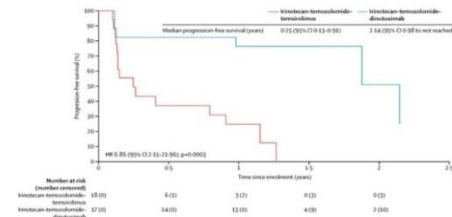


## Rationale for BEACON Immuno (anti-GD2) amendment in 2019

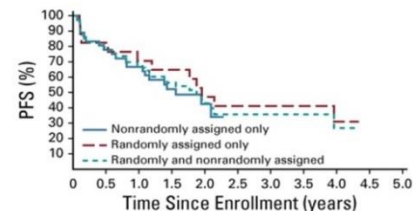
- Emerging evidence of benefit of chemo-immunotherapy
- ANBL1221; Tem-Iri-Dinutuximab-GM-CSF. n= 34 randomised (17 with chemo-antibody) plus expansion cohort n=36. (*Mody, Lancet Oncol 2017, JCO 2020*)
- St Jude: Hu14.18K322A-GM-CSF-IL2 + chemo (Topo-cyclo, Tem-Iri and ICE). n=13. (*Federico, CCR 2017*)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



**BEACON 2**



*Mody Lanc. Oncology 2017*



*Mody JCO 2020*



## ARRUOLAMENTO 3Y

**GE**  
**MI**  
**TO**  
**FI**  
**PD**  
**Roma**



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

Version: 1.0

Date: 19<sup>th</sup> March 2024

**Chief Investigator:**  
**Coordinating Sponsor:**

Dr Lucas Moreno  
University of Birmingham



### Protocol

#### Tier 1:

##### Arm A: dbIT

Dinutuximab beta 10 mg/m<sup>2</sup>/day iv days 1-7, Irinotecan 50 mg/m<sup>2</sup> iv days 1-5, Temozolomide 100 mg/m<sup>2</sup> po days 1-5  
3 weekly x12 cycles

##### Arm B: BIT

Bevacizumab 15 mg/kg iv day 1, Irinotecan 50 mg/m<sup>2</sup> iv days 1-5, Temozolomide 100 mg/m<sup>2</sup> po days 1-5  
3 weekly x12 cycles

#### Tier 2:

##### Arm C: dbBIT

Bevacizumab 15 mg/kg/day iv day 1, Dinutuximab beta 10 mg/m<sup>2</sup>/day iv days 1-7, Irinotecan 50 mg/m<sup>2</sup> iv days 1-5, Temozolomide 100 mg/m<sup>2</sup> po days 1-5  
3 weekly x12 cycles

### TIER 2 Relapsed Neuroblastoma

Subsequent  
relapse or  
ineligible to  
randomisation

1<sup>st</sup> analysis,  
n=10 per arm

Arm C - dbBIT

Arm D - tbc

Tier 2 arm added if successful

### TIER 1

#### Relapsed Neuroblastoma

1<sup>st</sup> analysis,  
n=40 per arm

2<sup>nd</sup> analysis,  
n=75 per arm

Arm A - dbIT

Arm B - BIT





cancers

2023



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	Naxitimb	2020
	Dinutuximab	2015
	Dinutuximab beta *	2017
RAS-MAPK	Selumetinib	2020
	Binimetinib	2018
	Sorafenib	2011
mTOR	Sirolimus	1999
	Temsirolimus	2007
	Palbociclib	2015
CDK4/6	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	NCT0373097
	iC9-GD2 T	NCT01822652
	C7R-GD2.CART	NCT03635632
	BCD-245	NCT05782959
	iC9.GD2.CAR.II-15 T	NCT03721068
	GINAKIT	NCT03294954
	Ex Vivo Expanded Allogeneic γδ T Cells	NCT05400603
	Naxitimb	NCT05489887, NCT03363373, NCT02650648, NCT01419834
	Dinutuximab beta	NCT02914405, NCT01704716, NCT05272371, 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



**MAGGIO 24 150 PTS**

A Pivotal Phase 2 Trial of Antibody Naxitamab (hu3F8) and Granulocyte-Macrophage Colony Stimulating Factor (GM-CSF) in High-Risk Neuroblastoma Patients with Primary Refractory Disease or Incomplete Response to Salvage Treatment in Bone and/or Bone Marrow

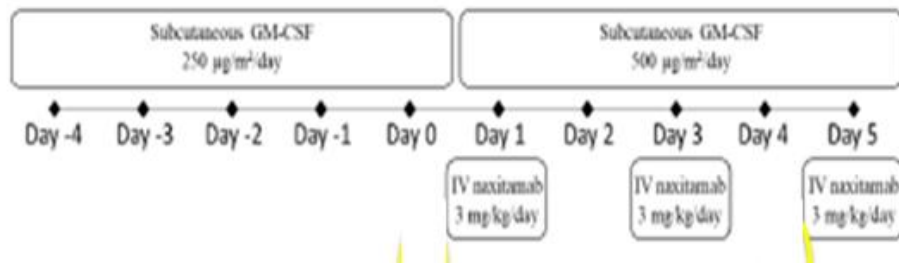


Figure 1: Eight countries have enrolled and treated patients in Trial 201

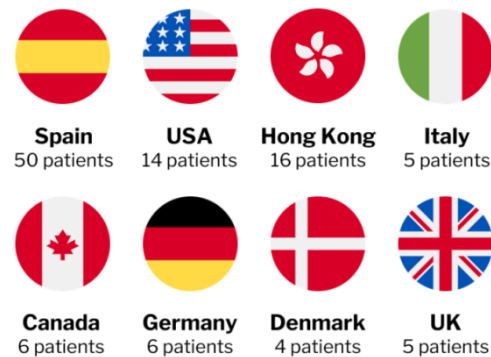
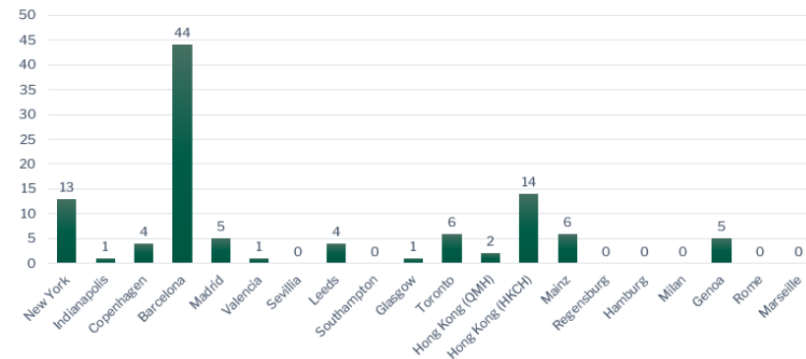


Figure 3 Distribution of treated patients per site in Trial 201





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

**Children < 18 y treated with Lornatinib + Topo/ex RR 63%**

....

13 of 27 (48%) responders achieved MIBG complete responses, supporting lorlatinib's rapid translation into active phase 3 trials for patients with newly diagnosed high-risk, ALK-driven neuroblastoma. ClinicalTrials.gov registration: [NCT03107988](https://clinicaltrials.gov/ct2/show/study/NCT03107988).





cancers

2023

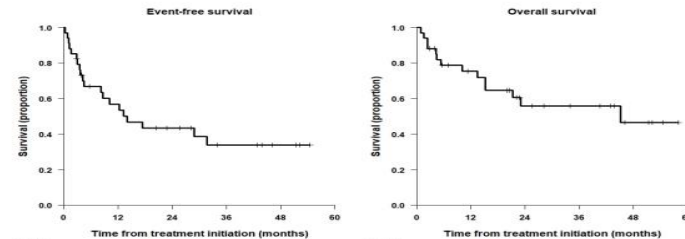
Casi 34



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



2024

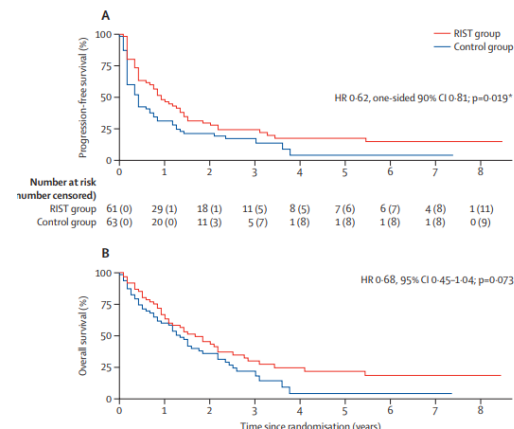
Casi 129



## 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 Suttrop, 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 Hundsdoerfer, 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 Crazzolar, Naghme Niktoeh, Gunnar Cario, Joerg Faber, Martin Demmert, Florian Babor, Birgit Fröhlich, Stefan Bielack, Toralf Bernig, Johann Greil, Angelika Eggert, Thorsten Simon, Juergen Foell







## PREME 65 CASI RECIDIVE/REFRATTARI

<u>Materiale</u>	<u>1 o più mutazioni</u>	MTB	Terapia target
43 Tessuto tumorale	30 (69.7%)	25/30	10 (40%)
22 Sangue midollare	18 (81,8%)	15/18	8 (53%)
65 Totale	48 (73,8%)	40/48	18 (45%)

**NB-HR ESORDIO O  
RECIDIVA**



## PREME

Journal of  
Translational Medicine



cancers



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

### RESEARCH

### Open Access



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

Mario Capasso<sup>1,3†</sup>, Chiara Brignole<sup>2†</sup>, Vito A. Lasorsa<sup>3†</sup>, Veronica Bensa<sup>2</sup>, Sueva Cantalupo<sup>1,3</sup>, Enrico Sebastiani<sup>4</sup>, Alessandro Quattrone<sup>4</sup>, Eleonora Ciampi<sup>2</sup>, Marianna Avitabile<sup>1,3</sup>, Angela R. Sementa<sup>5</sup>, Katia Mazzocco<sup>5</sup>, Barbara Cafferata<sup>5</sup>, Gabriele Gaggero<sup>5</sup>, Valerio G. Vellone<sup>5</sup>, Michele Cilli<sup>6</sup>, Enzo Calarco<sup>2</sup>, Elena Giusto<sup>2</sup>, Patrizia Perri<sup>2</sup>, Sanja Aveic<sup>7</sup>, Doriana Fruci<sup>8</sup>, Annalisa Tondo<sup>9</sup>, Roberto Luksch<sup>10</sup>, Rossella Mura<sup>11</sup>, Marco Rabusin<sup>12</sup>, Francesco De Leonardis<sup>13</sup>, Monica Cellini<sup>14</sup>, Paola Coccia<sup>15</sup>, Achille Iolascon<sup>1,3</sup>, Maria V. Corrias<sup>2</sup>, Massimo Conte<sup>16</sup>, Alberto Garaventa<sup>16</sup>, Loredana Amoroso<sup>16</sup>, Mirco Ponzoni<sup>2†</sup> and Fabio Pastorino<sup>2†</sup>



International Journal of  
*Molecular Sciences*



### Case Report

## Italian Precision Medicine in Pediatric Oncology: Moving beyond Actionable Alterations

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

### Article

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

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



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

Jose Genolla<sup>1</sup> · Trinidad Rodriguez<sup>1</sup> · Pablo Minguez<sup>2</sup> · Ricardo Lopez-Almaraz<sup>3</sup> · Veronica Llorens<sup>1</sup> · Aizpea Echebarria<sup>3</sup>



2022

ORIGINAL ARTICLES

## Tandem high-dose $^{131}\text{I}$ -MIBG therapy supported by dosimetry in pediatric patients with relapsed-refractory high-risk neuroblastoma: the Bambino Gesù' Children's Hospital experience

Altini, Claudio<sup>a</sup>; Villani, Maria F.<sup>a</sup>; Di Giannatale, Angela<sup>c</sup>; Cassano, Bartolomeo<sup>b</sup>; Pizzoferrero, Milena<sup>a</sup>; Serra, Annalisa<sup>c</sup>; Castellano, Aurora<sup>c</sup>; Cannatà, Vittorio<sup>b</sup>; Garganese, Maria C.<sup>a</sup>

Received: 3 May 2023 | Revised: 5 July 2023 | Accepted: 21 July 2023

DOI: 10.1002/jbc.30615

RESEARCH ARTICLE

2023

Pediatric  
Blood &  
Cancer



aspho  
The American Society of  
Pediatric Hematology/Oncology

WILEY

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

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

VECCHI RADIO-ISOTOPI

2021

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

**CONCLUSION** | Clin Oncol 39:3506-3514. © 2021 by American Society of Clinical Oncology toxicity.

Vincristine and irinotecan do not appear to improve the response rate to MIBG and are associated with increased toxicity.



A biomarker enriched phase I/II clinical trial of  $^{131}\text{I}$ -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)			
$^{131}\text{I}$ -mIBG			X														
PBSC rescue																	X

21 patients per group

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

**SIOPEN**  
AGM 2024 MEETING

18-20 September 2024

Vilnius, Lithuania



## MiNivAn – design

- Non-myeloablative dose  $^{131}\text{I}$ -mIBG (2 Gy) – fixed
- 3 mg/Kg Nivolumab (anti-PD-1) every 2 weeks – fixed
- Dose escalation of dinutuximab beta (anti-GD2):
  - Cohort 1: No dinutuximab beta (3-6 patients)
  - Cohort 2: 50% \*LTI dose of dinutuximab beta (50mg/m<sup>2</sup> over 10 days) (3-6 patients)
  - Cohort 3: 100% LTI dose of dinutuximab beta (100 mg/m<sup>2</sup> over 10 days) (initial 18 patients, extended to 30 patients)

4 sites

- Southampton, UCLH (UK)
- Madison (US)
- Greifswald (Germany)





ORIGINAL ARTICLE

2020



## NUOVI RADIO-ISOTOPI

2022



### A Phase II Trial of a Personalized, Dose-Intense Administration Schedule of <sup>177</sup>Lutetium-DOTATATE in Children With Primary Refractory or Relapsed High-Risk Neuroblastoma—LuDO-N

OPEN ACCESS

Edited by:

Sabine Sarnacki,

University of Basel, Switzerland

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

2020

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

Kong et al. J Ped Haem Oncol

A phase IIa trial of molecular radiotherapy with <sup>177</sup>-lutetium DOTATATE in children with primary refractory or relapsed high-risk neuroblastoma  
Gains et al. EJNMMI 2020

2024

iagnostics 2024, Vol. 14, Issue 3

1212



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 [<sup>64</sup>Cu]Cu-NOTA-ch14.18/CHO

Nils Florian Trautwein<sup>1,2</sup>, Johannes Schwenck<sup>1,2,3</sup>, Christian Seitz<sup>3,4</sup>, Ferdinand Seith<sup>5</sup>, Eduardo Calderón<sup>1</sup>, Sebastian von Beschwitz<sup>1</sup>, Stephan Singer<sup>6</sup>, Gerald Reischl<sup>2,3</sup>, Rupert Handgretinger<sup>4</sup>, Jürgen Schäfer<sup>5</sup>, Peter Lang<sup>4</sup>, Bernd J. Pichler<sup>2,3,7</sup>, Johannes H. Schulte<sup>4</sup>, Christian la Fougère<sup>1,3,7,8</sup> and Helmut Dittmann<sup>1</sup>



## Protocollo Studio Osservazionale

Vers. 1.0 30Mar2024



# 7 CENTRI

Autore del protocollo:

Dr. Roberto Luksch (Fondazione IRCCS Istituto Nazionale dei Tumori)

PI: Dr. Roberto Luksch

### Titolo

**Terapia radiometabolica con meta-iodo-benzil-guanidina per il trattamento del neuroblastoma: studio osservazionale (studio MIBGTER)**

<b>Obiettivi dello studio</b>	<p><i><b>OBIETTIVO PRIMARIO</b></i> Valutare l'impatto sulla sopravvivenza libera da eventi (EFS) del trattamento con radioterapia metabolica basato sull'utilizzo di ImIBG in pazienti affetti da neuroblastoma trattati presso i centri di riferimento della rete AIEOP.</p> <p><i><b>OBIETTIVI SECONDARI</b></i> -Valutare l'analisi di sopravvivenza -Descrivere gli effetti collaterali della terapia MIBG nella fase acuta e nella fase cronica -Eseguire sottogruppi di analisi dei risultati in base alle caratteristiche di presentazione della malattia al momento del trattamento con MIBG, i diversi tipi di radioterapia metabolica con mIBG effettuati</p>	<b>Tempi dello studio</b>	<p>Verranno inclusi nello studio pazienti affetti da neuroblastoma trattati con terapia MIBG a partire dal 1° gennaio 2007 fino al 31 dicembre 2022, con un periodo di follow-up che terminerà 36 mesi dopo la terapia MIBG dell'ultimo paziente incluso. Il numero delle visite cliniche sarà stabilito secondo la Buona Pratica Clinica e non verranno effettuate visite aggiuntive o valutazioni strumentali specificatamente legate al presente studio.</p> <p>Si prevede la conclusione dello studio entro 12 mesi una volta espletate tutte le pratiche presso i Centri partecipanti necessarie alla attivazione dello studio stesso, indicativamente entro Giugno 2025.</p>
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5 yrs EFS and OS rates of 43% and 53% respectively  
aGvHD rates 7.5%

## 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

2023

Journal of Clinical Oncology

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



Journal of  
*Clinical Medicine*

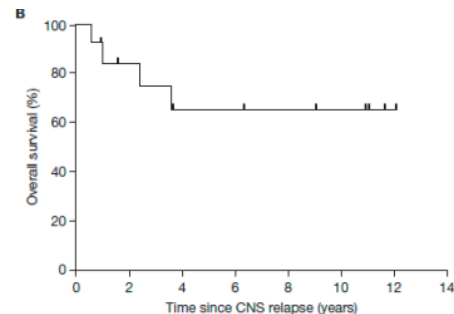
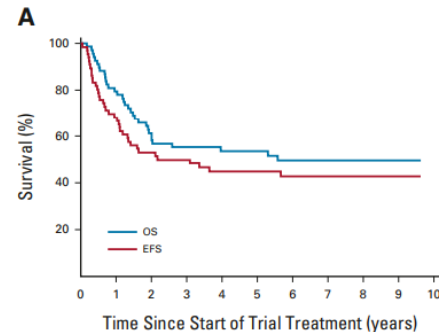
2023



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





# ATTIVAZIONE MAGGIO 23

**Trapianto aploidentico di cellule staminali emopoietiche  
con deplezione  $\text{TCR}\alpha\beta^+\text{CD}19^+$  seguito da immunoterapia  
in pazienti con Neuroblastoma alto rischio recidivato/resistente**

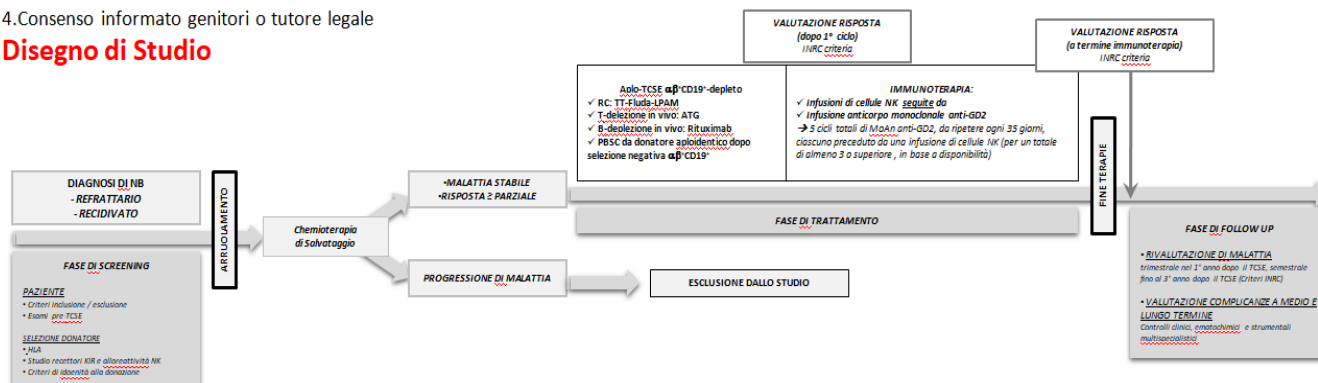
*Istituto Giannina Gaslini*



## CRITERI DI INCLUSIONE

1. Neuroblastoma alto rischio (stadio 4 con età > 12 mesi alla diagnosi, oppure stadio 2, 3, 4s con amplificazione di MYCN) in **recidiva locale, metastatica o combinata dopo protocollo di terapia di prima linea;**
2. **Stabilizzazione di malattia** (pari o superiore alla STABLE DISEASE secondo criteri INRC) ottenuta dopo chemioterapia di salvataggio;
3. **Disponibilità di un donatore familiare HLA aploidentico idoneo** ad eseguire una donazione di CSE da sangue periferico dopo stimolazione con GCSF(+/- Plerixafor);
4. Consenso informato genitori o tutore legale

## Disegno di Studio

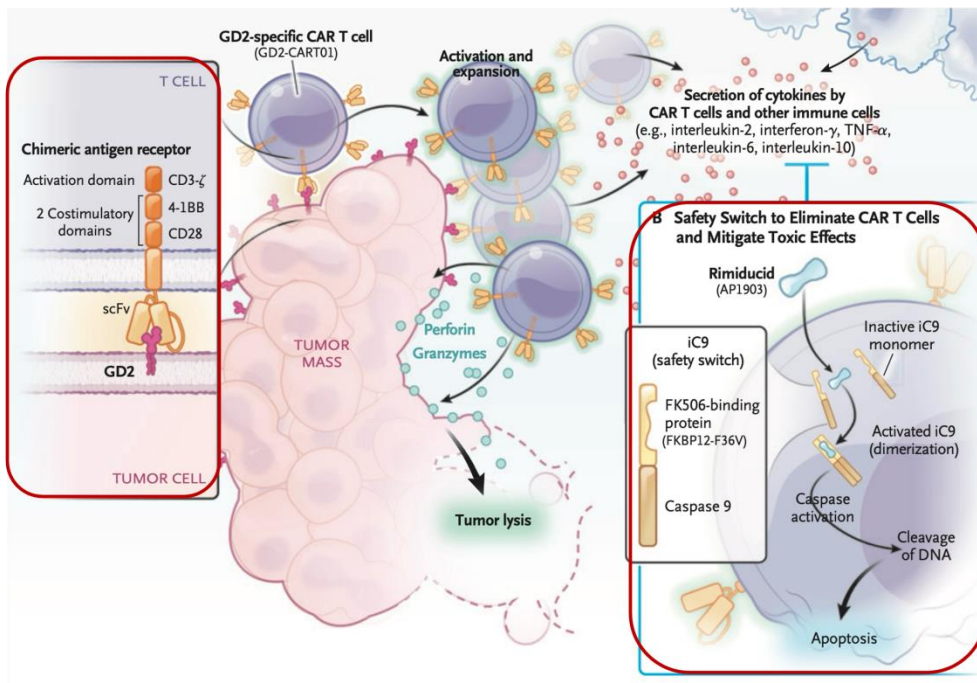




*Un cambio di rotta: CAR-T*



## Third Generation CAR Targeting GD2





2023

*The NEW ENGLAND JOURNAL of MEDICINE*

ORIGINAL ARTICLE

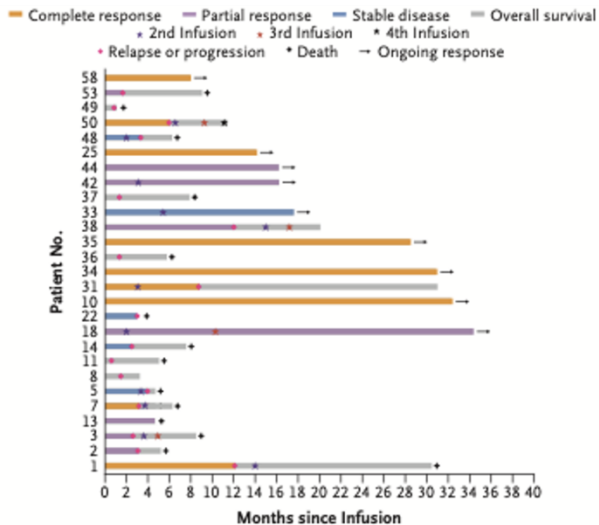
## GD2-CART01 for Relapsed or Refractory High-Risk Neuroblastoma

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\*



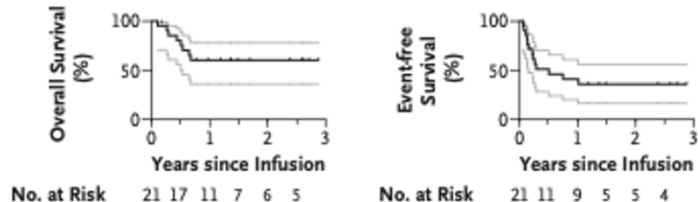


# Clinical response and outcome

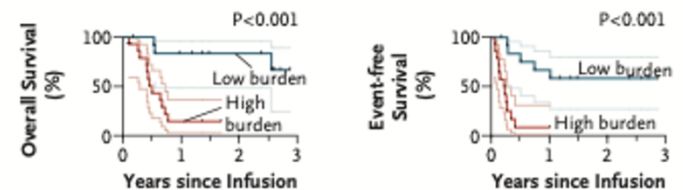


**ORR: 63%**

Patients Who Received Recommended Dose



According to Disease Burden\*



\*Low disease burden:

- SIOPEN skeletal score  $\leq 7$
- Tumor mass with longest diameter  $< 5\text{cm}$
- BM infiltration  $\leq 50\%$





## 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**

## 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



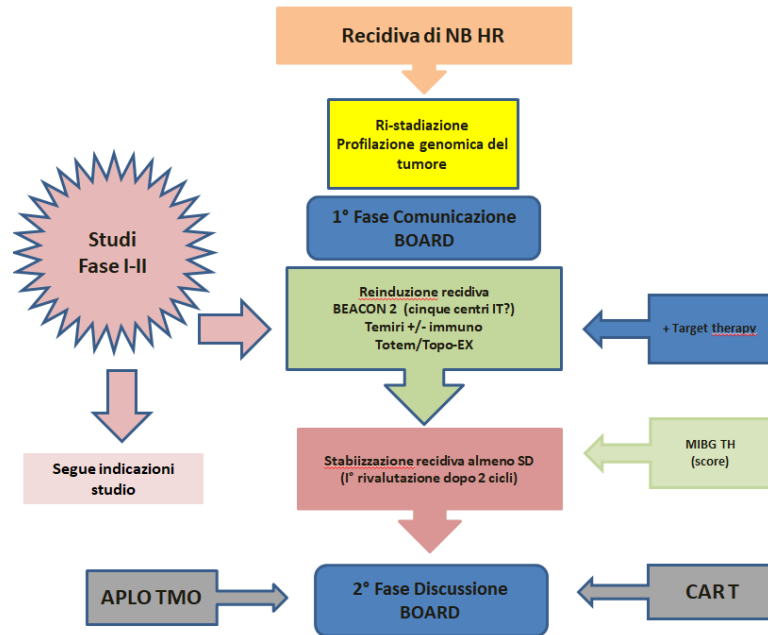
GD2-CAR01 infusion

## Suggerimenti per la gestione e trattamento di una recidiva di neuroblastoma (NB)



A cura del GDL-NB AIEOP

Versione 1 del 17 marzo 2024



**BOARD NB Componenti:** membri GDL-NB + esperti terapie cellulari-TMO-Nuovi Farmaci-Radioterapia  
*Una riunione mensile online*



## Take Home Message

**La terapia per un NB recidivato rimane una sfida aperta che deve tener conto di una serie di fattori :**

- Timing della recidiva
- Tipo di recidiva
- Precedente storia terapeutica
- Offerta possibile
- Condizioni del paziente
- Compliance del nucleo familiare



*... Le sfide sono ciò che rendono la vita interessante ...  
... Superarle e ciò che le dà significato ...*

*Grazie*

*Joshua J. Marine*

2024

2027

