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Neuroblastoma in childhood

Expert: **Prof Ruth Ladenstein**, St. Anna Children's Hospital, Vienna, Austria

Discussant: **Dr Dominique Valteau-Couanet**, Institute Gustave Roussy, Villejuif, France

NEUROBLASTOMA
Risk stratification and treatment concepts

“The Chameleon in Paediatric Oncology”

Prof. Ruth Ladenstein, MD, MBA
St. Anna Children’s Hospital and Research Institute, Vienna. Austria

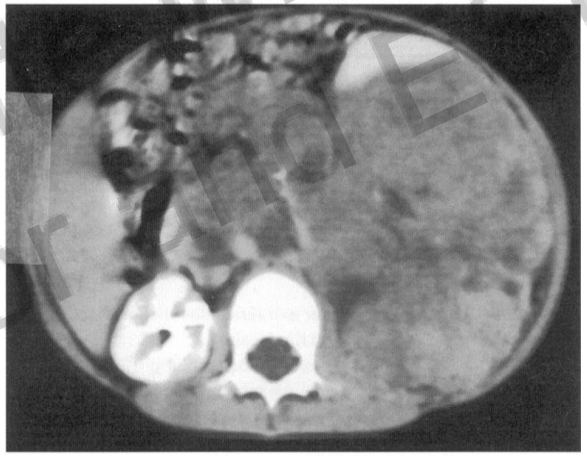
Dr. Domique Valteau- Couanet. MD, PhD
Gustave Roussy, Villejuif, France

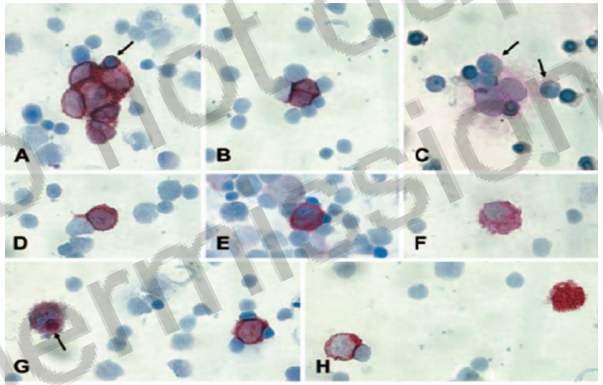
Neuroblastoma Introduction

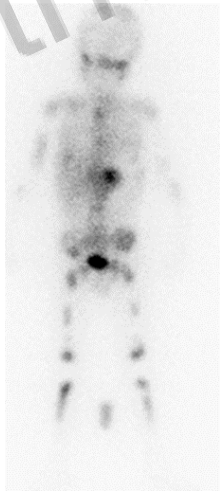
- Tumor of sympathetic neural crest origin, often in the adrenal gland
- Occurs in young children (median age 22 months)
- Most frequent pediatric extra-cranial solid tumor: 8-10%
  - Low and intermediate risk neuroblastoma:
    - ≈ >90% EFS survival with ongoing de-escalation strategies
  - High-Risk neuroblastoma:
    - ≈ 40% EFS in spite of intensive strategies

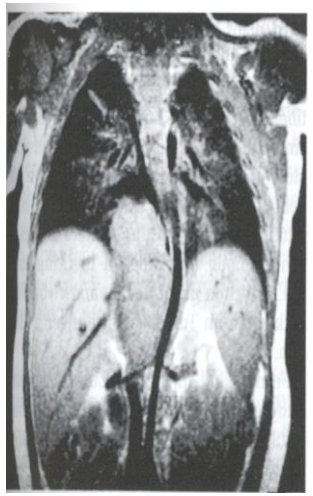
Standard Diagnostics

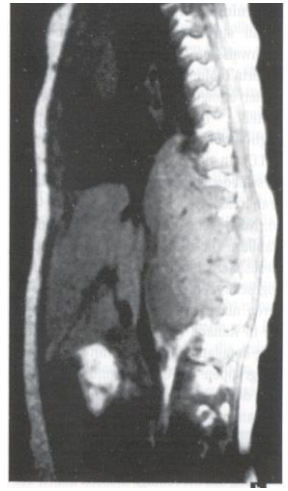
- Tumor markers:
  Urin Catecholamines: HVA, VMA, Dopamin
- Serum: neuronspezicische Enolase (NSE), Ferritin, LDH
- CT/MRI (Ultrasound)
- Uptake in mIBG-Scintigraphy
- Tumor biopsy: histology & tumor genetics
- Bone Marrow (aspirates, trephines)

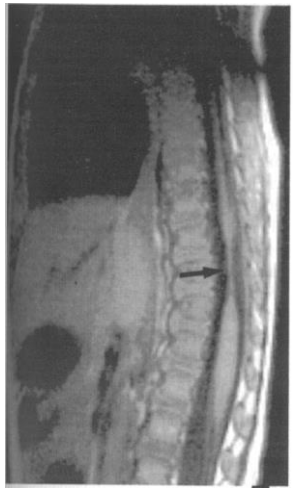




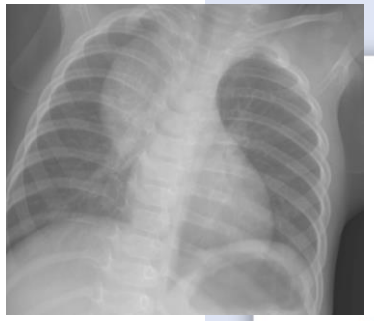


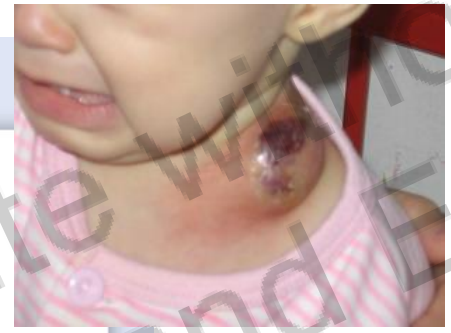


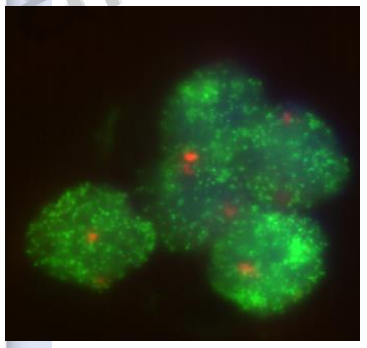


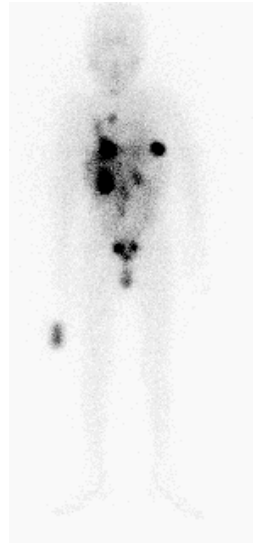


Genetic Markers in Neuroblastoma









~50%

3 N

LR
3 N

Kaum segmentale chromosomale Aberrationen

Geringe Mutationsfrequenz

Niedrige *TERT* mRNA Expression

Keine Telomer-Stabilisierung

Spontane Regression / Differenzierung

~50%

2 N

***MYCN*-Amplifikation**
Chr. 1p36 Del.

40 - 50 %

MNA
2 N

Hohe *TERT* mRNA Expression

***TERT*-Translokation**
Chr. 11q Del.

20 - 30 %

TERT- t
2 N / 4 N

Hohe *TERT* mRNA Expression

Telomeraseaktivität

***ATRX*-Mutation**
Chr. 11q Del.

20 - 30 %

ALT
2 N

Niedrige *TERT* mRNA Expression

Alt

Aktive Mechanismen zur Telomer-Stabilisierung

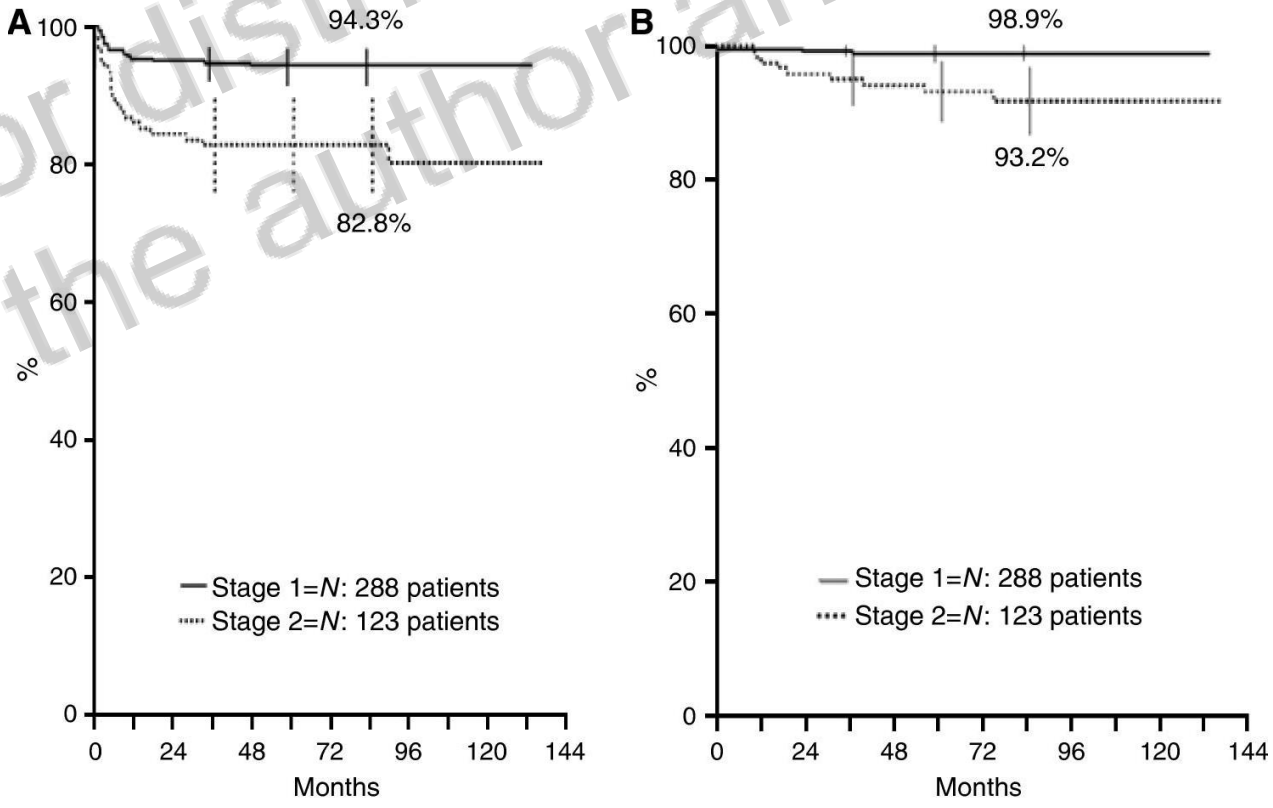
Progression / Aggressives Tumorwachstum

Background for Siopen Low & Intermediate Risk Strategy

- **LNESG1 Study**
  (Di Bernardi & J. Michon et al, Br J Cancer. 2008 Oct 7; 99(7): 1027–1033.

Conclusion:

- Surgery alone was effective and safe treatment for localised resectable neuroblastoma yielded by excellent OS for both stage 1 and 2 neuroblastoma without MYCNA,
- Stage 2 patients with unfavourable histopathology and elevated LDH suffered a high number of relapses.
- Both stage 1 and 2 patients with amplified MYCN gene (MYCNA) were at greater risk of relapse.



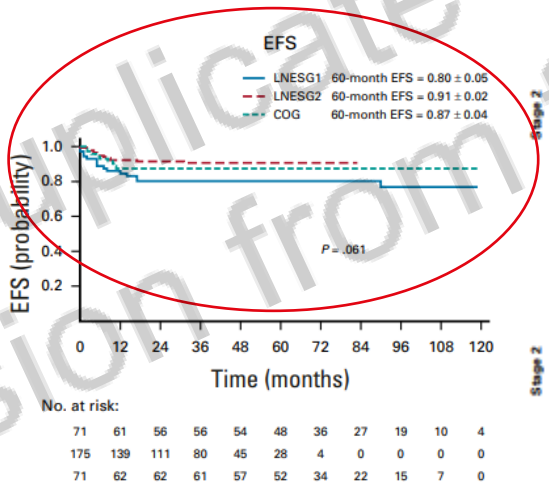
Background for Siopen Low & Intermediate Risk Strategy

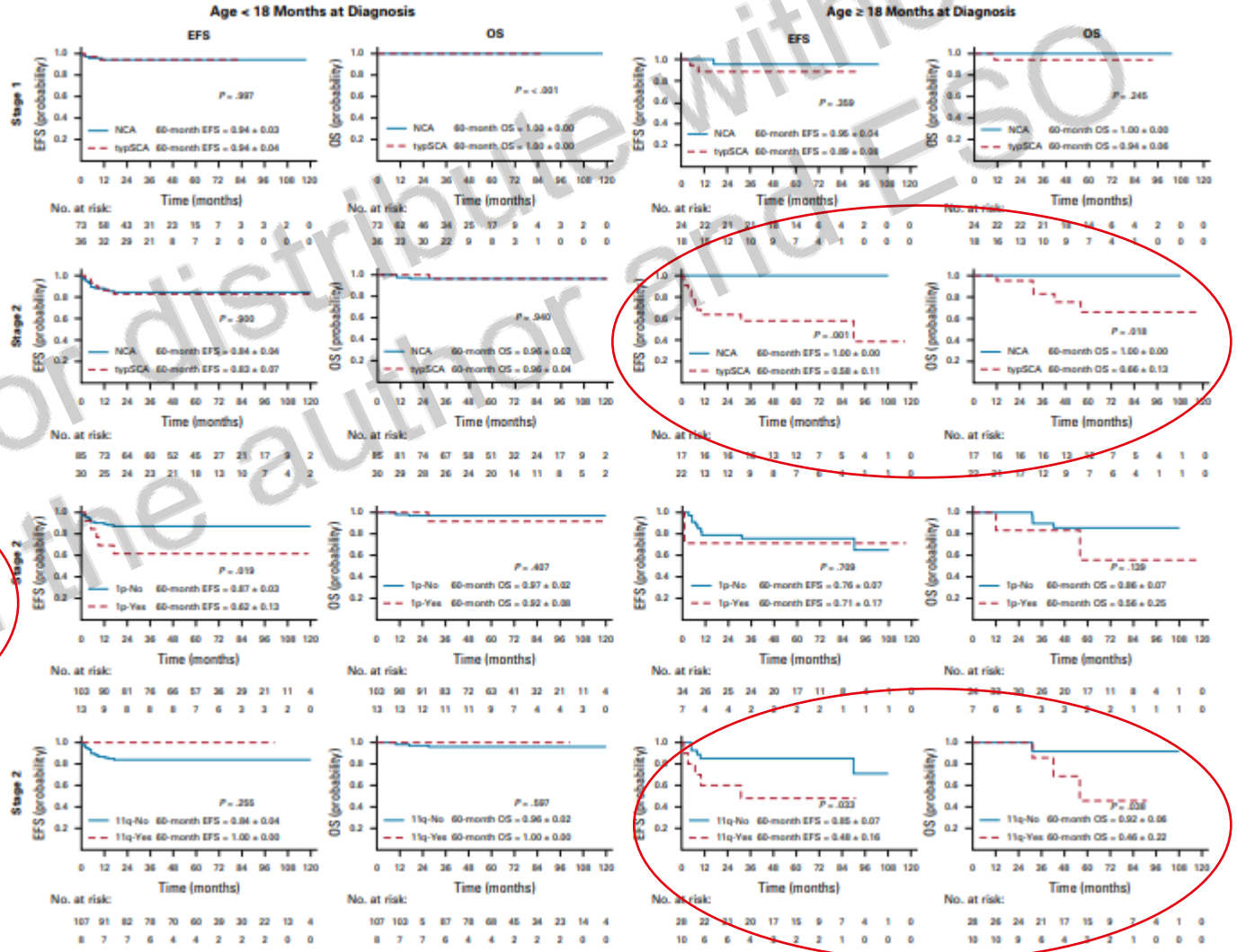
- Age Dependency of the Prognostic Impact of Tumor Genomics in Localized Resectable MYCN-Nonamplified Neuroblastomas. Report From the SIOPEN Biology Group on the LNESG Trials and a COG Validation Group

Ambros et al, J Clin Oncol 2020; 38:3685-3697

Conclusions:

- Genomic analyses of localized, resectable neuroblastomas from 2 consecutive European studies and a North American cohort revealed **a different prognostic impact of tumor genomics depending on patient age** (<or ≥ 18 months).
- The **presence of segmental chromosome aberrations, especially 11q loss, significantly reduced survival in patients ≥ 18 months of age with stage 2 neuroblastoma,** but not in the cohort < 18 months.





The International Neuroblastoma Risk Group (INRG) Staging System: An INRG Task Force Report

Tom Monclair, Garrett M. Brodeur, Peter F. Ambros, Hervé J. Brisse, Giovanni Cecchetto, Keith Holmes, Michio Kaneko, Wendy B. London, Katherine K. Matthay, Jed G. Nuchtern, Dietrich von Schweinitz, Thorsten Simon, Susan L. Cohn, and Andrew D.J. Pearson

J Clin Oncol. 2009 Jan 10; 27(2): 289–297.

Table 2. International Neuroblastoma Risk Group Staging System

Stage	Description
L1	Localized tumor not involving vital structures as defined by the list of image-defined risk factors and confined to one body compartment
L2	Locoregional tumor with presence of one or more image-defined risk factors
M	Distant metastatic disease (except stage MS)
MS	Metastatic disease in children younger than 18 months with metastases confined to skin, liver, and/or bone marrow

NOTE. See text for detailed criteria. Patients with multifocal primary tumors should be staged according to the greatest extent of disease as defined in the table.

Current standards:

MRI

MIBG

BM studies

- SIOPEN considerations for treatment strategy:
  - Age cut-off 12 months for M and MS .
  - All infants with M or Ms metastases are low risk except those with bony metastases demonstrated by CT, lung/pleura or CNS metastases (Intermediate risk).

Radiology

Guidelines for Imaging and Staging of Neuroblastic Tumors: Consensus Report from the International Neuroblastoma Risk Group Project[1]

Brisse H et al. Radiology . 2011 Oct;261(1):243-57. doi: 10.1148/radiol.11101352.

[1] From the Imaging Department, Institut Curie, 26 rue d'Ulm, 75005 Paris, France (H.J.B.). The complete list of the author affiliations is at the end of this article. Received August 27, 2010; revision requested October 21; revision received January 28, 2011; accepted March 1; final version accepted March 21. Supported in part by the William Guy Forbeck Research Foundation and Little Heroes Cancer Research Foundation. **Address correspondence to** H.J.B. (e-mail: *herve.brisse@curie.net*).

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J Clin Oncol. 2009 Jan 10; 27(2):

INRG Stage	Age (months)	Histologic Category	Grade of Tumor Differentiation	*MYCN*	11q Aberration	Ploidy	Pretreatment Risk Group
L1/L2		GN maturing; GNB intermixed					A Very low
L1		Any, except GN maturing or GNB intermixed		NA			B Very low
				Amp			K High
L2	< 18	Any, except GN maturing or GNB intermixed		NA	No		D Low
					Yes		G Intermediate
	≥ 18	GNB nodular; neuroblastoma	Differentiating	NA	No		E Low
					Yes		H Intermediate
			Poorly differentiated or undifferentiated	NA			H Intermediate
				Amp			N High
M	< 18			NA		Hyperdiploid	F Low
	< 12			NA		Diploid	I Intermediate
	12 to < 18			NA		Diploid	J Intermediate
	< 18			Amp			O High
	≥ 18						P High
MS	< 18			NA	No		C Very low
					Yes		Q High
				Amp			R High

Siopen Low Risk Group

Children with

- **L1 Neuroblastoma**, without Nmyc amplification.
- Children < 18 months with L2 neuroblastoma withouth MycN amplification.
- Infants (0-12 months) with M*/Ms* Neuroblastoma without MycN amplification.
- Neonatal adrenal masses MIBG positive.

Siopen Intermediate Risk Group

Children with

- Stage **INRG L2 > 18 months**, i.e. localised neuroblstoma without MycN amplification associated with image defined risk factors (IDRFs)

- **Stage INRG M ≤ 12 months** with disseminated neuroblastoma involving bone, pleura, lungs amd/or CNS without MycN amplification

-

- **Localised resected NBL** (stage INSS 1) **with MYCN amplification**

Treatment recommendations are based on algorithm combining:
age-stage-genomic profile-LTS

Siopen Life Threatening Symptoms:

The presence of any of these symptoms is an indication for chemotherapy.

Intraspinal neuroblastoma(See Appendix 13, page 182)
Patients who either have symptoms of spinal cord involvement or have a spinal tumour component that occupies more than one third of the spinal canal on the axial plane and/or the perimedullary leptomeningeal spaces are not visible and/or the spinal cord signal is abnormal.

Systemic upset

- **Pain requiring opiate treatment**
- **Gastrointestinal**
  - Vomiting needing nasogastric/IV support
  - Weight loss >10%body weight
    NOTE: diarrhoea with VIP does not respond to chemotherapy and is a definite indication for surgery
- **Respiratory**
  - Respiratory distress without evidence of infection
    - Tachypnoea >60
    - Oxygen need
    - Ventilatory support
- **Cardiovascular System**
  - Hypertension
  - IVC involvement +/- leg oedema
- **Renal**
  - Impaired renal function, creatinine increased x 2 ULN[1]
  - Poor urine output, less than 2mls/kg/hour
  - Hydroureter/hydronephrosis
- **Hepatic**
  - Abnormal liver function >2 ULN
  - Evidence of DIC
  - Platelets <50 x 10^9/l
- **Bladder/Bowel dysfunction** secondary to a mass effect.

A very larger tumour volume causing concern of possible tumour rupture and/or the possible rapid development of systemic upset.

Spinal Cord Compression (SCC)

- In neuroblastoma patients high expectation at diagnosis and during treatment
- Considered a **Life threatening symptom (LTS)** in LINES and for the low-risk NB guideline in both symptomatic and asymptomatic patients: recommendation to start urgent chemo (Vp/Carbo)

  - Symptomatic pts: pain and potentially irreversible loss of neurologic function)
  - Asymptomatic pts: concept of spinal cord involvement

- **Symptomatic patients are an emergency** (**urgent neurosurgery vs chemotherapy + high dose of glucocorticoids**)

  Discussion with Neurosurgery team!!

- SCC SIOPEN study

Opsoclonus Myoclonus Syndrome (OMS)

- Almost 50% of children with OMS have an underlying NB, but OMS precedes NB in 50% of cases

- Approx. 2% of children with NB develop paraneoplastic OMS, rather associated with favorable NBL
- Paraneoplastic syndrome (and non-paraneoplastic):
  - rare 0.18 cases per million per year*
  - mean age 1.5 to 2 years

- Importance of initiate as soon as possible specific treatment (independent of NB´s trt; glucocorticoids as first step *OMS/DES 2008 CT).

- Prognosis different from NB disease (independent and usually worse, residual symptoms)

* Pang KK, de Sousa C, Lang B, Pike MG. A prospective study of the presentation and management of dancing eye syndrome/opsoclonus-myoclonus syndrome in the United Kingdom. Eur J Paediatr Neurol. 2010;14(2):156.

LINES

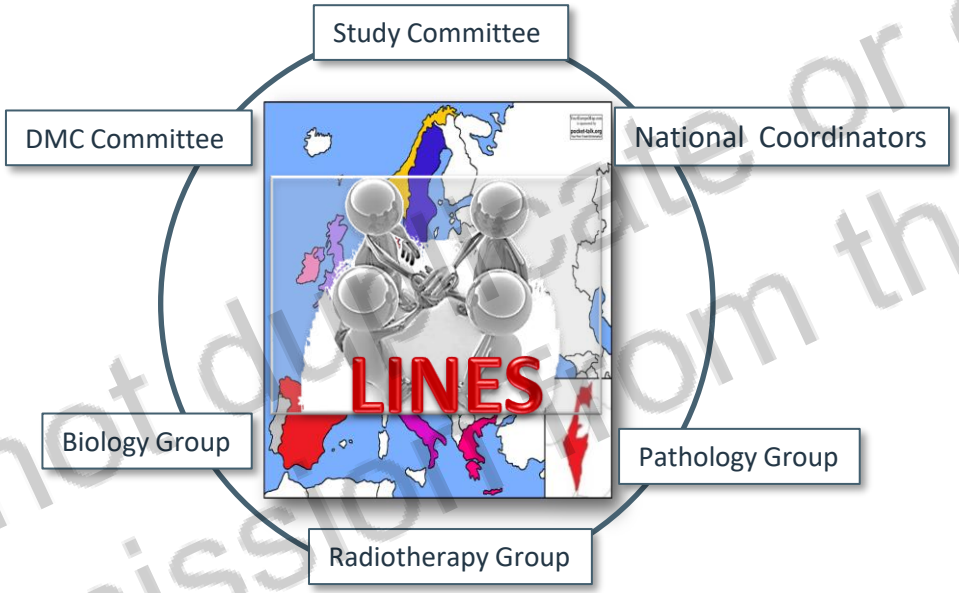
European Low and Intermediate Risk Neuroblastoma: A SIOPEN Study

Adela Cañete

Principal investigators:
Low Risk (LR): Gudrun Schleiermacher PI- Kate Wheeler co PI
Intermediate Risk (IR): Andrea di Cataldo PI- Adela Cañete co PI
Neonatal Suprarenal Mass (NSM): Adela Cañete PI, Vassilios Papadakis co PI
Vanessa Segura : Lines ISC

LINES Protocol: a Quick Glance
15 Participating Countries

International Sponsor
EudraCT:2010-021396-81
ClinicalTrials.Org:NCT01728155



Principal investigators:
Low Risk (LR): Gudrun Schleiermacher PI- Kate Wheeler coPI
Intermediate Risk (IR): Andrea di Cataldo PI- Adela Cañete coPI
Neonatal Suprarenal Mass (NSM): Adela Cañete PI, Vassilios Papadakis coPI

Country	Date of approval
Spain	2011
Italy	2012
Norway	2012
Denmark	2012
Austria	2012
France	2013
Belgium	2013
Israel	2013
Ireland	2014
Sweden	2015
Switzerland	2015
Portugal	2017
Australia	2018
Lithuania	2018
Greece	2020

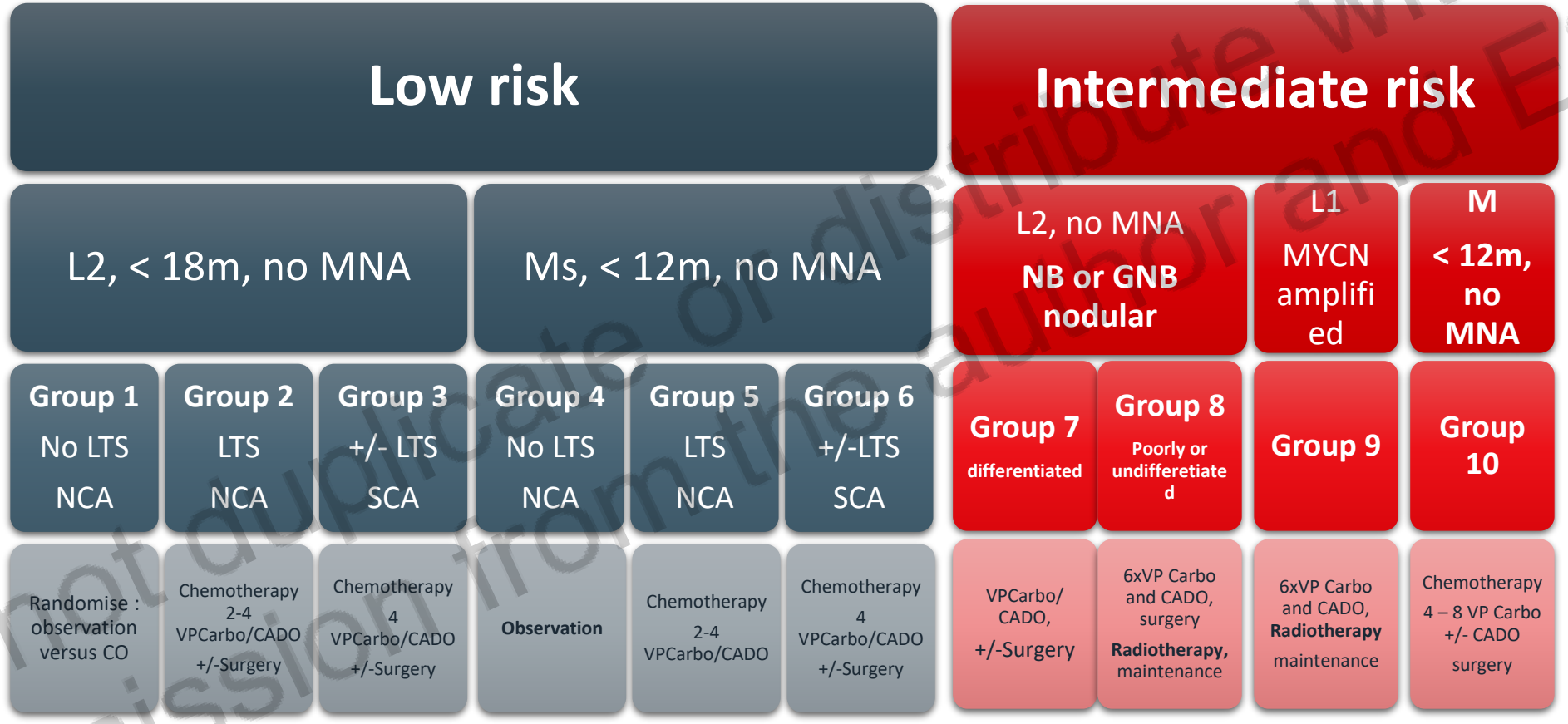
Independent Data Monitoring Commitee (IDMC)

SIOPEN database- AIT

LINES Protocol: a Quick Glance

Total patients enrolled into trial groups (G1-G6) =**271**

Total patients enrolled into trial groups (G7-G10) =**148**



Stratification of treatment according to Age, stage (IDRFs), clinical symptoms (LTS)

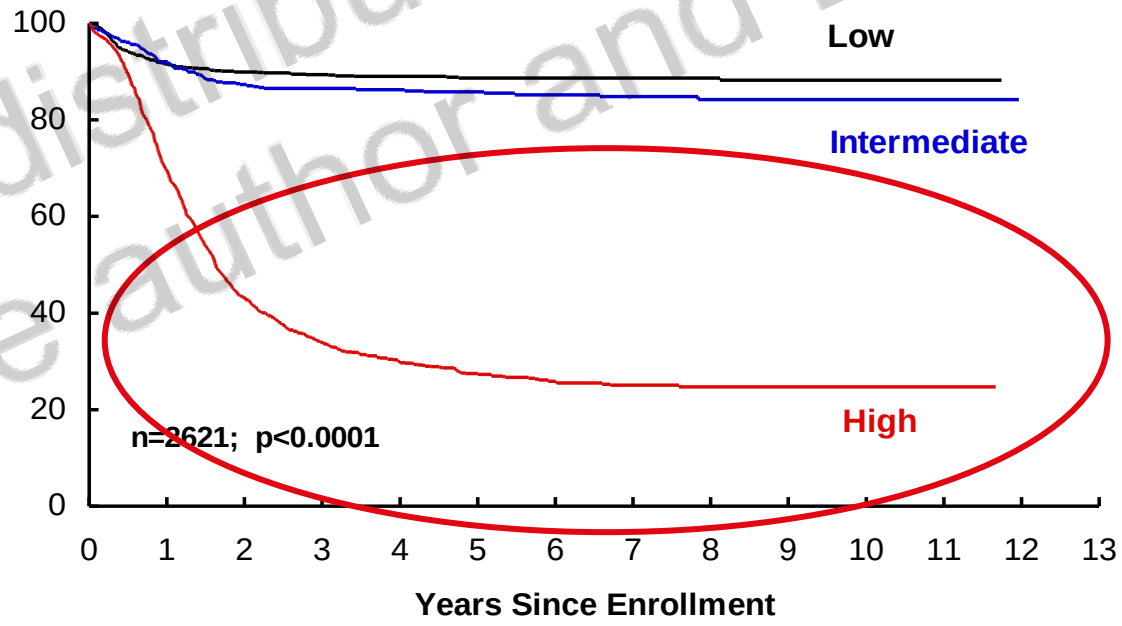
LR: Genomic satus : **MYCN,** genomic copy number profile **NCA:** numerical chromosomal alteration / **SCA**: segmental chromosomal altrations

IR: pathology

High-Risk Neuroblastoma

- Prognostic Features COG:
  - Age > 18 months,
  - Advanced stage disease,
  - Tumor MYCN amplification,
  - Poorly or undifferentiated tumor
  - Tumor diploid DNA content

- Prognostic Features SIOPEN / HR-NBL1:
  - Age > 12 months,
  - Tumor MYCN amplification in INSS stage ≥ 2
  - Metastatic disease > 12 months
  - Stage 4s with MycN Amplification



Building the evidence - Randomised trials in High–Risk neuroblastoma

ENSG-1(UK) : High dose melphalan in the treatment of advanced neuroblastoma: results of a randomised trial

Pritchard, Pediatric Blood & Cancer, 44, 2005

BACKGROUND

Additon of melphalan HDC in a randomised, multi-centre trial 1982 to 1985 including 167 children with stages IV and III neuroblastoma (123 stage IV > 1 year old at diagnosis and 44 stage III and stage IV from 6 to 12 months old at diagnosis) after induction with OPEC every 3 weeks, surgical excision of primary tumour:
90 patients (69% of the total) achieving CR or GPR)were randomised to either HD melphalan (180 mg/m^2) with autologous BMT or to no further treatment.

RESULTS

72% of eligible children were randomised with 21 surviving with a FU from randomisation of 14.3 years.
5-yr EFS was 38% in the HDC melphalan group and 27% in the "no-melphalan" group.
This difference was not statistically significant (P = 0.08, log rank test) but for the **48 randomised stage IV patients aged >1 year at diagnosis outcome was significantly better in the melphalan-treated group-5 year EFS 33% versus 17% (P = 0.01, log rank test).**

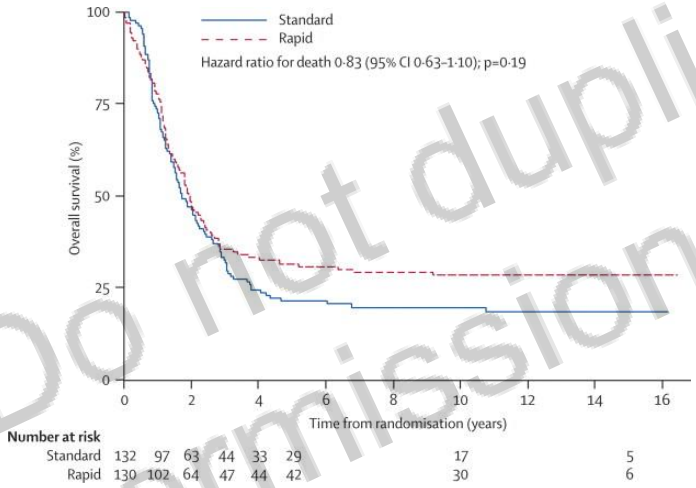
CONCLUSIONS

HD - melphalan improved EFS and OS who achieved CR or GPR after OPEC induction and surgery.

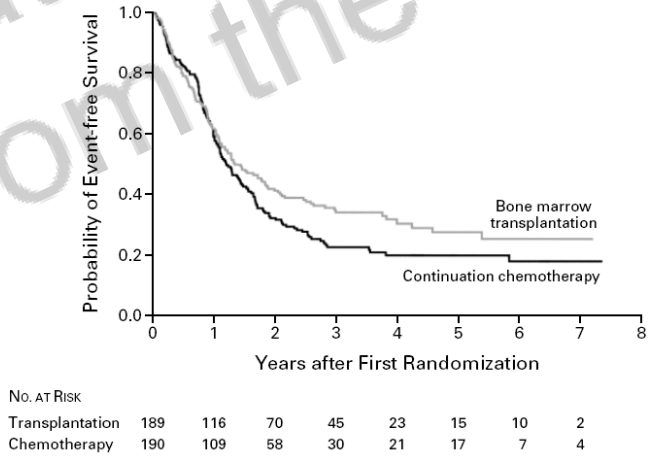
High Risk Neuroblastoma – First Randomised Evidence

Highly correlated components of front line strategies

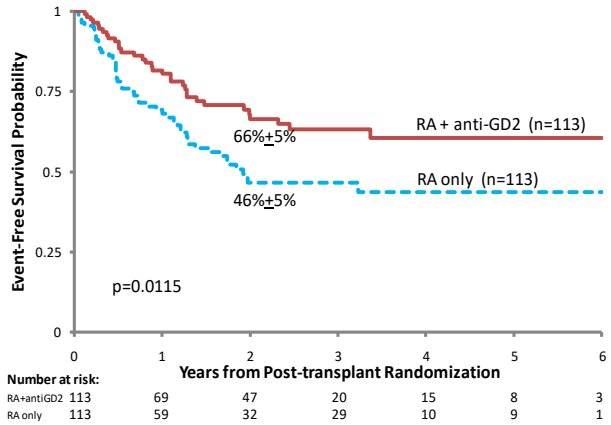
INDUCTION	CONSOLIDATION	POST-CONSOLIDATION
Multi-Agent Chemotherapy	HDC/SCT XRT	Anti-GD2 Ab (±cytokines) Isotretinoin
PBSC Harvest Surgery	PBSC Infusion	



Pearson, Lancet Oncology, 2008



Matthay, N Eng J Med, 1999



Yu, N Eng J Med, 2010

COG: LTFU of CCG-3891 HR-Neuroblastoma treated on a Randomized Trial of Myeloablative Therapy Followed by 13-cis-RA.

Matthay, Journal of Clinical Oncology, 2009

METHODS: Random assignment to HDC +TBI / purged bone marrow transplantation (ABMT) or 3 intense chemotherapy cycle and subsequent 13 cis-RA)

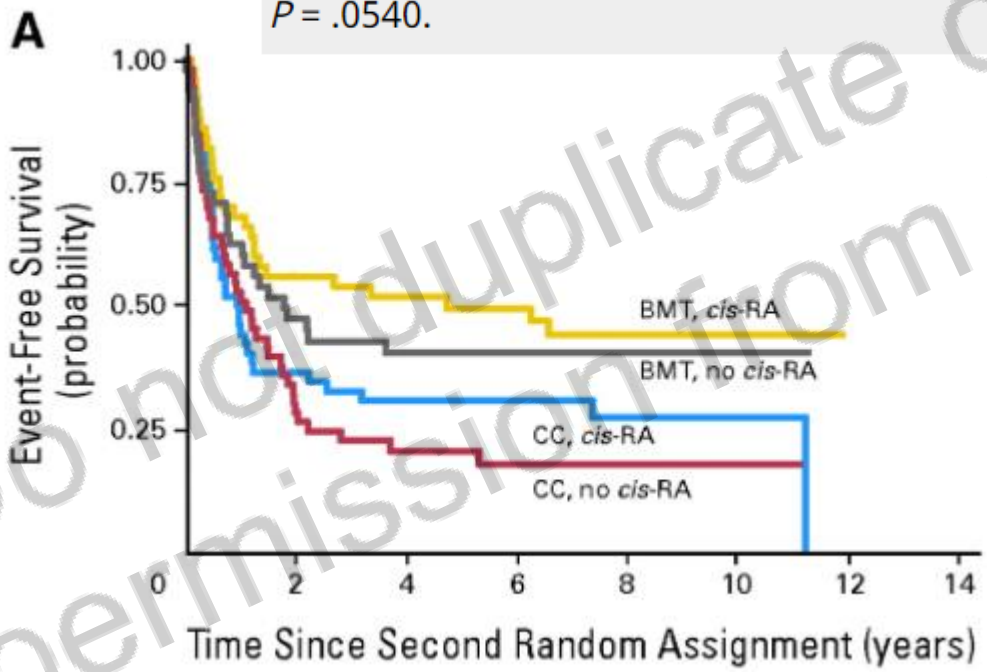
RESULTS: 5-yr EFS was significantly higher for HDC/ABMT than chemotherapy with 30% ± 4% versus 19% ± 3%, respectively (P = .04). The 5-year EFS (42% ± 5% v 31% ± 5%) from the time of second random assignment was higher for cis-RA than for no further therapy, though it was not significant.
The 5-yr OS from the second random assignment of patients who underwent both random assignments and who were assigned to ABMT/cis-RA was 59% ± 8%; for ABMT/no cis-RA, it was 41% ± 7%; for continuing chemotherapy/cis-RA, it was 38% ± 7%; and for chemotherapy/no cis-RA, it was 36% ± 7%.

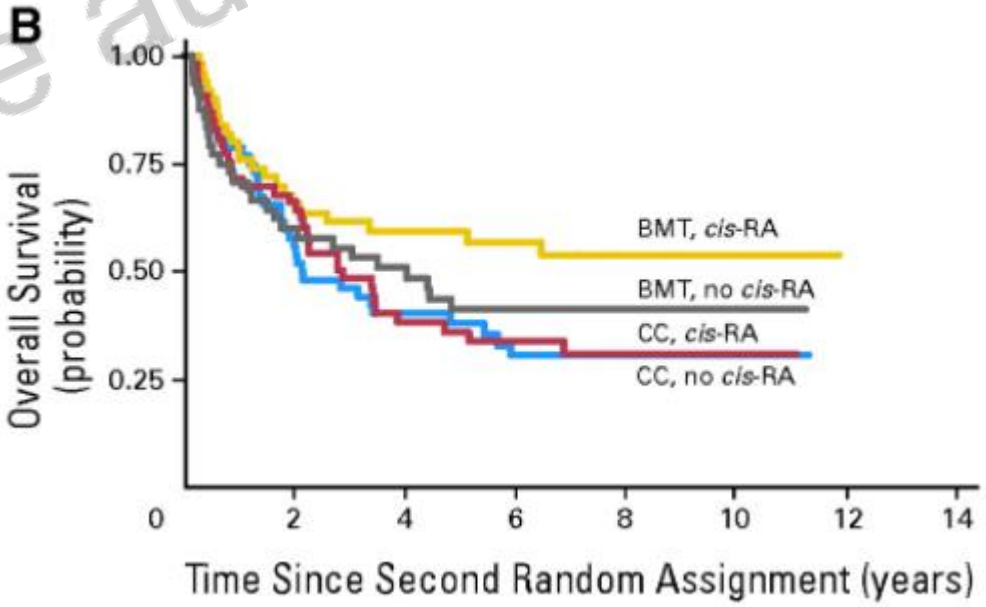
CONCLUSION

HDC/TBI /ABMT resulted in significantly better 5-yr EFS than intense chemotherapy; however, neither myeloablative therapy with autologous hematopoietic cell rescue nor cis-RA given after consolidation therapy significantly improved OS.

COG: LTFU of CCG-3891 HR-Neuroblastoma treated on a Randomized Trial of Myeloablative Therapy Followed by 13-cis-RA. *Matthay, Journal of Clinical Oncology, 2009*

(A) Event-free survival for patients who participated in both the first and second random assignments (autologous bone marrow transplantation + 13-*cis*-retinoic acid [*cis*-RA] [n = 50] versus continuing chemotherapy (CC) + no *cis*-RA [n = 53]). *P* = .0038. (B) Overall survival for patients who participated in both the first and second random assignments (autologous bone marrow transportation + *cis*-RA versus CC + no *cis*-RA) *P* = .0540.





GPOH: LTFU of the GPOH NB97 trial for high-risk neuroblastoma comparing HDCT/SCT and oral chemotherapy as consolidation

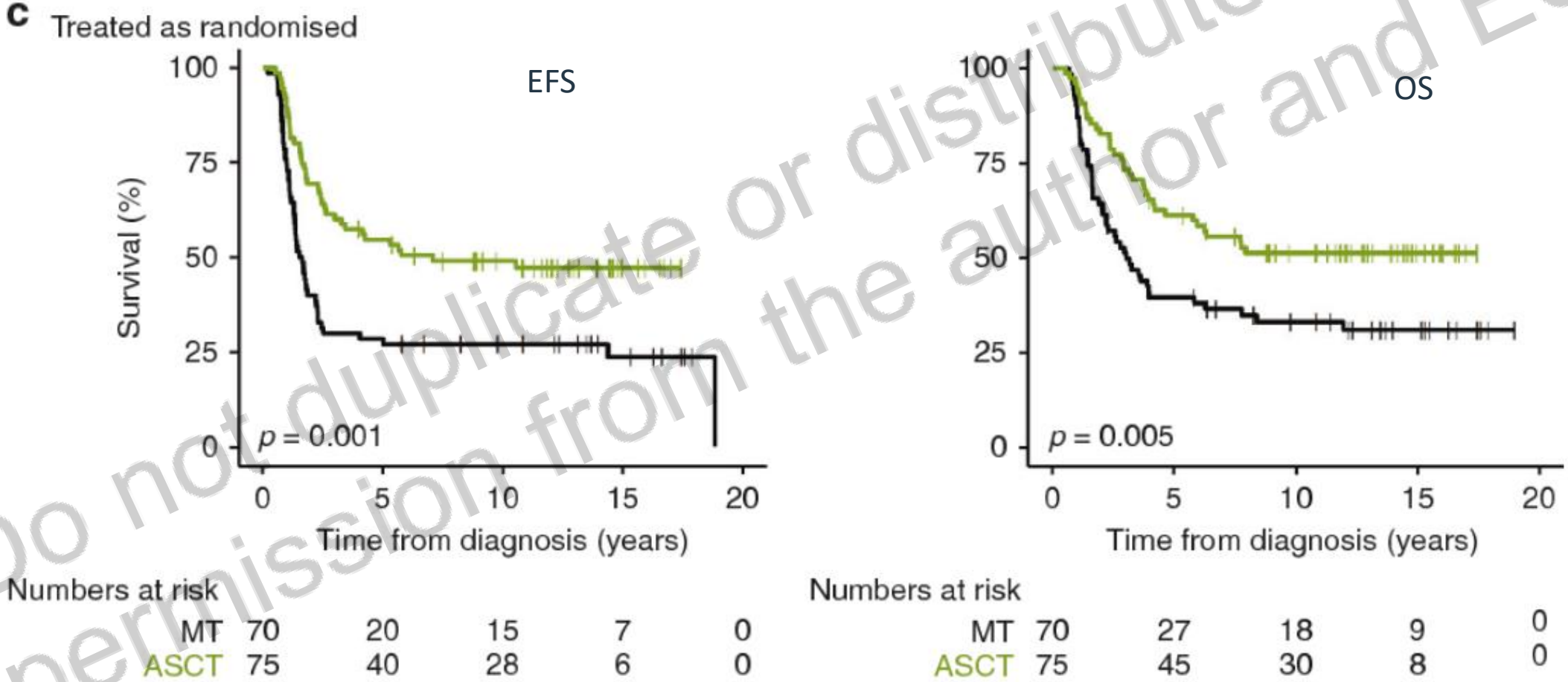
F. Berthold, British Journal of Cancer, 2018

METHODs:
A randomised open label trial 1997–2004 (Germany, Switzerland) with 295 patients with HR-NBL randomly assigned to HDC (MEC) /ASCT or maintenance chemotherapy (MT) for consolidation. Analyses were done by intention-to-treat (ITT: ASCT/MT N = 149/146), as treated (AT: N = 110/102), and treated as randomised (TAR: N = 75/70).

RESULTS The EFS suprior with ASCT compared to MT in all three cohorts (hazard ratio [HR] for ITT 1.39, 95% confidence interval (CI) 1.05-1.85, P = 0.022, HR for AT 1.75, CI 1.24-2.47, P = 0.001; HR for TAR 2.07, CI 1.36-3.16, P = 0.001).
OS also in favour of the ASCT groups (ITT: P = 0.075; AT: P = 0.017; TAR: P = 0.005). The frequencies of late sequelae were not different except for focal nodular hyperplasia of the liver observed more frequently in the ASCT arm

CONCLUSIONS
HDC /ASCT had a better long-term outcome compared to maintenance CHT.

GPOH: LTFU of the GPOH NB97 trial for high-risk neuroblastoma comparing HDCT/SCT and oral chemotherapy as consolidation



COG A3973: Purged versus non-purged PBSCT for HR-NBL *Kreissman, Lancet Oncol, 14; 2013*

BACKGROUND

Randomised study of tumour-selective PBSC purging in SCT HR-NBL pts between 2001 -2006 to receive either non-purged or immunomagnetically purged PBSC. (Strata on INSS &INPC, age, MYCN status)

6 cycles of induction CHT, HDC /SCT, and radiation therapy to the primary tumour site plus mIBG treatment to avid metastases present prior HDC followed by oral isotretinoin. PBSC collection was done after two induction cycles.

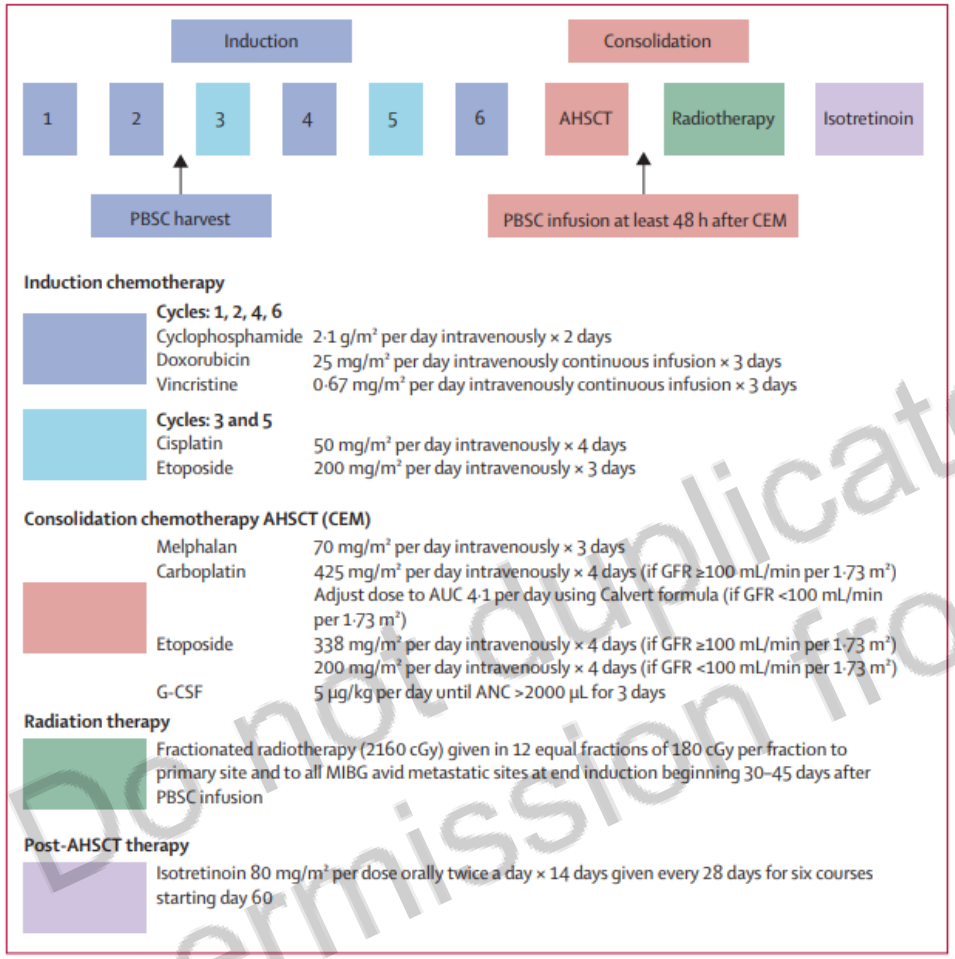
RESULTS

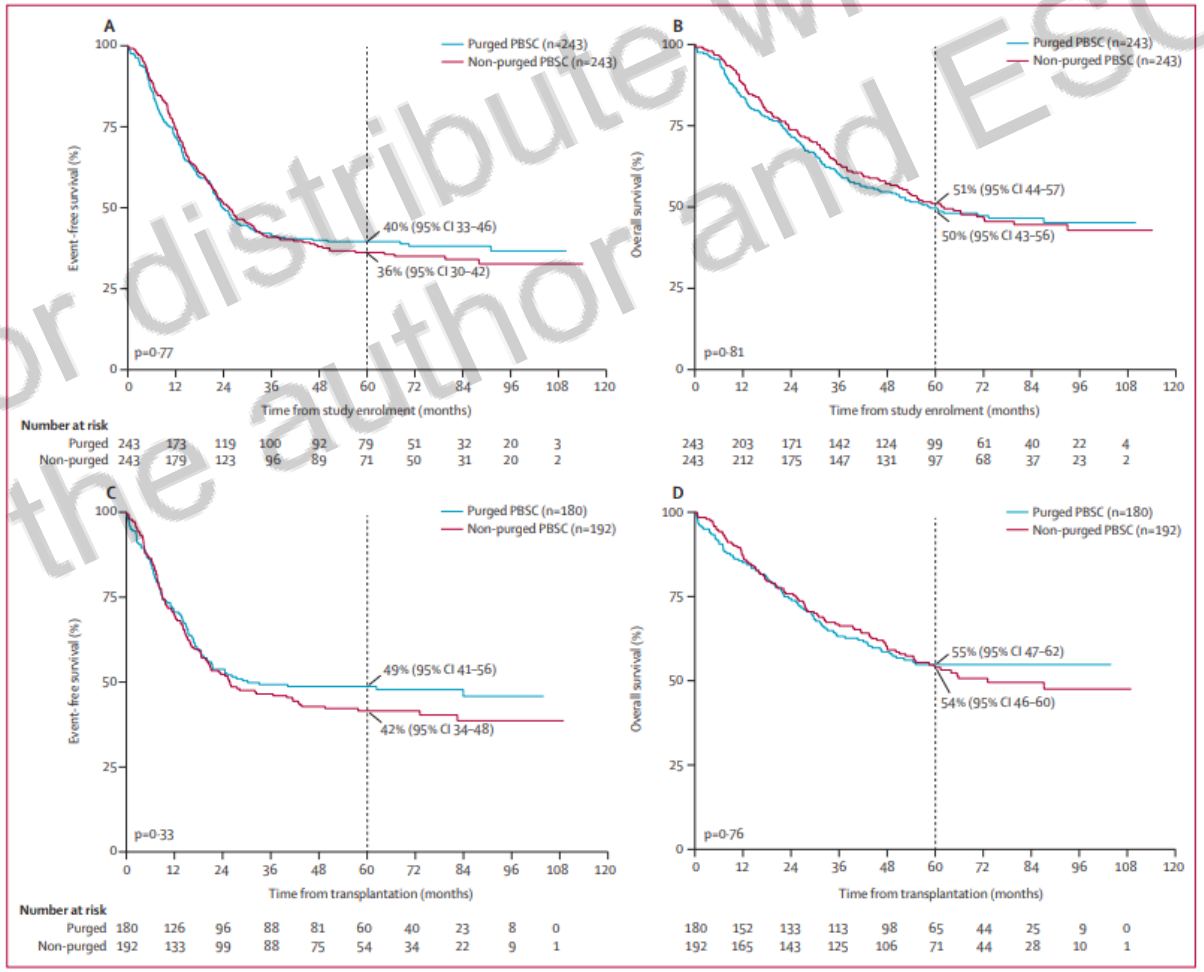
486 randomly assigned , of whom 243 patients to receive non-purged PBSC. 5-year EFS 40% (95% CI 33–46) in the purged group versus 36% (30–42) in the non-purged group (p=0·77); 5-year OS was 50% (95% CI 43–56) in the purged group compared with 51% (44–57) in the non-purged group (p=0·81).

INTERPRETATION

Immunomagnetic purging of PBSC for autologous stem-cell transplantation did not improve outcome, perhaps because of incomplete purging or residual tumour in patients. Non-purged PBSC are acceptable for support of myeloablative therapy of high-risk neuroblastoma.

COG A3973: Purged versus non-purged PBSCT for HR-NBL *Kreissman, Lancet Oncol, 14; 2013*





COG: ANBL0532 Effect of Tandem ASCT vs Single SCT on EFS in HR- Neuroblastoma

Park et al, JAMA, 2019 Aug 27;322(8):746-755.

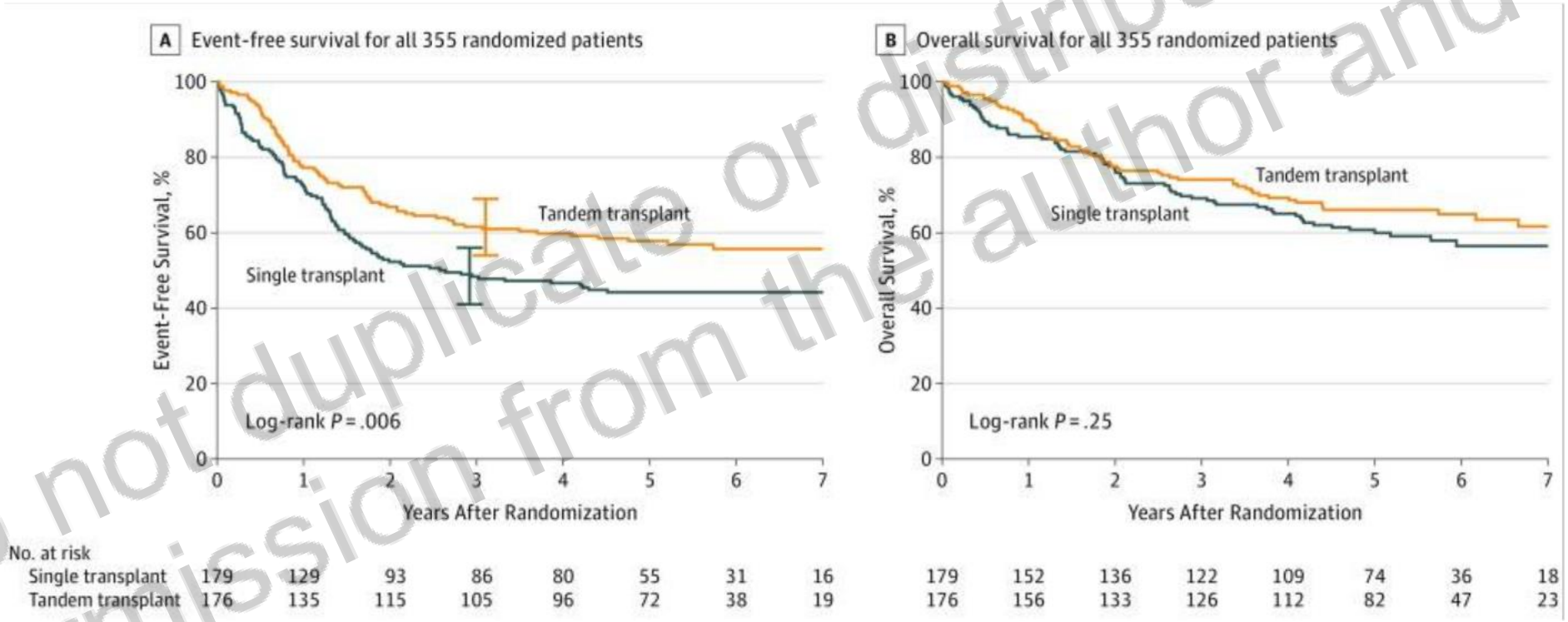
METHODS: 652 eligible patients enrolled (2007 – 2012) at 142 COG centers (US, Canada, Switzerland, Australia, and New Zealand) with protocol-defined high-risk neuroblastoma with 355 randomized to either Tandem SCT (thiotepa/cyclophosphamide followed by dose-reduced carboplatin/etoposide/melphalan (n = 176) or single SCT with carboplatin/etoposide/melphalan (n = 179).

RESULTS: In 355 patients randomized, 297 patients (83.7%) completed the study. 3 year EFS from the time of randomization was 61.6% (95% CI, 54.3%-68.9%) in the tandem transplant group and 48.4% (95% CI, 41.0%-55.7%) in the single transplant group (1-sided log-rank P=.006). FU was 5.6 (0.6-8.9) years. The most common significant toxicities following tandem vs single transplant were mucosal (11.7% vs 15.4%) and infectious (17.9% vs 18.3%).

CONCLUSIONS:
Tandem transplant resulted in a significantly better EFS than single transplant. However, because of the low randomization rate, the findings may not be representative of all patients with high-risk neuroblastoma.

COG: ANBL0532 Effect of Tandem ASCT vs Single SCT on EFS in HR- Neuroblastoma

Park et al, JAMA, 2019 Aug 27;322(8):746-755.



COG ANBL0532 Effect of Tandem ASCT vs Single SCT on EFS in HR-Neuroblastoma

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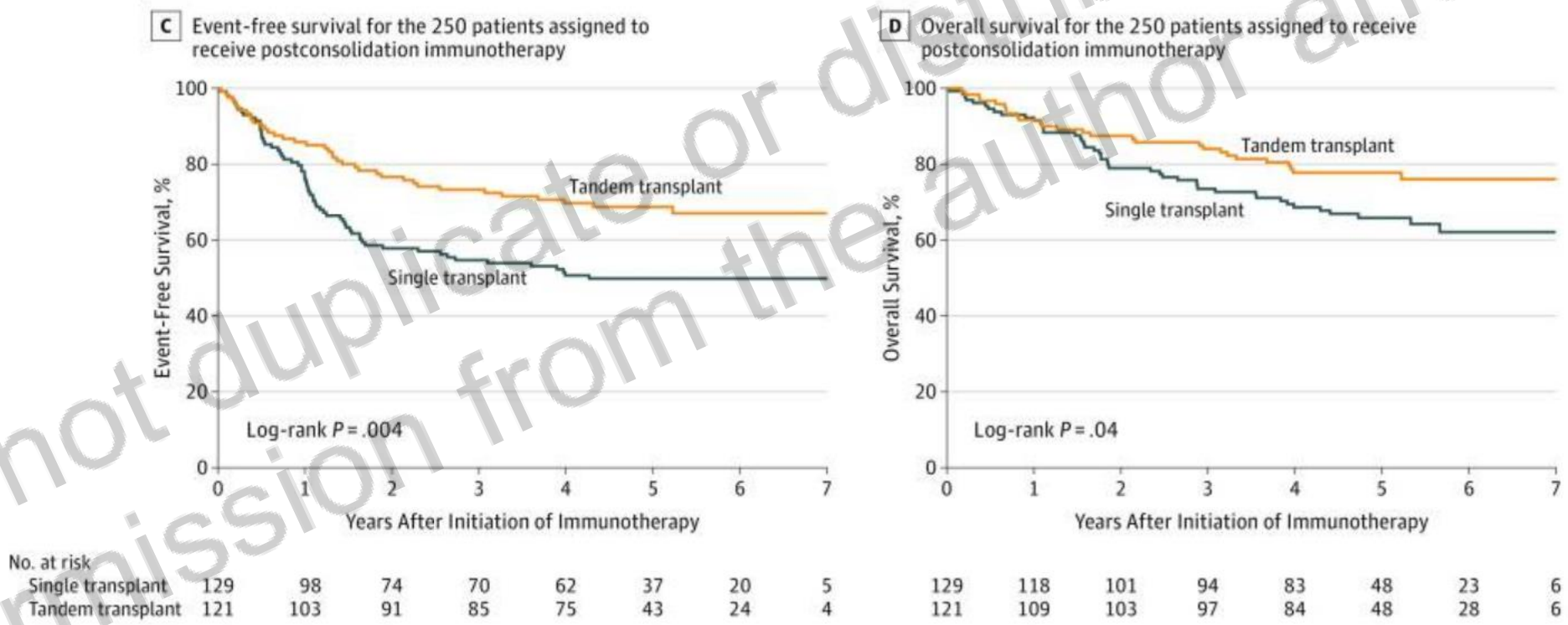
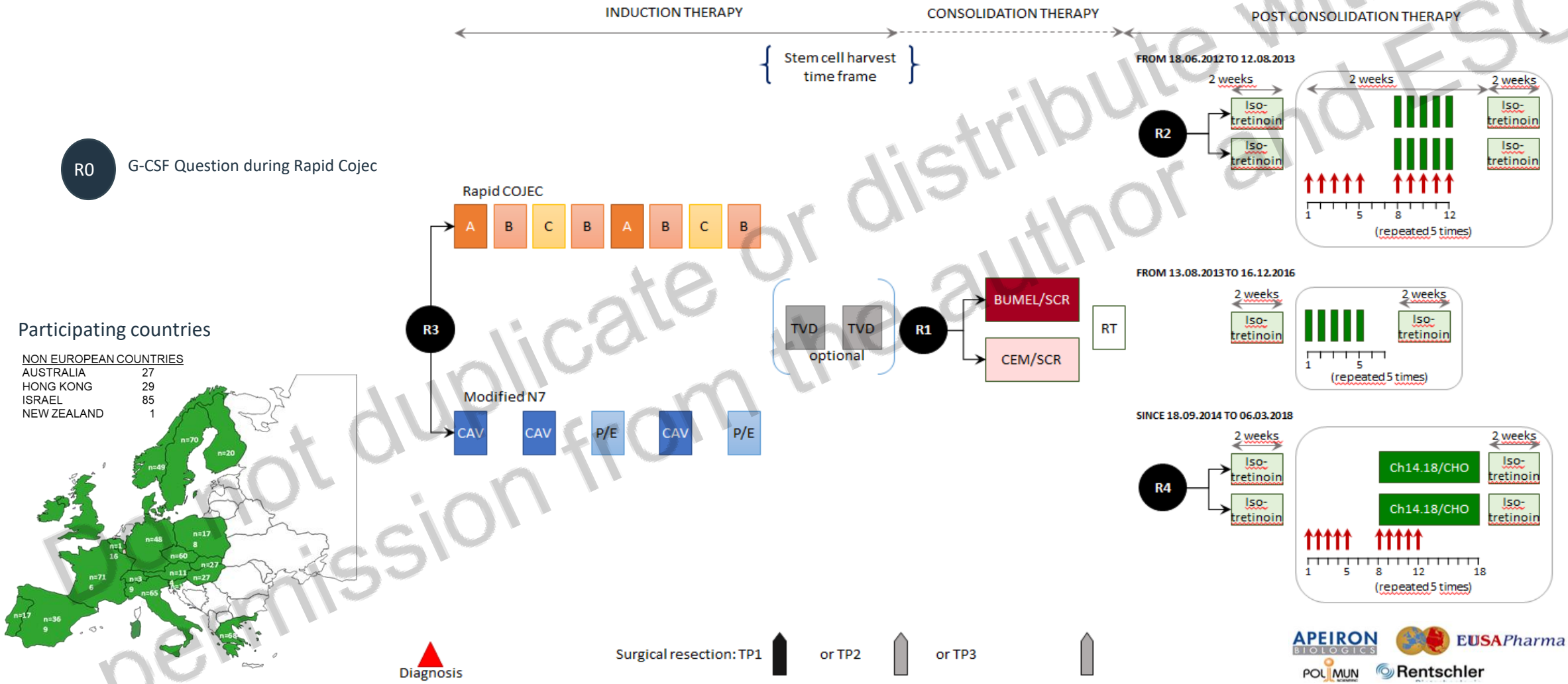


SIOPEN: High-Risk Neuroblastoma HR-NBL1/SIOPEN (2002-2021):>3500 pts

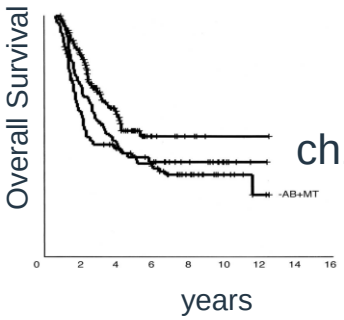
5 Randomizations - 4 Treatment Standards established , 14 publications to date



Participating countries

NON EUROPEAN COUNTRIES	
AUSTRALIA	27
HONG KONG	29
ISRAEL	85
NEW ZEALAND	1

CCRI driven dinutuximab beta development: 2002-2017



Simon et al., JCO, 44, 3549 – 57, 2004

ch14.18/SP2/0

Phase II

2003

Recloning in CHO

„Master working cell bank“

GMP production of ch14.18/CHO

2011

antibody structure and function
pharmacokinetics

APEIRON BIOLOGICS

EUSAPharma

2017

Preclinical

Phase I Bridging Study

2006

toxicity profile
pharmacokinetics

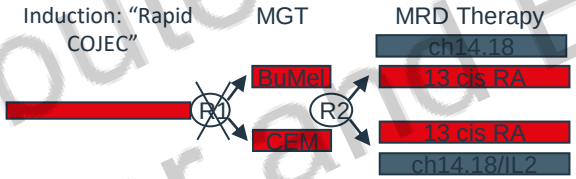
Siebert N,et al Lode HN, MAbs. 2016;8(3):604-16.
Ladenstein R, et al. Lode HN, MAbs. 2013; 5(5):801-9

Zeng Y, et al.. Lode HN.
Mol Immunol. 2005 Jul;42(11):1311-9.

2007

Phase III

HR-NBL-1 SIOPEN



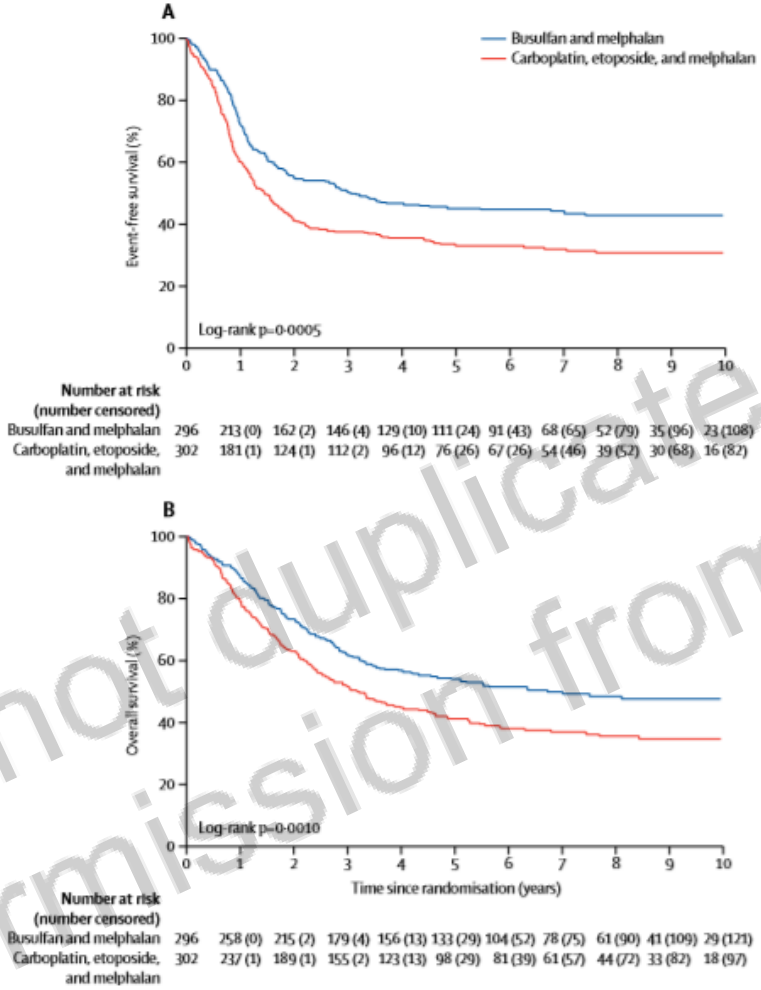
Ladenstein, et al Lode HN ASCO /ANR 2016

EMA Approval: Dinutuximab beta 08.05.2017

EC 5th Frame Work Grant QLRI-CT-2002-01768

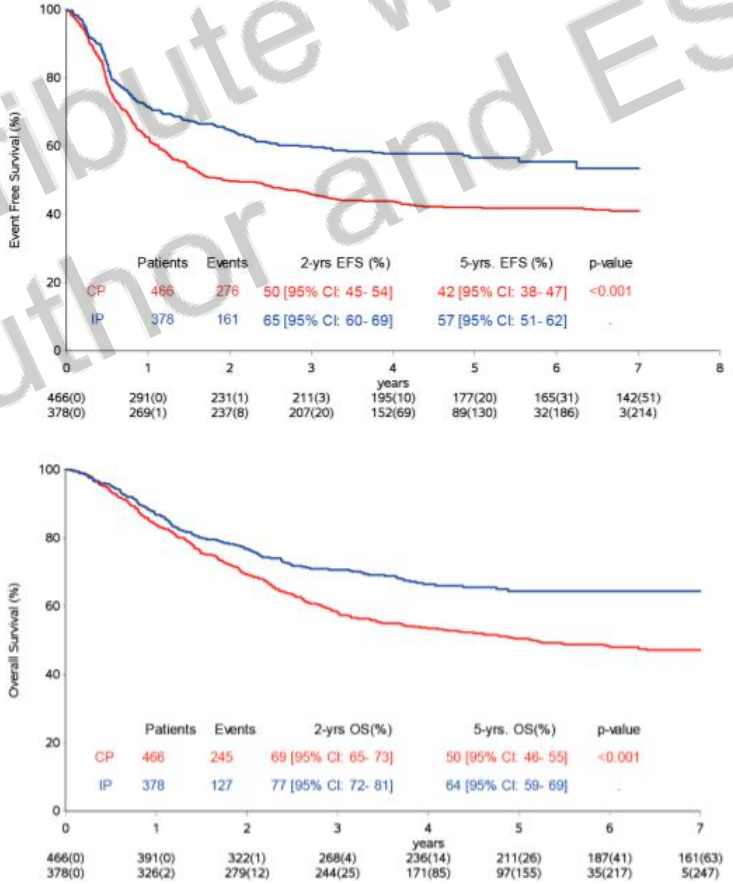
The European Experience: HR-NBL1/SIOPEN

BUMEL > CEM as HDT



Ladenstein et al; Lancet Oncol. 2017 Apr;18(4):500-514.

Dinutuximab beta improves outcome



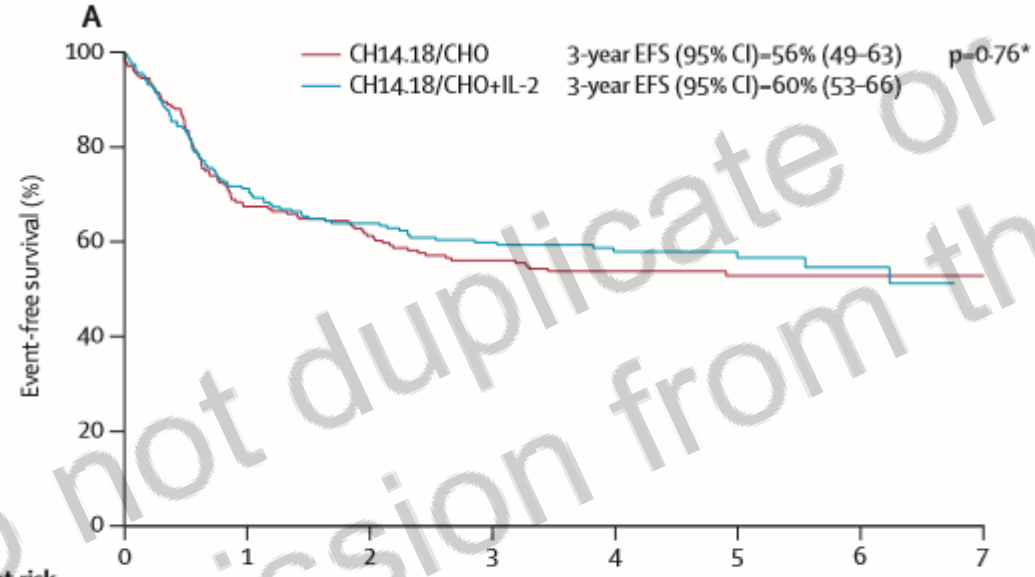
Ladenstein et al; Cancers (Basel). 2020 Jan 28;12(2):309.

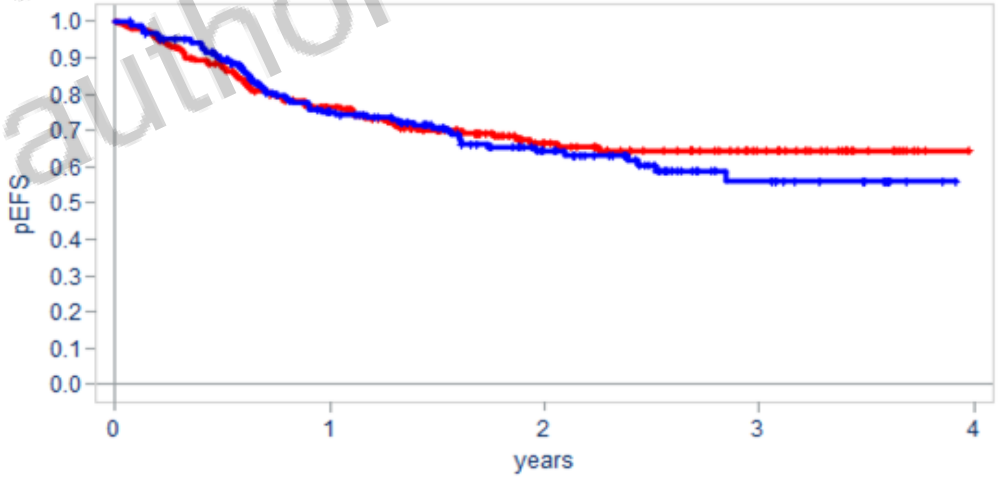
Scientific Outputs –HR-NBl1

Role of ch14.18/CHO (dinutuximab beta) R2 & R4 – Omit IL2c !

Short term (8h) dinutuximab beta infusion - total dose 100mg/m² over 5 days
+ s.c.IL2 6x10E6 IU/m2/ day s.c.IL2 (d 1-5, 8-12)

Long term dinutuximab beta infusion total dose 100mg/m² over 10 days ctn infusion
+ s.c.IL2 (50% of R2): 3x10E6 IU/m2/ day s.c.IL2 (d 1-5 & d 9,11,13,15,17)





	Patients	Events	1-yrs pEFS	2-yrs. pEFS	p-value
DB	205	61	0.76±0.03	0.67±0.04	0.649
DB+ IL2	203	61	0.75±0.03	0.64±0.04	

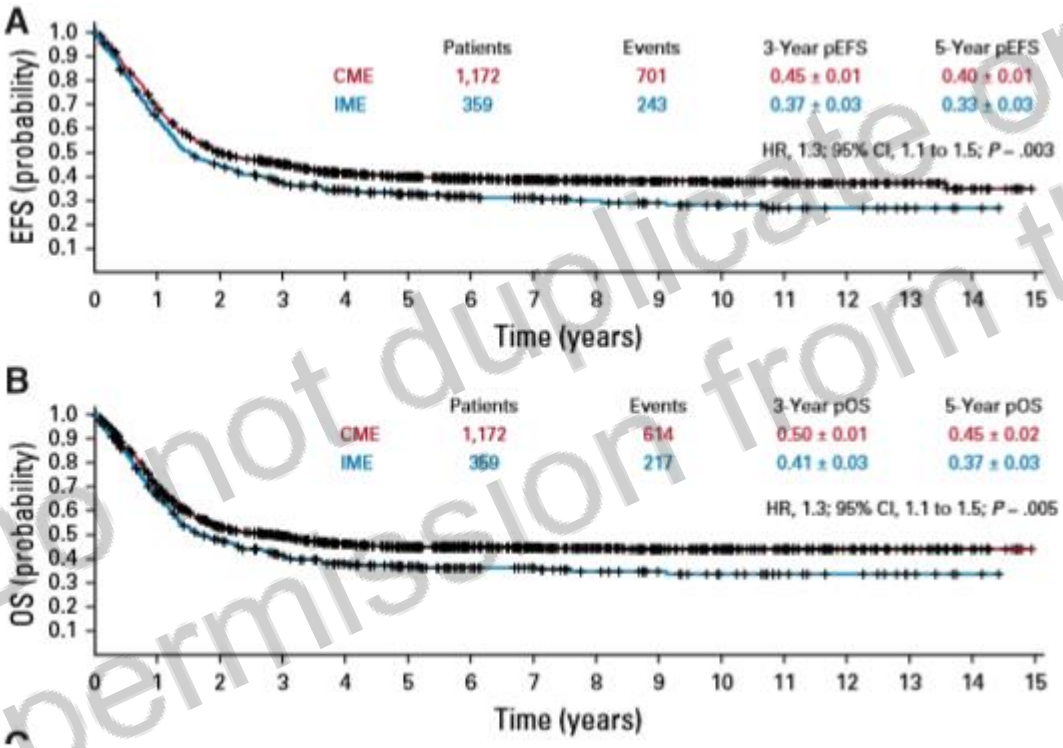
Lancet Oncol. 2018 Dec;19(12):1617-1629.

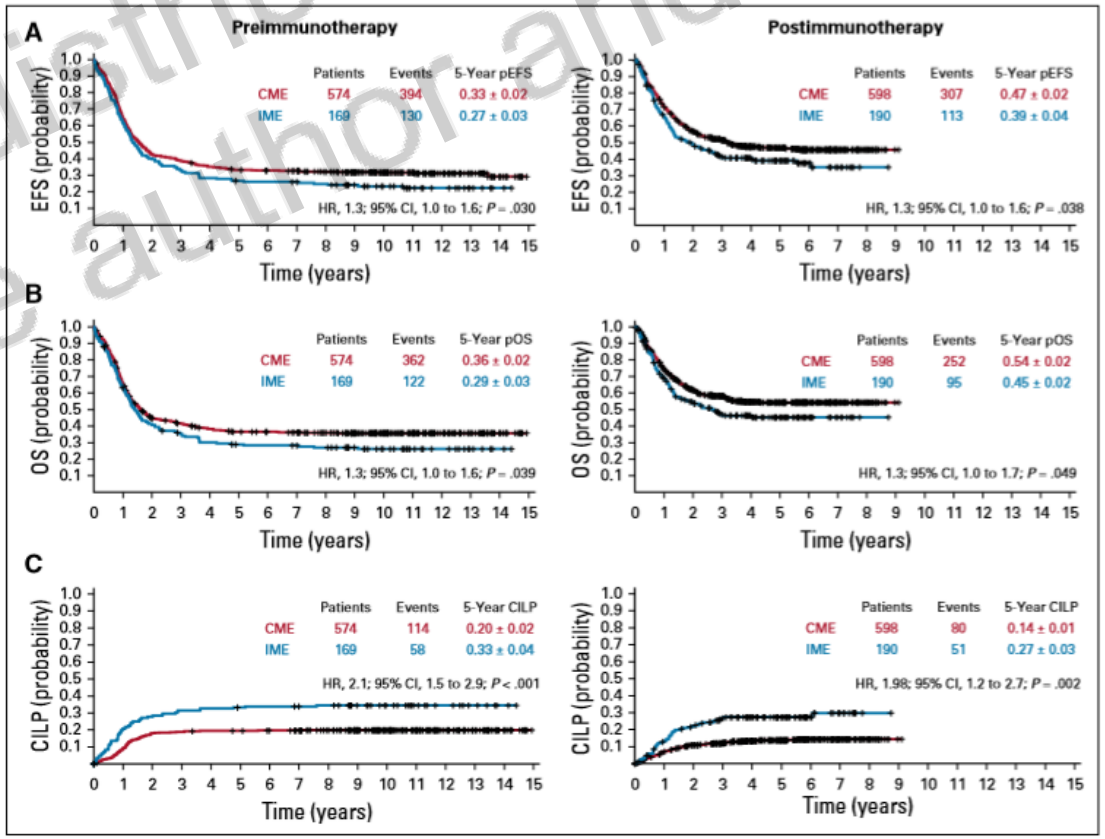
Scientific Outputs

Complete macroscopic excision results in survival advantage

Influence of Surgical Excision on the Survival of Patients With Stage 4 High-Risk Neuroblastoma: A Report From the HR-NBL1/SIOPEN Study

Keith Holmes, Ulrike Pötschger, et al ; (SA) Ruth Ladenstein,



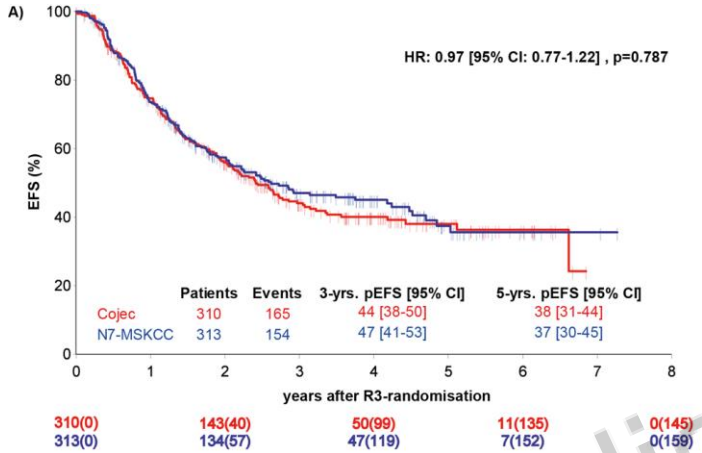


Journal of Clinical Oncology 2020 38:25, 2902-2915

2 recent HR-NBL1 publications

Rapid Cojec – Siopen Standard induction

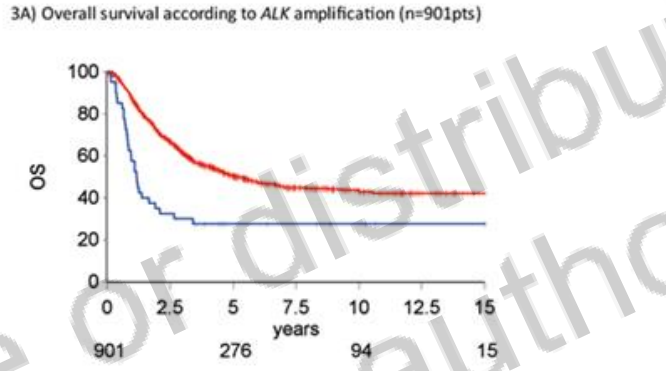
R3 *

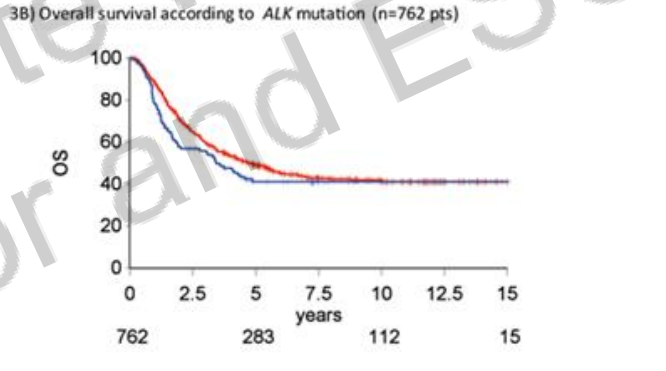


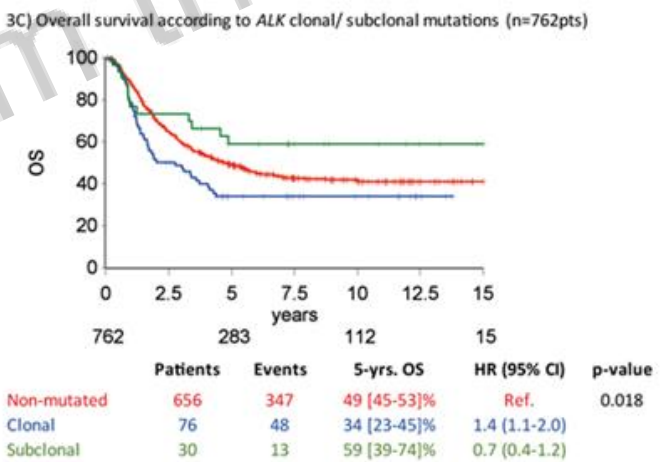
Garaventa ; J Clin Oncol, 39; 2021
Ladenstein ; J Clin Oncol. 28 , 2010

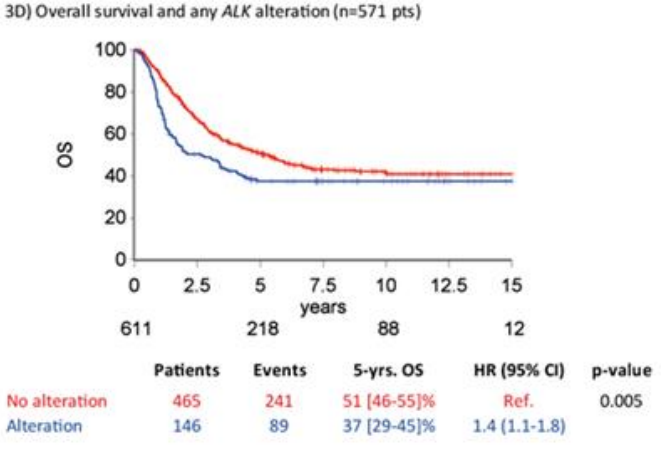
Inferior outcome of pts with Alk ampl. + clonal mutation

ALK



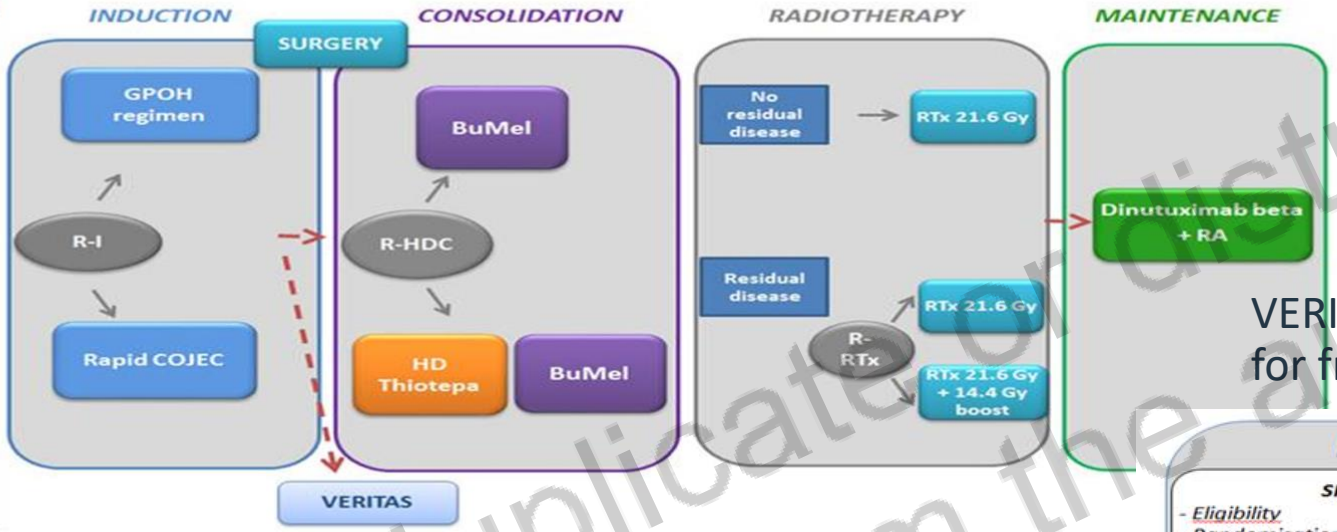






Bellini, J Clin Oncol 39, 2021

HR-NBL2/SIOPEN (PI: D. Valteau- Couanet)

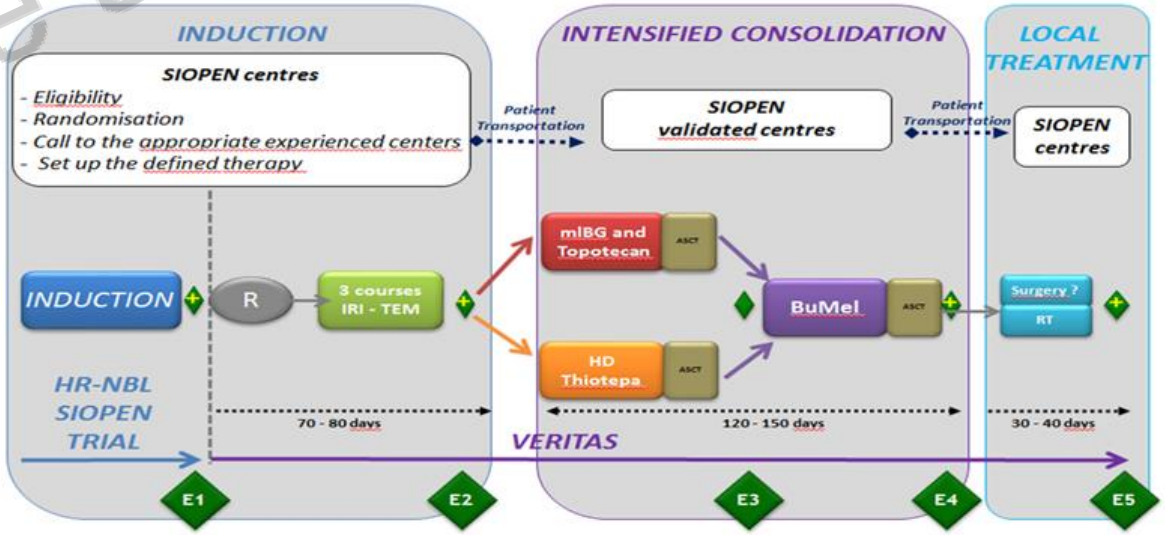


Intercontinental collaboration of SIOPEN & COG
to add **Loratinib** in ALK mutated/amplified pts

Children's Hospital of Philadelphia RESEARCH INSTITUTE

Collaboration with COG
Yael Mosse, Philadelphia

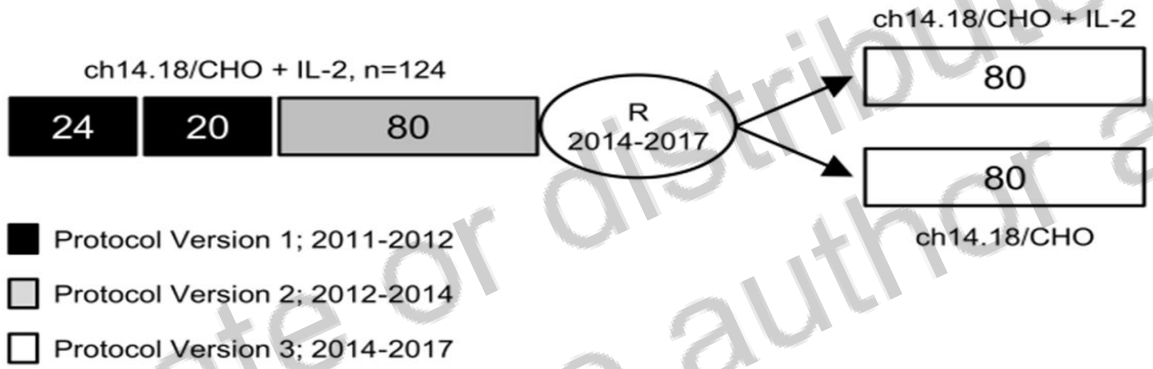
VERITAS Protokoll
for front line Refractory & poor responders



Long Term Infusion Study Dinutuximab beta in relapsed /refractory patients (accrual closed)

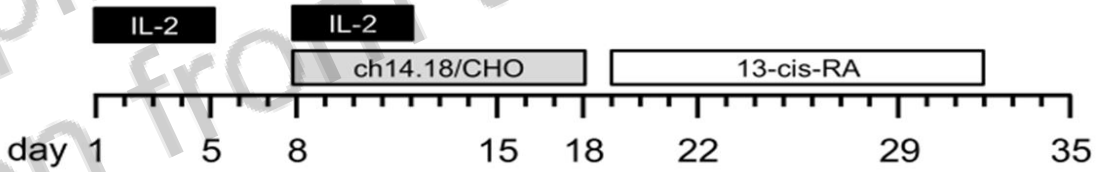
Single arm (124 pts)

Randomization (2x80pts 0 160 pts)



PI Prof. Holger Lode

Universitätsmedizin Greifswald



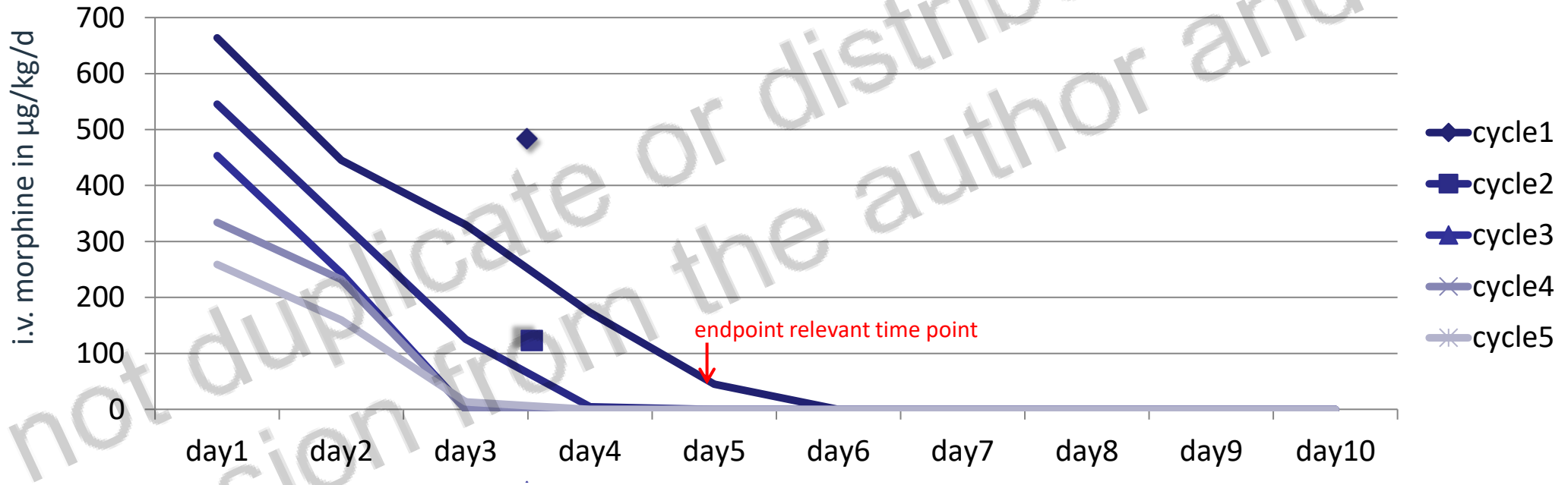
treatment: 5 cycles; 35 day/cycle

- aldesleukin (IL-2); s.c.; 6× 10^6 IU/m²/day; cum.: 60× 10^6 U/m²/cycle
- ch14.18/CHO; LTI; 10 mg/m²/day; cum.: 100 mg/m²/cycle
- isotretinoin (13-cis-RA); b.i.d. p.o.; 160 mg/m²/day; cum.: 2240 mg/m²/cycle

Senior PI

St. Anna Kinderkrebsforschung
Coordinating Sponsor

LTI: Endpoint (124-patients cohort): Intravenous Morphine usage



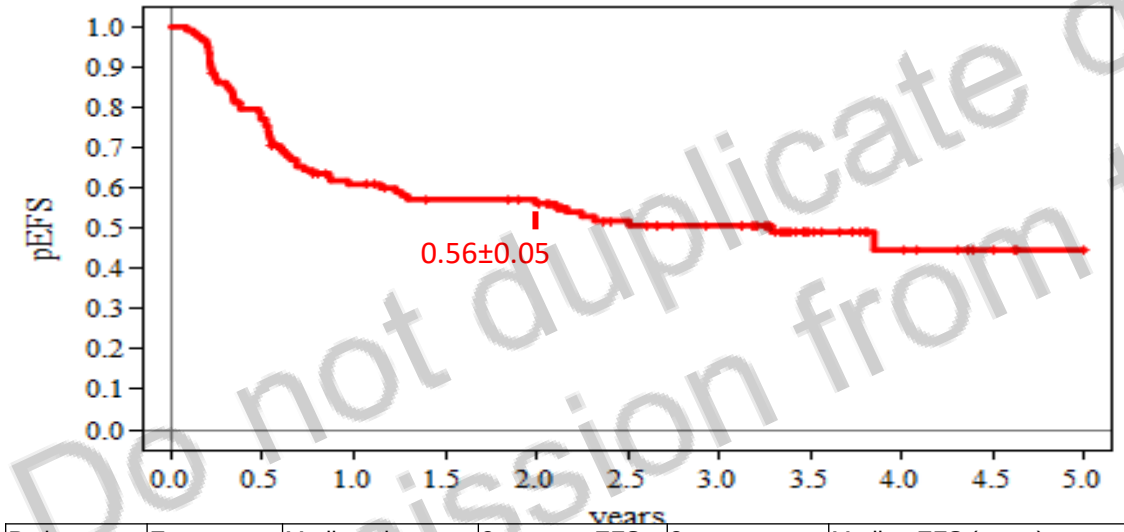
Reduced morphine within cycles and from cycle to cycle. 72% of the 124 patients were i.v. morphine-free on day 5.

LTI: Endpoints (124-patients cohort): Response Rate & Survival

79/124 patients with measurable disease

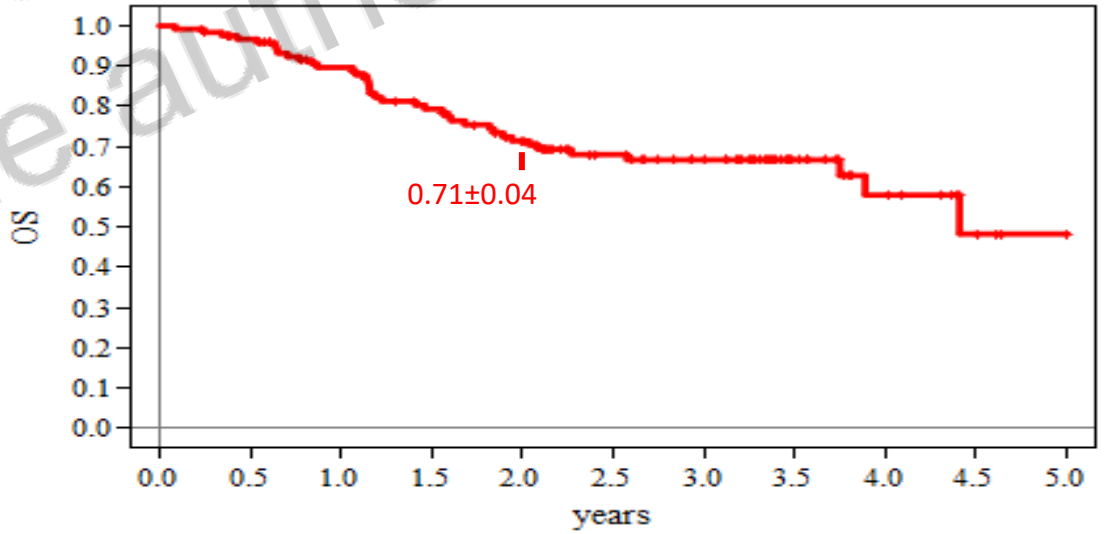
	CR	PR	SD	PD	missing	total	response rate	
mid	14	24	27	11	3	79	38/76	50%
end	14	19	15	28	3	79	33/76	43%

Event free survival



Patients	Events	Median observ. time	2 years - pEFS	3 years - pEFS	Median EFS (years)
124	59	3.12 y	0.56±0.05	0.51±0.05	3.29 y (95%CI: 1.2-5.4)

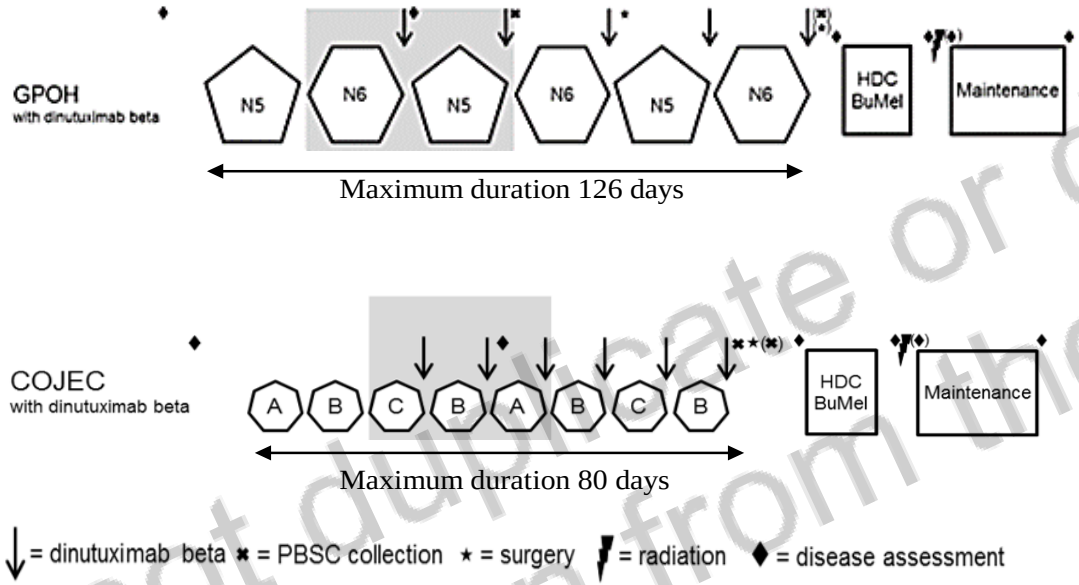
Overall survival



Patients	Events	Median observ. time	2 years - pEFS	3 years - pEFS	Median EFS (years)
124	38	3.12 y	0.71±0.04	0.67±0.05	4.41 y (95%CI: 3.89-4.93)

In preparation: Phase 1 study Combination of dinutuximab beta with induction chemotherapy regimens in newly diagnosed high-risk neuroblastoma
PI: H. Lode

Study Schema



Starting infusion durations:

- GPOH: starting dinutuximab beta infusion duration = 5 days 10 mg/m^2 × 5 days (50 mg/m^2/course) at 21-day treatment intervals.
- COJEC: starting dinutuximab beta infusion duration = 3 days 10 mg/m^2 × 3 days (30 mg/m2/course) at 10-day treatment intervals.

COJEC = cisplatin, vincristine, carboplatin, etoposide, and cyclophosphamide; GPOH = German Pediatric Oncology and Hematology; HDC BuMel = high-dose chemotherapy busulfan and melphalan; PBSC = peripheral blood stem cells.

Critical appraisal and Conclusions 1

- Neuroblastoma is marked by wide clinical and biological heterogeneity rendering comparisons across respective trials with varying eligibility and treatment intensities per se difficult.
- Over the past 4 decades, outcomes for children with high-risk neuroblastoma have improved by better identification of high-risk groups
- Therapy de-escalation in the low- intermediate risk group as important element for children with favourable biological profiles and no LTS.
- Therapy intensification was beneficial in high risk neuroblastoma with one of the most significant improvements achieved by introduction of HDC/autologous SCT.
- Hallmark randomized trials addressing HDC/SCT underpinned results of earlier single arm HDC /SCT trials in NBL overcoming poor long term outcome results of reviously 10 to 20% OS.

Critical appraisal and Conclusions 2

- However, unless we achieve long term survival rates in HR-NBL comparable to ALL with > 90% de-escalation strategies appear not advisable and rather synergistic approach of available treatment modalities including innovative ones should be further explored and new evidence be created.

- Continued collaborative efforts are necessary with a respectful, albeit critical appraisal of new insights to built together optimized treatment concepts and to create new evidence for children with high risk neuroblastoma to achieve our common vision:
  A long term survival for all our patients with reduced toxicity and minimal late effects!

St. Anna Kinderkrebsforschung
CHILDREN'S CANCER RESEARCH INSTITUTE

Thank you!