Neuroblastic Tumours for IPSO
4th October 2012

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Great Ormond Street Hospital for Children NHS Trust and Institute of Child Health London

Previously at the

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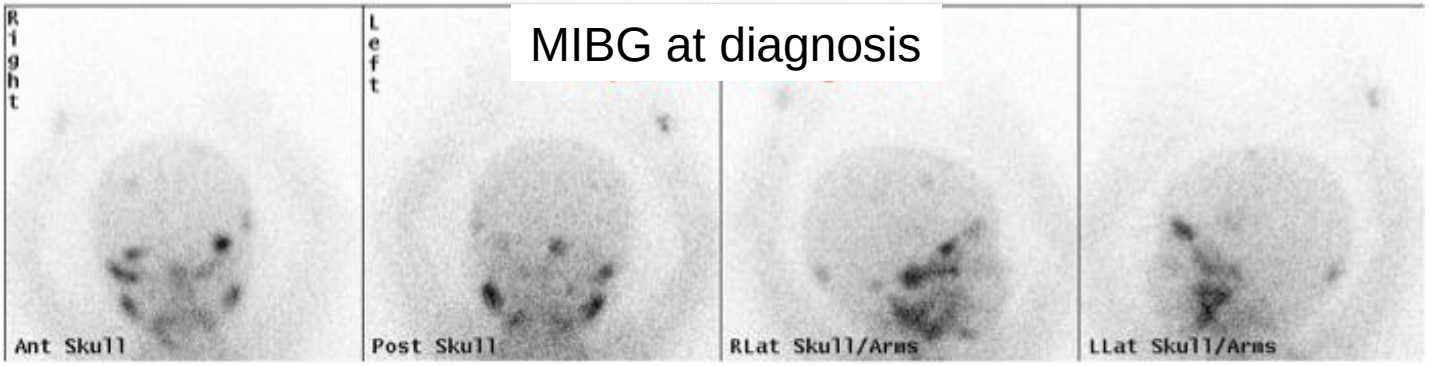
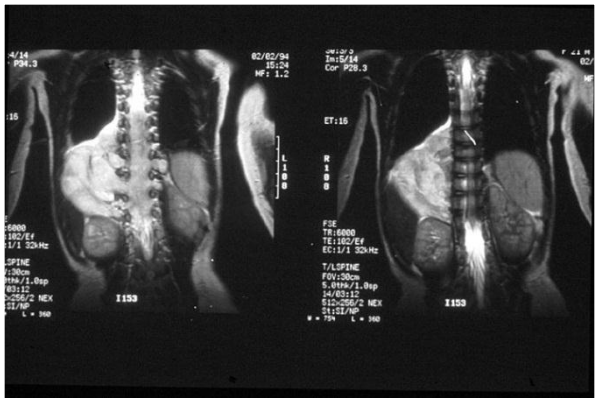
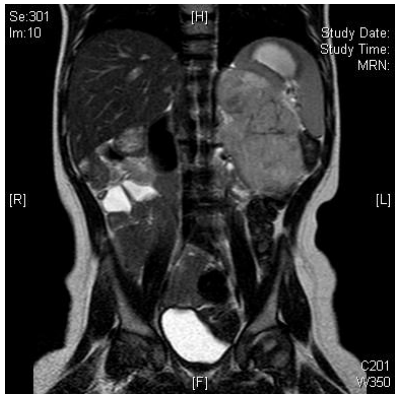
The child first and always

Neuroblastic tumour presentations



MIBG at diagnosis





EUROPEAN JOURNAL OF CANCER 47 (2011) 561–571

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ScienceDirect

journal homepage: www.ejconline.com

Changes over three decades in outcome and the prognostic influence of age-at-diagnosis in young patients with neuroblastoma: A report from the International Neuroblastoma Risk Group Project

Veronica Moroz [a,*], *David Machin* [a], *Andreas Faldum* [b], *Barbara Hero* [c], *Tomoko Iehara* [d], *Veronique Mosseri* [e], *Ruth Ladenstein* [f], *Bruno De Bernardi* [g], *Hervé Rubie* [h], *Frank Berthold* [c], *Katherine K. Matthay* [i], *Tom Mondair* [j], *Peter F. Ambros* [k], *Andrew D.J. Pearson* [l], *Susan L. Cohn* [m], *Wendy B. London* [n,*]

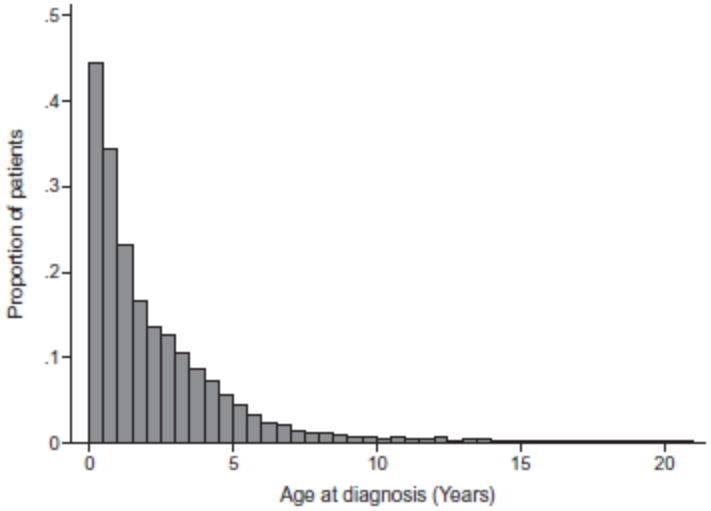


Fig. 2 – Distribution of age-at-diagnosis in 11,037 cases of neuroblastoma under 21 years of age.

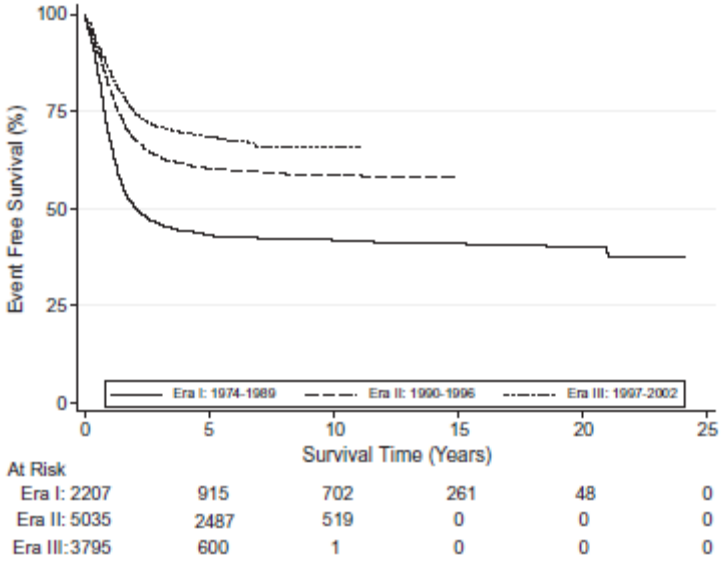


Fig. 1 – EFS from date of diagnosis of all 11,037 patients and by their respective Era of diagnosis (1974–1989, 1990–1996 and 1997–2002).

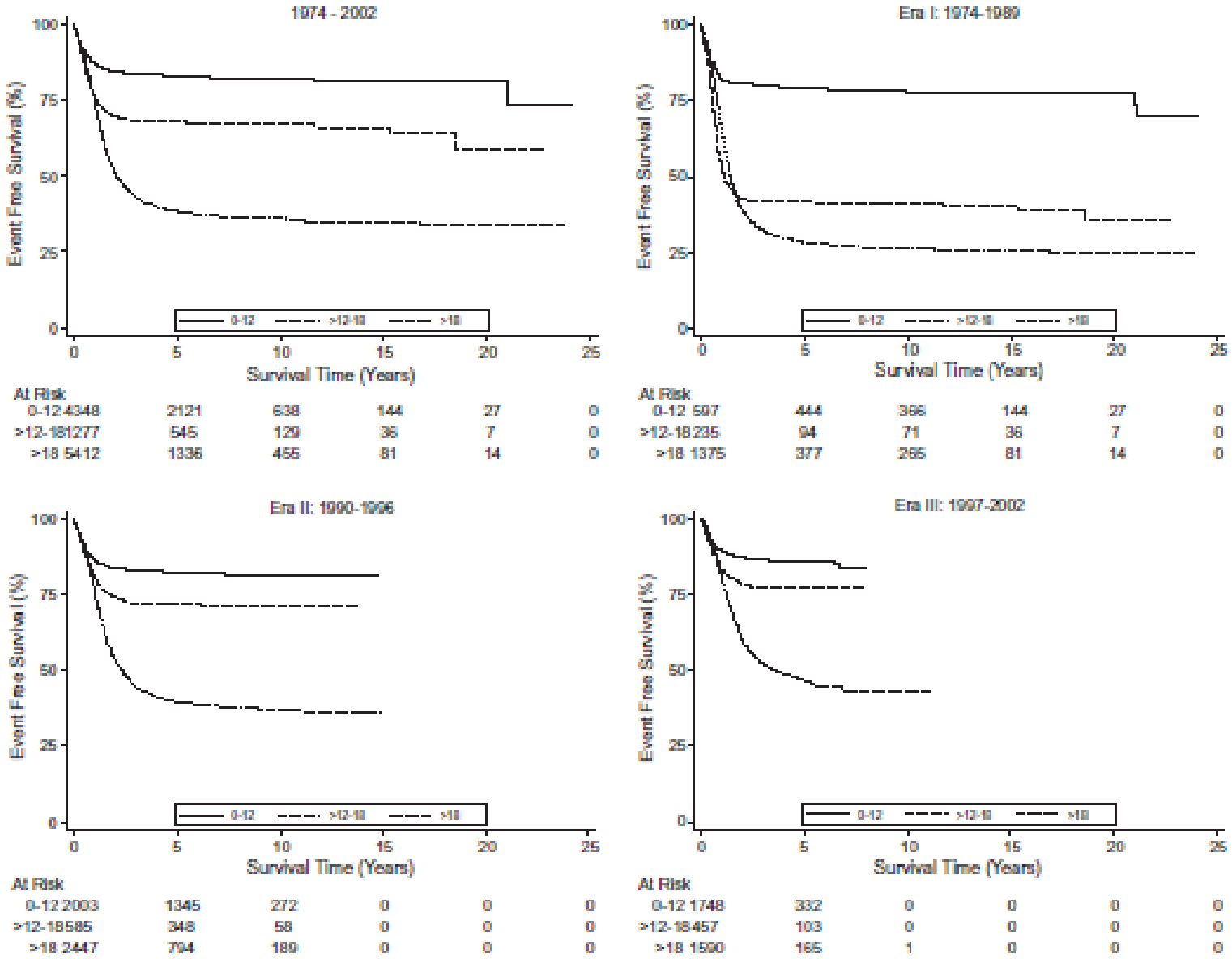


Fig. 3 – EFS for all 11,037 patients, and within each Era, for the age categories 0–12, 13–18 and 19 or more months.

VOLUME 27 · NUMBER 2 · JANUARY 10 2009

JOURNAL OF CLINICAL ONCOLOGY

SPECIAL ARTICLE

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

Oncology, Children's Hospital of Philadelphia, Philadelphia, PA; Children's Cancer Research Institute, St Anna Kinderkrebsforschung, Vienna, Austria; Department of Radiology, Institut Curie, Paris, France; Pediatric Surgery-Department of Pediatrics, University of Padova, Padova, Italy; Department of Paediatric Surgery, St George's

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.

Table 3. Distribution of SIOPEN Patients by INRGSS Versus INSS

INSS Stage	INRGSS L1		INRGSS L2		
	No.	%	No.	%	Total No.
1	239	79	64	21	303
2	81	55	66	45	147
3	12	6	199	94	211
Total	332	50	329	50	661

Abbreviations: SIOPEN, International Society of Pediatric Oncology Europe Neuroblastoma Group; INRGSS, International Neuroblastoma Risk Group Staging System; INSS, International Neuroblastoma Staging System.

Table 1. Image-Defined Risk Factors in Neuroblastic Tumors

Ipsilateral tumor extension within two body compartments
Neck-chest, chest-abdomen, abdomen-pelvis
Neck
Tumor encasing carotid and/or vertebral artery and/or internal jugular vein
Tumor extending to base of skull
Tumor compressing the trachea
Cervico-thoracic junction
Tumor encasing brachial plexus roots
Tumor encasing subclavian vessels and/or vertebral and/or carotid artery
Tumor compressing the trachea
Thorax
Tumor encasing the aorta and/or major branches
Tumor compressing the trachea and/or principal bronchi
Lower mediastinal tumor, infiltrating the costo-vertebral junction between T9 and T12
Thoraco-abdominal
Tumor encasing the aorta and/or vena cava
Abdomen/pelvis
Tumor infiltrating the porta hepatis and/or the hepatoduodenal ligament
Tumor encasing branches of the superior mesenteric artery at the mesenteric root
Tumor encasing the origin of the coeliac axis, and/or of the superior mesenteric artery
Tumor invading one or both renal pedicles
Tumor encasing the aorta and/or vena cava
Tumor encasing the iliac vessels
Pelvic tumor crossing the sciatic notch
Intraspinal tumor extension whatever the location provided that:
More than one third of the spinal canal in the axial plane is invaded and/or the perimedullary leptomeningeal spaces are not visible and/or the spinal cord signal is abnormal
Infiltration of adjacent organs/structures
Pericardium, diaphragm, kidney, liver, duodeno-pancreatic block, and mesentery
Conditions to be recorded, but *not* considered IDRFs
Multifocal primary tumors
Pleural effusion, with or without malignant cells
Ascites, with or without malignant cells

Abbreviation: IDRFs, image-defined risk factors.

Risk Grouping according to INRG

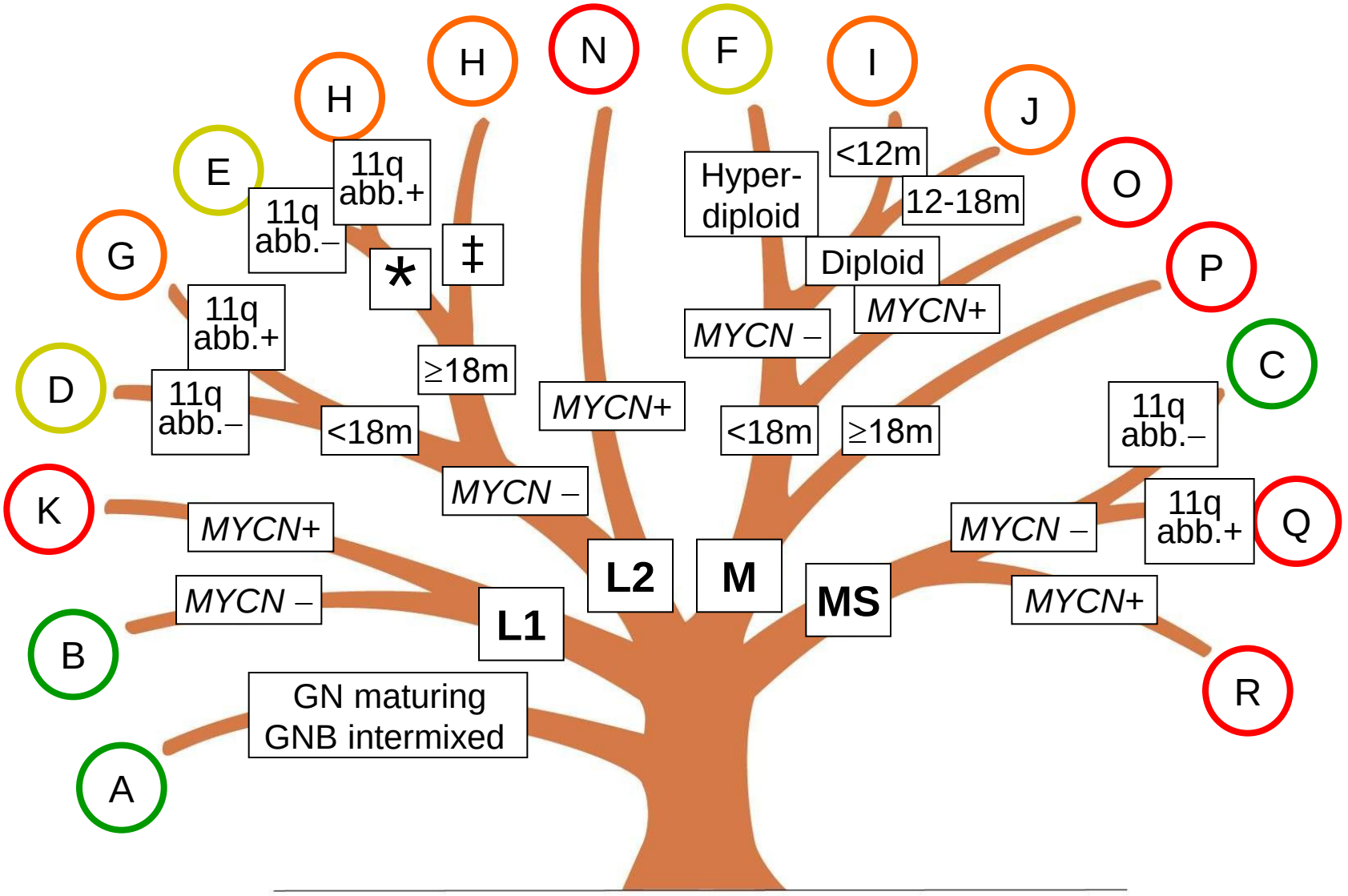
Risk Group	Pre-treatment Group	Predicted 5-year EFS	Proportion of patients
Very low	A B C	>85%	28%
Low	D E F	76-85%	27%
Intermediate	G H I J	50-75%	9%
High	K N O P Q R	<50%	36%

Tom Monclair 2012

The International Neuroblastoma Risk Group Pre-treatment Classification Schema

INRG Stage	Age months	Histologic Category	Grade of Tumor Differentiation	*MYCN*	11q aberration	Ploidy	Pre-treatment 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 m	Any, except GN maturing or GNB intermixed		NA	No		D Low
					Yes		G Intermediate
	≥18 m	GNB nodular Neuroblastoma	Differentiating	NA	No		E Low
					Yes		H Intermediate*
			Poorly differentiated or Undifferentiated	NA			
				Amp			N High
M	<18 m			NA		Hyperdiploid	F Low
	<12 m					Diploid	I Intermediate
	12 – <18m					Diploid	J Intermediate
	<18 m			Amp			O High
	≥18 m						P High
MS	<18 m			NA	No		C Very Low
					Yes		Q High
				Amp			R High

The INRG Survival Tree



* NB or GNB nodular, differentiating ‡ NB or GNB nodular, poorly - or un-differentiated

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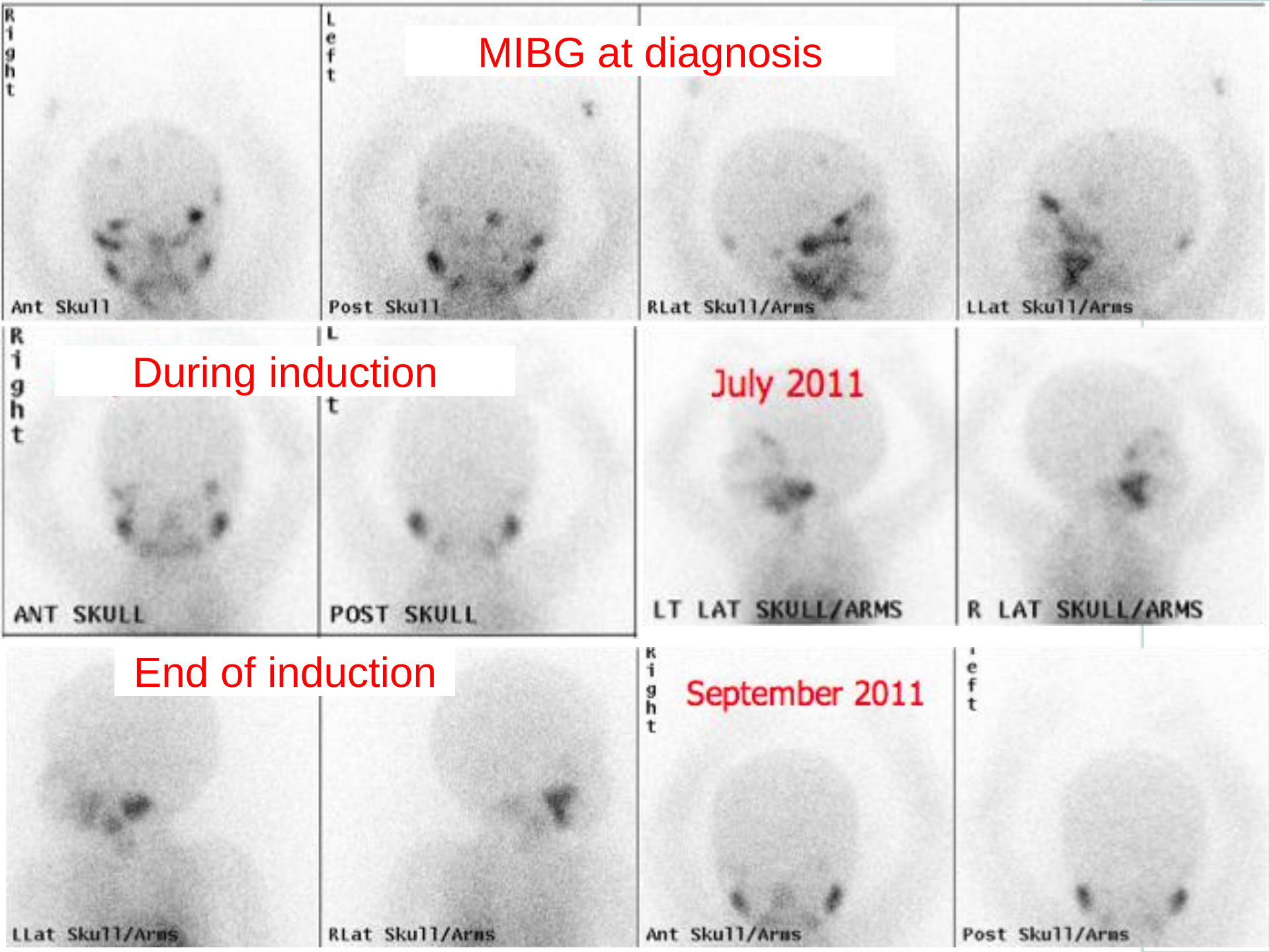
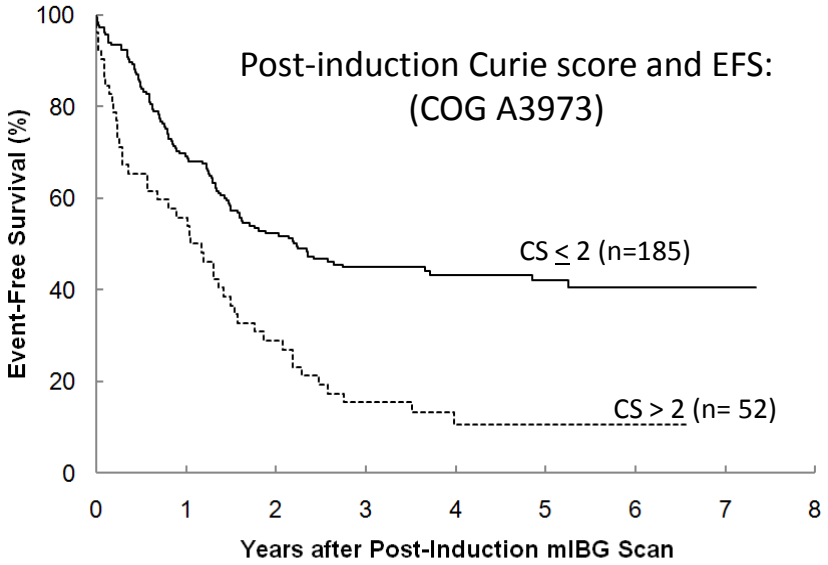

MIBG at diagnosis
Ant Skull
Post Skull
RLat Skull/Arms
LLat Skull/Arms
During induction
ANT SKULL
POST SKULL
July 2011
LT LAT SKULL/ARMS
R LAT SKULL/ARMS
End of induction
LLat Skull/Arms
RLat Skull/Arms
September 2011
Ant Skull/Arms
Post Skull/Arms

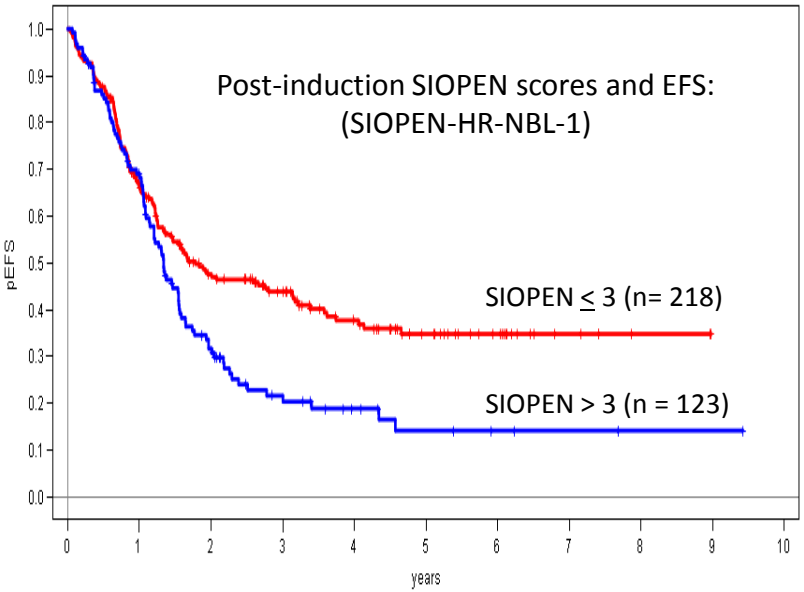
Curie score vs SIOPEN score Post-Induction and EFS

Poor EFS if Curie Score > 2 or SIOPEN score > 3



	No.	3-yrs. pEFS	p-value
0-2	185	0.44.9±0.04	.
> 2	52	0.15.4±0.05	p< 0.001

COG: > 90% of patients underwent BMT.
- Early separation in curves. Higher risk patients.



	Patients	3-yrs. pEFS	p-value
0-3	218	0.44±0.04	0.002
> 3	123	0.22±0.04	.

SIOPEN data: 74% underwent BMT.
- Highest risk patients did not undergo BMT.

Greg Yanik and Ariane Boubaker

NB INDUCTION PROTOCOLS

	MSK N7		COG		ENSG 5		SIOPEN	
1	CDV	1	CT	1	OJE	1	OJE
2	CDV	2	CT	2	OP	2	OP
3	CiE	3	CiE	3	OEC	3	OEC
4	CDV	4	CDV	4	OP	4	OP
5	CiE	5	CiE	5	OJE	5	OJE
		6	CDV	6	OP	6	OP
				7	OEC	7	OEC
				8	OP	8	OP
						9	TVD
						10	TVD
	Duration 140 days CR-VGPR 83% CR-PR 93%		Duration 170 days CR-VGPR 50% CR-PR 88%		Duration 100 days CR-VGPR 75% (assessed 82/130) CR-PR 85%		Duration 150 days CR-VGPR?? CR-PR?? ± 2 TVD
	BU-MEL		CEM		LPAM		CEM - BU-MEL

MoAb3F8 (CEM/TIC)

ME COMPOSITION : DRUG CYCLE DOSE (mg/1qm)												
C	CPM	4200	C	CPM	4000	O	VCR	1.5	O	VCR	1.5
D	DOXO	75	T	TOPO	7.5	J	CARBOPT	750	J	CARBOPT	750
V	VCR	2				E	VP	350	E	VP	350
			Ci	CDDP	200						
Ci	CisPt	200	E	VP	600	O	VCR	1.5	O	VCR	1.5
E	VP	600				P	CDDP	80	P	CDDP	80
			C	CPM	4200						
			D	DOXO	75	O	VCR	1.5	O	VCR	1.5
			V	VCR	2	E	VP	350	E	VP	350
						C	CPM	2100	C	CPM	2100
									T	TOPO	7.5
									V	VCR	2
									D	DOXO	45

DRUG- TOTAL DOSE (mg/bqm)											
	CPM	12600		CPM	16400		CPM	4200		CPM	4200
	ADR	225		ADR	150		ADR	--		ADR	90
	VCR	6		VCR	4		VCR	12		VCR	16
	CARBO	-		CARBO	-		CARBO	1500		CARBO	1500
	CDDP	400		CDDP	400		CDDP	320		CDDP	320
	VP16	1200		VP16	1200		VP16	1400		VP16	1400
	TOPO	-		TOPO	15		TOPO	-		TOPO	15

Alberto Garaventa

High dose melphalan in the treatment of advanced neuroblastoma: results of a randomised trial (ENSG –1) by the European Neuroblastoma Study Group

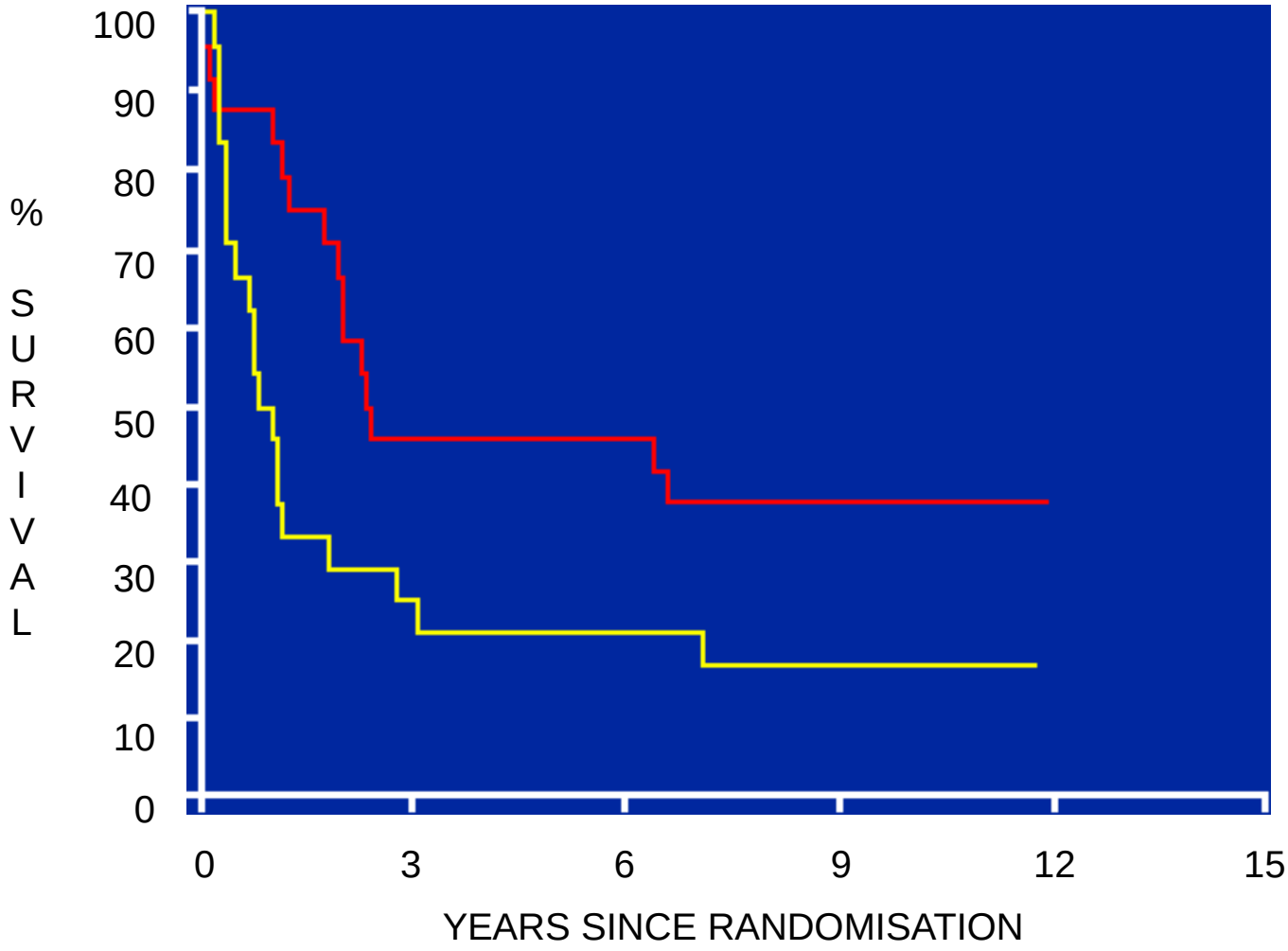
Recruitment 1982-1985

Pritchard J, Cotterill SJ, Germond SM, Imeson J, de Kraker J, Jones DR

Ped Blood Cancer 2005 Apr; 44(4):348-57

ENSG 1 Overall Survival - Stage 4 ≥ 1year

Time 0 = pre-transplant



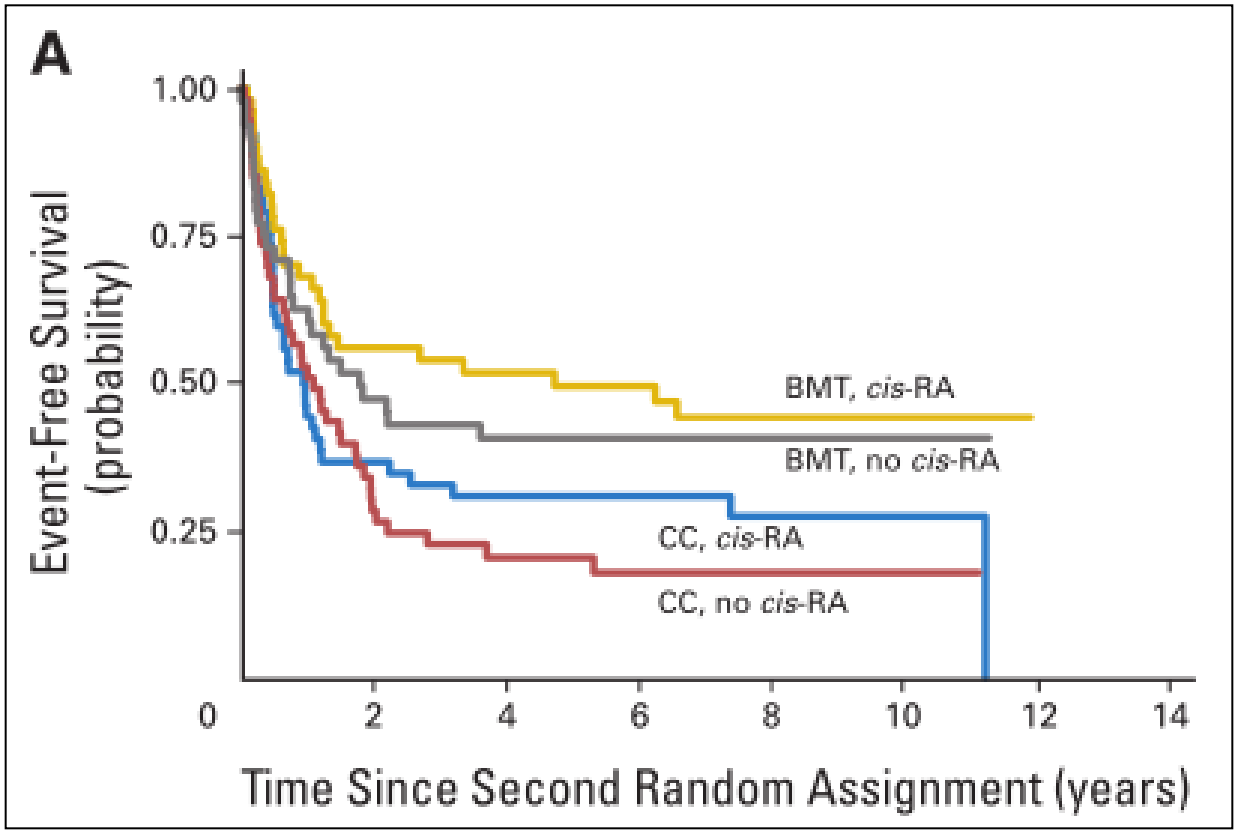
No FT	2yr	30%	3 yr	20%
HDM	2yr	55%	3 yr	46%

Long-Term Results for Children With High-Risk Neuroblastoma Treated on a Randomized Trial of Myeloablative Therapy Followed by 13-cis-Retinoic Acid: A Children's Oncology Group Study

Katherine K.Matthay, C.Patrick Reynolds, Robert C. Seeger, Hiroyuki Shimada, E. Stanton Adkins, Daphne Haas-Kogan, Robert B. Gerbing, Wendy B. London, and Judith G. Villablanca

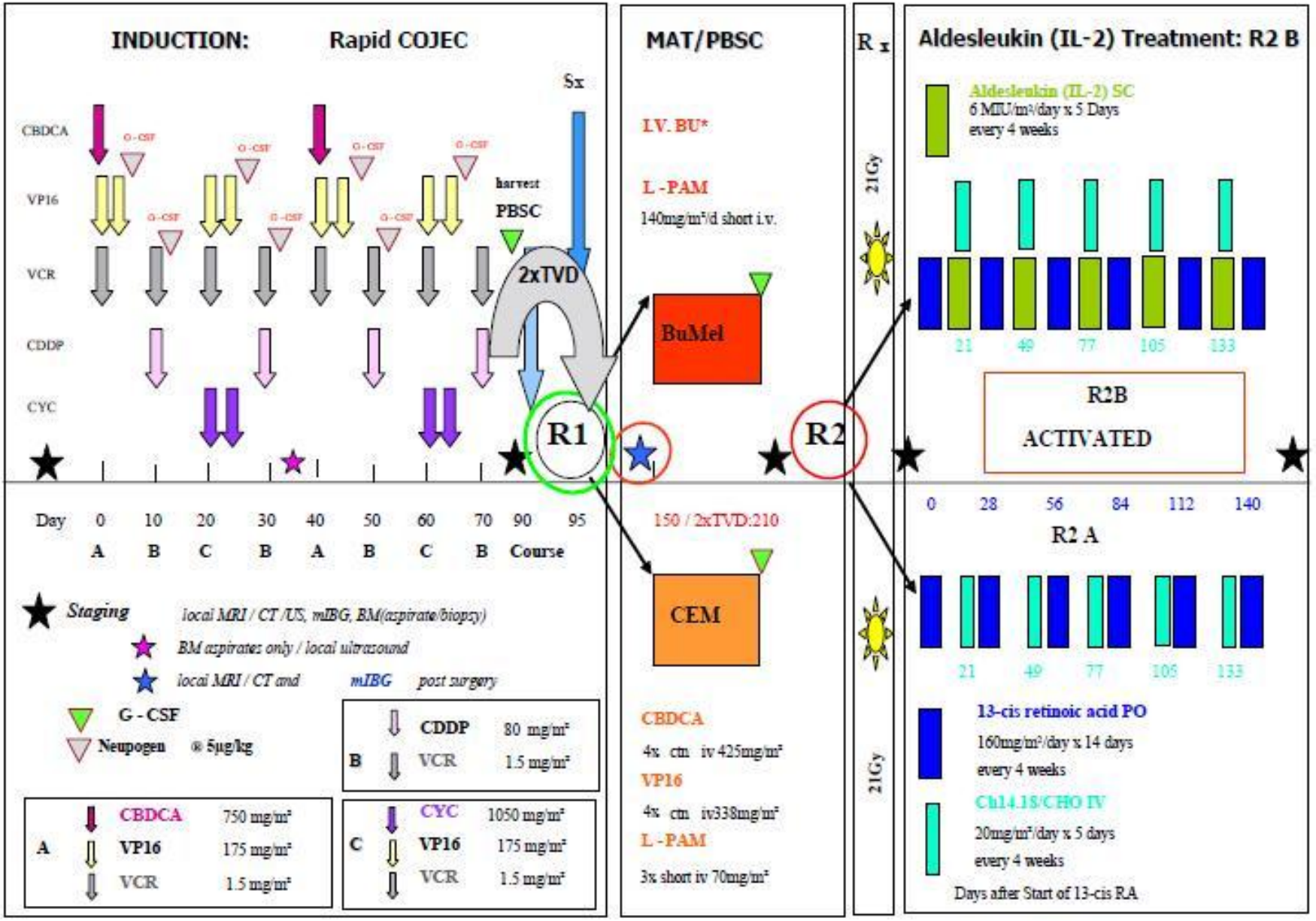
J Clin Oncol Jan 26, 2009

Randomized Trial of Myeloablative Therapy and 13-cis-Retinoic Acid



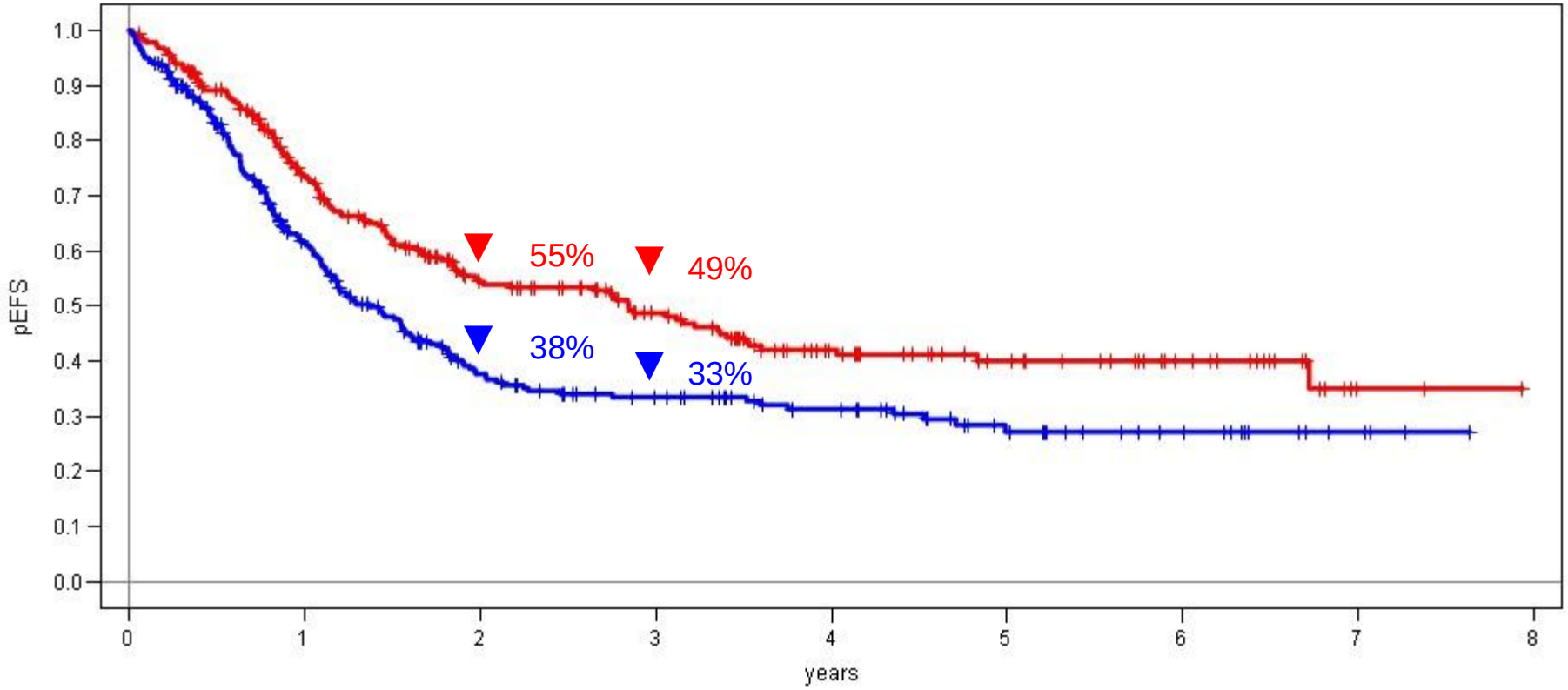
Event-free survival for patients who participated in both the first and second random assignments (autologous bone marrow transplantation + 13-cisretinoic acid [*cis*-RA] [n = 50] versus continuing chemotherapy (CC) + no *cis*-RA [n = 53]). *P* = .0038.

HR-NBL-1 / SIOPEN FLOWSHEET



EFS by Randomized Arm

Survivors are censored at the last follow up

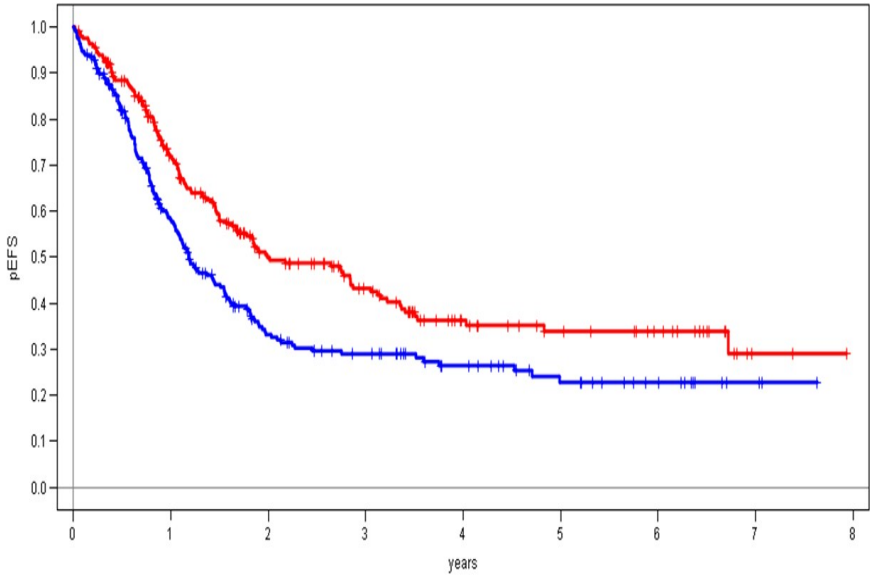


	Patients	Events	3-yrs. pEFS	p-value
BUMEL	281	136	49%±3	<0.001
CEM	282	169	33%±3	

EFS Impact of Regimens by Stage

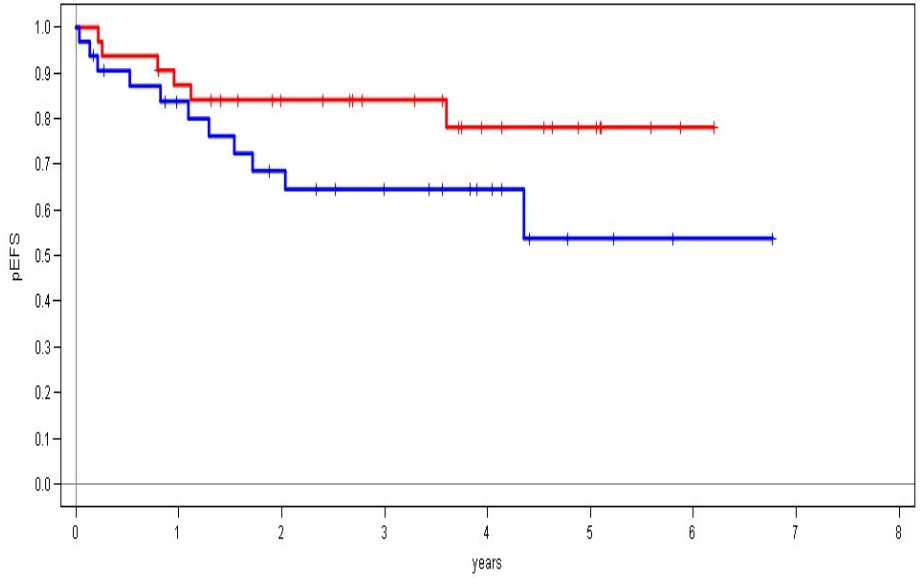
Survivors are censored at the last follow-up

Stage 4



	Patients	Events	3-yrs. pEFS	p-value
BUMEL	247	129	0.43±0.04	0.001
CEM	247	158	0.29±0.03	.

Stage 2 & 3



	Patients	Events	3-yrs. pEFS	p-value
BUMEL	32	6	0.84±0.07	0.120
CEM	32	11	0.65±0.09	

A Phase III Randomized Trial of Chimeric Anti-GD2 antibody + GM-CSF + IL2 Immunotherapy of High-Risk Neuroblastoma in First Response

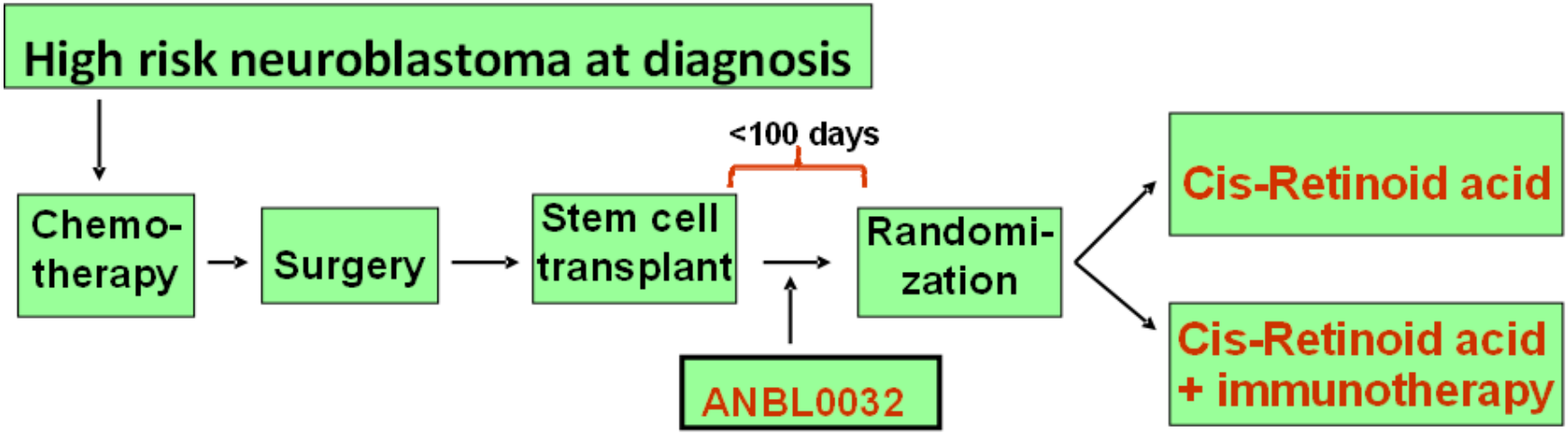
Children's Oncology Group (COG) study ANBL0032

A. L. Yu, A. L. Gilman, M. F. Ozkaynak,
W. B. London, S. Kreissman, H. Chen, K. K. Matthay,
S. L. Cohn, J. M. Maris, P. Sondel

N Engl J Med. 2010 September 30; 363(14): 1324–1334.

CureSearch
Children's Oncology Group

COG ANBL0032: phase III trial design for high risk neuroblastoma



Immunotherapy: monoclonal antibody (mAb) ch14.18 + GM-CSF + IL2

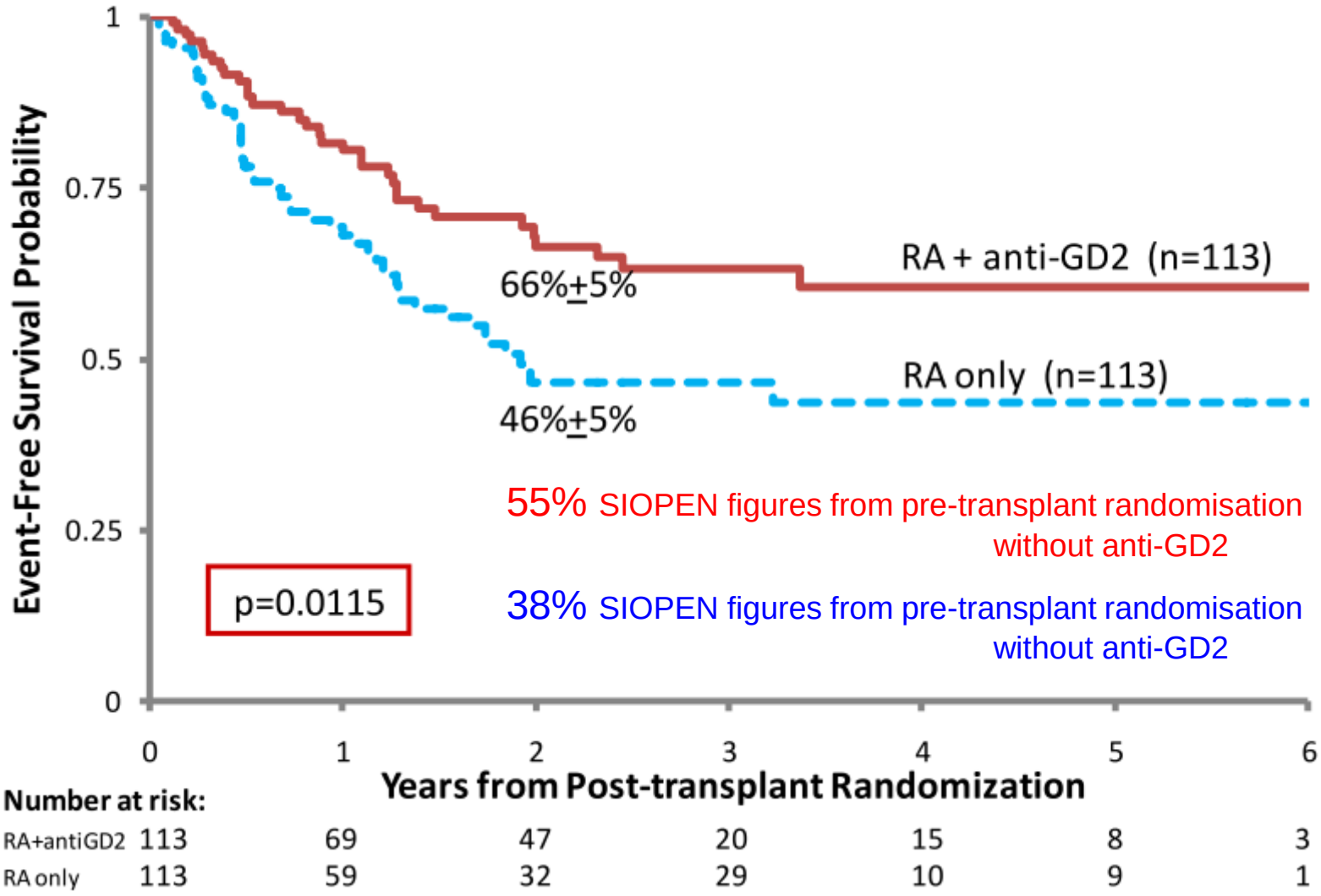
To stimulate immune effector cells to enhance ADCC:

GM-CSF : granulocytes & monocytes

IL2: NK cells

CureSearch
Children's Oncology Group

Results: Event-free Survival



Number at risk:

RA+antiGD2	113	69	47	20	15	8	3
RA only	113	59	32	29	10	9	1

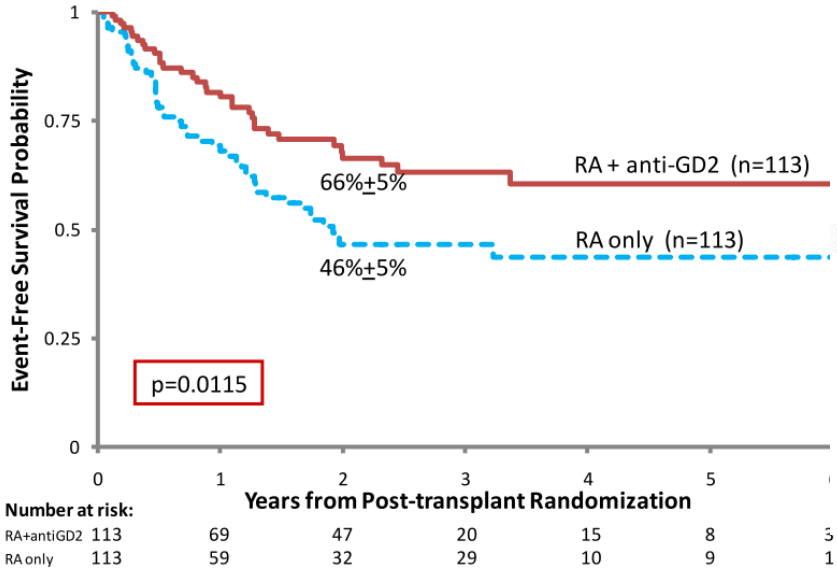
CureSearch
Children's Oncology Group

Comparison of figures

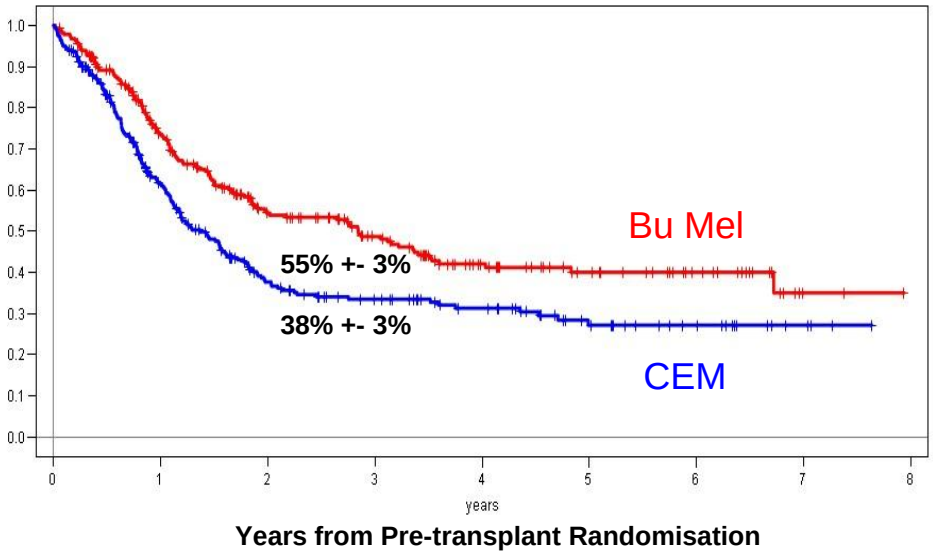
COG
Time 0: post transplant=later cohort
With and without antibody

SIOPEN
Time 0: pre transplant=earlier cohort
BuMel or CEM without antibody

Results: Event-free Survival



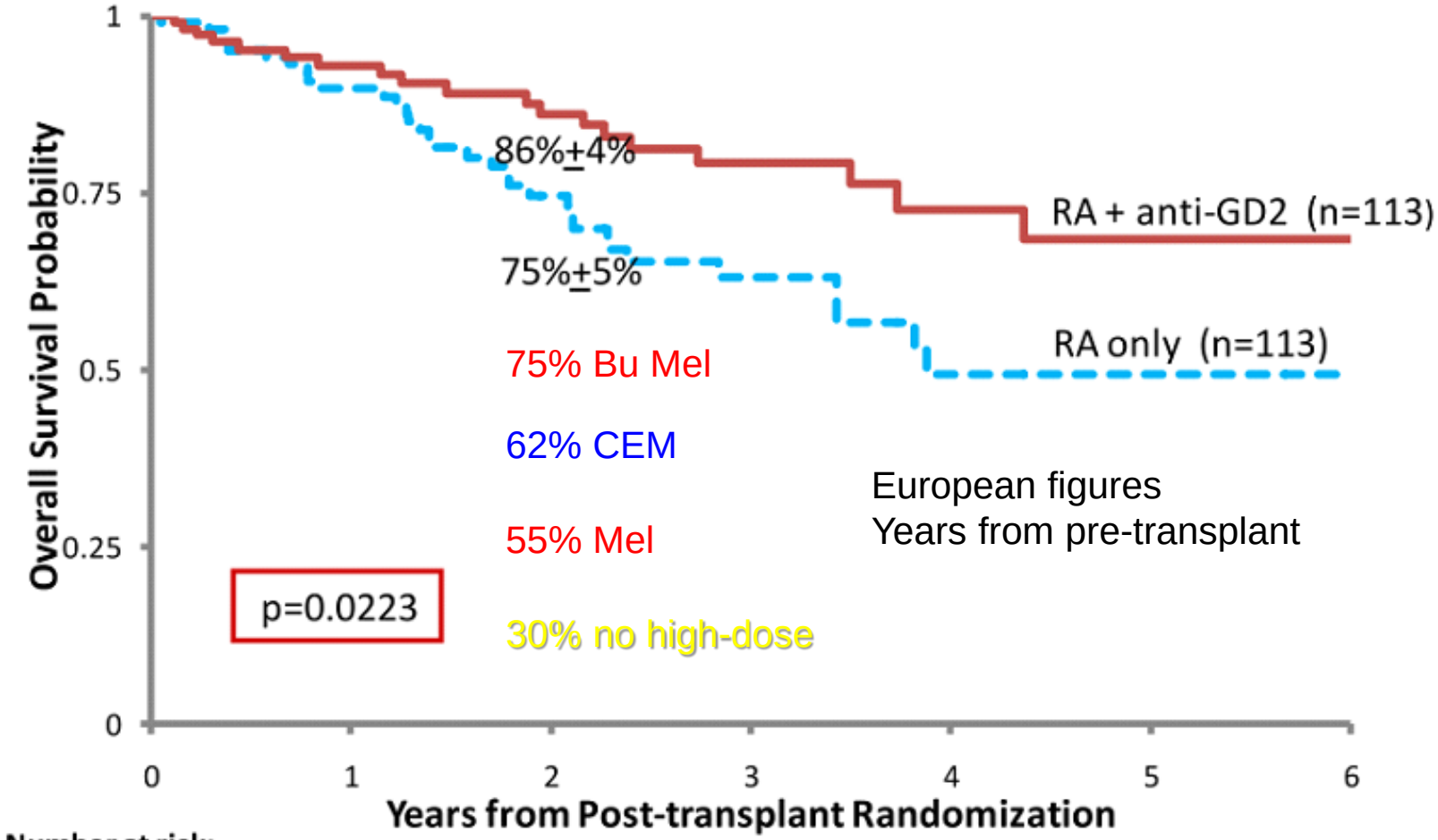
Results: Event-free Survival



CureSearch
Children's Oncology Group

SIOPEN R NET

Results: Overall Survival



Number at risk:

RA+antiGD2	113	77	59	37	20	10	3
RA only	113	79	51	26	12	9	1

Conclusions

- Survival is improving
- Treatment needs to be stratified
- Stratification requires tissue diagnosis
- Surgery remains essential particularly in high-risk disease
- Immunotherapy requires a minimal residual disease state