Neuroblastoma

Κλινικά χαρακτηριστικά -Θεραπευτική αντιμετώπιση των νευροβλαστικών όγκων στα παιδιά

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Ογκολογική Μονάδα Μαριάννα Β Βαρδινογιάννη ΕΛΠΙΔΑ

Νοσοκομείο Παίδων «Η Αγία Σοφία»

Αθήνα

Neuroblastoma

- NBL is the most common extra-cranial solid tumor during childhood
- Incidence: 1 case every 10,000 births

- Significant clinical heterogeneity:
  - Spontaneous regression
  - Disease evolution and resistant relapses despite current aggressive combination treatments

- Originates form the adrenal glands and along the sympathetic chain

Location

- Adrenal glands 50%

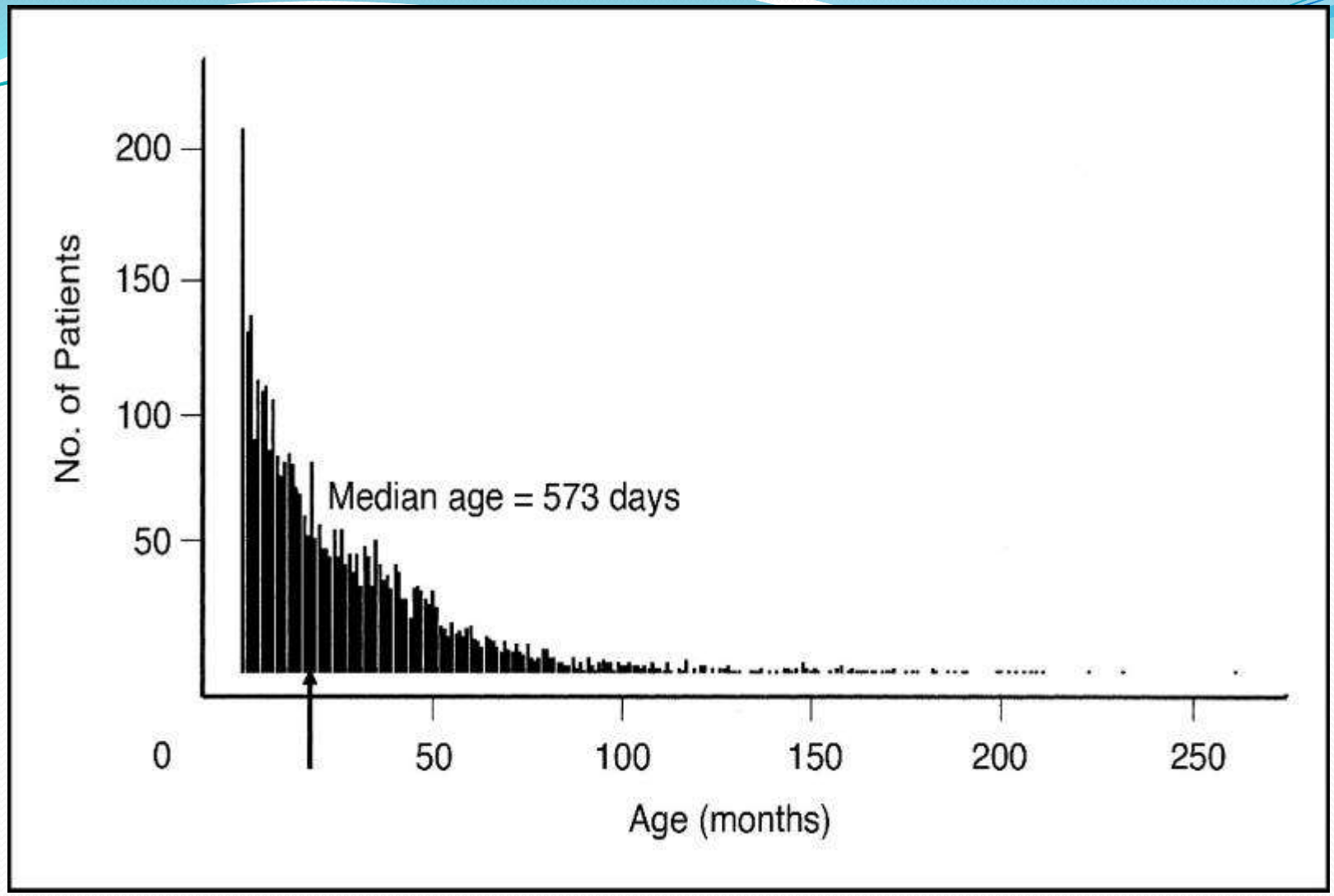
- Localized Disease 40 %
- Metastatic Disease 60 %

- Sympathetic chain 50 %

- Neck 1 %
- Thorax 19 %
- Abdomen 30 %
- Pelvis 1 %

Abdominal Cavity
80 %

High Risk
>50 %



London W et al. JCO 2005;23:6459-6465

JOURNAL OF CLINICAL ONCOLOGY

Νευροβλάστωμα : Κλινική Προβολή

Νευροβλάστωμα : Κλινική Προβολή Ενδομήτρια

- Προγεννητικά
  - Υπερνεφρική μάζα
  - Διηθήσεις ήπατος

- Επιβεβαίωση μετά τη γέννηση
  - Διερεύνηση
  - Αντιμετώπιση
    - Παρακολούθηση
    - Θεραπεία

Νευροβλάστωμα : Κλινική Προβολή

- Ασυμπτωματική ανεύρεση μάζας
- Άλγος, καχεξία, απώλεια βάρους, εφίδρωση
- Ψηλαφητικό εύρημα
- Οργανομεγαλία
- Νευρολογικές διαταραχές
  - Σ. Horner
  - Επώδυνο ισχίο
  - Μεταβολές σε ούρηση, κενώσεις
- Δερματικές διηθήσεις
- Περιοφθαλμικές εκχυμώσεις / Raccoon eyes
- Αιματολογικές μεταβολές
  - Αυξημένα αιμοπετάλια
  - Διήθηση μυελού έως και 100% (ΛΕΥΧΑΙΜΙΑ?)
- Διαρροϊκό σύνδρομο VIP
- Υπέρταση

Διερεύνηση Σταδιοποίηση

6.1.1 FULL HISTORY

- With attention to presence and duration of symptoms, such as pallor, sweating, weight loss, diarrhoea, irritability

6.1.2 CLINICAL EXAMINATION

- Measurements of weight, height and blood pressure
- Note signs of spinal cord compression

6.1.3 HAEMATOLOGY

- Full blood count including haemoglobin, white blood cell, neutrophil, lymphocyte and platelet counts.
- Coagulation profile

6.1.4 SERUM

- Renal and liver function (Na, K, Ca, Mg, PO_4, urea, creatinine, glucose, total protein, bilirubin, transaminases)
- Serum lactate dehydrogenase (LDH)
- Serum ferritin, serum NSE
- Pre-transfusion serum tests

6.1.5 URINE ANALYSIS

- Catecholamine metabolites: Determination of vanillomandelic acid (VMA), homovanillic acid (HVA) and dopamine, expressed in relation to creatinine excretion
- Strip test for albumin, glucose, ketones, blood, pH prior to platinum derivatives to exclude underlying renal disease

6.1.6 IMAGING

- Isotope scintigraphy preferably I^{123}-mIBG: mIBG scan assessing the uptake on the primary tumour, the number and the location of bone metastases and any other metastatic sites.
- If negative mIBG, bone scintigraphy with 99mTc-hydroxy-methylene-diphosphanate scintigraphy (T^{99} scan)
- AP chest x-ray
- CT or MRI scan of primary tumour (with 3D measurements) including search for dumbbell extension in relevant regions
- Radiological visualisation of any other evaluable disease

6.1.7 BONE MARROW, APHAERETIC PRODUCT AND PERIPHERAL BLOOD

Risk Classification

- High
- Intermediate
- Low to Very low

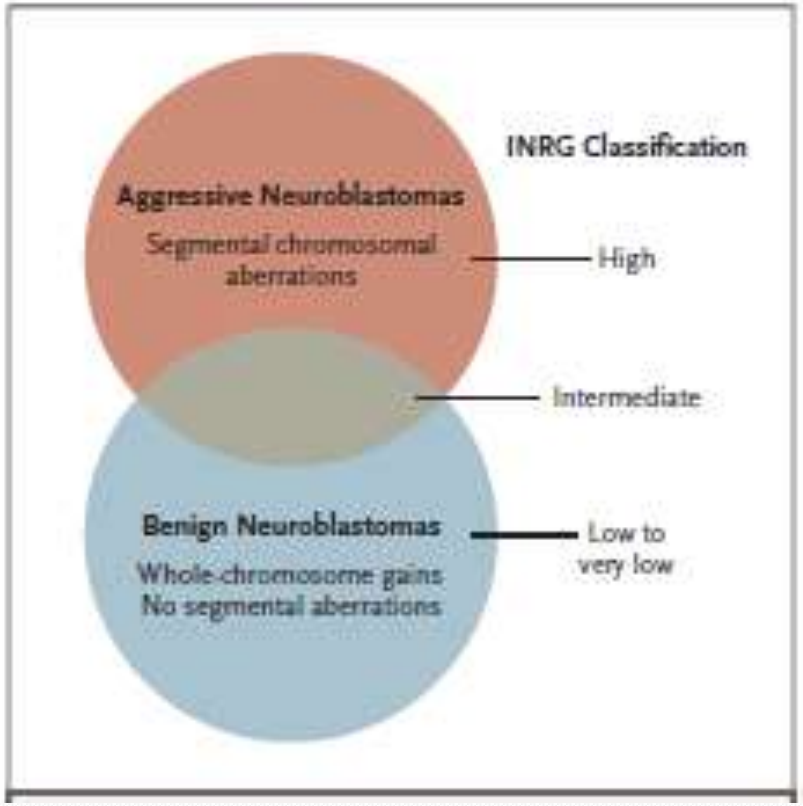


Figure 3. Genomic Basis of Neuroblastoma Risk Groups.

Two broad neuroblastoma phenotypes — aggressive and benign — are seen clinically, with the latter showing a high propensity for spontaneous regression or differentiation. These two groups are largely identifiable at a chromosomal level by the presence of segmental aberrations (translocations, amplifications, and deletions) in the more aggressive cases and by whole-chromosome gains in the more benign cases. Thus, the International Neuroblastoma Risk Group (INRG) classification is related to these chromosomal alterations, but the current system is imprecise, since the intermediate group in particular remains poorly defined. Current investigation is focused on the identification of molecular predictors of outcome in the high-risk group (as well as in patients with aggressive neuroblastomas masquerading as more benign forms of the disease).

Ανάπτυξη του Νευροβλαστώματος

Συγγενές

- Συγγενές NB: Μεταλλάξεις στη ΤΚ περιοχή του γονιδίου ALK
- Σποραδικό ή οικογενές NB σε συνδυασμό με σύνδρομο κεντρικού υποαερισμού ή νόσου Hirschsprung εμφανίζουν μεταλλάξεις απώλειας λειτουργίας στο homeobox gene PHOX2B

- Αν και οι μεταλλάξεις στο ALK και PHOX2B γονίδιο αφορούν τους περισσότερους ασθενείς με συγγενές NB, αλλά γονίδια μπορεί να βρεθούν

MEDICAL PROGRESS

Recent Advances in Neuroblastoma

John M. Maris, M.D.

N Engl J Med 2010;362:2202-11.

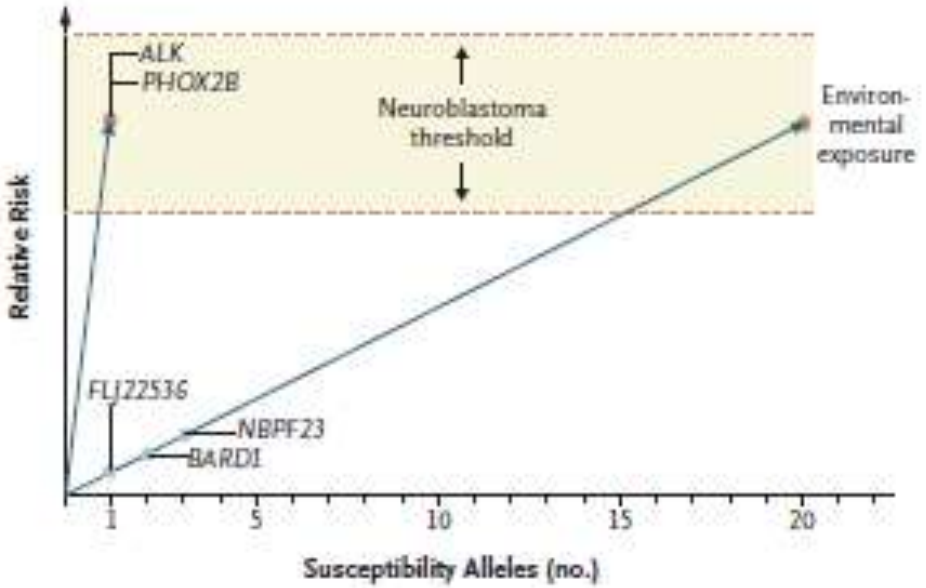


Figure 2. Model of Genetic Susceptibility to Neuroblastoma.

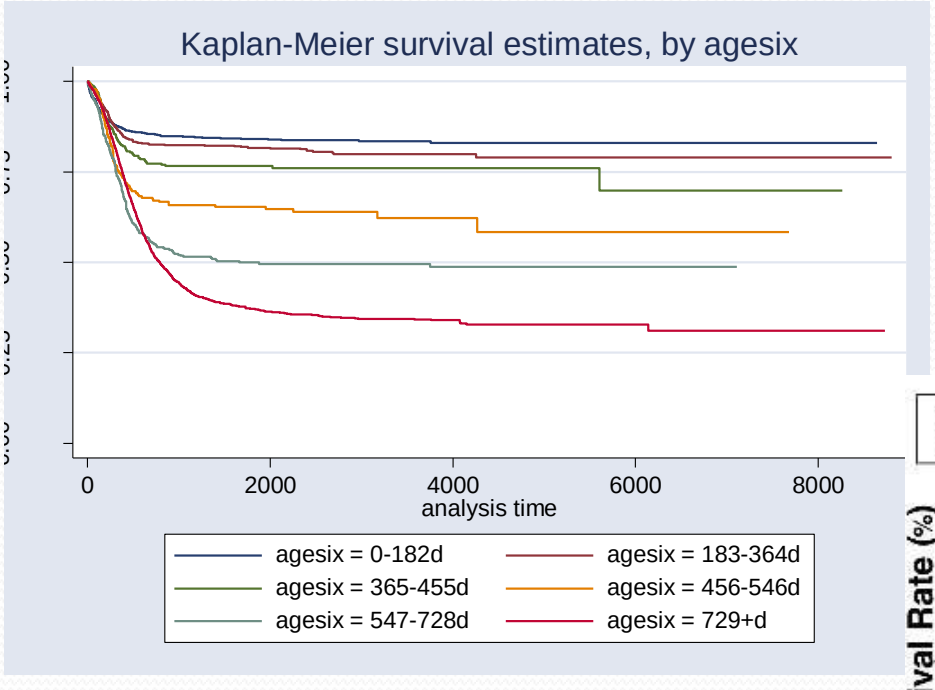
The y axis indicates the theoretical relative risk of neuroblastoma, and the x axis indicates the number of known and theoretical susceptibility alleles. A genetic threshold for the development of disease has been postulated, and malignant transformation is probably modified by interactions related to environmental exposure. A mutation in the *ALK* or *PHOX2B* gene results in a single, highly penetrant risk allele that allows developing neuroblastic tissue to meet or exceed this threshold for malignant transformation. These types of mutations are powerful enough to permit neuroblastoma to occur within families as a mendelian trait. On the other hand, there are multiple common DNA variations (polymorphisms) in a large number of genes that cooperate to reach this threshold in patients without *ALK* or *PHOX2B* mutations. For these sporadic cases of neuroblastoma, an excessive inheritance of "risk" variants has been postulated that increases susceptibility to the disease. Discovered susceptibility genes include *FLJ22536*, *BARDI*, and *NBPF23*. The total number of susceptibility loci is not currently known, nor is it known whether these polymorphisms act in an additive or synergistic (epistatic) fashion.

Προγνωστικοί Παράγοντες

- Ηλικία
- Στάδιο νόσου (INSS)
- Η ιστολογική εικόνα και κατηγοριοποίηση του όγκου (Shimada classification International Neuroblastoma Classification, INPC)
- Βιολογικοί δείκτες
- Γενετικοί Δείκτες

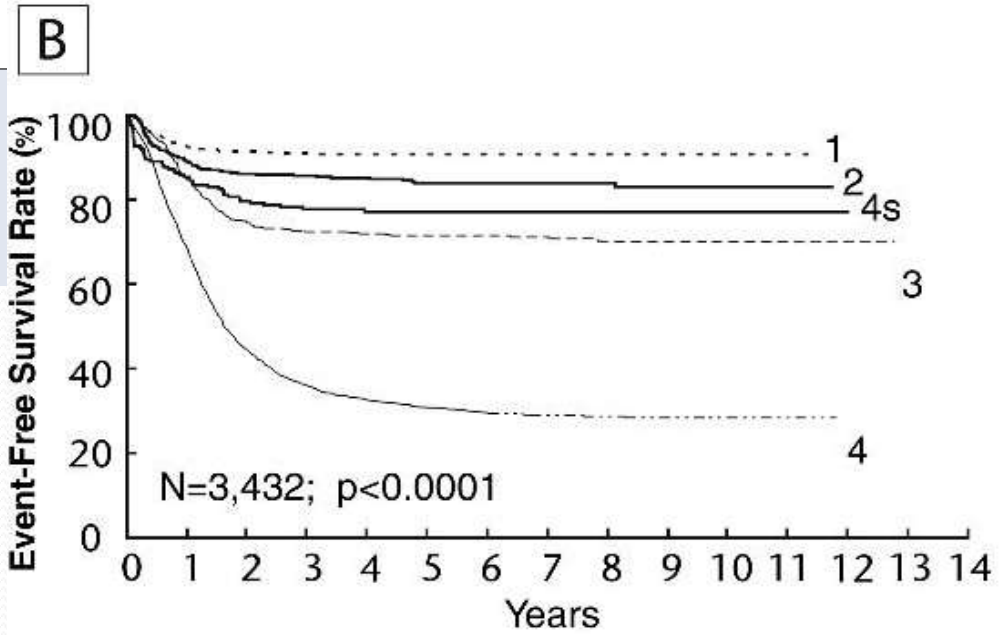
- Οι ανωτέρω παράγοντες πιθανολογούν με αρκετή ακρίβεια την προβολή και έκβαση της νόσου

Στοιχεία από το INRG 2005: Προγνωστικοί Παράγοντες



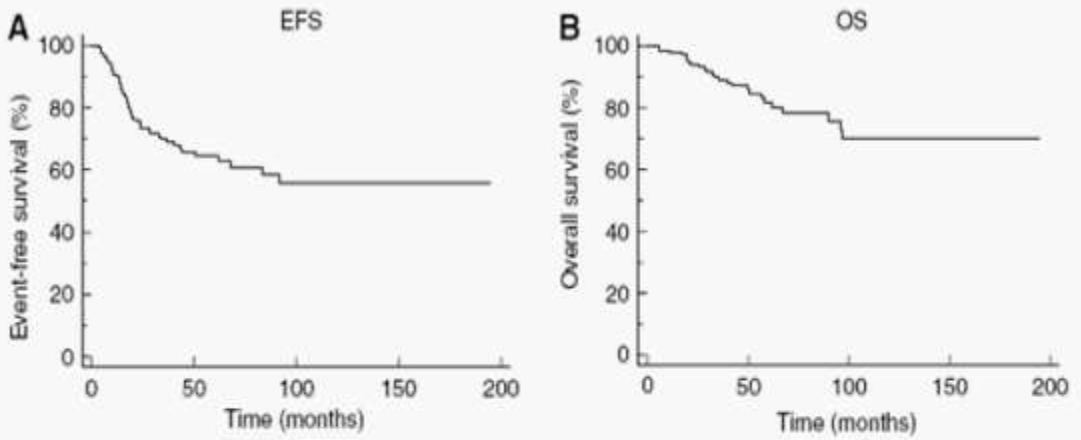
Ηλικία

Στάδιο



Στοιχεία από SFOP BJC 2007:

G Schleiermacher *et al*



Στάδιο

Ηλικία

Figure 3 Survival curves of 139 neuroblastoma patients. (**A**) Event-free survival of all patients. (**B**) Overall survival of all patients. (**C**) Event-free survival according to stage at diagnosis. (**D**) Event-free survival according to age at diagnosis.

Γενετικές Βλάβες

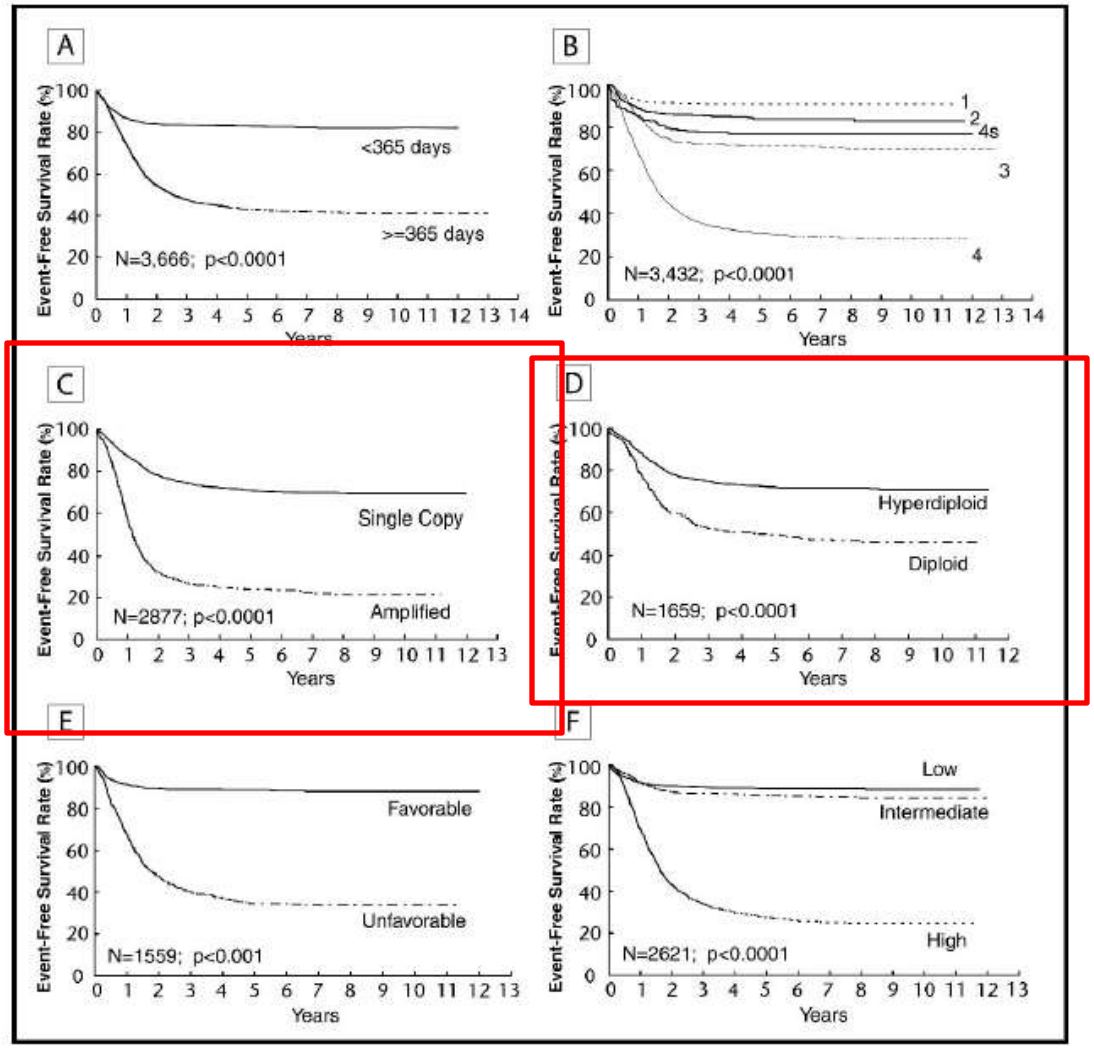
Γενετικές Βλάβες

- Στα κύτταρα του NB ανευρίσκονται γενετικές μεταβολές, αλλοιώσεις στο επίπεδο των χρωμοσωμάτων, με σαφή επαναληπτικότητα

- Μπορούν, όμως, αυτές οι βλάβες να αποτελέσουν επιπλέον σημαντικούς προγνωστικούς δείκτες για το NB?

Προγνωστικοί Παράγοντες

N-myc



Πλοειδία

Δεδομένα από Maris et al., 2005
(COG, USA)

Ενίσχυση του ογκογονιδίου N-myc

- Ενίσχυση του ογκογονιδίου N-myc εμφανίζεται σε περίπου 20% όλων των νευροβλαστικών όγκων
- Οι όγκοι με ενίσχυση του ογκογονιδίου N-myc έχουν σαφώς χειρότερη πρόγνωση και ανεξαρτήτως σταδίου της νόσου
- Η συσχέτιση αυτή δεν είναι καινούργια
- Παρά την εμφάνιση τόσο νεότερων δεικτών όσο και μοριακών βλαβών, η ανεύρεση ενίσχυσης του N-myc εξακολουθεί να παραμένει σημαντικός και ανεξάρτητος προγνωστικός δείκτης
- Σημασία έχει και το πώς ορίζεται και ελέγχεται εργαστηριακά αυτή η ενίσχυση και η τεχνική με την οποία αυτή αναδεικνύεται

Ενίσχυση του ογκογονιδίου N-myc

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- Σαφώς χειρότερη πρόγνωση και ανεξαρτήτως σταδίου της νόσου

- Η ανεύρεση ενίσχυσης του N-myc εξακολουθεί να παραμένει σημαντικός και ανεξάρτητος προγνωστικός δείκτης

British Journal of Cancer (2007), 1–9

www.bjcancer.com

Full Paper

Chromosomal CGH identifies patients with a higher risk of relapse in neuroblastoma without *MYCN* amplification

G Schleiermacher*[,1,2], J Michon[2], I Huon[3], C Dubois d'Enghien[3], J Klijanienko[4], H Brisse[5], A Ribeiro[3], V Mosseri[6], H Rubie[7], C Munzer[7], C Thomas[8], D Valteau-Couanet[9], A Auvrignon[10], D Plantaz[11], O Delattre[1] and J Couturier[1,3] on behalf of the Société Française des Cancers de l'Enfant (SFCE)

[1]INSERM U830, Institut Curie, Paris, France; [2]Département d'Oncologie Pédiatrique, Institut Curie, Paris, France; [3]Service de Génétique Oncologique, Institut Curie, Paris, France; [4]Service de Pathologie, Institut Curie, Paris, France; [5]Département d'Imagerie Médicale, Institut Curie, Paris, France; [6]Service de Biostatistique, Institut Curie, Paris, France; [7]Unité d'Hemato-Oncologie, Hôpital des Enfants, Toulouse, France; [8]Unité d'Onco-Hématologie Pédiatrique, Hôpital de la Mère et de l'Enfant- CHU de Nantes, Nantes, France; [9]Département de Pédiatrie, Institut Gustave-Roussy, Villejuif, France; [10]Service d'Hématologie et d'Oncologie Pédiatrique, Hôpital Trousseau, Paris, France; [11]Département de Pédiatrie, CHU, Grenoble, France

Whereas neuroblastoma (NB) with *MYCN* amplification presents a poor prognosis, no single marker allows to reliably predict outcome in tumours without *MYCN* amplification. We report here an extensive analysis of 147 NB samples at diag[nosis] *MYCN* amplification, by chromosomal comparative genomic hybridisation (CGH), providing a comprehensive ove[rview] genomic imbalances. Comparative genomic hybridisation profiles showed gains or losses of entire chromosomes (type 1) [in] 71 cases, whereas partial chromosome gains or losses (type 2), including gain involving 17q were observed in 68 cases. Atypical profiles were [found] cases. A type 1 profile was observed more frequently in localised disease ($P<0.0001$), and in patients of less than 12 [months] osis ($P<0.0001$). A type 2 genomic profile was associated with a higher risk of relapse in the overall population (log-[rank test, P] 0001), but also in the subgroup of patients with localised disease (log-rank test, $P=0.007$). In multivariate analysis, the [type 2 profile remained] . In conclusion, the genomic profile is of prognostic impact in patients without *MYCN* amplification, making it a help in the management of low-stage NB. Further studies using higher-resolution CGH are needed to better characterise atypical genomic alterations.

British Journal of Cancer advance online publication, 19 June 2007; doi:10.1038/sj.bjc.6603820 www.bjcancer.com

Keywords: neuroblastoma; pangenomic analysis; CGH; prognosis

Numerical

Segmental

Συνήθεις Προγνωστικοί Παράγοντες

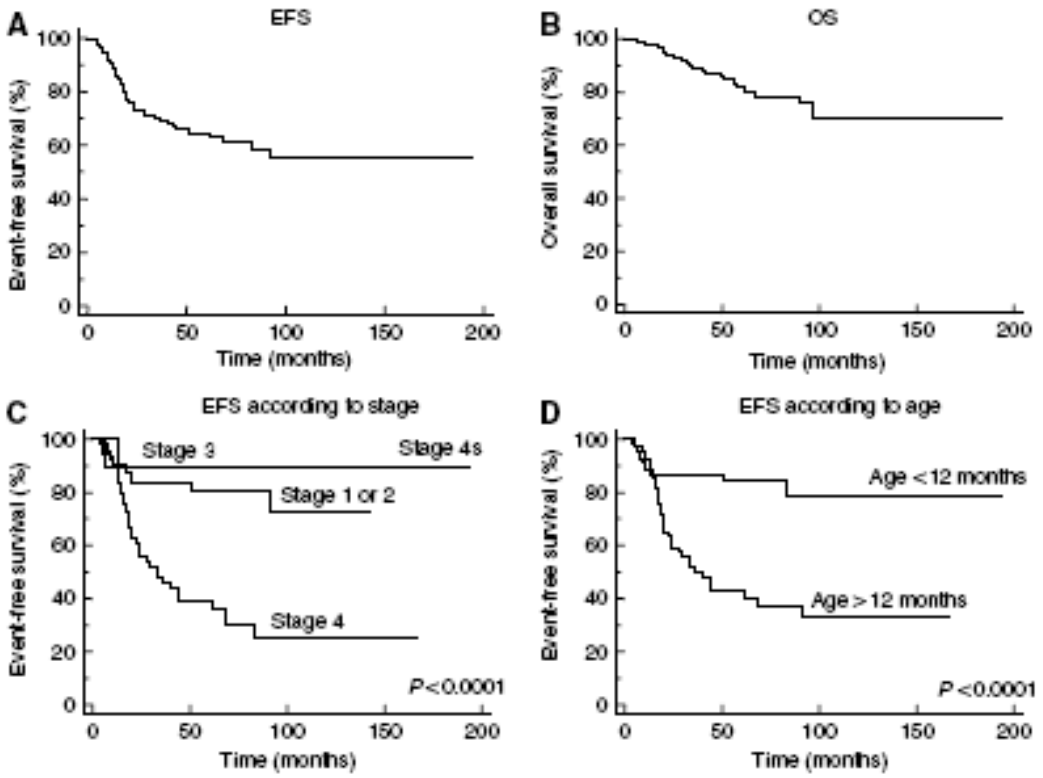
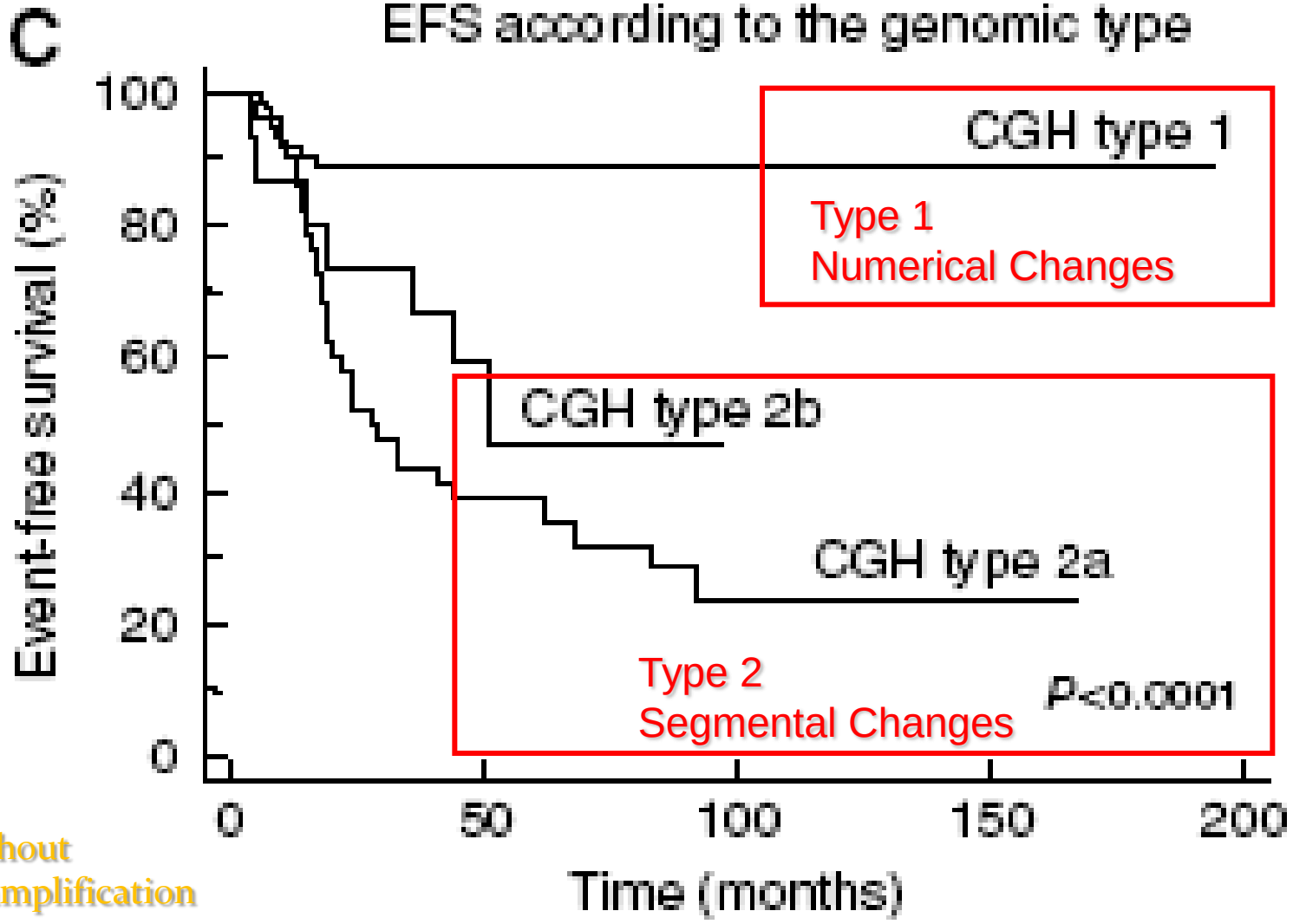


Figure 3 Survival curves of 139 neuroblastoma patients. (**A**) Event-free survival of all patients. (**B**) Overall survival of all patients. (**C**) Event-free survival according to stage at diagnosis. (**D**) Event-free survival according to age at diagnosis.

Στάδιο

Ηλικία

NB without
MYCN amplification



NB without
MYCN amplification

Συμπέρασμα

- Νευροβλάστωμα : παράδειγμα της χρησιμότητας σε κλινικό επίπεδο της γενετικής ανάλυσης των κυττάρων του όγκου
- Τύπος 1 NUMERICAL ABBERATIONS : Μεταβολές στον αριθμό ολόκληρων χρωμοσωμάτων
  - Χαρακτηρίζει το NB χαμηλού κινδύνου
  - Συνολική επιβίωση κοντά στο 100%
- Τύπος 2 SEGMENTAL ABERRATIONS: Μεταβολές τμηματικές σε χρωμοσώματα,
  που προκύπτουν από μη-σταθμισμένες μεταθέσεις
  (unbalanced chromosome translocations)
  - Χαρακτηρίζει το NB με μεγαλύτερη πιθανότητα υποτροπής και χειρότερης πρόγνωσης
- Ογκογονική δράση
  - Αύξηση στην περιοχή του χρωμοσώματος (17q) :
    υποθετικά ογκογονίδια
  - Απώλεια στις περιοχές (1p, 3p, 11q) :
    υποθετικά ογκο-κατασταλτικά γονίδια
- Ο μηχανισμός που οδηγεί σε αυτές τις μη-σταθμισμένες μεταθέσεις παραμένει άγνωστος

Structure of SIOPEN
Low and Intermediate Risk Neuroblastoma Protocol

Principal Investigators (PI)

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

Study Committee

Adela Cañete, Victoria Castel, Andrea di Cataldo, Ruth Ladenstein, Jean Michon, Vassilios Papadakis, Gudrun Schleiermacher, Kate Wheeler, Veronique Mosseri, José Bermudez

Initial Studies LNESG1

Localized Resectable Neuroblastoma European Study

LNESG1

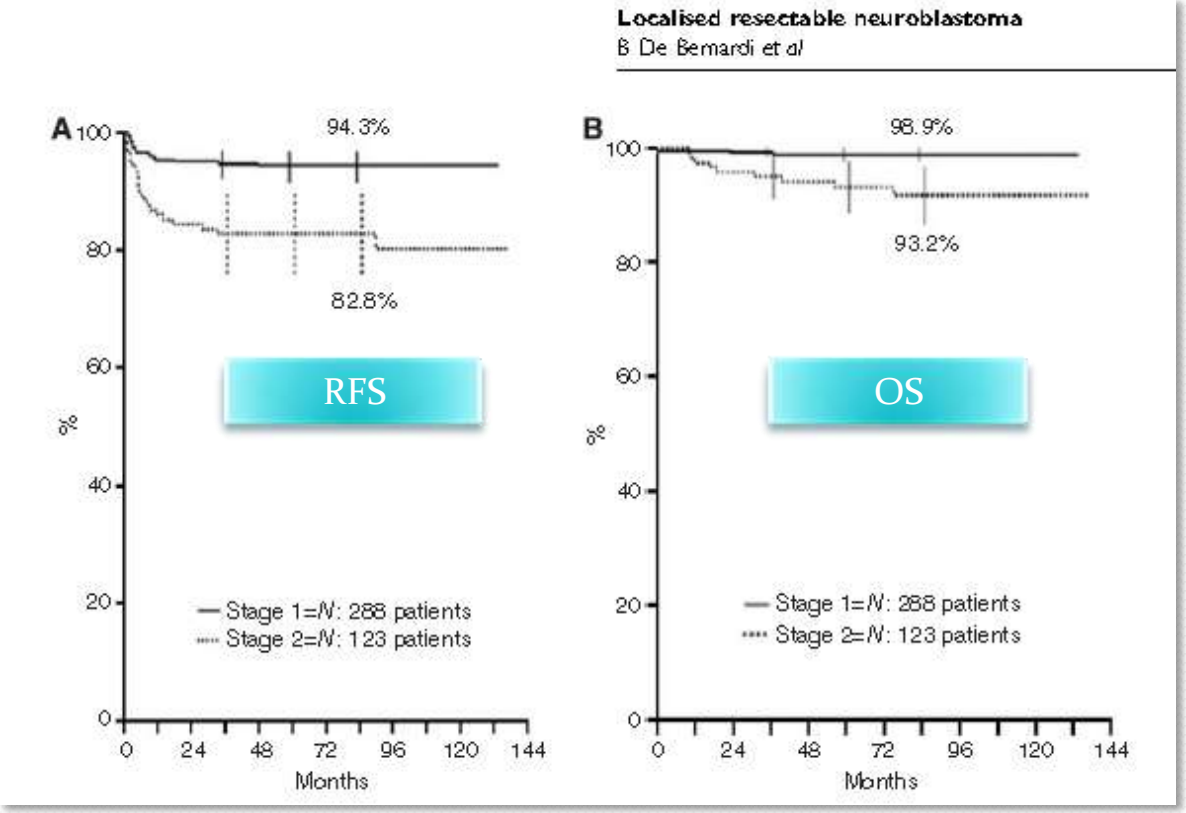
- Main objective of this study was to confirm that **surgery alone is an effective and safe treatment** for localized resectable neuroblastoma except stage 2 with amplified MYCN gene (MYCNA).
- Conclusion: **surgery alone yielded excellent OS** for both stage 1 and 2 neuroblastoma without MYCNA, although stage 2 patients with unfavorable histopathology and elevated LDH suffered a high number of relapses.
- Both stage 1 and 2 patients with MYCNA were at greater risk of relapse.

British Journal of Cancer (2008) 99, 1027 – 1033

LNESG1

Treatment of localised resectable neuroblastoma. Results of the LNESG1 study by the SIOP Europe Neuroblastoma Group

B De Bernardi*,[1], V Mosseri[2], H Rubie[3], V Castel[4], A Foot[5], R Ladenstein[6], G Laureys[7], M Beck-Popovic[8], AF de Lacerda[9], ADJ Pearson[10], J De Kraker[11], PF Ambros[12], Y de Rycke[2], M Conte[1], P Bruzzi[13] and J Michon[14]



Surgical Risk Factors

VOLUME 23 · NUMBER 33 · NOVEMBER 20 2005

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Surgical Risk Factors in Primary Surgery for Localized Neuroblastoma: The LNESG1 Study of the European International Society of Pediatric Oncology Neuroblastoma Group

Giovanni Cecchetto, Veronique Mosseri, Bruno De Bernardi, Pierre Helardot, Tom Monclair, Elisa Costa, Ernst Horcher, Sylvia Neuenschwander, Paolo Tomà, Antonino Rizzo, Jean Michon, and Keith Holmes

- Although tumor resection is the mainstay of treatment for localized neuroblastoma, there are no established guidelines indicating which patients should be operated on immediately and which should undergo surgery after tumor reduction with chemotherapy.
- In an effort to develop such guidelines, the LNESG1 study defined surgical risk factors (SRFs) based on the imaging characteristics.
- The adoption of SRFs as predictors of adverse surgical outcome was validated because their presence was associated with lower complete resection rate and greater risk of surgery related complications.

IDRF: Image Defined Risk Factors

Σταδιοποίηση του Νευροβλαστώματος

Χρήση του συστήματος σταδιοποίησης INRG

- L1 Tumors: No IDRF
- L2 Tumors: IDRF Positive
- M Tumors
- Ms Tumors

IDRF: Image defined risk factors

Ανάπτυξη του συστήματος σταδιοποίησης INRG

- Το στάδιο κάθε όγκου και κάθε ασθενούς με NB πρέπει να ισχύει:
- Ανεξάρτητα του ογκολόγου που το θεραπεύει
- Ανεξάρτητα του χειρουργού που επεμβαίνει
- Και να είναι το ίδιο σε όλα τα μήκη και πλάτη για τον ίδιο ασθενή

Table 1. International Neuroblastoma Staging System (INSS)

Stage 1	Localized tumor with complete gross excision, with or without microscopic residual disease; representative ipsilateral lymph nodes negative for tumor microscopically (nodes attached to and removed with the primary tumor may be positive).
Stage 2A	Localized tumor with incomplete gross excision; representative ipsilateral nonadherent lymph nodes negative for tumor microscopically.
Stage 2B	Localized tumor with or without complete gross excision, with ipsilateral nonadherent lymph nodes positive for tumor. Enlarged contralateral lymph nodes must be negative microscopically.
Stage 3	Unresectable unilateral tumor infiltrating across the midline[2], with or without regional lymph node involvement; or localized unilateral tumor with contralateral regional lymph node inv inf
Stage 4	An bo def
Stage 4S	Lo wi (limited to infants <1 year of age)

Μετεγχειρητικό στάδιο

Χωρίς επέμβαση, Στάδιο ≥ III

Σταδιοποίηση - Πρόγνωση

- Ένα σύστημα σταδιοποίησης πρέπει :

- **Να μπορεί να εφαρμοστεί κατά την αρχική διάγνωση με ακρίβεια**
- **Να ισχύει για τον ασθενή και τον όγκο του ανεξαρτήτως θεράποντος ιατρού και νοσοκομείου διερεύνησης**
- **Να είναι ανεξάρτητο όποιας χειρουργικής παρέμβασης**

Κατάταξη του NB όγκου κατά INRG

- Ο ασθενής σταδιοποιείται ως συνήθως (απεικονίσεις με US, CT, MRI, MIBG-scan)
- Ελέγχεται η πιθανή έκταση της νόσου
- Εάν η νόσος είναι μεταστατική:
  Στάδιο M (Metastatic)
- Εάν η νόσος είναι τοπική:
- Στάδιο L1 : No IDRF
- Στάδιο L2 : With IDRF (Local)

Πρωτοπαθής όγκος
IDRF: Image Defined Risk Factors

Ipsilateral tumour extension within two body compartments:

- Neck-chest, chest-abdomen, abdomen-pelvis

Neck

- Tumour encasing carotid and/or vertebral artery and/or internal jugular vein
- Tumour extending to base of skull
- Tumour compressing the trachea

Cervico-thoracic junction

- Tumour encasing brachial plexus roots
- Tumour encasing subclavian vessels and/or vertebral and /or carotid artery
- Tumour compressing the trachea

Thorax

- Tumour encasing the aorta and/or major branches
- Tumour compressing the trachea and/or principal bronchi
- Lower mediastinal tumour, infiltrating the costo-vertebral junction between T9 and T12

Thoraco-abdominal

- Tumour encasing the aorta and /or vena cava

Abdomen/pelvis

- Tumour infiltrating the porta hepatis and/or the hepatoduodenal ligament
- Tumour encasing branches of the superior mesenteric artery at the mesenteric root
- Tumour encasing the origin of the celiac axis, and/or of the superior mesenteric artery
- Tumour invading one or both renal pedicles
- Tumour encasing the aorta and/or vena cava
- Tumour encasing the iliac vessels
- Pelvic tumour crossing the sciatic notch

Intraspinal tumour extension whatever the location provided that:

- More than 1/3 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, duodenopancreatic block and mesentery.

Conditions recommended to be recorded, but NOT considered IDRFs:

- Multifocal primary tumours
- Pleural effusion (with or without malignant cells)
- Ascites (with or without malignant cells)

Χρήση του συστήματος σταδιοποίησης INRG

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- L2 Tumors: IDRF Positive
- M Tumors
- Ms Tumors

IDRF: Image defined risk factors

Current Studies

LINES
Low and Intermediate Neuroblastoma European Study

HR-NBL-SIOPEN
High Risk Neuroblastoma Study of SIOP-Europe (SIOPEN)

LINES

Low and Intermediate Neuroblastoma European Study

SUMMARY

SIOPEN R NET

Group 1
L2, ≤ 18 months, MYCN NA , NCA without LTS

Group 2
L2, ≤ 18months, MYCN NA, NMA with LTS.

Group 3
L2, ≤ 18 months, MYCN NA, SCA with/without LTS.

Group 4
Ms, ≤ 12 months, MYCN NA NMA without LTS

Group 5
Ms, ≤ 12 months, MYCN NA, NMA with LTS

Group 6
Ms, ≤ 12 months , MYCN NA SCA, with/without LTS.

Group 7
L2 NB o GN nodular, differentiated , MYCN NA, >18 months

Group 8
L2 NB, PD o INDEF , MYCN NA > 18 months.

Group 9
INSS 1, MYCN

Group 10
M NB, MYCN NA, <12 months

LOW RISK | NAM | INTERMEDIATE

Neonatal Adrenal Masses

Low Risk Group

L2, ≤ 18 months, MYCN non-amplified

- **Group 1 : Numerical genomic profile, no LTS**
  Randomization between observation and two-six courses of chemotherapy (CO x 2-4 ± VP/Carbo x 2)
  ± surgery
- **Group 2 : Numerical genomic profile, with LTS**
  Two-four courses of chemotherapy (VP/Carbo x 2 ± CADO x2)
  ± surgery
- **Group 3 : Segmental genomic profile, with or without LTS**
  Four courses of chemotherapy (VP/Carbo x 2-4 ± CADO x 2)
  ± surgery

NCA: Numerical SCA: Segmental Chromosomal Aberrations
LTS: Life Threatening Symptoms

Low Risk Group

Ms, ≤ 12 months, MYCN non-amplified

- **Group 4 : Numerical genomic profile, without LTS**
  Observation only
- **Group 5 : Numerical genomic profile, with LTS**
  Two-four courses of chemotherapy (VP/Carbo x 2 ± CADO x2)
- **Group 6 : Segmental genomic profile, with or without LTS**
  Four courses of chemotherapy (VP/Carbo x 2-4 ± CADO x 2) ± surgery

NCA: Numerical SCA: Segmental Chromosomal Aberrations
LTS: Life Threatening Symptoms

Intermediate Risk Group

- **Group 7 : INRG stage L2 neuroblastoma or ganglioneuroblastoma nodular, differentiating histology, MYCN non-amplified, age >18 month**
  Four courses of chemotherapy (VP/Carbo x 2 + CADO x 2 or VP/Carbo x 2) ± surgery
- **Group 8 : INRG stage L2 neuroblastoma or ganglioneuroblastoma nodular, poorly differentiated or undifferentiated histology, MYCN non-amplified, age >18 mo**
  Six courses of chemotherapy (VP/Carbo x 2, CADO x 2, VP/Carbo x 1 + CADO x 1 or CADO x 2), ± surgery, radiotherapy, and 6 courses of 13-cis-RA

Intermediate Risk Group

- **Group 9 : INSS stage 1 neuroblastoma, MYCN amplified, any age**
  Six courses of chemotherapy (VP/Carbo x 2, CADO x 2, VP/Carbo x 1, CADO x1) followed by radiotherapy and 6 courses of 13-cis-RA
- **Group 10 : INRG stage M neuroblastoma, MYCN non-amplified, age <12 months**
  Four-eight courses of chemotherapy (VP/Carbo x 2-4 ± CADO x 2-4), ± surgery

Neonatal Adrenal Mass

Observation Only

- Age less than or equal to 90 days when the supra mass is discovered
- Suprarenal mass detected by ultrasound and/or MRI. The suprarenal mass may be cystic and/or solid, but IT CANNOT REACH THE MIDLINE AND should MEASURE ≤ 5 CM AT THE LARGEST DIAMETER
- No regional involvement: MRI scan does not show evidence of positive ipsi/contralateral lymph nodes or other spread outside the suprarenal gland
- No metastatic involvement

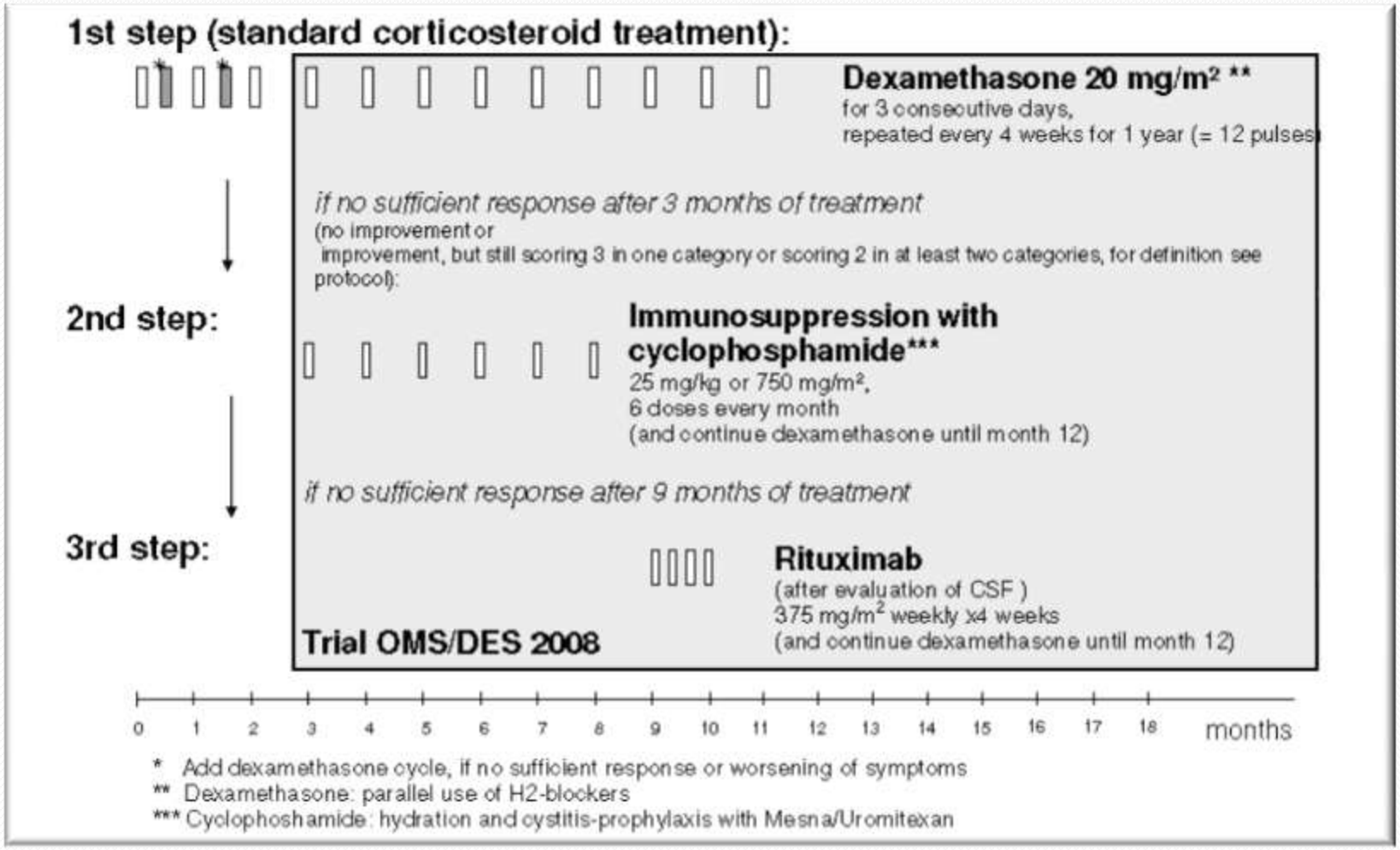
Detection on MYC-N Amplification in peripheral blood

Other Studies

Opsoclonus Myoclonus Study

Spinal Cord Involvement Registry

Opsoclonus Myoclonus Study Treatment Plan



HR-NBL-SIOPEN

High Risk Neuroblastoma Study of SIOP-Europe (SIOPEN)

International
High Risk Neuroblastoma Trial Centre

HR-NBL1/SIOPEN

Prof. **Ruth Ladenstein**, MD, MBA, cPM
on behalf of the SIOPEN Group

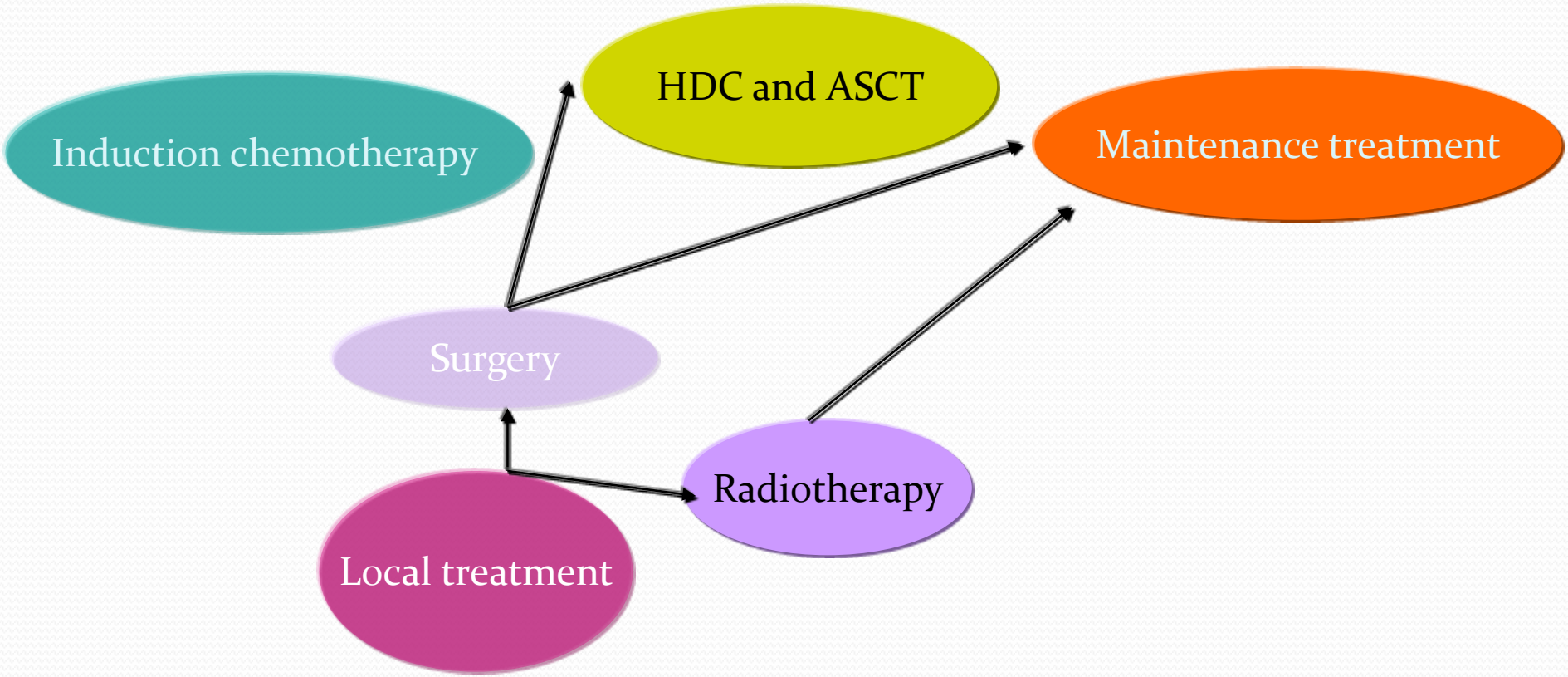
CRA: Dr. Ingrid Pribil
Statistics: Mag **Ulrike Pötschger**

High Risk Neuroblastoma

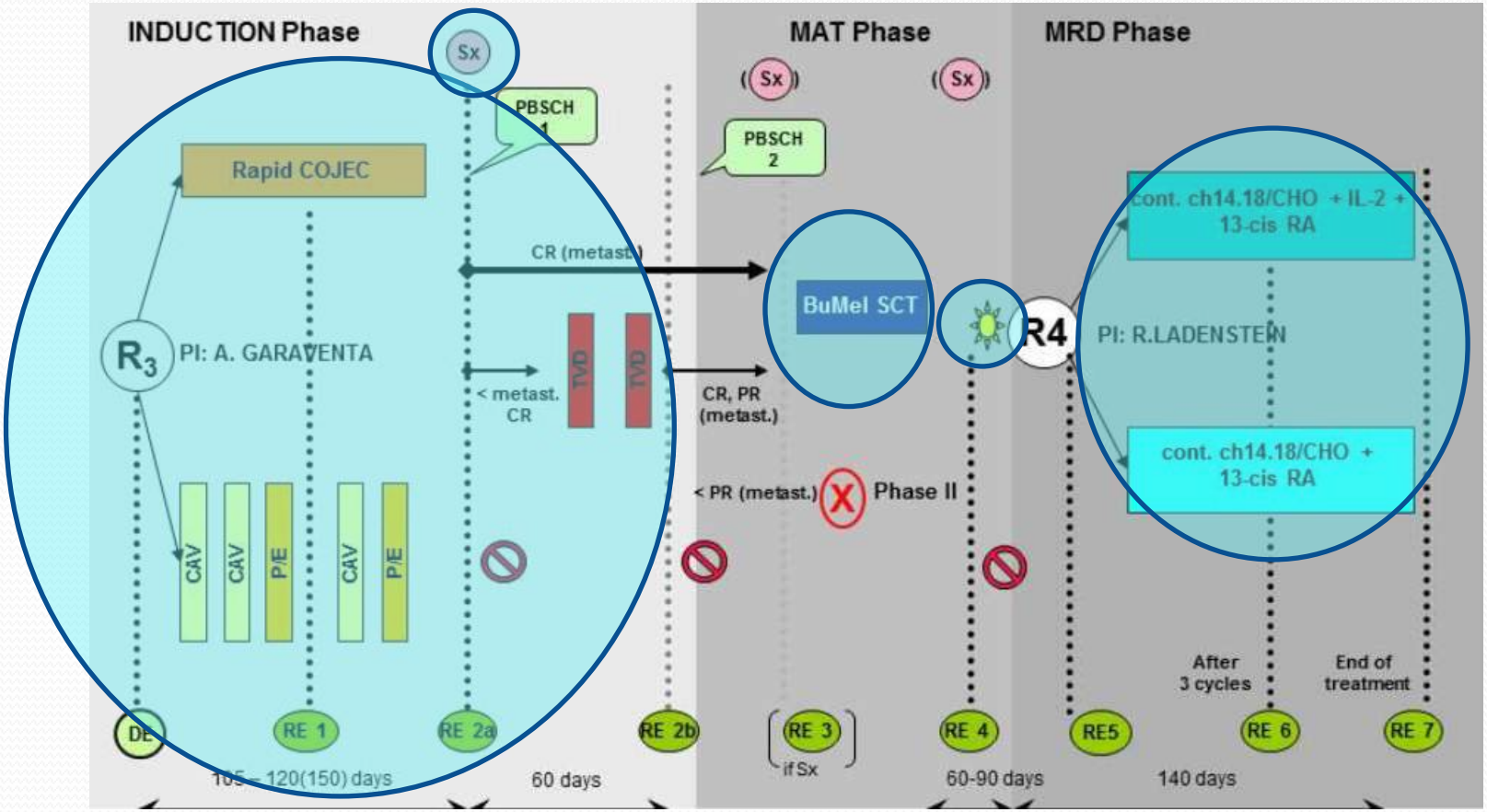
- More than 50 % of patients

- Metastatic disease, patient age > 1 year
- MYC-N Amplified tumors
  - Whatever the patient's age,
  - Whatever the stage (except stage 1)

High Risk Neuroblastoma Treatment



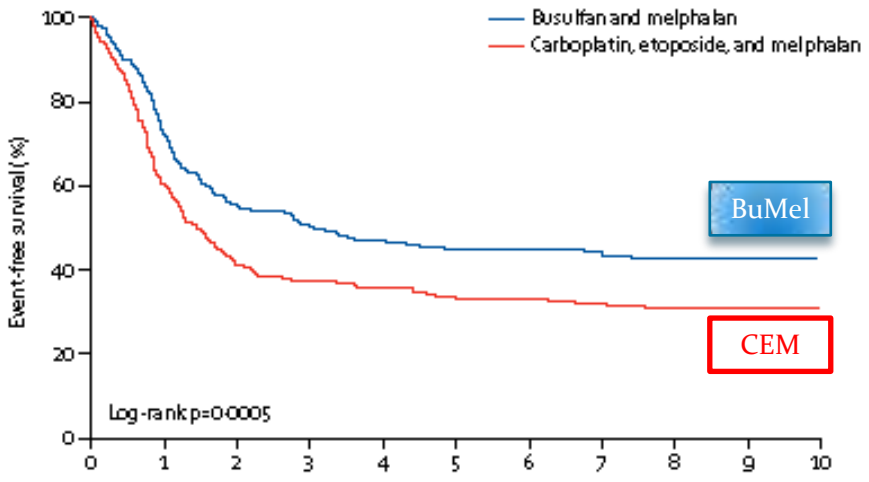
Current HR-NBL-SIOPEN Study

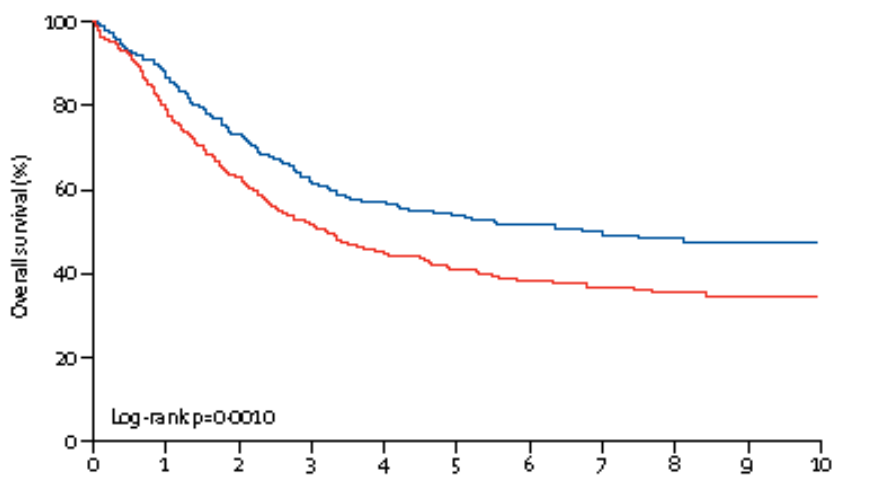


Busulfan and melphalan versus carboplatin, etoposide, and melphalan as high-dose chemotherapy for high-risk neuroblastoma (HR-NBL1/SIOPEN): an international, randomised, multi-arm, open-label, phase 3 trial

Ruth Ladenstein, Ulrike Pötschger, Andrew D J Pearson, Penelope Brock, Roberto Luksch, Victoria Castel, Isaac Yaniv, Vassilios Papadakis, Geneviève Laureys, Josef Malis, Walentyna Balwierz, Ellen Ruud, Per Kogner, Henrik Schroeder, Ana Forjaz de Lacerda, Maja Beck-Popovic, Pavel Bician, Miklós Garami, Toby Trahair, Adela Canete, Peter F Ambros, Keith Holmes, Mark Gaze, Günter Schreier, Alberto Garaventa, Gilles Vassal, Jean Michon, Dominique Valteau-Couanet, for the SIOP Europe Neuroblastoma Group (SIOPEN)*

Lancet Oncology March 1, 2017

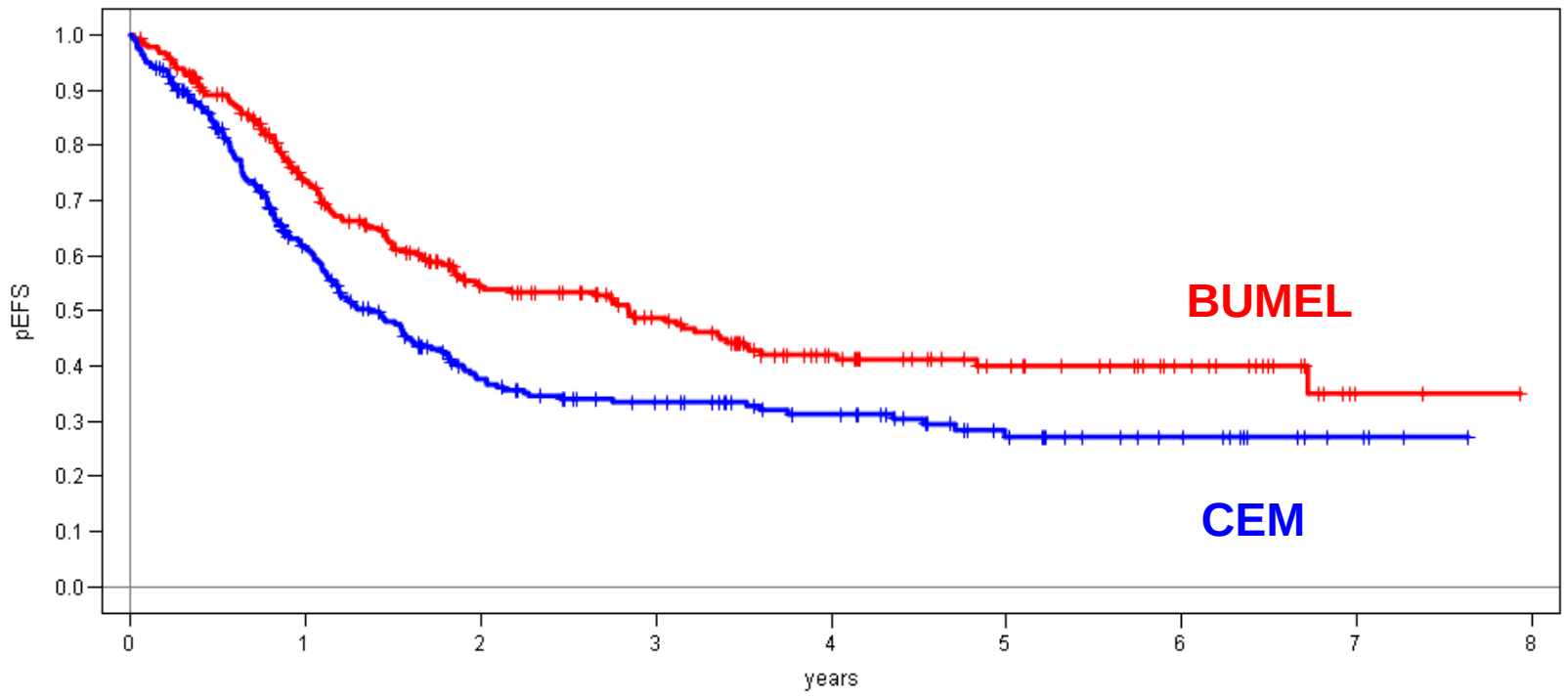




*Rochelle Bagatell, *Stephan A Grupp*
Refining megatherapy, improving outcome in neuroblastoma
Comment: ***Lancet Oncology 2017***

Primary Endpoint EFS by Randomized Arm

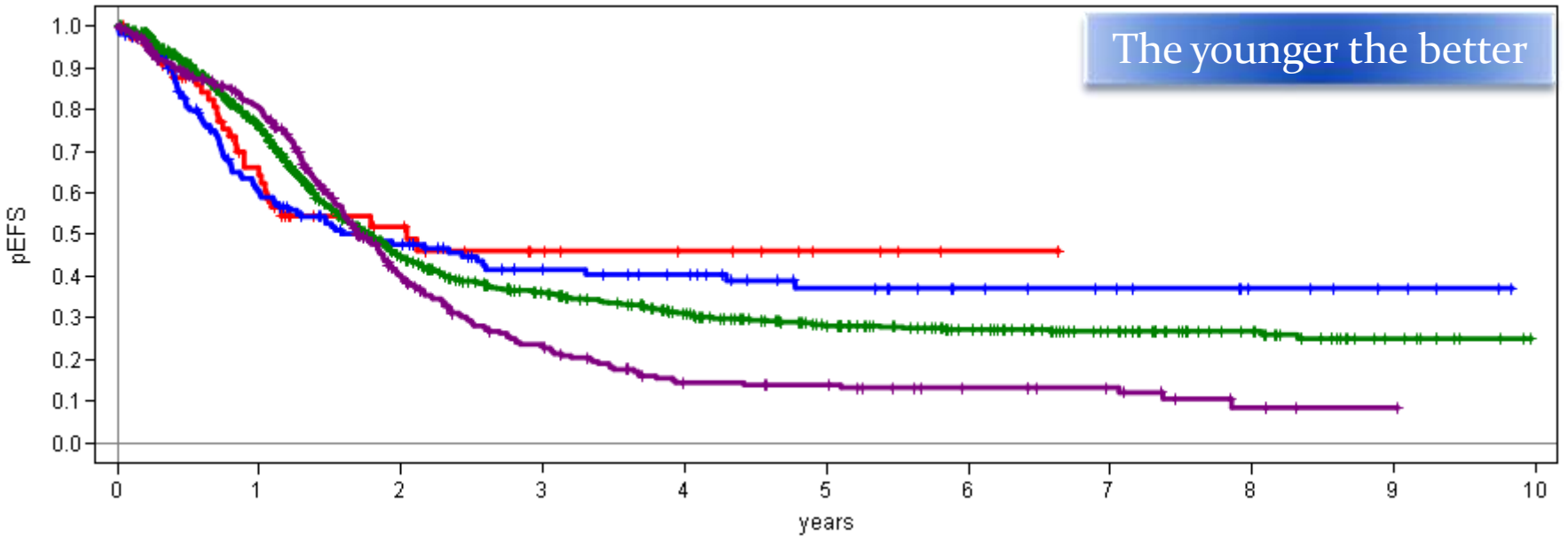
Intent to treat analysis from randomization



	Patients	Events	3-yrs. pEFS	p-value
BUMEL	281	136	0.49±0.03	<0.001
CEM	282	169	0.33±0.03	.

Other Important Messages

All Stage 4 neuroblastoma : impact of age

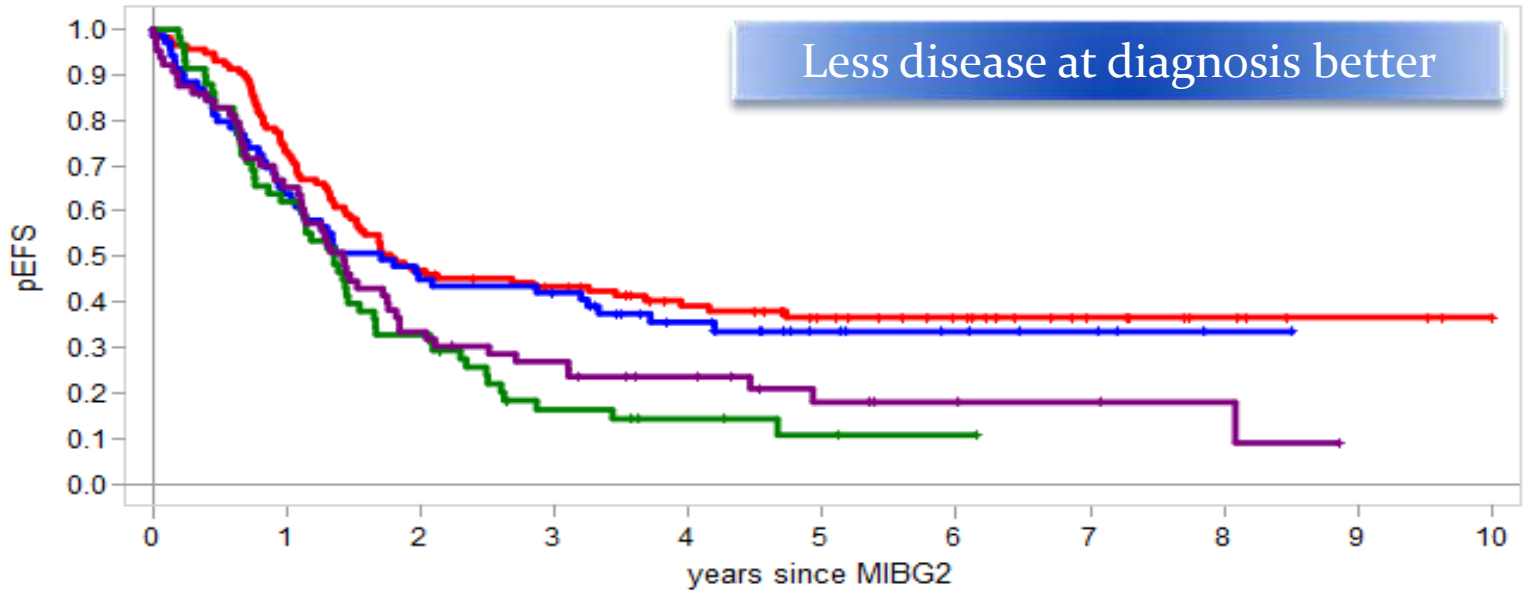


	Patients	Events	5-yrs. pEFS	p-value
< 1 year	67	29	0.46±0.07	0.025
1-1.5 yrs.	159	80	0.37±0.05	.
1.5-5	1080	597	0.28±0.02	.
>5 yrs.	355	241	0.14±0.02	.

SIOPEN R NET

Induction phase : MIBG score

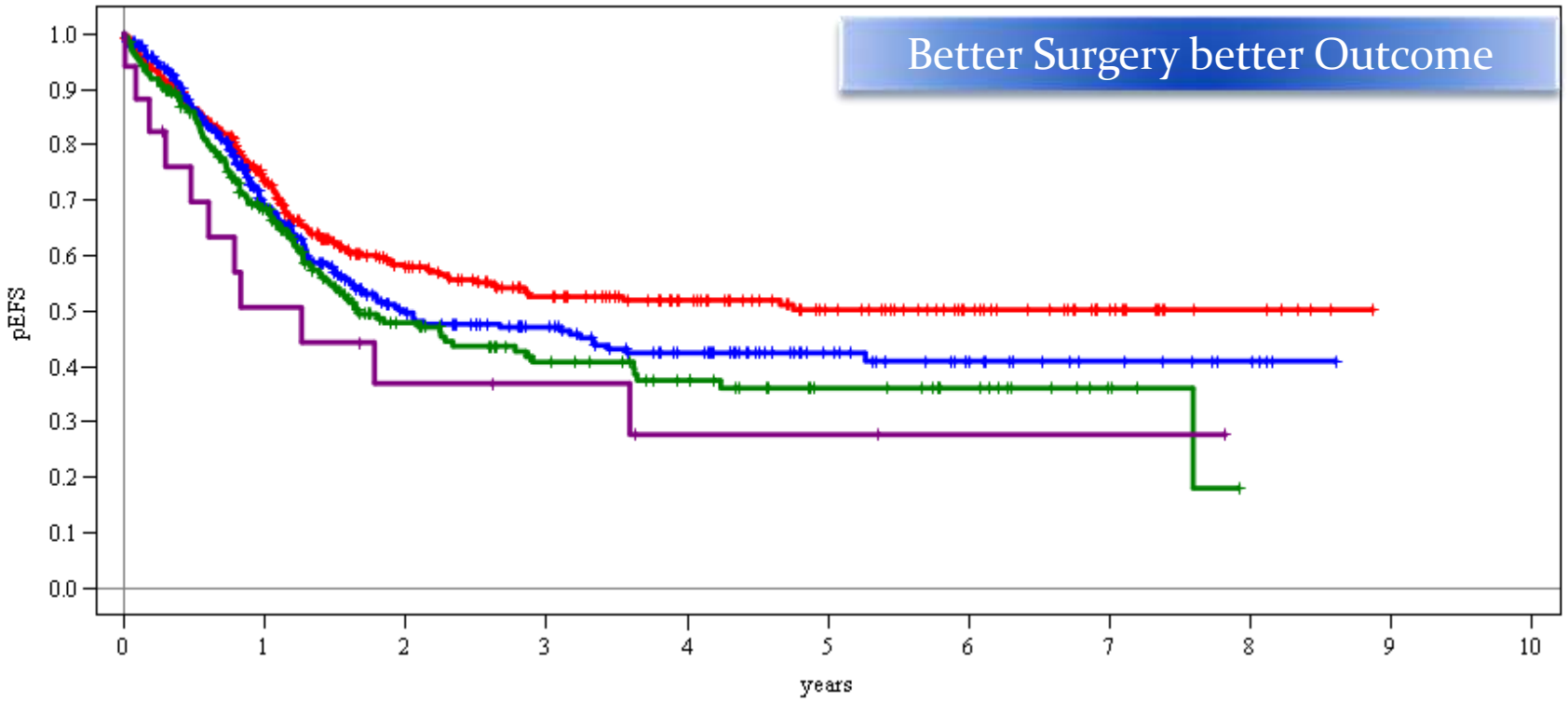
SIOPEN



	Patients	Events	5-yrs. pEFS	p-value
Neg	115	71	0.37±0.05	0.002
1-3	70	45	0.33±0.06	
4-17	58	50	0.11±0.05	
18+	64	51	0.18±0.05	

SIOPEN R NET

Local treatment : Surgery



	Patients	Events	3-yrs. pEFS	p-value
Complete excision	**373**	**146**	**0.53±0.03**	**0.024**
Complete excision - possible microscopic tumour re	**357**	**158**	**0.47±0.03**	**.**
Macroscopic tumour residue	**211**	**108**	**0.41±0.04**	**.**
Resection not possible	**17**	**11**	**0.37±0.12**	**.**

Neuroblastoma mRNAs Predict Outcome in Children With Stage 4 Neuroblastoma: A European HR-NBL1/SIOPEN Study

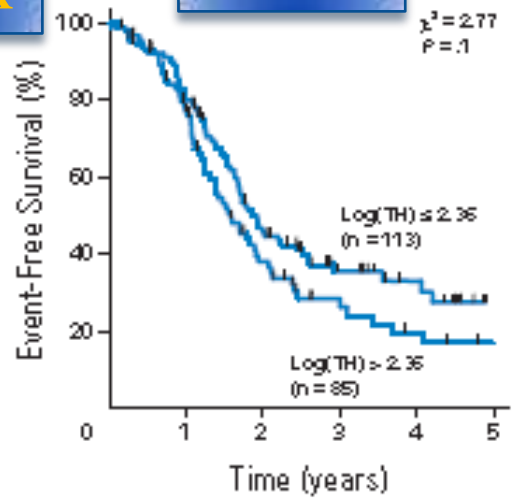
Virginie F. Viprey, Walter M. Gregory, Maria V. Corrias, Andrei Tchirkov, Katrien Swerts, Ales Vicha, Sandro Dallorso, Penelope Brock, Roberto Luksch, Dominique Valteau-Couanet, Vassilios Papadakis, Genevieve Laureys, Andrew D. Pearson, Ruth Ladenstein, and Susan A. Burchill

VOLUME 32 · NUMBER 10 · APRIL 1 2014

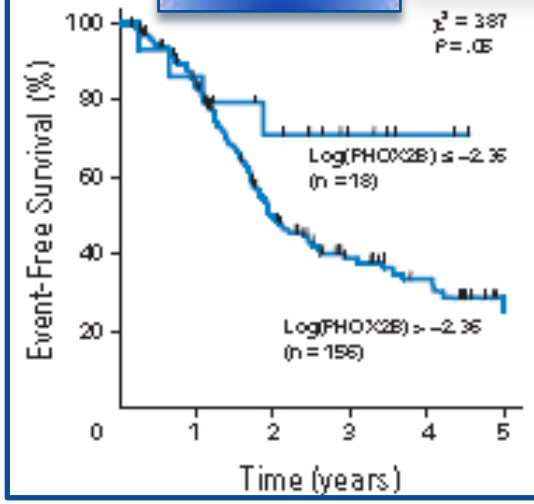
JOURNAL OF CLINICAL ONCOLOGY

EFS
BM Dx

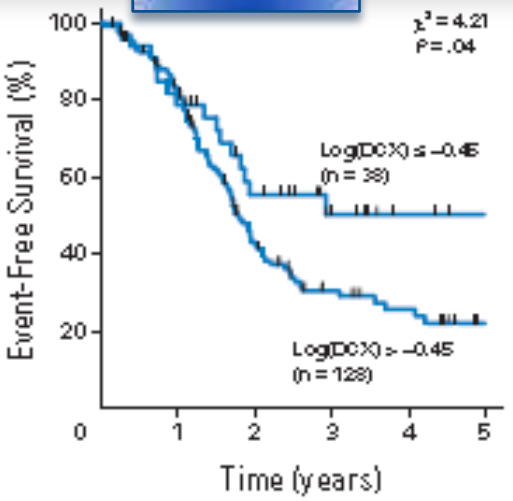
TH



PHOX2B



DCX



Time Years

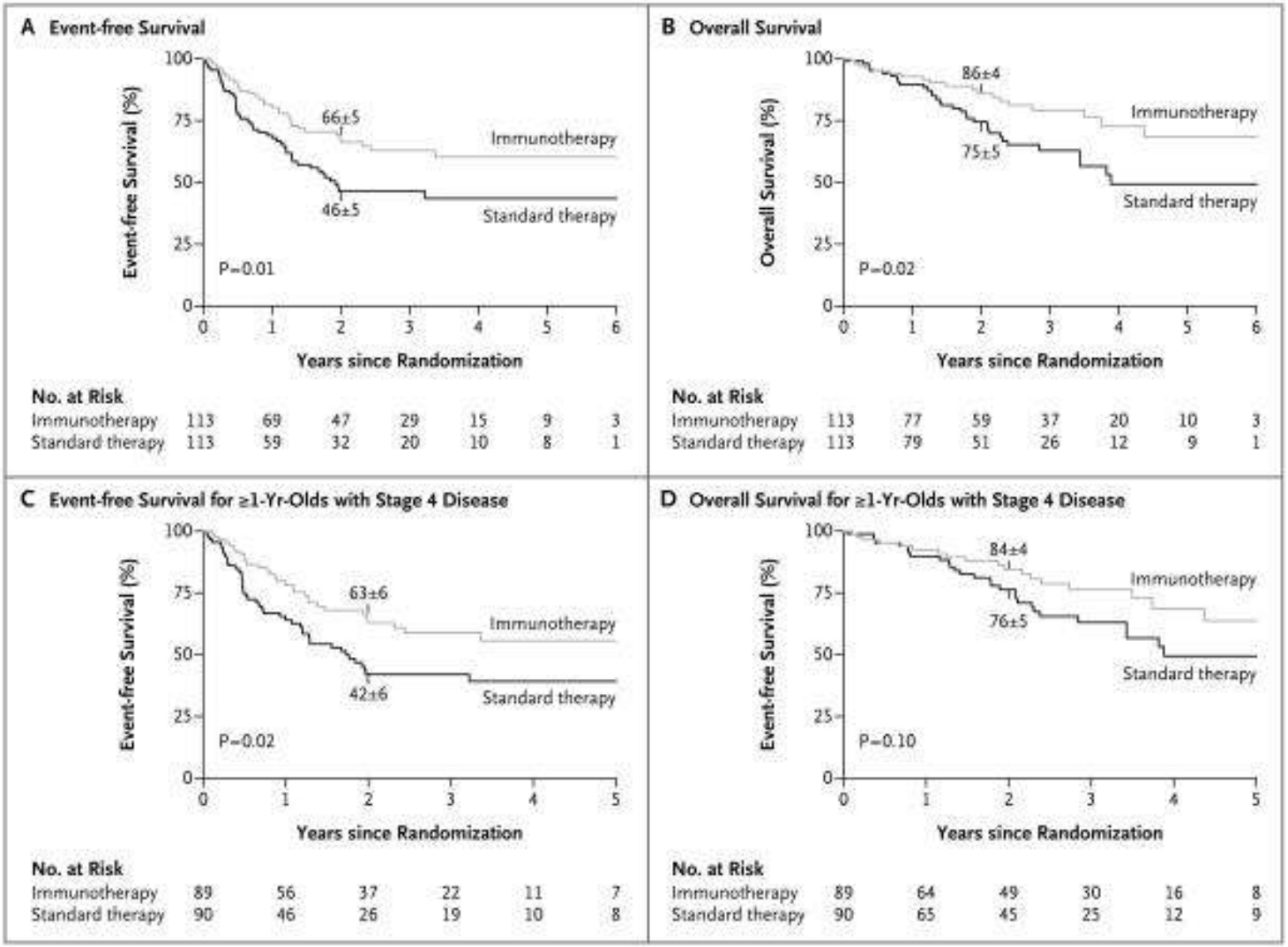
Log RTqPCR for mRNA **of**:

- tyrosine hydroxylase **(TH)**
- paired-like homeobox 2b **(PHOX2B)**
- doublecortin **(DCX)**

Immunotherapy Issues

COG ANBL0032: phase II trial design for high risk neuroblastoma

(Yu et al, N Engl J Med. 2010; 363(14): 1324–1334)

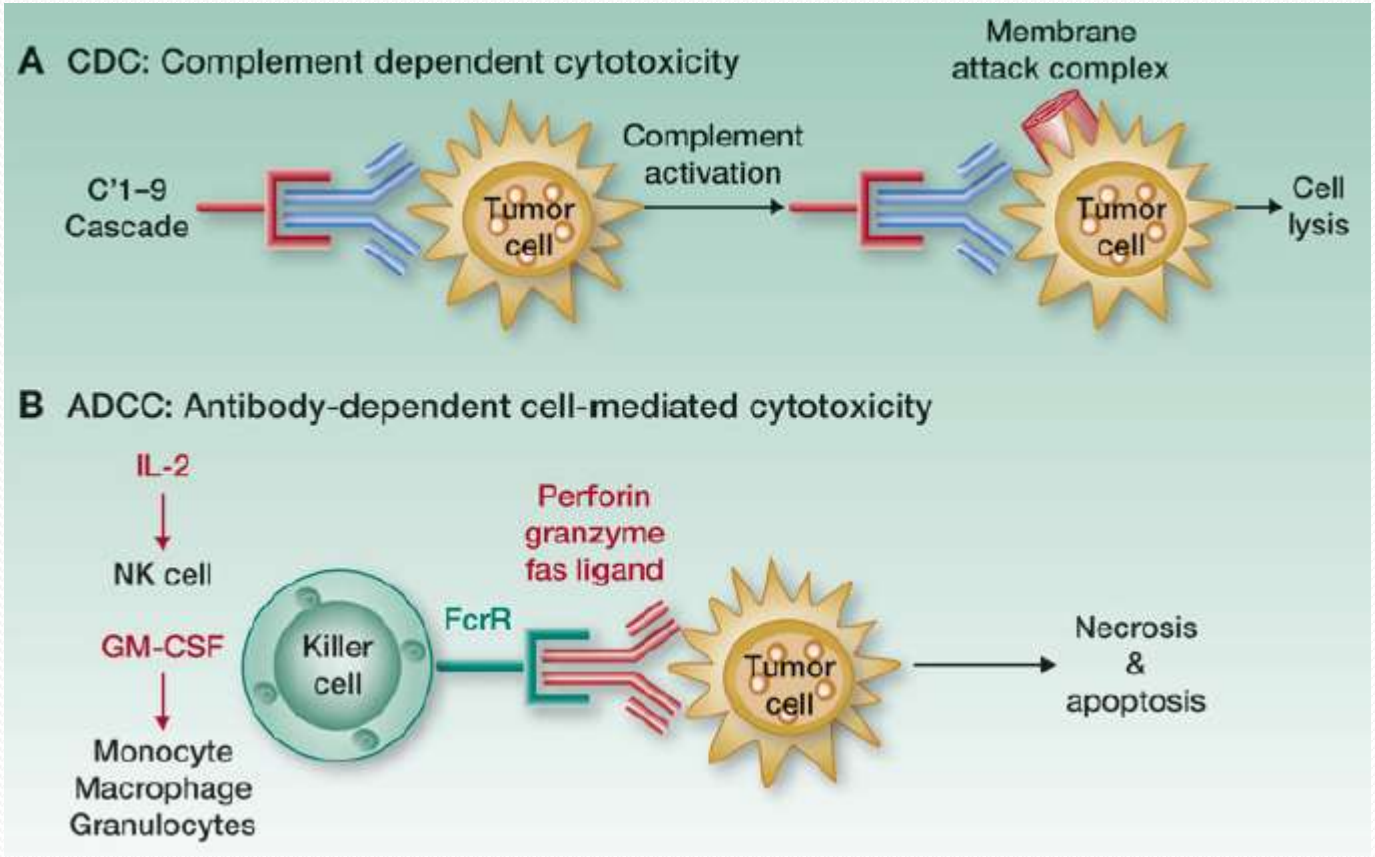


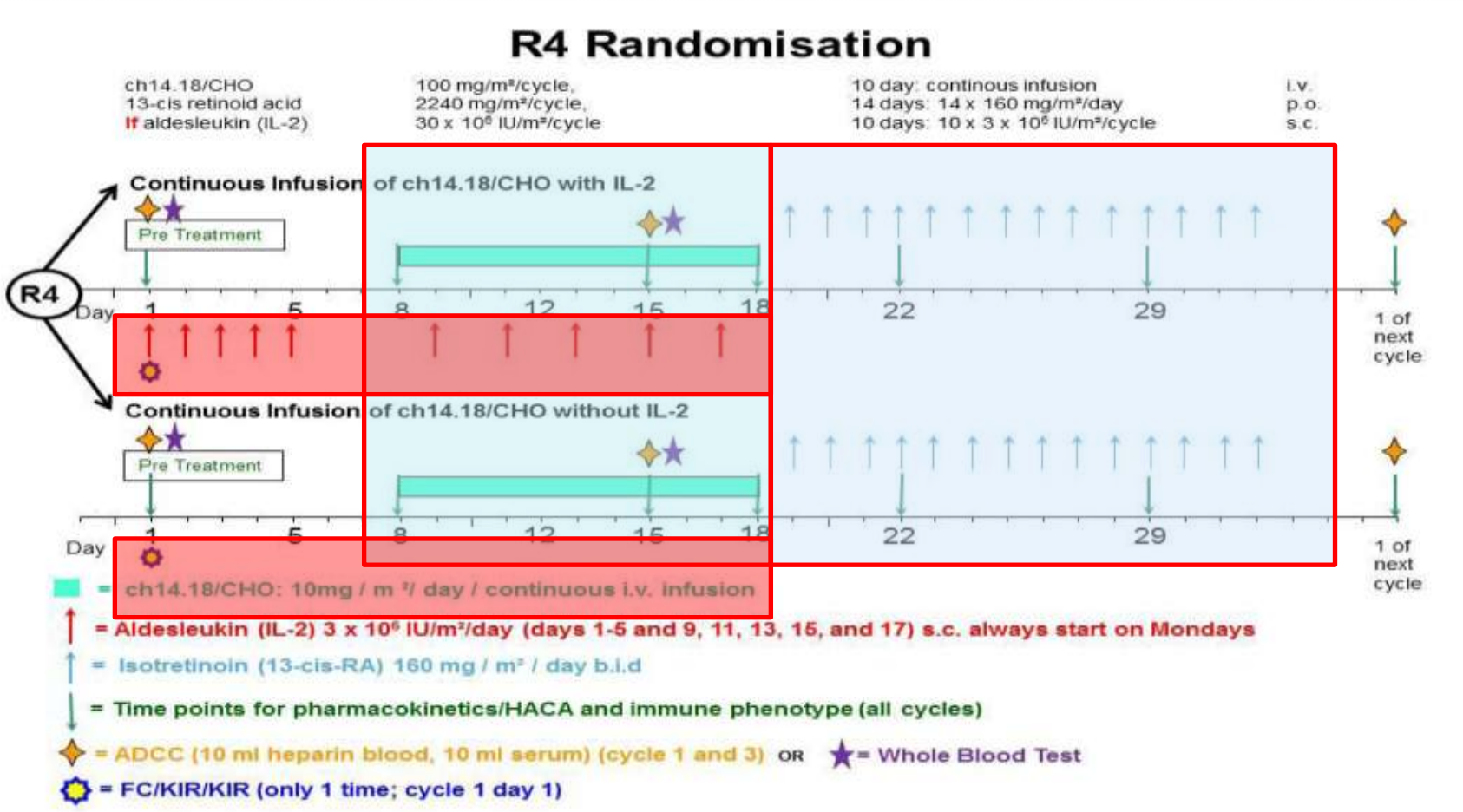
Promising Therapeutic Targets in Neuroblastoma

Katherine K. Matthay, Rani E. George and Alice L. Yu

Clin Cancer Res 2012;18:2740-2753.

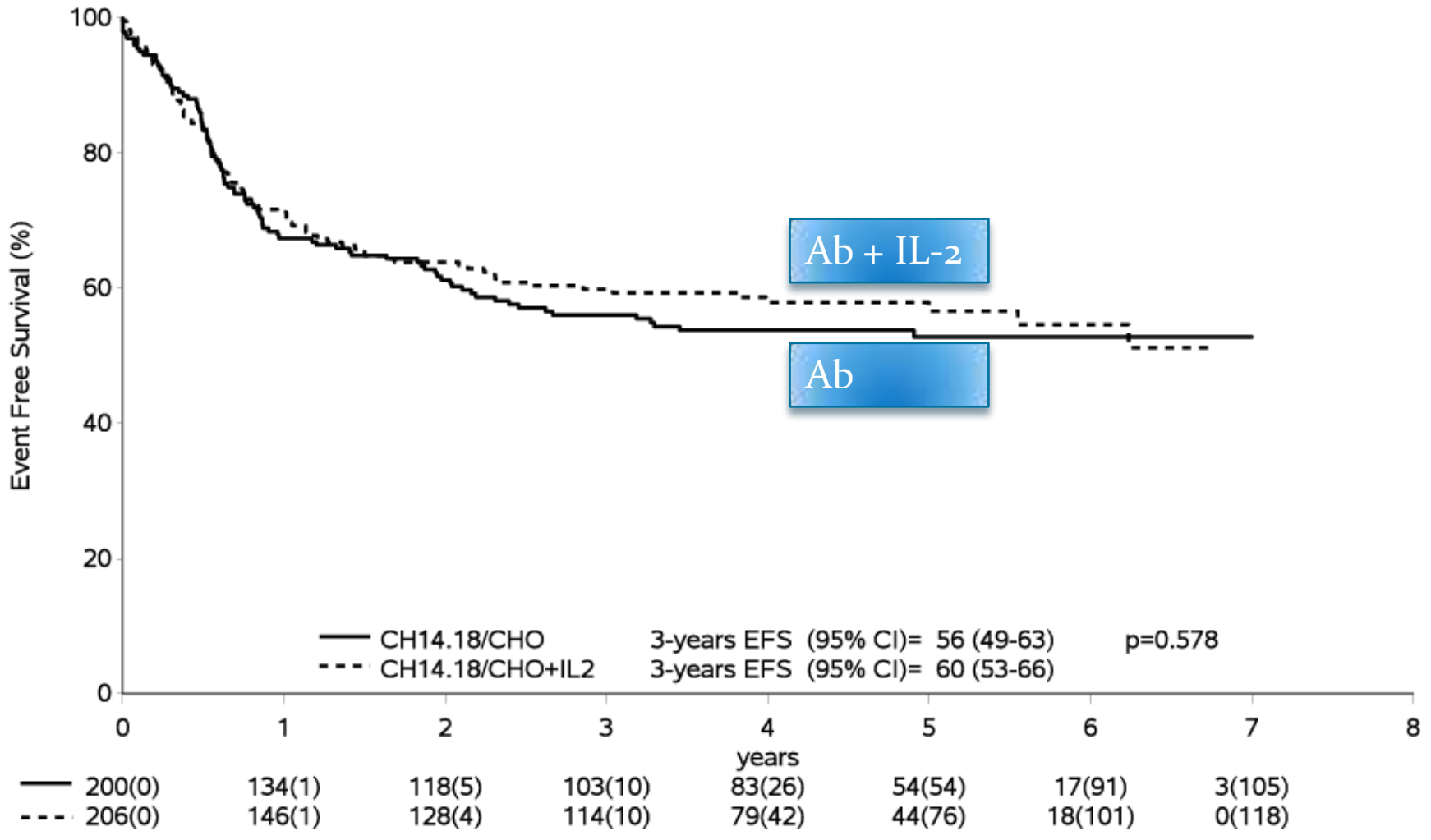
Ab mediated CDC, ADCC



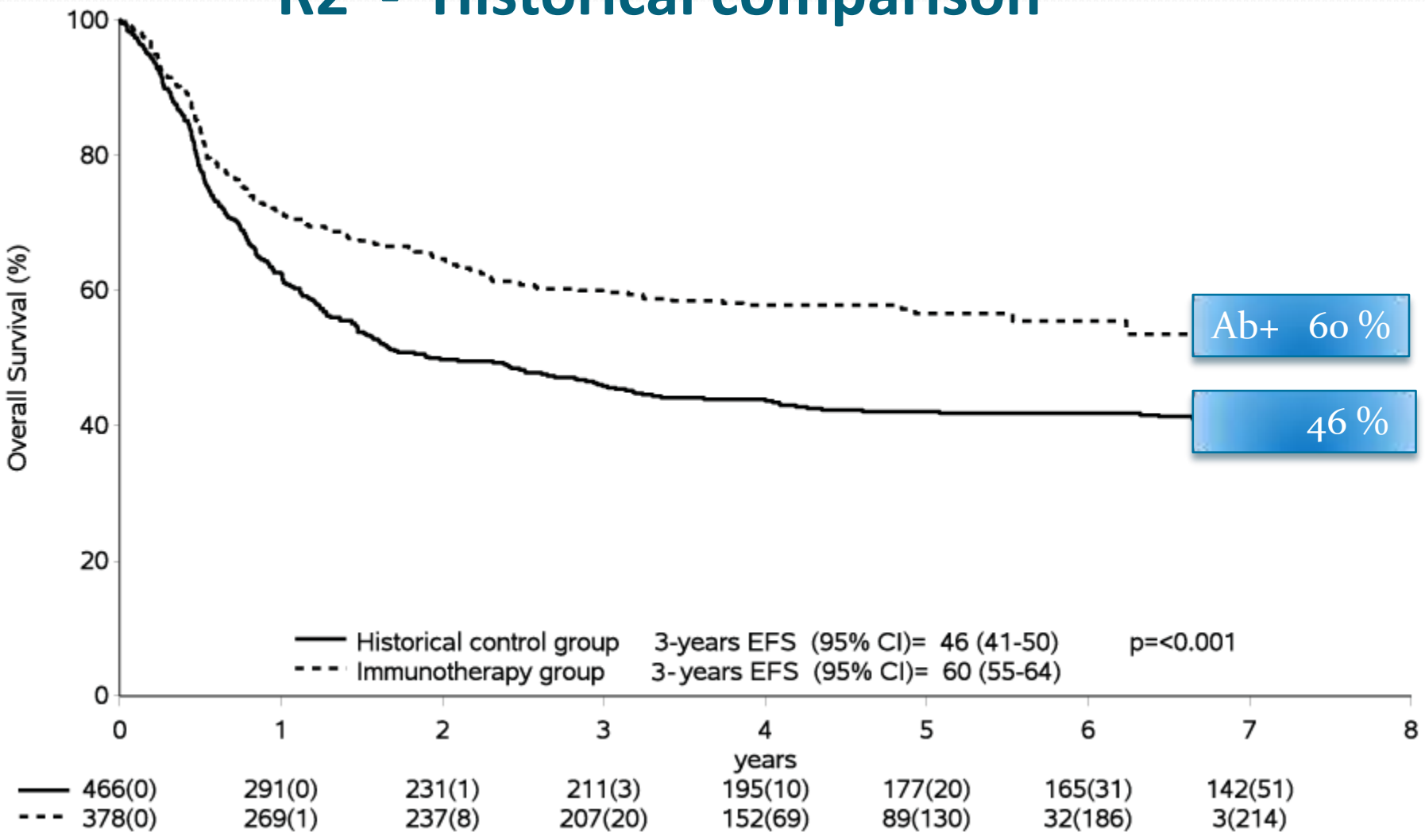


Current Immunotherapy
Long term infusion

R2: Event Free Survival



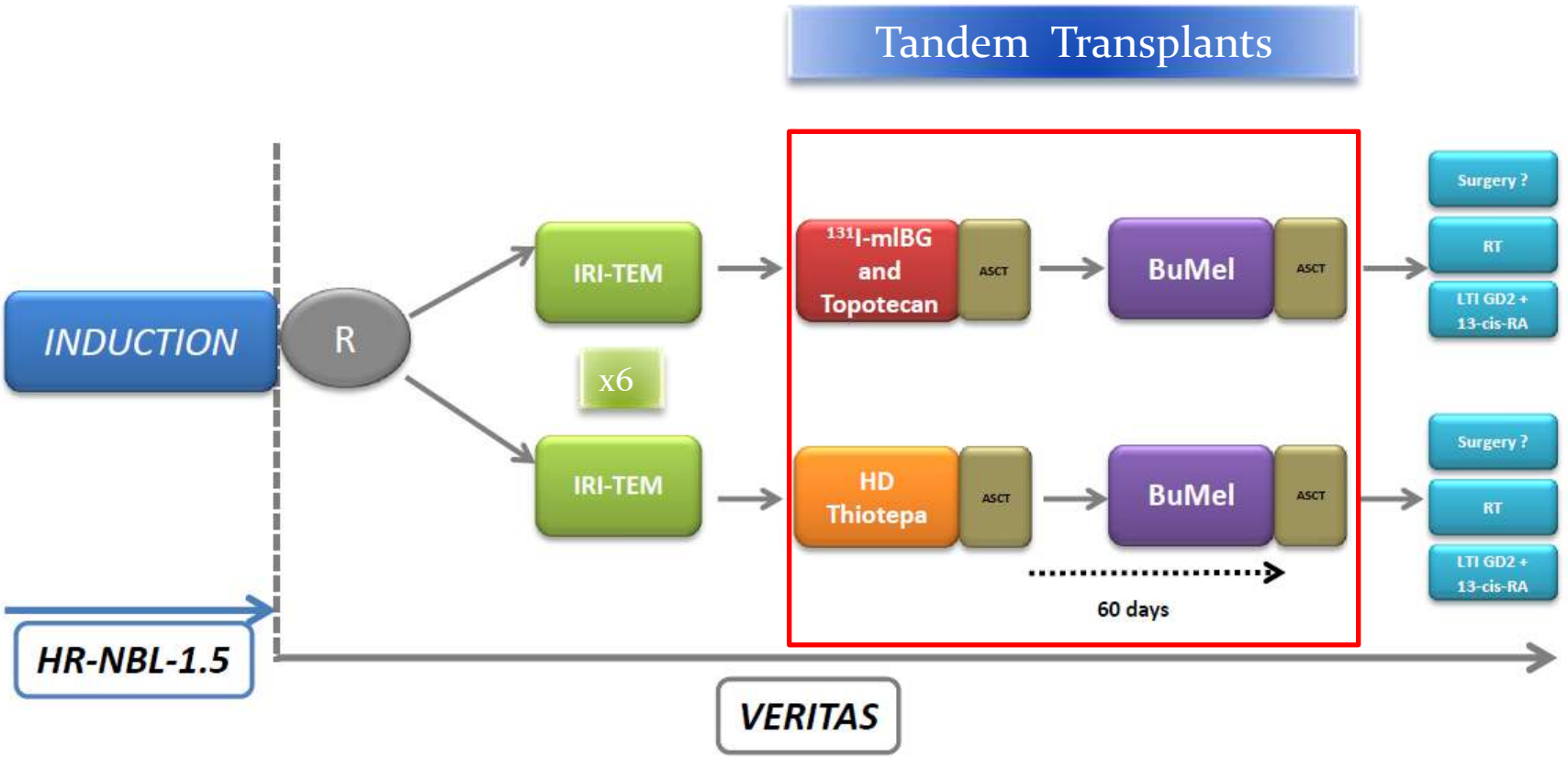
R2 - Historical comparison



Relapsed and Resistant Patients

VERITAS Protocol

VERITAS
Very High Risk NBL Protocol



Future Prospectives

Future Prospective

- Define the best induction chemotherapy
- Better utilize the ch14.18/CHO Ab. Upfront use?
- Introduction of new drugs
- Anti- ALK targeted therapy
- Other targeted therapies anti-PD1, anti-PDL1 treatments
- Early definition of Ultra High Risk patients
- Biology
- Minimal Residual Disease (MRD)
- Imaging (MIBG)
- Local treatment Surgery, RT to metastases?
- Best consolidation MAT (MIBG?)
- .....

SIOPEN R NET

SIOPEN Team Work

SIOPEN Team Work

- Founders
- Presidents and Members of the Executive Committee
- Principal Investigators of the Studies
- Researchers and Clinicians
- Committee Heads and Members
- Vienna office and Statisticians
- Hospital personnel
- Parents, families and children
- Parents associations
- ……

Marianna V. Vardinoyiannis- ΕΛΠΙΔΑ

Oncology Unit Athens Greece