E-SIOP NEUROBLASTOMA

a quarterly NEWSLETTER

#4 April 2003

Editorial

Dear friends,

no doubt, E-SIOP Neuroblastoma is growing, so are its challenges and potentials. Overtime Portugal, Israel, Hungary, Poland, Czech Republic, and Greece have joined the founding members Austria, Belgium, Denmark, France, Italy, Netherlands, Norway, Spain, Sweden, Switzerland, and UK.
Three clinical protocols are on-going and a fourth will open soon, thus covering all clinical conditions.

I would like to mention two recent achievements: (1) the Biology Sub-Committee is about to publish in JCO an article concerning the standardisation of the techniques used to characterise the tumour features; (2) the HR-NBL-1 has obtained substantial funding by the European Community, thanks to the great efforts of Ruth Ladenstein. The advantages of this financial support are under everybody's eyes, with the imaging transfer program being one ambitious example.

However, some relevant aspects for the development of E-SIOP Neuroblastoma Group need to be focused upon. Some of them will possibly be discussed during the final session of the Enlarged Board meeting scheduled on May 17, 2003, at the Middlesex Hospital, in London. This meeting was decided upon last November in Prague to give us the opportunity to analyse in depth the on-going clinical studies and research projects.

1. **E-SIOP Neuroblastoma Newsletter**. We definitively need an Editorial Board
2. **Board and Sub-Committees functioning. Membership. Statute**. We have to improve the inter relation between the Board and the Sub-Committees. We should discuss the advantages of establishing a membership for our Group. Do we need a Statute ?
3. **Discrepancies in participation of National Groups**. We have noticed that not all National Groups are equally enthusiastic and intense. This leads to inadequate patient recruitment and frustration of study chairmen. We must understand why this is happening and try to provide motivation for better compliance.
4. **Widening of E-SIOP Neuroblastoma.** As co-operative diagnostic guidelines and therapeutic protocols are developed, more an more requests are coming from colleagues of National Groups not yet part of E-SIOP Neuroblastoma. The problem stands in the lack of adequate infrastructures for some of these Groups. What to do ?
5. **Integration between clinical and basic science research.** So far, E-SIOP Neuroblastoma has paid prevalent attention to the development of clinical protocols and related laboratory aspects. We need to give more importance to basic research. In fact, more effective therapies will depend on progress of basic research.

Bruno De Bernardi,
Giannina Gaslini Children's Hospital, Genova, Italy
Chairman of E-SIOP Neuroblastoma

IMPORTANT FUTURE EVENTS

2003 ANNUAL MEETING

Toulouse, France,
November 7-8, 2003

ANR 2004

Advances in Neuroblastoma Research
Eleventh Conference
June 16-19, 2004, Genova, Italy
Abstract deadline: January 31, 2004.

E-SIOP Neuroblastoma

ENLARGED BOARD MEETING *

May 16-17, 2003

The Middlesex Hospital

Mortimer Street, London W1T 3AA, UK

Meeting organisers

Penelope Brock

Mark Gaze

Meeting Location

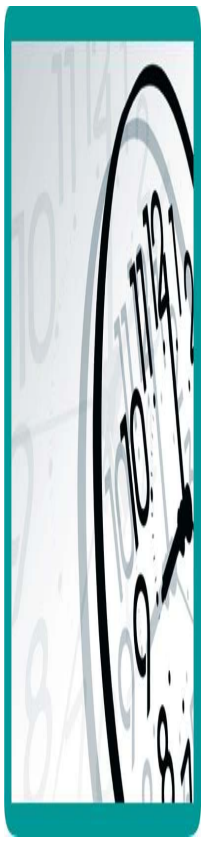
1 The Middlesex Hospital
Mortimer Street, London W1T 3AA

How to get to the Middlesex Hospital

By bus: Tottenham Court Road - North bound - Bus No's 10, 73, 24, 29, 134; Gower Street - South bound - Bus No's 10, 24, 29, 73, 134

By tube: Goodge Street (Northern Line); Oxford Circus (Central / Victoria / Bakerloo Lines)

FINAL AGENDA



Friday 16, AM	
9^{30}-11^{30}	**Infant Study** (*J Michon, H Rubie, M Gerrard, B De Bernardi, A Cañete*)
Break	
12^{00}-12^{30}	**Unresectable Study** (*A Garaventa*)
Friday 16, PM	
2^{00}-5^{00}	**HR-NBL-1 / ESIOP Study. Analysis and discussion of the first 100 patients** (*R Ladenstein and National Co-ordinators*)
Saturday 17, AM	
8^{30}-11^{30}	**New Studies and Research Projects** **1. TVD *vs* CADO** (*A Garaventa*) **2. mIBG-containing Protocols** - ***The use of dosimetry in evaluation of I-131 mIBG therapy*** (*G Flux*) - ***mIBG plus topotecan*** (*M Gaze*) - ***Italian proposal*** (*S Mastrangelo*) ***3.* MRD detection, phenotype and genotype, and targeting** (*B Kågedal*)
Break	
12^{00}-12^{30}	**LNESG-2 study** (*M Nenadov and Writing Committee*)
Saturday 17, PM	
2^{00}	**SIOPEN-R-NET. Update on IT structure** (*G Schreier*)
3^{00}	**Reports of Study Chairmen** (*M Gerrard 15'; A Garaventa 10'; R Ladenstein 15'; M Nenadov 10'*)
4^{00}	**Reports of Sub-Committee Chairmen** (*S Navarro 10'; G Amann 10'; S Helfré 10'; S Dallorso 10'; S Burchill 10'; K Beiske 10'; G Flux 10'*)
Break	
5^{30}-6^{30}	**Enlarged Board issues (general discussion)**

Sub-Committees' meetings: Pathology, Bone Marrow (Immunocytology and RT-PCR), Stem Cell

***Participants:** E-SIOP Neuroblastoma Board, E-SIOP Clinical Studies' Chairmen and National Co-ordinators, Presenters of new studies, ARC Seibersdorf Team

Biology Sub-Committee Report

ENQUA Meeting, Paris, March 14-16, 2003
Infant and Unresectable protocols

Participants: *Peter F. Ambros (Austria, CCRI), Jean Bénard (France, IGR), Maria Boavida (Portugal), Valérie Combaret (France, CLB), Jérôme Couturier (France, Curie), Raffaella Defferrari (Italy), Katia Mazzocco (Italy), Rosa Noguera (Spain), Gian Paolo Tonini (Italy), Alexandre Valent (France, IGR), Nadine Van Roy (Belgium).*

Excused: *Klaus Beiske (Norway), Nicole Gross (Switzerland), John Lunec (UK), Marta Jeison (Israel), Ales Vicha (Czech Republic)*

Reviewing of the FISH images and DI data:

220 cases included in Trials (INES update, February 2003) were reviewed for *MYCN* and DNA index data:

Austria:	22 cases
Belgium:	9 cases
Spain:	26 cases
France:	56 cases
Eire:	2 cases
Italy:	63 cases
Norway:	2 cases
Portugal:	1 case
UK:	38 cases
Switzerland:	1 case

The MYCN status was validated in 158 cases (71%). Missing data mainly concerned patients from the UK, because only very few FISH images were available.
13 *MYCN* amplifications were validated. In addition, one focal amplification was accepted. Four other cases were presented as having focal amplification. In order to clarify these ambiguous cases, *MYCN* FISH will be re-examined on tissue sections, and *MYCN* evaluation by a second method will be performed in all cases available; results will be presented at the next meeting (for further details: see below).

The DNA index was available in 114 cases (52%).
It was missing in all UK patients.

44 cases from the E-SIOP Unresectable Study were reviewed by the group.

Web based reviewing of the genetic data

It is agreed that the pictures from every case entered into one of the ongoing studies have to be displayed on the web page. This information should exclusively be accessible to the members of the Biology Group (password protection).
For each patient one page should be constructed that should contain: name 3+2 code, birth data, date sample arrived, lab, # tu cells, *MYCN*-, 1p-, ploidy- data. In addition, at least two pictures from every analysis (*MYCN*, 1p) with at least 3 cells per frame should be made visible. It should be possible to blow up these pictures and to be able to see also three different colors (red, green, blue) individually.

Decision making process

It was suggested that the *MYCN* data are immediately given to the responsible clinician by the local biology reference lab without reviewing. Nevertheless, the reviewing procedure will be done as fast as possible on all cases enrolled in the different studies to enable timely information of the clinician involved. In case of discordance, the clinician will be informed by the local reference lab about the result of the review.
The following procedure for the decision making process was discussed.

Acceptance of a case:
when the opinion of the original observer is in line with the opinion of the responsible study coordinator (biology) + respective assistant. These data are entered into the data bank - no more changes allowed!

Disagreement:
when one of the reviewers (study coordinator/assistant) and/or one member of the group has a different opinion, the case has to be reviewed by the whole group. Either slides are sent around or the pictures/slides are investigated in a review meeting. In case of a verified discrepancy the lab originating the data will be informed and it will be his/her responsibility to pass on this information to the clinician.

Time considerations:
The reviewing has to be done at least by two members (study coordinator/assistant) ideally within 5 days.

Different aspects of the logistics concerning this procedure will be discussed at the next meeting (e.g. who will review the data when the data are entered by the study coordinator or his/her assistant).

Responsibilities within the different studies

In order to establish a more simple procedure, it has been agreed that every study co-ordinator will be assisted by a member of the Biology Group.
So far the main responsibilities for the different studies are:

	Study coordinator	*Assistant*
Infant	Jerome Couturier	Klaus Beiske
Unresectable	Gian Paolo Tonini	
LNESG 2	Nicole Gross	Maria Boavida
High-Risk	Peter Ambros	Alexander Valent

MYCN in the serum of neuroblastoma patients

It was shown by Valerie Combaret that it is possible to determine the presence of *MYCN* copies in the serum from neuroblastoma patients. It was suggested to send serum samples, ideally deep frozen, to Lyon. All details can be obtained from Valerie Combaret.

Sample size

Participants stressed the fact that tumour samples received by the biologist are frequently (in some centres in about 50% of the cases) of very small size (micro-biopsies), making it impossible to study 1p aberrations by FISH and the ploidy level.
In cases where no sufficient and well preserved tumour cells are provided, no genetic report can be given. Furthermore, no further studies can be done and no storage of tumour samples for other biological/genetic studies is possible. The persons involved – paediatricians, surgeons and pathologists are therefore asked to strictly stick to these basic requirements. In order to enable appropriate genetic analyses, it is crucial that the responsible paediatrician/pathologist contacts the reference centre and discusses the most appropriate tumour handling procedure.

Gain of MYCN copies

As different members of the Biology Group observed a number of cases with additional *MYCN* copies, the group felt that special attention should be given to these cases at the next meeting.

Heterogeneity of MYCN amplification

Still, the clinical impact of focal *MYCN* amplifications has not been finally established. Therefore, it is a major concern to study the biological and clinical impact of this aberration. Besides the agreed and formulated definition of focal appearance of the genetically aberrant cells, e.g. *MYCN* amplification in at least 50 tumour cells present in a single focus, another type of heterogeneous tumours seems to be possible. A case was shown where only single cells or only very few *MYCN* amplified cells (< 50) had been found. For this type of tumour heterogeneity the term 'scattered' was suggested. To further elucidate the genomic changes which might precede the *MYCN* amplification, JC will perform CGH studies on these tumours. The Vienna group will study the amplicon size in the different foci to learn about the genesis of the *MYCN* amplification. In addition, JC will perform FISH studies on cryo-sections and PFA will analyse paraffin sections on the presence and distribution of *MYCN* amplified cells.

Next Meeting

The next meeting will be held in Vienna in June 2003 where *MYCN*, ploidy and 1p data from different studies will be reviewed. In addition, cases with *MYCN* gain and focally amplified or with scattered amplification will be looked at in great detail at the next Biology Meeting.
In addition, the web based review procedure will be discussed together with the representative(s) from Seibersdorf. PFA will provide suggestions concerning the date.

J Couturier **PF Ambros**

Radiotherapy Sub-Committee Report

April 25, 2003
Paris

Radiotherapy Sub-Committee Meets in Paris Spring Sunshine

Eight European clinical oncologists, ***Sylvie Helfre (Paris), Chairman Radiotherapy Subcommittee, Thomas Bjork-Eriksson (Gothenburg), Tom Boterberg (Gent), Karin Dieckmann (Wien), Mark Gaze (London), Jean-Louis Habrand (Paris), Bela Malinova (Prague), Nili Ramu (Jerusalem), met at the Intitut Curie, Paris, on 25 April 2003 with Bruno De Bernardi (Genova) Chairman and Ruth Ladenstein (Wien) Vice-Chairman of the ESIOP Board*** to discuss radiotherapy issues in relation to the High Risk Neuroblastoma protocol and the SIOPEN-R-NET project (Project Coordinator:Ruth Ladenstein).

Three case presentations stimulated discussion about the protocol as written, and how it should be interpreted. We clarified several ambiguous areas in the protocol. We agreed that metastatic sites would not be systematically irradiated. We agreed that regional lymph nodes adjacent to the primary tumour which remain enlarged on imaging following induction chemotherapy will be included in the GTV for planning local radiotherapy. More distant lymph node enlargement is metastatic disease, and will therefore not be systematically irradiated. Sometimes the volume to be irradiated may include too much normal tissue for the full protocol dose of 21Gy to be given safely. We agreed that the CTV should be the GTV + 2cm all round except where the organs at risk made this impractical. We reiterated that patients with thoracic primary tumours where a substantial volume of lung will necessarily require irradiation should not be randomised at R1, but should electively receive CEM to avoid the possibility of a radiotherapy/busulphan interaction on the lung.

Other more mundane issues we discussed related to quality assurance, minimum datasets, clinical governance issues in paediatric radiotherapy and technical definitions of the dose received by organs at risks. Pre-existing definitions from France and Germany shall be reviewed by SC members and shall get adopted to form standard SOPs.

To serve the image IT SIOPEN-R-NET project it was decided to circulate an amended questionnaire to relevant radiotherapists in each of the participating countries. Dr. Dickmann will care for the amendment and Ruth Ladenstein will circulate via the Vienna centre again to National Coordinators hoping that this time they will forward this questionnaire to the relevant radiotherapists in their country indeed.

Our meeting was such good fun that we plan to meet regularly. We intend to get together again in June in Lyon , at the International Paediatric Radiotherapy Congress, in November in Tolouse, at the SIOP Europe Annual Neuroblastoma Meeting and in Genova in June 2004, at the Advances in Neuroblastoma Research Meeting. We hope that by getting together at major international meetings, a larger group of interested paediatric clinical oncologists involved in giving radiotherapy to children with neuroblastoma will be able to participate. Please join us!

M. N. Gaze

Pathology Sub-Committee Report

January 17-18, 2003
Oslo

The Pathology Sub-committee (SC) held a meeting on the 17th-18th of January, 2003, in Oslo (Norway), Rikshospitalet, Department of Pathology. All members, i.e. ***Gabriele Amann (Austria), Catherine Cullinane (UK), Emanuele D'Amore (Italy), Claudio Gambini (Italy), Samuel Navarro (Spain), Michel Peuchmaur (France), and Klaus Beiske (local host)*** participated. The meeting had three major objectives:

1. COMPLETION OF THE REVIEW OF LNESG1 TRIAL CASES

The slides of seven tumours were brought to the meeting and finally reviewed according to the classification of the International Neuroblastoma Pathology Committee (INPC). Of 124 trial patients, 120 (96,7%) have been reviewed by the SC during the last three years, while four tumours still are missing. Three of the 120 reviewed cases were not interpretable, and another one represented a composite, neural crest-derived tumour. Thus, 116 tumours were assigned either a favourable or unfavourable prognosis. Veronique Mosseri is working on the statistical analysis of the prognostic significance of the INPC classification, and Samuel Navarro will present the results during the enlarged board meeting on May 17, 2003, in London.

2. BLINDED REVIEW OF RELAPSED/UNRELAPSED LNESG1 TUMOURS

The Pathology SC is currently reviewing 48 tumours, containing 19 relapsed, non-MYCN-amplified, blinded cases, for the possible identification of prognostically significant morphological criteria, not considered in the Shimada or INPC classification. As a pilot project, 22 tumours were looked at during the meeting in Oslo, and this pre-review led to a brain storm resulting in a list of 17 structural, histo- and cytological criteria which are suspected to discriminate between relapsed and unrelapsed cases. Since the analysis of candidate criteria in more than 40 tumours is time-consuming, every SC member performs it in his own laboratory and brings the data to the next meeting for statistical evaluation. A number of MYCN-amplified cases will also be analysed as controls, using the same morphological criteria. Gabriele Amann will inform about clinical purpose, morphological criteria and, possibly, some preliminary results of this investigation during the enlarged board meeting on May 17, 2003, in London.

3. SIOPEN-R-NET

The SC members agreed upon the latest, protocol-independent Pathology Form for primary tumours, and a revised Bone Marrow Form, to serve as basis for data collection in the SIOPEN-R-NET data base.

One of the deliverables of the Pathology SC concerns the teaching of pathologists unexperienced in the application of the INPC classification. The proposal of a large scale central European meeting/course was rejected in favour of more individual teaching in small groups. During future SC meetings, one day may be reserved to invite a few pathologists from the hosting country to join the SC members at the microscope.

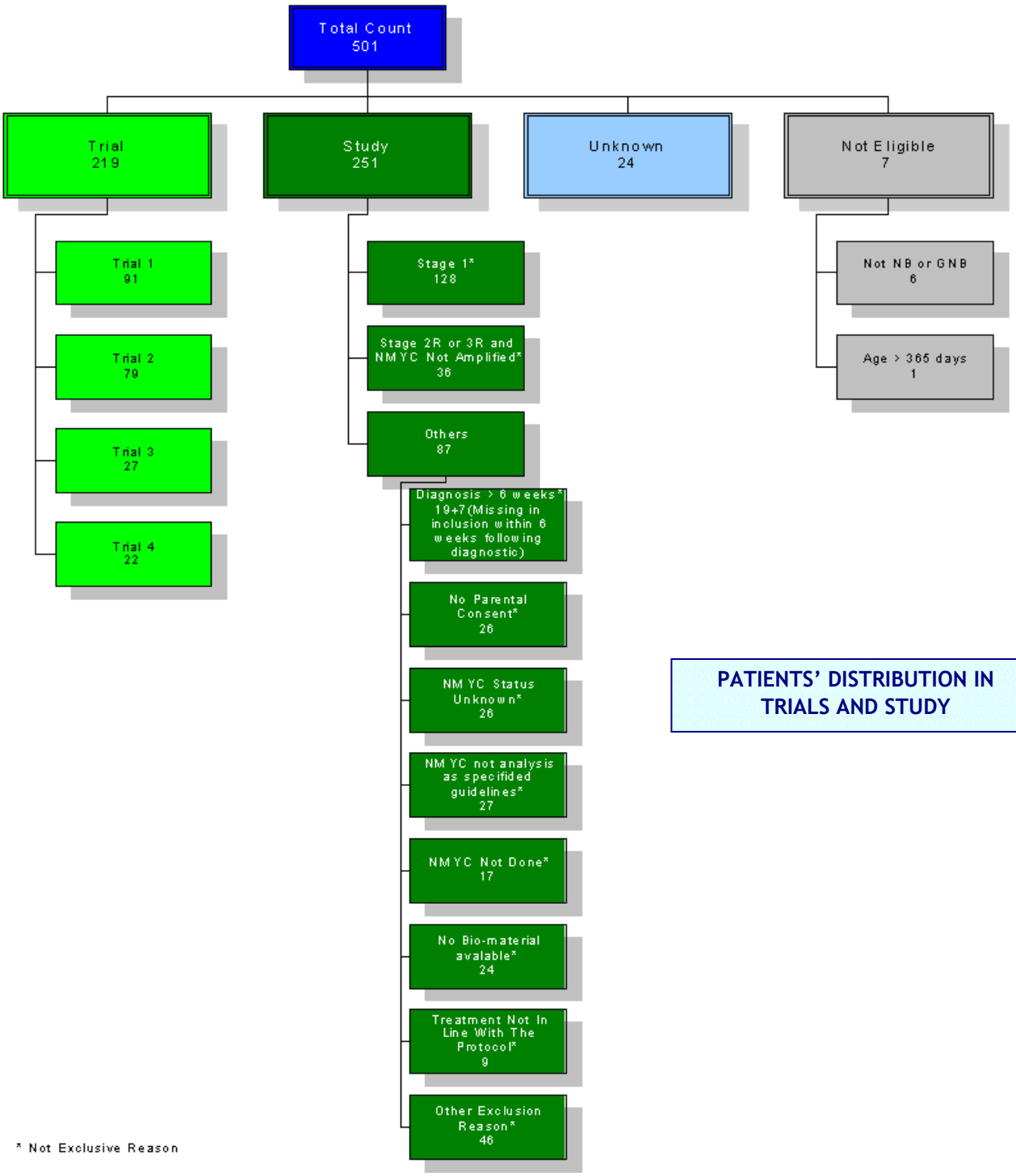
Finally, various possibilities of digital image transfer were discussed. The representative of a French company presented a soft ware which processed wide field pictures of tumour tissue into a virtual slide archive of higher magnifications, thus enabling the communication of histological, but not all necessary cytological details. Another company demonstrated a digital camera for net-based "life" transmission of microscopic pictures as a tool for on-line discussions of problematic cases (e.g. LNESG2). The quality of these digital pictures was very high, however, standard net connections will probably not be able to transmit such pictures with a speed required for on-line discussions.

Gabriele Amann
Klaus Beiske
Catherine Cullinane
Emanuele D'Amore
Claudio Gambini
Samuel Navarro
Michel Peuchmaur

Protocols Update (1)

INFANT NEUROBLASTOMA

Opened July 99
Update October 02
By Mary Gerrard



* Not Exclusive Reason

PATIENTS' DISTRIBUTION IN TRIALS AND STUDY

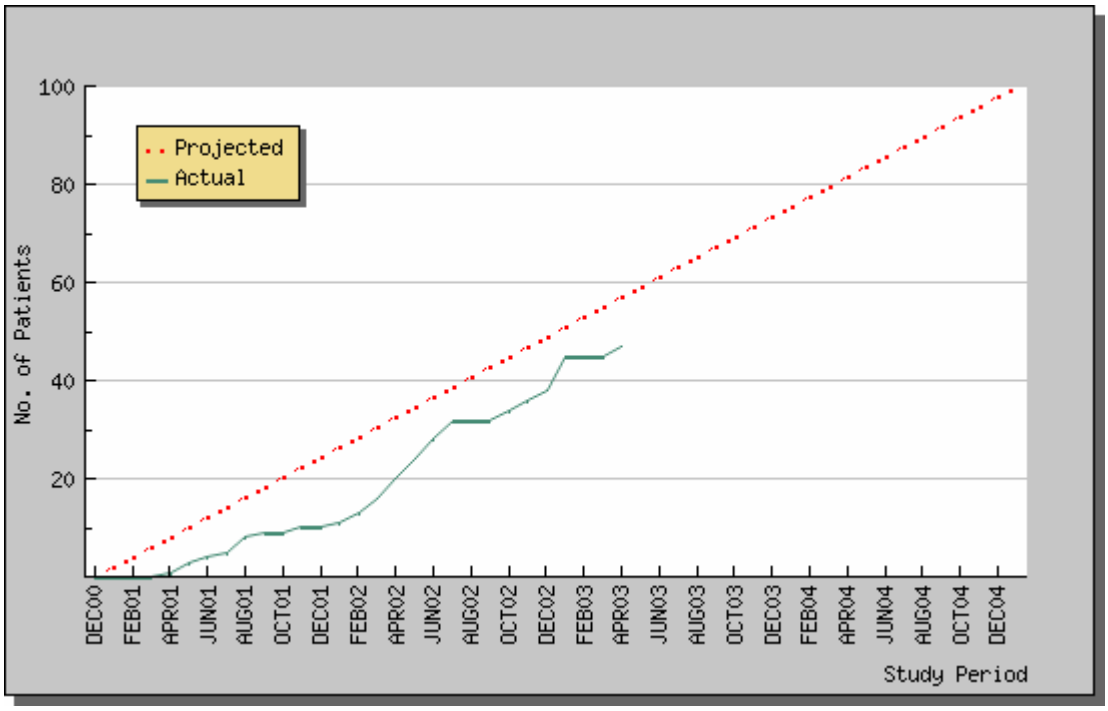
Protocols Update (2)

UNRESECTABLE NEUROBLASTOMA

Opened January 01
Update October 02

By Jan Kohler and Luca Boni

Country	Year			Total
	2001	2002	2003	
Austria	0 0.00	0 0.00	1 100.00	1 2.13
Belgium	2 66.67	1 33.33	0 0.00	3 6.38
France	0 0.00	5 62.50	3 37.50	8 17.02
Italy	7 53.85	5 38.46	1 7.69	13 27.66
Portugal	0 0.00	2 100.00	0 0.00	2 4.26
Spain	0 0.00	6 85.71	1 14.29	7 14.89
United Kingdom	1 7.69	9 69.23	3 23.08	13 27.66
Total	10 21.28	28 59.57	9 19.15	47 100.00



Protocols Update (3)

HR-NBL-1 Protocol

Opened July 99
Update October 02

Current Status of the High-Risk Study HR-NBL-1/ESIOP Study

Accrual status as of April 28th, 2003

1.	Countries registering patients	11
2.	Total Number of Patients	126
3.	Registering Institutions	138
4.	Users	198
5.	Logins to the system	4188
6.	Number of Patients per Country	
	▪ Austria	6 pts
	▪ Belgium	7 pts
	▪ Czech Republic	pts
	▪ Spain	26 pts
	▪ France	11 pts
	▪ Israel	5 pts
	▪ Italy	53 pts
	▪ Poland	3 pts
	▪ Sweden	3 pts
	▪ United Kingdom	8pts

So far no patient accrual on the study site from 6 countries:
Denmark, Hungary, Greece, Norway, Portugal, Switzerland

REMINDER - DATA ENTRY ON HR-NBL-1/ESIOP STUDY
DON'T FORGET THAT WE ONLY MAY DISCUSS, CONCLUDE AND DECIDE WHEN OUR DECISIONS ARE BASED ON FIRM DATA FOR WHICH DATA ENTRY IS AN ABSOLUTE PREREQUISITE!

As agreed in Prague the International Data Centre started a major effort to stimulate National Coordinators and 'Local Physicians' to reach complete data sets for the interim analysis of the first 100 patients entered on the HR-NBl-1/ESIOP Study to be analysed and presented at the enlarged board meeting in London May 16th, 2003. Based on the SIOPEN-R-NET Project Budget Dr. Ditha Modritz has been hired at the International Study Centre in Vienna as the International Data Manager to support the data flow, to contact national coordinators and local physicians and to communicate with ARC Seibersdorf to help to translate and implement necessary improvements on the study site, based on own daily data entry experience and taking into consideration the feed-back from our colleagues suggesting improvements. Some have been implemented and more are to come over the summer time when ARC Seibersdorf will recruit additional men-power for implementation tasks: in particular the opening of the official SIOPEN-R-NET WEB side followed by the migration of the HR-NBL-1/ESIOP study side to the official SIOPEN-R-NET WEB side (details to follow in London). These improvements will enable to transmit online basic information on the study progress and accrual rates in the participating countries and will include further improvements in the progress sections to make it even easier for study manager to follow data entries.

For the London meeting our principal tasks are to analyse response at Rapid Cojec induction, harvest feasibility, number of patients eligible for R0 (G-CSF question) and for R1 (MGT randomisation), and encountered toxicities and in particular SAEs.

Since the London meeting (16-17 May) is set shortly after the end of the first 6-month period of the EC grant SIOPEN-R-NET, we use the opportunity to demand all deliverables that will have been due at the end of April, as well as all the ones which have already been due at an earlier date. Please bring the deliverables along to the meeting as hard copy (paper) as well as on a disk, or email it to Isabelle Walters as attachment even before London. The study progress analysis of the HR-NBl-1/ESIOP is also an deliverable to the EC. An email reminder has been circulated to all participants listing the deliverables of individual partners due at the end of the first 6 month grant period via Isabelle Walters (Vienna Study Centre).
Fulfilling the deliverables and submitting them in time in the first year are a prerequisite to receiving your 2nd year budget. Please note that if you have not produced your tasks, and thus shown that you do not need the money, the EC will cut your 2nd year budget and/or ask first year's money back from your institutions!

Thank you for all the efforts made to our common project over then last months!

Sincerely yours

Ass. Prof. Dr. Ruth Ladenstein
(International study coordinator)

Dr. Ditha Modritz
(International data manager)

Mag. Isabelle Walters
(Scientific Secretary)

Unusual Cases

Infants with 4s neuroblastoma and *MYCN* amplification (MNA) are a rarity. Two such cases are presented herewith:

CASE 1

In 1997, a four-month-old boy, transferred to our hospital due to a *Meningococus B* septicemia, was discovered to have a huge nodular hepatomegaly. An ultrasound examination showed a left adrenal mass and multiple liver mets. He was considered to have stage 4s neuroblastoma (mIBG scan was positive at level of primary tumor and liver, but negative at level of bone, bone marrow biopsies negative too). Two courses of cyclophosphamide-adryamicin were administered by which a partial remission of tumor lesions was achieved. Radical resection of primary tumor was then carried out. Histology: undifferentiated neuroblastoma with high MKI. Biologic studies: amplified *MYCN; 1p* deletion triploid DNA index.

After careful literature review, a "wait and see" policy was adopted with close imaging and clinical follow-up, while waiting for a re-confirmation of our biological results in an abroad reference laboratory. Liver metastases progressively regressed. However, 6 months after diagnosis, while patient was asymptomatic, mIBG scan showed 2 isolated skeletal metastases, in absence of bone marrow infiltration. He was started on a high-risk protocol (Med Ped Oncol 2001; 37:537-542). Disease progressed in the early post-transplant period, with death shortly ensuing.

CASE 2

A left adrenal mass was detected prenatally. Ten days after birth, radical excision of the mass was carried out. Diagnosis of stage 4s neuroblastoma was done on the basis of complementary studies demonstrating presence of liver mets with normal bone and bone marrow.
Histology: undifferentiated neuroblastoma, with low MKI. Biologic studies: amplified *MYCN*, *1p* deletion, diploid DNA content and diploid tumor.

Patient was started on 99.4 Trial therapy, by which he achieved complete remission, which has been persisting since now (15 months from diagnosis).

Comment

The peculiar and favorable evolution of stage 4s neuroblastoma is well-known. Although rare, amplified *MCYN* in stage 4S may occur, and it may worsen the prognosis, therefore suggesting the application of aggressive therapeutic strategies.

These two cases could be considered in conjunction whit a recent publication of Rosa Noguera (Cancer Genet Cytogenet 2003; 140: 157-161) about a child with *MYCN* gain and 4s neuroblastoma, who suffered a metastatic relapse 26 months later. At time of relapse *MYCN* was amplified.

Overall, these three cases illustrate the difficulties the clinicians have to face with. The advances in biological knowledge have been overwhelming and clarifying in most circumstances, however, have raised new considerations and difficult situations, especially for stage 4s infants, considered so far to be one of the best-prognosis groups in neuroblastoma. These cases point out the importance of cooperative, well-designed and carried-out studies in these complex and scarce group of patients.

Adela Cañete and Victoria Castel.

Recent publications

Impact of Metaiodobenzylguanidine Scintigraphy on Assessing Response of High-Risk Neuroblastoma to Dose-Intensive Induction Chemotherapy

By Brian H. Kushner, Samuel D.J. Yeh, Kim Kramer, Steven M. Larson, and Nai-Kong V. Cheung

Journal Clinical Oncology 21:1082-1086, 2003

162 neuroblastoma patients from one institution were evaluated after either standard or dose intensive induction therapy. The authors found that with standard therapy, mIBG scintigraphy merely confirms findings of other staging modalities However, when dose-intensive therapy was initiated at diagnosis the reliable achievement of major disease responses made extensive BM tests and mIBG scintigraphy prerequisites for accurate determinations of disease status.

NEUROBLASTOMA: BIOLOGICAL INSIGHTS INTO A CLINICAL ENIGMA

Garrett M. Brodeur

Nature Reviews Cancer 3:2003 -2016, 2003

Recent advances in understanding the biology and genetic of neuroblastoma allowed 1) a classification into low-intermediate and high-risk groups, and 2) the most appropriate intensity of therapy to be selected. Future therapies will focus increasingly on the genes and biological pathways that contribute to malignant transformation or progression.

Oncogene (2003) 22, 2343–2351

www.nature.com/onc

Screening for gene mutations in a 500 kb neuroblastoma tumor suppressor candidate region in chromosome 1p; mutation and stage-specific expression in *UBE4B/UFD2*

Cecilia Krona[1], Katarina Ejeskär[1,2], Frida Abel[1], Per Kogner[3], Jill Bjelke[1], Elin Björk[1], Rose-Marie Sjöberg[1] and Tommy Martinsson[1]

[1]Department of Clinical Genetics, Institute for the Health of Women and Children, Göteborg University, Sahlgrenska University Hospital-East, SE-41685 Göteborg, Sweden; [2]Cell and Gene Therapy Group, Murdoch Children's Research Institute, Royal Children's Hospital, Parkville, Vic. 3052, Australia; [3]Childhood Cancer Research Unit, Karolinska Institute, Karolinska Hospital, SE-17176 Stockholm, Sweden

Oncogene 22:2343-2351, 2003

Despite deletion of the telomeric portion of 1p chromosome is associated with worse prognosis in neuroblastoma, no tumour suppressor gene has been identified in that region, yet. The shortest region of overlap of deletions, ranging from marker D1S80 to D1S244, was shown to partly overlap a 500 kb region that was homozygously deleted in a neuroblastoma cell line. The authors have screened seven genes known to reside in or very close to the overlap consensus region. A few deviations from the reference sequences were identified; most interestingly being a splice site mutation that was detected in *UBE4B/UFD2* in a stage 3 neuroblastoma with fatal outcome. This mutation was neither present in patients constitutional DNA nor in any of 192 control chromosomes analysed. Also, the expression of *UBE4B/UFD2* was markedly diminished in the high-stage/poor-outcome tumours as compared to the low-stage/favourable-outcome tumours. Given the data presented, *UBE4B/UFD2* stands out as the strongest candidate neuroblastoma tumour suppressor gene in the region at this stage.

[CANCER RESEARCH 63, 86–92, January 1, 2003]

Doxorubicin-loaded Fab′ Fragments of Anti-disialoganglioside Immunoliposomes Selectively Inhibit the Growth and Dissemination of Human Neuroblastoma in Nude Mice[1]

Fabio Pastorino,[2] Chiara Brignole,[2] Danilo Marimpietri, Puja Sapra, Elaine H. Moase, Theresa M. Allen, and Mirco Ponzoni[3]

Differentiation Therapy Unit, Laboratory of Oncology, G. Gaslini Children's Hospital, Genoa, Italy 16148 [F. P., C. B., D. M., M. P.], and Department of Pharmacology, University of Alberta, Edmonton, Alberta, Canada T6G2H7 [P. S., E. H. M., T. M. A.]

Cancer Research 63:86-92, 2003

This article documents significant improvements in the therapeutic effects of doxorubicin, when encapsulated in immunoliposomes targeted with the Fab' fragments of anti-disialoganglioside G_{D2}. Long term survival approaching 100% was observed for several doses and dosing schedules of the immunoliposomes, suggesting total inhibition of metastatic growth of human neuroblastoma grown in a xenograft nude mice model. This is the first publication demonstrating the possibility to prevent the growth of neuroblastoma cells as macro- and micrometastases by the use of immunospecific liposomes. The authors conclude that doxorubicin liposomal formulation deserves clinical evaluation as adjuvant therapy for advanced disease, or in case of minimal residual disease.

Disseminated Neuroblastoma in Children Older Than One Year at Diagnosis: Comparable Results With Three Consecutive High-Dose Protocols Adopted by the Italian Co-Operative Group for Neuroblastoma

By Bruno De Bernardi, Brigitte Nicolas, Luca Boni, Paolo Indolfi, Modesto Carli, Luca Cordero di Montezemolo, Alberto Donfrancesco, Andrea Pession, Massimo Provenzi, Andrea di Cataldo, Antonino Rizzo, Gian Paolo Tonini, Sandro Dallorso, Massimo Conte, Claudio Gambini, Alberto Garaventa, Federico Bonetti, Andrea Zanazzo, Paolo D'Angelo, and Paolo Bruzzi

Journal Clinical Oncology 21:1592-1601, 2003

330 children were treated between 1985-97 with three consecutive high-risk protocols, the second and third of which were modified compared to the first one in the hope to improve patients' outcome. However, major tumour response rates after induction therapy were comparable (66.7%, 69.2%, 68.6%), as well as 5-year overall survival (26%, 23%, 28%), and event free survival (19%, 17%, 17%). On the contrary, therapy-related deaths increased from 1.9% to 12.3% and 6.9%. The stability of these results overtime indicates that substantial therapeutic changes are needed.

Organised by Hervé Rubie
and SFOP
(Sociétée Française d'Oncologie Pédiatrique)

ADVANCES IN NEUROBLASTOMA RESEARCH

Eleventh Conference

June 16-19, 2004
Genova, Italy

ANR 2004

GE NOVA 04

Third Announcement & Call for Abstracts

Important dates !

January 31, 2004	Deadline for abstracts eligible for oral and poster presentation Deadline for early registration
March 15, 2004	Deadline for abstracts eligible for publication only
April 15, 2004	Confirmation of the abstracts
May 15, 2004	Deadline for regular registration
From May 16, 2004	Late and On-site registration

Main Topics

- Genetics and Molecular Biology
- Translational Research
- Clinical Research
- Novel Therapies

Workshops

- Microarray Technology *(June 16, PM)*
- Spinal Cord Compression *(June 19, PM)*
- Opsoclonus-Myoclonus *(June 19, PM)*

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Genova, May 5, 2003