SIOPEN

Newsletter #12

June 2010

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Edited by Sara Calmanti
Institut Gustave Roussy, Villejuif, France

President's introduction

Dear friends and colleagues,

Although volcanic ash has brought big turbulence upon us I am even more proud about the way the group has coped with crisis management. I wish to thank everybody for their understanding and flexibility to find new dates and to compromise to unusual solutions.

For these reasons we decided for a two step board meeting: Number one, replacing the original scheduled meeting, at the end of May in Toulouse. Number two in Stockholm on Sunday afternoon at the start of the ANR meeting we will meet again to continue our common work agenda and to update all those who did not have the opportunity to be with us in Toulouse for very good reasons. Together we will catch up with the news at the various meetings taking place in parallel! I wish to thank particularly Hervé Rubie for having hosted us in a difficult situation and having shown a lot of flexibility. Thank you Hervé for a wonderful and fruitful meeting! We really enjoyed Toulouse !

The association is flourishing well! Over the last months we have further increased our membership up to a total of 118 approved SIOPEN members. Also a big thank you to all colleagues who have supported us and engaged heavily with local fund raisers to develop a collaborative SIOPEN budget as we agreed.

We are happy to see two trials approaching finalization: LINES and OMS. This means major milestones for the groups after many years of very thoughtful study development and concerns. And this is a big thank you to the principal investigators and the study committees for having engaged so bravely over many years!

Having become partners within the SIOPE project ENCCA (European Network for clinical research in Cancer in Children and Adolescents) we are thrilled that the project was granted by the EC in March 2010. Neuroblastoma platforms that will benefit from this are the forthcoming LINES study and most importantly also the biological SIOPEN platform within LINES. Aspects of drug development, tumor banking, long term care and follow-up and more aspects will all be further developed within ENCCA and will also potentially help the SIOPEN platform to advance further.

The halpoidentical SCT study followed by immunotherapy with ch 14.18 antibody and IL2 has full ethical

approval in Austria and Tübingen and further centres are on their way. Additional questions raised by the German authorities are being addressed so that full approval in Germany is expected soon.

We were really excited to learn in Toulouse that the French authorities after all have approved the use of the ch 14.18/CHO antibody in France! Thank you for your input Dominique and the huge work that has led to success after all!

It is also very good news that the first randomized question of the high risk study has been accepted for publication by JCO and should appear soon.

Being in my fourth year of presidency, which I did enjoy very much and hope you all did, I need to announce that the time has almost come not so to say good bye but to happily announce a new president elect that will take over presidency in 2011 at a place to be decided!

I warmly welcome Peppy Brock ! Knowing SIOPEN needs so well for many years and always having shown a big engagement on SIOPEN affairs I trust she will be a superb future president reassuring the forthcoming tasks of the group! Hopefully the structures built over the last years will help her to facilitate, overlook and fulfil the SIOPEN task portfolio. We very much would like to congratulate Peppy on her election.

We also have rotations due within the Executive committee and very much would like to thank Vassilios Papadakis and Per Kogner for having engaged with the Executive committee over 4 years. We warmly welcome Klaus Beiske for Norway and Maja Beck for Switzerland as the two new members voted from the smaller countries to the Executive committee to serve for the next 4 years. We are most grateful to Victoria Castel for having provided us with her knowledge and support for many years in different functions at leadership level and last but not least updated and agreed upon recent publication rules. Many brilliant publications may follow! Victoria also deserves to be relieved from heavy duty over many years – thanks for the brilliant job done, Victoria! And Spain has nominated Adela Canete to follow her in the EXEC. We are very much looking forward to meet you all at the ANR meeting in Stockholm – hopefully nature will be with us! - which promises to be a scientifically exciting meeting.

It is my pleasure to see you all engaged with SIOPEN and supporting our common mission in so many ways!

Yours Ruth

Ruth Ladenstein

http://www.kinderkrebsforschung.at/

AGENDA
SIOPEN Catch-up Meeting
SIOPEN Executive Committee and SIOPEN Board
20/06/2010 11:00 – 18:00

Meeting site: Cancer Centre Karolinska, CCK, at Karolinska University Hospital, Stockholm (see enclosed map)
Local host: Per Kogner,
Mobile +46 70-5713907
E-mail: Per.Kogner@ki.se
Coffee provided. Sandwich lunch for those Executive Committee members pre-registered.

SUNDAY 20/06/10

Executive Committee Meeting

(closed with old and new Executive Committee members) 11:00 – 13:00

- Strategic roles within SIOPEN
- News from ENCCA
- Programme for SIOPEN AGM Oporto
- Planning of charity interactions
- New countries relationships
- Final decision on patent fees

13:00 – 13:30 Sandwich lunch

SIOPEN BOARD MEETING

PART 1: 13:30 - 15:30

➢ Report from the treasurer	Isaac	10 min.
➢ Approval of publication rules	Victoria	5 min.
➢ Update and next steps SIOPEN studies		
o HR-NBL-1	Ruth	
▪ Study progress		10 min.
o New High-Risk Study	Dominique	40 min.
o LINES	Adela	10 min.
o OMS	Gudrun	10 min.
o AYA	Isaac	10 min.
o HAPLO update	Peter Lang	5 min.
o GD2 continuous infusion study	Holger	15 min.

Coffee break 15:30 - 16:00

Part 2: 16:00 – 18:00

- Update from Specialty Committees

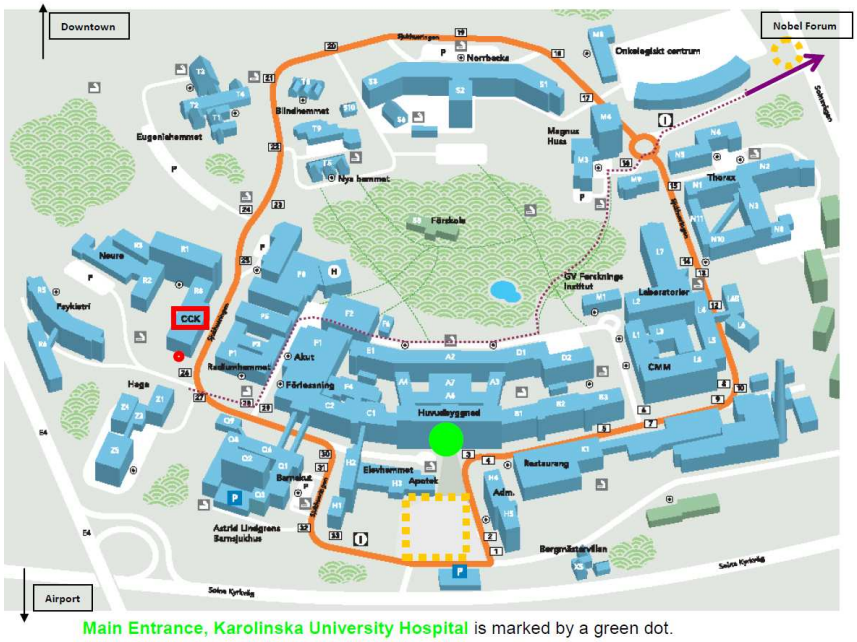
▪ Biology	Peter	10 min.
▪ Pathology	Klaus	10 min.
▪ Bone Marrow	Klaus & Peter	10 min.
▪ Molecular Monitoring Group	Sue	10 min.
▪ Nuclear Medicine	Val & Ruth	5 min.
▪ Surgery	Keith	10min.
▪ New Agents Development	Andy	60 min.

END 18:00

SIOPEN R NET

Welcome to SIOPEN EC and Board Catch- up meeting in Stockholm June 20!

Meeting place: Cancer Centre Karolinska, CCK, at Karolinska University Hospital, "Karolinska Sjukhuset" in Swedish (close to "Radiumhemmet" for taxi drivers to be familiar). Many of you were here 2006, remembering the snow...
You reach it by foot, taxi or local bus from downtown. From the airport a cab with fixed price is most convenient. The airport coach stops only a few hundred meters from the hospital. The airport train stops at the central railway station from which you take bus 59 to Karolinska.



Main Entrance, Karolinska University Hospital is marked by a green dot.

The main arrival and departure centre for buses at the hospital is marked by a semi dotted square in yellow (in the lower center) and **a bus stop at Karolinska Institutet and Nobel Forum** is marked by a semi dotted circle (upper right).

CCK (Cancer Centre Karolinska), entrance marked by a small red circle. This is where the meeting rooms for SIOPEN are. Ground floor or 5th floor, follow the signs!

Walking to Karolinska Institutet (Nobel Forum) and the ANR VIP-reception (invited only) is outlined by a semi dotted line and arrow in burgundy (appr. 10 min).

Local buses from downtown for the hospital are numbered 3 (blue buses, final stop Karolinska), 59,73,77 and 507 (red buses). Check time tables and bus stops at www.sl.se
NB! You need to have a ticket before you get on the bus!

Welcome!

Per Kogner

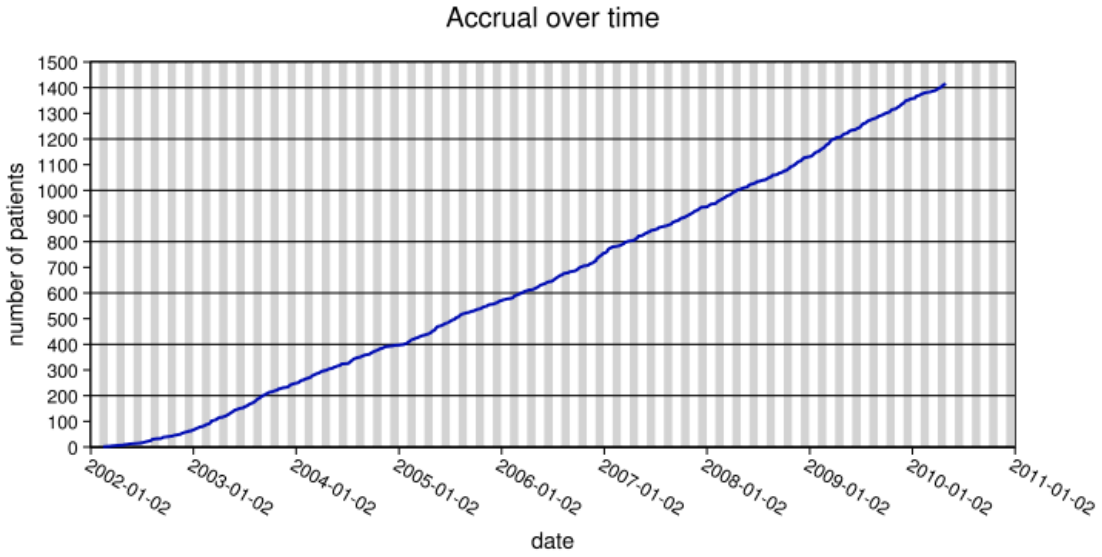
Clinical Trials' Corner

HR-NBL-1

High Risk Neuroblastoma Study

Ruth Ladenstein

Recruitment
The High-risk neuroblastoma trial is recruiting well and has now reached a total of 1424 patients.



R0 Randomisation
The R0 supportive care question is answered and the article has been submitted to JCO. All patients are now getting G-CSF during induction.

R1 Randomisation
There are currently 566 patients randomised to R1. The R1 question should be effectively answered in approximately 2 years.

New R2 Randomisation
In spring and at the ASCO meeting 2009 a major break through of immunotherapy has been reported when the COG was able to stop accrual into the immunotherapy arm in the COG Study ANBL0032 for early significance. This also had major implications for SIOPEN as the group felt the need to adopt the immunotherapy arm (R2-randomisation) of the current HR-NBL1/SIOPEN study. After intensive discussions and meetings the executive committee had approved the change towards a new SIOPEN immunotherapy strategy:
The amended version of the R2 randomisation (as of July 2009) compares the treatment with retinoic acid (RA) and antibody ch14.18/CHO versus ch14.18/CHO, RA and additional

subcutaneous Interleukin 2 (Aldesleukin). The amended protocol as of July 2009 has been approved by the Ethics Committee and the competent authorities in Austria.

The new R2 randomisation is available on the data base since November 1st 2009. 66 Patients have been randomised to R2. R2 randomisation can only be performed after all necessary documents (approval of the ethics committee, competent authorities, insurance, and sponsor-ship agreement) have been provided. So far, Austria, Belgium, Israel, Italy and the UK have managed to randomise and treat patients until now. All other countries are still in the process of receiving the necessary documents.
The SIOPEN group is currently the only organisation in Europe with access to the antibody having it developed over the last 8 years.

Low and Intermediate Risk Neuroblastoma Study LINES

from the LINES Writing Committee

The aim of this SIOPEN study is to have a clinical trial using a risk group stratification approach for the treatment of all non high risk neuroblastoma patients of any age who are MYCN non amplified. The risk groups will depend on age, stage, the presence or not of symptoms and the biological profile of the tumour.
There will be three well defined risk groups of patients included in this study: very low, low and intermediate.

- The Very Low Risk Study will be an observational study of Infants with adrenal masses, discovered antenatally or neonatally (ie suspected neuroblastoma). Our hypothesis is that these patients can be managed without initial surgery with close monitoring which does not jeopardise their outcome.

- The aim of treatment in the Low Risk Study will be to continue to reduce the amount of chemotherapy and surgery and therefore lessen the burden of treatment for all appropriate low risk patients, who in previous studies have been shown to have an excellent long term outcome (as in the SIOPEN 99.1-2 infant neuroblastoma studies when OS > 97%). This Low Risk study includes a randomisation for L2 patients >18 months of age, without segmental chromosomal aberrations and without life-threatening symptoms between 2 treatment arms either standard chemotherapy or observation with delayed chemotherapy if indicated clinically by the tumour progressing.

- The Intermediate Risk Study aims to unify treatment strategies to maintain the previously good EFS of > 80% and to intensify local treatment with radiotherapy for those intermediate risk patients with poorly differentiated or undifferentiated disease. A very small group of patients with L1, MYCN amplified tumours are included in this intermediate risk group.

The LINES study is about to be finalised in June 2010. The European sponsor has started the procedure to launch it in autumn. The EUDRACT-number has been applied. Most of the SIOPEN participating countries plus Australia confirmed their participation. The LINES study is also involved in the ENCCA project.

OMS
Opsoclonus-Myoclonus Protocol

Gudrun Schleiermacher
Barbara Hero
For the Opsoclonus Myoclonus Collaboration Group

Opsoclonus-myoclonus syndrome (OMS) in childhood is a rare, severe neurological disorder occuring mainly in children aged under 3 years old, and is frequently assocated with neuroblastoma (NB). In order to improve the understanding of the underlying pathological mechanism and work towards a better neurological outcome, an international European collaborative group, consisting of SIOPEN (Société Internationale d'Oncologie Pédiatrique – Europe Neuroblastoma), GPOH (German Society of Pediatric Oncology and Hematology), and EPNS (European Pediatric Neurology Society) is working on a common protocol, to be opened shortly, aiming at common guidelines and collaboration for biological studies, oncological and neurological diagnostic procedures, and a common treatment proposition.

The planned study, entitled "Multinational European Trial for Children with the Opsoclonus Myoclonus Syndrome / Dancing Eye Syndrome", will include children (aged between 6 months and 8 years) with newly diagnosed OMS/DES, with or without neuroblastoma. Search for and staging of neuroblastoma must have been performed according to the guidelines of the study. The study proposes patient registration, sampling and storage of biological material, and immunosuppressive treatment: the first step will consist of a standard immunosuppressive treatment with monthly dexamethasone bolus (20 mg/m2 for 3 days, repeated at monthly intervals) for one year. In case of insufficient response after three months, immunosuppressive treatment will be increased and cyclophosphamide will be given (cyclophosphamide 750 mg/m2 at monthly intervals) for 6 cycles. In case of insufficient response despite this treatment, immunosuppressive treatment with dexamethasone and rituximab will then be given. Centers will be given the possibility to include patients during the first 3 months of the standard treatment using dexamethasone.

Primary endpoints of the study are to evaluate the response to treatment and the long term neuropsychological outcome of patients with OMS with or without NB.

Secondary endpoints are to determine the percentage of OMS-NBpos patients among all patients with OMS, the comparison of OMS-NBpos and OMS-NBneg in terms of presentation, severity and treatment response, the evaluation of the treatment burden and the evaluation of factors influencing long term outcome

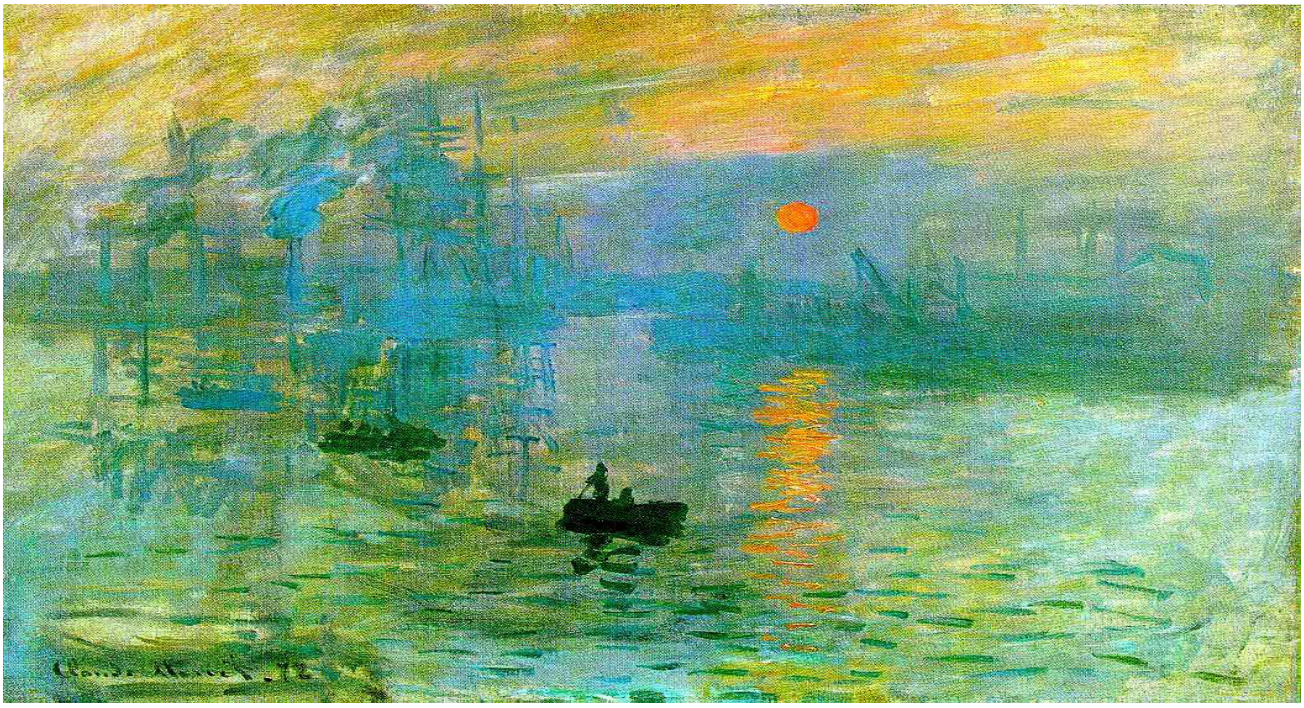
Further objectives are to develop a European multidisciplinary network of specialists in the treatment of patients with OMS/DES, to develop a European biomaterial bank and a Europe-wide collaboration of scientist interested in OMS/DES, to evaluate incidence of OMS/DES in Europe and per country, and to investigate the biology of OMS/DES.

The study protocol is now on version 26. There has been discussion to randomise between cyclophosphamide and rituximab but it was decided not to randomise as there is no epidemiological data and to keep the current statification stepwise according to the response

achieved by the respective treatment steps. (1st step steroid treatment, 2nd step cyclophosphamide, 3rd step Rituximab (plus supportive care with immunoglobulins)). The protocol and CRFs are to be completed in summer 2010.

On Monday 5th July 2010 there will be a working meeting in Vienna together with AIT, LINES and OMS study group members to produce the electronic CRFs for both studies based on the respective requirments and pre-existing electronic CRF modules.

Institut Curie will carry the international sponsorship. Currently, 14 countries have announced interest in participation. Contracts of delegation of responsibilities will be signed with Curie.



Committees' corner

Surgery

The group met last in Rome October 2009.

The group actively collaborates with the development of International. Treatment Protocols. This work particularly involves standardisation of operation strategies for each tumour type.
The outcome of all operations is recorded and all complications are examined carefully by the group. There is an active advice network for difficult patient problems.
The group works on the evaluation of surgical data and preparation of reports for publication.

Studies:
High risk HR-NBL-1/ESIOP
(analysis in October 2009 study remains open)
881 operations (800 in May 2009) - achieving 71% complete tumour excision. The complication rate is 10% in spite of operations of increasing complexity. There have been five deaths since the start of study.

Low risk LNESG1
The concept of Surgical Risk Factors (SRF) was developed based on images (CT MR) before operation. The presence of these factors predicted complete tumour removal and the risk of operation complication. (Published JCO 2005). SRF are incorporated in the International Neuroblastoma Risk Group (INRG).
The final draft of the paper has been submitted to the Publication Committee prior to submission to JCO. In summary both SRF and Operative Complication had an adverse effect of 5 year Relapse Free Survival.

LNESG2
This study opened in 2002 and develops the strategy of LNESG1.
The study is recruiting well and utilises the internet to allow real time International analysis of patient data.
Jean-Marc Joseph is leading for surgery.

Intermediate risk (unresectable localised)
This study ran from 2000 to 2008.
There are around 190 patients recruited and the comprehensive surgical and radiological data have been analysed By Riccardo Haupt and his colleagues.
Jan Kohler and Herve Rubie will lead on the oncology paper and Keith Holmes will lead on preparation of the surgical paper.

LINES
The surgery subcommittee is actively involved with the development of new studies for Infants and Intermediate Risk patients, led by Roly Squire and Sabine Sarnackie
This protocol is in the final stages of preparation and will incorporate the structure of the International Neuroblastoma Risk Group (INRG).

Keith Holmes
Chair - London, April 2010.

Nuclear Medicine

Val Lewington on behalf of the SIOPEN Nuclear Medicine Committee

The nuclear medicine Committee has made significant progress over the past year in raising the profile of the SIOPEN mIBG score method developed by its international team. Two interactive teaching symposia were held in London [May 2009] and Barcelona [October 2009], sponsored by educational grants from the charity Adam's Hats. Both meetings were well attended both by national representatives from SIOPEN participating centres and by senior opinion leaders from the wider paediatric nuclear medicine and oncology communities. Feedback was positive and we succeeded in attracting several new enthusiastic trainees and junior specialists who are keen to support the SIOPEN work package.

The SIOPEN score method was presented and well received at 3 major scientific conferences in 2009 [US Society of Nuclear Medicine Meeting, Toronto, SIOP Annual Conference, Sao Paulo and European Association of Nuclear Medicine Annual Congress, held in Barcelona].

Over the past six months, national representatives have been working hard to retrieve original mIBG image data from individual hospitals for central review. The committee is indebted to the IT team at CCRI, particularly Mr Marek Nykiel who has worked tirelessly to upload available scans for analysis. A further major effort will be required to maintain this momentum and ensure that remaining outstanding data are recovered and scored by the end of the year.

Key objectives for 2010 are, therefore, to complete the on-line mIBG scan review, submit the completed mIBG score method manuscript for peer review publication and to develop educational tools to raise standards of paediatric oncological nuclear medicine practice internationally. Funding will be required to support these activities, particularly to facilitate travel for young specialists to meet, learn, share expertise and develop new ideas.

Work has begun using the SIOPEN score method as a component of response evaluation in the MATIN study and the method will be applied prospectively in the forthcoming TOTEM trial. Invited reviews based on the work of the SIOPEN nuclear medicine group will be presented in 2010 at the World Nuclear Medicine Congress in Cape Town and at the International Cancer Imaging Society in Edinburgh. Both meetings will provide a useful platform to publicise the contribution of SIOPEN to oncology research and to highlight the success of building expert clinical networks to advance the management of rare cancers.

Having completed over three years as nuclear medicine Chair, I hope to hand over leadership of the committee in June, subject to Board approval. I am confident that we now have a strong, well motivated group who are committed to taking the project forward to its next stage and crucially, to exploring the potential of new radio-tracers for neuroblastoma diagnosis and treatment.

Biology

Toby Trahair (Australia), Inge Ambros (Austria), Frank Speleman, Nadine Van Roy (Belgium), Ales Vicha (Czech Republic), Jean Benard, Valérie Combaret, Jérome Couturier, Olivier Delattre, Gudrun Schleiermacher, Alexander Valent (France), Raymond L. Stallings (Ireland), Marta Jeison (Israel), Raffaella Defferrari, Katia Mazzocco, Gian Paolo Tonini (Italy), Klaus Beiske (Norway), Barbara Marques (Portugal), Nicole Gross (Switzerland), Rosa Noguera, Eva Villamón (Spain), Tommy Martinsson (Sweden), Clare Bedwell, Nick Bown, John Lunec, Deb Tweddle (UK), Peter F. Ambros (Austria, Chairman).

Challenge LINES Study
In order to be prepared to implement the information on the presence or absence of segmental aberrations for the decision-making process for patients enrolled within the LINES study in January 2010, three important aspects were discussed:
i) Necessity of clear-cut results for the stratification process
ii) Heterogeneity of the MYCN amplification (het MNA)
iii) Nomenclature of the MLPA/CGH-/SNP-array results

Ad i) a scenario was agreed upon what to do when a certain method does not give the adequate result. In case technique A yields an insufficient result – another technique will be applied and/or DNA to another reference laboratory will be sent to obtain another opinion.

Ad ii) clear-cut guidelines were developed as to how to handle tumours with het MNA. In addition, it was agreed to spend a separate meeting on this issue to work up all relevant cases from different genetic centres. All genetic information will be collected and discussed at this meeting. In order to learn about the clinical impact of het MNA tumours, it was also agreed to collect clinical data on these cases.

Ad iii) A nomenclature for MLPA/CGH-/SNP-array results was developed by the group which is now included in a manuscript on the inter-laboratory and inter-technique testing of different techniques to be used in neuroblastoma genetic diagnosis (I-FISH, array CGH and SNP arrays).

The SIOPEN Biology Speciality Committee came together once this year. We met on 21st -22nd, January 2010, at the Institut Curie, Paris, France. Main issues discussed in this meeting were: Biology update for: LINES Study, 2p gain Study, Unresectable Study, LNESGI and LNESGII, HR-NBL01 12–18 months; MLPA and arrayCGH inter-laboratory and inter-technique comparisons and nomenclature of MLPA results, miRNA predictors of response to chemotherapy in high risk patients.
The next meeting is planned for the 3. – 5. May 2010 at the CCRI in Vienna.

The SIOPEN Biology Group did send in three abstracts of their collaborative work at the forthcoming ANR Meeting in June 2010.

Segmental Chromosome Aberrations and Ploidy in Localized Neuroblastomas without MYCN Amplification – Report from the SIOP Europe Neuroblastoma (SIOPEN) Group on the LNESG I Trial
Ambros IM, Tonini GP, Couturier J, K. Beiske K, Benard J, Boavida M, Bown N, Caron H, Combaret V, Defferrari R, Gross N, Jeison M, Lunec J, Martinsson T, Mazzocco K, Noguera R, Valent A, Van Roy N, Amann G, Mosseri V, Ladenstein R, De Bernardi B, Michon J, Ambros PF.
The prognostic impact of segmental chromosome aberrations (SCA) and DNA content was assessed for 123 patients with stage 2A and 2B neuroblastoma without MYCN amplification. The patients were included in a multinational protocol

(the localized Neuroblastoma European Study Group trial 94.01, LNESG I, 1995-99) and were treated by surgery only. The neuroblastomas were analyzed by pan- and/or multigenomic techniques (array comparative genomic hybridization, aCGH; multiplex ligation-dependent probe amplification, MLPA), fluorescence in situ hybridization (FISH) and flow cytometry (FCM). Pan-/multigenomic data were available for 66 tumours, FISH for additional 40 tumours. All genetic data were quality controlled by the SIOPEN Biology Group. SCA have been found in 39.4% (FISH negative tumours excluded) being more frequently associated with near-di-/tetraploidy than with near-triploidy ($p<0.0009$). The most frequently affected loci were: 17q (18x), 1p/1q (11x) followed by 11q (4x). Relapse-free survival (RFS) was significantly related to 1p loss ($p<0.045$), whereas 17q gain had neither impact on RFS nor on overall survival (OS). OS was poorer in patients with diploid neuroblastomas, however with borderline significance ($p=0.53$). Moreover, while OS and RFS were significantly associated with SCA in patients over 1.5 years of age at diagnosis ($p<0.0015$ and $p<0.00035$, respectively), no such relationship was found for patients below 1.5 years ($p>0.28$ and $p>0.59$, respectively). Based on the analysis of this patient cohort, it is suspected that in neuroblastomas with normal MYCN status, SCA have a different clinical impact dependent on the age of the patient at diagnosis.

Segmental Chromosome Abnormalities and Age over 36 Months at Diagnosis are Associated with Increased Risk of Relapse in Localised Unresectable Neuroblastoma without MYCN Amplification - A Preliminary Report from the SIOP Europe Neuroblastoma (SIOPEN) Biology Group

Defferrari R, Mazzocco K, Ambros IM, Ambros PF, Bedwell C, Beiske K, Bénard J, Bown N, Castel V, Combaret V, Couturier J, De Bernardi B, Garaventa A, Haupt R, Kohler J, Ladenstein R, Lunec J, Marques B, Noguera R, Parodi S, Rubie H, Schleiermacher G, Speleman F, Valent A, Van Roy N, Villamon E and Tonini GP

Background/Aims: Recent reports suggest that segmental chromosome abnormalities (SCA) in neuroblastoma (NB) without MYCN gene amplification correlate with worse outcome. So far, no treatment modifications have been made for children with stage 2 and 3 disease over 1 year of age at diagnosis based on this information. The current study presents validated multigenomic data concerning the presence and the prognostic impact of SCA on a cohort of patients over one year with Localized Unresectable Neuroblastoma without MYCN amplification. Methods: Between January 2001 and October 2006, a total of 161 newly diagnosed children were enrolled in the SIOPEN Unresectable Neuroblastoma study (EUNB). Out of 161 tumors, 157 were analyzed by Interphase FISH (I-FISH) for MYCN amplification and 1p deletion, while Multiplex Ligation-dependent Probe Amplification (MLPA) and array-Comparative Genomic Hybridization (array-CGH) were performed on 56 and 38 tumors respectively. Genetic data were reviewed by members of the SIOPEN Biology Group. Results: One or more segmental chromosome abnormalities were detected in 49 (52%) tumors. Of the 7 recurrent chromosome aberrations (gain of 1q, 2p, 17q; loss of 1p, 3p, 4p, 11q), described in NB the most frequently observed were: 17q gain (33%), 11q loss (23%), 1p loss (22%) and 2p gain (12%). Compared to children at the age range 12-18 and 19-36 months, those>36 months showed the highest frequency of the number of SCA ($p=0.027$, Kruskal-Wallis test). In these patients the presence of at least one of these aberrations was associated with poor overall and progression free survival ($p=0.06$ and $p=0.043$, respectively). This effect was not evident in younger children. Conclusion of the study: In this cohort of patients with not MYCN amplified tumors, the presence of at least one SCA increased with age at diagnosis and was associated to poor overall and progression free survival only in children >36 months. Our data suggest that other chromosome abnormalities than MYCN could play an important role in tumor development and progression.

A MULTILOCUS TECHNIQUE FOR RISK EVALUATION OF PATIENTS WITH NEUROBLASTOMA

I.M. Ambros, B. Brunner, C. Bedwell, K. Beiske, J. Benard, N. Bown, V. Combaret, J. Couturier, R. Defferrari, N. Gross, M. Jeison, J. Lunec, B. Marques, T. Martinsson, K. Mazzocco, R. Noguera, G. Schleiermacher, F. Speleman, R. Stallings, G. Tonini, D.A. Tweddle, A. Valent, A. Vicha, N. Van Roy, E. Villamon, A. Ziegler, G. Schreier, G. Aigner, M. Drobics, R. Ladenstein, G. Amann, J. P. Schouten, U. Pötschger, P.F. Ambros

Background. Precise and comprehensive analysis of tumour genetics is essential for the most accurate risk evaluation and only pangenomic/multilocus approaches fulfil the present-day requirements. Here, we present the establishment of the multiplex ligation-dependent probe amplification technique (MLPA) for neuroblastoma.
Methods. A neuroblastoma specific MLPA kit was designed by the SIOPEN (SIOP Europe Neuroblastoma) Biology Committee in co-operation with MRC Holland. The kit used in this study contained target sequences for 106 genetic loci corresponding to 19 chromosomal arms and reference loci. The validation was performed by fluorescence in situ hybridization (FISH, n=125), BAC array (aCGH, n=39) and by SNP array (n=10). Dilution experiments for determination of minimal tumour cell percentage were performed as well as testing of reproducibility which was checked by inter-laboratory testing involving nine laboratories. Results. Inter-technique validation showed a high concordance rate (99.5%) as well as the inter-laboratory MLPA testing (kappa 0,95, $p<0.01$) with seven discrepant out of 1490 results (0.5%). Validation of MLPA results by SNP and aCGH showed a single discordance out of 190 consensus results (0.5%). The test results led to the formulation of interpretation standards and to a revision of the kit. The minimal amount of tumour cell content was fixed at 60% to detect segmental aberration, for detection of amplification, it can be lower.
Conclusions. The recently designed neuroblastoma specific MLPA kit not only covers the chromosomal regions demanded by the International Neuroblastoma Risk Group (INRG) for therapy stratification but also includes all hitherto described genetic loci of possible prognostic interest for future studies. Moreover, the technique turned out to be cost effective, reliable and robust with a high inter-laboratory and inter-technique concordance.

Immunotherapy

The treatment of stage 4 neuroblastoma with immunotherapy using anti-ganglioside GD2 antibody ch14.18 in combination with cytokines experienced a new momentum based on reports from COG trial ANBL0032. In this trial, the standard arm was closed in favour of ch14.18 in alternating combination with GMCSF and IL2.
Based on these findings, we decided to develop a protocol combining ch14.18 with IL2 aiming at a reduction in toxicity. The way to achieve this goal was to apply ch14.18 as a continuous infusion in combination with subcutaneous IL2 injections.
The incidence of neuropathic pain following ch14.18 infusion is dose dependent. Two lines of evidence support this contention.
First, the MTD of hu14.18-IL2, a genetically engineered antibody IL2 fusion protein, was reported to be 12 mg/m2, which is about half the amount of ch14.18 currently used (20 mg/m2). The dose limiting toxicities observed with hu14.18-IL2 were IL2 related. Pain was rarely observed as a side effect Second, it is well known that a decrease in the infusion rate of ch14.18 alleviates neuropathic pain.
As far as the application of IL2 is concerned, subcutaneous application of IL-2 (6 x 106 IU s.c. / day for 5 days) demonstrated a low toxicity profile.
Based on these considerations a combination of continuous infusion of increasing amounts of ch14.18/CHO in combination with subcutaneous application of IL-2 may synergize in anti-neuroblastoma activity with a toxicity profile acceptable to treat children in an outpatient setting.

Molecular Monitoring Group

Current Members:
Sue Burchill, United Kingdom (chair), Maria-Valeria Corrias, Italy (vice-chair), Sandro Dallorso, Italy, Bertil Kagedal, Sweden, xxxxx, Belgium, Andrei Tchirkov, France, Ales Vicha, Czech republic, Virginie Viprey, United-Kingdom (vice-chair)

Current Study Aims:
The minimal disease (MD) biological study in conjunction with the clinical trial HR-NBL1/ESIOP aims to determine the clinical significance of tumour cells detected by QRT-PCR for TH, DCX and Phox2B mRNA alone or in combination, in peripheral blood (PB), bone marrow (BM) and peripheral blood stem cell harvest (PBSC).

Interim Results:
A big thank you to Ulli Pötschger (SIOPEN, Vienna, Austria) for providing information on children entered into HR-NBL1/ESIOP that has made the interim analysis possible.

Quality control samples for the specific and sensitive detection of circulating neuroblastoma cells using QRT-PCR for all three markers (TH, Phox2B, and DCX mRNA) have been prepared and successfully tested by the participating European reference laboratories. Additional fields have been implemented into the SIOPEN-R-NET QRT-PCR database to allow incorporation of results from all three markers.
We have validated QRT-PCR results for TH and Phox2B mRNA at diagnosis and/or after induction chemotherapy from 341 patients across Europe (Italy, n=179; UK, n=108; France, n=19; Belgium, n=15; Czech Republic, n=13; Austria, n=4; Greece, n=2; Slovakia, n=1). These data are recorded, blinded on the SIOPEN database. End of induction therapy is a particularly interesting time to study minimal disease because at this point in treatment children may receive additional induction therapy prior to progression in the trial; if the presence of disease detected by QRT-PCR predicts disease course after induction therapy this may influence subsequent treatment and potentially outcome.

The SIOPEN board has recently approved the release of clinical information for correlation with QRT-PCR data, to allow an interim analysis and accurately inform how many more children we need to recruit into different stages of the biological study. The clinical data is currently being cleaned and updated prior to this analysis, which will be prepared for submission to the Advances in Neuroblastoma Research Meeting, Stockholm, 2010.

Quantitative PCR data showed that TH and Phox2B mRNA levels in BM at diagnosis vary greatly between patients, ranging from -3 to +5 (Log10 transformed values). After induction therapy, levels of mRNA detected are up to 6.7 Log10 values lower than at diagnosis in some patients (median Log10 reduction is 2.7). The clinical significance of differences in frequency and levels of TH and Phox2B mRNA detection are to be evaluated in the proposed interim analysis.

Countries entering children into Molecular Monitoring Group Studies

The following countries are actively collecting samples from children with neuroblastoma for studies of the SIOPEN Molecular Monitoring Committee: Austria, Czech Rebublic, Italy, France, Greece, Portugal, UK.
Thank you to the National Co-ordinators, clinicians, nurses, scientists, technicians, assistants, parents and children from these countries.
Children from Australia will soon be entered in to the studies; thank you to Dr Toby Trahair for making this possible.

Any other countries wishing to collect samples for this valuable clinical studies, please contact Professor Sue Burchill (s.a.burchill@leeds.ac.uk) or Dr Virginie Viprey (V.F.Viprey@leeds.ac.uk). We would welcome the opportunity to collaborate with you.

Future Studies of the SIOPEN Molecular Monitoring Group
The MMG continue to collect bone marrow, peripheral blood and peripheral blood stem cell harvests from children with neuroblastoma entered into HR-NBL1/ESIOP to

a. establish the clinical significance of disease detected by QRT-PCR in the BM compartment prior to treatment for minimal disease and at the end of therapy.
b. Compare the efficacy of minimal disease clearance from the BM when children treated with antiGD2 antibodies, 13 cis RA plus or minus IL-2.
c. Determine if the presence of disease detected by QRT-PCR for 3 markers (TH, PHoX2B, DCX) is more informative that the detection of disease using a single or two markers.
d. Determine if detection of disease in PB is as informative as detection of disease in BM.
e. Investigate the predictive and prognostic value of miRNA.

Meetings
The group last met on Tuesday 27th November 2009 in Rome, Italy.
We plan to meet again in Autumn 2010.

Thank you to all the people who are contributing to the success of these studies and to the funding bodies across Europe that continue to make our collaborative efforts possible.

Bone Marrow

During 2009, the members of the SIOPEN Bone Marrow SC continued to collect and analyse BM, PB and PBSC samples from patients enrolled into the HR study. Because of a number of reasons, among them lack of funding, delayed uploading of MD results into the SIOPEN data bank and unavailability of clinical data, our projects were temporarily deferred and no SC meeting was organized.

BM Data Base

As pointed out previously, any clinical study involving MD data depends on entering IC and/or FISH results into the data base. However, the burden of this work is unevenly distributed among the SC members as the national contributions vary greatly. This applies especially to our Italian colleagues, both because of the high number of patients from Italy and because MD analyses and review of pathological specimens are very well centralized on a few hands. In July 2009, I had the opportunity to visit the pathology department at the Gaslini Institute in Genoa where I met Angela Sementa and her enthusiastic co-workers. We reviewed a number of bone marrow specimens over a couple of days and trained the upload of results into the BM data bank.

An update of our data base at the end of December 2009 showed that MD results of 1.984 samples from 296 patients were entered. 1.634 samples from 205 patients had been analysed by light microscopic immunocytology (L-IC) and 350 samples from 81 patients by fluorescence immunocytology and FISH (AIPF). Moreover, 98 samples from 45 patients had been splitted and investigated by both L-IC and AIPF.

Clinical studies

The number of entries has further increased during the first half of 2010, but there is still a clear potential of improvement as we know about results which are not uploaded. Thus, we believe that the amount of MD data is now close to reach a level sufficient to design a clinical interim study which e.g. could look at the correlation between the number of tumour cells in the bone marrow before and after induction and patient survival. In order to retrieve relevant clinical information, we have for some time been in contact with the HR study coordinator and the CCRI statistician, but were asked to await the update of clinical data in the data base.

We have previously also discussed to compare the amount of BM disease in terms of numbers of infiltrating tumour cells to MIBG data in an attempt to identify appropriate response criteria. This project could neither be pushed forward because the number of patients fulfilling all criteria, i.e. uploaded MD data, updated clinical information, reviewable MIBG scans and a sufficiently long observation time was so far too small.

Future activities

As soon as the present update of the clinical data base is completed (hopefully July 2010) we are going to send to the data centre at the CCRI an updated list of patients who might be eligible for a clinical study due to a minimum number MD results and length of observation time. Depending on the number of patients whose files are clinically informative, we will try to organize a meeting of the Bone Marrow SC may be in October/November with the main goal of reviewing and quality controlling the samples of those patients who are eligible for our study. We will also try to pursue our collaboration with the NucMed SC and identify patients with quality controlled MD, MIBG and clinical data.

Klaus Beiske (on behalf of the SIOPEN Bone Marrow SC)

Pathology

Members: Amann Gabriele, Beiske Klaus, d'Amore Emanuele S.G., Cullinane Catherine, Gambini Claudio, Navarro Samuel, Peuchmaur Michel

In 2010, the Pathology SC members worked on guidelines for the review of tumour material from patients enrolled in the LINES protocol. These guidelines are summarized here:

Guidelines for the "real time" review process of tumours to be treated according to the forthcoming LINES protocol

If a child with a PNT is enrolled in the LINES protocol, please send the following to one of the members of the SIOPEN Pathology SC (names and addresses, see below) for review:

- One HE-stained section from each paraffin block
- In case of an undifferentiated tumour: 1 HE per block and either 1 paraffin block or 5 or 10 unstained sections (for immunohistochemical studies)
- Copy of the local pathology report
- Clinical information on catecholamines, site of tumour and MIBG data in order to ease the review process.

Note: The tumour cell content of the frozen specimen dedicated to biological studies will be analysed by the local pathologist.

Review process:

1. The local pathologists have to send slides and local pathological reports within 2 weeks after finalization of their report to the national member of the Pathology SC for review. The national Pathology SC member sends his/her review diagnosis within 4 weeks to the local pathologist, local paediatric oncologist and the national clinical coordinator
2. Review in real time means that it takes 3 to 6 weeks from the biopsy time point to complete the national review.
3. Names, address and function of local and national clinical coordinator of each participating country should be clearly identified and made available to the members of the SIOPEN Pathology SC.
4. The members of the SIOPEN Pathology SC agree to review cases from their own countries and cases from those countries which are not represented in the review panel. The local pathologists of countries not represented in the Pathology SC should be informed by their national clinical coordinator and the LINES clinical coordinator about the individual SC members' responsibility to review cases from:

G Amann: Austria + Czech Republic + Hungary
K Beiske: Scandinavian countries + Belgium + Greece
ES d'Amore and C Gambini: Italy + Serbia + Slovakia
C Cullinane: UK + Baltic countries + Ireland + Australia
S Navarro: Spain + Poland + Portugal
M Peuchmaur: France + Israel + Switzerland

To overcome possible difficulties caused by different languages in the local reports, the International Pathology Evaluation Form - including the International Neuroblastoma Pathology Classification and the grading of differentiation of the tumour - should be used by the local pathologists (see below: pathological assessment form and agreement form for local pathologist).

If a final review diagnosis cannot be established by the national responsible

SC member, he/she will send the case to another member of the Pathology SC in order to try to obtain a consensus on grading and classification.

Note: The time interval from the biopsy to the report of the consensus diagnosis must not exceed 12 weeks.

5. The members of the SIOPEN Pathology SC plan to organize 2 international meetings per year for the review and discussion of every case over a period of 2 working days per meeting. Such international review will be performed as a quality control system.

6. Addresses of responsible members of the SIOPEN Pathology SC:

- **Amann G.:**

Clinical Institute of Pathology
Medical University of Vienna, AKH
Waehringer Guertel 18-20
1090 Wien, Austria

- **Beiske K.:**

Department of Pathology
Oslo University Hospital Rikshospitalet
Sognsvannsveien 20
N-0027 Oslo, Norway

- **Cullinane C.:**

Department of Histopathology, Level 5, Bexley Wing,
St. James's University Hospital,
Beckett Street,
Leeds LS9 7TF, United Kingdom

- **d'Amore ES. :**

UO di Anatomia Patologica
Ospedale San Bortolo
Viale F. Rodolfi n.37
36100 Vicenza, Italy

- **Gambini C.:**

U.O. di Anatomia Patologica
Istituto G. Gaslini
Largo G. Gaslini 5
1648 Genova, Italy

- **Navarro S.:**

Departamento de Patologia
Facultad de Medicina AVDA
Blasco Ibanez 17 E-4610 Valencia, España

- **Peuchmaur M. :**

Service de Pathologie
APHP et Université Paris 7
Hôpital Robert Debré, 48 Boulevard Sérurier
75019 Paris, France

On behalf of the SIOPEN Pathology SC

Michel Peuchmaur

Meeting of the the SIOPEN Pathology Specialty Committee on May 27-29, 2010 in Genoa

The SIOPEN Pathology SC organized a 3-days combined SIOPEN/INPC meeting hosted by Dr. Claudio Gambini in Genoa on May 27-29, 2010. We are very grateful to Claudio who was able to raise funds and sponsor the meeting. All SIOPEN Pathology SC members joined the meeting. The combined meeting with the INPC was chaired by Dr. Hiro Shimada who also had invited Dr. Vijay Joshi and Dr. Jason Jarzembowski from USA.

A part of the first day was allocated to a separate meeting of the SIOPEN Pathology SC members. They discussed the further development of a digital imaging project which was designed to compare the diagnostic information provided by thru-cut biopsies to the information gained from sections of resected tumours or large surgical biopsies. The participants agreed to assess 345 biopsies for 20 histological criteria within the next two months. The individual results will be reviewed on a subsequent SC meeting which hopefully will take place in September before the data are analyzed by a statistician. If successful, this project might conclude with recommendations for minimal number and size of needle biopsies.

The SIOPEN SC members further discussed the proposal by Dr. Hiro Shimada to join the INPC. The SIOPEN pathologists thanked him for the invitation and agreed to participate in INPC efforts which aim to improve and adapt the classification to new insights into the biology of neuroblastoma. However, they reserved the right to review and publish independently all pathology data generated within European studies.

The two following days were set aside for the INPC meeting. Dr. Alberto Garaventa opened the meeting by presenting the ongoing LNESG2- and High Risk study, preliminary results from the closed EUNB study and the objectives of the future LINES study to the American participants. In context with the ”real time” pathology review of tumours to be treated according to the LINES protocol the SC members emphasized the importance of an efficient system of slide recruitment which largely will depend on the responsible clinical coordinators.
Most of the meeting time was spent on the slide review of about 120 cases which Dr. Shimada had brought from his files. Half of these cases belonged to the provisional entity of “composite” neuroblastoma comprising different histological features, while the others were cases characterized by genotype-phenotype discordances. The goal of the review was to test if experienced neuroblastoma pathologists would be able to identify sufficient histological criteria to discriminate these cases from conventional neuroblastoma. Unfortunately, time available was insufficient to complete the review which therefore will be continued at a separate meeting later this year.

Due to his retirement, Dr. Vijay Joshi, a most distinguished member of the INPC, joined the group for the last time. On behalf of the INPC, Dr. Shimada acknowledged his great contribution to the classification of neuroblastoma and thanked him for many years of fruitful collaboration.

On behalf of the SIOPEN Pathology SC

Klaus Beiske

Pharmacology

The SIOPEN Pharmacology Subcommittee was established with a remit to promote the design and instigation of European studies to learn more about the clinical pharmacology of agents used for the treatment of neuroblastoma. In this respect members of the group have participated in a number of collaborative projects and ongoing clinical studies in neuroblastoma and other paediatric cancers. These studies have utilised common protocols established by the group to ensure appropriate and standardised withdrawal, handling, storage and transport of blood samples for pharmacokinetic analysis. Members of the group met in Rome in October, 2009, to participate in a meeting in collaboration with the New Drug development Group and ITCC representatives, providing a forum for productive discussion relating to potential future studies.

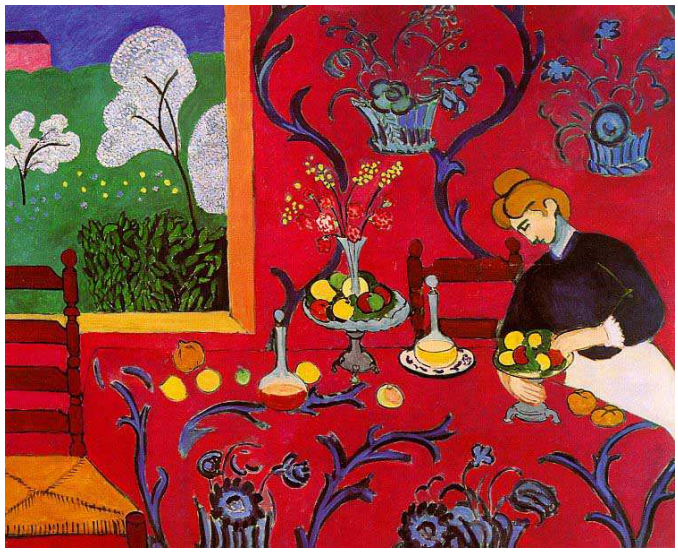
Since its initial founding, members have been involved in a number of studies and projects which are very much in line with the overall aims of the group. These activities include:

- Ongoing recruitment to clinical pharmacology studies associated with HR-NBL-1/ESIOP, investigating the pharmacokinetics of agents used in the high-dose myeloablative therapy treatment arm (BuMel and CEM). A total of over 80 patients have been recruited to the study to date, involving the collection and analysis of >700 clinical samples. Clinical data on patient characteristics, drug treatment, concomitant therapy and drug toxicity/adverse events, which will be essential for determining relationships between clinical parameters and drug pharmacokinetics, are being collected for all patients.
- Oral administration of busulphan has been replaced by the use of i.v. busulphan (Busilvex®) in the HR-NBL-1/ESIOP protocol. Clinical pharmacology studies are now ongoing to obtain Busilvex® pharmacokinetic data to compare with results obtained from patients who have received oral busulphan within the same study protocol.
- Clinical pharmacology studies incorporated into the HR-NBL-1/ESIOP protocol have been expanded to include pharmacokinetic and pharmacogenetic studies relating to treatment with 13-cis-retinoic acid following high-dose myeloablative therapy. Clinical samples for this study have been obtained from centres in both the UK and France.
- Results from a study designed to investigate the pharmacokinetics of etoposide and carboplatin in patients treated on the European Infant Neuroblastoma study (INES) have recently been published (Veal et al., Cancer Chemother Pharmacol 2010 65: 1057-1066). An additional CCLG/SFCE study to investigate the clinical pharmacology of a number of anticancer drugs in infants and very young children is now underway. This represents a patient population where very limited pharmacokinetic data exists and will generate data which may help to establish more appropriate dosage regimens for future treatment.
- Funding has been obtained for two European FP7 projects, involving partners in the UK, France, Germany and Italy. These studies are led by Professor Gilles Vassal and Professor Alan Boddy and will involve the recruitment of patients treated at centres in several European countries.

Over the past 5 years, we have made significant strides to achieving the long-term aims of the group. These aims include the future implementation of drug monitoring and adaptive dosing approaches to optimise the use of chemotherapy, with a view to improving the immediate tolerance, efficacy and long-term survival for children with neuroblastoma and other tumour types.

Radiotherapy

The Radiotherapy Committee met in Vienna last year with Marcus Hoermann from the Radiology Committee to review the data uploaded onto the SIOPEN-R-NET system for quality control assessment. Unfortunately, despite the excellent recruitment into the High-Risk study as a whole, the number of complete radiotherapy and radiology data sets is too few for meaningful results to be presented.



The Committee plans to meet again in the autumn, by which time we would like more data to be available for analysis. All national coordinators are requested to liaise with their radiology and radiotherapy teams to ensure that as many complete data sets are uploaded onto the specialty database sections. Of course not all of the >1000 patients registered will have data - some may, for one reason (for example early disease progression) or another (for example not having reached the timepoint for radiotherapy yet), have no data. Nonetheless even if data were entered on say one half of all patients in each centre, there would be enough information on the computerfor a very interesting analysis of protocol compliance in the first instance and its effect on outcome subsequently.

Please take this opportunity to ensure that the High-Risk study yields as much clinically relevant information as possible, in addition to answering the essential randomised questions.

Mark Gaze

Statistics

Jose D. Bermudez (ES), Riccardo Haupt (IT), David Machin (UK) Veronique Mosseri (FR), Caroline Munzer (FR), Ulrike Pötschger (AT), Keith Wheatley (UK)

As you all know, David Machin left us for his well-deserved retirement. The resignation of David has been a big loss to the SIOPEN statistical group. On both a professional and personal level, it was always a big pleasure working with him. He will be sorely missed.

On the other hand, we warmly welcome Keith Wheatley from the trial centre at the University of Birmingham. We are looking forward to his input and our future collaboration.

Aims

Our committee aims to contribute to biomedical science by providing expertise in the application and dissemination of statistical methods. In our function as study statisticians for various SIOPEN clinical trials, the focus was primarily on statistical issues in trial design, analysis, interpretation and decision making. This happens in close collaboration with the study committee.

The aim is to

1. assist clinicians and researchers of the SIOPEN with all issues related to statistical methodology from the design stage to the final publication of the results.
2. promote better understanding of the use and interpretation of biostatistics
3. promote high and harmonized standards of statistical practice
4. develop standards and be available to assist in the design of databases for research projects and clinical studies

Achievements 2009

Protocols in preparation

- The European low and intermediate risk Neuroblastoma study, LINES, will be launched soon. Veronique Mosseri and Jose Bermudez worked on the statistical design in their function as responsible study statisticians.
- Based on the results of the immunotherapy arm in the COG study ANBL0032, the HR-NBL 1/SIOPEN study has been amended with a completely revised randomised immunotherapy question. David Machin and Ulrike Pötschger worked on the statistical design of this new R2 randomisation.
- A phase II feasibility study using CH14.18/CHO antibody and subcutaneous Interleukin 2 after haploidentical stem cell transplantation has been launched recently. (responsible statistician: Ulrike Pötschger)

Ongoing studies

- The study progress of the ongoing trials LNESG2 and HR-NBL1/SIOPEN was summarized for the spring meeting in Villejuif and the AGM in Rome. A more comprehensive report including confidential information on outcome has been sent to the members of the data monitoring committees
- Based on the feedback from the DMC, which criticized data completeness of the HR-NBL1 study, a new comprehensive query system has been implemented. With the help of this system and repeated query rounds the study committee and the statistical committee hopes to improve data quality and completeness for the next study evaluation.

Closed studies.

- Members of the statistical subcommittee (Caroline Munzer, Bermudez Jose) were involved in the final analysis and publication of the INES studies.
- Within the HR-NBL1/SIOPEN study, the closed R0-randomisation (G-CSF question) was successfully published (statistical co-workers: David Machin, Ulrike Pötschger)
- The EUNB protocol is closed and we are in the process of retrieving the last missing data. A report was circulated among the protocol study members. At least 4 manuscripts are foreseen: The first will report the general clinical results; the other will focus on the surgical, pathologic, and biological aspects.

Collaborations with other sub-committees

In compliance with our aims, there are various links statistical subcommittee with other subcommittees. For example, there is an active collaboration between statisticians and members of the SIOPEN Biology group. Some subcommittees collaborate with statisticians outside the statistical subcommittee. For major research projects, involving data from clinical trials of SIOPEN, the statistical subcommittee invites these statisticians to get in contact with our committee or the study statistician, respectively.

International Neuroblastoma Risk Group (INRG) classification system

Veronique Mosseri and David Machin are members of the statistical committee of the INRG.

Aims 2010

- SIOP-EN plans a new phase I study using CH14.18/CHO antibody continuous infusion combined with subcutaneous interleukin 2. The statistical design of this study is pending
- The next DMC-report of the HR-NBL study will be prepared by the end of July. A feedback from the DMC is anticipated for the next study committee meeting in October 2010
- HR-NBL-1: The R1-randomisation (MAT-question) of the HR-NBL1 study is anticipated to reach it's final sample size by the end of this year
- HR-NBL-1: retinoic acid PK/PD analysis: a population pharmacokinetics model is carrying out to study the variability of PK parameters and the variability of concentration profiles of jointly 13-cisRA and its 4-oxo-13-cis metabolite.(Caroline Munzer is involved)
- To meet future challenges, harmonized standards of statistical practice and related issues are needed. We plan to 1) more formally define the way we work together as group and with other committees 2) define common approaches for all statistical issues related to statistical methodology (design, data-management, analysis, publication) of studies 3) to explore ways how data quality could be improved in SIOPEN studies.

Drug development

The SIOPEN-ITCC Drug Development Strategy is for there to be a pipeline of agents progressing through phase I studies (evaluating the toxicity profile and establishing the appropriate dose); phase II studies (determining efficacy) and relapse studies. The aim is that relapse studies will evaluate combinations in preparation for inclusion in front line phase III studies. Ideally there should be 3-5 Phase I studies and 2-3 Phase II - relapse studies to support this strategy.

The aim is for SIOPEN to work closely with ITCC in developing the portfolio of studies. ITCC is responsible for running Phase I and early Phase II studies in ITCC centres and SIOPEN is responsible for running late Phase II studies, relapse and Phase III studies.

A further aim is that these studies are coordinated with those being carried out by the Children Oncology's Group (COG) of North America.

A key concept is the establishment of "backbone" combinations, to which novel agents can be added in a randomised setting. The two potential "backbone" combinations are irinotecan and temozolomide and topotecan and temozolomide (TOTEM).

High priority targets include: - anti-angiogenesis; the PI3-kinase pathway (including PI3-kinase, mTOR and AKT); IGFR, MYCN and ALK.

The drug development strategy can be considered to have three themes:-

- Anti-angiogenics
- Chemotherapy Potentiation – chemotherapy and PARP
- Molecularly targeted therapy

Current Open Studies
Currently there is a Phase I study of an aurora kinase inhibitor (open in the UK) and a Phase II study of topotecan and temozolomide (TOTEM) (open in ITCC). A Phase I study of an IGFR inhibitor study will soon open in ITCC.

Future Relapse - Phase II studies
There are six potential Relapse - Phase II studies that are being considered by the SIOPEN Drug Development Group.

- Currently an important Phase I study of the combination of continuous intravenous infusion Ch 14.18 antibody over 10 days and subcutaneous IL2 is being evaluated. This study has been designed by Holge Lode and Ruth Ladenstein. Once completed a Phase II – relapsed study could be undertaken.

- A Phase I study of the combination of topotecan, vincristine and doxorubicin with Bortezomib is being prepared by Alberto Garaventa.

- A comparison of the two potential "backbone" combinations of irinotecan and temozolomide and topotecan and temozolomide (TOTEM). This could only be undertaken once the results of the current Phase II study of TOTEM in neuroblastoma are known.

- As neuroblastoma is an angiogenesis-dependent tumour and there is strong preclinical evidence suggesting that angiogenesis inhibition with several Receptor Tyrosine Kinase Inhibitors or monoclonal antibodies produces anti-tumour responses in vitro and in vivo, an anti- angiogenic approach is warranted. Consideration is being given to a randomised study of an anti-angiogenic added to a "back bone" of irinotecan and temozolomide in the first instance. This may be modified once the results of the current Phase II study of TOTEM in neuroblastoma are known.

- The Phase I Aurora kinase study is progressing well and consideration is being given whether this should progress to a phase II study.

- A Phase I study of an ALK inhibitor is ongoing in COG. Once completed the possibility of a Phase II study of an ALK inhibitor is being evaluated

Future Phase I studies
Agents that are being considered for Phase I studies include: - PI3K inhibitor: dual PI3K/mTOR inhibitor; IGF1R + mTOR inhibitor combination; PARP inhibitor and small molecule VEGFR inhibitor.

Newsreel: Charities Corner
A special thank-you

All members of the SIOPEN Association would like to thank all of the national charities for their support. Without their help our clinical trials would not be able to run as they do and we would not be able to bring the improvements in the treatment of neuroblastoma.

Particular mention in this newsletter goes to the

- **CCRI in Vienna** http://www.ccri.at/science/
- **Adam's Hats** http://www.adamshats.org/
- **The Italian Neuroblastoma, Association** http://www.neuroblastoma.org/
- **Israel Children Cancer Foundation** http://www.israelcancer.org/
- **The Cancer Research UK** http://www.cancerresearchuk.org/