SIOPEN

Newsletter #13
April 2011

Save the date
SIOPEN Board Meeting,
Oslo/Norway
April 28-29, 2011

Breaking News
BuMel significantly superior to CEM

Edited by Sara Calmanti
Institut Gustave Roussy, Villejuif, France

President's message

Dear friends and colleagues,

We hope you all had a great start this year.

I was happy to meet many of you during our successful Annual General Meeting in Porto, Portugal.

We were all very excited that the Data Monitoring Committee (DMC) of the High Risk Study decided to stop our high-dose regimen randomisation early. We learnt that the European approach with Busulfan / Melphalan had proved with high significance its superiority. We had very fruitful discussions and decided to amend the current High Risk Study accordingly. Because accrual is ongoing for the immunotherapy question, approval was given for a new randomised question on the induction regimen.

The results of the high-dose regimen randomisation were submitted as an abstract to ASCO 2011 which was accepted for oral presentation.

Particular warm thanks go to Ulrike our statistician not only for her great work in numerous DMC reports but also for her support in various abstracts and publications.

I express my warm thanks also to Gilles Vassal and Gareth Veal of the pharmacology Specialty Committee for having performed a very recent analysis on PK data of oral and intravenous Busulfan. We shall hear about the results in Oslo with the publication planned to follow soon thereafter.

Many of you have seen the amendment by now. Hopefully, we will receive feedback from our Austrian Ethics Committee prior to our upcoming Board Meeting in Oslo, Norway.

We had a very busy autumn and gained a new exciting experience asking for Scientific Advice at the European Medical Agency (EMA) in London, UK on how to take the antibody development forward. After a Letter of Intent was sent to EMA in August 2010 and the pre-submission meeting was held in September 2010 we ultimately submitted the final package in November 2010. EMA's Scientific Advice Working Party met at the beginning of December 2010. Finally, in January and February 2011 Holger Lode, Peppy Brock and I had two discussion meetings with EMA. The Scientific Advice in reply to all our questions was finally obtained in mid-February 2011 at the Scientific Advice Working Party meeting.

We are very thrilled that we found a new industrial partner interested in the antibody development. We shall give a further update on this in Oslo. Special thanks go to Ingrid Pribill who meticulously prepared all the documents needed to ask for Scientific Advice at EMA.

Peppy Brock's huge efforts and strong commitment have succeeded in obtaining a major funding for the production of a new antibody batch from the British government. We would like to take this opportunity to express our gratitude for Peppy's support and constructive involvement.

We are very proud that we were able to finalise the new long-term infusion study in collaboration with Holger Lode. This protocol already obtained the Ethics Committee and Competent Authority approvals in Austria and is well on its way in Austria.

At the Board Meeting in Porto, Portugal we welcomed Godfrey Chan from Hong Kong. Godfrey presented an overview on the social medical system and the neuroblastoma activities of his group in Hong Kong. All board members were equally happy to welcome Godfrey for future collaboration. To finalise the official membership application process the site visit will most probably take place in August 2011.
Godrey reported on Singapore's and Taiwan's interest to join the SIOPEN group as well.

Kim Vettenranta from Finland also joined us for the meeting. We are more than happy that on this occasion Kim announced Finland's willingness to join the SIOPEN Association as a member.
Meanwhile Vassilios Papadakis, SIOPEN's new country coordinator, received Finland's completed application forms for final approval by the SIOPEN Executive Committee.

The applications for becoming a member of the SIOPEN Association are flourishing. The number of members is continuously increasing and in due proportion to the size of the respective countries. It is a great pleasure for us to see that the SIOPEN group is constantly growing. Further informative advertising in your country is very much appreciated.

We are very happy to see LINES in its final preparations for opening internationally. The LINES protocol was heard at the meeting of the Spanish Ethics Committee in March 2011. The LINES database is in the final stages of development and it is expected to "go-live" at the beginning of May. Adela Cañete will provide a further update in Oslo.

The preparation of OMS also reached its final stage and is ready to be taken on by AIT to work on the database issues. We are equally excited to see the study online after many years of discussions.

Also our Specialty Committees have been very active over the last couple of months. The NucMed Specialty Committee under the leadership of Val Lewington and Ariane Boubaker made a major effort and scored online the uploaded mIBG scans of the High Risk Study. The result of these efforts was to generate an exciting abstract. We submitted this abstract to ASCO 2011 and it was accepted for oral presentation.

Mark Gaze and his colleagues of the radiotherapy Specialty Committee had a review meeting in Vienna in February 2011. Underlining the importance of reviewing radiotherapy data the results of this review meeting will be presented at the congress of the Paediatric Radiation Oncology Society (PROS) which will be held in Venice, Italy in June this year.

We would like to express our gratitude also to Peter Ambros and his colleagues of the SIOPEN tumour biology Specialty Committee for their fantastic work and input. Important results of his work were published in his manuscript "A Multilocus Technique for Risk Evaluation of Patients with Neuroblastoma" Clin Cancer Res. 2011 Feb 15;17(4):792-804.

I am very glad that our Specialty Committees founded on the occasion of the establishment of SIOPEN-R-NET are still active and highly motivated. So my special thanks also go to:

- Ulrike Pötschger for her brilliant statistical support,
- Sue Burchill and Sandro Dallorso for molecular monitoring and the news they brought at last ANR meeting,
- Keith Holmes for waving the flag for surgery and convincing us that attempted complete surgery is worthwhile and well performed on the European level,
- Holger Lode for his support in the manifold immunotherapy questions we had over the many years and his innovative ideas,
- Klaus Beiske as our special contact point to Michel Peuchmaur and Emanuele D'Amore for pathology and keeping reviews alive not only in the field of pathology but also for his ongoing interest in bone marrow evaluation,
- Marcus Hörmann for radiology support and being present at our meetings to help in particular in the difficult case discussions
- and Andy Pearson for the initiation of the phase I/II consortium.

Last but not least I would like to report on the very successful ENCCA kick-off meeting. The launch with all ENCCA partners took place in the EU hub Brussels in January 2011. We are very happy with the successful launch of the ENCCA Network of Excellence (the EU FP7-funded project ENCCA European Network for Cancer research in Children and Adolescents) that will undoubtedly pave the way for an improved environment for the European paediatric haemato-oncology field. This project is viewed as a major initiative that spans the entire paediatric oncology spectrum, from basic and translational research areas to drug development aspects integrating data from clinical trials, fostering clinical trial platforms, improving registry data, long-term follow-up and survivorship needs. It is our pride and joy that many key players of the SIOPEN group are involved in the various interesting work packages of the ENCCA project. For more information please visit the SIOP Europe website www.siope.eu.

Having said this I would like to thank you all for your excellent support throughout my 4-year presidency of the SIOPEN Association. I very much appreciate your enthusiasm and team spirit. Most proud of our superb achievements I pass on the baton to Peppy, our next SIOPEN president and wish her all the best for this exciting position.

Ruth Ladenstein

Report from the treasurer

Our common efforts to financially support the SIOPEN association activities have been very successful.

It was a bit of a struggle to begin with but eventually almost all countries have succeeded in getting the necessary funds and contributed in due time to our common account. This will allow us to maintain the database, hire part time secretary to run the association issues, continue the high risk study and support the opening of the new studies to come.

The contributions for 2010 are due by December 15 2010, and as had been decided upon during our last board meeting, we will be asking for the same annual contribution for 2011.

On behalf of the executive committee and are chairman I would like to thank all national representatives for their cooperation.

Isaac Yaniv MD
SIOPEN Treasurer

News summary from the OPORTO meeting

Introducing a future new collaborator: Prof. Chan from Hong Kong

Population of 7 Mio with a children's population < 15y of 1.1 Mio. There is important immigration of richer people from China. The social medical system allows 99% of children go to public hospitals for cancer treatment. The patients are concentrated in 2 university hospitals. There are 5-8 pts with neuroblastoma per year. For early stage NBL the POG protocol has been used with 100% survival of stage 1 and 2 pts . Major problem is overtreatment of early stage neuroblastoma. High-risk pts are treated according to MSKCC (modified N7). Antibody used since 1999. Which one? – to be clarified. Pts with persistent disease go to topo/cyclo or MIBG. 1y maintenance with retinoic acid one week on/off. Better results with antibody. Same side effects have been observed as per COG. For other disease, there is a participation in BFM, SIOP and EWS protocols,. Singapour and Taiwan would also like to participate. Both have the same social medical system and have treatment available. Prof. Chan's basic research is on interaction between stroma and NB cells. He concludes that there are many things to be shared.

SIOPEN-R-NET data base issues

Update of web-system is planned for in August 2010 and a preparation for upcoming new trials. Forms have improved. There is user support. New user accounts. Support for membership site. Support of radiotherapists training on the system in London. Preparation for upcoming LINES-trial. Update of biology review with next update. LINES will be launched by the end of January 2011. Interlink of user account, messages, biology actions, ev pathology (does not mean that biology data will be available to everyone – idea that conclusion will be linked to the clinical site for use). On-going trials supported.

Plans to move high-risk study to higher platform. Will be discussed at another moment. Aim to improve the data for the rest of the current study without losing the data.

Training for data managers needed for the new system? Apparently not as the new system will be improved. Otherwise possibility of organizing an on-line training. Parallel training session could be organized for autumn meeting.

Tumor banking strategies

Virtual bank containing information on where material is stored. Contributing specialties: pathology, biology, bone marrow, molecular monitoring

Material: paraffin blocks, frozen material, cytological specimens (imprints, FNAC). Extracted DNA, RNA. Stem cell products, frozen BM BM cell suspensions.

Procedure: SCs perform analyses of tumor according to SOPs; SC members upload results into group specific SIOPEN data-bank: results, information on sample date, type, amount, tumor cell content, quality of extracted RNA/DNA

Data saving: in a pre-existing, web-based, password-protected and ethically approved clinical data bank; but design of specific pages

Access to data bank: written research application, approved by involved SIOPEN specialty committees; local ethic committee, funding organizations; will got SIOPEN Research Committee for final approval.

Luigi: interphase needed with ENCA and European Virtual Institute of pediatric oncology, with new biobanks, local biobanks. BBMRI: inventory of existing biobanks in first phase; in second phase connect the biobanks in between them. Necessity to separate the biological resource center (where material is kept) from expert center. Expert center will take care of issues such as contact with companies, data sharing. Biobank is a center of excellence for future. Short term goals: definition of SIOPEN biobank; legal entity of resources centers and expert centers; legal and ethical issues; inventory; network of SIOPEN with other NB biobanks; interface with ENCA, BBMRI; fund raising

ENCCA European Network for Cancer research in children and adolescents

7th frame program: EC contribution of 12 Mio Euros for organizing the network. Harmonized therapies, strategies, improve quality of life, decrease side effects, effective joint training etc. K.Pritchard-Jones, Gilles Vassal, Martin Schrappe and Ruth Ladenstein very active. Important support by company Alma. Definition of working packages. One of major efforts to make it understand why there are so many different partners. Scientific advisory committee, ethics advisory committee, parents advocacy committee, European Clinical Research Council. Start up meeting for ENCCA meeting in January. Yearly lobbying in the European Parliament will be organized on the day of pediatric cancer in February. Joint research activities: Martin Schrappe; Integrating activities: K. Pritchard-Jones; Spread of excellence: Gilles Vassal; Project coordinator and net work of excellence manager: Ruth Ladenstein. New innovative strategies for small patient numbers etc by Maria Valsecchi.

HR-NBL-1

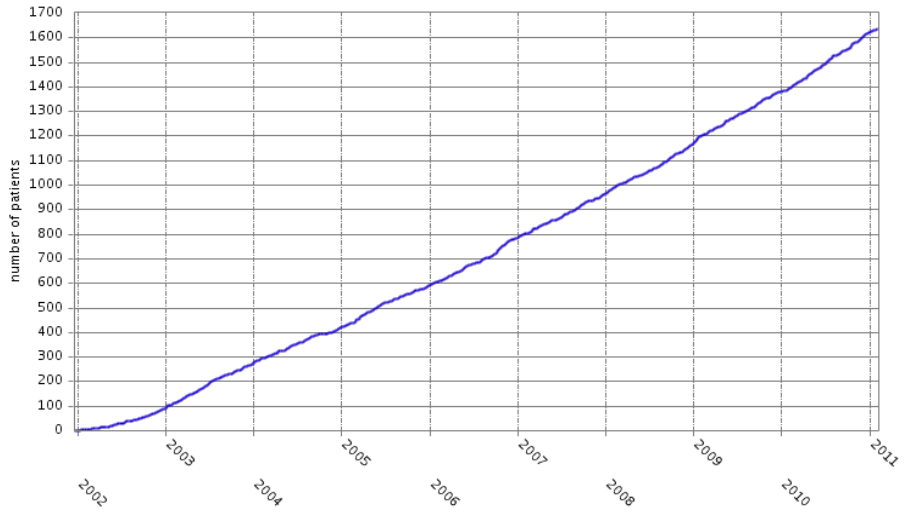
High Risk Neuroblastoma Study

Ruth Ladenstein

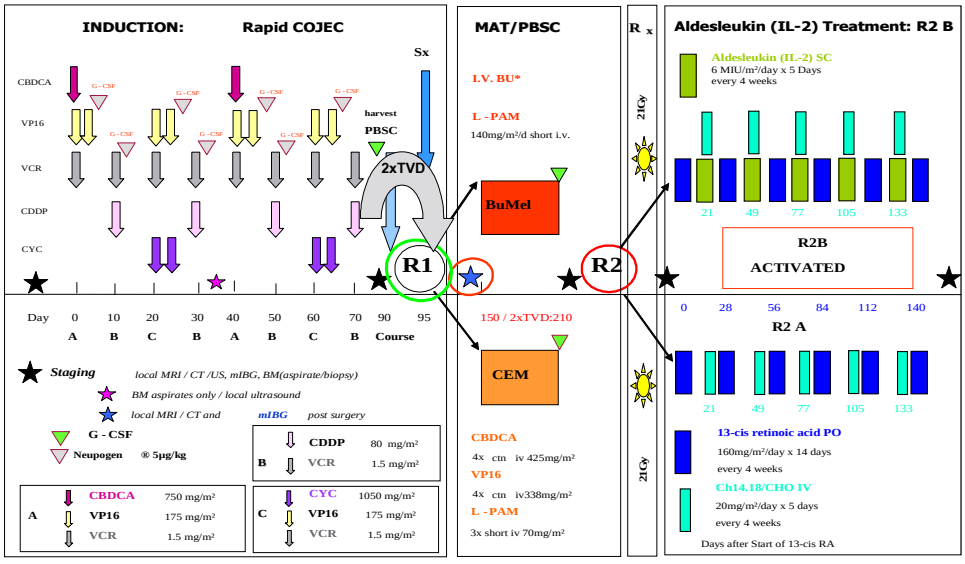
Recruitment

The high-risk neuroblastoma trial is recruiting well and as of 01.04.2011 has reached a total of 1637 patients.

Accrual Graph (2011/04/01)



HR-NBL-1 / SIOPEN FLOWSHEET



R0 Randomisation

The R0 supportive care question is answered and the article has recently been published in the Journal of Clinical Oncology. All patients now receive G-CSF during induction.

Ladenstein R, Valteau-Couanet D, Brock P, Yaniv I, Castel V, Laureys G, et al. Randomized Trial of prophylactic granulocyte colony-stimulating factor during rapid COJEC induction in pediatic patients with high-risk neuroblastoma: the European HR-NBL-1/SIOPEN study. J Clin Oncol. 2010 Jul 20;28(21):3516-24

Accrual numbers by country (2011/04/01)

Hint: The table can be sorted by selecting the corresponding table header.

Country	Patients registered ▼	Randomised patients			
		R0	R1	R2	R2 A4
National Data Centre UK for HRNBL1	355	65	95	44	44
National Data Centre FR for HRNBL1	344	46	117	23	23
National Data Centre IT for HRNBL1	316	1	126	32	14
National Data Centre ES for HRNBL1	185	17	64	9	9
National Data Centre IL for HRNBL1	81	27	30	11	8
National Data Centre AT for HRNBL1	60	25	33	16	3
National Data Centre PL for HRNBL1	58	2	20	0	0
National Data Centre BE for HRNBL1	52	16	22	6	6
National Data Centre CZ for HRNBL1	35	9	22	0	0
National Data Centre SE for HRNBL1	33	5	17	0	0
National Data Centre GR for HRNBL1	33	8	23	1	0
National Data Centre NO for HRNBL1	22	6	12	0	0
National Data Centre DK for HRNBL1	17	0	7	0	0
National Data Centre PT for HRNBL1	15	7	3	0	0
National Data Centre SK for HRNBL1	13	1	3	1	0
National Data Centre HU for HRNBL1	10	3	2	0	0
National Data Centre CH for HRNBL1	4	1	1	0	0
National Data Centre AU for HRNBL1	4	0	1	1	1
Totals:	**1637**	**239**	**598**	**144**	**108**

R1 Randomisation

A major European breakthrough was achieved in October 2010 when the DMC advised that the R1 randomisation MAT-question be stopped early.

At randomisation closure, 1577 high risk neuroblastoma patients (944 males) had been included since 2002; with INSS stage 4 disease (1369 pts) > 1 year, infants (65 pts) and stage 2&3 (143 pts) of any age with MYCN amplification.

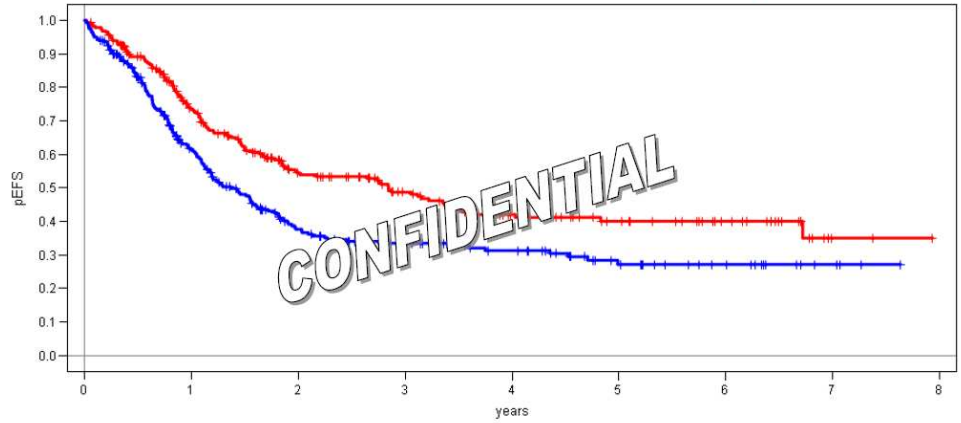
Response eligibility criteria prior to randomisation after Rapid COJEC Induction (J Clin Oncol, 2010) ± 2 courses of TVD (Cancer, 2003) included complete bone marrow remission and ≤ 3, but improved, mIBG positive spots. The MAT regimens were BuMel (oral busulfan till 2006, 4x150mg/m^2 in 4 equal doses, or after 2006 intravenous use according to body weight and melphalan 140mg/m^2/day) and CEM (carboplatin ctn. infusion (4xAUC 4.1mg/ml.min/day), etoposide ctn. infusion (4x338mg/m^2day or 4x200mg/m^2/day*), melphalan (3x70mg/m^2/day or 3x60mg/m^2/day*. *reduced if GFR<100ml/min/1.73m^2)). A minimum of 3x10E6 CD34/kgBW PBSC were requested. VOD prophylaxis included ursadiol, but not prophylactic defibrotide. Local control included surgery and radiotherapy of 21 Gy. A total of 598 patients were randomised (296 BuMel, 302 CEM). The median age at randomisation was 3 years (1-17.2) with a median follow up of 3 years.

At the last analysis, the Peto rule of p<0.001 was met. A significant difference in EFS in favour of BuMel (3-years EFS 49% vs. 33%) was observed as well as for overall survival (3-years OS 60% vs. 48%, p=0.004). This difference was mainly related to the relapse and progression incidence, which was significantly (p<0.001) lower with BuMel (48% vs. 60%). The severe toxicity rate up to day 100 (ICU and toxic deaths) was below 10%, but was significantly higher for CEM (p=0.014). The acute toxic death rate was 3% for BuMel and 5% for CEM (NS). The acute MAT toxicity profile favours the BuMel regimen in spite of a total VOD incidence of 18% (grade 3:5%). Based on these results and following advice from the DMC, the randomisation was closed early.

Hence, BuMel was demonstrated to be superior to CEM and is now recommended as standard treatment.

EFS by randomised arm after MAT

Survivors are censored at the last follow up



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

R2 Randomisation

The amended version of the R2 randomisation (July 2009) takes the standard isotretinoin (13-cis-RA) maintenance regime as a backbone and compares the addition of the following:

Arm A: ch14.18/CHO

Arm B: ch14.18/CHO and subcutaneous aldesleukin (IL-2)

As of 01.04.2011 a total of 108 patients have been randomised in 8 countries according to the amended R2 randomisation. Countries that have opened the amended R2 randomisation are: Australia, Austria, Belgium, Denmark, France, Ireland, Israel, Italy, Norway, Spain and the United Kingdom.

LNESG2

Guidedlines for the treatment of patients with localized resectable neuroblastoma and analysis of prognostic factors

Maja Beck Popovic

Since April 2005, 289 patients have been accrued in the LNESG2 protocol : 68.5% INSS stage 1, 29% INSS stage 2 and 2.5% INSS stage 3. An important effort has been done to improve data collection which resulted in much better data completeness : 100% for LDH, 82% for MIBG, 82% for IDRF, 88% for surgery, 88% for surgical complications and 84% for pathology. Data are still incomplete for surgical outcome (31%) and INPC (69%). The number of relapses has remained stable with 16 cases on the whole. At this point future tasks have been defined as follows :

1. data chasing for surgical outcome and INPC
2. analysis of the relapsed cases :
   a. Review of preoperative imaging with IDRF by panel of surgeons and radiologists in Lausanne (to be planned for spring)
   b. Review MIBG and Tc scintigraphy with members of Nuclear Medicine Subcommittee
   c. Complete entering of biology data (members of biology subcommittee)
   d. Complete pathology and INPC data (members of pathology subcommittee)

LNESG2 will remain open for patient accrual until the activation of LINES. L1 INSS stage 1 *MYCN* amplified patients will then be moved to intermediate risk group of LINES. There is an interest to keep LNESG2 for a small subgroup of patient , the L1 INSS stage 1 *MYCN* negative patients and stage 2 operated patients , in order to record their outome in a simplified data base.

Maja Beck Popovic, Lausanne, October 22nd 2010

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).*

The SIOPEN Biology Speciality Committee came together twice in 2010: we met on 21st – 22nd, January 2010, at the Institut Curie, Paris, France and on the 3. – 5. May 2010 at the CCRI in Vienna.
Main issues discussed in these 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. We plan to meet again in Paris, Institut Curie on the 7. – 8. February 2011.

Our manuscript: 'A MULTILOCUS TECHNIQUE FOR RISK EVALUATION OF PATIENTS WITH NEUROBLASTOMA' was accepted in Clinical Cancer Research.

Inge M. Ambros[1)], Bettina Brunner[1)], Gerhard Aigner[2)], Clare Bedwell[3)], Klaus Beiske[4)], Jean Benard[5)], Nick Bown[3)], Valerie Combaret[6)], Jerome Couturier[7)], Raffaella Defferrari[8)], Nicole Gross[9)], Marta Jeison[10)], John Lunec[11)], Barbara Marques[12)], Tommy Martinsson[13)], Katia Mazzocco[8)], Rosa Noguera[14)], Gudrun Schleiermacher[15)], Frank Speleman[16)], Ray Stallings[17)], Gian Paolo Tonini[8)], Deborah A. Tweddle[18)], Alexander Valent[5)], Ales Vicha[19)], Nadine Van Roy[16)], Eva Villamon[14)], Andrea Ziegler[1)], Sandra Preuner[1)], Mario Drobics[2)], Ruth Ladenstein[20)], Gabriele Amann[21)], Robert J.L. Schuit[22)], Ulrike Pötschger[1)], Peter F. Ambros[1)]

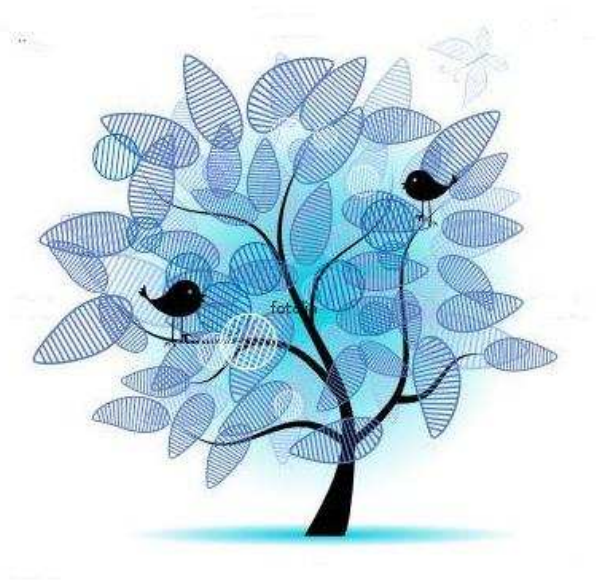
Statement of Translational Relevance:
Consensus exists in the International Neuroblastoma Risk Group (INRG) to use a series of tumor genomic features for risk evaluation. Increasing attention is now focused on utilizing pangenomic or multilocus datasets to better assign patients to certain genetic risk groups and also to discover new regions of interest exploring their potential clinical impact. So far, molecular-genetic investigations for routine diagnosis have been almost exclusively performed by FISH, PCR and flow cytometric analysis. The INRG Biology Committee suggests studying the prognostic impact of at least ten genomic changes in neuroblastoma. Consensus also exists on the use of commercialized platforms. We present a neuroblastoma specific MLPA kit fulfilling all these requirements including inter-laboratory and inter-technique validation as well as interpretation guidelines.

ABSTRACT
Purpose: Precise and comprehensive analysis of neuroblastoma genetics is essential for accurate risk evaluation and only pangenomic/multilocus approaches fulfill the present-day requirements. We present the establishment and validation of the PCR-based MLPA (multiplex ligation-dependent probe amplification) technique for neuroblastoma.
Experimental Design: A neuroblastoma specific MLPA kit was designed by the SIOP Europe Neuroblastoma Biology Committee in co-operation with MRC-Holland. The contained target sequences cover 19 chromosomal arms and reference loci. Validation was performed by single locus and pangenomic techniques (n=174). Dilution experiments for determination of minimal tumor cell percentage were performed and testing of reproducibility was checked by inter-laboratory testing (n=15). Further 156 neuroblastomas were used for establishing the amplification cut-off level.
Results: The MLPA technique was tested in 310 neuroblastomas and 8 neuroblastoma cell lines (including validation and amplification cut-off level testing). Inter-technique validation showed a high concordance rate (99.5%). Inter-laboratory MLPA testing (kappa 0.95, $p<0.01$) revealed seven discrepant of 1490 results (0.5%). Validation by pangenomic techniques showed a single discordance of 190 consensus results (0.5%). The test results led to formulation of interpretation standards and to a kit revision. The minimal tumor cell percentage was fixed at 60%.
Conclusions: The recently designed neuroblastoma specific MLPA kit covers all chromosomal regions demanded by the International Neuroblastoma Risk Group for therapy stratification and includes all hitherto described genetic loci of prognostic interest for future studies and can be modified or extended at any time. Moreover, the technique is cost effective, reliable and robust with a high inter-laboratory and inter-technique concordance.

Nuclear Medicine

Ariane Boubaker on behalf of the SIOPEN Nuclear Medicine Committee

The nuclear medicine Committee under the leadership of Val Lewington has been keeping his efforts in trying to have more scans uploaded into the SIOPEN-R-NET online scoring system. Great work has been achieved in using the new scoring method that appears to be a strong predictor for response and survival. This new method is very easy and appears to be robust and reproducible.
So far out of a total of 1465 (34%) included children, 474 (34%) pre- and post-therapeutic mIBG scintigraphies are available for on-line scoring. A first evaluation has been done by Val Lewington who scored 200 pre- and post-therapeutic scans from the UK children included in the HR-NBL-1 study. We are now going on with this project and aim to score more than 250 children examined in Austria, Belgium, Czech Republic, France, Spain, Italy, Denmark, Israel, Norway and Portugal. The goal is to submit an abstract for the annual meeting of the American Society for Clinical Oncology.
The retrieval and review of nuclear medicine imaging data from all participating SIOPEN Centres remains a major challenge. The committee continues to take a strong lead in building a network of expert reporters in Europe. Meetings dedicated to the role of nuclear medicine in the SIOPEN projects will be organised during the annual congress of the EANM.
Future perspectives remain to assess the role of FDG PET for staging and response evaluation particularly



in those children who are mIBG negative at diagnosis, and to further develop targeted radiotherapy.
I wish you all the best for 2011!

Radiotherapy

The main work of the radiotherapy committee has been to work on quality assurance for external beam radiotherapy.

In the high risk study, we have developed a system using the SIOPEN database, which has recently been published:

Mark N. Gaze, Tom Boterberg, Karin Dieckmann, Jean-Louis Habrand, Sylvie Helfr, Nili Peylan-Ramu, Elzbieta Korab Chrzanowska, Gnter Schreier, Ruth Ladenstein. Development of an electronic database for quality assurance of radiotherapy in the International Society of Paediatric Oncology (Europe) high risk neuroblastoma study. Radiotherapy and Oncology 97 (2010) 593595.

The main problem we have encountered is that although the database exists, not many clinicians have been using it routinely to store data. For quality assurance, we need not only radiotherapy data but also radiology images. We have tried to overcome this by raising awareness through the medium of this newsletter, at SIOPEN meetings, with the article in radiotherapy and oncology, and with a national training day in the UK for clinical oncologists and therapy radiographers, which was attended by Tom Boterberg, Mario Drobics and Peppy Brock.

The Committee is meeting again in Vienna on 18/19 February, so please ensure that the radiotherapy and radiology data for your patients are on the system for us to look at.

For the LINES study, we propose prospective review of radiotherapy plans before treatment starts. By doing it in this way, we hope that any suggested changes to the plan can be implemented. We have recommended that the necessary data are sent on CD to the Study Centre in Valencia for uploading, as we have demonstrated that it is not easy for centres to do this by remote data entry. Prospective review should result in data on a greater proportion of patients being collected. Also, by doing this in real-time rather than retrospectively, it will be changed from an academic exercise to one of potential benefit for patients.

Mark Gaze

Surgery

The group met last in Porto October 2010.

- 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 2010 study remains open)

938 operation data sets (881 in Oct 2010) - achieving 75% complete tumour excision. The overall complication rate is 9%. There have been six deaths since the start of study.

SIOPEN approved an interim analysis of outcome in relation to surgery.

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 is complete and will be submitted for publication. 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 will lead a multidisciplinary panel to validate imaging decisions.

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.

The final draft of this paper is nearing completion.

The surgery subcommittee will consider whether a separate 'surgery' paper is justified but much of the surgery data will be covered in the main 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, January 2011.

Newsreel: Charities Corner

SIOPEN AGM 6-8 October 2010 Porto, Portugal

Charities Meeting 8 Oct

Attending charities:
Acreditar (Portugal)
Fundacao Rui Osorio de Castro (Portugal)
Associacao Ines Botelho (Portugal)
Neuroblastoma Society (UK)
Adam's Hats (UK)

Attending SIOPEN Board members:
Ana Lacerda (Portugal), Mark Gaze (UK)

Chairing the meeting, Susan Hay (Adam's Hats) welcomed the attendees and put forward a scope for the meeting:

A each charity would make a brief presentation of its history and work, and its thoughts on how we might collaborate to support the work of SIOPEN

B we could then explore common interests around the themes of

- promoting research
- providing information for families
- facilitating better treatment
- other ways of supporting children with nbl and their families
- fundraising for SIOPEN

C hopefully, this would enable us to reach a clearer understanding of the role of charities for SIOPEN, which Susan would report to the final round up session of the AGM on Friday.

Each attendee introduced their charity and its work.

Neuroblastoma Society

Steve Smith, Chairman: The Society currently had c500 members who help to raise funds for bi-annual research grant cycle. The recent round resulted in E700 thousand being awarded. The Society produces a Newsletter, which attempts to remind readers of the human side of nbl, through relating families' stories and providing information on new developments in treatment. Advocacy has not traditionally been part of the Society's activities.
www.nsoc.co.uk

Associacao Ines Botelho
Isabel Botelho, founder of the charity, (presentation attached), explained that the charity's primary focus at the moment, was to encourage bone marrow donation. To this end, the Association has been inspired by the results the leukaemia sector has achieved, and works closely with the City Council in Lisbon.
www.**associacaoinesbotelho**.pt

Acreditar
The charity was represented by staff and parents closely involved with, and who founded the 17 year old charity, whose remit covers children with all types of cancer. The charity works country-wide, and develops 'foster homes' adjacent to hospitals and offers financial support to families whilst their child is in treatment. The local authority nominates families for support from Acreditar, which raises funds largely from private institutions. It relies on volunteers to support families., many of whom have been patients or parents of patients themselves. The charity is particularly interested in advocating for better services for 12-18 year olds.
www.**acreditar**.org.pt

Fundacao Rui Osorio de Castro
Marianna Oliveira explained that the charity's main function is to provide an internet portal for parents, children and oncologists to share information and promote clinical trials to increase research into all children's cancers. Collaboration with other organizations is critical to the quality and reach of the information

provided and in particular, the fun days and activities offered to young people.
www.fund-**ruiosoriodecastro**.org

Adam's Hats
Susan Hay, Chairman, I the essence of time, will circulate her presentation on Adam's Hats with the notes of this meeting.
www.adamshats.org

Ana Lacerda commented that she saw this meeting as a way of bringing charities together in the SIOPEN host country to explain SIOPEN's financial needs and to clarify how SIOPEN's work benefits the children of that country. This is a reciprocal arrangement between oncologists and charities, and Ana agreed to prepare a paper about SIOPEN work that charities can use when talking with sponsors and hospital heads, and others.

Mark Gaze hoped that charities would see themselves as equal members of SIOPEN, learning and contributing on behalf of families, to clinical developments.

Susan noted that at the 2009 SIOPEN AGM, charities attending had agreed that there needed to be collaboration between charities in each country before attempting to take collaboration to a European level. Clearly this is starting to happen in both Portugal and the UK and we should take the opportunity to describe these models as they develop, to other countries through the SIOPEN newsletter. In the last year, there has been some success where in-country clinical leads have achieved their SIOPEN Euro quota from charities.

It was generally agreed that

- SIOPEN is a vehicle for in-country charity collaboration, to identify the best use of charity funds; to push the nbl agenda forward using the strength of families' voices; and to utilize the policy-maker contacts held by charities.
- SIOPEN is the authoritative guide for nbl information for families, and repository for family feedback on SIOPEN activities.. The more family priorities can be seen to in fluence SIOPEN's work, the more charities can help SIOPEN.

- Charities should be positioned as a conduit between SIOPEN and families, and SIOPEN should see charities as a resource to help alleviate the communications task, both in-country and across Europe.
- Physical presence of charities at SIOPEN meetings is expensive, and becomes less necessary for those outside the host country, providing lay notes of both the scientific discussions, and local charities' discussions are circulated. The UK Neuroblastoma Society is happy to undertake the former role, and the SIOPEN Advisory Board's Charity Representative, the latter.
- This meeting's recommendation to the SIOPEN Executive will be that we want to regard SIOPEN as the central source for information on nbl developments. This relies on the SIOPEN in-country lead being available to charities to receive feedback from families on, say, a bi-annual plain-language bulletin.

We will also suggest that the SIOPEN Newsletter Sub Group extends its remit to communications on a broader scale, and includes charity representation.

Susan Hay
SIOPEN Advisory Board Charity Representative

TRAINING Corner

PhD thesis
Thesis: defence: 11/01/2011
Name Tom Van Maerken
University of Ghent, Belgium

Neuroblastoma is an aggressive childhood cancer of the developing peripheral autonomic nervous system. Approximately half of all neuroblastoma patients are diagnosed with high-risk disease, which has a fatal outcome in the majority of cases despite intensive multimodal therapy. Development of more effective and, if possible, less toxic treatment strategies is therefore a priority in neuroblastoma research. Our increasing understanding of tumor biology provides us with unprecedented opportunities to rationally target central molecular aberrations and vulnerabilities in tumor cells. This thesis aimed at investigating two promising molecular interventions for the treatment of neuroblastoma and at gaining insights into tumor defects that may direct the design and the development of molecular anticancer therapy.

The first part of the thesis was dedicated to the study of a new targeted anticancer agent, nutlin-3, which disrupts the interaction between a powerful tumor suppressor protein, p53, and a principal negative regulator of p53, namely MDM2. This investigation was fueled by pre-existing knowledge that inactivating p53 mutations are rare in neuroblastoma and by a growing body of evidence that positions inappropriately increased activity of MDM2 as a predominant mechanism by which neuroblastoma cells escape from p53-mediated growth control. Hence, we hypothesized that inhibition of the p53–MDM2 interaction by nutlin-3 would result in restoration of the antitumor activity of p53. We could indeed demonstrate that treatment with nutlin-3 results in stabilization of p53 and induction of expression of p53 target genes in neuroblastoma cells with wild-type p53, leading to G_1 cell cycle arrest and apoptosis. Of note, we uncovered alternative p53-dependent drug responses, consisting of premature senescence and neuronal differentiation, in neuroblastoma cells that survived nutlin-3 treatment, indicating that a single targeted intervention aimed at p53 reactivation is capable of engaging a multiplicity of potent antitumor programs. Further experiments revealed that nutlin-3 can also activate the p53 pathway, arrest the cell cycle, and elicit apoptosis in neuroblastoma cells that display a broad resistance to various conventional chemotherapeutic agents, provided that wild-type p53 is present. Oral administration of nutlin-3 to mice carrying chemoresistant neuroblastoma xenografts with wild-type p53 was well tolerated and reduced both the growth of the primary tumor and metastatic disease. As expected, no treatment effects were observed when nutlin-3 was given to mice with p53-mutant chemorefractory neuroblastoma tumors. These findings may stimulate the initiation of clinical trials with selective MDM2 antagonists for the treatment of advanced-stage and chemoresistant neuroblastoma with wild-type p53. To gain insight into the nature of p53 pathway defects in neuroblastoma, we decided to employ nutlin-3 as a tool for systematic interrogation of the functionality of the p53 pathway. Investigation of a panel of 34 neuroblastoma cell lines demonstrated that resistance to nutlin-3 due to *p53* mutation occurs in 26% of cell lines and that defects in effector molecules downstream of p53 are remarkably rare in neuroblastoma cells. We also identified $p14^{ARF}$ as a determinant of the outcome of the response to MDM2 inhibition. These observations may prove useful for the clinical translation of emerging p53-activating approaches and for the development of new therapeutic strategies. Finally, we optimized a reverse transcription–quantitative PCR workflow for assessment of the efficiency and functional effects of RNA interference–mediated gene silencing, as this was a central technology in several studies of this thesis.

In the second part of the thesis, we set out to investigate whether a promising growth-inhibitory gene that encodes an antitumor ribonuclease, *hPNPase*$^{old-35}$, could have utility for adenoviral gene therapy of neuroblastoma. Transgene expression was driven by either the cytomegalovirus (CMV) promoter or by a cancer-selective promoter derived from progression elevated gene-3 (*PEG-3*). We demonstrated that adenoviral vectors are able to efficiently transduce neuroblastoma cells and to provide robust transgene expression, that the *PEG-3* promoter is capable of specifically targeting gene expression in the majority of neuroblastoma cells, and that adenoviral gene transfer of *hPNPase*$^{old-35}$ selectively inhibits the growth and induces apoptosis of neuroblastoma cells. These results lend support to the potential use of adenovirus-based *hPNPase*$^{old-35}$ delivery in the treatment of neuroblastoma and suggest that combining the potent growth-suppressive properties of *hPNPase*$^{old-35}$ with the cancer-specific activity of the *PEG-3* promoter holds promise for creating an effective and selective therapeutic approach for neuroblastoma.

Taken together, this thesis illustrates that our improved understanding of tumor biology opens up exciting opportunities for molecular therapy of neuroblastoma. We anticipate that clinical trials with selective MDM2 antagonists will be initiated in patients with neuroblastoma in the near future and that gene therapy approaches are likely to become part of the treatment armatorium in the medium term.

SIOPEN publication corner 2010 – 2011

First authorships

Randomized Trial of prophylactic granulocyte colony-stimulating factor during rapid COJEC induction in pediatric patients with high-risk neuroblastoma: the European HR-NBL1/SIOPEN study.
Ladenstein R, Valteau-Couanet D, Brock P, Yaniv I, Castel V, Laureys G, Malis J, Papadakis V, Lacerda A, Ruud E, Kogner P, Garami M, Balwierz W, Schroeder H, Beck-Popovic M, Schreier G, Machin D, Pötschger U, Pearson A.
J Clin Oncol. 2010 Jul 20;28(21):3516-24. Epub 2010 Jun 21.
PMID: 20567002 [PubMed - indexed for MEDLINE]

Development of an electronic database for quality assurance of radiotherapy in the International Society of Paediatric Oncology (Europe) high risk neuroblastoma study.
Gaze MN, Boterberg T, Dieckmann K, Habrand JL, Helfré S, Peylan-Ramu N, Chrzanowska EK, Schreier G, Ladenstein R.
Radiother Oncol. 2010 Dec;97(3):593-5. Epub 2010 Sep 28.
PMID: 20851486 [PubMed - indexed for MEDLINE]

Dose finding study for the use of subcutaneous recombinant interleukin-2 to augment natural killer cell numbers in an outpatient setting for stage 4 neuroblastoma after megatherapy and autologous stem-cell reinfusion.
Ladenstein R, Pötschger U, Siabalis D, Garaventa A, Bergeron C, Lewis IJ, Stein J, Kohler J, Shaw PJ, Holter W, Pistoia V, Michon J.
J Clin Oncol. 2011 Feb 1;29(4):441-8. Epub 2010 Dec 13.
PMID: 21149662 [PubMed - indexed for MEDLINE]

Excellent outcome with reduced treatment in infants with nonmetastatic and unresectable neuroblastoma without MYCN amplification: results of the prospective INES 99.1.
Rubie H, De Bernardi B, Gerrard M, Canete A, Ladenstein R, Couturier J, Ambros P, Munzer C, Pearson AD, Garaventa A, Brock P, Castel V, Valteau-Couanet D, Holmes K, Di Cataldo A, Brichard B, Mosseri V, Marquez C, Plantaz D, Boni L, Michon J.
J Clin Oncol. 2011 Feb 1;29(4):449-55. Epub 2010 Dec 20.
PMID: 21172879 [PubMed - indexed for MEDLINE]

A multilocus technique for risk evaluation of patients with neuroblastoma.
Ambros IM, Brunner B, Aigner G, Bedwell C, Beiske K, Bénard J, Bown N, Combaret V, Couturier J, Defferrari R, Gross N, Jeison M, Lunec J, Marques B, Martinsson T, Mazzocco K, Noguera R, Schleiermacher G, Speleman F, Stallings R, Tonini GP, Tweddle DA, Valent A, Vicha A, Roy NV, Villamon E, Ziegler A, Preuner S, Drobics M, Ladenstein R, Amann G, Schuit RJ, Pötschger U, Ambros PF.
Clin Cancer Res. 2011 Feb 15;17(4):792-804. PMID: 21325297 [PubMed - in process]

INRG activities: Co-authorships

Changes over three decades in outcome and the prognostic influence of age-at-diagnosis in young patients with neuroblastoma: a report from the International Neuroblastoma Risk Group Project.
Moroz V, Machin D, Faldum A, Hero B, Iehara T, Mosseri V, Ladenstein R, De Bernardi B, Rubie H, Berthold F, Matthay KK, Monclair T, Ambros PF, Pearson AD, Cohn SL, London WB.
Eur J Cancer. 2011 Mar;47(4):561-71. Epub 2010 Nov 26.
PMID: 21112770 [PubMed - in process]

FINAL PROGRAMME
SIOPEN SPRING MEETING 2011
28-29/04/2011
Oslo University Hospital, Rikshospitalet
Oslo, Norway.

WEDNESDAY 27/04/11

- **Executive Committee Dinner: Rica Holberg Hotel at 20:00**
  - Programme for SIOPEN AGM London, UK, 12th -14th October 2011
  - Planning of charity interactions

THURSDAY 28/04/11
Oslo University Hospital, Rikshospitalet

- **Closed Executive Committee Meeting:**
  Meeting room B2.MØ13A/B **08:00 - 09:00**
  - Preparation of the Board Meeting
  - Practicalities related to presidency change

SIOPEN Clinical Trial Committees' Day
9:00 – 18:30
Place: Red lecture room (Rødt Auditorium) on lower floor in section B1 of the hospital
Note: The information desk has been moved from the hospital's entrance hall to the lower floor in front of the red lecture room. Your way from the entrance of the hospital to the red lecture room will be flagged.

Chairs: Ruth Ladenstein & Dominique Valteau-Couanet

- **High-Risk Study issues**
  - HR-NBL-1 — **09:00 – 09:45**
    - Study update — Ruth Ladenstein, Ulrike Pötschger
  - HR-NBL-1.5 — **09:45 - 10:30**
    - Status of the amendment — Ruth Ladenstein
    - Upfront induction practicalities — Alberto Garaventa
    - MRD practicalities — Sue Burchill, Klaus Beiske, Peter Ambros

Coffee break **10:30 – 11:00**

  - HR-NBL-1.5 cont'd — **11:00 - 12:30**
    - Pharmacokinetic studies practicalities — Gareth Veal
    - Immunotherapy practicalities — Holger Lode
    - mIBG scoring and review — Ariane Boubaker
    - Image and radiotherapy practicalities — Mark Gaze
    - Database issues — Mario Drobics

Lunch in the hospital's cantina
(to be entered from the main entrance hall) **12:30 – 13:30**

- **Poor responder and relapse studies**
  - Phase II poor responder HR-NBL patients **13:30 – 15:30**
    - Fusion protein crossover — Ruth Ladenstein
    - Tandem high dose results — Dominique Valteau-Couanet
    - mIBG feasibility and options — Mark Gaze
    - High dose treatment approach — Isaac Yaniv
    - Maintenance options — Holger Lode
  - Bevacizumab/Avastin in relapsed neuroblastoma pts. **15:30 – 16:00**
    Lucas Moreno, Andrew Pearson

Coffee break **16:00 - 16:30**

Chairs: Adela Cañete & Maja Beck-Popovic

- **LNESG2** Study update (Maja Beck-Popovic) **16:30 – 16:45**
- **LINES** Study update (Adela Cañete) **16:45 – 17:30**
- **LINES** Closed database meeting (Adela Cañete) **17:30 – 18:30**

Social Programme:

17:45: Bus leaves from the hospital to the city centre (Hotel Rica Holberg) (15 minutes).
18:15: Guided foot walk (optional) from the Hotel Rica Holberg to the National Opera (30 minutes).
18:30: Bus leaves from the Hotel Rica Holberg to the National Opera (for those who prefer not to walk).
18:30: Participants of LINES closed database meeting leave by taxi from the hospital to the National Opera.
19:00: All will be collected at entrance of the National Opera for a guided tour followed by a walk on the opera roof.
20:15: The bus leaves from the National Opera to the Old Sailors School for dinner.
Approx. 23:00: The bus leaves from the Old Sailors School to the city centre (Hotel Rica Holberg).

SIOPEN BOARD MEETING
FRIDAY 29/04/11
08:30 – 15:30
Place: Red lecture room (Rødt Auditorium) on lower floor in section B1 of the hospital

Chairs: Peppy Brock & Isaac Yaniv

1) SIOPEN Association **08:30 – 09:30**

a) SIOPEN activities and achievements (agreement on current and future tasks, recall lists, review, approval of roles within the SIOPEN Executive Committee — Ruth Ladenstein
b) Budget plan proposal and approval — Isaac Yaniv
   i) Budget 2011
   ii) Resources from charities
   iii) Resources raised by individual SIOPEN members
c) New country contacts, preparation for autumn AGM London (Introduction by the "mentor", questions to the persons, approval of new members) — Vassilios Papadakis
   (1) Finnland (Vassilios Papadakis/Per Kogner)
   (2) Baltic countries (Per Kogner)
   (3) Slovenia (Bruno De Bernardi, Vassilios Papadakis)
   (4) Jordan (Andrew Pearson)
   (5) Hong Kong (Ruth Ladenstein)

2) Charities **09:30 – 9:45**

a) update on recent activities and plans — Susan Hay

3) Public Affairs & Publications **09:45 -10:00**

- Links with SIOP Europe – news from Brussels — Ruth Ladenstein
- Summary on current group publications & ASCO abstracts — Dominique Valteau-Couanet
- Newsletter & website — Peppy Brock

Coffee break **10:00 – 10:30**

Chairs: Ruth Ladenstein & Alberto Garaventa

4) SIOPEN presidency hand-over **10:30 – 10:45**
(Peppy Brock: new president)

5) Reports on international collaborations **10:45 – 11:00**
a) Report on the COG Spring Meeting, Los Angeles — Ruth Ladenstein
b) Update on current INRG activities, publications — Peppy Brock on behalf of Andrew Pearson
c) Update on current common activities and plans with ITCC — Dominique Valteau-Couanet/Gilles Vassal

6) Study updates **11:00 – 12:00**
Short communications
- OMS — Gudrun Schleiermacher
- TOTEM — Hervé Rubie
- HAPLO, GD_2, IL-2 — Peter Lang
- Long term continuous infusion ch14.18/CHO plus s.c. aldesleukin (IL-2) — Holger Lode

7) IT-issues **12:00 – 12:30**
- Recent activities — Mario Drobics
- Presentation LINES database — Mario Drobics

Lunch in the hospital's cantina
(to be entered from the main entrance hall) **12:30 – 13:30**

Chairs: Geneviève Laureys & Klaus Beiske

8) Update from Specialty Committees **13:30 – 15:30**
- Surgery — Keith Holmes
- Tumour Biology — Peter Ambros
- Bone Marrow — Klaus Beiske
- Molecular Monitoring Group — Sue Burchill
- Radiotherapy/Radiology review — Mark Gaze
- Immunotherapy — Holger Lode
- NucMed: update on scoring mIBG — Ariane Boubaker
- Statistics — Ulrike Pötschger

9) Miscellaneous

END 15:30

Useful contacts

https://www.siopen-r-net.org/ for clinical trials
http://membership.siopen-r-net.org/ for membership