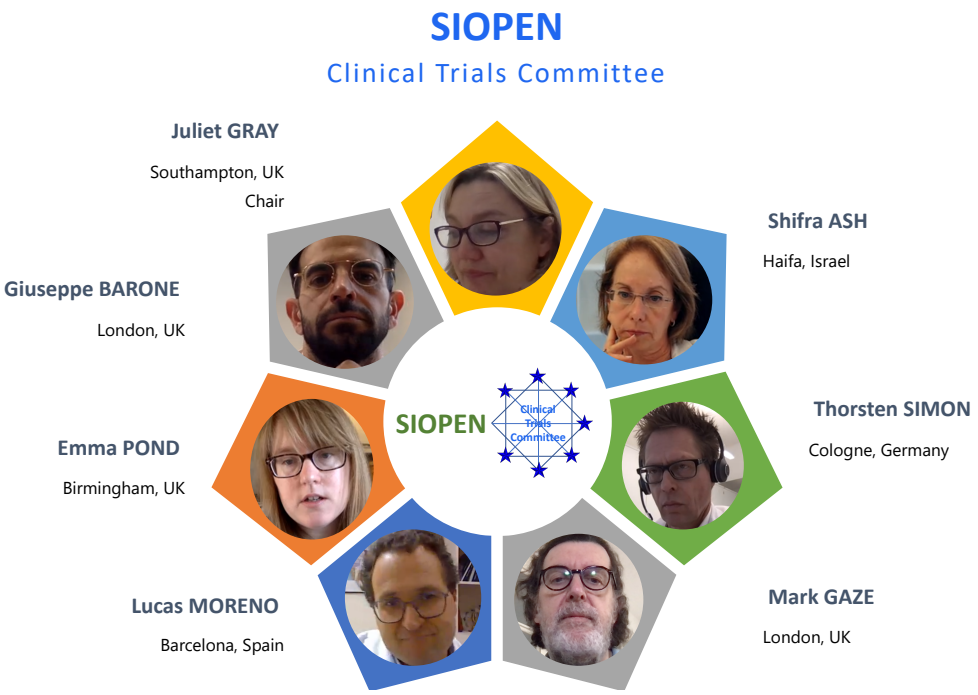
SIOPEN Clinical Trials Committee

Newsletter 1 – Spring 2021

HELLO!

Welcome to the first newsletter of the **SIOPEN Clinical Trials Committee**. This new subgroup reporting to the Executive Board was established in 2020 with the remit of maintaining an oversight of the clinical trials portfolio and associated translational research trials, reviewing their progress at least six-monthly, to promote good research governance, and to support timely delivery of trial results.

The committee meets monthly by videoconference, and will in addition meet within face-to-face SIOPEN conferences, when these restart after the pandemic. Nominations to be a member of the committee were invited by the Executive, and all applicants were appointed. At its first meeting, Juliet GRAY was unanimously selected by the group to be its first Chair. The group will keep the SIOPEN membership updated with six-monthly newsletters and presentations at meetings.



Membership

Juliet GRAY, Chair, has previously been a SIOPEN Executive Board member, and is Chair of the UK's National Cancer Research Institute's Neuroblastoma Clinical Studies Group. She is a paediatric oncologist in Southampton, and has special expertise in immunotherapy, and amongst other research projects is Chief Investigator of the transatlantic MINIVAN trial, exploring the combination of double immunotherapy with molecular radiotherapy for relapsed and refractory neuroblastoma.

Shifra ASH is the Director of the Division of Pediatric Haematology-Oncology and Bone Marrow Transplantation at the Rambam Healthcare Campus in Haifa, and Chair of the Israeli Society of Pediatric Haematology-Oncology. Formerly at the Schneider Medical centre in Tel Aviv, Shifra has a career-long interest in neuroblastoma, and published extensively in this field. She is currently Vice-President of SIOPEN and the principal co-investigator of the peripheral neuroblastic tumours presenting with spinal canal involvement registry.

Guiseppe BARONE is a paediatric oncologist and lead for neuroblastoma at Great Ormond Street Hospital for Children, the UK's largest centre for children with cancer. He has particular expertise in new drug development, and previously worked in this at the Institute of Cancer Research, University of London and Royal Marsden Hospital, gaining his PhD.

Mark GAZE is a clinical oncologist at University College London Hospitals and Great Ormond Street Hospital for Children. His career-long interest in neuroblastoma came from laboratory research work on mIBG therapy for his MD thesis, and continues into clinical trials of mIBG including MINIVAN and VERITAS. He has previously been Chair of the SIOPEN Radiotherapy Group, the NCRI Neuroblastoma Group and the Children's Cancer and Leukaemia Group.

Emma POND is Senior Trial Coordinator at the Cancer Research UK Clinical Trials Unit at the University of Birmingham, responsible for leading the neuroblastoma trials portfolio for the UK. This post is funded by Solving Kids' Cancer to accelerate the development of clinical trials in neuroblastoma. Emma is a member of the NCRI Neuroblastoma Group. She gained her PhD from the University of Manchester for research on skin barrier function in people with sun allergy.

Lucas MORENO leads the Division of Paediatric Haematology and Oncology of Vall d'Hebron Hospital in Barcelona, and was formerly a paediatric oncologist at Hospital Infantil Universitario del Niño Jesús, Madrid. He has been a member of the Clinical Trials Committee of the Innovative Therapies for Children with Cancer consortium and Chair of the SIOPEN Drug Development Committee. He is currently Vice-President of SIOPEN and the international Chief Investigator of the BEACON trial.

Thorsten SIMON is Director of the Department of Pediatric Oncology and Haematology at the University Children's Hospital of Cologne. Thorsten has been active for many years within the German/Swiss/Austrian Society of Paediatric Oncology and Haematology (GPOH), and has published extensively on neuroblastoma. More recently, as The GPOH neuroblastoma group has joined forces with SIOPEN to run trials together, he has become a leading SIOPEN figure.

Clinical trials portfolio

SIOPEN High-risk Neuroblastoma 2

The standard treatment of high-risk Neuroblastoma involves treatments using a combination of conventional chemotherapy (induction), surgery to the primary tumour, "consolidation" with high-dose chemotherapy (HDC) followed by autologous stem cell rescue (ASCR), radiotherapy to the primary tumour bed, and maintenance therapy with immunotherapy and retinoic acid.

The SIOPEN/HRNBL2 protocol aims to answer several questions:
1) Induction chemotherapy comparing Rapid-COJEC and the GPOH induction chemotherapy.
2) The impact of an intensified HDC with Thiotepa plus ASCR and then Busulfan-Melphalan (Bu-Mel) plus ASCR, in comparison with the standard Bu-Mel HDC.
3) In patients with a macroscopic residue before radiotherapy, the benefit of a boost on the residue to reach a total dose of 36 Gy in comparison to the standard 21 Gy dose delivered to the site of the primary tumour.

The principal coordinator of the study is Dr Dominique Valteau-Couanet. The total recruitment is planned to be 800 patients over 6 years. In France, the sponsor nation, the trial opened in 2018 and 28 centres are now open. The trial is opening in other countries as funding and research approvals permit, and it is anticipated that 26 countries will contribute. Plans for an amendment to evaluate the role of Lorlatinib in ALK positive patients are under discussion.

LINES

The Low and Intermediate Risk Neuroblastoma SIOPEN study (LINES) opened in 2011. It stratifies patients by biological and clinical markers in order to:
i) minimize the treatment burden in those low-risk patients who in previous studies were shown to have an excellent long-term outcome
ii) intensify treatment in those patients with biologically unfavourable disease to improve outcome.

The LINES trial (EudraCT: 2010-021396-81, ClinicalTrials.gov Identifier: NCT01728155) includes ten separate therapeutic groups, one of them randomized (Group 1). Neonatal adrenal masses (NAM) in infants below 3 months are also registered and observed, without initial surgery. The trial has run in Spain, Italy, France, Austria, Denmark, Norway, Israel, Ireland, Sweden, Belgium, Switzerland, Ireland, Australia and Portugal.

Following the closure of the majority of Low-risk trial groups (G1, G2, G3 and G6), one of our key focuses next year will be data clearance for low risk groups. The rest of the Intermediate risk patients are nonetheless important and their survival annual follow-up data entry should be up to date as well. Please ensure data is entered and collected in a timely manner that the database is as up to date as possible. This will allow Data Management and Medical reviewers to clean the data in a timely manner. The next analysis will be performed on April 2021.

Of note, when a LR and IR group is closed, patients can still be enrolled in LINES trial into the corresponding Registry Group with parents'/patient's consent and the appropriate information submitted via SIOPEN-R-NET. Real time quality control checks points in Biology and Histology are also established and functioning for these registry groups. News registry groups will be open for registration in your country once you get the approval for amended protocol v7.0.

VERITAS

VERITAS is a prospective, open-label, randomised, multi-centre phase 2 trial which aims to evaluate the efficacy of two intensified consolidation chemotherapy strategies randomly allocated among patients with poorly responding, metastatic high-risk neuroblastoma. These patients are recruited from those initially treated within or in a similar way to the SIOPEN high-risk protocol but who had an inadequate response to the induction chemotherapy (<PR or SIOPEN score >3).

The two strategies for the intensified consolidation treatment are:

- high administered activity 131I-mIBG and topotecan, and then Bu-Mel
  or
- high dose Thiotepa and Bu-Mel.

The principal coordinator of the study is Dr Dominique Valteau-Couanet. The trial opened in October 2018, and so far, 15 patients have been randomised. The trial is now open in France, Spain, the Netherlands, the UK and Italy. Austria, Germany and Israel will follow.

BEACON

The trial opened initially in 2013 to evaluate the role of bevacizumab, irinotecan and topotecan added to temozolomide-based chemotherapy in 160 patients. It is open to children and young adults aged 1 to 21 years of age with relapsed/refractory neuroblastoma. The Principal Investigator is Lucas Moreno. The trial is a collaboration between Innovative Therapies for Children with Cancer (ITCC) and SIOPEN.

Bevacizumab, irinotecan and topotecan randomisations have now closed. These results have been presented at ASCO and SIOP meetings in 2019 and 2020:
https://ascopubs.org/doi/abs/10.1200/JCO.2019.37.15_suppl.10001?af=R
https://ascopubs.org/doi/abs/10.1200/JCO.2020.38.15_suppl.10501

In 2019, the new dinutuximab beta randomisation was opened planning to recruit 64 patients. 43 sites are participating in BEACON Immuno trial, with 40 currently open for recruitment to the dinutuximab beta randomisation. The trial is now open in the UK, Denmark, Spain, Belgium, Ireland, Switzerland, Austria Netherlands and France. Approvals for Italy are awaited. It is expected that recruitment for this randomisation will be achieved during Q1 2021.
Further details about the trial can be found at clinicaltrials.gov database (NCT02308527): https://clinicaltrials.gov/ct2/show/NCT02308527?term=beacon+neuroblastoma&draw=2&rank=1

Recruitment is open until July 2021, but is now close to meeting the target of 224. 220 patients have been recruited: 60 to BEACON-Immuno (Dinutuximab beta [dB] randomisation, opened Aug 2019). On 28-Jan-2020, preliminary analysis of survival on the bevacizumab and irinotecan randomisations showed that the temozolomide alone arm in the initial Beacon trial had inferior outcomes and hence, temozolomide-only arms of the current BEACON-Immuno trial (temozolomide alone and temozolomide-dB) were closed. Patients are now randomised 2:1 to one of two arms: dinutuximab beta-topotecan-temozolomide (dBTTo) and topotecan-temozolomide (TTo).

MINIVAN

This is a phase I trial investigating combining 131-I mIBG therapy, anti-PD-1 antibody (nivolumab) and anti-GD2 antibody (dinutuximab beta) in children with relapsed or refractory neuroblastoma. The study is planned to have three cohorts of patients. Cohort 1 patients received only 131-I mIBG therapy and Nivolumab; Cohort 2 patients are receiving 131-I mIBG therapy, nivolumab and a 50% dose of dinutuximab beta, and Cohort 3 patients will receive all three treatments at the full dose. Cohort 2 is currently nearing completion of recruitment and has so far been well tolerated with no unexpected toxicity.

The study opened in the UK (Southampton Children's Hospital and UCLH London) in July 2018, and in the US (Madison Children's Hospital) in September 2020. It is hoped it will open in Greifswald in Germany very soon.

For more details about the study, please contact Dr Juliet Gray (jcgray@soton.ac.uk) or see:
https://www.solvingkidscancer.org.uk/minivan.

Spinal cord compression

This is the first prospective registry collecting clinical, pathological, biological, therapeutic and follow-up data on symptomatic and asymptomatic patients with spinal cord involvement. The first patient was enrolled on June 2014, and recruitment has been extended until June 2021.

The primary aim is to describe the natural history of peripheral neuroblastic tumours presenting with spinal cord involvement and the treatments used; to evaluate the combined effects of risk factors and to develop treatment guidelines. The secondary aims are: To correlate pathological and biological characteristics with clinical features, response to therapy and sequelae, to share the diagnostic and therapeutic approaches adopted in the participating centres, to increase the communication regarding this patient group.

The principal investigators are Shifra Ash and Riccardo Haupt. It is currently open in Italy, Israel, Ireland, The Netherlands, Poland, Slovakia, Norway, Spain, France, Sweden, Russia, Japan, Germany, Portugal, Belgium, Switzerland, Australia and Austria.

By August 2020, 184 patients had been registered from 18 countries. 68% are symptomatic. Motor deficit and pain were the most common symptoms at presentation. Chemotherapy is the prevalent treatment approach in 74% of the patients, while early neurosurgery is performed in 17% and correlates with the presence of symptoms. Neurosurgery allow quicker resolution of motor deficit, although the outcome is comparable to chemotherapy only. Improvement of symptoms (motor deficit), if any, was possible within the first 6-12 months since diagnosis. At last follow-up, the prevalence of patients with symptoms reduced by 37% for the whole group (from 68% to 43%).

Important recent publications – SIOPEN trials and SIOPEN authors

Central nervous system relapse in high-risk stage 4 neuroblastoma: The HR-NBL1/SIOPEN trial experience. Berlanga P, Pasqualini C, Pötschger U, Sangüesa C, Castellani MR, Cañete A, Luksch R, Elliot M, Schreier G, Kropf M, Morgenstern D, Papadakis V, Ash S, Ruud E, Brock P, Wieczorek A, Kogner P, Trahair T, Ambros P, Boterberg T, Castel V, Valteau-Couanet D, Ladenstein R. Eur J Cancer. 2021 Feb;144:1-8. doi: 10.1016/j.ejca.2020.10.020. Epub 2020 Dec 11.

A nomogram of clinical and biologic factors to predict survival in children newly diagnosed with high-risk neuroblastoma: An International Neuroblastoma Risk Group project. Moreno L, Guo D, Irwin MS, Berthold F, Hogarty M, Kamijo T, Morgenstern D, Pasqualini C, Ash S, Potschger U, Ladenstein R, Valteau-Couanet D, Cohn SL, Pearson ADJ, London WB. Pediatr Blood Cancer. 2021 Mar;68(3):e28794. doi: 10.1002/pbc.28794. Epub 2020 Nov 18.

Age Dependency of the Prognostic Impact of Tumor Genomics in Localized Resectable MYCN-Nonamplified Neuroblastomas. Report From the SIOPEN Biology Group on the LNESG Trials and a COG Validation Group. Ambros IM, Tonini GP, Pötschger U, Gross N, Mosseri V, Beiske K, Berbegall AP, Bénard J, Bown N, Caron H, Combaret V, Couturier J, Defferrari R, Delattre O, Jeison M, Kogner P, Lunec J, Marques B, Martinsson T, Mazzocco K, Noguera R, Schleiermacher G, Valent A, Van Roy N, Villamon E, Janousek D, Pribill I, Glogova E, Attiyeh EF, Hogarty MD, Monclair TF, Holmes K, Valteau-Couanet D, Castel V, Tweddle DA, Park JR, Cohn S, Ladenstein R, Beck-Popovic M, De Bernardi B, Michon J, Pearson ADJ, Ambros PF. J Clin Oncol. 2020 Nov 1;38(31):3685-3697. doi: 10.1200/JCO.18.02132. Epub 2020 Sep 9.

Accelerating drug development for neuroblastoma: Summary of the Second Neuroblastoma Drug Development Strategy forum from Innovative Therapies for Children with Cancer and International Society of Paediatric Oncology Europe Neuroblastoma. Moreno L, Barone G, DuBois SG, Molenaar J, Fischer M, Schulte J, Eggert A, Schleiermacher G, Speleman F, Chesler L, Geoerger B, Hogarty MD, Irwin MS, Bird N, Blanchard GB, Buckland S, Caron H, Davis S, De Wilde B, Deubzer HE, Dolman E, Eilers M, George RE, George S, Jaroslav Š, Maris JM, Marshall L, Merchant M, Mortimer P, Owens C, Philpott A, Poon E, Shay JW, Tonelli R, Valteau-Couanet D, Vassal G, Park JR, Pearson ADJ. Eur J Cancer. 2020 Sep;136:52-68. doi: 10.1016/j.ejca.2020.05.010. Epub 2020 Jul 9.

A Novel Standard for Systematic Reporting of Neuroblastoma Surgery: The International Neuroblastoma Surgical Report Form (INSRF): A Joint Initiative by the Pediatric Oncological Cooperative Groups SIOPEN, COG**, and GPOH***.* Matthyssens LE, Nuchtern JG, Van De Ven CP, Gabra HOS, Bjornland K, Irtan S, Stenman J, Pio L, Cross KM, Avanzini S, Inserra A, Chacon JG, Dall'igna P, Von Schweinitz D, Holmes K, Fuchs J, Squire R, Valteau-Couanet D, Park JR, Eggert A, Losty PD, La Quaglia MP, Sarnacki S; Surgical and Medical Committees of SIOPEN*, COG** and GPOH***. Ann Surg. 2020 Jul 7. doi: 10.1097/SLA.0000000000003947. Online ahead of print.

Influence of Surgical Excision on the Survival of Patients With Stage 4 High-Risk Neuroblastoma: A Report From the HR-NBL1/SIOPEN Study. Holmes K, Pötschger U, Pearson ADJ, Sarnacki S, Cecchetto G, Gomez-Chacon J, Squire R, Freud E, Bysiek A, Matthyssens LE, Metzelder M, Monclair T, Stenman J, Rygl M, Rasmussen L, Joseph JM, Irtan S, Avanzini S, Godzinski J, Björnland K, Elliott M, Luksch R, Castel V, Ash S, Balwierz W, Laureys G, Ruud E, Papadakis V, Malis J, Owens C, Schroeder H, Beck-Popovic M, Trahair T, Forjaz de Lacerda A, Ambros PF, Gaze MN, McHugh K, Valteau-Couanet D, Ladenstein RL; International Society of Paediatric Oncology Europe Neuroblastoma Group (SIOPEN). J Clin Oncol. 2020 Sep 1;38(25):2902-2915. doi: 10.1200/JCO.19.03117. Epub 2020 Jul 8.

Investigation of the Role of Dinutuximab Beta-Based Immunotherapy in the SIOPEN High-Risk Neuroblastoma 1 Trial (HR-NBL1). Ladenstein R, Pötschger U, Valteau-Couanet D, Luksch R, Castel V, Ash S, Laureys G, Brock P, Michon JM, Owens C, Trahair T, Chi Fung Chan G, Ruud E, Schroeder H, Beck-Popovic M, Schreier G, Loibner H, Ambros P, Holmes K, Castellani MR, Gaze MN, Garaventa A, Pearson ADJ, Lode HN. Cancers (Basel). 2020 Jan 28;12(2):309. doi: 10.3390/cancers12020309.