Intensification of treatment with immunochemotherapy in metastatic high-risk neuroblastoma patients after inadequate induction response (was selected for Fire-session)

S. Gunzer [1], C. Rosswog [1,2,3], M. Schmidt [4], S. Castelli [5], H.E. Deubzer [5], M. Fischer [1,2,3], A. Eggert [5], B. Hero [1], T. Simon [1]

[1] *Department of Pediatric Oncology and Hematology, University Children's Hospital of Cologne, Medical Faculty, University of Cologne, Cologne, Germany*
[2] *Department of Experimental Pediatric Oncology, University Children's Hospital of Cologne, Medical Faculty, University of Cologne, Köln, Germany*
[3] *Center for Molecular Medicine Cologne (CMMC), Medical Faculty, University of Cologne, Köln, Germany*
[4] *Department of Nuclear Medicine, University Hospital of Cologne, Medical Faculty, University of Cologne, Cologne, Germany*
[5] *Department of Pediatric Oncology and Hematology, Charité - Universitätsmedizin Berlin, Campus Virchow-Klinikum, Berlin, Germany*

Background: Incomplete response to induction chemotherapy correlates with poor outcomes in high-risk neuroblastoma. Immunochemotherapy has shown efficacy in relapsed high-risk neuroblastoma. It may improve response and outcomes in firstline-treatment. This study evaluates the effect of adding irinotecan, temozolomide, and dinutuximab beta (IT-dB) in patients with inadequate induction response.

Methods: We retrospectively analyzed patients with metastatic high-risk neuroblastoma from the German neuroblastoma registry (2018–2024) who received IT-dB after six cycles of GPOH N5/N6 induction due to insufficient response defined by >3 residual mIBG positive osteomedullary lesions

Results: Among the identified 28 patients (26 first-line, 2 chemotherapy-naïve relapses), median age at start of treatment was 47 months (range 15–453). MYCN amplification was present in 5 of 27 patients with available data. Patients with tumors characterized by alternative lengthening of telomeres (ALT) were overrepresented (50% vs. 24% in general high-risk-population).

Median SIOPEN score post-induction was 17.5 (range 5–43). Patients received 2–8 IT-dB cycles (median 2.5), resulting in reduced osteomedullary metastases in most. Based on relative MIBG score, patients were stratified into: 1) <0.5 (INRC partial response), 2) 0.5–0.8, and 3) >0.8. All patients in groups 1 and 2 responded to IT-dB, while responses in group 3 were heterogeneous.

Subsequent treatments included MIBG-therapy (n = 9), DOTATATE-therapy (n = 1), high-dose chemotherapy with autologous stem cell rescue (n = 20), tandem transplant (n = 3), haploidentical transplant (n = 1), or individualized therapy (n = 1). 18 patients already started immunotherapy.

8 patients are still receiving first-line therapy; 12 relapsed or progressed. 8 patients remain in remission (observation: 7-70 months). The 3-year-EFS is 0.41 ± 0.13.

Conclusions: Additional immunochemotherapy with IT-dB improves remission in patients with metastatic high-risk neuroblastoma showing poor response to induction. This intensified approach may improve short-term outcomes in this difficult-to-treat population.

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Genomic profiling in low and intermediate-risk neuroblastoma to refine treatment stratification and improve patient outcome. LINES: a SIOPEN trial (was selected for Fire-session)

I. Jiménez [a], V. Segura [b], V. Attignon [c], N. Auger [d], K. Beiske [e], J.F. de Mora [f], M. Jeison [g], T. Martinsson [h], J. Masliah-Planchon [i], K. Mazzocco [j], A. Mühlethaler-Mottet [k], R. Noguera [l], N. van Roy [m], T. Trahair [n], D. Tweddle [o], A. Canete [p], A. di Cataldo [q], V. Papadakis [r], K. Wheeler [s], S. Taschner-Mandl [t,11], G. Schleiermacher [u]

[a] *Department of Pediatric Hematology and Oncology, Clinical University Hospital Virgen de la Arrixaca, Murcia, Spain*
[b] *Clinical and Translational Research in Cancer Group, Paediatric Oncology, Instituto de Investigación Sanitaria La Fe, Valencia, Spain*
[c] *Centre Léon Berard, Lyon, France*
[d] *Gustave Roussy, Villejuif, France*
[e] *Department of Pathology, Oslo University Hospital and Medical Faculty, University of Oslo Oslo, Norway*
[f] *Instituto de Investigación Sanitaria La Fe, Valencia, Spain*
[g] *Schneider Children's Medical Center of Israel, Tel Aviv, Israel*
[h] *Sahlgrenska University Hospital, Göteborg, Sweden*
[i] *SIREDO Oncology Center, PSL Research University, Institut Curie, Paris, France*
[j] *Pathology Unit, IRCCS Istituto Giannina Gaslini, Genova, Italy*
[k] *Woman-Mother-Child Department, University Hospital CHUV and University of Lausanne, Lausanne, Switzerland*
[l] *Department of Pathology, Medical School, University of Valencia, Valencia, Spain; Incliva Health Research Institute/ CIBERONC, Madrid, Spain*
[m] *Center for Medical Genetics, Ghent University, Ghent, Belgium*
[n] *Kids Cancer Centre, Sydney Children's Hospital, Sydney, Australia*
[o] *Wolfson Childhood Cancer Research Centre, Translational & Clinical Research Institute, Newcastle Centre for Cancer, Newcastle University, Newcastle upon Tyne, United Kingdom*
[p] *Pediatric Oncohematology Unit, University and Polytechnic la Fe Hospital, Department of Pediatrics, Valencia, Spain*
[q] *Department of Clinical and Experimental Medicine, Unit of Pediatric Hematology and Oncology, University of Catania, Catania, Italy*
[r] *Department of Pediatric Hematology-Oncology, Agia Sofia Children's Hospital, Athens, Greece*
[s] *Department of Paediatric Oncology, Oxford Children's Hospital, Oxford, United Kingdom*
[t] *St. Anna Children's Cancer Research Institute, Vienna, Austria*
[u] *SIREDO Pediatric Oncology Center, RTOP (Recherche Translationelle en Oncologie Pédiatrique) U830 Inserm, Institut Curie, PSL Research University, Paris, France*
[11] *Sabine Taschner-Mandl and Gudrun Schleiermacher are CO-SENIOR authors of the abstract*

Background: In neuroblastoma, genomic profile with segmental chromosomal abnormalities (SCA) is associated with higher risk of relapse/poorer outcome. The SIOPEN LINES trial accrued low/intermediate-risk (LR/IR) neuroblastoma patients, aiming to maintain excellent outcome in LR-patients whilst diminishing treatment burden, by stratifying patients according to genomic profile and clinical parameters. In IR-patients, genomic profile was studied prospectively whenever possible.

Methods: Neuroblastoma samples with >60% cellularity were analyzed by multi-locus/pangenomic techniques (array-CGH n=49; SNP-arrays n=285; MLPA n=9). Genomic profiles were centrally reviewed, results entered in SIOPEN-R-NET-database, and clinically-relevant conclusion returned to clinicians within six weeks following diagnosis. According to genomic profile, *MYCN*-non-amplified tumors were classified in those containing only numerical chromosome abnormalities (NCA) and those harboring neuroblastoma recurrent SCA (1p/3p/4p/11q deletions; 1q/2p/17q gains), with/without NCA. Non-contributive genomic profiles included samples with low tumor-cell content, flat copy-number profile or non-recurrent SCA.

Results: 1190 samples from 1023 patients were analyzed (n=518 LR, n=263 IR, n=242 clinical screening-failure). A genomic profile could be determined in 621 patients (NCA n=387/SCA n=234); 402 patients showed non-contributive genomic profile (n=37 with non-recurrent SCA). A clinically decision-making genomic profile was determined in 595 patients: n=429 LR (NCA: n=313, 73%; SCA: n=116, 27%), n=166 IR (NCA: n=56, 34%; SCA: n=110, 66%). The frequency of NCA/SCA varied between different patient groups: in localized unresectable *MYCN*-non-amplified neuroblastoma patients ≤18 months (m) (n=175), n=135 (77%)/n=40 (23%); in same patients >18m (n=67), n=20 (30%)/n=47 (70%); in patients with disseminated *MYCN*-non-amplified neuroblastoma ≤12m (n=195), n=126 (65%)/n=69 (35%) respectively. Concerning recurrent SCA, 1p/3p/4p/11q-deletions and 1q/2p/17q-gains were present in 24.4%/15.8%/17.9%/36.3% and 11.5%/31.6%/60.6% of patients with SCA, respectively.

Conclusions: In SIOPEN-LINES trial, tumor genomic profiling at diagnosis identified recurrent SCA with higher frequency in older patients and those with disseminated disease. In-depth multiomics analyses including NGS-panel sequencing and expression profiling will be performed for patients with relapse whenever possible.

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Targeting ALK in relapsed high-risk neuroblastoma: real-world insights from the SACHA-France study (was selected for Fire-session)

P. Berlanga [1], B. Dumont [2], C. Pasqualini [1], I. Aerts [3], N. Corradini [2], S. Proust [4], J. Tandonnet [5], C. Coze [6], P. Chastagner [7], F. Millot [8], C. Briandet [9], E. Thebaud [10], K. Camille [11], S. Klein [12], D. Plantaz [13], S. Touvenin [14], L.A. Ndounga-Diakou [15], S. Laghouati [15], A.S. Defachelles [16], G. Schleiermacher [3]

[1] *Department of Pediatric and Adolescent Oncology, Gustave Roussy Cancer Campus, Université Paris-Saclay, Villejuif, France*
[2] *Pediatric Hematology and Oncology Institut, Léon Bérard Cancer Center, Lyon, France*
[3] *SIREDO Oncology Center (Care, Innovation and Research for Children and AYA with Cancer), Institut Curie, PSL Research University, Paris, France*
[4] *Department of Pediatric Oncology, University Hospital, Angers, France*
[5] *Paediatric Haematology-Oncology Department, Centre Hospitalier Universitaire (CHU), Bordeaux, France*
[6] *Department of Pediatric Hematology & Oncology, Hôpital de La Timone, AP-HM, Marseille, France*
[7] *Department of Pediatric Hematology-Oncology, Children's Hospital of Brabois, Vandoeuvre Les Nancy, France*
[8] *Department of Paediatric Haematology and Oncology, Centre Hospitalo-Universitaire de Poitiers, Poitiers, France*
[9] *Pediatric Oncology, CHU Dijon-Bourgogne, Dijon, France*
[10] *Pediatric Immuno-Hemato-Oncology Unit, CHU Nantes, Nantes, France*
[11] *Department of Pediatric Oncology, CHU Amiens Picardie, Amiens, France*
[12] *Pediatric Oncology and Hematology, CHU Jean-Minjoz, Besançon, France*
[13] *Department of Pediatric Onco-Immuno-Hematology, Grenoble Alpes University Hospital, Grenoble, France*
[14] *Department of Pediatric Hematology-Oncology, University Hospital St Etienne, St Etienne, France*
[15] *Pharmacovigilance Unit, Clinical Research Direction, Gustave Roussy Cancer Campus, Université Paris-Saclay, Villejuif, France*
[16] *Department of Pediatric Oncology, Oscar Lambret Cancer Center, Lille, France*

Background: ALK aberrations are the most frequent targetable identified alterations in patients with relapsed high-risk neuroblastoma. Current treatment for those patients consists mainly on third generation ALK inhibitor Lorlatinib, in most cases combined with chemotherapy.

Aims: To report real-world activity and safety data on patients with neuroblastoma included in the SACHA-France study and treated by Lorlatinib ± chemotherapy.

Methods: SACHA-France is a prospective national registry that documents safety and efficacy data on innovative anticancer therapies prescribed to patients ≤ 25 years old as compassionate or off-label use in France (NCT04477681).

Results: Between 01/01/2020 and 31/10/2024, 25 patients with relapsed high-risk neuroblastoma from 14 centers were included. Bobin et al. have already reported fifteen of these patients (Clin Cancer Re 2024). They had a median age of 5.9 years (range: 1.4-16.4) and a median of two previous lines of therapy (range: 1-6). Treatment consisted in Lorlatinib as single agent (n=10) or in combination (Topotecan/Cyclophosphamide, n= 9; Topotecan/Temozolomide, n= 5; Trametinib, n= 1). Twenty-three cases had ALK mutations, mostly F1174L (n=10) and R1275Q (n=4).

Three patients had previously received Lorlatinib therapy. Of the other 22 patients, the global objective response (OR) rate was 23% (5/22), with 1/9 as single-agent and 4/13 with chemotherapy. No OR was observed in patients with MYCN-amplified tumors (5 as single-agent, 6 with chemotherapy). 6-month and 12-month PFS were 23% and 14%, respectively. One patient had a grade 4 pneumonitis at 2.5 months after Bu-Mel (and before maintenance therapy) that recurred after Lorlatinib re-challenging, leading to permanent Lorlatinib discontinuation.

Conclusion: Our real-world data confirm the absence of anti-tumor activity of ALK inhibitors in a larger cohort of patients with MYCN-amplified neuroblastoma. Overlapping lung toxicities due to Lorlatinib and high-dose chemotherapy must be carefully considered and should influence future trial designs.

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Veno-occlusive disease in children with neuroblastoma following busulphan-melphalan high-dose chemotherapy

K O'Neill, F Clinton, S Alken, M Capra, N Cullinan, S Curry, J Pears, C Owens

Introduction: Children with high risk neuroblastoma generally undergo autologous stem cell transplant (SCT) with busulfan/melphalan (Bu/Mel) conditioning as part of their standard treatment. Veno-occlusive disease (VOD) remains a leading cause of morbidity