high-risk neuroblastoma (BARD1, $P_{51070096}$/MYCN-amplified vs $P_{1543310}/$MYCN-nonamplified = 0.34, CASC15-S: $P_{1543310}/$MYCN-amplified vs $P_{1543310}/$MYCN-nonamplified = 0.10). Conversely, LMO1 was significant only in patients with MYCN-nonamplified high-risk tumors ($P_{510419}/$MYCN-amplified vs $P_{510419}/$MYCN-nonamplified = 3.44 x 10^{-5}$).

**Conclusions:** We demonstrate MYCN-amplified and MYCN-nonamplified high-risk neuroblastoma arise under the influence of distinct germline susceptibility alleles. These results also suggest the etiology of MYCN-amplified neuroblastoma may result from attenuated DNA repair and/or impaired mitotic chromosome segregation. Further functional analysis of BARD1, CASC15-S, and KIF15 may provide insight into the pathogenesis of MYCN-amplification and identify potential therapeutic targets.

### 118 Pharmacogenetics of treatment response in patients with high-risk neuroblastoma, a Children's Oncology Group study

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**Background:** While outcomes for patients with high-risk neuroblastoma have improved over time, largely through intensification of therapy, biologic factors predictive of high-risk treatment failure remain elusive. Furthermore, the role of germline genetic variation in treatment failure has not been extensively investigated.

**Methods:** Single nucleotide polymorphism (SNP) genotyping was performed on selected genes in the pharmacokinetic pathway of cyclophosphamide (CY) for children with high-risk neuroblastoma enrolled on the Children's Oncology Group high-risk neuroblastoma protocol, ANBL0532. Response after two cycles of topotecan/CY (ranging from complete response to progressive disease) was used as a continuous outcome and with dominant model scoring of the SNP genotype as the independent variable for the association studies, adjusting for age at diagnosis, race (as determined by 30 genotyped SNPs serving as ancestry informative markers), stage, MYCN status and histology.

**Results:** Of the 652 patients enrolled on ANBL0532, 303 participated in the pharmacogenomics arm. We tested 110 SNPs (37 genes) that were either tagging or had associations of interest previously reported. ABCC1 and ABCC4 had SNPs with nominal p-values < 0.01. After correction for multiple testing, two intronic SNPs in ABBC1, rs4148353 and rs17287570, were significantly associated with response to two cycles of topotecan/CY, p

**Conclusions:** ABCC1 is a key regulator of chemotherapeutic cellular efflux, including CY. Genetic variants in ABCC1 which may alter the function of transporter impact outcome in children with high-risk neuroblastoma. Pediatric validation is underway in patients with rhabdomyosarcoma also treated with cyclophosphamide-containing regimens.
may benefit from alternative treatment approaches, a deeper understanding of the genomic alterations that drive rapidly progressive disease will be needed.

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Revised Children's Oncology Group (COG) risk stratification incorporating the international neuroblastoma risk group staging system

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Background: The COG risk classification system previously used the International Neuroblastoma Staging System (INSS). Because the INRG staging system (INRGSS) has been adopted for clinical trials we integrated INRG stage with biological and clinical prognostic factors to map patient categories, evaluate outcomes and develop a revised risk classification system. Methods: 4,255 newly diagnosed neuroblastoma patients were enrolled on COG Neuroblastoma Biology Study ANBL00B1 between 2006-2014. Staging per the INSS and INRG (using detection of Image Defined Risk Factor (IDRF) was determined. Tumor biological and histologic features assessed in the centralized COG Neuroblastoma Reference lab included MYCN status, ploidy, INPC histology, and 1p and 11q LOH. Survival analyses were performed to identify independent prognostic factors and to calculate event-free and overall survival (EFS, OS) for combinations of variables used to determine risk group assignments according to both COG and INRG classification templates. Results: Using the COG risk classification 1,309 low-, 1,007 intermediate- and 1,849 high-risk patients were identified. Concordance between INSS and INRG staging systems was higher for metastatic (4/M) as compared to loco-regional patients: 1,122 (67%) of loco-regional tumors had no IDRF (L1) and 545 (33%) had >1 IDRF (L2). Of the L1 patients 87% were INSS 1, while 61% of L2 patients were INSS 3. Subsets of L2 patients had sub-optimal outcomes (Table): Discussion: The COG revised risk classification will designate L2 patients >18mo with MYCN unfavorable INPC histology, and/or segmental chromosome aberrations as high risk. Efforts to identify additional prognostic biomarkers may enable further refinement of risk groups.

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High-dose 131I-MIBG treatment incorporated into tandem HDCT/auto-SCT for high-risk neuroblastoma: Results of SMC NB-2009 study

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Background: The strategy using tandem HDCT/auto-SCT for high-risk neuroblastoma in which TBI was incorporated into the second HDCT/auto-SCT (SMC NB-2004 study) demonstrated a very encouraging survival rate. However, most survivors experienced significant short- and long-term toxicities associated with tandem HDCT/auto-SCT, particularly TBI. Therefore, we incorporated high-dose 131I-MIBG treatment into the second HDCT/auto-SCT instead of TBI from 2009 (SMC NB-2009 study). Methods: From 2009 to 2013, 54 patients were assigned to receive tandem HDCT/auto-SCT after 9 cycles of induction chemotherapy. CEC (carboplatin + etoposide + cyclophosphamide) and TM (thiotepa + melphalan) with (for stage 4) or without (for stage 3) high-dose 131I-MIBG treatment were used as the first and second HDCT regimen, respectively. High-dose 131I-MIBG was infused on day -21 of the second HDCT/auto-SCT. Local radiotherapy, 13-cis-retinoid acid, and IL-2 were given after tandem HDCT/auto-SCT. Acute toxicities during the second HDCT/auto-SCT, late effects, and survival rates were compared between NB-2004 and NB-2009 studies. Results: All but 2 patients who experienced progression during induction treatment underwent the first HDCT/auto-SCT and 47 patients completed tandem HDCT/auto-SCT. Five patients died from toxicities during the first HDCT/auto-SCT. There was no significant immediate toxicity during 131I-MIBG infusion and no toxic death during the second HDCT/auto-SCT. The duration of high fever was shorter (P<0.001) and frequencies of grade 3/4 stomatitis, diarrhea, and liver enzyme elevation during the second HDCT/auto-SCT were lower in NB-2009 study than in NB-2004 study (P=0.005, 0.054, and 0.028, respectively). Late effects evaluated at 3 years after the second HDCT/auto-SCT were less significant in 2009 study than in 2004 study (less GH deficiency, SNHL, cataract, and glomerulopathy). There was no difference in 5-yr EFS (67.4 ± 6.7% vs. 64.9 ± 6.8%, P=0.833). Conclusions: High-dose 131I-MIBG treatment incorporated into tandem HDCT/auto-SCT was feasible and could reduce acute and chronic toxicities without jeopardizing survival rate.