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Predictors of Differential Response to Induction Therapy in High-Risk Neuroblastoma: A Report from the Children's Oncology Group (COG)

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Abstract

Background—Induction chemotherapy plays an important role in the management of patients with high-risk neuroblastoma. Predictors of response to induction therapy are largely lacking. We sought to describe clinical and biological features associated with induction response.

Methods—Patients from four consecutive COG high-risk trials were included. Response was evaluated by the 1993 International Neuroblastoma Response Criteria. The primary endpoint was end-induction partial response (PR) or better. Univariate analyses were performed to compare response as a function of clinical or biologic predictors. A multivariate logistic regression model using significant predictors from univariate analyses was constructed to model PR or better.

Results—The analytic cohort included 1,242 patients. End-induction response PR was significantly associated with higher event-free and overall survival. Baseline factors associated

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with PR included age <18 months (87.4% with PR vs. 78.7% if older; $p=0.0103$), INSS non-Stage 4 (89.0% vs. 78.4% if Stage 4; $p=0.0016$), *MYCN* amplification (85.5% vs. 77.1% if non-amplified; $p=0.0006$), 1p loss of heterozygosity (LOH; 85.6% vs. 76.0% if no LOH; $p=0.0085$), no 11q LOH (84.8% vs. 70.9% if 11q LOH; $p=0.0004$), and high mitosis-karyorrhexis index (84.5% vs. 77.5% if low-intermediate MKI; $p=0.0098$). On multivariable analysis ($n=407$), the absence of 11q LOH was the only factor that remained significantly associated with PR (odds ratio: 1.962 vs. 11q LOH; 95% confidence interval 1.104–3.487; $p=0.0216$).

Conclusions—Improved end-induction response in high-risk neuroblastoma is associated with longer survival. Patients with 11q LOH are less likely to respond to induction therapies and should be prioritized for novel approaches in future trials.

Keywords

Pediatric oncology; neuroblastoma; biomarkers

Introduction

Neuroblastoma is a malignancy of the sympathetic nervous system and the most common malignancy in infancy. Neuroblastoma is notable for its marked clinical heterogeneity ranging from spontaneous regression without intervention to highly fatal chemo-resistant disease(1). Several clinical and tumor biologic factors identify patients at low, intermediate or high risk of relapse and are used to assign upfront therapy(2). Outcomes for patients with high-risk neuroblastoma (representing approximately 40% of new neuroblastoma cases) are historically poor, with 5-year disease-free survival less than 50% (3–5). The addition of myeloablative chemotherapy followed by autologous stem cell transplant rescue (ASCT) after induction therapy, improved surgical and radiotherapy techniques, and the use of both a differentiating agent (cis-retinoic acid) and a chimeric anti-GD2 antibody after transplantation have all led to incremental improvements in disease-free survival (6). Despite multimodal therapy, durable remission rates remain low, with 10%–15% of patients progressing during induction therapy and another 40% progressing after an initial response to induction (4, 5). The ability to identify both clinical and biologic prognostic markers of response early in a patient's clinical course may significantly affect subsequent therapy, identifying individuals who may benefit from augmented or alternative therapy.

Induction therapy plays a critical role in the management of patients with high-risk neuroblastoma. The goal of induction therapy is to obtain maximal reduction in tumor burden prior to planned consolidation therapy with high-dose chemotherapy with stem cell rescue(7). Induction typically consists of intensive multiagent chemotherapy and surgical resection of the primary tumor. Prior studies have demonstrated that favorable response to induction therapy is associated with favorable event-free survival (8–10). However, predictors of response to induction therapy itself are surprisingly lacking. Increased dose intensity appears to be associated with higher response rate (11, 12), though little is known about the impact of treatment delays and dose reductions during induction in patients intended to receive similar chemotherapy regimens. Receipt of 5 vs. 6 cycles of induction chemotherapy does not appear to impact rate of response to induction (13). In a recent Children's Oncology Group (COG) analysis of *MYCN* copy number, patients with *MYCN*

amplification had a 25.1% complete induction response rate compared to 12.4% for patients with *MYCN* wild-type tumors (14). Whether other clinical or biological features impact likelihood of response to induction chemotherapy is largely unknown.

The COG has conducted a series of four clinical trials since 2001 that utilized intensive induction chemotherapy for 5–6 cycles (5, 13, 15, 16). During this same time period, response was graded uniformly using the 1993 version of the International Neuroblastoma Response Criteria (INRC), which uses a combination of radiographic, pathologic, and biochemical parameters to determine overall response to treatment(17). These trials enrolled a total of 1,315 eligible high-risk patients, providing a robust data set in which to perform a comprehensive evaluation of potential predictors of favorable and unfavorable response to induction therapy. In the current report, we used this data set to describe clinical and biological features associated with response to induction therapy using the following categories of response: partial response (PR) or better; complete response (CR); or progressive disease (PD). For patients that had an early response assessment (prior to the end of induction), we also sought to describe clinical and biological features that are associated with early response during induction therapy.

Materials and Methods

Patients

Patients from the following trials were considered for inclusion in the study: A3973(5); ANBL02P1(15); ANBL0532(16); and ANBL12P1(13). Patients with at least one disease evaluation during induction after initiating protocol therapy and those with early PD who were missing end-induction response were eligible for inclusion in the analytic cohort. Response was evaluated at two time points during induction: early response assessment and end-induction response assessment. The early response assessment was captured after 2 induction cycles for A3973, ANBL02P1, ANBL0532, and 4 cycles for ANBL12P1. The end-induction response assessment was captured after 5 cycles for ANBL12P1 and after 6 cycles for the other studies. Patients who developed PD after 2 cycles of therapy on studies ANBL02P1 and ANBL0532 were eligible to remain on study to complete the remainder of induction therapy as long as they did not continue to progress. Patients on ANBL12P1 with PD after 4 cycles could either end protocol therapy or remain on study at the discretion of the treating physician. Patients who developed PD on A3973 at an early timepoint were taken off protocol therapy. Patients with early PD who were missing end-induction response were coded as having progressive disease at end-induction.

Variables

End-induction overall response (PR or <PR) was the primary endpoint, while end-induction CR or PD were secondary response endpoints. Likewise, early PR or early PD were secondary response endpoints. All included trials utilized the 1993 INRC to evaluate response to induction therapy, with primary site response based upon response achieved from the combination of surgery and chemotherapy (Supplemental Table 1)(17).

Potential baseline predictor variables included: age at diagnosis; sex; race; ethnicity; International Neuroblastoma Staging System (INSS) stage(17); primary site; metastatic site; International Neuroblastoma Pathology Criteria (INPC) histology(18); mitosis-karyorrhexis index (MKI); tumor grade; *MYCN* status (amplified versus non-amplified); *ALK* status (wild-type vs mutant/amplified); chromosome 1p loss of heterozygosity (LOH); chromosome 11q LOH; tumor ploidy; and MIBG avidity (only available for A3973 and ANBL12P1). Age at diagnosis was evaluated using two binary variables: both an 18-month cut-off (optimized as prognostic of event-free survival)(19) and a 5-year cut-off (selected for descriptive purposes). LOH data were not collected on ANBL02P1. Potential predictor variables collected after initiation of chemotherapy included: response assessed at an early time point; chemotherapy dose modifications (only available for A3973 and ANBL02P1); and treatment delays (analyzed as duration of induction divided by total number of induction cycles). All induction cycles were 21 days long, and for each study, a treatment delay was defined as taking longer than 21 days times the number of induction cycles, plus 7 days per cycle completed, 14 days for surgery, and 12 days for transplant preparation if all induction cycles were completed [COG policy allows minor unavoidable departures of up to 72 hours from protocol directed therapy and up to 1 week for surgery for valid clinical, patient, and logistical issues]. Not all potential predictor variables were collected on all four clinical trials. As such, some variables have missing data for all patients enrolled to a trial in which the variable was not included on the trial case report forms.

Statistical Considerations

Kaplan-Meier methods and log-rank tests were used to compare event-free survival (EFS) and overall survival according to groups defined by end-induction response category. Event-free survival was calculated as time from initial diagnosis to first episode of disease relapse or progression, second malignancy, or death, with patients without event censored at last follow-up. Overall survival was calculated as time from initial diagnosis to death, with surviving patients censored at last follow-up.

A series of univariate analyses (Fisher's exact or chi-squared tests, depending on sample size with available data) were performed to compare response (PR or better) as a function of each predictor variable. These analyses were repeated to compare CR and PD as a function of each predictor variable. Early response assessment after 2–4 cycles of induction was a predictor variable, but we also assessed predictors of early response and early disease progression. For each predictor variable, the Holm-Bonferroni method was applied to p-values across the 3 different response dichotomizations (PR or better, CR, PD) to correct for multiple testing(20) using different cut-offs of the same response variable, using a family-wise error rate of 0.05.

A series of multivariable logistic regression models using the predictors that were statistically significant from the univariate analyses were constructed to model PR or better and separately to model CR or <CR. The goal of these models was to assess whether univariate significant predictors remained significant after controlling for other univariate significant predictors. For the model of CR, multivariable logistic regression models were run with and without MIBG avidity as a predictor because MIBG avidity data were available

from only two studies. Similarly, models were constructed with and without 1p and 11q status due to >50% missing data in the overall cohort. For all models, the odds ratios (OR) compared the more favorable category to the less favorable category (reference level) for each factor. P-values from multivariable models were not adjusted for multiple comparisons.

Results

Patient Characteristics

Of the 1,315 high-risk patients, 1,280 patients (A3973: 470; ANBL02P1: 31; ANBL0532: 638; ANBL12P1: 141) met eligibility for this study, with at least one disease evaluation or early PD after initiating protocol therapy (Figure 1). Thirty-five patients did not have a reported disease evaluation (see Figure 1) and were excluded. Nine hundred ninety-six (996) patients (A3973: 300; ANBL02P1: 30; ANBL0532: 545; ANBL12P1: 121) had early response evaluations and 1,242 patients (A3973: 457; ANBL02P1: 30; ANBL0532: 626; ANBL12P1: 129) had end-induction response evaluations. Clinical and biological features are shown in Table 1 and are as expected for this population. Data on tumor biological features other than *MYCN* status or ploidy (e.g., *ALK* status and segmental LOH at 1p or 11q) were missing in more than 50% of the dataset since these data were not collected on all four included trials. Among patients with available data on treatment delays or modifications, 13.3% met the definition of induction treatment delay and 11.7% had a reported chemotherapy dose modification during induction.

End-Induction Response is Associated with EFS and Overall Survival

We first sought to determine if end-induction response was associated with EFS and overall survival, as has been reported in prior analyses(10, 21). In the full cohort of 1,242 patients, 79.8% of patients had PR or better at end-induction. End-induction CR was reported in 20.8% of patients. Patients with either PR or CR at end-induction had significantly superior EFS (Figures 2A and B) and overall survival (Figures 2C and D) compared to patients with <PR or patients with <CR ($p<0.0001$ for all comparisons).

Univariate Predictors of PR or Better at End-Induction

The end-induction PR rate differed significantly by subgroups (Table 1). Among factors potentially known at initial presentation, the following variables were significantly associated with a PR or better, even after controlling for multiple testing: age <18 months (87.4% with PR or better vs. 78.7% if older; $p=0.0103$); age <5 years (82.0% vs. 70.6% if older; $p<0.0001$); INSS non-stage 4 (89.0% vs. 78.4% if Stage 4; $p=0.0016$); *MYCN* amplification (85.5% vs. 77.1% if non-amplified; $p=0.0006$); 1p loss of heterozygosity (LOH; 85.6% vs. 76.0% if no LOH; $p=0.0085$); no 11q LOH (84.8% vs. 70.9% if 11q LOH; $p=0.0004$); and high MKI (84.5% vs. 77.5% if low-intermediate MKI; $p=0.0098$).

We also evaluated potential predictors that occur after initial diagnosis, including early response or treatment delays/modifications. Early response was significantly associated with PR at end-induction (Table 1). In contrast, treatment delay or treatment modifications were not significantly associated with end-induction partial response or better.

Univariate Predictors of CR at End-Induction or Induction PD

We next assessed our secondary response endpoints of CR or PD. INSS non-stage 4, *MYCN* amplification, lack of 11q LOH, high MKI, and lack of MIBG avidity were the baseline variables significantly associated with higher rates of CR at end-induction (Table 2). Early PD and early PR were associated with lower and higher rates of subsequent CR, respectively.

End-induction PD was reported in 113/1,242 (9.1%) patients. 11q LOH was the sole baseline variable associated with PD at end-induction (Table 3). Among response-based variables, early PD and early PR were significantly associated with higher and lower rates of end-induction PD, respectively. Overall survival (OS) of patients who experienced PD was poor. The 3-year OS estimates were 31.2±4.3% (early or end-induction PD) versus 71.4±1.4% (no PD; log-rank test p-value< 0.0001; Figure 3).

Factors Associated with Early Responses to Induction Chemotherapy

We also assessed early PR and early PD as secondary outcomes of interest. Early PR was seen in 520/996 (52.2%) and early PD was seen in 41/996 (4.1%) patients. Patients with early PD were allowed to stay on protocol therapy at the discretion of their treating physician. Younger age at diagnosis (using either the 18-month or 5-year cut-offs), INSS non-stage 4, *MYCN* amplification, 1p LOH, lack of 11q LOH, and higher MKI were significantly associated with higher rates of early PR (Table 4). There were no variables significantly associated with early PD (Table 4).

Multivariable analyses

Multivariable logistic regression models were constructed to identify variables associated with end-induction PR and CR, starting from the variables that were statistically significant in the univariate analyses (Table 5).

Only lack of 11q LOH remained significantly associated with end-induction PR [OR=1.962 (95% confidence interval (CI): (1.104, 3.487))] compared to reference group with 11q LOH (p=0.0216). A separate model excluding 1p and 11q (due to missing data in >50% of the overall cohort and 100% of patients enrolled on ANBL02P1) and retaining age, stage, *MYCN* status, and MKI showed that non-stage 4 disease was the sole significant predictor of higher likelihood of end-induction PR [OR=2.520; 95% CI: (1.380, 4.602)] compared to reference group with stage 4 disease (p=0.0026).

Using CR at end-induction as the outcome of interest, we constructed three separate models (Table 5). The first model utilized all significant univariate predictors of CR. Only 99 patients had data available for all of these variables and no variables were significant on multivariate testing. Acknowledging the impact of missing data on this analysis, we next constructed a model excluding MIBG avidity. The resulting model included 408 patients and showed that non-stage 4 disease and *MYCN* amplification were associated with significantly higher likelihood of end-Induction CR. We repeated the analysis excluding 11q status and obtained similar results.

Discussion

In this comprehensive assessment of response to induction therapy for patients with high-risk neuroblastoma treated between 2001 and 2015, we confirmed that end-induction responses of PR or better or CR are associated with superior EFS and overall survival. We observed that clinical and biological factors present at the time of diagnosis of high-risk neuroblastoma are associated with differential responses to induction therapy. Features generally viewed as more favorable (younger age; lower stage) and others generally viewed as unfavorable (*MYCN* amplification; 1p LOH; high MKI) were associated with more favorable induction response. Interestingly, 11q LOH was shown to be a significant predictor of PD and lack of 11q LOH was associated with both higher rates of end-induction CR and of end-induction PR or better, the latter even after controlling for other factors. We also noted that end-induction response was associated with response assessments performed earlier in the course of induction. Another key finding was that treatment delays or modifications were not associated with a lower rate of induction response. We hypothesized that treatment delays would lead to inferior end-induction responses, and our definition sought to capture patients with fairly extreme delays in protocol directed therapy. The fact that this degree of delay did not affect outcome supports current practice, in the context of intensive multimodal therapy, that allows patients to fully recover between treatment cycles, prior to surgery and before proceeding to post-induction therapies. Whether there is an association between treatment delays/dose modifications and long-term outcomes is outside the scope of the current analysis focused on induction response.

Status at 11q appeared to be an important determinant of response to induction therapy. 11q LOH has been previously identified as an adverse prognostic feature in patients with neuroblastoma, and is often found in *MYCN* non-amplified high-risk neuroblastoma(22). 11q LOH is commonly found with other segmental chromosomal aberrations such as 1p deletion and 17q gain, and tumors with segmental chromosomal aberrations are much more frequently seen in patients with high-risk neuroblastoma, as opposed to numerical chromosomal aberrations, which are more frequently seen in patients with non-high-risk neuroblastoma (23). The role of 11q loss in mediating adverse outcomes in neuroblastoma is largely unknown, though our results suggest that 11q loss may be a marker of general chemoresistance. Proposed mechanisms of the impact of 11q loss on outcomes include loss of tumor suppressor genes (such as *CADMI*, *ATM* or *H2AFX*) or microRNAs (such as miR4301, miR125b-1, let-7a or miR100) versus the deletion of multiple genes and creation of a tumorigenic haploinsufficient state (24).

Both INSS non-stage 4 (INSS Stage 1–3, 4S) disease and *MYCN* amplification were independently associated with CR at end-induction. Patients with non-stage 4 disease were twice as likely to have a CR when compared to patients with metastatic disease (INSS Stage 4). Clinical stage has been previously shown to independently associate with outcome. In a prospective analysis of the INSS, the 4-year overall survival for patients >12 months with stage 1, 2A, 2B and 3 disease was 100% compared to 48.5% in patients with stage 4 disease ($p<0.0001$)(25). Similarly, amplification of the *MYCN* oncogene is a well-documented adverse prognostic feature that correlates with high-risk disease and is present in approximately 20% of neuroblastoma tumors (26–28). The finding of higher response rates

in patients with *MYCN* amplified tumors is noteworthy as we show that not all unfavorable prognostic factors are associated with unfavorable response to induction chemotherapy. *MYCN* amplified tumors often exhibit a greater degree of tumor necrosis in response to chemotherapy compared to *MYCN* non-amplified tumors(29). The higher proliferative rate associated with *MYCN* amplification may result in greater chemosensitivity, a hypothesis supported by higher response rates in patients with tumors with a high MKI.

Our analysis has certain strengths and weaknesses worthy of further note. We leveraged a large dataset with robust centralized assessment of baseline *MYCN* status and tumor histologic features. In addition, measurement of response using the 1993 version of the INRC was employed across all 4 studies included in this analysis. We evaluated several domains of induction response and utilized a strategy to control for multiple testing. However, given the size of the analytical cohort, central review of response was not possible. This weakness is noteworthy given that the included patients were diagnosed over a >10-year period of time when imaging approaches evolved. For example, MIBG imaging has become routine and is now almost exclusively performed with ¹²³I-MIBG as the preferred imaging agent compared to prior usage of ¹³¹I-MIBG or technetium-99 bone scan. Likewise, FDG-PET imaging is now more widely used for patients with MIBG non-avid tumors. It is possible that lack of FDG-PET imaging to fully evaluate these patients in earlier studies may have yielded the finding that patients with MIBG non-avid disease had differing CR rates. We also note that the induction regimens used in each of the four trials were not uniform, though all were intensive multiagent regimens. Data were missing in >50% of patients for several variables, including 11q status, for which data were missing disproportionately in patients enrolled on earlier trials in our analysis. We attempted to mitigate this limitation by constructing multivariable models with and without these variables, but a potential bias may remain. Finally, we acknowledge that our definition of treatment delay was an arbitrary (though *a priori*) definition and that other cut points to define delay could be considered.

Conclusions

The clinical and biological factors included in this analysis of induction response are the factors historically considered, and supported by statistical evidence, for assigning a risk group classifier and subsequent treatment. However, within the high-risk group, largely defined as patients with *MYCN* amplification or children over the age of 18 months with metastatic disease, reliable predictors of overall response to high-risk therapy and/or outcome are lacking. Efforts have been made to identify a so-called “ultra-high-risk” group of patients with a low predicted overall survival with standard high-risk therapies who may benefit from augmentation of traditional high-risk therapies to include targeted or alternative interventions. Our analysis demonstrates that patients who develop progressive disease during induction therapy are at high risk of subsequent death and should be prioritized for novel salvage approaches. In previous studies, the response to induction therapy appears to be a sensitive predictor of subsequent risk of relapse in patients with high-risk neuroblastoma (8–10). Our investigation represents the largest cohort of high-risk neuroblastoma patients analyzed for predictive biomarkers of induction response. Identification of reliable predictors of response to high-risk therapies has the potential to

further refine our risk classifiers and potentially spare some patients from the significant late effects of traditional high-risk therapies (30).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Predictors of induction therapy response in high-risk neuroblastoma are lacking.
- We evaluated baseline factors associated with induction response in 1242 patients
- Absence of 11q LOH is associated with PR to induction therapy
- This is the largest evaluation of induction response in neuroblastoma
- Novel approaches are needed for patients with 11q LOH

Figure 1.
CONSORT diagram of eligible and analyzed subjects.

Figure 2A.

Event-free survival according to end-induction partial response (PR) or better vs. less than PR. **B.** Event-free survival according to end-induction complete response (CR) vs. less than CR. **C.** Overall survival according to end-induction partial response (PR) or better vs. less than PR. **D.** Overall survival according to end-induction complete response (CR) vs. less than CR. Log-rank test $p < 0.0001$ for all panels.

Figure 3.
Overall survival according to PD (both early and end-induction PD) vs no PD during induction. Log-rank test $p < 0.0001$.

Table 1.

Clinical and biological features by end-induction response (PR vs <PR) in patients with high-risk neuroblastoma.

Feature	All Patients* N (%)	Partial Response or Better** N (%)	Less than Partial Response** N (%)	p-value#
Age ≥ 18 months at diagnosis Age < 18 months at diagnosis	1,083 (87.20) 159 (12.80)	852 (78.67) 139 (87.42)	231 (21.33) 20 (12.58)	0.0103#
Age ≥ 5 years at diagnosis Age < 5 years at diagnosis	245 (19.73) 997 (80.27)	173 (70.61) 818 (82.05)	72 (29.39) 179 (17.95)	<0.0001#
Male Female	714 (57.49) 528 (42.51)	570 (79.83) 421 (79.73)	144 (20.17) 107 (20.27)	0.9664
White Race Non-White Race Unknown	913 (81.08) 213 (18.92) 116	727 (79.63) 166 (77.93) 98	186 (20.37) 47 (22.07) 18	0.5828
Latino/Hispanic Non-Latino/Hispanic Unknown	131 (10.93) 1,067 (89.07) 44	101 (77.10) 853 (79.94) 37	30 (22.90) 214 (20.06) 7	0.4455
INSS Stage 4 All other stages	1,078 (86.80) 164 (13.20)	845 (78.39) 146 (89.02)	233 (21.61) 18 (10.98)	0.0016#
Adrenal primary Other primary sites Unknown	546 (46.19) 636 (53.81) 60	420 (76.92) 522 (82.08) 49	126 (23.08) 114 (17.92) 11	0.0281
Thoracic primary Other primary sites Unknown	72 (6.09) 1,110 (93.91) 60	63 (87.50) 879 (79.19) 49	9 (12.50) 231 (20.81) 11	0.0894
Presence of Bone Metastasis Absence of Bone Metastasis Unknown	252 (64.45) 139 (35.55) 851	215 (85.32) 111 (79.86) 665	37 (14.68) 28 (20.14) 186	0.1650
Presence of Bone Marrow Metastasis Absence of Bone Marrow Metastasis Unknown	296 (75.70) 95 (24.30) 851	245 (82.77) 81 (85.26) 665	51 (17.23) 14 (14.74) 186	0.5701
MYCN Amplified MYCN Non-amplified Unknown	469 (43.55) 608 (56.45) 165	401 (85.50) 469 (77.14) 121	68 (14.50) 139 (22.86) 44	0.0006#
ALK aberrant ALK wild type Unknown	96 (38.71) 152 (61.29) 994	79 (82.29) 127 (83.55) 785	17 (17.71) 25 (16.45) 209	0.7965
Diploid Hyperdiploid Unknown	532 (53.31) 466 (46.69) 244	420 (78.95) 383 (82.19) 188	112 (21.05) 83 (17.81) 56	0.1976
LOH at 1p No 1p LOH Unknown	215 (45.07) 262 (54.93) 765	184 (85.58) 199 (75.95) 608	31 (14.42) 63 (24.05) 157	0.0085#
LOH at 11q No 11q LOH Unknown	151 (32.40) 315 (67.60) 776	107 (70.86) 267 (84.76) 617	44 (29.14) 48 (15.24) 159	0.0004#
Presence of LOH at 1p and/or 11q No LOH at 1p or 11q Unknown	324 (68.79) 147 (31.21) 771	261 (80.56) 117 (79.59) 613	63 (19.44) 30 (20.41) 158	0.8077
Unfavorable Histology Favorable Histology Unknown	1,007 (96.00) 42 (4.00) 193	799 (79.34) 34 (80.95) 158	208 (20.66) 8 (19.05) 35	0.8007

Feature	All Patients[*] N (%)	Partial Response or Better^{**} N (%)	Less than Partial Response^{**} N (%)	p-value[#]
High MKI Low/Intermediate MKI Unknown	373 (42.00) 515 (58.00) 354	315 (84.45) 399 (77.48) 277	58 (15.55) 116 (22.52) 77	0.0098 [#]
Undifferentiated/Poorly Differentiated Differentiating Unknown	970 (95.94) 41 (4.06) 231	769 (79.28) 34 (82.93) 188	201 (20.72) 7 (17.07) 43	0.5713
Chemotherapy Modification No Chemotherapy Modification Unknown	56 (11.74) 421 (88.26) 765	50 (89.29) 340 (80.76) 601	6 (10.71) 81 (19.24) 164	0.1206
MIBG avid MIBG non-avid Unknown	433 (90.97) 43 (9.03) 766	353 (81.52) 40 (93.02) 598	80 (18.48) 3 (6.98) 168	0.0580
Induction Delay No Induction Delay Unknown	162(13.26) 1,060(86.74) 20	140 (86.42) 851 (80.28) --	22 (13.58) 209 (19.72) 20	0.0632
PD during early induction evaluation No PD during early induction evaluation Unknown	41 (4.28) 917 (95.72) 284	7 (17.07) 743 (81.03) 241	34 (82.93) 174 (18.97) 43	<0.0001 [#]
PR or better during early induction evaluation < PR during early induction evaluation Unknown	498 (51.98) 460 (48.02) 284	453 (90.96) 297 (64.57) 241	45 (9.04) 163 (35.43) 43	<0.0001 [#]

[#] Statistically significant p-values have been highlighted, after adjustment for multiple comparisons using a family-wise error rate of 0.05.

^{*} Percentages in this column sum to 100%, with patients with unknown values listed but not included in the reported percentages.

^{**} Percentages in each row of these two columns sum to 100% across these two columns, with patients with unknown values listed but not included in the reported percentages.

Table 2.

Clinical and biological features by end-induction response (CR vs <CR) in patients with high-risk neuroblastoma.

Feature	Complete Response* N (%)	Less than Complete Response* N (%)	p-value [#]
Age ≥ 18 months at diagnosis Age < 18 months at diagnosis	223 (20.59) 35 (22.01)	860 (79.41) 124 (77.99)	0.6799
Age ≥ 5 years at diagnosis Age < 5 years at diagnosis	42 (17.14) 216 (21.66)	203 (82.86) 781 (78.34)	0.1180
Male Female	139 (19.47) 119 (22.54)	575 (80.53) 409 (77.46)	0.1873
White Race Non-White Race Unknown	195 (21.36) 38 (17.84) 25	718 (78.64) 175 (82.16) 91	0.2538
Latino/Hispanic Non-Latino/Hispanic Unknown	25 (19.08) 226 (21.18) 7	106 (80.92) 841 (78.82) 37	0.5778
INSS Stage 4 All other stages	192 (17.81) 66 (40.24)	886 (82.19) 98 (59.76)	<0.0001 [#]
Adrenal primary Other primary sites Unknown	124 (22.71) 122 (19.18) 12	422 (77.29) 514 (80.82) 48	0.1363
Thoracic primary Other primary sites Unknown	11 (15.28) 235 (21.17) 12	61 (84.72) 875 (78.83) 48	0.2326
Presence of Bone Metastasis Absence of Bone Metastasis Unknown	47 (18.65) 37 (26.62) 174	205 (81.35) 102 (73.38) 677	0.0663
Presence of Bone Marrow Metastasis Absence of Bone Marrow Metastasis Unknown	66 (22.30) 18 (18.95) 174	230 (77.70) 77 (81.05) 677	0.4891
MYCN Amplified MYCN Non-amplified Unknown	127 (27.08) 98 (16.12) 33	342 (72.92) 510 (83.88) 132	<0.0001 [#]
ALK aberrant ALK wild type Unknown	25 (26.04) 43 (28.29) 190	71 (73.96) 109 (71.71) 804	0.6991
Diploid Hyperdiploid Unknown	110 (20.68) 99 (21.24) 49	422 (79.32) 367 (78.76) 195	0.8259
LOH at 1p No 1p LOH Unknown	54 (25.12) 46 (17.56) 158	161 (74.88) 216 (82.44) 607	0.0436
LOH at 11q No 11q LOH Unknown	21 (13.91) 73 (23.17) 164	130 (86.09) 242 (76.83) 612	0.0196 [#]
Presence of LOH at 1p and/or 11q No LOH at 1p or 11q Unknown	70 (21.60) 26 (17.69) 162	254 (78.40) 121 (82.31) 609	0.3281
Unfavorable Histology Favorable Histology Unknown	220 (21.85) 5 (11.90) 33	787 (78.15) 37 (88.10) 160	0.1240
High MKI Low/Intermediate MKI Unknown	98 (26.27) 96 (18.64) 64	275 (73.73) 419 (81.36) 290	0.0066 [#]

Feature	Complete Response* N (%)	Less than Complete Response* N (%)	p-value [#]
Undifferentiated/Poorly Differentiated Differentiating Unknown	208 (21.44) 7 (17.07) 43	762 (78.56) 34 (82.93) 188	0.5030
MIBG avid MIBG non-avid Unknown	95 (21.94) 22 (51.16) 141	338 (78.06) 21 (48.84) 625	<0.0001 [#]
Chemotherapy Modification No Chemotherapy Modification Unknown	18 (32.14) 94 (22.33) 146	38 (67.86) 327 (77.67) 619	0.1035
Induction Delay No Induction Delay Unknown	29 (17.90) 229 (21.60) --	133 (82.10) 831 (78.40) 20	0.2822
PD during early induction evaluation No PD during early induction evaluation Unknown	-- 190 (20.72) 68	41 (100.00) 727 (79.28) 216	0.0011 [#]
PR or better during early induction evaluation < PR during early induction evaluation Unknown	146 (29.32) 44 (9.57) 68	352 (70.68) 416 (90.43) 216	<0.0001 [#]

[#] Statistically significant p-values have been highlighted, after adjustment for multiple comparisons using a family-wise error rate of 0.05.

* Percentages in each row of these two columns sum to 100% across these two columns, with patients with unknown values listed but not included in the reported percentages.

Table 3.

Clinical and biological features according to documented progressive disease during induction therapy in patients with high-risk neuroblastoma.

Feature	Progressive Disease** N (%)	No Disease Progression** N (%)	p-value [#]
Age ≥ 18 months at diagnosis Age < 18 months at diagnosis	99 (9.14) 14 (8.81)	984 (90.86) 145 (91.19)	0.8905
Age ≥ 5 years at diagnosis Age < 5 years at diagnosis	20 (8.16) 93 (9.33)	225 (91.84) 904 (90.67)	0.5701
Male Female	60 (8.40) 53 (10.04)	654 (91.60) 475 (89.96)	0.3221
White Race Non-White Race Unknown	83 (9.09) 22 (10.33) 8	830 (90.91) 191 (89.67) 108	0.5759
Latino/Hispanic Non-Latino/Hispanic Unknown	13 (9.92) 93 (8.72) 7	118 (90.08) 974 (91.28) 37	0.6460
INSS Stage 4 All other stages	100 (9.28) 13 (7.93)	978 (90.72) 151 (92.07)	0.5755
Adrenal primary Other primary sites Unknown	57 (10.44) 52 (8.18) 4	489 (89.56) 584 (91.82) 56	0.1800
Thoracic primary Other primary sites Unknown	4 (5.56) 105 (9.46) 4	68 (94.44) 1,005 (90.54) 56	0.2672
Presence of Bone Metastasis Absence of Bone Metastasis Unknown	21 (8.33) 16 (11.51) 76	231 (91.67) 123 (88.49) 775	0.3042
Presence of Bone Marrow Metastasis Absence of Bone Marrow Metastasis Unknown	27 (9.12) 10 (10.53) 76	269 (90.88) 85 (89.47) 775	0.6840
MYCN Amplified MYCN Non-amplified Unknown	47 (10.02) 48 (7.89) 18	422 (89.98) 560 (92.11) 147	0.2224
ALK aberrant ALK wild type Unknown	10 (10.42) 8 (5.26) 95	86 (89.58) 144 (94.74) 899	0.1276
Diploid Hyperdiploid Unknown	53 (9.96) 37 (7.94) 23	479 (90.04) 429 (92.06) 221	0.2658
LOH at 1p No 1p LOH Unknown	14 (6.51) 17 (6.49) 82	201 (93.49) 245 (93.51) 683	0.9919
LOH at 11q No 11q LOH Unknown	15 (9.93) 16 (5.08) 82	136 (90.07) 299 (94.92) 694	0.0491 [#]
Presence of LOH at 1p and/or 11q No LOH at 1p or 11q Unknown	23 (7.10) 8 (5.44) 82	301 (92.90) 139 (94.56) 689	0.5017
Unfavorable Histology Favorable Histology Unknown	98 (9.73) 3 (7.14) 12	909 (90.27) 39 (92.86) 181	0.7905 [*]
High MKI Low/Intermediate MKI Unknown	37 (9.92) 42 (8.16) 34	336 (90.08) 473 (91.84) 320	0.3621

Feature	Progressive Disease** N (%)	No Disease Progression** N (%)	p-value#
Undifferentiated/Poorly Differentiated Differentiating Unknown	89 (9.18) 4 (9.76) 20	881 (90.82) 37 (90.24) 211	0.7851*
MIBG avid MIBG non-avid Unknown	34 (7.85) 1 (2.33) 78	399 (92.15) 42 (97.67) 688	0.3510*
Chemotherapy Modification No Chemotherapy Modification Unknown	5 (8.93) 43 (10.21) 65	51 (91.07) 378 (89.79) 700	0.7639
Induction Delay No Induction Delay Unknown	10 (6.17) 83 (7.83) 20	152 (93.83) 977 (92.17) --	0.4587
PD during early induction evaluation No PD during early induction evaluation Unknown	27 (65.85) 59 (6.43) 27	14 (34.15) 858 (93.57) 257	<0.0001 [#]
PR or better during early induction evaluation < PR during early induction evaluation Unknown	22 (4.42) 64 (13.91) 27	476 (95.58) 396 (86.09) 257	<0.0001 [#]

[#] Statistically significant p-values have been highlighted, after adjustment for multiple comparisons using a family-wise error rate of 0.05.

* Fisher's exact test was used in place of the chi-square test as expected counts were <5.

** Percentages in each row of these two columns sum to 100% across these two columns, with patients with unknown values listed but not included in the reported percentages.

Table 4.

Clinical and biological features by early response assessment performed mid-Induction therapy in patients with high-risk neuroblastoma.

Feature	Early PD ^{**} N (%)	No Early PD ^{**} N (%)	P-value	Early PR or Better ^{***} N (%)	<PR at Early Time Point ^{***} N (%)	p-value
Age 18 months at diagnosis Age < 18 months at diagnosis	35 (4.02) 6 (4.76)	835 (95.98) 120 (95.24)	0.6964	437 (50.23) 83 (65.87)	433 (49.77) 43 (34.13)	0.0010 [#]
Age 5 years at diagnosis Age < 5 years at diagnosis	10 (4.83) 31 (3.93)	197 (95.17) 758 (96.07)	0.5610	79 (38.16) 441 (55.89)	128 (61.84) 348 (44.11)	<0.0001 [#]
Male Female	26 (4.56) 15 (3.52)	544 (95.44) 411 (96.48)	0.4136	302 (52.98) 218 (51.17)	268 (47.02) 208 (48.83)	0.5718
White Race Non-White Race Unknown	31 (4.17) 6 (3.57) 4	712 (95.83) 162 (96.43) 81	0.7216	384 (51.68) 91 (54.17) 45	359 (48.32) 77 (45.83) 40	0.5605
Latino/Hispanic Non-Latino/Hispanic Unknown	4 (3.85) 36 (4.22) 1	100 (96.15) 818 (95.78) 37	1.0000 [*]	57 (54.81) 445 (52.11) 18	47 (45.19) 409 (47.89) 20	0.6027
INSS Stage 4 All other stages	36 (4.17) 5 (3.76)	827 (95.83) 128 (96.24)	0.8238	429 (49.71) 91 (68.42)	434 (50.29) 42 (31.58)	<0.0001 [#]
Adrenal primary Other primary sites Unknown	21 (4.90) 19 (3.68) 1	408 (95.10) 497 (96.32) 50	0.3565	220 (51.28) 272 (52.71) 28	209 (48.72) 244 (47.29) 23	0.6611
Thoracic primary Other primary sites Unknown	2 (3.45) 38 (4.28) 1	56 (96.55) 849 (95.72) 50	1.0000 [*]	27 (46.55) 465 (52.42) 28	31 (53.45) 422 (47.58) 23	0.3858
Presence of Bone Metastasis Absence of Bone Metastasis Unknown	2 (1.18) 5 (5.38) 34	167 (98.82) 88 (94.62) 700	0.1009 [*]	88 (52.07) 53 (56.99) 379	81 (47.93) 40 (43.01) 355	0.4448
Presence of Bone Marrow Metastasis Absence of Bone Marrow Metastasis Unknown	4 (2.04) 3 (4.55) 34	192 (97.96) 63 (95.45) 700	0.3731 [*]	107 (54.59) 34 (51.52) 379	89 (45.41) 32 (48.48) 355	0.6645
MYCN Amplified MYCN Non-amplified Unknown	18 (4.85) 19 (3.87) 4	353 (95.15) 472 (96.13) 130	0.4812	257 (69.27) 203 (41.34) 60	114 (30.73) 288 (58.66) 74	<0.0001 [#]
ALK aberrant ALK wild type Unknown	2 (2.90) 2 (1.71) 37	67 (97.10) 115 (98.29) 773	0.6282 [*]	50 (72.46) 75 (64.10) 395	19 (27.54) 42 (35.90) 415	0.2407
Diploid Hyperdiploid Unknown	13 (3.22) 19 (4.96) 9	391 (96.78) 364 (95.04) 200	0.2159	217 (53.71) 202 (52.74) 101	187 (46.29) 181 (47.26) 108	0.7849
LOH at 1p No 1p LOH Unknown	7 (3.83) 8 (3.62) 26	176 (96.17) 213 (96.38) 566	0.9135	123 (67.21) 102 (46.15) 295	60 (32.79) 119 (53.85) 297	<0.0001 [#]
LOH at 11q No 11q LOH Unknown	6 (4.84) 8 (2.97) 27	118 (95.16) 261 (97.03) 576	0.3852 [*]	54 (43.55) 164 (60.97) 302	70 (56.45) 105 (39.03) 201	0.0012 [#]
Presence of LOH at 1p and/or 11q No LOH at 1p or 11q Unknown	10 (3.65) 5 (4.03) 26	264 (96.35) 119 (95.97) 572	1.0000 [*]	161 (58.76) 59 (47.58) 300	113 (41.24) 65 (52.42) 298	0.0378
Unfavorable Histology Favorable Histology Unknown	35 (4.35) -- 6	769 (95.65) 38 (100.00) 148	0.3981 [*]	427 (53.11) 18 (47.37) 75	377 (46.89) 20 (52.63) 79	0.4885

Feature	Early PD ^{**} N (%)	No Early PD ^{**} N (%)	P-value	Early PR or Better ^{***} N (%)	<PR at Early Time Point ^{***} N (%)	p-value
High MKI Low/Intermediate MKI Unknown	12 (3.93) 18 (4.27) 11	293 (96.07) 404 (95.73) 258	0.8248	200 (65.57) 193 (45.73) 127	105 (34.43) 229 (54.27) 142	<0.0001 [#]
Undifferentiated/Poorly Differentiated Differentiating Unknown	33 (4.13) 2 (8.33) 6	766 (95.87) 22 (91.67) 167	0.2718 [*]	426 (53.32) 8 (33.33) 86	373 (46.68) 16 (66.67) 87	0.0533
MIBG avid MIBG non-avid Unknown	7 (2.27) -- 34	301 (97.73) 22 (100.00) 632	1.0000 [*]	187 (60.71) 17 (77.27) 316	121 (39.29) 5 (22.73) 350	0.1225
Chemotherapy Modification No Chemotherapy Modification Unknown	9 (2.88) 32	14 (100) 303 (97.12) 638	1.0000 [*]	11 (78.57) 166 (53.21) 343	3 (21.43) 146 (46.79) 327	0.0623
Induction Delay No Induction Delay Unknown	3 (3.09) 18 (2.06) 20	94 (96.91) 854 (97.94) 7	0.5093 [*]	55 (56.70) 461 (52.87) 4	42 (43.30) 411 (47.13) 23	0.4728

[#] Statistically significant p-values have been highlighted, after adjustment for multiple comparisons using a family-wise error rate of 0.05.

^{*} Fisher's exact test was used in place of the chi-square test as expected counts were <5.

^{**} Percentages in each row of these two columns sum to 100% across these two columns, with patients with unknown values listed but not included in the reported percentages.

^{***} Percentages in each row of these two columns sum to 100% across these two columns, with patients with unknown values listed but not included in the reported percentages.

Table 5. Multivariable logistic regression models of end-induction response in high-risk neuroblastoma.

Predictors of Partial Response or Better					
Feature	With 1p and 11q (n=407)		Without 1p and 11q (n=855)		
	Odds Ratio (95% CI)	p-value	Odds Ratio (95% CI)	p-value	
Age (<5 years vs. ≥ 5 years) [^]	1.611 (0.876,2.963)	0.1252	1.458 (0.951,2.235)	0.0838	
INSS Stage (Non-Stage 4 vs. Stage 4) [^]	1.378 (0.615,3.087)	0.4365	2.520 (1.380,4.602)	0.0026	
MYCN Status (Non-Amplified vs. Amplified)	1.061 (0.496,2.269)	0.8795	0.716 (0.471, 1.087)	0.1170	
1p LOH (No LOH vs. 1p LOH) [^]	0.772 (0.419, 1.425)	0.4085	--	--	
11q LOH (No LOH vs. 11q LOH) [^]	1.962 (1.104,3.487)	0.0216	--	--	
MKI (Low/Intermediate vs. High) [^]	0.784 (0.417, 1.474)	0.4492	0.846 (0.555, 1.287)	0.4343	
Predictors of Complete Response					
Feature	With MIBG (n=99)		Without MIBG (n=408)		Without MIBG and 11q (n=855)
	Odds Ratio (95% CI)	p-value	Odds Ratio (95% CI)	p-value	Odds Ratio (95% CI)
INSS Stage (Non-Stage 4 vs. Stage 4) [^]	1.607(0.420,6.155)	0.4887	2.015(1.080,3.760)	0.0276	2.916(1.965,4.327)
MYCN Status (Non-Amplified vs. Amplified) [^]	0.373(0.111, 1.252)	0.1105	0.318(0.165,0.612)	0.0006	0.491 (0.491, 0.333)
11q LOH (No LOH vs. 11q LOH) [^]	2.197(0.594,8.128)	0.2383	1.128(0.587,2.167)	0.7188	--
MKI (Low/Intermediate vs. High) [^]	1.262(0.409,3.893)	0.6859	1.393(0.772,2.512)	0.2708	0.958(0.651, 1.409)
MIBG avidity (Non-Avid vs. Avid) [^]	3.405 (0.837, 13.859)	0.0871	--	--	--

[^] Indicates the reference level for each variable.