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Association Between End-Induction Response According to the Revised International Neuroblastoma Response Criteria (INRC) and Outcome in High-Risk Neuroblastoma Patients

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Abstract

Background: The 1993 International Neuroblastoma Response Criteria (INRC) were revised in 2017 to include modern functional imaging studies and methods for quantifying disease in bone marrow. We hypothesized the 2017 INRC would enable more precise assessment of response to treatment and provide superior prognostic information compared to the 1993 criteria.

Methods: High-risk (HR) neuroblastoma patients from two institutions in Chicago diagnosed between 2006 and 2016 were identified. Patients were assessed post induction chemotherapy via the 1993 and 2017 INRC and classified as responder (mixed response (MXR) or minor response (MR), respectively) or non-responder (< MXR or < MR). Event free survival (EFS) and overall survival (OS) for responders versus non-responders were determined from end-induction and stratified by Cox regression. Patients with progressive disease at end-induction were eliminated from the EFS analyses but included in the OS analysis.

Results: The 1993 criteria classified 52 of the 60 HR patients as responders, whereas 54 responders were identified using the 2017 criteria (Spearman correlation $r=0.82$, $p<0.001$). No statistically significant difference in EFS was observed for responders versus non-responders using either criteria ($p=0.48$ and $p=0.08$). However, superior OS was observed for responders ($p=0.01$) using either criteria. Both criteria were sensitive in identifying responders among those with good outcomes. The specificity to identify non-responders among those with poor outcomes was poor.

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Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflict of interest statement

We have no conflicts of interest to disclose. All authors have significantly contributed to this work, reviewed the manuscript and agreed upon the content.

Conclusions: In HR neuroblastoma, end-induction response defined by the 1993 or 2017 INRC is associated with survival. Larger cohorts are needed to determine if the 2017 INRC provides more precise prognostication.

Keywords

Neuroblastoma; International neuroblastoma response criteria (INRC); Outcome

INTRODUCTION

Standardized response criteria are used in many types of cancer to enable comparisons of treatment response across and within clinical studies. In neuroblastoma, the most frequent extracranial solid tumor in children¹, International Neuroblastoma Response Criteria (INRC) were first established by expert consensus in 1988² and then revised in 1993 (Table 1)³. The prognostic strength of response defined by the 1993 INRC was subsequently demonstrated in a cohort of stage 4 patient⁴. During the past two decades, significant technological advances in functional imaging studies and new methods for quantifying disease in the bone marrow have significantly modified our ability to measure tumor response. Specifically, Iodine-123 (¹²³I) metaiodobenzylguanidine (MIBG) scans are now a standard method to evaluate and quantify soft tissue and skeletal sites of disease⁵⁻⁸. In addition, advances in immunohistochemistry and reverse transcriptase-quantitative polymerase chain reaction (RTqPCR) have allowed for improvements in the ability to detect minimal amounts of neuroblastoma within the bone marrow⁹. To incorporate these more modern approaches for measuring disease response, the INRC was revised in 2017 by consensus expert opinion (Table 2)¹⁰. However, the 2017 INRC has yet to be clinically validated.

A number of substantial changes have been incorporated into the revised 2017 INRC. Specifically, complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) are defined separately for the primary soft tissue site, metastatic soft tissue, bone sites, and the bone marrow (BM). As heterogeneous disease infiltration makes it difficult to serially assess low-level marrow disease, a new category of minimal disease (MD) was established to classify bone marrow with >0% but <5% tumor infiltration. Overall response is determined by the composite response of each of the components (Table 2). To be classified as CR, all components must meet criteria for CR. PR is defined as PR in at least one component and all other components are either CR, PR, MD, or not involved. A new minor response (MR) classification has also been added that includes PR or CR in at least one component but at least one other component with SD. SD is defined as SD in one component with no better than SD or site uninvolved in other components. Patients with PD in any component are classified as PD for overall response.

Treatment response, defined by MIBG Curie scores or the 1993 INRC is known to be significantly associated with outcome for children with HR neuroblastoma¹¹⁻¹⁵. We hypothesized that the revised 2017 INRC would enable a more refined assessment of response and be more highly prognostic of outcome in HR neuroblastoma patients compared to the 1993 INRC criteria. In this study, we analyzed the association between outcome and

response at end-of-induction defined by the 1993 and the 2017 INRC in a cohort of HR neuroblastoma patients and compared the prognostic strength of both INRC.

2 PATIENTS AND METHODS

2.1 Patients

HR neuroblastoma patients diagnosed between 2006 and 2016 at the University of Chicago and Lurie Children's Hospital were identified through in-house pediatric cancer registries. Eighty-seven HR neuroblastoma patients were treated at the participating sites between January 2006 and August 2016. Of these patients, 27 were excluded due to lack of required scans, death or progression prior to post induction evaluation, or evaluations done earlier in induction instead of at the end of induction per the treating clinician's discretion. Patients without available required scans for analysis fell into two categories: 1) patients who underwent bone scans instead of MIBG or PET scans as required by the 2017 INRC for evaluation, and 2) patients transferring care to study sites during therapy and access to diagnostic scans and evaluations could not be obtained. For the 60 patients meeting inclusion criteria, patient demographics, International Neuroblastoma Staging System (INSS) stage, the percentage of bone marrow disease, *MYCN* status, tumor ploidy, tumor histology defined by the International Neuroblastoma Pathology Classification (INPC)¹⁶, treatment, imaging studies and reports, pathology reports, and outcome as of August 2018 were abstracted from medical records. All patients were verified to be HR according to criteria defined by the Children's Oncology Group (COG) study ANBL0532¹⁷, and induction therapy was administered on or per the following clinical trials: ANBL02P1 (n=15)¹⁸, ANBL0532 (n=40)¹⁷, or ANBL09P1 (n=4) ([NCT01175356](#)). Three patients received one cycle of intermediate-risk chemotherapy per ANBL0531¹⁹ prior to confirmation of HR disease and were subsequently switched to high-risk therapy per ANBL0532. One 5-month-old, HR patient with a stage 3, localized, favorable histology, *MYCN* amplified tumor was treated with intermediate-risk therapy per ANBL0531 per physician preference. The study was approved by the Institutional Review Board at each participating institution. The University of Chicago served as the primary study site.

2.2 Study design

To be eligible for inclusion in this study, patients were required to have had CT scans, MIBG and or [¹⁸F] fluorodeoxyglucose (FDG)-positron emission, tomography (FDG-PET) scan, and bilateral bone marrow biopsy and aspirates both at diagnosis and after induction chemotherapy (unless, in stage 3 HR patients, BM was negative at diagnosis and not repeated). For each patient, response to induction chemotherapy, prior to consolidation with autologous stem cell transplant, was assessed using both the 1993 and 2017 INRC^{3,10}. One patient treated per ANBL0532 received 2 cycles of ANBL1221²⁰ after completion of induction therapy prior to receiving tandem transplants. In this case, INRC was classified prior to the ANBL1221 therapy. In cases in which multiple scans or BM studies were performed following induction chemotherapy (*i.e.* delay due to infection necessitating a repeat pre-transplant evaluation) response was determined using the studies obtained just prior to scheduled autologous stem cell transplant. MIBG Curie scores were determined using the modified Curie score method^{15,21}. For MIBG scans in which the Curie score was

not indicated in the medical record, scores were calculated by authors EKB or KL in consultation with imaging physicians at each respective institution. Surgery to resect the primary tumor was performed prior to the end of induction evaluation in 52 patients. Eight patients did not undergo surgery prior to end of induction evaluations.

For the 1993 criteria, response was classified as CR, very good partial response (VGPR), PR, mixed response (MXR), no response (NR), or PD³. Responders included patients with CR, VGPR, PR, and MXR whereas non-responders had NR or PD after induction therapy. For the 2017 criteria, response was classified as CR, PR, MR, SD, or PD¹⁰. Responders included patients with CR, PR, or MR whereas non-responders had SD or PD. A subgroup analysis was conducted evaluating only response at metastatic sites (*i.e.* non-primary site soft-tissue, bone, and bone marrow) for patients with stage 4 disease. Response for patients with metastatic disease was defined as CR versus non-CR. CR at metastatic sites was defined as resolution of all metastatic soft tissue sites by CT, skeletal sites by MIBG/PET scans, and bone marrow disease on bilateral bone marrow aspirate and biopsies. All others were classified as non-CR at metastatic sites. All patient information was recorded in a password protected REDCap database at the University of Chicago.

2.3 Statistical analysis

Using a landmark analysis approach²², event free survival (EFS) time was defined as months from end-of-induction to occurrence of the first event (relapse, progression, secondary malignancy, or death from any cause). Patients without an event were censored on the date of last contact as of August 2018. Patients with PD at the end of induction therapy were excluded from all EFS analyses. Overall survival (OS) time was defined as months from end induction evaluation to death due to any cause or last follow up as of August 2018. The Kaplan-Meier method was used to estimate EFS and OS according to response defined by the 1993 and 2017 INRC. Differences between curves were assessed by the stratified log-rank test, with treating hospital as the stratification factor. The association between INRC response and EFS and OS was analyzed using stratified, multivariate Cox regression using the full INRC scale with higher values indicating worse response (*i.e.* 1993: PD>NR>MXR>PR>VGPR>CR and 2017: PD>SD>MR>PR>CR) with treating hospital as the stratification factor and age at diagnosis and stage as covariates.

The C-statistic was calculated as a measure of discrimination between survivors and non-survivors (OS) or relapse/death and non-relapse survivors (EFS). Confidence intervals for the C-statistics were constructed based on 500 bootstrap replications. Larger C-statistics indicate greater discriminatory power; a C-statistic of 1 indicates perfect discrimination. The area under the receiver operating characteristic (ROC) curve (using the trapezoidal rule) with the full INRC scale and sensitivity/specificity for the 1993 and 2017 INRC (responders vs. non-responders) were calculated for 3-year OS and 3-year EFS in those patients experiencing an event by three years or who otherwise had at least three years of follow-up data (n=54). Analyses were performed using Stata (version 15; StataCorp., College Station, TX). P-values <0.05 were considered statistically significant.

3 RESULTS

3.1 Patient characteristics and treatments

87 HR neuroblastoma patients were treated at the participating sites between January 2006 and August 2016. Of these patients, 27 were excluded due to not having the required scans, death or progression prior to post induction evaluation, or evaluations done earlier in induction instead of at the end of induction per the treating clinician's discretion as detailed in the methods section of this paper. The final analytic cohort was comprised of 60 patients; 33 from the University of Chicago and 27 from Lurie Children's Hospital. The clinical characteristics of the patients and their tumor biology are shown in Table 3.

3.2 Patient response post induction therapy according to the 1993 and 2017 INRC

Following induction therapy, 52 patients were classified as responders according to the 1993 INRC [CR (n=9), VGPR (n=8), PR (n=18), MXR (n=17)] whereas 54 patients were classified as responders using the 2017 INRC [CR (n=13), PR (n=29), MR (n=12)] (Table 4, Supplemental Information Table S1). There were eight patients classified as non-responders according to the 1993 criteria [NR (n=3), PD (n=5)] whereas six patients were classified as non-responders using the 2017 INRC [SD (n=2), PD (n=4)] (Table 4, Supplemental Information Table S1). The 1993 and 2017 INRC classifications were highly correlated (Spearman rank $r=0.82$, $p<0.001$).

Eight of the nine patients classified as CR by both INRC criteria are alive with no events with 3 to 11 years follow-up from post induction therapy. The other patient relapsed and died. The most variability in classification between the two response criteria was seen among the patients classified as CR and PR/VGPR. There were two patients classified as CR in the 2017 INRC who were classified as VGPR using the 1993 INRC. Both patients had less than 10mm of residual soft tissue disease at their primary site, which accounted for the differing classifications per the two criteria, and neither patient had a subsequent event at 4 and 8 years post induction therapy. The 2017 INRC allows for less than 10mm of residual primary tumor to be classified as a CR whereas the 1993 INRC requires no residual primary tumor to be classified as a CR. There were also two patients classified as CR per the 2017 INRC who were classified as PR by the 1993 INRC. One of the patients was classified as PR based on elevated HVA and VMA in the urine, and this patient did subsequently relapse. Urine catecholamines were included in the 1993 but not the 2017 INRC. The second patient was classified as a PR using the 1993 INRC based on a residual < 10mm liver lesion. The 1993 INRC requires full resolution of metastatic disease to be classified as VPGR or CR, whereas nonprimary target and nontarget lesions that measure <10 mm that have resolution of MIBG or FDG-PET uptake are classified as CR according to the 2017 INRC. This patient remains alive and relapse free 6 years post induction therapy.

The 1993 criteria classified six patients as MXR (at least one primary and one metastatic lesion decreased by 50% but no increase of more than 25% and no new lesions) and two as NR, all of whom were classified as having a PR per the 2017 criteria. Of these eight patients, two relapsed and died, one relapsed and is still alive, one died during transplant, and four are relapse-free and alive. Of those called MXR by the 1993 INRC, five out of six had bilateral

bone marrow positivity of <5% post induction which the 2017 INRC classifies as MD, meeting the overall PR response. The 1993 INRC PR criteria requires no BM disease or only one side with residual disease. The sixth patient did not have a reduction of all metastases by 50-90% as required by the 1993 INRC for PR. In contrast the 2017 INRC allows for a PR to have 30% reduction in metastatic target lesions or stable to decreased in size metastatic non-target lesions. Both patients classified as NR according to the 1993 INRC and PR according to the 2017 INRC had < 50% reduction in primary lesion volume post induction; one relapsed and died while the other remains event free and alive. The 2017 INRC defines PR of the primary tumor as a decrease in the longest diameter of 30%, whereas the 1993 INRC requires a 50-90% decrease in tumor volume. There was one patient classified as PR by the 1993 INRC who was classified as MR according to the 2017 INRC due to different definitions of BM disease. The patient had >5% residual disease on only one side meeting the PR definition according to the 1993 INRC. In contrast, according to the 2017 INRC, >5% BM positivity on any side is defined as SD for BM. Thus, the best overall response score possible for this patient, who ultimately died of complications from veno-occlusive disease during their second transplant, is a MR using the revised response criteria.

3.3 Survival according to 1993 and 2017 INRC following induction therapy

EFS was not statistically different for responders compared to non-responders using either the 1993 INRC ($p=0.48$, Figure 1A) or the 2017 INRC ($p=0.08$, Figure 1B). However, very few patients were classified as non-responders in this analysis because all patients with progressive disease (i.e. an event) at end of induction were excluded. Utilizing all response categories, those with superior responses (i.e. 1993: CR>VGPR>PR>MXR>NR and 2017: CR>PR>MR>SD) were less likely to have an event using either the 1993 INRC ($p=0.02$ from log-rank trend test, Supporting Information Figure S1A) or 2017 INRC ($p=0.002$ from log-rank trend test, Supporting Information Figure S1B). Multivariate Cox models using the full INRC scale with higher values indicating worse response (i.e. 1993: NR>MXR>PR>VGPR>CR and 2017: SD>MR>PR>CR) confirmed that those with inferior responses were more likely than those with superior responses to have an event according to either the 1993 INRC (hazard ratio 1.51, 95% CI 1.01-2.27, $p=0.047$) or 2017 INRC (hazard ratio 2.00, 95% CI 1.21-3.32 $p=0.007$) (Table 5). The C-statistic was 0.62 (95% CI 0.50-0.74) for the 1993 INRC and 0.65 (95% CI 0.55-0.75) for the 2017 INRC. Further examination of 3-year EFS determined an area under the ROC curve of 0.70 (95% CI 0.57-0.84) for the 1993 INRC and 0.71 (95% CI 0.59-0.84) for the 2017 INRC. Both INRC criteria were able to identify responders among patients who ultimately had no event 3 years post induction (sensitivity 96.0%, 95% CI: 79.6-99.9 and 100%, 95% CI: 86.3-100, respectively). However, they had limited ability to identify non-responders among those who would go on to have an event (specificity: 7.1%, 95% CI: 0.9-23.5 and 6.9%, 95% CI: 0.8-22.8, respectively). In other words, both INRC were better at identifying those patients who would not have events than in determining those patients who would ultimately relapse.

OS was statistically superior for responders compared to non-responders using either the 1993 INRC ($p=0.01$, Figure 1C) or the 2017 INRC definitions ($p=0.01$, Figure 1D). The log-rank trend test across response categories showed those with superior responses (i.e. 1993: CR>VGPR>PR>MXR>NR>PD and 2017: CR>PR>MR>SD>PD) were less likely to die

using either the 1993 INRC ($p=0.02$, Supporting Information Figure S2A) or 2017 INRC ($p=0.003$, Supporting Information Figure S2B). Multivariate Cox models using the full INRC scale with higher values indicating worse response (i.e. 1993: PD>NR>MXR>PR>VGPR>CR and 2017: PD>SD>MR>PR>CR) confirmed these findings for both the 1993 INRC (hazard ratio 1.45, 95% CI 1.02-2.06, $p=0.04$) and 2017 INRC (hazard ratio 1.68, 95% CI 1.13-2.51, $p=0.01$) (Table 5). The C-statistic was 0.63 (95% CI 0.51-0.75) for the 1993 INRC and 0.65 (95% CI 0.53-0.76) for the 2017 INRC. Further analysis of 3-year OS demonstrated the area under the ROC curve was 0.66 (95% CI 0.51-0.81) for the 1993 INRC and 0.68 (95% CI 0.54-0.82) for the 2017 INRC. Both INRC criteria were able to identify responders among patients who ultimately survived 3 years post induction (sensitivity 91.2%, 95% CI: 76.3-98.1 and 94.1%, 95% CI: 80.3-99.3, respectively); however had limited ability to identify non-responders among those who would go on to die (specificity 25.0%, 95% CI: 8.7-49.1 and 20.0%, 95% CI: 5.7-43.7, respectively). In other words, both INRC were better at identifying those patients who would survive 3 years post induction than in determining those patients who would ultimately die.

3.4 Survival of stage 4 patients according to response at metastatic sites

EFS was significantly worse for patients who did not achieve a metastatic CR compared to those with a CR at metastatic sites (hazard ratio 2.84, 95% CI 1.12-7.20, $p=0.03$, C-statistic=0.61; Table 5). However, there was not a significant difference in OS between these groups (hazard ratio 2.49, 95% CI 0.89-6.96, $p=0.08$, C-statistic=0.60; Table 5).

4 DISCUSSION

In this study, we validated the prognostic value of the 2017 INRC in HR neuroblastoma patients. We also demonstrated that response at end-of-induction defined by either the 1993 INRC or 2017 INRC was highly correlated, although variability between the two response criteria was identified among the patients classified as CR in the 2017 INRC versus PR/VGPR in the 1993 INRC and those classified as PR in the 2017 INRC vs MXR/NR in the 1993 INRC. Despite these differences, both response criteria were highly associated with outcome. The incorporation of functional imaging studies and more sensitive methods for quantifying disease in bone marrow in the 2017 INRC did not provide superior prognostic information compared to the 1993 criteria in this small study cohort.

Previous studies have similarly demonstrated a strong correlation between response to treatment and outcome in patients with neuroblastoma^{13,14,23}. MIBG Curie score during and after induction therapy has been shown to be significantly correlated with EFS¹³. HR patients who had relative MIBG scores ≥ 0.5 after 2 cycles of induction therapy or ≥ 0.24 after 4 cycles of induction chemotherapy had improved EFS and were more likely to be classified as CR or VGPR at the end of induction by the 1993 INRC^{11,14}. Yanik *et al.* showed that Curie scores >2 post induction therapy were associated with inferior EFS, however the Curie score was not significantly correlated with OS^{13,14}. Decreased EFS was also found in neuroblastoma patients who had increasing numbers of tumor cells detected by immunocytologic analysis of bone marrow and blood samples at the time of diagnosis and through induction²⁴. More recently, Pinto *et al.* found post induction response of PR or

better in HR neuroblastoma patients, as determined by the 1993 INRC, was associated with improved OS and EFS¹².

The contribution of primary tumor response, as a result of either chemotherapy or surgical resection, to survival remains controversial²⁵. While Von Allmen *et al.* reported that patients with 90% resection of their primary tumor had higher EFS and decreased cumulative incidence of local progression compared to those with less than <90% resection²⁶, Simon *et al.* demonstrated that extent of surgical resection of the primary tumor was not associated with EFS or OS in HR NBL patients²⁷. Further, Bagatell *et al.* reported that primary tumor response to chemotherapy evaluated using either 3-dimensional or 1-dimensional measurements was not associated with OS or EFS²³. Based on these contradictory results, we hypothesized that response at only metastatic soft tissue, bone and bone marrow sites would replicate the association between full INRC and outcome. Indeed, we found that response at metastatic sites was statistically significantly associated with EFS but not OS. However, larger studies are needed to validate the degree to which primary site response may contribute to predicting outcomes.

In summary, our study demonstrates the prognostic value of the 2017 INRC in HR neuroblastoma patients. Because response was only evaluated at end-of-induction, additional studies will be required to assess the prognostic value of the 2017 INRC at different time points during therapy and to determine if different post-inductions treatments modifies the clinical value of this biomarker. Although each patient did serve as their own control using either the 1993 or 2017 INRC, the small size of our patient cohort and the lack of uniform treatment are limitations. Analysis of larger numbers of patients will be needed to determine if response at end-of-induction response using the 2017 INRC will provide more precise prognostication than the 1993 INRC.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

INRC	International Neuroblastoma Response Criteria
OS	Overall Survival
EFS	Event Free Survival
HR	High Risk

MIBG	Iodine-123 (¹²³ I) Metaiodobenzylguanidine
FDG-PET	[¹⁸ F] fluorodeoxyglucose (FDG)-positron emission, tomography
RTqPCR	Reverse transcriptase-quantitative polymerase chain reaction
BM	Bone Marrow
MD	Minimal Disease
INSS	International Neuroblastoma Staging System
CR	Complete Response
VGPR	Very Good Partial Response
PR	Partial Response
MXR	Mixed Response
MR	Minor Response
NR	No Response
SD	Stable Disease
PD	Progressive Disease
3D	3-Dimensional
1D	1-Dimensional
RECIST	Response Evaluation Criteria in Solid Tumors
COG	Children's Oncology Group

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FIGURE 1.

Event free survival (A) and overall survival (C) for responders (CR, VGPR, PR, MXR) vs non-responders (NR, PD*) based on 1993 INRC ($p=0.48$ and $p=0.01$ respectively). Event free survival (B) and overall survival (D) for responders (CR, PR, MR) vs non-responders (SD, PD*) based on 2017 INRC ($p=0.08$ and $p=0.01$ respectively)

*PD patients were excluded from EFS analysis

TABLE 11993 International Neuroblastoma Research Criteria (INRC). Adapted from Brodeur *et al*³

Response	Primary Tumor	Metastatic Sites
Complete Response (CR)	No Tumor	No tumor. Normal catecholamines
Very Good Partial Response (VGPR)	Decreased by 90-99%	No tumor. Normal catecholamines
Partial Response (PR)	Decreased by > 50%	All measurable sites decreased by >50%. Bone and bone marrow sites decreased by >50%. No more than one BM site can be positive.
Mixed Response (MXR)	At least one lesion decreased by >50%. No increase more than 25%	No new lesions. At least one lesion decreased by >50%. No increase more than 25%
No Response (NR)	Decreased by less than 50% but no increase more than 25%	No new lesions. No lesion decreased by greater than 50% but no increase more than 25%
Progressive Disease (PD)	Lesions increase by more than 25%.	Any new lesion. Lesions increase by more than 25%. Previous negative bone marrow now positive.

TABLE 2

2017 International Neuroblastoma Response Criteria (INRC) overall response. Components include individual assessments of response at primary site, metastatic sites, and bone marrow. Adapted from Park *et al*¹⁰

Response	Criterion
Complete Response (CR)	CR in all components.
Partial Response (PR)	PR in at least one component and all other components are CR, minimal disease (MD) *, PR, or not involved. No PD.
Minor Response (MR)	PR or CR in at least one component but at least one component with SD. No PD.
Stable Disease (SD)	No component better than SD or no involvement. No PD.
Progressive Disease (PD)	Any component with PD.

* MD is a unique response classification exclusive to the bone marrow assessment

TABLE 3

Patient characteristics and treatment received

Patient Cohort	Number (%)
Site	
University of Chicago	33 (55%)
Lurie Children's Hospital	27 (45%)
Age	
< 18 months	10 (17%)
18 months	50 (83%)
Gender	
Female	16 (27%)
Male	44 (73%)
INSS Stage	
Stage 3	10 (17%)
Stage 4	50 (83%)
MYCN Status	
Amplified	23 (38%)
Non-Amplified	24 (40%)
Unknown	13 (22%)
Histology	
Favorable	2 (3%)
Unfavorable	49 (82%)
Unknown	9 (15%)
Induction Protocol	
ANBL02P1	15 (25%)
ANBL0531	1 (2%)
ANBL0532	40 [*] (67%)
ANBL09P1	4 (6%)
Number of Transplants	
Zero	12 (20%)
One	37 (62%)
Two	9 (15%)
Three [#]	2 (3%)
Immunotherapy per ANBL0032	
Yes	33 (55%)
No	45%

^{*} 3 patients received one cycle of ANBL0531 prior to starting ANBL0532

[#] 2 patients were treated post induction on the Chicago pilot II study

TABLE 4

INRC assignment for each patient according to both the 1993 and 2017 INRC. Spearman correlation = 0.82 (p<0.001)

	1993 INRC						
	CR	VGPR	PR	MXR	NR	PD	Total
2017 INRC	CR	9	2	2	0	0	13
	PR	0	6	15	6	2	29
	MR	0	0	1	11	0	12
	SD	0	0	0	0	1	2
	PD	0	0	0	0	4	4
	Total	9	8	18	17	3	60

CR= complete response, VGPR=very good partial response, PR= partial response, MXR= mixed response, MR= minor response, NR= no response, SD= stable disease, PD= progressive disease

TABLE 5

Association between response and EFS and OS using multivariate Cox regression analysis stratified by site and adjusted for age and stage

Criteria	Hazard Ratio	95% CI	P value	C-Statistic (95% CI)
<i>Event Free Survival (EFS)[#]</i>				
1993 INRC *	1.51	1.01-2.27	0.047	0.62 (0.50-0.74)
2017 INRC *	2.00	1.21-3.32	0.007	0.65 (0.55-0.75)
Non-Complete vs. Complete Response at Metastatic Sites	2.84	1.12-7.20	0.03	0.61 (0.52-0.70)
<i>Overall Survival (OS)</i>				
1993 INRC *	1.45	1.02-2.06	0.04	0.63 (0.51-0.75)
2017 INRC *	1.68	1.13-2.51	0.01	0.65 (0.53-0.76)
Non-Complete vs. Complete Response at Metastatic Sites	2.49	0.89-6.96	0.08	0.60 (0.50-0.69)

* using the full scale with higher values indicating worse response.

[#] PD patients at the end of induction were excluded from EFS analysis.