Article:
Park, JR, Bagatell, R, Cohn, SL et al. (16 more authors) (2017) Revisions to the International Neuroblastoma Response Criteria: A Consensus Statement From the National Cancer Institute Clinical Trials Planning Meeting. Journal of Clinical Oncology, 35 (22). pp. 2580-2587. ISSN 0732-183X

https://doi.org/10.1200/JCO.2016.72.0177

VOLUME 35 · NUMBER 22 · AUGUST 1, 2017

JOURNAL OF CLINICAL ONCOLOGY

SPECIAL ARTICLE

Revisions to the International Neuroblastoma Response Criteria: A Consensus Statement From the National Cancer Institute Clinical Trials Planning Meeting

Julie R. Park, Rochelle Bagatell, Susan L. Cohn, Andrew D. Pearson, Judith G. Villablanca, Frank Berthold, Susan Burchill, Ariane Boubaker, Kieran McHugh, Jed G. Nuchtern, Wendy B. London, Nita L. Seibel, O. Wolf Lindwasser, John M. Maris, Penelope Brock, Gudrun Schleiermacher, Ruth Ladenstein, Katherine K. Matthay, and Dominique Valteau-Couanet

Author affiliations and support information (if applicable) appear at the end of this article.

Published at jco.org on May 4, 2017.

K.K.M and D.V.-C. contributed equally to this work.

Corresponding author: Julie R. Park, MD, Seattle Children's Hospital, 4800 Sandpoint Way NE, Seattle, WA 98105; e-mail: julie.park@seattlechildrens.org.

0732-183X/17/3522w-2580w/$20.00

ABSTRACT

Purpose

More than two decades ago, an international working group established the International Neuroblastoma Response Criteria (INRC) to assess treatment response in children with neuroblastoma. However, this system requires modification to incorporate modern imaging techniques and new methods for quantifying bone marrow disease that were not previously widely available. The National Cancer Institute sponsored a clinical trials planning meeting in 2012 to update and refine response criteria for patients with neuroblastoma.

Methods

Multidisciplinary investigators from 13 countries reviewed data from published trials performed through cooperative groups, consortia, and single institutions. Data from both prospective and retrospective trials were used to refine the INRC. Monthly international conference calls were held from 2011 to 2015, and consensus was reached through review by working group leadership and the National Cancer Institute Clinical Trials Planning Meeting leadership council.

Results

Overall response in the revised INRC will integrate tumor response in the primary tumor, soft tissue and bone metastases, and bone marrow. Primary and metastatic soft tissue sites will be assessed using Response Evaluation Criteria in Solid Tumors (RECIST) and iodine-123 (^{123}I) –metaiodobenzylguanidine (MIBG) scans or [^{18}F]fluorodeoxyglucose–positron emission tomography scans if the tumor is MIBG nonavid. ^{123}I-MIBG scans, or [^{18}F]fluorodeoxyglucose–positron emission tomography scans for MIBG-nonavid disease, replace technetium-99m diphosphonate bone scintigraphy for osteomedullary metastasis assessment. Bone marrow will be assessed by histology or immunohistochemistry and cytology or immunocytology. Bone marrow with ≤ 5% tumor involvement will be classified as minimal disease. Urinary catecholamine levels will not be included in response assessment. Overall response will be defined as complete response, partial response, minor response, stable disease, or progressive disease.

Conclusion

These revised criteria will provide a uniform assessment of disease response, improve the interpretability of clinical trial results, and facilitate collaborative trial designs.

J Clin Oncol 35:2580-2587. © 2017 by American Society of Clinical Oncology

INTRODUCTION

Neuroblastoma, a cancer of the sympathetic nervous system, is responsible for 12% of deaths associated with cancer in children younger than 15 years of age. It is a heterogeneous disease, with nearly 50% of patients having a high-risk phenotype characterized by widespread disease dissemination and poor long-term survival. In contrast, patients diagnosed with low- or intermediate-risk neuroblastoma have excellent long-term survival.[1]

Collaborative clinical trials have led to improved outcomes for patients with high-risk neuroblastoma and decreased therapy-related toxicity in patients with non–high-risk disease.[2-11] Unfortunately, a lack of consensus regarding the definition of clinically relevant disease

ASSOCIATED CONTENT

Appendix
DOI: https://doi.org/10.1200/JCO.2016.72.0177

DOI: https://doi.org/10.1200/JCO.2016.72.0177

response has hampered the development of more effective therapy for high-risk neuroblastoma and impaired our ability to define the optimal management for the majority of patients with low- and intermediate-risk neuroblastoma. Development of more effective therapeutic approaches for all children with neuroblastoma must be a primary goal in prospective clinical trials, in which standardized methods to interpret response are used to efficiently advance therapy for neuroblastoma.

The International Neuroblastoma Response Criteria (INRC) consensus was last updated in 1993[12] and has significant limitations in accurately defining response at metastatic bone and bone marrow sites, the most common sites of relapse.[13] Since 1993, iodine-123 (^{123}I) metaiodobenzylguanidine (MIBG) imaging has become widely available and provides more sensitive and specific imaging of neuroblastoma in soft tissue and bone sites.[14] For MIBG-nonavid neuroblastomas, [^{18}F]fluorodeoxyglucose (FDG) –positron emission tomography (PET) is also a useful imaging technique.[15-18] Limited guidance for using nuclear medicine modalities for response was included in the INRC published in 1993. In addition, further experience quantifying bone marrow disease using morphology and evolving molecular modalities to accurately quantify minimal marrow disease provide the basis for better assessment of bone marrow response.[19] Incorporation of these technical advances and cumulative clinical trial data into an international consensus on response is needed to identify optimally effective treatment strategies and facilitate the development of international collaborative clinical trials.

In 2005, an International Neuroblastoma Risk Group (INRG) task force evaluated the prognostic impact of biologic and clinical data and established criteria for an internationally accepted risk group classification system.[20,21] The INRG task force also released consensus statements on molecular and radiographic techniques and assessment of minimal residual disease,[22-25] setting the stage for the current revision in neuroblastoma response criteria. Single-institution retrospective analyses have confirmed that MIBG imaging rather than anatomic imaging is more likely to detect recurrent disease.[14] The New Approaches to Neuroblastoma Clinical Trials Consortium,[26-30] Children's Oncology Group (COG),[31-33] International Society of Pediatric Oncology European Neuroblastoma (SIOPEN),[34] and German Pediatric Oncology and Hematology (GPOH)[35,36] have also piloted novel response criteria incorporating MIBG scoring in anatomic sectors for bone metastases and developed definitions of bone marrow response using morphology. As a consequence of this previous work, neuroblastoma investigators are now poised to develop uniform response criteria using state-of-the-art imaging and molecular methods.

A National Cancer Institute–appointed executive planning committee, representing neuroblastoma leadership from COG and its international counterparts from SIOPEN, GPOH, and the Japan Children's Cancer Group, selected a panel of 52 international investigators from 13 countries with oncology, pathology, radiology, nuclear medicine, surgery, biology, and statistical expertise (Appendix Table A1, online only) to develop and implement a revised consensus response criteria for neuroblastoma.

METHODS

Methodology for determining response and definitions of response in pediatric neuroblastoma were reviewed using the previously published INRC and results from neuroblastoma clinical trials published from 2005 to 2015 (Appendix Table A2, online only).[2-11,14,23,26-28,31-34,37-39] A database established by the INRG task force[21,40] was used to identify prevalence and characteristics of metastatic sites of disease at diagnosis in patients with neuroblastoma.

Response assessment will include anatomic imaging for primary and metastatic soft tissue disease, nuclear medicine imaging using ^{123}I-MIBG or FDG-PET for assessment of soft tissue and bone disease and bilateral bone marrow aspirates and trephine biopsies for assessment of marrow disease. Tissue biopsies may be used as an adjunct to verify the presence of viable neuroblastoma or ganglioneuroblastoma that is evaluable for response. Urine catecholamine levels will not be used to evaluate response because of a lack of standardization in specimen collection and analysis and the influence of diet on results.[41,42]

Primary and Metastatic Soft Tissue Disease

Soft tissue disease should be evaluated using either computed tomography (CT) or magnetic resonance imaging (MRI) scans to determine if a lesion is considered measurable.[22] Measurement of irregularly shaped primary tumors in children with neuroblastoma presents significant challenges for assessment of response. The current INRC includes assessment of tumor volumes using three-dimensional reconstructions from CT and MRI scans.[12] Although the availability of three-dimensional reconstructions from anatomic imaging has increased in recent years, the trend in the broader field of oncology has been away from the use of multidimensional measurements and toward assessment of response using change in the single longest dimension. The RECIST guidance, published in 2000 and revised in 2009, relies on measurement of nonnodal target lesions based on the longest single diameter,[43-46] whereas discrete lymph nodes are assessed using the short axis as a single dimension.

A multi-institution, retrospective analysis of 229 patients with high-risk neuroblastoma was conducted to identify the preferred method of primary tumor response assessment for use in a revision of the INRC.[47] No statistically significant difference in outcome was observed when comparing the use of three-dimensional volumetric measurement versus RECIST single longest dimension measurement. Given the complexity of three-dimensional measurement followed by calculation of resultant volume, primary tumor sites in children should be defined as measurable in accordance with RECIST criteria, using the single longest dimension in any orthogonal plane. The RECIST criteria will also be used for defining measurable soft tissue metastatic lesions and response as defined by changes in longest dimension for non–lymph node tumor lesions and changes in the short-axis diameter of malignant lymph nodes.

^{123}I-MIBG in conjunction with anatomic imaging will define measurable lesions and will be used to assess primary and metastatic soft tissue tumor response in the majority of patients. Neuroblastoma is a tumor derived from the sympathetic nervous system, and neuroblastoma cells typically express the norepinephrine transporter, which mediates active intracellular uptake of radiolabeled MIBG in approximately 90% of patients,[18] regardless of stage of disease, risk group, or age at presentation. MIBG is a derivative of guanethidine and a norepinephrine analog, which is highly sensitive and specific for imaging both primary tumor and metastatic neuroblastoma when labeled with radioisotopes of iodine.[22,23] MIBG uptake resolves when a tumor is necrotic or involutes and often when maturation occurs (only 20% of ganglioneuromas concentrate MIBG).[48] In patients whose tumors do not concentrate MIBG, FDG-PET is an alternative modality for tumor detection, although FDG is less specific than MIBG because of uptake of FDG in inflammatory lesions, as well as normal and cytokine-stimulated bone marrow.[15-17,49] Because FDG is less specific for neuroblastoma, a tissue biopsy of at least one of the lesions may be required to confirm that FDG-avid, MIBG-nonavid lesions are

histologically confirmed to be neuroblastoma and/or ganglioneuroblastoma. Adding the use of ^{123}I-MIBG or FDG to the RECIST response by CT or MRI will provide a more specific and sensitive definition of response for soft tissue lesions in neuroblastoma.

Both ^{123}I-MIBG and FDG-PET scans must be interpreted carefully in light of physiologic sites of uptake. MIBG will normally concentrate in salivary glands, myocardium, liver, intestines, and brown fat and is excreted via the urinary tract. FDG is concentrated in the brain, myocardium, liver, and brown fat and is excreted via the urinary tract. Questions about uptake in tumor versus physiologic uptake or uptake in soft tissue versus bone are commonly resolved with three-dimensional imaging with combined ^{123}I-MIBG single-photon emission computed tomography (SPECT; or MIBG-SPECT/CT) or FDG-PET/CT.[15,24,49] Three-dimensional imaging may also identify lesions not seen with planar imaging. If a three-dimensional imaging modality is available and used at baseline, this same modality must be used for all disease response evaluations to ensure appropriate comparisons. In some cases, however, patients may require a biopsy in addition to nuclear imaging to confirm the presence of viable tumor.

MIBG uptake (or FDG for tumors that are not MIBG avid) will be used to determine which metastatic soft tissue lesions considered measurable by RECIST will be deemed target lesions for response assessment (Table 1). Nontarget soft tissue lesions will include leptomeningeal tumor, tumor in cerebrospinal fluid, ascites, or pleural effusion, and lesions smaller than 10 mm that are considered likely to be active tumor based on clinical correlation (eg, hepatic and pulmonary nodules). Small (< 10 mm) soft tissue lesions and lymph nodes that measure shorter than 15 mm on short axis will be considered nontarget lesions if they are biopsied and proven to consist of viable tumor. Non–lymph node soft tissue lesions at least 10 mm in diameter and lymph nodes larger than 15 mm on short axis that are not MIBG or FDG avid and do not contain viable tumor (if biopsied) will not be considered either target or nontarget lesions.

For certain subgroups of patients with localized tumors with favorable histology and genomics, differentiation of the tumor can occur during therapy and can be associated with an apparent increase in the size of the tumor, as well as persistent MIBG uptake.[48] In the absence of new tumor sites, serial evaluation of histology may be helpful to accurately define response.

Table 1. Key Terms

Term	Definition
Target lesions	Disease sites that meet criteria of measurable size (nonlymphoid soft tissue mass ≥ 10 mm in longest dimension or lymph node ≥ 15 mm in short axis) as well as either uptake on MIBG (or FDG for MIBG-nonavid tumors) OR biopsy positive for neuroblastoma or ganglioneuroblastoma
Nontarget lesions	Lesions that are considered to be active tumor sites but do not meet target lesion criteria*
Discrete lymph node	Single lymph node that can be discretely identified (ie, a cervical node); measure by short axis
Sum of diameters	Sum of the short axis of discrete lymph nodes (ie, cervical, axillary nodes) added to the sum of the longest diameters of non–lymph node soft tissue metastases; conglomerate masses of nondiscrete lymph nodes (ie, multiple contiguous retroperitoneal nodes) will be measured using longest diameter

Abbreviations: FDG, [^{18}F]fluorodeoxyglucose; MIBG, metaiodobenzylguanidine.
*Examples include leptomeningeal tumor, tumor in cerebrospinal fluid, ascites, and pleural effusion cytology.

Metastatic Bone Disease

Because of its higher sensitivity and specificity, ^{123}I-MIBG uptake will replace technetium-99m (^{99m}Tc) bone scintigraphy for evaluation of response at osteomedullary lesions.[22,23,50] For patients whose tumors do not concentrate MIBG, FDG-PET or PET/CT scan will be used for tumor detection in bone. Anatomic imaging will not be used to evaluate osteomedullary lesions, because these lesions may not shrink in size using CT/MRI even in the absence of residual viable tumor. In addition, osseous lesions without a soft tissue mass are considered nonmeasurable by RECIST. The measurable extramedullary soft tissue components of bone lesions will be assessed using the same criteria used for other soft tissue sites.

Metastatic Bone Marrow Disease

Assessment of bone marrow involvement is achieved via evaluation of bilateral aspirates and bilateral trephine biopsies, a total of four sampled sites. The 1993 INRC on bone marrow response are based on the number of sites positive for tumor but do not incorporate modern techniques to better quantitate disease burden within the bone marrow. The revised guidelines require assessment of bone marrow aspirates and trephines for neuroblastoma cells using morphologic criteria in conjunction with appropriate antibodies to confirm the identity of neuroblastoma cells by immunocytology (if available) and/or immunohistochemistry. Only bone marrow samples of suitable quality should be investigated, as detailed by Burchill et al.[19] Although more advanced techniques, including automatic immunofluorescence plus fluorescent in situ hybridization[51] and reverse transcription quantitative polymerase chain reaction (RTqPCR),[4,52-57] are available for assessment of bone marrow status, further prospective validation across clinical trials using standardized reporting is required before these can be incorporated into a revised INRC.

RESULTS

Data collected by the INRG task force was used to evaluate characteristics of metastatic disease at diagnosis in neuroblastoma.[21,40] This database consists of clinical data from 17,938 patients diagnosed with neuroblastoma from 1974 to 2015. Specifics of metastatic disease sites were not identified in 11,430 patient cases. Of the remaining 6,508 patients, 3,496 (54%) had documented metastatic disease at diagnosis. Bone marrow (n = 1,940; 56%) and bone (n = 1,625; 47%) are the most common sites of metastatic disease, highlighting the importance of including these sites as components of the proposed revised response criteria. Metastatic disease involving soft tissue sites includes lymph nodes (n = 846; 24%), liver (n = 727; 21%), and, less commonly, skin (n = 155; 4%), lung (n = 101; 3%), and CNS (n = 38; 1%).

On the basis of review of the scientific literature and consensus among the experts of this panel, the following revised INRC are proposed. Response will be based on all components of disease, taking into consideration soft tissue, bone, and bone marrow disease sites.

Primary Tumor

Response of primary tumor using both RECIST criteria and MIBG (or FDG if tumor is MIBG nonavid) uptake will be used (Table 2). In patients with bilateral adrenal lesions, response will be

Table 2. Primary (soft tissue) Tumor Response*

Response	Anatomic + MIBG (FDG-PET†) Imaging
CR	< 10 mm residual soft tissue at primary site AND Complete resolution of MIBG or FDG-PET uptake (for MIBG-nonavid tumors) at primary site
PR	≥ 30% decrease in longest diameter of primary site AND MIBG or FDG-PET uptake at primary site stable, improved, or resolved
PD	> 20% increase in longest diameter taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study) AND Minimum absolute increase of 5 mm in longest dimension‡
SD	Neither sufficient shrinkage for PR nor sufficient increase for PD at the primary site

Abbreviations: CR, complete response; FDG, [^{18}F]fluorodeoxyglucose; MIBG, metaiodobenzylguanidine; PD, progressive disease; PET, positron emission tomography; PR, partial response; SD, stable disease.
*Not for use in assessment of metastatic sites.
†Used for MIBG-nonavid tumors.
‡Mass that does not meet PD measurement criteria but has fluctuating MIBG avidity will not be considered PD.

based on the sum of the longest dimensions of both sites unless biopsy proves one to be ganglioneuroma. In patients with multifocal nonadrenal disease, the largest tumor will be considered the primary tumor, and additional lesions will be assessed as metastatic sites unless biopsy proven to be ganglioneuroma.

In some patients, it may be difficult to distinguish postoperative changes in soft tissues in the primary tumor bed from true residual neuroblastoma using anatomic imaging alone. This is particularly true when residual soft tissue masses are small (< 1 cm at longest diameter). For this reason, patients with MIBG-nonavid lesions measuring less than 1 cm in diameter would be considered to have achieved complete response (CR) in the primary site if the tumor was initially MIBG avid. For patients with MIBG-nonavid tumors at the time of diagnosis, small residual tumors must not demonstrate increased metabolic activity by FDG-PET imaging and, if biopsied, must not demonstrate neuroblastoma or ganglioneuroblastoma.

Metastatic Soft Tissue and Bone Disease

A combination of anatomic imaging and radionuclide scans will be used to assess response in soft tissue (including lymph node and non–lymph node) and bone metastases (Table 3). MIBG semiquantitative scoring systems have been previously used for response assessment,[37,50,58-62] with international consensus developed for use of these scoring systems in disease response.[23] Although differences exist in the approach to absolute scoring in the various systems, comparisons of the relative scores as defined by the SIOPEN scoring system[62] and the Curie scoring system[61] (used in COG) have yielded consistent designations of response and have validated MIBG relative scoring as prognostic for overall response and patient outcome in patients with newly diagnosed neuroblastoma.[36] The consensus recommendation is to use the MIBG relative score on bone sectors (the absolute score of bone lesions at time of response assessment divided by the absolute score of bone lesions at baseline before therapeutic interventions) for response assessment. The same scoring method (eg, Curie, SIOPEN) should be used at each time point of response assessment. MIBG-SPECT or MIBG-SPECT/CT may be used for scoring purposes, but the same imaging methodology should be used for all evaluations.

Bone Marrow Metastases

Exact quantification of bone marrow involvement at all sites should be reported; the percentage of tumor infiltration of bone marrow space assessed by histologic evaluation of trephine or biopsy (with immunohistochemical staining encouraged) or

Table 3. Tumor Response at Metastatic Soft Tissue and Bone Sites

Response	Anatomic + MIBG (FDG-PET*) Imaging
CR	Resolution of all sites of disease, defined as: Nonprimary target and nontarget lesions measure < 10 mm AND Lymph nodes identified as target lesions decrease to a short axis < 10 mm AND MIBG uptake or FDG-PET uptake (for MIBG-nonavid tumors) of nonprimary lesions resolves completely
PR	≥ 30% decrease in sum of diameters† of nonprimary target lesions compared with baseline AND all of the following: Nontarget lesions may be stable or smaller in size AND No new lesions AND ≥ 50% reduction in MIBG absolute bone score (relative MIBG bone score ≥ 0.1 to ≤ 0.5) or ≥ 50% reduction in number of FDG-PET–avid bone lesions‡§
PD	Any of the following: Any new soft tissue lesion detected by CT/MRI that is also MIBG avid or FDG-PET avid Any new soft tissue lesion seen on anatomic imaging that is biopsied and confirmed to be neuroblastoma or ganglioneuroblastoma Any new bone site that is MIBG avid A new bone site that is FDG-PET avid (for MIBG-nonavid tumors) AND has CT/MRI findings consistent with tumor OR has been confirmed histologically to be neuroblastoma or ganglioneuroblastoma > 20% increase in longest diameter taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study) AND minimum absolute increase of 5 mm in sum of diameters of target soft tissue lesions Relative MIBG score ≥ 1.2§
SD	Neither sufficient shrinkage for PR nor sufficient increase for PD of nonprimary lesions

Abbreviations: CR, complete response; CT, computed tomography; FDG, [^{18}F]fluorodeoxyglucose; MIBG, metaiodobenzylguanidine; MRI, magnetic resonance imaging; PD, progressive disease; PET, positron emission tomography; PR, partial response; SD, stable disease.
*Used for MIBG-nonavid tumors
†Sum of diameters is defined as the sum of the short axis of discrete lymph nodes (ie, cervical, axillary nodes) added to the sum of the longest diameters of non–lymph node soft tissue metastases. Masses of conglomerate nondiscrete lymph nodes will be measured using longest diameter.
‡For patients with soft tissue metastatic disease, resolution of MIBG and/or FDG-PET uptake at the soft tissue sites is not required; all size reduction criteria must be fulfilled.
§Relative MIBG score is the absolute score for bone lesions at time of response assessment divided by the absolute score for bone lesions at baseline before therapeutic interventions. The same scoring method (eg, Curie or International Society of Pediatric Oncology European Neuroblastoma) must be used at all assessment time points. MIBG single-photon emission computed tomography (SPECT) or MIBG-SPECT/CT may be used for scoring purposes, but the same imaging methodology should be used for all evaluations.

counting of the number of tumor cells in aspirates by cytology or immunocytology (recommended if available) divided by the number of hematopoietic or mononuclear cells evaluated to obtain a percentage of involvement (methodology described by Burchill et al[19]). The bone marrow sample with the highest percentage of tumor infiltration is used in the response algorithm. Neuroblastoma infiltration in the marrow can be heterogeneously distributed throughout the skeleton.[63,64] Because the clinical impact of this heterogeneity has not yet been fully evaluated, detection of more than 0% to ≤ 5% tumor infiltration in bone marrow will represent a new category of minimal disease (Table 4).

Overall Response

Overall response will be defined by combining response of the individual components (ie, soft tissue, bone, and bone marrow disease). All components must be evaluated and of sufficient quality to fully assess overall response (Table 5; Appendix Table A3, online only). An overall CR requires that all involved components have a CR. An overall partial response includes a partial response of all soft tissue and bone sites or noninvolvement in one of these components but allows residual minimal disease in the bone marrow. The prior category of mixed response has been eliminated, and a new category, minor response, has been included. Minor response requires a partial response or CR in at least one component, stable disease for at least one component, and no evidence of progressive disease in any component. Progressive disease in any one component defines overall progressive disease.

Table 4. Bone Marrow Metastasis Response*

Response	Cytology†/Histology‡
CR	Bone marrow with no tumor infiltration on reassessment, independent of baseline tumor involvement
PD	Any of the following: Bone marrow without tumor infiltration that becomes > 5% tumor infiltration on reassessment OR Bone marrow with tumor infiltration that increases by > two-fold and has > 20% tumor infiltration on reassessment
MD	Any of the following: Bone marrow with ≤ 5% tumor infiltration and remains > 0 to ≤ 5% tumor infiltration on reassessment OR Bone marrow with no tumor infiltration that has ≤ 5% tumor infiltration on reassessment OR Bone marrow with > 20% tumor infiltration that has > 0 to ≤ 5% tumor infiltration on reassessment
SD	Bone marrow with tumor infiltration that remains positive with > 5% tumor infiltration on reassessment but does not meet CR, MD, or PD criteria

NOTE. In the case of discrepant results between aspirations or core biopsies from two or more sites taken at the same time, the highest infiltration result should be reported using the criteria in this table.
Abbreviations: CR, complete response; MD, minimal disease; PD, progressive disease; SD, stable disease.
*Response will be compared with baseline disease evaluations before enrollment in a clinical trial or, for newly diagnosed patients, with baseline at specific times during therapy (ie, at diagnosis and before start of therapy, before specific phases of therapy such as induction, high-dose chemotherapy with stem-cell rescue consolidation, or postconsolidation immunotherapy).
†Accompanied by immunocytology (recommended, not mandatory).
‡Accompanied by immunohistochemistry; specific recommendations included in article by Burchill et al.[19]

Table 5. Determination of Overall Response

Response	Criterion
CR	All components meet criteria for CR
PR	PR in at least one component and all other components are either CR, MD* (bone marrow), PR (soft tissue or bone), or NI†; no component with PD
MR	PR or CR in at least one component but at least one other component with SD; no component with PD
SD	SD in one component with no better than SD or NI† in any other component; no component with PD
PD	Any component with PD

Abbreviations: CR, complete response; MD, minimal disease; MR, minor response; NI, not involved; PD, progressive disease; PR, partial response; SD, stable disease.
*For bone marrow assessment only.
†Site not involved at study entry and remains uninvolved.

DISCUSSION

The INRC revisions described in this consensus statement represent an evolution of neuroblastoma response criteria, with the incorporation of functional imaging, the widespread application of advanced techniques for analysis of marrow involvement, and the recognition that clinically significant minimal bone marrow disease can be assessed by discontinuous sampling. The goal of the current INRC revision is to eliminate modalities for tumor assessment that are less sensitive and/or specific for neuroblastoma (eg, bone scintigraphy and catecholamine levels) and replace these with nuclear imaging modalities (^{123}I-MIBG and FDG-PET imaging) that increase the likelihood of detection of viable neuroblastoma and/or ganglioneuroblastoma in soft tissue and bone metastatic sites and to include the use of histopathologic techniques that quantitate the extent of bone marrow involvement. These newer modalities are being widely used; however, until now, they have not been uniformly incorporated into neuroblastoma disease assessment. As a result, there have been significant challenges in interpretation of clinical trial results across institutions and consortia, highlighting the need for revisions to the INRC. In addition, the prior INRC were developed with a focus on newly diagnosed neuroblastoma and were not easily applicable to phase I or II clinical trials for patients with recurrent or refractory disease, where bone and bone marrow are frequently the only sites of tumor involvement.

Functional imaging is the cornerstone of these revised criteria for neuroblastoma response. Bone scintigraphy with ^{99m}Tc biphosphonates, although sensitive for detecting osseous metastatic sites at diagnosis, lacks specificity when assessing disease response to therapy, because of tracer uptake in remodeling bone.[65] ^{123}I-MIBG imaging provides superior sensitivity compared with bone scintigraphy for detecting viable neuroblastoma and will be used for assessment of response of bony metastatic disease. Postoperative changes in resected soft tissue sites and therapy-induced tumor differentiation require the use of functional imaging to complement the use of RECIST guidelines, which are based on anatomic imaging for response assessment of soft tissue sites. In the minority of patients with MIBG-nonavid disease, FDG-PET provides an alternative modality to assess disease status at primary or metastatic soft tissue sites and bony

sites. Thus, in contrast to the majority of adult trials that use only RECIST criteria to define response, the revised INRC will fully incorporate the sensitive and specific nuclear medicine modalities available to better define neuroblastoma response.

Bone marrow represents the most common site of metastatic disease at diagnosis and is one of the most common sites of relapse in patients with neuroblastoma. The INRC 1993 version[12] incorporated the number of involved bone marrow sites (assessing bilateral bone marrow aspirates and biopsies) into response assessment. However, the level of disease at each site was not assessed, and no distinction was made between patients who had a single neuroblastoma cell clump in the bone marrow and those who had near-complete replacement of the bone marrow compartment with tumor. Consequently, assessment of bone marrow response lacked precision, which could lead to over- or underestimation of response. Bone marrow response criteria piloted in the NANT consortium[27,29-31] and subsequently adopted in COG early-phase clinical trials have used the maximum percentage of tumor found at any of the four sampled bone marrow sites in response assessment and defined intermittently positive detection of low levels of tumor infiltration in the marrow as stable disease rather than progression. Multiple published early-phase clinical trials have confirmed the feasibility of incorporating these criteria to evaluate bone marrow response assessment in neuroblastoma.[27,29-31,33] The revised INRC now include quantitative assessment of bone marrow involvement, and the bone marrow response criteria reflect the current uncertainty regarding the clinical impact of detecting intermittent minimal disease. The optimal methodology for quantification of tumor in bone marrow is still under evaluation. The article by Burchill et al[19] provides details about the methodologies incorporated in the revised INRC to standardize the definition of bone marrow response. The precise amount of tumor cell infiltration in bone marrow aspirates and trephines or biopsies must be collected in future clinical trials, allowing for better assessment of the relationship between marrow response with overall outcome and providing data for evidence-based refinement of future revisions of the INRC.

Because minimal residual marrow disease is frequently observed post-therapy, these revised response criteria will include a new categorization of patients with minimal marrow disease. This will provide the opportunity to more uniformly study the prognostic importance of minimal disease and the effect of new agents in the setting of minimal marrow disease. Furthermore, this new classification provides the opportunity to prospectively study the clinical use of newer techniques, such as RTqPCR,[4,52-57] which provides an objective, rapid throughput method to precisely quantitate neuroblastoma load in the bone marrow. Although RTqPCR for neuroblastoma mRNAs has been shown to be of prognostic and predictive value in several clinical trials,[4,54] it has not yet been widely adopted in clinical practice and has not been incorporated into these revised INRC. Additional studies are required to define how best to incorporate such highly sensitive detection methods into future refinements of disease response criteria.

The revised INRC will apply to both newly diagnosed and recurrent or refractory neuroblastoma. Because these criteria can be used to assess disease response in patients with only bone and/or bone marrow metastases, they will enable the evaluation of disease response in patients without measurable soft tissue disease who are eligible for early-phase trials.

We anticipate that the INRC will continue to evolve as newer technologies are incorporated into clinical practice. In addition to novel techniques for marrow detection, detection of circulating tumor cells and use of novel functional imaging techniques, such as diffusion-weighted imaging MRI and PET-MRI, and new radiotracers, such as gallium-68–labeled somatostatin analogs,[66,67] Iodine-124–MIBG,[68] and [^{18}F]fluorodopa,[69] may further provide improved sensitivity for metastatic tumor detection. As these modalities become more widely available, their incorporation into future INRC revisions will require prospective study in the context of clinical trials for the validation of their utility and clinical applicability.

Great strides have been made in using clinical and biologic characteristics to more precisely assign therapy for children with neuroblastoma.[21] These international consensus response criteria are an additional step in providing a common international language to assess clinical trial outcomes and enhance the opportunity for international collaborative clinical trials.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

AUTHOR CONTRIBUTIONS

Conception and design: Julie R. Park, Rochelle Bagatell, Susan L. Cohn, Andrew D. Pearson, Judith G. Villablanca, Frank Berthold, Susan Burchill, Ariane Boubaker, Kieran McHugh, Jed G. Nuchtern, Nita L. Seibel, O. Wolf Lindwasser, John M. Maris, Penelope Brock, Gudrun Schleiermacher, Ruth Ladenstein, Katherine K. Matthay, Dominque Valteau-Couanet
Financial support: Julie R. Park
Administrative support: O. Wolf Lindwasser
Collection and assembly of data: Julie R. Park, Rochelle Bagatell, Susan L. Cohn, Andrew D. Pearson, Judith G. Villablanca, Frank Berthold, Susan Burchill, Kieran McHugh, Jed G. Nuchtern, Wendy B. London, John M. Maris, Ruth Ladenstein, Katherine K. Matthay, Dominque Valteau-Couanet
Data analysis and interpretation: Julie R. Park, Rochelle Bagatell, Susan L. Cohn, Andrew D. Pearson, Judith G. Villablanca, Frank Berthold, Susan Burchill, Ariane Boubaker, Kieran McHugh, Jed G. Nuchtern, Wendy B. London, Nita L. Seibel, John M. Maris, Penelope Brock, Ruth Ladenstein, Katherine K. Matthay, Dominque Valteau-Couanet
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

REFERENCES

1. Irwin MS, Park JR: Neuroblastoma: Paradigm for precision medicine. Pediatr Clin North Am 62: 225-256, 2015

2. Pearson AD, Pinkerton CR, Lewis IJ, et al: High-dose rapid and standard induction chemotherapy for patients aged over 1 year with stage 4 neuroblastoma: A randomised trial. Lancet Oncol 9: 247-256, 2008

3. Ladenstein R, Valteau-Couanet D, Brock P, et al: Randomized trial of prophylactic granulocyte colony-stimulating factor during rapid COJEC induction in pediatric patients with high-risk neuroblastoma: The European HR-NBL1/SIOPEN study. J Clin Oncol 28:3516-3524, 2010

4. Kreissman SG, Seeger RC, Matthay KK, et al: Purged versus non-purged peripheral blood stem-cell transplantation for high-risk neuroblastoma (COG A3973): A randomised phase 3 trial. Lancet Oncol 14: 999-1008, 2013

5. Simon T, Hero B, Faldum A, et al: Long term outcome of high-risk neuroblastoma patients after immunotherapy with antibody ch14.18 or oral metronomic chemotherapy. BMC Cancer 11:21, 2011

6. Berthold F, Boos J, Burdach S, et al: Myeloablative megatherapy with autologous stem-cell rescue versus oral maintenance chemotherapy as consolidation treatment in patients with high-risk neuroblastoma: A randomised controlled trial. Lancet Oncol 6:649-658, 2005

7. Baker DL, Schmidt ML, Cohn SL, et al: Outcome after reduced chemotherapy for intermediate-risk neuroblastoma. N Engl J Med 363:1313-1323, 2010

8. Strother DR, London WB, Schmidt ML, et al: Outcome after surgery alone or with restricted use of chemotherapy for patients with low-risk neuroblastoma: Results of Children's Oncology Group study P9641. J Clin Oncol 30:1842-1848, 2012

9. De Bernardi B, Gerrard M, Boni L, et al: Excellent outcome with reduced treatment for infants with disseminated neuroblastoma without *MYCN* gene amplification. J Clin Oncol 27:1034-1040, 2009

10. De Bernardi B, Mosseri V, Rubie H, et al: Treatment of localised resectable neuroblastoma: Results of the LNESG1 study by the SIOP Europe Neuroblastoma Group. Br J Cancer 99:1027-1033, 2008

11. Simon T, Hero B, Benz-Bohm G, et al: Review of image defined risk factors in localized neuroblastoma patients: Results of the GPOH NB97 trial. Pediatr Blood Cancer 50:965-969, 2008

12. Brodeur GM, Pritchard J, Berthold F, et al: Revisions of the international criteria for neuroblastoma diagnosis, staging, and response to treatment. J Clin Oncol 11:1466-1477, 1993

13. Matthay KK, Atkinson JB, Stram DO, et al: Patterns of relapse after autologous purged bone marrow transplantation for neuroblastoma: A Children's Cancer Group pilot study. J Clin Oncol 11: 2226-2233, 1993

14. Kushner BH, Kramer K, Modak S, et al: Sensitivity of surveillance studies for detecting asymptomatic and unsuspected relapse of high-risk neuroblastoma. J Clin Oncol 27:1041-1046, 2009

15. Taggart DR, Han MM, Quach A, et al: Comparison of iodine-123 metaiodobenzylguanidine (MIBG) scan and [^{18}F]fluorodeoxyglucose positron emission tomography to evaluate response after iodine-131 MIBG therapy for relapsed neuroblastoma. J Clin Oncol 27:5343-5349, 2009

16. Papathanasiou ND, Gaze MN, Sullivan K, et al: ^{18}F-FDG PET/CT and ^{123}I-metaiodobenzylguanidine imaging in high-risk neuroblastoma: Diagnostic comparison and survival analysis. J Nucl Med 52:519-525, 2011

17. Melzer HI, Coppenrath E, Schmid I, et al: ^{123}I-MIBG scintigraphy/SPECT versus ^{18}F-FDG PET in paediatric neuroblastoma. Eur J Nucl Med Mol Imaging 38:1648-1658, 2011

18. Shulkin BL, Shapiro B: Current concepts on the diagnostic use of MIBG in children. J Nucl Med 39:679-688, 1998

19. Burchill SA, Beiske K, Shimada H, et al: Recommendations for the standardization of bone marrow disease assessment and reporting in children with neuroblastoma: On behalf of the International Neuroblastoma Response Criteria Bone Marrow Working Group. Cancer [epub ahead of print on December 16, 2016]

20. Monclair T, Brodeur GM, Ambros PF, et al: The International Neuroblastoma Risk Group (INRG) staging system: An INRG Task Force report. J Clin Oncol 27:298-303, 2009

21. Cohn SL, Pearson AD, London WB, et al: The International Neuroblastoma Risk Group (INRG) classification system: An INRG Task Force report. J Clin Oncol 27:289-297, 2009

22. Brisse HJ, McCarville MB, Granata C, et al: Guidelines for imaging and staging of neuroblastic tumors: Consensus report from the International Neuroblastoma Risk Group project. Radiology 261: 243-257, 2011

23. Matthay KK, Shulkin B, Ladenstein R, et al: Criteria for evaluation of disease extent by (123)I-metaiodobenzylguanidine scans in neuroblastoma: A report for the International Neuroblastoma Risk Group (INRG) Task Force. Br J Cancer 102:1319-1326, 2010

24. Beiske K, Burchill SA, Cheung IY, et al: Consensus criteria for sensitive detection of minimal neuroblastoma cells in bone marrow, blood and stem cell preparations by immunocytology and QRT-PCR: Recommendations by the International Neuroblastoma Risk Group Task Force. Br J Cancer 100: 1627-1637, 2009

25. Ambros PF, Ambros IM, Brodeur GM, et al: International consensus for neuroblastoma molecular diagnostics: Report from the International Neuroblastoma Risk Group (INRG) Biology Committee. Br J Cancer 100:1471-1482, 2009

26. Matthay KK, Quach A, Huberty J, et al: Iodine-131–metaiodobenzylguanidine double infusion with autologous stem-cell rescue for neuroblastoma: A new approaches to neuroblastoma therapy phase I study. J Clin Oncol 27:1020-1025, 2009

27. Maurer BJ, Kang MH, Villablanca JG, et al: Phase I trial of fenretinide delivered orally in a novel organized lipid complex in patients with relapsed/refractory neuroblastoma: A report from the New Approaches to Neuroblastoma Therapy (NANT) consortium. Pediatr Blood Cancer 60:1801-1808, 2013

28. Yanik GA, Villablanca JG, Maris JM, et al: ^{131}I-metaiodobenzylguanidine with intensive chemotherapy and autologous stem cell transplantation for high-risk neuroblastoma: A new approaches to neuroblastoma therapy (NANT) phase II study. Biol Blood Marrow Transplant 21:673-681, 2015

29. Villablanca JG, Volchenboum SL, Cho H, et al: A phase I new approaches to neuroblastoma therapy study of buthionine sulfoximine and melphalan with autologous stem cells for recurrent/refractory high-risk neuroblastoma. Pediatr Blood Cancer 63: 1349-1356, 2016

30. DuBois SG, Marachelian A, Fox E, et al: Phase I study of the aurora A kinase inhibitor alisertib in combination with irinotecan and temozolomide for patients with relapsed or refractory neuroblastoma: A NANT (New Approaches to Neuroblastoma Therapy) trial. J Clin Oncol 34:1368-1375, 2016

31. Villablanca JG, London WB, Naranjo A, et al: Phase II study of oral capsular 4-hydroxyphenylretinamide (4-HPR/fenretinide) in pediatric patients with refractory or recurrent neuroblastoma: A report from the Children's Oncology Group. Clin Cancer Res 17: 6858-6866, 2011

32. Bagatell R, London WB, Wagner LM, et al: Phase II study of irinotecan and temozolomide in children with relapsed or refractory neuroblastoma: A Children's Oncology Group study. J Clin Oncol 29: 208-213, 2011

33. Shusterman S, London WB, Gillies SD, et al: Antitumor activity of hu14.18-IL2 in patients with relapsed/refractory neuroblastoma: A Children's Oncology Group (COG) phase II study. J Clin Oncol 28: 4969-4975, 2010

34. Di Giannatale A, Dias-Gastellier N, Devos A, et al: Phase II study of temozolomide in combination with topotecan (TOTEM) in relapsed or refractory neuroblastoma: A European Innovative Therapies for Children With Cancer-SIOP-European neuroblastoma study. Eur J Cancer 50:170-177, 2014

35. Simon T, Berthold F, Borkhardt A, et al: Treatment and outcomes of patients with relapsed, high-risk neuroblastoma: Results of German trials. Pediatr Blood Cancer 56:578-583, 2011

36. Decarolis B, Schneider C, Hero B, et al: Iodine-123 metaiodobenzylguanidine scintigraphy scoring allows prediction of outcome in patients with stage 4 neuroblastoma: Results of the Cologne interscore comparison study. J Clin Oncol 31:944-951, 2013

37. Yanik GA, Parisi MT, Shulkin BL, et al: Semiquantitative mIBG scoring as a prognostic indicator in patients with stage 4 neuroblastoma: A report from the Children's Oncology Group. J Nucl Med 54: 541-548, 2013

38. London WB, Castel V, Monclair T, et al: Clinical and biologic features predictive of survival after relapse of neuroblastoma: A report from the International Neuroblastoma Risk Group project. J Clin Oncol 29:3286-3292, 2011

39. DuBois SG, Allen S, Bent M, et al: Phase I/II study of (131)I-MIBG with vincristine and 5 days of irinotecan for advanced neuroblastoma. Br J Cancer 112:644-649, 2015

40. Pinto NR, Applebaum MA, Volchenboum SL, et al: Advances in risk classification and treatment strategies for neuroblastoma. J Clin Oncol 33: 3008-3017, 2015

41. Sundell IB, Hallmans G, Nilsson TK, et al: Plasma glucose and insulin, urinary catecholamine and cortisol responses to test breakfasts with high or low fibre content: The importance of the previous diet. Ann Nutr Metab 33:333-340, 1989

42. Weetman RM, Rider PS, Oei TO, et al: Effect of diet on urinary excretion of VMA, HVA, metanephrine, and total free catecholamine in normal preschool children. J Pediatr 88:46-50, 1976

43. Therasse P, Arbuck SG, Eisenhauer EA, et al: New guidelines to evaluate the response to treatment in solid tumors: European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 92:205-216, 2000

44. Eisenhauer EA, Therasse P, Bogaerts J, et al: New response evaluation criteria in solid tumours:

Revised RECIST guideline (version 1.1). Eur J Cancer 45:228-247, 2009

45. Schwartz LH, Bogaerts J, Ford R, et al: Evaluation of lymph nodes with RECIST 1.1. Eur J Cancer 45:261-267, 2009

46. Therasse P, Eisenhauer EA, Verweij J: RECIST revisited: A review of validation studies on tumour assessment. Eur J Cancer 42:1031-1039, 2006

47. Bagatell R, McHugh K, Naranjo A, et al: Assessment of primary site response in children with high-risk neuroblastoma: An international multicenter study. J Clin Oncol 34:740-746, 2016

48. Marachelian A, Shimada H, Sano H, et al: The significance of serial histopathology in a residual mass for outcome of intermediate risk stage 3 neuroblastoma. Pediatr Blood Cancer 58:675-681, 2012

49. Sharp SE, Shulkin BL, Gelfand MJ, et al: ^{123}I-MIBG scintigraphy and ^{18}F-FDG PET in neuroblastoma. J Nucl Med 50:1237-1243, 2009

50. Suc A, Lumbroso J, Rubie H, et al: Metastatic neuroblastoma in children older than one year: Prognostic significance of the initial metaiodobenzylguanidine scan and proposal for a scoring system. Cancer 77:805-811, 1996

51. Méhes G, Luegmayr A, Kornmüller R, et al: Detection of disseminated tumor cells in neuroblastoma: 3 log improvement in sensitivity by automatic immunofluorescence plus FISH (AIPF) analysis compared with classical bone marrow cytology. Am J Pathol 163:393-399, 2003

52. van Wezel EM, Stutterheim J, Vree F, et al: Minimal residual disease detection in autologous stem cell grafts from patients with high risk neuroblastoma. Pediatr Blood Cancer 62:1368-1373, 2015

53. Cheung IY, Lo Piccolo MS, Kushner BH, et al: Early molecular response of marrow disease to biologic therapy is highly prognostic in neuroblastoma. J Clin Oncol 21:3853-3858, 2003

54. Viprey VF, Gregory WM, Corrias MV, et al: Neuroblastoma mRNAs predict outcome in children with stage 4 neuroblastoma: A European HR-NBL1/SIOPEN study. J Clin Oncol 32:1074-1083, 2014

55. Cai JY, Pan C, Tang YJ, et al: Minimal residual disease is a prognostic marker for neuroblastoma with bone marrow infiltration. Am J Clin Oncol 35:275-278, 2012

56. Stutterheim J, Ichou FA, den Ouden E, et al: Methylated RASSF1a is the first specific DNA marker for minimal residual disease testing in neuroblastoma. Clin Cancer Res 18:808-814, 2012

57. Choi YB, Bae GE, Lee NH, et al: Clinical significance of persistent tumor in bone marrow during treatment of high-risk neuroblastoma. J Korean Med Sci 30:1062-1067, 2015

58. Schmidt M, Simon T, Hero B, et al: The prognostic impact of functional imaging with (123)I-mIBG in patients with stage 4 neuroblastoma >1 year of age on a high-risk treatment protocol: Results of the German neuroblastoma trial NB97. Eur J Cancer 44:1552-1558, 2008

59. Boubaker A, Bischof Delaloye A: MIBG scintigraphy for the diagnosis and follow-up of children with neuroblastoma. Q J Nucl Med Mol Imaging 52:388-402, 2008

60. Kushner BH, Yeh SD, Kramer K, et al: Impact of metaiodobenzylguanidine scintigraphy on assessing response of high-risk neuroblastoma to dose-intensive induction chemotherapy. J Clin Oncol 21:1082-1086, 2003

61. Matthay KK, Edeline V, Lumbroso J, et al: Correlation of early metastatic response by ^{123}I-metaiodobenzylguanidine scintigraphy with overall response and event-free survival in stage IV neuroblastoma. J Clin Oncol 21:2486-2491, 2003

62. Ady N, Zucker JM, Asselain B, et al: A new ^{123}I-MIBG whole body scan scoring method: Application to the prediction of the response of metastases to induction chemotherapy in stage IV neuroblastoma. Eur J Cancer 31A:256-261, 1995

63. Burchill SA: Micrometastases in neuroblastoma: Are they clinically important? J Clin Pathol 57:14-20, 2004

64. Cheung NK, Heller G, Kushner BH, et al: Detection of metastatic neuroblastoma in bone marrow: When is routine marrow histology insensitive? J Clin Oncol 15:2807-2817, 1997

65. Sisson JC, Shulkin BL: Nuclear medicine imaging of pheochromocytoma and neuroblastoma. Q J Nucl Med 43:217-223, 1999

66. Gains JE, Bomanji JB, Fersht NL, et al: ^{177}Lu-DOTATATE molecular radiotherapy for childhood neuroblastoma. J Nucl Med 52:1041-1047, 2011

67. Kiratli PO, Tuncel M, Bar-Sever Z: Nuclear medicine in pediatric and adolescent tumors. Semin Nucl Med 46:308-323, 2016

68. Cistaro A, Quartuccio N, Caobelli F, et al: 124I-MIBG: A new promising positron-emitting radiopharmaceutical for the evaluation of neuroblastoma. Nucl Med Rev Cent East Eur 18:102-106, 2015

69. Piccardo A, Lopci E, Conte M, et al: Comparison of ^{18}F-dopa PET/CT and ^{123}I-MIBG scintigraphy in stage 3 and 4 neuroblastoma: A pilot study. Eur J Nucl Med Mol Imaging 39:57-71, 2012

Affiliations

Julie R. Park, Seattle Children's Hospital and University of Washington School of Medicine, Seattle, WA; **Rochelle Bagatell** and **John M. Maris**, Children's Hospital of Philadelphia and University of Pennsylvania School of Medicine, Philadelphia, PA; **Susan L. Cohn**, University of Chicago, Chicago, IL; **Andrew D. Pearson**, Institute of Cancer Research and Royal Marsden National Health Service (NHS) Foundation Trust, Sutton, Surrey; **Susan Burchill**, Leeds Institute of Cancer and Pathology, St James University Hospital, Leeds; **Kieran McHugh** and **Penelope Brock**, Great Ormond Street Hospital for Children, NHS Trust, London, United Kingdom; **Judith G. Villablanca**, Children's Hospital Los Angeles and University of Southern California Keck School of Medicine, Los Angeles; **Katherine K. Matthay**, University of California San Francisco School of Medicine, San Francisco, CA; **Frank Berthold**, Children's Hospital and University of Cologne, Köln, Germany; **Ariane Boubaker**, Institute of Radiology, Clinique de La Source, Lausanne, Switzerland; **Jed G. Nuchtern**, Texas Children's Hospital and Baylor College of Medicine, Houston, TX; **Wendy B. London**, Dana-Farber/Boston Children's Cancer and Blood Disorder Center, Harvard Medical School, Boston, MA; **Nita L. Seibel** and **O. Wolf Lindwasser**, National Cancer Institute, Bethesda, MD; **Gudrun Schleiermacher**, Institut Curie, Paris; **Dominique Valteau-Couanet**, Gustave Roussy, Villejuif, France; and **Ruth Ladenstein**, Children's Cancer Research Institute, St Anna Children's Hospital, Vienna, Austria.

Support

Supported by the National Cancer Institute Pediatric and Adolescent Solid Tumor Steering Committee, Alex's Lemonade Stand Foundation, the Ben Towne Foundation, the EVAN Foundation, Cancer Research UK Institut of Cancer Research (ICR) Core Award No. C347/A15403, and the National Institute for Health Research Research Methods Programme/ICR Biomedical Research Centre.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Revisions to the International Neuroblastoma Response Criteria: A Consensus Statement From the National Cancer Institute Clinical Trials Planning Meeting

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/site/ifc.

Julie R. Park
Travel, Accommodations, Expenses: Roche

Rochelle Bagatell
No relationship to disclose

Susan L. Cohn
Stock or Other Ownership: United Therapeutics (I), Varian Medical Systems (I), Hansen Medical, United Therapeutics, Universal Health Services, Varian Medical Systems, Vermillion, Fresenius Medical Care (I), Resmed (I), Universal Health Services (I), AstraZeneca (I), Merck (I), Dr. Reddy's Laboratories, Novartis, Henry Schein, TEVA Pharmaceuticals Industries, AstraZeneca, Merck, Stryker (I), Cigna (I), Cigna, Ensign Group, Express Scripts, Perrigo, Smith & Nephew, Stryker, Valent Pharmaceuticals, Joint Chiropractic Company (I)
Research Funding: United Therapeutics (Inst), Merck (Inst)

Andrew D. Pearson
Travel, Accommodations, Expenses: Boehringer Ingelheim

Judith G. Villablanca
No relationship to disclose

Frank Berthold
Consulting or Advisory Role: United Therapeutics
Research Funding: United Therapeutics
Travel, Accommodations, Expenses: United Therapeutics

Susan Burchill
No relationship to disclose

Ariane Boubaker
No relationship to disclose

Kieran McHugh
No relationship to disclose

Jed G. Nuchtern
Stock or Other Ownership: Lexicon, Johnson & Johnson, CVS, Insulet, Dexcom, Tandem Diabetes Care

Wendy B. London
No relationship to disclose

Nita L. Seibel
No relationship to disclose

O. Wolf Lindwasser
No relationship to disclose

John M. Maris
No relationship to disclose

Penelope Brock
Honoraria: Fennec Pharma
Consulting or Advisory Role: Fennec Pharma
Travel, Accommodations, Expenses: Fennec Pharma

Gudrun Schleiermacher
No relationship to disclose

Ruth Ladenstein
Honoraria: Apeiron Biologics, Boehringer Ingelheim
Consulting or Advisory Role: Apeiron Biologics, Boehringer Ingelheim
Research Funding: Apeiron Biologics (Inst)
Patents, Royalties, Other Intellectual Property: Apeiron Biologics (Inst)
Expert Testimony: Apeiron Biologics
Travel, Accommodations, Expenses: Apeiron Biologics

Katherine K. Matthay
No relationship to disclose

Dominque Valteau-Couanet
No relationship to disclose

Acknowledgment

Presented at Advances in Neuroblastoma Research, Toronto, Canada, June 18-21, 2012, and Advances in Neuroblastoma Research, Cairns, Australia, June 19-23, 2016.

Appendix

Table A1. NCI Clinical Trial Planning Investigators

Name	Institution
Ambros, Peter	Children's Cancer Research Institute, Vienna, Austria
Asgharzadeh, Shahab	Children's Hospital of Los Angeles, Los Angeles, CA
Bagatell, Rochelle	Children's Hospital of Philadelphia, Philadelphia, PA
Baruchel, Sylvain	University of Toronto, Toronto, Ontario, Canada
Beiske, Klaus	Oslo University Hospital, Oslo, Norway
Berthold, Frank	University of Cologne, Cologne, Germany
Boubaker, Ariane	Institute of Radiology, Clinique de La Source, Lausanne, Switzerland
Brock, Penelope	Great Ormond Street Hospital for Children, London, United Kingdom
Burchill, Susan	Leeds Institute of Cancer and Pathology, Leeds, United Kingdom
Cohn, Sue	University of Chicago, Chicago, IL
Fischer, Matthias	University of Cologne, Cologne, Germany
Garaventa, Alberto	Instituto Giannina Gaslini, Genova, Italy
Gaze, Mark	Great Ormond Street Hospital for Children, London, United Kingdom
Gregory, Walter	Leeds Institute of Cancer and Pathology, Leeds, United Kingdom
Haber, Michelle	University of New South Wales, Sydney, New South Wales, Australia
Hero, Barbara	University of Cologne, Cologne, Germany
Hogarty, Michael	Children's Hospital of Philadelphia, Philadelphia, PA
Irwin, Meredith	University of Toronto, Toronto, Ontario, Canada
Kreissman, Susan	Duke University, Durham, SC
Kushner, Brian	Memorial Sloan Kettering Cancer Center, New York, NY
Ladenstein, Ruth	Children's Cancer Research Institute, Vienna, Austria
Lindwasser, O. Wolf	National Cancer Institute, Bethesda, MD
London, Wendy	Dana-Faber Cancer Institute/Harvard University, Boston, MA
Maris, John	Children's Hospital of Philadelphia, Philadelphia, PA
Matthay, Kate	University of California San Francisco, San Francisco, CA
McHugh, Kieran	Great Ormond Street Hospital for Children, London, United Kingdom
Mosse, Yael	Children's Hospital of Philadelphia, Philadelphia, PA
Nakagawara, Akira	Saga Medical Center, Koseikan, Japan
Nuchtern, Jed	Baylor College of Medicine, Houston, TX
Parisi, Marguerite	University of Washington, Seattle, WA
Park, Julie	University of Washington, Seattle, WA
Pearson, Andrew	Royal Marsden NHS Foundation Trust, Sutton, United Kingdom
Pfluger, Thomas	Ludwig Maximilians University of Munich, Munich, Germany
Potschiger, Ulriche	Children's Cancer Research Institute, Vienna, Austria

(continued on following page)

Table A1. NCI Clinical Trial Planning Investigators (continued)

Name	Institution
Sarnacki, Sabine	Hospital Necker-Enfants Malades/Paris Descartes University, Paris, France
Schleiermacher, Gudrun	Institut Curie, Paris, France
Schmidt, Matthias	University of Cologne, Cologne, Germany
Scott, Liz	Alex's Lemonade Stand Foundation, Bala Cynwyd, PA
Seeger, Robert	Children's Hospital of Los Angeles, Los Angeles, CA
Seibel, Nita	National Cancer Institute, Bethesda, MD
Shimada, Hiro	Children's Hospital of Los Angeles, Los Angeles, CA
Shulkin, Barry	St Jude's Children's Research Hospital, Memphis, TN
Simon, Thorsten	University of Cologne, Cologne, Germany
Katleen De Preter	University of Ghent, Ghent, Belgium
Sposto, Richard	Children's Hospital of Los Angeles, Los Angeles, CA
Stutterheim, Janine	University of Amsterdam, Amsterdam, the Netherlands
Tytgat, Godelieve	Prinses Maxima Center for Pediatric Oncology, Utrecht, the Netherlands
Valteau-Couanet, Dominique	Gustave Roussy, Paris, France
Villablanca, Judy	Children's Hospital of Los Angeles, Los Angeles, CA
von Schweinitz, Dietrich	University of Munich, Munich, Germany
Voss, Stephan	Dana-Faber Cancer Institute/Harvard University, Boston, MA
Wheatley, Keith	University of Birmingham, Birmingham, United Kingdom
Yanik, Greg	University of Michigan, Ann Arbor, MI

Abbreviations: NCI, National Cancer Institute; NHS, National Health Service.

Table A2. Clinical Trials Included in INRG Database

Consortium	Clinical Trial
Pediatric Oncology Group	POG8742
	POG8743
	POG9244
	POG9243
Children's Cancer Group	CCG321P2/3/4
	CCG3891
	CCG3881
	CCG3951
Children's Oncology Group	A3973
	A3961
	P9641
	ANBL0032
	ANBL00P1
	ANBL02P1
	ANBL0531
	ANBL0532
	ANBL0931
	ANBL00B1
European Neuroblastoma Study Group	ENSG IV
	ENSG V
	ENSG VI
	ENSG VIII
Spanish Neuroblastoma Study Group	SNSG N-I-87
	SNSG N-II-92
Italian Neuroblastoma Study Group	NB1992
	NB1997
International Society of Pediatric Oncology European Neuroblastoma	LNESG1
	INES
	EUNB
German Pediatric Oncology and Hematology	NB79
	NB82
	NB85
	NB90
	NB95-S
	NB97
Japan Study Group for Advanced Neuroblastoma	91A1

Abbreviations: CCG, Children's Cancer Group; ENSG, European Neuroblastoma Study Group; EUNB, European Unresectable Neuroblastoma; INES, Infant Neuroblastoma European Study; INRG, International Neuroblastoma Risk Group; LNESG1, Localized Neuroblastoma European Study G1; POG, Pediatric Oncology Group; SNSG, Spanish Neuroblastoma Study Group.

Table A3. Overall Response Criteria

Primary Tumor	Soft Tissue or Bone Metastatic Disease (MIBG or FDG-PET)	Bone Marrow Metastatic Disease (cytology*/histology†)	Overall
CR	CR	CR	CR
CR for one response component with either CR or NI for other components			CR
CR	CR	MD	PR
CR	PR	CR	PR
CR	PR	MD	PR
CR	PR	NI	PR
CR	NI	MD	PR
PR	CR	CR	PR
PR	CR	NI	PR
PR	CR	MD	PR
PR	PR	CR	PR
PR	PR	NI	PR
PR	PR	MD	PR
PR	NI	CR	PR
PR	NI	NI	PR
PR	NI	MD	PR
NI	CR	MD	PR
NI	PR	CR	PR
NI	PR	MD	PR
CR	CR	SD	MR
CR	PR	SD	MR
CR	SD	CR	MR
CR	SD	MD	MR
CR	SD	SD	MR
CR	SD	NI	MR
CR	NI	SD	MR
PR	CR	SD	MR
PR	PR	SD	MR
PR	SD	CR	MR
PR	SD	MD	MR
PR	SD	SD	MR
PR	SD	NI	MR
PR	NI	SD	MR
SD	CR	CR	MR
SD	CR	MD	MR
SD	CR	SD	MR
SD	CR	NI	MR
SD	PR	CR	MR
SD	PR	MD	MR
SD	PR	SD	MR
SD	PR	NI	MR
SD	SD	CR	MR
SD	NI	CR	MR
NI	CR	SD	MR
NI	PR	SD	MR
NI	SD	CR	MR
SD	SD	MD	SD
NI	SD	MD	SD
SD	NI	MD	SD
NI	NI	MD	SD
SD	SD	SD	SD
SD	NI	SD	SD
SD	NI	SD	SD
NI	SD	SD	SD
NI	SD	NI	SD
NI	NI	SD	SD
PD in any one component			PD
Response of not evaluable for any one of the three components that had measurable/evaluable tumor at study enrollment and no PD for any component			Not evaluable
No response evaluation performed for any of the three components			Not done

Abbreviations: CR, complete response; MD, minimal disease; MR, minor response; NI, not involved (site not involved at study entry and remains uninvolved); PD, progressive disease; PR, partial response; SD, stable disease.
*Accompanied by immunocytology (recommended, not mandatory).
†Accompanied by immunohistochemistry; specific recommendations included in article by Burchill et al.[19]