Early-phase clinical trial eligibility and response evaluation criteria for refractory, relapsed, or progressive neuroblastoma: A consensus statement from the National Cancer Institute Clinical Trials Planning Meeting

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BACKGROUND: International standardized criteria for eligibility, evaluable disease sites, and disease response assessment in patients with refractory, progressive, or relapsed high-risk neuroblastoma enrolled in early-phase clinical trials are lacking. **METHODS:** A National Cancer Institute–sponsored Clinical Trials Planning Meeting was convened to develop an international consensus to refine the tumor site eligibility criteria and evaluation of disease response for early-phase clinical trials in children with high-risk neuroblastoma. **RESULTS:** Standardized data collection of patient and disease characteristics (including specified genomic data), eligibility criteria, a definition of evaluable disease, and response evaluations for primary and metastatic sites of disease were developed. Eligibility included two distinct patient groups: progressive disease and refractory disease. The refractory disease group was subdivided into responding persistent disease and stable persistent disease to better capture the clinical heterogeneity of refractory neuroblastoma. Requirements for defining disease evaluable for a response assessment were provided; they included requirements for biopsy to confirm viable neuroblastoma and/or ganglioneuroblastoma in those patients with soft tissue or bone disease not avid for iodine-123 meta-iodobenzylguanidine. Standardized evaluations for response components and time intervals for response evaluations were established. **CONCLUSIONS:** The use of international consensus eligibility, evaluability, and response criteria for early-phase clinical studies will facilitate the collection of comparable data across international tri-als and promote more rapid identification of effective treatment regimens for high-risk neuroblastoma. ***Cancer* 2022;128:3775-3783**.

KEYWORDS: clinical trial, consensus criteria, early phase, neuroblastoma.

INTRODUCTION

Nearly 50% of children diagnosed with high-risk neuroblastoma (NB) experience a poor tumor response to frontline therapy or disease recurrence despite dose-intensive multimodal therapy.[1] Curative therapies are limited for patients with progressive disease (PD) or refractory disease.[2,3] Bone and bone marrow (BM) are the most common sites of NB recurrence, but they have been included only recently as evaluable sites for response in early-phase clinical trials.[4–6] Response Evaluation Criteria in Solid Tumors (RECIST) eligibility guidance requires measurable soft tissue disease,[7] and this limits its use in capturing responses at all sites of disease in patients with NB.[8] The revised International Neuroblastoma Response Criteria (INRC) addressed this issue by incorporating iodine-123 meta-iodobenzylguanidine (^{123}I-MIBG) scintigraphy and quantification of BM disease.[9] However, standardized eligibility criteria for disease characteristics of specific patient cohorts and more quantitative scoring of disease response are needed to optimize antitumor assessments of novel therapies. To address this issue, the National Cancer Institute (NCI)–sponsored Clinical Trials Planning Meeting for NB was formed.

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METHODS

To develop a consensus approach to the conduct of clinical trials for refractory, relapsed, or progressive high-risk NB, oncologists, surgeons, radiologists, pathologists, biologists, and statisticians with expertise in NB from major cancer centers and pediatric cooperative groups in Australia, Europe, Japan, and North America interacted under the auspices of the NCI. Data from published trials performed through the Children's Oncology Group, German Pediatric Oncology and Hematology, International Society of Paediatric Oncology European Neuroblastoma, New Approaches to Neuroblastoma Therapy, and single institutions were reviewed.[4,6,10–35] Consensus items were identified and approved by each international NB consortium, the NCI Clinical Trials Planning Meeting Executive Planning Committee, and the NCI Pediatric and Adolescent Solid Tumor Steering Committee. The revised INRC[9] were used in the committee's consensus recommendations.

RECOMMENDATIONS

Patient characteristics at enrollment (Table 1)

Standard clinical and biological features for high-risk NB, including segmental chromosomal aberrations,[36] ploidy,[37] histology by the International Neuroblastoma Pathology Classification,[38] and genomic aberrations (especially MYCN, ALK, and ATRX),[39–43] if available, will be collected. Analyses of biological factors such as these predict response and/or survival and may allow future biological stratification for choices of therapy. Treatment specifics outlined in Table 1 include the completion date of frontline therapy and the date of the last prior treatment. For patients with prior PD, the date of the first progression after the diagnosis of high-risk disease will be obtained along with the therapy (if any) that the patient was receiving at the time of PD. For patients who are initially diagnosed with localized non–high-risk NB but subsequently develop metastatic high-risk NB, the date of PD after the initiation of high-risk NB therapy will be recorded as the date of first progression. Required reporting will include whether the first progression occurred during or after the completion of frontline high-risk NB therapy because patients from all risk NB groups who relapse more than 12 months from their diagnosis demonstrate a longer time to subsequent progression than those relapsing while on therapy.[3,44]

The anatomic locations of NB (central nervous system, liver, lungs, regional or widespread lymph nodes, primary site, and other)[45] at the time of enrollment into an early-phase clinical trial will be collected to allow a descriptive assessment of the activity of a novel agent in specific patient cohorts, especially rare subgroups such as patients with central nervous system involvement. Additional details on patient cohorts may be collected according to the investigational treatment's predicted mechanism of antitumor activity (e.g., molecular data for specific targeted therapies), but these data will be study-specific.

TABLE 1. Patient Characteristics to be Obtained at Enrollment in Early-phase Clinical Trials

Characteristic	Specific details
Date of diagnosis of high-risk NB	
Date of diagnosis of non–high-risk NB, if applicable	
Characteristics at diagnosis	
Age	
Stage	INSS/INRGSS
INRG risk group	Very low, low, intermediate, high
MYCN amplification	Yes/no
MIBG avidity	Yes/no
Date of first disease progression (if applicable)	
Occurred during frontline therapy	Yes/no
Frontline therapy[a]	Dates (start through completion[b])
Induction regimen	Agents, protocol number if applicable
Surgical resection	Complete, incomplete, not done
Myeloablative therapy	Agents or not done
Stem cell infusion(s)	Date(s) or not done
Anti-GD2 immunotherapy	Agents used or not done
Isotretinoin	Number of cycles or not done
Radiotherapy	Dose and sites or not done
^{131}I-MIBG therapy	Dose (mCi/kg) or not done
Other	Agents used or not applicable
Overall response[c]	CR, PR, MR, SD, PD
Second-line/salvage therapy[d]	Date (start through completion)
Chemotherapy	Agents used or not done
Biologic or Molecular therapy[e]	Agents used or not done
Radiotherapy	Dose, sites or not done
^{131}I-MIBG therapy	Dose (mCi/kg) or not done
Other	Agents used or not applicable

Abbreviations: CR, complete response; INRG, International Neuroblastoma Risk Group; INRGSS, International Neuroblastoma Risk Group Staging System; INSS, International Neuroblastoma Staging System; MIBG, meta-iodobenzylguanidine; MR, minor response; NB, neuroblastoma; PD, progressive disease; PR, partial response; SD, stable disease.

[a]Frontline therapy is defined as the therapy chosen at diagnosis and includes all phases (induction, consolidation [including myeloablative therapy], and post-consolidation therapy) until the patient either completes the therapy as intended or the therapy is changed because of an inadequate response.

[b]The completion date is defined as the end of myeloablative consolidation treatment or biologic/immunotherapy residual disease therapy, whichever is later.

[c]Revised International Neuroblastoma Response Criteria.

[d]It is optimal to obtain all prior therapy received; if this is not possible, collect the details for the most recent therapy.

[e]This includes antibodies, vaccines, retinoids, small molecule inhibitors, anti-angiogenics, kinase inhibitors, and epigenetic modifiers.

Disease characteristics required for eligibility criteria (Table 2)

On the basis of data suggesting differences in prognosis,[4,12,46–48] patients will be classified into distinct groups (Table 2). The PD group includes those patients

TABLE 2. Disease Status Eligibility Requirements for Early-phase Clinical Trials

Disease status	Clinical history	Findings
Progressive disease group[a]	1. New soft tissue lesion detected by CT/MRI that is also avid for MIBG or FDG-PET or confirmed histologically 2. New bone site that is MIBG-avid 3. New bone site that is avid for FDG-PET (for MIBG-nonavid tumors) AND has CT/MRI findings consistent with tumor OR has been confirmed histologically 4. At least a 20% increase in the longest diameter, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study) AND a minimum absolute increase of 5 mm in the sum of the diameters of target soft tissue lesions 5. Relative MIBG score ≥ 1.2[b] 6. BM without tumor infiltration that becomes >5% tumor infiltration 7. BM involvement that increases by >2-fold and has >20% infiltration	Prior progressive disease AND at least one of the following: 1. Any amount of tumor in BM[c] 2. At least one MIBG-avid soft tissue or skeletal site 3. For MIBG-nonavid disease, at least one FDG-PET–positive soft tissue or skeletal site plus past histologic confirmation
Refractory disease group[d]	Best overall response to frontline therapy (a minimum of four cycles of induction chemotherapy) and no history of PD: 1. Responding persistent disease = PR but no PD 2. Stable persistent disease = MR or SD but no PD	Refractory disease AND one of the following present since diagnosis: 1. Any amount of tumor in BM 2. At least one MIBG-avid soft tissue or skeletal site 3. For MIBG-nonavid disease, at least one FDG-PET–positive soft tissue or skeletal site plus past histologic confirmation

Abbreviations: BM, bone marrow; CT, computed tomography; FDG, ^{18}F-fluorodeoxyglucose; MIBG, meta-iodobenzylguanidine; MR, minor response; MRI, magnetic resonance imaging; PD, progressive disease; PET, positron emission tomography; PR, partial response; SD, stable disease; SPECT, single-photon emission computed tomography.

[a]Defined as any disease progression occurring at any time after the diagnosis of high-risk neuroblastoma.

[b]The relative MIBG score is the absolute score for bone lesions at the time of the response assessment divided by the absolute score for bone lesions at entry into a clinical trial. The same scoring method (e.g., Curie or International Society of Pediatric Oncology European Neuroblastoma) and imaging methodology (MIBG-SPECT or MIBG-CT) must be used at all assessment time points.

[c]The percentage of tumor in BM is graded on the basis of the single sample with the highest percentage of tumor from bilateral aspirates and biopsies.

[d]Defined as an incomplete response of high-risk neuroblastoma to all treatments but without disease progression.

who develop INRC-defined PD[9] during any phase of treatment for newly diagnosed NB and those patients who develop PD or disease recurrence after the completion of therapy. The refractory disease group encompasses patients with incomplete responses of high-risk NB to all treatments who nonetheless never develop PD. This group is subdivided into two subsets based on the best overall response to frontline high-risk NB therapy that has included a minimum of four cycles of induction chemotherapy: responding persistent disease, which is defined as a partial response (PR) or minor response, and stable persistent disease, which is defined as stable disease. This distinction captures the clinical heterogeneity of refractory NB and provides an opportunity to prospectively assess whether responses and/or progression-free survival will differ between the subsets, as the literature is conflicting.[11,49] The definitions of *responding persistent disease* and *stable persistent disease* may be amended in future INRC consensus criteria to include factors such as an absolute or relative ^{123}I-MIBG score,[11,50] real-time quantitative polymerase chain reaction detection of tumor in BM,[13,27,46,47,51] or other variables that have sufficient validation.[48]

The requirements for the presence of disease characteristics for each distinct group are listed in Table 2. Elevated catecholamine levels and bone sites with uptake via technetium-99 scintigraphy will not be sufficient to meet eligibility criteria. Target soft tissue lesions at the time of enrollment into an early-phase clinical trial will be defined by RECIST[7], and must either be avid for meta-iodobenzylguanidine (MIBG), have uptake of ^{18}F-fluorodeoxyglucose (FDG)–positron emission tomography (PET), or proven viable tumor by biopsy. The definition of *soft tissue mass* also includes soft tissue associated with a bone metastasis (e.g., a dural-based mass extending outside the bone). Osteomedullary lesions detected on computed tomography (CT) or magnetic resonance imaging (MRI) scans will not meet eligibility criteria as measurable soft tissue target lesions but will meet eligibility criteria as bone sites on the basis of the uptake of ^{123}I-MIBG or, for MIBG-nonavid tumors, the uptake of FDG-PET (Table 2).

Disease evaluable for a response assessment (Table 3)

The defined eligibility groups will have different requirements for biopsies of tumor sites at the time of study

TABLE 3. Disease Sites Evaluable for Response

Disease site	Disease site characteristics	Biopsy requirements
Soft tissue site(s):target lesions[a]	Soft tissue site is ^{123}I-MIBG–avid AND is a new site of disease since most recent therapy.	Biopsy not required
	Soft tissue site is ^{123}I-MIBG–avid AND patient has responding persistent disease.[b]	Biopsy of at least one site (including BM) for histologic confirmation; biopsy not required if >1 soft tissue site of MIBG uptake
	Soft tissue site is ^{123}I-MIBG–avid AND patient has stable persistent disease[b] or prior progressive disease.	Biopsy not required
	Soft tissue site is ^{123}I-MIBG–nonavid BUT has increased FDG-PET uptake.	Biopsy of at least one soft tissue site for histologic confirmation
	Mass is NOT ^{123}I-MIBG–avid and does NOT have increased FDG-PET uptake.	Past biopsy documented disease AND mass has enlarged by ≥20% in the longest dimension, or biopsy performed within 4 weeks of enrollment and after the last dose of prior therapy confirmed disease.
Soft tissue site(s): nontarget lesions[c]	Soft tissue site is ^{123}I-MIBG–avid AND is a new site of disease since most recent therapy.	Biopsy not required
	Soft tissue site is NOT ^{123}I-MIBG–avid.	Biopsy of site for histologic confirmation
Bone site(s)	Bone site(s) are ^{123}I-MIBG–avid and are a new site of disease since most recent therapy.	Biopsy not required
	Bone site(s) are ^{123}I-MIBG–avid AND patient has responding persistent disease.[b]	Biopsy is not required if > 1 bone site with MIBG uptake
	Bone site(s) are ^{123}I-MIBG–avid AND patient has stable persistent disease[b] or prior progressive disease.	No biopsy required
	Bone site is ^{123}I-MIBG–nonavid BUT has increased FDG-PET uptake.	Past biopsy of at least one site confirmed disease, or MRI is consistent with metastasis.
	Bone site is NOT ^{123}I-MIBG–avid and does NOT have increased FDG-PET uptake.	Biopsy performed within 4 weeks of enrollment and after last dose of prior therapy confirms disease.
BM	Tumor present on cytology (with immunocytology if available) of an aspirate or standard histology ± immunohistochemistry of a biopsy Minimal disease includes any of the following[9]: 1. BM has ≤5% tumor infiltration at enrollment, and >0 to ≤5% tumor infiltration remains upon reassessment; it may have intermittent negatives. 2. BM does not have tumor infiltration at enrollment, but ≤5% is involved upon reassessment; it may have intermittent negatives. 3. BM has >20% tumor infiltration at enrollment, and becomes >0 to ≤5% upon reassessment.	Evaluable for response only if >5% tumor in any one sample of bilateral aspirates and biopsies

Abbreviations: BM, bone marrow; FDG, ^{18}F-fluorodeoxyglucose; MIBG, meta-iodobenzylguanidine; MRI, magnetic resonance imaging; PET, positron emission tomography.
[a]Target lesions are defined as a non–lymph node mass or coalesced lymph nodes ≥10 mm in one dimension or a discrete lymph node ≥15 mm on the short axis.
[b]The definitions of *responding persistent disease* and *stable persistent disease* are based on responses to frontline therapy including a minimum of four cycles of induction (see Table 2). Bone and soft tissue sites that have received prior focal radiation will remain evaluable if they meet the other criteria listed in the table.
[c]Nontarget lesions are defined as a non–lymph node soft tissue site or coalesced lymph nodes <10 mm in the longest diameter or a discrete lymph node <15 mm on the short axis.

enrollment for the purpose of defining evaluability for response (Table 3).

The comprehensive extent-of-disease evaluation required for early-phase clinical trials must be performed after the completion of the last prior therapy and less than 4 weeks before enrollment into the trial (Table 4). Further details on the timing of the tumor evaluation with respect to specific prior therapies will be delineated in individual protocols. Disease sites evaluable for response will include target and nontarget soft tissue masses (including primary and metastatic soft tissue sites), bone metastases, and BM metastases. Patients must have at least one tumor site that is evaluable for response among these three categories to be included in the analysis of response as the study end point (Table 3). Serum or urine catecholamines and technetium-99 scintigraphy are not required for response assessments.

Soft tissue sites (Table 3) will be assessed by CT scans and/or MRI to determine if they are measurable lesions per RECIST.[7] Limiting exposure to radiation should be considered when one is choosing the optimal imaging modality. MRI is suggested for the optimal imaging of epidural and hepatic sites, whereas CT is preferred for imaging the chest. Nontarget lesions include leptomeningeal tumors; tumors in cerebrospinal, ascites, or pleural fluid; and lesions smaller than 10 mm that are considered likely to be

TABLE 4. Response Assessment

Assessments	Schedule[a]	Extent of disease workup			
		CT or MRI[b]	MRI head + orbits[c]	^{123}I-MIBG[d]	BM[e]
Baseline	<4 weeks before enrollment	Yes	Yes, if cranial bones or CNS ever involved or if currently MIBG-avid	Yes	Yes
1	Completion of one to two cycles of study therapy	Yes	Yes, if involved at enrollment	Yes	Yes
2	Completion of three to four cycles of study therapy (<12 weeks from enrollment)	Yes, if involved at enrollment or to confirm CR; otherwise not required if MIBG-avid	Yes, if involved at enrollment	Yes	Yes, if involved at enrollment
3	Completion of six to eight cycles of study therapy (<24 weeks from enrollment)	Same as baseline assessment			
Subsequent	Every three to four cycles	Yes, if involved at enrollment or to confirm CR; otherwise not required if MIBG-avid	Yes, if involved at enrollment	Yes	Yes, if involved at enrollment; only required in alternating assessments if not involved at enrollment or two prior evaluations were without involvement
Completion of protocol	—	Same as baseline assessment			

Note: Urinary catecholamine levels are not required for a response assessment.
Abbreviations: BM, bone marrow; CNS, central nervous system; CR, complete response; CT, computed tomography; MIBG, meta-iodobenzylguanidine; MRI, magnetic resonance imaging; SPECT, single-photon emission computed tomography.
[a]Workups should be scheduled to coincide with the end of the cycle of study treatment if possible.
[b]This should include the chest, abdomen, and pelvis; the neck should be included if it was previously involved by disease. MRI should be considered if there is suspected liver or epidural disease.
[c]CT may be easier to perform and is most acceptable if cranial–orbital sites were previously irradiated.
[d]MIBG-CT, MIBG-SPECT, or both may be used, but the same modality must be used at each response evaluation. Positron emission tomography is required if the suspected disease is MIBG-nonavid, and is also recommended for evaluation of bone or soft sites that persist after focal radiation.
[e]BM aspirates and biopsies are from bilateral (posterior or anterior) iliac crests. Obtaining BM specimens can follow imaging studies because a BM evaluation might not be necessary if there is progressive disease.

active tumors on the basis of clinical correlation (e.g., hepatic and pulmonary nodules). Soft tissue lesions measuring <10 mm in the longest dimension and lymph nodes that measure <15 mm on the short axis must be biopsied to prove that they consist of viable tumor to be listed at study enrollment and considered as nontarget lesions. The eligibility for specific trials may exclude patients who have only nontarget lesions at study enrollment.

^{123}I-MIBG scanning should be performed for all patients at the time of enrollment, regardless of their prior history of MIBG-nonavid NB, to reassess for changes in MIBG avidity. ^{123}I-MIBG uptake and/or biopsy will be used as additional criteria to demonstrate that soft tissue sites are target lesions that are evaluable for response. Because tumor uptake of FDG-PET may occur with infection and/or inflammation, patients with tumors not avid for ^{123}I-MIBG will be required to meet additional criteria listed in Table 3. A soft tissue mass that is associated with a bone metastasis and meets the criteria for a target lesion is evaluable for response in the soft tissue category.[7,9]

Osteomedullary lesions that are avid for ^{123}I-MIBG are evaluable for response in the metastatic bone category. FDG-PET scans will be used for response assessment only if the tumor is known to be ^{123}I-MIBG–nonavid. FDG-PET scans will not be used for disease assessment in ^{123}I-MIBG–avid disease.

BM will be assessed by bilateral aspirates and biopsies, with cytology of aspirates (and immunocytology if available) and immunohistochemical staining for NB-specific antibodies of trephine biopsies per institutional standards strongly recommended.[52] The percentage of tumor infiltration at each response evaluation time point will be based on the highest percentage seen in any one sample among the bilateral aspirates and biopsies (a total of four samples). Early-phase clinical studies of agents targeting minimal residual disease may consider the use of more sensitive quantification of BM metastases such as real-time quantitative polymerase chain reaction[48]; however, further work is required to standardize the analytical platform specifications for minimal residual disease testing before its incorporation into the INRC.

Patients with ≤5% BM involvement will be placed into a new category labeled *minimal disease* (MD; Table 3). For early-phase clinical studies, patients with MD in BM as the only site of disease at study entry will be eligible for enrollment but will not be included in a

primary end point of overall response and instead will be descriptively tabulated separately. Such patients will be studied prospectively to further validate techniques that accurately measure low amounts of marrow involvement and further define complete response (CR), PR, or PD within this group. Until such techniques are validated, BM responses will be classified as CR, MD, stable disease, and PD.[9,52] In the category of BM MD, because of the known issue of accurate sampling of low levels of marrow disease, intermittent low-level positivity for a tumor not meeting the definition of PD will remain classified as MD.

Required observations for early-phase clinical trials (Table 4)

Patients must undergo a complete extent-of-disease evaluation, including anatomic imaging, ^{123}I-MIBG scintigraphy (or FDG-PET scanning if they are not avid for MIBG), and a BM evaluation, at least at the time points specified in Table 4. The same imaging modalities used to determine evaluable disease at enrollment should be repeated at subsequent response evaluations during protocol therapy.

Response assessments (Table 4) will occur after no more than two (assessment 1) and four cycles of therapy (assessment 2), with the length of a cycle predicted to be 3–4 weeks per cycle. Responses at all known sites of disease should be assessed; in addition, an examination of bilateral BM aspirates and biopsies should be performed at assessment 1, regardless of BM involvement at the time of enrollment.

Subsequent assessments will be performed at least every three to four cycles through at least the initial year of the protocol therapy. A BM evaluation must be included if the patient had documented BM involvement at enrollment. For patients without BM involvement at enrollment or for patients who achieve a BM CR confirmed by two consecutive BM evaluations, a BM evaluation will be required only at alternating evaluations (i.e., approximately every 24 weeks). A BM evaluation is not required if CT or ^{123}I-MIBG scanning demonstrates PD.

In the rare setting of prolonged stable disease, ongoing evaluations after 1 year of therapy will be study-specific. Although these evaluations must include the appropriate nuclear medicine scan (^{123}I-MIBG or FDG-PET), anatomic imaging (CT or MRI) is not required if there was no documented measurable soft tissue disease at enrollment and the tumor is known to be MIBG-avid. Imaging of the head is required only at alternating evaluations if it was involved at enrollment; it is not required if the patient is known to have an MIBG-avid tumor and there is no parenchymal brain involvement.

All patients who complete the prescribed early-phase clinical trial protocol therapy without PD should undergo "an end of protocol therapy" complete evaluation, which is identical to the one performed at study enrollment.

Overall tumor response assessment

The tumor response for each component of response (primary soft tissue, metastatic soft tissue and bone sites, and metastatic BM) will be assessed and considered in aggregate to determine an overall response assessment.[9] The objective response rate will be defined as patients who have achieved a CR, a PR, or a minor response. If PD is confirmed, the date of the first radiologic imaging or histopathology documenting PD should be considered as the date of PD. For equivocal findings of PD (e.g., small [<10 mm] or uncertain new lesions on imaging studies or an increase in the intensity of MIBG uptake at a known site but no new sites), treatment on study may continue until the next scheduled assessment, although an earlier follow-up evaluation might be advisable (e.g., after another cycle of the study treatment). If PD is confirmed, the date of PD should be the date when PD was confirmed on the second subsequent evaluation. The duration of the objective response rate and additional therapies received after the completion of the index clinical trial and before subsequent progression will also be collected.

Study design

The specifications of clinical trial study designs for early-phase clinical trials in relapsed and refractory high-risk NB will be dependent on the primary study aim and the anticipated patient accrual and cannot be mandated a priori. Expansion cohorts incorporated into phase 1 clinical trials (e.g., 10–26 patients) should be considered to detect early signals of antitumor activity. Further evaluation of antitumor activity within a phase 2 trial is required to assess whether investigation in a phase 3 trial is warranted.

Both single-arm phase 2 trials and randomized phase 2 trials can be used to assess antitumor activity. The advantages and disadvantages of each design have been the topic of ongoing debate.[53] Single-arm designs can use a single stage (e.g., A'Hern[54]) or two stages (e.g., Simon[55]) and require the assumption of a level of outcome that would make the novel treatment worthy of further evaluation and a level that would not. Randomized phase 2 trials, with a randomly assigned concurrent control group, minimize problems of patient selection and other factors that differ over time or geographically. Randomized phase 2 trials may have

a standard treatment control arm (e.g., Jung[56]) or compare experimental regimens with the objective of selecting the most promising for further comparative evaluation against a standard treatment (e.g., Sargent et al.[57]). Unfortunately, this design requires larger numbers of patients than single-arm studies and may not be feasible when one is studying extremely rare clinically or molecularly defined patient cohorts. An efficient design that is being increasingly used is the multi-arm, multistage trial,[5,53,58–61] which is also called "pick-a-winner" or "drop-a-loser." Arms that do not meet the phase 2 success criteria are dropped, whereas new arms can be brought in as they become available. Such designs can also use seamless phase 2 and phase 3 components, with arms that pass the phase 2 success criteria (often based on a short-term outcome measure) progressing straight into a larger phase 3 evaluation with a longer term outcome such as event-free or overall survival within the same trial.

This article defines consensus criteria for early phase clinical trial eligibilty criteria and evaluation of high-risk NB response that reflect the currently available methodology for defining tumor sites and their response. These criteria will facilitate comparisons between clinical trials; however, such comparisons will have important uncontrolled variables. For example, simply making the eligibility criteria for two studies identical does not mean that the patients actually enrolled will be a homogeneous population with the same prognostic and biological features, some of which will be unknown. These factors may affect the patient's response to a specific therapy.[49] Furthermore, several factors other than eligibility and response criteria can vary across time or between centers and regions (e.g., supportive care, differences in prior frontline therapy, or available radiologic techniques) and will make cross-study comparisons unreliable.

CONCLUSION

These international consensus guidelines will provide a framework in which early-phase clinical trials for novel high-risk NB therapies can be conducted worldwide. Although it is not statistically sound to make comparisons among different early-phase clinical trials, uniform definitions of eligible patients and tumor responses will allow a better understanding of the differences in results across clinical trials. Furthermore, a standardized language will encourage collaborative, multi-institutional trials and facilitate both enrollment in and completion of clinical trials with patient numbers adequate to provide reliable results. This is critical for rare tumors such as high-risk NB with an overall small population of available patients. Efficiently conducting clinical trials that use agreed-upon criteria for eligibility and response will enhance our ability to prioritize novel agents in the treatment of high-risk NB and ultimately improve patient outcomes. This consensus statement should be disseminated to cooperative groups involved in early-phase clinical trials across the globe through the involvement of key opinion leaders from cooperative groups as well as educational and dissemination activities, particularly those involving young investigators. This will ensure that it is rapidly incorporated into future clinical trials and that its impact can be maximized.

AUTHOR CONTRIBUTIONS

Julie R. Park: Funding acquisition. **Nita L. Seibel:** Funding acquisition. **Keith Wheatley:** Methodology. All authors contributed to the conceptualization, data curation, formal analysis, investigation, writing–original draft, and writing–review and editing.

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CONFLICTS OF INTEREST

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