European Reference Network
for rare or low prevalence complex diseases
Network Paediatric Cancer (ERN PaedCan)

February 15th, 2023

Dorus Kouwenberg & Maja Beck Popovic

New diagnostic possibilities in metastasized neuroblastoma

Moderation: Roelof van Ewijk

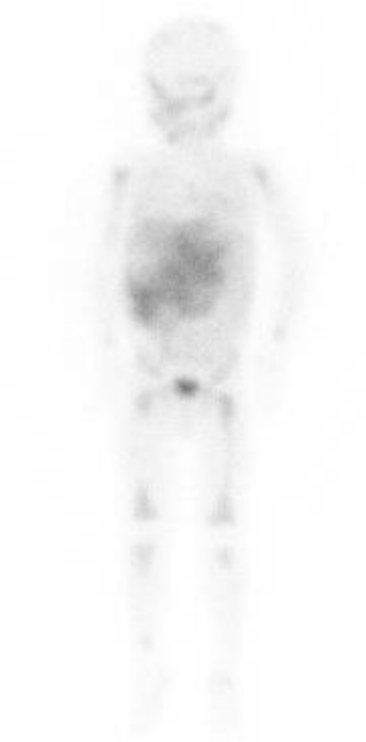
Funded by the European Union's EU4Health Programme

COI declaration

- Dorus Kouwenberg: nothing to declare
- Maja Beck Popovic: nothing to declare

Case description – diagnosis

- Boy, 2 years 11 months
- Neuroblastoma stage M
- NMYC amplified
- [^{123}I]mIBG SIOPEN score at diagnosis: 60/72



SIOPEN score

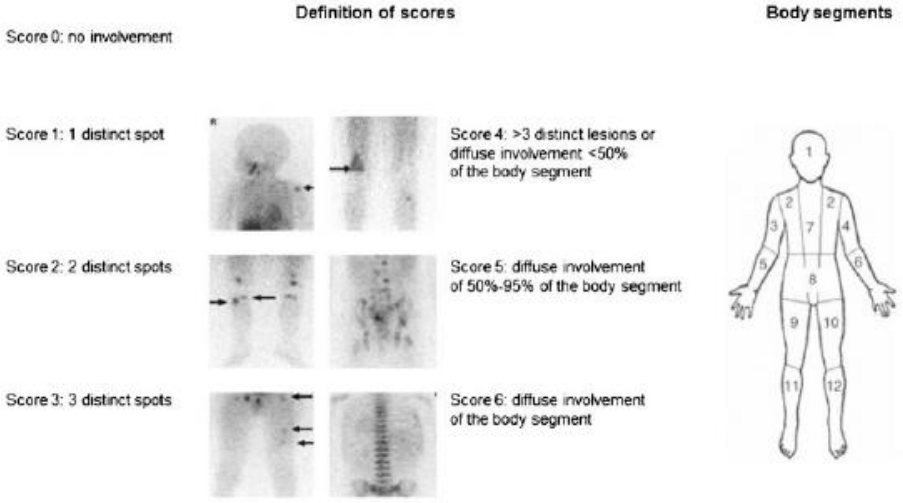
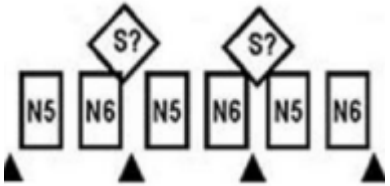


Fig. 1.
Definition of scores for the extension of the skeletal involvement with illustrative planar I-123-mIBG scans (arrows) of the various positive scores (left). The mIBG uptake over 12 body segments (right) is scored from 0 to 6 points per segment depending on the disease extension [13]

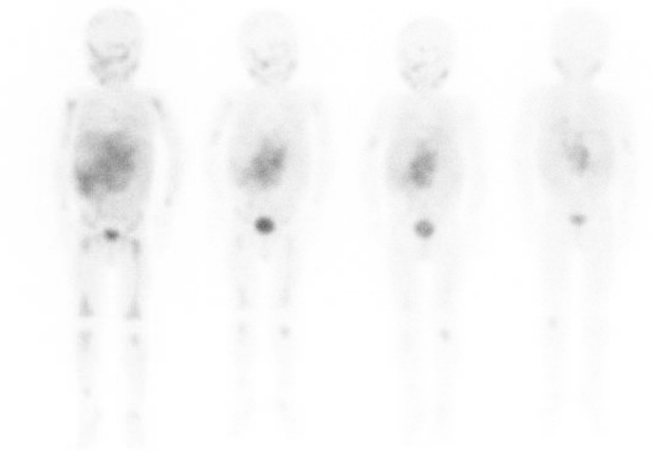
Ladenstein R et al, Eur J Nucl Med Mol Imaging. 2018 February ; 45(2): 292–305

Case description – induction treatment

- According to DCOG NBL 2009 protocol, high risk group



- Progressive decline of SIOPEN score after each cycle of N5/N6 (60 → 42 → 27 → 14)



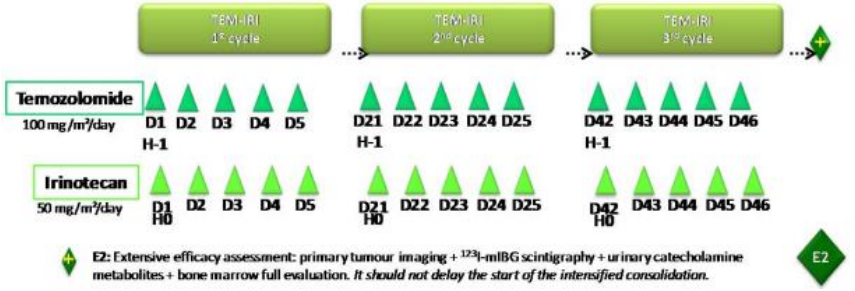
Question 1

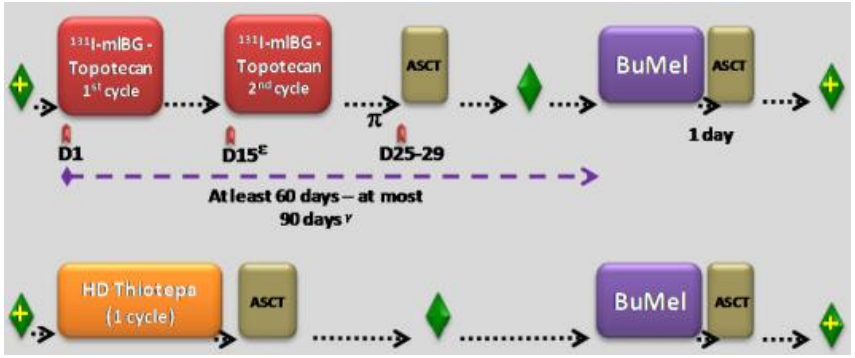
How would you interpret the response to treatment at the end of induction therapy and what would you suggest as next step in the treatment?

- ☐ Partial response, proceed with consolidation therapy per protocol
- ☐ Refractory disease, consider other treatment options

Case description – intensification treatment

- VERITAS trial
- High dose busulfan/melfalan with autologous stem cell reinfusion
- SIOPEN score after high dose: 3/72

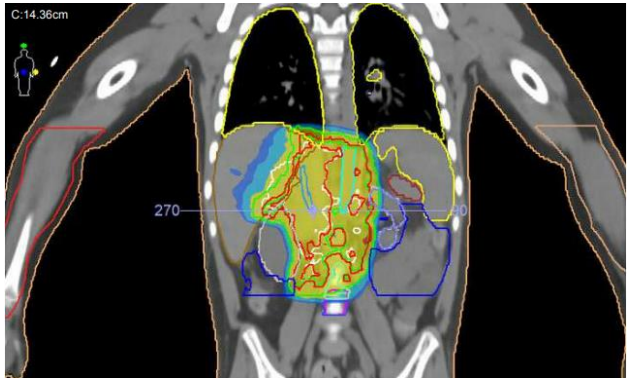




Case description – local treatment

- Tumor resection – necrotic tissue, no vital tumor

- Abdominal radiotherapy



Case description – immunotherapy

- SIOPEN score before immunotherapy: 1/72
- Dinutuximab (long-term infusion) and retinoic acid, six courses
- SIOPEN score after three courses of immunotherapy: 0/72

[^{18}F]mFBG PET-CT versus [^{123}I]mIBG SPECT

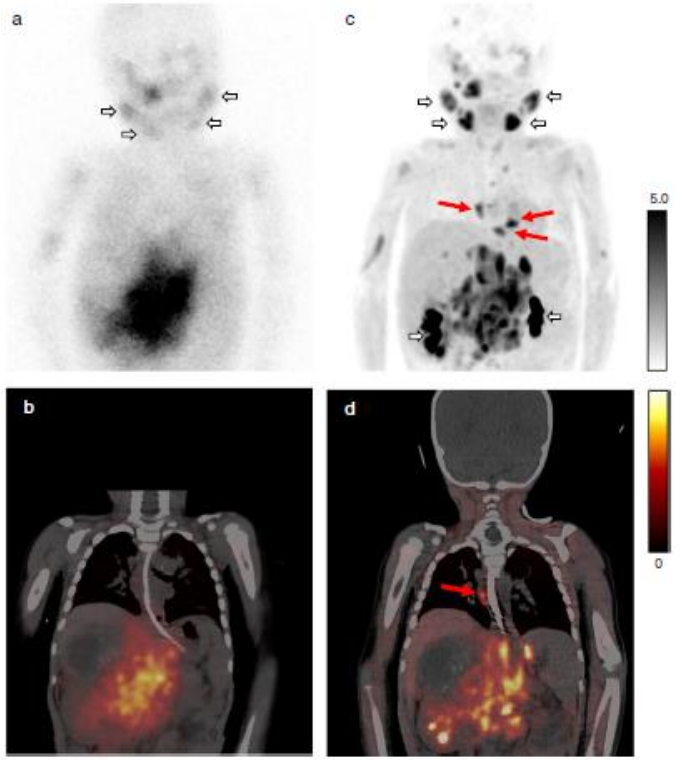
- Shorter scan time, reduced need for sedation
- No need for thyroid protecting medication
- Improved detection and localization due to higher image resolution and 3D-imaging

Samim et al., 2022

Pilot study

- 14 patients

- 20 paired [^{123}I]mIBG SPECT and [^{18}F]mFBG PET-CT scans



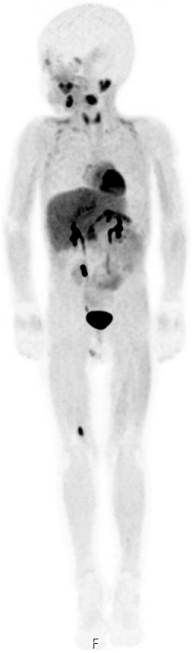
Comparison of mIBG and mFBG SIOPEN scores

Time point	[^{123}I]mIBG SPECT	[^{18}F]mFBG PET-CT
Diagnosis	60/72	-
After 1st N5/N6 cycle	42/72	44/72
After 2nd N5/N6 cycle	27/72	-
After 3rd N5/N6 cycle	14/72	21/72
After intensification and high dose	3/72	-
Before immunotherapy	1/72	-
During immunotherapy	0/72	-
End of therapy	-	1/72

Question 2

The mFBG scan suggests relapse. How would you confirm this?

- ☐ [^{123}I]mIBG SPECT
- ☐ Biopsy of suspected lesion



Question 3

What therapeutic options would you consider if relapse is confirmed?

Case description – relapse treatment

- CT-guided biopsy: infiltration of neuroblastoma
- 1st line: according to BEACON protocol, bevacizumab/irinotecan/temozolomide arm → progressive disease (SIOPEN score 4/72 after two courses)
- 2nd line: [^{177}Lu]DOTA-TATE therapy, evaluation end of February

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DISCUSSION

Co-funded by the European Union's Health Programme

Outcome of patients with relapsed/refractory disease

Moreno et al, Pediatr Blood Cancer 2017; 64: 25–31

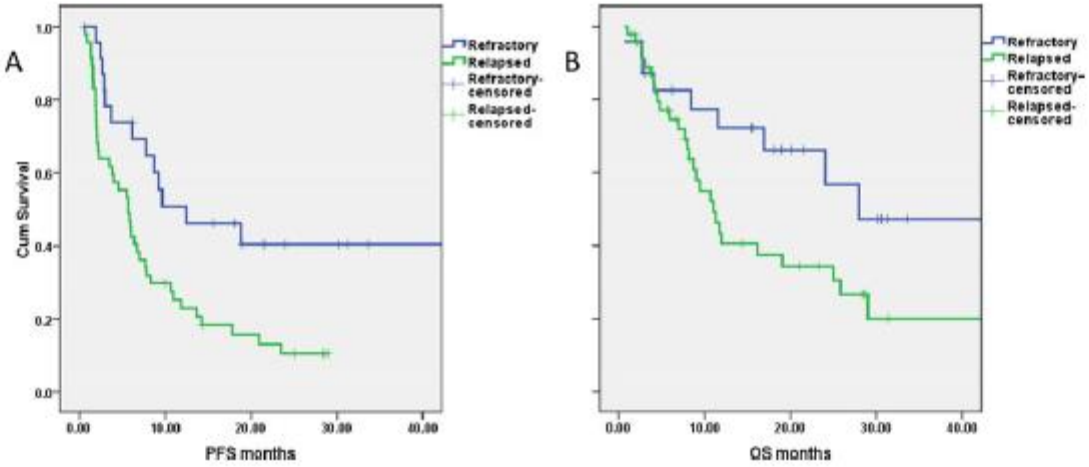
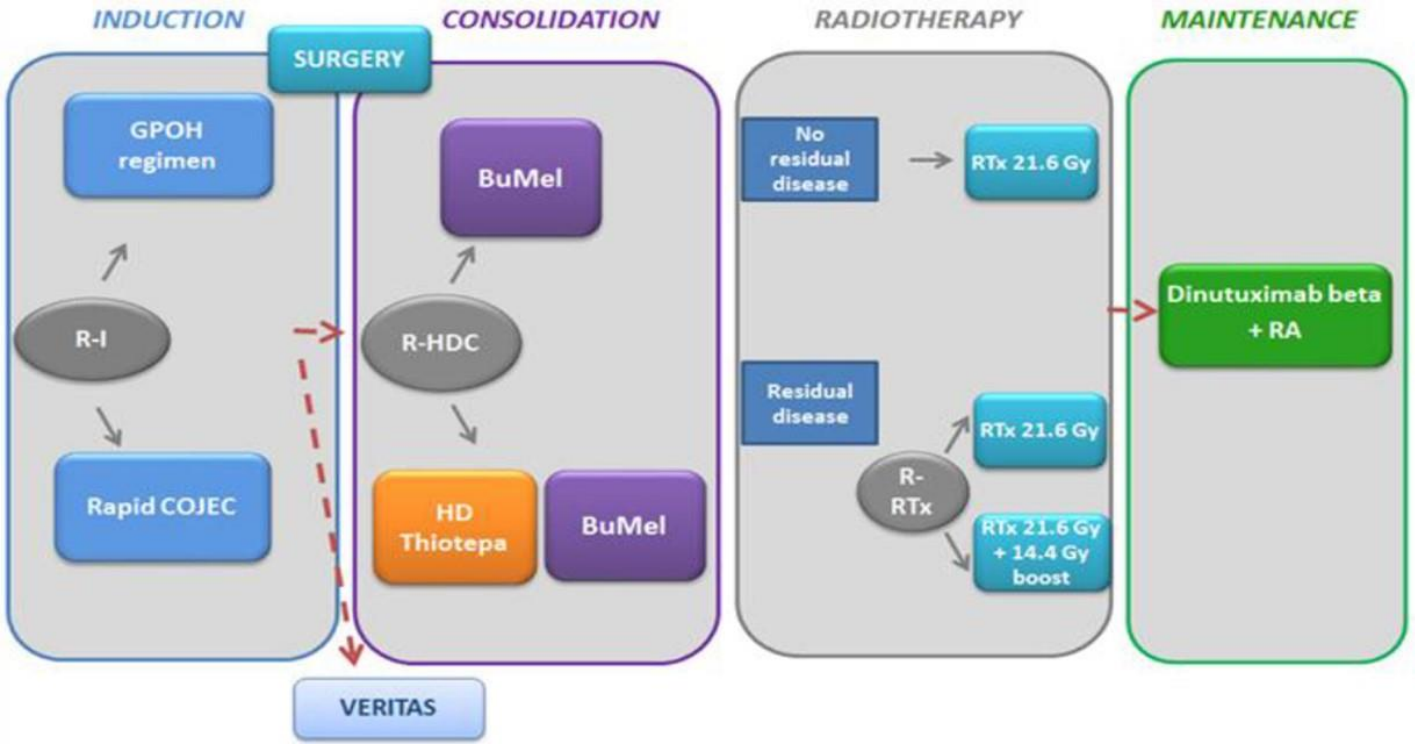
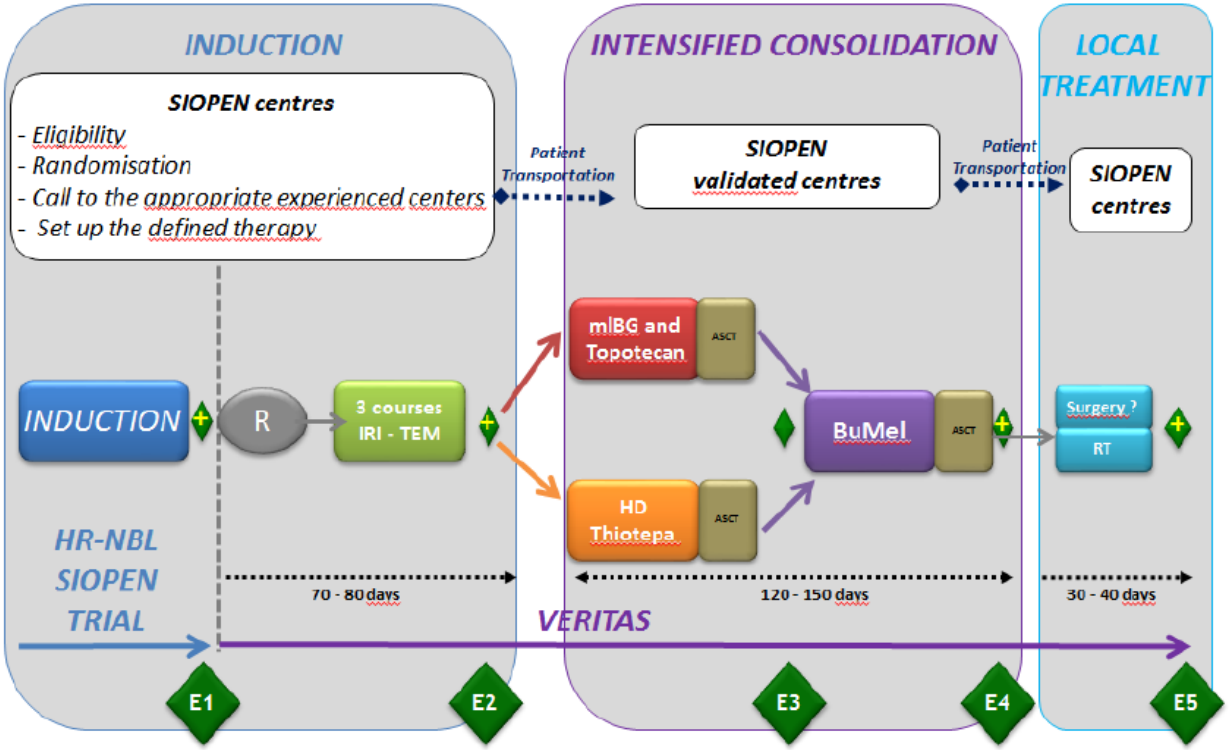


FIGURE 2 Outcome of patients with relapsed and refractory neuroblastoma treated in the three clinical trials: PFS from study entry (A) and OS from study entry (B) according to the type of disease at study entry: relapsed or refractory neuroblastoma

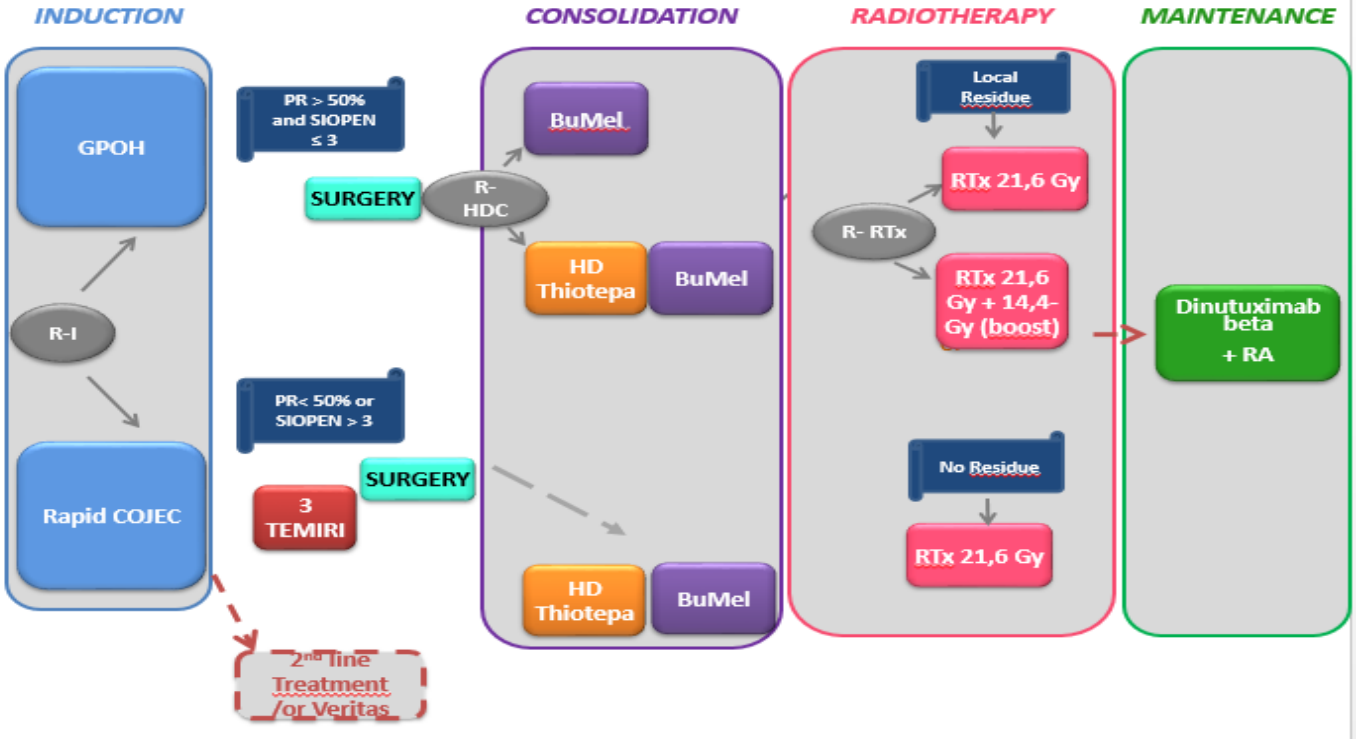
HR-NBL2


INDUCTION
CONSOLIDATION
RADIOTHERAPY
MAINTENANCE
SURGERY
GPOH regimen
R-I
Rapid COJEC
BuMel
R-HDC
HD Thiotepa
BuMel
No residual disease
RTx 21.6 Gy
Residual disease
R-RTx
RTx 21.6 Gy
RTx 21.6 Gy + 14.4 Gy boost
Dinutuximab beta + RA
VERITAS

Veritas


INDUCTION
SIOPEN centres
- Eligibility
- Randomisation
- Call to the appropriate experienced centers
- Set up the defined therapy
Patient Transportation
INTENSIFIED CONSOLIDATION
SIOPEN validated centres
Patient Transportation
LOCAL TREATMENT
SIOPEN centres
INDUCTION
R
3 courses IRI - TEM
mIBG and Topotecan
ASCT
HD Thiotepa
ASCT
BuMel
ASCT
Surgery ?
RT
HR-NBL SIOPEN TRIAL
70 - 80 days
120 - 150 days
30 - 40 days
VERITAS
E1
E2
E3
E4
E5

HR-NBL2/SIOPEN amendment V2.0 dated 03/10/2022



INRC

APPENDIX 4: INTERNATIONAL NEUROBLASTOMA RESPONSE CRITERIA

Data from both prospective and retrospective trials were used to refine the International Neuroblastoma Response Criteria (INRC [61, 15]

- Overall response integrates tumour response in the primary tumour, soft tissue and bone metastases, and bone marrow.
- Primary and metastatic soft tissue sites are assessed using Response Evaluation Criteria in Solid Tumours (RECIST) and ^{123}I–mIBG scans or [^{18}F] fluorodeoxyglucose–positron emission tomography scans if the tumour is mIBG nonavid.
- Bone marrow is assessed by histology or immunohistochemistry and cytology or immunocytology. BM with ≤ 5% tumour involvement will be classified as minimal disease.
- Urinary catecholamine levels are not included in response assessment.
- Overall response will be defined as complete response, partial response, minor response, stable disease, or progressive disease.

Park et al, J Clin Oncol 35:2580-2587, 2017

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

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

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

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

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Literature

- Outcome of children with relapsed or refractory neuroblastoma: A meta-analysis of ITCC/SIOPEN European phase II clinical trials. **Moreno et al, Pediatr Blood Cancer 2017; 64: 25–31**
- The challenge of defining "ultra-high-risk" neuroblastoma. **Morgenstern et al, Pediatr Blood Cancer. 2019;66:e27556**
- Revisions to the International Neuroblastoma Response Criteria: A Consensus Statement From the National Cancer Institute Clinical Trials Planning Meeting. **Park et al, J Clin Oncol 35:2580-2587, 2017**
- Pattern and predictors of sites of relapse in neuroblastoma: A report from the International Neuroblastoma Risk Group (INRG) project. **Vo et al, Pediatr Blood Cancer. 2022;69:e29616**.
- Accelerating drug development for neuroblastoma: Summary of the Second Neuroblastoma Drug Development Strategy forum from Innovative Therapies for Children with Cancer and International Society of Paediatric Oncology Europe Neuroblastoma. **Moreno et al, European Journal of Cancer 136 (2020) 52e68**
- 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. **Park et al, Cancer November 1, 2022**
- [18F]mFBG PET-CT for detection and localisation of neuroblastoma: a prospective pilot study. **Samim et al, European Journal of Nuclear Medicine and Molecular Imaging, published on-line 12 December 2022**
- [18F] MFBG PET imaging: biodistribution, pharmacokinetics, and comparison with [123I] MIBG in neural crest tumour patients. **Pauwels et al, European Journal of Nuclear Medicine and Molecular Imaging, published on-line 26 November 2022**
- 18F-meta-fluorobenzylguanidine (18F-mFBG) to monitor changes in norepinephrine transporter expression in response to therapeutic intervention in neuroblastoma models. **Turnock et al, Scientific Reports | (2020) 10:20918**

Take home messages

- Common and validated tools for uniform assessment of disease response
- Predictors of relapse
- Definition of prognostic subgroups
- Collaborative trial design to evaluate
  - New diagnostic/therapeutic tools
  - New drugs
  - The role of known and new biomarkers