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SCIENCE MEDICINES HEALTH

Current Treatment and Regulatory Insights – EMA and FDA – Part II

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Disclaimer

The views and opinions expressed in the following PowerPoint slides are those of the individual presenter and should not be understood or quoted as being made on behalf of the European Medicines Agency or its scientific Committees.

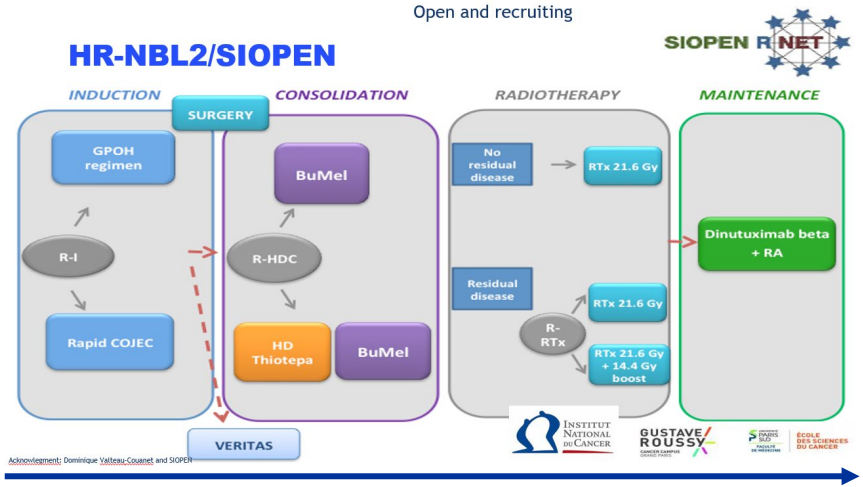
Regulatory decision making

- Objective: weighing up the benefits (B - survival) and risks (R - toxicities)

Including considerations related to e.g.:

- what is the individual contribution to B/R [1]

- Adequate data collection takes a long time



→ Need for innovative endpoint considerations

1) https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-evaluation-anticancer-medicinal-products-man-revision-5_en.pdf

Potential purposes of end of induction response

Strength of evidence

1. Supporting patient enrichment
2. Guiding prioritisation considerations of novel agents
3. Serving as (validated) surrogate endpoint, replacing survival endpoint in pivotal study(ies)

Conclusions

- End-induction response could have potential use in development of new drugs

- Collaboration amongst all stakeholders and early interactions with regulators key
  - Particularly to support its qualification/ validation [1]

1) https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-advice-protocol-assistance/qualification-novel-methodologies-medicine-development-0

Thank you very much!

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Diana Bradford, Martha Donoghue, Gregory Reaman

Any questions?

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Accelerating cure for high-risk neuroblastoma

Leona Knox
Advocate

My son, Oscar

- The most perfect little boy

- Diagnosed in 2011, aged 3
- Heavy disease burden
- Multiple lines of therapy
- Experienced significant toxicity
- Died in 2014, aged $5\frac{1}{2}$


Oscar Knox, forever 5

Front-line treatment: a poor chance of cure


Adam Bird, forever 9

- Despite intensive multimodality therapy, survival rates remain just over 50%.[1]
- Accounts for 10% to 12% of deaths from malignancy in childhood.[2]
- Approximately 7%-15% of patients experienced **early disease progression**, highlighting the importance of identifying the most effective initial treatment.[1]
- 20.2% of children do not achieve partial response or better at end-induction.[3]

1. Improving Outcomes in Children With High-Risk Neuroblastoma: The Role of Randomized Trials; Dubois et al, JCO 2021
2. Effect of tandem autologous stem cell transplant vs single transplant on event-free survival in patients with high-risk neuroblastoma: A randomized clinical trial; Park et al, JAMA 2019
3. Predictors of differential response to induction therapy in high-risk neuroblastoma: A report from the Children's Oncology Group (COG); Pinto et al, European Journal of Cancer 2019

Our children suffer…

- Embryonal cancer, diagnosed at a median age of 17.3 months[4] (US)
- Separated from family, peers, society, for long periods at a formative age
- Crippling impact on whole family

…infinitely

- Therapy for high-risk neuroblastoma is expected to be associated with long-term toxicities, including hearing impairment, kidney dysfunction, second cancer risk, infertility, and compromised growth.[2]
- Neuroblastoma survivors are at elevated risk for psychological impairment, which is associated with special education service usage and lower adult educational attainment.[4]

2. Effect of tandem autologous stem cell transplant vs single transplant on event-free survival in patients with high-risk neuroblastoma: A randomized clinical trial; Park et al, JAMA 2019
4. Long-term psychological and educational outcomes for survivors of neuroblastoma: A report from the Childhood Cancer Survivor Study; Zheng et al, Cancer 2018

Are we treading water?

- Significant progress made in treating childhood cancers since 1960s
- Progress has stalled, incremental improvements are now the norm

- More efficient approaches are needed in the most difficult-to-treat cancers – is that **the** problem of our generation?

- *Questions arise as to whether the results of a pediatric RCT that requires 5 years to accrue in a rare disease will still be relevant when the trial is completed.*[1]

1. Improving Outcomes in Children With High-Risk Neuroblastoma: The Role of Randomized Trials; Dubois et al, JCO 2021

Real progress is too slow

NIH U.S. National Library of Medicine

ClinicalTrials.gov

602 Studies found for: **Neuroblastoma**

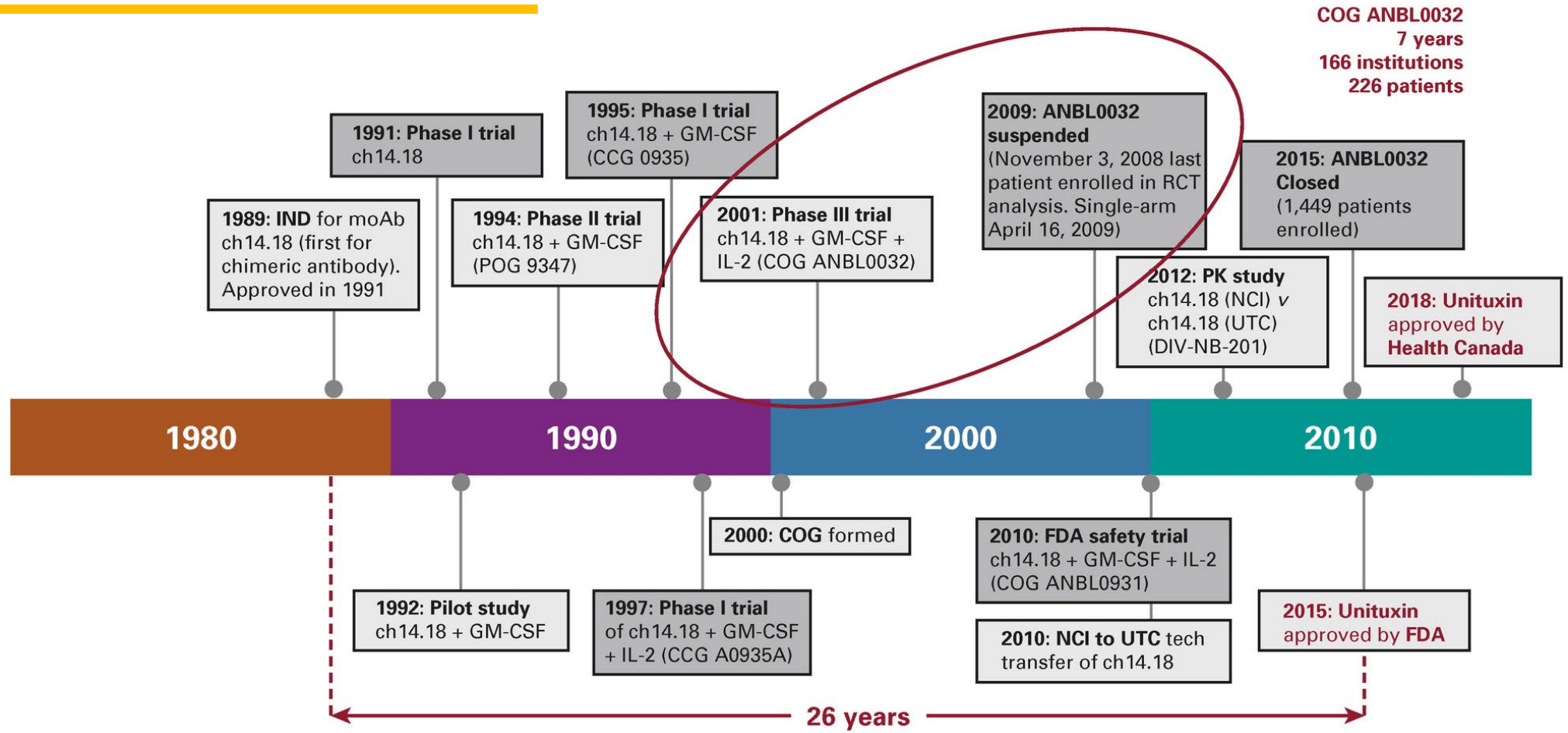
PubMed.gov

45,846 results

Only one class of targeted agents (anti-GD2 antibodies) has been incorporated into front-line therapy for neuroblastoma since the 1980s.[6]

6. 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 2020

Unituxin path to approval[7]



7. When Innovation and Commercialization Collide: A Patient Advocate View in Neuroblastoma; Nick Bird et al, Journal of Clinical Oncology 2022

What is needed?

ACCELERATE
INNOVATION FOR CHILDREN AND ADOLESCENTS WITH CANCER

- Assess efficacy of new drugs more rapidly but robustly – **how**?
- A more coordinated approach by cooperative groups, industry, regulators, payers, and *with patient advocates*
- Early interaction between all stakeholders is vital
- Major investment, including in infrastructure

Challenges

- Generating data to support regulatory filings in this ultra-rare disease, where research is driven by academia
- Gathering, comparing, and making sense of all the data – *learning from every child*
- Evaluating ‘response’ in the modern era
  - Improved imaging techniques may make comparison with historical controls more difficult – validity of datasets crucial
  - Application of new techniques including liquid biopsies
  - What is stable disease?
- Others?

What next?

- Define robust method(s) of using earlier endpoint(s)
- RAPID assessment of promising new therapeutic strategies:
  - Building on success of anti-GD2 approaches
  - Other immunotherapies
  - CAR-T cells including new targets such as GPC2
  - Targeting mechanisms of action including Telomere Maintenance Mechanism
  - +++

FDA and EMA have a major role to play in encouraging and supporting new drug development in this population with significant unmet needs

Improving Access to Novel Therapies in High-Risk Neuroblastoma

FDA Peds ODAC Meeting

Navin Pinto, MD

12 May 2022

Seattle Children's®

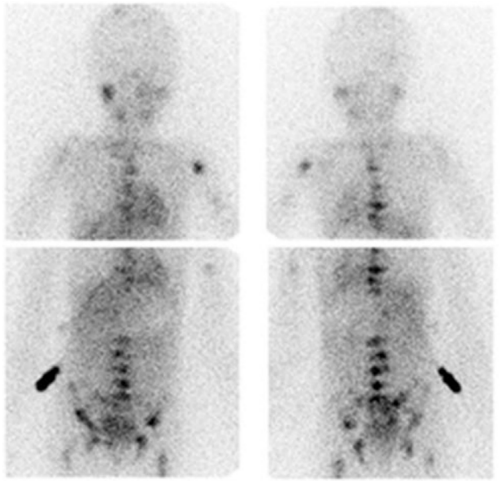
Disclosures

- I am an uncompensated member of the Y-Mabs Therapeutics Scientific Advisory Board

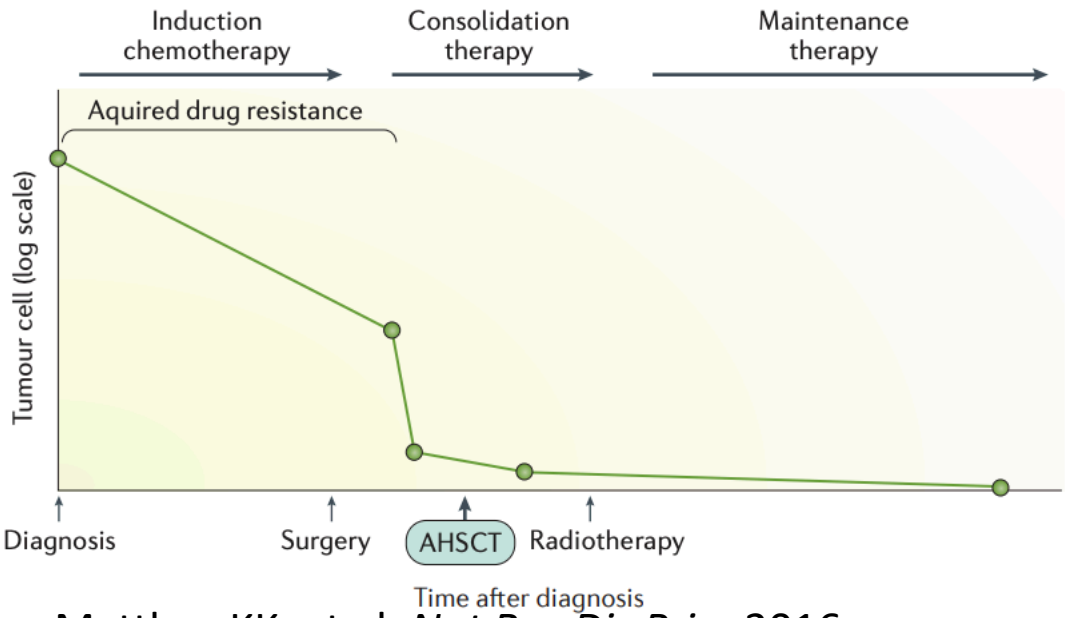
Seattle Children's®

Background

- High-risk neuroblastoma (HRNBL) affects <500 children/year in the United States
  - ~12-25 cases/million individuals
- Aggressive, multimodal therapy is necessary to achieve cure
- Relapsed HRNBL is generally fatal
- There are 2 FDA-approved therapies for patients with HRNBL
  - dinutuximab – post consolidation maintenance in upfront therapy
  - naxitamab – treatment of relapsed/refractory HRNBL isolated to bone/bone marrow

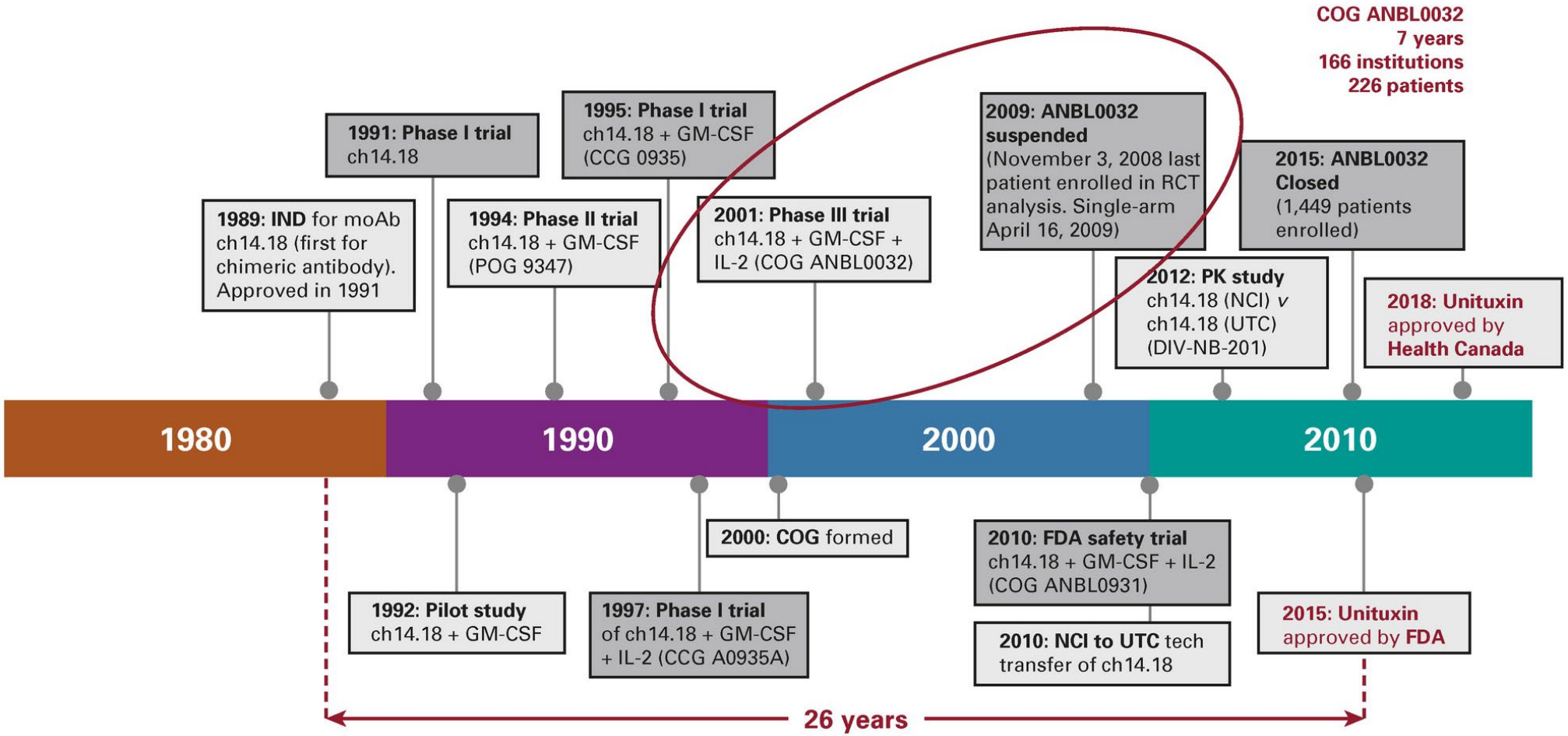


Pfluger T, et al.
Sem Nuc Med 2017



Matthay KK, et al. *Nat Rev Dis Prim* 2016

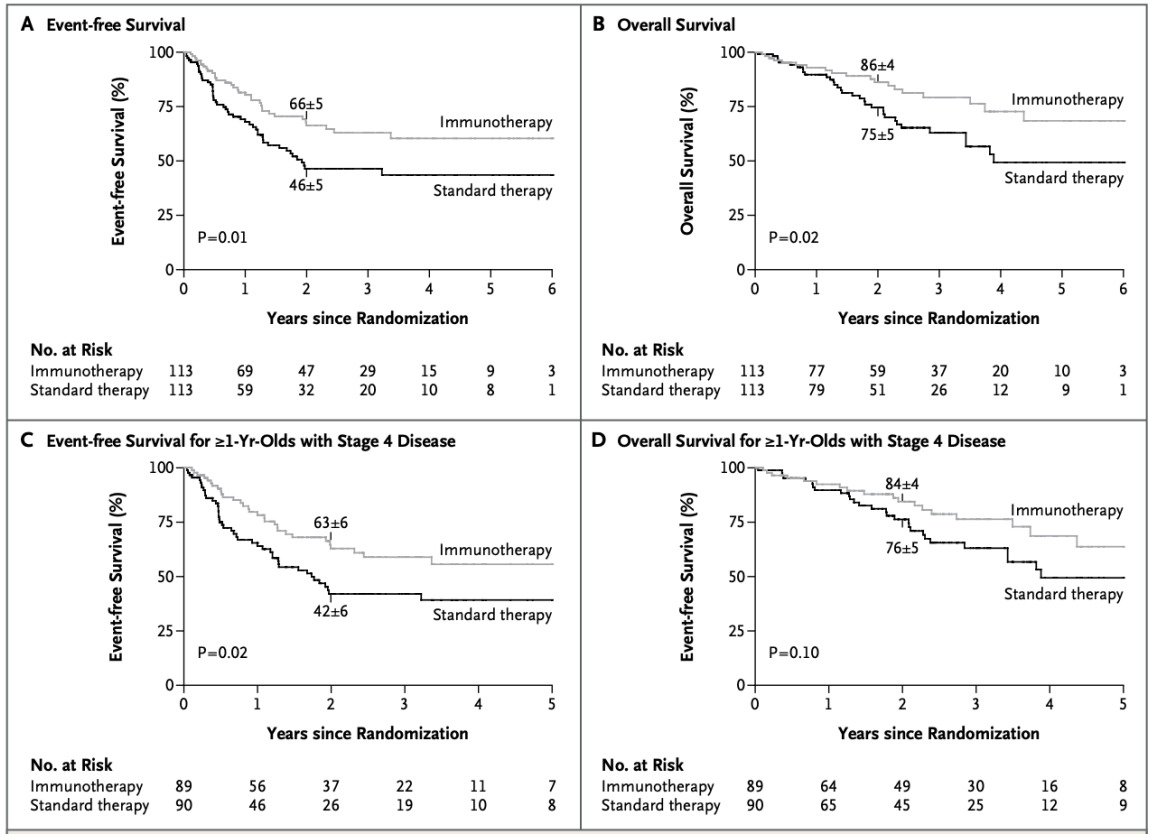
Drug Development in Pediatric Oncology is Painfully Slow



Bird N, et al. *JCO* 2022

Surrogate Biomarker Use in HRNBL

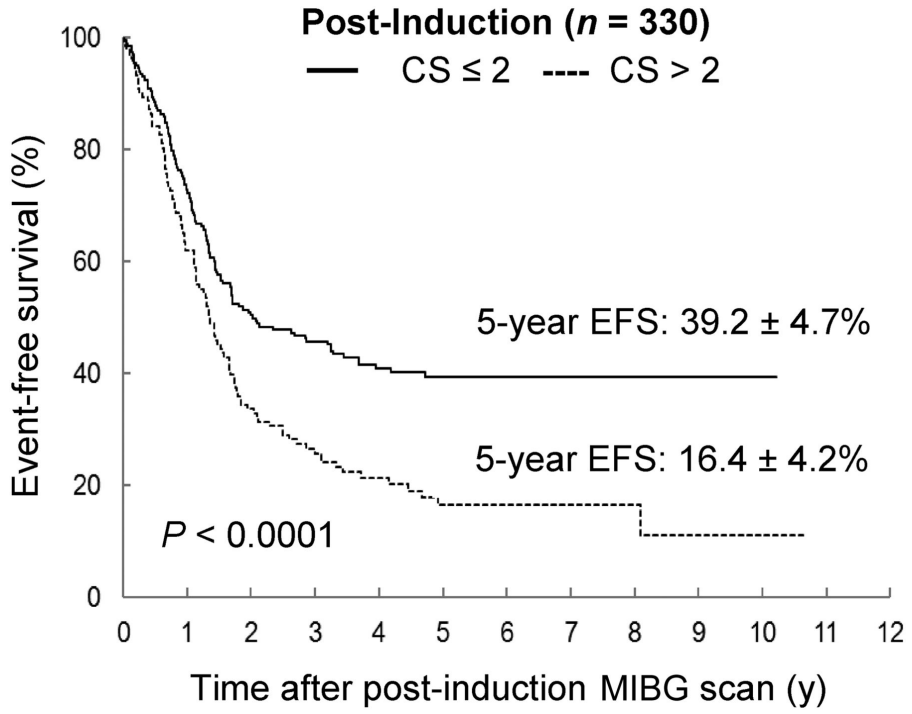
- Overall vs Event Free Survival
- Other than EFS, reliable biomarkers of OS are largely lacking
- Predicting which HRNBL patients will be failed by standard and novel therapies is critical to more rapid drug development



Yu AL, et al. *NEJM* 2010

End-Induction Response as a Surrogate Biomarker

- Induction chemotherapy
  - Goal = maximal reduction in tumor burden prior to planned consolidation therapy with high-dose chemotherapy
- Favorable responses to induction chemotherapy are associated with improved Event Free Survival
- Predictors of favorable response to induction are largely lacking



Yanik GA, et al. *J Nucl Med* 2018

End-Induction Response and Outcome

- Newly-diagnosed high-risk NBL enrolled to:
  - A3973: phase 3 trial assessing stem cell purging
  - ANBL02P1: pilot study of topo/cyclo in induction
  - ANBL0532: phase 3 trial assessing tandem transplant
  - ANBL12P1: pilot study of BuMel transplant

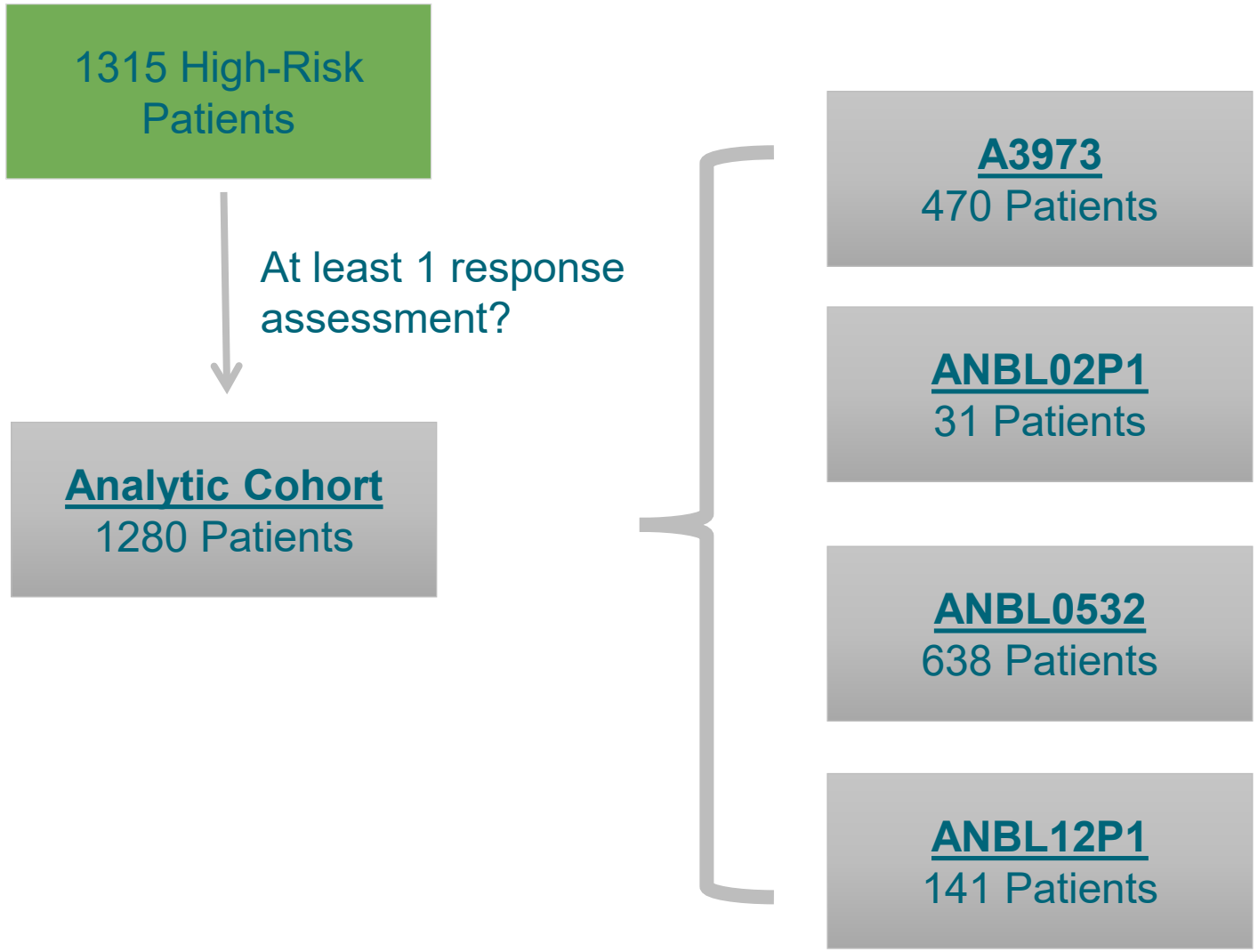
- Patients with at least 1 response assessment during induction were eligible for analysis

Outcome and Predictor Variables

- Outcome Variables (all using 1993 INRC)
  - Primary Outcome: Partial Response (PR) or better at end induction
  - Secondary Outcomes: Complete Response (CR) at end induction and Progressive Disease (PD) at end induction; PR or PD during induction

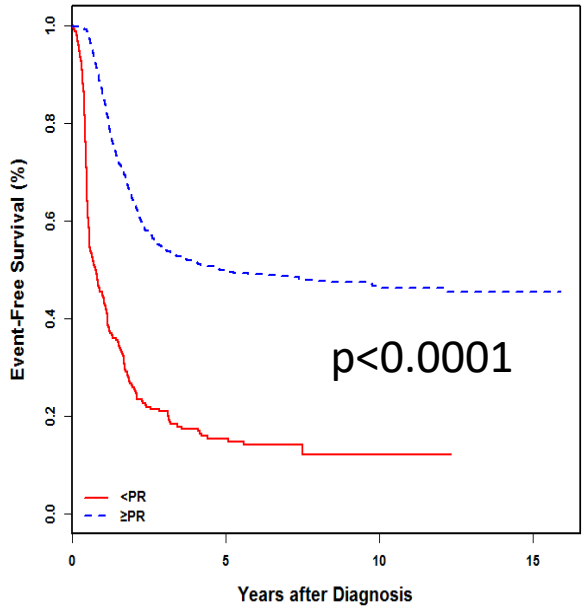
- Evaluated Predictor Variables
  - Baseline Clinical Variables
  - Biologic Variables
  - Treatment-related variables

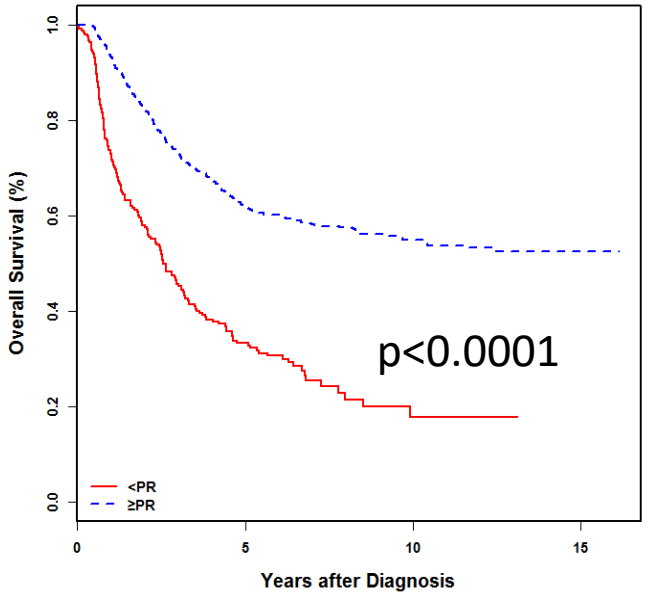
Patient Characteristics



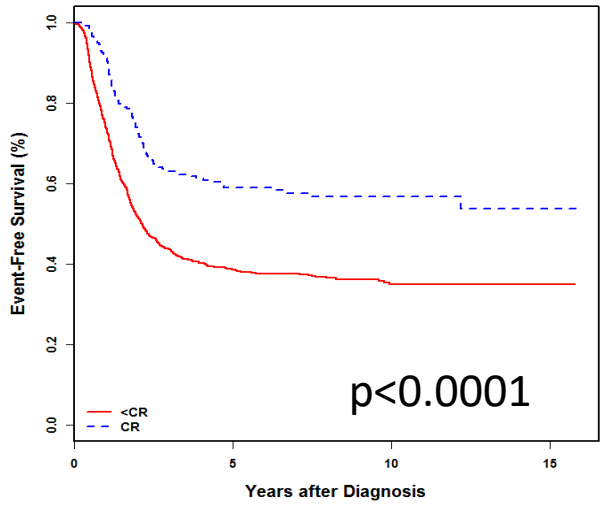
Impact of End-Induction Response on Outcome

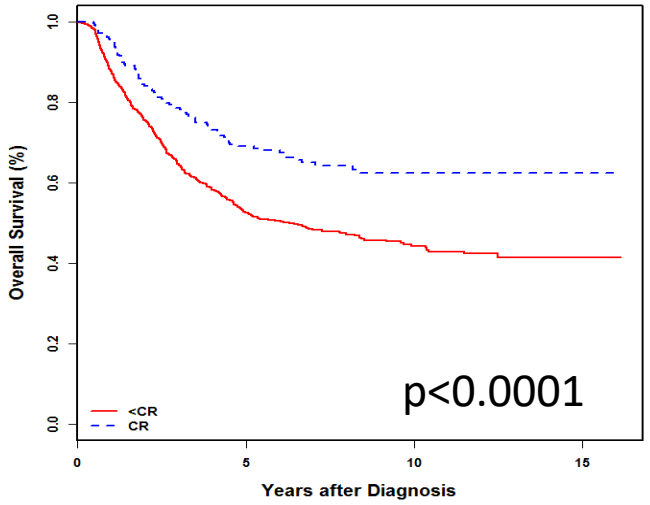
≥PR





CR

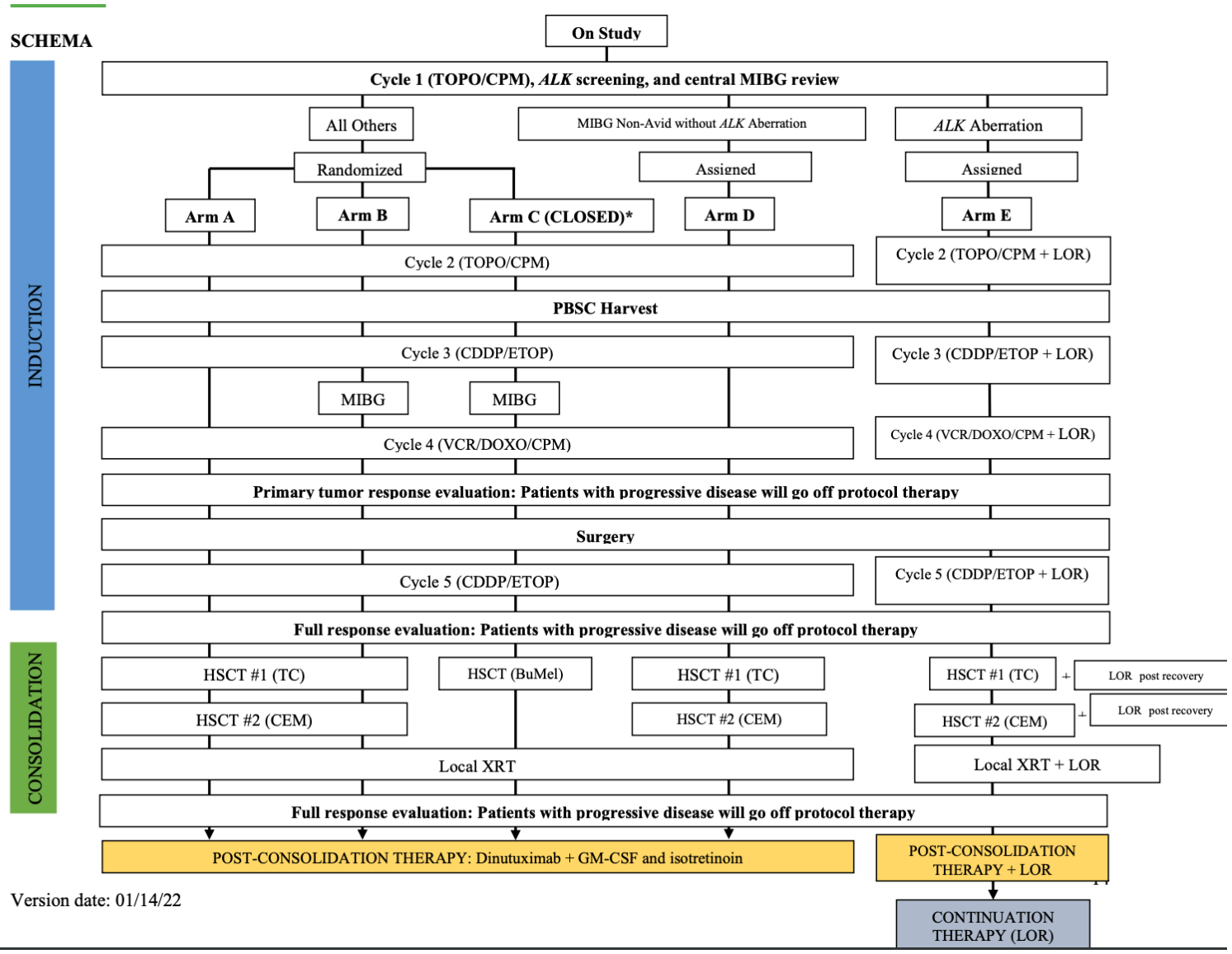




Conclusions

- International Neuroblastoma Response Criteria have international consensus but are complex
  - Incorporating anatomic, functional imaging and histologic response elements
- Patients that have a partial response or better to induction chemotherapy tend to have more favorable outcomes
- Interventions that improve end-induction PR rates will likely also improve EFS/OS

Future Directions – ANBL1531



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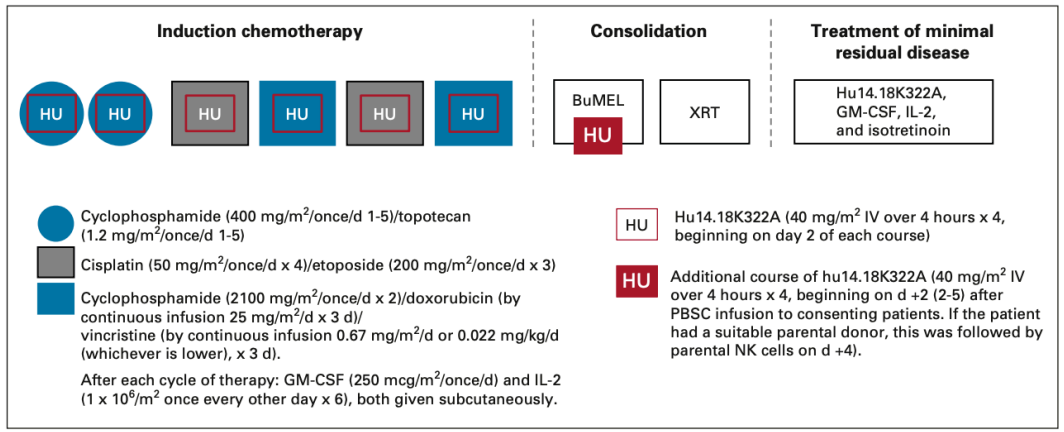
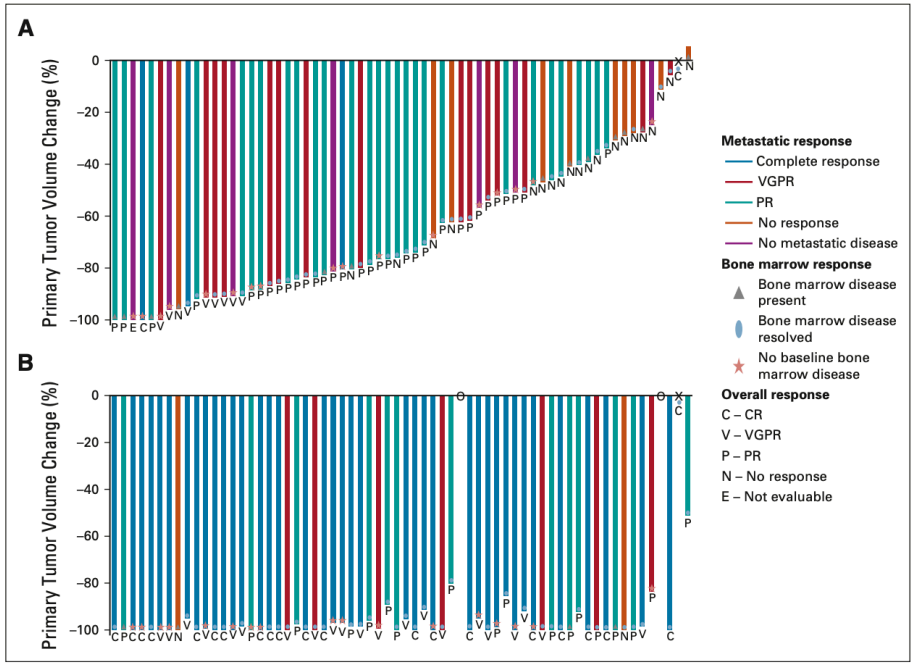
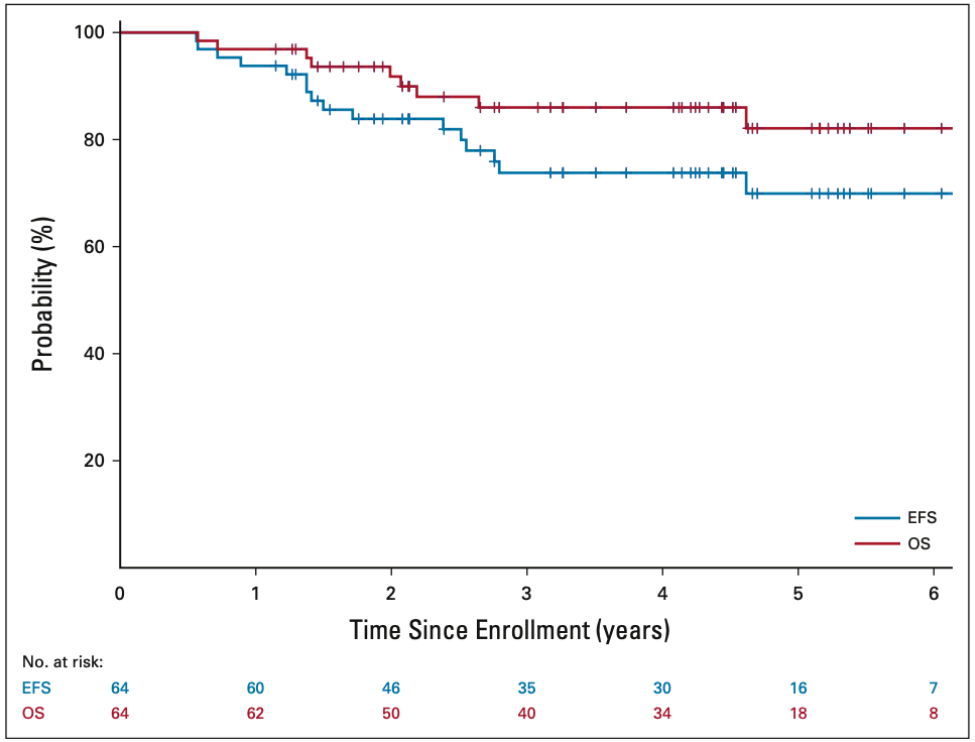
Future Directions – Chemo-immunotherapy

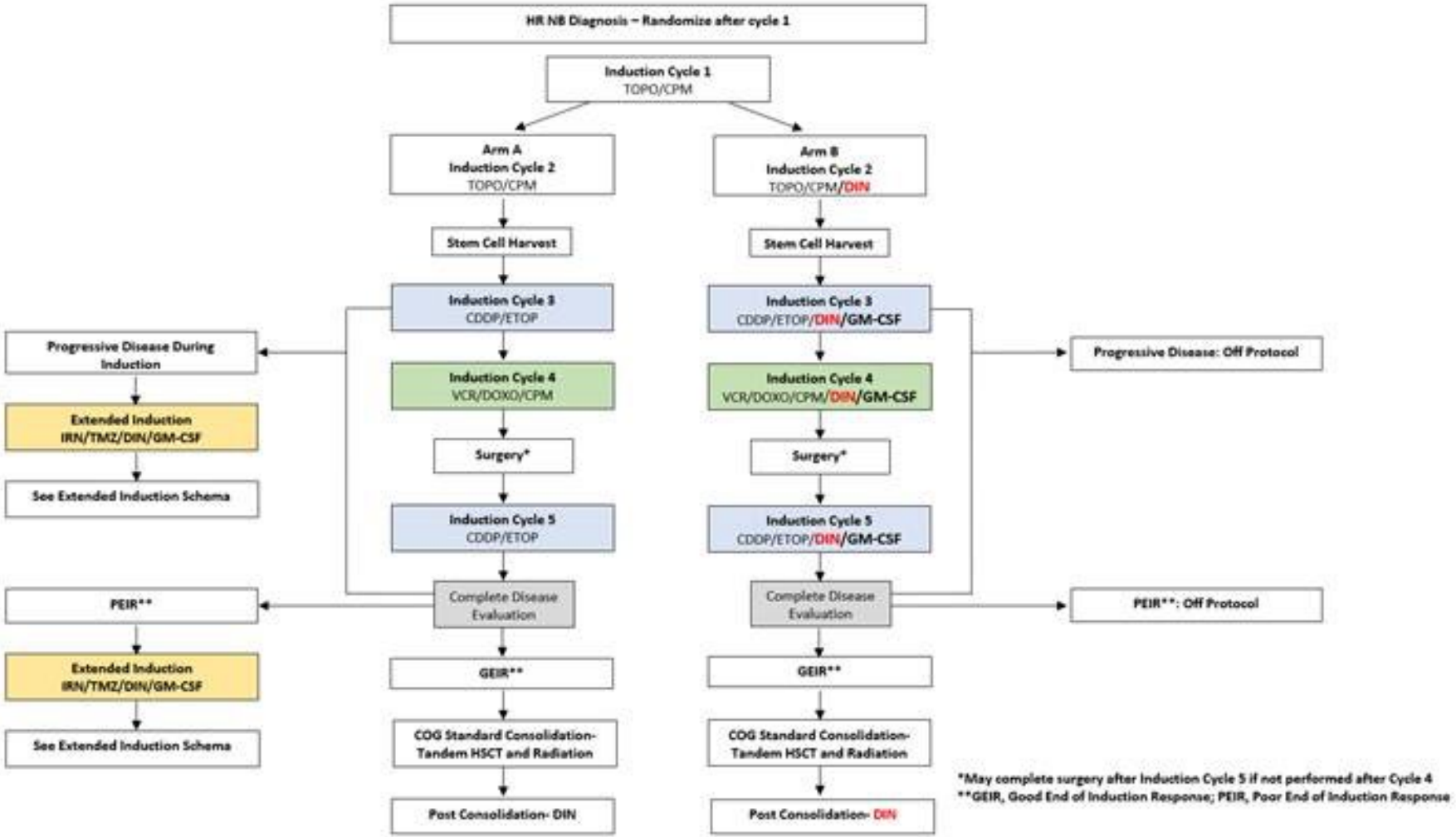






Furman W, et al. *JCO* 2022

Future Directions – ANBL2131



Conclusions

- MIBG therapy in induction is currently being studied groupwide in COG Phase 3 trial ANBL1531
- Chemo-immunotherapy in induction will be studied groupwide in an upcoming COG Phase 3 trial ANBL2131
- Prospective evaluation of a novel induction regimen and its impact on EFS/OS
- ANBL2131 may serve as a template for future novel strategies in induction
- Potential for more rapid evaluation of active agents in HRNBL

Thank You

Seattle Children's®

Multi-stakeholder Perspective on Current and Potential Future Use of End-Induction Response in Patient Care and Drug Development

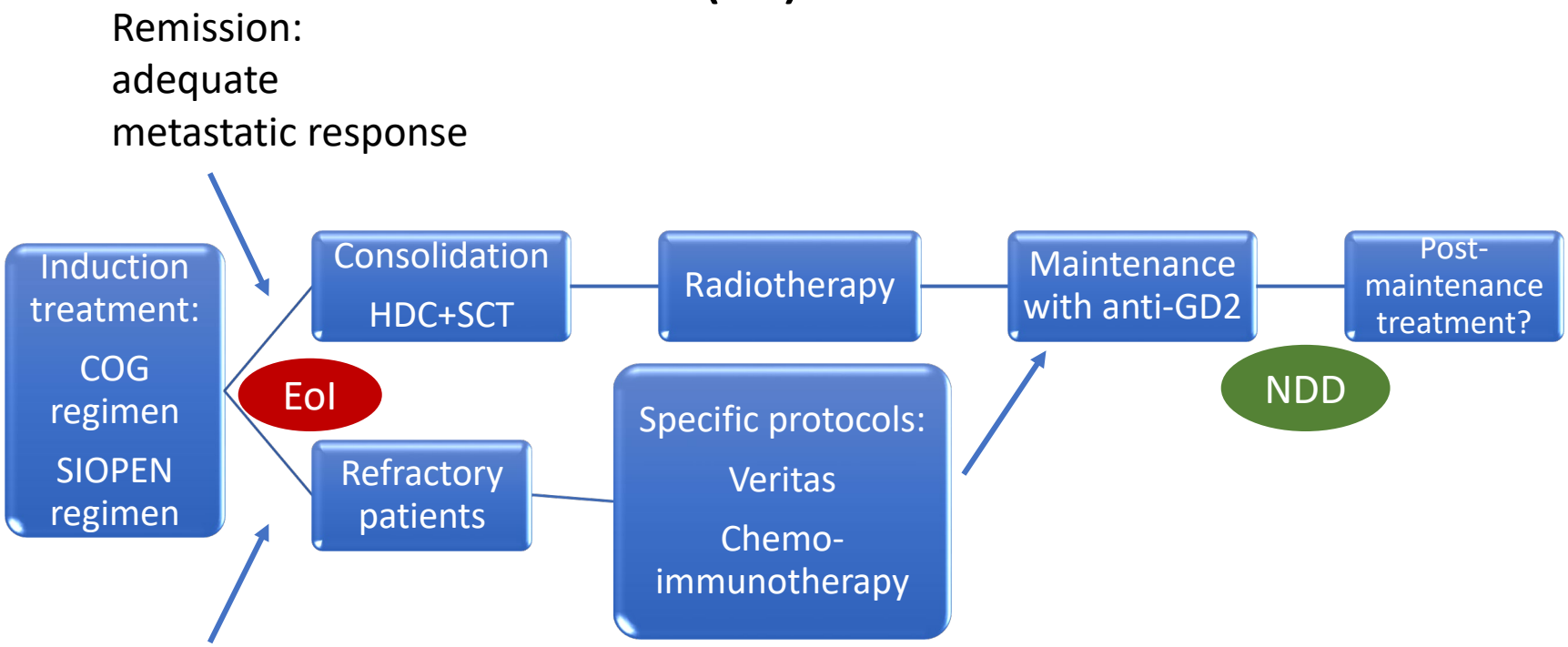
May 12th 2022

Maja Beck Popovic, MD

Disclosures

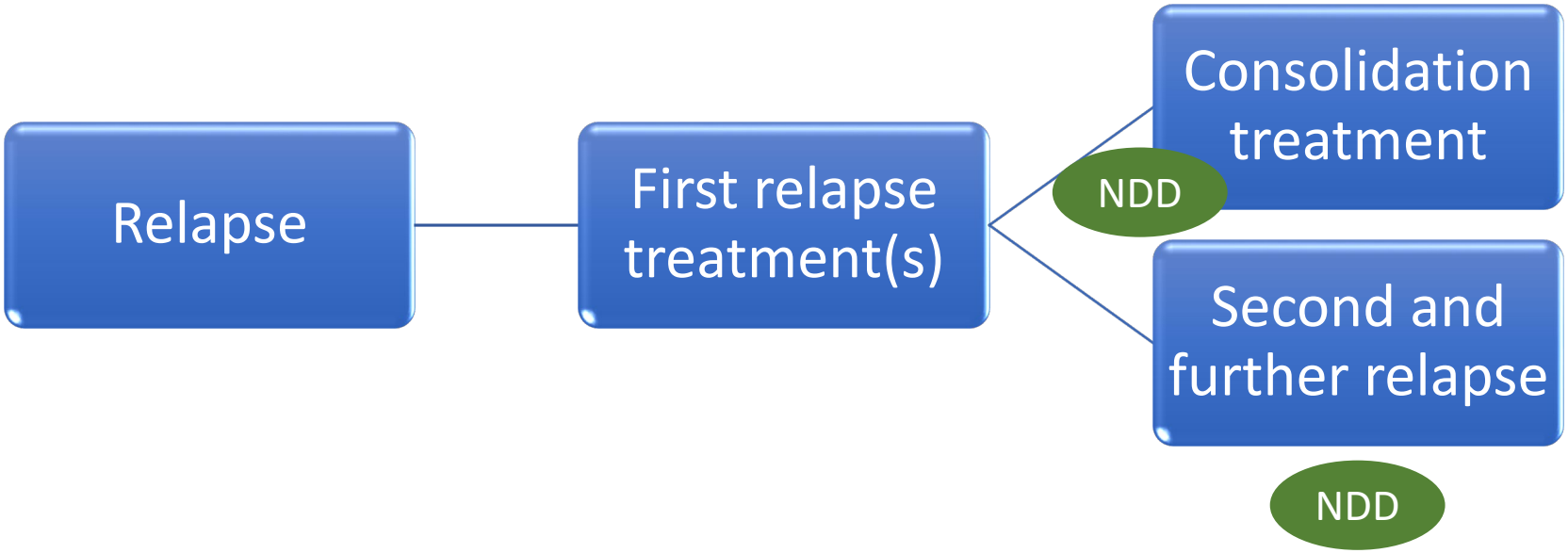
- Currently President of SIOPEN, receiving royalties for the sales of Dinutuximab beta
- Involved in discussion with Ymabs 2x

Summary of the patient's pathway (1)



EoI: end-of-induction
NDD: new drug development

Summary of the patient's pathway (2)

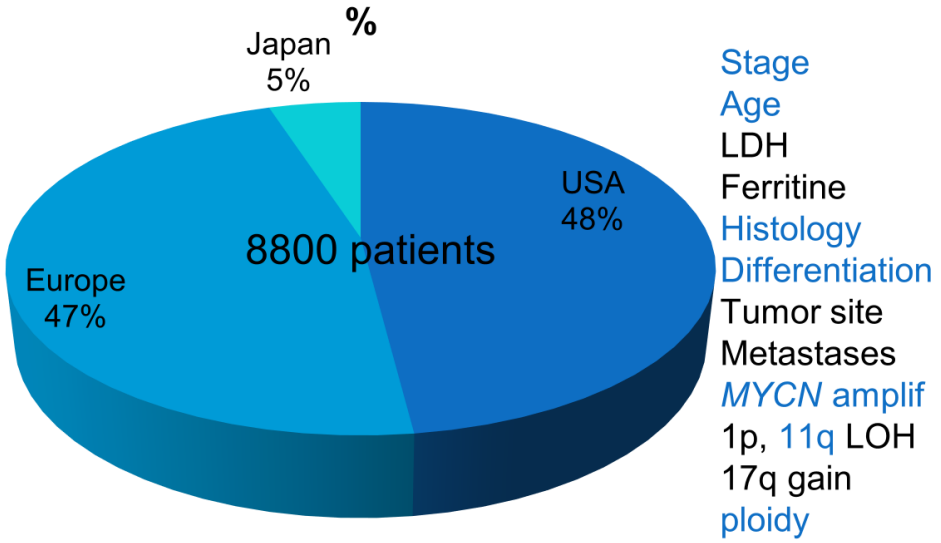


Question

- End-of-induction evaluation as surrogate endpoint to event free survival (EFS) in patients with high-risk neuroblastoma?
  - Important time point, but does not apply to evaluate other time points, other needs, such as
    - Post maintenance treatments
    - Treatments for relapse
    - Consolidation treatment after second or further relapse treatment
  - Quality of life as additional marker for evaluation
- EFS/OS still needed
- In discussion today: EoI in front-line therapy only for neuroblastoma high-risk patients

How do we define high-risk patients? An international collaboration

International task force, 2004



Cohn et al, JCO, 27:289-297, 2009

Sue Cohn and Andy Pearson

Currently data on 24,655 patients!

INRG staging system

Table 2. International Neuroblastoma Risk Group Staging System

Stage	Description
L1	Localized tumor not involving vital structures as defined by the list of image-defined risk factors and confined to one body compartment
L2	Locoregional tumor with presence of one or more image-defined risk factors
M	Distant metastatic disease (except stage MS)
MS	Metastatic disease in children younger than 18 months with metastases confined to skin, liver, and/or bone marrow

NOTE. See text for detailed criteria. Patients with multifocal primary tumors should be staged according to the greatest extent of disease as defined in the table.

Monclair et al, J Clin Oncol 27:298-303, 2009

INRG classification system

- International neuroblastoma risk group task force (2005) established criteria for an internationally accepted pre-treatment risk group classification based on clinical and biologic data
- Consensus statement on molecular and radiographic techniques
- Consensus statement on assessment of minimal residual disease

Risk group assignment

INRG Stage	Age (months)	Histologic Category	Grade of Tumor Differentiation	*MYCN*	11q Aberration	Ploidy	Pretreatment Risk Group
L1/L2		GN maturing; GNB intermixed					A Very low
L1		Any, except GN maturing or GNB intermixed		NA			B Very low
				Amp			K High
L2	< 18	Any, except GN maturing or GNB intermixed		NA	No		D Low
					Yes		G Intermediate
	≥ 18	GNB nodular; neuroblastoma	Differentiating	NA	No		E Low
					Yes		H Intermediate
			Poorly differentiated or undifferentiated	NA			
				Amp			N High
M	< 18			NA		Hyperdiploid	F Low
	< 12			NA		Diploid	I Intermediate
	12 to < 18			NA		Diploid	J Intermediate
	< 18			Amp			O High
	≥ 18						P High
MS	< 18			NA	No		C Very low
					Yes		Q High
				Amp			R High

Cohn S, Pearson A, et al, J Clin Oncol 27:289-297, 2009

NCI-CTPM, another international initiative

- 1988: Internationally accepted staging system for neuroblastoma, and consistent criteria for confirming diagnosis and determining response to therapy INSS & NRC, *Brodeur GM, et al: J Clin Oncol 6:1874-1881, 1988*
- 1993: Review experience with the INSS and INRC
  - Substantial changes:
    - redefinition of the midline
    - restrictions on age and bone marrow involvement for stage 4S
    - recommendation of meta-iodobenzylguanidine (MIBG) scanning for evaluating the extent of disease
  - *Brodeur et al, J Clin Oncol 11:1466-1477, 1993*

International neuroblastoma response criteria – INRC

- Modification in 2017
  - By incorporating modern imaging techniques
  - By incorporating new methods for quantifying bone marrow disease
- Multidisciplinary investigators (52) from 13 countries
  - Review from prospective and retrospective published trials
  - Monthly international conference calls 2011-2015
  - Consensus through review by working group leadership and the National Cancer Institute Clinical Trials Planning Meeting leadership Council

INRC (2)

- Assessment of
  - Primary tumor
    - Evaluated by RECIST (Response Evaluation Criteria on Solid Tumors)
  - Soft tissue metastases
    - Evaluated by RECIST (Response Evaluation Criteria on Solid Tumors)
  - Bone metastases
    - MIBG or FDG-PET (replaces Tc bone scintigraphy)
  - Bone marrow (aspirate and trephine biopsy)
    - Histology/immunohistochemostry and cytology/immunocytology
    - BM <- 5% = minimal disease
    - Validation still needed for RTqPCR

INRC (3)

- Overall response:
  - Complete response
  - Partial response
  - Minor response
  - Stable disease
  - Progressive disease

→ Uniform assessment of disease response

→ Improved interpretability

→ Facilitation of collaborative trial design

INRC (4)

- Primary and metastatic soft tissue disease
  - Anatomic imaging by CT and MRI
  - Evaluation by RECIST, also for soft tissue metastases
  - MIBG: to assess primary and soft tissue tumor response +/- three-dimensional imaging (MIBG-SPECT/CT or FDG-PET/CT)
- Metastatic bone disease
  - MIBG instead of Tc scintigraphy (or FDG-PET)
  - Osseous lesion without soft tissue mass = nonmeasurable by RECIST
- Metastatic bone marrow disease
  - 2 aspirates and 2 trephine biopsies
  - Morphologic criteria + appropriate antinbodies by immunocytology and/or immunohistochemistry

- Validation still needed for RTqPCR

Response by INRC

RECIST MIBG

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.

Response by INRC
Curie or SIOPEN score

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

Response by INRC: minimal marrow disease as new criterion – quantification of BM 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

INRC overall response

- Combination of response of the individual components

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.

Comments (1)

- Stratification into homogenous treatment groups
- Very low, low, intermediate, high-risk groups based on EFS cut-off
- EFS allows to modulate treatment
  - >80% - less treatment
  - < 50% - intensified treatment

allows

⟶ comparison of risk-based clinical trials conducted in different regions of the world

⟶ development of international collaborative studies

Thoughts on criteria needed for early phase trials?

- National Cancer Institute (NCI)-sponsored Clinical Trials Planning Meeting (CTPM)
  - Aim: establish consensus approach to conduct clinical trials
  - Definition of progressive and refractory disease:
    - Responding persistant disease
    - Stable persistant disease
  - Clear definition of eligibility criteria
  - Comprehensive extent-of-disease evaluation after at least 1 prior therapy and less than 4 weeks before enrollment on trial
  - Definition of response evaluation: BM disease as major challenge

→ Uniform definition of eligible patients and tumor response needed

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 J et al, submitted to Cancer

Comments (2)

- INRGSS: common tool for risk group assignment
- INRC: common tool for uniform response evaluation
- INRG: common international data base for data evaluation and developing research questions
- Clinical Trials Planning Meeting (CTPM) to develop a consensus on harmonized way to conduct early phase trials

Comments (3)

- Need to accelerate development of new drugs in patients with neuroblastoma to improve the patient's pathway – more quickly available endpoint than EFS needed
- Need to accelerate introduction into front-line treatment and then standard-of-care
- Close collaboration between academics - pharma – FDA/EMA
- Pivotal studies: end-of-induction as end-point acceptable
- Different needs for studies in relapse/refractory setting where safety, pharmacokinetics and preliminary activity data are needed
- International collaboration is set, also the tools to evaluate disease - common language
  - Metastatic CR by MIBG scans? → *Ladenstein et al, J Clin Oncol 39:2552-2563, 2021*

Conclusion

- Can we use EoI as endpoint? In what category of patients?
  - Yes, *but* only for induction in upfront HR-NB trials AND as an intermediate endpoint which will be complemented with EFS in the future
- What tools shall be used to evaluate EoI response?
  - INRC – simplified - **metastatic response by MIBG score** (literature)
- How shall this be done?
  - SIOPEN and COG hand in hand with FDA/EMA to agree on EoI response criteria
  - Previous collaboration INRG-INRC as basis to future work

THANK YOU FOR YOUR ATTENTION