High-Risk Neuroblastoma: Current Treatment and Regulatory Insights

Meeting of the Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee

May 12, 2022

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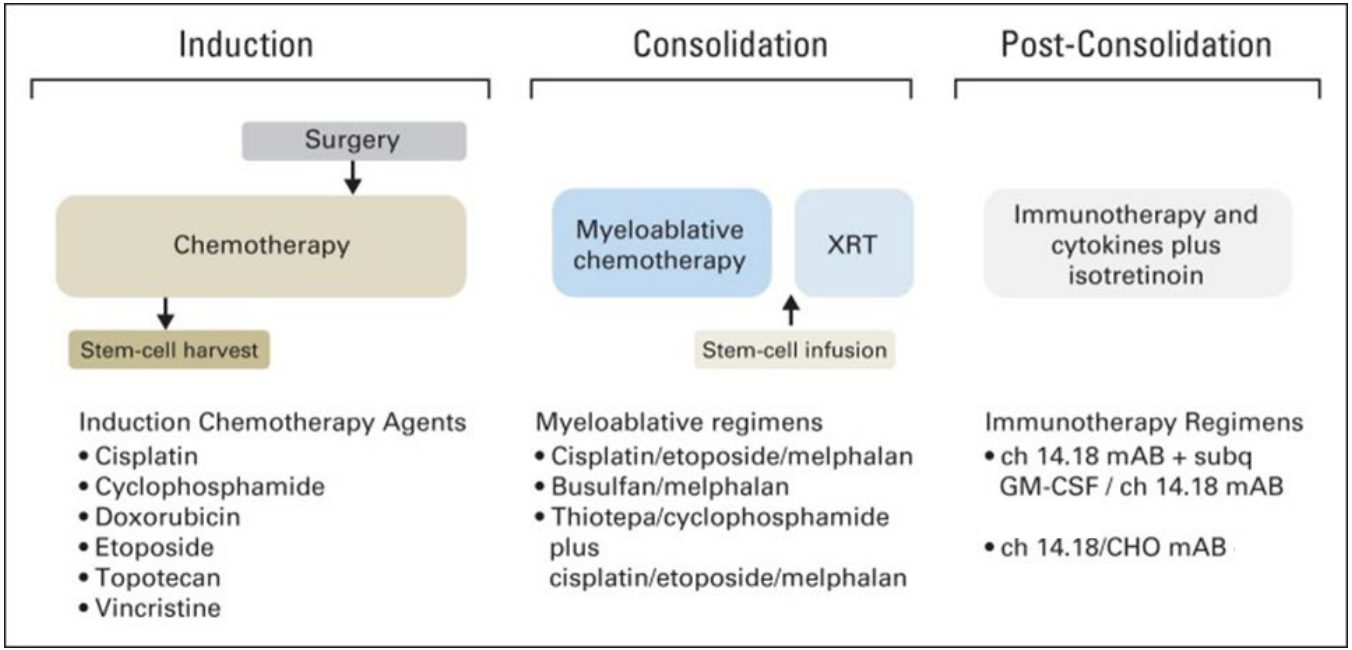
Neuroblastoma

- 650 new cases/ year in the U.S.
- Median age at diagnosis 19 months
- Heterogeneous disease
  - Risk group based on clinical and biological factors
  - Treatment dependent upon risk categorization
  - ~50% of patients have high-risk disease
  - High-risk: 40-50% long-term survival

Patients with high-risk neuroblastoma have an unmet medical need

High-Risk Neuroblastoma Treatment



Adapted from Pinto et al. 2015

XRT= radiation therapy, subq=subcutaneous, ch mAB= chimeric monoclonal antibody, CHO=Chinese hamster ovary

ANBL 1531

Arm	Population	Induction	Consolidation	Maintenance
A	MIBG+/ALK-	Standard	Tandem HSCT	Dinutuximab/GM-CSF/isotretinoin
B		Standard + MIBG	Tandem HSCT	
C*		Standard + MIBG	Single HSCT (BuMel)	
D	MIBG-/ALK-	Standard	Tandem HSCT	
E	ALK+	Standard + ALK inhibitor	Tandem HSCT + ALK inhibitor	Above + ALK inhibitor

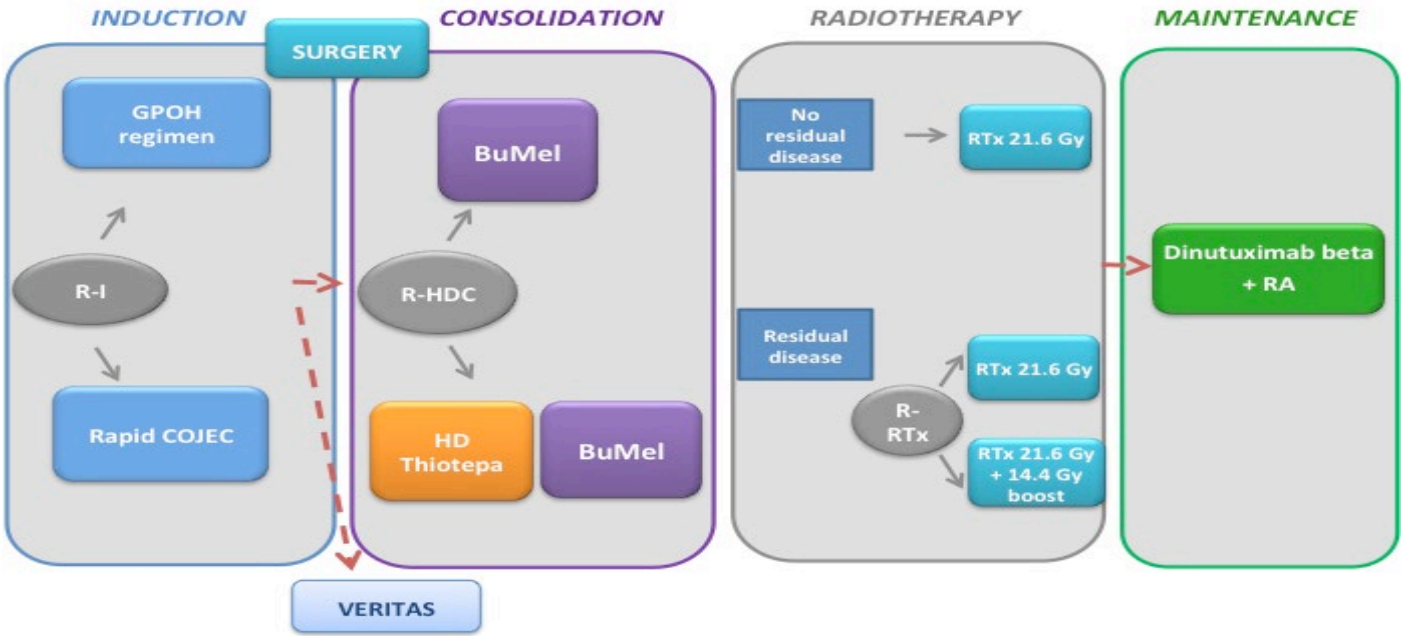
Primary Endpoint: Event-Free Survival
Secondary Endpoints: include Overall Survival

*Arm C closed to accrual

MIBG = metaiodobenzylguanidine, ALK=anaplastic lymphoma kinase , HSCT=hematopoietic stem cell transplant

HR-NBL2/SIOPEN

Open and recruiting



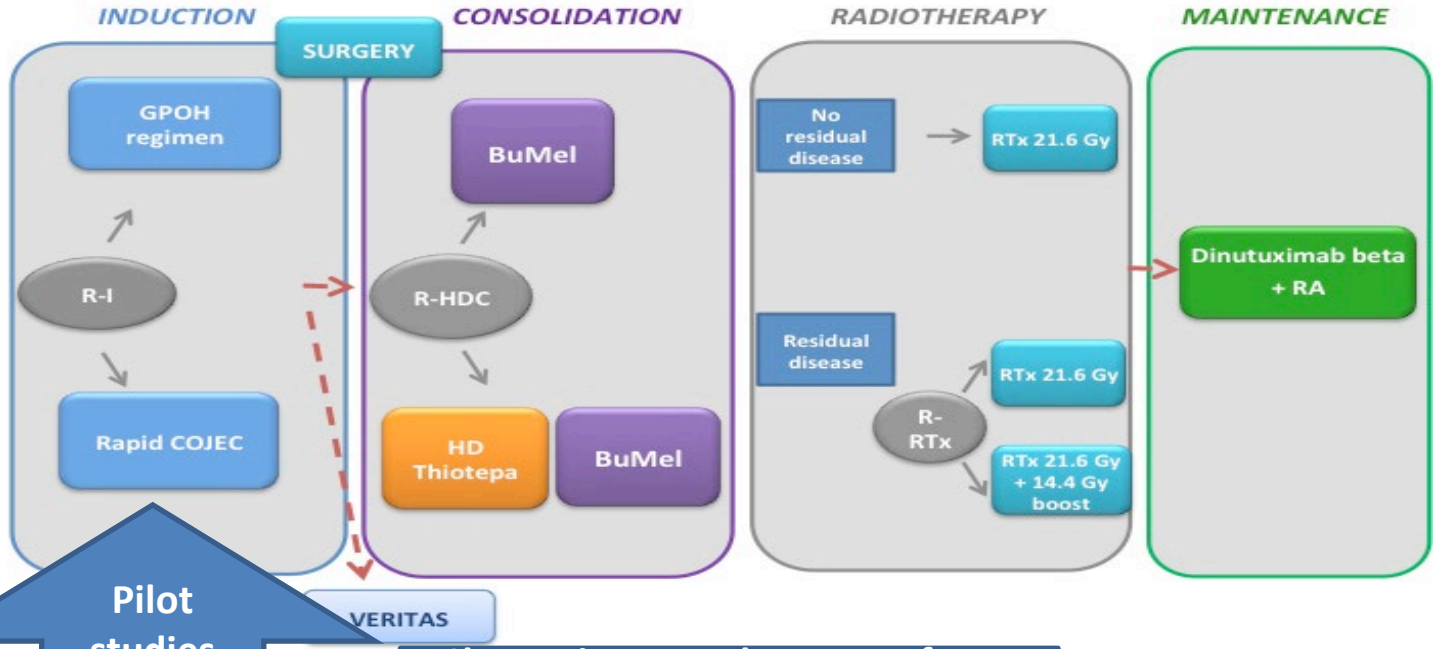
Primary Endpoint: Event-Free Survival

Slides courtesy Lucas Moreno & SIOPEN
PI: Dominique Valteau-Couanet

GPOH=German Pediatric Hematology and Oncology; COJEC=cisplatin, vincristine, carboplatin, etoposide, and cyclophosphamide; Gy= Gray; RA=retinoic acid

HR-NBL2/SIOPEN

Opening soon



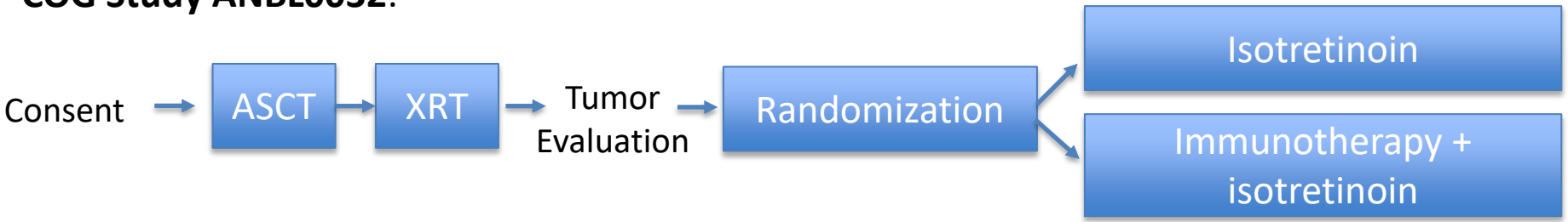
Pilot studies + ALK

Chemo-immunotherapy upfront, biomarker-driven upfront

R=randomization, R-I =induction, R-HDC=high dose chemotherapy, R-RTx=radiotherapy

FDA Approval of Dinutuximab

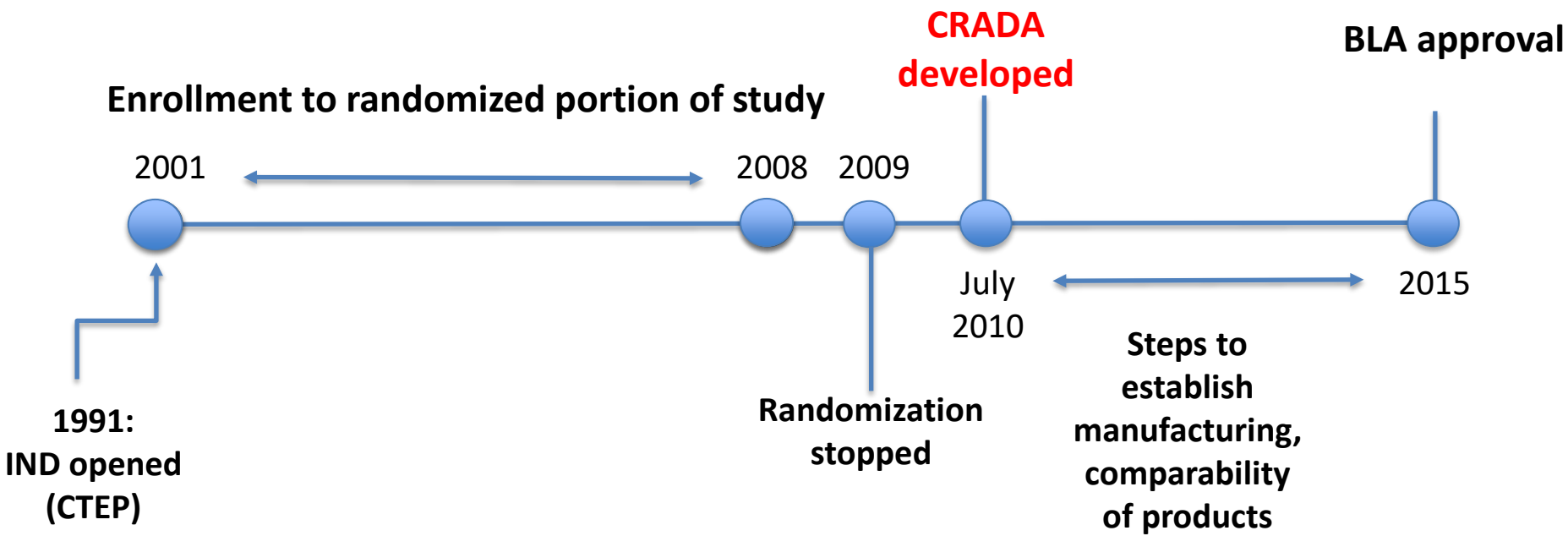
COG Study ANBL0032:



		Unituxin/RA (n=113)	RA (n=113)
EFS	No. Events (%)	33 (29%)	50 (44%)
	Median (95% CI, years)	NR (3.4, NR)	1.9 (1.3, NR)
	HR (95% CI)	**0.57** (0.37, 0.89), p value 0.01	

ASCT= autologous stem cell transplantation; XRT= radiation therapy; RA= retinoic acid; NR= not reached; HR= Hazard ratio

Timeline for Dinutuximab Development



IND= Investigational New Drug application, CTEP= Cancer Therapy Evaluation Program, CRADA=Cooperative Research and Development Agreement, BLA=Biologics License Application

Endpoints supporting FDA Approvals in High-Risk Neuroblastoma

- Dinutuximab (First line/ maintenance):
  - EFS/OS endpoint
  - Randomization allowed isolation of treatment effect of dinutuximab + GM-CSF +IL-2

- *Naxitamab (Relapsed/Refractory):*
  - *ORR endpoint*
  - *Challenges in conduct of a randomized trial*
    - *No previously approved therapies*
    - *Rarity of disease*

EFS= Event-Free Survival, OS= overall survival, ORR=overall response rate

Conclusions

- Patients with high-risk neuroblastoma have a high unmet medical need
  - Current trials to augment existing multimodality therapy
- Need for multi-stakeholder collaboration
  - Academic/cooperative group, industry, regulatory, patients
- Historically lengthy drug development timelines
  - Interest in use of an earlier endpoint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Early Endpoint Validation

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Important Questions for Consideration

- Would the benefit-risk assessment based on an early endpoint, which may or may not be indicator of clinical benefit, be the same had we waited for a trial to meet definitive endpoint?

- What magnitude of treatment effect for an early endpoint would predict a meaningful improvement in definitive clinical benefit?

Regulatory Pathways for Early Endpoints

- Regular Approval
  - Approval is based on demonstration of clinical benefit or an effect on an established surrogate
- Accelerated Approval
  - Approval is based on an effect on a surrogate endpoint or an intermediate clinical endpoint that is reasonably likely to predict clinical benefit
  - Takes into account the severity, rarity, or prevalence of the condition and the availability of lack of alternative treatments
  - May require post-approval trials to verify anticipated clinical benefit

21 CFR 314.510
FDA Guidance for Industry: Expedited Programs for Serious Conditions- Drugs and Biologics

Development of Early Endpoints for Regulatory Use

- Prentice Criteria
  - Stringent and unlikely to be met
- Meta-analytical methods
  - Proportion of treatment effect explained
  - The proportion of times the trials reached the same conclusion based on statistical significance testing for the two endpoints
  - Individual- and trial-level analysis
  - Weighted linear regression

Mechanisms for Novel Early Endpoint Development

Two mechanisms exist to obtain the Agency's feedback on the use of a novel surrogate endpoint to support approval.

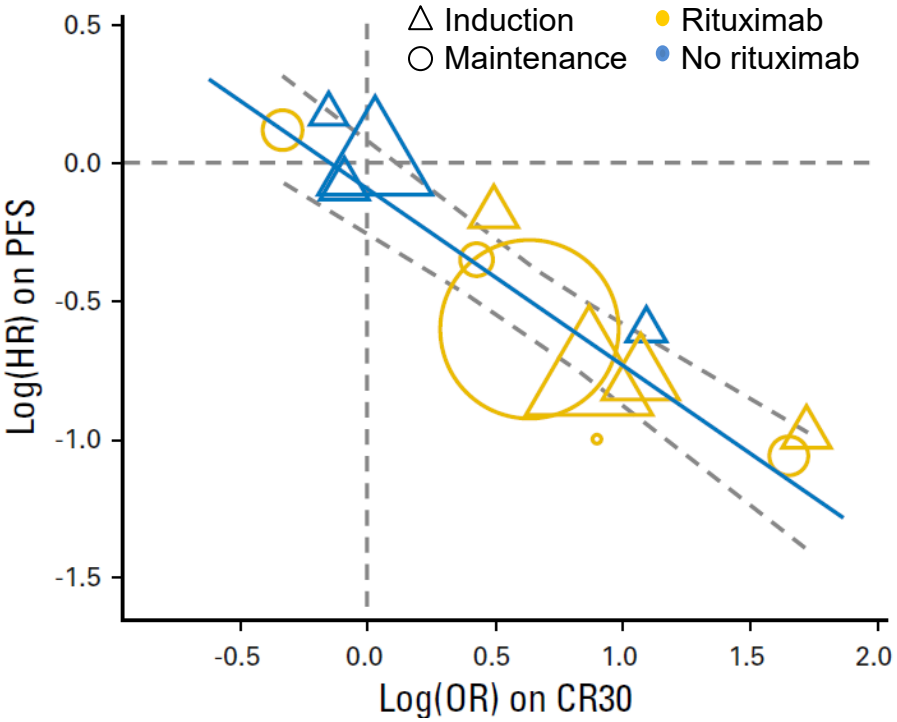
- Through FDA's Drug Development Tool (DDT) Qualification programs[1]

- Through discussions with the specific Center for Drug Evaluation and Research or Center for Biologics Evaluation and Research review division

[1]https://www.fda.gov/drugs/development-approval-process-drugs/drug-development-tool-ddt-qualification-programs

Example: Thirty-Month Complete Response

First-line Follicular Lymphoma



- Meta-analysis of analysis of randomized trials of chemotherapy and/or immunotherapy agents
  - Included eight induction and five maintenance randomized trials in 3,837 evaluable patients
- Demonstrated strong trial-level Correlation
  - R^2 WLS: 0.88 (95% CI: 0.77, 0.96)
  - R^2 Copula: 0.86 (95% CI: 0.75, 1.00)
- Sensitivity analyses showed consistently high levels of surrogacy
- Weaker among patients with stage I-III disease or low to intermediate risk scores

Shi et al. Journal of Clinical Oncology (2017)

CI: Confidence Interval
CR30: Thirty-month Complete Response

Development of Early Endpoints for Regulatory Use

- Caveats regarding use of early endpoints
  - May not be appropriate for therapeutic modalities that have substantially different mechanism of action (e.g., cytotoxic vs. immunotherapies).
  - May not be appropriate for subpopulations or future trial populations if there are significant differences between the population in the meta-analysis and the trial population.

Considerations for Early Endpoints

High-Risk Neuroblastoma

- Biologically plausible candidate early endpoints
- Standardization of early endpoint assessment techniques, thresholds, and timing
- Adequate number of Randomized clinical Trials (May be challenging)
  - Assess both early and definitive endpoints
  - Access to patient-level data
  - Seek national and international collaboration between stakeholders
- Appropriate statistical analysis
  - Establish strong correlation in patient- and trial-level
  - Proper accounting of potential confounders
- Acknowledge limitations
  - highly context dependent, and contingent on disease, stage, patient population, and therapy

Interactions with the Agency

- Definition of early and definitive clinical endpoints
- Details of the trials to be included in the Meta-analysis
- Detailed analysis plan
  - Strategies to harmonize endpoint definition
  - Strategies to handle missing or inadequate endpoint assessments
  - Sensitivity analyses
  - pre-specified timing/assessment methods for intermediate endpoint evaluation
  - Pre-specified criteria for concluding surrogacy

Summary

- Accelerated approval program may be used to expedite drug approval (provisionally) for serious life-threatening diseases based on early endpoints.
- The candidate early endpoints such as end-of-induction response should be validated to show that it is reasonably likely to predict clinical benefit, which generally requires multi-trial approach.
- Collaboration and cooperation between all stakeholders and early planning of future trials, including the ones conducted by academic investigators, will be crucial to accumulate and fully utilize limited number of trials that are feasible in pediatric diseases such as high-risk neuroblastoma.
- Additional research in methodology and alternative data sources may also be needed to overcome the limitations posed by multi-trial approach.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