

Venetoclax for Treatment of Pediatric Patients with Relapsed/Refractory Cancers

Pediatric Subcommittee of the
Oncologic Drugs Advisory Committee
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Venetoclax for Treatment of Pediatric Patients with Relapsed/Refractory Cancers

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Venetoclax Agenda

- Regulatory history
- Mechanism of action
- Clinical trial experience in adults
- Proposed pediatric plan
- Pediatric trial challenges identified

US Regulatory History of Venetoclax

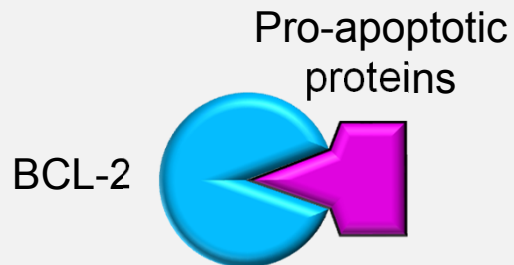
IND	Active	November 2010
Orphan Drug Designation Granted	CLL	September 2012
	DLBCL	March 2014
	AML	February 2016
Breakthrough Therapy Designation Granted	R/R CLL with 17p del	April 2015
	R/R CLL in combination with rituxumab	December 2015
	Treatment-naïve AML in combination with HMAs	January 2016
Approval	R/R CLL with 17p del	April 2016

Venetoclax

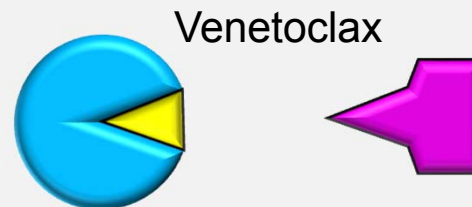
- Novel, orally bioavailable, small-molecule B-cell lymphoma (BCL-2) inhibitor
- Selective high affinity binding to BCL-2
- Lower affinity to other anti-apoptotic proteins
- Overexpression of anti-apoptotic proteins with
 - Tumor initiation
 - Disease progression
 - Resistance to chemotherapy

Venetoclax: Restoration of Apoptosis Through BCL-2 Inhibition

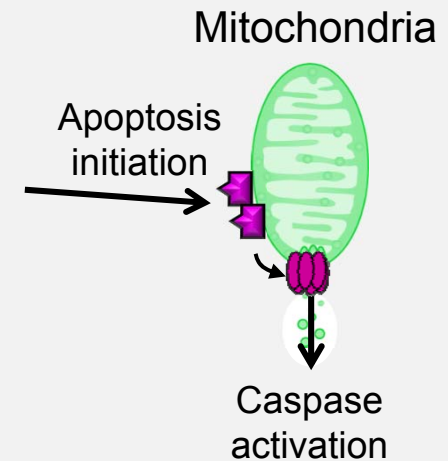
**BCL-2
Overexpression,
Cancer Cell Survival**



**Venetoclax Binds
to BCL-2**



Cancer Cell Death



Clinical Trial Experience in Adults

Current Trials in Adults

- Chronic lymphocytic leukemia (CLL)
 - Small lymphocytic leukemia (SLL)
- Acute myeloid leukemia (AML)
- Non-Hodgkin's lymphoma (NHL)
- Multiple myeloma (MM)

Accelerated Approval Venetoclax for Patients with 17p Deletion CLL

	Venetoclax N=106 n (%)
Overall response rate (ORR)	85 (80.2)
95% CI	(71.3, 87.3)
Complete remission (CR) + CRi, n (%)	8 (7.5)
CR, n (%)	6 (5.7)
CRi, n (%)	2 (1.9)
nPR, n (%)	3 (2.8)
PR, n (%)	74 (69.8)

CRi = complete remission with incomplete marrow recovery

nPR = nodular partial response

USPI, April 2016.

Activity in AML

	Venetoclax ¹ N=32 n (%)	Venetoclax + low- dose cytarabine ² N=18 n (%)
ORR	6 (19)	8 (44)
CR	2 (6)	4 (22)
CRi	4 (13)	4 (22)
PR	0	0
Treatment failure	20 (63)	10 (56)

1. Konopleva M, et al., ASH 2014.

2. Lin TJ, et al., ASCO 2016.

Activity in NHL

	Venetoclax ¹			Venetoclax + Bendamustine and Rituximab ²	
	DLBCL N=34 n (%)	FL N=29 n (%)	MCL N=28 n (%)	DLBCL N=16 n (%)	FL N=27 n (%)
ORR	6 (18)	11 (38)	21 (75)	6 (38)	21 (78)
CR	4 (12)	4 (14)	6 (21)	4 (25)	8 (30)
PR	2 (6)	7 (24)	15 (54)	2 (13)	13 (48)
Stable disease	8 (24)	17 (59)	5 (18)	2 (13)	1 (4)
Progressive disease	19 (56)	1 (4)	1 (4)	6 (38)	2 (7)

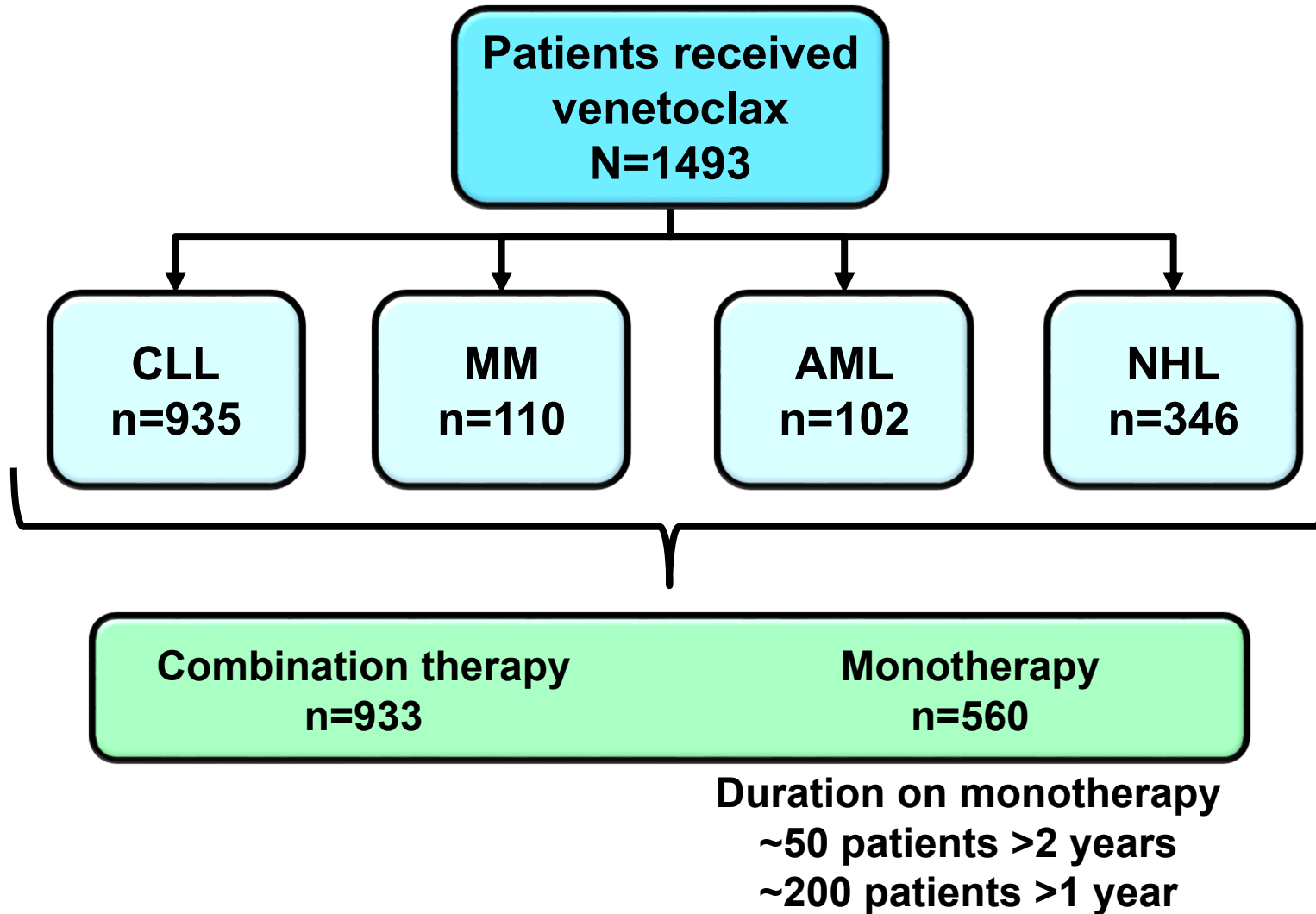
DLBCL = diffuse large b-cell, lymphoma, FL = follicular lymphoma, MCL = mantle cell lymphoma

1. Gerecitano J, et al., Blood 2015;126(23):254.

2. de Vos S, et al., Blood 2015;126(23):255.

Safety of Venetoclax

Venetoclax Exposure



Overall Safety Profile in Adults

- Most common AEs
 - Mild GI toxicity
- Grade 3/4 AEs
 - Cytopenias
- Identified risks
 - Tumor lysis syndrome (TLS)
 - Neutropenia

AEs in $\geq 20\%$ of Patients Across All Monotherapy Studies

MedDRA Preferred Term	Overall AE Frequency N=560 %
Nausea	41
Diarrhea	41
Fatigue	30
Neutropenia	29
Anemia	22
Upper respiratory tract infection	20

Includes patients with CLL, AML, NHL and MM in ongoing clinical studies as of November 2015

Grade 3/4 AEs in $\geq 5\%$ of Patients Across All Monotherapy Studies

MedDRA Preferred Term	Overall AE Frequency N=560 %
Neutropenia	26
Anemia	14
Thrombocytopenia	11
Febrile Neutropenia	6
Pneumonia	5
Neutrophil count decrease	5

Includes patients with CLL, AML, NHL and MM in ongoing clinical studies as of November 2015

Tumor Lysis Syndrome (TLS)

- Potent activity of venetoclax → rapid reduction in tumor burden → risk of TLS
- Clinical TLS observed only in early dose finding studies in CLL
- Mitigated by more gradual dose ramp-up
- Standard prophylaxis measures recommended
- Since December 2012 no cases of clinical TLS observed

Neutropenia in Monotherapy

- Common grade 3/4 AE
- Managed with standard of care
- Improved over time on study
- No trend towards increased infection rate

Safety Considerations Evaluated Before Pediatric Trial

- Clinical adult safety data well-characterized
 - Mild GI events and cytopenias
 - Expected to be similar in children
 - No additional concerns with long-term use
- Relevant nonclinical finding in adult animals
 - Decreased spermatogenesis
 - Risk to humans unknown
- Nonclinical juvenile toxicity study to characterize potential safety profile in pediatrics

Proposed Pediatric Plan

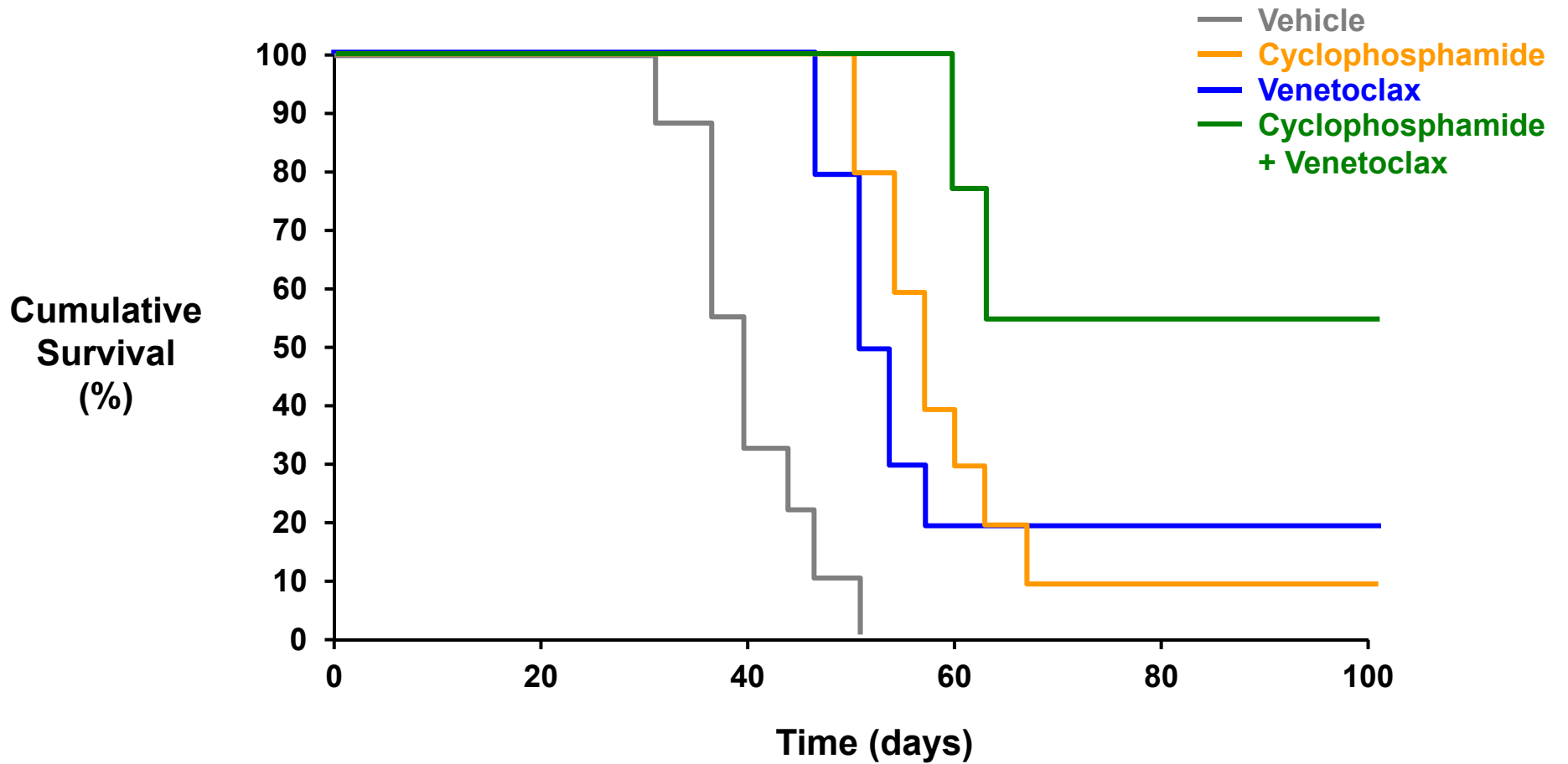
Mechanism Based Selection of Pediatric Tumor Types

Pediatric Cancer	BCL-2 Overexpression	Cell Line Response	Murine Xenograft Response	Clinical Response in Adults
AML	X	X	X	X
NHL*	X	X	X	X
ALL	X	X	X	Not tested
Neuroblastoma	X	X	X	Not tested

*Burkitt's lymphoma cell lines did not respond to venetoclax

Neuroblastoma: Preclinical Rationale BCL-2 Dependent Model

NB-1643 (BCL-2 Dependent)



Adapted from Tanos R, et al. BMC Cancer 2016.

Unmet Medical Need in Relapsed / Refractory Patients

- Newly diagnosed patients
 - ALL, NHL and neuroblastoma
 - OS rate >75%
 - AML
 - OS rate ~60%
- Relapsed / refractory setting
 - Prognosis remains dismal for all indications

Overview of Proposed Study

- Phase 1: dose escalation and cohort expansion study
- Multi center global study
 - ~40 sites in US, EU, Canada, Australia
- Proposed enrollment
 - ~150 patients
 - Age 1 to <18 years

Study Objectives

- Primary objectives
 - Safety (dose limiting toxicity)
 - Pharmacokinetics
- Secondary objectives
 - Efficacy (ORR, CR)
 - Safety in combination with chemotherapy
- Exploratory
 - Minimum residual disease (MRD) analysis
 - Biomarker analysis

Phase 1: Two Part Study Design

Part 1
Dose Escalation
N = 24-72

Using standard
3 + 3 + 3 design

Dose level 1
400 mg

Dose level 2
800 mg

Determines
recommended
dose for Part 2

Part 2
Cohort Expansion
N = 32-100

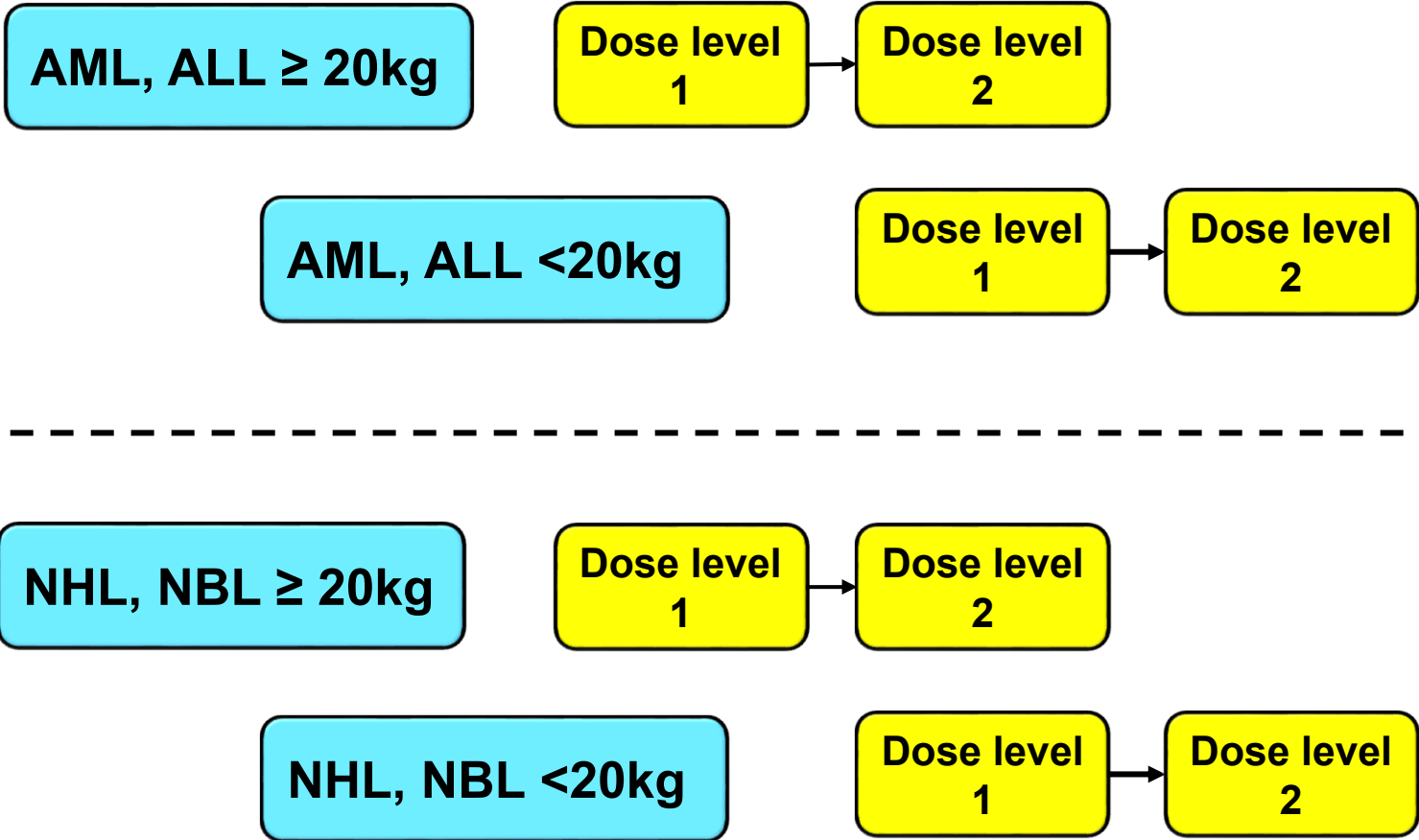
AML

ALL

NHL

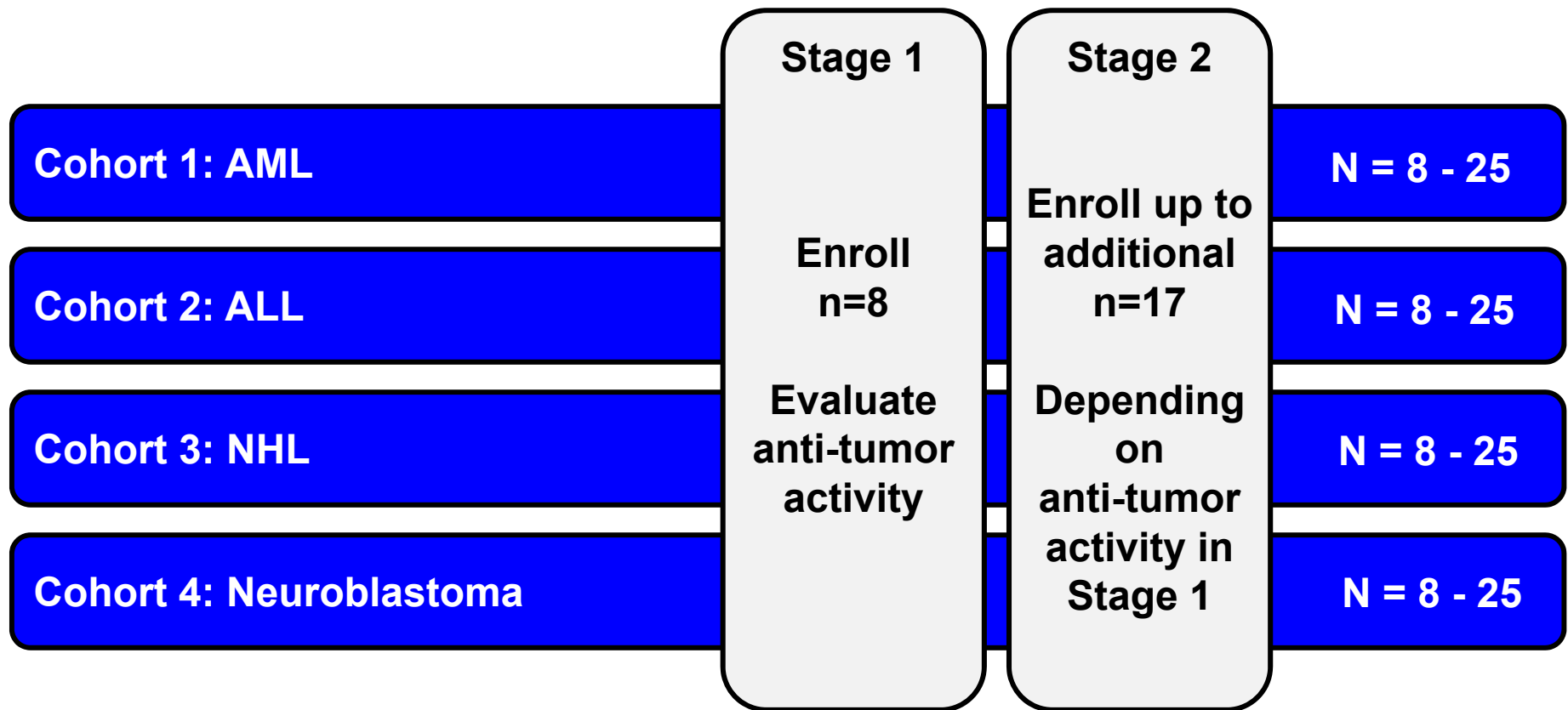
Neuroblastoma

Part 1: Dose Escalation Scheme



Part 2: Cohort Expansion

Gehan 2-Stage Design



- Targeting a response rate of 20%

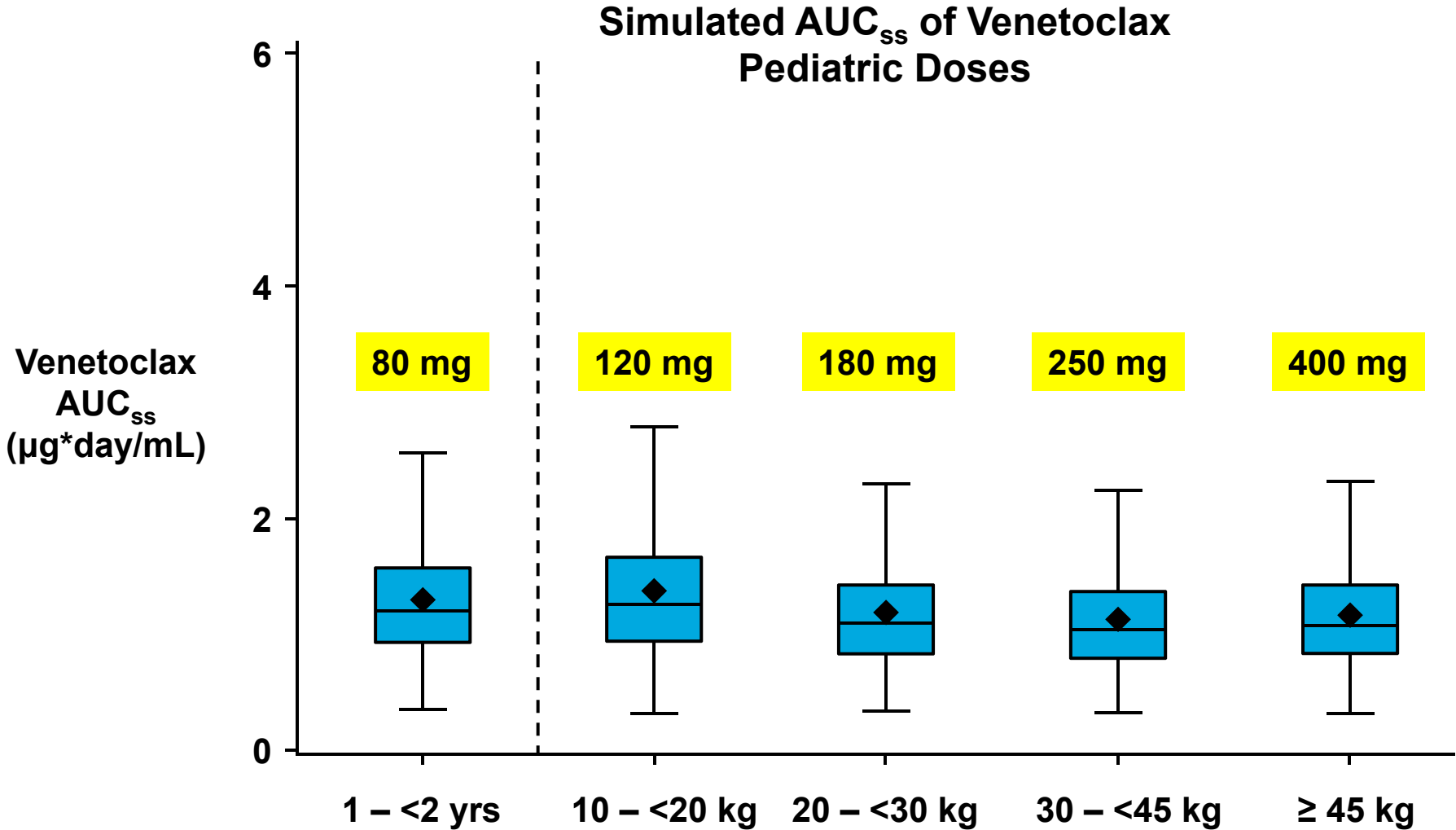
Venetoclax Pediatric Formulation

- Tablet formulation (recently approved)
 - 10 mg, 50 mg and 100 mg
- Rapidly disintegrating tablets
 - 2.5 mg, 10 mg and 25 mg
 - Used to make oral liquid suspension

Venetoclax Pediatric Dose Projections

- Impact on hepatic metabolism by CYP3A4 in patients <2 years
- Age band dosing: <2 years
- Weight band dosing: ≥ 2 years

Venetoclax Pediatric Dose Projections



Illustrative of dose level 1

Rationale for Venetoclax in Combination Therapy

- Acceptable safety profile first with monotherapy
- Meet efficacy endpoint
- Based on investigator discretion in best interest of the child
- Combination therapy may
 - Push tumor cell to apoptosis
 - Maintain response
 - Stop repeated progression

Allowed Combination Agents

- AML
 - Low dose cytarabine
- ALL
 - Dexamethasone and vincristine
- NHL
 - Rituximab
- Neuroblastoma
 - Cyclophosphamide

Potential Pediatric Challenges

Challenges	Mitigation
Suspension formulation palatability	Taste studies and dosing vehicle evaluation ongoing
Number of tablets for high dose groups	Combination of tablets and liquid dosing
Food effect on pediatric formulation	Bioavailability study
Trial enrollment across tumor types	NHL / DLBCL: outreach to encourage screening

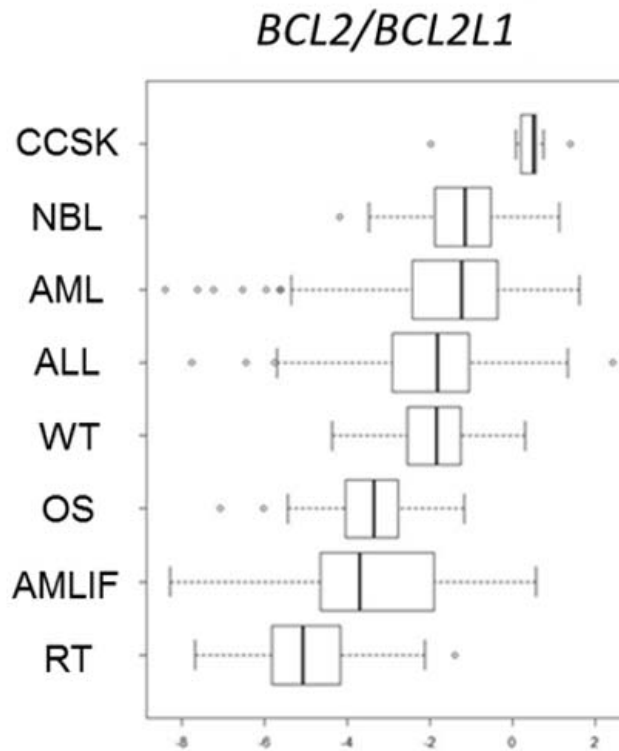
Venetoclax Summary

- Venetoclax
 - Showed activity in adults
 - Reasonable candidate for pediatric evaluation
- Morbidity and mortality in relapsed setting remains high
- Mechanistically venetoclax works differently than other therapies
 - May show response where other treatments failed
 - Will offer another treatment option
- Sponsors committed to continue development in pediatric oncology

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AbbVie Figure 2: BCL-2/BCL-X_L Expression Ratio Among Pediatric Tumor Types



CCSK = clear cell sarcoma of the kidney; NBL = neuroblastoma; AML = acute myeloid leukemia;
 ALL = acute lymphocytic leukemia; WT = Wilms tumor; OS = osteosarcoma; AMLIF = AML induction failure;
 RT = rhabdoid tumor

The ratio of BCL-2 mRNA expression relative to BCL-2L1 is plotted for pediatric tumor samples.