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Targeted Therapies in Pediatric Leukemia

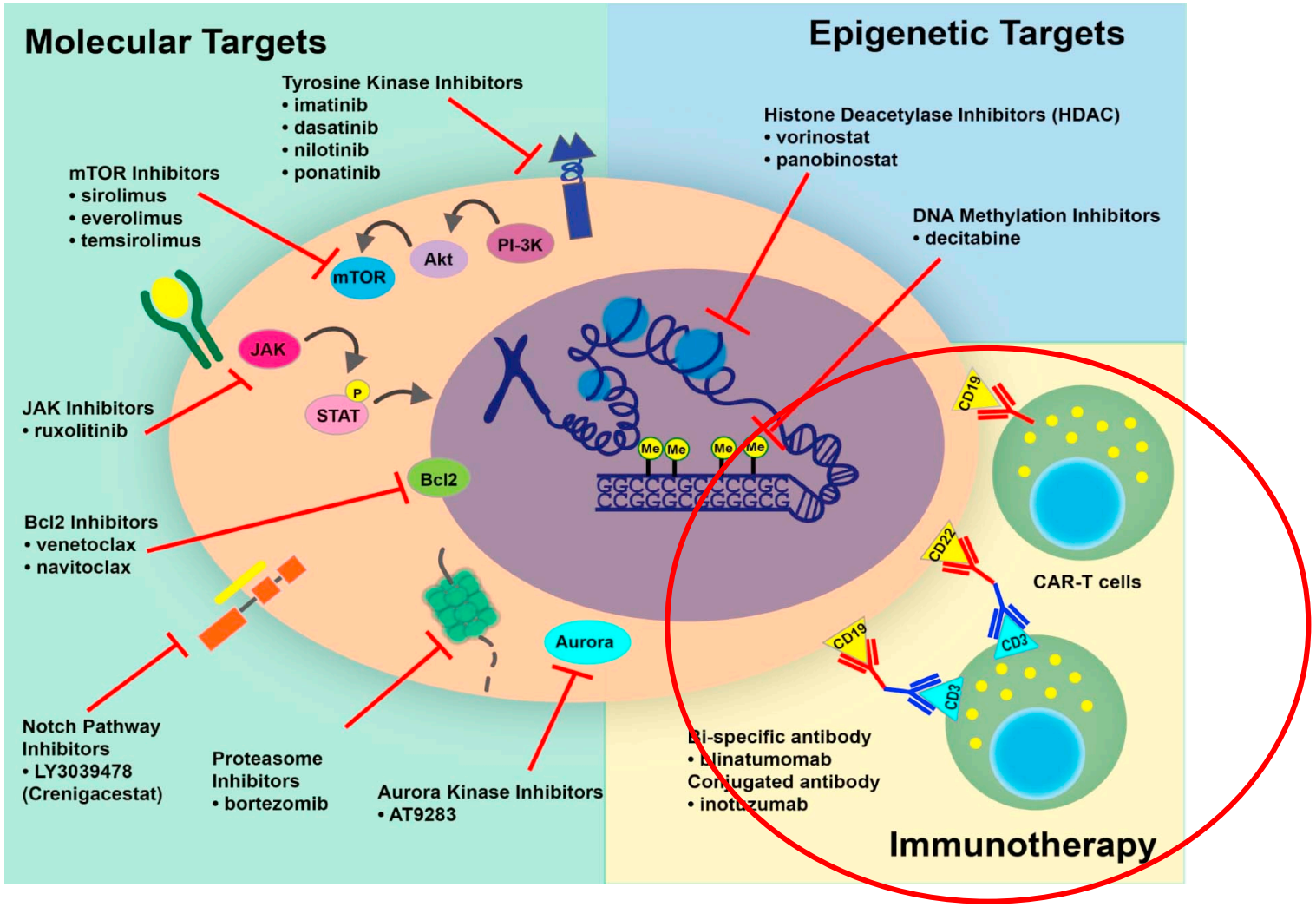
December 9th, 2022

Tara O'Donohue, MD

Objectives

- To discuss different types of targetable cell surface proteins/molecular aberrations found in pediatric leukemia
- To review mechanisms of action and notable adverse effects of select targeted therapeutics
- To review where molecular profiling/immunohistochemical information can be found in the EMR

Abbreviated Landscape of Targeted Therapies in Pediatric Leukemia

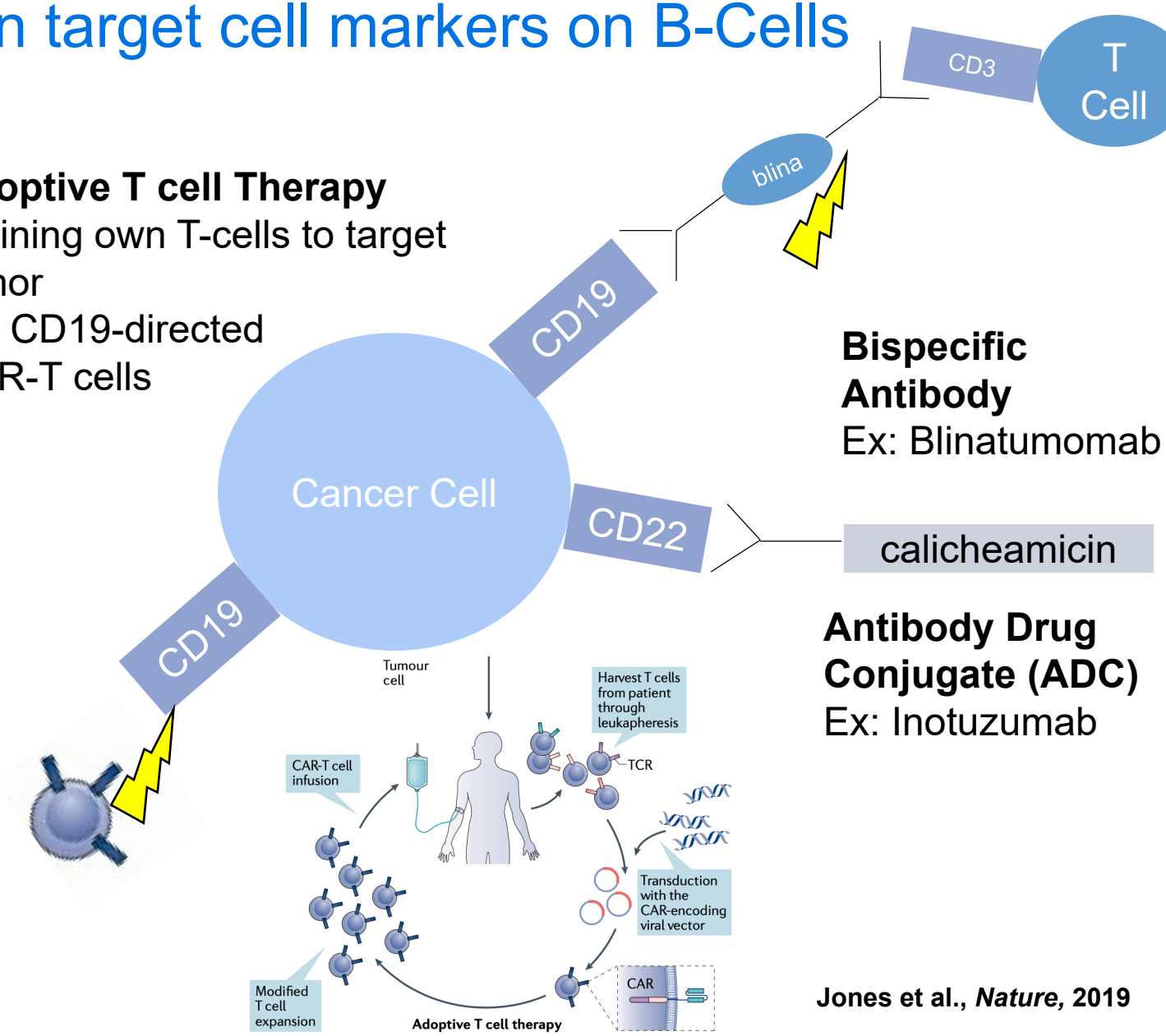


Heikamp and Pui, *Journal of Pediatrics, 2018*

Immunotherapeutic agents can target cell markers on B-Cells

- B-cell acute lymphoblastic leukemia
  - Most common pediatric cancer
  - Cure rate >90%, but relapsed/refractory patients are ongoing challenge
- Many targetable markers on immature B-cells for which novel therapies exist

Adoptive T cell Therapy
Training own T-cells to target tumor
Ex: CD19-directed CAR-T cells



Bispecific Antibody
Ex: Blinatumomab

Antibody Drug Conjugate (ADC)
Ex: Inotuzumab

Jones et al., *Nature,* 2019

Chimeric Antigen Receptor (CAR) T cells

- Form of cellular therapy; T cells genetically modified to express CD19 antibody on cell surface + T-cell receptor signaling domain inside cell
- Binding of CAR to CD19 leukemia cells activates CAR to kill leukemia cells
- Unique toxicities
    - Cytokine release syndrome (CRS)
    - Neurotoxicity
    - B-cell aplasia
- Tisagenlecleucel: autologous CAR T product, FDA approved for relapsed/refractory B-ALL in patients up to 25 yo
- Currently evaluating in phase 2 study for patients with high-risk disease and are end of consolidation MRD positive (NCT03876769)

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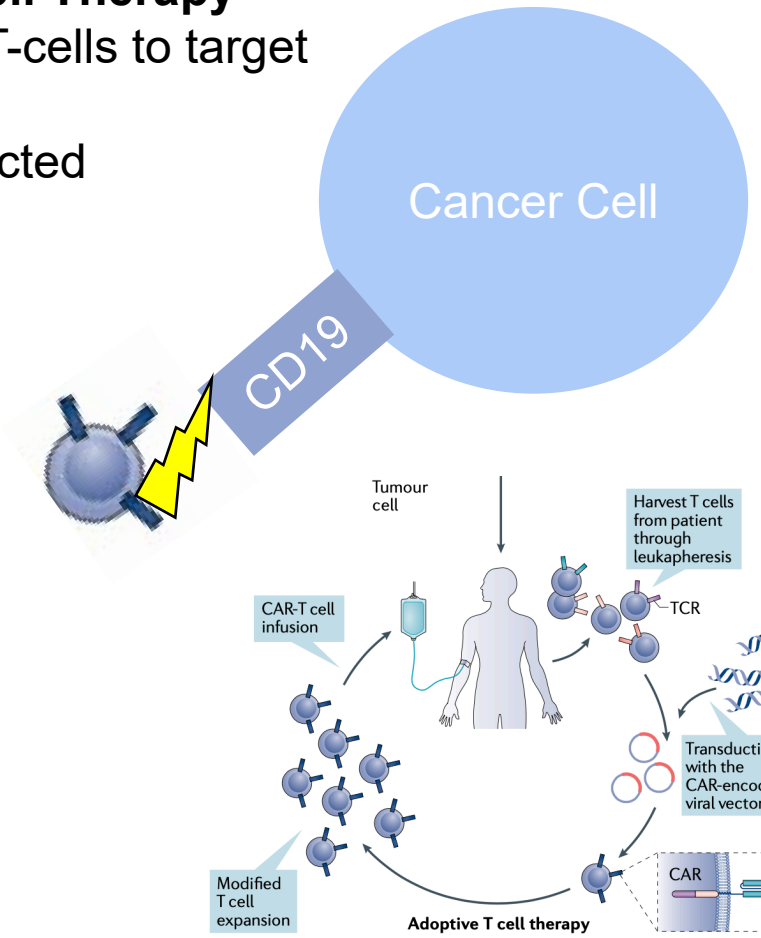
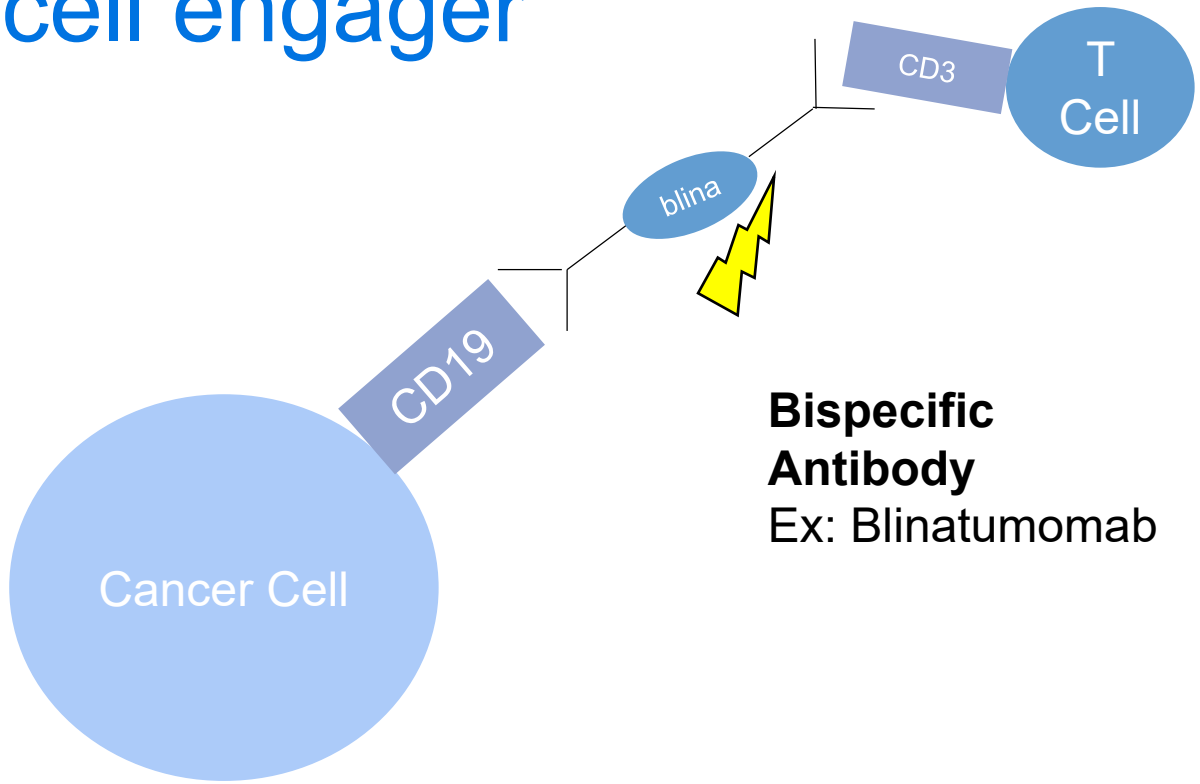


Jones et al., *Nature,* 2019
Butler *et al, Cancer Journal for Clin*, 2021

Blinatumomab: a bispecific T-cell engager

- Has antibody fragments directed to CD19 and CD3 (T-cell surface marker)
- Activates cytotoxic T cells to target/kill leukemic cells
- SHORT half-life (2 hours)
- When administered with chemotherapy, fewer toxicities than chemo-only arm and pts more likely to go to AlloSCT (AALL1331); but no difference in survival
- FDA approved for relapsed/refractory B-ALL in pediatric and adult patients
- Under active study in newly diagnosed B-ALL in combination with chemotherapy (AALL1731)

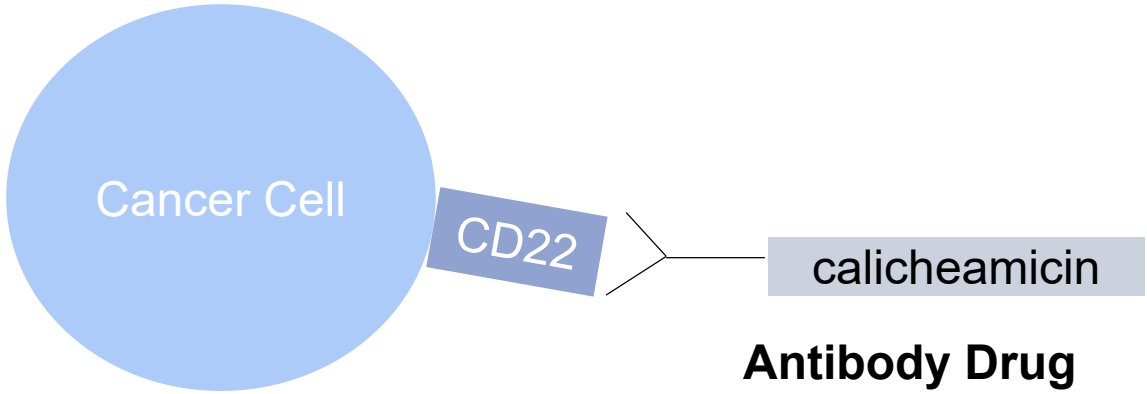


Bispecific Antibody
Ex: Blinatumomab

Butler *et al, Cancer Journal for Clin*, 2021
Brown *et al, JAMA*, 2021

Inotuzumab: Antibody-drug conjugate that targets CD22

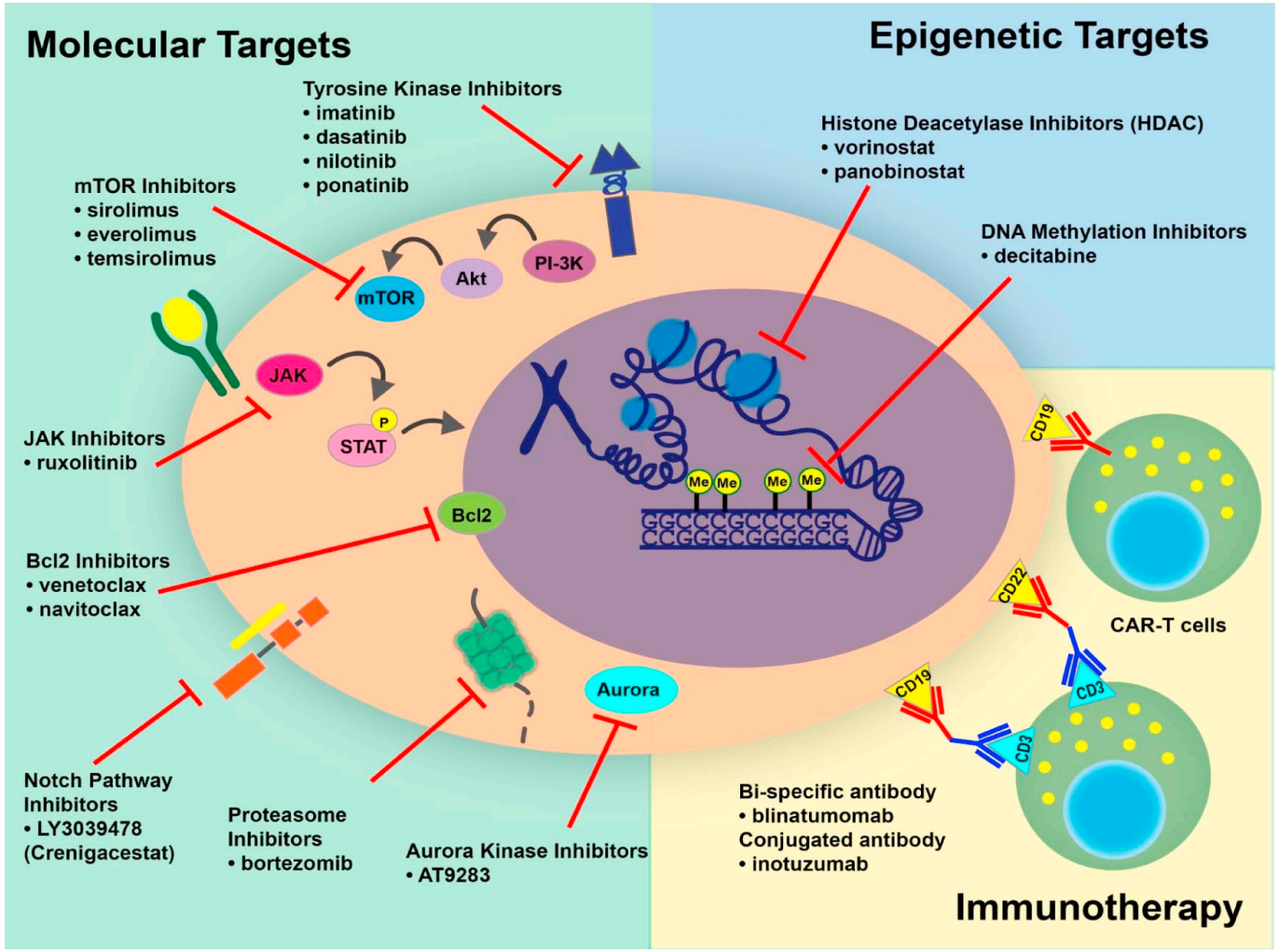
- Antibody targeting CD22 and linked to cytotoxic antitumor antibiotic (calicheamicin)
- Toxicities of interest
    - Sinusoidal obstruction syndrome (SOS, formerly known as VOD)
    - Particular caution post-transplant
- Attractive options for patients who lose CD19 positivity
- FDA approved for adults with B-ALL, but clinical activity in children as well
- Active investigation in high-risk patients when added to post induction chemotherapy (AALL1732)



Antibody Drug Conjugate (ADC)
Ex: Inotuzumab

Butler *et al, Cancer Journal for Clin*, 2021

Abbreviated Landscape of Targeted Therapies in Pediatric Leukemia



Heikamp and Pui, *Journal of Pediatrics, 2018*

Imatinib: The Poster Child for Targeted Therapy in Heme Malignancies

ORIGINAL ARTICLE

Efficacy and Safety of a Specific Inhibitor of the BCR-ABL Tyrosine Kinase in Chronic Myeloid Leukemia

Brian J. Druker, M.D., Moshe Talpaz, M.D., Debra J. Resta, R.N., Bin Peng, Ph.D., Elisabeth Buchdunger, Ph.D., John M. Ford, M.D., Nicholas B. Lydon, Ph.D., Hagop Kantarjian, M.D., Renaud Capdeville, M.D., Sayuri Ohno-Jones, B.S., and Charles L. Sawyers, M.D.

TABLE 3. HEMATOLOGIC RESPONSES.

DOSE (mg/DAY)	ALL PATIENTS	PATIENTS WITH RESPONSES	PATIENTS WITH COMPLETE RESPONSES
	no.	no. (%)	
25 or 50	6	2 (33)	0
85	4	2 (50)	1 (25)
140	3	3 (100)	1 (33)
200 or 250	16	16 (100)	9 (56)
300–1000	54	54 (100)	53 (98)
Total	83	77 (93)	64 (77)

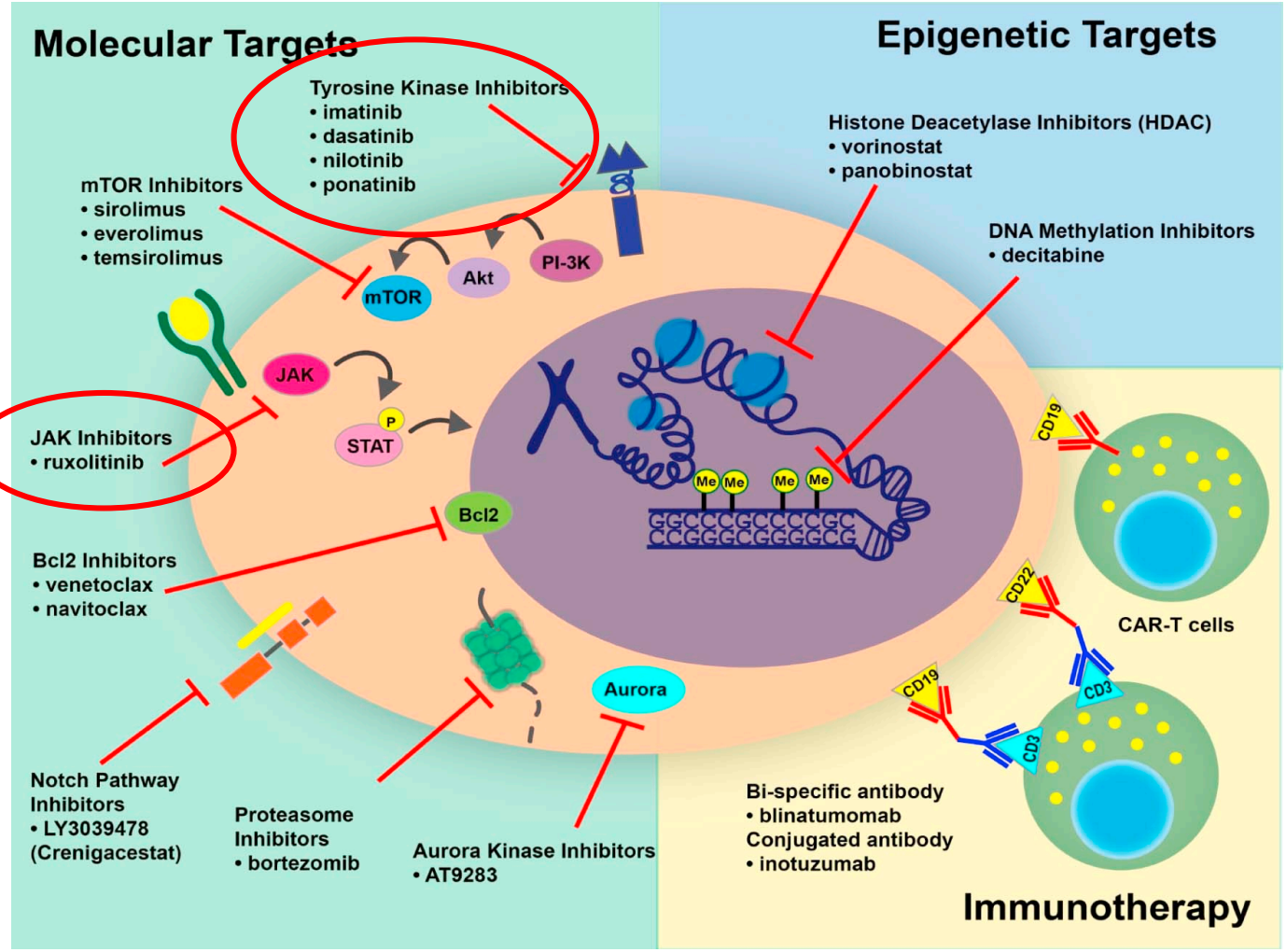
TABLE 4. CYTOGENETIC RESPONSES.

DOSE (mg/DAY)	ALL PATIENTS	PATIENTS WITH COMPLETE OR MAJOR RESPONSES	PATIENTS WITH MINOR RESPONSES
	no.	no. (%)	
300–350	13	5 (38)	2 (15)
400	6	3 (50)	2 (33)
500	6	1 (17)	1 (17)
600	8	4 (50)	4 (50)
750	6	2 (33)	0 (0)
800	8	1 (12)	2 (25)
1000	7	1 (14)	1 (14)
Total	54	17 (31)	12 (22)

Drucker *et al*, *NJEM*, 2001

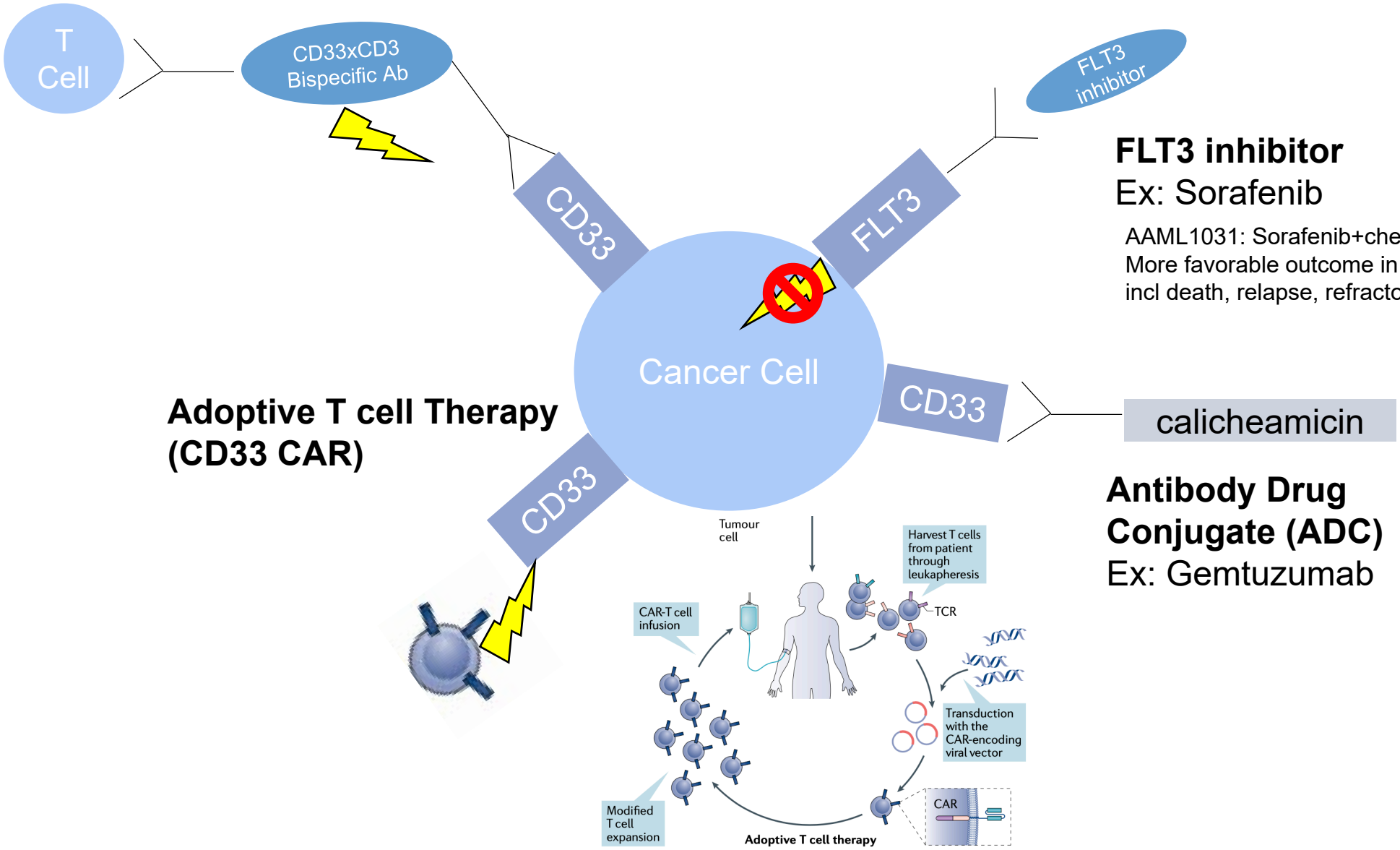
Abbreviated Landscape of Targeted Therapies in Pediatric Leukemia

- A subset of patients with B-ALL harbor the BCR-ABL1 (Philadelphia) translocation, and others fit a sub-class called “Ph-like ALL” (up to 15% of B-ALL)
    - Other ABL class fusions: ABL1, ABL2, CSF1R, PDGFRB, PDGFRA
    - Respond clinically to ABL1 tyrosine kinase inhibitors (TKIs)
    - Preclinical models with activating JAK-STAT pathway, amenable to treatment with JAK inhibitors
- Ongoing studies looking at response w/addition of TKI (AALL1131-dasatinib, AALL1521-ruxolitinib for CRLF2 fusion)



Heikamp and Pui, *Journal of Pediatrics, 2018*

Immunotherapeutic agents can target cell markers on myeloid cells (AML targets)



Adoptive T cell Therapy (CD33 CAR)

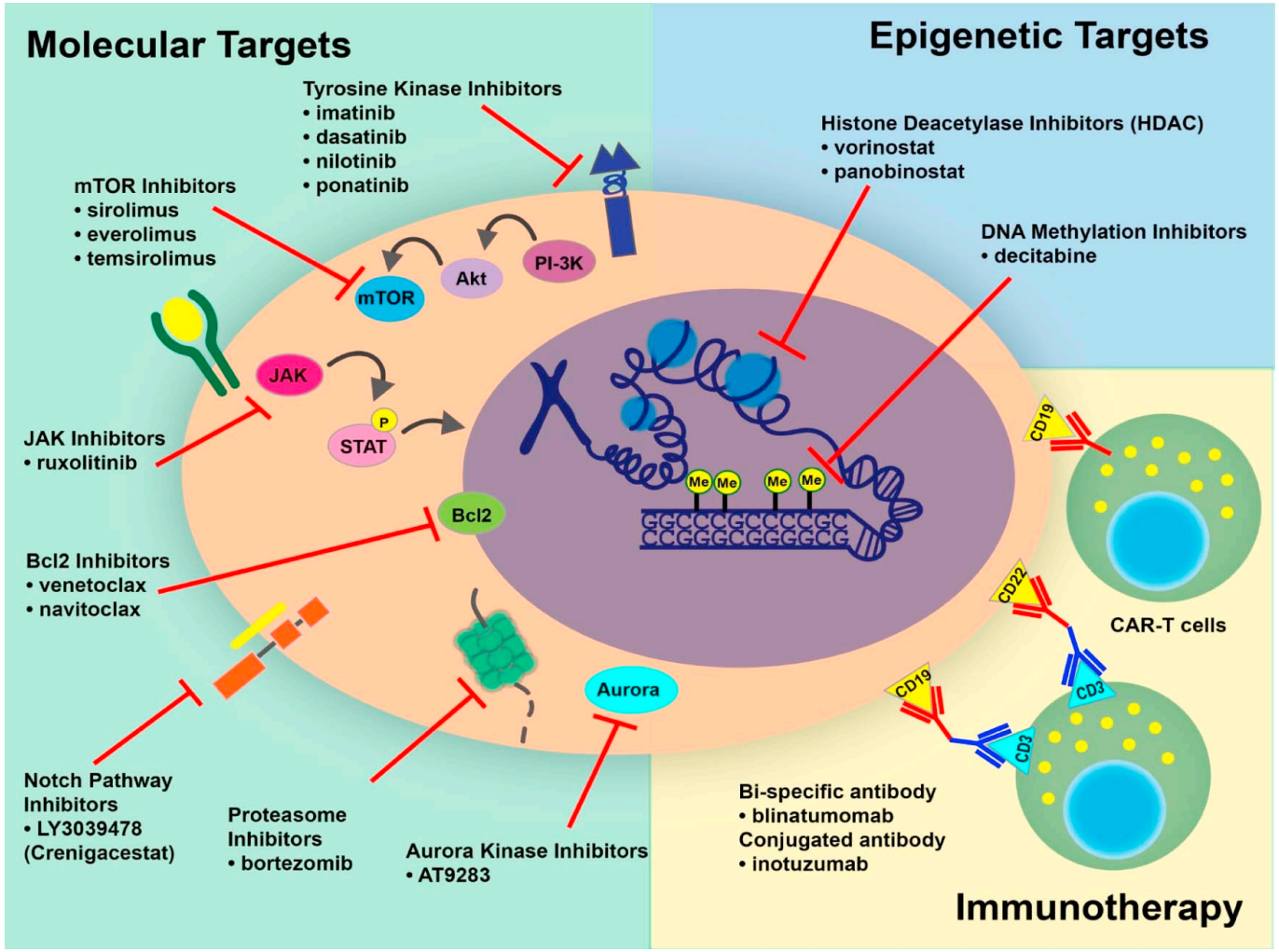
FLT3 inhibitor
Ex: Sorafenib

AAML1031: Sorafenib+chemo vs SOC chemo in HAR FLT3/ITD
More favorable outcome in sorafenib group (half as many events incl death, relapse, refractory disease)

Antibody Drug Conjugate (ADC)
Ex: Gemtuzumab

Jones et al., *Nature,* 2019
Pollard et al., *JCO*, 2022

Abbreviated Landscape of Targeted Therapies in Pediatric Leukemia



Heikamp and Pui, *Journal of Pediatrics, 2018*

Early Phase Targeted Therapies for Liquid Tumors at MSK Kids

Agent	Disease	Mechanism	Trial
SNDX-5613	ALL, AML (KMT2A rearranged or NPM1m)	Menin inhibitor	19-448- single agent 22-239- combination with chemo
Idasanutlin	ALL, AML	MDM2 inhibitor	20-140- IDASA + chemo or venetoclax
MRX-2843	ALL, AML, MPAL	MerTK/FLT3 inhibitor	22-080- Phase 1 single agent dose escalation
Venetoclax	ALL, AML, NHL, solid tumors	BCL-2 inhibitor	18-265 (CTA, Ph1 dose escalation/expansion)

Many unanswered questions…

- Timing of novel agent (at diagnosis or relapse)
- Administration of novel agent
  - monotherapy vs combination with chemotherapy or other novel agent(s)
    - If combination, which drugs are synergistic without overlapping toxicity profiles?
- How to prioritize drugs that hit same target
  - Blinatumomab vs CD19 CAR-T

Targetable Molecular Aberrations- How do I find this information?

Single Nucleotide Variant/Point mutation	**Fusion/Rearrangement**	**Amplification**
IMPACT/IMPACT-HEME	Archer/Archer-Heme	IMPACT Cytogenetics

OncoKB Levels of Evidence

1 Structural Variants (page 1 of 1)

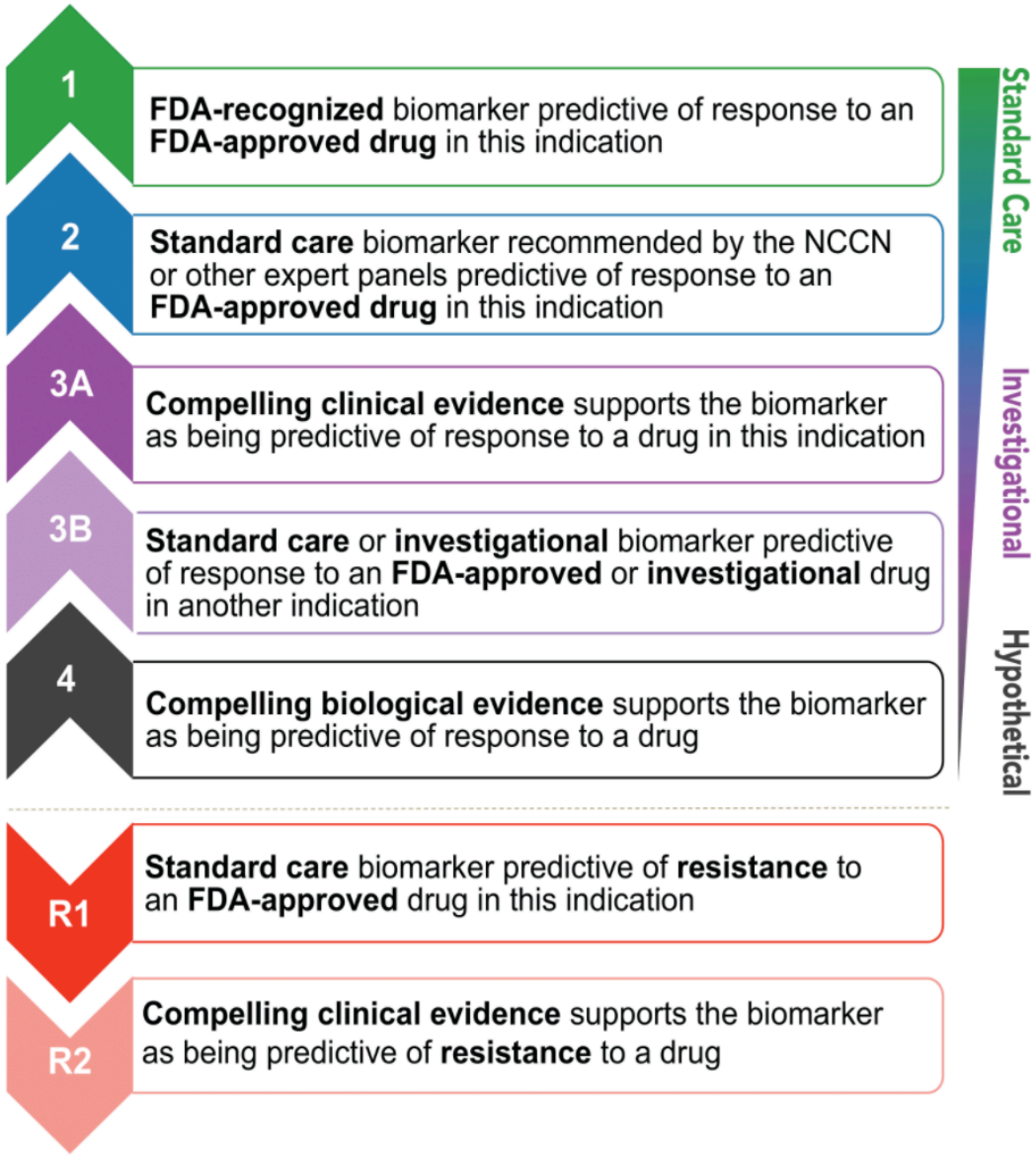
Columns

Gene 1	Gene 2	Status	Annotation	Variant Class	Event Info	Connection Type
BCR	ABL1	s	1	NA	BCR-ABL1 Fusion	NA

Showing 1-1 of 1 Structural Variants

Study is not profiled for copy number alterations.

OncoKB Levels of Evidence



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1 Structural Variants (page 1 of 1)

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BCR	ABL1	s	1

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BCR-ABL1 Fusion in acute myeloid leukemia

Oncogenic | **Gain-of-function**

ABL1, a tyrosine kinase, is frequently altered by chromosomal translocations in leukemia.

The BCR-ABL1 fusion is known to be oncogenic.

The presence of the BCR-ABL1 fusion in myeloproliferative neoplasms is diagnostic of chronic myelogenous leukemia (CML). While the multikinase inhibitors imatinib, dasatinib, nilotinib and bosutinib are FDA-approved for the treatment of patients with CML and imatinib, dasatinib and ponatinib are FDA-approved for the treatment of patients with BCR-ABL1 fusion-positive acute lymphoblastic leukemia, their clinical utility in patients with BCR-ABL1 fusion positive acute myeloid leukemia is unknown.

Biological Effect | 1 Diagnostic Implications

The BCR-ABL1 fusion protein (also known as the Philadelphia chromosome) juxtaposes part of the serine/threonine kinase BCR with the SH2/3, tyrosine kinase, DNA- and actin-binding domains of ABL1 (). This fusion is commonly found in chronic myelogenous leukemia and acute lymphocytic leukemia. This fusion is well-studied and results in constitutive downstream JAK/STAT and PI3K signaling, resulting in growth-factor independence, inhibited apoptosis, altered cell motility and transformation (). Small molecule inhibitors of ABL1, including FDA-approved imatinib, dasatinib, and nilotinib, have had high levels of clinical activity in patients with the BCR-ABL1 fusion ().

The information above is intended for research purposes only and should not be used as a substitute for professional diagnosis and treatment.

OncoKB

Feedback

Targetable Cell Surface Markers- How do I find this information?

Solid Tumors

Pathology report
Immunohistochemistry (IHC)

Liquid Tumors

Flow cytometry

Things to consider for interpretation:
IHC- percentage of cells with expression (>50%?); strength of staining (2+, 3+)

Flow cytometry- bright vs dim

Cutoffs in protocol may vary

Protocol may be histology specific OR biomarker specific (i.e. any histology so long as meets minimum threshold of expression)

Questions?

Abbreviated Landscape of Targeted Therapies in Pediatric Leukemia

Pathway/mechanism of action	(Genetic) target	Drug name	Adult trials	Pediatric trials	FLT3-ITD	KMT2A-r	Ph+	IDH1/2
Kinase inhibition	JAK-STAT pathway	Ruxolitinib	+	+			+	
	FLT3 inhibitor	Midostaurin, quizartinib, lestaurtinib	+	+	+	+		
	MEK inhibitor	Trametinib, selumetinib	+	+				
	Multi-kinase inhibitors	Imatinib, ponatinib, dasatinib, sorafenib	+	+	+		+	
Proteasome/ubiquitin system	Proteasome	Bortezomib, carfilzomib, ixazomib	+	+		+		
	MDM2	Idasanutlin, milademetan, ALRN-6924	+	+	+	(+)	(+)	
	NEDD8	Pevonedistat	+	+				
Epigenetic targeting	HDAC	Vorinostat, panobinostat	+	+				
	DNMT	Azacitidine, decitabine	+	+				
	DOT1L	Pinometostat	+	+		(+)		
Apoptosis	TP53	APR-246	+	No				
	MCL1	S64315	+	No				
	BCL2	navitoclax, venetoclax	+	+		(+)	(+)	+
	survivin	EZN-3042, LY2181308	No	No				
Other approaches	IDH1	Ivosidenib	+	+				+
	CDK4/6	Palbociclib, ribociclib	+	+		+	(+)	
	PARP	Olaparib, veliparib	+	No	+			+
	mTOR	Everolimus, temsirolimus, sirolimus	+	+				
	Menin	MI-463, MI-503, MI-1481, MI-525	No	No		(+)		
	CBFβ-SMMHC	AI-10-49	No	No				

Drug names are indicated. +, studies currently recruiting (adult trials or pediatric trials, respectively). FLT3-ITD, KMT2A-r, Ph+, IDH1: cases, in which these leukemia specific defects can be targeted by any of the mentioned drugs are designated by "+".

Kuhlen *et al, Frontiers in Pediatrics*, 2019