Society for Immunotherapy of Cancer

Cancer Immunotherapy GUIDELINES

Clinical Practice Guideline Webinar –

Immunotherapy for the Treatment of Acute Leukemia

Monday, January 11, 2021

Noon – 1 p.m. EST

Jointly provided by Postgraduate Institute for Medicine and the Society for Immunotherapy of Cancer

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Open access Position article and guidelines

Journal for ImmunoTherapy of Cancer

The Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immunotherapy for the treatment of acute leukemia

Michael M Boyiadzis,[1] Ivan Aksentijevich,[2] Daniel A Arber,[3] John Barrett,[4] Renier J Brentjens,[5] Jill Brufsky,[1] Jorge Cortes,[6] Marcos De Lima,[7] Stephen J Forman,[8] Ephraim J Fuchs,[9] Linda J Fukas,[10] Steven D Gore,[11] Mark R Litzow,[12] Jeffrey S Miller,[13] John M Pagel,[14] Edmund K Waller,[15] Martin S Tallman[5]

Webinar faculty

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Outline

- Introduction to acute leukemia
- Approved immunotherapies for ALL
  - Inotuzumab ozogamicin
  - Blinatumomab
  - Tiasagenlecleucel
- Approved immunotherapies for AML
  - Gemtuzumab ozogamicin
- Emerging therapies for acute leukemia

Acute leukemia

- Cytogenetic and molecular abnormalities have separated acute leukemia into distinct groups

- Risk stratification of acute leukemia has been used to guide therapeutic decisions

  -allogeneic hematopoietic cell transplantation for patients with high-risk disease

- Cytogenetic, immunophenotypic, and molecular studies including next generation sequencing should be performed to diagnose and classify disease characteristics

Diagnostic tests for ALL/AML

ASCO/CAP/ASH recommended tests	
Acute lymphoblastic leukemia	**Acute myeloid leukemia**
t(9;22)(q34;1;q11.2); PAX5	*FLT3-ITD; IDH1*
CRLF2; JAK1	*NPM1; IDH2*
BCR-ABL1; JAK2	*CEBPA; TET2*
KMT2A (MLL); *IKZF1* (for B-ALL)	*RUNX1; WT2*
CRLF2 overexpression (for B-ALL)	*PML-PARA; DNMT3A*
NOTCH1 and/or *FBXW7* (for T-ALL)	*KIT* (for CBF AML); *TP53*
	RUNX1-RUNXT1/CBFB-MYH1 (for CBF AML)

Immunotherapy-related diagnostic markers	
ALL	**AML**
CD19	CD33
CD22	
CD20	

Risk status based on cytogenetic and molecular abnormalities in AML

Risk category	Genetic abnormality
Favorable	t(8;21)(q22;q22.1); RUNX1-RUNX1T1
	inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBFB-MYH11
	Mutated NPM1 without FLT3-ITD or with FLT3-ITD^{low}
	Biallelic mutated CEBPA
Intermediate	Mutated NPM1 and FLT3-ITD^{high}
	Wild-type NPM1 without FLT3-ITD or with FLT3-ITD^{low} (without adverse-risk genetic lesions)
	t(9;11)(p21.3;q23.3); MLLT3-KMT2A
	Cytogenetic abnormalities not classified as favorable or adverse
Adverse	t(6;9)(p23;q34.1); DEK-NUP214
	t(v;11q23.3); KMT2A rearranged
	t(9;22)(q34.1;q11.2); BCR-ABL1
	inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); GATA2,MECOM(EVI1)
	−5 or del(5q); −7; −17/abn(17p)
	Complex karyotype, monosomal karyotype
	Wild-type NPM1 and FLT3-ITD^{high}
	Mutated RUNX1
	Mutated ASXL1
	Mutated TP53

Dohner et al , Blood 2017

Recently approved agents in acute leukemia- a complex treatment landscape

Acute myeloid leukemia	Acute lymphocytic leukemia
Midostaurin Gilteritinib Ivosidenib Enasidenib Venetoclax Glasdegib CPX-351 Gemtuzumab ozogamicin Oral azacitidine	Tyrosine kinase inhibitors (TKIs) Blinatumomab Inotuzumab ozogamicin Tisagenlecleucel

- **Approved immunotherapies**
- **How to incorporate immunotherapies at acute leukemia diagnosis and in the refractory/relapse setting**
- **Role of new immunotherapies in allogeneic hematopoietic cell transplantation**

Guideline development

- *The Institute of Medicine's Standards for Developing Trustworthy Practice Guidelines* used to develop these recommendations
- Panel consisted of 17 participants, including medical oncologists, hematologists, a hematopathologist, a leukemia research nurse, and a patient advocate
- Recommendations come from literature evidence, supplemented with clinical experience of the panel members where necessary
- Consensus defined as ≥75% agreement

Guideline development

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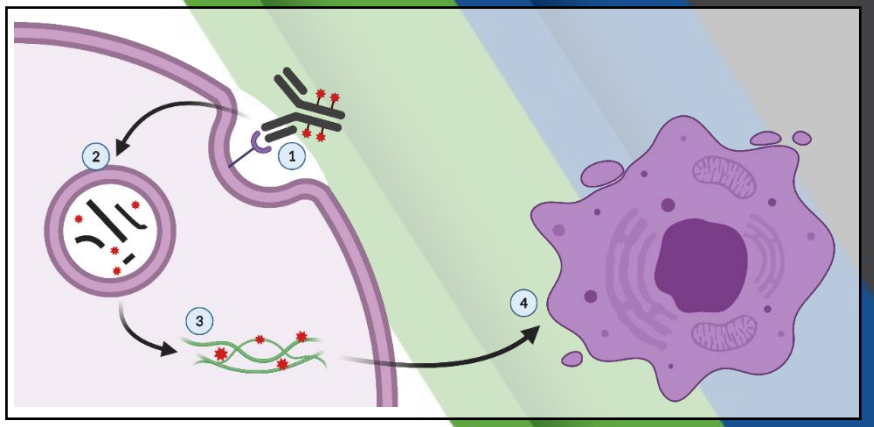
Approved immunotherapies for ALL

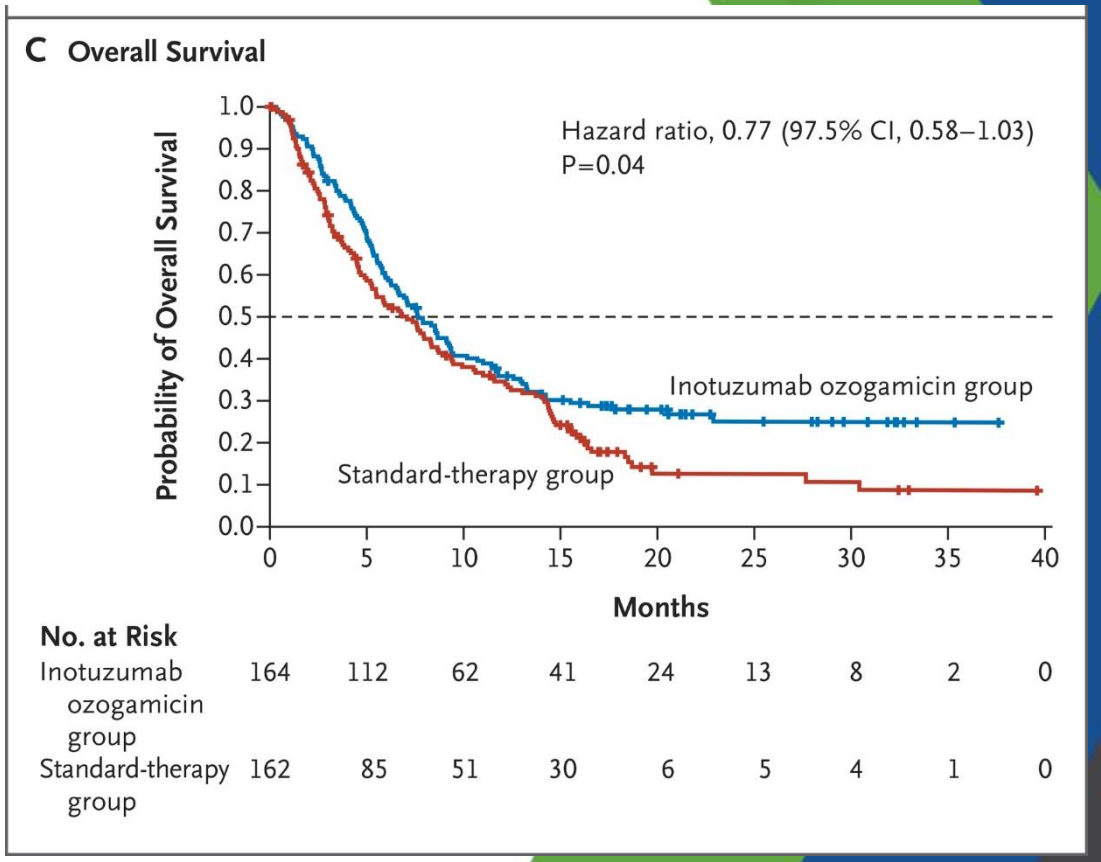
Drug	Type	Mechanism	Approval	Indications
Blinatumomab	Bispecific T cell engager (BiTE)	CD3 x CD19 bispecific	March 2018	Adult and pediatric patients with B-cell precursor ALL in first or second complete remission with MRD ≥0.1%
			July 2017	Relapsed or refractory B-cell precursor ALL in adults and children
			December 2014	Philadelphia chromosome-negative relapsed or refractory B-cell precursor ALL
Inotuzumab ozogamicin	Anti-CD22 antibody–drug conjugate	Antibody-drug conjugate, CD22 antibody + calicheamicin	August 2017	Adults with relapsed or refractory B-cell precursor ALL
Tisagenlecleucel	CAR T cell therapy	CD19 CAR T cells	August 2017	Patients up to 25 years of age with B-cell precursor ALL that is refractory or in second or later relapse

Inotuzumab ozogamicin

CD22 antibody linked to calicheamicin



Trial	Study design	Patient population	Enrolled patients	Primary endpoint	Results
INO-VATE	Phase III	R/R B-ALL	218 (109 in each arm)	OS and complete response rate	Median OS: 7.7 vs 6.7 months CR rate: 80.7 % vs 29.4%



Kantarjian, N Engl J Med 2016

Toxicities with inotuzumab ozogamicin

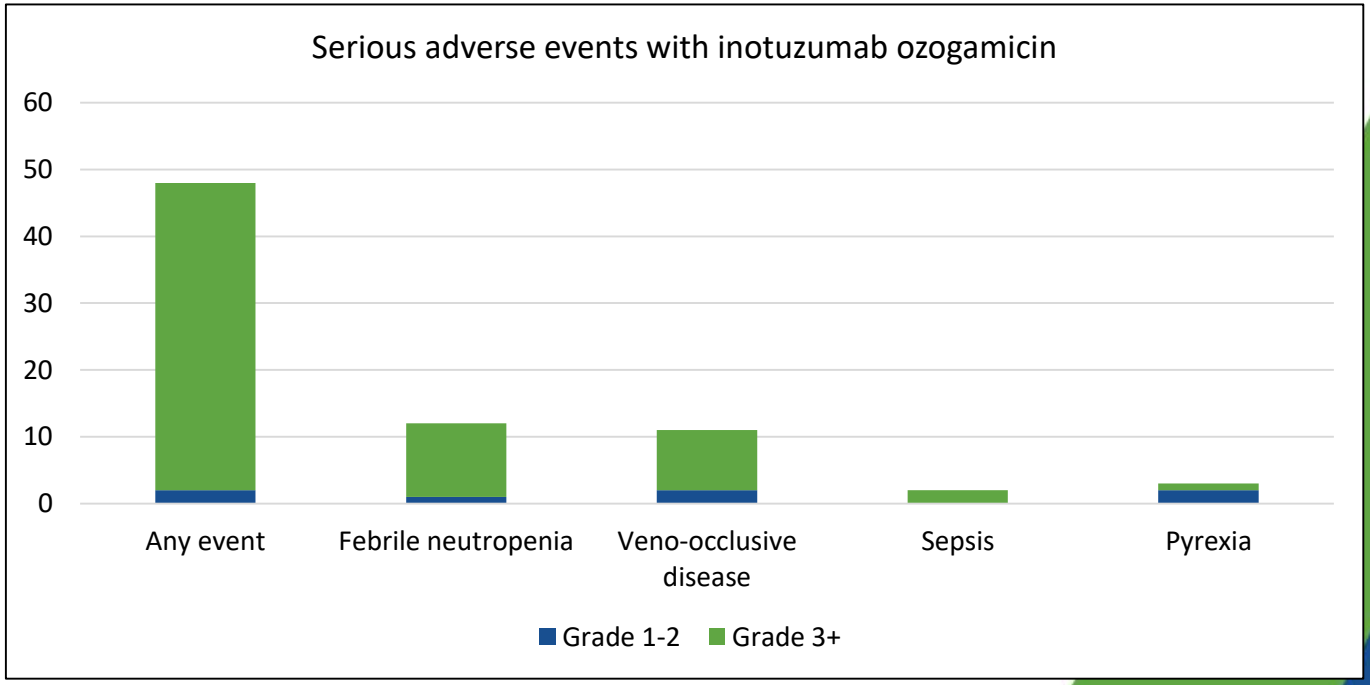
Panel recommendation:

Because inotuzumab ozogamicin increases the risk of SOS/VOD in subsequent transplants, the number of cycles should be limited if allo-HCT is planned.

WARNING: HEPATOTOXICITY, INCLUDING HEPATIC VENO-OCCLUSIVE DISEASE (VOD) (ALSO KNOWN AS SINUSOIDAL OBSTRUCTION SYNDROME and INCREASED RISK OF POST- HEMATOPOIETIC STEM CELL TRANSPLANT (HSCT) NON-RELAPSE MORTALITY

See full prescribing information for complete boxed warning.

- **Hepatotoxicity, including fatal and life-threatening VOD occurred in patients who received BESPONSA. (5.1)**
- **A higher post-HSCT non-relapse mortality rate occurred in patients receiving BESPONSA (5.2)**

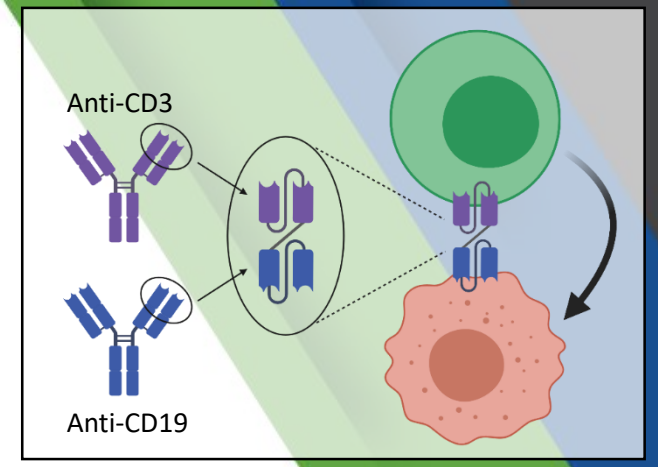


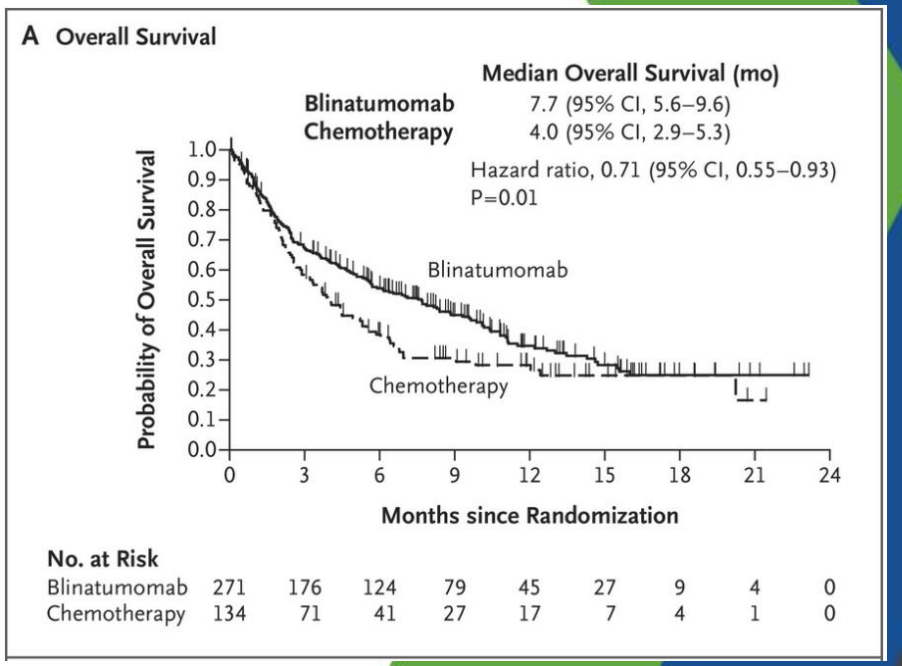
Kantarjian, N Engl J Med 2016.

Blinatumomab

CD3 x CD19 bispecific

Trial	Study design	Patient population	Enrolled patients	Primary endpoint	Results
TOWER	Prospective, randomized phase III	Adults with Ph− RR B-ALL	405	OS	Median OS 7.7 months in blinatumomab group versus 4.0 months in the chemotherapy group
ALCANTARA	Open-label-, single-arm phase II	Adults with Ph+ RR B-ALL	45	CR or CRh	CR or CRh rate 36% with 88% MRD−
MT103-205	Phase I/II	Children with RR B-ALL	93 total	MTD (phase I) CR (phase II)	CR rate 39% with 52% MRD−
BLAST	Open-label, single-arm phase II	Adults with B-ALL in first or later hematological CR and persistent or recurrent MRD $\geq 10^{-3}$	113	Complete MRD response	78% achieved MRD−





Kantarjian, N Engl J Med 2017; Martinelli, J Clin Oncol 2017; von Stackelberg, J Clin Oncol 2016; Gokbuget, Blook 2018.

Case Presentation

Sept, 2016: 54 yo woman with 1 month history of fatigue, dizziness, headache

- Pancytopenia with 58% blasts
- BM biopsy: 99% blasts, CD19 pos, CD20 neg, BCR-ABL1 neg, Cytogenetics normal, FISH IgH translocation at 14q32, CSF negative
- Enrolled on the E1910 regimen with a modified pediatric intensive regimen

Case Presentation

- Day 28 BM<5% blasts, MRD 3.85% by flow cytometry
- Oct-Dec, 2016: Cycle 2 of induction, BM <5% blasts, MRD+ 0.49%
- Jan, 2017: Intensification w/ HD MTX; BM <5% blasts, MRD+ 0.21%
- Feb, 2017: Randomized on protocol to 2 cycles of blinatumomab over 28 days each cycle
- Apr, 2017: BM biopsy <5% blasts, MRD negative!
- May, 2017: Myeloablative haploidentical BMT from her sister
- Remains in remission, MRD negative with 100% donor chimerism

Administration of blinatumomab (R/R B-ALL)

Induction cycle 1

7-day low-dose infusion

21-day normal dose infusion

14 days treatment-free

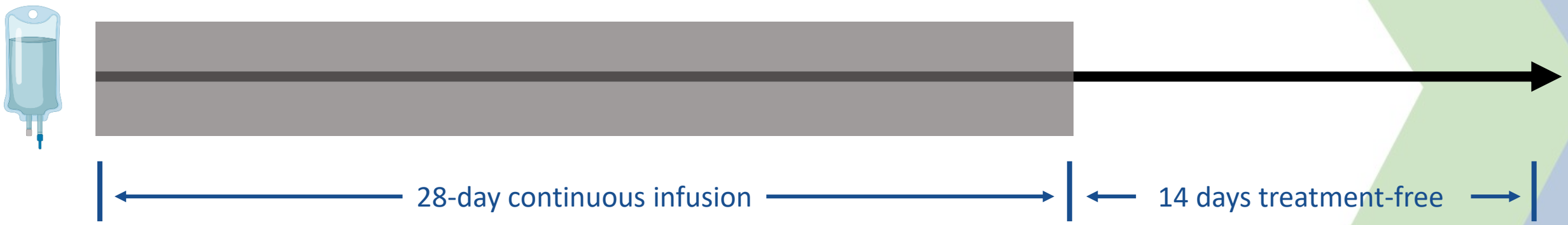
Induction 2, Consolidation

28-day continuous infusion

14 days treatment-free

Blinatumomab prescribing information.

Administration of blinatumomab (MRD+ B-ALL)



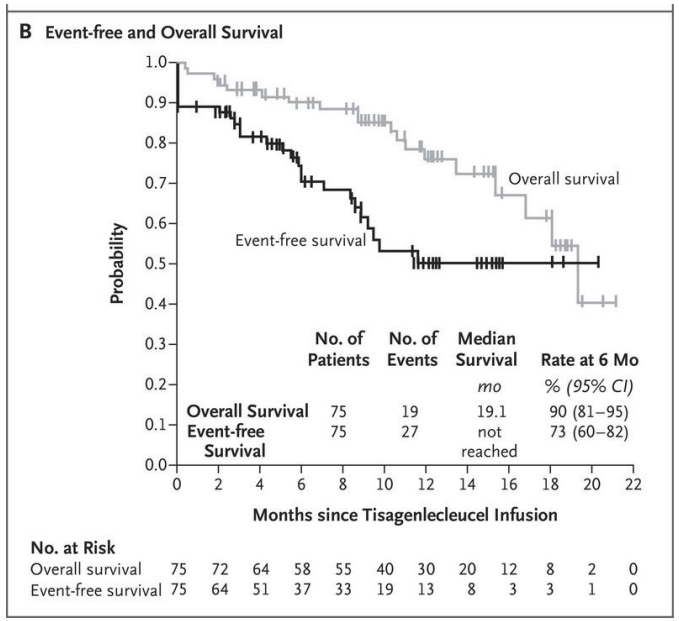
Blinatumomab prescribing information.

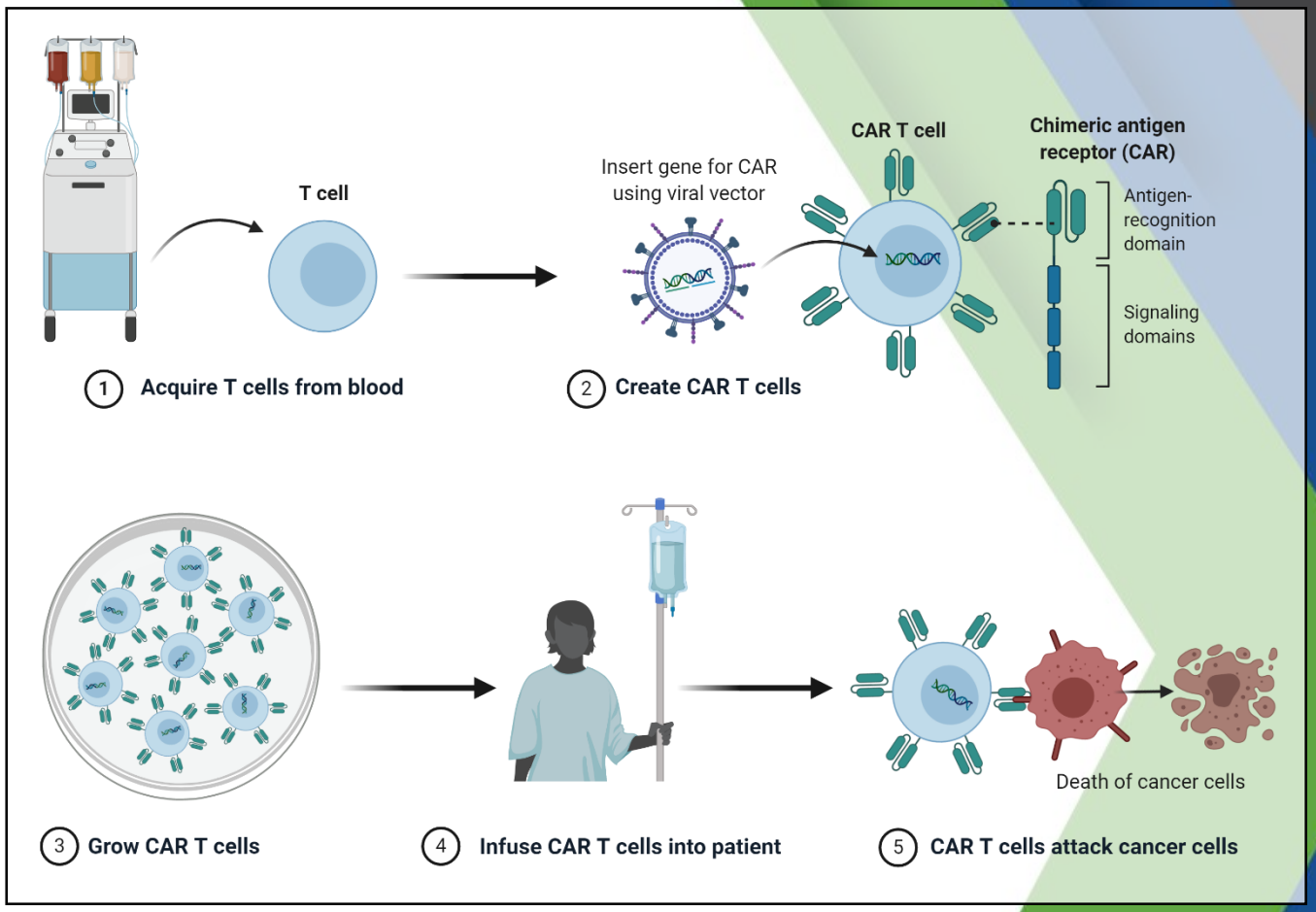
Panel recommendation

Patients with **newly diagnosed B-ALL who are MRD positive** after undergoing induction chemotherapy should be offered blinatumomab.

Tisagenlecleucel

CD19 CAR T therapy





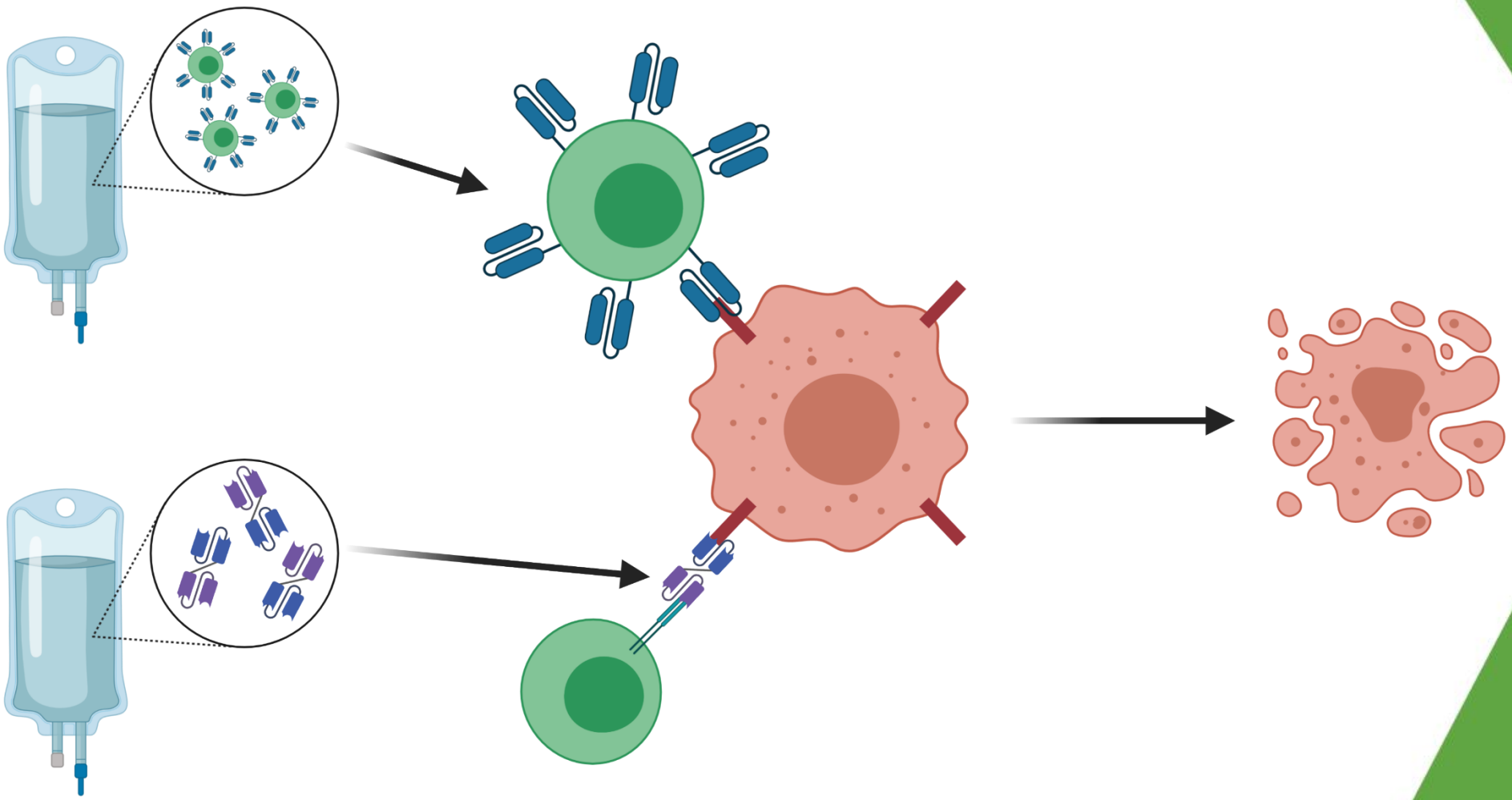
Trial	Study design	Patient population	Enrolled patients	Primary endpoint	Results
ELIANA	Phase I/II	Children/young adults with R/R B-ALL	75	Overall remission rate within 3 months	ORR: 81% 1-year OS: 76%

Maude, N Engl J Med 2018

Panel recommendation

CAR T cell therapy is strongly recommended for patients with relapsed ALL after second-line and/or third-line therapy.

T cell engagers vs. CAR T therapy



T cell engagers vs. CAR T therapy

	CAR T cells	T cell engagers
Structure	Synthetic gene construct encoding an scFv against tumor antigen linked to activation/costimulatory motifs	Recombinant protein with two specificities: one for tumor antigen and one for T cell antigen (usually CD3)
Effector cell types	Engineered CD8+ and CD4+ T cells	Endogenous CD8+ and CD4+ T cells
Immune synapse	Atypical	Typical
Serial killing	Yes	Yes
Killing mechanisms	Perforin and granzyme B, Fas-Fas-L, or TNF/TNF-R	Perforin and granzyme B
Trafficking	Active	Passive
Clinical applications	Pre-treatment lymphodepletion followed by a single infusion	No lymphodepletion; repeat administration and continuous infusions
Specificity	Manufactured for each patient	“Off-the-shelf”
Availability	Limited to REMS program facilities	Most cancer centers

Toxicities with blinatumomab and tisagenlecleucel

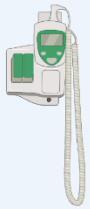
Cytokine release syndrome	Neurotoxicity	B cell aplasia

• Characterized by initial flu-like symptoms
• Can progress to shock-like syndrome
• Variable onset/course, but most common in first cycle
• Pre-treatment with dexamethasone required for blinatumomab
• Management options:
  • IL-6 and IL-6R antagonism
  • Corticosteroids
	• Manifests as confusion, delirium, seizures, cerebral edema
	• Largely unknown mechanisms
	• Incidence increases with more doses, increased age, more prior therapies
	• Management options:
	  • Supportive care
	  • Corticosteroids
		• Due to targeting of CD19, which is expressed by normal B cells
		• May result in hypogammaglobulinemia
		• Infectious prophylaxis required
		• Managed through intravenous immunoglobulin

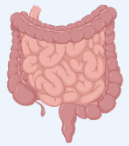
Cytokine release syndrome

Cytokine Release Syndrome symptoms

Constitutional
- Fever +/- rigors
- Malaise/fatigue
- Myalgias
- Arthralgias
- Headache

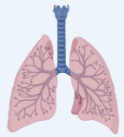


Gastrointestinal
- Nausea/vomiting
- Diarrhea
- Anorexia



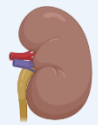
Skin
- Rash

Respiratory
- Tachypnea
- Hypoxia
- Pulmonary edema

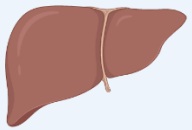


Coagulation
- Elevated D-dimer
- Hypofibrinogenemia +/- bleeding

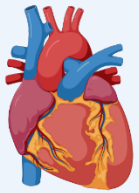
Renal function
- Azotemia



Hepatic dysfunction
- Transaminitis
- Hyperbilirubinemia



Cardiovascular
- Tachycardia
- Hypotension
- Capillary leak
- Widened pulse presssure
- Increased cardiac output (early)
- Potentially diminished cardiac output (late)



Symptoms often mimic sepsis, but treatment of CRS is quite different

Neurotoxicity

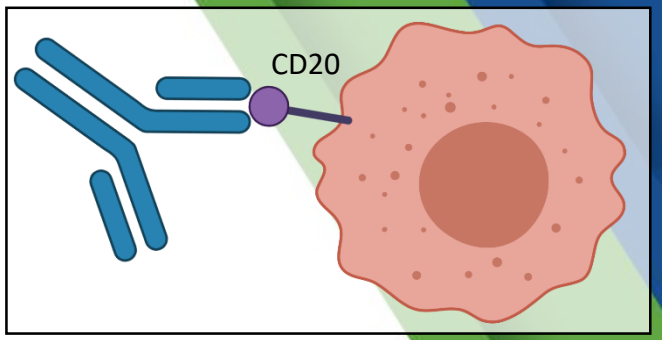
- Also called CAR-T Related Encephalopathy Syndrome (CRES) or IEC-associated neurologic syndrome (ICANS)
  - With CAR T: Occurs in 20-64% of patients, ≥ grade 3 in 11-42%
  - With blinatumomab: Occurs in 50-70% of patients, ≥ grade 3 in 10-15%

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score	7-9	3-6	0-2	0
Depressed level of consciousness	Awakens spontaneously	Awakens to voice	Awakens to tactile stimulus	Unrousable
Seizure	N/A	N/A	Any clinical seizure/on EEG	Prolonged/life-threatening seizure
Motor Findings	N/A	N/A	N/A	Hemi or paraparesis, deep focal motor weakness
Raised ICP/ cerebral edema	N/A	N/A	Focal edema on imaging	Diffuse cerebral edema on imaging, cranial N palsy, Cushing's triad, Decorticate posture

Wang Z. Biomark Res. 2018; Hunter BD. J Natl Cancer Inst. 2019; Jen, Clin Cancer Res 2019.

Rituximab

Note: Rituximab is *not* FDA-approved for this indication, but is widely used off-label



Trial	Study design	Patient population	Enrolled patients	Endpoints	Results
GRAAL	Randomized phase III	Adults with CD20+, Ph− B-ALL	209	EFS	65% with rituximab versus 52% with standard of care; HR=0.66
Thomas et al, JCO 2010	Prospective, non-randomized	Adolescents and adults with de novo Ph− B-ALL	282	CR rate; 3-year CRD rate; OS rate	In the younger (age <60 years) CD20-positive subset, rates of CRD and OS were superior with the modified hyper-CVAD and rituximab regimens compared with standard hyper-CVAD (70% v 38%; p<.001% and 75% v 47%, p=.003). Older patients with CD20-positive ALL did not benefit from rituximab-based chemoimmunotherapy

Recommendations for ALL management

- While a number of immunotherapies do have a role in the treatment of patients with acute leukemia in various settings, **clinical trial enrollment** should be considered at each juncture.
- New, experimental drugs should be administered at centers that have **proper support, infrastructure, and subspecialties**.
- Patients with relapsed B-ALL should receive **immunotherapy as a bridging therapy** to induce remission prior to allo-HCT.
- Outcomes for MRD-positive patients are generally poor; therefore, **enrollment into a clinical trial** should be considered to help achieve an MRD-negative status.

Recommendations for ALL management

- Options for patients with **relapsed ALL after one line of prior therapy** include clinical trial enrollment, treatment with blinatumomab or inotuzumab ozogamicin, or allo-HCT.
- For patients with **relapsed B-ALL and a high disease burden**, inotuzumab ozogamicin should be considered first followed by blinatumomab for persistent disease or MRD positivity, based on the clinical experience and consensus of the Expert Panel.

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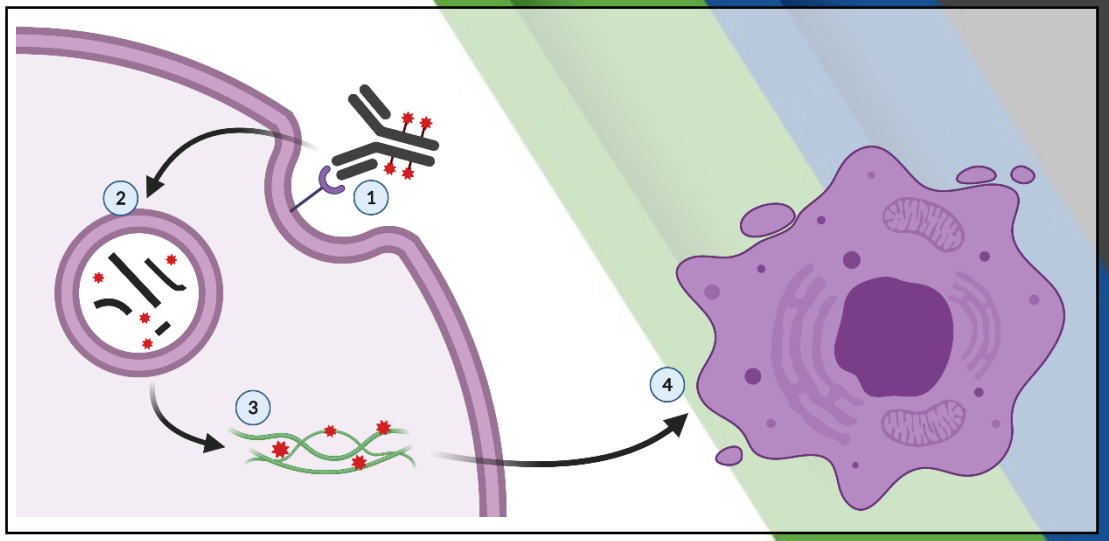
Current therapeutic options for AML

	Drug	Label
FLT3i	**Midostaurin**	In combination with standard cytarabine and daunorubicin induction and cytarabine consolidation chemotherapy, for the treatment of adult patients with newly diagnosed AML who are FLT3 mutation–positive, as detected by an FDA-approved test
	Gilteritinib	For the treatment of adult patients who have relapsed or refractory AML with a FLT3 mutation as detected by an FDA-approved test
IDHi	**Enasidenib**	For the treatment of adult patients with relapsed or refractory AML with an IDH2 mutation as detected by an FDA approved test
	Ivosidenib	For the treatment of AML with a susceptible IDH1 mutation as detected by an FDA-approved test in adult patients with newly-diagnosed AML who are ≥75 years old or who have comorbidities that preclude use of intensive induction chemotherapy; adult patients with relapsed or refractory AML
Unfit	**Venetoclax**	In combination with azacitidine or decitabine or low-dose cytarabine for the treatment of newly-diagnosed AML in adults who are age 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy
	Glasdegib	In combination with low-dose cytarabine, for the treatment of newly-diagnosed AML in adult patients who are ≥75 years old or who have comorbidities that preclude use of intensive induction chemotherapy
2°	**CPX-351**	For the treatment of adults with newly-diagnosed t-AML or AML with myelodysplasia-related changes
CD-33	**Gemtuzumab ozogamicin**	Treatment of newly-diagnosed (single agent or combination) CD33-positive AML in adults; treatment of relapsed or refractory (single agent) CD33-positive AML in adults and in pediatric patients 2 years and older
HMA	**Oral azacitidine**	Treatment of adult patients with AML who achieved 1st CR or CRi following intensive induction chemotherapy and are not able to complete intensive curative therapy

Gemtuzumab ozogamicin

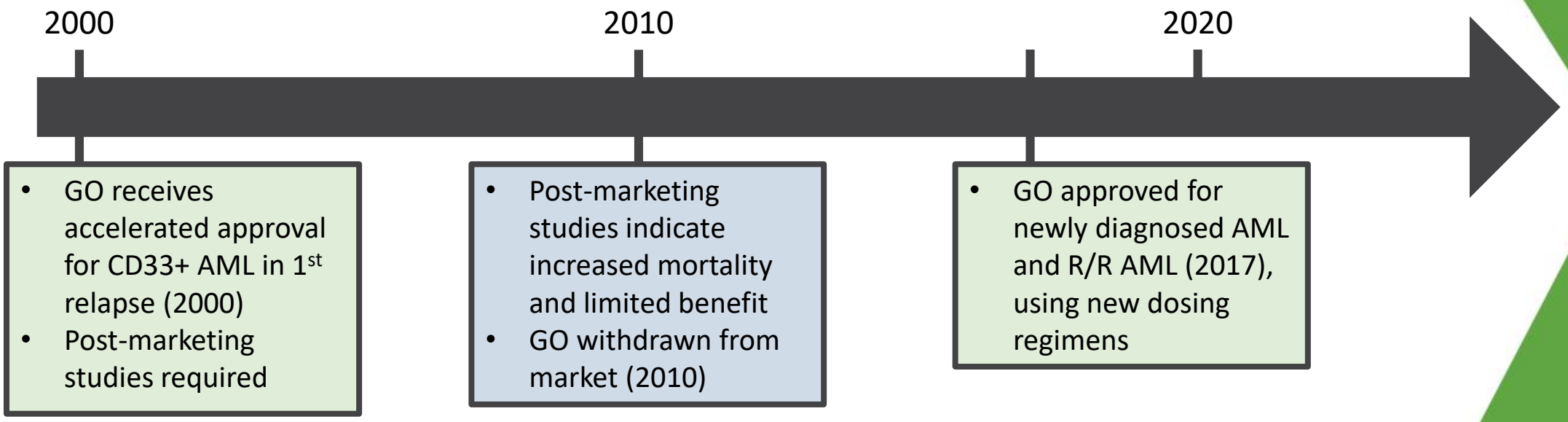
CD33 antibody linked to calicheamicin



Drug	Type	Mechanism	Indications	Dosing regimen
Gemtuzumab ozogamicin	Anti-CD33 antibody-drug conjugate	CD33 antibody + calicheamicin	Newly diagnosed, de novo AML	Combination with daunorubicin and cytarabine
			Newly diagnosed AML	Monotherapy
			R/R AML	Monotherapy

**All indications require premedication with a corticosteroid, antihistamine and acetaminophen.*

History of GO

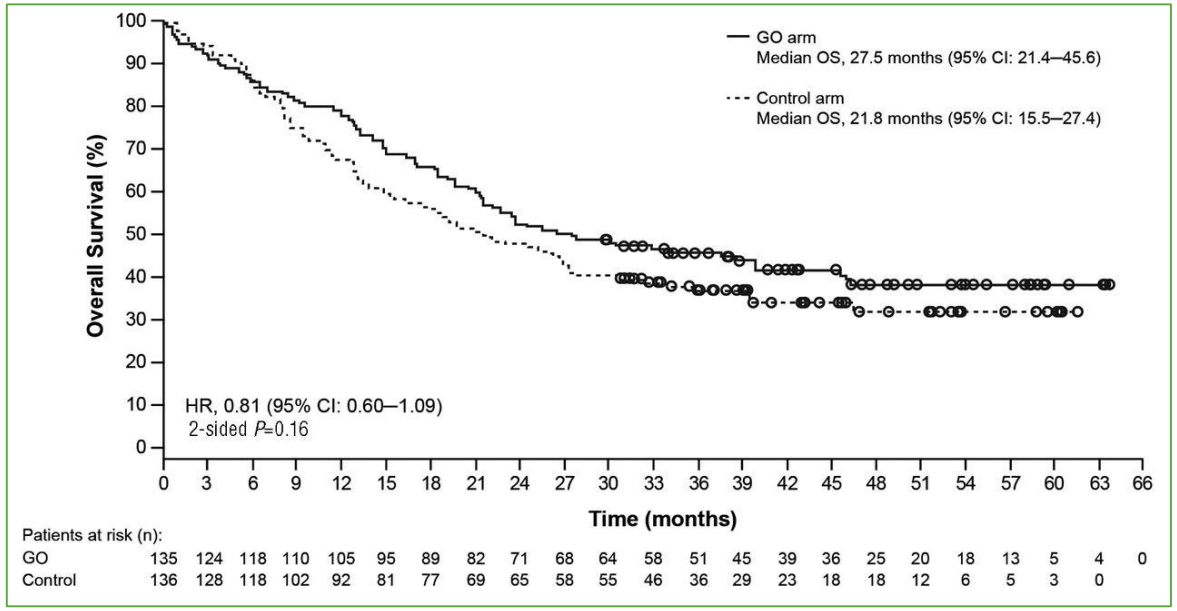


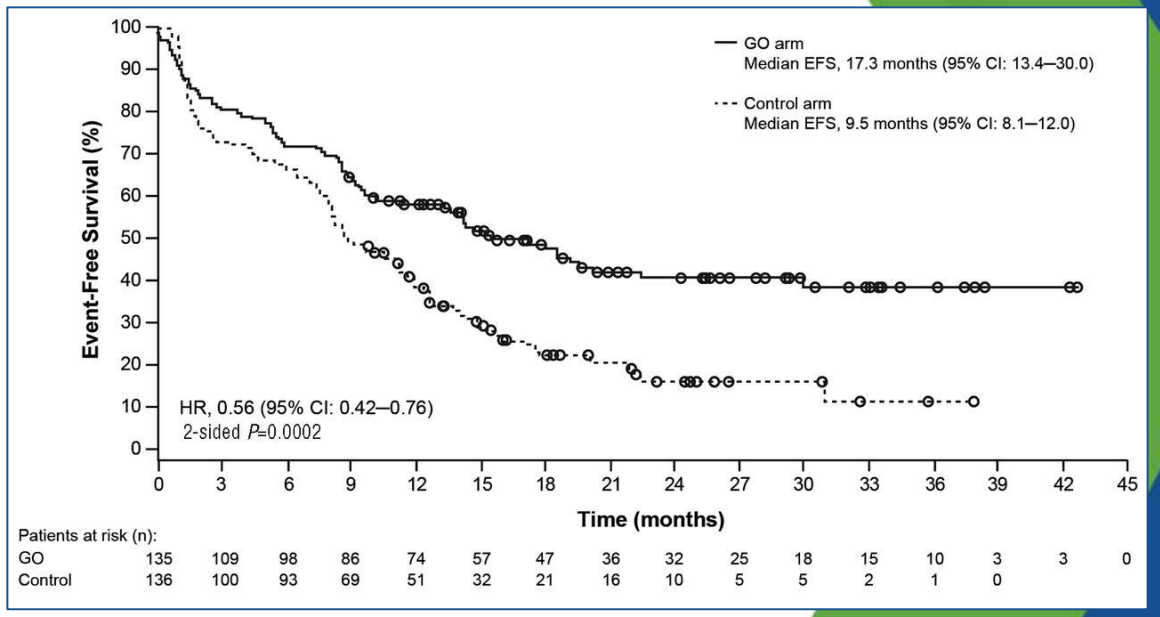
Recent clinical trials of GO

Trial	Study design	Patient population	Enrolled patients	Primary endpoint	Results
ALFA-0701	Randomized phase III	Patients aged 50–70 years with de novo AML	280	EFS	GO arm, median 17.3 months vs control arm, median 9.5 months; p=0.0002
EORTC-GIMEMA AML-19	Randomized phase III	Patients aged 61 years or older with de novo AML unsuitable for intensive chemotherapy	237	OS	Median OS 4.9 months vs 3.6 months (HR, 0.69; 95% CI, 0.53 to 0.90; p=0.005)
Mylo-France 1	Single-arm, open label phase II	Patients aged 18 years or older with RR AML	57	CRR	CRR 26% and 7% CR with incomplete platelet recovery
AAML0531	Multicenter randomized phase III	Patients aged 0 to 29 years with newly diagnosed AML	1022	EFS,OS	GO+chemotherapy improved EFS (3 years: 53.1% v 46.9%, p=0.04) OS, 3 years: 69.4% v 65.4%,p=0.39 GO+chemotherapy versus chemotherapy alone
MRC AML15	Open-label	De novo or secondary AML, 15 years or older	1113 induction; 948 consolidation	CR, DOR, OS	Induction: Patients with favorable risk: OS HR: 0.32 Consolidation: no significant differences

Castaigne, Lancet 2012; Lambert, Haematologica 2019; Amadori, J Clin Oncol 2016; Taksin, Leukemia 2007; Gamis, J Clin Oncol 2014; Burnett, J Clin Oncol 2011

Recent clinical trials of GO – ALFA-0701





Lambert, Haematologica 2019

Toxicities of gemtuzumab ozogamicin

WARNING: HEPATOTOXICITY

See full prescribing information for complete boxed warning.

Hepatotoxicity, including severe or fatal hepatic veno-occlusive disease (VOD), also known as sinusoidal obstruction syndrome (SOS), has been reported in association with the use of MYLOTARG. (5.1, 6.1)

- Current GO regimens of 3-6 mg/m^2 are associated with VOD/SOS incidence of 0-5%
- Incidence correlates with:
  - Higher GO dose
  - Baseline hepatic impairment
  - Prior/subsequent HSCT
- Trials recommended 2-3-month interval between last GO dose and HSCT

Recommendations for AML management

- While many immunotherapy approaches may have a role in the treatment of patients with AML in various settings, **clinical trial enrollment** should be considered at each juncture.
- GO may be added in **favorable and possibly intermediate-risk patients** with AML during induction chemotherapy.
- GO should be considered at the time of AML relapse and in newly diagnosed patients with AML who are **not eligible to receive intensive induction chemotherapy**.
- Outcomes are generally worse after allo-HCT for patients who achieve morphological remission after induction chemotherapy, yet display **persistent MRD**. Further studies are needed to identify therapeutic options for these patients. Therefore, enrollment into a clinical trial should be considered to help achieve an MRD-negative status.

AML case presentation – frontline therapy

A 52 year old policeman is diagnosed with AML. He has a history of smoking, stopped 8 years earlier. Co-morbidities include hypertension controlled with Lisinopril and obesity. His PS is 1. His WBC is 0.7 x 10^9/L, with 8% blasts; platelets are 87 x10^9/L, hemoglobin 7.9 g/dL. BM confirms AML with 74% MPO-positive blasts, t(8;21)(q22;q22). A c-kit mutation is identified. Your proposed initial treatment would be:

A. Hypomethylating agent alone
B. 3+7
C. Glasdegib + low-dose cytarabine
D. Venetoclax + hypomethylating agent
E. CPX-351
F. GO + 3+7
G. Miostaurin + 3+7

Outline

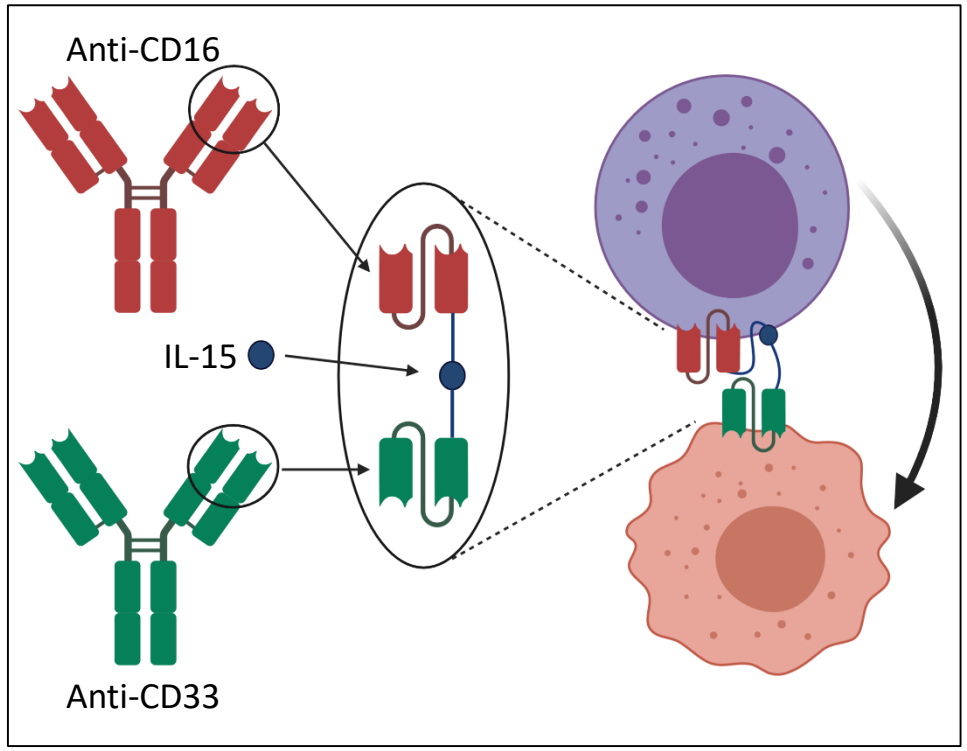
- Introduction to acute leukemia
- Approved immunotherapies for ALL
  - Inotuzumab ozogamicin
  - Blinatumomab
  - Tiasagenlecleucel
- Approved immunotherapies for AML
  - Gemtuzumab ozogamicin
- Emerging immunotherapies for acute leukemia

Emerging immunotherapies for acute leukemia

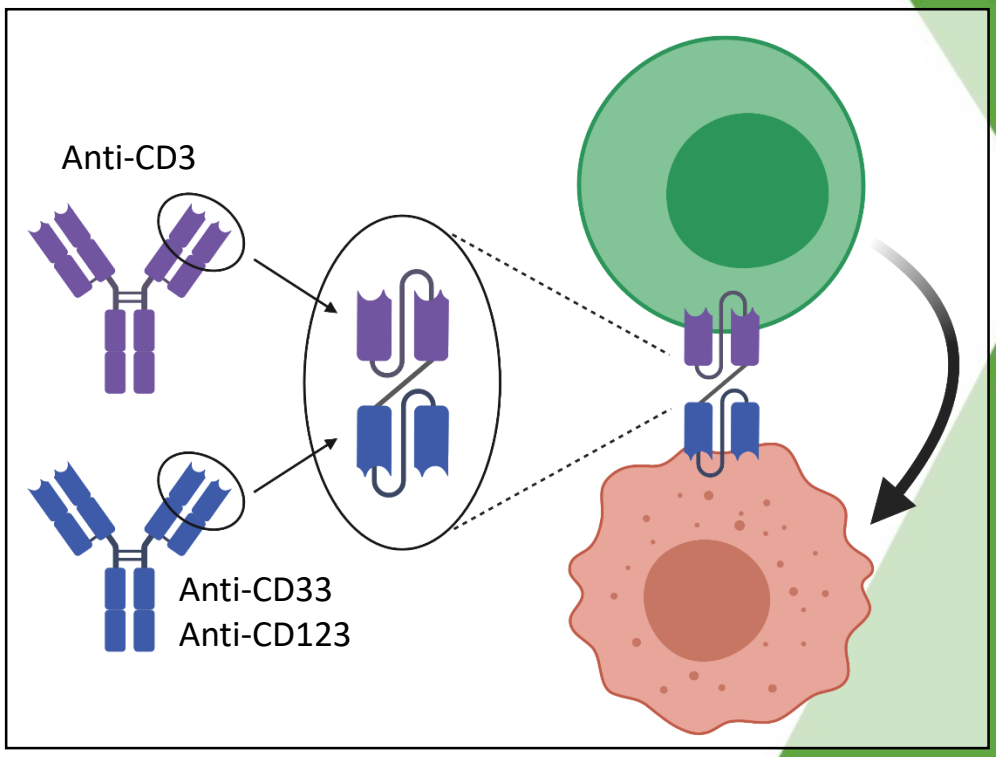
- Immune cell engagers
- Antibody-drug conjugates
- Checkpoint inhibitors
- Adoptive cellular therapies

Immune cell engagers

Trispecific NK cell engagers

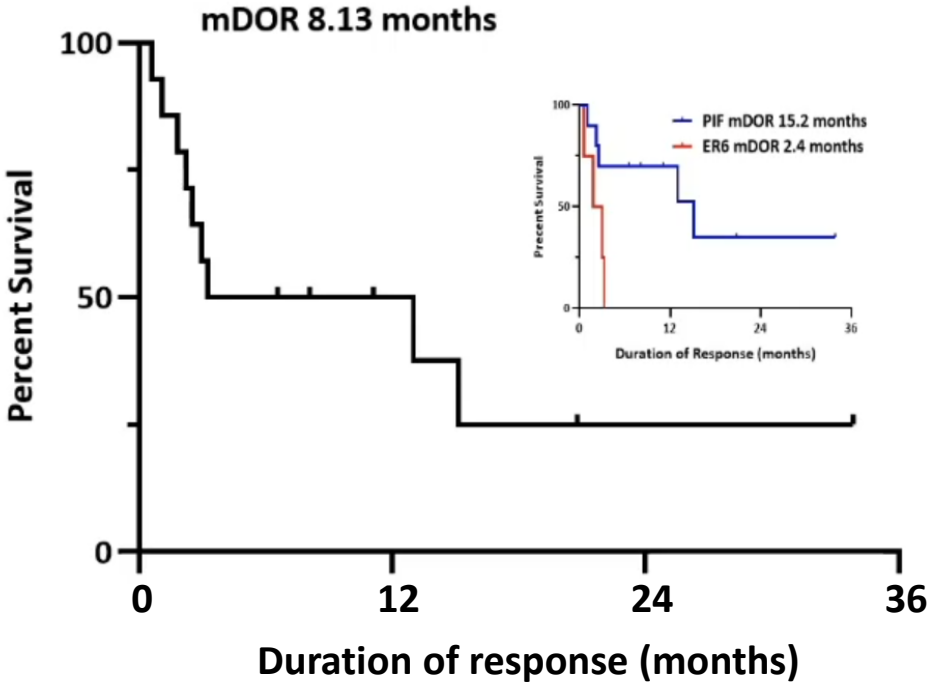


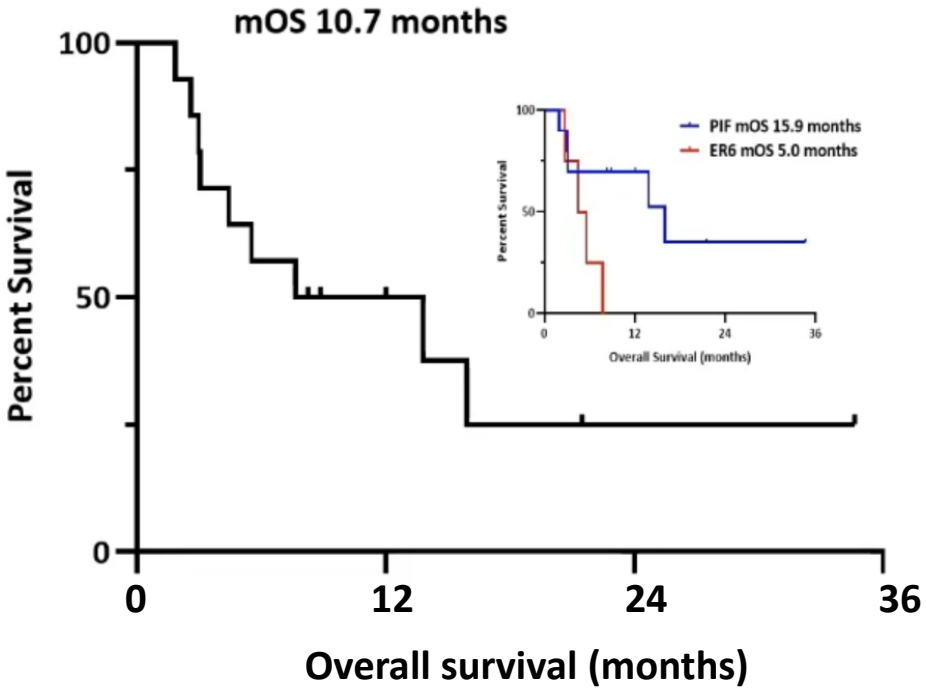
Bispecific T cell engagers



Flotetuzumab – CD3xCD123

	PIF/ER (n=44)	PIF (n=27)	ER (n=17)
CR/CRh	25%	33.3%	11.8%
CR/CRh/CRi	31.8%	37.0%	23.5%
Median BM reduction (%)	-81%	-83%	-13%

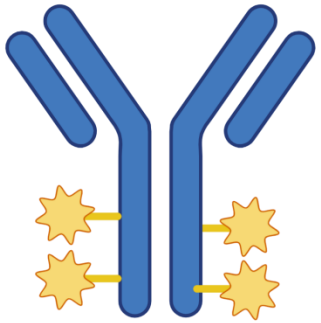




Aldoss, ASH 2020

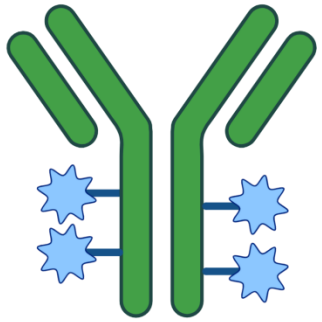
Antibody-drug conjugates

IMGN632



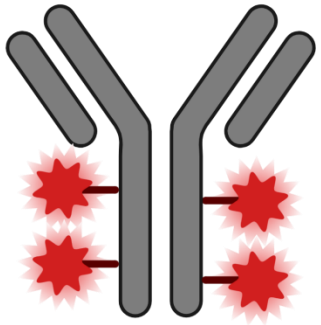
Anti-CD123 antibody
+
Novel DNA-alkylating agent

Brentuximab vedotin



Anti-CD30 antibody
+
MMAE

Iomab-B



Anti-CD45 antibody
+
^{131}I

Checkpoint inhibitors

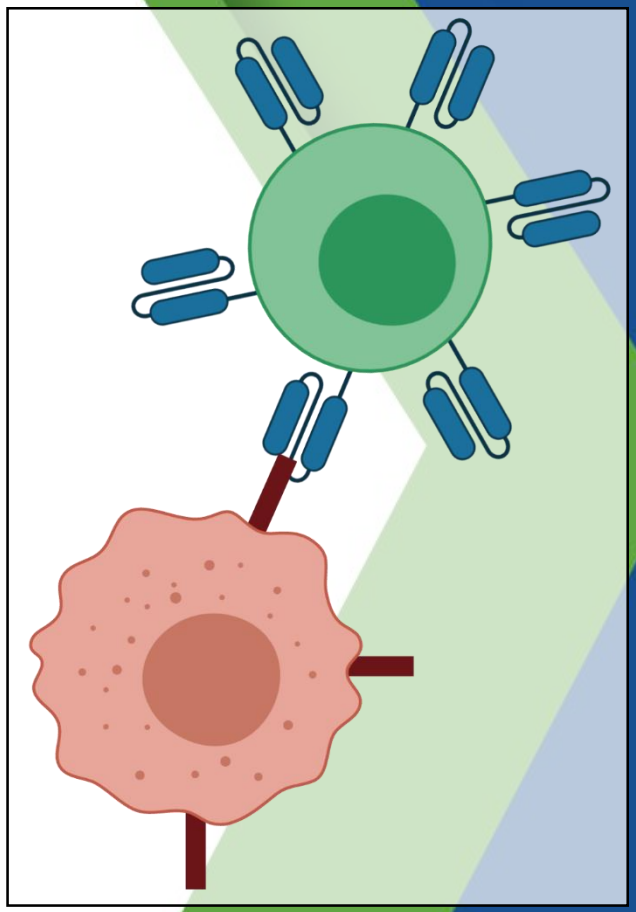
Checkpoint inhibitors + blinatumomab	Checkpoint inhibitors + hypomethylating agents	Checkpoint inhibitor maintenance after allo-HCT	CD47 – macrophage immune checkpoint
• NCT02879695 • Blinatumomab + nivolumab +/- ipilimumab • R/R B-ALL • 5 evaluable patients • MRD-negative CR rate: 80%	• NCT02397720 • Nivolumab + azacitidine • R/R AML • ORR: 33% • CR rate: 15%	• Checkpoint inhibition may improve graft-versus-leukemia effect • May result in unexpected toxicities	• Blocks “do not eat me” signals • 5F9005 study • Magrolimab + azacitidine • Untreated AML • ORR: 63% • CR rate: 42%

Webster, Blood 2018; Daver, Ca Discov 2019; Sallman, ASH 2020

Adoptive cellular therapies

ALL	AML

• CD22 CAR T cells
  • Potential use in CD19-negative disease
  • Reported CR rates: ~73%
  • Relapses often associated with CD22 expression modulation
• Dual CD19xCD20 CAR T cells being developed to prevent/overcome resistance
	• CAR T targets under investigation include:
	  • CD33
	  • CD123
	  • CD7
	  • FLT3
	  • CLL1
	• Off-the-shelf and personalized NK cell products being developed



Fry, Nat Med 2018

Conclusions

- Immunotherapy is an effective treatment option for acute leukemia, aiming to induce durable responses and improve survival
- Combinations of immunotherapies with traditional and newly approved therapies and with strategies to mitigate adaptive resistance by acute leukemia are under investigation
- Successful implementation of novel immunotherapeutic approaches requires, among others, determining the optimal antigenic targets, timing immunotherapy in relation to chemotherapy and allogeneic hematopoietic cell transplantation, determining toxicities to hematopoietic stem cells, clonal evolution of leukemia cells, immune cell exhaustion, and the identification of resistance mechanisms

Acknowledgements

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