POST-NEW ORLEANS 2022
Novità dal Meeting della Società Americana di Ematologia

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Milano
Teatro Dal Verme
2-3-4 Febbraio 2023

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Mila
Teat
2-3

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Sessione Leucemie acute

TERAPIE DI SALVATAGGIO CON ANTICORPI MONOCLONALI E CAR-T

Massimiliano Bonifacio (Verona)

DICHIARAZIONE

MASSIMILIANO BONIFACIO

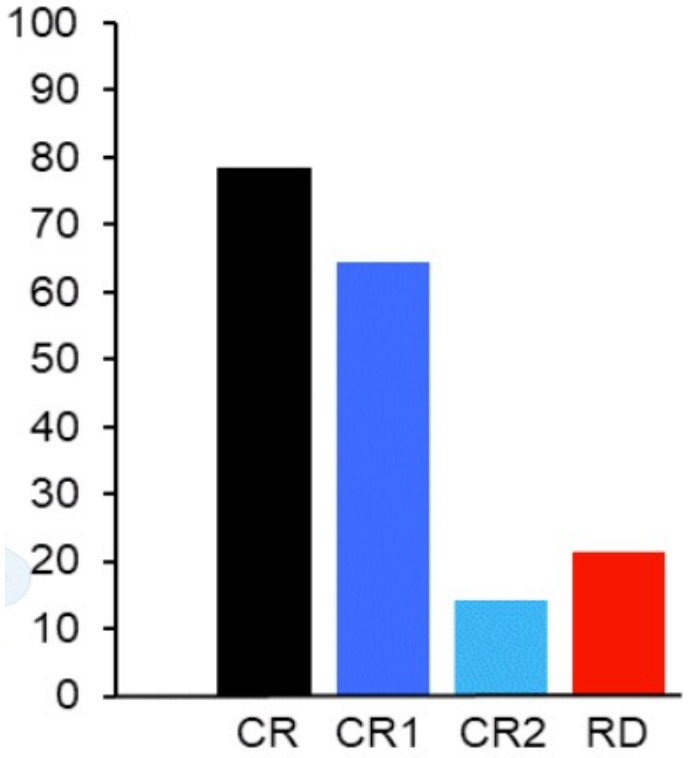
Come da nuova regolamentazione della Commissione Nazionale per la Formazione Continua del Ministero della Salute, è richiesta la trasparenza delle fonti di finanziamento e dei rapporti con soggetti portatori di interessi commerciali in campo sanitario.

- Posizione di dipendente in aziende con interessi commerciali in campo sanitario: **NIENTE DA DICHIARARE**
- Consulenza ad aziende con interessi commerciali in campo sanitario: **NIENTE DA DICHIARARE**
- Fondi per la ricerca da aziende con interessi commerciali in campo sanitario **NIENTE DA DICHIARARE**
- Partecipazione ad Advisory Board: **AMGEN, BRISTOL MYERS SQUIBB, CLINIGEN, INCYTE, PFIZER**
- Titolarietà di brevetti in compartecipazione ad aziende con interessi commerciali in campo sanitario: **NIENTE DA DICHIARARE**
- Partecipazioni azionarie in aziende con interessi commerciali in campo sanitario: **NIENTE DA DICHIARARE**
- Altro

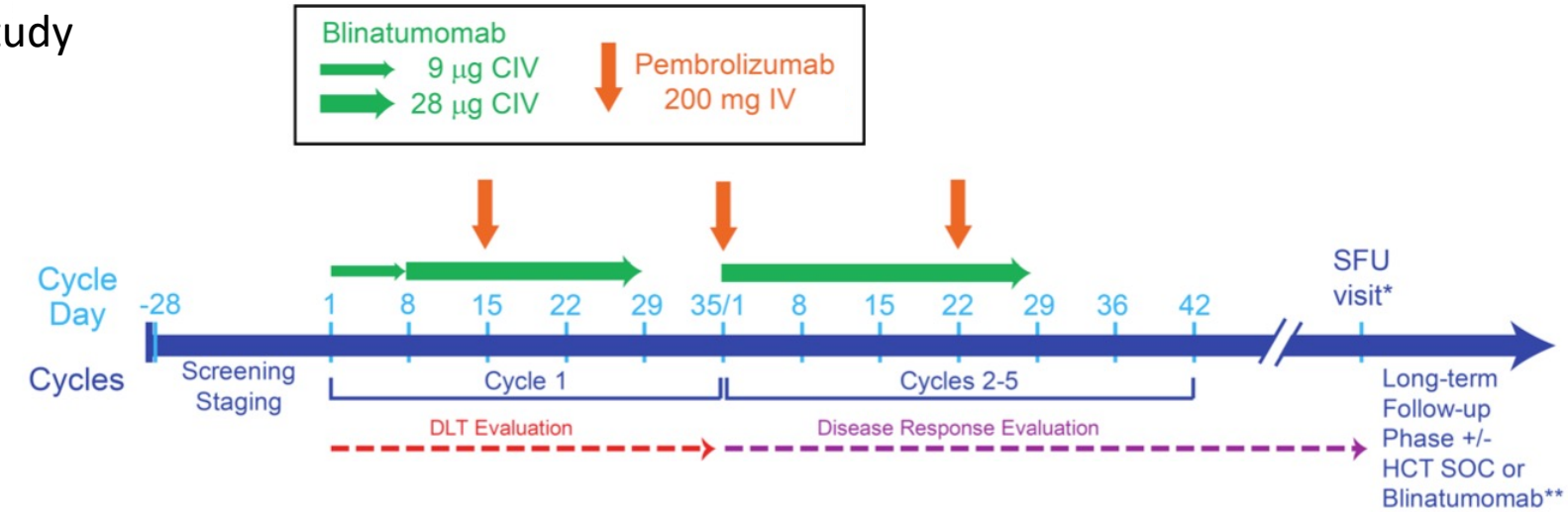
UPDATES ON CURRENTLY AVAILABLE IMMUNOTHERAPY FOR ACUTE LYMPHOBLASTIC LEUKEMIA

Blinatumomab and pembrolizumab in R/R B-ALL

- Single center, open label, phase 1/2 study
- 14 patients



Percentage of patients (n=14) by response category.
CR, complete remission; CR1, complete remission in cycle 1; complete remission in cycle 2; RD, refractory disease.



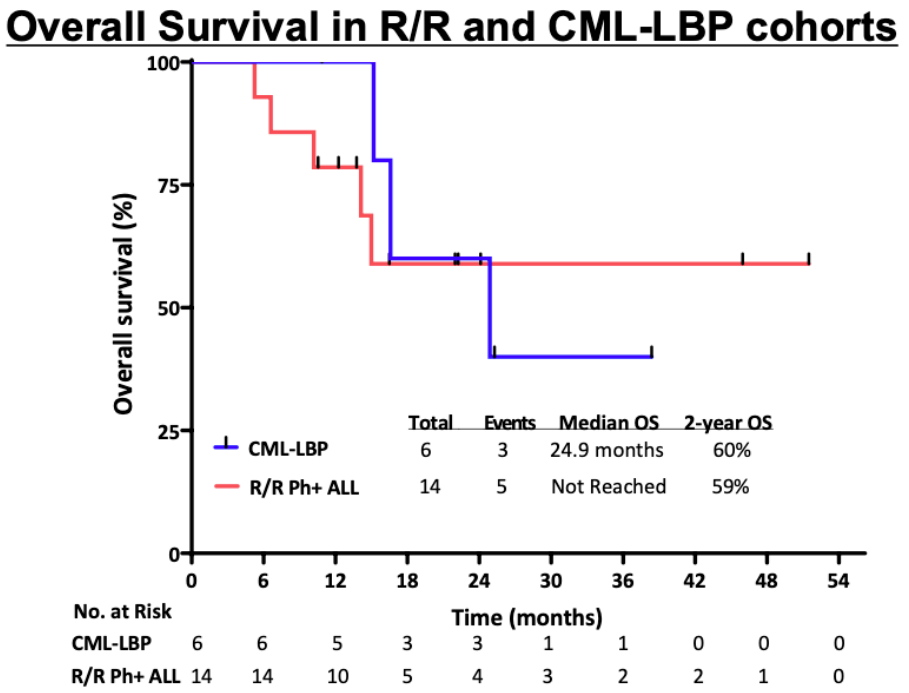
- Complete remission rate is 79% (11/14).
  - 10/14 evaluable patients (71%) achieved flow cytometry MRD- CR after a median of 1 cycle.
- 6/8 (75%) evaluable patients with blasts ≥ 50% achieved CR.
- Responders had higher pre- and post-treatment percentages of CD8+ T-cells.

Blinatumomab and ponatinib in R/R Ph+ ALL

- Single center study of **ponatinib** (cycle 1: 30 mg; cycle 2+ and maintenance: 15 mg) and **blinatumomab** (5 standard cycles) in newly diagnosed Ph+ ALL (reported separately), R/R Ph+ ALL (n=14) and CML in lymphoid blast crisis (n=6)

Response n/N (%)	R/R Ph+ ALL (n=14)	CML-LBP (n=6)
CR/CRi*	12/13 (92)	5/6 (83)
PR	0	1/6 (17)
No response	1/13 (8)	0
CMR	11/14 (79)	2/6 (33)
MMR or better	12/14 (86)	3/6 (50)

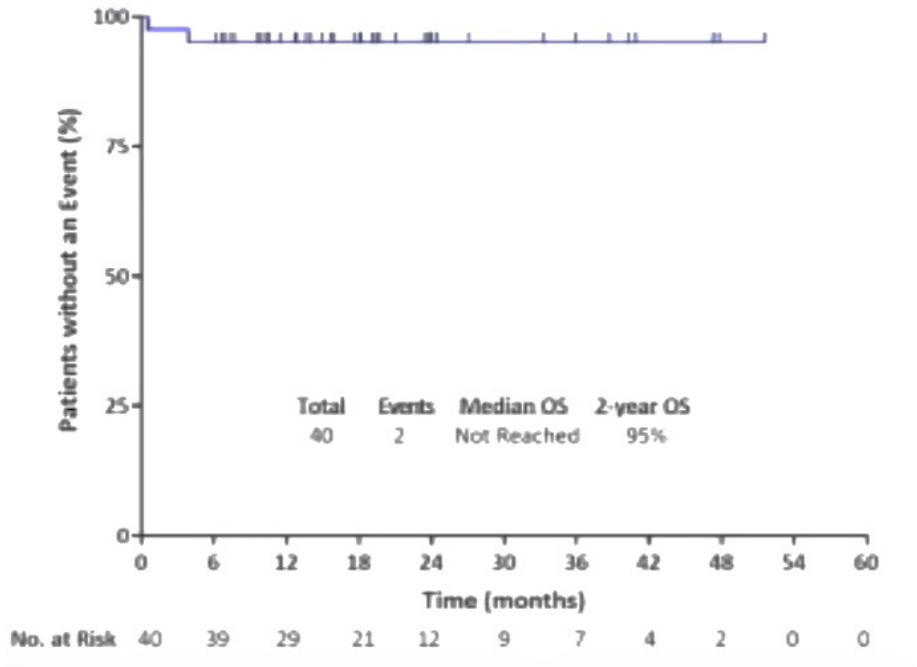
* 1 R/R Ph+ ALL patient was in CR at the start of therapy with detectable BCR::ABL1
Complete remission; CRi, complete remission with incomplete hematologic recovery; CMR, complete molecular response; MMR, major molecular response



Blinatumomab and ponatinib in frontline Ph+ ALL

Response, n/N (%)	Frontline Ph+ ALL N = 40
CR/CRi*	27/28 (96)
CR	26/28 (93)
CRi	1/28 (4)
PR	0
No Response	0
MMR*	36/37 (97)
CMR*	**33/38 (87)**
Early death	1/40 (3)**

Overall Survival in frontline cohort



- Median follow-up: 18 months (range 6-52)

* 12 patients were in CHR, 3 patients were in MMR and 2 patients were in CMR at the start of therapy

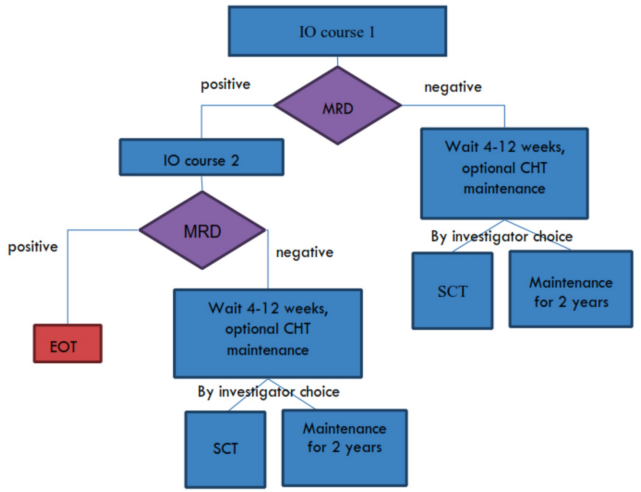
** This patient died from intracranial hemorrhage in the setting of thrombocytopenia from cytoreductive chemotherapy that was administered prior to trial enrollment

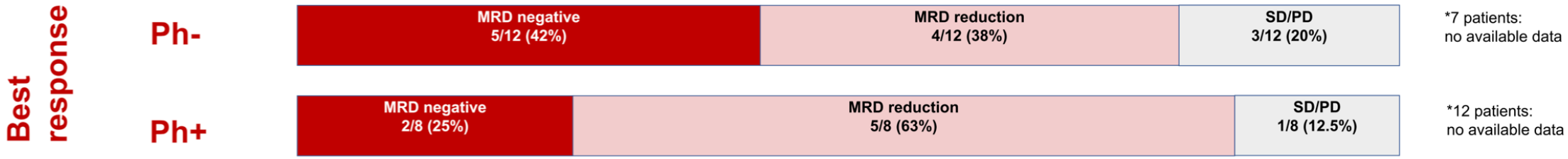
Inotuzumab ozogamicin in MRD+ B-ALL

Gimema multicenter study (ALL2418)

- 39 patients (20 Ph- / 19 Ph+ B-ALL) in CR with MRD^{pos} after induction/consolidation or at least 3 months of TKI
- Median no. of previous lines of therapy: 2
- Previously exposed to blinatumomab: 13%

Treatment scheme: IO 0.5 mg/sqm days 1,8,15 (max 2 cycles), then SCT or chemo/TKI maintenance

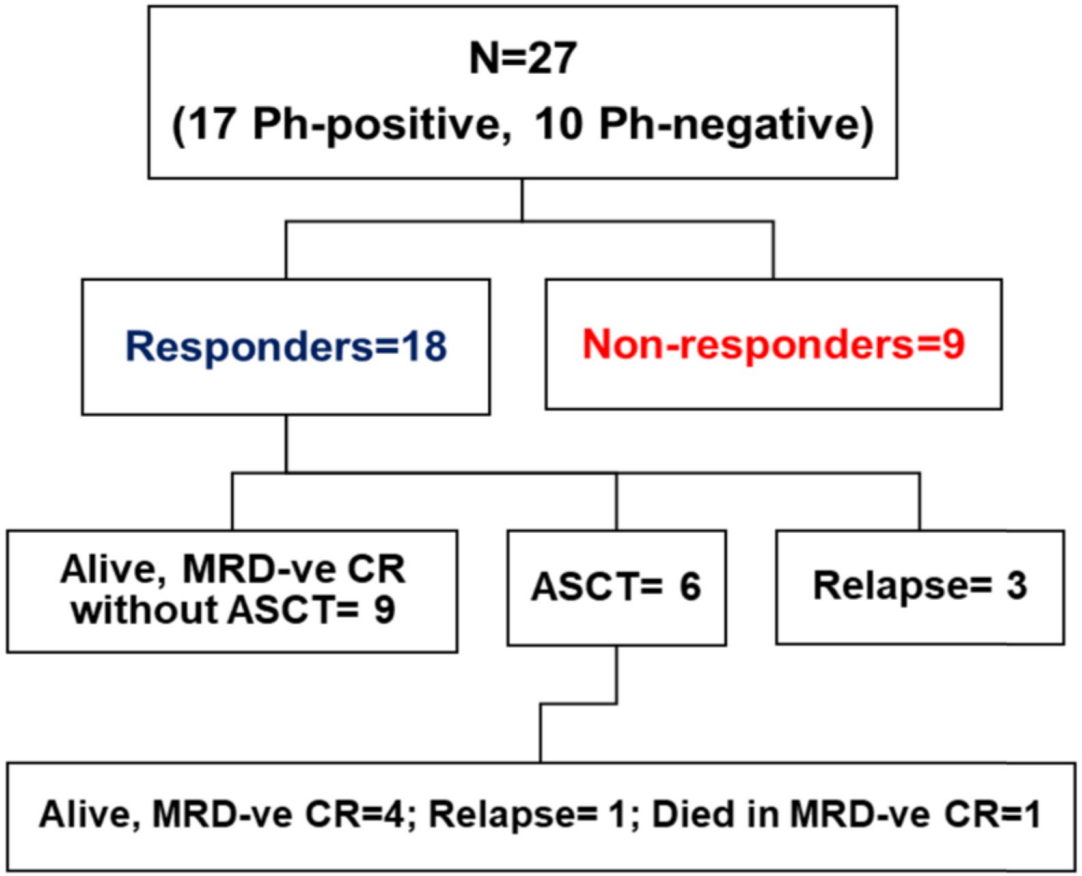




Safety: 1 case of Veno-Occlusive Disease (2.5%)

Inotuzumab ozogamicin in MRD+ B-ALL

MD Anderson phase II study



- **Treatment scheme:** IO 0.6 mg/sqm days 1,8 (cycle 1) then 0.3 mg/sqm days 1,8 (cycles 2-6)
- **Response:**
  - Ph-: MRD^{neg} **80%** (median cycles: 3, range 1-5)
  - Ph+: MRD^{neg} **59%** (median cycles: 4, range 1-6)
- 2 cases of Veno-Occlusive Disease (7%)

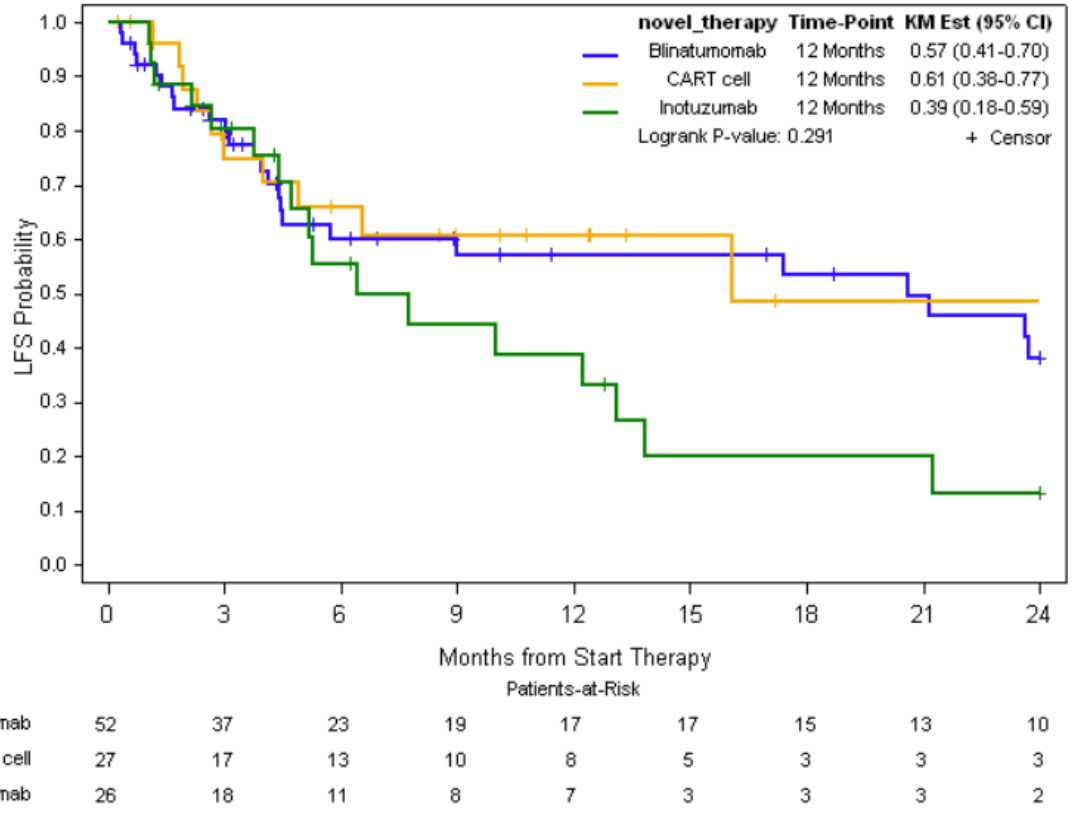
Salvage immunotherapy in Ph-like R/R B-ALL

- Retrospective analysis of patients with Ph-like R/R B-ALL who received at least one novel salvage treatment (blinatumomab, inotuzumab, or CD19CAR T-cells) at City of Hope from 2012 to 2022.

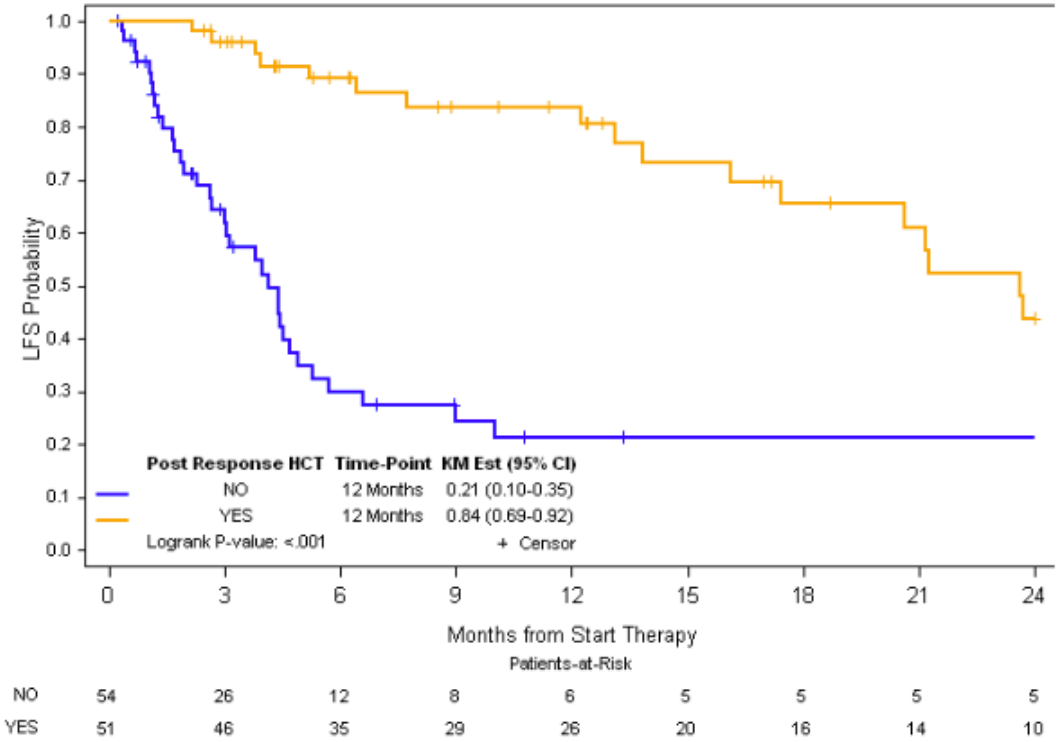
	Blinatumomab (n=83)	Inotuzumab (n=36)	CD19CAR T cells (n=30)	P-value
Median age	36 (18-71)	33 (19-71)	29 (18-66)	0.004
Median lines of therapies	1 (1-6)	2 (1-6)	3 (1-7)	<0.001
Median BM blasts	50% (0-95)	80% (0-100)	60% (0-97)	0.065
Extramedullary disease	0	2 (6%)	8 (27%)	<0.001
Prior alloHCT	10 (12%)	8 (22%)	17 (57%)	0.002
CR/CRi rate	**63%**	**72%**	**90%**	
MRD^{neg} in responders	86%	73%	96%	
AlloHCT realization rate in responders	50%	50%	44%	

Salvage immunotherapy in Ph-like R/R B-ALL

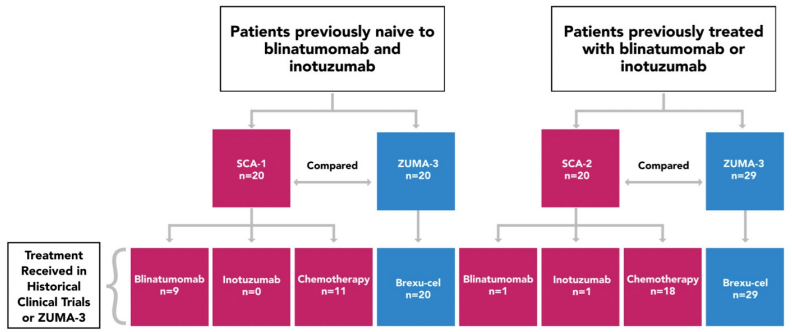
LFS according to received treatment



LFS according to post response HCT



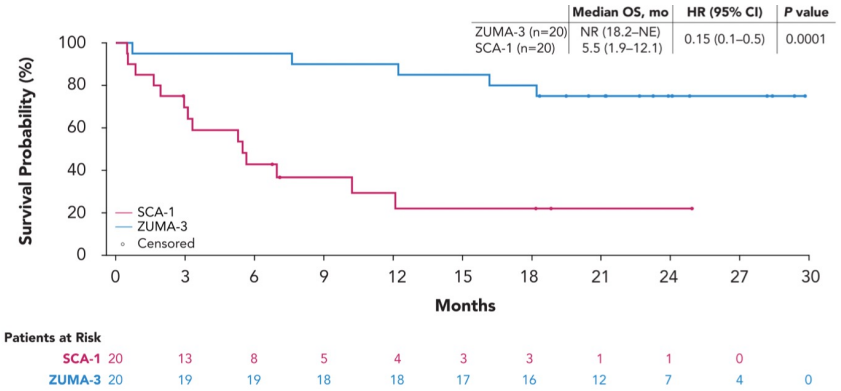
CAR-T cells in ALL: update of the ZUMA-3 study



Brexu-cel, brexucabtagene autoleucel; SCA, synthetic control arm.

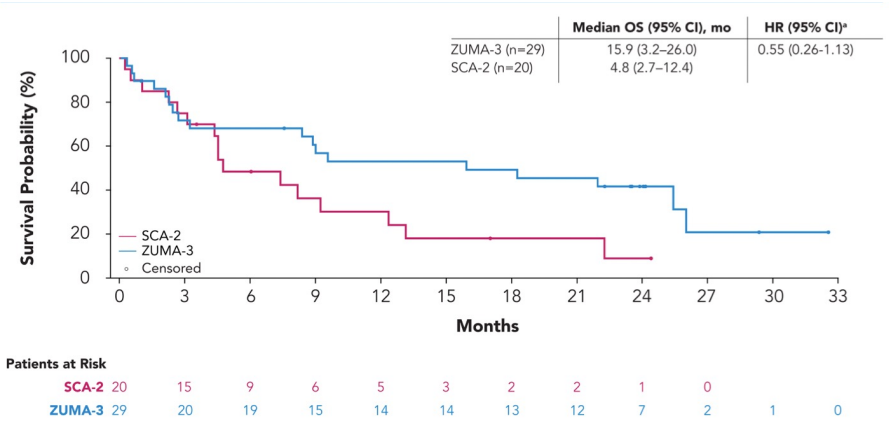
	Blinatumomab and Inotuzumab-Naive Patients	
	ZUMA-3 (n=20)	SCA-1 (n=20)[a]
Overall CR/CRi rate, % (95% CI)[b]	85.0 (62.1-96.8)	35.0 (15.4-59.2)
CR rate, % (95% CI)	75.0 (50.9-91.3)	30.0 (11.9-54.3)
Treatment difference (95% CI)	50.0 (17.9-73.7)	
Odds ratio (95% CI)	10.5 (2.3-48.7)	
P value	0.0031	
AlloSCT rate, % (95% CI)	35.0 (15.4-59.2)	20.0 (5.7-43.7)
Treatment difference (95% CI)	15.0 (–13.7-42.4)	
Odds ratio (95% CI)	2.2 (0.5-9.0)	
P value	0.4801	
Median RFS (95% CI), months	20.5 (2.8-NE)	0.0 (0.0-4.6)
Hazard ratio (95% CI)	0.18 (0.1-0.5)	
P value	0.0004	
Median OS (95% CI), months	NR (18.2-NE)	5.5 (1.9-12.1)
Hazard ratio (95% CI)	0.15 (0.1-0.5)	
P value	0.0001	

OS in patients previously naive to blinatumomab and inotuzumab



HR, hazard ratio; mo, month; NE, not estimable; NR, not reached; OS, overall survival; SCA, synthetic control arm.

OS in patients previously treated with blinatumomab or inotuzumab



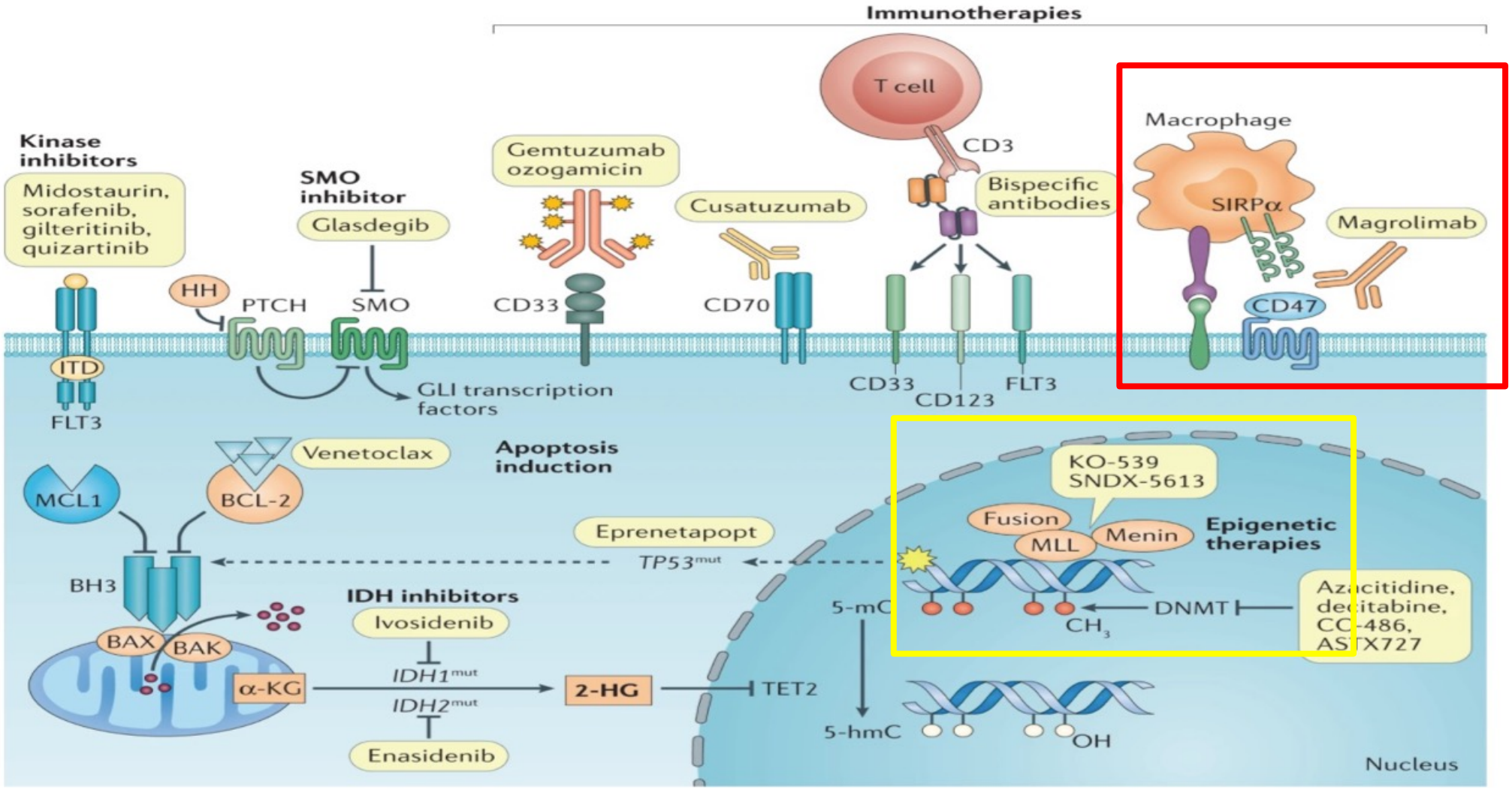
[a]Adjusted hazard ratio (95% CI) is based on the Cox proportional hazards model with treatment group, baseline bone marrow blasts (%) and number of prior lines of therapy (≤2 vs. >2) as the covariates. *P* value was not significant
mo, month; OS, overall survival; SCA, synthetic control arm.

Other clinical abstracts of CAR in ALL at ASH 2022

Abstract	Main results
Lu et al. (abs#980) Analysis of 60 patients with Relapsed or Refractory (R/R) T-cell Acute Lymphoblastic Leukemia (T-ALL) and T-cell Lymphoblastic Lymphoma (T-LBL) Treated with CD7-Targeted CAR-T Cell Therapy	• MRD^{neg} CR/CRi rate at day 28 post CAR: 94.4% • Patients with TP53 mutations, SIL::TAL1 or complex genetics had poorer PFS • At relapse 33% of patients lost CD7 expression
Jeyakumar et al. (abs#982) CD22 CAR T Cells Demonstrate Favorable Safety Profile and High Response Rates in Pediatric and Adult B-ALL: Results of a Phase 1b Study	• 8/8 (100%) adult and 4/8 (50%) pediatric patients achieved CR, with 63% MRD^{neg} • Responses were short-lived and associated with CD22+ expression
Myers et al. (abs#983) CD22-Targeted CAR-Modified T-Cells Safely Induce Remission in Children and Young Adults with Relapsed, CD19-Negative B-ALL after Treatment with CD19-Targeted CAR T-Cells	• CR rate: 77% (13/17), including patients previously refractory to inotuzumab • Median RFS: 5.3 months • 1-year OS: 37.5%
Roddie et al. (abs#3318) Safety, Efficiency and Long-Term Follow-up of AUTO1, a Fast-Off Rate CD19 CAR in Relapsed/Refractory B-Cell Acute Lymphoblastic Leukaemia and Other B-Cell Malignancies	• 8/20 (40%) are in ongoing CR at a median FU of 36 months post-AUTO1, without further therapies

A NOVEL CONCEPT: IMMUNOTHERAPY AS SALVAGE TREATMENT IN ACUTE MYELOID LEUKEMIA

Novel targets for precision medicine in AML

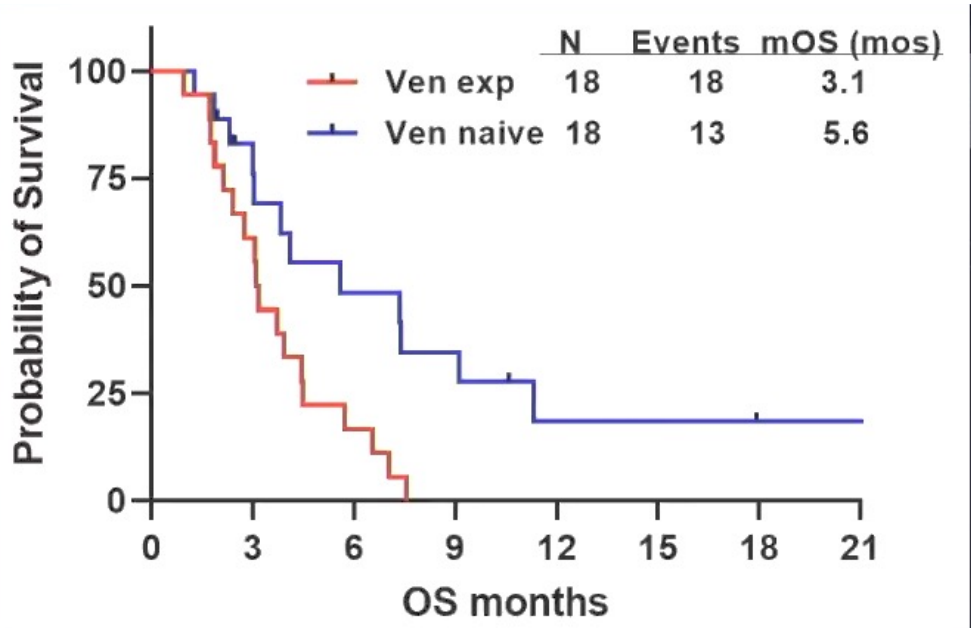


Dohner et al. *Nat Rev Clin Oncol*. 2021;18(9):577-590

Magrolimab, azacitidine and venetoclax in R/R AML

- Phase 1/2 study: **magrolimab** 1 mg/kg C1D1 and C1D4, 15 mg/kg C1D8, 30 mg/kg CD1D11 and subsequent doses (weekly), **azacitidine** 75 mg/sqm D1-D7, **venetoclax** 400 mg/day D1-D21/D28 every 28 days
- 36 patients with R/R AML (*2 cohorts according to prior exposure to venetoclax*)
- Prior lines of treatment: median 2 (range 1-5), including HMA (64%) and alloHCT (28%)
- Very high risk population: adverse cytogenetics 75%, TP53 mutation 64%

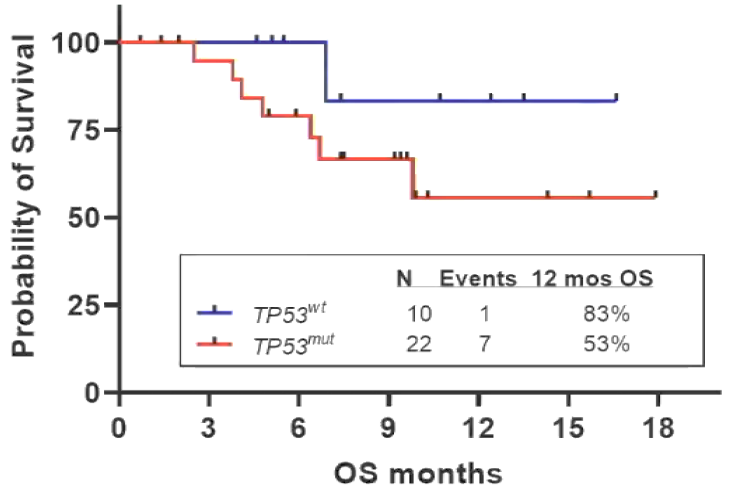
	Venetoclax exposed (n=18)	Venetoclax naïve (n=18)
CR/CRi	2 (11%)	8 (44%)
MLFS	0	1 (5%)
Time to best response	80 days (71-89)	41 days (31-126)
Median of cycles	2 (1-4)	2 (1-7)
8-week mortality	3 (17%)	1 (5%)



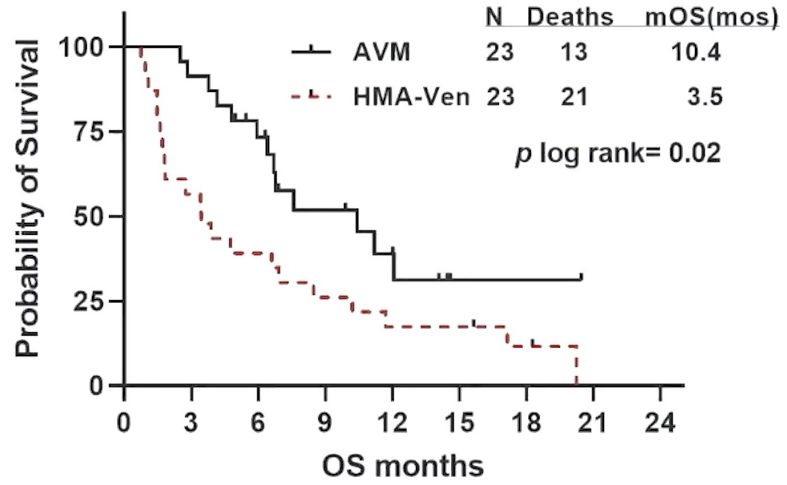
Magrolimab, azacitidine and venetoclax in frontline AML

- 43 patients front-line (33 *de novo*, 10 sAML)
- Very high risk population: adverse cytogenetics 65%, TP53 mutation 63%

	TP53^{mut} (n=27)	TP53^{wt} (n=16)
CR/CRi	17 (63%)	14 (87%)
MLFS	3 (11%)	1 (6%)
Time to best response	49 days (20-130)	33 days (20-88)
Median of cycles	3 (2-6)	3 (1-17)
8-week mortality	0	0



Propensity matched analysis AVM vs HMA-Ven in TP53^{mut}



Menin inhibitors in KMT2A-rearranged or *NPM1* mutant AML

AUGMENT-101 (SNDX-5613, revumenib)

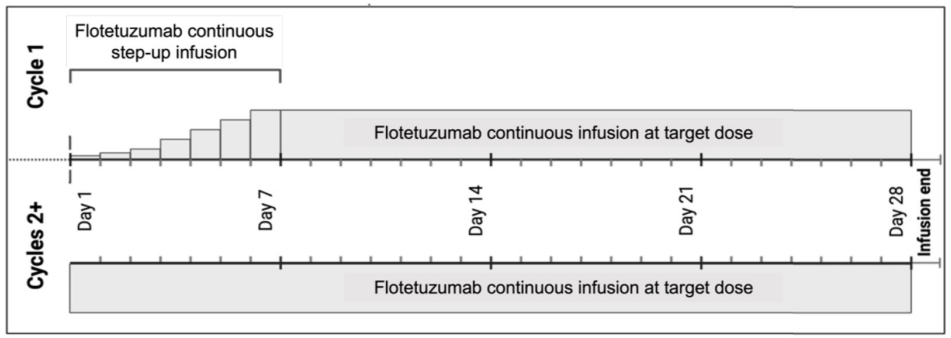
- Phase 1/2 study in R/R *KMT2A-r* or *NPM1m* AML (n=60)
- ORR: 53%
- CR/CRh rate: 30% (33% in *KMT2Ar*, 21% in *NPM1m*)
- Median duration of response: 9.1 months (2.7-NR), median OS: 7.0 months (4.3-11.6)
- Safety: differentiation syndrome (16%) and asymptomatic QTc prolongation (dose-limiting toxicity)

KOMET-001 (KO-539, ziftomenib)

- Phase 1/2 dose escalation in all comers (n=30) and validation / expansion in *KMT2A-r* or *NPM1m* (n=24) R/R AML
- KMT2A-rearranged (16 patients): ORR rate 18.9%, CR rate 0%
- NPM1-mutated (20 patients): ORR rate 40%, CR rate 30%
- Safety: differentiation syndrome and pneumonitis

Issa et al. Abs#63. Erba et al. Abs#64.

Flotetuzumab (CD123xCD3) in pediatric and young R/R AML



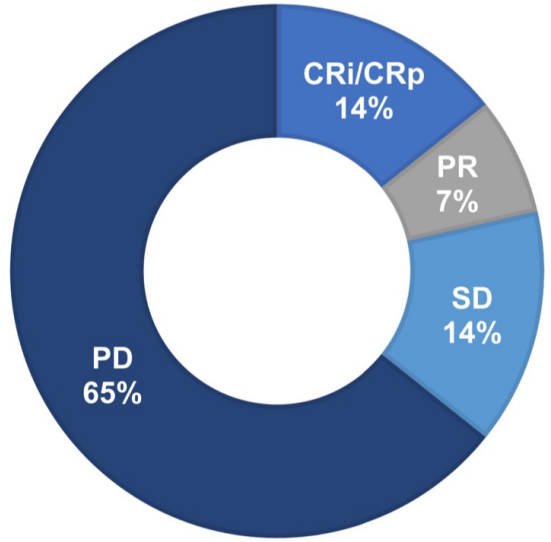
Dose Level 1

- 7 patients treated
  - Non-evaluable due to PD (n=1)
- Cycle 1 DLT
  - Grade 4 CRS (n=1)
- Cycle 2 DLT
  - None

Dose Level 2

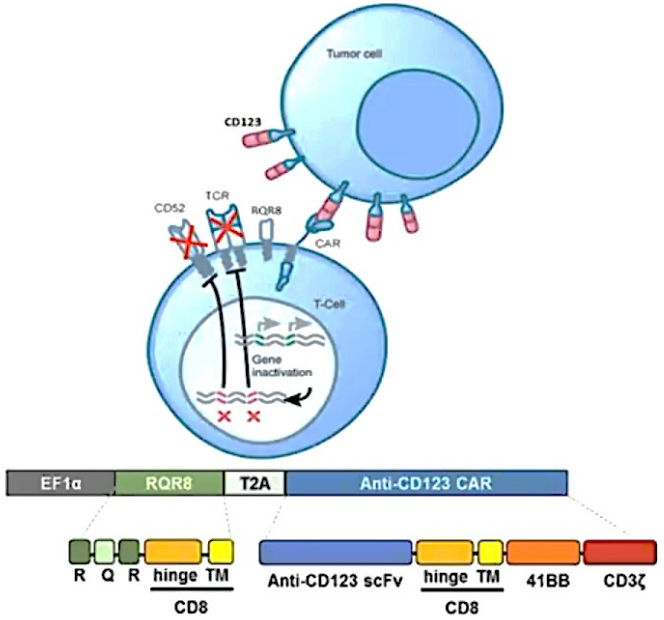
- 8 patients treated
  - Non-evaluable due to PD (n=3)
- Cycle 1 DLT
  - Grade 3 creatinine elevation (n=1)
- Cycle 2 DLT
  - Grade 3 CLS, Grade 4 pulmonary edema, Grade 4 pericardial effusion, Grade 4 pleural effusion, Grade 5 myocarditis (n=1)

Summary of adverse events	Grade 3/4	Any grade
• Anemia	27.3%	45.5%
• Lymphocyte count decreased	36.4%	36.4%
• Trhombocytopenia	36.4%	36.4%
• Neutrophil count decreased	27.3%	27.3%
• White blood cell decreased	27.3%	27.3%
• Cytokine release syndrome	18.2%	81.5%
• Capillary leak syndrome	36.4%	63.6%



AMELI-01: a phase 1 trial of anti-CD123 allogeneic CAR-T

- Phase 1, open-label, dose-escalation trial of UCART123v1.2 given with two different conditioning regimens
- Genetically modified allogeneic "Off-the-Shelf" T-cell product from non-HLA-matched healthy donors
  - *TRAC* disrupted to eliminate TCR$\alpha\beta$ from the CAR cell surface to avoid GvHD
  - *CD52* disrupted to eliminate sensitivity of CAR to conditioning regimen containing alemtuzumab



AMELI-01 trial design

FC arm

Fludarabine 30 mg/sqm x 4d + Cyclophosphamide 750 mg/sqm x 3d

FCA arm

FC + Alemtuzumab 12 mg/d x 4d

→ UCART123v1.2 (single dose)

DL from 1.25 x10^5 cells/kg to 3.30 x10^6 cells/kg

- 18 patients, median age 57 years, 4 median prior lines of treatment
- The addition of alemtuzumab to conditioning improves the leukemia clearance
- Anti-leukemic activity (2 CR) observed at the dose level of 6.25 x 10^5 cells/kg
- Protocol amendment for phase 2: addition of a second dose after 10-14 days to allow CAR expansion and activity

Sallman et al. Abs#981.

Other clinical abstracts of CAR in AML at ASH 2022

Abstract	Main results
Enhinger et al. (abs#979) Phase 1 Dose Escalation Study of the Rapidly Switchable Universal CAR-T Therapy Unicar-T-CD123 in Relapsed/Refractory AML	• n=14 • 4 PR, 2 CRi, 1 CR MRD^{neg}
Sallman et al. (abs#4633) Phase 1/1b Safety Study of Prgn-3006 Ultracar-T in Patients with Relapsed or Refractory CD33-Positive Acute Myeloid Leukemia and Higher Risk Myelodisplastic Syndromes	• 15 patients (11 AML, 1 CMML, 3 HR MDS) • 1 CRi, 1 CRh, 1 PR in the AML cohort
Naik et al. (abs#2003) Safety and Anti-Leukemic Activity of CD123-CAR T Cells in Pediatric Patients with AML: Preliminary Results from a Phase 1 Trial	• n=6 • 1 CR, 1 MRD^{pos} CR
Shelikhova et al. (abs#2010) Allogeneic Donor-Derived Myeloid Antigen Directed CAR-T Cells for Relapsed/Refractory Acute Myeloid Leukemia in Children after Allogeneic Hematopoietic Stem Cell Transplantation: Report of Three Cases	• CART123 n=1, CART33 n=2 • 2 CRi, 1 MRD^{pos} CR

Conclusions

- Blinatumomab and Inotuzumab ozogamicin are the current standards for **Relapsed/Refractory B-ALL**, including patients with unfavorable genetic risk, e.g. Ph-like. The combination of blinatumomab and checkpoint inhibitors might improve efficacy.

- The «chemo-free» combination of ponatinib and blinatumomab determines high rates of complete molecular response in frontline and **R/R Ph-positive ALL**.

- The use of inotuzumab ozogamicin in the setting of **MRD^{pos} B-ALL** seems promising.

- Immune-based therapy is a novel strategy in **relapsed/refractory AML**, and several targets have been identified. CAR-T cells demonstrated activity in R/R AML (lower than in ALL), however their use is still hampered by the on-target off-tumor toxicity.