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SOHO 2019 | Update on chemotherapy-free treatments for R/R AML

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Chemotherapy resistance and relapse are two of the main causes of death in patients with acute myeloid leukemia (AML). Thus, the development of novel chemotherapy-free approaches is crucial for these patients. Such targeted antibody-based or cell-based therapies including; chimeric antigen receptor T cells (CAR-T), antibody-drug conjugates (ADCs), bispecific T-cell engagers (BiTEs) and dual affinity retargeting (DART) antibodies.

During the 2019 Society of Hematologic Oncology (SOHO) annual meeting, in Houston, TX, US, two presentations showcased chemotherapy-free approaches for the treatment of AML. Elizabeth Budde from City of Hope National Medical Center, Duarte, CA, US, presented the current landscape of CAR-T trials for AML[1], while, John DiPersio from Washington University School of Medicine in St. Louis, St. Louis, MO, US, spoke about the use of ADCs, DARTs and BiTEs in the clinical setting of AML.[2] We hereby provide a summary of these talks regarding the latest updates on these chemotherapy-free approaches for the treatment of AML.

CAR-T trial landscape in AML[1]

One of the major challenges of CAR-T therapy for AML is the identification of a good CAR-T target, which should only or primarily be expressed by leukemic stem cells, so as to avoid CAR-T cell resistance and off-target toxicities. Such a target is yet to be identified with multiple options being evaluated pre-clinically (i.e. CD7, CD25, CD32, CD38, CD47 etc.). At the moment, the CAR-T constructs that have made it to the clinic target CD33, CD123, NKG2DL or LewisY.[1] Some of the ongoing clinical trials using the CAR-Ts mentioned above are shown in **Table 1**.

Table 1. Ongoing CAR-T trials in AML[1]

CAR-T target	Clinical trial ID	CAR	T cell source	Patient age (years)	Lymphodepletion	CAR-T dose	Efficacy & safety
CD33	NCT01864902 China	Lentivirus 4-1BB	Auto or allo	5-90	None in one patient	$4.25x10^8$ in one patient	One patient with transient blast reduction>50% at week 2 Fevers and hyperbilirubinemia
	NCT03126864	Lentivirus 4-1BB	Auto	1-80	Fludarabine (Flu) Cytarabine (Cy)	N/A	N/A
	NCT02958397China	N/A	Auto	14-75	yes	N/A	N/A
	NCT02799680China	Lentivirus	Allo	≥ 50	Idarubicin Cy	N/A	N/A
LewisY	NCT01716364	RetrovirusCD28	Auto	≥ 18	Fludarabine (Flu)Cytarabine (Cy)	$1.48\text{-}9.2x10^8$	One patient achieved cytogenic complete response (CR)

NKG2DL	NCT03018405	RetrovirusDAP10	Auto	≥ 18	None	$3x10^8$-$3x10^9$	3/8 patients responded41% CRS3/10 grade 3-4 CRS
CD123		Lentivirus CD28	Auto or allo	≥ 12	Flu/Cy	50-500$x10^6$	N/A
		mRNA electroporation 4-1BB	Auto	≥ 18	None or Cy	$4x10^6$/kg x 4 $4x10^6$/kg x 6	No anti-AML activityGrade1-4 CRS but no neurotoxicity or hematological toxicity
	NCT03190278	Lentivirus 4-1BB	Universal donor	18-75	Flu/Cy	$6.25x10^4$/kg $6.25x10^6$/kg	One patient death; trial reopened 11.2017
	NCT03766126	Lentivirus 4-1BB	Auto	≥ 18	Flu/Cy	$2x10^6$/kg	N/A (opened 02.2019)

The speaker highlighted that CAR-T therapy for AML is still at early stages with multiple ongoing and planned trials worldwide on different molecular targets (**Table 1**). CD123 and NKG2D targeted CAR-T treatment has led to encouraging early data with regards to feasibility, tolerability and patient responses. As Elizabeth Budde pinpointed, the ways to improve the effectiveness of CAR-T therapies for AML involve the optimization not only of the manufacturing but also the CAR-T design and dosing. Moreover, combination treatments with immunomodulatory drugs and dual-targeting therapies carry great potential for AML patients and should be further investigated.[1]

ADCs, DARTs & BiTEs for AML[2]

To date, there are eight clinical trials investigating the efficacy and safety of bispecific antibodies for the treatment of AML. These are shown in Table 2.[2]

Table 2. Bispecific DART antibodies in clinical trials for AML[2]

Dual targets	Clinical trial ID	Drug name	Sponsor	Status
CD123 & CD3	NCT02715011	JNJ-63709178	Janssen	Suspended
	NCT02730312	XmAb14045	Xencor	Recruiting
	NCT02152956	Flotetuzumab*	MacroGenics	Recruiting
CD33 & CD3	NCT02520427	AMG 330	Amgen	Recruiting
	NCT03224819	AMG 673	Amgen	Recruiting
	NCT03144245	AMV564*	Amphivena	Recruiting
	NCT03516760	GEM333	GEMoaB	Recruiting
CLL1 & CD3	NCT03038230	MCLA-117	Merus	Recruiting

*** Preliminary data are described below**

Flotetuzumab[2]

The speaker presented preliminary data from the phase I trial of flotetuzumab (FLZ), the humanized DART that targets CD3 and CD123 as explained below.

- FLZ was administered intravenously to n= 50 patients with relapsed/refractory AML at the stepwise dosing schedule from 30ng/kg at Day one to 500 ng/kg and at Day seven (week one)

- During weeks 2-4, patients received 500ng/kg of FLZ per day of cycle one and a four days on/ three days off schedule for cycle two onwards
- The recommended phase II dose of FLZ was 500ng/kg per day administered as a seven day/week continuous intravenous infusion
- Among the patients with primary refractory AML (62%), 32% achieved a complete response (CR)
- FLZ was well tolerated especially due to the stepwise escalation with mild tp moderate CRS events of short duration with a median of one day (grade one: 82%; grade two: 76%; grade three: 8%; grade four: 0%)

Last but not least, the investigators showed that PD-L1 expression was linked to decreased FLZ activity, as patients who progressed early (< 15 days) had significantly higher PD-L1 expression. Further results are expected the expansion cohort and an additionally planned FLZ plus MGA012 (anti-PD1) cohort.

AMV564-101 trial[2]

- n= 40 enrolled patients with R/R AML, aged ³ 18 with high-risk disease
- Study design 3+3
- AMV564 was administered on a 14-day continuous stepwise dose escalation from 0.5-15mg on Day one to 450mg on Day 14
- Thirty-three patients have been dosed to date
- Treatment was well-tolerated with no donor lymphocyte infusions and grade 1-2 CRS events
- One long duration (7 months) CRi was observed and one stable disease at seven months
- AMV564 led to quick and selective depletion of leukemic blasts and myeloid-derived suppressor cells (MDSCs) was observed by flow cytometry
- Further results are expected from this ongoing trial in the near future

Conclusions

This is an exciting time for the clinical setting of R/R AML as numerous CAR-Ts, ADCs, BiTEs/DARTs are under pre-clinical and early clinical investigation. With many of these chemotherapy-free therapies showing promising activity and tolerability, it is certain that the future of patients with R/R AML seems more hopeful than ever.

References

1. Budde E.L. Chimeric Antigen Receptor T-Cell Therapy for Acute Myeloid Leukemia. SOHO 2019 [Accessed Oct 14 2019]
2. DiPersio J.F. ADCs, DARTs and BiTEs in AML. SOHO 2019, [Accessed Oct 14 2019]