Safety and Efficacy of Combining Tagraxofusp (SL-401) with Azacitidine or Azacitidine and Venetoclax in a Phase 1b Study for CD123 Positive AML, MDS, or BPDCN

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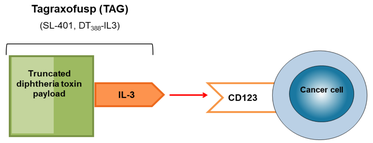
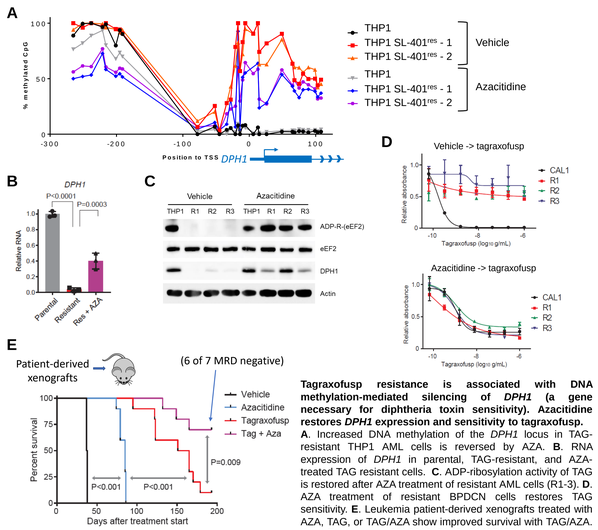
Overview

- CD123 is present on the surface of most AML and MDS blasts (and AML leukemia stem/initiating cells), and on BPDCN
- Tagraxofusp (TAG, SL-401) is a first-in-class CD123-targeted therapy that delivers a truncated diphtheria toxin payload to CD123-expressing cells, and is approved for BPDCN
- We previously found TAG resistance in AML cells is mediated by DNA methylation and silencing of diphthamide genes (Togami et al. JCI 2019)
- TAG resistance can be reversed in the laboratory by azacitidine (AZA), a DNA methyltransferase inhibitor
- Here, we performed a phase 1b study to test the combination of TAG with AZA, or TAG with AZA and venetoclax (VEN), in subjects with AML, MDS, and BPDCN



Preclinical Data

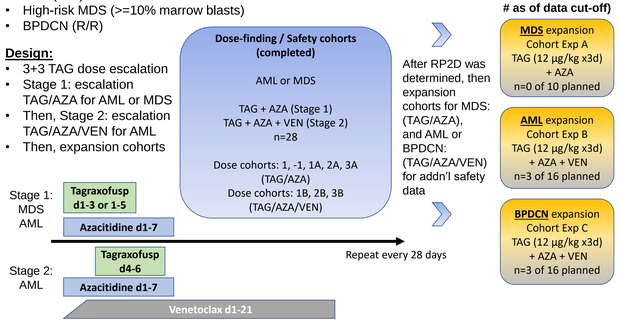


Tagraxofusp resistance is associated with DNA methylation-mediated silencing of *DPH1* (a gene necessary for diphtheria toxin sensitivity). Azacitidine restores *DPH1* expression and sensitivity to tagraxofusp. **A**. Increased DNA methylation of the *DPH1* locus in TAG-resistant THP1 AML cells is reversed by AZA. **B**. RNA expression of *DPH1* in parental, TAG-resistant, and AZA-treated TAG resistant cells. **C**. ADP-ribosylation activity of TAG is restored after AZA treatment of resistant AML cells (R1-3). **D**. AZA treatment of resistant BPDCN cells restores TAG sensitivity. **E**. Leukemia patient-derived xenografts treated with AZA, TAG, or TAG/AZA show improved survival with TAG/AZA. (from Togami et al. JCI 2019; PMID: 31437130)

Study Design

Eligible diagnoses:
- AML (newly diagnosed/first-line (1L), ineligible for intensive Rx)
- AML (R/R)
- High-risk MDS (>=10% marrow blasts)
- BPDCN (R/R)

Design:
- 3+3 TAG dose escalation
- Stage 1: escalation TAG/AZA for AML or MDS
- Then, Stage 2: escalation TAG/AZA/VEN for AML
- Then, expansion cohorts



- Inpatient hospitalization required in cycle 1 until completion of TAG for safety monitoring
- Early intervention and holding of TAG for possible capillary leak syndrome per tagraxofusp FDA prescribing information (including albumin supplementation if <3.2 g/dL or drop of >0.5 g/dL)

Other key eligibility:
CD123+ on blasts (determined locally by flow cytometry or IHC; any level of positivity), albumin >= 3.2 g/dl, normal cardiac ejection fraction

Objectives:
Primary: Determine MTD / RP2D of TAG/AZA and TAG/AZA/VEN and safety of regimen
Secondary: Response rate, PFS, OS
Exploratory: Biomarkers and correlative measures of response

Patient Characteristics / Dose Levels

Demographics	n
Enrolled and evaluable	34
TAG + AZA	19
TAG + AZA + VEN	15
Age	Range 21 - 86 (median 67)
Gender	23 M : 11 F
Disease	AML 1L (14), AML R/R (12), MDS (5), BPDCN (3)
Treatment received	Doublet (TAG/AZA): AML 1L (5), AML R/R (9), MDS (5) Triplet (TAG/AZA/VEN): AML 1L (9), AML R/R (3), BPDCN R/R (3)

Stage	Dose cohort	Dose of TAG	Days of TAG	Azacitidine	Venetoclax*	Subjects	Histology/Status
1 TAG/AZA	1	7 µg/kg	1,2,3,4,5	75 mg/m², D1-7		3	1L AML x3
		Two DLTs (prolonged hyperbilirubinemia and pericardial effusion) in Cohort 1, de-escalated to cohort -1 and amended study to escalate with 3-day dosing of TAG.					
	-1	5 µg/kg	1,2,3,4,5	75 mg/m², D1-7		4	1L AML, R/R AML x2, 1L MDS
	1A	7 µg/kg	1,2,3	75 mg/m², D1-7		3	R/R AML x3
	2A	9 µg/kg	1,2,3	75 mg/m², D1-7		6	1L AML, R/R AML x4, 1L MDS
	3A	12 µg/kg	1,2,3	75 mg/m², D1-7		3	1L MDS x3
2 TAG/AZA/ VEN	1B	7 µg/kg	4,5,6#	75 mg/m², D1-7	400 mg, D1-21	3	1L AML x2, R/R AML
	2B	9 µg/kg	4,5,6	75 mg/m², D1-7	400 mg, D1-21	3	1L AML, R/R AML x2
	3B +expan	12 µg/kg	4,5,6	75 mg/m², D1-7	400 mg, D1-21	9	1L AML x3 1L AML x3 (Exp B) R/R BPDCN x3 (Exp C)

*Venetoclax ramp up days 1-3 in Cycle 1, #Rationale for d4-6 TAG in triplet (in all cycles) was to ramp up VEN first in cycle 1 and confirm no TLS, and because preclinical data suggested AZA sensitizes to TAG and reverses resistance

Safety

Grade 2 or higher AEs in >10% Overall (n=34)	TAG/AZA (n=19)	TAG/AZA/VEN (n=15)
Neutrophil ct decreased	35%	26%	47%
Platelet ct decreased	35%	26%	47%
ALT increased	32%	47%	13%
Capillary leak syndrome	32%	47%	13%
Febrile neutropenia	24%	32%	13%
Anemia	24%	16%	33%
Hypotension	21%	32%	13%
Bilirubin increased	18%	21%	13%
Fatigue	18%	26%	13%
Fever	18%	26%	7%
Hypoalbuminemia	18%	21%	13%
Hypocalcemia	15%	11%	20%
Nausea	15%	16%	13%
Abdominal pain	12%	11%	13%
AST elevated	12%	11%	13%
Dyspnea	12%	11%	13%
Infusion related rxn	12%	11%	13%
Hypertension	12%	16%	7%
Hypokalemia	12%	11%	13%
Hypophosphatemia	12%	16%	7%
Lung infection	12%	16%	7%
Lymphocyte ct dec	12%	11%	13%

Events are per patient, during any cycle

Grade 3 or higher AEs in >10% Overall (n=34)	TAG/AZA (n=19)	TAG/AZA/VEN (n=15)
Neutrophil ct decreased	32%	21%	47%
Platelet ct decreased	29%	21%	40%
Febrile neutropenia	24%	33%	13%
Anemia	18%	11%	27%
ALT increased	12%	17%	7%
Bilirubin increased	12%	22%	0%

Capillary Leak Syndrome (CLS)

CLS Events	# (%)	Cohort (TAG dose)
Grade 2	8 (24%)	1 (7 µg x 5d) (n=2) -1 (5 µg x 5d) (n=1) 2A (9 µg x 3d) (n=3) 3A (12 µg x 3d) 3B (12 µg x 3d, with VEN)
Grade 3	2 (6%)	-1 (5 µg x 5d) 2A (9 µg x 3d)
Grade 4	1 (3%)*	3B (12 µg x 3d, with VEN)
Any grade	**11 of 34 (32%)**	

*One possibly treatment-related death occurred during C1 in a 79-year-old subject with AML who had multiple events including F&N and TLS during AZA/VEN, then CLS after TAG, in the setting of multiorgan system failure

Efficacy

Previously untreated (1L) AML that received triplet TAG/AZA/VEN (n=9)
8 of 9 CR/CRi = 89%; 6 CR (67%)/2 CRi (22%); 6 had MRD evaluation: 4 MRD neg / 2 MRD pos

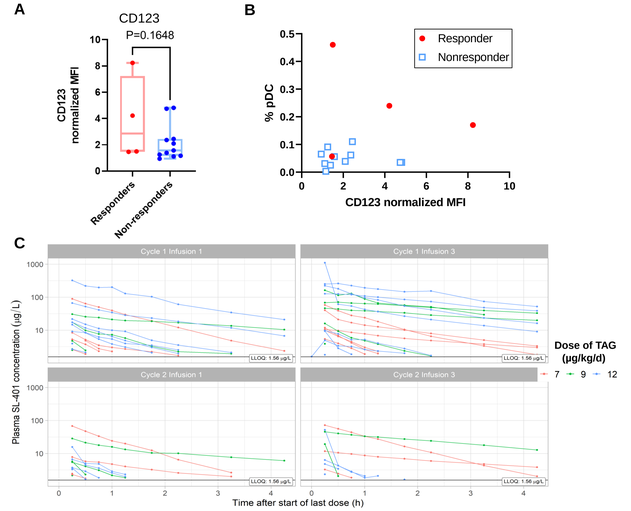
Subj	Cohort / Dose	Dem	AML Features	Best Response	Notes
1	1B / 7 µg	74M	sAML (after MDS); NK; ASXL1, BCOR	CR (MRD neg); achieved at C2	2 cycles then alloSCT
2	1B / 7 µg	59M	Complex karyotype, TP53	CR (MRD unk); achieved at C2	2 cycles then alloSCT
3	2B / 9 µg	81M	NK; FLT3-ITD, SF3B1	CR (MRD pos); achieved at C4	Progression after C7
4	3B / 12 µg	71F	+8; DNMT3A, IDH2, BCOR, WT1	CR (MRD neg); achieved at C1	3 cycles then alloSCT
5	3B / 12 µg	67M	sAML (after MDS); pDC-AML; NRAS, ASXL1, CBL, GATA2, PHF6, SF3B1, SMC1A, SMC3	CRi (MRD neg); achieved at C2	3 cycles then alloSCT
6	3B / 12 µg	81M	sAML (after CMML); pDC-AML; NRAS, KRAS, ASXL1, SRSF2, TET2, RUNX1	CRi (MRD unk); achieved at C2	Currently in C6
7	Exp B / 12 µg	78F	NK; SETBP1, SRSF2	CR (MRD neg); achieved at C4	Currently in C5
8	Exp B / 12 µg	79M	+8; ASXL1, NPM1, SRSF2, TET2	Not assessed, Gr5 event in C1	
9	Exp B / 12 µg	71M	Monosomal karyotype (-17,-5,-13,-18); TP53, GATA2, SF3B1	CR (MRD pos); achieved at C1	Currently in C5

NK, normal karyotype; genes listed are mutated; pDC-AML, AML with mature pDC proliferation (Xiao et al, Blood 2021)

Other groups	Regimen	N	CR/CRi/mCR	Notes
MDS, 1L	TAG/AZA	5	2 CR, 1 mCR (60%)	All 3 with CR/mCR had TP53 mutation
BPDCN, R/R	TAG/AZA/VEN	3	1 CRi, 1 CRc* (66%)	Both with CRi and CRc had relapsed after prior single agent TAG; both went to alloSCT after achieving CRi/CRc
AML, 1L or R/R	TAG/AZA	5 (1L) 9 (R/R)	1 CRi among 1L (20%)	Subject with CRi had complex karyotype and del(17p)

*CRc, BPDCN clinical complete response = CR in marrow and lymph nodes with minimal residual skin abnormality, per Pemmaraju et al, NEJM 2019, PMID: 3101806

Correlative Data



Measurement of potential biomarkers of response and pharmacokinetics. In **A** and **B,** we focused this interim analysis of responders vs non-responders only on patients who received TAG/AZA, because nearly all patients who received TAG/AZA/VEN with available data responded. **A**. CD123 mean fluorescence intensity on the surface of blasts by central flow cytometry, normalized to CAL1 BPDCN cells unstained (score=0) or stained (score=10). There is a trend toward higher CD123 in responders (AML or MDS that achieved CR/CRi), but we observed that some blasts with low-positive CD123 also responded. **B**. The same CD123 expression data are plotted, here also showing % pDC in the marrow at study entry, demonstrating that 3 of 4 responders had higher % pDC than any in the non-responder group (per Xiao et al, Blood 2021). **C**. TAG (SL-401) PK values available at the time of data cut-off are shown by dose of TAG (figures include subjects from all cohorts), LLOQ = lower limit of quantitation. Planned analyses with additional samples will include comparing PK in TAG/AZA vs TAG/AZA/VEN, relationship between PK and immunogenicity/anti-drug antibodies, and comparison to historical PK of single-agent TAG.

Conclusions

- An MTD was not reached. No dose-dependent toxicities of 3-day TAG were observed. The recommended Phase 2 dose (RP2D) of TAG is 12 µg/kg x 3d in each combination
- Encouraging activity of TAG/AZA/VEN in 1L AML (89% CR/CRi), longer follow-up needed for survival
- Activity seen in high-risk subsets of AML and MDS, including TP53-mutated AML/MDS and secondary AML
- Complete responses included subjects with blasts that had high and low CD123 positivity
- This study will be amended to include 1L BPDCN to receive up-front triplet TAG/AZA/VEN
- Comparison of TAG/AZA/VEN to standard-of-care AZA/VEN in previously untreated AML in a future study is warranted