Abstract 2577: Phase I dose escalation of LAVA-051, a novel bispecific γδ-T cell engager (Gammabody™), in relapsed/refractory hematological malignancies

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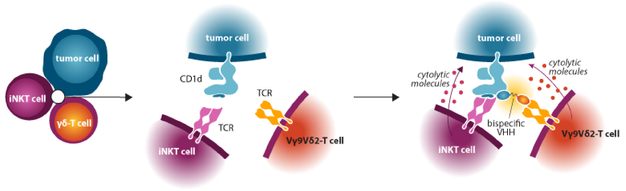
LAVA-051 is well tolerated early in dose escalation with on-mechanism pharmacodynamics consistent with Vγ9Vδ2-T cell engagement

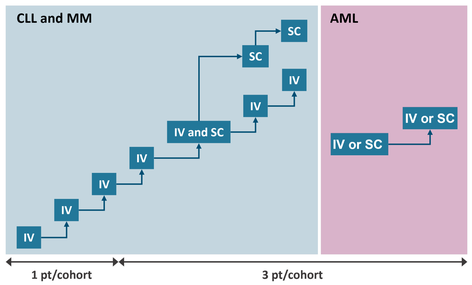
Introduction

- LAVA-051: 27kD humanized bispecific single domain antibody (VHH) that directly engages CD1d and the Vδ2-TCR chain of Vγ9Vδ2-T cells to mediate potent killing of CD1d-expressing tumor cells.
- Engages 2 innate-like T cell populations with inherent antitumor activity: type 1 NKT cells (Nature Cancer 2020;1:1054-1065) and Vγ9Vδ2-T cells.



- CD1d: expressed by tumor cells in the majority of patients with CLL (chronic lymphocytic leukemia) and MM (multiple myeloma), while expression in AML (acute myeloid leukemia) is most pronounced on (myelo)monocytic subtypes.
- LAVA-051 has high potency with low potential for cytokine release syndrome (CRS) affording an anticipated wide therapeutic window.

Trial Design and Objectives



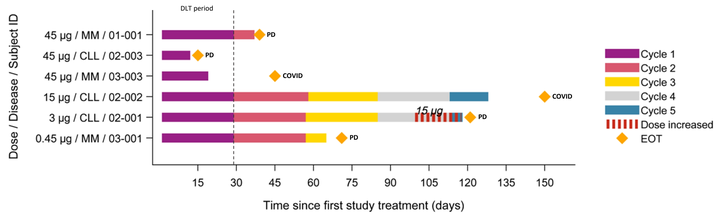
- Open label, accelerated titration design, phase 1/2a study in patients with relapsed/ refractory CLL, MM, and AML (NCT04887259).
- LAVA-051 administered via a 2 hr intravenous infusion, or subcutaneous injection (day 1, 8 and twice a week thereafter).
- Primary objectives: investigate safety and tolerability of LAVA-051 and determine the recommended Phase 2 dose (RP2D) of LAVA-051.
- Secondary objectives include evaluation of PK, PD, immunogenicity and preliminary antitumor activity.
- Data cut-off date of presented data was 2 May 2022.

Patient Characteristics

MM/CLL	3/3
Male/Female	5/1
Median age (range)	66 (60-75)
Prior therapies, median (range) – MM/CLL	5 (4-6) 4 (3-5)
CD1d MF index* on tumor cells, median (range)	3.2 (2.0-8.6)

* MF index = mean fluorescence index

Time on Treatment and Adverse Events



Cycle 1 Worst grade per patient TEAE Grade ≥2

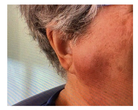
	0.45 µg (N=1)		3 µg (N=1)		15 µg (N=1)		45 µg (N=3)		Total (N=6)
Relatedness / AE	NS	S	NS	S	NS	S	NS	S	
Bone pain							1		1
Cancer pain	1								1
Contrast media allergy							1		1
Decreased appetite								1	1
Diarrhea							1		1
Drug hypersensitivity					1[A]				1
Dyspnea exertional							1		1
Fatigue							1		1
Hypercalcemia							1[C]		1
Hypoalbuminemia							1		1
Hypokalemia							1[C]		1
Hypomagnesemia							1[C]		1
Hypophosphatemia							1[C]		1
Infusion related reaction								1[E]	1
Lumbar vertebral fracture								1	1
Motor dysfunction							1		1
Neutropenia								1 1[D]	2
Pain in extremity							1		1
Pyrexia						1[B]			1
Rhinitis							1		1

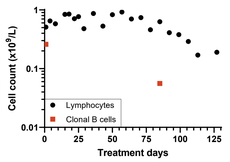
NS = not suspected; S = suspected
A: Drug hypersensitivity Gr3 reported for CLL patient to allopurinol administered as TLS prophylaxis; allergy to allopurinol confirmed through repeat occurrence to single agent prophylaxis.
B: Fever Gr2 reported for CLL patient in conjunction with 'tumor flare'.
C: Diverse electrolyte imbalances reported for MM patient: hypercalcemia Gr3 and hypomagnesemia Gr2 reported 2 days following 1st treatment - discontinuation of calcium carbonate and colecalciferol, all resolved; hypophosphatemia Gr2 reported 14 days following 1st treatment - all resolved; hypokalemia Gr2 reported 21 days following 1st treatment - resolved.
D: Neutropenia Gr3 reported for MM patient 14 days following first treatment - readily resolved with one dose of pegfilgrastim.
E: Infusion related reaction Gr2 within 15 minutes of end of infusion; no reappearance during following infusions administered following clemastine and paracetamol prophylaxis.

Potential Signs of Activity

CLL

- Patient with R/R CLL (15 µg) experienced enlargement and tenderness of several CLL-affected lymph nodes (LN) accompanied by grade 2 fever early during Cycle 1, followed by a regression of the size of the LNs; this resembled a tumor-flare reaction.
- Other causes of painful LN enlargement were ruled out.
- Patient was assessed as having stable disease per CT scan and iwCLL criteria (2018).
- Percent of clonal B cells in peripheral blood for this patient decreased from 41.8% at baseline to 8.9% at the start of Cycle 4.
- Patient stopped after Cycle 5 due to COVID.


(Permission for photo obtained)

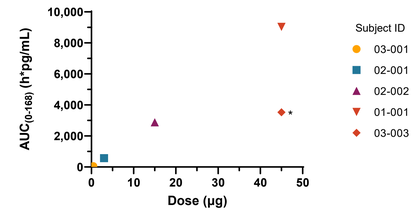


MM

- High risk R/R MM patient (45 µg)
- 4 prior lines of therapy within 6 years from diagnosis:
  - Bortezomib, Cyclo, Dex → auto HSCT
  - Carfilzomib, Lenalidomide, Dex
  - Pomalidomide, Dex
  - Daratumumab, Dex
- Refractory to last 3 lines of treatment
- 23% reduction in M-protein
- Patient stopped due to COVID.

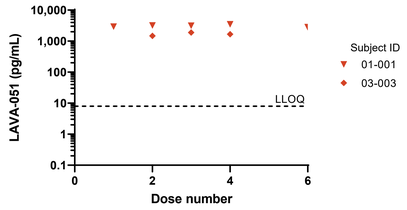
Pharmacokinetics

Dose vs AUC for Cycle 1 – Cohorts 1-4



* AUC could not be calculated accurately due to missing samples early after end of treatment

Cohort 4 LAVA-051 peak concentrations during Cycle 1: consistent

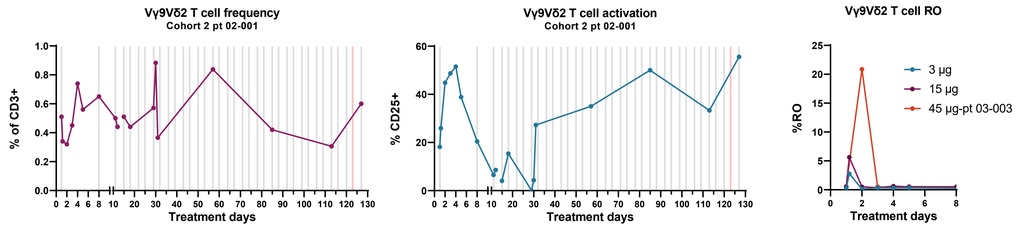


Note: Several sampling times at the end of the first infusion and immediately thereafter could not be collected for patient 03-003
LLOQ = lower limit of quantification

Selected PD Parameters - Vγ9Vδ2 T Cell Frequency, Activation and Receptor Occupancy

Dose/ patient ID	Vγ9Vδ2 T cell frequency (% of CD3+)		% CD25+		% CD69+		RO_{max} (%)
	Baseline	Post-dosing (range)	Baseline	Post-dosing (max)	Baseline	Post-dosing (max)	
0.45 µg/03-001	0.00	ND	ND	ND	ND	ND	NC
3 µg/02-001	0.51	0.31 - 0.74	18.2	51.5	48.5	88.9	2.8
15 µg/02-002	1.46	0.02 - 1.08	0.9	7.9	13.3	83.3	5.6
45 µg/03-003	0.41	0 - 0.42	15.2	35.6	30.3	86.7	20.9
45 µg/01-001	0.45	0 - 0.10	12.5	55.6	25	0	NC
45 µg/02-003	0.05	0 - 0.07	0	50.0	0	100	0.6*

RO = Vγ9Vδ2 T cell receptor occupancy; ND = not detectable; NC = RO_{max} could not be calculated; * RO_{max} could only be determined at 72 hr after end of infusion



Summary and Conclusions

- LAVA-051 is first of a novel class of bispecific γδ T cell engagers with expected broad therapeutic window:
  - Bispecific single domain antibody engaging CD1d and Vδ2-TCR chain of Vγ9Vδ2-T cells to mediate potent killing.
  - Low potential for CRS observed in preclinical models and clinical setting when Vγ9Vδ2-T cells are activated.
- LAVA-051 has reached 100x the starting dose in CLL and MM. To date:
  - No CRS and no ICANS (ASTCT).
  - No significant increase in the CRS-related cytokine IL-6.
  - Most observed AEs have not been suspected to be related.
  - No DLTs.
- No ADA's detected to date.
- Predictable and linear pharmacokinetics.
- PD parameters reflect changes as expected per MoA:
  - Vγ9Vδ2-T cell activation markers (CD25 and CD69) were consistently upregulated following dosing, in each dose cohort.
  - Maximum measured Vγ9Vδ2-T cell receptor occupancy increased with higher dose cohorts.
  - iNKT cell activation was assessable, and observed, in one patient (cohort 2).
- First hint of clinical activity in a CLL patient and a MM patient.
- Trial continuing to enroll and escalate without step-dosing or pre-medication:
  - Clearance of IND will allow US sites to participate.
  - Plan to evaluate s.c. dosing and impact on PD parameters.

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