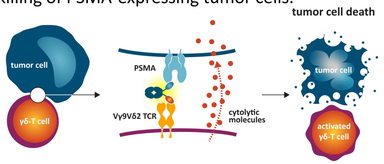
Early dose escalation of LAVA-1207, a novel bispecific gamma-delta T-cell engager (Gammabody™), in metastatic castration resistant prostate cancer patients

Niven Mehra[1] MD PhD, Debbie G.J. Robbrecht[2] MD PhD, Jens Voortman[3] MD PhD, Paul W.H.I Parren[4] PhD, Sonia Macia[4] MD PhD, Jorden M. Veeneman[4] PhD, Sanjana Umarale[4] MSc, Benjamin Winograd[4] MD PhD, Hans J. van der Vliet[3,4] MD PhD, David R. Wise[5] MD PhD

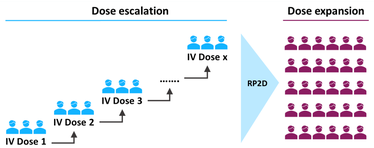
Introduction

- LAVA-1207: Fc-containing humanized bispecific antibody (~80 kD) that directly engages prostate-specific membrane antigen (PSMA) and the Vδ2-T cell receptor chain of Vγ9Vδ2-T cells to mediate potent killing of PSMA-expressing tumor cells.



- Preclinical data show that LAVA-1207 has high potency for selective tumor cell killing with low potential for CRS, affording an anticipated wide therapeutic window.

Trial Design and Objectives

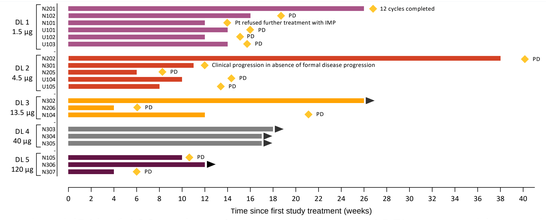


- Open-label, multi-center, Phase 1/2a dose escalation study in patients with therapy refractory metastatic castration resistant prostate cancer (mCRPC)(EU 1207-001: EudraCT Number: 2021-001789-39; US 1207-002: NCT05369000).
- LAVA-1207 administered via IV infusion every 2 weeks.
- Objectives: investigate safety and tolerability, evaluate PK, PD, immunogenicity and preliminary antitumor activity of LAVA-1207.
- Data cut-off date for presented data was 8 DEC 2022.

Patient Baseline Characteristics (n=20)

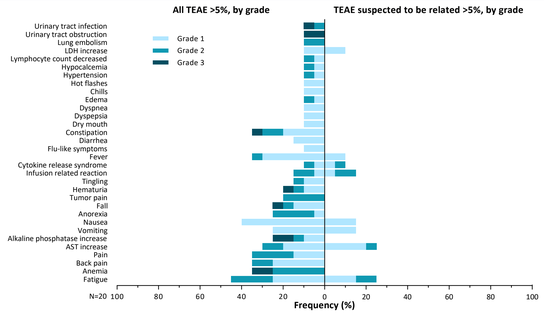
Age, median (range)	68 (51-76)
Years since diagnosis, median (range)	9 (3-21)
Prior systemic therapies, median (range)	4 (3-10)
Location of metastases	
Bone	19
Lymph node	14
Lung	2
Liver	5
Other visceral	2
Type of progression	
PSA	17
Bone	12
Nodal	12
Visceral	10

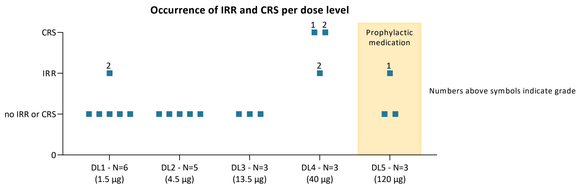
Time on Treatment



- A dose level (DL) of 120 µg (starting dose, 1.5 µg, MABEL approach) completed.
  - DL 1 included 6 pts, 3 from EU, 3 from US; DL 2 included 5 pts, 3 from EU, 2 from US.
- A total of 20 patients have been treated with LAVA-1207 with treatment duration ranging from 4 to 38 weeks.
- Next dose level: 360 µg.

Safety Profile

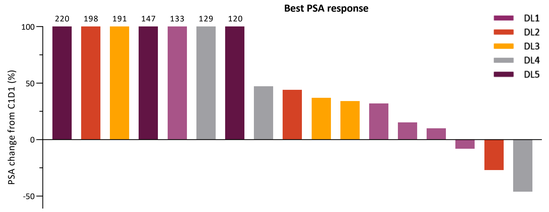


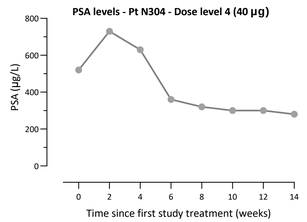


- Most observed AEs not suspected to be related and no DLT.
- Treatment emergent AEs (TEAEs) that were suspected to be related were grade 1 or 2.
- No increase in severity or frequency of TEAEs with increasing doses and no patient discontinued treatment due to AE.
- Only one grade 4 AE occurred (spinal cord compression, DL 5), which was non-related.
- As of 20 OCT 2022, prophylaxis with antipyretic and antihistaminic treatment to mitigate potential fever, IRR or CRS was implemented.

Preliminary Signs of Antitumor Activity

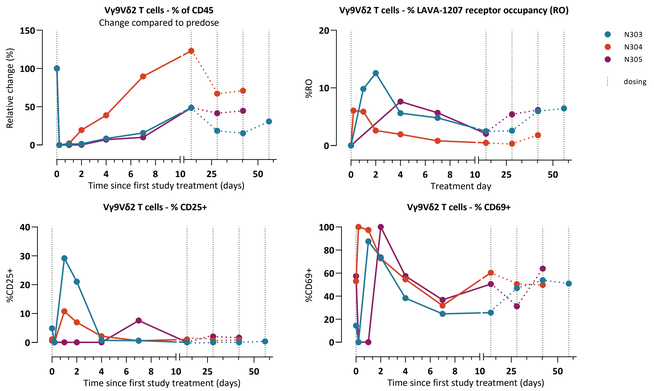
- Out of 14 iRECIST evaluable patients, 8 had iSD at week 8.





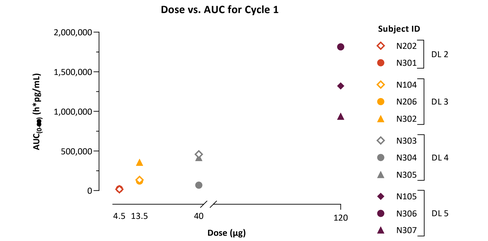
- Above: PSA response of patients with PSA progression at baseline who have had at least one PSA assessment on treatment. Shown is best PSA response and, for those patients with no PSA decline, PSA value at C5D1.
- Left: PSA over time for Pt N304, for whom the largest decrease in PSA (46%) was observed.
- This patient improved clinically with improvement in pain and fatigue.
- Patient is ongoing in the study.

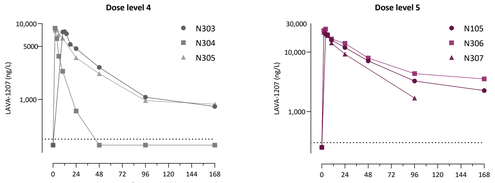
Pharmacodynamics – Dose Level 4



- Pharmacodynamics reflect changes expected as per MoA.
  - Pronounced drop in Vγ9Vδ2-T cell frequency 2 hr after dosing, likely reflective of Vγ9Vδ2-T cell re-distribution with subsequent recovery.
  - Vγ9Vδ2-T cell activation markers (CD25 and CD69) upregulated following dosing.
  - Receptor occupancy (RO) was detectable up to day 14 after EoI, with peak levels ranging from 6.1% to 12.6%.

Pharmacokinetics





- Pharmacokinetics of LAVA-1207 appears linear.
- Pt N304 (DL 4): faster plasma clearance may be related to higher target mediated disposition.

Conclusions

- LAVA-1207 is a PSMA targeting bispecific antibody belonging to a novel class of γδ T cell engagers (Gammabody™).
- LAVA-1207 has reached a dose of 120 µg without occurrence of DLTs in therapy refractory mCRPC patients.
  - Frequency and severity of AEs do not appear to be dose-dependent.
  - Most observed AEs were not suspected to be related.
  - Any CRS occurring was low grade and manageable.
  - Next dose level (360 µg) is ongoing.
- Pharmacodynamics reflect changes as expected per MoA.
- Clinical benefit observed with disease stabilization and PSA reduction during dose escalation.
- Dose escalation continues in both EU and US.

[1]Department of Medical Oncology, Radboud UMC, Nijmegen, The Netherlands; [2]Department of Medical Oncology, Erasmus UMC, Rotterdam, The Netherlands; [3]Department of Medical Oncology, Amsterdam UMC, Amsterdam, The Netherlands; [4]LAVA Therapeutics NV, Utrecht, The Netherlands; [5]Perlmutter Cancer Center, NYU Langone, New York, USA
Contact: Niven.Mehra@radboudumc.nl