MECHANISM OF ACTION OF LAVA-051, A BISPECIFIC Vg9Vδ2 T-CELL ENGAGER (BSTCE), CONFIRMED IN THE CLINICAL SETTING


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Background LAVA-051, a CD1d-targeting first-in-class bispecific single domain antibody (27 kDa), was brought into the clinic based on its high potency antitumor activity through dual engagement of Vγ9Vδ2-T and iNKT cells, and a low risk of cytokine release syndrome (CRS).

Methods A phase I study using LAVA-051 is ongoing in patients with relapsed/refractory MM or CLL to determine the recommended phase 2 dose (RP2D). This study has been approved by relevant ethics committees (NCT04887259). A panel of specific pharmacodynamic assays is included to determine the pattern of change in the binding of LAVA-051 to patients’ peripheral blood Vγ9Vδ2-T cells (i.e. Vγ9Vδ2-TCR occupancy) and in the frequency and activation status of Vγ9Vδ2-T and iNKT cells in circulation. Data presented are focused on the comparison of clinical to pre-clinical observations.

Results LAVA-051 triggers Vγ9Vδ2-T and iNKT cell mediated pro-inflammatory cytokine production, proliferation and anti-tumor activity in in vitro and ex vivo assays using patient CD1d+ AML, CLL and MM cells. In addition, LAVA-051 induced a strong anti-tumor effect in vivo in a CDX model using NSG mice with intermittent dosing. In a non-human primate (NHP) model utilizing a cross-reactive CD1d-Vγ9 bsTCE there was clear observation of Vγ9Vδ2-T cell engagement as reflected by a (temporary) decrease in circulating Vγ9Vδ2-T cells after dosing and concomitant upregulation of the activation marker CD69. As of July 2022, doses up to 100x the starting dose have been evaluated as safe in the clinical setting with 8 patients treated in total; importantly no CRS was observed. A similar temporary decrease in Vγ9Vδ2-T cells with consistent upregulation of activation markers (CD25 and CD69) as was seen in the NHP study has been observed in the clinic. In the NHP model, dose-dependent binding of the bsTCE to peripheral blood Vγ9-T cells was observed up to several days after injection. Similarly in the clinic, Vγ9Vδ2-TCR occupancy was shown to increase with higher dose cohorts with a current maximum of 20.9% receptor occupancy after dosing (45μg). The frequency and activation status of iNKT cells has been assessable in the clinic and will continue to be evaluated with escalating doses.

Conclusions LAVA-051 has demonstrated on-mechanism pharmacodynamics in the clinic, reflective of pre-clinical findings. The differentiating importance of these pharmacodynamic parameters with any correlating preliminary antitumor activity will be further elucidated in determining the RP2D and schedule; updated comparative data will be presented at the congress.

Trial Registration NCT04887259

Ethics Approval This study has been approved by relevant ethics committees in the Netherlands, Spain and Italy