Preliminary phase 1 dose escalation results of VIR-5500 (AMX-500), a dual-masked PRO-XTEN T-cell engager, in metastatic castration resistant prostate cancer (mCRPC).

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Background: VIR-5500, a dual-masked, PSMA-targeted bispecific T-cell engager, is designed to be specifically activated in the tumor microenvironment where protease activity is dysregulated relative to healthy tissues, potentially expanding the safety margin and therapeutic index. **Methods:** VIR-5500 was administered IV weekly (QW) and every 3 weeks (Q3W) at doses of 30 - 4000 ug/kg to eligible participants (pts) with progressive mCRPC after receiving SOC. Objectives were to characterize safety, pharmacokinetics (PK) profiles, anti-tumor activity, and determine the dose(s)/regimen(s) for expansion (NCT05997615). **Results:** As of 23 September 2025, 51 heavily pretreated mCRPC pts (~95% post-taxane) received ≥ 1 dose of VIR-5500. No dose limiting toxicities (pre-defined toxicities occurring during cycle 1) were reported. The incidence of related Grade ≥ 3 AEs was low and CRS was mostly limited to grade 1 and 2 (see Table). PSA declines were noted in all pts dosed at ≥ 3000 ug/kg Q3W, including clinically significant and deep PSA reductions (91% PSA_{50} and 55% PSA_{90}). Preliminary evidence of durable PSA responses lasting over one year was noted in select patients undergoing intra-patient dose escalation. An objective response rate of 67% was observed in 4 out of 6 RECIST-evaluable patients treated at doses ≥ 3000 μg/kg Q3W, including one confirmed partial response and three additional partial responses pending confirmation. PSMA-PET imaging confirmed anti-tumor activity, demonstrating strong concordance with PSA_{90} responses. Evidence of T-cell activation and target engagement included increased on-treatment CD3+ T-cell tumor infiltration and serum IFN-γ, including minimal elevation of IL-6 levels, consistent with generally low-grade CRS. Preliminary analyses indicated PK was dose-proportional for VIR-5500, with a half-life of approximately 8-10 days and minimal systemic unmasking to the fully unmasked metabolite. Dose escalation continues with both QW and Q3W regimen, and updated data will be provided at the time of the presentation. **Conclusions:** Pending further clinical validation, available data are suggestive of a generally favorable safety profile, with evidence of meaningful anti-tumor activity, including RECIST responses, and preliminary evidence of durable benefit in a heavily pretreated population with substantial disease burden. Clinical trial information: NCT05997615. Research Sponsor: Vir Biotechnology.

	All Participants (n/N, %)	≥ 3000 ug/kg Q3W (n/N, %)
Gr 1 CRS	24/51, 47%	9/15, 60%
Gr 2 CRS	4/51, 8%	1/15, 7%
Gr ≥ 3 CRS	1/51, 2%	0/15, 0%
Related Gr ≥ 3 TEAE	8/51, 16%	3/15, 20%
Any PSA Decline	34/45, 76%	11/11, 100%
PSA_{50}	24/45, 53%	10/11, 91%
PSA_{90}	11/45, 24%	6/11, 55%
Objective Response Rate	4/22, 18%	4/6, 67%