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BEHOLD-1: Exploratory analysis of biomarkers associated with mocertatug rezetecan (Mo-Rez) response in patients with platinum-resistant ovarian cancer (PROC)

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Background

Mo-Rez (GSK5733584) is a novel ADC comprising an IgG1 monoclonal antibody targeting B7-H4 (an immunomodulatory ligand) conjugated to a TOP1 inhibitor payload via a protease-cleavable linker. In the global BEHOLD-1 study (NCT06431594), Mo-Rez showed promising anti-tumour activity in patients with PROC (confirmed ORR: 62% at 5.8 mg/kg Q3W). Exploratory biomarker analysis of Mo-Rez response in BEHOLD-1 phase 1b (dose expansion) is presented.

Methods

B7-H4 immunohistochemistry (IHC; n=111) and whole-transcriptome sequencing (WTS; n=79) were performed on archival/fresh tumour tissue collected at screening. Tumour cell B7-H4 IHC was assessed as a continuous variable and using prespecified cutoffs. WTS was analysed by fast gene set enrichment analysis (fgSEA; Hallmark pathways using DESeq2 statistics) and gene set variation analysis (GSVA; immune/tumour microenvironment [TME] signatures). Biomarkers were correlated with response (RECIST 1.1) across all doses; responders (R) had confirmed response and non-responders (NR) had stable/progressive disease or were unevaluable. Data cutoff: 12 Nov 2025.

Results

B7-H4 was expressed in 96% of tumours and was not associated with response. fgSEA identified enrichment of immune-related pathways in R vs NR; TNFα-NF-κB signalling was the top enriched pathway (NES=2.6). GSVA of immune/TME signatures showed higher macrophage (p=0.02), Treg/Th2 traffic (p=0.0065) and myeloid cell traffic (p=0.049) scores in R vs NR, with matrix remodelling the most significantly associated signature (p=0.00065). Cathepsin B (*CTSB*) expression was elevated in R vs NR (p=0.02). *CTSB* expression, macrophage and matrix remodelling signatures were correlated with each other (r=0.5–0.63; p<0.00001).

Conclusions

Mo-Rez response correlated with immune/TME signatures and *CTSB* expression, consistent with a model where a macrophage-enriched, matrix remodelling TME with high *CTSB* facilitates linker cleavage, payload release and bystander effect. In PROC, where B7-H4 is expressed in >95% of tumours, predictive biomarkers of Mo-Rez response may require composite signatures that integrate elements of its mechanism of action beyond target expression.

Clinical trial identification

NCT06431594.

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Legal entity responsible for the study

GSK.

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Disclosure

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