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Safety and efficacy of first-in-class, YAP/TEAD inhibitor, VT3989 in refractory pleural and non-pleural mesothelioma: A phase I/II study

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Background

Dysregulated Hippo pathway, leading to YAP activation, is prevalent in mesothelioma. VT3989, a potent oral inhibitor of TEAD palmitoylation that disrupts YAP function, was assessed in a Phase I/II trial.

Methods

Dose escalation evaluated continuous (25-200 mg) and intermittent (50-200mg) dosing, with urine albumin creatinine ratio (UACR) guiding dose adjustments in advanced cancer pts. Expansion cohorts in refractory mesothelioma pts compared intermittent schedules and UACR thresholds to optimize safety, pharmacokinetics and efficacy.

Results

As of March 2025, 172 pts were enrolled: 135 mesothelioma, 9 epithelioid hemangioendothelioma (EHE), 9 meningioma and 19 other solid tumors. VT3989 was safe and well tolerated with mostly low grade (≤ grade(G) 2) toxicities, including treatment related increased UACR (all grade 31%; G3-G4 1.4%), proteinuria (28%; 0%), peripheral edema (23%; 0%) and fatigue (20%; 0.6%). Proteinuria was reversible upon dose reduction and not associated with decrease in renal function, hypoalbuminemia or nephrotic syndrome. As VT3989 has long half-life (9 days), intermittent scheduling limits long-term drug accumulation while maintaining therapeutic levels during off periods. Doses of 50 or 100 mg on a 2-weeks-on/2-weeks-off (2W/2W) schedule were clinically active, with 100 mg selected as the recommended dose for expansion. Anti-tumor activity with durable RECIST/mRECIST PRs was observed across different doses in mesothelioma, EHE and *NF2*-mutant spindle cell sarcoma. 22 pts with mesothelioma were treated at 50 or 100mg 2W/2W and optimal UACR thresholds for dose modification. All mesothelioma pts had received prior immunotherapy and 82% had previously received platinum-based chemotherapy. 7 of 22 mesothelioma pts achieved RECIST PRs (ORR 32%), 12 pts had SD (including 5 pts with >10% tumor regression), with DCR of 86%. Median PFS was 40 weeks [95% CI: 23-NE]. Responses were seen in pts with *NF2* mutant tumors, as well as those without identified *NF2* mutations.

Conclusions

VT3989 is well tolerated with promising antitumor activity in pts with refractory mesothelioma. Based on these data, a randomized phase 3 study is planned for further evaluation of VT3989 in mesothelioma.

Clinical trial identification

NCT04665206.

Legal entity responsible for the study

Vivace Therapeutics.

Funding

Vivace Therapeutics.

Disclosure

T.A. Yap: Financial Interests, Personal, Other, Consultant: Almac, Aduro, AstraZeneca, Atrin, Axiom, Bayer, Bristol Myers Squibb, Clovis, Cybrexa, EMD Serono, Guidepoint, Ignyta, I-Mab, Jansen, Merck, Pfizer, Repare, Roche, Schrodinger, Varian, Zai Labs, AbbVie, Acrivon, Adagene, Amphista, Artios, Athena, Avoro, Baptist Health Systems, Beigene, Boxer, C4 Therapeutics, Calithera, Cancer Research UK, Diffusion, F-Star, Genmab, Glenmark, GLG, Globe Life Sciences, GSK, Idience, ImmuneSensor, Institut Gustave Roussy, Intellisphere, Kyn, MEI Pharma, Mereo, Natera, Nexus Pharmaceuticals, Novocure, OHSU, OncoSec, Ono Pharma, Piper-Sandler, Prolynx, resTORbio, Theragnostics, Versant, Vibliome, Xinthera, Radiopharm Theranostics, Sanofi, Ellipses Pharma, Pliant Therapeutics, Synthis, Tessellate Bio, TD2 Theragonostics, Tome Biosciences, Amgen Inc., Astex, Avenzo, BioCity Pharma, Blueprint, Carrick Therapeutics, Circle Pharma, Daiichi Sankyo, Dark Blue Therapeuticcs, Duke Street Bio, 858 Therapeutics, EcoR1 Capital, Entos, FoRx Therapeutics AG, Genesis Therapeutics, Ideaya Biosciences, Impact Therapeutics, Merit, Monte Rosa Therapeutics, Nested Therapeutics, Nimbus, Odyssey, Onxeo, Protai Bio, Ryvu Therapeutics, SAKK, Servier, Synnovation, Tango, TCG Crossover, Terremoto Biosciences, Terns Pharmaceuticals, Tolremo, Thryv Therapeutics, Trevarx Biomedical, Veeva, Voronoi Inc., Aeneid Therapeutics, Alterome Therapeutics Inc., Atavistik, Bicycle Therapeutics, Bloom Burton, Bluestar Bio, Cancer Research Horizons, Clasp, DAiNA, Dawn Manco, Eikon, Flagship Pioneering, Forbion, Guardant, Jazz Pharmaceuticals, Kyowa Kirin, Lumanity, Plexium Inc., PSIM, Stablix, Techspert.io, Vivace; Financial Interests, Personal, Advisory Board, Advisor: BridGene Biosciences, Debiopharm, Grey Wolf Therapeutics, Institut Gustave Roussy, Joint Scientific Committee for Phase I Trials in Hong Kong, Prelude Therapeutics; Financial Interests, Personal, Other, University of Texas MD Anderson Cancer Center, where I am VP, Head of Clinical Development in the Therapeutics Discovery Division, which has a commercial interest in drug discovery and development: MD Anderson Cancer Center, Institute for Applied Cancer Sciences; Financial Interests, Institutional, Other, Grant/Research support: Bayer, Cyteir, EMD Serono, GSK, Karyopharm, Pfizer, Repare, Sanofi, Artios, AstraZeneca, Beigene, BioNTech, Blueprint, BMS, Clovis, Constellation, Eli Lilly, Forbius, F-Star, Genentech, Haihe, ImmuneSensor, Ionis, Ipsen, Jounce, KSQ, Kyowa, Merck, Mirati, Novartis, Ribon Therapeutics, Regeneron, Rubius, Scholar Rock, Seattle Genetics, Tesaro, Vivace, Zenith, Tango, Department of Defense; Financial Interests, Institutional, Research Grant, Principal Investigator: Boundless Bio, Ideaya; Financial Interests, Institutional, Local PI, Principal Investigator: CPRIT, Gilead, Golfers against Cancer, Exelixis, NIH/NCI, Pliant, Prelude, Roche, Synnovation, V Foundation, Zentalis; Financial Interests, Institutional, Other, Grant/Research Support: 858 Therapeutics, Accent, Aprea Therapeutics, BridGene BioScience, Circle Pharma, Eisbach Bio, Insilico Medicine, Loxo Oncology, SpringWorks. 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