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Enucleation prevention and vision preservation in primary uveal melanoma (UM): Preliminary results from a phase II study of neoadjuvant darovasertib

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Background

Primary UM treatment (Rx) requires vision-compromising enucleation or plaque brachytherapy (PB). Approximately 95% of UMs harbor GNAQ/GNA11 mutations with activated oncogenic PKC signaling. Darovasertib (D), a selective PKC inhibitor that inhibits growth of UM tumors in vivo, could alter the treatment paradigm for primary UM.

Methods

IDE196-009 is a phase 2 study (NCT05907954) testing the safety & efficacy of D as neoadjuvant Rx in primary UM requiring enucleation (Cohort 1: Co1) or PB (Cohort 2: Co2). Primary endpoints: Enucleation Prevention (EP) for Co1 & radiation Dose Reduction (DR) for Co2. Tumor shrinkage by Product of Diameters (PoD: height (ht) * longest basal diameter {lbd}) (Co1 & 2) & best corrected visual acuity (BCVA) loss of ≥ 15 letters post PB (Co2) are secondary endpoints, while risk of 20/200 vision assessed by a prognostic tool is exploratory (Co2).

Results

Safety population: 90 patients {pts} (n=51 Co1, n=39 Co2) received D at 300 mg BID in 28-day cycles. Median age: 58 yrs (23-85); median tumor ht: Co1: 11mm (2-15), Co2: 7mm (3-14); lbd: Co1: 17 mm (10-22); Co2: 14 mm (7-21). All grade treatment related adverse events (TRAEs) in ≥20%; diarrhea (48%), nausea (43%) & fatigue (30%). The only Grade ≥3 TRAE in ≥ 5% pts was hypotension (6.7%). Drug interruption, modification, or discontinuation due to TRAEs was seen in 16 (18%), 7 (8%) & 4 (4%) pts, resp. Efficacy population: N= 62 (n= 32 Co1, n = 30 Co2) defined as pts with tumor assessment after ≥ 3 cycles of D (or progression/AE requiring early discontinuation). In this efficacy population, 59% (19/32) of pts in Co1 became eligible for EP; in Co2 for pts with available paired simulations, DR was seen in 14/17 (82%) pts with 59% (10/17) showing both ≥ 20% DR and a lower 3-year predicted risk of 20/200 vision. Tumor shrinkage ≥ ⊠ 20% in the PoD was noted in 62% (Co1) & 63% (Co2) of pts. Among pts who had EP or DR, the majority had this magnitude of tumor shrinkage.

Conclusions

Darovasertib is well-tolerated & is the first Rx to show tumor shrinkage in primary UM resulting in EP, radiation dose reduction & potential for vision preservation. Based on these promising results, a registrational study is planned.

Clinical trial identification

NCT05907954.

Legal entity responsible for the study

IDEAYA Biosciences.

Funding

IDEAYA Biosciences.

Disclosure

M.O. Butler: Financial Interests, Personal, Advisory Board: BMS, Merck, Novartis, Adaptimmune, Iovance, GSK, Sanofi, La Roche-Possey, Pfizer, Medison, IDEAYA, Regeneron; Financial Interests, Personal, Invited Speaker: BMS, Merck, Novartis, Sanofi, Pfizer; Financial Interests, Personal, Advisory Board, Safety Review Committee: Adaptimmune; Financial Interests, Institutional, Other, Conduct Clinical Trial: TCR2, Novartis, Sanofi, Immunocore, GSK, Pfizer, Merck, Bristol Myers Squibb, Regeneron, AstraZeneca, Adaptimmune, IDEAYA Biosciences, Amgen, Instil Bio, Turnstone Biologics, Iovance, Ankara; Financial Interests, Institutional, Research Grant, support clinical trial: Merck; Financial Interests, Institutional, Funding, support clinical trial: Takara Bio; Financial Interests, Institutional, Funding, support quality improvement project: Novartis. D. Reichstein: Financial Interests, Personal, Invited Speaker: Regeneron, Genentech, Castle; Financial Interests, Personal, Advisory Board: Immunocore, Aura, IDEAYA. M. Mckean: Financial Interests, Institutional, Other, Consulting: Pfizer, Castle Biosciences, IQVIA, Merck, Moderna, AbbVie, Bristol Myers Squibb, Daiichi Sankyo, IDEAYA Biosciences, Pierre Fabre, Regeneron, Revolution Medicine; Financial Interests, Institutional, Research Grant: Ascentage Pharma Group, Bicycle Therapeutics, Dragonfly Therapeutics, Epizyme, Exelixis, Genentech, GSK, IDEAYA Biosciences, Ikena Oncology, Infinity Pharmaceuticals, Jacobio Pharmaceuticals, Moderna, NBE Therapeutics, Novartis, Oncorus, Plexxikon, Prelude Therapeutics, Regeneron, Sapience Therapeutics, Seattle Genetics, Tizona Therpeutics, TMUNITY Therapeutics, TopAlliance Biosciences, Aadi Biosciences, Alpine Immune Sciences, Arcus Biosciences, Arvinas, ASCO, Astellas, Bayer, BioMed Valley Discoveries, BioNTech, C4 Therapeutics, EMD Serono, Erasca, Foghorn Therapeutics, G1 Therapeutics, Gilead Sciences, ImmVira Pharma, Kechow Pharma, Kezar Life Sciences, Kinnate BioPharma, MedImmune, Mereo BioPharma, Metabomed, Nektar, OncoC4, PACT Pharma, Pfizer, Poseida, Pyramid Biosciences, Scholar Rock, Synthrox, Takeda Pharmaceuticals, Teneobio, Tempest Therapeutics, Xilio, Aulos Bioscienc, Boehringer Ingelheim, Bristol Myers Squibb, Daiichi Sankyo, InconVir, Jazz Pharmaceutical, Krystal Biotech, NucMito Pharmaceuticals, OnKure, Remix Therapeutics. A.M. Joshua: Financial Interests, Institutional, Advisory Board: IDEAYA Biosciences, Immunocore, Replimmune. M. Shackleton, S. Chandana: Financial Interests, Personal and Institutional, Advisory Board: IDEAYA Biosciences. L.A. Dalvin: Financial Interests, Personal, Advisory Board, Consultant: Aura Biosciences, Ideaya Biosciences. M. Angi: Financial Interests, Personal, Advisory Board: Immunocore, Aura Biosciences, Alimera Sciences Limited. E. Rossi: Financial Interests, Personal, Advisory Board: Immunocore, MSD, Novartis, Pfizer, Gentili; Financial Interests, Personal, Invited Speaker: Pierre Fabre, Bristol Myers Squibb International. J. Lutzky: Financial Interests, Personal, Advisory Board: immunocore; Financial Interests, Personal, Other, safety monitoring committee: agenus, Celldex; Financial Interests, Institutional, Research Grant, Funding for institutional trial: BMS; Financial Interests, Institutional, Local PI: Tango, Immunocore, Replimune, Oncohost, Dragonfly, Iovance, Ideaya; Financial Interests, Institutional, Local PI, Phase I/II clinical trial: Immatics; Financial Interests, Institutional, Local PI, clinical trial: Syntrix; Financial Interests, Institutional, Local PI, Phase I/II Clinical Trial: TScan; Financial Interests, Institutional, Local PI, Phase I Clinical Trial: AsherBio. M.M. Chao, J.C. Sachdev: Financial Interests, Personal, Financially compensated role: IDEAYA Biosciences. M. Orloff: Financial Interests, Personal and Institutional, Advisory Board: Immunocore, Ideaya, Replimmune, Trisalus, Delcath. D. Beaupre: Financial Interests, Personal, Full or part-time Employment, Employee: IDEAYA; Financial Interests, Personal, Stocks/Shares: IDEAYA Biosciences; Non-Financial Interests, Leadership Role, CMO of organization: IDEAYA; Non-Financial Interests, Institutional, Proprietary Information, Access to company confidential information: IDEAYA. C. Shields: Financial Interests, Personal and Institutional, Advisory Board: IDEAYA Biosciences. All other authors have declared no conflicts of interest.