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Phase I safety and efficacy of brenetafusp, a PRAME × CD3 ImmTAC T cell engager, in platinum resistant ovarian cancer (PROC)

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Background

Brenetafusp (brene), an ImmTAC bispecific T cell engager (PRAME × CD3), showed robust disease control and tumor reduction in Ph1 (NCT04262466; Hamid 2022, Hamid 2024) in HLA-A*02:01+ patients (pts). We present monotherapy (mono) and chemotherapy combination (CC) data in PROC, and association with a baseline blood T cell fitness (TCF) signature that was also linked with tebentafusp benefit in uveal melanoma (ESMO 2024). Preclinically, chemo increased antigen presentation and ImmTAC activity (ESMO 2024).

Methods

Brene was dosed IV weekly with step-up to target dose of 40-320 mcg in mono escalation or 160 mcg in expansion & in CC. Chemo options were gemcitabine (Gem), nab-paclitaxel (NP), and PLD. Primary objectives: Safety, dose selection, and efficacy (RECIST v1.1). Exploratory endpoints included molecular response (≥ 0.5 log ctDNA reduction by week 9) and TCF (mean RNAseq expression of TESPA1, CD28 and GRP183 in blood at baseline). Data cutoff: Mar 2024.

Results

47 pts with high-grade serous PROC received brene (mono 32, CC 15) at active doses in escalation and expansion. Pts had a median 4 prior regimens. Most common adverse event (AE) was Grade 1/2 cytokine release syndrome (mono 53%, CC 80%). No drug-related AE led to treatment discontinuation or death. CC safety was consistent with individual agents. 40 pts were efficacy evaluable (mono 28, CC 12). Mono disease control rate (DCR; PR+SD) was 61% (17/28) with 2 PR (ORR 7%); mPFS was 3.3 mo and 6-mo OS rate was 73%. In CC, DCR was 67% (8/12) with 3 PR (Gem 1/9; NP 1/2; PLD 1/1). Molecular response (mono 6/25 [24%]; CC 9/10 [90%]) trended with longer PFS and OS. 28 mono pts were TCF-evaluable. Pts with $\geq$ median TCF had higher DCR (80%) than pts with $<$ median TCF (38%) and longer mPFS (3.7 vs. 2.2 mo, respectively; HR 0.39 [95% CI 0.15-0.97]).

Conclusions

Brenetafusp was well tolerated, alone and with chemotherapy. Monotherapy was active in PROC, demonstrated by DCR and molecular response, which are surrogates of benefit for the ImmTAC platform. Clinical activity associated with blood TCF signature, which is another ImmTAC hallmark. Enhanced activity with chemo and potential for greater TCF in earlier lines support assessing additional combinations in PROC and platinum sensitive disease.

Clinical trial identification

NCT04262466.

Legal entity responsible for the study

Immunocore Ltd.

Funding

Immunocore.

Disclosure

C. Friedman: Financial Interests, Personal, Advisory Board: Loxo@Lilly; Financial Interests, Personal, Other, One time consulting meeting: Johnson and Johnson; Financial Interests, Institutional, Local PI: AstraZeneca, Hotspot Therapeutics, Immunocore, Mersana, Volastra; Financial Interests, Personal, Steering Committee Member: Marengo, Genentech/Roche; Financial Interests, Institutional, Steering Committee Member: Merck; Other, Travel Support: PUMA. J.S. Lopez: Financial Interests, Personal, Advisory Board: Roche Genentech, Basilea, Ellipses Pharma, Cureteq, Pierre Faber, GSK; Financial Interests, Institutional, Research Grant: Roche Genentech, Basilea, Astex. K. 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I am director and my salary (0.2WTE) is supported through this work as a grant to my institution (The Christie NHS foundation trust - not for profit NHS hospital) from IUK: iMATCH director; Financial Interests, Institutional, Local PI, NCT02890069: Novartis; Financial Interests, Institutional, Research Grant, Sarcoma pathways project and CAR-T PROMs study: GSK; Financial Interests, Institutional, Local PI, NCT02493751: Pfizer; Financial Interests, Institutional, Local PI, NCT03245736, NCT02988817, NCT02552121, NCT02001623, NCT05180474: GenMab; Financial Interests, Institutional, Local PI, NCT02277717: Synthron; Financial Interests, Institutional, Local PI, NCT03013491: CytomX; Financial Interests, Institutional, Local PI, NCT03314935: Incyte; Financial Interests, Institutional, Local PI, NCT02908906 and CAR-T referrals project: Janssen; Financial Interests, Institutional, Local PI, NCT03132792, NCT04044768,: Adaptimmune; Financial Interests, Institutional, Local PI, NCT03400332: BMS; Financial Interests, Institutional, Local PI, NCT04262466, NCT03973333, NCT03515551: Immunocore; Financial Interests, Institutional, Local PI, EudraCT Number: 2018-001005-85, 2018-003446-16: Achilles Ltd; Financial Interests, Institutional, Local PI: Agalimmune Ltd; Financial Interests, Institutional, Local PI, NCT02834247: Millenium Pharmaceuticals/Takeda; Financial Interests, Institutional, Local PI, NCT02690350: Daiichi Sankyo; Financial Interests, Institutional, Local PI, NCT04839991: Crescendo; Financial Interests, Institutional, Local PI, NCT05104515: Oxford Vacmedix Ltd; Financial Interests, Institutional, Local PI, NCT05278975: RS Oncology LLC; Financial Interests, Institutional, Coordinating PI, NCT03697824, NCT03391778: GSK; Financial Interests, Institutional, Coordinating PI, NCT04140500, NCT04857138, NCT04826003: Roche; Financial Interests, Personal, Coordinating PI, NCT05008913, NCT04949425, NCT0331509, NCT03313557: AstraZeneca; Financial Interests, Institutional, Coordinating PI, NCT03829501: Kymab Ltd/Sanofi; Financial Interests, Institutional, Coordinating PI, EUDRACT ID No: 2019-003329-11: Chugai; Financial Interests, Institutional, Coordinating PI, NCT05430555: T-Knife Therapeutics; Financial Interests, Institutional, Coordinating PI, NCT03621982: ADCT Therapeutics; Financial Interests, Institutional, Research Grant, IRAS Project ID: 227414: Novartis; Financial Interests, Institutional, Coordinating PI, ITIL-306-202: Instil Bio; Financial Interests, Institutional, Funding, CAR-T referrals project: Gilead, Autolus; Financial Interests, Institutional, Local PI, NCT04763083: Novalgen; Financial Interests, Institutional, Local PI, NCT05714553: Nucana; Non-Financial Interests, Other, Panel member for a funding committee (MRC is a UK government NFP organisation) 2020-2024: MRC DPFS panel member; Non-Financial Interests, Advisory Role, Sarcoma UK is a not-for-profit charity. 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