253P Immunopheresis to remove soluble TNF receptors as a novel immunotherapy for patients with advanced breast cancer

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Background: Endogenous tumor necrosis factor-α (TNF-α) has known anti-tumor effects; however, its activity is inhibited by soluble TNF receptors (sTNF-R1, -R2) produced by tumors. Systemic administration of recombinant TNF-α is limited due to unacceptable toxicity (except in isolated limb perfusion). Triple-negative breast cancers, including those with BRCA1/2 mutations, are candidates for novel immunotherapies. This study used extracorporeal apheresis (Immunopheresis) with the LW-02 Column to selectively remove sTNF-Rs from plasma to promote TNF-α's anticancer action resulting in objective tumor responses.

Methods: This trial [NCT04004910] evaluated column performance (removal of sTNF-Rs), safety, and clinical efficacy (via RECIST 1.1) of LW-02 Column Immunopheresis in advanced breast cancer patients who failed 2 or more lines of systemic therapy. The trial enrolled 46 patients, 3 with germline BRCA1 mutations. Patients received LW-02 Column Immunopheresis 3x/week, as monotherapy or combined with chemotherapy for 16 weeks (or longer if patients were stable or improved clinically). Each treatment processed up to 2 plasma volumes.

Results: Column performance data (from a prior data cutoff for 1700 procedures) found median reductions of sTNF-Rs from plasma after 30-minutes of Immunopheresis of 95.6% and 82.2% for sTNF-R1 and sTNF-R2, respectively. Safety and efficacy results are from data through 31 January 2023. About safety, of 665 AEs, 22 (3.3%) were deemed to have had a causal relationship to treatment with the LW-02 Column (including 2 SAEs). Median treatment durations were 9.7 and 14.5 wks for all patients and for patients treated ≥4 wks, respectively (and 55.9 wks for the subset of 3 patients with confirmed BRCA1 mutations, 2 are still being treated). Similarly, median OS was 17.9 and 27.6 and 55.9 wks for the same groups. CBR results for patients treated ≥4 wks was 39% and 67% for the 3 BRCA1 patients (the latter reflecting 1 CR and 1 PR).

Conclusions: LW-02 Column Immunopheresis is safe and effectively removes sTNF-Rs from advanced breast cancer patients and contributes to efficacy improvements. Additional trials will examine its role in patients with BRCA1 mutations and other tumor profiles.

Clinical trial identification: NCT04004910.

Legal entity responsible for the study: Immunicom, Inc.

Funding: Immunicom, Inc.

Disclosure: P.J. Wysocki, P. Tomczak, T. Jankowski, T. Nowikiewicz: Financial Interests, Personal and Institutional, Principal Investigator: Immunicom, Inc. V. Manax, L. Florin, R. Segal, K.M. Djazouli, S. Bilgrami, A. Marleau, A. Ostrowski: Financial Interests, Personal, Full or part-time Employment: Immunicom, Inc.

https://doi.org/10.1016/j.esmoop.2023.101441

254P The invasive lobular cancer of the breast (ILC): A collection of clinical and pathological data in patients with (non-) metastatic breast cancer (BC)

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Background: ILC is the second most common BC type after the invasive carcinoma of no special type (NST). It mostly presents as estrogen receptor (ER) and progesterone receptor (PR) positive, human epidermal growth receptor 2 (HER2) negative and with a low marker of proliferation (Ki67) which results in a luminal A subtype and E-cadherin loss. Additionally, it appears to have a metastatic pattern that differs from the NST. This registry study aims to show clinical and pathological parameters in patients with early and advanced ILC.

Methods: Clinical and pathological data of 683 patients diagnosed with ILC were retrospectively collected and descriptively analyzed. Of these, 206 patients (30.2%) subsequently developed a local recurrence and/or distant metastasis.

Results: The majority of ILC patients presented with low Ki67, positive ER and PR, HER2-negativity and an intermediate grade tumor. E-cadherin loss was detected in 96.2% (n=427, 256 unknown). In summary, 0.4% of patients exhibited a pTis, 45.7% a pT1, 37.3% a pT2, 15.5% a pT3 and 1.1% a pT4 tumor (n=451, 26 unknown), while 68% of patients had pN0, 20.3% pN1, 7.3% pN2 and 4.3% pN3 status (n=438, 39 unknown). ILC tumors with a subsequent metastatic event initially showed similar data to non-metastatic tumors, although metastatic tumors have the highest rate in pT2 with 44.4% but 39.2% presented with pN0 in. Distant metastases were detected at the following sites: bones (43.7%; n=90), local recurrence (33.4%; n =69), peritoneum (12.6%; n=26), liver (11.2%; n=23), gynecological metastasis (10.7%; n=22) (multiple sites per person possible). Patients who progressed showed a slightly different profile, with a particular increase in cerebral lesions (24%, n=24).

Conclusions: This registry study summarizes histopathological data of ILC patients and shows a high rate of metastatic events despite initially good prognostic factors. The metastatic sites in this cohort resemble other studies and differ from NST in the frequency of visceral metastasis or metastasis inside the abdominal cavity (28.2%, n=58) in our cohort. This should be taken into consideration for planning surveillance for ILC patients in survivorship care.

Legal entity responsible for the study: AG Karsten-Speiser, Department of Gynecology with Breast Center, Charité - Universitätsmedizin Berlin.

Funding: Has not received any funding.

Disclosure: P. Jank: Financial Interests, Personal and Institutional, Stocks/Shares: Myriad Genetics Inc. M.M. Karsten: Financial Interests, Personal, Invited Speaker: Roche, Gilead, Sysmex. All other authors have declared no conflicts of interest.

https://doi.org/10.1016/j.esmoop.2023.101442

255TiP AIPAC-003: A randomized, double-blind, placebo-controlled phase III trial testing eftilagimod alpha (soluble LAG-3) in HER2-neg/low metastatic breast cancer patients receiving paclitaxel, following an open-label dose optimization

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Background: Eftilagimod alpha (efti), a soluble LAG-3 protein, acts as an MHC class II agonist that enhances immunity by mediating antigen presenting cell and CD8 T-cell activation. Data from a randomized, phase IIb trial of efti plus paclitaxel compared to placebo plus paclitaxel in patients (pts) with HR+ HER2− metastatic breast cancer (MBC) (AIPAC; NCT02614833) showed sustained pharmacodynamic activity that was linked to improved overall survival (OS) in the efti arm. AIPAC-003 is a randomized, double-blind, placebo-controlled phase III trial testing efti plus paclitaxel in HER2-neg/low MBC pts, including an initial open-label dose optimization lead-in (DOL) component to determine the optimal biological dose (OBD) of efti in this combination.

Trial design: Enrolment for the DOL will begin in March 2023 in max. 66 pts. Primary endpoints (EP) in the DOL include safety and tolerability of 90 mg vs 30 mg efti and defining the OBD of efti in combination with weekly paclitaxel. Determination of the OBD will be based on the totality of safety and tolerability data together with overall response rate (ORR) and pharmacodynamic marker (CD8+ T cells, absolute lymphocyte count) data. In the phase III component approx. 771 pts will be randomized to receive either paclitaxel + efti or paclitaxel + placebo in a double-blinded fashion. The primary EP for the proposed phase III is OS. Key secondary EPs include progression free survival and ORR by RECIST 1.1, quality of life and safety. Pts will receive paclitaxel (80 mg/m2 I.V. on D1, 8 and 15 in a 4-week cycle), in combination with efti or placebo (DOL: 30 or 90 mg efti; Phase III: OBD of efti or placebo) S.C. on D1 and 15 in a 4-week cycle for up to 12 months. Key inclusion criteria: Pts with either a) HR+ and HER2-neg/low and endocrine therapy-resistant MBC or b) TNBC not eligible for anti-PD-1-based therapy. Pts must have measurable disease, ECOG PS 0-1 and no prior chemo for metastatic disease.

Legal entity responsible for the study: Immutep S.A.

Funding: Immutep S.A.

Disclosure: F.P. Duhoux: Other, Consulting or Advisory: Roche,Pfizer, AstraZeneca, Lilly, Novartis, Amgen, Daiichi Sankyo, Pierre Fabre, Gilead Sciences, Seattle Genetics, MSD Oncology; Other, Travel, Accommodations, Expenses: Amgen, Roche, Teva, Pfizer, Daiichi Sankyo/AstraZeneca. M. Oliveira: Other, Consulting or Advisory Role: Roche/Genentech, AstraZeneca, Seattle Genetics, ITeos Therapeutics, Daiichi Sankyo/AstraZeneca, Gilead Sciences, Relay Therapeutics; Other, Travel, Accommodations, Expenses: Eisai, Pierre Fabre, Gilead Sciences, AstraZeneca Spain; Other, Honoraria: Roche, Novartis, Pfizer, MSD, Eisai Europe, Seattle Genetics, Gilead Sciences; Other, Research Funding: Roche/Genentech, AstraZeneca, Seattle Genetics, Boehringer Ingelheim, GlaxoSmithKline, Zenith Epigenetics, Gilead Sciences, Ayala Pharmaceuticals. J. Peguero: Other, Employment: Oncology

Consultants; Other, Leadership Role: Director, Research Department. F. Triebel: Other, Employment: Immutep SAS; Other, Stock and Other Ownership Interests: Immutep Ltd.; Other, Patents, Royalties, Other Intellectual Property: Being an inventor on patents on LAG-3 owned by Immutep SAS. All other authors have declared no conflicts of interest.

https://doi.org/10.1016/j.esmoop.2023.101443

256TiP TACTIVE-E: Phase Ib study of ARV-471, a PROteolysis TArgeting Chimera (PROTAC) estrogen receptor (ER) degrader, in combination with everolimus in ER+/human epidermal growth factor receptor 2 (HER2)- advanced breast cancer

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Background: ARV-471 is an oral PROTAC ER degrader that binds to and degrades both wild-type ER and *ESR1* mutants. ARV-471 was well tolerated and showed clinical activity in a phase I/II study in heavily pretreated patients (pts) with ER+/HER2- advanced breast cancer. Everolimus, an inhibitor of mammalian target of rapamycin (mTOR), is approved with exemestane for pts with ER+/HER2- breast cancer after progression on aromatase inhibitors and has shown clinical activity after cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitor treatment. In pts with prior CDK4/6 inhibitor therapy, the combination of ARV-471 and everolimus may offer additional advantages as ARV-471 can degrade mutant forms of ER, and *ESR1* mutations are enriched in this setting. Preclinical studies in ER-expressing breast cancer cell lines showed evidence of cell growth inhibition with ARV-471 plus everolimus, including in cells expressing Y537S or D538G *ESR1* mutations. ARV-471 plus everolimus demonstrated greater tumor growth inhibition in a xenograft breast cancer model than either monotherapy. Here we describe the open-label, phase Ib TACTIVE-E study (NCT05501769) of ARV-471 plus everolimus in pts with ER+/HER2- advanced breast cancer.

Trial design: Eligible pts (aged $\geq$18 years) have histologically or cytologically confirmed ER+/HER2- metastatic, recurrent, or unresectable breast cancer; received 1–3 prior lines systemic therapy in the advanced/metastatic setting, including $\geq$1 endocrine therapy and $\leq$1 chemotherapy; and progression on or intolerance to a CDK4/6 inhibitor. Pts may not have received prior ARV-471 or an mTOR-targeting therapy. ARV-471 combined with everolimus is administered orally in 28-day cycles. The primary endpoints are dose-limiting toxicities to determine the recommended phase II dose for ARV-471 in combination with everolimus, and type, frequency, and severity of adverse events and laboratory abnormalities. Secondary endpoints are preliminary antitumor activity (overall response rate, clinical benefit rate, and duration of response) and pharmacokinetic parameters of ARV-471 plus everolimus.

Clinical trial identification: NCT05501769.

Editorial acknowledgement: Medical writing support: Justine Lempart, PhD, of Apollo Medical Communications, and funded by Arvinas Operations, Inc.

Legal entity responsible for the study: Arvinas Estrogen Receptor, Inc.

Funding: Arvinas Estrogen Receptor, Inc.

Disclosure: A. Schott: Financial Interests, Personal, Other, Contracted Research: Pfizer, Takeda, Genentech, Arvinas; Financial Interests, Personal, Other, Receipt of Intellectual Property Rights/Patent Holder: Imbio, LLC. J. Cortés: Financial Interests, Personal, Advisory Board: Roche, Celgene, Cellestia, AstraZeneca, Seattle Genetics, Daiichi Sankyo, Erytech, Athenex, Polyphor, Lilly, Merck Sharp& Dohme, GSK, Leuko, Bioasis, Clovis oncology, Boehringer Ingelheim, Ellipses, Hibercell, BioInvent, Gemoab, Gilead, Menarini, Zymeworks, Reveal Genomics; Financial Interests, Personal, Invited Speaker: Roche, Novartis, Celgene, Eisai, Pfizer, Samsung Bioepis, Lilly, Merck Sharp & Dohme, Daiichi Sankyo; Financial Interests, Personal, Other, Consulting/advisor: Expres2ion Biotechnologies; Financial Interests, Personal, Stocks/Shares: MedSIR, Nektar Therapeutics; Financial Interests, Institutional, Research Grant: Roche, Ariad Pharmaceuticals, AstraZeneca, Baxalta GMBH/Servier Affaires, Bayer healthcare, Eisai, Guardant Health, Merck Sharp&Dohme, Pfizer, Piqur Therapeutics, Puma B, Queen Mary University of London; Other, Travel cost and expenses: Roche, Novartis, Eisai, Daiichi Sankyo, Pfizer, Gilead, AstraZeneca. S. Ivie: Financial Interests, Personal, Full or part-time Employment: Arvinas Operations, Inc. R. Gedrich: Financial Interests, Personal, Full or part-time Employment: Arvinas Operations, Inc.; Financial Interests, Personal, Stocks/Shares: Arvinas Operations, Inc. E. Zhi: Financial Interests, Personal, Full or part-time Employment: Arvinas; Financial Interests, Personal, Stocks/Shares: Arvinas; Financial Interests, Personal, Project Lead: Arvinas. J. Ranciato: Financial Interests, Personal, Full or part-time Employment: Arvinas. J. Perkins: Financial Interests, Personal, Full or part-time Employment: Pfizer; Financial Interests, Personal, Stocks/Shares: Pfizer; Financial Interests, Personal, Other, Patent Holder: Pfizer. E. Hamilton: Financial Interests, Institutional, Other, Consulting/Advisory Role: Genentech/Roche, Novartis, Lilly, Pfizer, Mersana, iTeos, Janssen, Loxo, Relay Therapeutics, Olema Pharmaceuticals, Orum Therapeutics, Stemline Therapeutics, Arcus, AstraZeneca, Daiichi Sankyo, Seagen, Ellipses Pharma, Greenwich LifeSciences, Tubulis, Verascity Science; Financial Interests, Institutional, Research Grant: Oncomed, Genentech/Roche, Zymeworks, Rgenix, Arqule, Clovis, Millennium, Acerta Pharma, Sermonix Pharmaceuticals, Black Diamond, Immunomedics, Karyopharm, Curis, Syndax, Novartis, Boehringer Ingelheim, FujiFilm, Taiho, Deciphera, Molecular Templates, Onconova Therapeutics, Dana Farber Cancer Hospital, Hutchinson MediPharma, MedImmune, Seagen, Compugen, TapImmune, Lilly, Pfizer, H3 Biomedicine, Merus, Regeneron, Arvinas, StemCentRx, InventisBio, Verastem, eFFECTOR Therapeutics, CytomX, Lycera, Mersana, Radius Health, AbbVie, Nucana, Leap Therapeutics, Zenith Epigenetics, Harpoon, Orinove, AstraZeneca, Tesaro, Macrogenics, EMD Serono, Daiichi Sankyo, Syros, Sutro, G1 Therapeutics, PharmaMar, Olema, Immunogen, Plexxicon, Amgen, Akesobio Australia, Shattuck Labs, ADC Therapeutics, Aravive, Jacobio, Atlas MedX, Ellipses, Incyte, Mabspace Biosciences, ORIC Pharmaceuticals, Pieris Pharmaceuticals, Pionyr Immunotherapeutics, Repertoire Immune Medicine, Treadwell Therapeutics, Accutar Biotechnology, Cascadian Therapeutics, Artios, BeiGene, Bliss BioPharmaceuticals, Context Therapeutics, Cullinan-Florentine, Dantari, Duality Biologics, Elucida Oncology, Infinity Pharmaceuticals, K-Group Beta, Kind Pharmaceuticals, Loxo Oncology, Oncothyreon, Relay Therapeutics, Orum Therapeutics, Prelude Therapeutics, Profound Bio, Tolmar, Torque Therapeutics. All other authors have declared no conflicts of interest.

https://doi.org/10.1016/j.esmoop.2023.101444

257TiP VERITAC-2: A global, randomized phase III study of ARV-471, a PROteolysis TArgeting Chimera (PROTAC) estrogen receptor (ER) degrader, vs fulvestrant in ER+/human epidermal growth factor receptor 2 (HER2)- advanced breast cancer

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Background: ARV-471 is an oral PROTAC ER degrader that binds to and degrades wild-type ER and clinically relevant mutants. ARV-471 directly recruits the ubiquitin-proteasome system to degrade ER, whereas selective ER degraders (SERDs) indirectly cause ER degradation. In a first-in-human phase I/II study, ARV-471 monotherapy was well tolerated and showed clinical activity in heavily pretreated patients with ER+/HER2- advanced breast cancer. The phase III monotherapy dose (200 mg once daily [QD]) was chosen due to comparable efficacy and favorable tolerability relative to 500 mg QD and robust ER degradation in paired tumor biopsies. The randomized phase III VERITAC-2 study (NCT05654623) will compare efficacy and safety of ARV-471 vs the SERD fulvestrant in patients with ER+/HER2- advanced breast cancer after prior combination cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitor therapy and endocrine therapy (ET).

Trial design: Eligible patients (aged $\geq$18 years) have a confirmed diagnosis of ER+/HER2- locoregional recurrent or metastatic breast cancer not amenable to surgical resection or radiation; 1 prior line of combination CDK4/6 inhibitor therapy and ET; $\leq$1 additional line of ET; most recent ET given for $\geq$6 months before disease progression; and radiological disease progression during or after the last line of therapy. Prior chemotherapy in the locally advanced or metastatic setting and prior fulvestrant are not permitted. Patients (N ~ 560) are randomized 1:1 to receive 200 mg ARV-471 orally QD continuously or fulvestrant intramuscularly on days 1 and 15 in the first 28-day cycle and on day 1 in subsequent cycles; patients are stratified by *ESR1* mutation status and presence of visceral disease. The primary endpoint, progression-free survival, will be assessed by blinded independent central review in the intention-to-treat population and the *ESR1* mutation sub-population. Secondary outcome measures include overall survival, antitumor activity (objective response rate, duration of response, and clinical benefit rate), safety, and quality of life assessments.

Clinical trial identification: NCT05654623.

Editorial acknowledgement: Medical writing support: Justine Lempart, PhD, of Apollo Medical Communications, and funded by Arvinas Operations, Inc.

Legal entity responsible for the study: Arvinas Estrogen Receptor, Inc.

Funding: Arvinas Estrogen Receptor, Inc.

Disclosure: E. Hamilton: Financial Interests, Institutional, Other, Consulting/Advisory Role: Genentech/Roche, Novartis, Lilly, Pfizer, Mersana, iTeos, Janssen, Loxo, Relay Therapeutics, Olema Pharmaceuticals, Orum Therapeutics, Stemline Therapeutics, Arcus, AstraZeneca, Daiichi Sankyo, Seagen, Ellipses Pharma, Greenwich LifeSciences, Tubulis, Verascity Science; Financial Interests, Institutional, Research Grant: Oncomed, Genentech/Roche, Zymeworks, Millennium, Rgenix, Arqule, Clovis, Acerta Pharma, Sermonix Pharmaceuticals, Black Diamond, Karyopharm, Curis, Syndax, FujiFilm, Novartis, Boehringer Ingelheim, Immunomedics, Taiho, Deciphera, Molecular Templates, Onconova Therapeutics, Dana Farber Cancer Hospital, Hutchinson MediPharma, MedImmune, Seagen, Compugen, TapImmune, Lilly, Pfizer, H3 Biomedicine, Merus, Regeneron, Arvinas, StemCentRx, InventisBio, Verastem, eFFECTOR Therapeutics, CytomX, Lycera, Mersana, Radius Health, AbbVie, Nucana, Leap Therapeutics, Zenith Epigenetics, Harpoon, Orinove, AstraZeneca, Tesaro, Macrogenics, EMD Serono, Daiichi Sankyo, Syros, Sutro, G1 Therapeutics, PharmaMar, Olema, Immunogen, Plexxicon, Amgen, Akesobio Australia, Shattuck Labs, ADC Therapeutics, Aravive, Jacobio, Atlas MedX, Ellipses, Incyte, Mabspace Biosciences, ORIC Pharmaceuticals, Pieris Pharmaceuticals, Pionyr Immunotherapeutics, Repertoire Immune Medicine, Treadwell Therapeutics, Accutar Biotechnology, Artios, BeiGene, Bliss BioPharmaceuticals, Cascadian Therapeutics, Context Therapeutics, Cullinan-Florentine, Dantari, Duality Biologics, Elucida Oncology, Infinity