678P ExoDS: A bioengineered exosome-based capsule for targeted delivery of chemotherapy drugs to cancer cells and cancer stem cells

A. Dutta, S. Paul, S. Bhagat

R&D, Exsure, Bhubaneswar, India

Background: Cancer stem cells (CSCs) are the major cause of therapy failure. CSCs are responsible for cancer relapse, metastasis, chemo-resistance, and radiation resistance. Therefore, targeting CSCs is imperative for better therapy outcomes. To date, there is no therapy precisely targeting CSCs. To fill these lacunae we have developed ExoDS a bioengineered exosome-based platform to precisely deliver chemotherapy drugs directly to CSCs effectively eliminating them.

Methods: ExoDS is an exosome-based platform that has been isolated and purified from immune cells that have been treated with a patented bioformulation and the specific drug to be incorporated within exosomes. To test the efficacy of ExoDS in targeting CSCs, we first generated and isolated CSCs from breast cancer cell lines, MCF7, MDA-MB-231, and MDA-MB-468. We next isolated CSCs from chemo-naïve breast tumor tissue samples to test the efficacy of ExoDS in targeting breast CSCs. We extensively used flow cytometric dependent analysis of AnnexinV to determine apoptosis in CSCs.

Results: Our results have shown that ExoDS can specifically identify and target CSCs with a 12-fold higher efficiency as compared to free drugs. At a cellular level, we established that ExoDS gets internalized inside CSCs within 6hrs of treatment. ExoDS was also found to target CTCs isolated from patient blood (n=5). Further analysis revealed that ExoDS spared healthy PBMCs isolated from healthy donors (n=9) as well as breast cancer patients (n=7). Our data confirmed that ExoDS can reduce chemotoxicity by more than 30%. Broadly, our results highlight the benefits of using ExoDS as compared to free chemotherapy drugs. ExoDS is a potential chemotherapy alternative.

Conclusions: Collectively, ExoDS efficiently targeted CSC in-vitro and also ex-vivo. Its specificity towards CSCs was established by the inability of ExoDS to target PBMCs derived from healthy individuals as well as patients. ExoDS can potentially target CSCs in a clinical setting making it a first-of-its-kind therapy vehicle. Targeting CSCs will revolutionize cancer treatments and will lead to better therapy outcomes. Currently, we are testing ExoDS in murine models to test it's in vivo efficacy and efficiency.

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679P Lurbinectedin (LRB) pharmacokinetics (PK) and safety when co-administered with itraconazole (ITZ) in patients with advanced solid tumor

I. Moreno[1], T. Hernandez[2], E. Calvo[1], S. Fudio[3], C. Kahatt[3], S. Martinez[3], J. Iglesias[3], R.O. Calafati[3], L. Pérez Ramos[3], L. Montilla[3], A. Zeaiter[3], R. Lubomirov[3]

[1]Oncology, START Madrid-CIOCC, Centro Integral Oncológico Clara Campal, Madrid, Spain; [2]Oncology, START Madrid-FJD, Hospital Universitario Fundación Jiménez Díaz, Madrid, Spain-Current address: START Barcelona-HM CIOCC Early Phase Program, Hospital HM Nou Delfos, Barcelona, Spain; [3]Clinical Development, PharmaMar, Colmenar Viejo, Madrid, Spain

Background: LRB is a highly selective inhibitor of oncogenic transcription primarily metabolized by CYP3A4. This study investigated whether the PK and safety profile of LRB is affected by co-administration with ITZ, a strong CYP3A4 inhibitor, in adult patients with advanced solid tumors.

Methods: This was a 2-part crossover, open-label, phase Ib drug-drug interaction study (NCT05063318). In Part A, 3 patients were assigned to sequence 1 (TR) receiving a cycle (C) 1 of LRB (0.8 mg/m^2, 1 hour [h], iv) co-administered with ITZ (200 mg/day oral; 12-days), followed by a C2 of LRB alone (3.2 mg/m^2, 1 h, iv). In Part B, 11 patients were randomized (1:1) to receive either sequence 1 (TR) or 2 (RT). Plasma samples for LRB and ITZ PK were collected.

Results: 11 patients were evaluable for the primary objective of the study: 3 patients in Part A and 8 patients in Part B (4 in each of sequences 1 and 2). The systemic exposure of LRB was increased [15% for C_{max}, 2.4-fold for $AUC_{0\text{-}t}$ and 2.7-fold for $AUC_{0\text{-}\infty}$] with ITZ co-administration. This correlated with reduced clearance (CL) by 63% and prolonged elimination half-life ($t_{1/2}$) by 2.2-fold. Co-administration with ITZ produced statistically significant modifications in the unbound plasma LRB PK parameters of similar extent than in total plasma with a 2.2-fold and 2.4-fold increase in $AUC_{0\text{-}t}$ and $AUC_{0\text{-}\infty}$, respectively compared to LRB alone. Unbound LRB CL decreased by 58% and $t_{1/2}$ was 2-fold longer. Consistent with previous studies, the most common treatment-related adverse events of LRB alone at dose of 3.2 mg/m^2 were neutropenia, nausea, vomiting and fatigue. Safety profile of LRB at a dose of 0.9 mg/m^2 when co-administered with ITZ was no worse than that of LRB administered alone at 3.2 mg/m^2.

Conclusions: In comparison with LRB alone, the co-administration with multiple doses of ITZ, significantly altered LRB systemic exposure reducing total plasma (by 63%) and unbound (by 58%) LRB CL. The magnitude of these changes showed a clinically relevant effect of ITZ co-administration on LRB PKs. To avoid LRB overexposure and a worst safety profile when co-administered with strong CYP3A4 inhibitors a LRB dose reduction proportional to CL reduction should be applied.

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680P First results from the phase I trial of the ATR inhibitor, ART0380, in advanced solid tumors

K. Moore[1], M.R. Patel[2], G.S. Falchook[3], E. Fontana[4], B. Bashir[5], C.A. Perez[6], M. Barve[7], S. Ulahannan[8], H. Milward[9], A. Fielding[9], B. Harrop[10], N. Little[9], T. Coleman[11], A. Wilby[12], S. Busacca[13], S. Holt[14], S. Menon[15], D. Headley[16], I. Smith[17], M.L. Johnson[18]

[1]Department of Obstetrics and Gynecology University, Stephenson Cancer Center/University of Oklahoma, Oklahoma City, OK, USA; [2]Drug Development, Florida Cancer Specialists, Fort Myers, FL, USA; [3]Drug Development Unit, Sarah Cannon Research Institute (SCRI) at HealthONE, Denver, CO, USA; [4]Drug Development, Sarah Cannon Research Institute SCRI UK, London, UK; [5]Medical Oncology, Sidney Kimmel Cancer Center - Thomas Jefferson University, Philadelphia, PA, USA; [6]Department of Medicine, Florida Cancer Specialists, Fort Myers, FL, USA; [7]Research Oncology, Mary Crowley Cancer Research Center, Dallas, TX, USA; [8]Hematology Oncology, Stephenson Cancer Center/University of Oklahoma, Oklahoma City, OK, USA; [9]Drug Development, Artios Pharma Limited, Cambridge, UK; [10]Oncology Business Unit, Artios Pharma Limited, Cambridge, UK; [11]Clinical Pharmacology, Artios Pharma Limited, Cambridge, UK; [12]Clinical Pharmacology, Seda Pharmaceutical Development Services, Manchester, UK; [13]Leicester Cancer Research Centre, University of Leicester-Leicester Cancer Research Centre, Leicester, UK; [14]Translational Science, Artios Pharma Limited, Cambridge, UK; [15]Bioinformatics, Artios Pharma Limited, Cambridge, UK; [16]Clinical Development, Artios Pharma Limited, Naples, FL, USA; [17]Clinical Development, Artios Pharma Limited, Cambridge, UK; [18]Lung Cancer Research, Sarah Cannon Research Institute-Cancer Centre, Nashville, TN, USA

Background: Ataxia telangiectasia and Rad3-related (ATR) is a critical protein in sensing DNA damage and activating the DNA damage checkpoint. ART0380 is a potent and selective, orally administered ATR inhibitor. This is the first report of the ongoing phase I trial (NCT04657068).

Methods: Patients (pts) with advanced solid cancers received escalating doses of ART0380 on a continuous daily (QD) or intermittent (3 days on, 4 days off) schedule. Investigators were guided to enroll pts with cancers that harbored DNA damage response deficiencies as identified by the Artios DcoDeR platform. Key study objectives included evaluation of safety and tolerability, preliminary efficacy, pharmacokinetics (PK), and pharmacodynamics.

Results: 49 pts were dosed with ART0380 monotherapy: 39 pts on intermittent doses between 100mg and 1200mg, and 10 pts on QD doses of 200mg and 400mg. PK data show ART0380 is rapidly absorbed followed by immediate decline to a low level succeeded by a longer mean elimination half-life of 8.3 hours. ART0380 exposure is dose proportional with increasing dose from 100mg to 1200mg in terms of Cmax and AUC0-24ss. The recommended phase II doses have been established as 600mg intermittent and 200mg QD. Approximately 36% of pts experienced the only Grade 3 treatment-related adverse event of anemia. Pts on QD dosing experienced fewer unplanned dose interruptions due to adverse events compared to intermittent dosing. Confirmed partial responses were observed in 3 pts with endometrial adenocarcinoma and 1 pt with anal cancer. One pt with cholangiocarcinoma had a profound reduction in their tumor marker associated with a reduction in non-measurable disease. There was a 25% confirmed objective response rate in pts with measurable disease treated on the QD regimens. Target engagement was