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Ad-RTS-hIL-12+Veledimex bench to bedside in the treatment of metastatic breast cancer

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Immunotherapy has been shown to be effective in breast cancer patients. In breast cancer, CD8+ T-cells are activated by IL-12 have been shown to correlate with anti-tumor activity and prolonged survival. Ad-RTS-IL-12 (Ad) is a replication incompetent adenovirus engineered to express IL-12 via our RheoSwitch Therapeutic System® gene switch. When injected directly into a tumor. IL-12 expression is off devoid of the activator ligand, veledimex (V), while IL-12 production is turned on in a dose-dependent manner by V p.o. Mechanistic studies in the 4T1 syngeneic mouse breast tumor model with Ad+V have shown a dose related increase in tumor IL-12 mRNA and IL-12 protein expression. Cessation of V resulted in a return to baseline IL-12 mRNA and IL-12 protein expression. These changes correlated with a local and systemic immune and anti tumor response. Low dose chemotherapy primes the immune system and in combination with immunotherapy may augment tumor specific T-cells resulting in enhanced efficacy. In the 4T1 mouse mammary tumor model Ad (1e10vp)+V (30 mg/m2) with low dose chemotherapy significantly inhibited tumor growth in a supra-additive fashion concomitant with increased median survival vs. single agent alone. Based on these results an open label, phase-2 trial evaluating the safety of inducible IL-12 expression in heavily pretreated subjects with recurrent/metastatic breast cancer was performed. In this study, treatment with Ad+V resulted in increase in IL-12, downstream IFNg followed by rapid increase in IL-10 and IP-10. In the 12 subjects administrated Ad+V there was a total of 16 non-injected evaluable lesions in 7 subjects. Of the 16 lesions, 1 lesion had decrease in lesion diameter ranging from 10-19%, 2 lesions 30-49% and 3 lesions 50-100%. Most common ≥Grade 3 treatment emergent adverse events in BC and melanoma included neutropenia and hyponatremia (16% each), hypotension, cytokine release syndrome, AST increase (11% each), dehydration, fatigue, pyrexia (8% each). All TEAEs and SAEs≥Grade 3 reversed rapidly upon discontinuation of veledimex. The results of this study showed biologic activity with an acceptable therapeutic index. In summary, Ad+V are a novel gene therapy which controls local expression of IL-12, which may result in the collapse of tumor stroma and stimulating an anti-cancer T-cell immune response. The ability to regulate the production of IL-12 by modulating V dosing may result in an improved therapeutic index in combination with standard of care.

Biography

John A Barrett has completed his PhD from Saint John's University, NY. He is presently a Vice President of R&D and Head of Translational Research at Ziopharm Oncology with a research focus in immunotherapy, oncology, targeted radiopharmaceuticals and biomarkers. During his career, he was responsible for numerous INDs and NDAs and has authored 45 papers in peer review journals.

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