

Abstract: EMI-1725 Demonstrates Broad Antagonist Activity Against Drug-Resistant AR Mutations and Tumor Growth Suppression in Preclinical Models of mCRPC

Authors: Steven Kregel¹, Raymond J. Kostlan^{1,2}, John T. Phoenix^{1,2}, Audris Budreika^{1,2}, Carleen D. Deegan^{1,2}, Jonathan Katz^{3,4}, Jerry S.H. Lee^{3,5,6}, Charles McKenna⁷, David B Agus^{3,4,8}, Katherin Patsch³

Affiliations:

¹Department of Cancer Biology, Stritch School of Medicine, Loyola University Chicago, Maywood, IL, USA 60153

²Integrated Program in Biomedical Science, Biochemistry, Molecular and Cancer Biology, Loyola University Chicago, Maywood, IL, USA 60153

³Ellison Medical Institute, Los Angeles, CA 90064, USA

⁴Department of Medicine, Keck School of Medicine, University of Southern California, Los Angeles, CA 90033, USA

⁵Chemical Engineering and Material Science, Viterbi School of Engineering, University of Southern California, Los Angeles, CA 90089 USA

⁶Quantitative and Computational Biology, Dornsife College of Letters and Sciences, University of Southern California, Los Angeles, CA 90089 USA

⁷Department of Chemistry, University of Southern California, Los Angeles, CA 90089, USA

⁸Alfred E. Mann Department of Biomedical Engineering, Viterbi School of Engineering, University of Southern California, Los Angeles, CA 90089, USA

Background: Metastatic castration-resistant prostate cancer (mCRPC) remains a leading cause of cancer-related mortality in men, with over 35,000 deaths annually in the United States and a 5-year survival rate of approximately 30%. Although AR-targeted therapies such as enzalutamide and darolutamide delay disease progression, resistance inevitably emerges, underscoring a critical unmet need for next-generation therapeutics. Here, we describe EMI-1725, a novel androgen receptor (AR) antagonist developed to overcome resistance-associated AR mutations.

Methods: EMI-1725 binds the AR ligand-binding domain with affinities comparable to or higher than enzalutamide and darolutamide. In cell-based transcriptional assays, both enantiomers inhibit wild-type AR activity at potencies comparable to approved agents and retain activity against the most prevalent AR mutation T878A, where EMI-1725 is approximately 5-fold more potent than darolutamide. Critically, EMI-1725 also demonstrates antagonist activity against the enzalutamide-resistant double mutant AR F877L/T878A, a target not addressed by current therapies. In cell viability assays, EMI-1725 inhibits proliferation of two prostate cancer models (AR-amplified VCaP and LNCaP cells expressing the AR T878A mutation).

Results: In an AR-amplified xenograft model of mCRPC (VCaP), EMI-1725 reduced tumor growth as well as enzalutamide and suppressed PSA levels below those achieved with enzalutamide at standard dosing. Treatment across all groups was well tolerated over 47 days of daily oral gavage, with no significant weight loss. EMI-1725 showed improved biodistribution across organs, and importantly, displayed less accumulation in the brain compared to enzalutamide, where off-target binding leads to risk of seizure.

Conclusions: Collectively, these *in vitro* and *in vivo* findings support the advancement of EMI-1725 as a promising therapeutic candidate for mCRPC.

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