The androgen receptor (AR) pathway continues to drive most castrate-resistant prostate cancers even in late stages of the disease through resistance mechanisms, including gain-of-function mutations in the C-terminal ligand binding domain (LBD) and expression of constitutively active truncated AR splice variants lacking the LBD, such as AR-V7. Selective inhibition of the N-terminal domain (NTD) of the AR can inhibit its transcriptional activity even in the presence of LBD driven anti-androgen resistance.

A Phase I clinical trial of the first-generation AR NTD inhibitor, EPI-002, (a triacetate produg of EPI-506) demonstrated PSA declines in enzalutamide and/or abiraterone resistant metastatic CRPC patients. However, these declines were only 50% and of short duration. The drug was well-tolerated but required high doses to achieve meaningful exposure, and steady-state concentrations were well below those required for full NTD inhibition.

EPI-7386 represents a new generation of NTD inhibitors (Antinen) and its characteristics are presented.