Novel androgen/androgen receptor (AR) directed therapies have demonstrated prolongation of survival in castration-resistant prostate cancer (CRPC). However, most CRPC patients progress during treatment with abiraterone acetate (AA) or enzalutamide (Enza); this is associated with rising PSA, suggesting that persistent AR signaling is responsible for treatment failure.

Galeterone (TOK-001) is a small molecule oral drug that disrupts AR signaling by a novel triple mechanism: it potently and selectively inhibits CYP17 lyase, potently antagonizes AR and decreases AR protein levels (wild-type and mutant), leading to antitumor activity.

In preclinical models, galeterone demonstrates potent inhibition of testosterone synthesis via selective inhibition of CYP17 lyase. Unlike AA, ketoconazole and orteronel, galeterone caused minimal changes in cortisol and other intermediate corticosteroids, suggesting that pharmacological levels will not cause secondary mineralocorticoid excess (ME). ME is characterized by hypertension, peripheral edema, and hypokalemia. ME is a clinical sequelae of AA treatment because of its selective inhibition of CYP17 hydroxylase leading to elevated progesterone and decreased cortisol (activating the ACTH feedback loop), and co-administration with prednisone is therefore required.

A phase I trial of galeterone (ARMOR1) showed significant antitumor activity demonstrated by PSA declines along with soft tissue tumor shrinkage (Taplin, ME et al., AACR 2012 and Montgomery, B et al., ASCO 2012). At the maximal tested dose (2600 mg PO QD), 75% and 42% of patients had > 30% and > 50% decline in PSA, respectively, and in some cases corresponding radiological responses were seen. Galeterone demonstrated a favorable risk benefit ratio with 90% of AEs ≤ grade 2 (e.g. nausea and diarrhea). Similar to AA, some patients had increases in transaminases. In all cases these increases were reversible and the majority of those patients were rechallenged with no further rise in transaminases. With galeterone treatment, ME was not observed, prednisone or eplerenone were not required, and no CNS AEs occurred. The MTD was not reached.

A phase 2 study of galeterone in CRPC, ARMOR2, using a new tablet formulation is accruing AA and Enza naive and AA treated patients.