The androgen receptor (AR) pathway continues to drive most castration-resistant prostate cancer (CRPC) even in late stages of the disease through resistance mechanisms including gain-of-function mutations in the C-terminus 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 anti-androgen resistance.

A Phase I clinical trial of the first-generation AR NTD inhibitor, EPI-006, (a triacetate prodrug of EPI-002 – Ralaniten) demonstrated PSA declines in enzalutamide and/or abiraterone resistant metastatic CRPC patients. However, these declines were less than 50% and of short duration (see abstract 257, poster board L14), revealing the need for more potent and metabolically stable NTD inhibitors.

A new generation of NTD transcriptional inhibitors (Anitens) has been generated. Examples of this new class, demonstrating improved potency, metabolic stability and pharmaceutical properties, will be discussed in this poster.

Next generation Anitens demonstrate a 10-20 fold improvement on the inhibition of androgen-induced AR transcriptional activity

Figure 2: Activity against androgen-induced PSA-luciferase activity in LNCaP cells

A: A dosedependent decrease in AR transcriptional activity was demonstrated in LNCaP cells transfected with the PSA reporter gene and stimulated with androgen (R1881). B: Summary of ES50 calculated across multiple independent experiments.

Next generation Anitens are active and well tolerated in castrated mice bearing AR dependent LNCaP xenographs

Figure 4: Anitens are metabolically stable and show adequate PK profile for high and sustained plasma exposure

Conclusions

- Promising next-generation Anitens compounds have been identified
- Major chemistry efforts led to the identification of several Anitens with >10 20 fold improvement in cellular potency compared to EPI-506 and which are also metabolically stable
- These compounds showed in vivo activity in an AR full length model, but also in an enzalutamide resistant model driven by AR-V7
- IND-selection preclinical studies are underway on the most promising Anitens with an IND submission planned shortly

CONCLUSION

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