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BACKGROUND

Androgen Receptor (AR) and PI3K/Akt Signaling are Two of the Most Frequently Dysregulated Pathways in Prostate Cancer

- Prostate cancer remains sensitive to inhibition of the androgen pathway, including in the castration-resistant state.
- More than 90% of metastatic prostate cancer cells exhibit activation of phosphomonoesterase 3 (PMEPA1) pathways, frequently through loss of PTEN.

Primary Objective of the Phase II Portion of the Study

- Assess the effect on numbers of circulating tumor cells
- Estimate the clinical activity, as measured by prostate-specific antigen (PSA) response rate, confirmed objective tumor response rate
- Assess the effect on numbers of circulating tumor cells

Secondary End Points

- The study consists of two stages
- The study will attempt to define a biomarker of sensitivity to combination treatment
- Tumor samples will be assayed for PTEN status using IHC
- Patient-reported outcomes: BPI and EORTC QLQ-C30

Study Design

- A Phase II open-label stage in which the recommended Phase II dose (RP2D) will be determined for GDC-0068 and GDC-0980 in combination with abiraterone 1000 mg qd and prednisone 5 mg bid
- Two dose levels of GDC-0068 (600 mg, 5 mg bid; 400 mg, 5 mg bid) and GDC-0980 (30 mg, 40 mg bid; 2 mg/kg PO, 3 mg/kg PO) will be evaluated
- The decision to escalate to the higher dose level (600 mg and 40 mg for GDC-0068 and GDC-0980, respectively) will be made using standard 3+3 dose escalation rules

PREDICTIVE BIOMARKERS

- The study will attempt to define a biomarker of sensitivity to combination treatment
- The lead biomarker for GDC-0068 is PTEN loss
- Circulating tumor cells (CTCs) will be enumerated and assessed for PTEN gene copy number by Fluorescence in Situ Hybridization (FISH)

STUDY PATIENTS

Main Inclusion Criteria

- Histologically or cytologically confirmed metastatic or advanced prostate adenocarcinoma previously treated with docetaxel and progressed on 2 or more lines of therapy
- Availability of adequate organ function

Secondary Inclusion Criteria

- Previous therapy with Akt, PI3K, and/or mTOR inhibitors
- Adequate hematologic and end organ function
- ECOG PS (0-1)
- Adenocarcinoma of prostate
- Histologically or cytologically confirmed metastatic or advanced prostate cancer
- There is robust scientific rationale to concurrently inhibit AR and PI3K/Akt signaling in prostate cancer

Main Exclusion Criteria

- Previous therapy with CYP17 inhibitors, including abiraterone
- Abiraterone Acetate
- GDC-0068
- GDC-0980

STUDY OBJECTIVES

- The study will consist of two stages
- The phase II open-label stage in which the recommended dose will be determined for GDC-0068 and GDC-0980 in combination with abiraterone 1000 mg qd and prednisone 5 mg bid
- Two dose levels of GDC-0068 (600 mg, 5 mg bid; 400 mg, 5 mg bid) and GDC-0980 (30 mg, 40 mg bid) will be evaluated
- The decision to escalate to the higher dose level (600 mg and 40 mg for GDC-0068 and GDC-0980, respectively) will be made using standard 3+3 dose escalation rules

STUDY ASSESSMENTS

- Screening within 28 days prior to cycle 1
- PSA Day 1 of every cycle beginning with Cycle 4

PREDICTIVE BIOMARKERS

- The study will attempt to define a biomarker of sensitivity to combination treatment
- The lead biomarker for GDC-0068 is PTEN loss
- GDC-0980 has broad anti-proliferative activity in a range of PTEN- and PTEN+ prostate cell lines
- Tumor samples will be assayed for PTEN status using IHC
- Circulating tumor cells (CTCs) will be enumerated and assessed for PTEN gene copy number by Fluorescence in Situ Hybridization (FISH)

ACKNOWLEDGMENTS


TRIAL KEYWORDS:

- Prostate cancer
- PI3K/Akt
- mTOR
- abiraterone
- PTEN
- circulating tumor cells (CTCs)

REFERENCES


SUMMARY

- There is robust scientific rationale to concurrently inhibit AR and PI3K/Akt signaling in late-stage prostate cancer
- Three-arm trial design will allow evaluation of safety/efficacy of abiraterone + Akt inhibition and abiraterone + PTEN/MIF inhibition
- Trial is currently enrolling patients

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