Phase 2 Study of AZD4635 in Combination With Durvalumab or Oleclumab in Patients With Metastatic Castrate-resistant Prostate Cancer (mCRPC)

Emerson Lim1, James Reeves2, Sunil Gandhi3, David Spigel4, Edward Arrowsmith5, Daniel J. George5, Janet Karl5, Gayle Poulot5, Maureen M. Hattersley1, Eric Gangi1, Gareth James1, Jeff Thompson1, Deanna L. Russell1, Bhavikumar Patel1, Rakesh Kumar1, Gerald S. Falchook6

1Emory University Hospital, Atlanta, GA, USA; 2Fred H. West Cancer Center, New York, NY, USA; 3Turks Cancer Specialists SouthEast Cancer Research Institute, Fortworth, TX, USA; 4Fred Cancer Specialists NorthEast Cancer Research Institute, St. Petersburg, FL, USA; 5Emory University; 6Sarah Cannon Research Institute, Nashville, TN, United States; 7Karman Cancer Research Institute, Garwood, FL, USA; 8University of Illinois at Chicago, Chicago, IL, USA; 9Sarah Cannon Research Institute, Nashville, TN, United States; 10Sarah Cannon Research Institute at HealthONE, Denver, CO, USA.

Current Affiliation: Spectrum Health Medical Group, Medical Oncology & Hematology - LHD; Grand Rapids, MI, United States.

Introduction

The current standard of care for metastatic castration-resistant prostate cancer (mCRPC) includes testosterone and novel hormones agents (ARs), neo-adjuvant or adjuvant androgen ablation, and sipuleucel-T. 1

Patients with mCRPC can progress on treatments and have limited therapeutic options. 2

Due to the low adenine A(2a) receptor (A2AR) expression, ADAs reduce the intrinsic suppressive effects of adenosine and may complement immune-targeting agents such as durvalumab (anti-PD-L1) 3

A2ARs on tumor and immune cells could potentially modulate adenosine signaling of PD-L1 and T-cell activity. 4

Durvalumab is a human IgG4 kappa Fab that blocks the interaction of PD-L1 with PD-1 and CD80 (B7.1) on tumor cells. 5

The phase 3 study (ORCHID) evaluated the combination of durvalumab with sipuleucel-T. 6

Preclinical data demonstrate improved anti-tumour efficacy through co-targeting of A2AR and PD-L1. 7

The phase II study (IMAGINE) evaluated the safety and efficacy of AZD4635 in combination with durvalumab (Module 1) or oleclumab (Module 2) in patients with mCRPC. 8

Module 1

Methods

Eligible patients had histologically or cytologically confirmed mCRPC and had previously received and progressed on ≥ 2 approved lines of treatment before enrollment in this study (Table 1). Patients were randomized 1:1 to receive AZD4635 1500 mg IV Q4W or placebo for 1 year. Patients received durvalumab (1500 mg IV Q4W or 75 mg capsule PO QD) at study outset (Figure 1).

Patients were randomized into 2 arms: 9

- Arm A (μm): AZD4635 1500 mg IV Q4W + durvalumab 1500 mg IV Q4W
- Arm B (μm): Placebo + durvalumab 1500 mg IV Q4W

Assessment of primary efficacy was conducted every 10 weeks from the first dose, and included a tumor response to the treatment regimen, survival status, and safety. 10

Antitumor Activity

Patients were eligible for Arm A if they were determined to be responders with objective tumor shrinkage of 20% or greater. Patients were determined to be responders with objective tumor shrinkage of 20% or greater, with a best change from baseline of at least 20% in tumor size, confirmed either by CT or MRI. 11

Patients who were non-responders were randomly assigned to either modules 1 or 2.

Primary endpoints were objective response rate (ORR) per RECIST v1.1 and prostate-specific antigen (PSA)-confirmed response. 12 ORR was determined based on radiological progression-free survival (rPFS) at 6 months, overall survival (OS), safety, and tolerability.

Secondary endpoints included radiological progression-free survival (rPFS) at 6 months, overall survival (OS), safety, and tolerability.

All patients were required to give written informed consent prior to the first dose of study drug.

Results

ORR (iRECIST)

<table>
<thead>
<tr>
<th>ORR (iRECIST)</th>
<th>Module 1 (AZD4635 + Durvalumab)</th>
<th>Module 2 (AZD4635 + Oleclumab)</th>
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Median OS was 10.7 months (95% CI: 7.2–NE) in Module 1 and not reached in Module 2 (Figure 4A).

OS at 12 months was 69.9% (95% CI: 60.2–80.1) in Module 1 and 87.0% (95% CI: 78.1–93.9) in Module 2 (Figure 4B).

Median rPFS was 2.3 months [95% CI: 1.6–3.8] and 1.5 months [95% CI: 1.3–4.0] in Module 1 and Module 2, respectively (Figure 4A).

Probability of Progression-free Survival

Men aged 18 years or older are included in the study. 13

Exclusion criteria for the study were men aged 18 years or older are included in the study. 14

Conflicts of interest

None of the authors have any conflicts of interest.

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References


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