AZD5363, a catalytic pan-AKT inhibitor, in AKT1 E17K mutation positive advanced solid tumors


Introduction

AZT1 E17K mutation

• AZT1, a catalytic pan-AKT inhibitor, in tumors (NCT01226316).
• Assess the safety and tolerability of AZD5363.

Methods

Study design

• Open-label, multicenter, 2-stage, non-comparative, phase 1 study in patients aged ≥18 years with advanced solid tumors with ≥1 measurable lesion.
• The study is ongoing.

Patients and dosing

• Eligibility: ≥18 years, ≥1 prior line of systemic therapy, ECOG ≤1, ≥1 measurable lesion, tumor harboring AKT1 E17K mutation.
• Treatment: AZD5363 100 mg twice daily (bid) for at least 28 days.

Patients with tumors harboring AKT1 E17K mutation

• All 12 patients had ≥1 prior line of therapy, 2 patients (16%) treated with AZD5363 plus fulvestrant, 10 (83%) with AZD5363 alone, 1 (8%) on study drug at the dose level of 100 mg bid.

Combination of fulvestrant and AZD5363: clinical data

• For patients treated with AZD5363 plus fulvestrant for ≥12 weeks, the combination was generally well tolerated.

Assessments

• Primary endpoints: RECIST data are available for 11 patients with gynecological tumors.

Results

Patient demographics

• Median age (SD), years 56.8 (9.7)
• Mean number of regimens (SD) 5.9 (3.5).

Tumors

• N = 12, 10/12 patients demonstrated target lesion shrinkage (Figure 6):

AZD5363: 10/12

• 400 aa

• AKT1

• On-study duration from start of study drug to discontinuation or data cut-off (months)

• Safety was assessed throughout.

Combination of fulvestrant and AZD5363: preclinical data

• Preclinical studies: combination of fulvestrant and AZD5363 demonstrated synergistic antitumor activity in vitro.

Conclusions

• AZD5363, a pan-AKT inhibitor, was well tolerated in the current study.
• Integration of AKT1 E17K mutation status in clinical decision-making is under active consideration.

Figure 1. (a) Mutations in AKT1 triggered by fulvestrant. (b) Fulvestrant added on day 121 with disease progression. (c) Missense mutations in AKT1.