Evidence of Immune Activation in the First-in-Human Phase Ia Dose Escalation Study of the Adenosine 2a Receptor Antagonist, AZD4635, in Patients with Advanced Solid Tumors

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Introduction

- Adenosine in the tumor microenvironment plays an important role in innate and adaptive immunity, affecting immune function.
- Pharmacologic blockade of signaling through the adenosine 2a receptor (A2aR) may counteract the immunosuppressive effects of adenosine.
- AZD4635 is an oral inhibitor of A2aR signaling, and has been shown in preclinical models to increase dendritic cell activation, antigen presentation, and cytotoxic T cells.
- Modulating the tumor microenvironment with AZD4635 may allow for a more robust anti-tumor immune response, particularly when used in combination with immune checkpoint inhibitors.
- This first-in-human study was designed to determine the safety, tolerability, pharmacokinetics, and preliminary clinical activity of AZD4635 in patients with advanced solid tumors, both as monotherapy and in combination with anti-PDL1 durvalumab.

Methods

- This multicenter phase 1 study enrolled patients with refractory solid tumors in three monotherapy dose level cohorts, and two cohorts in combination therapy with durvalumab. Initial monotherapy dosing started at 125mg BID.
- Eligible patients had advanced solid tumors, an ECOG performance status of 0 or 1, and at least one prior treatment regimen.
- AZD4635 was administered orally as a nanosuspension on a continuous daily dosing schedule.
- Peripheral blood was analyzed for PK and TCR sequencing.
- Tumor biopsy samples were also collected and analyzed for gene expression and changes to the tumor microenvironment by Nanostring technology.

Baseline Patient Demographics and Clinical Characteristics (N=38)

Characteristic	Value
Median age, years (range)	64 (21-81)
Sex, n (%)	
Male	23 (61)
Female	15 (39)
Primary diagnosis, n (%)	
CRPC/mCRPC	12 (32)
Colorectal	6 (16)
Sarcomas	4 (11)
Ovary	3 (8)
Breast	2 (5)
Pancreas	2 (5)
Other: Uterus, Urinary Bladder, Head and Neck, Kidney, Melanoma, Bile Duct, Esophageal, Appendix, SCLC	9 (24)
Prior Therapies, n (%)	
Chemotherapy	31 (82)
Radiotherapy	22 (58)
Hormonal	14 (37)
Vaccine	5 (13)
Immune Checkpoint Inhibitor	5 (13)
Other	22 (58)
No. of prior therapies	
Median (range)	3 (1-10)

Results

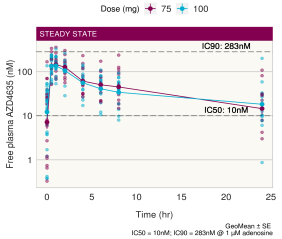
Safety and Tolerability

- Two dose-limiting toxicities were noted in the 125mg BID cohort (grade 3 nausea and grade 2 abdominal pain). There were no other DLTs noted in the monotherapy cohorts.
- AZD4635 100 mg QD was well-tolerated as monotherapy and in combination with durvalumab.
- In the 75mg QD plus durvalumab cohort, one DLT was noted (grade 2 nausea with grade 2 fatigue). No other DLTs were noted in the combination cohorts.

Monotherapy Treatment-Related Adverse Events ≥ 10%, n (%)	Cohort A (125 mg, BID) N=3	Cohort B (75 mg, QD) N=4	Cohort C (100 mg, QD) N=8
Nausea	3 (100)	0	4 (50)
Dizziness	2 (67)	1 (25)	1 (13)
Fatigue	2 (67)	3 (75)	2 (25)
Diarrhea	1 (33)	1 (25)	1 (13)
Myalgia	0	1 (25)	2 (25)
Decreased Appetite	0	0	0
Abdominal Pain	1 (33)	0	0

AZD4635+durvalumab Treatment-Related Adverse Events ≥ 10%, n (%)	Cohort D (75 mg + durva) N=13	Cohort E (100 mg + durva) N=10
Nausea	8 (62)	4 (40)
Dizziness	2 (15)	2 (20)
Fatigue	5 (39)	2 (20)
Diarrhea	0	2 (20)
Myalgia	0	1 (10)
Decreased Appetite	2 (15)	0

Pharmacokinetics



Steady state free AZD4635 plasma concentration are above *in vitro* IC50 over the dosing interval.

The metabolism is predominantly CYP1A2.

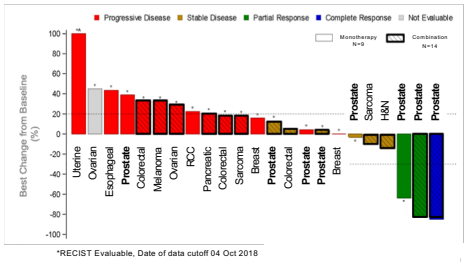
Primary pharmacokinetic parameters of AZD4635 on Day 1 and Day 15

AZD4635 DOSE	PK Parameter	75 mg QD	100 mg QD
DAY 1	N	16	102
	Cmax, ng/mL	594.13 (55.9)	580.21 (42.6)
	AUC, ng*hr/mL	4780.3 (47)	4364.8 (60.4)
	Half-life, hr	18.134 (32.3)	13.134 (65.3)
	Tmax, hr	0.5 (0.5 - 4)	1 (0 - 6)
DAY 15	N	15	52
	Cmax, ng/mL	650.6 (51.2)	663.5 (43)
	AUC, ng*hr/mL	5339.3 (114)	5709.9 (63.5)
	Tmax, hr	1 (0.5 - 4)	1 (0.5 - 8)

Cmax and AUC reported as Geo Mean (CV% Geometric Mean), Tmax as Median (Range), Half-life as mean (CV%)

Preliminary Clinical Activity

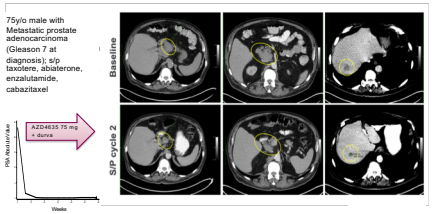
Best percentage change from baseline*:



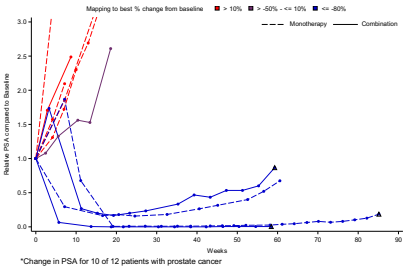
*RECIST Evaluable, Date of data cutoff 04 Oct 2018

Representative Scan Images:

mCRPC patient with response post cycle 2.

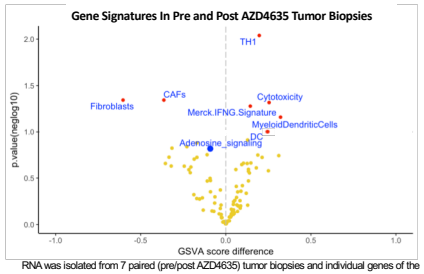


Changes in PSA over time (N=10*)

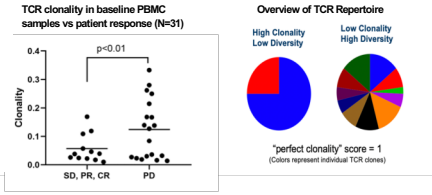


*Change in PSA for 10 of 12 patients with prostate cancer

Trend of gene expression signatures consistent with immune activation



RNA was isolated from 7 paired (pre/post AZD4635) tumor biopsies and individual genes of the PanCancer Immune panel were quantified using nanostring technology. Genes forming part of the indicated immune-related signatures are shown.



DNA was isolated from pretreatment peripheral blood samples of AZD4635-treated subjects and the TCR repertoire (TCRB) repertoire was sequenced at Adaptive Biotechnologies. The repertoire clonality is shown for patients by best overall response.

Conclusions

- AZD4635, an oral inhibitor of A2aR, was well-tolerated both as a monotherapy and in combination with durvalumab.
- AZD4635 pharmacokinetics and safety profile support once a day dosing at the recommended phase 2 dose of 100mg.
- Gene expression analysis showed post-treatment increases in both innate and adaptive immunity.
- Tumor and PSA responses were seen in patients with metastatic castration resistant prostate cancer.
- Peripheral TCR clonality at baseline was significantly lower in patients with stable disease or partial/complete responses, compared to progressive disease.
- Further evaluation of AZD4635 is ongoing in monotherapy, combination with durvalumab (NCT02740985) and combination with oleclumab (NCT03381274).

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