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Activity of ERK1/2 Inhibitor ASTX029 in Patients with Gynecological Malignancies Harboring Genomic Alterations in the MAPK Pathway

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Background

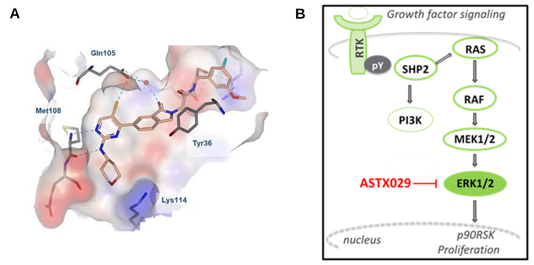
Aberrant activation of the mitogen-activated protein kinase (MAPK) pathway is a common occurrence, with about 20% of all cancers, including gynaecological (GYN) cancers, harboring genomic alterations activating the pathway (1).

Targeting of the MAPK pathway has been clinically validated, with approval of multiple agents, including the combination of BRAF and MEK inhibitors in advanced solid tumours with $BRAF^{V600E}$ mutation (2). Additionally, MEK inhibition has shown clinical activity in low-grade serous ovarian cancers and is a treatment option in this setting (3). As such, targeting the primary downstream effector of the MAPK pathway, extracellular signal-regulated kinase 1/2 (ERK1/2), is an attractive therapeutic strategy.

ASTX029 is a potent and selective dual-mechanism inhibitor of ERK1/2. Due to its distinctive ERK-binding mode, ASTX029 inhibits both ERK catalytic activity and the phosphorylation of ERK by MEK (4). Notably, ASTX029 demonstrates preclinical activity in cancer models showing resistance to inhibitors of upstream components of the MAPK pathway (5).

Here we report on the GYN cohort of an open-label phase 2 clinical study investigating ASTX029 in subjects with relapsed/refractory solid tumours (ASTX029-01, NCT03520075). The recommended phase 2 dose (RP2D) of 200 mg ASTX029 oral once daily in a 21-day cycle was previously established in the phase 1 clinical study (6,7).

Figure 1: (A) X-ray Crystal Structure of ASTX029 bound to human ERK2; (B) MAPK Signalling Pathway



Methods

The primary objective of the phase 2 portion of the ASTX029-01 clinical study was to assess the preliminary single agent antitumor activity of ASTX029 at the RP2D, as measured by overall response rate (ORR).

The phase 2 study followed a Simon's Optimal 2-stage design in each of 6 cohorts, including a cohort for MAPK pathway-altered GYN cancers (Cohort E). 10 subjects were enrolled in the first stage. If ≥2 subjects achieved a response, an additional 19 subjects were enrolled in the second stage.

Key eligibility criteria for trial participation included:

- 18 years of age or older
- Histologically or cytologically confirmed advanced solid tumors that are metastatic or unresectable
- Documented gene alterations in the MAPK pathway
- Measurable disease according to RECIST v1.1
- ECOG performance status of 0 to 2
- Acceptable organ function

Figure 2: Phase 2 cohorts of ASTX029-01 clinical study

A. NRAS-mutant melanoma	D BRAF-fusion cancers
B. KRAS-mutant or KRAS-amplified NSCLC	**E. Gynecological cancers with alterations in the MAPK pathway**
C. BRAF V600-mutant cancers (non-CRC)	F. Tumors with other gene aberrations (HRAS, GNAQ/GNA11, MEK)

Results

Patient demographics

Thirty-two subjects with GYN cancers with MAPK pathway alterations were treated with ASTX029.

Table 1: Baseline Characteristics for Subjects in Cohort E GYN Cancers (N=32)

Age (year)	
n	32
Mean	63.7
SD	9.26
Median	64.5
Min-max	42, 76
Race, n (%)	
Asian	0
Black or African American	0
White	27 (84.4)
Other	5 (15.6)
Mutational Status, n (%)	
KRAS	21 (65.6)
HRAS	1 (3.1)
NRAS	3 (9.4)
Other	7 (21.9)
Number of Regimen, n (%)*	
1	4 (12.5)
2	10 (31.2)
3	6 (18.8)
4+	12 (37.5)

*Two subjects had prior MEK inhibitor; Database extract 1Aug2024

Table 2: Disease Classification	N=32; n (%)
Epithelial ovarian, fallopian tube, primary peritoneal	16 (50)
Endometrial	11 (34)
Other gynecologic cancers	5 (16)

Safety

No serious adverse events (SAEs) or deaths related to ASTX029 were reported.

Most common treatment-related AEs (TRAE) were diarrhoea (56.3%), fatigue (37.5%), nausea (37.5%).

Six subjects (18.8%) interrupted treatment due to a TRAE and two subjects required dose reductions (6.3%), but none permanently discontinued treatment due to TRAEs.

The most frequent reason for treatment discontinuation was progressive disease (n=27; 84.4%).

Table 3: Treatment-Related Adverse Events (>5%) for Cohort E GYN Cancers

Adverse Event Term	All subjects (N=32) n (%)		
	All	G1/2	≥G3
Subjects with any AE	28 (87.5)	24 (75.0)	4 (12.5)
Diarrhoea	18 (56.3)	18 (56.3)	0
Fatigue	12 (37.5)	11 (34.4)	1 (3.1)
Nausea	12 (37.5)	12 (37.5)	0
Anaemia	10 (31.3)	7 (21.9)	3 (9.4)
Dermatitis acneiform	9 (28.1)	9 (28.1)	0
Vomiting	7 (21.9)	7 (21.9)	0
Decreased appetite	5 (15.6)	4 (12.5)	1 (3.1)
Alanine aminotransferase increased	3 (9.4)	3 (9.4)	0
Aspartate aminotransferase increased	3 (9.4)	3 (9.4)	0
Hyponatraemia	3 (9.4)	3 (9.4)	0
Platelet count decreased	3 (9.4)	3 (9.4)	0
Stomatitis	3 (9.4)	3 (9.4)	0
Vision blurred	3 (9.4)	3 (9.4)	0
Visual impairment	3 (9.4)	3 (9.4)	0
Asthenia	2 (6.3)	1 (3.1)	1 (3.1)
Constipation	2 (6.3)	2 (6.3)	0
Ejection fraction decreased	2 (6.3)	2 (6.3)	0
Rash	2 (6.3)	2 (6.3)	0
Rash maculo-papular	2 (6.3)	2 (6.3)	0

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Pharmacokinetics

PK exposures were in the predicted pharmacologically active range with mean cycle 1 AUC_{0_24} as 10321 ng*hr/ml (76% CV) and C_{max} as 3457 ng/ml (160% CV), n=11.

These data are consistent with previously presented data from the phase 1 study (6,7).

Table 4: Pharmacokinetic Data for Cohort E GYN Cancers

Visit	Dose (mg)	N	AUC_{0_24}[1] (ng*hr/mL)	C_{max}[1] (ng/mL)	T_{max}[2] (hr)
C1D1	200	11	10321 (76%)	3457 (160%)	2 (0.5-4)

[1]Geometric mean (%CV); [2]Median (range)

Activity

Four subjects had a partial response:

- $NRAS^{Q61K}$ ovarian adenocarcinoma
- $KRAS^{G12V}$ mesonephric adenocarcinoma of the cervix
- $KRAS^{G12D}$ endometrioid ovarian carcinoma
- $KRAS^{G12D}$ endometrioid endometrial carcinoma

Table 5: Clinical Activity Data for Cohort E GYN Cancers (N=32)

PR (n, %, 95% CI)	4, 12.5 (1.0. 24.0)
SD (n, %, 95% CI)	18, 56.3 (39.1, 73.4)
PD (n, %, 95% CI)	6, 18.8 (5.2, 32.3)
NE (n, %, 95% CI)	4, 12.5 (1.0, 24.0)
ORR (CR+PR) (n, %, 95% CI)	4, 12.5 (1.0, 24.0)
DCR (CR+PR+SD*) (n, %, 95% CI)	10, 31.3 (15.2, 47.3)
Duration of response (months, 95% CI)	8.54 (3.35, NE)
Follow-up (months, 95% CI)	9.49 (7.39, 13.86)
Overall survival (months, 95% CI)	11.17 (6.80, NE)
Progression free survival (months, 95% CI)	2.74 (1.48, 5.39)

*SD>24 weeks; Database extract 1Aug2024

Figure 3: Chart for Treatment Duration and Best Response for Cohort E GYN Cancers

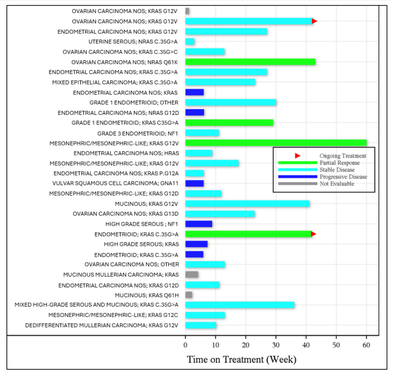

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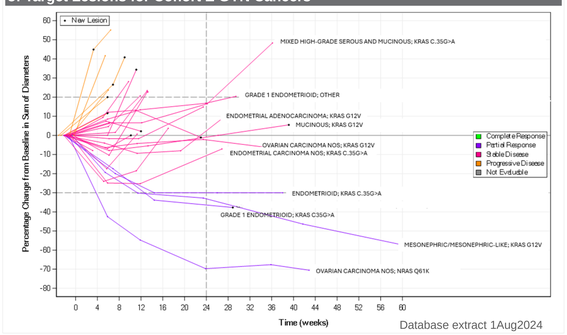
Figure 4: Spider Plot of Percentage Change from Baseline in Sum of Diameters of Target Lesions for Cohort E GYN Cancers



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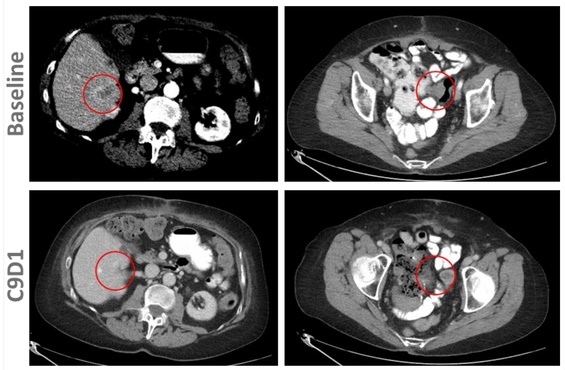
Case study

67 year old female with history of sarcoidosis, anaemia, asthma, and COPD with a locally advanced/unresectable endometrioid ovarian carcinoma, with an $NRAS^{Q61K}$ mutation, who had previous progressive disease on trametinib/navitoclax. Partial response to ASTX029 on cycle 3. Discontinued treatment on cycle 14 due to progressive disease.

Figure 5: Radiological images of Case Study Subject Treated with ASTX029



Conclusions

- ASTX029 shows preliminary antitumor activity in GYN cancers with MAPK pathway alterations at the recommended phase 2 dose (200 mg, orally, daily, given continuously in a 21-day cycle).
  - ASTX029 induced partial responses in four subjects (ORR 12.5%).
- ASTX029 was well-tolerated at the clinically active dose investigated, consistent with prior experience in the phase 1 study
  - Relatively infrequent dose interruptions and reductions, and no treatment discontinuation due to treatment-related adverse events.
- The ASTX029 PK exposures were in the predicted pharmacologically active range and consistent with previously presented phase 1 PK data.
- The response to ASTX029 in a patient previously treated with MEK inhibitor therapy suggests further study in this population is warranted.
- Further investigation of ASTX029 in rational combinations in GYN cancers with MAPK pathway alterations merits consideration.

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Notes

Study sponsored by Astex Pharmaceuticals Inc (now part of Taiho Oncology Inc).
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DOI of the presenting authors - E. Lee: research funding (paid to the institution) from: Merck, OnCusp Therapeutics, Repare Therapeutics, Seagen, KSQ Therapeutics / Roche, ProfoundBio / GenMab, Eli Lilly; advisory board participation with: Aadi Biosciences, OnCusp Therapeutics. J.E. Ang: principal investigator of clinical trials sponsored by GSK, AZ, Astex/Taiho, MSD, Incyte; received honoraria for advisory roles and speaker at events sponsored by GSK, AZ and MSD.

 Poster presented at ESMO Congress 2024, Barcelona.