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A Phase 1 Study of E7386, a CREB-Binding Protein/β-Catenin Interaction Inhibitor, in Patients With Advanced Solid Tumors Including Colorectal Cancer

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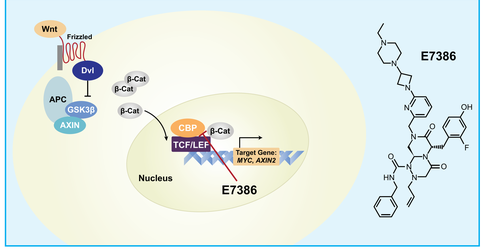
INTRODUCTION

- E7386 is a novel oral anti-cancer agent that inhibits the binding of β-catenin to its transcriptional co-activator, CREB-binding protein, thereby modulating Wnt/β-catenin signaling (**Figure 1**).[1]
- The Wnt/β-catenin signaling pathway is associated with the development of numerous types of cancers.[2]
  - Abnormal activation of this signaling pathway affords cancer cells an escape mechanism from immune checkpoint inhibitors.
- Notably, over 90% of colorectal cancers (CRCs) have mutations related to the activation of the Wnt pathway; over 80% of CRCs have *APC* and/or *CTNNB1* mutations.[3]
- Here, we report preliminary results from a phase 1 safety and efficacy study of E7386 in patients with advanced solid tumors including CRC.

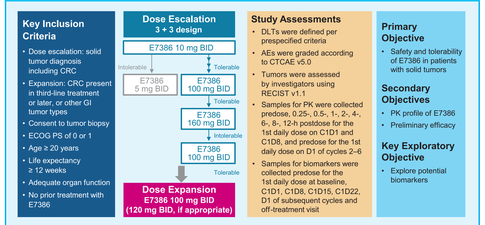
Figure 1. E7386 Structure and Mechanism of Action



METHODS

- This open-label phase 1 study of E7386 was conducted in Japanese patients with solid tumors including CRC.
  - Eligible patients were ≥ 20 years of age, had an Eastern Cooperative Oncology Group performance status of 0–1, and a life expectancy ≥ 12 weeks.
- The data presented here are from the dose-escalation part of the study that determined the recommended dose for expansion using a 3 + 3 design (**Figure 2**).
  - E7386 was administered orally in escalating doses on a twice-daily (BID) continuous schedule in 28-day cycles.

Figure 2. Study Design



AE, adverse event; BID, twice daily; C, cycle; CRC, colorectal cancer: CTCAE v5.0, Common Terminology Criteria for Adverse Events version 5.0; D, day; DLT, dose-limiting toxicity; ECOG PS, Eastern Cooperative Oncology Group performance status; GI, gastrointestinal; PK, pharmacokinetics, RECIST v1.1, Response Evaluation Criteria In Solid Tumors version 1.1.

- The primary objectives of the dose-escalation part were to determine the tolerability and the safety of E7386 in patients with solid tumors.
  - Secondary objectives were to assess the pharmacokinetic profile of E7386 and the preliminary efficacy.
- Dose-limiting toxicities (DLTs) were adverse events (graded using the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0) that occurred during cycle 1, were defined per the protocol, and were related to E7386.
- Efficacy endpoints were assessed by Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1, per investigator assessment.
- An expansion part enrolling patients with CRC and other selected tumor types to E7386 100 mg BID is ongoing.

RESULTS

Demographics

- 28 Patients were included in the dose-escalation part of the study; most patients (82.1%) had an Eastern Cooperative Oncology Group performance status of 0.
- Additional baseline patient demographics and characteristics are shown in **Table 1**.

Table 1. Baseline Patient Demographics and Characteristics

Characteristics	Total (N = 28)
Median age, year (range)	59.5 (36–77)
Sex, n (%)	
Male	17 (60.7)
Female	11 (39.3)
ECOG performance status, n (%)	
0	23 (82.1)
1	5 (17.9)
Median weight, kg (range)	60.85 (42.2, 89.9)
Tumor type, n (%)	
Colorectal cancer	16 (57.1)
Endometrial cancer	2 (7.1)
Pancreatic cancer	2 (7.1)
Small bowel carcinoma	2 (7.1)
Gastric cancer	1 (3.6)
Hepatocellular carcinoma	1 (3.6)
Other	4 (14.3)
Number of previous anticancer systemic medications, patient n (%)	
0	3 (10.7)
1	0
2	1 (3.6)
3	2 (7.1)
≥ 4	22 (78.6)
***NRAS* mutation, n (%)** Yes / no / unknown	1 (3.6) / 7 (25.0) / 20 (71.4)
***KRAS* mutation, n (%)** Yes / no / unknown	7 (25.0) / 5 (17.9) / 16 (57.1)
***APC* mutation, n (%)** Yes / no / unknown	10 (35.7) / 1 (3.6) / 17 (60.7)
***CTNNB1* mutation, n (%)** Yes / no / unknown	2 (7.1) / 0 / 26 (92.9)

ECOG, Eastern Cooperative Oncology Group.

Dose-Limiting Toxicities

- 2 DLTs (both grade 3 decreased appetite) were reported with E7386 160 mg BID.
  - As such, the recommended dose selected for the expansion phase was E7386 100 mg BID.

Safety

- Overall, 25 (89.3%) of 28 patients had treatment-related treatment-emergent adverse events (TEAEs) (**Table 2**).
  - The most common treatment-related TEAEs were nausea (78.6%) and vomiting (67.9%); nausea and vomiting were controlled with anti-emetics including 5HT3 antagonists, except in the E7386 160 mg BID cohort.
  - The most common grade ≥ 3 treatment-related TEAE was decreased appetite (7.1%).
- Serious TEAEs occurred in 6 (21.4%) of 28 patients.
  - There were no fatal events in the dose-escalation part of this study.
- Overall, 1 patient (E7386 15 mg BID) had TEAEs leading to withdrawal of study drug and 1 patient (E7386 160 mg BID) had TEAEs resulting in dose reduction.
  - 10 Patients had TEAEs resulting in dose interruption of E7386 (15 mg BID, n = 2; 20 mg BID, n = 1; 45 mg BID, n = 1; 80 mg BID, n = 2; 100 mg BID, n = 2; 160 mg BID, n = 2).
- Values of a bone metabolic marker, β-CTX, did not change markedly from baseline levels following treatment with E7386 (data not shown).

Table 2. Treatment-Related TEAEs of Any Grade

	E7386 Dose Group, n (%)																	
	10 mg (n = 3)		15 mg (n = 4)		20 mg (n = 3)		30 mg (n = 3)		45 mg (n = 4)		80 mg (n = 3)		100 mg (n = 6)		160 mg (n = 2)		Total (N = 28)	
Preferred Term	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Patients with any treatment-related TEAEs	2 (66.7)	0	3 (75.0)	0	3 (100.0)	1 (33.3)	2 (66.7)	0	4 (100.0)	0	3 (100.0)	0	6 (100.0)	0	2 (100.0)	2 (100.0)	25 (89.3)	3 (10.7)
Nausea	2 (66.7)	0	2 (50.0)	0	2 (66.7)	0	2 (66.7)	0	4 (100.0)	0	3 (100.0)	0	5 (83.3)	0	2 (100.0)	0	22 (78.6)	0
Vomiting	2 (66.7)	0	1 (25.0)	0	2 (66.7)	0	0	0	3 (75.0)	0	3 (100.0)	0	6 (100.0)	0	2 (100.0)	0	19 (67.9)	0
ALT increased	0	0	0	0	0	0	0	0	0	0	1 (33.3)	0	2 (33.3)	0	1 (50.0)	0	4 (14.3)	0
AST increased	1 (33.3)	0	0	0	0	0	0	0	0	0	0	0	2 (33.3)	0	1 (50.0)	0	4 (14.3)	0
Anemia	1 (33.3)	0	0	0	0	0	0	0	0	0	0	0	1 (16.7)	0	1 (50.0)	0	3 (10.7)	0
Decreased appetite	0	0	0	0	0	0	0	0	0	0	0	0	1 (16.7)	0	2 (100.0)	2 (100.0)	3 (10.7)	2 (7.1)
Diarrhea	0	0	0	0	0	0	1 (33.3)	0	0	0	0	0	0	0	1 (50.0)	0	2 (7.1)	0
White blood cell count decreased	0	0	0	0	0	0	1 (33.3)	0	0	0	0	0	1 (16.7)	0	0	0	2 (7.1)	0
Amylase increased	0	0	0	0	1 (33.3)	0	0	0	0	0	0	0	0	0	0	0	1 (3.6)	0
C-telopeptide increased	0	0	0	0	0	0	0	0	1 (25.0)	0	0	0	0	0	0	0	1 (3.6)	0
Electrocardiogram QT prolonged	0	0	0	0	0	0	1 (33.3)	0	0	0	0	0	0	0	0	0	1 (3.6)	0
Hyperphosphatemia	0	0	0	0	1 (33.3)	0	0	0	0	0	0	0	0	0	0	0	1 (3.6)	0
Lipase increased	0	0	0	0	1 (33.3)	1 (33.3)	0	0	0	0	0	0	0	0	0	0	1 (3.6)	1 (3.6)
Liver disorder	0	0	0	0	1 (33.3)	0	0	0	0	0	0	0	0	0	0	0	1 (3.6)	0
Osteoporosis	0	0	0	0	0	0	0	0	0	0	0	0	1 (16.7)	0	0	0	1 (3.6)	0
Rash	0	0	0	0	0	0	0	0	0	0	0	0	1 (16.7)	0	0	0	1 (3.6)	0
Sinus tachycardia	0	0	0	0	0	0	0	0	0	0	0	0	1 (16.7)	0	0	0	1 (3.6)	0
Stomatitis	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1 (50.0)	0	1 (3.6)	0

ALT, alanine aminotransferase; AST, aspartate aminotransferase; TEAE, treatment-emergent adverse event.

Preliminary Pharmacokinetics

- With the exception of the E7386 30 mg dose, exposure of E7386 appeared to increase with increasing doses from 10 to 100 mg BID at steady state (cycle 1 day 8) (**Table 3**).

Table 3. Preliminary Pharmacokinetic Parameter Results for E7386

E7386 Dose, mg BID	Cycle 1 Day 1			Cycle 1 Day 8				
	C_{max} (ng/mL)	t_{max} (h)	$AUC_{(0-12h)}$ (h*ng/mL)	$C_{max,ss}$ (ng/mL)	$t_{max,ss}$ (h)	$AUC_{(0-\tau)ss}$ (h*ng/mL)	$R_{ac(AUC)}$	$R_{ac(Cmax)}$	Effective $t_{1/2}$ (h)
10 (n = 3)	37.2 (42.6)	2.00 (0.25–2.00)	131 (39.7)	53.9 (272)	2.00 (1.00–2.00)	210 (168)	1.60 (113)	1.45 (178)	9.03, 27.9[b]
15 (n = 4)	135 (28.9)	0.75 (0.50–2.00)	310 (42.5)	159 (38.1)	0.75 (0.50-2.00)	504 (34.3)	1.62 (52.6)	1.17 (67.3)	7.10 (118)
20 (n = 3)	146 (209)	1.00 (0.50–2.00)	501 (76.8)	278 (161)	0.50 (0.50–1.00)	866 (96.6)	1.73 (58.6)	1.90 (36.5)	12.2, 18.0[b]
30 (n = 3)	105 (17.7)	2.00 (2.00–2.00)	349 (55.5)	68.3 (31.9)	2.00 (0.50–4.00)	396 (41.2)	1.13 (20.6)	0.653 (14.4)	3.27, 6.81[b]
45 (n = 4)	209 (201)	1.00 (1.00–2.00)	865 (109)	199 (124)	3.00 (1.00–4.00)	1070 (69.6)	1.24 (37.0)	0.95 (63.3)	6.59 (56.3)[c]
80 (n = 3)	279 (251)	2.00 (1.00–2.00)	758 (182)	737 (59.1)	1.00 (0.50–1.00)	2100 (51.8)	2.79 (85.6)	2.64 (106)	17.4 (120)
100 (n = 6)	443 (93.9)	0.50 (0.25–4.00)	1420 (70.5)	862 (115)	1.00 (0.50–1.00)	2700[a] (127)	2.18 (41.3)	2.13[a] (50.6)	13.0 (61.1)
160 (n = 2)	481, 1750	0.50, 1.00	2510, 8060	2980, 3850	1.00, 1.00	9060, 21300	2.64, 3.60	2.20, 6.20	17.5, 25.6

[a]Based on 5 patients; [b]based on 2 patients; [c]based on 3 patients.

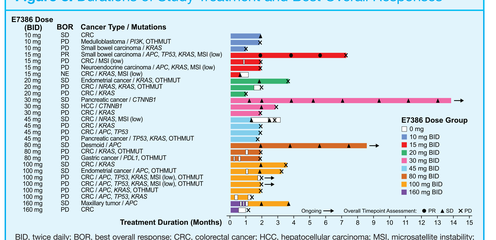
t_{max} is reported as median (range). All other values are reported as geometric mean (%CV). Summary statistics could not be performed for groups with 2 patients.

AUC, area under the plasma concentration-time curve; $AUC_{(0-12h)}$, area under the plasma concentration-time curve from zero time to 12 hours after first dose on Day 1; $AUC_{(0-\tau)ss}$, area under the plasma concentration-time curve at steady state after first dose on Day 8 from time zero to τ, where τ is the length of time of the dosing interval (τ = 12 hours); BID, twice daily; C_{max}, maximum observed plasma concentration after 1st dose on Day 1; $C_{max,ss}$, maximum observed plasma concentration at steady state after 1st dose on Day 8; CV, coefficient of variation; Effective $t_{1/2}$, half-life reflecting drug accumulation based on $R_{ac(AUC)}$; $R_{ac(AUC)}$, accumulation ratio calculated from $AUC_{(0-\tau)ss}$ and AUC, after single dosing; $R_{ac(Cmax)}$, accumulation ratio calculated from $C_{max,ss}$ and C_{max}; t_{max}, time to reach maximum (peak) plasma concentration after 1st dose on Day 1; $t_{max,ss}$, time to reach maximum (peak) plasma concentration at steady state after 1st dose on Day 8.

Efficacy

- 1 Patient with small bowel adenocarcinoma and an *APC* mutation, who received E7386 15 mg BID, had a partial response (tumor shrinkage: –69%; duration of response: 165 days) (**Figure 3**).
- Across doses, the overall objective response rate was 3.6% (95% CI 0.1–18.3) and the disease control rate was 35.7% (95% CI 18.6–55.9).
- Patients' durations of treatment and best overall responses are shown in **Figure 3**.

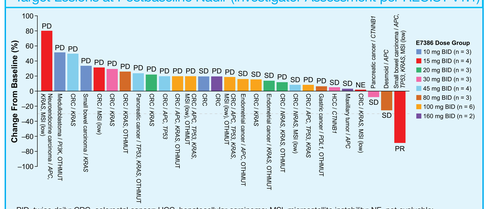
Figure 3. Durations of Study Treatment and Best Overall Responses



BID, twice daily; BOR, best overall response; CRC, colorectal cancer; HCC, hepatocellular carcinoma; MSI, microsatellite instability; NE, not evaluable; OTHMUT, other mutation; PD, progressive disease; PR, partial response; SD, stable disease.

- Maximum change in tumor size from baseline for each patient is shown in **Figure 4**.

Figure 4. Maximum Percent Change from Baseline in Sums of Diameters of Target Lesions at Postbaseline Nadir (Investigator Assessment per RECIST v1.1)

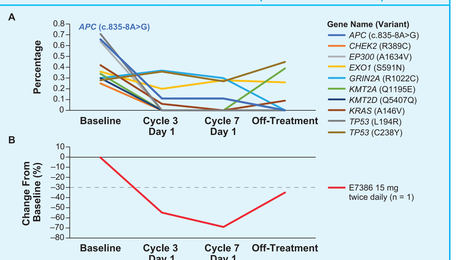


BID, twice daily; CRC, colorectal cancer; HCC, hepatocellular carcinoma; MSI, microsatellite instability; NE, not evaluable; OTHMUT, other mutation; PD, progressive disease; PR, partial response; RECIST v1.1, Response Evaluation Criteria In Solid Tumors version 1.1; SD, stable disease.

Biomarkers

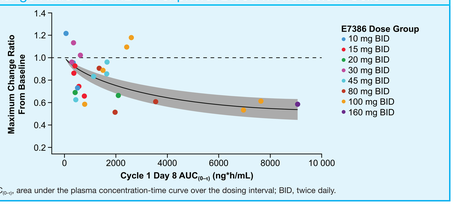
- Analysis of circulating tumor DNA in plasma showed a decrease in variant allele frequency of *APC* after E7386 treatment in the patient with a partial response (**Figure 5**).

Figure 5. Circulating Tumor DNA Analysis (A) and Percentage Change in Sums of Diameters of Target Lesions Over Time (B) in 1 Patient With Small Bowel Adenocarcinoma and With a Best Overall Response of Partial Response



- A trend in decreased *AXIN2* levels was observed with E7386 80 mg BID or higher doses (**Figure 6**).

Figure 6. Pharmacokinetic–Pharmacodynamic Analysis Using Maximum Change Ratio of *AXIN2* in Peripheral Blood Mononuclear Cells



$AUC_{(0-\tau)}$, area under the plasma concentration-time curve over the dosing interval; BID, twice daily.

CONCLUSIONS

- E7386 was well tolerated at doses up to 100 mg BID—the dose selected as the recommended dose for the expansion part.
- 2 DLTs were reported with E7386 160 mg BID.
- 1 Patient with small bowel adenocarcinoma had a partial response to treatment with E7386.
  - Several gene mutations, including *APC*, were decreased as assessed by circulating tumor DNA analysis in association with tumor shrinkage.
- Further investigations of safety, preliminary efficacy, pharmacokinetics, and biomarker analyses of E7386 are ongoing.

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Conflict of Interest

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