SUPPLEMENTARY TABLES

Supplementary Table S1. Patient disposition

No. (%)	Arm A (docetaxel) *n* = 27	Arm B (mFOLFOX6) *n* = 34	Arm C (paclitaxel) *n* = 27	Arm D (enzalutamide) *n* = 34
Patient status in study				
Off study	27 (100.0)	34 (100.0)	27 (100.0)	31 (91.2)
Reasons for discontinuation				
Disease progression	22 (81.5)	25 (73.5)	18 (66.7)	11 (32.4)
Adverse event	2 (7.4)	1 (2.9)	1 (3.7)	3 (8.8)
Physician decision	1 (3.7)	2 (5.9)	1 (3.7)	4 (11.8)
Withdrawal by patient	2 (7.4)	6 (17.6)	4 (14.8)	3 (8.8)
Death	0	0	2 (7.4)	0
Use of another anticancer therapy	0	0	1 (3.7)	0
Other	0	0	0	10 (29.4)

mFOLFOX6, modified leucovorin, 5-fluorouracil, and oxaliplatin.

Supplementary Table S2. Ipatasertib-related AEs reported in ≥ 10% of all patients

Ipatasertib-related AEs, No. (%)	**Arm A (docetaxel) *n* = 27**	**Arm B (mFOLFOX6) *n* = 34**	**Arm C (paclitaxel) *n* = 27**	**Arm D (enzalutamide) *n* = 34**
Nausea	20 (74.1)	24 (70.6)	15 (55.6)	16 (47.1)
Diarrhea	19 (70.4)	20 (58.8)	21 (77.8)	30 (88.2)
Vomiting	18 (66.7)	19 (55.9)	10 (37.0)	7 (20.6)
Decreased appetite	7 (25.9)	14 (41.2)	5 (18.5)	10 (29.4)
Asthenia	6 (2.2)	12 (35.3)	0	0
Fatigue	5 (18.5)	13 (38.2)	9 (33.3)	16 (47.1)
Dyspepsia	4 (14.8)	4 (11.8)	0	0
Hyperglycemia	4 (14.8)	6 (17.6)	4 (14.8)	0
Rash	4 (14.8)	6 (17.6)	3 (11.1)	7 (20.6)
Hypomagnesemia	3 (11.1)	0	0	0
Mucosal inflammation	3 (11.1)	10 (29.4)	0	0
Neutropenia	0	8 (23.5)	0	0
Dry mouth	0	4 (11.8)	0	0
Dysgeusia	0	4 (11.8)	0	5 (14.7)
Thrombocytopenia	0	4 (11.8)	0	0
Abdominal pain	0	0	4 (14.8)	0
Maculopapular rash	0	0	4 (14.8)	0
Dehydration	0	0	3 (11.1)	0

Flatulence	0	0	0	8 (23.5)
Dizziness	0	0	0	6 (17.6)
Hypertriglyceridemia	0	0	0	4 (11.8)

AE, adverse event; mFOLFOX6, modified leucovorin, 5-fluorouracil, and oxaliplatin.

Supplementary Table S3. Ipatasertib-related AEs reported in ⩾ 10% of all patients by dose level

Ipatasertib-related AEs in arm A, No. (%)	**Docetaxel + 100 mg (*n* = 3)**	**Docetaxel + 200 mg (*n* = 4)**	**Docetaxel + 400 mg (*n* = 7)**	**Docetaxel + 600 mg (*n* = 13)**	**Total (*N* = 27)**
Overall	3 (100.0)	4 (100.0)	6 (85.7)	13 (100.0)	26 (96.3)
Nausea	2 (66.7)	3 (75.0)	5 (71.4)	10 (76.9)	20 (74.1)
Diarrhea	1 (33.3)	3 (75.0)	4 (57.1)	11 (84.6)	19 (70.4)
Vomiting	2 (66.7)	2 (50.0)	5 (71.4)	9 (69.2)	18 (66.7)
Decreased appetite	2 (66.7)	0	0	5 (38.5)	7 (25.9)
Asthenia	0	1 (25.0)	0	5 (38.5)	6 (22.2)
Fatigue	1 (33.3)	1 (25.0)	2 (28.6)	1 (7.7)	5 (18.5)
Dyspepsia	0	2 (50.0)	2 (28.6)	0	4 (14.8)
Hyperglycemia	0	2 (50.0)	1 (14.3)	1 (7.7)	4 (14.8)
Rash	0	0	0	4 (30.8)	4 (14.8)
Hypomagnesemia	0	1 (25.0)	0	2 (15.4)	3 (11.1)
Mucosal inflammation	0	1 (25.0)	0	2 (15.4)	3 (11.1)
Ipatasertib-Related AEs in arm B, No. (%)	**mFOLFOX + 100 mg (*n* = 6)**	**mFOLFOX + 200 mg (*n* = 9)**	**mFOLFOX + 400 mg (*n* = 6)**	**mFOLFOX + 600 mg (*n* = 13)**	**Total (*N* = 34)**
Overall	6 (100.0)	6 (66.7)	6 (100.0)	12 (92.3)	30 (88.2)

Nausea	4 (66.7)	5 (55.6)	4 (66.7)	11 (84.6)	24 (70.6)
Diarrhea	2 (33.3)	4 (44.4)	4 (66.7)	10 (76.9)	20 (58.8)
Vomiting	3(50.0)	4 (44.4)	2 (33.3)	10 (76.9)	19 (55.9)
Decreased appetite	2 (33.3)	2 (22.2)	2 (33.3)	8 (61.5)	14 (41.2)
Fatigue	3 (50.0)	2 (22.2)	2 (33.3)	6 (46.2)	13 (38.2)
Asthenia	2 (33.3)	3 (33.3)	3 (50.0)	4 (30.8)	12 (35.3)
Mucosal inflammation	1 (16.7)	1 (11.1)	3 (50.0)	5 (38.5)	10 (29.4)
Neutropenia	1 (16.7)	1 (11.1)	2 (33.3)	4 (30.8)	8 (23.5)
Hyperglycemia	1 (16.7)	1 (11.1)	1 (16.7)	3 (23.1)	6 (17.6)
Rash	2 (33.3)	0	1 (16.7)	3 (23.1)	6 (17.6)
Dry mouth	1 (16.7)	2 (22.2)	0	1 (7.7)	4 (11.8)
Dysgeusia	2 (33.3)	1 (11.1)	0	1 (7.7)	4 (11.8)
Dyspepsia	0	1 (11.1)	1 (16.7)	2 (15.4)	4 (11.8)
Thrombocytopenia	1 (16.7)	1 (11.1)	1 (16.7)	1 (7.7)	4 (11.8)
Ipatasertib-related AEs in arm C, No. (%)			**Paclitaxel + 400 mg (*n* = 21)**	**Paclitaxel + 600 mg (*n* = 6)**	**Total (*N* = 27)**
Overall			19 (90.5)	6 (100.0)	25 (92.6)
Diarrhea			15 (71.4)	6 (100.0)	21 (77.8)
Nausea			11 (52.4)	4 (66.7)	15 (55.6)
Fatigue			5 (23.8)	4 (66.7)	9 (33.3)

Decreased appetite			5 (23.8)	0	5 (18.5)
Abdominal pain			3 (14.3)	1 (16.7)	4 (14.8)
Hyperglycemia			2 (9.5)	2 (33.3)	4 (14.8)
Rash maculopapular			3 (14.3)	1 (16.7)	4 (14.8)
Dehydration			1 (4.8)	2 (33.3)	3 (11.1)
Rash			1 (4.8)	2 (33.3)	3 (11.1)
Ipatasertib-related AEs in arm D, n (%)		**Enza + 400 mg (*n* = 6)**	**Enza + 600 mg (*n* = 7)**	**Enza + 400–600 mg (*n* =21)**	**Total (*N* = 34)**
Overall		6 (100.0)	7 (100.0)	20 (95.2)	33 (97.1)
Diarrhea		5 (83.3)	7 (100.0)	18 (85.7)	30 (88.2)
Fatigue		2 (33.3)	3 (42.9)	11 (52.4)	16 (47.1)
Nausea		2 (33.3)	5 (71.4)	9 (42.9)	16 (47.1)
Decreased appetite		1 (16.7)	2 (28.6)	7 (33.3)	10 (29.4)
Flatulence		0	1 (14.3)	7 (33.3)	8 (23.5)
Rash		0	1 (14.3)	6 (28.6)	7 (20.6)
Vomiting		1 (16.7)	0	6 (28.6)	7 (20.6)
Dizziness		0	1 (14.3)	5 (23.8)	6 (17.6)
Dysgeusia		1 (16.7)	1 (14.3)	3 (14.3)	5 (14.7)
Hypertriglyceridemia		0	1 (14.3)	3 (14.3)	4 (11.8)

AE, adverse event; Enza, enzalutamide; mFOLFOX6, modified leucovorin, 5-fluorouracil, and oxaliplatin.

Supplementary Table S4. Summary of drug exposure

	Arm A (docetaxel) *n* = 27	**Arm B (mFOLFOX6) *n* = 34**	**Arm C (paclitaxel) *n* = 27**	**Arm D (enzalutamide) *n* = 34**
Cumulative total dose, median (range), mg				
Ipatasertib	17,300.0 (1800-117,000)	11,700.0 (100-59,500)	25,200.0 (2400-136,400)	35,000.0 (2800-418,800)
Chemotherapy	501.3 (123-2141)	5-FU: 20,944.0 (2880-362,962) Leucovorin: 3078.0 (600-45,494) Oxaliplatin: 702.5 (128-3239)	1160.0 (399-5568)	12,800.0 (800-116,320)
No. of cycles, median (range)				
Ipatasertib	4.0 (1-16)	4.5 (1-64)	3.0 (1-18)	3.0 (1-26)

Chemotherapy	4.0 (1-16)	–	3.0 (1-18)	3.0 (1-26)
Duration of exposure, median (range), weeks				
Ipatasertib	10.9 (0-49)	8.2 (0-221)	11.0 (3-75)	12.8 (1-105)
Chemotherapy	9.0 (0-47)		10.1 (2-73)	11.9 (1-104)
Dose modification, n (%)				
Ipatasertib	9 (33)	9 (27)	11 (41)	16 (47)
Chemotherapy	7 (26)		8 (30)	5 (15)

5-FU, 5-fluorouracil; mFOLFOX6, modified leucovorin, 5-fluorouracil, and oxaliplatin.

Supplementary Table S5. Pharmacokinetic parameters of ipatasertib and its metabolite, G-037220, in each arm

Agent	Dose, mg	Arm A			Arm B			Arm C			Arm D					
		Ipatasertib + docetaxel			Ipatasertib + mFOLFOX6			Ipatasertib + paclitaxel			Ipatasertib alone			Ipatasertib + enzalutamide		
		No.	$C_{max,ss}$, ng/mL (geo-metric %CV)	$AUC_{0-24,ss}$, ng · hr/mL (geometric %CV)	No.	$C_{max,ss}$, ng/mL (geo-metric %CV)	$AUC_{0-24,ss}$, ng · hr/mL (geometric %CV)	n	$C_{max,ss}$, ng/mL (geo-metric %CV)	$AUC_{0-24,ss}$, ng · hr/mL (geometric %CV)	n	$C_{max,ss}$, ng/mL (geo-metric %CV)	$AUC_{0-24,ss}$, ng · hr/mL (geometric %CV)	n	$C_{max,ss}$, ng/mL (geo-metric %CV)	$AUC_{0-24,ss}$, ng · hr/mL (geometric %CV)
Ipatasertib	100	3	36.3 (8.31)	174 (14.1)	6	67.8 (89.4)	351 (65.0)									
	200	3	123 (61.6)	447 (76.7)	9	176 (41.1)	865 (38.6)									
	400	7	264 (52.8)	1370 (44.5)[a]	6	296 (29.4)	2020 (26.7)[b]	19	388 (84.4)	3180 (38.9)[c]	5	273 (66.5)	2070 (47.0)	4	121 (54.7)	1050 (5.14)
	400 (Expansion)										18	287 (68.8)	2200 (57.0)[c]	15	120 (73.6)	1140 (36.9)[d]
	600	13	496 (39.6)	2720 (41.2)	13	619 (50.2)	4580 (38.5)[e]	5	540 (54.1)	4210 (95.2)[f]	6	314 (58.2)	2690 (34.0)[b]	3	198 (58.3)	1420 (54.1)
Metabolite G-037220	100	3	14.8 (38.6)	109 (37.0)	6	10.7 (106)	93.6 (85.6)									

	200	3	48.4 (75.0)	251 (82.9)	9	51.8 (76.3)	331 (50.7)									
	400	7	122 (70.7)	899 (62.3)[b]	6	63.9 (64.4)	552 (37.4)[b]	19	163 (117)	1650 (71.3)[c]	5	141 (90.0)	1310 (94.4)	4	129 (89.3)	1260 (63.5)
	400 (expansion)										18	122 (48.4)	1220 (37.5)c	15	109 (72.1)	1480 (47.0)[e]
	600	13	232 (37.7)	1510 (42.5)	13	173 (58.9)	1500 (73.0)[e]	5	246 (65.2)	2270 (96.6)[f]	6	151 (71.6)	1550 (47.4)[b]	3	203 (34.2)	1920 (38.0)

$AUC_{0–24}$, area under the concentration-time curve from time 0 to 24 hours; C_{max}, highest observed plasma concentration;

CV, coefficient of variation.

[a] *n* = 6.

[b] *n* = 5.

[c] *n* = 17.

[d] *n* = 13.

[e] *n* = 12.

[f] *n* = 4.

Supplementary Table S6. Summary of antitumor activity in patients with baseline measurable disease[a]

ORR, n (%)[b]	Arm A (docetaxel)[c] *n* = 26	Arm B (mFOLFOX6)[d] *n* = 33	Arm C (paclitaxel)[e] *n* = 25	Arm D (enzalutamide)[f] *n* = 17
CR	0	0	0	0
PR	2 (7.7)	2 (6.1)	2 (8.0)	2 (11.8)
SD	14 (53.8)	17 (51.5)	14 (56.0)	4 (23.5)
PD	7 (26.9)	10 (30.3)	6 (24.0)	7 (41.2)
Missing/ unevaluable	3 (11.5)	4 (12.1)	3 (12.0)	4 (23.5)

CR, complete response; mFOLFOX6, modified leucovorin, 5-fluorouracil, and oxaliplatin; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease (≥6 weeks for arm A, ≥8 weeks for arm B, and ≥12 weeks for arms C and D).

[a] *N* = 101.

[b] Confirmed objective response per Response Evaluation Criteria in Solid Tumors v1.1.

[c] The most common locations of primary tumors were lung (non-small cell) or breast (5 patients [18.5%] each), esophageal (4 patients [14.8%]), and bladder (3 patients [11.1%]).

[d] The most common locations of primary tumors were colorectal (14 patients [41.2%]), esophageal (3 patients [8.8%]), and cholangiocarcinoma, unknown, and pancreatic (2 patients [5.9%] each).

[e] The most common location of primary tumors among patients in arm C was breast (15 patients [55.6%]). In addition, 2 patients (7.4%) each had primary tumors in the bladder or lung (non-small cell).

[f] All 34 patients in arm D had primary prostate tumors.

Supplementary Table S7. Summary of antitumor activity in patients with baseline measurable disease by mutation status[a]

***AKT1/PIK3CA* Status**	**Arm A (docetaxel)[†] *n* = 26**	**Arm B (mFOLFOX6)[‡] *n* = 33**	**Arm C (paclitaxel)[§] *n* = 25**	**Arm D (enzalutamide)[‖] *n* = 17**
Activating mutation, No. (%)				
CR	0	0	0	0
PR	1 (3.8)	1 (3.0)	2 (8.0)	0
SD	1 (3.8)	3 (9.1)	4 (16.0)	0
PD	1 (3.8)	0	0	0
Not evaluated	1 (3.8)	0	0	0
Nonaltered, No. (%)				
CR	0	0	0	0
PR	1 (3.8)	1 (3.0)	0	0
SD	9 (34.6)	10 (30.3)	5 (20.0)	0
PD	3 (11.5)	7 (21.2)	2 (8.0)	0
Not evaluated	1 (3.8)	3 (9.1)	3 (12.0)	1 (5.9)
Unknown, No. (%)				
CR	0	0	0	0
PR	0	0	0	2 (11.8)
SD	4 (15.4)	4 (12.1)	5 (20.0)	4 (23.5)
PD	3 (11.5)	3 (9.1)	4 (16.0)	7 (41.2)

Not evaluated	1 (3.8)	1 (3.0)	0	3 (17.6)

CR, complete response; mFOLFOX6, modified leucovorin, 5-fluorouracil, and oxaliplatin; PD, progressive disease; PR, partial response; SD, stable disease.

[a] *N* = 101. Confirmed objective response per RECIST v1.1. Activating mutations included: AKT1, E17K; PIK3CA, R88Q, N345K, C420R, E542K, E545A, E545D, E545G, E545K, Q546K, Q546R, Q546E, Q546L, M1043I, M1043V, H1047L, H1047R, H1047Y, and G1049R.

[b] The most common locations of primary tumors were lung (non-small cell) or breast (5 patients [18.5%] each), esophageal (4 patients [14.8%]), and bladder (3 patients [11.1%]).

[c] The most common locations of primary tumors were colorectal (14 patients [41.2%]), esophageal (3 patients [8.8%]), and cholangiocarcinoma, unknown, and pancreatic (2 patients [5.9%] each).

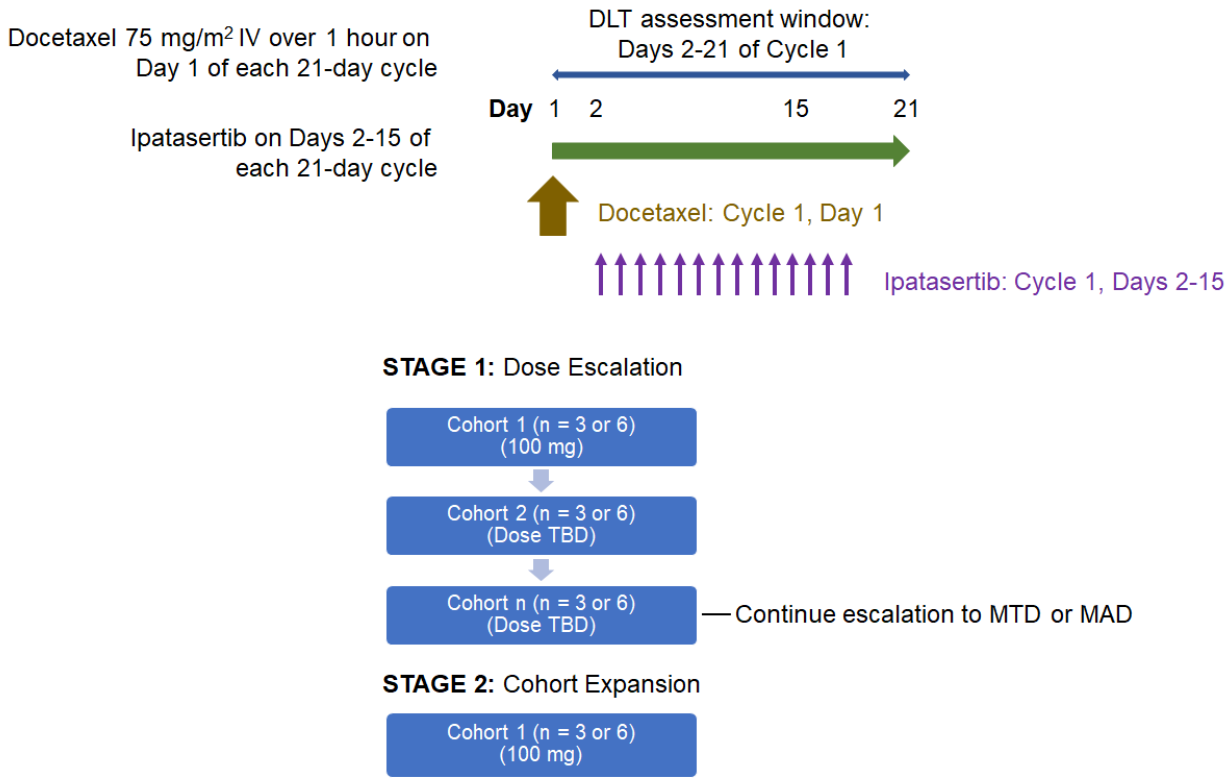
[d] The most common location of primary tumors among patients in arm C was breast (15 patients [55.6%]). In addition, 2 patients (7.4%) each had primary tumors in the bladder or lung (non-small cell).

[e] All 34 patients in arm D had primary prostate tumors**.**

SUPPLEMENTARY FIGURES

Supplementary Figure S1. Study design schematics for arms A-D

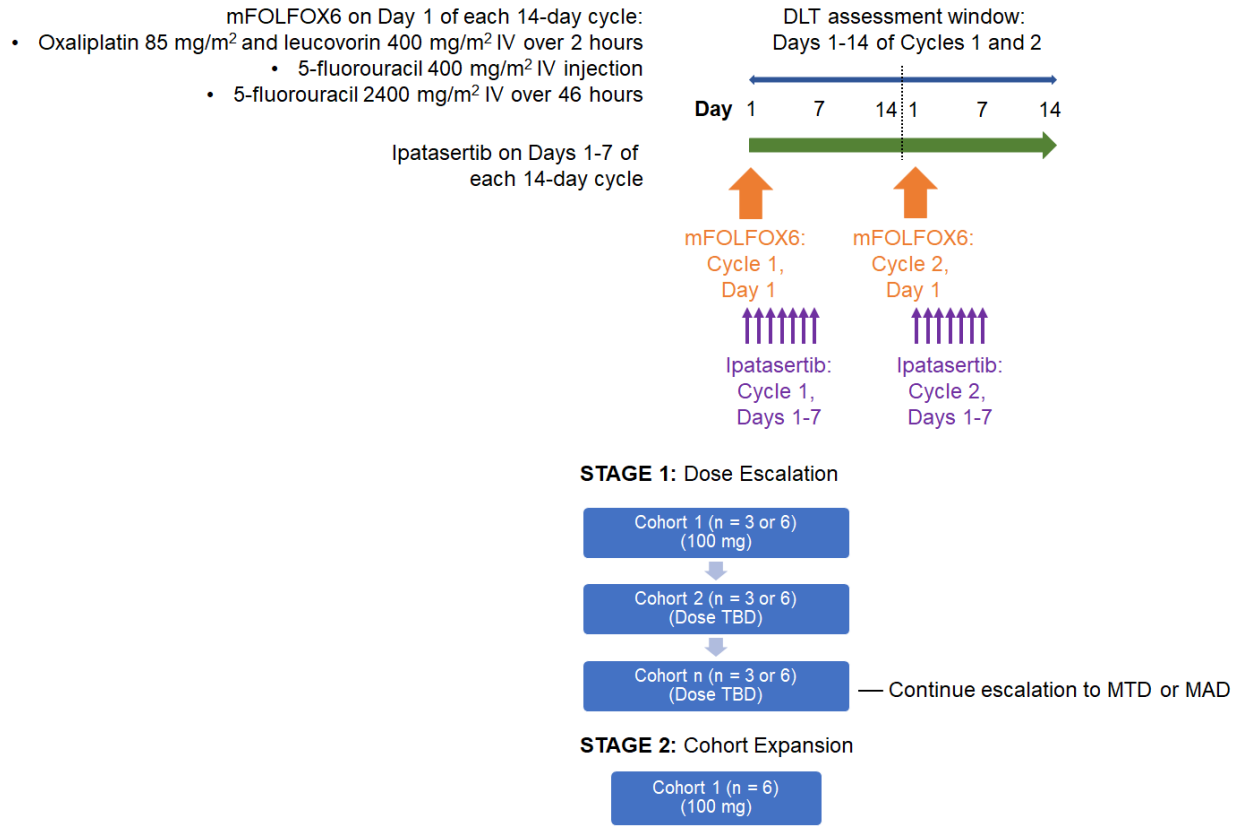
Arm A: docetaxel + ipatasertib[a]



DLT, dose-limiting toxicity; IV, intravenous; MAD, maximum assessed dose; MTD, maximum tolerated dose; TBD, to be determined.

[a] Ipatasertib dose increased by 100% until a safety signal was observed in that cohort, defined in Section 3.1.1.c of the protocol. During stage 1 escalation, cohort 2 received 200 mg, cohort 3 received 400 mg, and cohort 4 received 600 mg. During stage 2 cohort expansion, patients received ipatasertib 600 mg.

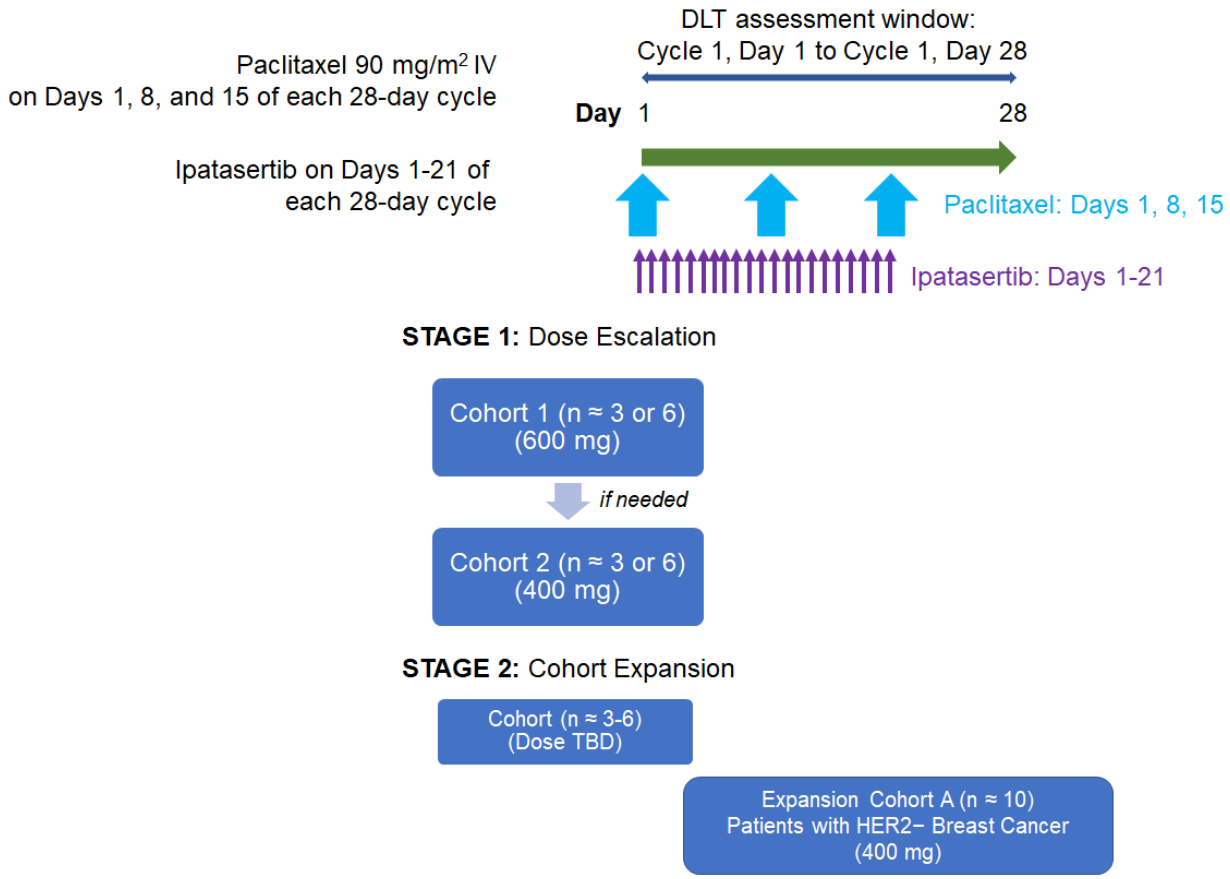
Arm B: mFOLFOX6 + ipatasertib[a]



DLT, dose-limiting toxicity; IV, intravenous; MAD, maximum assessed dose; mFOLFOX6, modified leucovorin, 5-fluorouracil, and oxaliplatin; MTD, maximum tolerated dose; TBD, to be determined.

[a] Ipatasertib dose increased by 100% until a safety signal was observed in that cohort, defined in Section 3.1.1.c of the protocol. During stage 1 escalation, cohort 2 received 200 mg, cohort 3 received 400 mg, and cohort 4 received 600 mg. During stage 2 cohort expansion, patients received ipatasertib 600 mg.

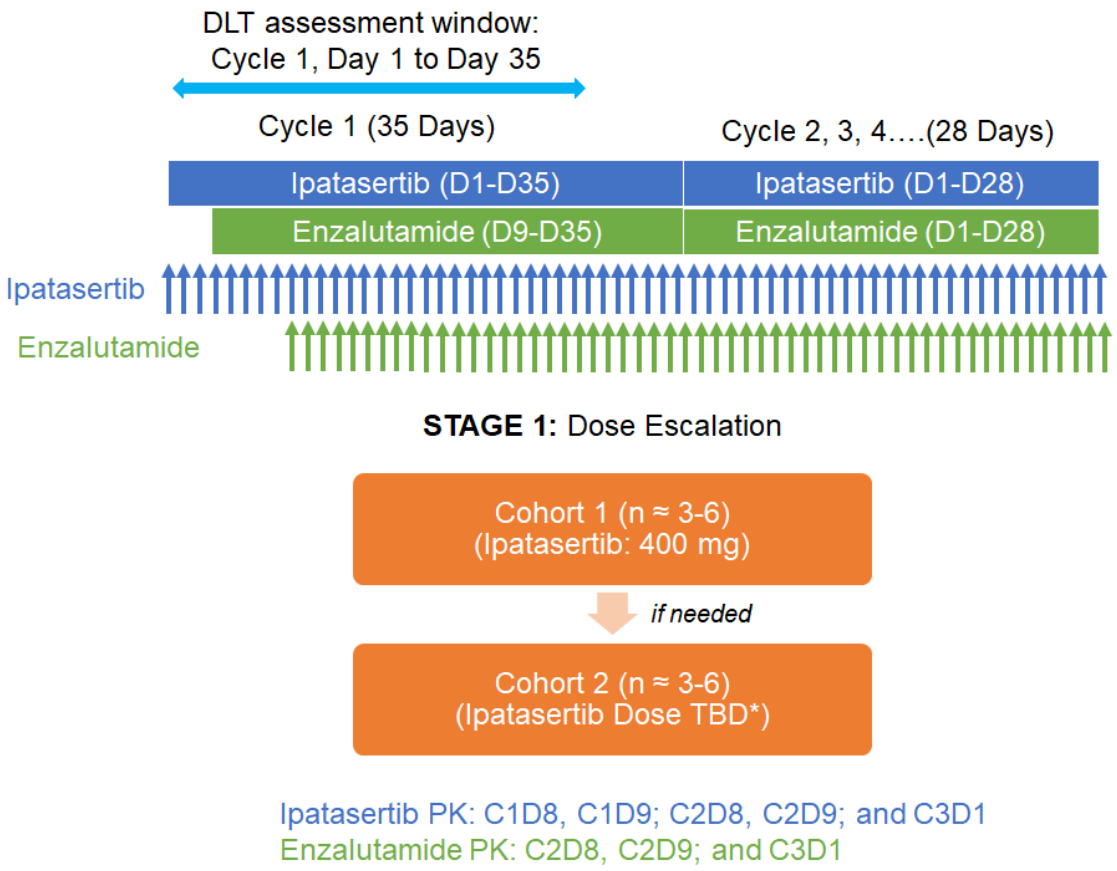
Arm C: paclitaxel + ipatasertib[a]



DLT, dose-limiting toxicity; HER2, human epidermal growth factor receptor 2; IV, intravenous; TBD, to be determined.

[a] Cohort 2 was included in arm C. During stage 2 cohort expansion, patients received ipatasertib 400 mg.

Arm D: enzalutamide + ipatasertib[a]

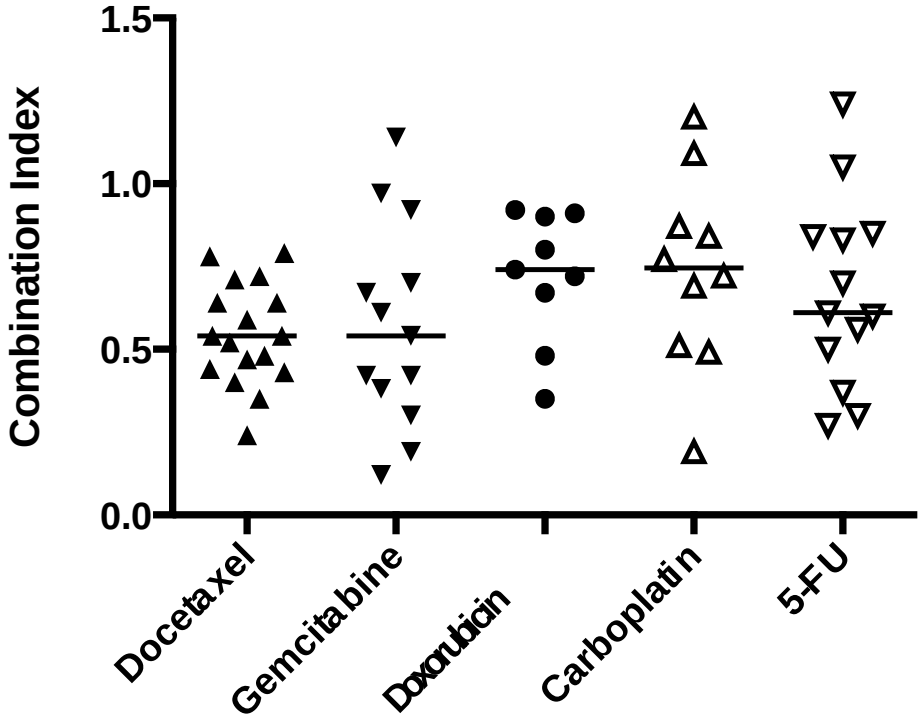


C, cycle; D, day; DLT, dose-limiting toxicity; PK, pharmacokinetics; TBD, to be determined.

[a] During stage 1 dose escalation, cohort 2 received ipatasertib 600 mg. The ipatasertib dose could be:

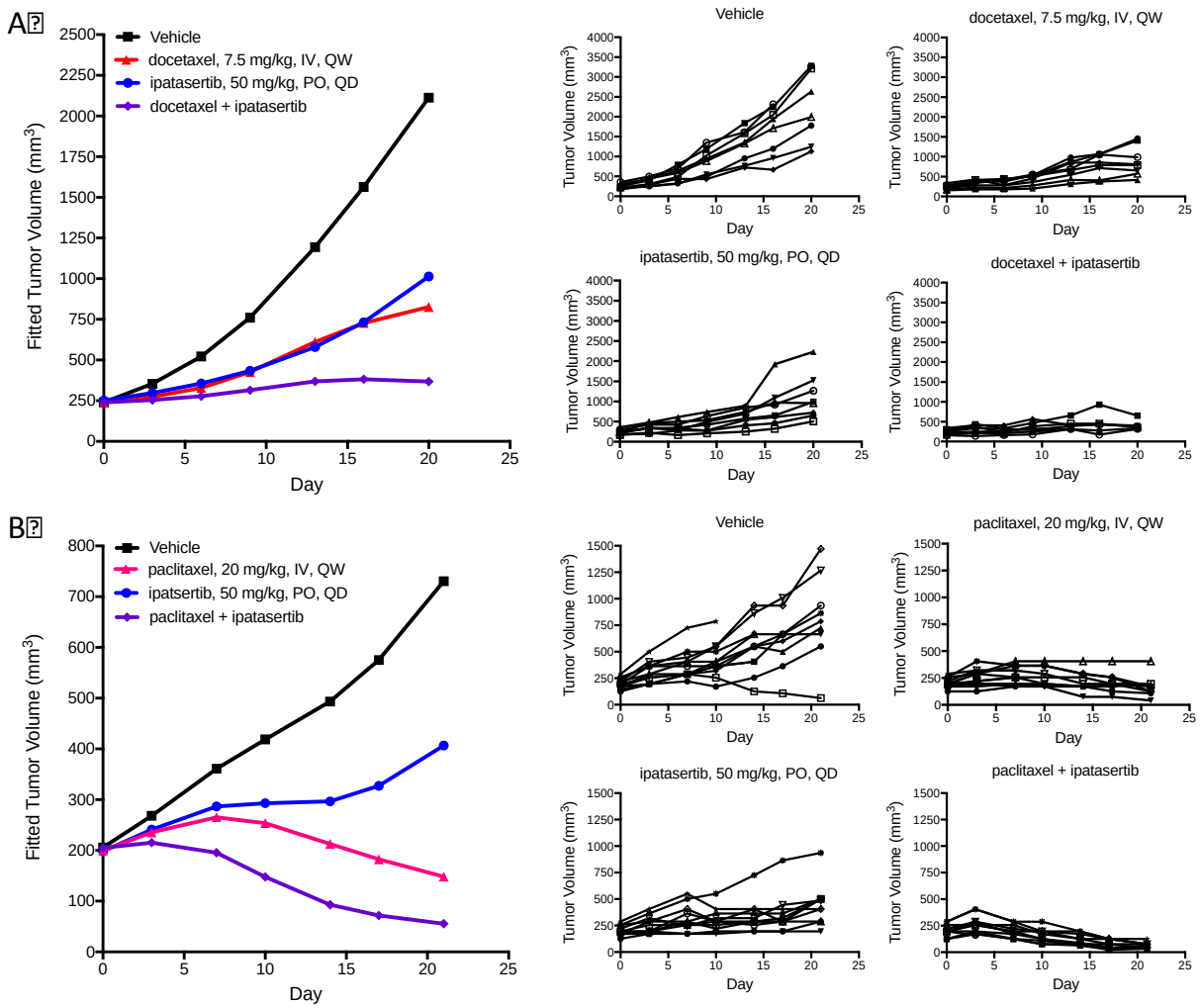
1. Increased up to a dose level ≤ 600 mg of single-agent exposure if drug-drug interaction resulted in decreased ipatasertib exposure ***or***
2. Decreased for tolerability, provided that ipatasertib exposure was adequate in cohort 1.

Supplementary Figure S2. Preclinical combination studies of ipatasertib and chemotherapeutic agents in human cancer cell lines in vitro. Each data point represents 1 cell line and the corresponding combination index value between ipatasertib and the indicated chemotherapeutic agent in that cell line.

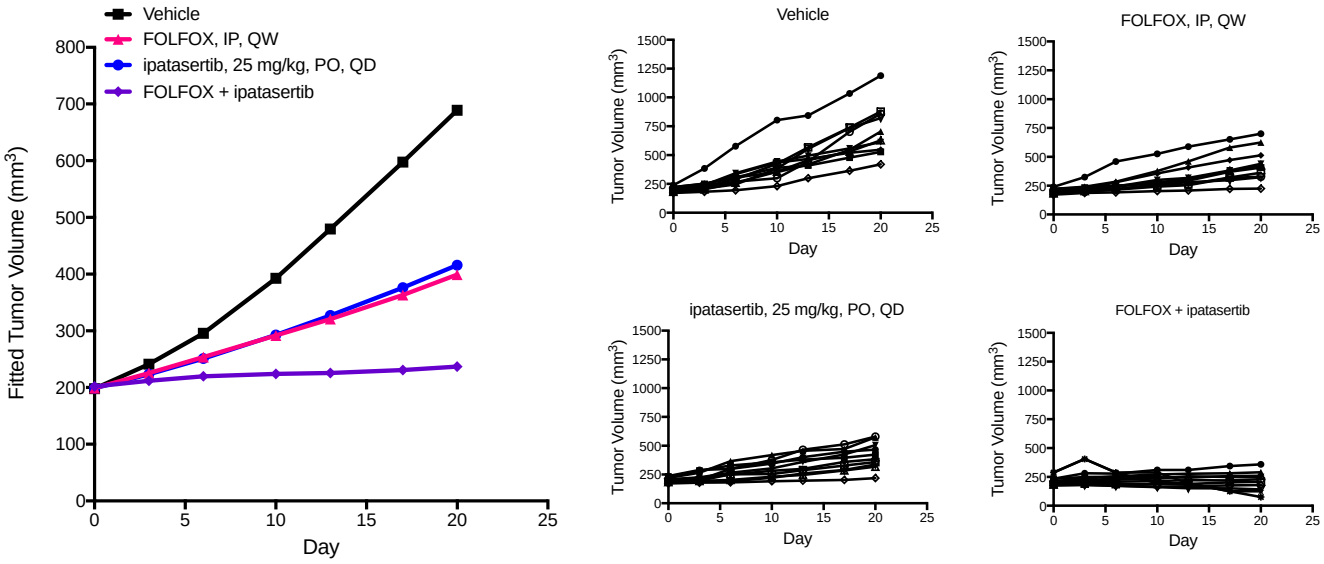


5-FU, 5-fluorouracil.

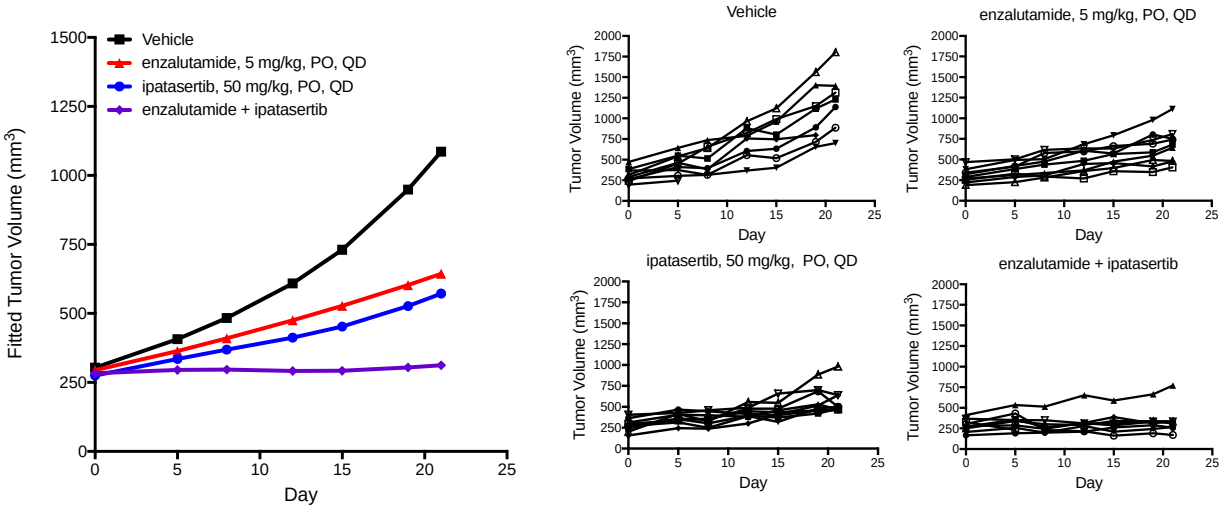
Supplementary Figure S3. In vivo efficacy of ipatasertib in combination with taxanes in breast cancer models. (A) Combination of ipatasertib with docetaxel showed enhanced efficacy compared with each single agent alone in the HCI-001 TNBC PDX model, which has a low level of PTEN expression as defined by IHC (H score of 100). Left panel: curve fitting of tumor volume for each group. Right panels: individual tumor volumes. Ipatasertib was administered daily at 50 mg/kg PO; docetaxel was administered IV at 7.5 mg/kg once weekly. (B) Combination of ipatasertib with paclitaxel showed enhanced efficacy compared with each single agent alone in the MCF-7 HR^+ breast cancer model that harbors a hot-spot *PIK3CA* mutation (E545K). Left panel, curve fitting of tumor volume for each group. Right panels, individual tumor volumes. Ipatasertib was administered daily at 50 mg/kg PO; paclitaxel was administered IV at 20 mg/kg once weekly. IHC, immunohistochemistry; IV, intravenous; PDX, patient-derived xenograft; PIK3CA, phosphatidylinositol 4,5-bisphosphate 3-kinase catalytic subunit α; PO, oral; PTEN, phosphatase and tensin homolog; QD, once daily; QW, once weekly; TNBC, triple-negative breast cancer.


A
Vehicle
docetaxel, 7.5 mg/kg, IV, QW
ipatasertib, 50 mg/kg, PO, QD
docetaxel + ipatasertib
Fitted Tumor Volume (mm3)
Day
Vehicle
docetaxel, 7.5 mg/kg, IV, QW
ipatasertib, 50 mg/kg, PO, QD
docetaxel + ipatasertib
Tumor Volume (mm3)
Day
B
Vehicle
paclitaxel, 20 mg/kg, IV, QW
ipatsertib, 50 mg/kg, PO, QD
paclitaxel + ipatasertib
Fitted Tumor Volume (mm3)
Day
Vehicle
paclitaxel, 20 mg/kg, IV, QW
ipatasertib, 50 mg/kg, PO, QD
paclitaxel + ipatasertib
Tumor Volume (mm3)
Day

Supplementary Fig. S4. In vivo efficacy of ipatasertib in combination with FOLFOX in the STO#240 gastric PDX model (PTEN-null, HER2^{-}). Left panel: curve fitting of tumor volume for each group. Right panels: individual tumor volumes. Ipatasertib was administered daily at 50 mg/kg PO; FOLFOX (oxaliplatin 5 mg/kg IP, calcium folinate 100 mg/kg IP, 5-fluorouracil 25 mg/kg IP and 25 mg/kg SC) was given once weekly. FOLFOX, leucovorin, 5-fluorouracil, and oxaliplatin; HER2, human epidermal growth factor receptor; IP, intraperitoneal; PDX, patient-derived xenograft; PO, oral; PTEN, phosphatase and tensin homolog; QD, once daily; QW, once weekly; SC, subcutaneous.



Supplementary Fig. S5. In vivo efficacy of ipatasertib in combination with enzalutamide in the LuCaP 35V AR^{+} CRPC PDX model (PTEN-low based on an IHC H score of 200) in castrated SCID beige male mice. Left panel: curve fitting of tumor volumes for each group. Right panels: individual tumor volumes. Ipatasertib was administered daily at 50 mg/kg and enzalutamide was administered daily at 5 mg/kg, both PO. AR, androgen receptor; CRPC, castration-resistant prostate cancer; IHC, immunohistochemistry; PDX, patient-derived xenograft; PO, oral; PTEN, phosphatase and tensin homolog; QD, once daily; SCID, severe combined immunodeficient.



Supplementary Fig. S6. Maximum reduction in prostate-specific antigen (PSA) from baseline among patients in arm D. (A) Patients with prostate cancer without prior abiraterone therapy. (B) Patients with prostate cancer with prior abiraterone therapy.