

Supplementary Tables

Supplementary Table 1. Dosing levels for dose-finding portion of trial

Dose Level^a	Gemcitabine	Nab-paclitaxel	L-glutamine^b
-2	600 mg/m ² IV D1, 8, 15	75 mg/m ² IV D1, 8, 15	0.1 g/kg oral BID
-1	800 mg/m ² IV D1, 8, 15	100 mg/m ² IV D1, 8, 15	0.1 g/kg oral BID
0	1000 mg/m ² IV D1, 8, 15	125 mg/m ² IV D1, 8, 15	0.1 g/kg oral BID
1	1000 mg/m ² IV D1, 8, 15	125 mg/m ² IV D1, 8, 15	0.2 g/kg oral BID
2	1000 mg/m ² IV D1, 8, 15	125 mg/m ² IV D1, 8, 15	0.3 g/kg oral BID

Supplementary Table 2. Treatment-related adverse events

	Event-level (N=169)		Patient-level (N=18)	
All grade AEs	169 (100.0%)		17 (94.4%)	
Any grade ≥3 AEs	43 (25.4%)		12 (66.7%)	
Adverse event type	All grade	Grade ≥3	All grade	Grade ≥3
Abdominal pain	1 (0.6%)	0	1 (5.6%)	0
Alanine aminotransferase increased	1 (0.6%)	0	1 (5.6%)	0
Alopecia	3 (1.8%)	0	3 (16.7%)	0
Anemia	22 (13.0%)	11 (6.5%)	8 (44.4%)	5 (27.8%)
Anorexia	5 (3.0%)	1 (0.6%)	5 (27.8%)	1 (5.6%)
Anxiety	1 (0.6%)	0	1 (5.6%)	0
Arthralgia	1 (0.6%)	0	1 (5.6%)	0
Aspartate aminotransferase increased	3 (1.8%)	0	2 (11.1%)	0
Blood bilirubin increased	2 (1.2%)	0	1 (5.6%)	0
Constipation	2 (1.2%)	0	2 (11.1%)	0
Cough	1 (0.6%)	0	1 (5.6%)	0
Dehydration	1 (0.6%)	0	1 (5.6%)	0
Diarrhea	6 (3.6%)	1 (0.6%)	5 (27.8%)	1 (5.6%)
Dizziness	1 (0.6%)	0	1 (5.6%)	0
Dysgeusia	1 (0.6%)	0	1 (5.6%)	0
Dyspnea	1 (0.6%)	0	1 (5.6%)	0
Edema limbs	9 (5.3%)	0	6 (33.3%)	0
Fall	1 (0.6%)	0	1 (5.6%)	0
Fatigue	15 (8.9%)	2 (1.2%)	10 (55.6%)	2 (11.1%)
Febrile neutropenia	2 (1.2%)	2 (1.2%)	2 (11.1%)	2 (11.1%)
Flatulence	1 (0.6%)	0	1 (5.6%)	0
Heart failure	1 (0.6%)	0	1 (5.6%)	0
Hypokalemia	3 (1.8%)	0	3 (16.7%)	0
Hyponatremia	1 (0.6%)	0	1 (5.6%)	0
Muscle weakness lower limb	1 (0.6%)	0	1 (5.6%)	0
Nausea	3 (1.8%)	0	3 (16.7%)	0
Neutrophil count decreased	19 (11.2%)	10 (5.9%)	9 (50.0%)	7 (38.9%)
Peripheral sensory neuropathy	9 (5.3%)	1 (0.6%)	5 (27.8%)	1 (5.6%)
Platelet count decreased	19 (11.2%)	7 (4.1%)	7 (38.9%)	4 (22.2%)
Pneumonitis	1 (0.6%)	1 (0.6%)	1 (5.6%)	1 (5.6%)
Pruritus	1 (0.6%)	0	1 (5.6%)	0
Rash maculo-papular	7 (4.1%)	0	4 (22.2%)	0
Scalp pain	1 (0.6%)	0	1 (5.6%)	0
Superficial thrombophlebitis	1 (0.6%)	0	1 (5.6%)	0
Syncope	1 (0.6%)	1 (0.6%)	1 (5.6%)	1 (5.6%)
Thrush	2 (1.2%)	0	2 (11.1%)	0
Vomiting	3 (1.8%)	0	3 (16.7%)	0
Weight loss	1 (0.6%)	0	1 (5.6%)	0
White blood cell decreased	15 (8.9%)	6 (3.6%)	8 (44.4%)	5 (27.8%)

AE, adverse event

Supplementary Table 3. All adverse events treatment-related or treatment-unrelated

	E v e n t - l e v e l (N=245)		Patient-level (N=18)	
Any AEs	245 (100.0%)		17 (94.4%)	
Any grade ≥3 AEs	61 (24.9%)		15 (83.3%)	
Adverse event type	All grade	Grade ≥3	All grade	Grade ≥3
Abdominal pain	2 (0.8%)	0	2 (11.1%)	0
Alanine aminotransferase increased	1 (0.4%)	0	1 (5.6%)	0
Alkaline phosphatase increased	4 (1.6%)	1 (0.4%)	2 (11.1%)	1 (5.6%)
Alopecia	3 (1.2%)	0	3 (16.7%)	0
Anemia	23 (9.4%)	12 (4.9%)	9 (50.0%)	6 (33.3%)
Anorexia	5 (2.0%)	1 (0.4%)	5 (27.8%)	1 (5.6%)
Anxiety	2 (0.8%)	0	2 (11.1%)	0
Arthralgia	1 (0.4%)	0	1 (5.6%)	0
Ascites	2 (0.8%)	0	1 (5.6%)	0
Aspartate aminotransferase increased	3 (1.2%)	0	2 (11.1%)	0
Back pain	1 (0.4%)	0	1 (5.6%)	0
Bloating	1 (0.4%)	0	1 (5.6%)	0
Blood bilirubin increased	5 (2.0%)	0	2 (11.1%)	0
Cardiac troponin I increased	1 (0.4%)	0	1 (5.6%)	0
Chest pain - cardiac	1 (0.4%)	0	1 (5.6%)	0
Colitis	1 (0.4%)	0	1 (5.6%)	0
Constipation	3 (1.2%)	0	3 (16.7%)	0
Cough	2 (0.8%)	0	2 (11.1%)	0
Creatinine increased	1 (0.4%)	0	1 (5.6%)	0
Dehydration	2 (0.8%)	0	2 (11.1%)	0
Delirium	1 (0.4%)	0	1 (5.6%)	0
Diarrhea	7 (2.9%)	1 (0.4%)	6 (33.3%)	1 (5.6%)
Disseminated intravascular coagulation	1 (0.4%)	0	1 (5.6%)	0
Dizziness	1 (0.4%)	0	1 (5.6%)	0
Dysgeusia	1 (0.4%)	0	1 (5.6%)	0
Dysphagia	1 (0.4%)	1 (0.4%)	1 (5.6%)	1 (5.6%)
Dyspnea	4 (1.6%)	0	4 (22.2%)	0
Edema limbs	11 (4.5%)	0	7 (38.9%)	0
Epistaxis	1 (0.4%)	0	1 (5.6%)	0
Fall	1 (0.4%)	0	1 (5.6%)	0
Fatigue	16 (6.5%)	2 (0.8%)	11 (61.1%)	2 (11.1%)

Febrile neutropenia	2 (0.8%)	2 (0.8%)	2 (11.1%)	2 (11.1%)
Fever	1 (0.4%)	0	1 (5.6%)	0
Flatulence	1 (0.4%)	0	1 (5.6%)	0
Heart failure	1 (0.4%)	0	1 (5.6%)	0
Hypertension	5 (2.0%)	3 (1.2%)	3 (16.7%)	3 (16.7%)
Hypocalcemia	1 (0.4%)	0	1 (5.6%)	0
Hypoglycemia	1 (0.4%)	0	1 (5.6%)	0
Hypokalemia	5 (2.0%)	1 (0.4%)	4 (22.2%)	1 (5.6%)
Hyponatremia	2 (0.8%)	0	2 (11.1%)	0
Infections and infestations - Other, specify	1 (0.4%)	0	1 (5.6%)	0
Insomnia	3 (1.2%)	0	3 (16.7%)	0
Ischemia cerebrovascular	1 (0.4%)	0	1 (5.6%)	0
Leukocytosis	1 (0.4%)	1 (0.4%)	1 (5.6%)	1 (5.6%)
Lung infection	1 (0.4%)	0	1 (5.6%)	0
Muscle weakness lower limb	1 (0.4%)	0	1 (5.6%)	0
Myocardial infarction	1 (0.4%)	1 (0.4%)	1 (5.6%)	1 (5.6%)
Nasal congestion	1 (0.4%)	0	1 (5.6%)	0
Nausea	5 (2.0%)	1 (0.4%)	5 (27.8%)	1 (5.6%)
Neck pain	1 (0.4%)	0	1 (5.6%)	0
Neutrophil count decreased	19 (7.8%)	10 (4.1%)	9 (50.0%)	7 (38.9%)
Obstruction gastric	1 (0.4%)	1 (0.4%)	1 (5.6%)	1 (5.6%)
Pain	1 (0.4%)	0	1 (5.6%)	0
Peripheral sensory neuropathy	10 (4.1%)	1 (0.4%)	6 (33.3%)	1 (5.6%)
Platelet count decreased	19 (7.8%)	7 (2.9%)	7 (38.9%)	4 (22.2%)
Pleural effusion	1 (0.4%)	0	1 (5.6%)	0
Pneumonitis	1 (0.4%)	1 (0.4%)	1 (5.6%)	1 (5.6%)
Presyncope	1 (0.4%)	1 (0.4%)	1 (5.6%)	1 (5.6%)
Pruritus	1 (0.4%)	0	1 (5.6%)	0
Rash maculo-papular	7 (2.9%)	0	4 (22.2%)	0
Rhinorrhea	1 (0.4%)	0	1 (5.6%)	0
Scalp pain	1 (0.4%)	0	1 (5.6%)	0
Sepsis	3 (1.2%)	3	2 (11.1%)	2

		(1.2%)		(11.1%)
Skin and subcutaneous tissue disorders - Other, specify	1 (0.4%)	0	1 (5.6%)	0
Skin infection	1 (0.4%)	1 (0.4%)	1 (5.6%)	1 (5.6%)
Skin ulceration	1 (0.4%)	0	1 (5.6%)	0
Stroke	1 (0.4%)	0	1 (5.6%)	0
Superficial thrombophlebitis	1 (0.4%)	0	1 (5.6%)	0
Syncope	2 (0.8%)	2 (0.8%)	2 (11.1%)	2 (11.1%)
Thromboembolic event	2 (0.8%)	1 (0.4%)	2 (11.1%)	1 (5.6%)
Thrush	2 (0.8%)	0	2 (11.1%)	0
Upper respiratory infection	1 (0.4%)	0	1 (5.6%)	0
Urinary tract infection	1 (0.4%)	0	1 (5.6%)	0
Vaginal infection	1 (0.4%)	0	1 (5.6%)	0
Vomiting	5 (2.0%)	0	4 (22.2%)	0
Weight loss	1 (0.4%)	0	1 (5.6%)	0
White blood cell decreased	15 (6.1%)	6 (2.4%)	8 (44.4%)	5 (27.8%)

AE, adverse event

Supplementary Table 4. Post-progression therapies and progression-free survival.

Characteristic (n=14)^a	n (%)
Lines of therapy	
1 ^b	2 (14%)
2	5 (36%)
3	2 (14%)
4	5 (36%)
Post-progression regimens	
<u>Second-line (n=12):</u>	
FOLFIRINOX	5 (42%)
5-FU/liposomal irinotecan	4 (33%)
Gemcitabine/capecitabine	2 (17%)
NALIRIFOX	1 (8%)
<u>Third-line (n=7):</u>	
Gemcitabine/nab-paclitaxel	1 (14%)
FOLFIRINOX	1 (14%)
IROX	1 (14%)
Clinical trial	4 (58%)
<u>Fourth-line (n=5):</u>	
Cisplatin/gemcitabine	2 (40%)
Cisplatin/gemcitabine/nab-paclitaxel	1 (20%)
FOLFOX	1 (20%)
Post-progression PFS (median, range)	
Second-line PFS	2 months (0.7-13.2 months)
Third-line PFS	1.6 months (0.5-4.3 months)
Fourth-line PFS	1.2 months (0.7-3.0 months)

^aTwo subjects did not have disease progression at time of data cut off

^bTwo subjects did not receive subsequent systemic therapies upon progression to study treatment FOLFIRINOX, 5-fluorouracil or 5-FU, leucovorin, irinotecan, oxaliplatin; NALIRIFOX, liposomal irinotecan, 5-FU, leucovorin, oxaliplatin; IROX, irinotecan and oxaliplatin; FOLFOX, 5-FU, leucovorin, oxaliplatin; PFS, progression-free survival

Supplementary Table 5. Plasma metabolites that exhibited significant changes either between baseline and C1D1 or between C1D1 and C1D8 are bolded.

		Baseline			Wilcoxon matched-pairs signed rank test – two-sided P Value	
		Baseline	C1D1	C1D8	Baseline vs C1D1	C1D1 vs C1D8
1	2-Deoxy-D-glucose 6-phosphate	158	365	465	0.0276	0.9097
2	2-Ketobutyrate	486	290	478	0.0479	0.1294
3	2-Methyl-1-butanol	2609	4488	1676	0.1465	0.0161
4	3-2-Hydroxyethylindole	34	22	22	0.0386	0.5771
5	3-Methylglutaric acid	15032	24336	10660	0.0215	0.0005
6	alpha-Ketoglutaric acid	28679	39224	20901	0.0681	0.0049
7	Cellobiose	1068	1705	1202	0.0479	0.1348
8	cis-Aconitic acid	771321	780217	680450	0.7354	0.0425
9	Cytidine-5-monophosphate	33	41	25	0.2439	0.0269
10	D-Mannose	360349	470598	502376	0.0002	0.3013
11	Glyoxylic acid	140	256	43	0.3396	0.0186
12	Inosine 5-monophosphate	531	636	127	0.5879	0.02
13	L-Arabitol	1554	3578	1450	0.3757	0.0425
15	L-Hydroxyglutaric acid	3116	4451	3180	0.1099	0.021
16	L-Malic acid	236776	273681	230564	0.0574	0.0068
17	L-Sorbose	360349	470598	502376	0.0002	0.3013
18	Lactic acid	462716	551143	484296	0.0479	0.2036
19	Mevalonic acid	264	1572	233	0.0398	0.0449
20	Myo-Inositol	9287040	10788618	11126479	0.0007	0.6221
21	N-Carbamoyl-DL-aspartic acid	786	1191	1455	0.0266	0.5693
22	Nicotinic acid mononucleotide	182	104	107	0.0425	0.7334
23	Phenylpyruvic acid	1282	2074	1194	0.1099	0.021
24	Pyridoxal hydrochloride	1060	1501	426	0.3757	0.0034
25	Pyruvic acid	1435	3898	1869	0.0398	0.2334
26	Quinic acid	5971	8570	3300	0.1677	0.0122
27	Taurocholic acid	5952	890	2988	0.0046	0.0161
28	trans-Aconitic acid	607771	631649	573170	0.3054	0.0122
29	Trehalose	155	262	250	0.0171	0.8501
30	Uridine 5-diphosphate	129	131	92	0.7354	0.0171

Supplementary Table 6. The impact of L-glutamine on overall survival (OS) and progression free survival (PFS) based on alpha diversity of the gut microbiome in patients treated with L-glutamine and gemcitabine plus nab-paclitaxel (in reference to Extended Data Figure 5a comparisons). Long OS was defined by patients whose median OS surpassed the historical median OS (258 days), while long PFS was defined by those patients having surpassed historical median PFS (165 days) of first-line gemcitabine and nab-paclitaxel alone.

	N	Baseline N = 12 (%)	L-Glutamine N = 11 (%)
OS	23		
Long OS		10 (83%)	9 (82%)
Short OS		2 (17%)	2 (18%)
PFS	23		
Long PFS		9 (75%)	8 (73%)
Short PFS		3 (25%)	3 (27%)

Supplementary Table 7. Baseline characteristics and evidence of weight stabilizing effects from L-glutamine and first-line gemcitabine and nab-paclitaxel (n = 16).

Characteristic	Frequency (%) or mean $\pm$ SD
Median age in years (range)	71 (55-92)
Female	11/16 (69%)
Cachexia at study entry ^a	13/16 (81%)
Mean weight (kg) at study entry	73.1 (21.3)
Mean BMI (kg/m ²) at study entry	26.2 (6.4)
Weight stability ^b	8/16 (50%)
Median duration of treatment	8.6 months (95% CI 6-15)
Weight increase from baseline	8/16 (50%)
BMI increase from baseline	8/16 (50%)
Mean weight change (kg) from baseline	-0.39 (6.7)
Mean BMI change (kg/m ²) from baseline	-0.17 (2.7)

^aDefined as >5% unexplained weight loss within 6 months prior to screening

^bDefined as weight change less than 0.1 kg/baseline BMI-unit from cycle 1, day 1 of study treatment to end of treatment (median duration of treatment 8.6 months)

SD, standard deviation; CI, confidence interval

Supplementary Table 8. Association between weight stability and overall survival (OS) and progression free survival (PFS; n=16).

	p-value from Fisher's exact two- sided test	p-value from exact log-rank two-sided test	
	Best overall response CR+PR vs. SD+PD	OS dead vs. alive	PFS PD vs. PF
Weight stability^a Yes vs. No	>0.999	0.682	0.742

^aDefined as weight change less than 0.1 kg/baseline BMI-unit from cycle 1, day 1 of study treatment to end of treatment (median duration of treatment 8.6 months)

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; OS, overall survival; PFS, progression-free survival; PF, progression free

Supplementary Table 9. Association between weight stability and efficacy end points (n=16).

	Mean ± standard deviation		p-value (Mann-Whitney U two-sided test)	p-value (Cox regression, two-sided test)
Tumor shrinkage^a, %	Weight stability ^b Yes n=8	Weight stability No n=8	0.958	.
	-36.09 ± 45.47	-32.04 ± 31.13		
Weight change, kg	Best overall response CR+PR n=7	Best overall response SD+PD n=9	0.289	.
	-2.39 ± 7.11	1.17 ± 6.77		
	OS dead n=10	OS alive n=6	0.871	0.790
	-0.97 ± 7.74	0.58 ± 5.86		
	PFS PD n=14	PFS PF n=2	0.382	0.515
	-1.06 ± 6.88	4.30 ± 7.35		
BMI change	Best overall response CR+PR n=7	Best overall response SD+PD n=9	0.091	.
	-1.30 ± 2.57	0.72 ± 2.86		
	OS dead n=10	OS alive n=6	0.492	0.966
	-0.52 ± 3.22	0.42 ± 2.20		
	PFS PD n=14	PFS PF n=2	0.600	0.470
	-0.36 ± 2.89	1.21 ± 2.80		

^aTumor shrinkage defined as any reduction in tumor target lesions from baseline

^bDefined as weight change less than 0.1 kg/baseline BMI-unit from cycle 1, day 1 of study treatment to end of treatment (median duration of treatment 8.6 months)

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; OS, overall survival; OS, overall survival; PF, progression free; BMI, body mass index; PFS, progression-free survival