A Phase 2b Study of Eryaspase in Combination with Gemcitabine or FOLFOX as Second-line Therapy in Patients with Metastatic Pancreatic Adenocarcinoma (NCT02195180)

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Background

- Erythrocytes as a carrier for asparaginase (ASNase) lead to prolonged ASNase activity with reduced toxicity.
- The presumed mechanism of action is predominantly via elimination of a circulating pool of asparagine actively transported into erythrocytes where it is hydrolyzed by the encapsulated ASNase.
- Additional complementing mechanism of action is the elimination of circulating asparagine by the free ASNase component in eryaspase (GRASPA®) (approximately 5-10%).

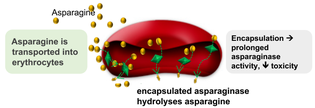


Figure 1. Encapsulated Asparaginase in Erythrocytes

- KRAS mutations are present in over 90% of pancreatic ductal adenocarcinomas (PDAC), resulting in the constitutive activation of RAF/MEK/ERK and PI3K/AKT-mTOR pathways, enhanced nutrient uptake, and uncontrolled cellular growth. A key feature of constitutive KRAS signaling is the dysregulation of metabolic pathways, which can be modulated by additional therapeutic strategies that involve tumor metabolism.[1]
- Asparagine synthetase (ASNS) expression status is believed to play a role in determining sensitivity to ASNase treatment in several solid tumors including pancreatic cancer.[1] Enhanced expression of ASNS has been shown to be a component of adaptation responses to hypoxic conditions and glucose deprivation, leading to the neo-synthesis of asparagine, and is therefore hypothesized to be a predictive factor for ASNase sensitivity in PDAC.[2]
- ASNase has been shown to have growth inhibitory effects in pancreatic cell lines and in xenograft models.[3-6]
- Excessive toxicity of other ASNase formulations has been observed in early clinical studies in various solid tumors (pancreatic, ovarian) and multiple myeloma.[7-10]
- The clinical activity and lower incidence of adverse events associated with eryaspase[11] suggest a potential therapeutic strategy in PDAC.

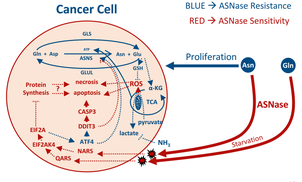


Figure 2. Rationale for Therapy with L-Asparaginase in PDAC[12]

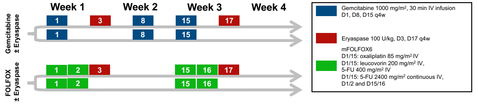
Study Design

Co-primary endpoints:

- PFS and OS in ASNS 0/1+, positive study if HR <0.85 irrespective of statistical significance

Key secondary endpoints:

- PFS and OS in key treatment populations (ASNS all comers with minimum target for 0/1+)
- Safety, ORR, QoL



Patient Results

Baseline Characteristics

Status	Eryaspase + Chemotherapy N=95 (%)	Chemotherapy Alone N=46 (%)	Total (N=141)
Gender, n (%)	**95**	**46**	**141**
Male	53 (55.8)	30 (65.2)	83 (58.9)
Female	42 (44.2)	16 (34.8)	58 (41.1)
Age at randomization, n	**95**	**46**	**141**
Mean (SD)	62.7 (10.24)	62.4 (8.68)	62.6 (9.72)
Median	63	63	63
Range	(37, 84)	(43, 80)	(37, 84)
ECOG PS, n (%)	**92**	**43**	**135**
0	29 (31.5)	11 (25.6)	40 (29.6)
1	63 (68.5)	32 (74.4)	95 (70.4)
CA19-9, n (%)	**83**	**37**	**120**
Normal	19 (22.9)	6 (16.2)	25 (20.8)
Elevated	64 (77.1)	31 (83.8)	95 (79.2)
Time from initial diagnosis, mo	**95**	**46**	**141**
Mean (SD)	10.7 (10.53)	10.7 (7.87)	10.7 (9.72)
Median	8	9	8
Range	(2, 87)	(3, 39)	(2, 87)
Stage at initial diagnosis, n (%)	**95**	**46**	**141**
I/II	15 (15.8)	7 (15.2)	22 (15.6)
III	8 (8.4)	6 (13.0)	14 (9.9)
IV	72 (75.8)	33 (71.7)	105 (74.5)
Main sites of metastasis, n (%)	**93**	**46**	**139**
Liver	74 (79.6)	37 (80.4)	111 (79.9)
Lung	22 (23.7)	8 (17.4)	30 (21.6)
Peritoneal	21 (22.6)	10 (21.7)	31 (22.3)
Number of metastatic sites, n (%)	**95**	**46**	**141**
0–1	60 (63.2)	34 (73.9)	94 (66.7)
2	29 (30.5)	10 (21.7)	39 (27.7)
≥3	6 (6.3)	2 (4.3)	8 (5.7)
ASNS scoring intensity, n (%)	**95**	**46**	**141**
0/1+	66 (69.5)	32 (69.6)	98 (69.5)
2+/3+	29 (30.5)	14 (30.4)	43 (30.5)
Prior systemic therapy, n (%)	**95**	**46**	**141**
Yes	94 (98.9)	46 (100.0)	140 (99.3)
Prior best overall response, n (%)	**94**	**46**	**140**
Objective response	28 (29.8)	6 (13.0)	34 (24.3)
Stable disease	36 (38.3)	23 (50.0)	59 (42.1)
Progressive disease	29 (30.9)	17 (37.0)	46 (32.9)
Non-evaluable	1 (1.1)	0	1 (0.7)

Patient Disposition

	Eryaspase + Chemotherapy N=95 (%)	Chemotherapy Alone N=46 (%)	Total (N=141)
Randomized (ITT), n	95	46	141
Safety population, n (%)	93 (97.9)	44 (95.7)	137 (97.2)
Chemotherapy regimen, n (%)			
Gemcitabine	84 (88.4)	41 (89.1)	125 (88.7)
FOLFOX	11 (11.6)	5 (10.9)	16 (11.3)
Discontinued study, primary reasons, n (%)			
Adverse event	7 (7.4)	2 (4.3)	9 (6.4)
Disease progression	62 (65.3)	35 (76.1)	97 (68.8)
Investigator's decision	16 (16.8)	5 (10.9)	21 (14.9)
Consent withdrawal	3 (3.2)	1 (2.2)	4 (2.8)
Others	5 (5.3)	0	5 (3.5)

Efficacy Results

Summary of Efficacy Data

Overall Survival	ITT		ASNS 0/1+		ASNS 2+/3+	
	E + CT (n=95)	CT (n=46)	E + CT (n=66)	CT (n=32)	E + CT (n=29)	CT (n=14)
Event rate, n (%)	79 (83.2)	40 (87.0)	54 (81.8)	27 (84.4)	25 (86.2)	13 (92.9)
OS (weeks), Median (95% CI)	26.1 (21.0, 28.4)	19.0 (12.3, 26.3)	27.0 (22.3, 31.1)	21.7 (13.0, 31.0)	21.0 (14.9, 29.4)	11.9 (6.9, 19.7)
HR (95% CI)	0.60 (0.40, 0.88)		0.65 (0.40, 1.05)		0.45 (0.22, 0.95)	
Log-Rank p-value	0.009		0.077		0.036	
OS rate at 24 wks	56.2%	36.6%	59.8%	47.6%	48.1%	14.3%

Progression Free Survival*	ITT		ASNS 0/1+		ASNS 2+/3+	
	E + CT (n=95)	CT (n=46)	E + CT (n=66)	CT (n=32)	E + CT (n=29)	CT (n=14)
Event rate, n (%)	80 (84.2)	36 (78.3)	57 (86.4)	24 (75.0)	23 (79.3)	12 (85.7)
PFS (weeks), Median (95% CI)	8.6 (7.6, 14.6)	7.0 (6.1, 7.6)	8.6 (7.6, 14.6)	7.6 (6.1, 14.6)	8.4 (7.0, 14.9)	6.1 (2.1, 7.0)
HR (95% CI)	0.59 (0.40, 0.89)		0.72 (0.44, 1.17)		0.38 (0.18, 0.82)	
Log-Rank p-value	0.011		0.184		0.014	
PFS rate at 24 wks	16.9%	5.8%	17.0%	8.6%	16.7%	0%

Objective Response Rate*	ITT		ASNS 0/1+		ASNS 2+/3+	
	E + CT (n=95)	CT (n=46)	E + CT (n=66)	CT (n=32)	E + CT (n=29)	CT (n=14)
Response rate, n (%) (95% CI)	11 (11.6) (5.9, 19.8)	3 (6.5) (1.4, 17.9)	9 (13.6) (6.4, 24.3)	3 (9.4) (2.0, 25.0)	2 (6.9) (0.8, 22.8)	0 (0.0, 23.2)
SD, n (%)	34 (35.8)	8 (17.4)	21 (31.8)	7 (21.9)	13 (44.8)	1 (7.1)
DCR (CR+PR+SD), n (%) (95% CI)	45 (47.4) (37.0, 57.9)	11 (23.9) (12.6, 38.8)	30 (45.5) (33.1, 58.2)	10 (31.3) (16.1, 50.0)	15 (51.7) (32.5, 70.6)	1 (7.1) (0.2, 33.9)
PD, n (%)	43 (45.3)	31 (67.4)	32 (48.5)	18 (56.3)	11 (37.9)	13 (92.9)
NE, n (%)	7 (7.4)	4 (8.7)	4 (6.1)	4 (12.5)	3 (10.3)	0

Per RECIST criteria, DCR: disease control rate, CR: complete response, PR: partial response, SD: Stable disease, PD: progressive disease, NE: No follow-up scans [4 consent withdrawal; 4 randomized but not treated; 1 fatal event; 1 target lesions unassessed; 1 treated but discontinued treatment before follow-up scans]. The NE was similar between investigator and independent review.
E+CT: Eryaspase Arm; CT: Chemotherapy Arm

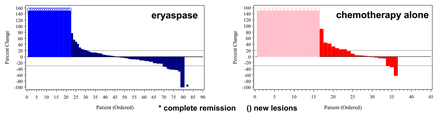
*Based on independent radiological review

The main efficacy and safety results presented in this interim report are based on data cutoff date of **31 July 2017**.

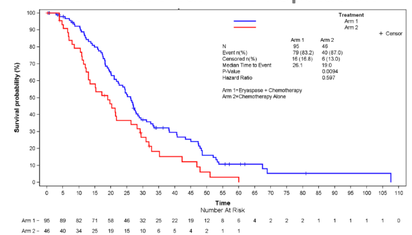
Post-Study Anti-Cancer Therapy

	Eryaspase + Chemotherapy (N=95)	Chemotherapy Alone (N=46)
Any anti-neoplastic agent, n (%)	41 (43.2)	15 (32.6)
Single agent	17 (41.4)	6 (40)
Combination	24 (58.5)	9 (60)
Combination chemotherapy agents		
FOLFOX	7 (29.2)	4 (44.4)
Mitomycin/5-FU or capecitabine	5 (20.8)	1 (11.1)
Gemcitabine/paclitaxel	4 (16.7)	1 (11.1)
Irinotecan/5-FU	3 (12.5)	2 (22.2)
Paclitaxel/5-FU	3 (12.5)	0 (0)
Cisplatin/5-FU	1 (4.2)	1 (11.1)
Erlotinib/capecitabine	1 (4.2)	0 (0)

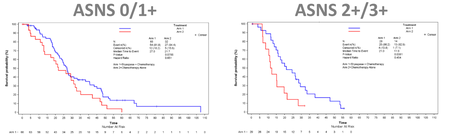
Best Response (RECIST 1.1) – Waterfall Plot
% Change from Baseline



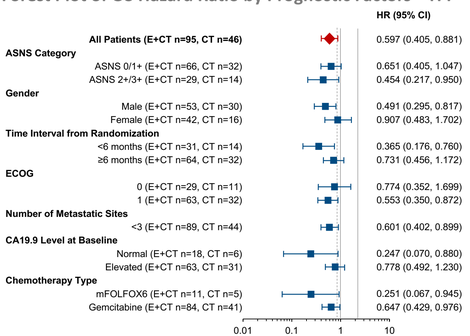
Overall Survival – ITT Population



Overall Survival – ASNS Subsets

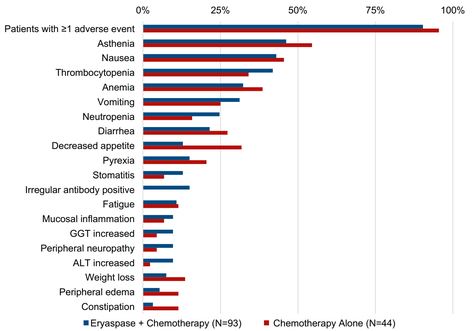


Forest Plot of OS Hazard Ratio by Prognostic Factors – ITT



Safety Results

Key Treatment-Emergent Related Adverse Events



Conclusions and Future Direction

- The baseline characteristics in the ITT and in the ASNS 0/1+ were similar between the two treatment groups. Most of the patients received gemcitabine (approximately 90%).
- The study has met its pre-specified primary endpoints. The combination of eryaspase plus chemotherapy led to a trend of improvement of co-primary endpoints of OS and PFS in patients whose tumors had low expression of ASNS (ASNS 0/1+).
- The combination of eryaspase plus chemotherapy significantly prolonged OS and PFS in the ITT population, and led to an improvement of DCR. Sensitivity analyses confirmed that these results were robust, again supporting the conclusion that eryaspase added to chemotherapy significantly improved OS and PFS.
- The safety profile of eryaspase combined with chemotherapy was comparable with the known safety profile for each chemotherapy used, respectively.
- Biomarker work is in progress to further decipher the effect of eryaspase in this disease, in particular the impact on metabolic pathways.
- Together, these data support the sponsor's proposal to conduct a confirmatory study of eryaspase in pancreatic adenocarcinoma. A global phase 3 study is currently being planned.

Acknowledgements: The authors wish to express their sincere thanks to the patients and their families, all investigators and their research staff, the CRO (Biotrial) and lab vendors, Richard Kay (consultant statistician), Adam Hamm (statistician, Cytel), Anu Gupta (Study Team Leader at Erytech), and the entire project team. Editorial assistance was provided by Cadence Research & Consulting, funded by Erytech Pharma.

Disclosures: I. El-Hariry is the Chief Medical Officer of Erytech Pharma; P. Hammel is a consultant or advisor for AstraZeneca, Celgene, Erytech Pharma, Ipsen, Merck Serono, and Shire.

Study sponsored by: Erytech Pharma

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