

**Supplemental Table 1. Demographic and clinical-pathological characteristics in patients with a diagnosis of Mixed Neuroendocrine Non-Neuroendocrine Neoplasm (MiNEN) according to the disease stage at diagnosis**

		Localised stage		Advanced stage				Localised stage		Advanced stage	
VARIABLE	CATEGORY	N	%	N	%	VARIABLE	CATEGORY	N	%	N	%
AGE AT DIAGNOSIS	Median (years)	66		61		PREDOMINANT COMPONENT	NE	14	37.8	13	43.3
	Range (years)	36-86		34-89			Non-NE	9	24.3	3	10.0
							Equal proportion	2	5.4	5	16.7
GENDER	Female	14	37.8	9	30.0		n.a.	12	32.4	9	30.0
	Male	23	62.2	21	70.0						
ECOG PS	0-1	27	73.0	15	50.0	MORPHOLOGY OF NE COMPONENT	Large cell	7	18.9	6	20
	≥ 2	5	13.5	10	33.3		Small cell	2	5.4	3	10
	n.a.	5	13.5	5	16.7		Others	0	0	1	3.3
							n.a.	28	75.6	20	
PRIMARY TUMOUR SITE	Colon	14	37.8	7	23.3	GRADING OF NE COMPONENT	Grade 1	2	5.4	0	0
	Oesophagus/OGJ	5	13.5	6	20.0		Grade 2	3	8.1	3	10.0
	Rectum	5	13.5	3	10.0		Grade 3	31	83.8	26	86.7
	Pancreas	4	10.8	2	6.7		n.a.	1	2.7	1	3.3
	Small bowel/ICJ	3	8.1	5	16.7						
	Stomach	1	2.7	2	6.7	Ki-67 OF NE COMPONENT	Median (%)	60		75	
	Anus	3	8.1	1	3.3		95%-CI (%)	49.8- 66.2		54.7-75.3	
	Biliary tract	1	2.7	2	6.7		Ki-67<55%	11	29.7	8	26.7
	Appendix	1	2.7	1	3.3		Ki-67≥55%	18	48.6	19	63.3
	Unknown	0	0	1	3.3		n.a.	8	21.6	3	10
	Lower GI	26	70.3	17	56.7	GRADING OF NON-NE COMPONENT	Grade 1	3	8.1	6	20.0
	Upper GI	6	16.2	8	26.7		Grade 2	10	27.0	4	13.3
	PB	5	13.5	4	13.3		Grade 3	11	29.7	8	26.7
	Unknown	0	0	1	3.3		Adenoma	1	2.7	1	3.3
							n.a.	12	32.4	11	36.7

N = number of patients, ECOG = Eastern Cooperative Oncology Group, PS = performance status, Loc = localised stage, Adv = advanced stage, NE = neuroendocrine, ADC = adenocarcinoma, OGJ = oesophago-gastric junction, ICJ = ileo-caecal junction, Lower GI = lower gastrointestinal tract (colon, rectum, small bowel, ICJ, anus), Upper GI = upper gastrointestinal tract (oesophagus, stomach, OGJ), PB = pancreatico-biliary tract, 95%-CI = 95% Confidence Interval, n.a. = information not available. Note: the sum of the percentages might not reach 100% due to rounding.

**Supplemental Table 2. Association between the predominant/most aggressive component and choice of first-line treatment regimen in patients with advanced stage Mixed Neuroendocrine Non-Neuroendocrine Neoplasm (MiNEN) (30 patients)**

PREDOMINANT COMPONENT*	PRIMARY TUMOUR SITE	GRADING OF NE*	GRADING OF ADC*	CHEMOTHERAPY REGIMEN		CHOICE OF REGIMEN IN LINE WITH PREDOMINANT COMPONENT	CHOICE OF REGIMEN IN LINE WITH MOST AGGRESSIVE COMPONENT	CHOICE OF REGIMEN IN LINE WITH PREDOMINANT OR MOST AGGRESSIVE COMPONENT
NE	pancreas	G3	G3	Gem	ADC-LIKE	NO	not applicable	
NE	oesophagus/OGJ	G3	G3	Epi/fluo/plat	ADC-LIKE	NO	not applicable	
EQUAL	colon	G3	G2	Fluo/plat	ADC-LIKE	not applicable	NO	
NE	oesophagus/OGJ	G3	n.a.	Epi/fluo/plat	ADC-LIKE	NO	not applicable	
ADC	ICJ	G3	G2	Fluo + RT	ADC-LIKE	YES	NO	✓
EQUAL	colon	G3	G3	Eto/plat	NEC-LIKE	not applicable	not applicable	
NE	rectum	G3	G2	Fluo/iri	ADC-LIKE	NO	NO	
ADC	ICJ	G3	G3	Fluo/plat	ADC-LIKE	YES	not applicable	✓
EQUAL	ICJ	G3	G3	Fluo/plat	ADC-LIKE	not applicable	not applicable	
NE	ICJ	G3	n.a.	Eto/plat	NEC-LIKE	YES	not applicable	✓
NE	oesophagus/OGJ	G3	G3	Eto/plat	NEC-LIKE	YES	YES	✓
NE	small bowel	G3	G2	Fluo/plat	ADC-LIKE	NO	NO	
NE	colon	G3	n.a.	Eto/plat	NEC-LIKE	YES	not applicable	✓
NE	rectum	G3	adenoma	Eto/plat	NEC-LIKE	YES	YES	✓
NE	rectum	G3	G3	Fluo/iri	ADC-LIKE	NO	not applicable	
NE	anus	G3	G2	Eto/plat	NEC-LIKE	YES	YES	✓
NE	pancreas	G3	G2	Eto/plat	NEC-LIKE	YES	YES	✓
n.a.	oesophagus/OGJ	G3	G2	Eto/plat	NEC-LIKE	not applicable	YES	✓
EQUAL	pancreas	G3	G1	Eto/plat	NEC-LIKE	not applicable	YES	✓
NE	colon	G3	G2	Eto/plat	NEC-LIKE	YES	YES	✓
NE	colon	G3	G3	Eto/plat	NEC-LIKE	YES	not applicable	✓
ADC	ICJ	G2	G1	Fluo/iri + mAB	ADC-LIKE	YES	YES**	✓
NE	colon	G3	G1	Eto/plat	NEC-LIKE	YES	YES	✓
ADC	rectum	G3	G2	Eto/plat	NEC-LIKE	NO	YES	✓
NE	small bowel	G3	G1	Eto/plat	NEC-LIKE	YES	YES	✓
NE	rectum	G3	G1	Eto/plat	NEC-LIKE	YES	YES	✓
EQUAL	biliary tract	G2	G1	Gem/plat	ADC-LIKE	not applicable	YES**	✓
ADC	colon	G3	G2	Eto/plat	NEC-LIKE	NO	YES	✓
NE	rectum	G3	G3	Fluo/plat + mAb	ADC-LIKE	NO	not applicable	
ADC	colon	G2	n.a.	Fluo alone	ADC-LIKE	YES	not applicable	✓

NE = neuroendocrine, ADC = adenocarcinoma/adenoma, OGJ = oesophago-gastric junction, ICJ = ileo-caecal junction, n.a. = information not available, gem = gemcitabine, fluo = fluoropyrimidine (5-fluorouracil or capecitabine), plat = platinum (cisplatin, carboplatin or oxaliplatin), iri = irinotecan, eto = etoposide, mAB = monoclonal antibody (cetuximab, panitumumab or bevacizumab), ADC-like = in accordance with the standard of care first-line treatment for pure adenocarcinomas from the same site of origin, NEC-like = in accordance with the standard of care first-line treatment for pure neuroendocrine carcinomas. \*In diagnostic samples or metastases identified at the time of diagnosis of advanced disease (pre-treatment). \*\*A NE component with a grading of ≤2 is usually less aggressive compared to an ADC component of any grade, but more aggressive than an adenoma.

**Supplemental Table 3. Cox-regression multivariable analysis for progression-free survival (PFS) and overall survival (OS) in advanced Mixed Neuroendocrine Non-Neuroendocrine Neoplasms (MiNENs)**

			PFS		OS	
		N	HR (95%-CI)	p	HR (95%-CI)	p
<i>Primary tumour</i>	Lower GI (ref.)	23	0.180 (0.031-1.051)	0.057	0.104 (0.017-0.654)	0.016
	Upper GI	2				
	Pancreato-biliary	4				
<i>Age</i>	<70 y (ref.)	16	0.664 (0.262-1.682)	0.388	0.816 (0.292-2.285)	0.699
	≥70 y	13				
<i>ECOG PS</i>	0-1	22	1.343 (0.314-5.736)	0.691	0.154 (0.031-0.769)	0.023
	≥2	7				
<i>Gender</i>	Female (ref.)	11	3.919 (1.260-12.186)	0.018	0.475 (0.145-1.564)	0.221
	Male	18				
<i>Predominant component</i>	NE (ref.)	18	6.929 (1.464-32.786)	0.015	1.221 (0.275-5.417)	0.792
	ADC	5				
	Equal	6				
<i>Grading of NE component</i>	G1-G2(ref.)	2	2.844 (0.321-25.179)	0.348	0.055 (0.002-1.441)	0.082
	G3	27				
<i>Ki-67 NE component</i>	<55% (ref.)	10	0.505 (0.180-1.415)	0.194	1.035 (0.341-3.138)	0.952
	≥55%	19				
<i>First line active treatment</i>	No (ref.)	5	2.207 (0.594-8.198)	0.237	1.590 (0.383-6.600)	0.523
	Yes	24				
<i>% cases not included because of incomplete data</i>		47.3%				

N = number of patients, ECOG = Eastern Cooperative Oncology Group, PS = performance status, Loc = localised stage, Adv = advanced stage, NE = neuroendocrine, ADC = adenocarcinoma, OGJ = oesophago-gastric junction, ICJ = ileo-caecal junction, Lower GI = lower gastrointestinal tract (colon, rectum, small bowel, ICJ, anus), Upper GI = upper gastrointestinal tract (oesophagus, stomach, OGJ), PB = pancreatico-biliary tract, 95%-CI = 95% Confidence Interval, n.a. = information not available. First line active treatment includes palliative surgery alone, palliative surgery combined with chemotherapy, chemotherapy alone, chemo-radiotherapy.