

Prognosis and management of advanced digestive well-differentiated grade 3 neuroendocrine tumors (G3 NETs): a NET-CONNECT study performed in four expert centers



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Context : The prognosis and management of G3 NETs are poorly defined and differ from those of neuroendocrine carcinoma (NECs)

The most appropriate treatment for patients with advanced G3 NETs has yet to be determined

Aim : Describe a retrospective cohort of patients with advanced digestive G3 NETs and depict their prognosis and treatment

Patients : Patients with advanced digestive G3 NET from 4 expert centers

Design : A central virtual pathological review of all cases was performed after digitalization of Haematin-Eosin and Ki67 slides

The Objective response rates (ORR) to the two first treatment lines (primary endpoint) was analyzed depending on the type of treatment: NEC-like, alkylating agent (temozolomide or streptozotocin) (ALK), or somatostatin analogs (SSAs)

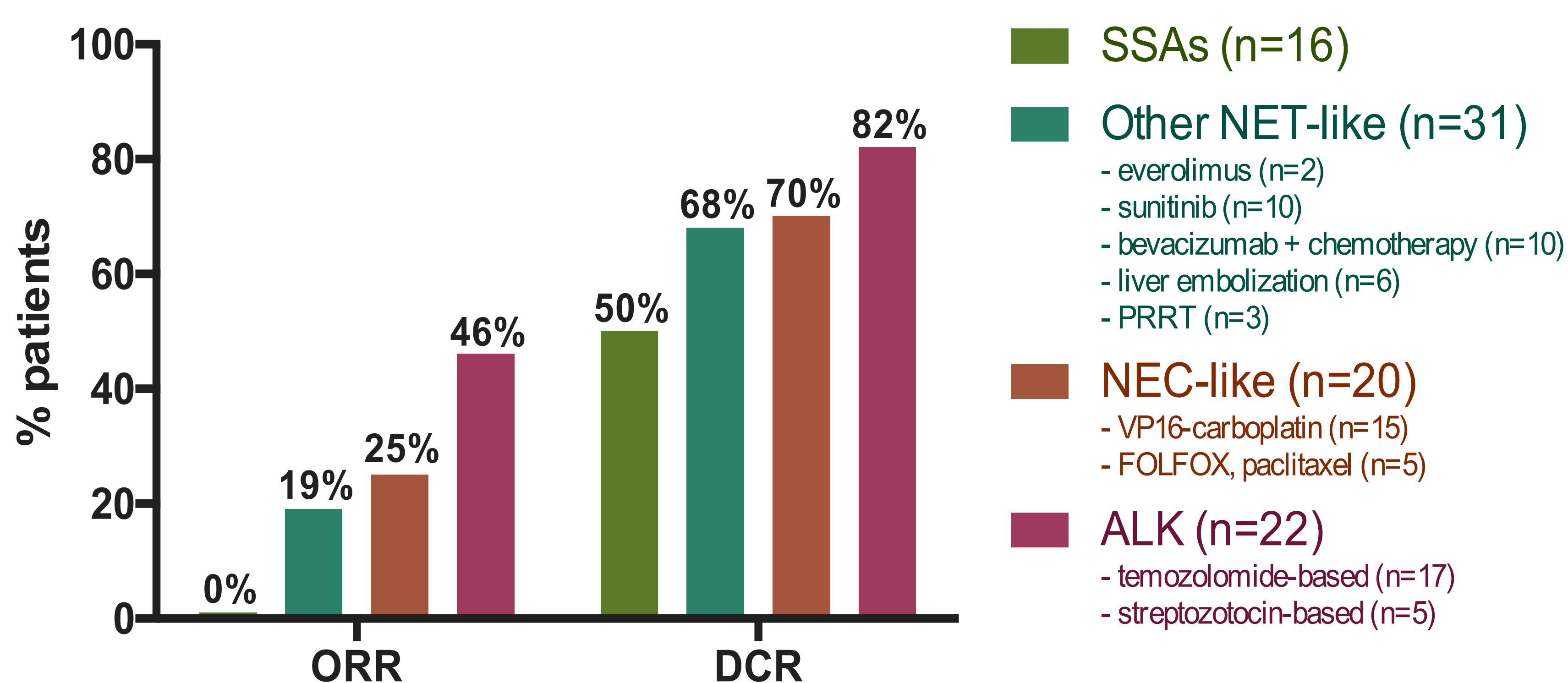
Factors associated with ORR and overall survival (OS) were assessed using logistic or Cox regression models, respectively

Characteristics of the 55 patients

	N or median	% or IQR
Age (years)	55.9	45.4 - 65.8
Male gender	31	56.4
Chromogranin A staining	49	89.1
Synaptophysin staining	46/47	97.9
Ki67 (%)	30	25 - 40
Primary tumor	Pancreas/Biliary	37
	Colon/Intestine/Stomach	12
	Unknown/Other	6
Previous primary tumor surgery	12	21.8
Performance status at L1	PS-0	24
	PS-1	26
	PS-2	5
Tumor-related symptoms	35	63.6
Functioning syndrome	14	25.2
Stage	Locally advanced	1
	M1a (liver mets)	25
	M1b (extra-hepatic mets)	18
	M1c (liver and bone mets)	11
Extrahepatic metastases	29/54	52.7
Synchronous metastases	47/54	85.5
FDG-PET avidity > liver	25/30	83.3
SST imaging positive	42/48	76.4
Chromogranin A plasma (xULN) (n=48)	6.5	1.8 - 17.5
NSE plasma (xULN) (n=23)	1.6	1.0 - 2.4
LDH plasma (xULN) (n=31)	0.9	0.7 - 1.2
ALP plasma (xULN) (n=51)	1.4	1.0 - 3.5

Tumour response to treatments (89 L1 or L2 treatment lines)

ORR = objective response rate, DCR = disease control rate (OR + stability)



Factors associated with objective response (89 L1 or L2 treatment lines)

Multivariable logistic regression	OR	95% CI	P
Age (each additional year)	0.98	0.94-1.03	0.420
Male gender (vs. female)	0.27	0.09-0.86	0.026
Ki67 (each additional 1%)	1.06	0.98-1.14	0.145
Pancreas primary NET (vs. other)	1.96	0.41-9.24	0.397
Second line (vs. L1)	1.20	0.38-3.82	0.754
Alkylating agent (vs. other treatment)	4.86	1.42-16.65	0.012

Factors associated with overall survival (OS)

Median OS from the first treatment was 29.7 months (95% CI, 16.2-43.3)

1-, 2- and 5-year OS rates were 81%, 63% and 13%, respectively

Multivariable Cox model	HR	95% CI	P
Age (each additional year)	1.03	1-1.06	0.07
Male gender (vs. female)	0.79	0.31 - 2.03	0.62
Ki67 (each additional 1%)	1.07	1.01 - 1.14	0.02
Pancreas primary NET (vs. other)	0.60	0.22 - 1.66	0.33
Primary tumor resected (vs. no)	0.16	0.34 - 0.76	0.02
Performance status 1-2 (vs. 0)	2.88	0.91 - 9.07	0.07

Factors associated with somatostatin analogs

Multivariable	OR	95% CI	P
Age (each additional year)	1.06	1.01-1.12	0.020
Ki67 (each additional 1%)	0.94	0.86-1.02	0.138
Second line (vs. L1)	0.06	0.01-0.49	0.009

Factors associated with alkylating chemotherapy

Multivariable	OR	95% CI	P
Pancreas primary NET (vs. other)	5.56	1.15-26.99	0.033
Functioning syndrome (vs. no)	2.85	0.61-13.42	0.184
Ki67 (each additional 1%)	0.96	0.90-1.03	0.295

Factors associated with NEC-like chemotherapy

Multivariable	OR	95% CI	P
Age (each additional year)	0.96	0.92-1.01	0.104
Second line (vs. L1)	0.34	0.09-1.26	0.106
Pancreas primary NET (vs. other)	0.37	0.08-1.71	0.202
Ki67 (each additional 1%)	1.18	1.08-1.28	<0.001

Conclusion

In this cohort of centrally-reviewed advanced digestive G3 NETs, **alkylating agents achieved the highest response rate**, regardless of Ki67