Supplementary Materials

Table S1. Characteristics of studies reporting outcomes of TMZ in NENs.

CI: Confidence Intervals; CR: Complete Response; MGMT: O6-methylguanine DNA methyltransferase; NENs: NeuroEndocrine Neoplasms; NR: Nor Reported; OS: Overall Survival; PR: Partial Response; PS: Performance Status; pts: patients; PD: Progressive Disease; RFA: Radio-Frequency Ablation; RT: RadioTherapy; SD: Stable Disease; TACE: Trans-Arterial Chemo-Embolization; TAE: Trans-Arterial Embolization; TMZ: temozolomide; TTP: time-to-progression.

Year, First Author No. of pts	Type of NENs	PS of pts	Line of therapy	Associa tion with other drugs	Prospecti ve	TMZ doses	Treatmen t exposure	Toxicity (G3/G4 total events)	Objective responses	Time– to– outcom e results	MGMT evaluatio n
2006, Kulke MH 29	Locally unresectab le or metastatic neuroendo crine tumors, excluding small–cell carcinoma.	ECOG 0: 20 1: 9	Pts received from 0 to 4 previous systemic therapies. Previous TACE in 3 pts. Eleven patients received prior therapy with octreotide and remained on octreotide during study.	Yes (Thalido mide)	Yes (phase II, primary objective was to determine the response rate)	150 mg/mq, days 1–7 and days 15–21 every 28 days.	Median: 7.3 months (range: 1– 23).	Hematolog ic: 29 Non– hematologi c: 30	28 evaluable pts CR: 1 PR: 6 SD: 19 PD: 2	Median TTP: not reached. Median OS: not reached. The 1– year survival rate was 79%, and the 2–year survival rate was 61%.	Not done.
2007, Eklebad S 36	All advanced or progressin g NENs.	NR	Pts received from 0 to 6 previous systemic therapies.	No	No	100–150 mg/mq, days 1–5 every 28. (dose was escalated to 200 mg/mq/d in 20 pts).	Median: 4.5 cycles (range: 0– 17).	Hematolog ic: 8 Non– hematologi c: 3	CR: 0 PR: 5 SD: 19 PD: 12	Median TTP: 7 months (95%CI: 3–10). Median OS: 16 months (95%CI: 11–22).	Yes (23/36). No predictive power.
2011, Welin S 25	Poorly differentiat ed endocrine carcinoma progressed on first– line chemother apy.	Not detaile d. All patien ts had a PS ECOG of 0–2.	Twenty– four patients received cisplatin and etoposide as first line treatment, and 1 patient received docetaxel and doxorubici	Yes (TMZ alon –5 pts–or in combina tion with capecita bine -19 pts–. A subset -7pts– received also	No	Alone: 150–200 mg/mq, days 1–5 every 28 days. In combina tion: 150 mg/m2, days 10– 14 every 28 days.	NR	Hematolog ic: 2 Non– hematologi c: 2	CR: 1 PR: 7 SD: 10 PD: 7	Median TTP: 6 months (95% CI, 4– 14). Median OS: 22 months (95% CI, 8– 27).	Only 1 patient had a MGMT methylatio n (This patient had a PR for 15 months and an OS of 22 months).

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	and pNETs), excluding small–cell carcinoma.		systemic therapies including octreotide, chemother apy, interferons , sunitinib. Previous TAE in 11 pts, RFA in 3, RT in 4.		activity and toxicity)				SD: 22 PD: 4	(95%CI, 7.3–Not reached). Median OS: 33.3 months (95%CI, 13.4– 41.7).	
2012, Holsen IH 28	Metastatic NEC (Ki–67 > 20%).	ECOG 0–1: 22 2: 6	Second– line after previous exposure to carboplati n and etoposide.	No	No	200 mg/mq, days 1–5 every 28 days.	Median: 3 cycles (range 1– 12).	Hematolog ic: 3 Non– hematologi c: NR	16 evaluable pts CR: 0 PR: 0 SD: 10 PD: 6	Median TTP: 2.4 months. Median OS: 3.5 months.	Not done.
2013, Saif MW 7	Metastatic pNETs	ECOG 0: 1 1: 4 2: 2	Pts received from 1 to 3 previous systemic therapies. Previous TAE/TAC E in 4 pts. One resection of PT.	Yes (capecita bine)	No	200 mg/mq, days 10– 14 of a 28–day cycle	NR	Hematolog ic: 1 Non– hematologi c: 1	CR: 0 PR: 3 SD: 2 PD: 2	Median TTP: 12 months (range: 10–16). Median OS: 24 months. (range: NR)	Not done.
2013, Chan JA 43	Low– or intermedia te– grade metastatic or locally unresectab le pNETs.	ECOG 0: 20 1: 23	Number of previous sistemic terapies (other than octreotide) were 0 in 77%, 1 in 16% and 2 in 7% of pts. One patients received also TACE, 3 pts RT.	Yes (everoli mus)	Yes (phase I/II, primary objective was to determine the response rate).	150 mg/mq, days 1–7 and days 15–21 every 28 days.	Median: 8.5 cycles (range 1– 28).	Hematolog ic: 36 Non– hematologi c: 29	40 evaluable pts CR:0 PR: 16 SD: 21 PD: 3	Median TTP: 15.4 months (95% CI, 9.4– 20.4). Median OS was not reached.	Not done.
2013, Fine RL 18	Metastatic , well differentiat ed neuroendo crine cancers.	ECOG 0: 4 1: 9 2: 5	All pts progressed on Sandostati n LAR 60 mg/month. Pts received a median of 2 previuos chemother apy lines (range: 1– 5). Previous	Yes (capecita bine)	No	150–200 mg/mq, days 10– 14 every 28 days.	NR	Hematolog ic: 2 Non– hematologi c: 1	18 evaluable pts CR: 1 PR: 10 SD: 4 PD: 3	Median TTP: 14.0 months (range: 4.2–18). Median OS: 83 months (range 18.5– 140).	Not done.

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Table S2. Clinico-pathological characteristics of patients according to treatment response.

		Response	s (CR+PR)	P^*
Characteristics	No. (%)	Yes	No	
Age, years				
≤ 65	13 (50.0)	3	10	
> 65	13 (50.0)	2	11	0.6256
Gender				
Male	13 (50.0)	3	10	
Female	13 (50.0)	2	11	0.6256
Grading				
G1	0 (0.0)	0	0	
G2	11 (42.3)	1	10	
G3	15 (57.7)	4	11	0.2706
KI–67 level				
3–20	11 (42.3)	1	10	
20–55	10 (38.5)	2	8	
> 55	5 (19.2)	2	3	0.3464
Performance Status				
0	0 (0.0)	0	0	
1	11 (42.3)	2	9	

2	15 (57.7)	3	12	0.9093
Site of primary tumor				
GI	13 (50.0)	2	11	
Non-GI	13 (50.0)	3	10	0.6256
No. of involved metastatic sites				
1	13 (50.0)	3	10	
2	8 (30.8)	2	6	
≥3	5 (19.2)	0	5	0.4758
Previous treatments				
Platinum-based CT	12 (46.1)	3	9	
Non-platinum based CT	2 (7.7)	0	2	
Somatostatin analogues	8 (30.8)	1	7	
Clinical trials drugs	4 (15.4)	1	3	0.7886

* At Chi-square test with Yates correction for small datasets.