Optimizing Chemotherapy in G1-G2 GEP-NET

Jonathan Strosberg, MD
Professor, Moffitt Cancer Center

September, 2019

Potential indications for chemotherapy

CONSENSUS	UNCERTAINTY	PROBABLE LACK OF ACTIVITY
Pancreatic NETs	Bronchial, thymic, gastric, colorectal NETs	Midgut

The New England
Journal of Medicine

Volume 303 NOVEMBER 20, 1980 Number 21

STREPTOZOCIN ALONE COMPARED WITH STREPTOZOCIN PLUS FLUOROURACIL IN THE TREATMENT OF ADVANCED ISLET-CELL CARCINOMA

CHARLES G. MOERTEL, M.D., JAMES A. HANLEY, PH.D., AND LEWIS A. JOHNSON, M.D.

Abstract To evaluate the treatment of advanced islet-cell carcinoma, we randomly assigned 84 patients to streptozocin alone or streptozocin plus fluorouracil. Each regimen was given in five-day courses. The most frequent toxic effects were nausea and vomiting, mild and reversible renal toxicity, and bone-marrow depression with the combination regimen.

The combination had advantages over streptozocin alone in overall rate of response (63 vs. 36 per cent) and in rates of complete response (33 vs. 12 per cent). There was no evidence of a preferential response among types of functional tumors. Objective responses were generally of long duration (median, 17 months) and of substantive clinical benefit. Treatment with the combination also yielded a survival advantage over treatment with streptozocin alone (medians, 26 and 16½ months), but this difference is not statistically significant.

In spite of gastrointestinal side effects, streptozocin combined with fluorouracil appears to be a valuable treatment for advanced islet-cell carcinoma. (N Engl J Med. 1980; 303:1189-94.)

Moertel CG et al. *N Engl J Med* 1980;303:1189–1194

“Response rate”

RESPONSE RATE ACCORDING TO TREATMENT REGIMEN			
CATEGORY	STREPTOZOCIN ALONE n (%)	STREPTOZOCIN + FLUOROURACIL n (%)	MEDIAN DURATION (MONTHS)
ALL RESPONSES	15/42 (36)	25/40 (63)	17

Moertel CG et al. *N Engl J Med* 1980;303:1189–1194

STREPTOZOCIN–DOXORUBICIN, STREPTOZOCIN–FLUOROURACIL, OR CHLOROZOTOCIN IN THE TREATMENT OF ADVANCED ISLET-CELL CARCINOMA

CHARLES G. MOERTEL, M.D., MYRTO LEFKOPOULO, SC.D., STUART LIPSITZ, SC.D., RICHARD G. HAHN, M.D., AND DAVID KLAASSEN, M.D.

Abstract *Background.* The combination of streptozocin and fluorouracil has become the standard therapy for advanced islet-cell carcinoma. However, doxorubicin has also been shown to be active against this type of tumor, as has chlorozotocin, a drug that is structurally similar to streptozocin but less frequently causes vomiting.

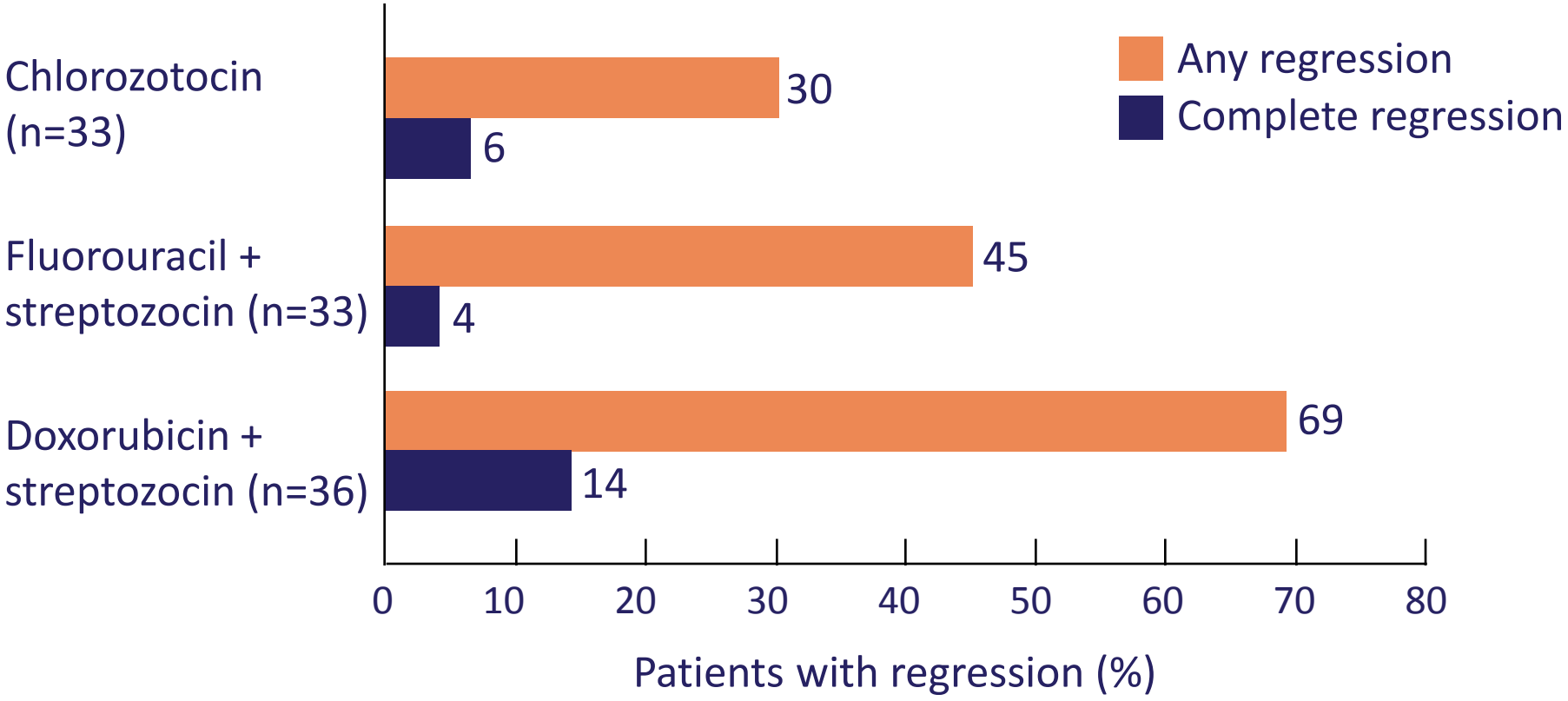
Methods. In this multicenter trial, we randomly assigned 105 patients with advanced islet-cell carcinoma to receive one of three treatment regimens: streptozocin plus fluorouracil, streptozocin plus doxorubicin, or chlorozotocin alone. The 31 patients in whom the disease did not respond to treatment were crossed over to chlorozotocin alone or to one of the combination regimens.

Results. Streptozocin plus doxorubicin was superior to streptozocin plus fluorouracil in terms of the rate of tumor regression, measured objectively (69 percent vs. 45 percent, $P = 0.05$), and the length of time to tumor progression (median, 20 vs. 6.9 months; $P = 0.001$). Streptozocin plus doxorubicin also had a significant advantage in terms of survival (median, 2.2 vs. 1.4 years; $P = 0.004$) that was accentuated when we considered long-term survival (>2 years). Chlorozotocin alone produced a 30 percent regression rate, with the length of time to tumor progression and the survival time equivalent to those observed with streptozocin plus fluorouracil. Crossover therapy after the failure of either chlorozotocin alone or one of the combination regimens produced an overall response rate of only 17 percent, and the responses were transient. Toxic reactions to all regimens included vomiting, which was least severe with chlorozotocin; hematologic depression; and, with long-term therapy, renal insufficiency.

Conclusions. The combination of streptozocin and doxorubicin is superior to the current standard regimen of streptozocin plus fluorouracil in the treatment of advanced islet-cell carcinoma. Chlorozotocin alone is similar in efficacy to streptozocin plus fluorouracil, but it produces fewer gastrointestinal side effects than the regimens containing streptozocin. It therefore merits study as a constituent of combination drug regimens. (N Engl J Med 1992; 326:519-23.)

Moertel CG et al. *N Engl J Med* 1992;326:519–523

Rates of tumor regression, measured objectively, according to treatment group



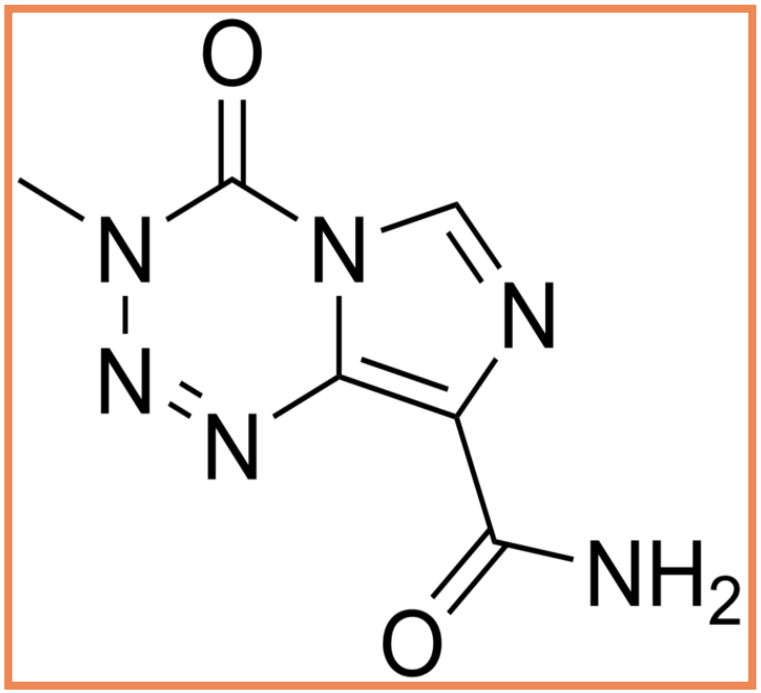
Moertel CG et al. *N Engl J Med* 1992;326:519–523

Streptozocin-based regimens

	REGIMEN	N	AUTHOR	YEAR	RESPONSE RATE (%)
Historical Prospective	Streptozocin + fluorouracil[1]	42	Moertel	1980	63%
	Streptozocin + doxorubicin[2]	38	Moertel	1992	69%
Modern Retrospective	Streptozocin + doxorubicin[3]	16	Cheng	1999	6%
	Streptozocin + doxorubicin[4]	45	Delaunoit	2004	36%
	Streptozocin + Cisplatin+ fluorouracil[5]	47	Turner	2008	38%
	Streptozocin + doxorubicin + fluorouracil[6]	84	Kouvaraki	2004	39%

1. Moertel CG et al. *N Engl J Med* 1980;303:1189-1194; 2. Moertel CG et al. *N Engl J Med* 1992;326:519-523;
3. Cheng PN and Saltz LB. *Cancer* 1999;86:944-948; 4. Delaunoit T et al. *Eur J Cancer* 2004;40(4):515-20 5. Turner N. et al Br J Cancer 2010 102(7): 1106-12 6. Kouvaraki MA et al. *J Clin Oncol* 2004;22:4762–4771

Temozolomide



Oral alkylating agent

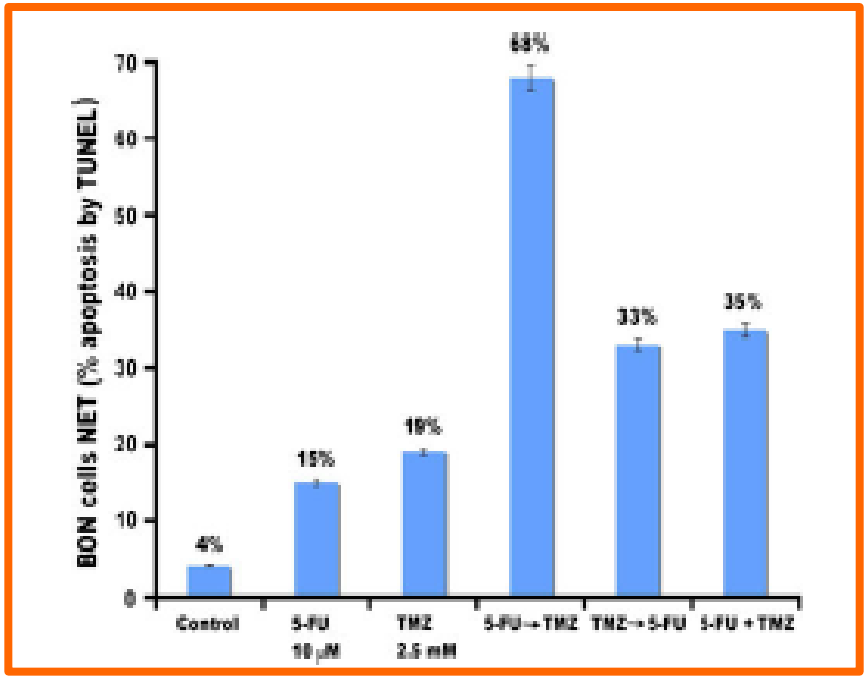
Prodrug of MTIC

Alkylation/methylation of DNA occurs at the N-7 or O-6 positions of guanine residues

Activity is diminished by DNA repair enzyme O^6-methylguanine-DNA-methyltransferase (MGMT)

MTIC: 3-methyl-(triazen-1-yl)imidazole-4-carboxamide

Synergistic Cytotoxicity of Cape/Tem in BON cell line



Maximal induction of apoptosis observed with pre-exposure to 5-FU for 7 days prior to TMZ for 2 days

Fine R, et al. *Cancer Chemother Pharmacol.* 2013;71:663–670

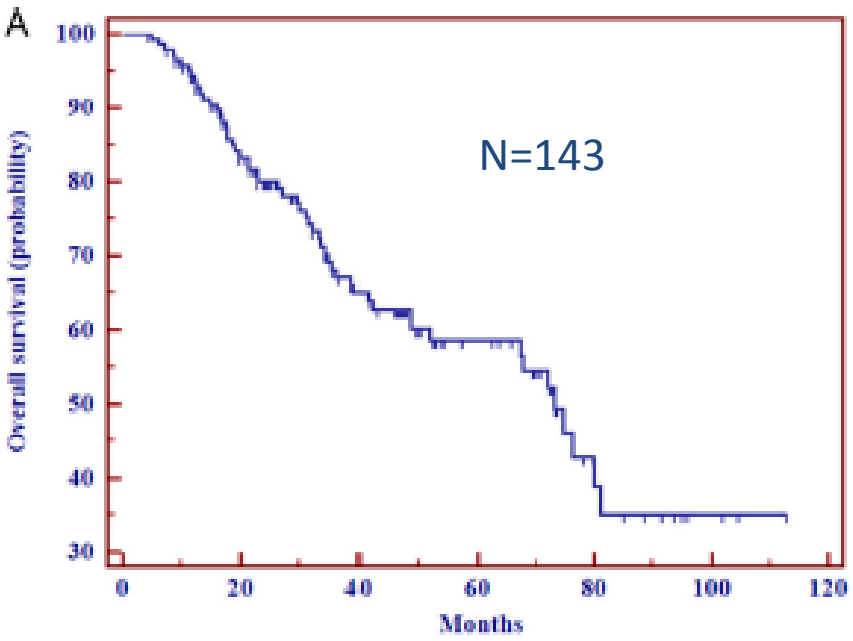
Temozolomide-based regimens

	REGIMEN	N	AUTHOR	YEAR	RESPONSE RATE (%)
Prospective	Temozolomide + thalidomide[1]	11*	Kulke	2006	45%
Prospective	Temozolomide + bevacizumab[2]	15*	Chan	2012	33%
Retrospective	Temozolomide + capecitabine[3]	30	Strosberg	2010	70%
Retrospective	Temozolomide + capecitabine[4]	18	Fine	2013	60%
Retrospective	Temozolomide + capecitabine[4]	143	Cives	2016	54%

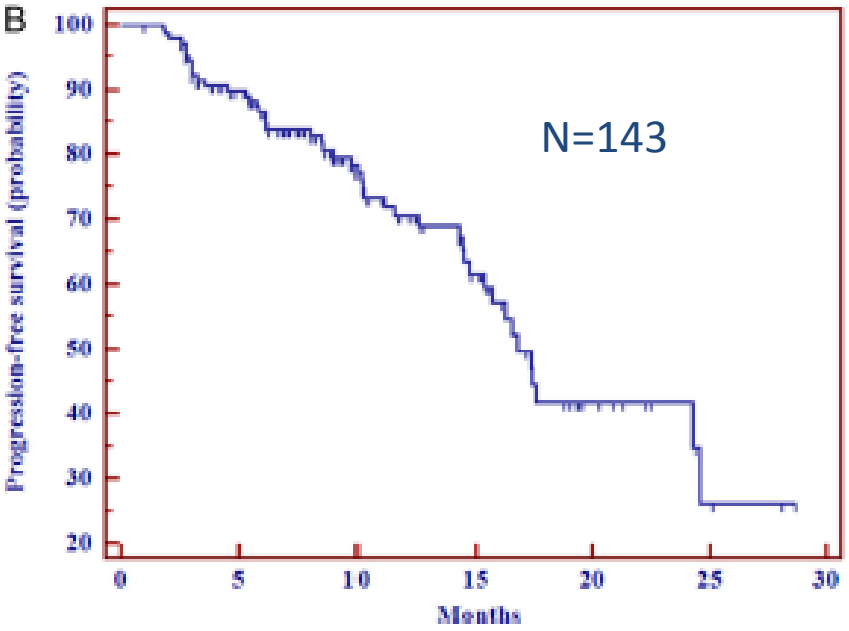
*pancreatic NET cohort of trial

1. Kulke M, et al. *J Clin Oncol.* 2006;24:401–406; 2. Chan, JA et al. *J Clin Oncol.* 2012;30:2963–2968;
3. Strosberg J, et al. *Cancer.* 2011;117:268–275; 4. Fine R, et al. *Cancer Chemother Pharmacol.* 2013;71:663–670;
5. Cives M, et al. *Endocr Relat Cancer.* 2016;23(9):759-767.

Progression-free and overall survival



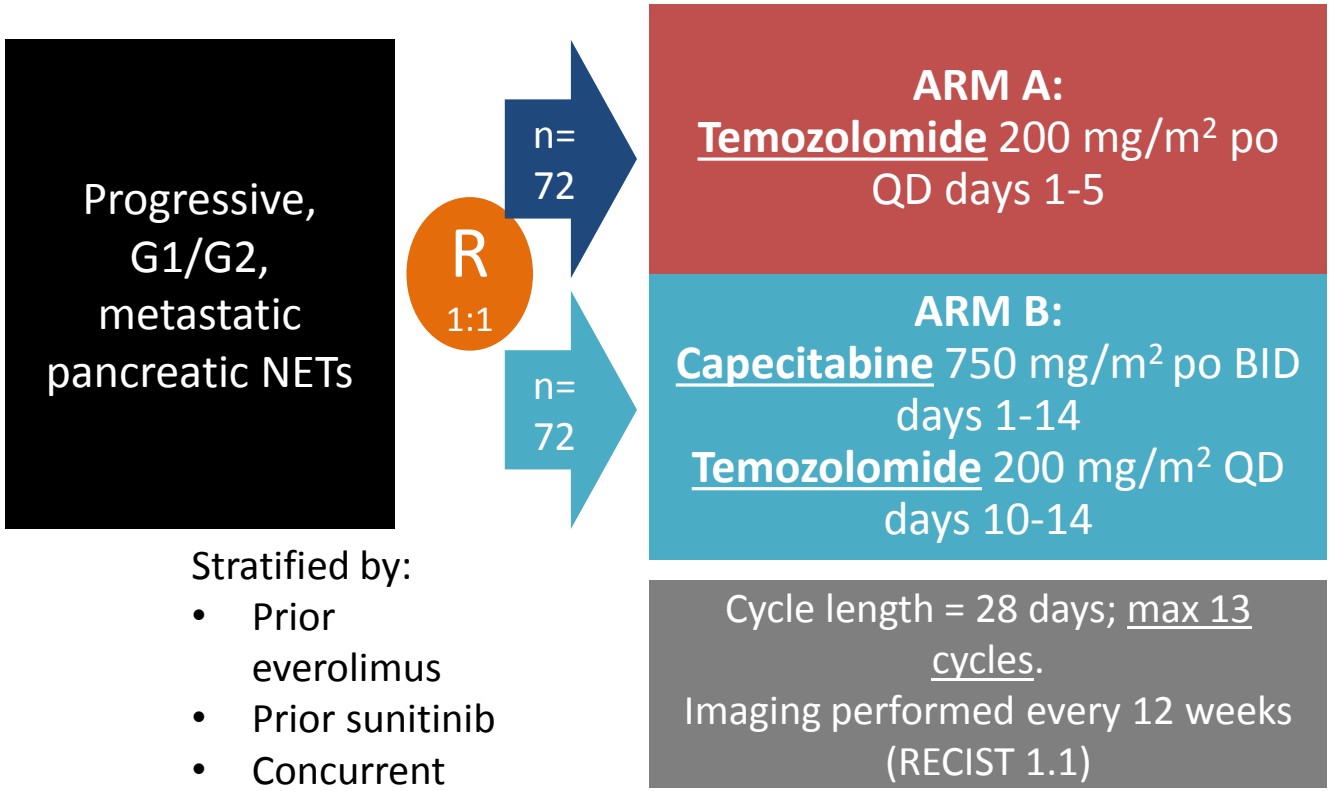
Median OS 73 months (95% CI 52-81)



Median PFS 17 months (95% CI 15-25)

Cives M, et al. *Endocr Relat Cancer.* 2016;23(9):759-767.

E2211 Study Design



Stratified by:

- Prior everolimus
- Prior sunitinib
- Concurrent octreotide

Primary Endpoint:

- PFS (local review)

Secondary Endpoints:

- RR
- OS
- Toxicity

Correlative Endpoints:

- MGMT by IHC
- MGMT by promoter methylation

NCT01824875

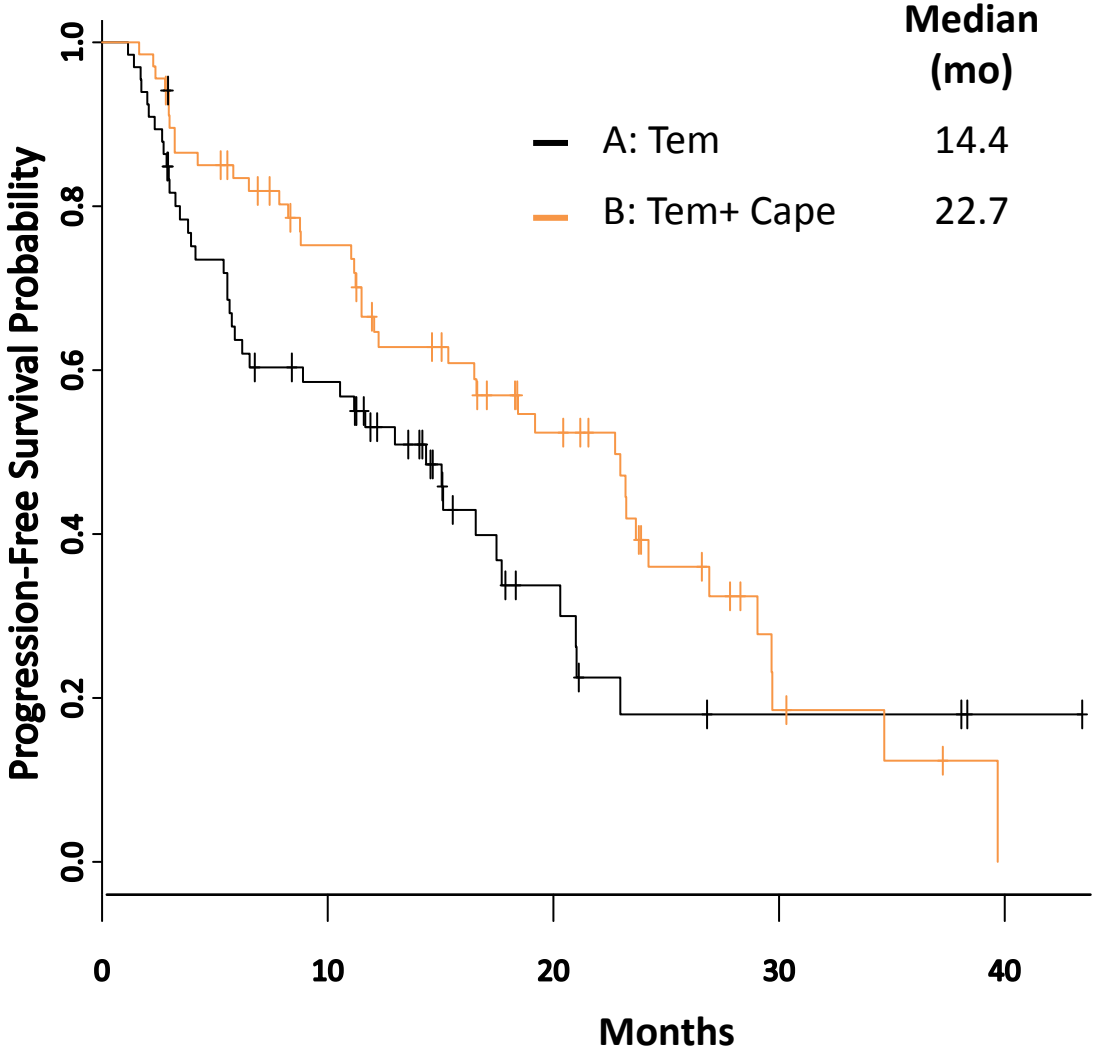
Kunz PL, et al. *J Clin Oncol.* 2018;36 [ASCO 2018: Abstract 4004]

Baseline characteristics

	Temozolomide (N = 72)	Temozolomide + Capecitabine (N = 72)
Time from Diagnosis (months)	24.4 mo	34.0 mo
WHO Grade		
Low (Grade 1)	45.1%	68.1%
Intermediate (Grade 2)	54.9%	31.9%
Sites of Metastasis		
Liver	93.1%	93.1%
Bone	12.5%	11.1%
Lung	6.9%	13.9%
Peritoneum	5.6%	9.7%
Prior Treatment		
Everolimus	34.7%	36.1%
Sunitinib	12.5%	11.1%
Concurrent SSA	54.2%	52.8%

Kunz PL, et al. *J Clin Oncol.* 2018;36 [ASCO 2018: Abstract 4004]

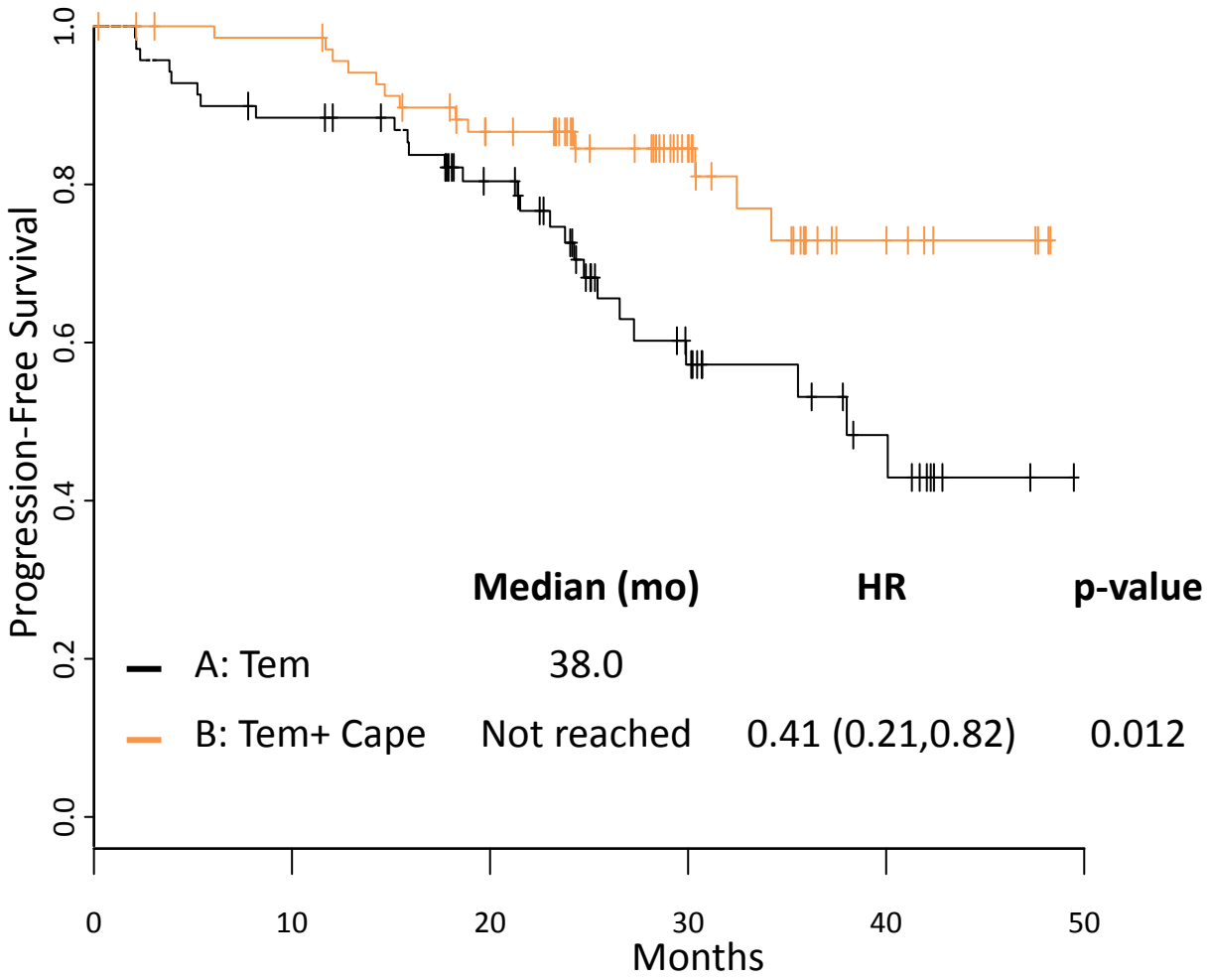
Progression Free Survival



	Median (mo)	HR (95% CI)	p-value
A: Tem	14.4		
B: Tem+ Cape	22.7	0.58 (0.36, 0.93)	0.023

Kunz PL, et al. *J Clin Oncol*. 2018;36 [ASCO 2018: Abstract 4004]

Overall Survival

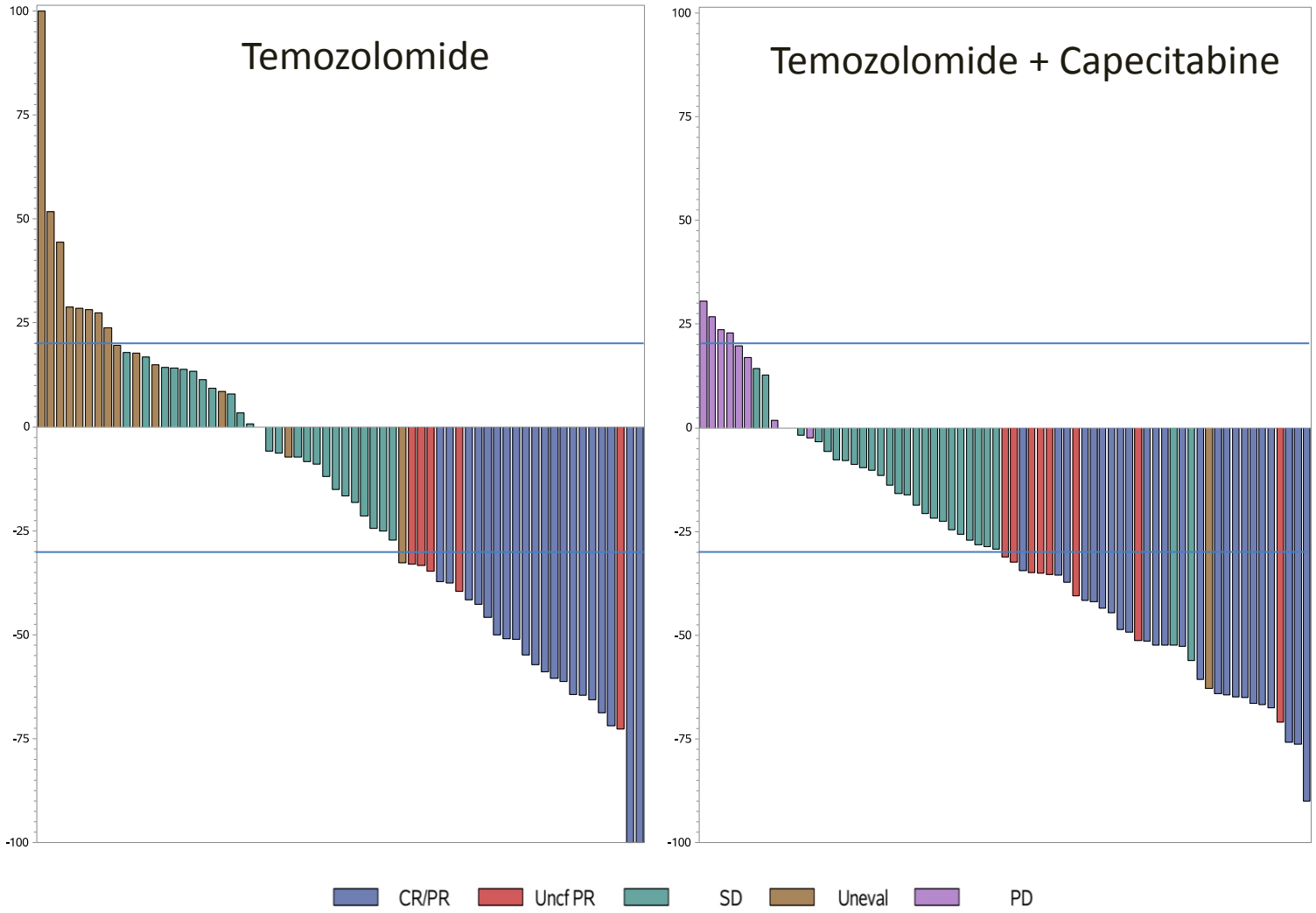


Kunz PL, et al. *J Clin Oncol.* 2018;36 [ASCO 2018: Abstract 4004]

Confirmed Response Rates

	Temozolomide	Temozolomide + Capecitabine	p-value
Stable / Progressive disease (%)	72.2	66.7	
Partial response (%)	25.0	33.3	
Complete response (%)	2.8	0	
Objective RR (%)	**27.8**	**33.3**	**0.47**

Waterfall Plot of Best Response



Kunz PL, et al. *J Clin Oncol.* 2018;36 [ASCO 2018: Abstract 4004]

Safety Profile

AE Category	AE Term	Temozolomide (N= 68)	Temozolomide + Capecitabine (N= 71)	p-value
Worst degree for all treatment-related, Grade 3-4 AEs				
		22%	44%	p=0.007
Treatment related, Grade 3-4 AEs ≥ 5%				
Hematologic	Neutropenia	4%	13%	
	Lymphopenia	4%	5%	
	Thrombocytopenia	13%	8%	
Gastrointestinal	Nausea	0	8%	
	Vomiting	0	8%	
	Diarrhea	0	8%	
Constitutional	Fatigue	1%	8%	

Kunz PL, et al. *J Clin Oncol.* 2018;36 [ASCO 2018: Abstract 4004]

Key points on cap/tem

1. Myelotoxicity is delayed: check CBC *shortly* before each cycle. If platelet count <100, hold treatment and monitor closely.
2. Ondansetron 30-60 min before temozolomide
3. Round doses *down* for patient convenience:

   -Target dose cap **750**mg/m2 bid days 1-14; tem **200**mg/m2 days 10-14 every 28 days

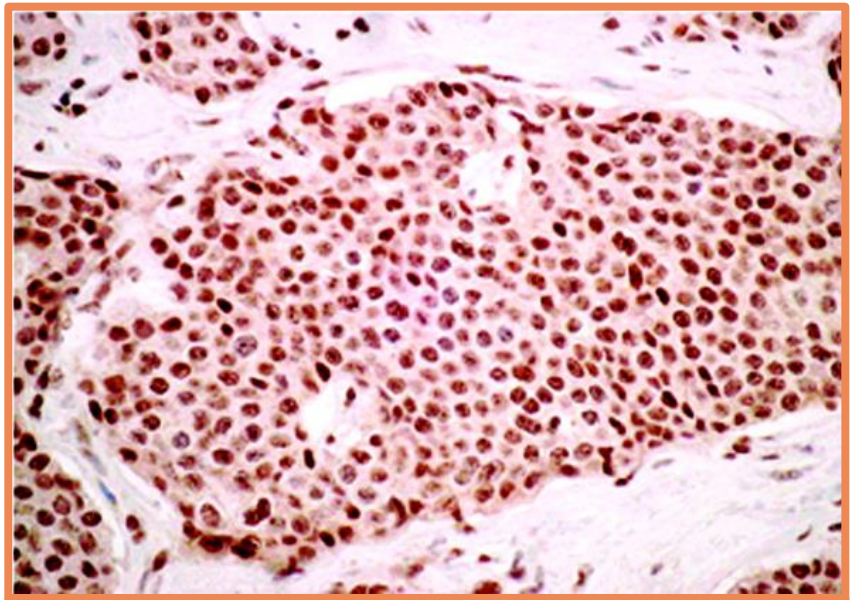
   -Actual dose: cap **714**mg/m2 bid days 1-14, tem **175**mg/m2 days 10-14 every 28 days[1]
4. When to stop???

1. Strosberg J, et al. *Cancer.* 2011;117:268–275

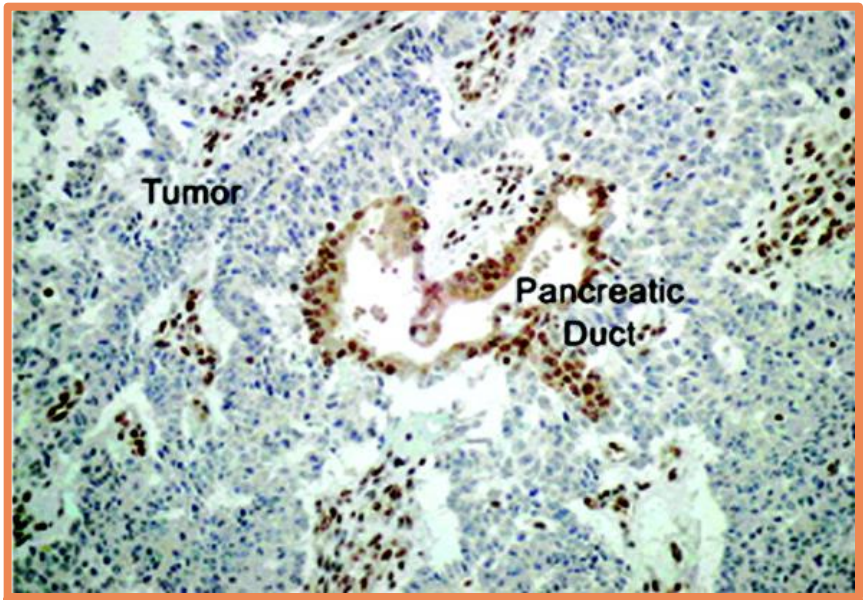
Predictive factors?

O^6-Methylguanine DNA Methyltransferase Deficiency and Response to Temozolomide-Based Therapy in Patients with Neuroendocrine Tumors

Matthew H. Kulke, Jason L. Hornick, Christine Frauenhoffer, et al.



MGMT intact carcinoid tumor



MGMT deficient pancreatic NET

MGMT (by IHC) measured in 97 archival NET specimens

Kulke M et al. *Clin Cancer Res.* 2009;15:338–345

IHC: immunohistochemistry;
MGMT: O-6-methylguanine-DNA-methyltransferase

MGMT deficiency

MGMT DEFICIENCY — OBSERVED IN

51% (19/38)	PANCREATIC NETs
0% (0/60)	CARCINOID TUMORS

AMONG 21 PATIENTS WHO RECEIVED — TEMOZOLOMIDE

4/5	PATIENTS WITH MGMT-DEFICIENT TUMORS RESPONDED

VERSUS

0/16	PATIENTS WITH MGMT INTACT TUMORS

P=0.001

Kulke M et al. *Clin Cancer Res* 2009;15:338–345

MGMT: O-6-methylguanine-DNA-methyltransferase

Predictive factors for response

Criteria of stratification	Interpretable cases (*n*)	ORR (%)	*P*
MGMT (Intact: nuclear staining in any tumor cells)	52		0.10
MGMT Intact		65	
MGMT deficient		40	
MGMT (Intact: nuclear staining in ≥10% of tumor cells)	52		0.37
MGMT Intact		63	
MGMT deficient		50	
MGMT (Intact: Allred score ≥4)	52		0.25
MGMT Intact		64	
MGMT deficient		47	
Grade	128		0.29
Low grade		65	
Intermediate grade		52	
High grade		69	
Mitotic count/10 HPF	96		0.93
<2		54	
2 <MC<20		50	
>20		50	
KI-67 labeling index	80		0.38
<3%		65	
Between 3 and 20%		50	
>20%		42	
ALT status	46		0.37
ALT-positive		63	
ALT-negative		47	
DAXX/ATRX status	31		0.34
DAXX/ATRX-positive		52	
DAXX/ATRX-negative		69	

Cives M, et al. *Endocr Relat Cancer.* 2016;23(9):759-767.

Chemotherapy in other NETs

Temozolomide as Monotherapy Is Effective in Treatment of Advanced Malignant Neuroendocrine Tumors

Sara Ekeblad,[1] Anders Sundin,[2] Eva Tiensuu Janson,[1] Staffan Welin,[1] Dan Granberg,[1] Henrik Kindmark,[1] Kristina Dunder,[1] Gordana Kozlovacki,[1] Håkan Örlefors,[1] Mattias Sigurd,[1] Kjell Öberg,[1] Barbro Eriksson,[1] and Britt Skogseid[1]

Abstract

Purpose: A retrospective analysis of the toxicity and efficacy of temozolomide in advanced neuroendocrine tumors.

Experimental Design: Thirty-six patients with advanced stages of neuroendocrine tumor (1 gastric, 7 thymic and 13 bronchial carcinoids, 12 pancreatic endocrine tumors, 1 paraganglioma, 1 neuroendocrine foregut, and 1 neuroendocrine cecal cancer) were treated with temozolomide (200 mg/m^2) for 5 days every 4 weeks. Patients had previously received a mean of 2.4 antitumoral medical regimens. Tumor response was evaluated radiologically according to the Response Evaluation Criteria in Solid Tumors every 3 months on an intent-to-treat basis. The circulating tumor marker plasma chromogranin A was also assessed. The expression of O^6-methylguanine DNA methyltransferase, an enzyme implicated in chemotherapy resistance, was studied by immunohistochemistry ($n = 23$) and compared with response to temozolomide.

Results: Median overall time to progression was 7 months (95% confidence interval, 3-10). Radiologic response was seen in 14% of patients and stable disease in 53%. Side effects were mainly hematologic; 14% experienced grade 3 or 4 thrombocytopenia (National Cancer Institute toxicity criteria). Ten patients had tumors with O^6-methylguanine DNA methyltransferase immunoreactivity in <10% of nuclei, whereas four patients showed radiologic responses.

Conclusions: Temozolomide as monotherapy had acceptable toxicity and antitumoral effects in a small series of patients with advanced malignant neuroendocrine tumors and four of these showed radiologic responses.

Ekeblad S et al. *Clin Can Res* 2007;13:2986–2991

Radiologic response

	ALL PATIENTS (N=36)	Pancreatic NET (n=12)	BRONCHIAL NET (n=13)	THYMIC NET (n=7)	OTHER (n=4)
COMPLETE RESPONSE	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
PARTIAL RESPONSE	5 (14%)	1 (8%)	4 (31%)	0 (0%)	0 (0%)
STABLE DISEASE	19 (53%)	8 (67%)	4 (31%)	5 (71%)	2 (50%)
PROGRESSIVE DISEASE	12 (33%)	3 (25%)	5 (38%)	2 (29%)	2 (50%)

Trend towards correlation with MGMT expression which was not statistically significant

Ekeblad S et al. *Clin Can Res* 2007;13:2986–2991

Cap/Tem in lung NETs

- 20 patients
- ORR 30%
- Median PFS 13 months (95% CI 4-21)
- Median OS 68 months (95% CI 35-100)

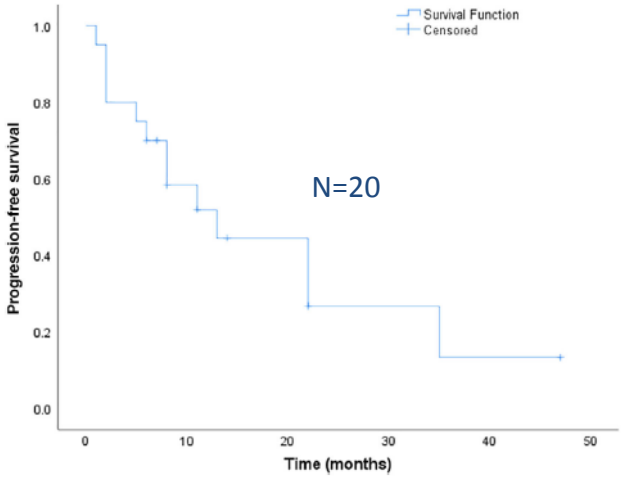


Figure 1. Progression-free survival.

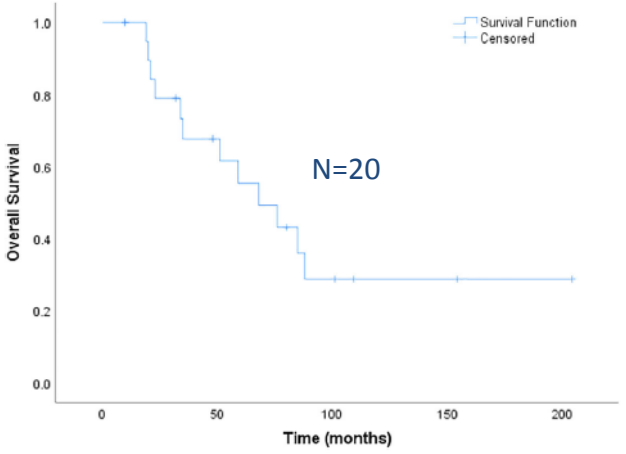


Figure 2. Overall survival.

Al-Toubah et al. Oncologist. 2019 Aug 27. pii: theoncologist.2019-0361

5-Fluorouracil/Dacarbazine

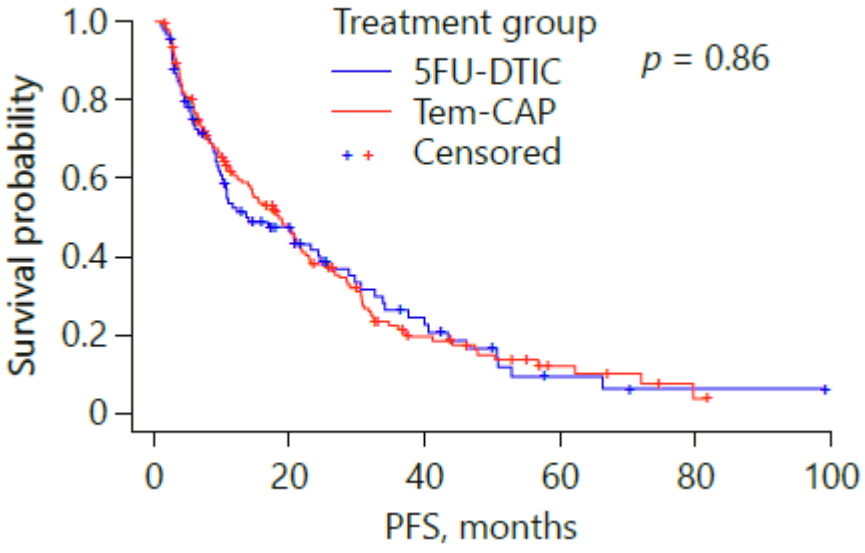
Non-Randomized Retrospective Study: Cap/Tem vs. 5-FU/Dacarbazine in pNETs and midgut NETs

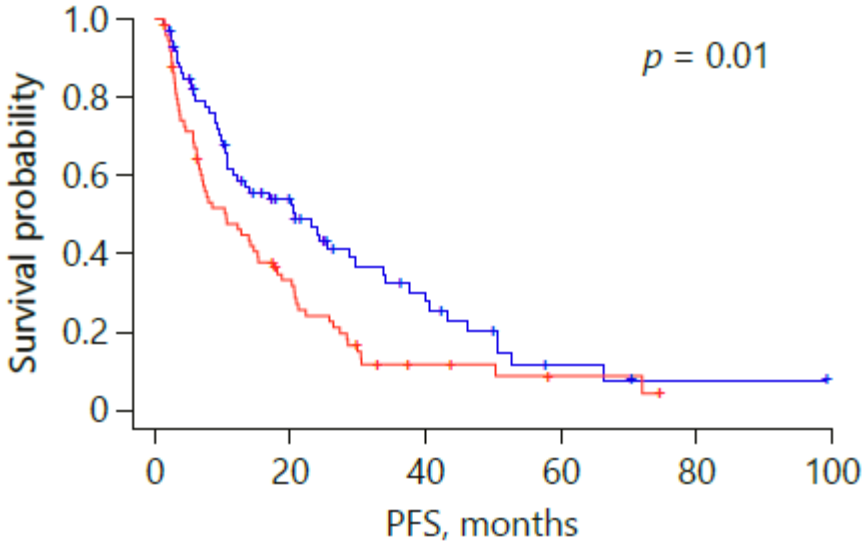
Table 2. Efficacy of chemotherapy using 5FU-DTIC or TEM-CAP in 247 patients with advanced pancreatic or small-intestine neuroendocrine tumors

	5FU-DTIC (n = 94)	TEM-CAP (n = 153)	p value
Best RECIST response, n (%)			0.411
Complete response	0	4 (2.6)	
Partial response	36 (38.3)	60 (39.2)	
Stable disease	44 (46.8)	64 (41.8)	
Progression	14 (14.9)	25 (16.3)	
Overall response rate, n (%)	36 (38.3)	64 (41.8)	0.596
Disease control rate, n (%)	80 (85.1)	128 (83.7)	0.858
PFS, months, median (95% CI)			
Global	13.9 (9.6–24.4)	18.3 (13.8–21.7)	0.86
Pancreas	20.5 (10.6–29.5)	20.6 (14.6–23.0)	0.86
Midgut	9.0 (4.9–24.4)	6.9 (4.4–13.8)	0.18
OS, months, median (95% CI)			
Global	47.1 (30.2–63.9)	60.5 (54.3–66.8)	0.24
Pancreas	59.3 (34.2–84.5)	64.3 (53.6–74.9)	0.39
Midgut	42.6 (34.9–50.3)	27.7 (15.8–39.5)	0.23

5FU-DTIC, 5-fluorouracile-dacarbazine; TEM, temozolomide; CAP, capecitabine; OS, overall survival; PFS, progression-free survival.

De Mestier et al. Neuroendocrinology 2019;108(4):343-353





De Mestier et al. Neuroendocrinology 2019;108(4):343-353

Capecitabine/Oxaliplatin

Cancer Chemother Pharmacol (2007) 59:637–642
DOI 10.1007/s00280-006-0306-6

ORIGINAL ARTICLE

Are capecitabine and oxaliplatin (XELOX) suitable treatments for progressing low-grade and high-grade neuroendocrine tumours?

Emilio Bajetta · Laura Catena · Giuseppe Procopio · Sara De Dosso · Ettore Bichisao · Leonardo Ferrari · Antonia Martinetti · Marco Platania · Elena Verzoni · Barbara Formisano · Roberto Bajetta

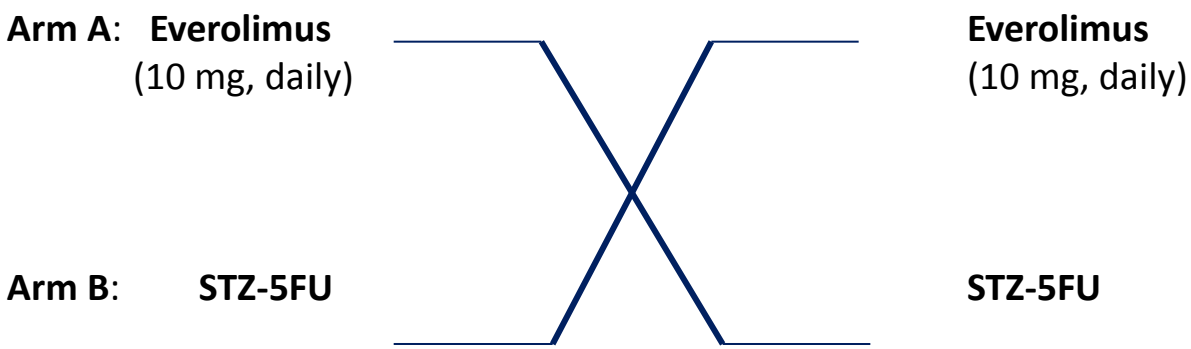
	Poorly Diff (N=13)	Pancreatic NET (n=11)	BRONCHIAL NET (n=5)	MIDGUT NET (n=7)
PARTIAL RESPONSE	3 (23%)	3 (27%)	3 (60%)	0 (0%)
STABLE DISEASE	1 (7%)	5 (45%)	1 (20%)	7 (100%)
PROGRESSIVE DISEASE	9 (70%)	1 (20%)	1 (20%)	0 (0%)

A phase II study of capecitabine, Oxaliplatin and Bevacizumab

	Pancreatic NET	Small bowel NET	Other/unknown
PARTIAL RESPONSE	6 (30%)	0 (0%)	1 (6%)
STABLE/PROGRESSIVE	14 (70%)	5 (100%)	14 (94%)

Kunz P et al. *J Clin Oncol* 28 15(s) ASCO 2010

Chemotherapy vs. 'biological' agent



- Accrual goal = 180 pts
- Study population: progressive, metastatic pNET, 1st line after SSA, G1/G2
- Locations: Denmark, France, Germany, Italy, Netherlands, Spain, Sweden, UK
- Primary EP: PFS2; Secondary EP: OS, RR, biochemical response

Slide courtesy of R. Salazar, Study Lead, Barcelona

Does chemo increase risk of MDS/AML in PRRT treated patients?

Table 2 Prognostic factors of occurrence of MDS and AML in patients treated with PRRT

	Patients who developed MDS/AML, *n* (%)	Other patients, *n* (%)	*P*-value
Total	4 (20)	16 (80)	
Gender (F/M)	3 (75)	4 (25)	0.16
Median age at diagnosis (years) (range)	53.8 (45–66)	51 (16–71)	0.63
Mean number of cycles of previous chemotherapy (range)	13.8 (6–25)	4.7 (0–19)	**0.001**
Alkylating-based chemotherapy mean number of cycles (range)	12.5 (6–20)	3.75 (0–9)	**0.001**
Bone metastases before PRRT	3 (75)	8 (50)	0.39
Immunosuppressive treatment	2 (50)	0 (0)	**0.006**
Mean dose of PRRT (GBq)	29	30.5	0.94
Mean number of cycles of PRRT	4	4	0.97
Early hematological toxicity grade 3–4	3 (75)	2 (13)	**0.03**
Number of deaths	4 (100)	4 (29)	–
Cause of deaths: underlying tumor	0 (0)	4 (29)	–
MDS/AML	4 (100)	0 (0)	–

Abbreviations: AML, acute myeloid leukemia; F, female; M, male; MDS, myelodysplastic syndrome; PRRT, peptide receptor radionuclide therapy. Bold indicates significant values.

Brieau et al. Endocr Relat Cancer. 2016 May;23(5):L17-23

Conclusions

- Alkylating agent based chemotherapy (streptozocin/dacarbazine/temozolomide) highly effective in pNETs.
- Typically combine with fluoropyrimidine (capecitabine/5-FU)
- Lesser activity in other NETs (lung, thymus). Relative lack of activity in midgut.
- Need to consider implications of chemo with respect to other myelotoxic drugs (i.e. PRRT).