Efficacy and Toxicity Analysis of Capecitabine and Temozolomide in Neuroendocrine Neoplasms

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ABSTRACT

Background: The capecitabine/temozolomide (CAPTEM) regimen has significant activity in advanced neuroendocrine tumors (NETs). Questions exist regarding activity in pancreatic versus nonpancreatic NETs, risk of opportunistic infections, long-term myelotoxicity, and safety of prolonged treatment duration. Analysis of large patient cohorts is needed for the evaluation of rare toxicities and assessment of risk factors. **Methods:** We conducted a retrospective study of all patients with advanced NETs seen at Moffitt Cancer Center between January 2008 and June 2019 who received treatment with CAPTEM. **Results:** A total of 462 patients were eligible. The objective radiographic response rate was 46%, and the disease control rate was 81%. Median progression-free survival (PFS) was 18 months (95% CI, 14.0–21.9 months) and median overall survival was 51 months (95% CI, 42.8–59.2 months): 62 months in well-differentiated NETs versus 14 months in poorly differentiated neuroendocrine carcinomas ($P<.0001$). Patients with primary pancreatic tumors had the highest partial response rates and longest median PFS. Incidences of grade 4 thrombocytopenia and neutropenia were 7% and 3%, respectively, and substantially higher in women than men ($P=.02$ and $P=.004$, respectively). Only 1 case (0.2%) of suspected *Pneumocystis* pneumonia (PCP) was observed in a patient receiving corticosteroids. Three patients developed myelodysplastic disease, all of whom had received prior peptide receptor radiotherapy (PRRT). There were no acute treatment-related deaths; 1 patient died 2 months after a thrombocytopenic bleed. **Conclusions:** The CAPTEM regimen is exceptionally safe. Efficacy is particularly robust in well-differentiated pancreatic NETs. Severe myelotoxicity is rare; the risk of grade 4 cytopenias is significantly increased in women, and therefore sex-based dosing should be considered. There were no cases of myelodysplastic syndromes, except among patients who had received PRRT, a known risk factor. The risk of PCP is negligible.

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Background

The capecitabine/temozolomide (CAPTEM) regimen has shown significant activity in neuroendocrine tumors (NETs), particularly in pancreatic NETs, for which objective radiographic response rates (ORRs) have ranged from roughly 30% to 70%.[1–5] A recent randomized phase II study sponsored by the ECOG compared CAPTEM with temozolomide monotherapy in 144 patients with advanced, progressive, low- and intermediate-grade pancreatic NETs.[2] The study showed a clinically and statistically significant improvement in progression-free survival (PFS) with the combination regimen, with a median PFS of 22.7 versus 14.4 months (hazard ratio [HR], 0.58; $P=.023$). Moreover, the trial also showed a significant improvement in overall survival (OS) with CAPTEM (not reached vs 38.0 months; HR, 0.41; $P=.012$).

The CAPTEM regimen has also showed efficacy in other types of NETs, albeit with lower response rates. Retrospective studies of CAPTEM in lung NETs have shown response rates of 18% to 30% in lung NETs and anecdotal responses in thymic NETs.[6–9] Several studies have enrolled heterogeneous populations of patients, generally showing the highest ORRs in pancreatic NETs, an intermediate response in lung/thymic NETs, and the lowest response in gastrointestinal NETs.

Although moderately powered studies are sufficient to determine critical outcomes such as ORR and PFS, larger databases are key to answering other important questions. These include the frequency of rare toxicities, risk factors for toxicities, and efficacy across all subtypes of NETs. A real-world clinical database with long-term follow-up is also important to address other questions, such as duration of treatment, dose adjustments, and other patterns of practice.

With respect to the CAPTEM regimen, central questions are as follows: is the regimen active in nonpancreatic NETs? Does temozolomide (an alkylating agent) cause

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myelodysplastic syndromes (MDS), and is this risk associated with long-term use? Is the risk of *Pneumocystis* pneumonia (PCP) and other opportunistic infections similar to that seen in the brain tumor population?[10] What are the rates of grade 4 cytopenias? Are there clinical risk factors for severe myelotoxicity? Can patients be safely treated for >1 year (as was the strategy in the randomized ECOG study)? What is the treatment-associated mortality rate? To address these and other clinical questions, we analyzed a database of 462 patients with advanced gastroenteropancreatic and lung NETs treated with CAPTEM at Moffitt Cancer Center.

Methods

We reviewed the records of patients with advanced neuroendocrine neoplasms seen at Moffitt Cancer Center between January 2008 and June 2019 who received treatment with CAPTEM. Patients who initiated treatment at outside institutions were included if they were prescribed treatment at appropriate doses and if complete records were available. The local Institutional Review Board approved the study protocol, and a waiver of consent was granted due to the retrospective nature of the study.

Demographic and pathologic data included age, primary disease site, Ki-67 proliferation index, histologic grade and differentiation, prior oncologic therapy, date of treatment initiation, and date of last follow-up and death, if applicable. We collected data on outcomes (ORR, PFS, OS, and disease control rate), duration of treatment, starting doses, dose reductions and interruptions, toxicities associated with treatment, and reasons for discontinuation.

PFS was defined as the time from initiation of treatment to either clinical or radiographic progression (whichever was shortest) or death of any cause. Assessments of radiographic response and progression were based on chart review rather than formal RECIST analysis. Partial response (PR) was defined as significant tumor regression on radiology reports and noted by the treating physician. Stable disease was defined as overall no significant change on radiology reports or minor disease improvement. Increase in tumor burden (size and/or number of tumors) and significant clinical progression as assessed by the treating physician defined progression of disease. OS was measured from the date of treatment initiation until death of any cause or last known follow-up date. Data were analyzed using SPSS Statistics, version 25 (IBM Corp). Survival curves were estimated using the Kaplan-Meier method, and categorical variables were analyzed using logistic regression or categorical response models. A *P* value set at 0.05 was used for Pearson correlations and chi-square analyses.

Table 1. Tumor Characteristics

Characteristic	n (%)
Primary disease site	
Pancreas	330 (71.43)
Small bowel	40 (8.66)
Lung	33 (7.14)
Unknown	27 (5.84)
Thymus	11 (2.38)
Rectal	8 (1.73)
Gastric	7 (1.51)
Cervical	3 (0.65)
Ampulla	1 (0.22)
Gallbladder	1 (0.22)
Presacrum	1 (0.22)
Ki-67 proliferation index	
≤2%	49 (10.61)
3%–20%	185 (40.04)
21%–50%	59 (12.77)
>50%	13 (2.81)
Unknown	156 (33.77)
Tumor grade	
1	70 (15.15)
2	189 (40.91)
3	93 (20.13)
Unknown	110 (23.81)
Tumor differentiation	
Well-differentiated	365 (79.00)
Poorly differentiated	39 (8.44)
Unknown	58 (12.56)

Results

Patient Characteristics

Supplemental eTable 1 presents patient demographics (available with this article at JNCCN.org), and Table 1 presents tumor characteristics. A total of 462 patients met eligibility criteria for analysis, including 252 men (55%) and 210 women (45%) with a median age of 59 years (range, 16–88 years) at the time of treatment initiation. Ten percent of patients began their treatment at an outside institution. Most patients had a primary pancreatic tumor (n=330; 71.4%). A total of 365 patients (79%) had well-differentiated tumors, 39 (8.4%) had poorly differentiated neuroendocrine carcinomas (NECs), and 58 (12.6%) had undefined differentiation status. A plurality of patients (n=189; 41%) had grade 2 histology. A total of 132 patients (28.6%) were treatment-naïve, and 187 (40.5%) had received 1 prior line of therapy. Tables 2 and 3 outline additional patient treatments before and after CAPTEM.

Table 2. Pre-CAPTEM Treatment Summary

	Primary Site				
Treatment	**Pancreas, n**	**Small Bowel, n**	**Lung, n**	**Unknown, n**	**Other, n**
Total, N	330	40	33	27	32
Locoregional therapies					
Surgery	57	11	8	3	5
Chemoembolization	12	0	0	0	1
Bland embolization	20	12	5	4	3
Radioembolization	7	1	2	2	1
Ablation	15	2	1	1	1
Radiation	20	1	10	5	7
Systemic therapies					
Platinum/Etoposide	33	0	9	10	17
Streptozocin-based chemo	19	2	1	0	1
5-FU–based chemo	10	0	0	0	0
Gemcitabine-based chemo	6	1	0	0	0
Interferon	2	4	0	1	2
Sunitinib	20	0	1	2	1
Everolimus	40	5	14	4	5
Somatostatin analogues	172	32	21	14	16
Immunotherapy	0	0	0	1	3
Clinical trial	6	3	4	1	4
PRRT	2	4	1	1	3
Other systemic therapy	13	0	5	1	4

Abbreviations: CAPTEM, capecitabine/temozolomide; chemo, chemotherapy; PRRT, peptide receptor radiotherapy.

Regimen

The target dose of capecitabine was 750 mg/m^2 twice daily on days 1 through 14, and the target dose of temozolomide was 200 mg/m^2 at bedtime on days 10 through 14 every 28 days, with ondansetron prophylactically administered 30 to 60 minutes before temozolomide. However, starting doses were frequently rounded down or reduced mildly at baseline. Consequently, the actual average starting dose of capecitabine was 675 mg/m^2 twice daily, and the average starting dose of temozolomide was 180 mg/m^2. The median duration on treatment was 8 months (range, 0–136 months). Median time to maximal response was 6 months. The median treatment-free interval for patients who discontinued treatment for reasons other than toxicity or disease progression was 14 months. A dose reduction was required for 113 patients (25%), and 72 (16%) discontinued treatment because of toxicity of any grade. A total of 193 patients (42%) discontinued treatment because of progressive disease, and 129 (28%) completed their course of treatment before progression because they achieved maximal response or reaching an arbitrary time point such as 1 year. The remaining patients discontinued because of other complications (nononcologic health issues, n=10; 2%) or insurance coverage issues or by personal request (n=16; 3%). A total of 42 patients (9%) remained on active treatment at the time of data cutoff.

Efficacy

Radiographic responses were assessed by review of patient progress notes and radiology reports, including tumor measurements provided. As the best response, 8 patients (2%) had a complete response, 204 (44%) had a PR, 161 (35%) had stable disease, and 76 (16%) had progressive disease. In 13 patients, response was not assessable. Median PFS was 18 months (95% CI, 14.0–21.9 months) and median OS was 51 months (95% CI, 42.8–59.2 months) (eFigure 1A, B).

When comparing patients with pancreatic versus nonpancreatic primary tumors, we found that median PFS was 23 versus 10 months ($P<.0001$) and median OS was 62 versus 28 months ($P<.0001$) (eFigure 2A, B). Patients with a pancreatic primary tumor had an ORR of 51.5%, whereas those with a nonpancreatic primary tumor had an ORR of 31.8% ($P<.0001$). Of note, all complete responses were in patients with pancreatic primary

Table 3. Post-CAPTEM Treatment Summary

Treatment	Primary Site				
	Pancreas, n	Small Bowel, n	Lung, n	Unknown, n	Other, n
Total, N	330	40	33	27	32
Locoregional therapies					
Surgery	43	4	4	1	2
Chemoembolization	5	0	0	0	0
Bland embolization	46	5	1	3	4
Radioembolization	19	1	0	0	0
Ablation	15	0	0	0	0
Radiation	32	2	3	3	4
Systemic therapies					
Platinum/Etoposide	15	1	3	2	7
Streptozocin-based chemo	8	1	0	0	2
5-FU–based chemo	54	2	0	3	3
Gemcitabine-based chemo	1	0	1	0	0
Interferon	0	2	0	0	0
Sunitinib	70	0	0	1	1
Everolimus	108	7	4	4	11
Somatostatin analogues	62	6	0	4	1
Immunotherapy	13	1	3	3	5
Clinical trial	14	1	3	1	4
PRRT	62	6	1	2	3
Other systemic therapy	41	1	1	2	1

Abbreviations: CAPTEM, capecitabine/temozolomide; chemo, chemotherapy; PRRT, peptide receptor radiotherapy.

tumors. Patients with well-differentiated tumors had significantly better outcomes than those with poorly differentiated carcinomas, with a median PFS of 24 versus 7 months ($P<.0001$) and a median OS of 62 versus 14 months ($P<.0001$) (Figure 1A, B). Patients with grades 1, 2, and 3 tumors had a median PFS of 30, 23, and 10 months, respectively ($P=.081$) and median OS of 81, 57, and 23 months, respectively ($P<.0001$) (Figure 2A, B). Among patients with grade 3 tumors (n=77; 38 NETs and 39 NECs), those with well-differentiated grade 3 NETs had significantly better outcomes than those with poorly differentiated NECs, with median PFS of 28 versus 7 months ($P=.005$) and median OS of 36 versus 14 months ($P<.001$); however, no difference was observed in ORR (42% and 33%, respectively; $P=.388$). Patients with pancreatic primary or well-differentiated tumors were more likely to have PR as the best response ($P<.001$ and $P=.001$, respectively). Table 4 outlines ORR, PFS, and OS by patient subgroup.

Adverse Effects

Treatment-related adverse effects were graded per CTCAE version 5.0 and are outlined in Table 5. Seventy percent (n=322) of patients experienced at least grade 1 treatment-related toxicity. Particular attention was paid to grade 4 hematologic events, opportunistic infections, and the development of hematologic malignancies or disorders. The incidence of grade 4 thrombocytopenia was 7% (10% in women and 5% in men; $P=.02$), and 4 cases were complicated by bleeding (0.8%). The incidence of grade 4 neutropenia was 3% (5% in women and 1% in men; $P=.004$), and the incidence of grade 4 lymphopenia was only 2%. There were no differences in prescribed doses between men and women. There was no difference between male and female patients with regard to prior exposure to chemotherapy or duration on CAPTEM ($P=.850$ and $P=.536$, respectively).

Only 1 case (0.2%) of suspected PCP was observed in a patient receiving corticosteroids. There were 5 cases of herpes zoster virus and no other opportunistic infections. Three patients developed myelodysplastic disease, all of whom had also received peptide receptor radiotherapy (PRRT) with ^{177}Lu-DOTATATE ($P<.0001$). Two of the patients had received PRRT approximately 5 years earlier and developed MDS during or shortly after completing CAPTEM. The third patient received PRRT roughly 20

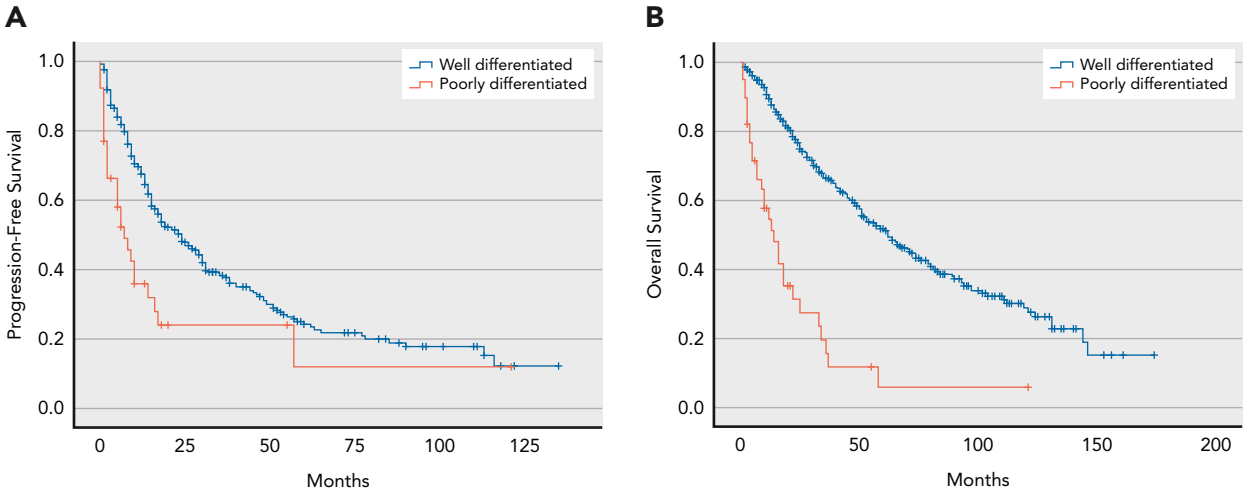

Figure 1. **(A)** Progression-free and **(B)** overall survival, stratified by tumor differentiation.

months after completing CAPTEM and developed MDS 3 months after PRRT ended. There was no statistically significant increase in the risk of developing grade 3 or 4 hematologic toxicity among patients who received prior PRRT (P=.480). There were no acute treatment-related deaths, although 1 patient died 2 months after a thrombocytopenic bleed.

Of the 113 patients who required dose reductions, 15 (13%) underwent dose reduction of temozolomide alone, and 1 (0.8%) was unable to tolerate dose reduction and continued on capecitabine monotherapy. Thirty-eight patients (34%) had a dose reduction of capecitabine alone, 7 (6%) of whom continued on temozolomide monotherapy. A total of 60 patients (53%) required dose reduction of both drugs, 4 (4%) of whom could not tolerate dose reductions and permanently discontinued therapy.

Discussion

Our analysis of a large database of patients with NETs treated with CAPTEM yielded many new insights. One key finding is that the regimen is safe and that treatment-related deaths are exceedingly rare: only 1 patient (0.2%) death was likely attributable to treatment. Another finding is that the opportunistic infection risk is negligible and that serious opportunistic infections such as PCP are absent among otherwise immunocompetent patients. This stands in contrast to the brain tumor literature, in which prophylactic PCP therapy is recommended, likely because many patients are receiving chronic immunosuppressive corticosteroids.[10] It is important to note that previous data on opportunistic infections in patients with neuroendocrine neoplasms involved patients who were receiving temozolomide at a higher dose intensity (every other week), which may contribute to the higher risk observed.[11]

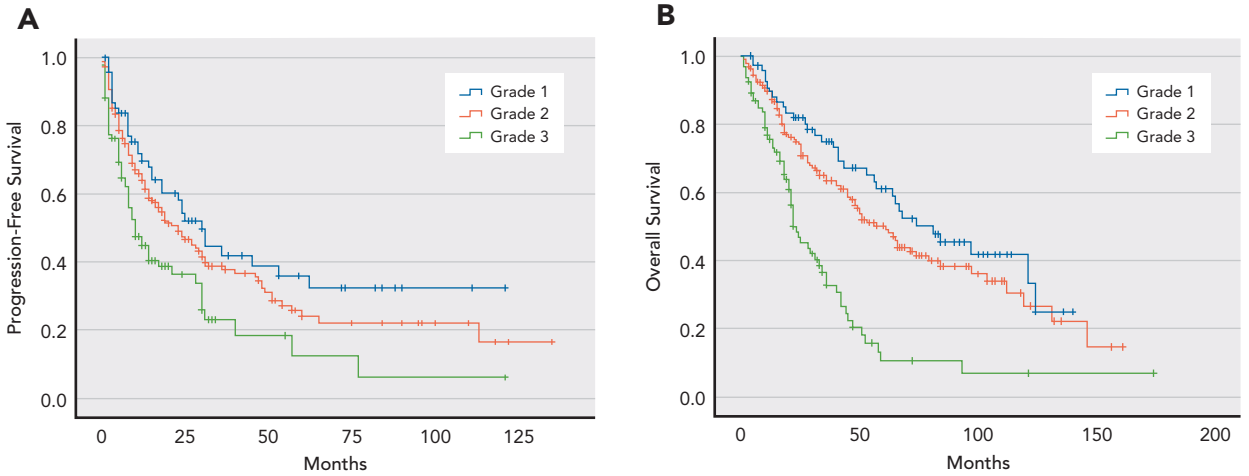

Figure 2. **(A)** Progression-free and **(B)** overall survival, stratified by tumor grade.

Table 4. Response Data per Primary Site of Disease

Primary Site	ORR n (%)	Median PFS (95% CI), in Months	Median OS From Treatment (95% CI), in Months	Median OS From Diagnosis (95% CI), in Months
Pancreas	170/330 (51.5)	23 (17.2–28.8)	62 (51.5–72.5)	105 (87.9–122.0)
Small intestine	9/40 (22.5)	15 (0.0–31.5)	36 (9.4–62.6)	76 (46.9–105.0)
Lung	14/33 (42.4)	12 (5.5–18.5)	22 (13.9–30.1)	53 (27.6–78.4)
Unknown	8/27 (29.6)	7 (0.0–15.3)	33 (5.7–60.3)	87 (3.8–170.2)
Other	11/32 (34.4)	9 (6.5–11.5)	32 (15.8–48.2)	54 (34.8–73.2)

Abbreviations: ORR, objective radiographic response rate; OS, overall survival; PFS, progression-free survival.

Alkylating cytotoxic drugs, as a class, are associated with development of MDS.[12] However, with our study's median follow-up of 2.4 years, we identified no cases of treatment-associated MDS or acute leukemia, apart from 3 patients who had also received PRRT with ^{177}Lu-DOTATATE, a known risk factor for myelodysplasia. Consequently, it appears that temozolomide in itself does not present a significant risk for subsequent development of

Table 5. Treatment-Related Adverse Effects per CTCAE Version 5.0

Adverse Effect	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)
Fatigue	111 (24.0)	41 (8.9)	9 (1.9)	0 (0.0)
Nausea	76 (16.5)	16 (3.5)	8 (1.7)	0 (0.0)
Platelet count decreased	73 (15.8)	23 (5.0)	12 (2.6)	28 (6.1)
Anemia	70 (15.2)	41 (8.9)	10 (2.2)	5 (1.1)
Lymphocyte count decreased	51 (11.0)	49 (10.6)	39 (8.4)	8 (1.7)
Palmar plantar erythrodysesthesia	42 (9.1)	10 (2.2)	14 (3.0)	0 (0.0)
Neutrophil count decreased	30 (6.5)	28 (6.1)	6 (1.3)	10 (2.2)
Constipation	28 (6.1)	6 (1.3)	1 (0.2)	0 (0.0)
Abdominal pain	20 (4.3)	13 (2.8)	11 (2.4)	0 (0.0)
Diarrhea	17 (3.7)	10 (2.2)	9 (1.9)	0 (0.0)
Vomiting	15 (3.2)	4 (0.9)	4 (0.9)	0 (0.0)
Rash	13 (2.8)	5 (1.1)	1 (0.2)	0 (0.0)
Myalgia	10 (2.2)	3 (0.6)	0 (0.0)	0 (0.0)
Skin hyperpigmentation	10 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)
Mucositis	9 (1.9)	3 (0.6)	4 (0.9)	0 (0.0)
Dizziness	7 (1.5)	3 (0.6)	0 (0.0)	0 (0.0)
Pruritus	7 (1.5)	2 (0.4)	0 (0.0)	0 (0.0)
Fever	6 (1.3)	0 (0.0)	1 (0.2)	0 (0.0)
Anorexia	5 (1.1)	5 (1.1)	0 (0.0)	0 (0.0)
Edema, limbs	4 (0.9)	3 (0.6)	0 (0.0)	0 (0.0)
Confusion	4 (0.9)	4 (0.9)	1 (0.2)	0 (0.0)
Bloating	4 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)
Headaches	3 (0.6)	1 (0.2)	4 (0.9)	0 (0.0)
Insomnia	3 (0.6)	5 (1.1)	0 (0.0)	0 (0.0)
Arthralgia	2 (0.4)	3 (0.6)	0 (0.0)	0 (0.0)
Dehydration	0 (0.0)	3 (0.6)	4 (0.9)	0 (0.0)
Dyspnea	0 (0.0)	5 (1.1)	1 (0.2)	0 (0.0)

MDS. It is unclear, however, whether sequential treatment with CAPTEM and ^{177}Lu-DOTATATE increases the risk of MDS significantly above the risk of ^{177}Lu-DOTATATE alone. Of note, in a recent study of 38 patients, researchers evaluated long-term outcomes of patients treated with a CAPTEM-PRRT regimen in which no long-term cases of MDS or leukemia were reported.[13]

The rates of grade 4 acute myelotoxicities were similar to those reported in the randomized ECOG study.[2] However, the size of our database allowed us to show significant sex disparities in grade 4 thrombocytopenia and neutropenia, with women at substantially higher risk. We conclude that mild sex-based dosing adjustments should be considered, particularly among older female patients, in whom risks of grade 4 thrombocytopenia or neutropenia can be quite significant.

Response rates in our cohort of patients support those previously reported in the literature, with well-differentiated tumors and patients with pancreatic primary tumors exhibiting significantly higher PFS, OS, and ORR.[14–16] We also note that our average starting doses were 10% lower than the target doses of 750 mg/m^2 twice daily of capecitabine and 200 mg/m^2 of temozolomide and that our prior analyses of outcomes using these doses showed highly favorable results in the pancreatic and lung NET population.

Limitations of the study include lack of Ki-67 percentage in approximately one-third of patients, primarily due to the fact that many were treated during a time when mitotic activity was the primary determinant of grade. Although the average follow-up duration was relatively long (median, 2.4 years), cases of treatment-related MDS occurring many years after onset of therapy may have been missed.

Conclusions

The CAPTEM regimen is exceptionally safe, with a treatment-associated mortality rate of 0.2%. It is particularly active in well-differentiated pancreatic NETs but appears to have significant activity in other NET subtypes. Severe myelotoxicity is rare, but risks of grade 4 thrombocytopenia and neutropenia are significantly increased in women compared with men. Sex-based dosing should be considered. The risk of MDS or acute leukemia appears to be negligible in patients who are unexposed to other known risks, such as PRRT, although cases occurring many years after onset of therapy may have been missed. The risk of a serious opportunistic infection likewise appears to be negligible in otherwise immunocompetent patients.

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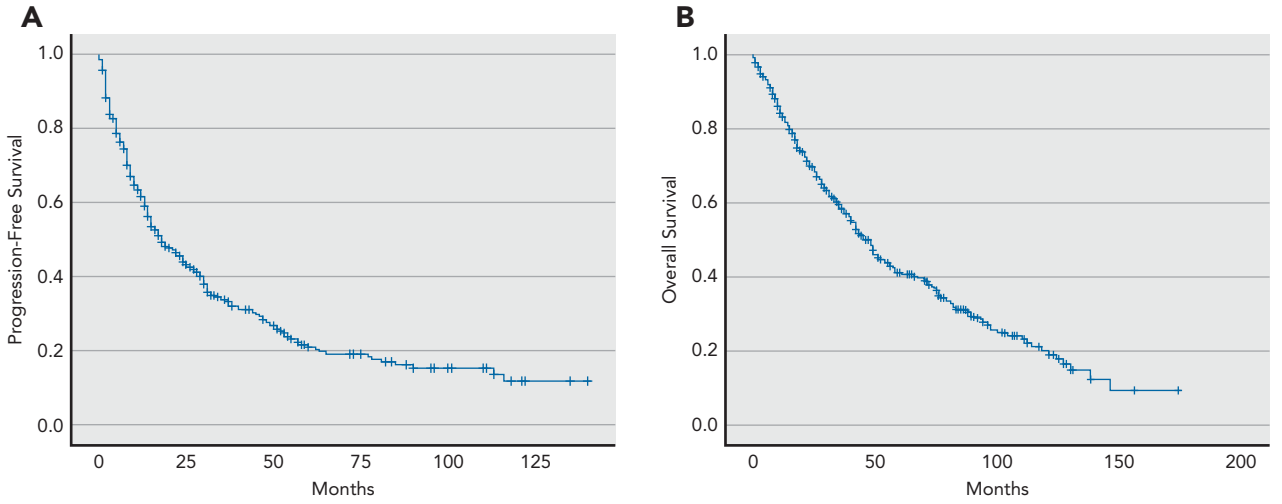
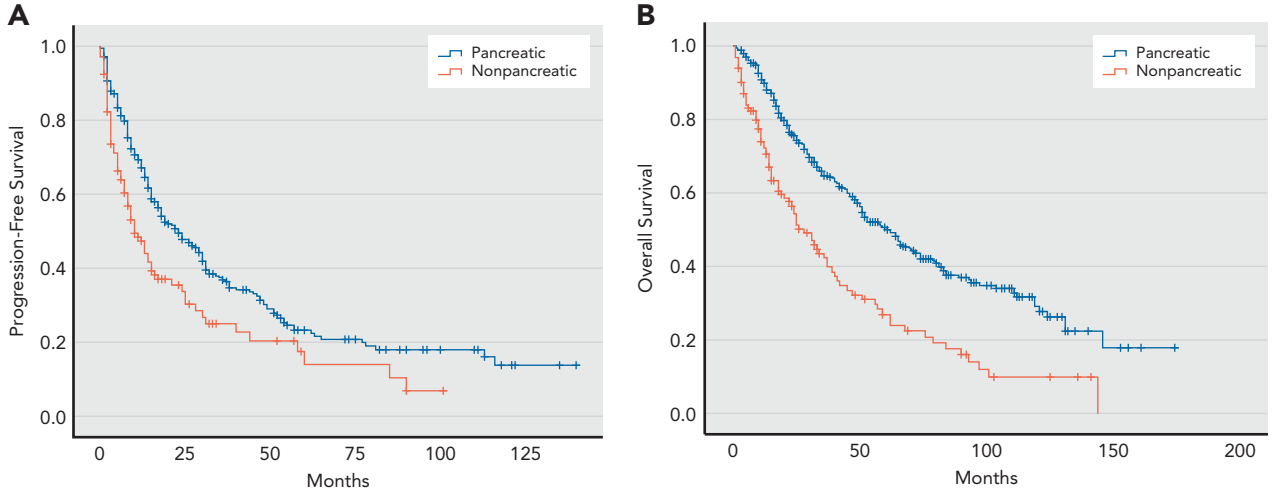


eFigure 1. **(A)** Progression-free and **(B)** overall survival.



eFigure 2. **(A)** Progression-free and **(B)** overall survival by primary site of disease.

eTable 1. Patient Demographics

Characteristic	n (%)
Sex	
Male	252 (54.55)
Female	210 (45.45)
Age, y	
16–29	11 (2.38)
30–44	55 (11.90)
45–59	170 (36.80)
60–74	181 (39.18)
≥75	45 (9.74)
Number of prior lines	
0	132 (28.57)
1	187 (40.48)
2	78 (16.88)
3	46 (9.96)
4	7 (1.52)
5	6 (1.30)
6	2 (0.43)
≥7	4 (0.86)