Re-examining NCTN Clinical Trials for Sex Differences in Outcomes and Toxicities in Patients with Neuroendocrine Neoplasms

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Background

- Epidemiologic and retrospective studies on treatment-related side effects revealed potential sex-based differences in neuroendocrine neoplasms (NEN).
- The purpose of this study was to examine sex differences in treatment-related toxicities and outcomes in three NCTN clinical trials.

Methods

- A retrospective analysis of three randomized clinical trials for patients with NEN conducted through the NCTN was performed:
  - ECOG-ACRIN E2211 [Phase II Capecitabine + Temozolomide vs Temozolomide in advanced pancreatic NEN]
  - SWOG S0518 [Phase III Octreotide + Interferon (IFN) vs Octreotide + Bevacizumab in advanced gastrointestinal NEN]
  - Alliance CALGB 80701 [Phase II Everolimus vs Everolimus + Bevacizumab in advanced pancreatic NEN].
- Sex differences in progression free survival (PFS), overall survival (OS), response rate (RR), and treatment-related toxicities as measured through the NCI Clinical Trial Adverse Event Criteria were examined.

Results

- The total number of males (M) and females (F) in each trial were E2211 (N = 73 M and 60 F), S0518 (N = 192 M and 210 F), and CALGB 80701 (N = 84 M and 66 F) [Table 1].

NCTN Clinical Trials	Males	Females
ECOG-ACRIN E2211		
Capecitabine + Temozolomide	38	30
Temozolomide	35	30
Total	73	60
SWOG S0518		
Octreotide + IFN	90	112
Octreotide + Bevacizumab	102	98
Total	192	210
Alliance CALGB 80701		
Everolimus	40	35
Everolimus + Bevacizumab	44	31
Total	84	66

Table 1: Total number of male and female patients in each arms of all three clinical trials

- There were no statistically significant sex differences in PFS, OS and RR within the treatment arms of each trials [Figures 1 and 2; Tables 2 to 4].

Sex Differences in PFS

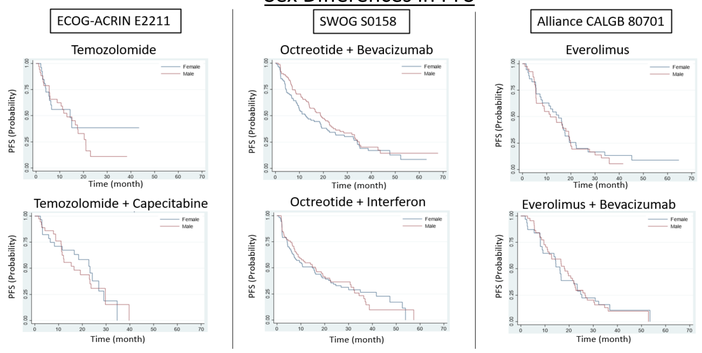


Figure 1 (above): PFS of male vs female in each clinical trial.

NCTN Clinical Trials	Median PFS (months)		Hazard Ratio (Females to Males) (95% Confidence Interval, p-value)
	Females	Males	
ECOG-ACRIN E2211			
Capecitabine + Temozolomide	23.2	16.5	0.90 (0.48-1.70, p=0.75)
Temozolomide	14.4	13.0	0.83 (0.42-1.64, p=0.59)
SWOG S0518			
Octreotide + IFN	14.8	16.1	1.02 (0.72-1.44, p=0.93)
Octreotide + Bevacizumab	12.6	18.9	1.23 (0.89-1.71, p=0.21)
Alliance CALGB 80701			
Everolimus	15.0	11.5	0.90 (0.55-1.47, p=0.68)
Everolimus + Bevacizumab	16.2	18.0	0.99 (0.61-1.61, p=0.96)

Table 2: Sex differences in median months of PFS in each clinical trial

MAIN TAKEAWAY & FUTURE DIRECTION:

Sex differences in treatment-related toxicities in NEN may be more prevalent than previously recognized and highlight the need for further study in this area.

Sex Differences in OS

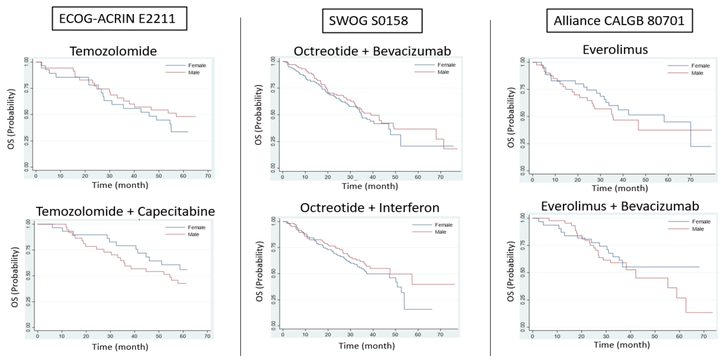


Figure 2 (right): OS of male vs female in each clinical trial.

NCTN Clinical Trials	Median OS (months)		Hazard Ratio (Females to Males) (95% Confidence Interval, p-value)
	Females	Males	
ECOG-ACRIN E2211			
Capecitabine + Temozolomide	N/A	54.5	0.66 (0.32-1.34, p=0.25)
Temozolomide	46.0	57.1	1.39 (0.72-2.68, p=0.32)
SWOG S0518			
Octreotide + IFN	37.2	47.6	1.25 (0.83-1.90, p=0.28)
Octreotide + Bevacizumab	34.8	39.1	1.17 (0.80-1.71, p=0.41)
Alliance CALGB 80701			
Everolimus	58.2	35.5	0.76 (0.40-1.42, p=0.39)
Everolimus + Bevacizumab	N/A	42.1	0.75 (0.38-1.49, p=0.42)

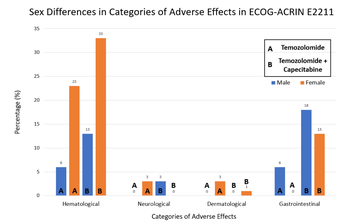
Table 3: Sex differences of median months in each clinical trial

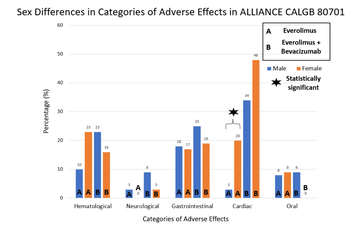
Sex Differences in Response Rate

ECOG-ACRIN E2211						
Response Category	Temozolomide		p-value	Temozolomide + Capecitabine		p-value
	Female	Male	0.43	Female	Male	0.77
CR/PR	9 (30.0%)	13 (37.1%)		10 (33.3%)	17 (44.7%)	
Stable disease	11 (36.7%)	15 (42.9%)		14 (46.7%)	16 (42.1%)	
Progressive disease	6 (20.0%)	6 (17.1%)		5 (16.7%)	4 (10.5%)	
Missing/Unevaluable	4 (13.3%)	1 (2.9%)		1 (3.3%)	1 (2.6%)	
SWOG S0518						
Response Category	Octreotide + Bevacizumab		p-value	Octreotide + IFN		p-value
	Female	Male	0.30	Female	Male	0.18
CR/PR	11 (11.2%)	18 (17.6%)		11 (9.8%)	4 (4.4%)	
Stable disease	67 (68.4%)	68 (66.7%)		69 (61.6%)	68 (75.6%)	
Progressive disease	13 (13.3%)	7 (6.9%)		21 (18.8%)	12 (13.3%)	
Missing/Unevaluable	7 (7.1%)	9 (8.8%)		11 (9.8%)	6 (6.7%)	
Alliance CALGB 80701						
Response Category	Everolimus		p-value	Everolimus + Bevacizumab		p-value
	Female	Male	0.61	Female	Male	0.67
CR/PR	6 (17.1%)	3 (7.5%)		10 (32.3%)	13 (29.5%)	
Stable disease	24 (68.6%)	32 (80.0%)		18 (58.1%)	28 (63.6%)	
Progressive disease	3 (8.6%)	3 (7.5%)		3 (9.7%)	2 (4.5%)	
Missing/Unevaluable	2 (5.7%)	2 (5.0%)		0 (0.0%)	1 (2.3%)	

Table 4: Sex differences in RR in each clinical trial

- There were sex differences in treatment-related toxicities in CALGB 80701 [Figure 3].
- In CALGB 80701, there was a higher occurrence of cardiac-related toxicities among females in Everolimus treatment (20% vs 3%; p=0.022) but not in Everolimus + Bevacizumab.
- In E2211, hematological toxicities showed a trend of female predominance in both treatment arms.





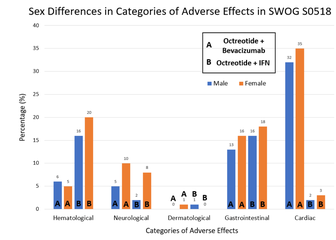


Figure 3 (above and right): Sex differences in categories of adverse effects in each clinical trial.

Conclusions

- Sex differences were present in cardiac treatment-related toxicities in CALGB 80701. However, there were no statistically significant sex-based differences in PFS, OS, and RR in the three clinical trials examined.

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