Capecitabine and Temozolomide (C/T) Combination Therapy in Patients (pts) with Advanced Neuroendocrine Neoplasms (aNEN) and the Role of O6-methylguanine-methyltransferase (MGMT) as a Potential Biomarker for Response

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Background: Tumor O^6-methylguanine-methyltransferase (MGMT) reverses temozolomide-induced DNA injury, and low MGMT tumor expression is a predictor of response to temozolomide in glioblastoma. C/T therapy induces partial responses in up to 70% of pts with grade 1-2 pancreatic NEN but the role of MGMT expression as a predictor is unclear. We evaluated C/T combination therapy in patients with aNEN of all grades and primary sites, and assessed MGMT expression by immunohistochemistry (IHC) as a prognostic and predictive biomarker.

Methods: A retrospective review was carried out at Ohio State University of 38 pts with aNEN receiving C/T therapy from 2009 to 2013, with 29 pts evaluable for RECIST response. Tumor MGMT expression was assessed in 20 pts by IHC to evaluate whether low MGMT expression (<10%) predicted response to C/T therapy vs high levels (≥10%).

Results: Primary NEN site was pancreas in 18 pts, and non-pancreas in 11 pts. Objective response, progression-free survival (PFS) and overall survival (OS) data are outlined in the Table. Partial response (PR) rate was 50% in pts with pancreas primary vs 18% for non-pancreas primary. High PRs were observed in pts with grade 3 NEN (57%). Median PFS in the MGMT-low group was 16.6 months vs 9.5 months in the MGMT-high group (p=0.19). Median OS in the MGMT low group was 42.9 months vs 18.1 months in the MGMT-high group (p=0.16). There was a trend toward higher rate of PR (63%) in pts whose tumors had low levels of MGMT expression compared to those with high levels (17%) (p=0.18).

Conclusion: We observed a trend towards increased PR, median PFS, and median OS in aNEN pts whose tumors had low MGMT protein expression by IHC. Results of this trial serve as strong rationale for future prospective trials to clarify role of MGMT expression in choosing C/T therapy for pts with NET.

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Table 1: Objective response rate, progression-free survival (PFS), and overall survival (OS) for patients with aNEN treated with C/T

	All patients evaluable for response	Low MGMT* (<10%)	High MGMT (>10%)
N	29	12	8
%PR	38	63	17
%SD	52	37	66
%PD	10		17
Median PFS (months)	13	16.6	9.5
Median OS (months)	29.3	42.9	18.1
Survival rate at 2 years (%)	58	75	38

*MGMT IHC was assessed on tumor samples of 20 patients