

# B-18

## Testicular Receptor-4 (TR4): Novel Predictive Biomarker for Disease Related Survival in pNETs

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**BACKGROUND:** Pancreatic neuroendocrine tumors (pNETs) exhibit a variable disease course, ranging from slowly progressive tumors with high functional status to rapidly progressive widely metastatic disease with increased mortality. The WHO 2010 disease classification integrates tumor staging, metastatic status and grade based on proliferation index and provides some insight into clinic outcome. However, no reliable predictive biomarker of disease specific survival that helps guide appropriate patient therapy currently exists. We recently demonstrated overexpression of the orphan nuclear receptor, Testicular receptor-4 (TR4, also known as NR2C2), in adrenocorticotrophin (ACTH)-secreting pituitary- NETs and we sought to examine its broader role in pNETs.

**METHODS:** This study retrospectively analyzed a cohort of 85 surgically resected pNET tissues collected at UCLA Medical Center between 1989-2009 which according to American Joint Committee on Cancer 7th staging criteria composed 17 (20%) stage IA, 26 (30.6%) stage IB, 4 (4.7%) stage IIA, 21 (24.7%) stage IIB, and 17 (20%) stage IV with 15 (17.6%) exhibiting hepatic metastasis. A tissue microarray of the primary pancreatic tumors was developed and TR4 immunocytochemical staining was performed and quantitated by a single pathologist (DD), using the histoscore (range 0-300) representing the product of nuclear staining intensity (0-absent, 1-weak, 2 – moderate, 3-strong) and percent tumor cell staining (0-100).

**RESULTS:** A Kaplan Meier analysis demonstrated that high nuclear TR4 staining (>200, n=33 patients) was significantly associated with increased disease-specific

survival ( $p=0.004$ ). Additionally, lower TR4 was significantly correlated with pM1 status ( $p=0.005$ ) and pN1 status ( $p=0.024$ ) by Fisher Exact test, as well as higher pT status ( $p=0.023$ ) by Chi-square test.

**CONCLUSION:** Immunocytochemical TR4 expression in 85 pNETs demonstrated that high TR4 nuclear staining predicts long term disease-specific survival. Further understanding of the mechanism(s) by which TR4 regulates pNET metastasis may lead to a novel therapeutic approach to treat neuroendocrine tumors.