

PRRT 2.0: Definition and Prediction of Efficacy with Circulating Neuroendocrine Tumor Transcripts

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Background: Peptide receptor radionuclide therapy (PRRT) is an effective treatment for neuroendocrine tumors (NETs) and somatostatin receptor imaging (SRI) uptake is used to identify candidates as well as predict therapeutic efficacy. A blood-based 51 multigene NET transcript analysis (NETest) including gene clusters provides a direct measure of tumor behavior. We evaluated whether the NETest was a predictive biomarker in PRRT.

Methods: 177Lu-PRRT treated NETs (n=72; advanced disease: 30% salvage treatment) followed for 33 months. Baseline evaluation included: histological grade, SRI, CgA (ELISA, normal<108ng/ml) and NETest (qPCR with multianalyte algorithmic analyses). A mathematical predictive response index comprising NETest genes regulating metabolism and growth factor signaling integrated with grade was developed as a predictive quotient (PRI). RECIST criteria were used to evaluate disease control (responder vs non-responder). Statistical analyses: multiple regression, Kaplan-Meier survival, Chi2 analyses.

Results: PRRT demonstrated a 68% disease control rate response with median PFS of 21 months (median follow-up 16 months). NETest decreased in 88% of responders; and increased in 90% of non-responders accurately correlating with RECIST-determined responses. Although 77% low grade and 50% high-grade tumors responded, grade alone was not predictive (p=0.12). Neither baseline SRI measurement (p=0.58) nor CgA were predictive (p=0.53). Baseline gene cluster expression for metabolism and growth factor signaling had 76% accuracy for predicting PRRT-response. The predictive response index (PRI: NETest/grade) accurately predicted responders (97%; mPFS undefined) and non-responders (91%: mPFS: 17 months). This was significantly better than SRI (94% vs. 38% accuracy, p<0.0001). Baseline NETest >40% accurately (89%) predicted treatment response and a longer PFS (HR 2.97, p=0.05).

Conclusion: The blood-based NETest provides a predictive multi-molecular biomarker for PRRT. The PRI is highly accurate (94%) in predicting efficacy and significantly outperforms SRI assessment. Alterations in NETest correlate with RECIST responses and assess real time treatment efficacy. NET multigene measurement in blood can predict patients responsive to PRRT.