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

Lisa Bodei, Mark S. Kidd, Irvin M. Modlin, Stefano Severi, Ignat Drozdov, Silvia Nicolini, Dik J. Kwekkeboom, Eric Krenning, Richard P. Baum, Giovanni Paganelli,
Memorial Sloan Kettering Cancer Center, New York, NY; Yale School of Medicine, New Haven, CT; Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori-IRST IRCCS, Meldola, Italy;
Zentralklinik Bad Berka, Bad Berka, Germany; King's College, London, England; Erasmus Medical Center, Rotterdam, Netherlands; Wren Laboratories, Branford CT

Principal Message

The NETest is a predictive multi-molecular biomarker for PRRT efficacy. Alterations in levels correlate with treatment responses.
The NETest accurately (94%) predicted PRRT efficacy and significantly outperforms SRI.

Background

Peptide receptor radionuclide therapy (PRRT) is an effective NET treatment. Predicting response is based on somatostatin receptor expression and efficacy evaluated by RECIST criteria. Both have limited accuracy. The NETest measures tumor activity in blood and correlates cell signaling and metabolism directly with tumor activity.

Aim

Examine the effectiveness of the NETest as a PRRT predictive marker.

Methods

^{177}Lu-octreotate treated NETs (*n*=72; advanced disease: 30% salvage treatment) followed for 33 months. Histological grade, somatostatin receptor imaging (SRI), CgA (ELISA, normal≤108ng/ml) and NETest (qPCR with multianalyte algorithmic analyses) were evaluated. A mathematical response index comprising NETest genes regulating metabolism and growth factor signaling and grade was developed as a Predictive Response Index (PRI). RECIST criteria were used to evaluate disease control (responder vs non-responder). Statistical analyses: multiple regression, Kaplan-Meier survival, Chi^2 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).

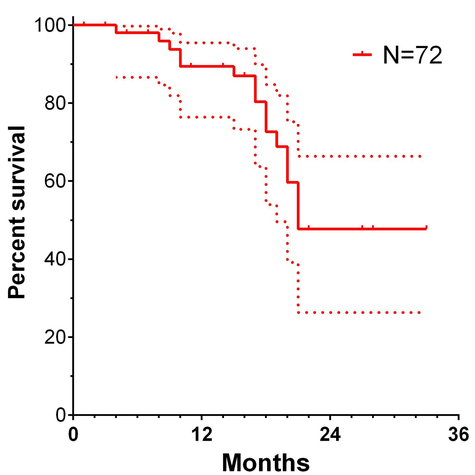

Figure 1
Progression free survival with 95% confidence interval (dotted line). Median survival 21 months (*top*).

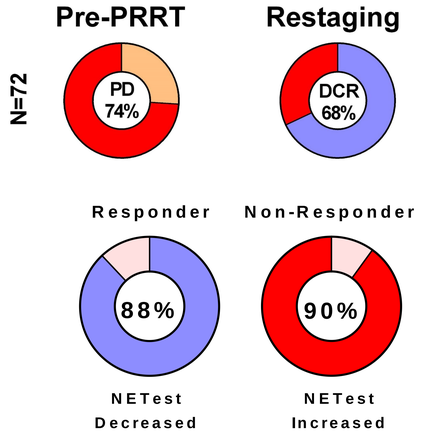

Figure 2
Proportion of patients with progressive disease (PD) was 74% at start of therapy. Sixty-eight percent achieved disease control (DCR = disease control rate) (*top*). In PRRT responders, NETest decreased in 88% or was unchanged in 12%. Changes in NETest were concordant with imaging (*p*=0.0002) (*bottom*) In non-responders, NETest increased in 90% (unchanged in 10%); NETest alterations were concordant with image-based disease changes (*p*<0.007).

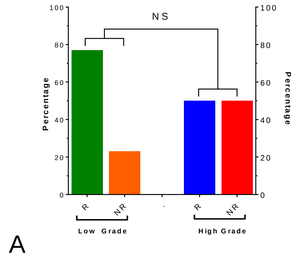

Figure 3A
Low grade (G1/G2 and typical/atypical BP carcinoids) responded to therapy in 77% of cases while high grade lesions (G3/undifferentiated BPs) responded 50% of the time. This was not significant: *p*=0.12

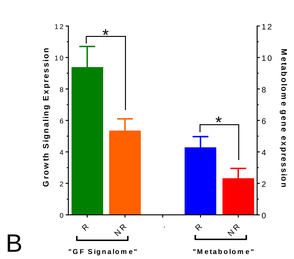

Figure 3B
Growth factor signaling (GF signalome) and genes involved in regulating metabolism (metabolome) were significantly elevated in responders (R) prior to initiation of PRRT therapy. *p<0.05 vs. Non-responders (NR). These genes form the biological basis of the PRI

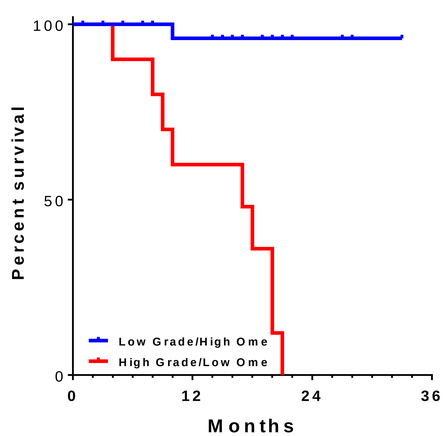

Figure 4
PFS was significantly different between those with a high ome/low grade prediction response index (median not reached) and those with a low ome/high grade PRI (median PFS 17 months, Log Rank 26.8, p<0.0001, HR = 53.3).

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.

NANETs Jackson Hole, September 30, 2016