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PRRT Neuroendocrine Tumor Response Monitored Using Circulating Transcript Analysis: The NETest



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BACKGROUND: Peptide receptor radionuclide therapy (PRRT) is effective for metastatic/inoperable neuroendocrine tumors (NETs). Imaging response assessment is usually efficient subsequent to treatment completion. Blood biomarkers such as PRRT Predictive Quotient (PPQ) and NETest are effective in real-time. PPQ predicts PRRT efficacy; NETest monitors disease. We prospectively evaluated: (1) NETest as a surrogate biomarker for RECIST; (2) the correlation of NETest levels with PPQ prediction.

METHODS: Three independent ¹⁷⁷Lu-PRRT-treated GEP-NET and lung cohorts (Meldola, Italy: n=72; Bad-Berka, Germany: n=44; Rotterdam, Netherlands: n=41). Treatment response: RECIST1.1 (responder (stable, partial, and complete response) vs non-responder). Blood sampling: pre-PRRT, before each cycle and follow-up (2-12 months). PPQ (positive/negative) and NETest (0-100 score) by PCR. Stable <40; progressive >40). CgA (ELISA) as comparator. Samples de-identified, measurement and analyses blinded. Kaplan-Meier survival and standard statistics.

RESULTS: One hundred twenty-two of 157 were evaluable. RECIST-stabilization or response in 67%; 33% progressed. NETest significantly ($p<0.0001$) decreased in RECIST "responders" ($-47\pm 3\%$); in "non-responders," it remained increased ($+79\pm 19\%$) ($p<0.0005$). NETest monitoring accuracy was 98% (119/122). Follow-up levels >40 (progressive) vs stable (<40) significantly correlated with mPFS (not reached vs. 10 months; HR 0.04 (95%CI, 0.02-0.07)). PPQ response prediction was accurate in 118 (97%) with a 99% accurate positive and 93% accurate negative prediction. NETest significantly ($p<0.0001$) decreased in PPQ-predicted responders ($-46\pm 3\%$) and remained elevated or increased in PPQ-predicted non-responders ($+75\pm 19\%$). Follow-up NETest categories stable vs progressive significantly correlated with PPQ prediction and mPFS (not reached vs. 10 months; HR 0.06 (95%CI, 0.03-0.12)). CgA did not reflect PRRT treatment: in RECIST responders decrease in 38% and in non-responders 56% ($p=NS$).

CONCLUSION: PPQ predicts PRRT response in 97%. NETest accurately monitors PRRT response and is an effective surrogate marker of PRRT radiological response. NETest decrease identified responders and correlated ($> 97\%$) with the pretreatment PPQ response predictor. CgA was non-informative.

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