Evaluation of Chromogranin A and Neuron-specific Enolase as Predictors of Response to Everolimus Therapy in Patients with Advanced Pancreatic Neuroendocrine Tumors (pNET)

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BACKGROUND AND RATIONALE

- Patients with pNET often have advanced disease at time of diagnosis, resulting in a high mortality rate.[1–3]
- Currently, there are limited treatment options after chemotherapy failure and treatment for pNET remains a significant unmet need.
- In 2007, the National Cancer Institute (NCI) identified priorities for improving the management of neuroendocrine tumors (NET):
  - Develop more effective and specific therapies for advanced disease (preferably based on improved understanding of molecular pathogenesis)
  - Identify biomarkers for early diagnosis, monitoring, treatment, and prognostication[4]
- For patients with advanced pNET, there is a definitive benefit with targeted agents, everolimus ± octreotide LAR.[5,6]
- Two circulating proteins are promising biomarkers in NET:
  - Chromogranin A (CgA) is elevated in pNET and present in the secretory granules of neuroendocrine cells[7]
  - Neuron-specific enolase (NSE), which is present in the cytoplasmic compartment of cells, is also a potential NET serum biomarker[8–10]
- Here, we prospectively evaluated the prognostic and predictive values of CgA and NSE in a non-randomized trial of everolimus treatment ± octreotide LAR.

METHODS

- Stratum 1: Patients not receiving octreotide LAR therapy (n=115):
  - Treated with everolimus 10 mg/day orally (Figure 1)
- Stratum 2: Patients on stable dose of octreotide LAR for ≥3 months before study entry (n=45):
  - Treated with everolimus 10 mg/day orally and octreotide LAR at the pre-study dose of ≤30 mg intramuscularly every 28 days (Figure 1)
- Data from Stratum 1 and 2 were combined for analysis to obtain greater statistical power, all *P* values and hazard ratios (HR) were adjusted for the strata.
- Elevated baseline of blood biomarkers were defined as:
  - CgA levels >2× upper limit of normal (ULN) (2× 36.4 ng/mL) and NSE levels >ULN (8.6 ng/mL)
- Biomarker blood samples were repeated monthly if >ULN at baseline collection.
- Early CgA and/or NSE responses were defined as a ≥30% decrease from baseline or normalization at week 4.
- Progression-free survival (PFS) and overall survival (OS) distributions were estimated using the Kaplan-Meier method and all comparisons used a 2-sided stratified log-rank test.
- HR was obtained using a stratified Cox model, adjusted for the two strata.

Figure 1. Trial Design

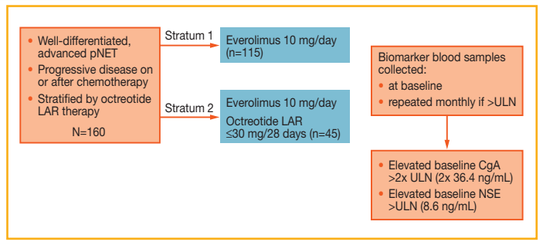


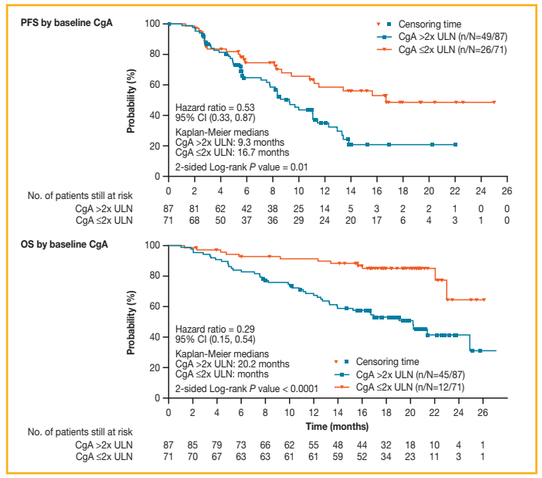
Table 1. Disease Characteristics by Baseline Biomarkers

	Non-elevated CgA Non-elevated NSE n=53	Elevated CgA Non-elevated NSE n=40	Non-elevated CgA Elevated NSE n=17	Elevated CgA Elevated NSE n=46
Histological grade, n (%)				
Well differentiated	41 (77.4)	32 (80.0)	13 (76.5)	35 (76.1)
Moderately differentiated	9 (17.0)	7 (17.5)	3 (17.6)	8 (17.4)
Undifferentiated	0	0	0	1 (2.2)
Unknown	3 (5.7)	1 (2.5)	1 (5.9)	2 (4.3)
Median time since first diagnosis Months (range)	46.3 (4.0–231.7)	47.5 (4.2–189.8)	48.9 (4.0–118.9)	42.0 (4.2–178.6)

RESULTS

- Disease characteristics by baseline biomarkers are shown in Table 1.
- PFS and OS were significantly longer for patients without elevated baseline levels of CgA (Figure 2 and Table 2):
  - PFS with elevated versus non-elevated CgA was 9.3 months versus 16.7 months, respectively [HR=0.53; *P*=0.01]
  - OS with elevated versus non-elevated CgA was 20.2 months versus not yet reached, respectively [HR=0.29; *P*<0.0001]

Figure 2. PFS and OS of Patients by Baseline CgA



- PFS and OS were significantly longer for patients without elevated baseline levels of NSE (Figure 3 and Table 2):
  - PFS with elevated versus non-elevated NSE was 7.5 months versus 15.6 months, respectively [HR=0.42; *P*=0.0002]
  - OS with elevated versus non-elevated NSE was 16.6 months versus not yet reached, respectively [HR=0.33; *P*<0.0001]

Figure 3. PFS and OS of Patients by Baseline NSE

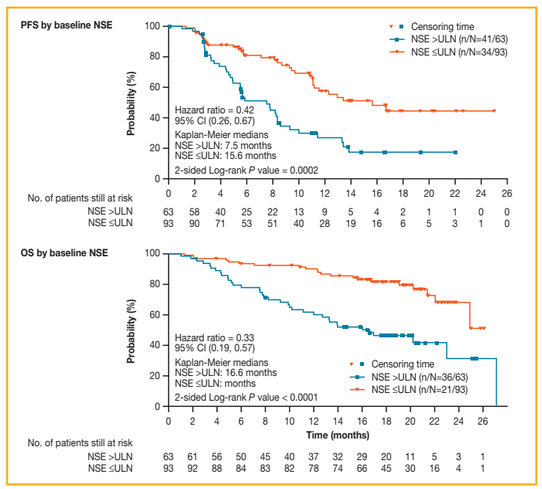


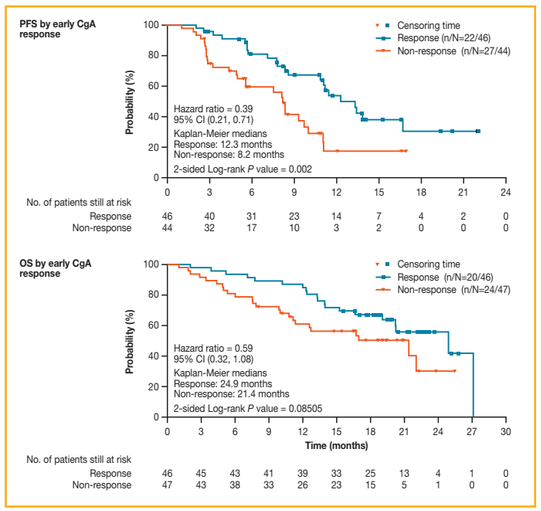
Table 2. PFS and OS of Patients by Baseline CgA and NSE

	Non-elevated CgA Non-elevated NSE n=53	Elevated CgA Non-elevated NSE n=40	Non-elevated CgA Elevated NSE n=17	Elevated CgA Elevated NSE n=46
Median PFS, months (95% CI)	NR (11.53, NR)	11.1 (9.26, NR)	5.9 (2.73, NR)	7.8 (4.9, 8.57)
Median OS, months (95% CI)	NR (NR, NR)	24.9 (19.06, NR)	23.0 (16.03, NR)	12.7 (7.85, 16.95)

NR = not (yet) reached

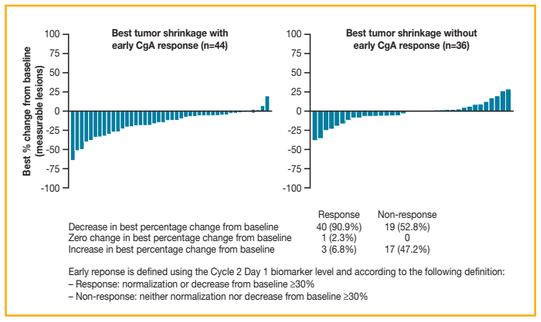
- PFS was longer among patients with early CgA response to everolimus-based therapy than among patients not achieving an early response (Figure 4):
  - Median PFS for patients without early CgA response versus early response was 8.2 months versus 12.3 months, respectively [HR=0.39; *P*=0.002]

Figure 4. PFS and OS of Patients by Early CgA Response



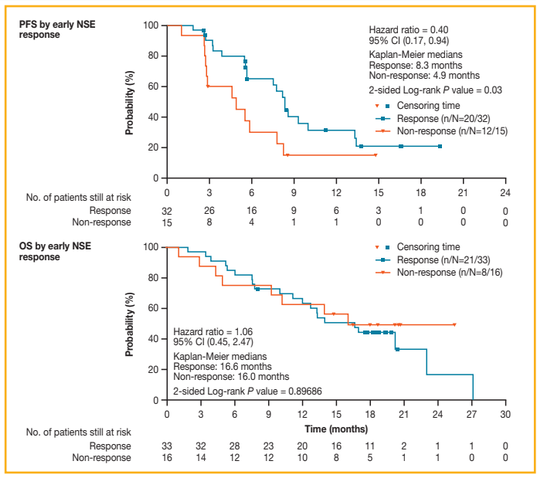
- Per central radiology review, a measurable tumor reduction (best percentage decrease from baseline) was seen in 90.9% of patients with early CgA response (40/44) compared to 52.8% (19/36) without an early CgA response (Figure 5).

Figure 5. Waterfall Plots of Best Tumor Shrinkage by Early CgA Response



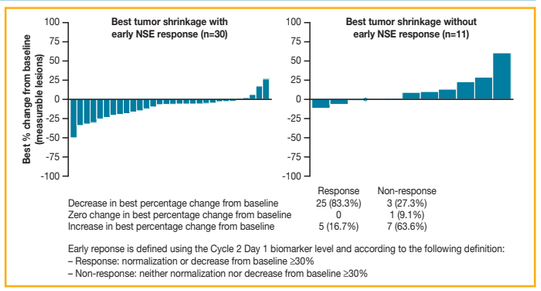
- PFS was longer among patients with early NSE response to everolimus-based therapy than among patients not achieving an early response (Figure 6):
  - Median PFS for patients without early NSE response versus early response was 4.9 months versus 8.3 months, respectively [HR=0.40; *P*=0.03]

Figure 6. PFS and OS of Patients by Early NSE Response



- Per central radiology review, a measurable tumor reduction (best percentage decrease from baseline) was seen in 83.3% of patients with an early NSE response (25/30) compared to 27.3% of patients (3/11) without an early NSE response (Figure 7).

Figure 7. Waterfall Plots of Best Tumor Shrinkage by Early NSE Response



CONCLUSIONS

- **Elevated baseline levels of either CgA or NSE were associated with shorter median PFS and OS in patients treated with everolimus.**
- **An elevated baseline level of both CgA and NSE was associated with the shortest median PFS and OS in patients treated with everolimus.**
- **An early reduction in either CgA or NSE in response to everolimus-based therapy correlated with longer PFS and OS.**
- **An early response to everolimus treatment in either CgA or NSE levels correlates with an increased probability of tumor reduction.**
- **Early CgA and NSE responses to everolimus-based therapy hold promise as predictive biomarkers for favorable PFS outcome in patients with pNET.**
- **Baseline CgA and NSE are prognostic biomarkers for PFS and OS among patients with pNET treated with everolimus.**

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