MEN1/*DAXX* alterations are associated with improved overall survival and treatment response in patients with pancreatic neuroendocrine tumors

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Introduction

- Alterations in the *MEN1* and *DAXX* genes are common in pancreatic neuroendocrine tumors (PNETs).
- Approximately 40-50% of sporadic PNETs are reported to have somatic *MEN1* mutations.[1]
- Approximately 45%, may show mutations in the *DAXX* gene.[1]
- Previous data show that *MEN1*- and *DAXX*-altered tumors show longer overall survival in patients with metastatic PNETs.[2]
- These alterations may increase radiation sensitivity in tumor cells.[3]
- We explored the associations of *MEN1* and *DAXX* alterations with clinical outcomes in PNETs, with a focus on three treatments: peptide receptor radionuclide therapy (PRRT; utilizing ^{177}Lu-DOTATATE), capecitabine/temozolomide (CAPTEM), and surgical debulking.

Methods

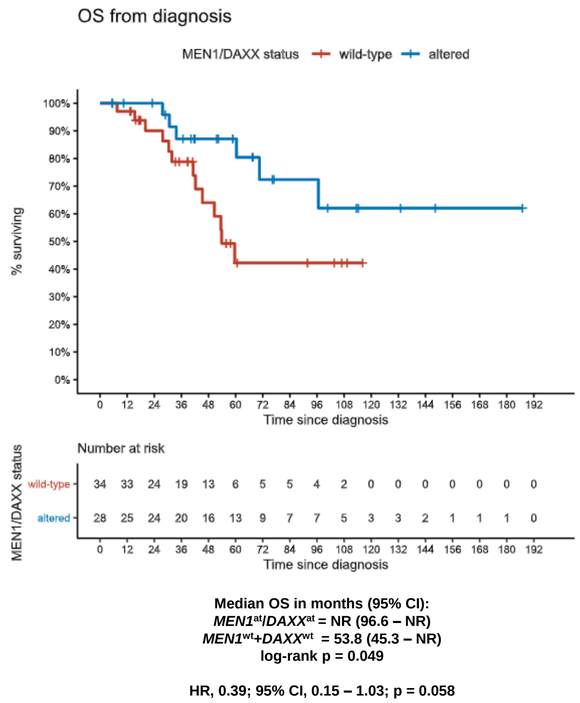
- A retrospective chart review was conducted.
- PNETs seen between 2013 to 2024 at a specialized tertiary NET center with tumor based NGS were included.
- Cases with deleterious alterations (truncating mutations, missense mutations considered pathogenic, copy number losses) in the *MEN1* and *DAXX* genes were considered as *MEN1*/*DAXX* altered (*MEN1*/*DAXX*^{at}).
- The primary outcome was OS.
- The secondary outcome was progression free survival (PFS), after PRRT, CAPTEM, and surgical debulking.
- Study outcomes were analyzed using Kaplan Meier estimations, log-rank tests, and Cox proportional hazards regression analyses.

Results

Table 1. Clinicopathological characteristics of the study cohort stratified by *MEN1*/*DAXX* status

	MEN1^{at}/*DAXX*^{at}		*MEN1*^{wt}+*DAXX*^{wt}		p-value
	n	%	n	%	
Number	28		34		
Male SAAB (vs. Female)	16	57.1%	19	55.9%	0.99
Median Age at Diagnosis (IQR)	54.2 (46.0 - 59.1)		55.5 (40.4 – 60.8)		0.99
Grade 3 (vs. 2/1)	2	7.1%	12	35.3%	0.01
Metastases at Presentation	22	78.6%	26	76.5%	0.99
Extrahepatic Metastases	11	39.3%	12	35.3%	0.8
Bone Metastases	2	7.1%	7	20.6%	0.17
Baseline chromogranin A levels > 2 ULN (N = 51)	10/25	40%	13/26	50%	0.58

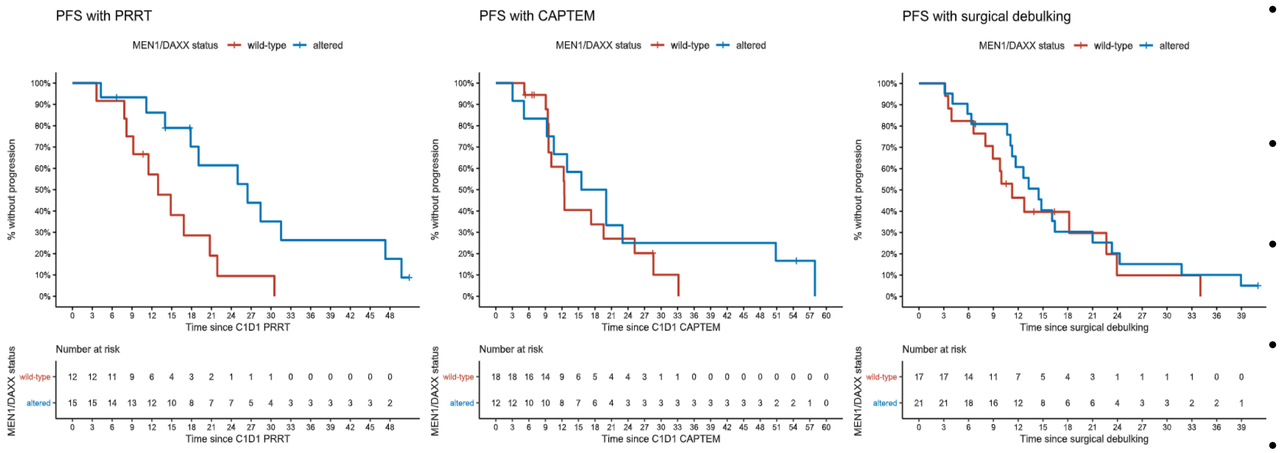
MEN1^{at}/*DAXX*^{at} = alteration in either *MEN1*/*DAXX*; *MEN1*^{wt}+*DAXX*^{wt} = wild-type for **both** *MEN1* and *DAXX*; SAAB = Sex Assigned at Birth; ULN = Upper Limits of Normal.



Median OS in months (95% CI):
***MEN1*^{at}/*DAXX*^{at} = NR (96.6 – NR)**
***MEN1*^{wt}+*DAXX*^{wt} = 53.8 (45.3 – NR)**
log-rank p = 0.049

HR, 0.39; 95% CI, 0.15 – 1.03; p = 0.058

Figure 1. Kaplan-Meier plot for overall survival after diagnosis



Median PFS in months (95% CI):
***MEN1*^{at}/*DAXX*^{at} = 26.5 (17.9 – NR)**
***MEN1*^{wt}+*DAXX*^{wt} = 12.9 (9.2 – NR)**

HR, 0.30; 95% CI, 0.12 – 0.77; p = 0.01

Median PFS in months (95% CI):
***MEN1*^{at}/*DAXX*^{at} = 17.8 (10.5 – NR)**
***MEN1*^{wt}+*DAXX*^{wt} = 12.4 (9.6 – NR)**

HR, 0.65; 95% CI, 0.28 – 1.53; p = 0.32

Median PFS in months (95% CI):
***MEN1*^{at}/*DAXX*^{at} = 14.5 (11.3 – 23.3)**
***MEN1*^{wt}+*DAXX*^{wt} = 11.3 (8.9 – NR)**

HR, 0.77; 95% CI, 0.38 – 1.55; p = 0.46

Figure 2. Kaplan-Meier plots for progression free survival after PRRT, CAPTEM, and surgical debulking

MEN1/*DAXX* alterations were associated with:

- **Significantly longer PFS with PRRT [^{177}Lu-DOTATATE]. (mPFS, 26.5 months vs. 12.9 months; p = 0.01)**
- **Significantly longer OS from diagnosis. mOS, NR vs. 53.8 months; log-rank p = 0.049).**
- Median Follow-up among survivors = 51.6 months.

No differences noted in:

- No significant difference in PFS after CAPTEM.
- No significant difference in PFS after surgical debulking for metastatic disease.

Conclusions and Limitations

- Our analysis of survival outcomes and real-world treatment outcomes in patients with PNETs treated showed that *MEN1*/*DAXX* alterations may hold prognostic relevance.
- Progression free survival with PRRT was prolonged for patients with *MEN1*/*DAXX* alterations.
- Patients with *MEN1*/*DAXX* alterations also showed improved overall survival from diagnosis as well as date of metastases.
- The retrospective and single-center nature of our study limits the generalizability of our results and external validation is necessary.
- Prospective evaluations are warranted to further investigate the prognostic and predictive significance of these alterations in PNETs.

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