Distinctive Chromosomal Instability (CIN) Patterns and its Prognostic Value in Pancreatic Neuroendocrine Tumors (pNET)

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Background: MEN1, DAXX and ATRX are frequently mutated in pNET. Their associations with chromosomal aberrations, disease progression, and efficacy of targeted therapy have not been established. We explored these biomarkers in patients from RADIANT-3, a randomized phase 3 trial of everolimus (EVE) vs placebo in advanced pNET (Yao JC et al, NEJM 2011).

Methods: Mutations and copy number analysis was performed on 65 archival tumor samples (15% of the trial population) using next-generation sequencing. Cox PH modeling was used to assess the association between groups defined by CIN and clinical outcome.

Results: MEN1, DAXX, and ATRX were mutated in 42, 28, and 11% of pNET, respectively. DAXX and ATRX mutations were mutually exclusive; while 60% of DAXX and no ATRX mutation co-exist with MEN1. Three distinct CIN patterns were identified based on 2 mutually exclusive sets of chromosome aberrations; group 1 with loss of heterozygosity (LOH) in 1st set of chromosomes; group 2 with copy-neutral LOH in 1st set and gains in 2nd set of chromosomes; and group 3 with no recurring gains or loss. MEN1/DAXX/ATRX mutations were associated with CIN in group 1 and 2 ($P < 1.8 \times 10\text{-}10$; Table).

Group 1 and 2 had better prognosis than group 3 (median overall survival, 62.6 vs 37.9 mo; HR 1.86; 95% CI 0.96-3.6). All patients derived similar PFS benefit from EVE over placebo (Table), consistent to that observed in overall study population (median PFS, 11.0 vs 4.6 mo; HR 0.35; 95% CI 0.27-0.45, $P < 0.001$).

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Conclusion: pNET showed 3 distinct CIN groups, with two groups tightly associated with commonly mutated genes. These molecular subtypes may have different disease prognosis, but all benefited similarly from EVE. Results upon statistical validation in larger cohorts may have far-reaching clinical applications.

Table 1:

CIN Group N = 65 (n/%)	% Samples with MEN1, DAXX or ATRX aberrations	Median PFS (EVE vs PBO, mos) HR (95% CI)	Copy number aberrations	Copy number aberrations
			Chromosome: 1, 2, 3, 6, 8, 10, 11, 15, 16, 21, and 22	Chromosome: 4, 5, 7, 9, 12, 13, 14, 17, 18, 19, and 20
Group 1 (30/46)	97	12.5 vs 5.4 0.45 (0.21-10)	LOH	Wild-type
Group 2 (5/8)	100	12.5 vs 5.4 0.45 (0.21-10)	Copy-neutral LOH	Gain
Group 3 (30/46)	23	10.8 vs 4.6 0.57 (0.22-1.46)	Mostly wild-type	Mostly wild-type