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Translational biomarkers in G2-3 NENs: Analysis from NET-001 and NET-002 trials

Jose E. Nunez[1], Jeffrey Bruce[2], Arnavaz Danesh[2], David L. Chan[3], Victor Rodriguez-Freixinos[4], Julie Hallet[1], Sten Myrehaug[1], Calvin Law[1], Trevor Pugh[2], Simron Singh[1].

[1]Sunnybrook Health Sciences Centre, [2]University Health Network, [3]University of Sydney, [4]Debiopharm.

BACKGROUND

The treatment of neuroendocrine neoplasms (NENs) of higher grade remains a dilemma. In these patients the role of immunotherapy is still unclear and predictive biomarkers are an unmet need. Herein, we present a revised translational analysis of the NET001 and NET002 (NCT03278405, NCT03278379) clinical trials.

METHODS

Patients with advanced WHO G2-3 NENs who had a gastroenteropancreatic (GEP) or a bronchial primary (excluding typical carcinoid) and had 0-2 prior lines of systemic therapy were given avelumab 10mg/kg/iv every 2 weeks as their treatment. NET001 explored G3 neuroendocrine carcinomas (NECs) with poor differentiation (PD), whereas NET002 investigated G2-3 well differentiated (WD) neuroendocrine tumors (NETs). We identified genetic abnormalities in pre-treatment samples by doing whole-exome sequencing and whole transcriptome RNA sequencing in order to find potential predictive biomarkers.

RESULTS

This analysis included samples from seven patients (2 small bowel, 1 pancreas, 1 lung, and 3 others; 4 from NET-001 and 3 from NET-002). Four samples were previously discarded as a result of contamination and sample exchange problems. The median age was 72 (range: 37-80), 28% of patients had ECOG PS 1-2, and 71% had prior therapy with 1 or more lines. The median Ki-67 index was 50% (10-100). The median progression free survival (PFS) was 60 days (NET-001 median PFS = 44 days versus NET-002 median PFS = 69 days, p=0.19) and the median overall survival (OS) was 85 days (NET-001 median OS=75 days versus NET-002 median OS = 85 days, p=0.78). Exome sequencing revealed only one RB1 mutation and one MEN1 mutation in a PD NEC and a WD NET, respectively. Two PD NECs exhibited p53 mutations. In PD NECs, differential gene expression analysis revealed that stem-cell-associated genes such as E2F1/2/7/8, SOX2, and 17 HOX genes were overexpressed (fdr<0.05). Neither the tumor mutational burden (TMB) nor PD-L1 expression differed significantly between WD NETs and PD NECs. Interestingly, TMB was approximately 10 per MB within all the samples.

CONCLUSIONS

Patients with Grade 2-3 NENs who were treated with avelumab exhibited a distinct genomic and transcriptomic profile, according to our observations. There was no discernible difference in the expression of TMB or PD-L1 between PD NECs and WD NETs. In addition to that, a high TMB was found in all the samples. The development of more accurate predictive biomarkers for NENs should be a primary focus of future translational research.

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