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Abstracts

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Guest Editors
Furio Pacini, Siena, Italy
Clara V. Alvarez, Santiago de Compostela, Spain
The observations infer Foxa1 and Foxa2 as novel biomarkers of neuroendocrine thyroid cancer. While Foxa1 seems to participate in MTC tumor cell proliferation Foxa2 may promote the tumor epithelial phenotype that is transiently lost in invasive MTC cells. Distinct functions of Foxa1 and Foxa2 in tumors may be related to the evolutionary determined diversification of these two gene paralogs.

**OP18**

**EXOME SEQUENCING REVEALS THAT SOS1 GENE MUTATIONS CAUSE A SYNDROME WITH PHENOTYPIC FEATURES OF MULTIPLE ENDOCRINE NEOPLASIA TYPE 2B BUT NO ENDOCRINOPATHY**

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**Objective:** Multiple Endocrine Neoplasia type 2B (MEN2B) is characterized by medullary thyroid carcinoma (MTC), phaeochromocytoma, and typical physical features (including mucosal neuromas, Marfanoid habitus and prominent corneal nerves). Rarely, patients present with physical features of MEN2B without endocrinopathy or RET gene mutations, thought to represent a distinct subgroup termed ‘mucosal neuroma syndrome’. We aimed to investigate genetic basis of this syndrome.

**Methods:** We studied two families. *Family 1:* 13-year-old girl presented with photophobia. She had prominent corneal nerves, mucosal neuromas and Marfanoid habitus (Spyer et al., 2006). Urinary catecholamines were normal but pentagastrin-stimulated calcitonin levels were equivocal (baseline 0.09 μg/L, peak 0.14 μg/L). She underwent prophylactic thyroidectomy; histology was normal. Subsequent genetic testing showed no RET gene mutations. Her parents are unaffected. *Family 2:* 37-year-old man also presented with eye symptoms and was found to have prominent corneal nerves, mucosal neuromas and Marfanoid habitus. Plasma metanephrines and pentagastrin-stimulated calcitonin levels were normal. No RET mutations were detected. His 64-year-old mother has similar clinical features and no biochemical evidence of endocrinopathy. We undertook exome sequencing in the probands to detect a shared gene with a rare or novel non-synonymous variant.

**Results:** We identified a heterozygous *SOS1* frameshift mutation, c.3248dup or c.3266dup, in each family. Sanger sequencing showed that the c.3248dup mutation had arisen de-novo in the proband of Family 1 and the c.3266dup mutation was inherited from the proband’s affected mother in Family 2. SOS1 is a RAS-specific guanine nucleotide exchange factor which catalyses the activation of the RAS-MAPK pathway. The c.3248dup mutation has previously been reported in patients with Hereditary Gingival Fibromatosis, and generates a truncated protein lacking functional domains that maintain the down-regulated state.

**Conclusions:** Our results demonstrate the existence of mucosal neuroma syndrome as a clinical entity distinct from MEN2B that can now be diagnosed by genetic testing.

**OP19**

**EFFICACY AND SAFETY OF VANDETANIB IN AGGRESSIVE AND SYMPTOMATIC MEDULLARY THYROID CANCER (MTC) – POST-HOC ANALYSIS FROM THE ZETA TRIAL (NCT00410761)**

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In the Phase III ZETA trial (JCO 2012;30:134–141), vandetanib conferred a statistically significant progression-free survival (PFS) benefit versus placebo for patients with measurable, unresectable locally advanced or metastatic, hereditary or sporadic MTC. Based on ZETA, vandetanib was approved in the EU for the treatment of a smaller cohort: aggressive and symptomatic MTC.

**Objectives:** This analysis determined PFS, objective response rate (ORR), and adverse events (AEs) for vandetanib versus placebo among a sub-population of ZETA patients with symptomatic and progressive disease, reflecting EU approval.

**Methods:** Patients with symptomatic and progressive disease at baseline were identified. ‘Progressive’ was defined as documented progression ≤12 months prior to enrolment and ‘symptomatic’ defined as at least one of the following symptoms at baseline: pain score >4, ≥10 mg/day opioid use, diarrhoea, flushing, fatigue, pain, nausea, dysphagia, dysphonia, respiratory symptoms, weight loss. Endpoints: Central Read PFS, investigator-assessed PFS, ORR, AEs grade ≥3.

**Results:** Of the 331 ZETA patients, 186 had symptomatic and progressive disease at baseline (126 vandetanib; 60 placebo). After discontinuation of randomized drug open-label vandetanib was started in 38 (88%; placebo arm) and 26 (38%; vandetanib arm) patients. PFS and ORR are presented in the table below. Seventy-seven (61%) of vandetanib-treated patients and 14 (24%) placebo-treated patients had AEs grade ≥3.

**Conclusions:** Vandetanib is well tolerated and offers clinical benefit over a wide spectrum of patients with MTC, with a statistically significant prolonged PFS among ‘symptomatic and progressive disease’ patients from ZETA, in line with the EU label.

**Table 1.** (for Abstract OP19)

<table>
<thead>
<tr>
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<th>Median PFS (months)</th>
<th>Hazard ratio</th>
<th>P value</th>
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<tr>
<td></td>
<td>Vandetanib (n = 126)</td>
<td>Placebo (n = 60)</td>
<td></td>
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<tr>
<td>Central Read, excluding open-label vandetanib</td>
<td>30.11</td>
<td>11.1</td>
<td>0.32</td>
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<tr>
<td>Investigator-assessed</td>
<td>22.1</td>
<td>8.3</td>
<td>0.33</td>
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<tr>
<td>ORR, n (%)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Vandetanib (n = 126)</td>
<td>Placebo (n = 60)</td>
<td>Odds ratio</td>
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<tr>
<td>55 (43.7%)</td>
<td>1 (1.7%)</td>
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<td>45.70</td>
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1Median not reached. The reported median is estimated based on a Weibull model.