133 gene panel reported no germline mutations in menin, RET, CDKN1B, NF12, VHL, SDH and other genes tested but there were variants of uncertain significance (VUS) identified in CHEK2 c.14C>T (p.Ser5Leu) and PTCH2 c.2812G>A (p.Gly938Ser). Patient successfully underwent left adrenalectomy after alpha blockage. Paired tumor-normal sequencing of the resected tumor detected a pathogenic deletion frameshift mutation in NF1 with loss of heterozygosity (LOH) along with copy number alterations with losses in 1p34.1-p11.2, 11p11.2-15.4, 11q14.1-q25 and 17q11.2 (including NF1). VUSs were also detected including CDKN1A C117Y variant, and CHD2P80L. Since germline and tumor testing failed to reveal any known pathogenic variants, whole exome sequencing (pending) will be pursued.

The presentation with RCC, pheochromocytoma, pituitary adenoma and parathyroid adenoma is consistent with a MEN syndrome in this patient despite no known pathogenic MEN mutations detected. Somatic mutation in NF1 is a common finding in pheochromocytoma. The biochemical phenotype of pheochromocytoma (elevated metanephrines) is consistent with cluster 2 tumors of kinase signaling pathway as seen in tumors of MEN syndrome and neurofibromatosis. We hope to gain more insight via whole exome sequencing to evaluate for potential novel gene mutation(s).

Reproductive Endocrinology

CHALLENGES IN REPRODUCTIVE ENDOCRINOLOGY: LATE BREAKING INSIGHTS

NT-814, a Non-Hormonal Dual Neurokinin 1,3 Receptor Antagonist Markedly Improves Vasomotor Symptoms in Post-Menopausal Women; Results of a Randomised, Double-Blind, Placebo-Controlled, Dose-Finding Study (SWITCH-1)

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Introduction: Vasomotor symptoms (VMS), caused by declining estrogen in menopausal women, are common and debilitating. Hormone therapy is effective in many women but carries risks and may be contraindicated. Biological and clinical evidence shows a modulatory role for neurokinin (NK) receptor antagonists acting primarily via hypothalamic KNDy (kisspeptin, NK, dynorphin) neurons on VMS. NT-814 is an oral non-hormonal dual NK1,3 receptor antagonist which has previously been shown to cause rapid and marked improvements in VMS in post-menopausal women. This Phase-2b trial (SWITCH-1) was undertaken to further evaluate efficacy and safety and to establish the optimum dose(s) for Phase 3 studies.

Methods: SWITCH-1 was a double-blind, placebo-controlled, adaptive-randomization, dose-finding trial in 199 post-menopausal women. After a 2-week single-blind placebo run-in to establish symptom stability, women (40 to 65 years) with ≥7 moderate and/or severe VMS per day at baseline were randomized to 12 weeks of once daily treatment with placebo or one of 4 doses of NT-814: 40 mg, 80 mg, 120 mg, 160 mg. Subjects recorded the frequency and severity of VMS in electronic diaries twice daily throughout the study. Patient-reported measures of quality-of-life, sleep and mood were collected periodically. Adverse events (AEs) were recorded at each clinic visit.

Results: VMS frequency was reduced in all treatment groups, including placebo. VMS reductions were significantly greater with the 2 higher NT-814 doses at most timepoints, as early as the first week of treatment. Least squares mean reductions from baseline in moderate/severe VMS per day at week 4 were: placebo, 2.7; 40 mg, 4.3 (p=0.161 vs placebo); 80 mg, 4.1 (p=0.326); 120 mg, 6.7 (p<0.0001); 160 mg, 5.5 (p=0.007). In week 12 the reductions were: placebo, 4.7; 40 mg, 6.5 (p=0.185); 80 mg, 5.6 (p=0.599); 120 mg, 7.8 (p=0.009); 160 mg, 6.6 (p=0.109). At the 160 mg dose the median reduction in week 12 was significantly greater than placebo (6.9 vs 4.4, p=0.0023), indicating an effect of high outliers on the mean. Average HF severity was also improved in a dose-related manner, with greater reductions compared to placebo with the 2 higher NT-814 doses. Improvements in HF were accompanied by statistically significant benefits on sleep (assessed using the Insomnia Severity Index and Pittsburgh Sleep Quality Index), mood (measured using the Beck Depression Inventory), and all four domains of the MenQoL menopause-specific quality-of-life instrument. NT-814 was well-tolerated; most AEs were mild or moderate and there were no serious AEs related to treatment.

Conclusions: NT-814, a once daily non-hormonal NK antagonist, at doses of 120 & 160 mg reduced the frequency and severity of VMS and significantly improved quality of life, mood and sleep, in postmenopausal women. NT-814 was well tolerated, with a safety profile that supports further evaluation in Phase 3 trials.

Tumor Biology

ENDOCRINE NEOPLASIA CASE REPORTS III

Case of the Broken Hearted

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Phaeochromocytomas are rare neuroendocrine tumours which, usually present with headache, diaphoresis, episodic tachycardia and hypertension. Takotsubo-pattern cardiomyopathy is an unusual initial presentation of phaeochromocytomas, however has been reported[1]. Approximately 10% of phaeochromocytomas present with cardiomyopathy. It is associated with a high mortality risk and early intervention with surgery is the key to recovery. We report a case of a previously healthy, 68 year old man who presented with symptoms of left ventricular failure, and feeling anxious. Physical examination