OR05-06
There is strong interest in targeting the androgen receptor (AR) in estrogen receptor (ER) positive breast cancer, but widespread confusion exits as to what therapeutic strategy - agonism or antagonism - is appropriate. Current understanding of AR predominantly stems from the field of prostate cancer, where AR is the key oncogenic driver and therapeutic target. An ensuing assumption is that AR promotes malignancy in breast cancer and should be therapeutically antagonised. However, compelling pre-clinical data to support this assumption is lacking. Since estrogen stimulates and androgen inhibits the development of normal breast tissue, we hypothesized that AR acts as a tumour suppressor in the breast and that AR agonism is the appropriate therapeutic strategy for ER-driven breast cancer. We tested this hypothesis using a large suite of cell line and patient-derived explant (PDE) and xenograft (PDX) models of breast cancer, including those that were resistant to current therapies and those harbouring genomic anomalies of ESR1 associated with treatment-resistant disease. Across the diverse models we found compelling evidence that AR agonism, but not antagonism, potently and durably inhibited tumour growth. A signature of AR activity derived from the xenograft models positively predicted disease survival in multiple large clinical cohorts of ER+ breast cancer, out-performing other breast cancer-specific prognostic signatures. We also show that an AR agonist can be combined with current ER target therapies such as Tamoxifen or a CDK4/6 inhibitor to maximize growth inhibition. Mechanistically, agonist-bound AR opposed ER signalling by repositioning ER and the co-activator p300 in the chromatin landscape, resulting in down-regulation of cell cycle genes. Introduction of an AR DNA binding mutant had no effect on ER signalling or estrogen-stimulated growth in ER- lines and ER+ tumours that provide a new understanding of AR activity and clearly show differences to those associated with prostate cancer cell lines and tumours. In conclusion, our data provides a compelling biological rationale for AR agonism as a therapeutic strategy in multiple, clinically relevant contexts of ER-positive breast cancer. These findings should dispel widespread confusion over the role of AR in ER-driven breast cancer, an issue that currently hinders progress in leveraging modern AR-targeted therapies (e.g. selective androgen receptor modulators) that lack the undesirable side-effects of androgens for clinical benefit.

SAT-477
Background: Pembrolizumab (PD-1) is an immune checkpoint inhibitor used for treating melanoma and has been associated endocrine immune-related adverse events.

Case Presentation: 76-year-old Caucasian male presented for evaluation of abnormal thyroid labs. Significant co-morbidities included recurrent melanoma, heart failure, atrial fibrillation, coronary artery disease, type 2 diabetes, hypertension. Patient’s melanoma was being treated with Pembrolizumab. Further history revealed no family/personal history of thyroid disease but a history of mouth cancer treated with radiation over 30 years ago. He denied any recent glucocorticoid or biotin use. Symptoms included worsening fatigue, weight loss, and diarrhea. He was afebrile and vitally stable. Physical exam was unremarkable. Prior to this year, patient had normal thyroid labs. Recent thyroid labs showed TSH of 0.01 uIU/mL (normal 0.34-4.94 uIU/mL), confirmed with repeat labs a week later (TSH: < 0.01, Free T4: 2.23 ng/dL, normal Free T4: 0.7-1.48 ng/dL). There was a high suspicion that these labs were related to Pembrolizumab, but other etiologies were evaluated. Completed thyroid uptake and scan showed no evidence of increased activity (4-hour uptake: 1.6%, 24-hour update: 1.2%). Repeat thyroid labs indicated recovering thyroid function with a TSH: 0.14 uIU/mL, Free T4: 0.49 ng/dL, Free T3: 1.5 pg/mL (normal Free T3 2.3-4.2 pg/mL), TSI: 96% (normal < 140%), TPO Ab: 111 IU/mL (normal TPO Ab < 9 IU/mL). One month later thyroid tests resulted as TSH: 72.81 uIU/mL, Free T4: < 0.40. He was started on levothyroxine, which was titrated over several weeks.

Discussion: Pembrolizumab (PD-1) is an IgG4 programmed cell death 1-directed monoclonal antibody, whose mechanism of action is to inhibit cancer cells ability impede T-cell activation. However, because of this mechanism, some T-cells, will remain activated, leading to autoimmune diseases. PD-1 has been associated with thyroid dysfunction, with an incidence rate as high as 14-20%. The clinical presentation varies from isolated thyrotoxicosis to overt hypothyroidism. In our patient, he developed thyrotoxicosis with subsequent development of hypothyroidism. Generally, the timing of thyroid dysfunction after the initiation of PD-1 ranges from 3 to 40 weeks, with the median onset at week 6. Baseline TSH and free T4 should be obtained with rechecking of these labs monthly for the first 6 months. For patients who present with thyrotoxicosis, Grave’s disease should be ruled out, and initial treatment should include beta-blockers. Hypothyroidism should be treated with levothyroxine with titration to normal thyroid function tests. What remains to be determined is the mechanism in which PD-1 causes thyroid dysfunction and if specific patient characteristics, such as thyroid antibodies, can be used to risk stratify the likelihood of a patient developing thyroid dysfunction.

Diabetes Mellitus and Glucose Metabolism

TYPE 2 DIABETES MELLITUS

Fournier’s Gangrene and Diabetic Ketoacidosis Caused by Canagliflozin
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Thyroid

THYROID DISORDERS CASE REPORTS II

Melanoma Treated with Pembrolizumab Leading to Thyroiditis and Subsequent Hypothyroidism
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SUN-700

Introduction
Sodium glucose co-transporter 2 (SGLT2) inhibitors have become an appealing treatment for diabetes due to their favorable cardiac and renal outcomes. However, reports continue to emerge describing potentially life-threatening adverse events such as Fournier’s gangrene (FG) and diabetic ketoacidosis (DKA) associated with their use. Herein, we report a case of simultaneous FG and DKA in a patient taking canagliflozin.

Case Presentation
A 37-year-old woman with a history of type 2 diabetes mellitus, peripheral neuropathy, and morbid obesity (BMI of 45.8 kg/m²) presented to the hospital with left gluteal pain associated with dysuria despite 5-day treatment with trimethoprim/sulfamethoxazole for a presumed urinary tract infection. Approximately 1 month prior, sitagliptin and canagliflozin were added to her regimen due to poor glycemic control on metformin (HbA1c 9.8%). On examination her temperature was 36.9°C, pulse 117 beats/minute, blood pressure 144/79 mmHg and respiratory rate was 19 bpm. She appeared lethargic and had suprapubic tenderness and induration in the left gluteal region extending to the perineum. Laboratory findings revealed an arterial pH of 7.23 and PCO₂ of 34 mmHg, a blood glucose of 402 mg/dL, serum bicarbonate 12 mmol/L (20-30 mmol/L), an elevated anion gap of 24 mmol/L (7-17 mmol/L) and a lactate of 1.8 mmol/L. Urinalysis showed 4+ glucose and 1+ ketones. Serum β-hydroxybutyrate was 2.49 mmol/L (0.02-0.27 mmol/L). A CT scan of the abdomen and pelvis showed marked inflammatory changes with subcutaneous edema and air within the medial left gluteal soft tissues and locules of gas. Probable diagnosis was Fournier’s gangrene. The diagnoses of Fournier’s gangrene and DKA were made. The patient was started on empirical antibiotic treatment and required six surgical explorations with debridement. Interestingly, initial DKA management included only subcutaneous insulin. Only when serum ketones were identified and the anion gap persisted, insulin infusion with aggressive fluid resuscitation was initiated with successful resolution of anion gap metabolic acidosis. She was discharged with continued oral anti-diabetic medications. 

Discussion
To the best of our knowledge, this is the first case describing the simultaneous occurrence of two potentially fatal adverse effects of SGLT2 inhibitor therapy; Fournier’s gangrene and DKA. In light of the FDA’s warnings and the growing popularity of SGLT2 inhibitor therapy it is important to be mindful of their more serious and potentially fatal complications. It is also important to promptly terminate SGLT2 inhibitors when harmful adverse effects are suspected to prevent further progression.