that irreversibly inhibits generation of adrenal steroids, would have anti-tumour activity in ERα+ or ERα−/AR+ patients.
Patients and Methods: Post-menopausal women with ERα+ or ERα-/AR+ advanced or metastatic breast cancer who had failed at least 2 lines of hormone therapies were enrolled on a phase I/II study of once daily abiraterone at increasing doses (250 to 2000 mg) in 6-patient cohorts. Abiraterone was initially administered as a single agent to allow endocrine evaluation, with low dose hydrocortisone being commenced for hypermineralocorticoid toxicity.
Results: To date, 18 patients have been treated in this ongoing phase I trial (250, 500 and 1000 mg dose levels). Abiraterone has been well-tolerated in this patient population with the majority of related adverse events (AEs) such as fatigue, nausea, anorexia, dyspnoea, dizziness and hot flushes, classified as Common Toxicity Criteria (CTCAE) grades 1 or 2. Hypokalemia was commonly seen as might be expected from a secondary mineralocorticoid syndrome; in 3 patients, CTCAE grade 3/4 hypokalemia occurred. This was easily and effectively managed with a combination of potassium supplementation, hydrocortisone (20 mg bd) and eplerenone (50–200 mg). CTCAE grade 3 neutropenia and grade 3 reduction in left ventricular ejection fraction were observed in one patient. To date, two patients on 1000 mg daily abiraterone have continued on study beyond 4 months. One of these patients has shown an unconfirmed partial response by RECIST criteria, with a 69% reduction in Ca15.3 tumour marker from baseline, following 4 cycles of treatment.
Conclusions: Abiraterone is well tolerated in advanced breast cancer patients with preliminary evidence of antitumour activity. Mechanism based side-effects eg. hypokalemia are the predominant AEs and are managed expectantly and effectively.

656 POSTER

Suppression of testosterone release by chronic administration of investigational novel metastin analogues in male dogs and monkeys, and in healthy male volunteers

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Background: Metastin/kisspeptin is the cognate endogenous ligand for GPR54 and a key regulator of the gonadotropin-releasing hormone (GnRH) system. We previously reported that chronic administration of novel investigational metastin analogues TAK-448 or TAK-683, strongly suppresses testosterone release in normal male rats with superior activity compared to leuprolide acetate (LA). Here, we describe the effects of chronic administration of TAK-448 or TAK-683 vs LA on testosterone (T) release in intact male dogs and monkeys, as well as a phase I evaluation of TAK-448 in healthy male volunteers.
Materials and Methods: Adult male beagle dogs and cynomolgus monkeys received continuous infusion of TAK-448, TAK-683 or LA subcutaneously (sc) using osmotic ALZET® mini pumps (n = 3 animals/group). Plasma T levels were determined by radioimmunoassay (RIA) in dogs and monkeys; plasma TAK-448 and/or TAK-683 levels in monkeys were measured by liquid chromatography-tandem mass spectrometry (LC/MS/MS). Healthy male volunteers (n = 30) aged ⩾50 yrs received an sc bolus of TAK-448 0.1 mg (Day 1), followed by 13 days' continuous sc infusion (TAK-448: 0.01, 0.1, 0.3, or 1 mg/day or placebo). Blood samples were collected at 6,12,24 hrs post-dose on days 2,4,8,11,14 to determine plasma T levels via RIA; tolerability of TAK-448 was also assessed.

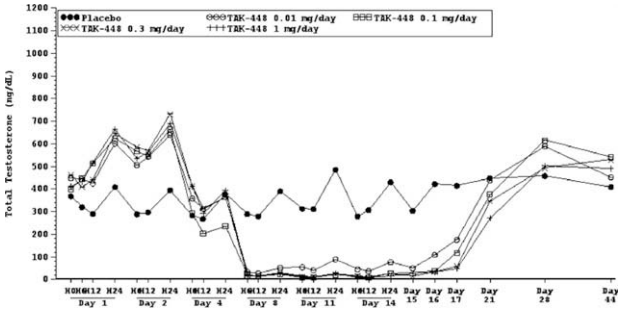

Figure. Mean testosterone concentrations in male volunteers (n = 30)

Results: Chronic administration of TAK-448 or TAK-683 exerted rapid and continuous suppressive effects on T release in a dose-dependent manner in dogs/monkeys. Suppression of T appeared greater with TAK-448 or TAK-683 vs LA, in terms of required dose and time to onset-of-effect. TAK-448 required 3-fold smaller dose than TAK-683 to achieve equivalent testosterone reduction both in dogs and monkeys. TAK-448 plasma concentrations at a given dose were approximately 3-fold higher than those of TAK-683. In healthy volunteers, continuous sc infusion of TAK-448 rapidly decreased T at all doses (Figure). 14/23 volunteers experienced an AE considered to be related to TAK-448.
Conclusions: TAK-448 and TAK-683 showed greater and more rapid reduction in plasma T vs LA in dogs and monkeys, and TAK-448 achieved superior *in vivo* T reducing activity compared with TAK-683. In healthy volunteers, continuous infusion resulted in rapid decreases in T levels. These findings suggest metastin analogues could be novel effective hormonal agents in prostate cancer therapy.

657 POSTER

Anti-tumor growth effect of TAK-683, a metastin analogue, in preclinical androgen-dependent prostate cancer models

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Background: The G-protein-coupled receptor GPR54 and its ligand metastin/kisspeptin are considered to play a pivotal role in the secretion of gonadotropin-releasing hormone (GnRH). We previously showed that chronic administration of metastin analogues, TAK-683 and TAK-448, reduced plasma testosterone levels in male SD rats. In this study, we compared the effects of chronic administration of TAK-683 with a GnRH analogue leuprolide acetate (LA) or orchiectomy (ORX) on testosterone levels and tumor growth in prostate cancer model *in vivo*.
Materials and Methods: (1) Tumor volume and plasma testosterone levels were assessed in male Copenhagen rats bearing subcutaneous R3327-G tumors (n = 7−8). Rats were treated with either ORX, chronic administration of TAK-683 (5.2, 16, or 52 nmol/kg/W) or LA (16, 52, or 700 nmol/kg/W), starting 12 days post-inoculation. (2) Serum prostate-specific antigen (PSA) levels as a biomarker of tumor growth were assessed in male F344/N nude rats bearing JDCaP human prostate cancer tumors, transplanted under the renal capsule (n = 7). Treatment involved either ORX, chronic administration of TAK-683 (10 or 50 nmol/kg/W) or LA (10 or 50 nmol/kg/W), starting 48 days post-tumor transplantation.
Results: In Copenhagen rats bearing R3327-G tumors, TAK-683 rapidly reduced testosterone vs LA. At 10 weeks after initiation of dosing, both TAK-683 (16 nmol/kg/W, p = 0.018) and LA (52 nmol/kg/W, p = 0.023) significantly reduced tumor volume compared with vehicle control. ORX showed a trend (p = 0.072) to reduce tumor volume in this setting. In nude rats bearing JDCaP xenografts, serum PSA levels were reduced below the detectable limit in all rats by Day 7 (ORX), Day 14 (TAK-683), or Day ⩾42 (LA) after treatment initiation; suggesting a more rapid PSA reduction by TAK-683 vs LA in this model. The observed PSA reducing effects associated with TAK-683 may reflect an earlier (vs LA) onset of testosterone reduction by metastin analogue.
Conclusions: TAK-683 exhibited anti-tumor activity in both the R3327-G and JDCaP prostate cancer models. Metastin analogues may have promise as potential new therapeutic agents for prostate cancer.

Immune system

658 POSTER

Prevalence, phenotype and prognostic significance of IL-17-producing cells infiltrating human colorectal cancers

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Background: Lymphocytic infiltration is known to be associated with a favourable prognosis in human colorectal cancer (CRC). In particular, the presence of CD8+ T cells and, unexpectedly, of Foxp3+ regulatory T cells, has been found to be associated with improved patient survival. Recent evidence suggests that IL-17 and T helper (Th) 17 cells might also have an impact on anti-tumour immune responses. We have investigated prevalence, phenotype and prognostic significance of IL-17-producing cells in human CRC.
Material and Methods: IL-17 expression was evaluated by immunohisto-chemistry on a tissue micro-array (TMA) including 1420 cases of primary