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Phase II study of AEZS-108 (AN-152), a targeted cytotoxic LHRH analog, in patients with LHRH receptor positive endometrial cancer. Protocol AGO-GYN 5, AGO Study Group, Germany

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Background: Gynecological cancers commonly express receptors for luteinizing hormone releasing hormone (LHRH-R). AEZS-108 (AN-152) is a targeted cytotoxic drug in which doxorubicin is linked to [D-Lys(6)]-LHRH. A phase I study in patients (pts) with LHRH-R positive tumors recommended a dose of 267 mg/m^2 by 2-hour intravenous infusion in 3-week cycles. We aimed to assess the efficacy and tolerability of AEZS-108 in endometrial cancer.
Material and Methods: Pts with histologically confirmed LHRH-R positive advanced (FIGO III or IV) or recurrent endometrial cancer received AEZS-108 for a planned duration of 6 treatment courses. At least 1 measurable lesion was required at baseline. An independent radiologic review was performed. Response rate per RECIST was defined as primary endpoint. Secondary endpoints were safety, time-to-progression (TTP) and overall survival (OS).
Results: In all, 43 pts with a median age of 68 years (range 25−88) entered the study. Tumors of all patients were confirmed as LHRH-R positive; percentages of tumor cells staining for LHRH-R ranged 30% to 90% (median 70%). 27 pts had primary diagnosis of EC FIGO III/IV. Majority of tumors with endometrioid (31 pts) or serous (8 pts) histology. Prior treatment included surgery (42 pts), radiotherapy (29 pts), chemotherapy (9 pts) and hormonal therapy (11pts). 28 pts (62.8%) received AEZS-108 for 6 courses (2 pts with 8 courses), only one pt was retreated at a reduced dose. Possibly drug related adverse events, except for hematologic toxicity Grade 3/4 (rapidly reversible neutropenia: 60%, anemia: 5%), was commonly limited to CTCAE grade 1/2. There was 1 pt each with febrile neutropenia and a Grade 2 hand-foot-syndrome. There was no evidence of cardiotoxicity in serial controls of LVEF. Only one pt stopped therapy for toxicity (recurrent anemia). Serial measurements of LH and FSH showed partial suppression (median 25−50%).
Independent review, which is currently ongoing, has confirmed the target minimum of 5 responses. Definite results for further reported responses with preliminary judgement as 4 CR, 10 PR and − at end of course 6 − 15 SD are expected.
Conclusions: AEZS-108 was well tolerated in pts with endometrial cancer and confirmed the recommended dose of 267 mg/m^2. Therapeutic activity exceeded the minimum response rate for continuing development. Follow-up is ongoing to define TTP and survival.
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A first in human phase I study of the proteasome inhibitor CEP-18770 in patients (pts) with advanced solid tumors, non-Hodgkin's lymphomas (NHL) and multiple myeloma (MM)

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Background: CEP-18770 (CEP) is a new boronic acid inhibitor of mammalian proteasome. Preclinical data showed antitumor activity in a wide range of solid and haematological malignancies. Aim of this multicentric study was to determine the CEP maximum tolerated dose (MTD) and its pharmacokinetic (PK) and proteasome inhibition (PD) profile, in pts with advanced solid tumors, NHL and MM.
Methods: Treatment consisted of D1, 4, 8, 11 i.v. administration Q21D for 6 cycles (cys), unless progression or toxicity. A modified accelerated dose titration design (2 cohorts) and a 3 + 3 dose-escalation design were followed. MTD was 1 level below the dose at which $\geqslant$2/6 pts experienced dose limiting toxicity (DLT) in the 1st cy. Eligible pts received $\leqslant$3 previous chemotherapies for advanced disease and $\leqslant$5 in case of MM. Adverse Events (AEs) were graded by the NCI CTCAE. Tumor response was assessed every 2 cys. PK and proteasome inhibition were evaluated on blood collected on cy 1.
Results: Thirty-one solid tumours and 7 MM were treated. Pts characteristics: median age 60 yrs (35−74), ECOG PS 0/1 39.5/60.5%, 34% received $\geqslant$2 lines prior therapy for metastatic disease and 42.9% of MM pts received bortezomib. Pts received a median of 2 cys (1−7). Eight dose levels were explored from 0.1 up to 1.8 mg/m^2; at MTD (1.5 mg/m^2) 16 pts were treated (7 MM). Three pts experienced DLTs: 1 at level 0.6 mg/m^2 (diarrhea G3) and 2 at level 1.8 mg/m^2 (the Maximum Administered Dose) respectively rash G3 in one pt and diarrhea/vomiting/anorexia/asthenia G3 in the other one. More frequent G1-G3 AEs were cutaneous (rash 50%, pruritus 10.5% and erithema 5.3%). Other common AEs, were asthenia (23.7%), stomatitis (21.1%), nausea and diarrhea (18.4%), anorexia (13.2%). Three possibly drug related Serious AEs were reported: asthenia, acute renal failure and pneumonia. Neurological effects were limited: 1 pt had paresthesia G2 and neuralgia G3, other 4 pts experienced neurotoxicity G1 without any evidence of cumulative toxicity. One pt experienced atrial fibrillation and palpitation G3. Two objective responses were recorded in MM pts both not previously treated with bortezomib; disease stabilization was reported in 15 pts (27%) for a median time of 4 mos. (2.8−6.1).
CEP showed a linear PK with about 50% inhibition of proteasome activity at the MTD (1.5 mg/m^2).
Conclusion: When administered on days 1, 4, 8, and 11 of a 21 day cycle, the MTD of CEP-18770 is 1.5 mg/m^2. The promising activity of CEP in 2 of 7 MM pts justifies further testing also in combination.

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Phase I trial of OXi4503: positron emission tomography (PET) analysis shows early effects on tumour perfusion that predict metabolic response

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Background: OXi4503 (OXiGENE Inc.) is the diphosphate pro-drug of combretastatin A1, a second-generation tubulin-binding vascular disruptive agent (VDA). As part of a phase I trial (Zweifel et al., ASCO Proceedings 2010), we used positron emission tomography (PET) analysis to assess the anti-vascular and metabolic effects of OXi4503 in normal and metastatic regions of interest (ROI; n = 28) in seven patients with advanced solid tumours.
Materials and Methods: [^{15}O]-H_2O and [^{18}F]-fluorodeoxyglucose (FDG) scans were performed before (baseline) and after (90 mins, 24 hrs and 28 days) administration of OXi4503 (1.92–15.4 mg/m^2) on days 1, 8 and 15 (1 cycle). FDG standardized uptake value (SUV) was semi-quantitatively derived to assess metabolic changes. The rate of tumour/tissue blood flow (TBF) and the volume of distribution (Vt; the partition co-efficient) were derived from compartmental blood flow modelling of [^{15}O]-H_2O scan data to assess perfusion.
Results: Analysis in all metastases showed mean TBF decreased by 22.8% at 24hrs post-infusion compared with baseline measurements (p = 0.006). Mean Vt decreased by 6.5% at 90 mins (p = 0.025) and 6% at 24 hrs (p = 0.028). Mean changes per patient are shown in Figs 1A+B. No significant changes were observed in normal tissues, showing a specificity of OXi4503 for tumour. Excluding one patient who showed rapid clinical progression, mean FDG decreased by 15% at 28 days (p = 0.015; Fig 1C), demonstrating inhibition of tumour growth in 6/7 patients. The % change in TBF at 24 hrs correlated significantly with % change in FDG at 28 days (p = 0.022; Fig 1D), indicating a predictive relationship between early mechanistic drug action and tumour response. When compared with an earlier PET study of combretastatin A4 phosphate (CA4P; Anderson et al., JCO 2003), similar acute changes were observed for TBF and cardiac output reductions. However, OXi4503 induced a greater reduction in mean TBF at 24 hrs compared with CA4P (22.8% vs 2%, respectively; p = 0.019), suggesting a more sustained effect. Different acute effects were also observed on normal kidney blood flow, with a reduction of 6.2% with