Conclusion: These data suggest safety and promising efficacy of oxaliplatin and pemetrexed for 2nd and 3rd line treatment of CRPC, with a majority of patients achieving stable disease or better.

7028 POSTER

Dasatinib and docetaxel combination treatment for patients with metastatic castration-resistant prostate cancer (CRPC): analysis of Study CA180−086

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Background: SRC and SRC-family kinases (SFK) play a key role in proliferative, invasive, and bone-metastatic processes in solid tumors. Dasatinib (Bristol-Myers Squibb) is a potent SRC and SFK inhibitor that inhibits prostate cancer cell proliferation and migration *in vitro*. In clinical studies, dasatinib treatment was associated with downregulation of osteoclast activity and bone turnover. Following preliminary reports from Study CA180−086 (ASCO 2009, abs. 5061), we report an intent-to-treat analysis for dasatinib and docetaxel combination treatment 5 months after completion of accrual.
Methods: CA180−086 is a phase 1/2 study in men with CRPC progressing despite castrate levels of testosterone (⩽50 ng/dL) and requiring chemotherapy. Patients (pts) (phase 1) received dasatinib 50–120 mg once daily (QD) and docetaxel 60−75 mg/m^2 every 21 days (Q21D), with selected doses of dasatinib 100 mg QD plus docetaxel 75 mg/m^2 Q21D and prednisone 5 mg twice daily administered to all pts enrolled in phase 2. Bisphosphonate continuation was permitted but anti-androgens were discontinued. Responses were determined according to PSWG2 criteria. To assess bone turnover, urinary N-telopeptide (uNTX) and serum bone alkaline phosphatase (BAP) levels were measured.
Results: At the time of analysis, median treatment duration was 4.8 mos (range 0.1−9.6) and 18/46 treated pts remain on therapy. The most common grade 1/2 adverse events (AEs) were fatigue, dysgeusia, and GI and skin disorders. A grade 3 AE was reported in 9 pts and a grade 4 AE in 2 pts. A prostate-specific antigen (PSA) response was observed in 21/43 evaluable pts (49%). Bone scans showed reduction in size and number of lesions in 11/39 (28%) pts and stable lesions in 27 (69%) pts (n = 8 at ≈6 wks; n = 6 at ≈12 wks; n = 6 at ≈18 wks; n = 5 at ≈24 wks; n = 2 at ≈30 wks). Of 31 pts with RECIST-evaluable lesions, best response was: partial response (PR) in 14; unconfirmed PR in 4 (still on study); stable disease in 12 (6−21 wks); and progressive disease in 1 pt. Of pts evaluated for bone markers, 17/34 (50%) had a ⩾35% uNTx decrease (2 received bisphosphonates) and 24/32 (75%) had a BAP decrease from baseline (9 received bisphosphonates).
Conclusions: Dasatinib and docetaxel treatment is well tolerated. These promising data, showing modulation of bone markers and PSA at a higher-than-expected rate, support combined anti-tumor and anti-osteoclast targeting and serve as the basis for the ongoing phase 3 study of this combination.

7029 POSTER

CYP17 gene polymorphism in prostate cancer

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Background: The cytochrome P450c17a mediates both steroid 17a-hydroxylase and 17, 20-lyase activities and functions at key steps in the genesis of human sex steroid hormones. The 5′-untranslated promoter region of the *CYP17* gene contains a polymorphic T-to-C substitution that gives rise to *A1* (T) and *A2* (C) alleles. The *CYP17* polymorphism may play a crucial role in the etiology of hormone-related cancers such as prostate cancer and breast cancer. The aim of our study was to investigate the distribution of the *CYP17* genotype between a control group and prostate cancer patients.
Material and Methods: Blood samples from 200 subjects (mean age 59.5±7.4 years, range 50 - 78 years) were obtained from healthy, unrelated subjects. A total of 195 prostate cancer patients (mean age 67.0±8.2 years, range 50−85 years) with histologically verified prostate cancer were invited to participate in the project. Both patients and controls were interviewed regarding age, smoking habits, drinking habits, possible chemical exposure, previous and/or current prostate diseases, incidence of cancer and chronic diseases. PCR-RFLP (polymerase chain reaction-restriction fragment length polymorphism analysis) was used to detect *CYP17* polymorphisms. The χ^2 method was used to test frequencies of genotypes/allele in prostate cancer patients and controls.
Results: The frequency of the *A2* allele was similar in cases and controls. Compared with men with the *A1*/*A1* genotype, the adjusted odds ratio was 1.06 (95% CI = 0.68 to 1.64) for the *A1*/*A2* and 0.66 (95% CI = 0.37 to 1.20) for the *A2*/*A2* genotype. The multivariate analysis confirmed the association between PSA levels and *CYP17* genotypes (*A1*/*A1 vs. A1*/*A2; A2*/*A2*). Prostate cancer patients with PSA levels (4−10 ng/ml) and *A1*/*A2; A2*/*A2* genotypes had an excess risk to develop prostate cancer (OR = 2.84, 95% CI = 1.06 to 7.62; OR = 3.15, 95% CI = 0.75 to 13.3, respectively).
Conclusions: These results suggest that the *CYP17 A1*/*A2* and *A2*/*A2* genotypes predict susceptibility to prostate cancer in men with serum PSA levels above 4 ng/ml. It is also possible that *CYP17* interacts with other genes that influence risk of prostate cancer.
Acknowledgements: This work was supported by grants MH SR 2007/45-UK-10, MH SR 2007/57-UK-17, UK/264/2006, MVTS Bil/CR/SR/UK/06 and AV 4/0013/05.

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Dose finding and safety analysis of inecalcitol in combination with docetaxel-prednisone regimen in hormone-refractory prostate cancer (HRPC) patients (pts)

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Introduction: Inecalcitol is a novel synthetic vitamin D3 analogue with potent antiproliferative effects in human cancer cell lines and a 100-fold lower hypercalcemic activity than calcitriol in animal models.
Methods: In this study, escalating dosages of inecalcitol was combined to chemotherapy in naive HRPC pts. Safety and efficacy were evaluated in groups of 3−6 patients receiving inecalcitol daily or every other day on a 21-day cycle in combination with docetaxel (75 mg/m^2 q3w) and oral prednisone (5 mg bid). Biphosphonates were prohibited during the first cycle. Patients received up to six cycles unless unacceptable toxicity or disease progression. Primary endpoint was dose limiting toxicity (DLT) defined as grade 3 hypercalcemia within the first cycle. Calcemia, creatininemia and CBC were assessed weekly; biochemistry, ECG and PSA every 3 weeks. Efficacy endpoint was PSA response defined as ⩾30% decline within 3 months.
Results: Five dose levels: 40, 80, 160, 300, 600 μg have been evaluated in 34 pts; 9 pts are still being treated at 600 μg; 25 pts have completed 6 cycles (13 bone metastases; 3 extrasqueletic metastasis, 8 bone and extrasqueletic metastases; 1 PSA-only disease). Median age was 72 years [range 53−87], median Gleason score (Gs) 7 [36% Gs 10−8, 64% Gs 7−6] and median PSA 41.5 ng/mL [range 0.9−962.4]. No increased calcemia was reported. Most adverse events (AE) were G1−2, asthenia (19pts), constipation (14pts), diarrhea (13pts). G3−4 AEs were neutropenia (11pts) lymphopenia (9pts), asthenia (3pts), arrhythmia (2 pts), general health deterioration (2pts) and diarrhea (1pt). None of these AEs was considered related to inecalcitol. Of the 23 evaluable pts for PSA response, 20 (87%) had ⩾30% PSA decline.
Conclusion: Results from this ongoing study show the safe toxicity profile of inecalcitol when given daily in HRPC pts. PSA responses with this combination are encouraging. As DLT was not reached, higher dose of inecalcitol (1000 μg/day) are being tested.

7031 POSTER

The impact of neoadjuvant and concurrent MAB for intermediate & high risk localized prostate cancer treated with IMRT

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Background: The sensitivity to hormonal therapy in Japanese prostate cancer patients is though to be much higher than that in other countries.