13 months, the addition of BEV to IFN-α 2a significantly improved duration of PFS in all evaluable patients (10.2 vs 5.4 months, HR = 0.63, p < 0.0001). Analysis of PFS in the prespecified patient subgroups showed that the hazard ratio was consistently <1.
Conclusions: These results demonstrate that BEV plus IFN-α 2a provides a consistent clinical benefit irrespective of baseline prognosis factors and patient characteristics.

4009 POSTER

Urine is the preferred remote body fluid for early identification of prostate cancer using real-time PCR detection of DNA methylation markers

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Background: A prostate cancer (PCa) screening biomarker with improved specificity relative to PSA or with the diagnostic ability to discriminate PCa from BPH in patients with elevated PSA would offer a valuable tool for the public health management of PCa. Aberrant DNA methylation occurs early in tumorigenesis, is stable, and can be assayed in tissues and body fluids, making targets of aberrant DNA methylation attractive biomarker candidates. We previously identified candidate DNA methylation markers to discriminate PCa from benign epithelium. We have now validated those markers in a clinical trial and determined the optimal remote body fluid for PCa screening and diagnostics.
Materials & Methods: A clinical study was initiated to determine the optimal remote analyte for a methylation biomarker and to validate the performance of real-time quantitative HeavyMethyl® PCR assays associated with the genes GSTP1, RASSF2, HIST1H4Kand TFAP2E in body fluids. Matched plasma and urine were collected from 100 PCa patients, 51 biopsy negative patients (diagnosed with BPH subsequent to biopsy referral for elevated PSA) and 50 young healthy control males with no known family history of PCa. ROC curves were generated for each marker and cut-off values for methylation were optimized.
Results: In all negative class comparisons and for all markers, urine was the more sensitive analyte. RASSF2 was the best performing screening marker candidate with 74% sensitivity at 96% specificity in urine (37% sens, 100% spec in plasma). HIST1H4K was the best performing diagnostic marker candidate with 28% sensitivity at 95% specificity in urine (16% sens, 96% spec in plasma). None of the markers correlated with PSA values, indicating that they contribute additional information not provided by the PSA value alone. All markers correlated with Gleason score in both urine and plasma DNA. A quantitative screening panel of markers RASSF2 and HIST1H4K yielded 94% sensitivity at 88% specificity. A quantitative diagnostic panel of markers GSTP1 and PSA yielded 83% sensitivity at 45% specificity.
Conclusions: In a series of matched urine and plasma samples we have shown that urine is a superior remote analyte for PCa detection and diagnosis as compared to plasma. We have also shown that a screening panel of only two markers can achieve 94% sens with a spec of 88%. While we have clearly identified markers that discriminate PCa patients from healthy controls, the current markers do not sufficiently discriminate PCa patients from those with BPH as a diagnostic follow-on test to PSA. Identification of markers that improve discrimination of PCa from BPH with elevated PSA is currently underway.

4010 POSTER

Satraplatin increases progression-free survival (PFS) and delays pain progression in hormone refractory prostate cancer (HRPC): Results of SPARC, an international phase III trial with 950 patients

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Background: Satraplatin (S) is a novel oral platinum agent with demonstrated activity in many tumors, including HRPC. The SPARC study, a large, randomized, phase III trial, was conducted to compare the effects of S + prednisone (P) and placebo (PL) + P in patients (pts) with HRPC who had failed 1 prior chemotherapy regimen.
Methods: Eligible pts were had stage D2 metastatic HRPC and ECOG performance status 0−2. Pts were randomized to S (80 mg/m^2 qd × 5 d q5w) +P (5 mg bid qd) or to PL+P. The primary endpoint was PFS. Secondary endpoints included time to pain progression (TPP), as indicated by increased present pain index (PPI) score or increased opioid use, and PSA response (⩾50% reduction from baseline). Exploratory analyses measured PFS and TPP for subsets of pts based on prognostic variables: age (<65 or ⩾65 years), baseline PPI score (0 or ⩾1), baseline ECOG score (0−1 or 2), prior docetaxel use, type of tumor progression, and bisphosphonate use.
Results: 950 pts were randomized to S (n = 635) or PL (n = 315). Most pts were Caucasian (89%), age ⩾65 years (71%, median 70 yrs), ECOG score 0−1 (90%), and PPI score 0−1 (65%). In the ITT analyses, pts in the S arm had 33% reduced risk of PFS or death vs the PL arm (median 11.1 vs 9.7 weeks, respectively; HR = 0.67, 95% CI: 0.57−0.77; p < 0.001) and significantly longer median TPP (66.1 vs 22.3 weeks, respectively, HR = 0.64, 95% CI: 0.51, 0.79; p < 0.001). PSA response was also significantly higher in the S arm (25.4% vs 12.4%, p < 0.001). Robust findings across patient subgroups showed significant and comparable treatment effects of S on PFS and TPP irrespective of prior docetaxel use, age, or bisphosphonate use; as well as in pts with baseline PPI scores ⩾1, ECOG scores 0−1, and pts with tumor progression with or without PSA increase. S was well tolerated; the most common adverse events were mild to moderate myelosuppression and GI disturbances. When analyzed by age, neutropenia was more frequent in pts ⩾75 yrs, but no pt in this group had febrile neutropenia and the overall incidence of Grade 3−4 infections remained low.
Conclusions: Second line chemotherapy for pts with HRPC is an unmet medical need. Benefits of satraplatin use on PFS, TPP, and PSA in the ITT population are clear. These results are highly robust. Comparable treatment effects are revealed in different subsets of pts defined by prognostic variables. Satraplatin is well tolerated and will be a welcome addition to the therapeutic armamentarium.

4011 POSTER

Results of a phase 3, randomized study of patients with advanced renal cell carcinoma (RCC) and poor prognostic features treated with temsirolimus, interferon-α or the combination of temsirolimus + interferon-α

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Background: Temsirolimus is a specific inhibitor of mTOR, a signaling protein that regulates cell growth and angiogenesis. A phase 3, randomized study was designed to determine the effects of first-line treatment with temsirolimus, interferon-α (IFN), or the combination temsirolimus + IFN on patients (pts) with advanced RCC and poor prognostic features. In a second interim analysis, the O'Brien-Fleming Boundary for early success was crossed for the primary endpoint of overall survival (OS; Hudes et al. J Clin Oncol 24: LBA4, 2006). Pts receiving temsirolimus had significantly longer OS compared with IFN (hazard ratio [HR] 0.73; 95% confidence interval [CI] 0.57−0.92; p = 0.007). Pts receiving temsirolimus + IFN did not have significantly longer OS compared with IFN (HR 0.95; 95% CI 0.76, 1.20; p = 0.691). We report the final supportive analysis of this study.
Methods: Pts with previously untreated RCC and poor prognostic features (⩾3 of 6 prognostic factors [Hudes et al. J Clin Oncol 24:LBA4, 2006]) were randomly assigned to 1 of 3 treatment arms: temsirolimus 25 mg IV once weekly (n = 209); IFN 3 million units (MU) escalating to 18 MU subcutaneously (SC) 3 times weekly (n = 207); or temsirolimus 15 mg IV once weekly + IFN 6 MU SC 3 times weekly (n = 210).
Results: This final supportive analysis of 626 pts enrolled was completed when 514 deaths had occurred and confirmed the results of the second interim analysis. Pts receiving temsirolimus continued to have longer OS compared with IFN (HR 0.78; 95% CI 0.63, 0.97; p = 0.0252). OS of pts receiving temsirolimus + IFN was not significantly longer than that for pts receiving IFN (HR 0.93; 95% CI 0.75, 1.15; p = 0.4902). Median OS for temsirolimus, IFN, and combination groups was 10.9, 7.3, and 8.4 months, respectively. Progression-free survival (PFS; investigator assessed) was significantly longer for pts receiving temsirolimus vs. IFN (HR 0.74; 95% CI 0.60, 0.90; p = 0.003). Median PFS was 3.8 and 1.9 months, respectively.

The most frequently occurring (>10%) grade 3−4 adverse events for pts receiving temsirolimus were anemia (20%), asthenia (11%), and hyperglycemia (11%). A greater proportion of pts receiving IFN (79%) experienced grade 3−4 adverse events compared with temsirolimus (69%, p = 0.024).
Conclusions: Temsirolimus increased OS and PFS when used as first-line treatment for pts with advanced RCC and poor prognostic features, compared with IFN, with an acceptable safety profile.

4012 POSTER

Preliminary results of the 2-year prostate re-biopsy in a phase II randomized study of conventional fractionation vs. hypofractionation on patients with high risk prostate cancer

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Background: Several recent studies suggested a great sensitivity of prostate cancer to high dose fractions, due to a low α/β ratio of this tumor. To test this hypothesis we designed a randomized study comparing conventional fractionation with a biologically equivalent hypofractionated regimen, based on an α/β value of 1.5, as suggested by Fowler et al. (Int J Radiat Oncol Biol Phys 2003; 56: 1093). This is a preliminary report on histologic results from biopsies taken 2 years after the end of radiotherapy.
Material and Methods: From January 2003 to March 2007, 144 patients with histologically proven high risk prostate cancer were recruited to this study. High risk were patients with PSA > 20 ng/ml or with at least 2 of the following characteristics: PSA of 11 to 20, Gleason Score >6, T > 2b. All patients received hormonal therapy for 9 months. Seventy four patients were randomized to receive 80 Gy in 40 fractions in 8 weeks (control arm), and 73 were allocated to receive 62 Gy in 20 fractions in 5 weeks, 4 fractions per week, (hypofractionated arm). All patients were treated with 3D conformal radiation therapy (3DCRT). The median follow-up (FU) is 25 months (range 2−47). Of the 71 patients with a >2 year FU, 48 patients, 23 in the control and 25 in the hypofractionated arm, underwent a 2-yr prostate re-biopsy with, at least, 6 specimens for each lobe, depending on the size of the residual prostate.
Results: In 43 of the 48 patients (89.5%) undergone prostate re-biopsy, the histological examination showed only extended post-XRT modifications. Residual atypic cells were found in the remaining 5 patients (10%), 1 in the control and 4 in the hypofractionation arm. Only 1 of the 5 patients with positive biopsies is presently showing a PSA rise due to pelvic node metastases, while the remaining 4 are still b-NED with a PSA < 0.5 ng/ml.
Conclusions: Despite all patients in this study had a poor prognosis, only few patients, 5/48 (10%) showed a local tumour persistence. Since 4 of these 5 patients with a positive biopsy are showing no biochemical progression, a longer FU is necessary to explain the meaning of this finding.

4013 POSTER

Hypofractionation versus standard fraction in prostate cancer: analysis of the acute toxicity

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Background: The aim of this study is to evaluate the tolerance and the acute toxicity of a hypofractionation in comparison to a conventional fractionation regimen in the radiotherapy of prostate cancer.
Material and Methods: From January 2003 to March 2007, 144 patients with histologically proven, high risk prostate cancer were recruited to this study. All patients received a total androgen deprivation (AD) for 9 months. After 2 months of AD, all patients underwent a 3D conformal radiotherapy to the prostate and seminal vesicles. Patients were randomized to receive a conventional fractionation of 80 Gy in 40 fractions in 8 weeks, or 62 Gy in 20 fractions in 5 weeks, (4 fractions per week). Acute hematological, gastrointestinal (GI) and genitourinary (GU) toxicities were weekly evaluated according to the RTOG/EORTC score system.
Results: No patient experienced acute hematological toxicity or grade 3 gastrointestinal (GI) or genitourinary (GU) toxicity.
The acute grade 2 GI and GU toxicities were observed in the 20% and 34% of patients, respectively, in the control arm and in 33% and 41%, of patients, respectively, in the hypofractionation arm (p = 0.02 for GI and 0.04 for GU toxicity). The actuarial analysis showed an earlier appearence of both toxicities in the hypofractionation arm in comparison to the standard arm. However, when both toxicities were analyzed as a function of the normalized total dose in 2 Gy fraction equivalents (NTD2) using α/β value of 10 for acute reactions, the statistical significance disappeared for both toxicities, suggesting that the acute toxicity is simply anticipated in the hypofractionation with respect to conventional fractionation. This observation was confirmed by the evaluation of the Mucositis Index which did not result in a significant difference between the 2 arms, analyzed either as a function of time or of NTD2.
Conclusions: These preliminary results suggest that the hypofractionation schedule is well tolerated although the acute G2 toxicity in this group, was observed earlier than in conventional fractionation.

4014 POSTER

A new inhibitor of EGFR/SRC activation is able to block several key molecular events in prostate cancer progression

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Background: The encouraging results obtained in the last years by molecular therapy have induced researchers to intensify their efforts in developing new drugs with higher anticancer potency. One of the more promising targets of anticancer agents is the class of tyrosine kinases, including several growth factor receptors and signal transducing molecules.
Materials and Methods: Starting from the scaffold of pyrazolo[3,4-d]-pyrimidine c-Src kinase inhibitors we have synthesized new compounds that demonstrated an effective antiproliferative activity against different tumor cell lines. After a preliminary screening of their kinase inhibition capacity we selected the molecule SI35 that demonstrated a submicromolar inhibitory activity against EGFR and c-SRC.
Results: SI35 demonstrated in vitro to block the proliferation of prostate carcinoma cells PC3 and LnCaP (IC50 is about 30uM), while it had no effect in modulating vitality/proliferation of normal human fibroblasts, Hs27, and of primary human endothelial cells, HUVEC. Moreover we observed a strong inhibition by SI35 in modulating PC3 cells migration and invasion. In fact PC3 cells responded to the presence of EGF by increasing their migratory ability and this effect was strongly reduced by the addition of SI35 at concentrations below its IC50. Further observations demonstrated that SI35 molecule modulated PC3 cells morphology and their adhesive capacity on different physiological substrates. At the same time SI35 blocked invasive and sprouting capabilities of endothelial cells when seeded in Matrigel, inhibiting the formation of lamellipodia and of actin stress fibers. The action of SI35 molecule appeared to involve, in parallel with c-Src and EGFR inhibition, the downmodulation of the active forms FAK/paxillin and ERK.
Conclusions: These data suggest that pharmacological use of pyrazolo-[3,4-d]pyrimidines EGFR/Src inhibitors is potentially able to block several aspects of tumor progression including tumor growth, migratory/invasive capacity and angiogenesis by interference with transduction pathways emanating from EGFR and involving c-Src and FAK activation.

4015 POSTER

Arachidonic acid sustains prostate tumor growth in bone metastasis through the COX-2-mediated production of TNF-α

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Background: Diets high in n-6 fatty acids are associated with an increased risk of bone metastasis from prostate carcinoma (PCa). Although the bone represents, mainly in elderly, a rich repository of fatty acids, the molecular mechanism underlying this phenomenon is largely unknown. Arachidonic acid (AA) can be metabolized through lypoxigenase and cyclooxygenase (COX) pathways producing pro-inflammatory cytokines and mitogenic factors that act as autocrine and paracrine regulators of cancer behaviour. We and other Authors have previously reported that factors released by PCa cells play a key role in inducing an aberrant response in bone cells and favouring PCa cells growth. The aim of this study was to investigate how exogenous AA may modulate in vitro the interaction between PCa cells and bone cells.
Results: First we observed that exogenous AA is in PCa cells an effective inducer of gene transcription. In particular COX-2 activity stimulates the production of pro-inflammatory cytokines, including TNF-α and IL-1β. The blockade of COX-2 activity through a specific inhibitor is sufficient to repress