MPM in a phase I study of single agent vorinostat experienced stable disease lasting 4−13 months. Therefore, Merck Sharp & Dohme sponsored Vantage 014 (NCT00128102), a global, multicenter, phase III, randomized, double-blind study to investigate the overall survival and tolerability of V plus best supportive care (BSC) vs placebo plus BSC in patients with advanced MPM.
Material and Methods: Patients with pathologically confirmed MPM, measurable pleural disease based on modified RECIST criteria, and disease progression following 1 or 2 prior systemic regimens were eligible. Patients received oral V 300 mg (or matching placebo) twice daily for 3 days each week of a 21-day cycle. Primary endpoints included overall survival (OS) and safety/tolerability, per NCI-CTCAE (version 3.0). Secondary endpoints included progression-free survival (PFS), objective response rate, pulmonary function, and patient-reported symptoms. Enrollment of 660 patients provided 80% power, accounting for futility analyses, at the two-sided significance level of 4% to detect a hazard difference of 25% (e.g. improvement in median OS from 6 to 8 months).
Results: Baseline characteristics of the 661 patients randomized at 92 sites were well balanced between V and placebo: median age (64:65 years), median Karnofsky performance status (90%:85%), male (86%:81%), epithelioid histology (83%:81%), one line of prior therapy (77%:77%). The median OS for V vs placebo was 30.7 vs 27.1 weeks with a hazard ratio (HR) of 0.98 (95% confidence interval [CI] 0.83–1.17, two-sided p-value = 0.858). The median PFS (independent assessment) for V vs placebo was 6.3 vs 6.1 weeks with a HR of 0.75 (95% CI 0.63–0.88, two-sided p-value <0.001), favoring V. There was not a statistically significant difference between the arms for response rate (independent assessment, 2 patients vs 1 patient), forced vital capacity, or dyspnea score for the Lung Cancer Symptom Score-Mesothelioma. There was no statistically significant difference in the percentage of patients with grade 3−5 or serious adverse events during treatment between the arms.
Conclusions: In the largest randomized trial to complete enrollment in MPM, V did not significantly extend the overall survival of patients with advanced MPM who have failed prior chemotherapy compared to placebo. Subgroup analyses and biomarker evaluation are underway.

Presidential Session IV

Tuesday 27 September 2011, 09:00−11:00

4BA BEST ABSTRACT

Blood Pressure and Risk of Incident and Fatal Cancer in the Metabolic Syndrome and Cancer Project (Me-Can) − Analysis of Seven Prospective Cohorts

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Background: Observational studies have often found contradicting results for the association between hypertension and risk of different cancers. We assessed the relation between blood pressure (BP) and incident and fatal cancer in a prospective study of seven European cohorts.
Material and Methods: The Metabolic syndrome and Cancer project (Me-Can) includes cohorts from Norway, Austria, and Sweden; the current study included 289,454 men and 288,345 women. Mean age at baseline was 44 years and mean follow-up time was 12 years. Excluding the first year of follow-up, 22,184 men and 14,744 women were diagnosed with cancer, and 8,724 men and 4,525 women died of cancer. Cox proportional hazard regression was used to calculate hazard ratios (HR) of incident and fatal cancer by mid-blood pressure (BP) quintiles and 10 mmHg increments. All models used attained age as time scale, were stratified by cohort, sex, and birth year, and adjusted for baseline age, BMI, and smoking status. In addition, we adjusted for random error in the exposure classification of BP.
Results: For men, a positive association was found between BP and incident risk of cancer (HR per 10 mmHg increment: 1.07 (95% CI: 1.04–1.09)). Furthermore, a positive linear association was observed between BP and risk of oral cancers, and cancer of the colon, rectum, lung, bladder, renal cell, and melanoma and non-melanoma skin cancer. In women, BP was not significantly related to overall incident cancer, but was positively associated with cancer of the liver, pancreas, cervix uteri, endometrium, and melanoma skin cancer. A positive trend by quintiles and 10 mmHg increments of BP was also found for fatal cancer [e.g. HR per 10 mmHg increment in men: 1.19 (1.16–1.22) and women: 1.12 (1.08–1.15)].
We further calculated the absolute risk difference (ARD) for the fifth (Q5) vs first quintile (Q1) of mid-BP for incident and fatal cancer. A statistically significant ARD was found for incident male cancer (ARD: 3.0% with absolute risk of 12.8% for Q1 and 15.8% for Q5), as well as fatal cancer in men (ARD: 2.3% with absolute risk of 5.2% for Q1 and 7.5% for Q5) and women (ARD: 1.0% with absolute risk of 4.3% for Q1 and 5.3% for Q5).
Conclusions: Elevated BP was statistically significantly associated with incident cancer in men and fatal cancer in men and women, as well as several specific cancers. The association was stronger among men than among women and stronger for fatal compared to incident cancer.

Presidential Session I

Saturday 24 September 2011, 13:45−15:35

1LBA LATE BREAKING ABSTRACT

Overall Survival Benefit of Radium-223 Chloride (Alpharadin™) in the Treatment of Patients with Symptomatic Bone Metastases in Castration-resistant Prostate Cancer (CRPC): a Phase III Randomized Trial (ALSYMPCA)

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Background: Radium-223 chloride (Alpharadin™) is a first-in-class alpha-pharmaceutical that targets bone metastases with high-energy alpha-particles of extremely short range (<100 μm). ALSYMPCA is a phase III, double-blind, randomized, multinational study designed to compare the efficacy, in terms of overall survival (OS), and safety of radium-223 plus best standard of care (BSC) versus placebo plus BSC in patients with symptomatic bone metastases in CRPC.
Methods: Eligible patients had progressive, symptomatic CRPC with at least 2 bone metastases on bone scintigraphy and no known visceral metastases; were receiving BSC; and either had previously received docetaxel, were docetaxel ineligible, or had refused docetaxel. Patients were randomized 2:1 to receive 6 injections of radium-223 (50 kBq/kg IV) every 4 weeks or matching placebo and stratified according to prior docetaxel use, baseline alkaline phosphatase level, and current bisphosphonate use. A pre-planned interim analysis was conducted to assess the effect of radium-223 on the primary endpoint (OS) using a predefined threshold. Survival data for the 2 treatment arms were compared using a stratified log-rank test. The Independent Data Monitoring Committee (IDMC) evaluated the results of the pre-planned interim analysis, based on 314 deaths, on June 3, 2011; the findings are communicated here.
Results: 922 patients (radium-223, n = 615; placebo, n = 307) were randomized from June 2008 to February 2011. 445 (58.4%) of the 809 patients in the interim analysis data set had received prior treatment with docetaxel. Based on results of the interim analysis, radium-223 significantly improved OS in patients with CRPC with bone metastases (two-sided *P* value = 0.00185; HR = 0.695; 95% CI, 0.552–0.875). The median OS was 14.0 months for radium-223 and 11.2 months for placebo. Secondary endpoints were met and will be presented. The safety and tolerability data for radium-223 were highly favorable and showed a low incidence of myelosuppression (eg, grades 3/4 neutropenia in 1.8% and 0.8% of the radium-223 and placebo groups, respectively).
Conclusion: Based on results of the pre-planned interim analysis, the IDMC recommended the trial be stopped early due to evidence of a significant treatment benefit that surpassed the pre-defined threshold for OS. Radium-223 is an effective therapy with a highly favorable safety profile and may provide a new standard of care for the treatment of CRPC patients with bone metastases.