"HER2-positive" and "Triple-negative". The need for specific trials for each of these subtypes is an obvious evolution within the field of adjuvant systemic therapies. While research on HER2-positive disease has progressed rapidly, clinical research on the adjuvant treatment of "Triple-negative" or "Luminal B" breast cancers lack initiatives. Reasons for such limited clinical research include the relatively small size of subpopulations in which niche trials should be performed and the enormous costs involved in conducting and monitoring an adjuvant trial. Nevertheless, results from past trials indicate the need to improve outcomes for several cohorts of breast cancer patients. These include treatment strategies for young women, improved endocrine therapies to reduce the risk of late relapse in endocrine-responsive cohorts, and combined targeted therapy such as novel cytotoxic combinations together with DNA repair inhibitors for patients with triple negative disease.

Presidential Session I
Saturday 24 September 2011, 13:45−15:35
1BA BEST ABSTRACT

A Pivotal Multicenter Trial Evaluating Efficacy and Safety of the Hedgehog Pathway Inhibitor (HPI) Vismodegib in Patients With Advanced Basal Cell Carcinoma (BCC)

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Background: The Hedgehog (Hh) signaling pathway is implicated in pathogenesis of BCC. While most BCCs are mostly surgically managed, rare BCCs can become locally advanced (laBCC) or metastatic (mBCC), leaving no effective therapeutic alternatives. Vismodegib (GDC-0449) is a first-in-class small-molecule inhibitor of Hh signaling. In a phase 1 trial, a 55% response rate was seen in 33 patients (pts) with advanced BCC, and treatment was generally well tolerated (Von Hoff, NEJM 2009), leading to this pivotal trial of vismodegib.
Materials and Methods: This pivotal, multicenter, 2-cohort (laBCC and mBCC) nonrandomized study (NCT00833417; ERIVANCE BCC, SHH4476g; sponsored by Genentech; closed to enrollment). Pts with laBCC had histologically-confirmed BCC that was inoperable or for whom surgery would be significantly disfiguring. Pts with mBCC had histologically-confirmed RECIST-measurable disease. Pts received 150 mg oral vismodegib daily until disease progression. The primary endpoint is overall response rate (ORR) by independent review (IRF), using RECIST for mBCC and a composite endpoint for laBCC including improvements in tumor dimension and ulceration, pathologic clearance of BCC, and RECIST if applicable. Primary hypotheses tested are that ORR is significantly >20% for laBCC and >10% for mBCC. Secondary endpoints include duration of response, response per investigator (INV), and safety.
Results: 104 pts (71 laBCC/33 mBCC) were enrolled at 31 sites in US, Europe and Australia. For laBCC, the IRF ORR was 43% (95% CI 31−56%; $p < 0.0001$) and INV ORR was 60% (95% CI 47−72%). For mBCC, the IRF ORR was 30% (95% CI 16−48%; $p = 0.0011$) and INV ORR was 46% (95% CI 28−62%). Adverse events (AEs) in >30% of pts were muscle spasms, alopecia, taste disturbance, weight loss and fatigue. Serious AEs were reported in 26 pts (25%); 4 patients (4%) experienced serious AEs considered related to vismodegib. Fatal AEs were reported in 7 pts (7%), none considered related to vismodegib. Duration of response, histopathology, and detailed safety will be presented.
Conclusions: This pivotal study confirms the significant clinical benefit of vismodegib in both laBCC and mBCC, as measured by tumor response, and further characterizes the AE profile. These results demonstrate the potential role of vismodegib for the treatment of advanced BCC.

Presidential Session II
Sunday 25 September 2011, 12:20−14:40
2BA BEST ABSTRACT

Synchronous Chemo-radiation Can Reduce Local Recurrence in Early Stage Breast Cancer: Results of the SECRAB Trial (ISRCTN: 84214355) Presented on Behalf of the SECRAB Steering Committee

I. Fernando[1], S.J. Bowden[2], C.L. Brookes[2], R. Grieve[3], D. Spooner[4], R.K. Agrawal[5], A.M. Brunt[6], M. Churn[7], D.W. Rea[2], P. Canney[8]. *[1]University Hospitals Birmingham NHS Foundation Trust, Cancer Centre, Birmingham, United Kingdom; [2]University of Birmingham, Cancer Research UK Clinical Trials Unit, Birmingham, United Kingdom; [3]University Hospital, Arden Cancer Centre, Coventry, United Kingdom; [4]City Hospital, Birmingham Treatment Centre Oncology Department, Birmingham, United Kingdom; [5]The Shrewsbury and Telford Hospital NHS Trust, Department of Oncology, Shrewsbury, United Kingdom; [6]University Hospital North Staffordshire, The Cancer Centre, Stoke-on-Trent, United Kingdom; [7]New Cross Hospital, Deansley Centre, Wolverhampton, United Kingdom; [8]Beatson West of Scotland Cancer Centre, Oncology Department, Birmingham, United Kingdom*

Background: The sequencing of chemotherapy (CT) and radiotherapy (RT) after surgery for early breast cancer (EBC) remains controversial. Previous studies using a mitozantrone based regimen have shown that synchronous (Syn) CT-RT does not significantly improve loco-regional recurrence (LLR) and resulted in worse toxicity. SECRAB was designed to determine the optimal sequence of CT and RT in patients having a CMF or anthracycline (A)-CMF regime. The results of a planned analysis looking at local recurrence (LR) are presented.
Materials and Methods: SECRAB was a prospective, randomised multicentre trial comparing sequential (Seq) to Syn RT. RT schedules included 40 Gy/15F over 3 weeks, 45 Gy/20F over 4 weeks and 50 Gy/25F over 5 weeks. Syn RT was administered between cycles 2 and 3 for CMF or 5 and 6 for A-CMF. Seq RT was delivered on CT completion. Key eligibility criteria were completely excised EBC, fit for and requiring adjuvant CT and RT. Between Jul 98 and Mar 04, 2296 women were randomised. LR was defined as a recurrence in the ipsilateral breast or chest wall. Time to LR was calculated as the time from entry until first LR or date of censor.
Results: With a median follow-up of 8.8 years there were 63 and 41 LR in the Seq and Syn arms and 5-year LR rates were 5.1% (95% CI: 3.8%, 6.4%) and 2.8% (95% CI: 1.8%, 3.8%) respectively. There was a significant benefit for Syn RT with a 35% reduction in the risk of LR ($HR_{Syn} = 0.65$, 95% CI: 0.44, 0.96; $p = 0.03$). There was benefit for Syn RT across all treatment (CT regimen, duration of RT, RT boost) and biological subgroups (grade, lymph node status, tumour size, vascular invasion and excision margin). A previous analysis of LRR rates showed no significant difference between Seq and Syn RT ($HR_{Syn} = 0.82$, 95% CI: 0.60, 1.10; $p = 0.19$). Benefit for Syn RT was not seen in patients with regional recurrence, as 80% of these were outside the radiation field. Previously presented results showed an increase in acute skin toxicity in patients treated with Syn treatment however a recent analysis of quality of life data has shown no difference between the two arms.
Conclusions: Syn RT using a CMF or A-CMF regimen has resulted in a significant reduction in LR. The magnitude of benefit is comparable to the effects of chemo-radiation seen in other tumour sites. This is the first study to show this effect in EBC.
Sponsor: University Hospitals Birmingham NHS Foundation Trust

Presidential Session III
Monday 26 September 2011, 12:15−14:25
3BA BEST ABSTRACT

VANTAGE 014: Vorinostat (V) in Patients With Advanced Malignant Pleural Mesothelioma (MPM) who Have Failed Prior Pemetrexed and Either Cisplatin or Carboplatin Therapy: A Phase III, Randomized, Double-Blind, Placebo-Controlled Trial

L.M. Krug[1], H. Kindler[2], H. Calvert[3], C. Manegold[4], A.S. Tsao[5], D. Fennell[6], G.M. Lubiniecki[7], X. Sun[7], M. Smith[7], P. Baas[8]. *[1]Memorial Sloan-Kettering Cancer Center, New York, NY, USA; [2]University of Chicago, Chicago, IL, USA; [3]University College London Cancer Institute, London, UK; [4]Heidelberg University Medical Center, Mannheim, Germany; [5]MD Anderson Cancer Center, Houston, TX, USA; [6]Queen's University Belfast & Northern Ireland Cancer Centre, Belfast, Northern Ireland; [7]Merck Research Laboratories, Merck Sharp & Dohme Corporation, Upper Gwynedd, PA, USA; [8]The Netherlands Cancer Institute, Amsterdam, The Netherlands*

Background: V is a histone deacetylase inhibitor that alters gene expression and protein activity. Five of 13 previously treated patients with

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)

C. Parker[1], D. Heinrich[2], J.M. O'Sullivan[3], S. Fosså[4], A. Chodacki[5], T. Demkow[6], A. Cross[7], B. Bolstad[8], J. Garcia-Vargas[9], O. Sartor[10]. *[1]The Royal Marsden Hospital, Surrey, United Kingdom; [2]Haukeland University Hospital, Bergen, Norway; [3]Centre for Cancer Research and Cell Biology Queen's University, Belfast, Ireland; [4]Radiumhospitalet, Oslo, Norway; [5]Hospital Kochova, Chomutov, Czech Republic; [6]Centrum Onkologii − Instytut im Sklodowskiej-Curie, Warsaw, Poland; [7]PharmaNet, Hemel Hempstead, United Kingdom; [8]Algeta ASA (at time of study), Oslo, Norway; [9]Bayer Healthcare Pharmaceuticals, Montville NJ, USA; [10]Tulane Cancer Center, New Orleans LA, USA*

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.