Lung Cancer − Metastatic

Saturday 24 September 2011, 11:15−13:55

27LBA LATE BREAKING ABSTRACT

A Phase II Study of Sorafenib in Patients with Locally Advanced And/or Metastatic (stage IIIB or IV) Non-small Cell Lung Cancer (NSCLC) with a K-Ras Mutation

A.M. Dingemans[1], W.W. Mellema[2], H.J.M. Groen[3], A. van Wijk[2], S. Burgers[4], P.W.A. Kunst[5], F.B. Thunnissen[6], D.A.M. Heideman[6], E.F. Smit[2]. *[1]Maastricht University Medical Center, Pulmonary Diseases, Maastricht, The Netherlands; [2]VU University Medical Center, Pulmonary Diseases, Amsterdam, The Netherlands; [3]University Medical Center Groningen, Pulmonary Diseases, Groningen, The Netherlands; [4]Netherlands Cancer Institute, Thoracic Oncology, Amsterdam, The Netherlands; [5]Academic Medical Center, Pulmonary Diseases, Amsterdam, The Netherlands; [6]VU University Medical Center, Pathology, Amsterdam, The Netherlands*

Background: In a pilot study [1] we found sorafenib to display clinical activity against patients with K-Ras positive NSCLC, sufficient for formal phase II testing.
Methods: Patients with K-Ras mutated NSCLC that progressed after at least 1 platinum containing regimen with adequate organ reserve, ECOG 0−2, who provided written informed consent according to local IRB regulations were eligible. A tumor biopsy confirming the presence of a K-Ras mutation was mandatory. Treatment consisted of sorafenib 400 mg BID until disease progression or unacceptable toxicity. Dose reductions and delays were specified per protocol in the face of CTC toxicities grade 3 and 4. Primary endpoint: Rate of No Progression (NPR) at 6 weeks. Secondary endpoints: duration of response, progression free survival (PFS), overall survival and treatment related toxicities. A 2-stage design was implemented (Simon's optimal design; p0 = 40%, p1 = 60%, alpha = 0.05, beta = 0.20) for a total number of 48 pts.
Results: 59 patients were entered between May 1st 2010 and February 18 2011. Median age was 58 (range 46−79) years, 17 Male/42 Female, ECOG PS 0/1/2 23/32/4. 57 patients started treatment. At 6 weeks 7 PR, 23 SD, 27 PD were observed; NPR 52.8%. Four patients stopped treatment before 2nd tumor assessment. They were regarded as progressive disease and censored from the PFS analysis. At time of analysis the median follow-up was 8.1 months (range 1−12 months), 36 patients had died. Median duration of treatment was 2.1 (range 0−12) months, 4 patients are still on treatment. Median duration of response was 4.9 (range 0−11) months. Median PFS was 2.6 (range 0−12) months, 8 patients were censored. Median OS 4.9 (range 0−12) months, 21 patients were censored. Dose modifications were realized in 16 patients, of whom 4 discontinued treatment. Most common adverse events were fatigue, hand-foot reaction, dyspnea, diarrhea and cough. Grade 3 skin toxicity was reported in 6 patients (10.5%), grade 3 gastrointestinal toxicity was reported in 7 patients (12.3%), grade 3−4 metabolic abnormalities was reported in 5 patients (8.8%), grade 3−4 pulmonary toxicity in 13 patients (22.8%).
Conclusion: Treatment with sorafenib has relevant clinical activity in patients with K-Ras mutational status. Further randomized study with this agent is warranted.

References

[1] E.F. Smit, et al. J. Thor. Oncol. 5, 719, 2010.

Melanoma and Skin Cancer

Saturday 24 September 2011, 11:15−13:15

28LBA LATE BREAKING ABSTRACT

Vemurafenib Improves Overall Survival Compared to Dacarbazine in Advanced BRAFV600E-mutated Melanoma: Updated Survival Results From a Phase III Randomised, Open-label, Multicentre Trial

G. McArthur[1], A. Hauschild[2], C. Robert[3], J.B. Haanen[4], P. Ascierto[5], R.J. Lee[6], K. Nolop[7], B. Nelson[8], K.T. Flaherty[9], P.B. Chapman[10]. *[1]Peter MacCallum Cancer Centre, Medical Oncology, Melbourne, Australia; [2]Universitaetsklinikum Schleswig-Holstein, Dermatology, Kiel, Germany; [3]Cancer Institute Gustave Roussy, Villejuif, France; [4]The Netherlands Cancer Institute, Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands; [5]Instituto Nazionale Tumori Pascale, Medical Oncology and Innovative Therapy, Naples, Italy; [6]Hoffman La Roche, Nutley NJ, USA; [7]Plexxikon Inc, Berkeley CA, USA; [8]Genentech, South San Francisco CA, USA; [9]Massachusetts General Hospital, Boston MA, USA; [10]Memorial Sloan-Kettering Cancer Center, New York NY, USA*

Background: Median overall survival (OS) for metastatic melanoma patients (pts) has consistently been 6−8 months in chemotherapy clinical trials. Vemurafenib (PLX4032/RG7204/RO5185426) is an orally administered inhibitor of oncogenic BRAF kinase for which median OS has not been reached after a median of 10 months' follow-up in 132 pts in a Phase II study (BRIM2). In a Phase I melanoma extension cohort of 32 pts, the median OS was 12.6 months and the 2-year survival rate estimate was 35%. The aim of the Phase III BRAF In Melanoma (BRIM3) trial (NCT01006980; Hoffmann-La Roche) was to determine if vemurafenib improves OS and progression-free survival (PFS) in melanoma pts with the $BRAF^{V600E}$ mutation.
Material and Methods: Pts with previously untreated, unresectable stage IIIC or IV melanoma that tested positive for $BRAF^{V600E}$ mutation by the cobas® 4800 V600 Mutation Test (Roche Molecular Systems, Inc.) were randomised (1:1) to vemurafenib (960 mg po bid) or dacarbazine (DTIC; 1000 mg/m^2 IV q3w). Randomisation was stratified by performance status, stage, LDH and region. At the planned OS interim analysis in January 2011 (50% of the 196 deaths needed for final analysis) the independent Data and Safety Monitoring Board recommended release of results due to compelling efficacy (OS hazard ratio [HR] 0.37; 95% CI 0.26–0.55; p < 0.0001) and to permit crossover from DTIC to vemurafenib. An updated analysis of OS with an additional 3 months' follow-up was performed. Survival data were censored at time of crossover for the 50 pts who had crossed over to vemurafenib after release of results.
Results: 675 pts were enrolled at 104 centres worldwide between January and December 2010. Median follow-up in this update was 6.21 months for vemurafenib (range <1–13.9) and 4.46 months for DTIC (range <1–11.7). The updated HR for OS was 0.44 (95% CI 0.33–0.59) favouring vemurafenib. Kaplan–Meier (KM) estimate of median OS has not been reached in the vemurafenib group (95% CI 9.59−NR) and was 7.89 months (95% CI 7.26–9.63) with DTIC. KM estimate of 6-month survival was 83% for vemurafenib and 63% for DTIC. The safety profile in vemurafenib-treated pts was consistent with that reported in previous studies.
Conclusions: In this updated OS analysis of the BRIM3 trial in pts with previously untreated $BRAF^{V600E}$-mutated metastatic melanoma, vemurafenib was associated with continued improvement in OS. Median OS after 6.2 months' follow-up has not been reached.

Nursing − Supportive Care

Monday 26 September 2011, 09:00−11:15

29LBA LATE BREAKING ABSTRACT

Unrecognised and Underprepared: an Exploratory Mixed Method Study of Informal Carers' Experiences of Supporting Someone Through Chemotherapy

E. Ream[1], V. Pedersen[1], C. Oakley[1], A. Richardson[2], C. Taylor[1], R. Verity[1]. *[1]The Florence Nightingale School of Nursing and Midwifery King's College London, Specialist Care, London, United Kingdom; [2]University of Southampton, Faculty of Health Sciences, Southampton, United Kingdom*

Background: Patients having chemotherapy in outpatient settings assume responsibility for monitoring and managing side effects at home. They are supported by informal carers (relatives/friends). Informal carers are important for patients' safety and wellbeing during chemotherapy, yet little is known about their needs for information and support. This study investigated informal carers' needs and experiences whilst supporting patients through chemotherapy.
Materials and Methods: A mixed methods study design was used. Data were gathered by self-completion questionnaires which were analysed descriptively. These data subsequently informed semi-structured interviews conducted with a purposively selected subsample of survey respondents. Interviews were digitally recorded, transcribed and analysed using the 'Framework' approach.
Results: Forty-eight informal carers returned questionnaires (RR: 70%) − 13 of these were interviewed. Informal carers reported their needs were met in relation to information on chemotherapy and its side-effects, but a large proportion had unmet needs regarding financial support and their own needs as carers. Few informal carers were given information on their own, and thus had little opportunity to raise issues concerning their own needs and/or worries regarding patients' care. Further, not all carers had contact details for the chemotherapy service.
Informal carers adopted 4 roles in support of patients: 'advocate', 'protector', 'symptom monitor' and 'assertive companion'. Interaction between patients and informal carers influenced the roles carers adopted. Carers felt assertiveness was important; it enabled them to enhance patients' accurate and early reporting of concerning symptoms, communicate effectively with health professionals and contribute to decision-making regarding patients' care. Not all carers felt sufficiently empowered to be assertive.
Conclusion: Informal carers are important for patient safety during chemotherapy. However, their contribution in the chemotherapy setting is generally not recognised formally by health professionals and some carers appear ill-prepared to undertake the roles they adopt during patients' treatment. Lack of preparation for, and clarity regarding, their caring role and high unmet need for support can impact negatively on carers and the support they provide patients. Research is needed to develop interventions which prepare informal carers thoroughly for their carer role. This will

enhance their experience, improve carer involvement and may enhance patient outcomes.

Sarcoma

Tuesday 27 September 2011, 09:00−11:30

30LBA LATE BREAKING ABSTRACT

A Randomized Clinical Trial of Adjuvant Chemotherapy with Doxorubicin, Ifosfamide, and Cisplatin in Localized Uterine Sarcomas. Results On 81 Randomized Patients

P. Pautier[1], A. Floquet[2], L. Gladieff[3], D. Berton-Rigaud[4], S. Piperno-Neumann[5], F. Selle[6], I. Ray-Coquard[7], C. Guillemet[8], B. Weber[9], A. Rey[10]. *[1]Institut Gustave-Roussy, Medecine, Villejuif, France; [2]Institut Bergonié, Medecine, Bordeaux, France; [3]Institut Claudius Regaud, Medecine, Toulouse, France; [4]Centre René Gauducheau, Medecine, Nantes, France; [5]Institut Curie, Medecine, Paris, France; [6]Hôpital Tenon, Medecine, Paris, France; [7]Centre Léon Bérard, Medecine, Lyon, France; [8]Centre Henri Becquerel, Medecine, Rouen, France; [9]Centre Alexis Vautrin, Medecine, Nancy, France; [10]Institut Gustave-Roussy, Biostatistics, Villejuif, France*

Background: Uterine sarcomas (US) have a high risk of metastatic relapse. No benefit was shown with doxorubicin as adjuvant treatment even though a trend emerged in favor of chemotherapy (CT) (Omura 1985). A multichemotherapy approach in US achieved a good response rate (DECAV therapy: 54% overall response rate), though toxic. Adjuvant API (doxorubicin, ifosfamide and cisplatin) followed by radiotherapy (RT) is a feasible protocol. We conducted a phase III multicenter study of adjuvant CT with API. The objective was to detect an increase $\geqslant$20% of 3 years PFS (a = 5%, power = 80%) in the CT arm. Study was stopped because of lack of recruitment. We present the results of the 81 pts who actually entered the study.

Material and Methods: Pts with FIGO stage $\leqslant$III US after complet surgery, normal thoracic, abdominal and pelvic CT scan, physiological age $\leqslant$65 years, PS $\leqslant$ 2, left ventricular ejection fraction >50%, were randomized (stratification carcinosarcomas [CS] versus others). All patients received pelvic RT (45 grays); vaginal brachytherapy was optional. Chemotherapy consisted in 4 cycles of doxorubicin 50 mg/m^2 d1, ifosfamide 3 g/m^2/d d1d2 + mesna, cisplatin 75 mg/m^2 d3, + lenograstim 150 μg/m^2/d d 7−14; q 3 wks.

Results: 81 patients randomized, 39 in arm A (CT + RT) and 42 in arm B (RT); median age 55 y (39−69), 52 stage I, 16 stage II, 13 stage III; 53 leiomyosarcomas, 9 indifferenciated sarcomas, 19 CS. Gr 3−4 toxicity during API (/37 pts): hematologic gr3 (16%) and 4 (68%); febrile neutropenia (22%) with 2 toxic deaths; renal gr 4 (1 pt); nausea-vomiting gr 3−4 (24%); 28% of pts needed dose reduction. With median follow-up of 4.3 years, 41/81 pts recurred at a median time of 13 mo (5−43 mo), 15 in arm A (38%) and 26 in arm B (62%); median DFS is 33 mo; recurrences sites was: pelvis 11, pelvis + meta 3, meta 27 (25/30 meta: lung). 3 years DFS is 55% in arm A (IC95: 40−70) and 41% in arm B (IC95: 27−57) p = 0.048. 3 years OS is 81% in arm A (IC95: 66−91) and 69% in arm B (IC95: 52−82) NS.

Conclusions: With median follow-up of 4.3 years, API adjuvant chemotherapy increases statistically the 3 year-DFS of patients with uterine sarcoma.. Results have to be confirmed with longer follow-up to see real impact on OS. The 2 toxic deaths may impact the global prognosis. A selection of less toxic chemotherapy is mandatory.

Sarcoma

Tuesday 27 September 2011, 09:00−11:30

31LBA LATE BREAKING ABSTRACT

Response to Imatinib Rechallenge of GIST That Recurs Following Completion of Adjuvant Imatinib Treatment − the First Analysis in the SSGXVIII/AIO Trial Patient Population

P. Reichardt[1], J.T. Hartmann[2], K. Sundby Hall[3], M. Eriksson[4], J. Schütte[5], G. Ramadori[6], P. Hohenberger[7], J. Duyster[8], M. Leinonen[9], H. Joensuu[10]. *[1]HELIOS Klinikum Bad Saarow, Sarcoma Center Berlin-Brandenburg, Bad Saarow, Germany; [2]Medical Center Eberhad-Karls-University, Medical Oncology/Hematology/Immunology/Rheumatology and Pulmonology, Tübingen, Germany; [3]The Norwegian Radium Hospital Oslo University Hospital, Oncology, Oslo, Norway; [4]Skane University Hospital Lund University, Oncology, Lund, Sweden; [5]Marien Hospital, Oncology/Hematology, Düsseldorf, Germany; [6]University of Göttingen, Gastroenterology/Endocrinology, Göttingen, Germany; [7]Mannheim University Medical Center, Surgical Oncology/Thoracic Surgery, Mannheim, Germany; [8]Klinikum rechts der Isar, Internal Medicine III, München, Germany; [9]4Pharma Ltd., Turku, Finland; [10]Helsinki University Central Hospital, Oncology, Helsinki, Finland*

Background: Adjuvant imatinib improves outcome of patients with operable GIST, but many GISTs recur after completion of adjuvant therapy. Efficacy of imatinib in recurrent GIST following adjuvant treatment is unknown, and concern has been expressed that prior exposure to imatinib may reduce efficacy of the drug in the advanced setting. The SSGXVIII/AIO trial recruited patients with KIT-positive GIST, estimated to have a high risk of tumor recurrence based on the modified NIH Consensus Classification from February 2004 to September 2008.

Patients and Methods: The intention-to-treat population consisted of 397 patients, of whom 199 were randomly assigned to receive 12 months of imatinib and 198 36 months of imatinib. Imatinib was administered orally at a dose of 400 mg/d in both groups. The patients were monitored with computed tomography at 6-month intervals during follow-up. With a median follow-up time of 54 months, 84 and 50 patients were diagnosed with recurrent GIST or died in the 1-year and 3-years groups, respectively. Patients who did not have GIST at central pathology review (n = 15) and those with metastatic GIST at the time of randomization (n = 24) were excluded from the current analysis.

Results: Eighty-one patients were treated with imatinib for recurred GIST (1-year group, 54; 3-years group, 27). Forty-six (56.8%) out of the 81 patients were evaluable for response (6 were not evaluable, and 29 had missing data or were too early for evaluation). Imatinib was administered at a dose of 400 mg/d for 71 patients (87.7%). The remaining 10 patients received 100 mg (n = 3), 600 mg (n = 1) or 800 mg (n = 6), respectively. Fifteen (32.6%) patients achieved a CR, 14 (30.4%) a PR, 10 (21.7%) had SD and 7 (15.2%) PD as the best response yielding a clinical benefit rate CBR (CR + PR + SD) of 84.8%. There was no difference in the CBR between patients assigned to the 1-year and 3-years groups (87.9% vs. 76.9%, respectively; p = 0.385). The median time to progression after starting imatinib for advanced GIST was 35.7 months (1-year group: 39.6 months; 3-year group: 20.8 months; HR 1.60, 95% CI, 0.67–3.85; p = 0.289).

Conclusions: Most patients diagnosed with recurrent GIST after having received imatinib in the adjuvant setting respond to imatinib. The CR rate observed was high, possibly due to early detection of recurrent disease during follow-up. The observed median time to disease progression appears similar to the times found in patient populations that have not been exposed to imatinib in the adjuvant setting.

Sarcoma

Tuesday 27 September 2011, 09:00−11:30

32LBA LATE BREAKING ABSTRACT

Denosumab Treatment for Giant Cell Tumor of Bone (GCTB) in Adolescent Patients: Interim Results From a Phase II Study

J. Engellau[1], S. Chawla[2], R. Grimer[3], A. Powell[4], S. Schuetze[5], K. Skubitz[6], A. Staddon[7], C. Atchison[8], Y. Zhao[8], I. Jacobs[8]. *[1]Skåne University Hospital, Lund, Sweden; [2]Sarcoma Oncology Center, Santa Monica, USA; [3]Royal Orthopaedic Hospital, Birmingham, United Kingdom; [4]Sir Charles Gairdner Hospital, Nedlands, Australia; [5]University of Michigan, Ann Arbor, USA; [6]Masonic Cancer Center University of Minnesota, Minneapolis, USA; [7]University of Pennsylvania School of Medicine, Philadelphia, USA; [8]Amgen Inc., Thousand Oaks, USA*

Background: GCTB is characterized by RANKL-mediated bone destruction. Symptoms include localized tenderness, swelling, fractures, and often severe, intractable pain. In a previous phase 2 GCTB study, 86% of patients had a response to the RANKL inhibitor denosumab, as demonstrated by an elimination of $\geqslant$90% of giant cells or no radiological progression of the target lesion. We report data from a preplanned interim analysis of a 2nd phase 2 study, describing denosumab effects on the adolescent subset of patients with GCTB (Amgen, Inc. ClinicalTrials.gov identifier NCT00680992).

Materials and Methods: Skeletally mature adolescent patients with surgically unsalvageable GCTB (Cohort 1, n = 8) or salvageable GCTB (Cohort 2, n = 2), $\geqslant$12 to <18 years of age, received subcutaneous denosumab 120 mg every 4 weeks with additional doses on days 8 and 15. The primary objective was to evaluate denosumab safety. We also analyzed investigators' assessments of disease progression and the proportion of patients for whom surgery was delayed, reduced in scope, or no longer deemed required. Safety analyses included all patients who received denosumab; efficacy analyses included patients who received $\geqslant$1 dose of denosumab and had the opportunity to be on study for $\geqslant$6 months. Pain was evaluated in patients who had $\geqslant$1 post-baseline pain assessment (Brief Pain Inventory-Short Form [BPI-SF] 0: no pain − 10: pain as bad as can be imagined). The BPI-SF was administered at baseline and before each dose. Analgesic use was quantified using the 8-point Analgesic Quantification Algorithm (AQA 0: no analgesics − 7: strong opioids with >600 mg oral morphine equivalent per day).

Results: Patients included 2 males and 8 females (mean age 15.6 years, range 13−17) who were on denosumab treatment for a median of 9.0 months (range 3.3–17.3). All patients had skeletal lesions. Adverse