Gastrointestinal Malignancies - Colorectal Cancer

Saturday 24 September 2011, 11:15−13:50

19LBA LATE BREAKING ABSTRACT

A Phase 2b, Double-Blind, Randomized Study Evaluating the Efficacy and Safety of Sorafenib (SOR) Compared With Placebo (PBO) When Administered in Combination With Chemotherapy (Modified FOLFOX6) for First-line Treatment (tx) of Patients (Pts) With Metastatic Colorectal Cancer (mCRC). The RESPECT Trial

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Background: SOR, an oral multikinase inhibitor targeting angiogenesis and tumor growth, is indicated for renal and hepatic carcinomas. The RESPECT trial was an initial assessment of SOR in first-line mCRC in a randomized PBO-controlled setting.
Methods: Pts with mCRC and no prior therapy were randomized to SOR 400 mg or PBO twice daily with mFOLFOX6. Pts received mFOLFOX6 every 14 days. The primary endpoint was progression-free survival (PFS); secondary endpoints were overall survival (OS), time to progression (TTP), overall response rate (ORR), disease control rate (DCR), and duration of response (DOR). (ClinicalTrials.gov: NCT00865709. Sponsors: Bayer Healthcare and Onyx Pharmaceuticals)
Results: 198 pts were randomized: SOR arm (N = 97), PBO arm (N = 101). Baseline factors were balanced between SOR and PBO arms, except for gender (female, 57% v 38%) and *KRAS* status (wild type, 43% v 41%; mutant, 34% v 43%). To date, *KRAS* status has not yet been determined for ~20% of patients. There was no statistical difference between SOR and PBO arms for PFS (median, 9.1 v 8.7 mo; HR = 0.88, 95% CI 0.64–1.23; P = 0.23) or TTP (9.2 v 9.0 mo; HR = 0.83, 95% CI 0.59–1.17; P = 0.14). OS data are pending. ORR was 46% and 60% and DCR was 95% and 93% in the SOR and PBO arms, respectively. Exploratory subgroup analysis of PFS (SOR v PBO) by *KRAS* status showed a median of 9.6 v 9.2 mo for wild type (HR = 0.79; 95% CI 0.47–1.30) and 8.9 v 7.6 mo for mutant (HR = 0.89; 95% CI 0.53–1.51). The most common Grade 3/4 adverse events (AEs) in the SOR and PBO arms were neutropenia (48% v 22%), peripheral sensory neuropathy (6% v 12%), and Grade 3 hand-foot skin reaction (20% v 0%). Discontinuation of study treatment due to AEs was 9% in the SOR and 6% in the PBO arm.
Conclusions: The addition of SOR to first-line mFOLFOX6 in mCRC pts did not lead to a statistically significant improvement in PFS in unselected patients although a potential trend was suggested. A prespecified analysis of the *KRAS* mutant subgroup showed potential benefit of SOR, although the sample size was small. Safety data were consistent with SOR and mFOLFOX6 profiles with increased rates of some AEs.

Genitourinary Malignancies − Prostate Cancer

Sunday 25 September 2011, 09:00−11:00

20LBA LATE BREAKING ABSTRACT

Celecoxib Plus Hormone Therapy Vs Hormone Therapy Alone for Hormone-sensitive Prostate Cancer: First Results From the STAMPEDE Randomised Controlled Trial (MRC PR08)

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Background: Long-term hormone therapy (HT) alone is the standard of care for men with metastatic or high-risk non-metastatic prostate cancer (PCa). The STAMPEDE trial is investigating whether early use of additional therapies can improve overall survival. STAMPEDE is an international randomised controlled trial (NCT00268476), sponsored by the UK Medical Research Council. It uses novel multi-arm, multi-stage methods to assess the addition of 1 or 2 of three agents (docetaxel, zoledronic acid, celecoxib) in 5 research arms in men with PCa starting long-term HT for the first time.
Materials and Methods: HT was given as per standard care. Celecoxib was planned as 400 mg *bid* until the sooner of 1 year or disease (including PSA) progression. The trial has 3 intermediate activity stages (I−III) where the outcome measure (OM) is failure-free survival (FFS) and one final efficacy stage (IV) with overall survival as primary OM. At the end of each stage, research arms are compared pairwise to the control arm. Accrual of further patients is discontinued early for any research arm either showing (a) safety concerns or (b) insufficient evidence of activity (lack-of-benefit) where the treatment effect on FFS is compared against a pre-defined stopping guideline. The interim activity "hurdle" becomes increasingly stringent stage-by-stage, with the hazard ratio (HR) used when the hazards are proportional and restricted-mean survival time when they are not.
Results: From October 2008 to February 2011, 2,114 patients were consented and randomised, including 875 in this comparison. With 305 FFS events, there was no evidence of an advantage to HT+celecoxib over HT-alone: HR 0.98 (95% CI 0.90–1.06). The Independent Data Monitoring Committee recommended stopping accrual to this arm; stopping celecoxib was also recommended for patients currently on treatment. There was no evidence of differences in toxicity: 25% and 23% of patients reporting grade $\geqslant$3 toxicities or adverse events with or without celecoxib. Control arm FFS was 51% at 2 years, in line with expectations.
Conclusions: Celecoxib shows no evidence of activity in this setting. Accrual continues seamlessly to the other research arms. Follow-up of all arms is ongoing.
Support: The trial is supported by the MRC, CRUK, Novartis, Sanofi-Aventis and Pfizer

Genitourinary Malignancies − Prostate Cancer

Sunday 25 September 2011, 09:00-11:00

21LBA LATE BREAKING ABSTRACT

Escalated-dose Conformal Radiotherapy for Localised Prostate Cancer: Long-term Overall Survival Results From the MRC RT01 Randomised Controlled Trial

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Background: Radiotherapy (RT) is one standard of care for men with localised prostate cancer (PCa). Conformal radiotherapy (CFRT) can deliver higher doses of radiation than standard-dose conventional radical external-beam radiotherapy and could improve long-term efficacy, potentially with increased toxicity.
Materials and Methods: Between Jan-1998 and Dec-2002, 862 consenting men with histologically confirmed T1b–T3a, N0, M0 PCa with PSA < 50 ng/mL, WHO performance status 0−1, normal blood counts and no previous PCa treatment joined RT01 (ISRCTN47772397). N = 843 were eligible to be randomised to standard-dose CFRT (Std: 64 Gy/32f; n = 421) or escalated-dose CFRT (Esc 74 Gy/37f; n = 422). Randomisation was stratified on hospital and risk for seminal vesicle (SV) involvement (T-category, PSA, Gleason score). All received neo-adjuvant hormone therapy (HT) for 3 to 6 months pre-RT until the end of RT. The main efficacy outcome measures were biochemical progression-free survival (bPFS; time from randomisation until the first of: biochemical progression, re-start of HT, local progression, lymph node involvement, bone or other metastases or prostate-cancer death) and overall survival (OS; time from randomisation to death). Standard survival analysis methods were used. First activity results published in 2007 with ~5 years median follow-up showed an advantage to escalated-dose CFRT in terms of bPFS and some evidence of an advantage in metastases-free survival.
Results: At entry, median age was 67 yr; two thirds were at moderate risk for SV involvement, one third low risk. With median follow-up of 10 years, 239 deaths were reported (120 Std, 119 Esc). OS at 10 yr was 70% (95% CI = 65−75%) in each arm: hazard ratio (HR) from an adjusted Cox model 0.99 (95% CI = 0.77–1.28; p = 0.942). The assumption of proportional hazards was met (p = 0.337). 396 bPFS events were observed (224 Std, 172 Esc) and the previously observed advantage in bPFS was maintained: HR = 0.688 (95% CI = 0.56–0.84; p < 0.0001) in

favour of Esc. At 10 yr, bPFS was 42% (95% CI = 37−47%) Std and 54% (95% CI = 49−60%) Esc. Long-term HT was reported for 220 with fewer men starting HT and later on Esc: HR = 0.77 (95% CI = 0.59–1.00; p = 0.05). Further data, including prostate-cancer specific survival and metastases-free survival will be presented; a blinded death review is ongoing.

Conclusions: Escalated dose radiotherapy with neo-adjuvant HT showed an advantage in early efficacy outcome measures but this did not translate into an improvement in overall survival. Five extra fractions of RT may have led to less exposure to long-term HT. Survival rates in both arms were much higher than originally expected.

Support: The trial is supported by the UK Medical Research Council

Gynaecological Cancer

Monday 26 September 2011, 09:00−11:55

22LBA LATE BREAKING ABSTRACT

Quality of Life in the ICON7 GCIG Phase III Randomised Clinical Trial

D. Stark[1], M. Nankivell[2], F. Hilpert[3], L. Elit[4], J. Brown[5], A. Lanceley[6], G. Valikova[7], A. Oza[8], A.M. Swart[2], T. Perren[1]. *[1]St James' University Hospital, Institute of Oncology, Leeds, United Kingdom; [2]Medical Research Council, Clinical Trials Unit, London, United Kingdom; [3]University Hospital Schleswig-Holstein, Department of Gynecology and Obstetrics, Kiel, Germany; [4]Henderson Hospital, Juravinski Cancer Centre, Ontario, Canada; [5]Leeds Institute of Molecular Medicine, Clinical Trials Research Unit, Leeds, United Kingdom; [6]UCL, Institute for Women's Health, London, United Kingdom; [7]St James' Institute of Oncology, Cancer Research UK Clinical Centre, Leeds, United Kingdom; [8]Princess Margaret Hospital, University of Toronto, Toronto, Canada*

Background: ICON7 (ISRCTN 91273375) evaluated the addition of bevacizumab (bev) to standard chemotherapy (CT) in the first line treatment of ovarian cancer. Bev was scheduled concurrently with CT (18 weeks) and as maintenance (54 weeks). 1,528 patients were recruited. MRC sponsored the trial, and Roche provided bev for all patients.

The primary endpoint, progression free survival, showed a 15% improvement at 12 months and an overall 1.5 month improvement with bev (restricted mean). This quality of life (QL) sub-study addresses short-term QL of patients during the period on and immediately after trial treatment.

Materials and Methods: QL was collected using the EORTC QLQ-C30 questionnaire at regular intervals until disease progression. The primary QL outcome was Global QL at 54 weeks. Three QL hypotheses were prospectively generated for the addition of bev

1. gastro-intestinal symptoms resolve more rapidly during chemotherapy
2. problems associated with wound healing (pain, body image, social and physical function) are greater at the midpoint of chemotherapy and
3. improvement in fatigue and social functioning is less during continuation of bev.

Other subscales were explored including subgroups from initial survival analyses.

Comparisons were by analysis of variance, controlling for baseline scores. A benefit for bev is indicated by a positive difference in global QL.

Results: Those receiving bev had a clinically small but statistically significant detriment in global quality of life at 54 weeks (table).

None of the hypothesised differences between the treatment arms were supported (all p > 0.05).

Bev was associated with clinically small but statistically significant detriments in exploratory analyses of role and emotional function, appetite, financial worries and chemotherapy side effects (all p < 0.01).

Missing data were present. Sensitivity analyses indicate caution is required in interpreting these observations.

Parameter	N	Comparison	Difference (Bev −CT)	P-value
Global QL	777	Difference in mean QL at 54 weeks	−6.38	<0.0001

Conclusions: Results suggest clinically small deficits in global quality of life and several other patient-reported outcomes associated with the addition of bev to standard CT in ovarian cancer. This should be considered in determining the optimal treatment.

Gynaecological Cancer

Monday 26 September 2011, 09:00−11:55

23LBA LATE BREAKING ABSTRACT

Quality of Life Outcomes of a Randomized, Placebo-Controlled Trial of Bevacizumab in the Front-Line Treatment of Ovarian Cancer: a Gynecologic Oncology Group Study

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Background: Results of a randomized, double-blind, placebo-controlled phase 3 trial indicate that the addition of bevacizumab to concurrent carboplatin and paclitaxel chemotherapy followed by maintenance bevacizumab (R3) prolongs progression-free survival in the front-line treatment of advanced epithelial ovarian cancer compared to chemotherapy alone (R1) or chemotherapy concurrent with bevacizumab in cycles 2−6 only (R2). Quality of Life (QOL) was compared among groups.

Methods: The Trial Outcome Index of the Functional Assessment of Cancer Therapy-Ovary (FACT-O TOI) was used to assess QOL before cycles 1, 4, 7, 13, and 21; and 6 months after completing study therapy. Differences in QOL scores between groups were assessed using a linear mixed model, adjusting for baseline score and age. Treatment effect size was calculated as the ratio of the treatment difference to the baseline standard deviation in the control group (R1). The significance level is set at 0.0167 to account for multiple comparisons.

Results: A total of 1,693 patients (566 in R1, 554 in R2, and 573 in R3) comprised the sample for the QOL comparisons. At cycle 4, the patients in R2 (p < 0.001) and R3 (p < 0.001) reported QOL scores that were 2.7 points (98.3% CI: 0.88–4.57; p < 0.001; effect size = 0.18) and 3.0 points (98.3% CI: 1.13–4.78; p < 0.001; effect size = 2.0) lower respectively, than those in R1. While the observed differences in QOL were statistically significant, they were not considered clinically significant. The difference in QOL scores between R1 and R3 remained statistically significant up to cycle 7, 2.3 points lower (98.3% CI: 0.33–4.14; p = 0.005; effect size = 0.15) in group R3. These scores were not statistically different between patients in R2 and R3. A similar trend was evident in subscale analyses, in which the patients in R2 and R3 reported statistically (not clinically) lower functioning than those in R1. The percentage of patients who reported abdominal discomfort (AD score >0) dropped over time, without significant differences between study arms.

Conclusion: The addition of bevacizumab compromised QOL to a mild extent during chemotherapy, but had no prolonged effect on QOL after chemotherapy completion. Quality of life improved from baseline to cycle 13 for each treatment group, as did abdominal discomfort.

Gynaecological Cancer

Monday 26 September 2011, 09:00−11:55

24LBA LATE BREAKING ABSTRACT

Mutation and Protein Expression Biomarkers Correlate with Response to AKT Inhibition in a Phase I Trial of the Oral Pan AKT Inhibitor GSK2141795 (GSK795) in Patients (pts) with Platinum Resistant Ovarian Cancer

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Background: AKT pathway activation is central to clinical platinum resistance. Molecular analysis of paired tumour biopsies (PTB) was undertaken in a GSK sponsored phase I trial of GSK795, PCS113124, with investigator led translational component in platinum resistant ovarian cancer pts.

Methods: 11 pts received GSK795 in 3 cohorts of 25–50–75 mg for 2 or 4 weeks, escalating to 75 mg following pharmacodynamics (PD) assessment. SUV, Ki and MRglu PET PD parameters were derived by 3 sequential FDG-PET scans. Response assessment was by RECISTv1.1