Latest advances in the medical treatment of cancer: a 2011 snapshot

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The 16th ECCO – 36th ESMO Multidisciplinary Cancer Congress was held in Stockholm, 23–27 September, 2011. This editorial features highlights of late-breaking and best abstracts in medical oncology presented at the conference.

Breast cancer

Breast cancer recurrence in postmenopausal women reduced by zoledronic acid

Professor Robert Coleman (Weston Park Hospital, Sheffield, UK) presented his subgroup analysis of the AZURE trial results [Coleman *et al.* 2011]. This study comprised 3360 patients with stage II/III breast cancer (BC) who were given standard adjuvant treatment plus randomization to zoledronic acid (4 mg IV every 3–4 weeks for six doses, then 3-monthly for eight doses, then 6-monthly for five doses). After 5 years, disease-free survival (DFS; the primary endpoint) was similar between the two groups; however, subgroup analysis showed a difference according to menopausal status. In patients who were >5 years postmenopausal, zoledronic acid was shown to have a significantly better DFS effect than in other age groups: the rates of invasive DFS in postmenopausal patients were 78.2% for zoledronic acid *versus* 71.0% in the control group (adjusted hazard ratio [HR] 0.75, 95% confidence interval [CI] 0.59–0.96, $p = 0.02$) compared with 74.1% for zoledronic acid and 77.2% in the control group for the other age groups. This result seems to be due to a consistent and significant difference in the effects of zoledronic acid according to menopausal status, with an apparent benefit in postmenopausal women and potential harm in all other women ($\chi^2_1 = 14.00$, $p < 0.001$), and is not due to differences between the groups in distant skeletal recurrence

($\chi^2_1 = 0.14$, $p = 0.70$). Oestrogen-receptor status, tumour stage, and lymph-node involvement did not contribute towards treatment effect.

In addition, the 5-year overall survival (OS) rate (the secondary endpoint) in the >5 year postmenopausal cohort showed a significant difference between zoledronic acid and control groups: 84.6% for zoledronic acid *versus* 78.7% for the control group (adjusted HR 0.74, 95% CI 0.55–0.98, $p = 0.04$); however, OS was not significantly different in the other age groups (85.7% for zoledronic acid *versus* 85.1% for placebo). Professor Coleman suggests these initial results shed light on the important role that bone plays in disease progress. He expects that other studies in progress will provide further affirmative data on the effectiveness of zoledronic acid as adjuvant therapy for early BC in postmenopausal women.

Adjuvant letrozole still outperforms tamoxifen after 12 years

The BIG1-98 phase III trial showed that the aromatase inhibitor, letrozole, was better than tamoxifen at improving DFS and distant recurrence-free interval (DRFI) when given as adjuvant therapy (postsurgery, given for 5 years) for endocrine-responsive early BC in postmenopausal women [Thürlimann *et al.* 2005]. Sequential therapy (i.e. letrozole followed by tamoxifen or tamoxifen followed by letrozole) did not improve outcomes over letrozole alone. Professor Richard Gelber (Dana-Farber Cancer Institute, Boston, MA, USA) presented a 12-year update of results and showed that over a median of 8 years, the patients who had received letrozole had an 18% reduced risk of relapse ($p = 0.0002$), improved DRFI ($p = 0.003$) and a 21% reduced risk of death ($p = 0.0006$) compared with those given tamoxifen. Letrozole

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monotherapy tended to be superior also to tamoxifen/letrozole in sequence and similar in outcome to letrozole/tamoxifen in sequence. Thus, adjuvant letrozole continues to show significantly better disease control and OS advantage compared with tamoxifen at this follow-up assessment. A further 5 years of follow up is planned.

Ageism occurs with exemestane treatment

Professor Christos Markopoulos (Athens University Medical School, Athens, Greece) has used the Tamoxifen Exemestane Adjuvant Multinational (TEAM) trial database to determine causes of death among postmenopausal women with early BC (Abstract 5015). The patients had hormone receptor positive tumours (total of 9766 patients, 50% node negative, 68% radiotherapy, 36% chemotherapy [exemestane for 5 years or tamoxifen then exemestane for 2.5 years each]). The researchers compared younger *versus* older patient groups and found that risk of dying due to BC was higher among older patients than younger patients. Whilst most of the older patients died from noncancer-related causes, the authors stated that the portion of patients who died from BC may have been undertreated compared with their younger cohorts. They found that older patients received less radiotherapy and chemotherapy compared with younger patients. This study underscores the need to clarify how elderly patients are treated, and that age *per se* should not preclude them from best available treatments.

Everolimus plus exemestane improves PFS in hormone therapy-resistant advanced BC

Professor José Baselga (Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA) presented results of the BOLERO2 phase III study, which investigated PFS in 724 patients with advanced BC refractory to letrozole or anastrozole, who were given exemestane (25 mg/day) with and without everolimus (10 mg/day) (Abstract 9LBA). The preplanned interim analysis found that the trial had met its primary endpoint: centrally assessed PFS was 10.6 months in patients receiving everolimus plus exemestane *versus* 4.1 months given exemestane monotherapy (HR 0.36, 95% CI 0.27–0.47, $p = 3.3 \times 10^{-15}$). Response rates were also significantly better for the combined drugs than for exemestane monotherapy (9.5% *versus* 0.4%, $p < 0.0001$).

Professor Baselga believes that exemestane plus everolimus therapy represents a new therapeutic option in women with hormone therapy-resistant advanced BC.

Sorafenib provides no added benefit in HER2-negative metastatic breast cancer

The potential benefit of adding sorafenib (400 mg twice daily) to docetaxel (75 mg/m² IV every 3 weeks for a maximum of six cycles) and/or letrozole (2.5 mg orally) therapy for first-line therapy in patients with HER2-negative metastatic BC (FM-B07-01 trial) has been investigated by G. Mariani and colleagues (Fonazione IRCCS Istituto Nazionale Tumori, Milan, Italy; Abstract 17LBA). Docetaxel and letrozole were administered according to hormone receptor status and visceral or nonvisceral disease, and sorafenib or placebo were given by randomized, double-blind methods. There were 218 enrolled patients (75% visceral presentation treated for 43 weeks, 22% hormone-receptor negative treated for 26 weeks). Median PFS in the 146 patients alive at analysis was not significantly different between sorafenib and placebo groups (8.43 months in each group; HR 1.22, 95% CI 0.91–1.62). Two further randomized phase II studies are yet to be reported.

T-DM1 improves progression-free survival in phase II study in metastatic breast cancer

Dr Sara Hurvitz (UCLA School of Medicine, Los Angeles, LA, USA) presented primary efficacy and safety results of a phase II study of trastuzumab emtansine (T-DM1), an antibody-guided drug for the initial treatment of HER2-positive metastatic BC. (We previously reported their preliminary results from ESMO 2010 [Mallarkey and Coombes, 2011].) The study comprised 137 patients with HER2-positive metastatic BC who were randomized to trastuzumab plus docetaxel (T+D; 6 mg/kg IV [8 mg/kg in cycle 1] + 75 or 100 mg/m² IV every 3 weeks) or T-DM1 (3.6 mg/kg IV every 3 weeks) until disease progression or unacceptable toxicity. The median PFS (the primary endpoint) was 14.2 months for those who received T-DM1 compared with 9.2 months for T+D (HR 0.59, 95% CI 0.36–0.97, $p = 0.035$). Similar overall response rates (ORRs) were achieved but T-DM1 produced more durable responses than T+D (64.2% median duration not reached *versus* 58.0% median duration 9.5 months, respectively). The most common adverse events (AEs) for T+D were alopecia, neutropenia, diarrhoea and fatigue,

and for T-DM1 were fatigue, nausea, increased AST and pyrexia. Grade ≥ 3 AEs, serious AEs and treatment discontinuations were less frequent among T-DM1 patients than T+D patients (46.4% *versus* 89.4%, 18.8% *versus* 28.8%, and 7.2% *versus* 28.8%, respectively). The authors concluded that first-line T-DM1 treatment produces a significant improved PFS compared with T+D therapy as well as improved tolerability. They believe the results validate the hypothesis that the unique properties of T-DM1 may lead to an improved therapeutic index; that is, the improved PFS with T-DM1 may be the result of improved tolerability/duration of treatment/response and intrinsic potency of HER2-targeted T-DM1. T-DM1 is being evaluated in phase III clinical trials for HER2-positive metastatic BC.

Skin cancer

Vismodegib produces good overall response in basal cell carcinoma

Luc Dirix (Iridiumkankernetwerk, Antwerp, Belgium) presented results of a pivotal phase II study of vismodegib, a small molecule inhibitor of the hedgehog (Hh) signalling pathway, in advanced basal cell cancer (BCC) (Abstract 1BA). A total of 104 BCC patients (71 locally advanced [laBCC], 33 metastatic BCC [mBCC]) received oral vismodegib 150 mg/day until disease progression (or intolerable toxicity or withdrawal from study). ORR assessed by independent review was the primary endpoint and was 43% for laBCC (95% CI 31–56%, $p < 0.0001$) and 30% for mBCC (95% CI 16–48%, $p < 0.0011$). Secondary endpoints including investigator assessment of ORR and duration of response also corroborated the positive efficacy of the drug. Mild-to-moderate AEs included muscle spasm, alopecia taste disturbance, weight loss and fatigue. There were 26 serious AEs (four possibly related to vismodegib) and seven fatal events though none thought to be drug related. The authors suggest that vismodegib provided substantial clinical benefit in this phase II study and thus holds potential as a potential new targeted therapy for patients with advanced BCC.

Velaparib improves PFS in metastatic melanoma but not significantly

The poly ADP ribose polymerase (PARP) inhibitor, velaparib (VEL), has been studied in combination with temozolomide (TMZ) in a phase II

trial in metastatic melanoma (Mark Middleton *et al.*, Churchill Hospital, Oxford, UK; Abstract 13LBA). There were 346 patients with stage III/IV metastatic melanoma who were randomised to receive TEM (150 mg/m² daily for 5 days every 28 days) with VEL (20/40 mg twice daily for 7 days every 28 days) or placebo. Median PFS (primary endpoint) was nearly doubled with VEL+TMZ *versus* TMZ alone (113 and 110 days for VEL 20 and 40 mg, respectively, *versus* 60 days for TMA alone) although this was not significant. A trend towards improved OS was seen at the higher VEL dosage.

Vemurafenib overall survival still not reached in BRIM3 trial

Updated OS data from the phase III BRAF in melanoma (BRIM3) trial were presented by Grant McArthur (Peter MacCallum Cancer Centre, Melbourne, Australia; Abstract 28LBA). The ongoing study consists of 675 previously untreated patients with unresectable stage III or IV melanoma, positive for the *BRAF*^{V600E} mutation randomized to vemurafenib (960 mg twice daily, VEM) or intravenous (IV) dacarbazine (1000 mg/m² every three weeks, DTIC). At an interim analysis in January 2011, it had been decided to release results and allow crossover from DTIC to VEM because of clear OS benefit. The latest results (i.e. 3 further months of follow up) show that after a median follow up of 6.2 months, median OS for VEM has still not been reached (95% CI 9.59–NR *versus* 7.9 months in the DTIC group, 95% CI 7.26–9.63). The updated HR for OS is 0.44 (95% CI 0.33–0.59) in favour of VEM. The Kaplan–Meier estimate of 6-month survival was 83% for VEM *versus* 63% for DTIC. A consistent ORR of 50% has been confirmed across the entire VEM clinical trial program. VEM has a manageable safety profile (e.g. includes arthralgia, rash, fatigue, photosensitivity) with few drug-related discontinuations. The results suggest VEM is a promising drug for future combination therapies for metastatic melanoma.

Percutaneous hepatic perfusion improves PFS in patients with liver melanoma metastases

James Pingpank (University of Pittsburgh Cancer Institute, Pittsburgh, PA, USA) presented final results from a phase III trial of a new treatment, percutaneous hepatic perfusion (PHP), in patients with melanoma liver metastases. Melanoma of the eye is nonresponsive to BRAF inhibitors and

usually spreads to the liver where no current effective treatment exists and the median OS is 2–4 months (1-year survival 10%). PHP is designed to deliver high-dose chemotherapy to the liver and thus minimize drug exposure to the rest of the body. In this study, melphalan (3 mg/kg ideal body weight infused *via* the hepatic artery for 30 minutes, every 4–8 weeks) was chosen for PHP and was compared against best alternative care (BAC). The hepatic venous return was captured and externally filtered for drug extraction then returned ‘cleaned’ to the body. A total of 93 patients were randomized to PHP or BAC. Overall PFS was significantly better in the PHP group than in the BAC group (median 6.1 *versus* 1.6 months, HR 0.41, $p < 0.0001$). OS (secondary outcome) was not significant owing to the fact that BAC patients were allowed to transfer to PHP once its benefits became apparent (11.4 *versus* 9.9 months, PHP *versus* BAC, respectively). Dr Pingpank concluded that the results show PHP provides a new treatment option for unresectable metastatic melanoma in the liver.

Prostate cancer

Denosumab delays onset of metastases in castration-resistant prostate cancer

A double-blind, randomized, placebo-controlled trial has been conducted to evaluate the efficacy and safety of denosumab (120 mg subcutaneously [SC] every 4 weeks) in 1432 patients with castration-resistant prostate cancer (CRPC; total serum testosterone level <50 ng/dl; high risk for bone metastases, e.g. high prostate-specific antigen [PSA] or low PSA doubling time). Stéphane Oudard (Georges Pompidou Hospital, Paris, France) reiterated results that had been presented at the American Urology Association congress in May 2011. Denosumab was found to increase the median bone metastasis-free survival (primary endpoint) compared with placebo (29.5 *versus* 25.2 months, respectively; HR 0.85, 95% CI 0.73–0.98, $p = 0.03$). This benefit was observed in all patient subgroups (PSA risk factors, Gleason score and demographic factors such as age, region and race). Denosumab also delayed the time to first symptomatic bone metastasis (secondary endpoint). This is the first large randomized study to demonstrate that targeting the bone microenvironment can significantly delay bone metastasis in men with CRPC. Whether or not this leads to a survival benefit remains to be determined.

Single-dose ibandronate is effective for metastatic bone pain in prostate cancer

Peter Hoskin (Mount Vernon Cancer Centre, Northwood, UK) presented results of the first large randomised phase III trial of a bisphosphonate drug for pain control in prostate cancer patients with bone metastases (Abstract 7LBA). There were 470 prostate cancer patients with metastatic bone pain who were randomized to standard single-dose radiotherapy or ibandronate (single 6 mg IV infusion). Pain assessment (WHO pain ladder or Mercadante score) was conducted at baseline and at regular intervals up to 52 weeks after treatment. The only noticeable difference was worse Mercadante scores in the ibandronate group at 4 weeks requiring retreatment. In general, pain assessments over 12 months showed no substantial differences between radiotherapy and ibandronate groups. Further research will look at biomarkers for bone resorption to see which patients might respond best to radiotherapy of ibandronate.

Celecoxib fails in STAMPEDE trial

First results from the STAMPEDE trial of celecoxib added to hormone therapy for hormone-sensitive prostate cancer were presented by Professor Noel Clarke (Christie and Salford Royal Hospitals, Manchester, UK; Abstract 20LBA). The study features a multi-arm, multistage design where men starting standard hormone therapy for prostate cancer are given additional drugs. One arm includes early addition of celecoxib (400 mg twice daily). The study also includes zoledronic acid and docetaxel arms (not reported yet). Patients are assessed for improvement in outcome (measured as failure-free survival [FFS] in early stages and OS in the final stage). So far, there are 2114 patients in the study, and 875 were included in this comparison with results showing that celecoxib plus hormone therapy was no better than hormone monotherapy (305 FFS events; HR 0.98, 95% CI 0.90–1.06). Accrual to this arm of the study has been stopped and the cohort of patients taking celecoxib has been advised to stop taking it. Accrual into the remaining arms continues, including addition of abiraterone.

Abiraterone improves fatigue in metastatic castration-resistant prostate cancer patients

Abiraterone (1 g twice daily) plus prednisone (5 mg twice daily) has been found to improve OS in metastatic CRPC after docetaxel therapy (compared with placebo plus prednisone) in a double-blind study of 1195 patients [de Bono *et al.* 2011]. Dr Cora Sternberg (San Camillo and Forlanini Hospitals,

Rome, Italy) presented a retrospective assessment of patient-reported fatigue from this study. The Brief Fatigue Inventory (BFI) was assessed at baseline and each treatment cycle. Baseline BFI scores were similar for abiraterone and placebo groups; however, abiraterone therapy produced better fatigue outcomes. It significantly improved scores for BFI intensity and BFI interference compared with placebo. The fact that abiraterone may delay fatigue progression and improve fatigue scores shows that, in addition to improving OS, it also improves quality of life in affected patients.

Colorectal cancer

Aflibercept subgroup analyses confirms primary efficacy VELOUR results

Josep Tabernero (Vall D'Hebron University Hospital, Barcelona, Spain) presented results from the VELOUR placebo-controlled phase III trial of aflibercept in combination with FOLFIRI (folinic acid, fluorouracil, irinotecan) in 1226 previously treated metastatic colorectal cancer (mCRC) (Abstract 6LBA). Primary efficacy results were presented earlier in 2011 showing that aflibercept (4 mg/kg IV, 1 hour infusion) significantly improved OS and PFS compared with placebo. In this presentation Professor Tabernero presented results of prespecified subgroups analysis. The subgroups included age (<65 years and ≥65 years), gender, race, prior hypertension, number of organs involved, liver metastases only, and location of primary cancer (colon, sigmoid, rectum). Analysis showed that the OS and PFS improvement with aflibercept was consistent among all subgroups except for those patients with liver metastases only where the treatment effect was greater than in those with disease not confined to the liver. Further, aflibercept's effect was consistent between patients who had and had not received prior bevacizumab. The authors concluded the subgroup analysis confirmed the primary OS and PFS results.

RESPECT shows no PFS benefit for sorafenib

The RESPECT trial is a phase IIb placebo-controlled study of sorafenib (400 mg twice daily, SOR) combined with chemotherapy (modified FOLFOX6 [folinic acid, fluorouracil, oxaliplatin]) in first-line treatment of mCRC. Josep Tabernero (Vall D'Hebron University Hospital, Barcelona, Spain) presented results showing that among the 198 randomized patients there was no difference in PFS (primary endpoint) between the SOR and

placebo groups (median 9.1 *versus* 8.7 months; HR 0.88, 95% CI 0.64–1.23) or time to progression (secondary endpoint) (Abstract 19LBA). Subgroup analysis by KRAS status showed no statistical PFS differences for mutant or wild-type genes between the groups. Grade 3/4 adverse events included neutropenia (more common with SOR than placebo), peripheral sensory neuropathy (placebo > SOR) and grade 3 hand-foot syndrome (20% SOR *versus* 0% placebo)

Head and neck

Panitumumab improves survival in human papilloma virus negative patients with recurrent/metastatic head and neck cancer

Jan Vermorken (Antwerp University Hospital, Antwerp, Belgium) presented an analysis of the phase III SPECTRUM trial looking specifically at outcomes by tumour HPV (human papilloma virus) status in patients with recurrent/metastatic squamous cell cancer of the head and neck (SCCHN) randomized to platinum-based chemotherapy with or without panitumumab (Abstract 25LBA). There were 377 samples evaluable for testing from the total of 657 patients recruited to date, and 83 (22%) and 294 (78%) were found to be HPV+ and HPV-, respectively. Patients with HPV+ tumours were more likely to be nonsmokers, have oropharyngeal primary tumours and more poorly differentiated tumours than those with HPV- tumours. Efficacy results showed that panitumumab plus CT improved OS and PFS in HPV- tumours. The OS HR was 0.71 (95% CI 0.54–0.94), median OS 11.8 *versus* 8.7 months. There was no incremental benefit in patients with HPV+ tumours. There were more serious adverse events in the panitumumab groups than in those who received CT alone (e.g. 53% *versus* 41% for HPV- patients, respectively). This is first report of treatment outcomes related to HPV status in first-line R/M SCCHN. The trend for more favourable outcomes in HPV- disease needs to be confirmed in further studies.

Non-small cell lung cancer

Pemetrexed added to bevacizumab maintenance therapy improves PFS in nonsquamous non-small cell lung cancer

Final efficacy outcomes of the phase III AVEPERL study were presented by F. Barlesi (University of Méditerranée-Assistance Publique Hôpitaux de

Marseille, France; Abstract 34LBA). This is an ongoing study of continuation maintenance with bevacizumab (BEV) with or without pemetrexed (PEM) following first-line BEV–cisplatin–PEM treatment in patients with nonsquamous non-small cell lung cancer (nsNSCLC). There were 253 patients with advanced/metastatic/recurrent nsNSCLC who achieved complete response/partial response/stable disease with first-line treatment and were randomized to continuous maintenance with BEV alone or BEV+PEM. Median PFS (primary endpoint) was significantly better with BEV+PEM than with BEV alone (10.2 *versus* 6.6 months; HR 0.50, $p < 0.001$). This PFS benefit is unprecedented and occurred across all different subgroups. OS data also favours BEV+PEM but are currently immature. Both regimens well tolerated but AEs were more frequent in the BEV+PEM arm. The overall results strongly favour the use of BEV+PEM as continuation maintenance treatment in nsNSCLC patients.

Acknowledgements

This report was compiled following attendance at the 2011 European Multidisciplinary Cancer Congress in Stockholm (23–27 September). The authors have summarized the presentations so that the key points are given together with extra material (e.g. session discussions and personal clinical viewpoints). Our aim has been to collate the key studies in medical oncology as a starting point for further reading. Fuller descriptions of

study methodologies, limitations and results are given in the full abstracts, which have been published in 2011 *Eur J Cancer* 47(Suppl. 1): S3–S673 and 47(Suppl. 2): 1–16, and many of the reported studies are either in press or will be published.

Conflict of interest statement

The authors declare no conflict of interest in preparing this article.

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