Latest advances in medical oncology: highlights from Milan ESMO 2010 annual congress

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The 35th European Society for Medical Oncology (ESMO) Congress was recently held in Milan, Italy. Many exciting new clinical studies were presented at the conference, several of which are summarized in this editorial. Professor David Kerr (ESMO President) said that ‘we still need to understand more about cancer—its biology as well as better insights about treating the right patient, at the right time, with the right drug at the right dose’. With increasing use of molecular classification of cancer, he emphasized the need for a multi-disciplinary approach for every tumour type.

One of the most important clinical studies reported at ESMO was the trial of abiraterone acetate in prostate cancer patients who had previously failed hormone and chemotherapy. Professor Fortunato Ciardiello (ESMO2010 Press Officer) commented that we can now change the approach to treatment because we now have a drug that provides a novel and well-tolerated hormone therapy to patients for which no other treatment options are available. Another practice-changing trial is the OPTIMAL trial presented by Professor Caicun Zhou, which brings new hope to lung cancer patients. Other notable presentations included the ICON7 trial of bevacizumab in ovarian cancer presented by Dr Tim Perren, and results with trastuzumab-DM1 (T-DM1), a monoclonal antibody/cytotoxic conjugate drug with low toxicity, in advanced breast cancer presented by Dr Edith Perez.

Trastuzumab-DM1 is effective and less toxic for first-line therapy of HER2-positive metastatic breast cancer

Edith Perez (Mayo Clinic, Jacksonville, FL, USA) presented the results of the first

randomized trial of T-DM1 as a first-line treatment for metastatic breast cancer. T-DM1 is an antibody–drug conjugate consisting of trastuzumab, which targets cells that overproduce human epidermal growth factor receptor 2 (HER2) protein, and DM1, a cell-killing agent that targets microtubules.

There were 137 women with HER2-positive metastatic breast cancer (with no prior chemotherapy for their metastatic disease) who received trastuzumab plus docetaxel or T-DM1. Median follow up at approximately 6 months revealed an overall response rate of 48% in patients administered T-DM1 compared with 41% in the trastuzumab plus docetaxel group. Notably, clinically relevant adverse events were significantly lower with T-DM1 (37%) compared with trastuzumab plus docetaxel (75%).

Professor Perez explained that the trial is ongoing; however, the early results have prompted a phase II trial to begin, MARIANNE, which will evaluate taxane plus trastuzumab *versus* T-DM1 *versus* T-DM1 plus pertuzumab.

These initial results are heartening because they suggest that future therapies may be as effective but less toxic. Linking of a monoclonal antibody to a cytotoxic drug may thus become a therapeutic possibility not only for HER2 targeting but also for other specific cancers.

Adding cetuximab doubles response rate in triple-negative breast cancer

A phase II study provides first proof that targeting the epidermal growth factor receptor (EGFR) provides substantial clinical benefit for triple-negative breast cancer patients. Adding cetuximab to cisplatin chemotherapy doubled the

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response rate and time to progression when compared with cisplatin chemotherapy given alone in a study of 173 heavily pretreated women. The research was led by Professor Jose Baselga (Vall d'Hebron Hospitals, Barcelona, Spain, now at Massachusetts General Hospital Cancer Center, Boston, MA, USA) and included researchers from Spain, Belgium, Austria, Portugal, the UK and Israel. The study included 173 women with metastatic cancer, randomized to receive cetuximab (400 mg/m² initial dose and then 250 mg/m² weekly) plus up to six 3-weekly cycles of cisplatin, or cisplatin alone. The best overall response rate was seen with the cetuximab/cisplatin combination (20%), which was double the overall response rate with cisplatin alone (10.3%). Adding cetuximab to cisplatin also more than doubled the median length of progression-free survival (PFS) from 1.5 to 3.7 months. Professor Baselga commented that type of improvement is rarely seen in advanced disease and is highly significant. While the results are impressive they now need to be confirmed in a large randomized trial. The implications however are enormous. It suggests that EGFR may play a role in the progression of triple-negative breast cancer. Further research aims at identifying different subtypes within this population, then tailoring appropriate targeted treatment should be able to change the natural history of this disease.

Iniparib in metastatic triple-negative breast cancer: overall survival extended in a phase II study

Joyce O'Shaughnessy (Baylor-Charles A. Sammons Cancer Center and Texas Oncology, Dallas, TX, USA) presented final efficacy and safety results from a trial of iniparib in 123 women with metastatic triple-negative breast cancer (mTNBC) who had previously received up to two prior regimens for metastatic disease. They were randomly assigned to receive gemcitabine-carboplatin alone or with iniparib. Iniparib is a poly (ADP-ribose) polymerase-1 (PARP-1) inhibitor that may prevent cancer cells from repairing their DNA, therefore enhancing the effectiveness of DNA-damaging chemotherapy.

Overall survival (OS) was 12.3 months in the iniparib group compared with 7.7 months with chemotherapy alone. A survival improvement of almost 5 months is unusual in breast cancer and in metastatic tumours in general, so this is an exciting finding. Clinical benefit (complete or partial response or stable disease for at least

6 months) was experienced by 55.7% of patients receiving iniparib *versus* 33.9% with chemotherapy alone. Little or no difference in adverse events was found between the two groups.

Ongoing trials will attempt to establish which chemotherapy treatment is the best partner for iniparib. Agents such as cisplatin, cyclophosphamide and anthracyclines may also be good chemotherapy drugs to combine with iniparib. Iniparib is also being studied in squamous cell non-small-cell lung cancer (NSCLC) and in other difficult-to-treat cancers, including ovarian, pancreatic and brain cancers.

Extending first-line chemotherapy in metastatic breast cancer: meta-analysis shows improved outcomes

The question of how long chemotherapy should be continued in metastatic breast cancer after achieving disease control is subject to considerable debate. The number of chemotherapy cycles given is usually based on response to treatment, symptoms improvement and toxicity of treatment.

Dr Alessandra Gennari (Galliera Hospital, Genova, Italy) presented results of a study to determine whether prolonging chemotherapy after disease response or stabilization was associated with prolonged survival and time to progression. They identified 11 randomized studies comparing longer and shorter durations of chemotherapy in a total of 2269 patients with metastatic breast cancer.

They found that longer chemotherapy duration was associated with a 34% reduction in the rate of disease progression (defined as a significant increase in the size of metastatic lesions and/or the appearance of new metastatic lesions). Longer chemotherapy durations were also associated with a 9% reduction in the rate of death during the course of the studies.

Dr Gennari commented that the results justify a policy of prolonging chemotherapy until disease progression or unacceptable toxicity in metastatic breast cancer. Most oncologists stop chemotherapy when the disease is controlled, and continuing with endocrine therapy in the case of hormone-sensitive disease. In patients with negative hormone receptors this is of course not possible, making the question of duration of chemotherapy even more important. Data on

subgroups (e.g. hormone-receptor positive and negative tumours) would be invaluable to see how continuation of chemotherapy affects them.

Which subsets of patients with metastatic breast cancer benefit from subsequent lines of chemotherapy?

Dr Giovanni Bernardo (Fondazione Maugeri, Pavia, Italy) and colleagues have analysed data from 980 women treated with chemotherapy for metastatic breast cancer in their centre between 1992 and 2006. They presented results suggesting it may be possible to identify subsets of metastatic breast cancer patients who are likely to respond to subsequent lines of chemotherapy.

Their results showed that the median OS shortened with each successive chemotherapy regimen that patients were given. Time to treatment failure also decreased with each new regimen from a median of 9.2 months for first-line therapy to 7.8 and 6.4 months for the second- and third-line drugs, respectively. Beyond third-line therapy there was no significant decrease in the median time to treatment failure of successive therapies.

The researchers found that only one factor they analysed affected a patient's OS time. This was the time to treatment failure for each line of chemotherapy. That is, the more benefit one type of therapy offered, the more benefit the subsequent therapy was likely to offer.

Delayed progression of ovarian cancer with bevacizumab

The early results from the large ICON7 phase III trial were presented by Dr Tim Perren (Leeds Teaching Hospitals NHS Trust, UK). This study includes 1528 women with high-risk early or advanced stage epithelial ovarian cancer, primary peritoneal cancer or fallopian tube cancer. Following preparatory surgery, patients were randomly assigned to six cycles of carboplatin and paclitaxel chemotherapy (once every 3 weeks) or the same chemotherapy plus bevacizumab given concurrently and then as maintenance monotherapy for up to a further 12 cycles. At 12 months, the risk of developing further progression of ovarian cancer was reduced by 15% in bevacizumab-treated patients compared with those who received only chemotherapy (primary endpoint). Preliminary survival data is showing fewer deaths among bevacizumab-treated patients; however, full survival data will not be mature for a further 2 years.

An interesting comment from Dr Perren was that the amount of benefit seen from the addition of bevacizumab varies and diminishes over time. This is the second large randomized trial in ovarian cancer that shows that adding bevacizumab to standard therapy improves PFS. The final results as well as results of ICON 7 translational studies should identify the population who benefits from this treatment.

MLN8237 shows single-agent activity in platinum-resistant ovarian cancer: phase II trial

MLN8237 is a selective inhibitor of Aurora A kinase: a member of a family of kinase enzymes involved in normal cell division, which researchers have found to be overexpressed in some cancer cells including ovarian cancer. Thus, MLN8237 is being investigated as a potential new monotherapy or combined with standard agents such as paclitaxel.

Dr Ursula Matulonis (Dana-Farber Cancer Institute, Boston, MA, USA) reported results of a study of 31 patients (25 ovarian cancer, five primary peritoneal cancer, one fallopian tube carcinoma) whose cancer was resistant or refractory to platinum-based chemotherapy and who had tried at least three other therapies. Patients received oral MLN8237 50 mg twice daily for 7 days in 21-day cycles. Three patients had a partial response to treatment and five had stable disease that was sustained for at least four 21-day cycles.

Dr Matulonis commented that the single-agent activity of the drug is encouraging as well as its durable disease control in some patients. Several patients have remained on the study drug for over 12 months. The most common serious toxicities included neutropenia, stomatitis, leukopenia, thrombocytopenia and fatigue, which were generally reversible during the 14-day break in treatment. Five patients discontinued due to adverse events.

Future development of MLN8237 in combination with other active agents may be a promising avenue to investigate.

IPASS: final results confirm survival benefits of EGFR mutations in lung cancer

Professor Chih-Hsin James Yang (National Taiwan University Hospital, Taiwan) reported final OS results from the landmark IPASS

phase III trial. They confirm that patients with EGFR mutation-positive advanced NSCLC have better OS when treated with gefitinib or chemotherapy than patients whose tumours do not carry such mutations.

Primary endpoint results were presented at ESMO 2008 and compared PFS and OS in 1217 East Asian patients with advanced NSCLC treated with first-line gefitinib or carboplatin and paclitaxel. The matured results showed a median OS of 18.8 months in patients who began treatment with gefitinib, while survival in the chemotherapy group was 17.4 months. This was not significantly different, and is probably explained by the fact that the majority of patients received gefitinib as second choice. In the gefitinib arm, 60% of patients received subsequent platinum-based combination chemotherapy, while 51% of patients in the chemotherapy arm received subsequent gefitinib or erlotinib treatment. Only 31% of patients in the gefitinib arm and 38% in the paclitaxel and carboplatin arm did not receive further systemic anticancer treatment.

Median survival was 21.6 months (first-line gefitinib) and 21.9 months (combination chemotherapy) among patients whose tumour tissue contained EGFR mutations. This was compared with 11.2 months median survival in gefitinib patients whose tumours tested negative for EGFR mutations and 12.7 months for EGFR-negative patients treated with chemotherapy. Thus, mature OS data show that patients with EGFR mutation-positive advanced NSCLC have better outcomes than patients with EGFR mutation-negative disease.

This demonstrates that EGFR mutation status is a predictive factor for better PFS with gefitinib and adds to the body of evidence that different types of NSCLC exist. It is fundamental to tailor each patient's treatment on the basis of genetic characteristics.

Afatinib provides benefit after lung cancer progression following EGFR inhibitor treatment

Dr Vincent Miller (Memorial Sloan-Kettering Cancer Center, New York, USA) reported findings of the LUX-Lung 1 phase IIb/III trial showing that patients with advanced NSCLC, already treated with EGFR inhibitors (erlotinib or gefitinib), gained further benefits (PFS, tumour

shrinkage) when treated with afatinib, an irreversible inhibitor of EGFR and HER2.

There were 585 patients with lung adenocarcinoma whose cancer had progressed after chemotherapy with erlotinib or gefitinib who were randomly assigned to best supportive care plus placebo, or supportive care plus afatinib.

Median OS was 10.78 months in the afatinib group *versus* 11.96 months for placebo: more than expected for both groups. Median PFS was 3.3 months with afatinib *versus* 1.1 month for placebo. Disease control rate at 8 weeks was 58% for afatinib *versus* 19% for placebo, and the investigator analysis saw an overall response rate of 11% for afatinib *versus* 0.5% for placebo. The trial did not achieve its primary endpoint of extending OS; however, Dr Miller commented that this did not fully diminish afatinib's potential value in treating this most lethal of cancers.

First-line erlotinib improves PFS in advanced NSCLC: results of the OPTIMAL trial

New results from the OPTIMAL trial were reported by Professor Caicun Zhou (Shanghai Pulmonary Hospital, Tongji University, China). This study included 165 patients whose lung cancer carried mutations activating EGFR. Participants had not received systemic treatment for their cancer. There were 83 who were randomly assigned to receive erlotinib 150 mg/day and 82 patients received a 'doublet' combination chemotherapy of gemcitabine and carboplatin.

The median PFS (primary endpoint) among erlotinib patients was 13.1 months compared with 4.6 months those receiving chemotherapy. The objective response rate with erlotinib was 83%, compared with 36% for chemotherapy. Currently, there are 31 patients still under study in the erlotinib group that are progression free compared with only 1 in the chemotherapy group. Safety analyses showed lower rates of adverse events with erlotinib than with chemotherapy.

This is the first reported prospective phase III study to confirm the role of erlotinib in advanced NSCLC patients with EGFR-activating mutations. Professor Zhou commented that the fact that it nearly tripled PFS compared with standard chemotherapy suggests it should be used as soon as possible after the diagnosis of

advanced NSCLC with EGFR-activating mutations.

These results combined with data emerging phase III studies with gefitinib show that erlotinib or gefitinib are very good prospects for frontline therapy in metastatic NSCLC with activating EGFR mutations. The studies so far have been conducted in Asian populations but a confirmatory study in Caucasian patients is currently ongoing.

The 'pan-HER' inhibitor, PF-299, slows disease progression in advanced NSCLC: first results

PF-299 irreversibly inhibits several members of the HER family, including EGFR, HER-2 and HER-4. This makes it substantially different from drugs such as erlotinib and gefitinib. Preclinical work shows that it inhibits both wild-type and mutant EGFR signalling, including forms of NSCLC that are resistant to EGFR inhibitors such as erlotinib and gefitinib.

Preliminary results from an ongoing phase II trial of PF-299 were reported by Dr Tony Mok (Chinese University of Hong Kong). It included patients with advanced NSCLC and no prior systemic treatment for their disease. All were either nonsmokers or light smokers, or were known to have EGFR mutations.

To date, 74 of 80 planned patients have enrolled: 41 had known EGFR status and 27 had activating mutations. Patients received PF-299, 30 mg or 45 mg once daily. After 9 months of treatment, PFS was 57.1% across all patients and 84.7% in patients with EGFR mutations (the expected median PFS with standard-of-care chemotherapy in this patient population is approximately 6 months).

Targeting MET in addition to EGFR benefits some patients with advanced NSCLC

Dr David Spigel (Sarah Cannon Research Institute, Nashville, TN, USA) reported the results of double-blind phase II trial of 128 patients with advanced NSCLC randomly assigned to treatment with erlotinib plus placebo, or erlotinib plus MetMab, a monoclonal antibody that binds specifically to the MET receptor on cancer cells.

There were 51% of patients whose tumours expressed MET. In this subset, MetMab plus erlotinib produced better OS and longer PFS

than erlotinib plus placebo. Ironically, the patients whose tumours did not express the MET protein appeared to do worse when treated with MetMab plus erlotinib. Dr Spigel suggested that MetMab may interfere with erlotinib's activity in these patients; however, this needs to be investigated further.

MET is an important switch in cancer cells: when turned on, it influences the growth of these cells. MET activation has also been associated with resistance of lung cancers to EGFR inhibitors such as erlotinib. MetMab helps target this switch and turn it off. This is the second trial in lung cancer where MET targeting with erlotinib suggests a better warrants validation in a phase III trial.

Early signs of pazopanib's promise in relapsed/refractory urothelial cancer

Median survival in metastatic urothelial cancer is approximately 12–15 months with only a 10–15% chance of prolongation with use of standard chemotherapy regimens. In those patients whose cancers relapse or do not respond to upfront therapy, there are few second-line treatment options and palliative care is the option in the majority of cases.

Dr Andrea Necchi (Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy) presented results to date of a phase II trial using pazopanib in such patients. To date, they have enrolled 18 of 41 planned patients with metastatic urothelial cancer that had already failed to respond to at least one prior chemotherapy regimen. Patients received pazopanib 800 mg once daily until their disease progressed or they experienced unacceptable toxicity. Tumour shrinkage has occurred in 4 of 18 patients and death of metastatic tumour has begun in 12 of 18 patients (observed by monthly computed tomography and positron emission tomography scans). As part of pazopanib's activity is anti-angiogenic, this is not surprising; however, the positive result in so many patients is encouraging and longer-term results in more patients are eagerly awaited.

Survival improvement with abiraterone in metastatic castration-resistant prostate cancer

Exciting results from a large phase III multicentre study of 1195 patients with metastatic castration-resistant prostate cancer (CRPC) who have progressed after chemotherapy (including docetaxel)

show they live significantly longer after treatment with abiraterone acetate compared with placebo. Dr Johann de Bono (Institute of Cancer Research and Royal Marsden NHS Foundation Trust, London, UK) presented the study results and commented that we are now looking at a new standard of care for men with advanced prostate cancer who progress despite receiving docetaxel-based chemotherapy.

Median OS was 10.9 months in 398 patients who randomly received prednisone plus placebo whereas it was extended to 14.8 months in 797 patients who received abiraterone acetate plus prednisone. There were also significant differences between abiraterone and placebo groups with respect to all of the trial's secondary end-points, including time to prostate-specific antigen (PSA) progression, radiographic PFS and PSA response rate.

Because the benefits of abiraterone became known during a prespecified interim analysis of the study, it was deemed ethically responsible to unblind the trial and allow placebo patients to receive abiraterone acetate. While abiraterone acetate represents an important addition to the treatment of CRPC, a further step is to determine which patients benefit most from the drug.

Everolimus delays tumour progression in hard-to-treat neuroendocrine tumours

Dr Marianne Pavel (Charité University, Berlin, Germany) presented results of a phase III trial showing that everolimus plus octreotide LAR improved PFS by 5.1 months over placebo plus octreotide LAR in patients with advanced neuroendocrine tumours. In the new RADIANT-2 trial, researchers in several European countries and the USA treated 429 patients with progressing, well or moderately differentiated advanced neuroendocrine tumours. Overall, the median PFS in the everolimus-treated patients was 16.4 months, which was significantly longer than the median 11.3 months for placebo plus octreotide LAR.

This is the first phase III trial combining everolimus with octreotide LAR in neuroendocrine tumours and it offers the hope of antitumour efficacy in addition to the currently available agents, somatostatin analogues and interferon. Further steps will be to identify patients that may benefit most from everolimus plus octreotide LAR compared with octreotide LAR alone.

Oral drug GSK2118436 shrinks secondary tumours in melanoma patients

Of all solid tumours, melanoma has the greatest capacity to spread via the blood stream to the brain. Overall, 15–20% of patients with melanoma that has spread beyond the skin have brain metastases at initial diagnosis, and nearly 75% have them at autopsy. Currently, there is no evidence that any therapy prolongs survival in patients with multiple melanoma brain metastases. The median OS time for all patients with melanoma brain metastases is 16 weeks from diagnosis of brain involvement.

The oral drug, GSK2118436, is being developed to treat melanoma skin cancers. Dr Georgina Long (Melanoma Institute Australia and Westmead Hospital, Sydney, Australia) reported the results in a subgroup of 10 melanoma patients with previously untreated brain metastases from an international phase I/II trial. Dr Long and colleagues tested GSK2118436 among melanoma patients with a mutation of the gene for BRAF protein, which is mutated in 50% of human melanomas. The drug binds to the activated form of the BRAF protein in the melanoma cell, causing the cell to stop proliferating.

All 10 patients experienced control of melanoma brain metastases: 9 had reductions in the overall size of their brain metastases. The overall reductions ranged from 20% to 100% of brain metastases that were 3 mm or larger in diameter before treatment.

An update of activity and safety in all subjects of the phase I/II trial will be presented in November 2010 at the meeting of the Society for Melanoma Research in Sydney.

Questions remain for cetuximab in first-line metastatic colorectal cancer

Disappointing and unexpected results from the NORDIC VII study were presented by Professor Kjell Magne Tveit (Oslo University Hospital, Oslo, Norway). The study included 566 patients with metastatic colorectal cancer (mCRC) who were randomly assigned to first-line therapy of a combination of 5-fluorouracil, folinate and oxaliplatin (NORDIC FLOX), FLOX plus cetuximab until disease progression, or FLOX intermittently plus continuous cetuximab. The addition of cetuximab did not improve response rate, PFS or OS.

Cetuximab has a documented beneficial effect in later stages of mCRC when given alone or with chemotherapy. Thus, the researchers expected similar findings would be found in early stage when given together with the oxaliplatin regimen. Also unexpectedly, the lack of significant benefit was found in subgroups with wild-type KRAS gene.

Mixed results have been found in other trials where cetuximab was added to chemotherapy as first-line treatment in colorectal cancer. In the phase-III CRYSTAL study, cetuximab combined with an irinotecan-based FOLFIRI had a positive effect. Similarly, cetuximab was beneficial when combined with FOLFOX in the phase-II

OPUS study. However, the recent phase III COIN study, which also used oxaliplatin combination as standard, did not show a positive effect with cetuximab addition.

Thus, the current study and the COIN study question whether cetuximab has a clinically significant effect in first-line therapy of mCRC when combined with oxaliplatin. It is essential that all of the separate study results are subjected to meta-analysis to see whether or not adding cetuximab is an efficacious strategy.

Conflict of interest statement

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

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