From the podium to the patient: bringing the 2008 ASCO meeting to the clinic

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Around 4,800 abstracts on preclinical and clinical research in different oncology areas were presented and discussed by oncology clinicians and scientists at the 44th American Society of Clinical Oncology meeting, the largest international forum in the field. As expected, the meeting provided valuable insights into future developments as well as enlightening clinicians regarding current controversies. This manuscript is an opinion-based review of the studies presented at the meeting, focusing on findings from randomized phase III trials and translational researches that, in the authors' opinion, are most likely to modify clinical practice or help scientists in designing future translational and clinical studies. ***Anti-Cancer Drugs***

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Introduction

The 44th annual meeting of the American Society of Clinical Oncology (ASCO) was held from 30 May to 3 June 2008 in Chicago, Illinois, USA. In line with its principal mission, this year's conference sought to facilitate the dissemination of clinical and translational research in the diagnosis, prevention, and treatment of cancer through communication among experts from different parts of the world. Among the most interesting advances, there are the findings of a study showing that patients with colon cancer expressing a wild-type form of the KRAS gene respond better to epidermal growth factor receptor (EGFR) inhibitors than those in whom KRAS is mutated [1]. Notably, with immediate effect, the European Medicines Agency has restricted the use of cetuximab as a first-line treatment for patients with colon cancer to those whose tumors have the wild-type KRAS gene.

This review focuses on randomized phase III trials and translational research presented at the 44th ASCO meeting that, in the authors' opinion, may have an impact on clinical practice or help cancer researchers plan future studies. These advances are grouped into four major tracks, namely breast cancer, colorectal cancer (CRC), non-small cell lung cancer (NSCLC), and miscellaneous.

Breast cancer

Adjuvant treatment

Recent years have seen important advances in adjuvant therapy, in particular, the introduction of aromatase inhibitors for postmenopausal women with receptor-positive disease and the widespread use of taxanes. Nevertheless, important questions remain; some were answered and others highlighted at ASCO 2008.

Hormonal therapy and bisphosphonates

The Austrian Breast and Colorectal Cancer Study Group Trial 12 This randomized, open-label, phase III, modified 2×2, four-arm trial addressed two questions. First, the efficacy and tolerability of oral tamoxifen and goserelin was compared with anastrozole and goserelin. Second, the potential benefits of zoledronic acid as adjuvant therapy were studied in women randomized to receive the bisphosphonate or placebo for 3 years [2]. In all, 1893 premenopausal women, with endocrine responsive stage I/II breast cancer and fewer than 10 involved lymph nodes were studied. Adjuvant chemotherapy was not permitted, but preoperative chemotherapy was administered to about 5% of patients; disease-free survival (DFS) was the primary endpoint.

With a median follow-up of 60 months outcomes were good, overall 5-year DFS being 94% and overall survival (OS) 98.2%. With regard to the comparison of endocrine therapies, no significant difference was observed in terms of DFS [hazard ratio (HR) = 1.09, 95% confidence interval (CI) 0.78–1.53, $P = 0.59$], relapse-free survival (RFS) (HR = 1.11, 95% CI: 0.80–1.56, $P = 0.52$), and OS (HR = 1.79, 95% CI: 0.95–3.37, $P = 0.06$) between the tamoxifen and anastrozole arms. The dominant effect of ovarian suppression with the luteinizing hormone-releasing hormone agonist goserelin was hypothesized as a possible explanation.

The second question generated intriguing results. The addition of zoledronic acid to endocrine therapy

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significantly decreased the risk of DFS events by 36% (HR = 0.64, 95% CI: 0.46–0.91, $P = 0.01$) and the risk of RFS events by 35% (HR = 0.65, 95% CI: 0.46–0.92, $P = 0.01$). Notably, this therapeutic benefit was observed with regard to reduction of bone metastases recurrence, non-bone metastases recurrence, loco-regional recurrence, and contralateral recurrence. Forest plots showed that the effect for all subgroups clustered around the main effect with no interaction. The use of the bisphosphonate also resulted in a trend toward improved OS (HR = 0.60, $P = 0.1$). Interestingly, these benefits were most apparent in those women who received the aromatase inhibitor as adjuvant endocrine therapy.

The toxicity profiles of the different treatments were as expected, with the observation of higher rates of arthralgia, bone pain, and fever in the anastrozole/zoledronate arm, and higher occurrence of thrombosis and uterine polyps in the tamoxifen/zoledronate arm. No confirmed cases of osteonecrosis of the jaw or renal toxicity were found.

Although fascinating, these findings are not yet practice changing for several reasons. The 'control' endocrine arm (goserelin and tamoxifen for 3 years) was not standard, and the trial was underpowered to answer the endocrine comparison. The open-label design and absence of stratification for HER-2 status were also limitations. The value of combining a luteinizing hormone-releasing hormone agonist with an aromatase inhibitor in premenopausal women will be clarified by the results of the ongoing Suppression of Ovarian Function Trial and the Tamoxifen and Exemestane Trial of the Breast International Group [3]. Likewise, the results of ongoing trials including the AZURE/Breast International Group-1-04 trial [4], will clarify the role of bisphosphonates as anticancer agents in the adjuvant setting.

Adjuvant tamoxifen to offer more The optimal duration of adjuvant tamoxifen was investigated in this randomized trial, initially designed to recruit 8000 women in the UK and Ireland [5]. Between 1991 and 2005, 6952 women with estrogen receptor positive (39%), or estrogen receptor untested (61%) invasive breast cancer, who had completed at least 4 years of adjuvant tamoxifen, were randomized between continuing tamoxifen for another 5 years or stopping. Notably, 81% of patients allocated to continue, and 3% of those allocated to stop, continued adjuvant tamoxifen after randomization.

With a median follow-up of 4.2 years, fewer recurrences occurred (relative risk = 0.95, 95% CI: 0.83–1.09, $P = 0.4$) among patients allocated to long-term tamoxifen. Although data are still immature, breast cancer mortality was lower in patients receiving extended treatment. Despite a doubling in the incidence of endometrial cancer (2.2 vs. 1.1%) with extended tamoxifen, there was no increase in deaths from endometrial cancer nor from any other non-breast cancer. These results are consistent with preliminary findings from the Adjuvant Tamoxifen Longer Against Shorter trial, which reported a DFS but not OS benefit with extended tamoxifen [6]. Importantly, earlier trials showing conflicting results were largely underpowered [7]. A pooled analysis combining results from the 'adjuvant tamoxifen to offer more' and 'Adjuvant Tamoxifen Longer Against Shorter' studies indicates that continuation of tamoxifen beyond the first 5 years reduces recurrence over the following years (odds ratio = 0.90, 95% CI: 0.84–0.98, $P = 0.01$), but longer follow-up is needed to assess the effect, if any, on mortality.

Where do the preliminary results of the 'adjuvant tamoxifen to offer more' trial sit in relation to the question of the optimal duration of adjuvant endocrine therapy? Ongoing studies will answer this important question in relation to the role of aromatase inhibitors. For now, extended tamoxifen may be considered for premenopausal women or postmenopausal patients in whom aromatase inhibitors are contraindicated. It is also an option for women in countries with limited resources where aromatase inhibitors are not available.

Chemotherapy

Perhaps the two most interesting adjuvant studies were 'negative', but both carried important messages.

tAnGo Increasing acceptance of taxanes as 'standard' therapy highlights the question of how to further improve outcomes. In this UK randomized, open-label, multicenter phase III trial women received adjuvant treatment with epirubicin/cyclophosphamide 90/600 mg/m^2 every 3 weeks for four cycles followed by paclitaxel (175 mg/m^2 every 3 weeks) either alone or combined with gemcitabine (1250 mg/m^2 on days 1 and 8, every 3 weeks) for a further four cycles [8].

Between August 2001 and November 2005, 3141 patients with operable breast cancer (any node or hormonal receptor status) were accrued, with DFS as the primary endpoint. Results were presented with a median follow-up of 34.9 months after the occurrence of 339 deaths and 524 recurrences. No significant difference was observed in DFS (HR = 1.0, 95% CI: 0.8–1.2, $P = 0.96$) or in OS (HR = 1.1, 95% CI: 0.9–1.4, $P = 0.35$) between the paclitaxel and paclitaxel plus gemcitabine treatment arms.

The trial was powered adequately. These results are, therefore, a valuable reminder that benefits observed in women with advanced disease [9] do not always translate into survival benefit in the adjuvant setting.

CALGB-49907 A second study looked at adjuvant therapy in women aged above 65 years with pT1 (> 1 cm)-T4, N0-3, M0 BC. This randomized, phase III intergroup trial compared four cycles of doxorubicin/cyclophosphamide (AC) or six cycles of cyclophosphamide/methotrexate/5-fluorouracil (CMF) to capecitabine (1000 mg/m^2 twice daily on days 1–14 every 3 weeks for six cycles) [10], the choice of AC or CMF as standard therapy was at the investigators discretion. The study, conducted through the Cancer Trials Support Unit of the National Cancer Institute, was designed as a noninferiority trial, with RFS as the primary endpoint, the hope being that oral chemotherapy could be as effective as standard intravenous therapy in older patients. According to an adaptive sample size calculation based on Bayesian prediction, 633 patients were assigned randomly to capecitabine ($n = 307$) or AC/CMF ($n = 326$). Accrual stopped when the first planned analysis showed a statistically high probability that capecitabine was inferior to AC/CMF. With a median follow-up of 2.4 years, in a multivariate analysis, patients receiving capecitabine had a significantly higher risk of relapse (HR = 2.09, 95% CI: 1.4–3.2, $P = 0.0006$) or death (HR = 1.85, 95% CI: 1.1–3.1, $P = 0.02$) than those on standard therapy. An unplanned subset analysis showed that this negative impact appeared greatest in patients with hormonal receptor negative disease (HR for relapse = 4.39, 95% CI: 2.9–6.7, $P < 0.0001$).

Given the activity of capecitabine in women with chemoresistant advanced breast cancer, these results might be considered surprising. The results of the TACT2 study, in which women are randomized to receive CMF or capecitabine after anthracycline-based chemotherapy as adjuvant therapy are awaited with interest. For now, perhaps the most important finding from this study is that older women do tolerate standard therapy, especially the AC regimen. Although only about 60% of patients received all six cycles of CMF, and about 80% received six cycles of capecitabine, 90% completed all four courses of AC. This reinforces the notion that older patients with a good life expectancy should receive the best available therapies, independently of their chronological age.

Advanced disease

The armamentarium of treatments for metastatic breast cancer is increasing thanks to the introduction of new targets and biologic therapies. One of these targets, HER-2 is the most clinically relevant, with trastuzumab established as standard therapy but we still not fully understand how best it should be used. Another new biologic, bevacizumab, the humanized monoclonal antibody that binds to the vascular endothelial growth factor (VEGF) family member VEGF-A certainly enhances the activity of chemotherapy, and emerging data are defining better its clinical value.

The AVADO trial

Results from preclinical and clinical studies seem to indicate a synergy between chemotherapy and bevacizumab. This could be explained by the mechanism of vascular normalization induced by bevacizumab [11,12] leading to enhanced delivery of chemotherapy to the tumor.

Bevacizumab has previously been approved by the US Food and Drug Administration (FDA) for use in combination regimens for the first-line treatment of metastatic colon cancer and metastatic NSCLC. It has now also been provisionally approved for use in combination with paclitaxel for the first-line treatment of women with HER2-negative metastatic breast cancer. This was based on the E2100 phase III study that showed the addition of bevacizumab to weekly paclitaxel doubled progression-free survival (PFS) compared with paclitaxel alone (HR = 0.48, $P < 0.0001$) [13].

Before converting this provisional approval into a full approval, the FDA will review results from additional phase III studies. These include AVADO the results of which were reported at this year's ASCO and were among the most discussed [14]. AVADO was an international, randomized, placebo-controlled trial that enrolled 736 patients with previously untreated, locally recurrent, or metastatic HER-2-negative breast cancer. They were randomized to one of two doses of bevacizumab (7.5 or 15 mg/kg) or placebo, each given every 3 weeks in combination with docetaxel at 100 mg/m^2 for up to nine cycles. Patients discontinuing docetaxel for toxicity or after nine cycles continued bevacizumab or placebo until disease progression. The primary endpoint was PFS and assuming a median PFS of 6 months in the control arm, the study was designed to detect an increase to 8.6 months in each of the bevacizumab arms. This study was not powered to detect a difference between the two bevacizumab arms.

With median follow-up of around 11 months, PFS was statistically significantly superior for the bevacizumab-containing arms compared with docetaxel alone (HR = 0.79, 95% CI: 0.63–0.98, $P = 0.0318$ and 0.72, 95% CI: 0.57–0.90, $P = 0.0099$, respectively, for 7.5 and 15 mg/kg arms). Although subgroup analyses were not adequately powered to demonstrate differences, the effect on PFS observed for each subgroup was consistent with that for the overall population. In addition, both bevacizumab arms resulted in a statistically higher response rate than docetaxel alone (placebo vs. bevacizumab 7.5 mg/kg: 44 vs. 55%, $P = 0.03$; placebo vs. bevacizumab 15 mg/kg: 44 vs. 63% $P = 0.0001$). Data on OS are still immature and expected in April 2009. In terms of toxicity, bevacizumab caused a modest increase in adverse events but the overall findings did not reveal any new safety signals.

Although it achieved its primary endpoint, the AVADO trial was widely perceived as a positive study with disappointing results. The magnitude of absolute improvement in PFS was much smaller than in E2100 (less than 1 month and 5.5 months, respectively). Although cross-trial comparisons are fraught with danger, these differences are substantial and several hypotheses were formulated in an attempt to explain them. Weekly paclitaxel may have greater antiangiogenic activity and exert a 'dual hit' on angiogenesis when combined with bevacizumab. Tolerability, may also favor partnering bevacizumab with paclitaxel rather than docetaxel.

Trastuzumab

In pivotal trials trastuzumab was administered to disease progression, but preclinical models and nonrandomized data support its use beyond progression. Despite the cost implications, this has become routine practice for many oncologists without prospective data in its support. At ASCO 2008 von Minckwitz and colleagues [15] presented compelling data justifying the continuation of trastuzumab beyond progression.

Women with HER-2-positive advanced breast cancer, whose disease had progressed on trastuzumab, had received one cycle or no chemotherapy with a left ventricular ejection fraction of greater than 50% were randomized between continuing or stopping trastuzumab while starting capecitabine. The study aimed to recruit nearly 500 patients but closed early when lapatinib was approved in this indication; at this point 156 women had been randomized (111 previously treated with docetaxel/trastuzumab and 42 with other chemotherapy and trastuzumab as first-line metastatic therapy; three had received adjuvant docetaxel/trastuzumab). Despite this early closure, the study generated strikingly clear results. Continuing rather than stopping trastuzumab with the capecitabine led to improvement in the primary endpoint of time to progression (8.2 and 5.6 months, respectively; HR = 0.69, $P = 0.03$), response rate (48 and 27%; $P = 0.01$), and a trend toward better survival (25.5 and 20.5 months; P = NS).

Now there are three proven, effective strategies for targeting HER-2 after progression on trastuzumab/chemotherapy, and the prospect of more. When changing chemotherapy, trastuzumab can simply be continued. Alternatively, the oral HER-1/HER-2 tyrosine kinase inhibitor lapatinib may be introduced in place of trastuzumab, in combination with chemotherapy [16] or lapatinib can be added to trastuzumab. Another HER-2-targeted monoclonal antibody, pertuzumab, is also active when added to trastuzumab in patients progressing on treatment [17].

Lapatinib

This orally active, small molecule inhibitor of both EGFR and HER-2 tyrosine kinases adds to the efficacy of capecitabine in women with HER2-positive metastatic disease previously treated with trastuzumab [16].

A phase III trial compared the efficacy of lapatinib alone (1500 mg/day) and at the same dose in combination with trastuzumab (trastuzumab 2 mg/kg weekly) in patients with HER-2-positive metastatic breast cancer who progressed on trastuzumab [18]. Notably, 28% allocated to lapatinib and 34% of patients allocated to lapatinib and trastuzumab had received at least six earlier chemotherapy regimens. In addition, median earlier trastuzumab regimens for metastatic disease were three for both arms.

A significant improvement was seen in PFS, the primary endpoint, with the combination in the intention to treat population (12 vs. 8.1 months, HR = 0.73, 95% CI: 0.57–0.93, $P = 0.008$). Moreover, in a multivariate analysis the combination of lapatinib and trastuzumab treatment had an independent beneficial effect, together with good performance status, absence of liver involvement, and less than three metastatic sites of disease. Toxicity was similar between treatment arms with the exception of a statistically higher incidence of diarrhea with the combination (60 vs. 48%, $P = 0.03$).

This is the first phase III trial to demonstrate benefit from combining two HER2-targeted agents. It also identifies a valuable chemotherapy-free option for women with HER2-positive metastatic disease. Finally, these results support the evaluation of 'total HER-2 blockade' in earlier stages of breast cancer, as in the combination arm of the Adjuvant Lapatinib and/or Trastuzumab Treatment Optimisation trial.

Colorectal cancer

Despite many recent therapeutic advances CRC remains a major problem throughout the world, affecting close to 1 000 000 people, with half of them dying within 10 years of surgery. Significant management advances in the adjuvant and advanced settings were presented, improving our understanding of the biology of the disease, and allowing better individualization of patient treatment.

Adjuvant treatment

Two important abstracts from the National Surgical Adjuvant Breast and Bowel Project (NSABP), focused on adjuvant chemotherapy. The first updated DFS and OS results of weekly adjuvant oxaliplatin-based chemotherapy. The second reported the safety of bevacizumab administered with chemotherapy after radical surgery.

NSABP C-07

This study [19] enrolled over 2400 patients after radical surgery. They received either a weekly schedule of 5-fluorouracil (5-FU; 500 mg/m^2 bolus) followed by folinic acid (FA; 500 mg/m^2) weekly for 6 weeks repeated

three times, or the same combination given with intravenous oxaliplatin, 85 mg/m^2, on days 1, 15, and 28 (the FLOX regimen).

DFS results, the primary end-point of the trial, have already been published, showing significant benefit for the FLOX arm [20]. Here, results of the secondary endpoint, OS, were presented with a median follow-up of 67 months. The number of deaths recorded in both arms was lower than expected, reducing the power of the trial. Nonetheless, a survival advantage was reported for the FLOX arm (OS rate at 6 years, 77.7 vs. 73.5%). Although not reaching statistical significance ($P = 0.06$), the results are clinically meaningful, given the 15% decrease in the risk of recurrence, developing a second primary or dying of any cause. With a lower cumulative dose of oxaliplatin, the results of the study parallel and reinforce those of the Multicenter International Study for Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colorectal Cancer (MOSAIC) trial [21] confirming oxaliplatin-based regimens as the gold standard adjuvant treatment for patients with stage III CRC, irrespective of the partner 5-FU regimen.

NSABP C-08

When new active agents are proposed in the adjuvant setting, where many patients are already cured and others will die irrespective of such treatment, tolerability is a major concern. In this trial, 2700 patients with CRC were assigned randomly to bevacizumab or placebo in addition to oxaliplatin-based chemotherapy [22]. No unexpected toxicity was observed in the experimental arm, although the most severe toxicities did appear greater in the small number of patients aged over 80 years. Serious cardiovascular complications (cardiac or CNS ischemia, arterial thrombotic events), gastrointestinal perforations, or significant hemorrhages were no greater in the bevacizumab arm. As expected, there was a higher rate of grades 3–4 hypertension (12.7 vs. 1.8%, $P < 0.001$), proteinuria (0.9 vs. 0.2%, $P = 0.035$), and wound complications (1.7 vs. 0.3%, $P < 0.001$) in patients receiving the VEGF inhibitor. For reasons that were not clear, severe thrombocytopenia and allergic reactions were significantly less frequent in patients receiving bevacizumab (1.4 and 3.1% vs. 3.4 and 4.7%, respectively) but these patients had a significantly higher rate of moderate or severe pain (11.1 and 6.3%, $P < 0.001$), specifically chest, muscle, or joint. Although it is reassuring that the addition of bevacizumab did not substantially increase toxicity, its incorporation into adjuvant regimens cannot be recommended until efficacy data become available.

CPT-GMA-301

The previously reported Pan-European Trials in Adjuvant Colon Cancer (PETACC) III [23], ACCORD-02 [24], and Cancer and Leukemia Group B (CALGB) 89803 [25] trials of irinotecan-based therapies have all failed to show significant benefit in the adjuvant setting, not even those enrolling high-risk stage III CRC patients, who are at the highest risk of recurrence. Nevertheless, given the undisputed activity of irinotecan in patients with advanced disease, there remains interest in defining its role in patients with 'early' disease. The CPT-GMA-301 study [26] evaluated postoperative irinotecan combined with 5-FU (the FOLFIRI regimen) versus 5-FU in patients with radically resected liver metastasis, and no evidence of extrahepatic spread, who had not received preoperative chemotherapy. The study aimed to detect a 36% decrease in the primary endpoint of DFS. Preplanned stratification factors were number of hepatic lesions (one vs. more than one), earlier adjuvant chemotherapy (yes vs. no), and time from initial colorectal surgery to liver recurrence metastasis (within or beyond the first year). With 321 patients randomized in 15 countries median DFS was 21.6 and 24.7 months for the 5-FU and FOLFIRI groups, respectively. The HR for DFS, adjusted for the stratification factors, was 0.89 (95% CI: 0.66–1.19, $P = 0.47$). FOLFIRI did, however, cause significantly more toxicity, especially neutropenia.

This latest negative trial shows that irinotecan-based regimens are not effective in the adjuvant setting. After potentially curative surgery, irinotecan does not yet have a proven role.

Advanced disease

Prolonged administration of oxaliplatin is associated with cumulative peripheral neurosensory impairment, and the best strategy to counteract this dose-limiting toxicity remains unclear. Two abstracts addressed the question and tested the putative neuroprotective role of calcium/magnesium supplementation.

Combined oxaliplatin neurotoxicity prevention trial and NO04C7

These studies investigated two approaches to reduce oxaliplatin-induced neurotoxicity: intermittent administration of oxaliplatin, and intravenous calcium/magnesium supplementation.

In Combined Oxaliplatin Neurotoxicity Prevention trial patients with metastatic disease were randomized to intermittent or continuous FOLFOX with bevacizumab at the standard dose of 5 mg/kg every 2 weeks, and to intravenous calcium/magnesium supplementation or placebo in a 2×2 design [27]. The study planned to enroll 532 patients but closed early at the recommendation of the Independent Data Monitoring Committee when an unplanned interim analysis seemed to show a substantially lower response rate in patients receiving calcium/magnesium supplementation (17.7 and 32.8%, respectively). Subsequent formal independent radiological review did not confirm any negative effect of supple-

mentation in patients receiving either oxaliplatin regimen. Despite early termination, the study did meet its primary endpoint, showing a longer time to treatment failure for patients exposed to oxaliplatin intermittently (5.6 vs. 4.2 months, $P = 0.002$). Notably, there was markedly less neurotoxicity in the intermittent oxaliplatin arm, with fewer dose delays, reductions, or discontinuations. Intermittent oxaliplatin can, therefore, be considered standard as in OPTIMal use of Oxaliplatin (OPTIMOX) 1.

N04C7, a randomized trial from the North Central Cancer Treatment Group, again investigating the role of salt supplementation but in the adjuvant setting, also closed prematurely because of the interim analysis of Combined Oxaliplatin Neurotoxicity Prevention trial. With 102 patients randomized to intravenous calcium/magnesium ($n = 50$) or not ($n = 52$), there was a significantly lower rate of moderate-to-severe sensitive neurotoxicity (22 vs. 41%, $P = 0.038$) in those patients who received calcium/magnesium supplementation [28].

Unfortunately, both trials closed prematurely and definitive conclusions are hard to draw. These data do not show any deleterious effect of calcium/magnesium supplementation in patients receiving oxaliplatin-based chemotherapy. Indeed, such supplementation may reduce neurotoxicity. Nevertheless, in the authors' opinion with data from fewer than 300 patients, calcium/magnesium supplementation cannot be recommended.

Capecitabine, Irinotecan, and Oxaliplatin in Advanced Colorectal Cancer (CAIRO)-2

The novel randomized phase II Bowel Oncology with Cetuximab Antibody (BOND)-2 trial [29] showed striking activity for the bevacizumab and cetuximab biologic doublet in heavily pretreated patients. Response rates for the biologics alone and in combination with irinotecan were 23 and 38%, respectively, with times to progression of 6.9 and 8.5 months, respectively.

In Europe, the Dutch Colorectal Cancer Group have conducted a phase III trial to investigate the simultaneous use of agents inhibiting the VEGF and the EGFR pathways in the first-line setting [30]. Capecitabine, Irinotecan, and Oxaliplatin in Advanced Colorectal Cancer-2 randomized over 700 previously untreated patients with metastatic CRC to receive the XELOX regimen (capecitabine 1000 mg/m^2 twice daily on days 1–14 q21 + oxaliplatin 130 mg/m^2 on day 1 q21) and either bevacizumab alone (7.5 mg/kg on day 1 q21) or bevacizumab at the same dose with cetuximab (cetuximab 400 mg/m^2 on day 1, followed by 250 mg/m^2 given weekly). Although median OS did not differ (20.4 vs. 20.3 months) PFS (the primary endpoint) was significantly shorter for patients who received both antibodies (9.6 vs. 10.7 months, $P = 0.018$), with a 20% increase in the risk of disease progression. Moreover, the double monoclonal antibody regimen carried the greatest risk of grades 3 and 4 toxicity, especially diarrhea.

These results should be viewed in the context of recently presented preliminary results from the Panitumumab Advanced Colorectal Cancer Evaluation trial [31,32]. The upfront combination of fluoropyrimidine/oxaliplatin chemotherapy with an anti-EGFR monoclonal antibody (cetuximab or panitumumab) and bevacizumab was more toxic in both trials, was detrimental to PFS in both trials, and may even cause a reduced OS (in PACCE). Although the mechanism of any interaction is not known, these data serve as a note of caution regarding the combination of antibodies with different mechanisms of action. It remains to be seen whether similar effects are observed with other EGFR inhibitors and antiangiogenic combinations, or in other diseases.

Predictive value of KRAS

Most physicians, if asked about the greatest challenge in using newer high-priced potentially toxic drugs, would agree that it is to define more appropriate patient selection. Proving drug efficacy is not easy with respect to 'targeted' biological cancer therapies [33], especially where no functionally useful biomarker has been identified. This has led to FDA and European Medicines Agency approval of drugs with a modest overall benefit and questionable cost-effectiveness. It has also highlighted the distinction between statistical significance in very large (and arguably overpowered) trials and clinical relevance. By contrast, the identification of a relevant predictive biomarker for therapies targeting HER-2 allowed the selection of women with breast cancer who may benefit from trastuzumab (and more recently lapatinib), and avoided their use in patients who will not benefit.

The Cetuximab combined with irinotecan in first-line therapy for metastatic colorectal cancer (CRYSTAL) study

The ASCO 2008 plenary session audience welcomed, therefore, the results of studies addressing this question with respect to KRAS mutation status in patients with CRC receiving cetuximab.

The pan-European phase III Cetuximab combined with irinotecan in first-line therapy for metastatic colorectal cancer trial met its primary endpoint [34], demonstrating that the upfront combination of cetuximab with FOLFIRI regimen was superior to the same chemotherapy alone in terms of PFS (8.9 vs. 8 months, $P = 0.048$), decreasing the absolute risk of progression at 1 year by 10% and increasing objective response rates (47 and 39%, respectively; $P = 0.004$). Although statistically signifi-

cant, the improvement in PFS was clinically modest and arguably not cost-effective.

Blocks from archived tumor material from 540 out of the 1198 total population enrolled in the study were retrieved and analyzed for KRAS mutation status (codons 12 and 13), after isolation of genomic DNA performed directly from the slides, to reevaluate treatment effect according to KRAS status [1]. KRAS mutations were detected in 35.6% (192) of these patients, tumors whereas 348 had KRAS wild-type. Importantly, the KRAS population was representative in that their outcomes closely reflected those of the overall population. No significant difference was observed in terms of PFS for patients whose tumors were KRAS mutant irrespective of whether they did or did not receive cetuximab (median PFS 7.6 vs. 8.1 months, HR = 1.07, $P = 0.47$). By contrast, there was a clear advantage for the upfront combination when given to patients with KRAS wild-type tumors (median PFS 9.9 vs. 8.7 months, HR = 0.68, $P = 0.017$); indeed, there was a trend for these to have worse outcomes if treated with cetuximab.

OPUS and Cetuximab dose-escalation study in patients with metastatic colorectal cancer (MCRC) with no or slight skin reactions on cetuximab standard dose treatment (EVEREST)

These two trials supported key findings of the Cetuximab combined with irinotecan in first-line therapy for metastatic colorectal cancer trial.

Oxaliplatin and cetuximab in first-line therapy treatment of metastatic colorectal cancer (OPUS), a first-line randomized phase II trial enrolled 340 patients who received either FOLFOX alone or with cetuximab [35]. The primary endpoint, response rate, was higher in the combination arm although this did not reach statistical significance (45.6 vs. 35.7%, $P = 0.06$), and did not impact on PFS (median PFS 7.2 months in both arms). Analyses of KRAS status in relation to efficacy showed that patients with KRAS wild-type tumors had significantly better outcomes with FOLFOX and cetuximab than FOLFOX alone (response rate 61 and 37%, respectively; $P = 0.01$ and PFS 7.7 and 7.2 months, respectively; $P = 0.016$). By contrast, those with KRAS-mutated tumors did significantly worse when cetuximab was added to chemotherapy (response rate 33 and 49%, respectively; $P = 0.01$ and PFS (5.5 and 8.6 months, respectively; $P = 0.02$).

In the EVEREST trial [36] patients were treated with first-line irinotecan and cetuximab then randomized either to continue standard dose cetuximab or receive dose-escalated cetuximab in the absence of clinically significant skin toxicity after 3 weeks of treatment. Several key messages are available. First, patients with wild-type KRAS had better outcome in terms of response rate and PFS than those with KRAS-mutated tumors. Second, escalating the dose of cetuximab appeared to enhance efficacy (both response rate and PFS) only in patients with KRAS wild-type tumors. In conclusion, skin toxicity and KRAS wild-type status were independent predictors of better outcome in patients receiving cetuximab. Dose escalation did not overcome the adverse impact of having a KRAS-mutated tumor.

Taken as a whole, these data represent a major milestone in our ability to personalize therapy and increase the cost-effectiveness of treating patients with advanced CRC using anti-EGFR antibodies. KRAS testing represents the first predictive biomarker that differentiates patients who are likely to respond to EGFR inhibitors (i.e. those with wild-type tumors) from those who are not (i.e. with KRAS tumor mutations). The term 'paradigm shift' is overused but appropriate here. Now there are several good reasons to test the KRAS status of a patient's tumor. It can identify those patients most likely to derive clinically significant benefit from EGFR inhibitors; it can also reduce the likelihood of the increased toxicity and costs of treating patients who have KRAS-mutated tumors and are unlikely to benefit from agents such as cetuximab.

On the basis of these findings, both the PETACC VIII and the NO147 trials, testing the role of cetuximab in combination with FOLFOX in the adjuvant setting, have been amended, and now allow only the randomization of patients with KRAS wild-type tumors. In routine clinical practice, the KRAS testing of tumor tissue with satisfactory quality control will be a challenge similar to that when HER-2 testing became clinically relevant in women with breast cancer.

In conclusion, further significant advances were presented this year, but many questions are still to be answered. The optimal partner for EGFR inhibitors has yet to be defined. The detrimental effect of combining cetuximab with FOLFOX chemotherapy in patients with KRAS mutant tumors is as yet unexplained. The benefits of using EGFR inhibitors 'upfront', or even as adjuvant therapy, as opposed to later in the course of disease are unclear. Obviously, the fascinating KRAS story has not been fully revealed and the optimal use of anti-EGFR molecules is far away from its complete definition.

Lung cancer

Non-small cell lung cancer

The FLEX trial in the plenary session was the main highlight for lung cancer specialists. This randomized study has finally demonstrated the effectiveness of an anti-EGFR agent in combination with chemotherapy in advanced NSCLC. Other relevant studies in NSCLC addressed the role of maintenance therapy with pemetrexed in the advanced setting, the role of neoadjuvant chemotherapy

and the value of genetic profiling in the adjuvant setting. Disappointing long-term follow-up results of the International Adjuvant Lung trial highlighted the need for long-term follow-up for adjuvant studies.

First-line treatment

The FLEX trial Several randomized phase III trials failed to demonstrate a survival benefit from the addition of an EGFR tyrosine kinase inhibitor to standard first-line platinum-based chemotherapy in advanced NSCLC. In the ASCO 2008 plenary session final results of the FLEX trial, a large international randomized phase III trial evaluating the effectiveness of the addition of the anti-EGFR monoclonal antibody cetuximab to a standard platinum-based chemotherapy as first-line treatment in advanced EGFR-expressing NSCLC were presented [37]. It followed encouraging results in the LUCAS randomized phase II trial of of cisplatin and vinorelbine +/− cetuximab as first-line treatment of patients with NSCLC [38].

In the FLEX trial patients with stage wet IIIB or IV NSCLC that were EGFR positive (defined as ≥ 1 EGFR-positive cell), with performance status 0–2, and not known to have brain metastases were randomized to receive either cisplatin and vinorelbine or the same chemotherapy and weekly cetuximab. Chemotherapy was continued up to six cycles; cetuximab continued as maintenance therapy until progression or unacceptable toxicity; the primary endpoint was OS. Overall 1125 patients were randomized; the median number of chemotherapy cycles was four in both arms and median duration of cetuximab treatment was 18 weeks.

A statistically significant survival benefit was available for patients in the cetuximab arm (median survival 11.3 and 10.1 months, respectively; HR = 0.87, 95% CI: 0.76–0.99, $P = 0.04$) with 1-year survival rates of 47 and 42%, and response rates of 36 vs. 29% ($P = 0.01$). The survival benefit was confirmed across all major subgroups, that is, ECOG performance status, smoking status, histology, sex, age, and tumor stage. Notably, Asian patients ($n = 121$) had a significantly longer OS compared with Caucasians ($n = 946$; median survival 19.5 and 9.6 months, respectively). In a preplanned subgroup analysis, this benefit in survival was confirmed for Caucasian patients (median survival 10.5 and 9.1 months, HR = 0.80, 95% CI: 0.69–0.93, $P = 0.003$). By contrast, in the Asian population no survival advantage was observed from the addition of cetuximab (median survival 17.6 and 20.4 months, respectively). No difference was observed between the two arms in terms of PFS (4.8 months in both arms, HR = 0.94, 95% CI: 0.825–1.077) although time to treatment failure favored the cetuximab arm (4.2 and 3.7 months, HR = 0.86, 95% CI: 0.761–0.971, $P = 0.015$). In terms of toxicity, an unexpectedly high incidence of febrile neutropenia was observed in both arms, and was significantly higher in the cetuximab arm (22 vs. 15%, $P < 0.05$). Typical cetuximab-related toxicity was observed in the experimental arm, including grade 3 acne-like rash (10 and $< 1\%$), diarrhea (5 and 2%), and infusion-related reactions (4 and $< 1\%$).

The FLEX trial demonstrates for the first time survival benefit for the addition of an EGFR inhibitor to first-line chemotherapy in patients with NSCLC. The accrual of patients with tumors expressing EGFR does not fully explain these positive results, compared with the negative U.S. phase III trial of carboplatin and paclitaxel +/− cetuximab [39]. The enrichment of patient populations in clinical practice by molecular profiling, specifically KRAS status and EGFR copy number analysis by FISH, should be investigated to improve the cost-effectiveness of cetuximab added to chemotherapy in patients with advanced NSCLC.

PF-3512676 and chemotherapy in first-line NSCLC PF-3512676 is a synthetic oligodeoxynucleotide targeting the Toll-like receptor 9 expressed on B and T cells, plasmacytoid cells, and dendritic cells. TLR-9 activation may enhance innate antitumor immunity. In a phase II trial in advanced NSCLC, the addition of PF-3512676 to chemotherapy improved the response rate with a trend to improved PFS and OS survival compared with chemotherapy alone [40].

Two phase III trials evaluated the role of PF-3512676 in combination with standard chemotherapy as first-line treatment of NSCLC [41,42]. Previously untreated patients with advanced NSCLC were randomized to receive chemotherapy (either carboplatin/paclitaxel or cisplatin/gemcitabine) with or without PF-3512676 (0.2 mg/kg subcutaneously on days 8 and 15 of each 3-week cycle), with OS the primary endpoint; patients in the experimental arm could receive maintenance PF-3512676.

After more than 1660 patients accrued in both studies, a planned interim analysis showed an increased rate of neutropenia, infections, septic events in the PF-3512676 arm compared with the chemotherapy arm in both studies. Accordingly, the Data Safety Monitoring Committee recommended the early termination of both studies because of increased toxicity and lack of benefit. In the absence of a strategy for identifying patients who may benefit from its addition to combination chemotherapy, PF-3512676 appears not to have a role in advanced NSCLC.

Maintenance therapy

Pemetrexed: *the JMEN trial* Over the past decade, several trials have demonstrated the feasibility of maintenance

chemotherapy in advanced NSCLC although its effectiveness has not been definitely proven [43].

At ASCO 2008, the results of a multicenter, double-blind, placebo-controlled phase III trial evaluating the efficacy and safety of pemetrexed as 'maintenance' treatment in patients with advanced NSCLC were presented [44]. Overall, 663 patients with advanced NSCLC, not progressing after four cycles of standard first-line platinum-based chemotherapy, were randomized 2 : 1 to then receive, or not receive, maintenance pemetrexed. At progression, however, approximately half the patients in the placebo arm received second-line therapy, but for only 11% was this pemetrexed. Vitamin B12 and folate supplementation, and dexamethasone were given in both arms.

The primary endpoint was met with a doubling of PFS in the pemetrexed arm (4.04 and 1.97 months, respectively; HR = 0.59, 95% CI: 0.49–0.73, $P < 0.00001$), and a trend toward improvement of OS in a preliminary analysis (13.01 and 10.18 months; HR = 0.8, 95% CI: 0.63–1.01, $P = 0.060$). Maintenance pemetrexed was well tolerated with no unexpected toxicity [45]. The prespecified analysis of efficacy by histological subtypes demonstrated a significant benefit in OS for patients with non-squamous histology. Pending the final OS results, which should be available in early 2009, this is the first positive trial of maintenance chemotherapy in patients with advanced NSCLC. The use of maintenance pemetrexed in patients with non-squamous NSCLC after first-line standard platinum-based chemotherapy cannot, however, be considered proven without answering the key question of whether maintenance pemetrexed offers any advantage compared with the same drug on progression.

Gefitinib: *the West Japan Thoracic Oncology Group trial 0203 trial* This Japanese phase III trial evaluated the role of maintenance gefitinib in patients with advanced NSCLC, irrespective of the histological subtype or smoking history; the primary endpoint was OS [46]. Overall, 598 previously untreated patients with stage IIIB/IV NSCLC were randomized up front to receive standard platinum-based chemotherapy for three to six cycles or three cycles of the same chemotherapy followed by gefitinib (250 mg daily) until progression or unacceptable toxicity.

Despite a significant improvement in PFS favoring the maintenance arm (4.60 and 4.27 months, respectively; HR = 0.68, 95% CI: 0.57–0.80, $P < 0.001$), there was no difference in OS between the two arms (13.7 and 12.9 months, respectively; HR = 0.86, 95% CI: 0.72–1.03, $P = 0.10$). A prespecified subgroup analysis did, however, show survival benefit in patients with adenocarcinoma ($P = 0.03$). Interpretation of this study is complicated by nearly half the patients in the chemotherapy alone arm having crossed over to receive gefitinib poststudy; by contrast, perhaps because patients were randomized upfront, only 57% of those allocated to maintenance gefitinib received it.

Early stage NSCLC

Long-term results of the International Adjuvant Lung Cancer trial When first presented at ASCO 2004 with a median follow-up of 4.7 years, this trial showed a survival advantage for adjuvant platinum-based chemotherapy compared with observation in radically resected NSCLC patients, with a 3.9% absolute survival benefit at 5 years (HR = 0.86; 95% CI: 0.76–0.98; $P < 0.03$) [47].

At ASCO 2008, updated results were reported, with 7.5 years follow-up [48]. Disappointingly, the initial survival benefit for patients in the chemotherapy arm was no longer significant (HR = 0.91, 95% CI: 0.81–1.02, $P = 0.10$) with further follow-up. DFS (HR = 0.88, 95% CI: 0.78–0.98, $P = 0.02$), local recurrence rate ($P = 0.002$) as well as risk of distant metastasis ($P = 0.02$) remain in favor of the chemotherapy arm, but non-lung cancer mortality was significantly higher in the chemotherapy arm (HR = 1.34, $P = 0.06$). Interestingly, with 7.5-year follow-up, the previously reported predictive value of ERCC1 status for survival benefit was confirmed [49]. Mature results of other large phase III trials (ALPI, JBR.10, ANITA, and Big Lung Trial) will define the long-term impact of adjuvant chemotherapy.

The ChEST study The role of neoadjuvant chemotherapy in early stage NSCLC is still unclear. In the ChEST study patients with stage IB, II, and selected IIIA NSCLC were randomized to either surgery or chemotherapy with a standard regimen of cisplatin and gemcitabine for three cycles followed by radical surgery [50]. The primary endpoint was 3-year PFS rate. After the publication of positive results for several large randomized trials of adjuvant chemotherapy in this setting, the ChEST investigators considered the surgery alone arm unethical and in December 2004 decided upon early closure of accrual when only 270 patients out of the 712 planned had entered the study.

Nevertheless, there was a significant difference in favor of the chemotherapy arm with a median PFS of 4.0 years compared with 2.9 years for the surgery alone arm (HR = 0.71, 95% CI: 0.50–0.99, $P = 0.011$). Breaking the results down by disease stage, there was no significant benefit for stages IB–IIA, whereas there was a statistically significant benefit in favor of neoadjuvant chemotherapy for clinical stages IIB–IIIA patients for PFS (median PFS 4.0 vs. 1.1 years, $P = 0.002$) and OS (5.7 vs. 2.1 years, $P = 0.001$). These results support the use of perioperative chemotherapy in early stage NSCLC, but it remains unclear whether this approach is superior to adjuvant chemotherapy, and further randomized trials are necessary.

Fifteen-gene signature prognostic for survival and predictive for benefit from adjuvant chemotherapy The selection of patients with radically resected NSCLC for adjuvant chemotherapy is currently based on clinical prognostic parameters (mainly performance status, stage of disease). In the era of molecular medicine, there is the potential to integrate this clinical information with molecular data to identify high-risk patients more likely to benefit from adjuvant chemotherapy and spare low-risk patients from unnecessary chemotherapy and its side effects.

Gene expression profiling was performed using Affymetrix U133A technology on RNA from snap frozen tumors of 62 and 71 patients, respectively, in the observation and chemotherapy arms of the JBR.10 trial [51]; this study previously showed a significant survival benefit from adjuvant cisplatin and vinorelbine chemotherapy compared with observation in stages IB and II NSCLC [52]. A 15-gene expression signature was identified in the observation arm, which distinguished between patients at low and high risk of death (HR = 15.02, 95% CI: 5.12–44.04, $P < 0.0001$), that is, it had 'prognostic' significance; it was also validated in three independent datasets, overall including 360 stages I–II NSCLC patients. When this 15-gene expression signature was applied to the chemotherapy-treated JBR.10 group, benefit from adjuvant therapy was seen in the 'high-risk' (HR = 0.33, 95% CI: 0.17–0.63, $P = 0.0005$) population, but not in the remainder, that is, it was 'predictive' of benefit. Prospective studies are now needed to further validate the selection of NSCLC patients for adjuvant chemotherapy based on this 15-gene expression signature.

The ELPET study PET/CT versus conventional imaging staging for resectable NSCLC Where available, positron emission tomography (PET) and PET/computed tomography (CT) are routinely used to stage NSCLC patients who are candidates for radical surgery. The role of PET in this setting compared with conventional imaging is, however, still unclear. To address this issue, the ELPET study group conducted a randomized controlled trial comparing conventional staging (CT liver/adrenals, total body bone scan, CT, or MRI brain) to PET imaging (whole-body PET and CT or MRI brain) [53]. A total of 337 NSCLC patients considered resectable based on chest CT, were randomized. PET findings resulting in upstaging required pathological confirmation. The primary aim was to compare the two imaging approaches in terms of correctly upstaging the tumor and avoiding inappropriate therapy in patients with NSCLC being considered for surgery.

PET/CT was superior to conventional imaging in correctly upstaging patients, identifying more with mediastinal and extrathoracic disease than conventional imaging (14 vs. 7% patients, $P = 0.046$). PET/CT also understaged fewer patients than conventional imaging (11 and 30%, respectively; $P = 0.00003$). PET/CT would, therefore, spare more patients potentially inappropriate surgery. The ELPET investigators conclude that PET can replace conventional staging in early stage NSCLC.

Small cell lung cancer

For decades, the combination of cisplatin and etoposide has been the standard first-line treatment for small cell lung cancer (SCLC). This was challenged in three important randomized phase III trials reported this year at the ASCO annual meeting. The effectiveness of high-dose prophylactic cranial irradiation (PCI) in patients with limited stage SCLC achieving a complete response was also addressed in a large randomized phase III trial.

Extensive-disease SCLC

The SWOG0124 trial irinotecan/cisplatin versus cisplatin/etoposide The SWOG 0124 trial [54] aimed to (i) confirm in a North American population the significant survival benefit observed for irinotecan/cisplatin over etoposide/cisplatin in Japanese patients with extensive-disease SCLC (ED-SCLC) [55], and (ii) investigate the association of genetic polymorphism with clinical outcomes.

In all, 671 patients with ED-SCLC, performance status 0–1 not known to have brain metastases were randomized to receive either irinotecan (60 mg/m^2 on days 1, 8, 15) and cisplatin (60 mg/m^2 on day 1) every 4 weeks or etoposide (100 mg/m^2 on days 1–3) and cisplatin (80 mg/m^2 on day 1) every 3 weeks; each regimen was given for up to four cycles. Both regimens were well tolerated and there was no unexpected toxicity, a higher incidence of hematological toxicity being observed in the etoposide/cisplatin arm whereas the administration of irinotecan/cisplatin was associated with more diarrhea. No significant difference was seen in OS (median survival of 9.9 months for irinotecan/cisplatin and 9.1 months for etoposide/cisplatin, respectively; $P = 0.71$), 1-year survival rate (41 and 34%, respectively), response rate (60 and 57%) or PFS (5.7 and 5.2 months, respectively). Pharmacogenomics analyses showed a correlation between specific genotypes and the risk of neutropenia and diarrhea, but no correlation was observed between genotypic profile and efficacy.

This large, well-conducted randomized trial failed, therefore, to confirm in a North American population the previously reported survival benefit of irinotecan/cisplatin in Japanese patients. Etoposide/cisplatin remains the reference chemotherapy regimen for SCLC in North America.

The ABC study topotecan/cisplatin versus cisplatin/etoposide Single agent topotecan is a common second-line treatment for SCLC. An earlier randomized phase II trial showed that the administration of topotecan upfront in

combination with cisplatin is feasible and has comparable efficacy to cisplatin/etoposide [56].

The ABC study group conducted a phase III trial in previously untreated patients with ED-SCLC comparing cisplatin (75 mg/m^2 on day 1) and etoposide (100 mg/m^2 intravenous on days 1–3) to cisplatin (75 mg/m^2 on day 1) and topotecan (1 mg intravenous on days 1–5) every 3 weeks; a third arm of topotecan (1 mg/m^2 intravenous on days 1–5) and etoposide (80–100 mg/m^2 intravenous on days 3–5) was discontinued because of an excess of treatment-related deaths [57]. This trial was designed to demonstrate the superiority of topotecan/etoposide over cisplatin/etoposide in terms of OS. If superiority was not shown, a noninferiority test was prespecified. Noninferiority of cisplatin/topotecan versus cisplatin/etoposide was reported (median survival 10.5 and 9.5 months in the topotecan/cisplatin and cisplatin/etoposide arms, respectively, HR = 0.931, 95% CI: 0.788–1.099, $P = 0.3$). Significantly longer time to progression (7.0 vs. 6.0 months, log-rank $P = 0.004$) and higher response rate (55.5 vs. 45.5%, $P = 0.01$) were observed in the experimental arm but the incidence of grades 3–4 hematological toxicity (in particular, anemia and thrombocytopenia) and treatment-related deaths was also higher (5.2 and 2.7% deaths, respectively). Despite its efficacy, the unfavorable toxicity profile and the less convenient schedule of topotecan/cisplatin, make it unlikely this will become a standard regimen.

The GALES/JMHO trial carboplatin/pemetrexed versus carboplatin/etoposide This study was designed as a noninferiority trial comparing the effectiveness of pemetrexed/carboplatin to etoposide/carboplatin in ED-SCLC [58]. Previously untreated ED-SCLC with performance status 0–2 were randomized to either pemetrexed (500 mg/m^2 on day 1) and carboplatin [area under the curve (AUC) 5 on day 1] every 3 weeks or etoposide (100 mg/m^2 on days 1–3) and carboplatin (AUC 5 on day 1) every 3 weeks for up to six cycles. An interim analysis, performed after enrolment of 733 of the planned 1820 patients, prompted early termination of the study because of a significantly inferior PFS (median: 3.88 vs. 5.32 months, respectively; HR = 1.79, 95% CI: 1.49–2.15, $P < 0.0001$) and lower preliminary OS (median: OS 7.3 vs. 9.6 months) in the pemetrexed/carboplatin arm, leaving etoposide/cisplatin as the standard regimen.

Limited disease SCLC

High-dose versus standard dose prophylactic cranial irradiation in LD-SCLC The PCI99 intergroup study compared standard with high-dose PCI in patients with limited disease SCLC (LD-SCLC) who achieved a complete response to induction therapy [59]. They were randomized to standard cranial radiotherapy (25 Gy in 10 fractions over 12 days), or to a higher dose (36 Gy dose given either as 18 fractions over 24 days or an accelerated schedule of 24 twice daily fractions over 16 days). A total of 720 patients were randomized and there was no difference in the incidence of brain metastasis at 2-year follow-up between the two arms (24 vs. 30% in the standard and higher dose radiotherapy, respectively, HR = 0.77, 95% CI: 0.55–1.08, $P = 0.13$). Moreover, survival was significantly worse in the higher dose arm with 37% alive at 2 years compared with 42% with standard dose (HR = 1.22, 95% CI: 1.02–1.47, $P = 0.03$), higher dose cranial irradiation being associated with an increased higher incidence of chest relapse. PCI with 25 Gy remains, therefore, the standard of care for patients with LD-SCLC.

Other tumors (miscellaneous)

Genitourinary cancers

Adjuvant treatment of stage I seminoma: the MRC TE19/EORTC 30982 trial

In the MRC TE19/EORTC 30982 trial, between 1996 and 2001, 1447 patients who underwent orchidectomy for stage I seminoma were randomized 3 : 5 to receive either one cycle of carboplatin (AUC 7; $n = 573$ patients) or radiotherapy (para-aortic strip or dog-leg field at 20–30 Gy; $n = 904$ patients) [60]. Updated results of this important trial were presented in the ASCO 2008 plenary session. With a median follow-up of 6.5 years, the previously reported noninferiority of carboplatin to standard radiotherapy was confirmed [61]. No statistically significant difference was observed in terms of relapse-free rate, the primary endpoint of the study. In particular, at 5 years, RFS was 94.7% for carboplatin and 96% for radiation therapy (HR = 1.25, 90% CI: 0.83–1.89, $P = 0.37$). Less acute toxicity and a more rapid return to work for patients in the chemotherapy arm compared with radiotherapy were also confirmed. Notably, chemotherapy resulted in significantly lower rate of second germ cell tumors in the contralateral testis (HR = 0.22, 95% CI: 0.05–0.95, $P = 0.03$). The importance of carboplatin dosing was also highlighted as a higher 5-year RFS rate was observed for patients treated with at least the planned dose of carboplatin ($n = 347$) compared with a lower dose ($n = 212$) (96.1 and 92.6% for AUC ≥ 7 and AUC < 7, respectively). This observation also supports the investigation of higher doses of carboplatin in this setting. Now there are three options for stage I seminoma patients after orchidectomy: surveillance, radiotherapy, or carboplatin.

Sunitinib and mTOR inhibitors for the treatment of advanced renal cell carcinoma

The 44th ASCO meeting again highlighted significant advances in the field of advanced renal cell carcinoma (RCC). The final survival data of the randomized study comparing the multitargeted receptor tyrosine kinase inhibitor sunitinib to interferon α-2a were presented [62]. By demonstrating a significant advantage in PFS

with sunitinib ($P < 0.000001$), the study met its primary endpoint. Moreover, sunitinib resulted in a significantly longer OS (26.4 vs. 21.8 months, HR = 0.82, 95% CI: 0.67–1.00, log-rank test: $P = 0.05$, Wilcoxon test: $P = 0.01$). The mature results of this study provide further support for sunitinib as standard first-line therapy in patients with metastatic RCC.

Another randomized phase III study compared everolimus (RAD001), an oral mammalian target of rapamycin (mTOR) inhibitor, with placebo in patients with RCC progressing on or less than 6 months after antiangiogenic therapy with sorafenib, sunitinib, or both [63]. Patients were randomized 2 : 1 to receive everolimus 10 mg/day ($n = 272$) or placebo ($n = 138$) and best supportive care. The primary endpoint PFS was achieved with highly significant risk reduction in patients receiving everolimus (HR = 0.30, 95% CI: 0.22–0.40, $P < 0.0001$) that was seen in all subgroups evaluated. No advantage in OS in patients randomized to receive the mTOR inhibitor, but survival data may have been confounded by crossover to everolimus after disclosure of the interim analysis. Everolimus was associated with higher rates of all grades stomatitis (40 vs. 8%), infections (10 vs. 2%), pneumonitis (8 vs. 0%), and hyperglycemia (12 vs. 1%) than placebo. The importance of these results is two-fold; first, everolimus is the first agent to show significant clinical efficacy in patients previously treated with sunitinib or sorafenib; second, this benefit was obtained with an acceptable safety profile.

Second-line chemotherapy for hormone-refractory prostate cancer: the Satraplatin and Prednisone Against Refractory Cancer trial

The Satraplatin and Prednisone Against Refractory Cancer trial is the largest randomized study to evaluate second-line chemotherapy in patients with advanced hormone-refractory prostate cancer [64].

The trial randomized 950 patients to receive satraplatin, an oral platinum compound (80 mg/m^2 on days 1–5 every 35 days) along with prednisone (5 mg orally twice daily), or placebo and prednisone; approximately half the patients had received docetaxel as first-line treatment. The primary endpoint was PFS, defined as a composite of radiological progression, symptomatic progression, skeletal events or death, and OS. Notably, according to an independent review committee, satraplatin resulted in a 37% reduction in the risk of disease progression compared with placebo (HR = 0.67; 95% CI: 0.57–0.77; $P < 0.0001$), although there was no significant advantage in OS (HR = 0.98; 95% CI: 0.84–1.15; $P = 0.79$). As previously reported [65], the pain response rate was significantly higher in patients receiving the platinum agent ($P < 0.005$), as was the PSA response rate ($P < 0.0001$). Treatment with satraplatin was generally well tolerated, the most common toxicities being neutropenia (22%) and thrombocytopenia (23%). Nonetheless, the modest advantage in PFS (11 weeks for satraplatin and 9.7 weeks for placebo) and the absence of benefit in OS, do not support the adoption of satraplatin as standard second-line treatment of hormone-refractory prostate cancer.

Head and neck cancer

The efficacy of adding induction chemotherapy to concomitant chemoradiotherapy (CT/RT) as a treatment of locally advanced head and neck cancer was investigated in an Italian randomized phase II study [66]. The control arm was two cycles of cisplatin and 5-FU chemotherapy concomitant with radiotherapy (66–70 Gy); patients in the experimental arm received three cycles of induction chemotherapy with docetaxel, cisplatin, and 5-fluorouracil (TPF) before the same CT/RT treatment. The primary endpoint was radiological complete response rate at the end of concomitant CT/RT. Overall, 101 patients with stage III or IV M0, inoperable, squamous cell carinoma of the oral cavity, oral pharynx, or hypopharynx were randomized (51 to TPF → CT/RT and 51 to CT/RT alone). The complete response rate favored induction chemotherapy (50 and 21%, respectively, $P = 0.004$); induction chemotherapy also significantly reduced the need for salvage surgery (34 vs. 11%, $P = 0.012$). One-year OS was 86% in the TPF → CT/RT arm and 77.6% in the CT/RT arm. These results support further investigation of induction chemotherapy and specifically TPF induction chemotherapy in large phase III trials.

Pancreatic cancer

Despite its low activity and modest survival benefit, gemcitabine has been the key drug in the treatment of advanced pancreatic cancer over the past decade [67]. The role of this drug with or without radiation therapy has been also investigated in the adjuvant setting. Most of the randomized trials so far are, however, underpowered and results are conflicting. Recently, the CONKO-001 trial demonstrated a significant advantage in DFS for resected patients receiving 6 months of postoperative gemcitabine compared with observation [68]. Updated results of the CONKO-001 trial were presented this year, confirming the DFS advantage (median DFS 13.4 and 6.9 months, respectively; $P < 0.001$) regardless of T stage ($P < 0.01$ for T3–T4, $P < 0.05$ for T1–T2), lymph node involvement ($P < 0.006$ if node is positive, $P < 0.01$ if node is negative) or even microscopic residual disease ($P < 0.001$ if R0, $P < 0.001$ if R1) [69]. The advantage in terms of OS is disappointing (median survival 22.8 and 20.2 months in the gemcitabine and observation arm, respectively; log-rank $P = 0.005$), probably diluted by the large use of gemcitabine at disease recurrence. Five-year survival rate was, however, more than doubled for patients in the chemotherapy arm (21 vs. 9%).

Combining upfront erlotinib and gemcitabine in the advance setting, even if statistically beneficial in terms of OS [70], has been extensively debated in the oncology community owing to its uncertain cost-effectiveness. Accepting gemcitabine–erlotinib as standard first-line treatment, the randomized, double-blind, placebo controlled AVITA trial investigated the effectiveness of adding bevacizumab to erlotinib and gemcitabine in patients with advanced pancreatic cancer [71]. Results showed a PFS benefit (4.6 vs. 3.6 months, HR = 0.73, $P = 0.0002$), but failed to show any improvement in OS (HR = 0.89, $P = 0.2$), primary endpoint of the study. These negative results are consistent with the CALGB 80303 study [72], which failed to show any advantage when bevacizumab was added to gemcitabine (PFS 4.9 vs. 4.7 months, OS 5.8 vs. 6.1 months for bevacizumab/gemcitabine vs. gemcitabine, respectively).

Supportive care

Cancer-related fatigue, sleep disorders, and depression

Depression, insomnia, and cancer-related fatigue (CRF), are common, but often underdiagnosed and undertreated in patients with cancer. Several studies presented at the ASCO 2008 meeting in the Patient Care sessions investigated new treatments for these patients.

In a secondary analysis of a large randomized, placebo-controlled trial primarily designed to evaluate the effect of paroxetine on depression and fatigue in patients receiving chemotherapy, the effect of paroxetine on insomnia was studied [73]. After cycle 2 of chemotherapy, patients reporting CRF were randomized to receive either paroxetine (20 mg orally, daily) or placebo. Insomnia was assessed at each cycle using an established evaluation tool. During cycle 1, almost 85% of patients reported insomnia, and 52% fulfilled diagnostic criteria for clinical insomnia. Although paroxetine reduced depression, it was no better than placebo in improving insomnia. The authors concluded that it is necessary to identify effective treatments for insomnia in these patients, as sleep disruption may persist even if depressive symptoms are controlled.

Another interesting study investigated the effect of modafinil on CRF [74]. Modafinil stimulates the CNS, improving wakefulness and well-being and has been approved by the FDA to treat narcolepsy [75] and other common sleep disorders [76]. In the phase III trial presented at the ASCO meeting, 888 cancer patients reporting fatigue (>1 on a 10-point scale) were randomized to receive either 200 mg/day of oral modafinil or daily placebo starting on day 5 of chemotherapy cycle 2 until 7 days after completion of cycle 4. Patient-reported fatigue, sleepiness and depression were assessed at baseline, cycle 2, and cycle 4. With complete data available for 642 patients, modafinil improved CRF ($P = 0.03$) and reduced sleepiness ($P = 0.002$), but had no effect on depression ($P = 0.83$). Of note, modafinil was particularly effective in patients with severe fatigue (scoring ≥ 7; $P = 0.0017$).

Quality of life

Two important abstracts addressed the prognostic value of quality of life (QOL) in cancer patients.

In the first study, pooled data from over 10 000 patients with 11 types of cancer and enrolled in 30 EORTC randomized controlled trials were studied to evaluate whether baseline QOL (assessed by the standardized EORTC-QLQ-C30 questionnaire) predicts survival [77]. Several QOL parameters were capable of predicting survival after adjustment for age, sex, performance status, and stage of disease. These included physical functioning ($P < 0.0001$), cognitive functioning ($P = 0.01$), global health status ($P = 0.0006$), fatigue ($P = 0.01$), nausea and vomiting ($P = 0.0004$), pain ($P = 0.0003$), dyspnea ($P < 0.0001$), and appetite loss ($P < 0.0001$).

The second was a meta-analysis of 24 North Central Cancer Treatment Group clinical trials, overall involving close to 4000 cancer patients with different types of cancer [78]. In this study, OS was tested for association with overall QOL. Patients were categorized by baseline overall QOL score on a 100-point scale (above vs. below median baseline value 83), and by clinical efficiency (clinically deficient patients with score 0–50 vs. clinically efficient patients with score 51–100). Patients with baseline QOL scoring less than 83 had worse OS than those who scored 83 or higher (median survival 12.3 vs. 18.4 months, $P < 0.0001$), and those who were not clinically efficient at baseline had a shorter survival than the others (median survival 9.3 vs. 16.8 months). The survival disadvantage for poor QOL patients was independent of type of cancer or initial performance status.

Both trials demonstrate that QOL is a strong prognostic factor, perhaps independent of other conventional factors. Baseline QOL scoring should, perhaps, be included as a stratification factor in at least some future randomized controlled trials.

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