Hot topics and landmark studies from the 43rd annual meeting of the American Society of Clinical Oncology

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The results of several preclinical and clinical studies were reported by oncology professionals at the 43rd American Society of Clinical Oncology (ASCO) meeting, the largest international forum in which the latest achievements in cancer research are annually presented. The central theme this year was 'Translating Research into Practice', emphasizing the goal of forging stronger links between basic research and clinical practice. This review offers a critical, summarized selection of several of the foremost studies presented at the meeting. The focus is on the findings from randomized phase III trials that, in the authors' opinion, are most likely to have an immediate effect on clinical practice. ***Anti-Cancer Drugs*** **19:221–233 © 2008 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Introduction

The 43rd annual meeting of the American Society of Clinical Oncology (ASCO) was held on 1–5 June 2007 in Chicago, Illinois, USA. Once again, the meeting confirmed its premise, playing the role of the leading educational and scientific forum for oncologists to present and discuss the latest advances in translational and clinical cancer research. In continuity with the previous edition [1], this year also there were a relevant number of abstract submissions on emerging key topics dealing with research on anticancer drugs. Interesting findings from randomized phase III trials have been reported in several topical areas. Some of these results are expected to reach the clinical scenario soon. Among the most important advances are the results obtained with the use of sorafenib in hepatocellular carcinoma, the third highest cause of cancer deaths globally, which still lacks a standard treatment protocol when diagnosed in the late stages.

Breast cancer

Adjuvant treatment

Hormonal therapy

The National Cancer Institute of Canada Clinical Trials Group (NCIC CTG MA.17) trial investigated the efficacy and tolerability of extended adjuvant letrozole vs. placebo in 5187 postmenopausal women with early-stage breast cancer (BC), who had completed about 5 years of tamoxifen therapy [2]. Chapman *et al.* [3] analyzed several baseline factors of the patients in the trial, to identify their effects on the type of death, by means of the competing-risks analysis. The types of death were classified into three categories: death from BC, from other malignancies, or from other causes. Interestingly, women with cardiovascular disease were more likely to die from other causes ($P = 0.02$), whereas those with osteoporosis had the highest likelihood of dying from other malignancies ($P = 0.03$). In addition, older women showed shorter survival from all three causes of death ($P < 0.001$), and patients with node-positive disease experienced the shortest survival ($P < 0.001$). The results of this analysis have a relevant impact on the process of clinical decision-making, underscoring the importance of evaluating the competing causes of death when planning treatment.

Chemotherapy

In a further attempt to improve the clinical benefit obtained with adjuvant chemotherapy (CT), the taxanes, paclitaxel (P) and docetaxel (D), were incorporated into several therapeutic regimens for women with early-stage BC.

Results from second-generation taxane-based trials evaluating the best way to administer these drugs were reported at the 2007 ASCO meeting.

Sparano *et al.* [4] presented the fourth interim analysis (median follow-up: 47 months) of the E1199 multicenter phase III trial, in which 4950 patients with node-positive or large (≥ 2 cm) node-negative BC initially received four cycles of doxorubicin and cyclophosphamide (AC) at standard doses, and were then randomized to either P (175 mg/m^2 every 3 weeks for four cycles or 80 mg/m^2

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weekly for 12 weeks) or D (100 mg/m^2 every 3 weeks for four cycles or 35 mg/m^2 weekly for 12 weeks). Initial findings according to the 2×2 factorial trial design were presented at the 2005 San Antonio Breast Cancer Symposium, whereas the report at the 2007 ASCO meeting was based on a comparison of all the treatment arms. Thanks to the results of this analysis, for the first time after the previous observations in advanced and neoadjuvant settings, the impact of the P schedule in influencing outcome measures was also demonstrated in the adjuvant setting. Of note, when the weekly P arm was compared with the other arms, a statistically significant advantage was observed in disease-free survival (DFS) [hazard ratio (HR) = 1.27; 95% confidence interval (CI): 1.07–1.51; $P = 0.006$] and overall survival (OS) (HR = 1.32; 95% CI: 1.06–1.63; $P = 0.01$). Interestingly, the highest survival benefit was noted in patients with hormone receptor-negative tumors. This study also supported the value of the 3-weekly D regimen over the other regimens in terms of DFS (HR = 1.23; 95% CI: 1.04–1.46; $P = 0.02$), whereas no significant advantage was observed in OS (HR = 1.13; 95% CI: 0.92–1.39). The toxicity profiles of the different schedules were as expected, with the observation of higher rates of peripheral neuropathy in the weekly P arm and the highest rates of neutropenia and febrile neutropenia in the 3-weekly D arm.

This trial also provided a methodological lesson, indicating a caveat in the interpretation of trials with 2×2 factorial designs. In particular, the negative results from the first analysis of the study were probably due to an initially unforeseen interaction among the treatment arms. With a smaller sample size, the advantage of weekly P could not be observed.

Loesch *et al.* [5] presented the update of a phase III trial in which 1830 patients with operable node-positive or high-risk node-negative BC were randomized after surgery to receive four cycles of the conventional 3-weekly AC, followed by four cycles of 3-weekly P (175 mg/m^2), or the experimental combination of 3-weekly doxorubicin (50 mg/m^2) and P (200 mg/m^2) for four cycles, followed by weekly P (80 mg/m^2) for 12 weeks.

After a median follow-up of 5 years, although the significant advantage in terms of DFS previously observed with the arm 3-weekly doxorubicin (50 mg/m^2) and P (200 mg/m^2) followed by P had been lost, a marginal but statistically significant advantage was observed with the experimental regimen in terms of OS (90 vs. 87%; HR = 0.76; $P = 0.04$). Notably, patients with triple-negative phenotype tumors experienced the greatest survival benefit (87 vs. 79%; HR = 0.59; $P = 0.037$).

The bigger change in OS than in DFS is a somewhat unusual observation, differing from the scenario typically observed in most clinical trials, in which DFS is often used as a surrogate marker for OS. Despite the interesting findings, the 'multiple-variables' design of the trial does not permit the attribution of merit to one strategy rather than to another (e.g. substitution of P for cyclophosphamide, or the use of weekly P vs. 3-weekly P).

Trastuzumab

Perez *et al.* [6] reported an update on the combined analysis of the National Surgical Adjuvant Breast and Bowel Project (NSABP) B31 and the North Central Cancer Treatment Group (NCCTG) N9831 – the two trials that evaluated either the concurrent or the sequential use of trastuzumab combined with the standard US regimen of AC followed by P. At 4 years' follow-up, the use of trastuzumab was associated with a 50% relative reduction in the risk of recurrence, conferring an absolute benefit of 13% in terms of DFS (86 vs. 73%). Notably, even though a significant proportion of patients crossed over to adjuvant trastuzumab or received the agent at the time of disease progression, a statistically significant advantage in OS was still observed.

The issue of HER-2-status determination in BC was recently addressed by an expert panel from the ASCO and the College of American Pathologists, which developed recommendations for optimal HER-2-testing performance [7].

At the ASCO meeting, provocative results were reported by Paik *et al.* [8], challenging the knowledge of a strong relationship between HER-2 status and benefit from trastuzumab. Unexpectedly, after analysis of the central HER-2 testing by immunohistochemistry or fluorescence in-situ hybridization, the benefit from trastuzumab in the context of the NSABP B31 trial was not limited to patients with HER-2-positive tumors.

Moreover, a statistically significant advantage in DFS was observed even for the 174 women (about 10% of the trial population) with immunohistochemistry and fluorescence in-situ hybridization-negative tumors (risk ratio = 0.34; 95% CI: 0.14–0.80; $P = 0.014$). Although these findings have practice-changing potential, they need to be interpreted with caution and further confirmed in bigger clinical studies, before considering their clinical implications. Such results, nonetheless, add fuel to the ongoing debate on the quality of HER-2 testing that might vary according to the laboratory (local vs. central) and on the need to refine criteria to assess HER-2 status (e.g. correction for chromosome 17 polysomy and avoidance of arbitrary cut off points) [9].

Advanced disease

Chemotherapy

Ixabepilone (BMS-247550) is an epothilone B analog that stabilizes microtubules and has antitumor activity in

taxane-refractory metastatic BC. A phase III registration trial compared a 3-weekly regimen of ixabepilone 40 mg/m^2 on day 1 in combination with capecitabine 1000 mg/m^2 twice a day on days 1–14 vs. single-agent capecitabine 1250 mg/m^2 twice a day on days 1–14 in patients with anthracycline pretreated, taxane-resistant metastatic BC [10]. The primary endpoint was progression-free survival (PFS). After a blinded independent radiologic review, the addition of ixabepilone to capecitabine resulted in a significantly better response rate (RR) (35 vs. 14%; $P < 0.0001$) and PFS (5.8 vs. 4.2 months; HR = 0.75; $P = 0.0003$). As expected, the combination was, however, more toxic, resulting in more grade 3/4 hematologic adverse events such as leukopenia (57 vs. 6%; $P < 0.0001$), neutropenia (68 vs. 11%; $P < 0.0001$), and febrile neutropenia (4 vs. < 1%; $P = 0.001$). In addition, patients receiving ixabepilone experienced more grades 3/4 peripheral neuropathy (23 vs. 0%) that, although rapidly reversible (median time to baseline or grade 1: 6 weeks), is a clinical concern in patients pretreated with taxanes. Unfortunately, as crossover was not planned, the trial does not allow us to draw any conclusions about the potential superiority of the combination over the same agents given sequentially.

Lapatinib

Lapatinib is an oral selective inhibitor of both epidermal growth factor receptor (EGFR) and HER-2 tyrosine kinases. A large randomized placebo-controlled phase III trial ($n = 579$) compared the efficacy of lapatinib (1500 mg/day) in combination with P (175 mg/m^2 every 3 weeks) vs. P alone, in patients with HER-2-negative or HER-2 untested advanced (stage IIIb/IIIc/IV) BC [11].

Central HER-2 testing later established that a reasonable percentage (more than 15%) of the enrolled patients had HER-2-positive disease. Time to progression (TTP) was the primary endpoint of the study. Interestingly, although no significant improvement in TTP was obtained with the addition of lapatinib to P for the total population (6.7 vs. 5.3 months; HR = 0.87; $P = 0.14$), the subset of patients with HER-2-positive BC experienced significantly higher RR (60 vs. 36%; $P = 0.027$) and TTP (8.1 vs. 5.8 months; $P = 0.011$). These findings suggest that HER-2 is probably the main target of lapatinib. The added value of targeting EGFR in the mechanism of action of this 'dual' kinase inhibitor, however, remains to be elucidated. In terms of toxicity, the combination of lapatinib and P was reasonably well tolerated, with a statistically significant increase in rash, diarrhea, and mucositis ($P < 0.0001$).

Colorectal cancer

Adjuvant treatment

In the Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC) trial, over 2000 stage II/III colorectal cancer (CRC) patients were randomized to receive 12 cycles of adjuvant 5-fluorouracil (5-FU), leucovorin, and oxaliplatin (FOLFOX-4) or 5-FU in combination with folinic acid regimen [12]. Oxaliplatin-based CT had a clear advantage. After the presentation of such convincing data, FOLFOX-4 regimen quickly became the new worldwide standard at least for radically resected stage III CRC patients. Now, the longer follow-up confirmed that the remarkable absolute DFS benefit reported at 5 years (7.5% for stage III, 7.2% for high-risk stage II, 5.9% for the entire population, and 3.8% for stage II) converted into a clear survival advantage. The absolute survival benefit at 6 years was 4.6% for stage III and 2.7% for the whole series of patients [13]. MOSAIC results get better with time, just like good French wine does, as an Italian commentator apostrophized. Despite this striking evidence for lymph-node-positive carcinomas, considering that an equally compelling survival advantage for stage II has not been reported, the uncertainty regarding oxaliplatin-based CT for Dukes B patients still continues. Hope can be found in fully, specifically designed ongoing trials that can help dissipate the haziness, and help clinicians to identify the patients who would benefit the most.

Another sobering finding is the long-term persistence of sensorial neuropathy, which was still present after 4 years, in the 11.4% of the people who received oxaliplatin. As the oxaliplatin-induced neurotoxicity is both dose cumulative and dose limiting, research is quickly moving forward to verify the activity of neuroprotective agents and to test whether more limited oxaliplatin exposure could be equally effective while being less toxic.

Metastatic disease

Chemotherapy

In less than 4 years, 364 patients have been enrolled in the European Organisation for Research and Treatment of Cancer (EORTC) 40983, a randomized phase III controlled trial, conveniently designed to prove the benefit of 12 perioperative FOLFOX-4 cycles for patients potentially curable for resectable CRC liver metastases [14]. More importantly, this trial looks at perioperative CT as a whole, and is not intended to compare preoperative vs. adjuvant treatment. Baseline characteristics were similar: no significant differences were reported between treatment arms in terms of median age, median number of liver metastases (up to three in about 90% of the population), number of patients with early (< 2 years) liver recurrence, and pathologic features of the primary tumor. Owing to the nature of the study, evaluation of resectability was based on the preoperative imaging. About 17% of the patients in each arm could, nevertheless, not undergo resection. Overall, the data favor patients who received both CT and radical liver

surgery: the absolute benefit in terms of PFS at 3 years is about 8%, and it is similar to what the MOSAIC and NSABP C-07 trials have confirmed for stage III CRC patients who were treated with an adjuvant oxaliplatin-based regimen [12,15]. Upon a closer examination, the reported statistical significance is not easy to decipher, as it was reached by excluding ineligible patients from the analysis.

At the same time, we have to be conscious that systemic CT is grossly beneficial for originally unresectable metastatic disease: it later allows about one fifth of the patients to receive potentially curative surgery [16]. When considering resectable disease at onset, however, the role of preoperative treatment remains essentially unknown [17], and its risk-to-benefit ratio is still to be demonstrated [18]. Concerns and questions might, thus conceivably, arise: is a healthy, potentially curable patient with an easily resectable liver deposit the best candidate for primary systemic treatment? Would we pursue the same strategy if the patient had both a resectable CRC and resectable metastases? According to other reports, if treated with surgery alone, such a patient would have a 20% chance of being alive, with no evidence of disease at 10 years. A recent study claims no increased risk for hepatic recurrence even when suboptimal surgery is performed [19]. Moreover, the selected control arm for the EORTC trial was surgery alone. Considering the currently available reports [20], however, it would be quite unusual in clinical practice not to offer post-operative treatment to radically resected patients.

Cetuximab

Cetuximab, a humanized monoclonal EGFR inhibitor, proved to be effective when combined with irinotecan-based regimens, and is the first biologic therapy approved for the treatment of patients with advanced disease that progressed after a irinotecan-11-based chemotherapy. Recently, a pan-European randomized phase III trial [cetuximab combined with irinotecan in first-line therapy for metastatic colorectal cancer (CRYSTAL) study] was planned, to demonstrate whether the upfront combination of the EGFR inhibitor cetuximab at a standard dose (400 mg/m^2 followed by 250 mg/m^2 weekly) with a regimen of leucovorin, 5-FU, and irinotecan (FOLFIRI) could confer survival advantage vs. only CT [21]. According to the trial design, approximately 1200 patients were needed for the accrual of 633 events required to statistically differentiate PFS among groups. The primary endpoint was met, and a PFS increase of nearly 1 month (from 8 to 8.9 months) was reported for the group treated with the combination therapy ($P = 0.036$). Although statistically significant, the clinical repercussion of this data could be fragile, with the caveat of comparison across trials. It might be useful to point out that other authors have reported a 8.8-month PFS with intermittent FOLFIRI [22], and a 9.9-month PFS when FOLFIRI was combined with bevacizumab for previously untreated patients [23]. The CRYSTAL study, nevertheless, demonstrated an absolute 8% RR increase for patients who received the combined therapy (46.9 vs. 38.7%, $P = 0.005$). This improvement, even if not striking, is similar to the one reported by those who received an upfront FOLFOX/cetuximab combination [24]. Definitely a drug synergy can be hypothesized, but a plain additive effect seems sufficient to justify the higher RR. The increased activity might, however, be helpful in offering salvage surgery to a greater number of metastatic patients, and allegedly enhance the possibility of curing them. In conclusion, the upfront addition of cetuximab to the FOLFIRI scheme has modestly prolonged PFS, reducing the risk of progression of about 15%, but the practical improvement does not sound so meaningful. Studies looking for K-*ras* mutations, gene amplification/overexpression, and insulin-like growth factor pathways are on the way. Which subset of patients will benefit the most from the use of EGFR inhibitors in general and of cetuximab in particular is, however, still to be defined.

Bevacizumab

At least two trials have addressed the question regarding the upfront combination of bevacizumab with backbone standard CTs (FOLFOX or FOLFIRI).

The BICC-C trial, a randomized trial of first-line irinotecan/fluoropyrimidine combinations with or without celecoxib in metastatic colorectal cancer, already presented at ASCO 2006, was updated later this year [25]. Initially, 430 patients were randomized to receive an irinotecan-based CT with or without celecoxib. Starting from May 2004, soon after bevacizumab obtained the approval of the US Food and Drug Administration (FDA), the trial was emended, allowing the patients to receive the vascular endothelial growth factor (VEGF) inhibitor upfront as well, and 120 more patients were randomized. Concisely, it might be stated that the addition of bevacizumab improved the efficacy results without worsening tolerability. In addition, first-line FOLFIRI, whether combined with bevacizumab or not, seemed to be superior in efficacy (both in PFS and OS) over the other irinotecan-based CTs.

The capecitabine combined with oxaliplatin (XELOX-1/NO16966) trial shares with the previous study a similar story [26]. The study primarily enquired about the noninferiority of oral vs. intravenous 5-FU when combined with oxaliplatin; once bevacizumab became available and the first 634 patients had already been enrolled, the trial design was emended, and a second randomization to bevacizumab or placebo was incorporated. Reporting a median PFS of 9.4 months for patients who received bevacizumab vs. an 8-month PFS for patients who received placebo, the results showed that the

addition of bevacizumab to a first-line oxaliplatin-based CT could significantly improve PFS.

'Which is the right time to conveniently stop bevacizumab treatment?' is another unanswered key question. On this matter, no consistent data were available before the 2007 ASCO meeting. Similar to what happened with the use of trastuzumab in BC, a significant proportion of US physicians, nevertheless, used to maintain the patients who had already failed a bevacizumab-containing regimen on the VEGF inhibitor. Basically, to understand whether or not an extended use of bevacizumab might be beneficial beyond the first disease progression, clinical information has been extrapolated from the large BRiTE (first-line Bevacizumab Regimens: Investigation of Treatment Effects and Safety) database [27]. This registry started in 2004 with the aim of capturing, in a large, less-selected, community-based population, safety and efficacy information regarding first-line bevacizumab use. The exploratory, observational, nonrandomized, and noncontrolled analysis presented at the ASCO meeting focused on the 1445 CRC patients who progressed after being initially treated with a first-line combination of bevacizumab and CT outside a clinical trial. Of these patients, 253 received no further treatment, 531 a second-line treatment without bevacizumab, and 642 a second-line treatment that included the antiangiogenic compound. Data were prospectively recollected every 3 months. While bearing in mind all the limitations quoted above, the multivariate analysis indicated that the use of bevacizumab beyond first disease progression had a clear impact on 1-year OS (87.7%), median OS (31.8 months), and median OS after first progression (19.2 months). As the authors conveniently highlighted in their conclusion, this cohort study provided important clinical outcome data that generated hypotheses to be tested in future randomized controlled trials. Until validated, however, outcomes and long-term results become unambiguous; caution should be used in generalizing, and discussion with the patient should be the drive for a tailored clinical decision.

Opportunely, the intergroup irinotecan-based therapy (S0600/iBET) phase III trial has already started to validate the observational results in a randomized controlled clinical setting. Does anyone else want to bet?

Other gastrointestinal and hepatobiliary malignancies

Stomach and esophagogastric junction

Two significant studies addressed the role of preoperative therapeutic strategies in localized gastric and esophagogastric junction carcinomas. The first trial focuses on the role of neoadjuvant CT, which was not a standard treatment in the mid-1990s, at the time when the study began [28]. A total of 224 patients were randomized either to surgery alone or to 2–3 cycles of neoadjuvant cisplatin/5-FU followed by surgery and eventually by adjuvant CT. for a maximum of six total cycles. Preoperative CT influenced neither postoperative mortality (4 vs. 5%) nor surgical morbidity (19 vs. 26%), although three patients allocated to the sequential arm were not operated upon, owing to rapid disease progression. Microscopically radical (R0) rate of resection was superior for the preoperative arm (87 vs. 74% $P = 0.04$), and a lower incidence of lymph node involvement was also detected (67 vs. 80%, $P = 0.054$). According to the Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial results [29], preoperative CT clearly improved both DFS (absolute benefit of 13%) and OS (absolute benefit of 14%).

By enrolling patients with locally advanced carcinomas of the gastroesophageal junction, the second trial tests in a preoperative setting whether a chemoradiation regimen is superior to the sole CT, the latter being considered the standard induction treatment [30]. The rationale for the trial is that combining radiation with antiblastic drugs in the preoperative setting could increase the R0 resection rate, lessen lymph node involvement, enhance major histologic responses, and ultimately improve survival. Before radical surgery, 126 patients received either three cycles of cisplatin, folinic acid, and 5-FU or two cycles of the same regimen, followed by a cisplatin/etoposide cycle together with radiotherapy (15×2 Gy). Epoetin α was recommended to keep the hemoglobin value above 12.5 g/dl. After 45 months of median follow-up, the reported 3-year OS was 47% for patients treated with the combined modality and 27.7% for those who received CT alone.

In conclusion, the results of the two reports provided even further evidence on the use of a preoperative strategy for resectable gastric and esophagogastric junction cancers. Even if expected, it represented the highest progress that we have had for gastric cancers in recent years.

We must, nevertheless, wait for the results of a randomized comparison between preoperative and postoperative treatment before neoadjuvant strategy can be definitively recommended.

Hepatocellular carcinoma

Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide and its incidence is constantly growing over time, both globally and in the US [31,32]. Regrettably, no standard therapy is currently available for the advanced phase of the disease. Substantial toxicities with disappointing outcome results emerged from clinical phase II/III trials testing systemic CTs [33]. Best supportive care remains a reasonable approach to palliate

advanced liver cancer patients, for whom surgical resection, liver transplantation, ablation, or even transarterial chemoembolization are no longer appropriate options. In such an unwelcoming scenario, the purpose of the Sorafenib HCC Assessment Randomized Protocol (SHARP) trial is to verify whether the orally active raf-kinase inhibitor sorafenib can confer an advantage on patients being administered the drug over those treated with placebo [34]. In fact, not only does sorafenib have a broad antiproliferative activity inhibiting the raf/mitogen-acitivated protein kinase/extracellular signal regulated kinase, c-Kit, REarranged during Transfection, and Flt-3 pathways, but it also holds an antiangiogenic effect, blocking VEGF receptor and platelet-derived growth factor receptor. A previously reported pivotal phase II trial supported the use of sorafenib in this setting [35].

Over 600 patients entered the SHARP trial. They were stratified by vascular invasion, extrahepatic spread, Eastern Cooperative Oncology Group performance status, and geographic origin, and randomized 1 : 1 to 400 mg of sorafenib twice a day continuously, or to a placebo. As soon as the second interim analysis was carried out, this large study was stopped by the data safety monitory board, and the positive results were prematurely disclosed. As a result of this recommendation, the sponsors allowed all enrolled patients access to the drug. For patients treated with sorafenib, Llouvet *et al.* [34] proudly presented a significantly prolonged OS (10.7 vs. 7.9 months; HR = 0.69; $P = 0.00058$,) and a notably increased TTP of symptoms (5.5 vs. 2.8 months; HR = 0.58; $P = 0.000007$), the coprimary efficacy endpoints of the study. The advantages were maintained when considering subcategories. Doubtless, the compound was very well tolerated: mild-to-moderate diarrhea, hand–foot syndrome, and anorexia were frequently reported in the sorafenib-exposed patients (39, 21, 14% of any-grade toxicity, respectively). Severe cases were, however, very few, and no life-treating adverse events were observed. Moreover, few absolute differences in moderate toxicities were reported between the two arms, confirming a favorable toxicity profile (sorafenib vs. placebo: diarrhea 8 vs. 2%; hand–foot syndrome 8 vs. 1%).

More thrilled than surprised, the ASCO 2007 plenary session audience welcomed the meaningful results of this landmark study, and shared the awareness that a new standard of treatment had been outlined for advanced liver cancer patients – at least for the Child–Pugh class A patients, who represented the vast majority of the treated population in this trial. Still, the role of the oral agent in patients with more impaired liver function remains to be explored. Whether those patients would require a dose reduction remains to be determined. In addition, even as trials testing the efficacy of sorafenib in the adjuvant setting are ongoing, researchers are planning studies and considering how to combine the drug with other targeted therapies. We hope and expect these studies to be much more appealing, as sorafenib, and no longer placebo, will be the control arm.

Pancreatic cancer

Over the past 10 years, gemcitabine has been the backbone of the armamentarium that oncologists possess to treat advanced pancreatic cancer [36]. Recently, the upfront combination of erlotinib and gemcitabine, even if statistically beneficial in terms of OS over gemcitabine alone [37], has been extensively debated in the oncologic community, owing to its questionable cost-effectiveness. While the question is ongoing, it lingers on in consciousness that, for the very first time, a biologic compound has marked a new dawn in the management of pancreatic cancer.

In this moving landscape, two major comparative studies have been presented. Both the trials brought negative results: paradoxically, they are, just for this reason, very important. The Cancer and Leukemia Group B (CALGB) 80303 study investigated the use of bevacizumab in 590 patients randomized to receive the standard dose of weekly gemcitabine either with placebo or with bevacizumab, at 10 mg/kg every 14 days [38]. On the basis of a planned protocol-specific interim analysis, after obtaining 64% of the information on OS, the trial was stopped early because a futile boundary had been crossed; the patients were unblinded, notified of the results, and offered the continuation of bevacizumab treatment upon request. The updated results presented at ASCO 2007 failed to show any differences in outcome (PFS 4.9 vs. 4.7 months; OS 5.8 vs. 6.1 months for bevacizumab/gemcitabine vs. gemcitabine, respectively).

In the Southwest Oncology Group (SWOG) protocol SO205, over 700 patients with locally advanced (20%) or metastatic disease (80%) received a standard weekly dose of gemcitabine, with or without cetuximab (400-mg/m^2 induction dose, followed by a 250-mg/m^2 weekly dose) [39]. The statistic was calculated to determine a 33% increase in median survival. Philip *et al.* [39] did not report any improvement in terms of OS (6.4 vs. 5.9 months, HR = 1.09, $P = 0.14$) or PFS (3.5 vs. 3 months, HR = 1.13, $P = 0.058$) for the cetuximab arm, although an increased time to treatment failure (2.5 vs. 1.8 months; HR = 1.25; $P = 0.0014$) was presented.

In conclusion, bevacizumab failed to improve survival or clinical benefit when added to standard CT in advanced pancreatic cancer, whereas the extensive use of EGFR inhibitors needs further efforts to design appropriate trials rationally, and to select patients who would probably benefit from targeted agents. Moreover, considering all the randomized trials that failed to show any further benefit for a gemcitabine-based doublet over gemcitabine

alone, whatever the selected partner was, one should ask whether antimetabolite is really the best drug to add a compound to, and whether the right time for gemcitabine-free regimens has really arrived.

Lung cancer

Non-small cell lung cancer

Neoadjuvant and adjuvant setting

Non-small cell lung cancer (NSCLC) is often diagnosed at an advanced, incurable stage [40]. The patients with early disease are, nevertheless, candidates for radical surgery, with (stage II and IIIA) or without (stage I) platinum-based adjuvant CT [41].

Further information on this topic became available at this ASCO meeting.

In a European intergroup collaborative trial, 519 patients with potentially resectable NSCLC were randomized to receive either surgery alone or three cycles of platinum-based CT before surgery. In the neoadjuvant arm, 49% of patients obtained a response (complete and partial) with CT and only 2% of them progressed. No differences between the two arms in terms of PFS (HR = 0.98; 95% CI: 0.77–1.23) and OS (HR = 1.04; 95% CI: 0.81–1.35) were observed [42].

An updated analysis of the SWOG 9900 study was presented. In this phase III trial, 354 patients with early-stage NSCLC were accrued and randomized to either surgery alone or induction P/carboplatin treatment followed by surgery. In the CT group, there was a positive trend for both PFS (33 vs. 21 months) and OS (50 vs. 47 months), although statistical significance was not reached, probably owing to the reduced power of the study. The trial was, in fact, closed before accrual completion, when adjuvant CT became the standard of care [43]. These trials confirm that preoperative therapy is feasible and does not affect subsequent surgery.

A meta-analysis of individual patient data from 11 randomized clinical trials measured the impact of adjuvant CT after surgery and radiotherapy on 2626 early-stage NSCLC patients [44]. Results confirmed the advantage for adjuvant CT: after a median follow-up of 6.3 years, OS was significantly better in patients receiving CT (HR = 0.88; 95% CI: 0.80–0.96; $P < 0.006$), with an absolute gain of 4.7% at 5 years. Adjuvant CT was equally effective both in patients receiving postoperative radiotherapy and in those not treated with radiation therapy, with a modest but clinically significant survival benefit.

Locally advanced disease

The SWOG 0023 phase III trial enrolled 571 unresectable stage IIIA or IIIB patients [45]. After definitive chemoradiation treatment (cisplatin at 50 mg/m^2 on days 1 and 8 in addition to etoposide at 50 mg/m^2 on days 1–5, every 28 days for two cycles, with concurrent radiation at 1.8–2 Gy/day to 61 Gy) followed by consolidation D (75 mg/m^2 for three cycles), nonprogressing patients were randomized to gefitinib (initially at 500 mg/day, then lowered to 250 mg/day) or placebo.

Median OS was 23 months for gefitinib vs. 35 months for placebo ($P < 0.01$). In this unselected population, maintenance treatment with gefitinib not only failed to improve survival but also had a detrimental effect. This statistically significant disadvantage follows preliminary results presented in 2005, when a trend toward inferior survival was observed among patients receiving gefitinib. Imbalance in EGFR expression has been proposed as one of the possible explanations for these findings. Median OS for all enrolled patients (19 months), however, has been quite favorable in this setting, especially for a large intergroup trial.

A total of 203 patients with inoperable stage III A/B NSCLC were enrolled in the Hoosier Oncology Group LUN (HOG-LUN) 01–24/-0023 trial, to test the eventual benefit of D consolidation CT [46]. After concurrent cisplatin-based chemoradiation (cisplatin/etoposide for two cycles and concurrent chest radiation to 5940 cGy), 147 of 203 patients were randomized to either D or observation. Median survival was not improved by addition of D: 12.9 months for the observation arm and 12.3 months for the consolidation arm ($P = 0.94$). Otherwise, there was a statistically significant increase of toxicity (including pneumonitis) with a higher rate of hospitalization. Consolidation D should no longer be used in unresectable stage III NSCLC.

In another phase III trial, induction CT followed by concurrent chemoradiation treatment was compared with immediate chemoradiation, to evaluate whether the addition of induction CT would result in improved survival [47]. A total of 134 patients with unresectable stage III NSCLC received weekly cisplatin/P concurrent with definitive thoracic irradiation. Half of the patients received two courses of induction gemcitabine and cisplatin. A trend toward a detrimental effect in PFS was observed for induction CT (7.5 vs. 11.6 months; $P = 0.04$), whereas median OS did not significantly differ between the two treatment arms (12.6 vs. 18.2 months; $P = 0.18$). Today, the optimal treatment for unresectable stage III NSCLC remains concurrent platinum-based chemoradiation.

Metastatic disease

In the Avastin in Lung (AVAiL) trial, a total of 1043 treatment-naive nonsquamous NSCLC patients without brain metastases were randomized to receive either cisplatin and gemcitabine with bevacizumab at two

different doses (7.5 or 15 mg/kg), or placebo [48]. The primary endpoint PFS was significantly better for both bevacizumab arms compared with the CT alone arm (HR = 0.75; 95% CI: 0.62–0.91; $P < 0.0026$ in the 7.5-mg/kg arm and HR = 0.82; 95% CI: 0.68–0.98; $P < 0.0301$ in the 15-mg/kg arm). RR was also increased, with the addition of the antiangiogenic agent (20% in control arm; 34% in bevacizumab at 7.5 mg/kg, $P < 0.0001$; and 30% in bevacizumab at 15 mg/kg, $P < 0.0017$), as median duration of response (4.7, 6.1, and 6.1 months, respectively). Data on OS are still awaited, owing to the short follow-up. Toxicity was mild, with a low rate of severe hemoptysis, and no differences between the two dose levels of bevacizumab were observed. AVAiL is the second phase III trial showing benefit from bevacizumab in advanced NSCLC in terms of PFS and RR. Evidence that the 7.5-mg/kg dose was as effective as the full dose suggests that further studies are needed, to identify the optimal schedule of bevacizumab in NSCLC in a better manner.

A very intriguing trial, known as the MADelT study (Molecular Analyses-Directed Individualized Therapy in Advanced Lung Cancer), focused on the feasibility of individualizing doublet CT in the first-line setting by tumor gene expression [49]. Quantitative reverse transcriptase polymerase chain reaction (RT-PCR) of *ERCC1* (E1) (excision repair cross-complementing group 1 gene) and *RRM1* (R1) (ribonucleotide reductase subunit 1), potential predictors for sensitivity to platinum and to gemcitabine, respectively, were measured on 55 patients out of 60. Dual agent CT was selected (among carboplatin, gemcitabine, D, and vinorelbine) on the basis of gene expression: gemcitabine/carboplatin for low R1/low E1; gemcitabine/D for low R1/high E1; D/carboplatin for high R1/low E1; and D/vinorelbine for high R1/high E1. For the 53 patients who were ultimately treated, RR was 44%; 1-year survival, 59%; and of note, 2-year survival, 37%. These exciting results need urgent confirmation in a phase III trial, to overcome the possible selection biases and limitations of a single-institution phase II study.

A phase III trial enrolled 562 previously untreated patients (IIIB with pleural effusion or stage IV NSCLC), to test optimal timing of second-line therapy [50]. After four cycles of carboplatin in addition to gemcitabine, 307 patients with nonprogressive disease were randomized to either immediate D (75 mg/m^2 every 21 days) or to delayed treatment with the same regimen. Despite an absolute difference of more than 2 months in terms of OS (11.9 in immediate D vs. 9.1 in delayed arm), no statistical significance was obtained ($P = 0.071$). Immediate treatment was, nevertheless, associated with a significant PFS benefit (6.5 vs. 2.8 months; $P < 0.0001$), and the likelihood of not progressing at 1 year was 20% for the immediate-treatment vs. only 9% for the delayed-treatment arm. These data suggest that a timely transition to second-line D might be able to confer a substantial clinical benefit, without differences in the quality of life, as assessed by the Lung Cancer Symptom Scale.

Small cell lung cancer

Small cell lung cancer (SCLC) accounts for less than 20% of all bronchogenic malignant tumors. The trend toward a decreased scientific interest in these topics was reversed at the 2007 ASCO meeting. A pivotal phase III EORTC trial, reported at the plenary session, evaluated the role of prophylactic cranial irradiation (PCI) in patients with SCLC extended disease [51]. A total 286 patients (18–75 years) with any response after 4–6 cycles of CT were randomly selected to receive PCI (dose ranging from 20 Gy/5F to 30 Gy/12F). The primary endpoint was the development of symptomatic brain metastases. Acute toxicity was mild: the most common side effect was headache, with grades 2 and 3 occurring in 9 and 4% of the patients, respectively. About 30% of the patients reported late headache, mostly G1–G2. The addition of PCI resulted in a significant decrease of the 1-year risk of symptomatic brain metastases (HR = 0.27; 95% CI: 0.16–0.44; $P < 0.0001$) and improved both PFS (HR = 0.76; 95% CI: 0.59–0.96; $P < 0.021$) and OS (HR = 0.68; 95% CI: 0.52–0.88; $P < 0.003$). The 1-year survival rates were, respectively, 27.1% (95% CI: 19.4–35.5) in the PCI and 13.3% (95% CI: 8.1–19.9) in the control group.

PCI did not adversely influence the global quality of life, as assessed with the QLQ-C30 of the EORTC. The relevant take-home message from this study is going to change clinical practice, driving organizational outcomes: extended-disease SCLC patients who respond to CT should routinely be offered PCI and brain irradiation as part of the standard treatment arm in future studies.

Other tumors (miscellanea)

Head and neck cancer

A randomized phase III trial (the recurrent and/or metastatic squamous cell carcinoma of the head and neck study or Extreme study) investigated the role of cetuximab in patients with advanced head and neck cancer [52]. A total of 442 patients were randomized to receive 5-FU infusion at 1 g/m^2 on days 1–4 in addition to either cisplatin or carboplatin (six cycles, maximum), either alone or in combination with cetuximab (initial dose of 400 mg/m^2, then at 250 mg/m^2, weekly), up to disease progression or unacceptable toxicity. Apart from rashes, no other relevant toxicities were observed with the addition of cetuximab. The study met its primary endpoint: median survival was significantly longer in the cetuximab arm (10 months, with 39% of the patients remaining alive at 1 year) than in the control arm

(7.4 months, with 31% of patients remaining alive at 1 year) (HR = 0.79; 95% CI: 0.64–0.98).

The findings of the Extreme study represent a landmark advance in first-line treatment for this group of patients and substantiate the role of cetuximab in combination with standard CT in advanced head and neck cancer.

Ovarian cancer

No clinical studies in ovarian cancer have demonstrated an OS benefit associated with maintenance therapy.

The study of Conte *et al.* [53], presented at the ASCO meeting this year, explored the role of additional CT after cytoreduction with six cycles of platinum/taxane-based CT, in patients with stage IIb–IV ovarian cancer who obtained complete clinical and/or pathologic response. From 1999 to 2006, a total of 200 patients were randomized either to observation ($n = 99$) or to receive six cycles of P at 175 mg/m^2 every 3 weeks. No difference was observed in the primary endpoint PFS ($P = 0.68$) or in OS ($P = 0.13$) between the two arms. Although the results of this trial are in line with those of previous ones, a note of caution is needed, especially because of the small sample size and the fact that 14% of the controls received CT.

In the effort to identify the best single-agent therapy in the treatment of recurrent ovarian cancer, Ferrandina *et al.* [54] carried out a phase III trial comparing gemcitabine (1000 mg/m^2; days 1, 8, and 15, every 4 weeks) vs. pegylated liposomal doxorubicin (PLD) (40 mg/m^2, every 4 weeks). No difference was observed in terms of TTP ($P = 0.4$) and OS ($P = 0.17$) between the two agents. As expected, gemcitabine resulted in higher hematologic toxicity, whereas hand–foot syndrome was typically associated with PLD treatment. With respect to quality of life, PLD resulted superior to gemcitabine. Longer follow-up is, nevertheless, needed to acquire more confidence with these results.

Prostate cancer

Satraplatin is a new oral platinum compound that is being investigated for the treatment of advanced hormone-refractory prostate cancer. An international randomized clinical trial testing this new agent in patients who experienced disease progression after first-line CT was presented by Sternberg *et al.* [55]. A total of 950 patients were randomized to satraplatin at 80 mg/m^2 daily on days 1–5 every 35 days along with prednisone vs. placebo in combination with prednisone. Nearly 70% of the patients were at aged least 65, and more than one third of them had severe pain. Approximately one half of the patients had received D-based CT as first-line treatment. The primary endpoint was PFS, defined as a composite endpoint of radiologic progression, symptomatic progression, skeletal events, or death. Results were independently analyzed by investigators blinded to the treatment assignment. Treatment with satraplatin was well tolerated, with the most common toxicities being myelosuppression (neutropenia and thrombocytopenia) and gastrointestinal toxicities (nausea/vomiting and diarrhea). Notably, the use of the platinum agent resulted in a 40% reduction in the risk of disease progression over placebo (HR = 0.6; 95% CI: 0.5–0.7; $P < 0.001$). In addition, pain RR was significantly higher in patients receiving satraplatin (24.2 vs. 13.8%; $P = 0.005$), as was prostatic-specific antigen RR (25.4 vs. 12.4%, $P < 0.001$). Survival data were not presented, as enough events had not occurred yet. The US FDA will probably wait for the final survival analysis of this trial before deciding whether this platinum compound is approvable for the treatment of hormone-refractory prostate cancer patients in the second-line setting.

Acute leukemia

Acute promyelocytic leukemia (APL), a subtype of acute myeloid leukemia, accounts for about 10% of cases, mostly in young and middle-aged adults. A randomized phase III North American intergroup study (protocol C 9710) evaluated arsenic trioxide (As_2O_3) as consolidation first postremission treatment in newly diagnosed APL patients [56]. The eligible population included 537 patients. A total of 243 adult patients were randomized to receive two courses of As_2O_3 (0.15 mg/kg/day for 5 days each week for 5 weeks; cycle after 2 weeks' rest) as first consolidation if they achieved remission (complete or partial response) after standard induction therapy [all-*trans* retinoic acid (ATRA), daunorubicin, and cytarabine]. A total of 237 adults and 57 children (below 15 years of age) were assigned to the non-As_2O_3 arm. Subsequent consolidation on both arms included two courses of ATRA in addition to daunorubicin. The patients who obtained complete response were then randomized to 1 year of ATRA maintenance, with or without 6-mercaptopurine and methotrexate. RRs were 90, 90, and 88% in the As_2O_3, non-As_2O_3, and children groups, respectively. Event-free survival (EFS), the primary endpoint, was significantly better for the patients on the As_2O_3 arm (81 vs. 66% at 3 years; $P < 0.0007$). OS at 3 years also favored patients receiving As_2O_3 as consolidation therapy (86 vs. 79%; $P < 0.063$). EFS and OS in pediatric patients did not statistically differ from those in the adult control arm. Grades 3/4 hematologic and nonhematologic toxicities were similar for the standard and study arms, and in the pediatric population. In conclusion, the addition of two courses of As_2O_3 consolidation treatment showed a substantial benefit in EFS and OS in adults with APL, and was associated with acceptable toxicity.

On the basis of these results, which deserved to be discussed in the plenary session, As_2O_3 should be

included in first-line therapy for patients with acute promyelocytic leukemia.

Supportive care

Cancer-related fatigue

Cancer-related fatigue is a disturbing symptom, frequently reported among patients being treated for advanced cancer: it might adversely impact quality of life [57]. No FDA-approved, standard treatment is currently available to counteract this problem.

For hundreds of years, ginseng has been revered in the Orient as a natural supplement with remarkable benefits for those who use it regularly. More recently, ergogenic experimental data showed that American ginseng (*Panax quinquefolious*) is useful to increase endurance and to decrease fatigue in mice when given in large amounts [58]. Furthermore, several uncontrolled, non-evidence-based reports define ginseng as a potential herb to treat weakness and fatigue, even though a Swedish study showed that most commercially sold ginseng products contained only trace amounts of ginsenoides [59]. In the NCCTG N03CA trial, 282 patients were randomized to either placebo or ginseng administered twice daily for 8 weeks at three different dose levels (750, 1000, or 2000 mg/day) to test in a controlled setting whether ginseng was superior to placebo in treating fatigue [60]. Main eligibility criteria were as follows: (i) a score of 4 or more on a validated cancer-related fatigue test, (ii) reference to the symptom throughout the previous month at least, (iii) a life expectancy of >6 months, (iv) absence of other detectable causes for fatigue, and (v) absence of other potentially confounding treatment. Barton *et al.* [60] did not report any differences in adverse events among the four treated groups. In contrast, patients randomized to the higher doses of ginseng reported improved vitality, enhanced endurance, decreased fatigue level, and a superior satisfaction with the treatment assigned. In conclusion, this randomized pivotal trial cautiously suggests that Wisconsin ginseng might be effective for alleviating cancer-related fatigue, but further studies are warranted to validate its real impact.

In another small, randomized, double-blind, placebo-controlled trial, donepezil, an acetylcholinesterase inhibitor already licensed for the symptomatic treatment of severe Alzheimer's disease and mild-to-moderate dementias, was evaluated for fatigue in advanced cancer patients [61]. Close to 100 patients were allocated to donepezil (5 mg orally; daily in the morning for 1 week) or to placebo. They were frequently assessed by means of a daily phone call from a nurse, using the Edmonton Symptom Assessment System, Sleeping Pattern Assessment, and FACIT-Fatigue, which are all validated questionnaires. Possibly owing to the well known placebo effect, both treated groups resulted in noteworthy fatigue improvement ($P < 0.001$). Data, nevertheless, remain vague, as donepezil did not seem to be significantly superior to placebo. Given these results, the regular use of the drug in cancer-related fatigue management is not recommended.

Depression in advanced cancer patients

Major depression is common among patients with cancer, and antidepressant treatment with selective serotonin reuptake inhibitors (SSRis) was proven effective in improving the symptoms for this population [62,63]. Common symptoms and signs that support a subthreshold depression are sadness, moodiness, minor anxiety, uneasiness, fatigue, impaired well-being, and sleep disorders. They often cluster together in advanced cancer patients, and closely relate to one another. Sertraline is a well tolerated, FDA-approved SSRi antidepressant.

A randomized controlled trial was presented at the 43rd ASCO meeting [64], and recently published in its extended form [65]. Stockler *et al.* [65] reported on the Zoloft's Effect on Symptom and Survival Time (ZEST) trial, properly planned to compare the usefulness of sertraline with placebo in advanced cancer patients who did not match the criteria for major depression. The 189 enrolled patients were randomly assigned to either placebo (94 patients) or to 50-mg sertraline daily (95 patients), and the treatment cohorts were compared in terms of depression, anxiety, and fatigue by means of validated scales. Effectively, Centre for Epidemiologic Studies Depression scale, Hospital Anxiety and Depression scale, Functional Assessment of Cancer Therapy – General and Functional Assessment of Cancer Therapy – Fatigue (FACT-G/F), and Spitzer's Quality of Life Index were used to comparatively evaluate depression, anxiety, fatigue, and quality of life, respectively. The main flaw of this well conducted study, nonetheless, is that the diagnosis of major depression (main exclusion criteria) was basically arbitrary, and left to a personal clinical judgment. No significant advantage was reported for patients treated with sertraline for all main outcomes. Therefore, the analyses ruled out a clinically important benefit for sertraline in this setting, and the recruitment was prematurely stopped for futility. In contrast with the results of the above-cited studies, in which cancer patients with depression did benefit from the treatment, the take-home message of the ZEST trial is that antidepressants do not confer any advantage on cancer patients who do not have a clear indication for them. In other words, SSRis are worthless in this setting, but are they harmful? It is noteworthy that a shortened survival was reported for patients who received sertraline (unadjusted HR = 1.6; $P = 0.04$) and this observation was not modified by adjustment for other independently significant prognostic factors (adjusted HR = 1.62; $P = 0.02$). This data should not, however, pessimistically

influence the clinical practice of prescribing antidepressants when indicated: further studies are needed to clarify whether a small survival disadvantage does really exist.

Hot flashes

Hot flashes are referred to as a bothersome, troubling manifestation in men being treated with androgen deprivations for prostate carcinoma, and are often associated with depression, nervousness, insomnia, and inability to concentrate. The pathophysiology leading to the symptoms is not fully understood, but it is clear that a nonhormonal treatment is definitively warranted to alleviate this significant side effect. Used at therapeutic doses (up to 3600 mg/day), gabapentin acts as an anticonvulsant drug. Moreover, if prescribed at lower doses, gabapentin recently showed great activity in decreasing hot flashes in women with BC [66], even in those for whom antidepressants have not provided an adequate control [67]. The double-blind phase III NCCTG trial was designed to compare the drug with placebo in prostate cancer patients complaining of hot flashes due to androgen suppression [68]. Differences among the treatment arms, to which almost 200 patients had been allocated to receive either placebo or gabapentin (at doses of 300, 600, or 900 mg/day), were measured calculating the percentage of variation in hot-flash scores and their frequencies. With the exceptions of mild appetite loss and constipation, the treatment was generally well tolerated, and did not significantly worsen the toxicity profile compared with placebo. Overall, the patients receiving the highest gabapentin dose reported significantly less hot-flash distress and more symptom control than the controls did. In fact, compared with the placebo group, treated patients profited from a higher decrease both in terms of median hot-flash score (44 vs. 21%; $P = 0.02$) and frequency (45 vs. 21%; $P = 0.02$). These data led the authors to conclude that gabapentin at 900 mg/day moderately decreased hot flashes related to androgen deprivation and could, therefore, be considered to treat this side effect in men with prostate cancer.

Central venous catheter antithrombotic prophylaxis

In cancer patients, the presence of a central venous catheter (CVC) is a well known risk factor for vein thrombosis and consequent pulmonary embolism. Despite these data, the role of anticoagulation for thrombosis prophylaxis in cancer patients with CVC still remains an unresolved topic. At least nine controlled randomized trials have already addressed the question, alternately reporting conflicting results: the recently updated cochrane meta-analysis indicates a potential (but not statistically significant) preventive role for low-molecular-weight heparins (LMWHs) [69].

Another systematic review of the literature (available in the *MEDLINE* and *EMBASE* databases) was presented this year at the ASCO meeting [70]. With the use of appropriately chosen search keywords, 831 trials were identified, 11 among them selected, and finally five high-quality randomized trials, comparing LMWHs with placebo altogether in 1367 patients, were included in the analysis. The pooled analysis was not able to identify any clear advantage for the prophylactic use of LMWHs, even if a possible small risk reduction for thrombosis (of about 2–3%) could be hypothesized. In conclusion, whether to suggest antithrombotic prophylaxis or not to cancer patients with CVC still remains questionable, and it should be discussed individually, cautiously considering the risk/benefit ratio for each single patient. Further well designed randomized studies testing the efficacy of newer molecules such as fondaparinux and ximelagatran are definitely warranted.

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