



Report

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Introduction

From 5–8 July 2007, more than 1,000 delegates attended the first ESMO Conference Lugano (ECLU). This educational event, organized by the European Society for Medical Oncology (ESMO), gave an overview of important topics in oncology. The delegates attended keynote lectures, lectures on highlights in oncology given by internationally recognized specialists, special symposia and meet-the-professor sessions. Also, the meeting allowed the presentation of scientific data, which were commented on and placed in perspective by expert speakers. The Conference was organized in such a way that interaction was facilitated and all participants could interact with the speakers. Most of the symposia are reported in a special issue of *Annals of Oncology* (18, 2007 Supplement 9). Because the highlights session gave an update of all important recent findings, they could not be included in the *Educational Book* and are therefore reported here.

Highlights in lung cancer

The optimal non-surgical therapy of non-small cell lung cancer (NSCLC) was discussed in 2 different sessions: 'Highlights in lung cancer' session presented by G. Giaccone and a 'Hot topics in lung cancer' session presented by B. Besse, E. Felip, R.A. Stahel and P. Jänne.

Localized NSCLC

Preoperative chemotherapy

G. Giaccone discussed the early results of a randomized prospective multi-center trial which had been performed in patients with stage I, II or III NSCLC under supervision of MRC, NVALT and EORTC. In this trial ($n=519$), preoperative chemotherapy with a cisplatin (CDDP)-based regimen appeared feasible and safe in terms of quality of life and complication rate. The response rate was 45% and downstaging was reached in about 20% of patients. This however did not result in

longer progression-free survival (PFS) or overall survival (OS). An updated meta-analysis among 751 patients also indicates that there is no indication for neo-adjuvant chemotherapy in the everyday treatment setting.

Chemoradiation

CDDP-based chemoradiation is broadly applied in patients with locally advanced NSCLC, which sometimes results in downstaging and subsequent operation. E. Felip discussed the results of a study presented at ASCO 2005 by Albain et al. Chemoradiation appeared to increase survival in patients who underwent a lobectomy (median survival 34 vs. 22 months, $P=0.02$), whereas it decreased survival in patients treated with a pneumonectomy. The latter finding was probably caused by postoperative complications and tumor recurrence. G. Giaccone discussed the results of the HOG Lun 01-24/USO 02-033-trial and the SWOG 9504-trial, which addressed the question whether docetaxel-consolidation after chemoradiation with CDDP and etoposide prolonged PFS and/or OS in patients with inoperable stage III NSCLC. This appeared not to be the case, leaving chemoradiation alone as the gold standard.

Adjuvant chemotherapy

E. Felip discussed the results of the LACE meta-analysis presented at ASCO 2006. This analysis encompassed 4,584 patients who had been entered in five randomized prospective trials that compared adjuvant CDDP-based chemotherapy with observation. A significant survival benefit (HR 0.83; 95% CI 0.73-0.95) was only found for patients with stage II or IIIA NSCLC. It was unclear whether patients with a WHO performance status of 2 or an age older than 75 years benefited in the same way, because they were underrepresented. In conclusion, adjuvant (CDDP/etoposide) chemotherapy should only be given to patients operated on for stage II/IIIA NSCLC.

Advanced NSCLC

First-line systemic treatment of advanced NSCLC

G. Giaccone concluded that the maximum effect of traditional chemotherapy combinations has probably been reached. Several different doublets appear to have the same efficacy. Four cycles (more in case of a continued response and good tolerance) should suffice. Further progress should be made by the addition of molecular targeted agents.

Bevacizumab

Bevacizumab is a recombinant humanized monoclonal antibody, which selectively binds to and neutralizes the biologic activity of vascular endothelial growth factor (VEGF). G. Giaccone discussed the results of 2 phase III trials. In the ECOG 4599-study, 855 patients with stage IIIB/IV NSCLC were randomized to treatment with carboplatin AUC 6/paclitaxel 200 mg/m² every 3 weeks

or carboplatin/paclitaxel and bevacizumab (15 mg/kg) every 3 weeks. In the bevacizumab treatment arm the response rate was significantly higher (35% vs. 15%, $P<0.001$). The addition of bevacizumab also appeared to increase median PFS (6.2 vs. 4.5 months, HR 0.66, $P<0.001$) and median survival (12.3 vs. 10.3 months, HR 0.80, $P=0.003$). Bevacizumab-based treatment was however associated with a significantly higher rate of proteinuria, hypertension and hemorrhage. In the AVAIL trial, which was carried out in 1,050 patients to identify the optimal bevacizumab dose, low-dose bevacizumab (7.5 mg/kg every 3 weeks) and high-dose bevacizumab (15mg/kg every 3 weeks) appeared equally effective in terms of response rate (RR) (30 vs. 34%) and displayed the same PFS benefit in comparison with chemotherapy alone (median response duration 6.1 months vs. 4.7 months). To date, the number of events has not sufficed to present mature survival data. Based on the results of these 2 trials, Giaccone concluded that platinum-based chemotherapy combined with 7.5 mg/kg bevacizumab every 3 weeks will probably become the new gold standard for first-line systemic treatment in stage IIIB/IV NSCLC.

Second-line systemic treatment of advanced NSCLC

The epidermal growth factor receptor (EGFR) is a member of the tyrosine kinase family. Overexpression of EGFR results in tumor cell proliferation, angiogenesis and inhibition of apoptosis. EGFR overexpression occurs in 12% of NSCLC patients from Caucasian origin. In Asians, overexpression occurs in about 40% of patients. R. Stahel discussed the strong association between smoking and K-ras mutations. K-ras mutations are associated with a downstream lack of EGFR-activating mutations. This may partly explain why EGFR overexpression is seen more often in non-smokers (75%) and passive smokers (61%) than in ex-smokers (36%) and current smokers (19%).

Erlotinib is a specific EGFR blocker. It has been shown to induce response rates up to 100% in NSCLC patients with EGFR-activating mutations identified by DNA analysis. EGFR-mutation analysis is laborious and expensive. Immunohistochemical staining of paraffin-embedded tumor samples is however far less predictive for response. Both erlotinib and docetaxel have shown a 2-month median survival benefit in comparison with best supportive care, when administered in second line. Pemetrexed, an antifolate antimetabolite, has also been registered for second-line treatment based on an equivalence study with docetaxel.

This leaves the oncologist with 3 treatment options: erlotinib may be most suitable for women, Asians, non-smokers or adenocarcinoma patients, because EGFR overexpression is more often seen in these subgroups. For other patients, chemotherapy is the treatment of choice. Pemetrexed is usually better tolerated than docetaxel, which should be taken into account in older patients or patients with a poorer performance status.

Small-cell lung cancer (SCLC): state of the art

G. Giaccone gave a treatment overview for limited and extensive disease.

Limited disease

At present, chemoradiation with cisplatin and etoposide is the treatment of choice. In case of a complete response, prophylactic cranial irradiation (PCI) should be performed.

Extensive disease

At ASCO 2007, Hermes et al. presented the results of a randomized phase III trial, which compared the carboplatin/etoposide combination with carboplatin/irinotecan. Patients treated with carboplatin/irinotecan showed a higher response rate (34% vs. 24%, $P=0.02$) and survival was prolonged significantly (HR 1.41; 95%-CI 1.06-1.87). In a previous trial comparing cisplatin/etoposide and cisplatin/irinotecan, the latter regimen had also shown a significant survival benefit (Noda et al., NEJM 2000). Both studies support the use of platinum-based chemotherapy with irinotecan in first line.

The EORTC 08993-22993 study addressed the question whether PCI reduces the incidence of symptomatic brain metastases in patients who have responded to first-line chemotherapy. PCI was well tolerated and significantly reduced the 1-year percentage of symptomatic brain metastases in comparison with observation (14.6 % vs. 40.4%, $P<0.001$). This reduction was associated with an improved 1-year OS (27.1% vs. 13.3%, $P=0.003$).

Highlights in gynecological oncology

J. Vermorken reported on highlights in gynecological oncology and reviewed ovarian and cervical cancer.

Ovarian cancer

According to the data of the International Agency for Research on Cancer (IARC), in 2000 there were 20,2520 women who developed ovarian cancer, of whom 22,801 lived in the USA and 61,757 in Europe. The mortality figure was 124,381 worldwide and 14,417 and 43,801 in the USA and Europe, respectively. In the 30 years that the International Federation of Gynecology and Obstetrics (FIGO) registered the survival of women with ovarian cancer, there has been a steady increase in survival in each disease stage with OS increasing from around 26% in the 1960s to 47% in the 1990s.

Milestones in the treatment of ovarian cancer were surgery according to FIGO guidelines with at least a lymph node sampling and peritoneal staging and upfront maximal surgical debulking and the evolution of chemotherapy with the introduction of platinum compounds and taxanes.

Primary disease

The place of adjuvant chemotherapy in early stage ovarian cancer

Patients with early ovarian cancer (stage I or II) can be divided into a low risk (grade I, intact capsule, no tumor on the external surface of the ovary, negative washings, no ascites, and growth confined to the ovaries) or high risk (grade 2-3, ruptured capsule, tumor on the external surface, positive washings; ascites or growth outside the ovaries) category. Two parallel randomized phase III trials of adjuvant chemotherapy in patients with early stage epithelial ovarian cancer (ICON I and ACTION) did address the question on the value of adjuvant chemotherapy in this patient population. In patients with high-risk ovarian cancer, adjuvant chemotherapy improved recurrence-free survival by 11% (65%-76%) and OS by 7% (75%-82%) at 5 years. In the ACTION trial, the benefit of adjuvant chemotherapy was only apparent in the group that was suboptimally staged. J. Vermorken concluded that chemotherapy improves DFS and OS in clinical early ovarian cancer, possibly by affecting occult residual disease, while optimal surgical staging might effectively exclude residual disease so that it does not result in an additional benefit in this patient group. However in an update of the ICON I trial after 10 years, there was a survival benefit in patients with high-risk ovarian cancer treated with adjuvant chemotherapy, while those with low or intermediate risk did not benefit. Adjuvant chemotherapy should still be considered in patients with high-risk localized ovarian cancer.

Interval debulking

Interval debulking still has a place in the treatment of advanced ovarian cancer. Two big studies addressed the role of interval debulking in stage III and IV ovarian cancer: the EORTC study showed a risk reduction in death of 49% in a group of patients that were treated with interval debulking while the GOG did not show a reduction by this approach. Since ovarian cancer is a very chemosensitive disease, the role of induction chemotherapy is further explored. In an Indian phase

III trial, 128 patients with stage III/IV (pleural effusion only) ovarian cancer were treated by primary surgery followed by 6 cycles of combination chemotherapy or 3 cycles of induction chemotherapy followed by interval surgery followed by 3 cycles of adjuvant chemotherapy. In the latter arm there was a higher optimal debulking rate ($P<0.0001$), decreased blood loss ($P<0.003$), a reduction in postoperative infections ($P<0.04$) and a better quality of life score. There was no difference in DFS and OS at the date of the report. The final answer will come from the EORTC 55971 and the Intergroup trial that addressed this question.

Consolidation and/or maintenance therapy after primary treatment

Several studies have looked at the role of consolidation and/or maintenance treatment after primary treatment for advanced disease. Studies with epirubicin and topotecan after primary treatment could not show superiority in DFS and OS compared with observation in this patient population. While an American study could show an improvement in DFS with continuation of paclitaxel (12, 3-weekly cycles vs. 3, 3-weekly cycles), an Italian study in 200 patients in complete response after 6 cycles platinum/paclitaxel and randomized to observation or 6, 3-weekly cycles of paclitaxel showed no difference in PFS or OS. These data indicate that there is no place for maintenance therapy in this patient population in daily clinical practice.

Intraperitoneal chemotherapy

Intraperitoneal (IP) chemotherapy is a valid treatment option in patients with advanced ovarian cancer. Since the 1970s, intraperitoneal chemotherapy has been explored based on the character of the disease and the possibility of administering high local doses with limited systemic side effects. Based on pooled data of several randomized studies on the combined use of intravenous (IV) and IP chemotherapy, it was shown that this approach leads to a significant survival benefit in women with optimally debulked ovarian cancer (median survival increase of more than 12 months). Based on the most recent trials, strong consideration should be given to a regimen with IP cisplatin (100 mg/m²) and a taxane (whether IV or IP). However, one should consider also the toxicities, inconvenience and costs of IP therapy but these seem justified by the improved survival.

Recurrent disease

When to start treatment for recurrent disease? Since ovarian cancer can be evaluated by a tumor marker (CA125), it is possible to detect a subclinical recurrence. It is not known whether early treatment is better than treatment with clinically symptomatic disease. However, one should not wait until there is bulky disease and the performance status of the patient has worsened to a performance status of 3 or 4. An Intergroup study is looking into this question.

Other important findings from randomized studies are that some dose schedules or routes of administration

are better than others for a specific drug; some drugs are better than others in terms of efficacy; in specific circumstances some drugs are to be preferred with respect to toxicity; and in specific circumstances combination chemotherapy is superior to single agent chemotherapy. This last statement was shown in a systematic review of 8 randomized trials with 2,312 patients that showed an improved response rate (HR 1.32), progression-free (HR 0.67) and OS (HR 0.77) with a doublet but only in platinum-sensitive patients.

Several targeted agents have been tested in patients with ovarian cancer, but studies with agents interfering with anti-angiogenesis are the most far advanced. These agents may specifically inhibit newly sprouting vessels (ligand antibodies, receptor antibodies, soluble decoy receptors, ribozymes, tyrosine kinase inhibitors, radioligands); may specifically target the vascular endothelium (vasculotoxins, adhesion inhibitors); or may be both cytotoxic to tumor cells and the endothelial cell (cytotoxic agents, coagulation products). The toxicity of the anti-angiogenic agents are relatively favorable with side effects such as fatigue, fever, chills, neurotoxicity, vertigo, ataxia, loss of concentration, headache, nose bleeds, rash, nausea, vomiting, hypercoagulability, asymptomatic QT prolongation, hypertension, proteinuria, transaminases, or change in bowel habits but may also lead to lethal hemorrhage and bowel perforation. Bevacizumab proved to be active in this disease with a response rate of around 15% but bowel perforation and thrombo-embolic events did lead to the discontinuation of the studies with this drug in patients with ovarian cancer.

Cervical cancer

Cervical cancer is the second most common form of cancer among women worldwide and the leading cause of death from cancer among women in developing countries. At least 493,000 new cases of cervical cancer per year (83% in developing countries) and 274,000 deaths are seen and in the USA, 10,370 cases of invasive cervical cancer and 3,700 deaths were reported in 2005.

Milestones in the treatment of cervical cancer have been the role of surgery versus radiotherapy in early cervical cancer; the NCI consensus statement in 1999 on the role of concurrent chemotherapy and radiation; the importance of hemoglobin-level during radiation therapy and the potential of hyperthermia.

This year highlights are the use of neo-adjuvant chemotherapy in locally advanced cervical cancer, the role of chemotherapy in recurrent and metastatic disease, the emergence of targeted therapy and human papillomavirus (HPV) vaccines.

Prevention

Specific strains of human papillomavirus (HPV-16 and -18) have been implicated in the development of cervical cancer. Several studies have demonstrated that combined vaccines against HPV could prevent the evolution to cervical intraepithelial neoplasia (CIN).

Local disease

Neoadjuvant chemotherapy

A meta-analysis of the role of neo-adjuvant chemotherapy in radiotherapy showed no improved DFS and OS from the addition of chemotherapy in patients with locally advanced cervical cancer. When a subgroup analysis was performed there was a beneficial effect of chemotherapy when radiotherapy treatment started within 14 days of chemotherapy (risk reduction for death, 17%) and when the dose intensity of cisplatin was higher or equal to 25 mg/m²/week (risk reduction for death, 9%). However, when induction chemotherapy was added to surgery and compared with radical radiotherapy, there was a benefit in local relapse, distant relapse, disease-free and OS for the combination therapy. In view of these findings, the EORTC initiated a study comparing induction chemotherapy followed by surgery, and concomitant chemoradiation in patients with FIGO stage IB2, IIA > 4 cm or IIB.

Advanced disease

Several of the newer chemotherapeutic agents (docetaxel, paclitaxel, vinorelbine, irinotecan, gemcitabine) have shown activity in patients with metastatic and/or recurrent cervical cancer. For the first time, there has been a beneficial effect of adding one of these drugs (topotecan) to cisplatin, compared with cisplatin alone, on DFS and OS. Targeted agents have also been tested in cervical cancer.

EGFR expression is observed in 75-100% of cervical cancers. However, anti-EGFR agents such as ZD1839 (500mg/d) induced no responses. Inhibition of angiogenesis by bevacizumab in combination with 5-fluorouracil (5-FU) induced responses in this patient population.

Highlights in prostate cancer

I. Tannock reviewed the highlights in prostate cancer. He discussed the use of maximum androgen blockade (MAB), the use of continuous versus intermittent hormonal therapy in patients with advanced disease, the role of second and third-line hormonal therapies, and the toxicity of hormonal therapy. He also looked at the role of androgen deprivation therapy (ADT) as an adjuvant to surgery or radiotherapy and in the patient with rising prostate-specific antigen (PSA) after local therapy.

Hormonal treatment

After the 2000 meta-analysis, published in *The Lancet*, he concluded that there was no indication for MAB in patients with advanced prostate cancer. This patient-based meta-analysis showed no significant benefit of MAB after more than 8,000 patients and 27 trials. MAB is expensive, has increased toxicity and his conclusion was that it should not be used.

The use of intermittent versus continuous androgen blockade for patients with advanced prostate cancer has been a matter of debate. In an animal model it was

shown that intermittent androgen blockade delays the development of androgen-independent prostate cancer. There was only 1 small published randomized trial of continuous versus intermittent treatment showing that intermittent androgen blockade had a beneficial effect on PSA progression and that patients in the intermittent arm were 60% of the time off treatment. In 2007, 3 randomized trials were presented at ASCO showing that there was no difference in PFS and OS, no difference in adverse events, and that 88% of patients were off therapy in the intermittent arm for more than 50% of time. There are now 4 randomized controlled trials with a total of more than 1,000 patients to support non-inferiority of intermittent ADT for PFS and OS. He concluded that intermittent ADT is standard in this patient population with the advantage that patients are exposed for less time to a potentially toxic therapy with a marked decrease in costs.

About 90% of men respond to initial therapy with orchidectomy or a luteinizing hormone-releasing hormone (LHRH) agonist. At progression, about 1/3 respond to addition of a peripheral anti-androgen (e.g. flutamide, bicalutamide) and of those who respond and then progress about 20% respond to withdrawal of the peripheral anti-androgen. Men may respond to further hormonal treatments such as dexamethasone, estrogen, or ketoconazole and hydrocortisone.

Hormonal manipulation in men with prostate cancer may lead to impotence, gynecomastia (increased breast tissue, sometimes with tenderness); hot flashes ('male menopause'), loss of muscle and bone, anemia and an increased risk of cardiovascular events.

Osteoporosis is also an important side effect of hormonal treatment. Several randomized trials have shown that pamidronate or zoledronate can prevent bone loss due to hormone treatment and a trial presented at ASCO 2006 suggested that zoledronic acid given annually is effective in preventing bone loss. Zoledronic acid 4 mg once yearly did lead to an increase of 4% in bone density at 1 year, in men starting hormonal therapy. In an observational study in more than 73,000 men older than 65 years and treated for localized prostate cancer between 1992-1999, hormonal manipulation with orchiectomy or an LHRH agonist led to an increase in diabetes, chronic heart failure, myocardial infarction and sudden death compared with placebo.

The addition of ADT as adjuvant to prostatectomy or radiotherapy has been studied extensively leading to the following findings:

Radiotherapy with concomitant and 3 years of adjuvant ADT improves progression-free and OS for men with locally advanced prostate cancer compared with radiotherapy alone.

Long-term adjuvant ADT after radiotherapy improved progression-free and OS compared with radiotherapy alone.

Neo-adjuvant and concurrent short course ADT improves progression-free survival with a trend to improved OS.

There is no benefit of neo-adjuvant ADT pre-surgery

but small randomized clinical trials suggest a benefit of adjuvant ADT for high-risk patients.

During ASCO 2007, results of a phase III study of radiotherapy plus concurrent and 6 months versus 3 years of adjuvant ADT for locally advanced prostate cancer were presented by Bolla et al. (EORTC 22961). This study showed that non-inferiority of short-term ADT cannot be confirmed with a shorter PFS with short-term ADT. This is not surprising and many patients will have remission with reintroduction of ADT. However, although this was not the endpoint of the study, there was a strong trend to improved survival with concurrent and long-term ADT with radiotherapy, indicating that this should remain the standard of care.

The role of ADT in patients with rising PSA after local treatment is also a matter of debate. In a follow up study, the probability of death was studied in 498 and 661 men who had a PSA failure after radical prostatectomy and radiotherapy, respectively. The 5-year prostate-specific mortality was 31% in men with a PSA doubling time of less than 3 months and 1% in men with a PSA doubling time of more than 3 months. A Gleason score >7 was also predictive of mortality. Another study looked also at the prostate-specific death in patients with a PSA failure after radical prostatectomy. After a median follow up time of 16 years the median survival was not yet reached. Survival was correlated with the interval of PSA relapse (more or less than 3 years) and with the Gleason score (more or equal or less than 7). Based on this information, it has been shown that the interval between first detected rise in PSA and development of symptomatic metastases may be several years. Only for men with rapid PSA doubling time hormonal therapy should be considered. An ASCO guideline on prostate cancer states that 'in metastatic or progressive prostate cancer immediate versus symptom-onset institution of ADT results in a moderate decrease (17%) in relative risk (RR) for prostate cancer-specific mortality, a moderate increase (15%) in RR for non-prostate cancer-specific mortality, and no OS advantage. Therefore, the panel does not make a strong recommendation for early ADT initiation.' I. Tannock concluded that all we are doing by measuring PSA and then not acting on the information is causing anxiety and that we are converting healthy men into PSA cripples. The solution to this problem is to stop measuring PSA.

Chemotherapy

Chemotherapy has a proven effect in prostate cancer. Docetaxel and prednisone is established as the preferred first-line chemotherapy for hormone-refractory disease since it provides a survival benefit. The question of whether additional agents can improve outcome still remains. Also the question of whether chemotherapy should be used in minimally symptomatic patients is unanswered as well as which agents should be used in men that are well enough to receive second-line chemotherapy.

Principles of management for symptomatic hormone-refractory prostate cancer (HRPC) are to optimize pain

control with regular dosing of narcotic medication, such as morphine; give regular laxatives to control the constipation that will be caused by morphine; give local radiotherapy to dominant sites of pain and consider chemotherapy or bone-seeking radioisotopes for those with general symptoms or rapidly progressive disease.

Studies confirm the palliative benefit of mitoxantrone + prednisone, and this remains appropriate treatment for patients who are averse to side effects of docetaxel, while estramustine adds only toxicity and should not be used. Several studies looked at second-line treatment in prostate cancer after mitoxantrone or docetaxel treatment. It seems that the results of these small studies showed that docetaxel remains active independent of sequence, while second-line mitoxantrone induces a low response rate (6-20%) after docetaxel. In a randomized study, comparing satraplatin with prednisone, the former drugs resulted in a higher PFS ($P=0.0000003$), better time to pain progression ($P<0.001$), PSA response rate ($P<0.001$), pain RR ($P<0.005$), and measurable disease RR ($P=0.001$). Major concerns about this trial were that the aim of a phase III trial is the comparison of an experimental therapy with the current standard of care and whether the control arm should be a therapy that has been approved by regulatory bodies such as the FDA (or minimal treatment if there are no approved therapies) or a therapy that is most commonly applied in the oncological community. I. Tannock also referred to 2 poster presentations on the drug abiraterone, an oral inhibitor of the enzyme CYP450c17, which is critical to the production of the male hormones. This drug given in a dose of 1,000 mg led to a PSA response (in 60% of pre-docetaxel patients; in 50% of post-docetaxel patients) and objective response in patients in hormone-independent prostate cancer or after chemotherapy in 2 different phase II studies.

Bisphosphonates should be used in men with bone metastases. Zoledronate is a useful drug to decrease bone events in selected patients and fewer bone events were observed with the 4 mg dose (44%) compared to placebo (33%, $P=0.02$). However there was no difference in quality of life and some cases of osteonecrosis of the jaw were seen. Annual zoledronate is sufficient to prevent osteopenia in patients on long-term anti-androgen therapy and I. Tannock advised a 3-monthly interval since the 3-weekly interval is very expensive.

Highlights in colorectal cancer

C. H. Köhne reviewed important findings in patients with locoregional and metastatic colorectal cancer.

Adjuvant chemotherapy

Since the 1990s adjuvant chemotherapy have been used in certain patient population with colorectal cancer since consecutive studies showed a benefit with this approach (1990: survival with 5-FU/levamisole > surgery alone; 1994: 5-FU/LV > surgery alone; 1998: 5-FU/LV > 5-FU/levamisole; 1998 6 months = 12 months; 2002: LV5FU2 > bolus 5-FU). However many patients are already cured by surgery alone, while adjuvant chemotherapy induces a clinical benefit in only 20% of patients, indicating that around 80% of patients are treated with chemotherapy unnecessarily.

Since 2002, many drugs have been tested in the adjuvant setting in patients with stage II and III colorectal cancer.

In stage III colorectal cancer, the use of the oral fluoropyrimidine capecitabine is not inferior to 5FU/LV with 3-year OS rates of 81% and 78%, respectively.

In patients with stage III colorectal cancer, the addition of oxaliplatin to 5-FU/LV proved to be superior in terms of DFS (risk reduction of 22%) and OS (risk reduction 20%) compared with 5-FU/LV alone, while in patients with stage II disease no benefit could be demonstrated. The addition of oxaliplatin results in a neuropathy that decreases after treatment but 11.4% of patients still suffer from this side effect 5 years after ending treatment (grade 3: 0.5%).

The addition of irinotecan to 5-FU/LV in adjuvant setting did not lead to an improved survival.

In several adjuvant studies, it has been shown that when there is a benefit in DFS in patients with stage III colorectal cancer, there is also a benefit in OS. This finding might lead to a faster completion of clinical studies since a surrogate endpoint might be used in this patient population.

The survival outcome of patients with stage II colon cancer correlated with the number of resected lymph nodes: if there are only 10 or fewer lymph nodes, the survival is significantly shorter than when there are 11 or more, indicating that the first group might be of higher stage. While there was no benefit in the whole group of stage II colon cancer, there was a benefit in DFS when certain risk factors were taken into account: T4, tumor perforation, bowel obstruction, poorly differentiated tumor, venous invasion, or ≤ 10 lymph nodes examined. Therefore a small benefit on PFS is possible with 5-FU/FA and/or FOLFOX while the impact on survival is likely to be small and toxicity and co-morbidity should be considered when choosing adjuvant chemotherapy in this patient population.

Several studies are looking at the place of targeted therapies in the adjuvant setting (PETACC 8: FOLFOX vs. FOLFOX + cetuximab; AVANT: FOLFOX vs. FOLFOX + bevacizumab vs. CapeOx + bevacizumab; QUASAR 2: capecitabine vs. capecitabine + bevacizumab).

Metastatic disease

The median survival of patients with metastatic colorectal cancer has increased from 6 months to 22 months due to the new treatment strategies and drugs.

The use of adjuvant chemotherapy after metastasectomy of liver metastases does not bring a survival benefit. However, with the use of new cytotoxic combination, the place of chemotherapy in this patient population was re-evaluated. Patients with potentially resectable liver metastases were randomized to 6 cycles of FOLF-FOX4 followed by surgery followed by 6 more cycles or surgery alone. After 3 years, there was a significant benefit in survival in the combination treatment group when patients were eligible (8.1% absolute difference) or when a complete resection could be performed (9.2% absolute difference). Survival data are awaited for before this strategy can be introduced in clinical practice.

Several studies have been looking at the use of oral fluoropyrimidines (e.g. CapeOx vs. FOLFOX or FOLFIRI vs. Capelri); doublets versus triplets (e.g. FOLF-FOXIRI vs. FOLFIRI); doublets plus biologicals (e.g. FOLFIRI+bevacizumab vs. IFL+bevacizumab vs. IFL; FOLFOX+bevacizumab vs. FOLFOX); the role of different combinations in patients with resectable liver metastases and in elderly patients or these with a bad performance status and the possibility of intermittent treatment:

In a randomized study comparing FOLFOX with FOLF-FOXIRI, the latter combination resulted in a higher response rate (34% vs. 60%) and R0 resection rate in patients with liver metastases only (12% vs. 36%). Other studies also show that the resection rate in patients with liver metastases is higher with a higher response rate. This indicates that when one is considering metastasectomy, the most active regimen should be used.

While infusional combination therapy has already shown a beneficial effect in patients with good performance status compared with bolus regimens, this was also the case in patients with a performance status of 2.

Bevacizumab, a monoclonal antibody against VEGF was tested in patients with metastatic disease. The addition of bevacizumab to an irinotecan-containing regimen resulted in a higher response rate and OS compared with a non-bevacizumab regimen.

At ASCO 2007, Cassidy et al. presented the data of their 4-arm study comparing XELOX with or without bevacizumab with FOLFOX4 with or without bevacizumab. The protocol was amended to 2x2 placebo-controlled design after bevacizumab phase III data became available ($n=1401$). There was no difference in response rate among the different groups, while the DFS was lower in the XELOX arm compared with XELOX plus bevacizumab.

The conclusion of the overview was that bevacizumab may improve the lower activity regimen as a higher progression-free and OS when combined with 5-FU/FA; IFL in first-line treatment and its effect might be more pronounced with irinotecan-containing regimens.

Cetuximab is a monoclonal antibody against the EGFR and was also used in the treatment of metastatic colorectal cancer. In patients pretreated with both oxaliplatin and irinotecan, cetuximab did lead to a higher OS compared with placebo (6.4 vs. 4.6 months, $P=0.0046$). The addition of cetuximab to irinotecan in the second-line treatment (EPIC) increased PFS compared with placebo (4.0 vs. 2.6 months, $P<0.0001$) but there was no difference in OS. In first-line treatment (CRYSTAL) with FOLFOX4 the addition of cetuximab increased the 1-year progression-free rate from 23% with placebo to 34% with cetuximab. In conclusion, cetuximab improves FOLFIRI and FOLFOX, and it has single agent activity leading to a survival benefit in heavily pre-treated patients compared with best supportive care.

Highlights in upper gastrointestinal cancer

D. Cunningham presented the highlights in different cancers in the upper gastrointestinal tract.

Pancreatic cancer

Locally advanced and metastatic pancreatic cancer

In patients with locally advanced and metastatic pancreatic cancer, the use of a doublet (gemcitabine 1,000mg/m² weekly × 3 q 4 weeks plus capecitabine 1,660mg/m²/day for 21 days q 4 weeks) proved superior than standard treatment with gemcitabine alone (1,000mg/m² weekly × 7 q 8 weeks and thereafter weekly × 3 q 4 weeks). The median OS was 6.0 versus 7.4 months and the 1-year survival 19% versus 26%, with an advantage for the combination treatment. Toxicity was higher in the combination arm with more hematological toxicity, lethargy and hand-foot syndrome. A phase III study by the SAKK with a similar design could not show a benefit for the combination in OS (the primary endpoint); while in the subgroup of patients with good performance status a benefit was present.

Gemcitabine was also combined with erlotinib (gemcitabine 1,000mg/m² weekly × 7 followed by 1 week rest, then weekly × 3 q 4 w + erlotinib 100mg/day or 150mg/day) and compared with gemcitabine alone. There was a benefit for the combination arm with a 1-year survival of 24% compared with 17% for the single-agent arm. Rash and diarrhea were more frequently observed in the erlotinib arm and there seemed to be a correlation between rash and survival.

Gemcitabine was also combined with bevacizumab but this trial was negative with no beneficial effect on PFS and OS of the addition of bevacizumab. Also the addition of cetuximab did not improve treatment outcome.

Local pancreatic cancer

The role of adjuvant treatment in resected pancreatic cancer was studied in the ESPAC-1 trial. Patients were randomized to chemotherapy, chemoradiotherapy, chemoradiation plus chemotherapy or observation. There was a benefit on survival when chemotherapy was added compared with observation (median OS 15.5 vs. 20.1 months, 2-year OS rate 30% vs. 40%; HR 0.71; 95% CI, 0.55 - 0.92; $P=0.009$).

Similar results were found in the CONKO-001 trial in which gemcitabine was given in the adjuvant setting and compared with observation. There was a better progression-free survival in patients treated in the gemcitabine arm.

These data indicate that adjuvant chemotherapy might be of benefit in patients with local pancreatic cancer after local resection.

Hepatocellular carcinoma

The use of chemotherapy in patients with hepatocellular carcinoma has been disappointing, with doxorubicin being the most active agent with a survival benefit compared with best supportive care.

Since Raf-kinase is over-expressed in patients with hepatocellular carcinoma and the Raf/MEK/ERK seems to be implicated in this tumor type, sorafenib (a multi-targeted tyrosine kinase inhibitor with activity against the RAF family), VEGF, platelet-derived growth factor beta (PDGFb), and cKIT were compared in this patient population with placebo. There was a survival benefit (46.3 vs. 34.4 weeks) in the sorafenib arm, although there was no difference in time to symptomatic progression.

Esophagogastric cancer

Advanced disease

In patients with locally advanced and/or metastatic disease, the combination of an anthracycline, cisplatin and 5-FU has been the standard treatment for many years. A phase III trial compared the activity of oxaliplatin and capecitabine in patients with esophagogastric cancer. There was no superiority of any one of the regimens tested, while the capecitabine arms were slightly better than the 5-FU arms. Cunningham concluded that the combination of an anthracycline, oxaliplatin and capecitabine [OS 9.9 (ECF) vs. 11.2 months (EOX); 1-year OS 37.7% (31.8-43.6%) vs. 46.8% (40.4-52.9%); HR: 0.80 (95% CI: 0.66-0.97), Log rank $P=0.02$) should be the new standard. Diarrhea was more pronounced in the capecitabine treatment arms, while hematological toxicity and thromboembolic events occurred less than in the standard arm.

In his conclusion Cunningham stated that capecitabine could replace 5-FU and oxaliplatin cisplatin in this tumor type. Several studies are investigating how to integrate targeted agents (cetuximab, panitumumab and trastuzumab) into the treatment of advanced esophagogastric cancer. Results are awaited.

Local disease

Adjuvant chemotherapy did not improve the survival in patients treated with surgery. The MAGIC study evaluated induction chemotherapy followed by surgery followed by adjuvant chemotherapy in patients with a local esophagogastric cancer and showed a 2-year survival benefit (23% vs. 36, $P < 0.009$). There was no increased perioperative toxicity in the combination arm.

Another randomized trial showed a similar benefit of this approach compared with surgery alone.

He concluded that no patients should be treated with surgery alone when they suffer from a local esophagogastric cancer.

Highlights in lymphoma

F. Cavalli's lecture looked at rare presentations of lymphoma.

Since the 1970s, different classification systems have been used to classify lymphomas [Rappaport classification; Lukes and Collins classification; British National Lymphoma Investigation (BNLI) classification; Kiel classification (Europe, revised in 1988); NCI Working Formulation (1982); Revised European-American Lymphoma Classification (REAL) (1994); WHO classification of Hematopoietic and lymphoid tissues tumors (2001)].

Based on chromosomal and molecular analyses, it has been recognized that lymphomas constitute a large number of distinct diseases associated with distinctive epidemiology, morphology, immunophenotype, genetic features and clinical features. This will soon lead to a revision of the classification system actually used.

There has been an increase of around 4% in non-Hodgkin's lymphoma incidence in Europe while the incidence of Hodgkin's lymphoma is decreasing. The number of patients with nodal involvement increased by 1.7- 2.5% per year, while patients with extranodal involvement increased with 3.0 - 6.9% per year. The sites with the greatest increase are skin, stomach, intestine, brain and eyes.

The survival of extranodal lymphomas depends on the site of disease: the 5-year survival of patients with testicular (48%) and central nervous system lymphomas is poor while it is good for patients with mucosa-associated lymphoid tissue (MALT) lymphomas. Since these lymphomas are very rare, the International Extranodal Lymphoma Study Group (<http://www.ielsg.org>) has opened a registry and performs studies in these rare patient populations:

Central nervous system lymphoma (PCNSL)

In patients with PCNSL they could show, in 370 immune-competent patients treated at 23 cancer centers from 5 countries, that chemotherapy followed by radiotherapy is superior to radiotherapy alone and that the best treatment regimen is high-dose methotrexate and high-dose cytarabine.

The IELSG prognostic score for PCNSL is based on age, performance status, lactate dehydrogenase (LDH) serum level, cerebrospinal fluid (CSF) protein concentration, and involvement of deep structures of the brain and is a predictor of survival in this patient population.

MALT lymphoma

The MALT concept states that there are different forms of mucosa-associated lymphocytes.

Lymphocytes that are normally present in certain extranodal sites (e.g., Peyer's patches) (= native MALT); acquired MALT where lymphoid tissue is not a natural component (e.g. Sjögren, Hashimoto, *Helicobacter pylori*-gastritis); and MALT lymphoma that can arise from a wide variety of extranodal tissues (usually at acquired MALT sites). MALT lymphoma has typical histological and phenotypical features: they are centrocyte-like cells (usually) in lymphoepithelial lesions, show a plasma cell differentiation with scattered transformed blasts and are admixed with non-neoplastic T-cells; they have a follicular colonization and express surface immunoglobulins (slg) (usually IgM + and IgD -), and are CD20, CD21, CD35 positive and CD5, CD10, CD23 negative.

There is a relationship between *Helicobacter pylori* and MALT lymphoma. *H. pylori* can stimulate mucosal T lymphocytes to proliferate leading to contact-dependent B-cell stimulation by CD40-CD40L interaction. This can induce genetic alterations that results in *H. pylori*-dependent MALT lymphoma. *H. pylori* can also induce activation of neutrophils with release of genotoxic radicals that transforms B-cells to MALT lymphoma.

Additional mutations lead to disease progression. Several different chromosomal translocations have been described [e.g. t(1;14) leading to BCL10 deregulation (rare); t(11;18) resulting in CagA+ strains and API2/MALT1 fusion (common); t(3;14) giving FOXP1 overexpression; and at non-GI sites t(14;18) with MALT 1 deregulation] that lead to NF- κ B activation and development of antibiotic-resistant gastric lymphoma.

The different translocations lead to MALT lymphoma at different sites. The response rate to antibiotics in gastric MALT lymphoma ranges from 56-100%.

Diffuse large B-cell lymphoma (DLBCL)

The treatment and outcome of diffuse large B-cell lymphoma (DLBCL) has dramatically changed in recent years.

DLBCL is the most common form of non-Hodgkin's lymphoma (30%) and has an aggressive histology (most lymphoma cells are highly atypical: large and irregular, with vesicular nuclei and prominent nucleoli) and behavior (untreated, most patients die within 1-2 years).

The WHO classification (2001) has different sub-classifications of DLBCL:

Diffuse large B-cell lymphoma, not otherwise specified

(NOS), including germinal center B-cell type; activated B-cell type; DLBCL associated with chronic inflammation; EBV-positive DLBCL, NOS; and T cell/histiocyte rich large B-cell lymphoma,

- Primary mediastinal (thymic) large B-cell lymphoma
- Primary DLBCL of the CNS
- Primary cutaneous DLBCL-leg type
- Intravascular large B-cell lymphoma
- Anaplastic lymphoma kinase (ALK)-positive DLBCL
- Plasmablastic lymphoma
- Primary effusion lymphoma
- DLBCL associated with HHV8+ multicentric Castleman disease

The prognosis of DLBCL can be classified according to the International Prognostic Index (IPI) based on age (<60 vs. >60 years), stage (I/II vs. III/IV); performance status (0/1 vs. 2-4), LDH (normal vs. increased) and involvement of extranodal sites (1 vs. >1).

CHOP is no longer the standard treatment in patients with DLBCL. Randomized trials showed that either the addition of rituximab (R-CHOP), CHOP-14, CHOEP, or ACVBP are better than CHOP in various clinical settings. A specific therapeutic approach may be needed for each extranodal presentation.

Myeloablative therapy with autologous stem cell transplantation (ASCT) is the standard treatment at first relapse in patients <65 years. Upfront treatment of poor risk patients with ASCT is at this moment controversial.

Follicular lymphoma

Follicular lymphoma (FL) is a tumor of follicle center B-cells, composed of a mixture of centrocytes and centroblasts, with at least a partially follicular growth pattern. Grading of FL depends on the number of centroblasts: grade 1: 0-5 centroblasts per high-power field; grade 2: 6-15 centroblasts per high-power field; and grade 3: >15 centroblasts per high-power field. The immunophenotype of FL is CD19+, CD20+, CD22+ sIg+, CD10+/-, CD5-, CD43- and Bcl-2+ with nuclear Bcl-6 expression. FL has the following genetic features: t(14;18) with BCL-2/JH rearrangement and BCL-6 is frequently mutated/rearranged.

The prognosis of FL is according to the Follicular Lymphoma International Prognostic Index (FLIPI) based on age (<60 vs. ≥ 60 years); hemoglobin (≥12g/dL vs. <12g/dL), serum LDH [≤ upper normal limit (ULN) vs. > ULN], Ann Arbor stage (I-II vs. III-IV) and number of nodal sites (≤4 vs. >4). Based on these factors, patients are grouped into good prognosis (0-1 factors, 5-year OS 91%; 10-year OS 71%), intermediate prognosis (2 factors, 5-year OS 78%, 10-year survival 51%) and poor prognosis groups (≥ 3, 5-year survival 53%, 10-year survival 36%).

The introduction of rituximab improved OS in patients with FL compared with historical controls.

Highlights in breast cancer

M. Piccart-Gebhart concluded the day with the highlights in breast cancer.

Cancer biology

Research in cancer biology has shown that invasive breast cancer is at least 4 diseases.

Basal-like cancers show racial differences; BRCA-1-directed therapy is attractive but not yet evidence-based; its outcome is poorer unless a pathological complete response is reached, which is twice as common as for HER-2-disease (25% vs. 11%)

HER-2 positive disease, in which brain metastases are frequent but have better prognosis than in HER2-negative disease; and there is a hypothesis that it may be a gene signature for brain metastases; and at relapse under taxomifen estrogen receptor(ER)-positive tumors originally HER-2 negative can become HER-2 positive. In small T1 tumors if screen-detected, there is a 90% OS at 10 years with or without therapy; the event rate at 5 years is 15-20% (5-8% distant); and HER-2 positive, ER positive do better than HER-2 positive, ER negative (75 vs. 61% 10 years relapse-free survival.

Luminal A and B tumors in which luminal A may not be a homogenous group (Oncotype DX R.S. low in 62% only). The difference between luminal A and B is the level of expression of luminal genes (ER/GATA3); the proliferation, p53 mutations and HER-2 amplification.

Minimally detectable disease

Minimally detectable disease, defined as circulating tumor cells (CTC) or bone marrow micrometastases (DTC), is neither necessary, nor sufficient for macrometastatic disease to develop, but is relevant to the disease course.

CTC predict a poorer outcome, especially in ER-negative breast cancer; have a distinct phenotype compared with primary and metastases and frequently express HER2 and NOTCH1 transcripts.

DTC also predict a poorer outcome; show fewer genomic aberrations than the primary tumor; and do not correlate with sentinel node positivity, ER or HER2 status.

The evidence of minimally detectable disease indicates that dissemination could occur much earlier than initially thought and that breast cancer may be a systemic disease from the start. At the moment this has no clinical implications and one should wait for clinical trial results such as the FAME trial that compares anastrozole to anastrozole + fulvestrant in DTC-positive patients before changing clinical practice.

Multigene prognostic signatures

Multigene prognostic signatures should also not be used in daily clinical practice. Several trials [TAILORx (n=10500); MINDACT (n=6000)] are looking at the value of molecular prognostic signatures in daily clinical practice and the results of these trials should be awaited.

Endocrine therapy

Advanced disease

In advanced disease a potential sequence of endocrine therapies for ER-positive disease in postmenopausal women was discussed.

Patients who received tamoxifen as adjuvant treatment may be treated by:

Fulvestrant followed by an aromatase inhibitor (AI) followed by exemestane followed by medroxyprogesterone acetate or estrogens; or an AI followed by fulvestrant (or tamoxifen) followed by exemestane followed by medroxyprogesterone acetate or estrogens; or an AI followed by exemestane followed by fulvestrant (or tamoxifen) followed by medroxyprogesterone acetate or estrogens. Patients who received an AI as adjuvant treatment may be treated by:

Fulvestrant (or tamoxifen) followed by exemestane followed by medroxyprogesterone acetate or estrogens; or exemestane followed by fulvestrant (or tamoxifen) followed by medroxyprogesterone acetate or estrogens.

In patients failing a non-steroidal AI, the choice between fulvestrant and exemestane can be made on grounds of patient preference, toxicity and cost.

Adjuvant setting

In the adjuvant setting tamoxifen is still a valid option in this patient population. It was shown that the levels of endoxifen vary with the number of mutant alleles of *cyt P450 CYP 2D6*: wt/wt \approx 72%; wt/* \approx 21%; and */* \approx 7%. Modelling suggests that tamoxifen might be superior compared with AI in wt/wt patients. Adjuvant tamoxifen given for 2-3 years and followed by an AI is still a reasonable choice on grounds of toxicity and cost in patients at low-medium risk. *CYP2D6* inhibitors (fluoxetine, paroxetine) should be avoided.

Extended AI therapy after 5 years of tamoxifen is level 1 evidence-based. The NSABP-B33 results show an improvement in relapse-free ($P=0.004$), disease-free and distant DFS of similar magnitude as seen in MA 17. An update on cardiovascular adverse events in BIG 1-98 shows a slightly increased risk (from 1% to 2%, HR=1.63, $P=0.004$) at a 30 month follow up.

Targeted therapy

The role of targeted therapy in delaying development of hormonal resistance in patients with luminal-type breast cancers was further clarified. Studies showed that mTOR inhibition with temsirolimus was not able to improve the activity of letrozole in advanced breast cancer.

The results of the combination of fulvestrant + tipifarnib, a signal transduction inhibitor, were also disappointing: in a phase II study, the clinical benefit rate of 43% did not meet the predicted clinical benefit of 70% in 33 patients.

Chemotherapy

Advanced disease

In patients with advanced disease, several new findings in relation to chemotherapy were discussed.

In patients with metastatic disease, maintenance liposomal doxorubicin (Doxil) after anthracyclines/taxanes for 5 cycles improved time to tumor progression by 3 months in a randomized trial in ER-positive women but there was no crossover and no OS gain.

Nab-paclitaxel (Abraxane) is paclitaxel encapsulated in albumin and its weekly administration resulted in a higher response rate compared with docetaxel in a randomized phase II trial (60% vs. 36%).

Ixabepilone + capecitabine is superior to capecitabine alone as shown in a randomized trial with 752 patients and resulted in a better PFS (HR=0.75) and response rate (35% vs. 14%) but was more toxic. Capecitabine showed a better OS than CMF in a randomized trial of 325 ER-positive women.

Early disease

In patients with early disease, different chemotherapy regimens have been tested:

In the NCIC MA-21 patients were randomized to 6 cycles of CEF, 4 cycles of AC followed by 4 cycles of taxanes or 6, 2-weekly cycles of EC followed by 4 cycles of taxanes. The relapse-free survival was not different between the epirubicin-containing regimens (HR EC/T to CEF: 0.89; $P=0.46$) but the epirubicin-containing schedules were superior to the doxorubicin-containing schedule (HR AC/T to CEF: 1.49; $P=0.005$; HR AC/T to EC/T: 1.68; $P=0.0006$). This study shows that AC/T every 3 weeks is significantly inferior to CEF or EC/T.

A pooled analysis of PACS 01 and BCRIG 01 in 3490 patients and a follow up of around 6 years showed that docetaxel treatment resulted in a benefit: the HR for death was 0.69 and 0.70 and the absolute benefit 7% and 4% in ER-negative and ER-positive patients, respectively.

Both docetaxel and paclitaxel in weekly or 3-weekly administration were tested after AC in a randomized trial: there was no difference among the docetaxel and paclitaxel arms. However, when the 3-weekly paclitaxel arm was compared with the other arms, there was a DFS benefit for the weekly paclitaxel and 3-weekly docetaxel arm and an OS benefit for the weekly paclitaxel arm. M. Piccart concluded that weekly paclitaxel is superior both in advanced and early disease.

HER-2 positive breast cancer

HER-2 positive breast cancer has become an important subgroup in breast cancer treatment.

The ASCO/College of American Pathologists published new guidelines for HER2 testing in breast cancer:

Positive for HER-2 is either immunohistochemistry (IHC) HER-2, 3+ (defined as uniform intense membrane staining of > 30% of invasive tumor cells) or fluorescence *in situ* hybridization (FISH) amplified (ratio of HER-2 to CEP17 of > 2.2 or average HER-2 gene

copy number > 6 signals/nucleus for those test systems without an internal control probe).

Equivocal for HER-2 is defined as either IHC 2+ or FISH ratio of 1.8-2.2 or average HER-2 gene copy number four to 6 signals/nucleus for test systems without an internal control probe.

Negative for HER-2 is defined as either IHC 0-1+ or FISH ratio of < 1.8 or average HER2 gene copy number of < 4 signals/nucleus for test systems without an internal control probe.

Several targeted therapies (trastuzumab, lapatinib, pertuzumab and bevacizumab) have been tested in advanced breast cancer:

Trastuzumab

In patients with advanced disease in need for chemotherapy, the addition of carboplatin (BCRIG 007) or capecitabine (CHAT study) to the combination of docetaxel and trastuzumab did not translate in an OS benefit.

In patients with advanced disease without indication for immediate chemotherapy, the addition of trastuzumab to an AI induced a higher response rate and time-to-progression (TTP) but not in an OS benefit (TANDEM study).

Lapatinib

The addition of lapatinib to capecitabine resulted in an increased TTP (HR=0.57), increased response rate (24% vs. 14%) but not in an OS [OS HR=0.78 (NS)].

The combination of lapatinib plus paclitaxel resulted in a higher response rate and TTP compared with paclitaxel alone.

In patients with brain metastases, lapatinib induced a response rate of 6%, a median PFS of 4 months and the 6-month PFS rate was 22%. There is a pharmacokinetic interaction between lapatinib and paclitaxel, but not with docetaxel

Lapatinib is potentially less cardiotoxic because it activates AMP kinase in cardiomyocytes

Trastuzumab + lapatinib shows little cardiotoxicity.

Pertuzumab

Binds to the HER-2 dimerization domain and blocks homo- and hetero- dimerization of HER-2

It is given every 3 weeks intravenously (loading dose = 840 mg; then 420 mg) and showed activity in trastuzumab failures, while continuing trastuzumab (response rate 21%).

Bevacizumab

The combination of trastuzumab + bevacizumab is highly active but there are some worrying cardiac side effects: in a phase II trial in 37 women, the response rate was 54% but 5 cardiac events \geq grade 2 were observed. There has been an update of 'benefit versus harm' of trastuzumab in the adjuvant setting:

In the BCRIG 006 study there was a cross-over of only 1.6%, and after a median follow up of 3 years the disease-free (HR AC -> TH 0.49 -> 0.61; TCH 0.61 -> 0.67) and OS (HR AC -> TH 0.59 both; TCH 0.66) benefit for the trastuzumab arm was confirmed. It was shown that topoisomerase II amplification is no longer predictive for benefit.

In the B31 and N9831 after a median follow up of 2.9 years and a cross-over of 21%, the benefit was maintained (DFS HR: 0.48; OS HR: 0.65). The increased risk of cardiotoxicity of adding trastuzumab was confirmed but at 5 years, there was a high recovery rate of confirmed chronic heart failure.

Conclusion

ECLU 2007 provided a very good overview of all major tumor types and made a direct interaction between attendees and speakers possible. ECLU 2008 will be held in Lugano from 3-6 July 2008: a date to note in your agenda.

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