44th annual meeting of the American Society of Clinical Oncology (ASCO)

Highlights of the 44th annual ASCO meeting, 30 May – 3 June 2008, Chicago, Illinois, USA

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Summary

From the 30th of May until the 3rd of June, the 44th annual meeting of the American Society of Clinical Oncology (ASCO) was held at the McCormick place in Chicago, Illinois. The ASCO meeting attracted more than 30,000 attendees and again proved to be the premier educational and scientific event in the oncology community. Due to the vast amount of data presented at the ASCO meeting it is impossible to address everything in this brief congress report. Therefore, this report aims at summarizing the important take home messages in the different fields of oncology presented at the meeting. All abstracts referred to in this report can be consulted at the ASCO website (www.asco.org)

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Breast Cancer: ASCO 2008 Highlights

Zoledronic acid improves outcome

There is increasing evidence that the use of adjuvant bisphosphonates might have benefits in breast cancer beyond their ability to improve bone mineral density.

Dr. Grant presented the first efficacy results from ABCSG-12. This study was a randomized, open-label, phase III, modified 2x2, four-arm trial of tamoxifen and goserelin with or without zoledronic acid compared with anastrozole and goserelin with or without zoledronic acid for 3 years (4mg given intravenously every 6 months). 1,803 premenopausal women with hormone-responsive breast cancer were included.

After a median follow-up of 60 months, overall disease-free and overall survival were 94.0% and 98.2%. No difference in DFS were detected among patients who received tamoxifen and those who received anastrozole. In the analysis of zoledronic acid, the bisphosphonate improved the primary endpoint of DFS (HR=0.64; p=0.011). Of the 137 DFS events, 54 occurred in women who had received zoledronic acid, with the remaining 83 in those who had not received the drug. The incidences of contralateral breast cancer, distant metastases and local-regional recurrence were all significantly reduced by zoledronic acid. The benefit was seen in and outside of bone. No renal toxicity or confirmed cases of osteonecrosis of the jaw occurred.

Invited to discuss this study, *Dr. Piccart-Gebhart*, said that ABCSG-12 is an important trial announcing a paradigm shift: targeting both seed and soil but that the findings are not yet practice changing. She also commented on some of the study's limitations (not double-blind, the control arm is not widely accepted and no stratification for HER2) and noted that there is a long list of remaining open questions that need to be addressed. The results of other phase III studies, such as the National Surgical Adjuvant Breast and Bowel Project's B-24 trial, the Breast International Group's AZURE trial, and the Southwest Oncology Group's SO307 trial are eagerly awaited. (abs LBA4)

No superior adjuvant chemotherapy regimens reported

CALGB 49907 investigators found that capecitabine was inferior to standard adjuvant chemotherapy for older women (≥65) with breast cancer. Standard chemotherapy was defined as either CMF or AC, per physicians choice. Patients who were randomly assigned to receive capecitabine were 2.4 times more likely to experience a relapse-free survival event (adjusted p=0.0003) and 2.1 times likely to die (p=0.02). (abs 507)

In the tAnGo trial, a randomized, open-label, multicenter phase III trial, the addition of gemcitabine to paclitaxel following epirubicin plus cyclophosphamide in the adjuvant treatment of 3,141 early breast cancer patients was investigated. The rationale behind the trial was that promising trends in progression-free and overall survival had been seen with the gemcitabine paclitaxel combination versus taxane alone in patients with metastatic breast cancer. Surprisingly, the addition of gemcitabine to adjuvant chemotherapy did not confer any additional benefit. After a median follow-up of 34.9 months, there was no difference between the two treatment arms in terms of disease-free survival (HR=1.0; p=0.96) or overall survival (HR=1.1; p=0.35). (abs 506)

Importance of good nutrition

Previous studies have found vitamin D receptors on normal and malignant breast tissue, and low levels of vitamin D have been associated with increased breast cancer risk. *Dr. Goodwin and colleagues* measured vitamin D levels in frozen blood samples taken at the time of diagnosis of 512 newly diagnosed breast cancer patients enrolled between 1989 and 1996. About 38% of the women had vitamin D levels low enough to be considered "deficient" and 39% had levels that were "insufficient." Just 24% of the women in the study had "adequate" vitamin D levels.

The risk of distant disease recurrence was significantly increased for patients with deficient vitamin D levels (HR=1.94; p=0.02). Overall 10-year survival rates were 74%, 85% and 85% for patients with deficient, insufficient and adequate vitamin D respectively (HR=1.73; p=0.02). For distant DFS and OS, adjustment for patient and tumor characteristics had little effect on the hazard ratio.

Confirmation of these results is required. Until more is known, current findings do not support vitamin D supplementation for women with breast cancer at doses higher than needed to maintain bone health. (abs 511)

AVADO trial confirms bevacizumab benefit in metastatic breast cancer

Dr. Miles presented a randomized, double-blind, placebo-controlled, phase III study comparing bevacizumab (7,5mg/kg or 15mg/kg) with docetaxel (100mg/m^2) to docetaxel with placebo as first-line therapy for patients with HER-2 negative, locally recurrent or metastatic breast cancer (the AVADO trial). The first endpoint was PFS, secondary endpoints were time to treatment failure, OS, best overall response, duration of response and safety. From March 2006 to April 2007, 736 patients were randomized in 24 countries. With a median follow-up of 11 months, PFS was significantly superior for both bevacizumab containing arms compared to docetaxel alone (HR 0,69 and p= 0,0035 for bevacizumab low-dose, HR 0,61 and p= 0,0001 for bevacizumab high-dose). The median time to disease progression was 8 months with docetaxel alone, compared to 8.7 months with docetaxel plus low-dose bevacizumab, and 8.8 months with docetaxel plus high-dose bevacizumab. ORR was superior in both combination arms compared to docetaxel alone. OS results are immature due to short follow-up. No new safety signals were detected and bevacizumab had little effect on the established safety profile of docetaxel.

In conclusion, the AVADO trial supports the use of bevacizumab in metastatic breast cancer. However, the AVADO data are not as robust as in the E2100 study. The E2100 study, conducted with 722 patients, found that bevacizumab added to paclitaxel nearly doubled median PFS from 5.8 months with paclitaxel alone to 11.3 months with the combination. (abs LBA 1,011)

More complete HER2 blockade improves patient outcome

Dr O'Shaughnessy presented the results of a randomized study of lapatinib alone or in combination with trastuzumab in heavily pre-treated HER2+ metastatic breast cancer progressing on trastuzumab therapy. The primary endpoint was PFS; secondary endpoints were clinical benefit rate (CBR), RR and OS. 269 patients were randomized. All patients had received prior taxanes, the median number of previous chemotherapy regimens was 6. Combination therapy improved significantly PFS (6-months PFS 13% versus 28%) and doubled CBR from 12.4% to 24.7% (HR 0,77, p=0,029 and HR 2,1 p=0,020 re-

spectively). ORR and OS were similar in both arms. (abs 1,015)

Anastrozole and gefitinib combination holds promise

Preclinical data suggest crosstalk between growth factor receptor pathways and the estrogen receptor. Inhibition of both epidermal growth factor receptor and ER signalling could be a potential intervention to overcome hormonal resistance. A phase II double blind randomized trial comparing anastrozole plus gefitinib (A+G) with anastrozole plus placebo (A+P) in postmenopausal HR+ first line metastatic breast cancer showed superior PFS for the combination of A+G compared to A+P (HR 0,55; median PFS 14,5 months vs. 8,2 months). As this is a small phase II trial (94 patients), this combination should be further investigated in a randomized Phase III trial. (abs 1,012)

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Digestive Oncology: ASCO 2008 Highlights

Summary

This year, the most striking presentations at the ASCO 2008 meeting concerned the role and the impact of Ki-ras status in predicting efficacy of cetuximab in metastatic colorectal cancer, mainly in first line therapy in combination with standard chemotherapy. Many abstracts attempted to provide results on predictive biomarkers in GI malignancies. *Ki-ras status evaluation* will now become a prerequisite before any therapy with anti-EGFR is started. Combining anti-VEGF and anti-EGFR seems to be unbeneficial and harmful in pancreatic and colon cancer, respectively. Gemcitabine was reported as the new adjuvant standard therapy in resected pancreatic cancer.

Ki-ras superstar

The most striking novelty in GI oncology presented at the 2008 ASCO meeting was undoubtfully the role of Ki-ras mutation status in predicting efficacy of cetuximab in metastatic colorectal cancer, mainly in first line therapy. *Dr. E. Van Cutsem* discussed an abstract (abs 2) in which the influence of Ki-ras mutation status on the efficacy analyses in the CRYSTAL study comparing FOLFIRI to FOLFIRI + cetuximab (improved PFS for the whole pts population) in the first line therapy of mCRC was presented; Ki-ras mutations (mt) were detected in 35.6% (192/540) pts with evaluable samples. Several other abstracts reported on concordant data. A statistically significant difference in favour of cetuximab was seen in Ki-ras wild type (WT) for PFS (HR=0.68) and response rate (59,3 vs 43,2%, p=0.0025). However, no differences were seen in the mt Ki-ras subgroup. *The authors concluded that the mutation status of Ki-ras has a predictive role for cetuximab efficacy in first line therapy.*

Similar results were observed with the combination of FOLFOX + cetuximab in the OPUS study (*Bokenmeyer et al,* abs 4.000). Again, the benefit from addition of cetuximab to FOLFOX was only seen in the Ki-ras WT population (PFS and RR) while no benefit could be shown in the mutated population. In this small number of mutated Ki-ras pts, PFS and overall RR data were slightly better in the FOLFOX alone arm but it is unclear whether this combination could be truly deleterious in mt ki-ras tumors.

Data from the Everest study presented by *S. Tejpar* (abs 4.001) in irinotecan refractory mCRC also showed a concordant role for Ki-ras status and in

mt Ki-ras population. Escalation of cetuximab dose did not increase responses.
Reduced PTEN expression (by IHC), a downstream effector of the EGFR-cascade, was also suggested to be predictive of cetuximab activity. (*Loupakis et al,* abs 4.003)
Predicting the efficacy of anti-angiogenic drugs remains difficult. Data from the CONFIRM 1 and 2 studies exploring the role of PTK/ZK, an VEGFR TK inhibitor, suggested that mRNA levels of genes involved in angiogenesis and in the HIF pathway may predict outcome with VEGFR TK inhibitors. (abs 4.002)

The use of FDG-PET before hepatic surgery

An interesting randomized study (n = 150) concluded that the addition of FDG-PET to CT imaging alone before surgical resection of CRC liver metastases prevents unnecessary surgery in 1/6 pts (relative RR of 38%) (*Wiering et al*, abs 4.004). Another retrospective study demonstrated that complete metabolic response after neoadjuvant therapy of mCRC does not correlate with histological response (PPV of only 75%) and showed that hepatic resection of CRC liver metastasis should not be deferred on the basis of FDG –PET. (*Covas et al*, abs 4.070)

Improving oxaliplatin administration

Two abstracts derived from the randomized, phase III CONCEPT trial (2x2 design) reported that intravenous calcium and magnesium is a neuroprotectant against oxaliplatin-induced neuropathy in patients with mCRC receiving FOLFOX6 regimen and can be recommended as a standard component of oxaliplatin-based regimen (*Nikcevich et al*, abs 4.009). This study also showed that an intermittent oxaliplatin schedule of FOLFOX/beva resulted in an increased time on therapy compared to the conventional "treat to failure" approach (25 vs 18 weeks) (*Grothey et al*, abs 4.010). These data confirmed the previously reported results of the OPTIMOX -1 study.

Addition of bevacizumab and cetuximab to front line chemotherapy in mCRC is deleterious

The CAIRO-2 study was designed to investigate the effect of adding cetuximab to capecitabine, oxaliplatin (CapOx) and bevacizumab in mCRC. 755 pts were randomized and the primary endpoint was PFS. The combination of both antibodies resulted in increased grade 3-4 toxicities (71.8 vs 81.9%). Median PFS was 10.7 in the bevacizumab arm and 9.6 months in the cetuximab/bevacizumab arm (p=0.019,HR1.22). This finding was also confirmed in mutant Ki-ras pts 12.5 vs 8.6 months. However, OS was not affected. (*Punt et al*, abs 4.011)
In another abstract, *Ychou et al* reported the results of a randomized phase III trial comparing 5FU/FA infusional vs. FOLFIRI after complete resection of liver metastases from CRC. 321 pts were randomized and the two arms were well balanced. The overall HR for DFS adjusted for stratification factors was 0.89, p=0.47, indicating that there was no overall advantage to use FOLFIRI in this adjuvant setting (abs 4.013)

Pancreatic cancer

In the adjuvant setting, the final results of the CONKO001 trial provided a new standard of care after resection of pancreatic cancer. Patients were randomized between observation vs. gemcitabine during 6 months after R0 or R1 surgery. Mature results showed that gemcitabine improves median survival (22.8 vs 20.2 months, p=0.0051) and 5 year survival (21 vs 9%). (*Neuhaus et al*, abs 4.504) Observations from translational studies in pts treated with surgery and neoadjuvant gemcitabine-based chemotherapy plus radiation therapy suggested that polymorphic variants of gemcitabine metabolic genes (nucleoside transporters) affect the efficacy of gemcitabine therapy in patients with pancreatic cancer.
Two randomized studies (1 phase II, 1 phase III) failed to demonstrate any significant survival benefit in advanced pancreatic cancer of the combination of gemcitabine, erlotinib or cetuximab and bevacizumab. This confirms the lack of benefit of antiVEGF and antiEGFR combinations (*Kindler et al*, abs 4.502; *Vervenne et al*, abs 4.507)
A strategic FFCD trial compared two strategies in metastatic pancreatic cancer: gemcitabine followed by LV5FU2-CDDP vs. the reverse sequence. 102 pts were included and the primary endpoint was OS. Both sequences achieved a similar efficacy with similar OS reached (6.6 vs 8.2 months) However, the study was probably underpowered to demonstrate a superior effect. (*Mitry et al*, abs 4.513)
The CONKO 003 randomized trial was the first study able to enroll patients in 2nd line therapy of advanced pancreatic cancer after failure of gemcitabine. This trial compared oxaliplatin 85mg/m^2 + 5FU infusional 2gr/m^2 and folinic acid 200mg/m^2 24h weekly (OFF regimen) with OFF regimens without oxaliplatin. 168 pts were recruited. PFS

(13 vs 9 weeks, p=0.001) and OS (26 vs 13 weeks, p=0.001) were improved by the OFF regimen (*Kubica et al*, abs 4.508), suggesting that this regimen could be proposed in 2nd line therapy.

Oesogastric cancers

A Japanese phase III trial compared neoadjuvant chemotherapy to adjuvant chemotherapy in stage II/III squamous cell cancer of the thoracic esophagus. Patients received 2 cycles of CDDP/5FU before or after surgery. 330 patients were randomized. OS (HR=0.64, p=0.014) was clearly in favour of preoperative chemotherapy which is now regarded as the new standard of care in Japan. (*Igaki et al*, abs 4.510)

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New drugs: ASCO 2008 Highlights

Introduction

Next to many new drugs belonging to already known classes, drugs that have novel targets are being developed. Many of the activities reported here are preliminary. It appears that the new molecular drugs will have impact on small fractions of patients and that predictive biomarkers to identify these patients are needed. This also means that the number of patients that will have ultimately benefit might be small or very small which determines the ultimate market potential. As a consequence, the development of these drugs using the current path of large phase III trials or even randomized phase II trials, might become too cumbersome. Regulatory authorities should work together with drug developers and the academic world on alternative development strategies for most of the new targeted treatments and consider these as "orphan drugs", even if these molecules are applicable in subsets of the most frequently occurring cancers.
As melanoma and sarcoma are tumors for which therapeutic options are rapidly running out, these rare tumor types are overrepresented in early studies. In some phase I studies more than half of the patient population consists of sarcomas.

Rank and Rank ligand

The era in which sarcomas were treated with a single type of palliative chemotherapy is history. There is growing data showing that specific treatments work better in specific types of sarcomas. In view of the emerging diversity of treatments for sarcomas and other rare cancers, it would be good to have a national registration for the treatment of sarcomas including a database of available experimental treatments and trials running in the different centers.
Denosumab is a fully humanized monoclonal antibody that binds and neutralizes the human receptor activator of the NF-kappaB ligand (RANKL), an important mediator of osteoclast activation, differentiation, and survival. An impressive response rate of 87% was seen in preliminary data on 15 patients with giant cell tumors of the bone. (abs 10.500) Giant-cell tumor of bone represents 5% of all primary bone tumors and is a locally aggressive lytic bone lesion that has the propensity to metastasize. Current standard treatment for giant-cell tumor of bone is curettage and cementation or bone-grafting. The pathogenesis is based on a functional interaction between Rank ligand secreting cells and the tumor cells derived from the osteoclast that expresses the receptor for the Rank ligand. It is yet unclear how long the treatment should be pursued in the patients

going into remission. Responses were typically slow and there was evidence for bone repair in lesions in remission. The use of denosumab in the treatment of osteoporosis and malignant osteolysis is also under investigation.

Insulin-like growth factor 1 (IGF-1) and its receptor (IGF-1R)

Inhibition of the Insuline-like Growth Factor-1 Receptor (IGF-1R) is a promising novel therapy investigated in many cancers. The IGF-1R pathway is involved in cell growth and IGF-1R inhibition slows tumor growth in preclinical models. IGF-1R is implicated in autocrine and paracrine control of sarcoma and IGF-1R blockage increases apoptosis and decreases the malignant phenotype. In Ewing sarcoma, the pathogenic IGF-1 rearrangement has a direct effect on the transcription. It is currently unclear in what other cancers this pathway might be constitutionally activated.

CP-751,871 is a fully human IgG2 monoclonal IGF-1R antibody that is currently investigated in a wide range of cancers. In the current phase I/II studies the drug is investigated in combination with chemotherapy which makes it difficult to ascertain the contribution of the antibody to the overall effect (despite insinuations made in some abstract titles). Preliminary results of single agent activity in 24 sarcomas (of which 11 Ewing sarcomas) indicated that 2 patients (both Ewing sarcoma) responded and 6 had prolonged stable disease. (abs 10.501) Responses took months to be achieved. This antibody was very well tolerated in a pediatric population without detrimental effect on growth during study treatment despite the importance of this pathway for growth. There is currently no indication of strong activity of this anti-IGF-1R in other malignancies.

Heat-shock protein 90 (HSP90)

HSP90 is a chaperone for various proteins including oncogenic receptors such as HER2 and MET. Various HSP90 inhibitors are being developed. Inhibition of HSP90 results in the selective increased degradation of mutant receptors which are more dependent on HSP90 than the wild type copy. This provides an additional therapeutic method to downregulate oncogenic receptors, in particular receptors that have become resistant to primary small molecule inhibition.

IPI-504 is a water-soluble HSP90 inhibitor that has higher bioavailability than other HSP90 inhibitors. (abs 10.503) In GISTs that have acquired resistance to imatinib through secondary mutations in the targeted receptors a 5/21 partial metabolic response, 70% disease control at 6 weeks and one PR were obtained. A response was also observed in liposarcoma. A phase III trial is planned in imatinib resistant GISTs.

BIIB021 is an oral synthetic selective HSP90 inhibitor in early phase study in patients with cancer and chronic lymphocytic leukemia (CLL). Pharmacodynamic endpoints include the induction of HSP70 and inhibition of the Her2/neu extracellular domain (ECD). The drug is well tolerated and some activity in CLL was noted. (abs 2.503)

Polo-like kinase (Plk)

Plk is a key regulator of mitotic progression. ***BI2536*** is a highly selective inhibitor of Plk1 and has demonstrated favorable tolerability and antitumor activity in Phase I trials and is now investigated in combination with chemotherapy. (abs 8.115 & 8.030)

Vascular disrupting agents

Vascular disrupting agents are a relatively new class of anticancer agents with a peculiar and poorly understood mechanism of action. These drugs are microtubule inhibitors and are toxic for endothelial cells. However, the vascular toxicity occurs at doses much lower than needed for microtubule inhibition and indeed they do not produce clinical neurotoxicity. Most of these agents are still in phase I/II and the early signs of activity are poor.

Angiogenesis

A flood of anti-angiogenic agents is being explored in various cancer types.

Sunitinib. Few treatment options exist for patients with refractory differentiated (DTC) and medullary thyroid cancers (MTC). Recent data suggest that thyroid cancers respond to antiangiogenic agents. In addition, a subgroup of thyroid cancers harbour activating alterations in the RET gene. Sunitinib has inhibitory activity against RET, VEGFR, PDGFR, c-Kit and Flt-3. Sunitinib was shown to be very active in MTC with 3/7 RR en 3/7 SD. (abs 6.025) In 31 evaluable DTC patients PR 13%, SD 68%, was obtained and in MTC patients SD and PR were 83% and 17%.

In 10 patients with uveal melanoma that typically have late liver metastasis and who are currently not eligible for vaccination trials, 1 partial response (PR) and 7 stable disease (SD) (overall clinical benefit rate 80%) were observed. Sunitinib should be tested in

a larger cohort of these patients. (abs 9.047) A modest activity was observed in high grade glioma. (abs 13.001). In 23 patients with pleural mesothelioma, 3 PR (15%) and 11 SD (55%) were observed. A metabolic response occurred in 3 of 10 assessable patients (30%). There was one possible treatment-related death caused by pulmonary infiltrates and respiratory failure. This phase II study is being expanded. (abs 8.063) In alveolar sarcoma 2/4 responses were reported. (abs 10.592)

Axitinib is an oral, selective inhibitor of VEGFRs 1, 2, 3 with preliminary evidence of clinical activity as monotherapy against renal cell carcinoma. In 32 melanoma patients an ORR of 15.6% was observed. (abs 3.543 & 9.006) The median OS of patients experiencing dBP ≥ 90mm Hg on axitinib therapy was 13.0 months vs 6.2 months for those with dBP < 90mm Hg (n= 9).

E7080 is an inhibitor of VEGFRs 1 and 2, FGFR-1, PDGFR-β, Kdr, IGF-1R and Flt1. (abs 3.526 & 3.527) E7080 produces partial remissions in melanoma, sarcoma, renal cell cancer and colorectal cancer and thus might become an interesting drug. At present, it is unclear whether these remissions are entirely due to the anti-angiogenic effect. It would be very interesting to investigate the affected targets specifically for characterising the activation in the tumors that have responded well.

Vandetanib is an oral inhibitor of RET, VEGFR and EGFR. In hereditary MTC the drug was shown to produce remissions at 300mg. In the current study a 100mg dose was investigated. 3/18 PR and 12/18 SD were obtained. An impressive CBR of 15/18 was shown. Fifteen of the patients had a confirmed RET germline mutation, the mutation status of the other 3 patients was unknown. A randomized, placebo-controlled, international phase III study of vandetanib 300mg in MTC is ongoing. (abs 6.024)

XL647. The relationship between EGFR- and VEGFR2-mediated signaling pathways suggests that simultaneous inhibition of these pathways may provide improved efficacy. XL647 is a small molecular inhibitor of EGFR, HER2, and VEGFR2 and has preliminary activity in NSCLC with mutant EGFR and relapsing after previous reversible EGFR inhibition. (abs 8.053)

Cediranib. Blocking of angiogenesis can lead to ovarian cancer regression as has been demonstrated in clinical studies with bevacizumab and sunitinib. (abs 5.522) Cediranib (AZD2171) is a highly selective oral tyrosine kinase inhibitor (TKI) of VEGFR1, VEGFR2, VEGFR3, and c-Kit. In 27 ovarian cancer patients, 6 PR and 4 SD or a CBR of 31% was observed. Hypothyroidism occurred in 36%. (abs 5.501 & 5.521) In prostate cancer 2 PR amongst 11 evaluable patients were observed. (abs 5.136) Impressive activity was seen in renal cell cancer: in 32 evaluable patients a partial response was observed in 12/32 (38%) pts and stable disease in 15/32 (47%). Overall tumor control rate was 27/32 or 84%. Median PFS was 8.7 months. (abs 5.047)

Aflibercept is a recombinant fusion protein of the human VEGFR1 and R2 extracellular domains and the Fc portion of human IgG1. The drug was studied in metastatic renal cell cancer; both in bevacizumab (BEV) pretreated and untreated patients. In the BEV naïve cohort the disease control rate (PR + SD > 16 wks) was 29%. In the prior BEV cohort (n=27) there was 1 confirmed PR and a disease control rate of 30%. The drug is well tolerated. Single agent in the prior BEV cohort is being expanded. (abs 4.027) The drug also produces response in bevacizumab pretreated CRC. Significant activity was observed in TMZ resistant brain tumors with a 50% response rate for the anaplastic glioma cohort (4 SD, 5 PR, 2 CR of 14 evaluable patients) and a 30% response rate for patients with glioblastoma (14 SD, 8 PR of 27 evaluable patients). (abs 2.020) The drug is further assessed in combination with chemotherapy in various cancer types.

Pazopanib is a well tolerated oral inhibitor targeting VEGFR, PDGFR, and c-Kit. In a Phase II study in metastatic RCC the PR rate was 27%. A biomarker study now reveals that response was not correlated to the VHL gene variations (mutations or methylation) which were observed in 90% (70/78) of the patients. (abs 7.557) A decrease in sVEGFR2 was significantly correlated with tumor response (P=0.00002). (abs 5.046) In a preoperative phase II trial in patients with stage I-II NSCLC twenty pts (87%) had a reduction in tumor volume after pazopanib treatment. Three patients had a partial response. Further clinical development in this setting is planned.

XL184 is an oral inhibitor of RET, MET & VEGFR2 and strongly inhibits cell proliferation in MTC cell lines harboring activated RET. Pharmacodynamic studies showed substantial inhibition of RET & MET phosphorylation in TT (MTC model) xenograft tumors. XL184 produces PR in MTC. (abs 3.522)

XL880 is an oral small molecular inhibitor of MET and VEGFR2/KDR. Of 18 evaluable pts with papillary renal cell cancer 12/18 and 10/17 had disease control (SD or PR) at >8 and >10 months, respectively. (abs 5.103) The drug is also active in MET-amplified, poorly differentiated gastric cancer. (abs 4.572)

Raf/MEK/ERK signaling pathway

The Raf/MEK/ERK pathway is constitutively activated in melanoma. ***AZD6244*** is a selective, non-competitive inhibitor of MEK1/2 being tested in phase II clinical trials for a number of solid tumors. (abs 3.535) One patient with melanoma (pretreated with dacarbazine with PD after 6 cycles) had a complete response within 16 weeks. In another study six patients receiving AZD6244 had a PR, of which 5 were BRAF+ (12% of BRAF+ pts). (abs 9.033) AZD6244 has cutaneous toxicity similar to EGF targeting molecules but can also induce depigmentation. (abs 9.075). A rare response was also observed in NSCLC (1/40). (abs 8.029)

Chemotherapy

S-1, an oral fluoropyrimidine combination drug, is an active agent against many types of cancer. In uterine cervical cancer, S-1 was given twice daily for 28 days, followed by 14 days of rest in 36 eligible patients. The ORR was 33.3% (12/36). The most frequent grade 3/4 toxicities were anemia (16.2%), neutropenia (8.1%), diarrhoea (21.6%) and anorexia (16.2%). S-1 monotherapy seems highly active and well tolerated in women with advanced or recurrent carcinoma of the uterine cervix. (abs 5.514). The drug is also active as SA in gastric cancer. (abs 4.533)

mTOR inhibitors

Inhibition of mTOR with ***temsirolimus*** has demonstrated promising activity in chemotherapy-naïve endometrial cancer with an objective response rate of 21% and prolonged stable disease in 48%, irrespective of PTEN loss. In the current study patients who previously received chemotherapy were enrolled. Two patients have had a partial response (PR) (7.4%) and 12 patients had stable disease (SD) (44%), median duration 3.5 months. (abs 5.516)

Immunotherapy

Ipilimumab represents a new class of immunotherapeutic agents. Antitumor activity to ipilimumab in melanoma can take weeks to months and 3 main clinical patterns are observed: immediate, late (after initial progression) and the appearance of new lesions. Modified World Health Organization (mWHO) response criteria do not recognize the latter 2 patterns. PD by mWHO prompts cessation of treatment. To capture these patterns of activity, broader assessment criteria are needed. Novel immune-related response criteria (irRC) were developed that may describe the response to immunotherapy more accurately and may avoid premature treatment cessation in patients with PD prior to response. Possible mechanisms underlying late clinical activity patterns are late effects of the immune system, sufficient availability of antigen for immune recognition and increase of tumor volume through lymphocytic infiltration/edema before response. irRC needs prospective validation and confirmation by survival data. (abs 3.008)

RTA 402 (CDDO-Me) is an antioxidant inflammation modulator. The drug suppresses ROS-mediated signaling through suppression of pro-inflammatory transcription factors NF-κB and STAT3, induction of antioxidant/detoxification transcription factor Nrf2 and upregulation of the leucine zipper. (abs 3.517) Early evidence revealed a CR in melanoma (1/16) and a PR in anaplastic thyroid cancer. Now the drug is in phase 1/2 in pancreatic cancer.

Hedgehog pathway antagonist

Aberrant Hedgehog (Hh) signaling has been implicated in a variety of cancers.

GDC-0449 is a first-in-human, first-in-class, systemic inhibitor of Hh signal transduction. A pharmacodynamic parameter, Gli1, was down-regulated >2-fold in skin biopsies. (abs 3.516) For the moment only responses in basal cell cancer (6/9 PR, 8/9 CBR) were observed. The drug has a very long half-life and very good tolerance (hyponatremia, fatigue and dysgeusia).

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Sarcoma: ASCO 2008 Highlights

New therapeutic options

As discussed in the 'new drugs' section of this ASCO report, *David Thomas et al* reported on the use of denosumab in a phase II study in patients with giant cell tumour of bone (GCT). (abs 10.500) Denosumab is a fully human monoclonal antibody directed against the receptor activator of nuclear factor-kappa B ligand (RANKL). RANKL is critical for the survival of osteoclasts and GCT show very high expression levels of RANKL. In total 25 patients were treated with 120mg denosumab once a month, after a loading schedule. Of 15 evaluable patients, 13 (87%) had a tumor response, including nine out of nine by histology. Biochemical analysis showed a steep decrease in bone resorption markers after treatment with denosumab.

Combination therapy with temozolomide and bevacizumab in the treatment of hemangiopericytoma/malignant solitary fibrous tumor was reported by *Park et al.* (abs 10.512) 14 patients were treated with temozolomide 150mg/m^2 orally on days 1-7 and days 15-21, bevacizumab 5mg/kg was given intravenously on days 8 and 22, to be repeated at 28-day intervals. Choi criteria were used to determine the best response to therapy. Assessment showed that 11/14 (79%) achieved partial response (PR), 2/14 (14%) achieved stable disease (SD), while 1/14 (7%) developed progression. Combination therapy with temozolomide and bevacizumab is a well-tolerated and clinically beneficial regimen for the HPC/SFT spectrum of tumors.

Gelderblom and coworkers reported on the actvity of aromatase inhibition in chondrosarcoma (CS). (abs 10.542) Estrogen signalling is active in CS and estrogen and its precursor androstenedione promote growth of CS cells *in vitro* which can be inhibited by aromatase inhibition. Ten patients were included in this phase II study. Aromatase inhibitors being used were letrozole (4), anastrozole (4) and exemestane (2). All patients had progressive disease upon initiation of therapy. Of the 7 evaluable patients the median time to progression (TTP) for the primary tumor was 6 months (range 4-31 months). For the metastatic tumors the median TTP was 9 months (2-14$^+$ months), including the dedifferentiated CS with TTP of 2 months. In conclusion, aromatase inhibition seems to yield some activity in CS.

Dumez et al reported on the addition of everolimus (RAD001) to imatinib (I) in patients with GIST progressing on I. (abs 10.519) Synergism *in vitro* between I and RAD001 has been shown in human GIST cell lines resistant to I. All patients received I 600mg/d and RAD001 2.5mg/d. In patients with progression beyond second line, the addition of RAD001 to I showed that the PFS was 37.1% at 4 months. *Marrari et al* reported on 7 progressive, advanced chordoma patients with a secondary resistance to I and biochemical evidence of AKT expression and activation. (abs 10.541) Patients were treated with I 400mg/day + sirolimus (2-3mg/day). After 4-6 weeks, 3 pts had a PET response (SUV max decrease >25%) with subjective improvement and stable disease confirmed on CT/MRI after 3 months of treatment. In one patient, an ulcerated lesion shrunk in a few weeks. In 3 out of 4 evaluable advanced chordoma patients with progression on I, tumor response was re-established by adding sirolimus to I.

Ha et al reported on the activity of EGFR inhibition with cetuximab in sarcomas. (abs 10.537) The study included 22 evaluable pts with EGFR-positive sarcomas. Subtypes included synovial sarcoma (32%), liposarcoma (27%), malignant fibrous histiocytoma (18%), leiomyosarcoma (14%), myxofibrosarcoma (4%) and malignant peripheral nerve sheath (4%). Only one patient was free of progression for over 4 months. No objective responses were seen. No EGFR mutations were detected in exons tested in available specimens.

The activity of sorafenib (SOR) in patients with imatinib (I) and sunitinib (SU)-resistant GIST was reported in abstract 10.502. Therapeutic options are limited in GIST patients who have progressed on I and SU. A phase II trial of SOR in patients with unresectable, c-kit-expressing GIST that progressed on I per RECIST criteria and/or after both I and SU, was reported. SOR was administered orally, 400mg twice daily. 26 pts (6 I-RES, 20 I/SU-RES) were enrolled. 3 pts (13%) (1 I-RES, 2 I/SU-RES) had PR; 14 pts (58%) (3 I-RES, 11 I/SU-RES) had stable disease (SD). Disease control rate (PR + SD) was 71% with a median progression-free survival of 5.3 months. These data suggest that SOR is active and well-tolerated in pts with I- and SU-resistant GIST and might be an option in third line.

Novelties in the Ewing sarcoma family of tumors (EFST)

Chemotherapy with alternating cycles of vincristine-doxorubicin-cyclophosphamide and ifosfamide-etoposide following primary tumor treatment with surgery and/or radiation therapy is the standard approach in EFST. *Womer et al* reported on a prospective randomized-controlled trial for patients

with extra-dural EFST, without distant metastases, comparing every-two-week vs. every-three-week chemotherapy. (abs 10.504) Patients were treated with vincristine (2mg/m^2, max. 2mg), doxorubicin (75mg/m^2) and cyclophosphamide (1.2g/m^2) alternating with ifosfamide (9g/m^2) and etoposide (100mg/m^2) for 14 cycles, with filgrastim (5mg/kg/day, maximum 300mg) between cycles. Patients assigned to regimen A were scheduled to begin chemotherapy cycles every 21 days, and patients assigned to regimen B were scheduled to begin cycles every 14 days, or when ANC >750 and platelets >75. The primary endpoint was event-free survival. 587 patients were enrolled and randomized. For all courses, the median cycle interval for regimen A was 21 days (mean 23.3 days). In case of regimen B, the median interval was 15 days (mean 18.5 days). Event-free survival at a median of 3 years was 65% with regimen A and 76% with regimen B, p=0.028. In conclusion, every-two-week chemotherapy is more effective than every-three-week chemotherapy for localized EFST, without increase in toxicity.

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Gynaecological Oncology: ASCO 2008 highlights

Ovarian cancer

Topotecan was evaluated in a novel combination regimen in comparison to standard therapy in front-line epithelial ovarian cancer (EOC). (abs 5.505) The first 4 cycles in arm 1 were cisplatin 50mg/m^2 d1 plus topotecan 0.75 mg/m^2 d1-5 IV. Cycles 5 to 8 were paclitaxel 175mg/m^2 over 3 hrs d1 followed by carboplatin AUC5 d1. In arm 2, the standard arm, 8 cycles of paclitaxel plus carboplatin were given as described for arm 1. 819 pts (409 Arm 1, 410 Arm 2) were enrolled. 650 pts had a progression event and 406 died. Arm 1 had more hematological toxicity (gr 3/4 febrile neutropenia 9.9% vs. 2.7%) and hospitalizations (11.3% vs. 7.1%) compared to arm 2. The HR for PFS was 1.1 (0.94-1.28), not significantly favouring arm 2. In conclusion, topotecan/cisplatin followed by carboplatin/paclitaxel was more toxic but did not show any evidence of improved efficacy compared to standard therapy.

The three-weekly administration of paclitaxel and carboplatin (c-TC) is considered the standard of care in the treatment of ovarian carcinoma. (abs 5.506) This standard treatment was compared with dose dense weekly administration of TC (dd-TC) as first-line chemotherapy for stage II-IV epithelial ovarian, fallopian tube or primary peritoneal cancer. Patients were randomly assigned to receive carboplatin AUC 6 either with paclitaxel 180mg/m^2 on day 1 or paclitaxel 80mg/m^2 on days 1, 8, and 15. Treatment was repeated every 3 weeks for six cycles. Three additional cycles were administered in responding patients. Primary endpoint was progression-free survival (PFS). 631 pts were eligible for analysis. After a median follow-up of 29 months, median duration of PFS in the c-TC group and dd-TC group was 17.1 and 27.9 months, respectively (p=0.0014 by the log-rank test). Overall survival at 2 years was 77.7% and 83.6% respectively (p=0.05). Among 282 patients with measurable disease, objective response rates were 53.3% and 55.8% in the c-TC and dd-TC groups respectively (P=0.91). Grade 3 and 4 anemia was reported more frequently in the dd-TC group. Other toxicities were similar in both groups. In conclusion, the dd-TC regimen significantly improved PFS in patients with advanced EOC.

AZD2281 is a novel, potent poly (ADP-ribose)

polymerase (PARP) inhibitor. AZD2281 induces cancer specific lethality in homologous recombination repair defective cells, including BRCA-deficient tumours. (abs 5.510) In previous work the MTD was shown to be 400mg bd. In a study of BRCA-deficient ovarian cancer (BDOC) 92 patients were treated with doses of 40mg daily, 100mg bd, 200mg bd, 400mg bd and 600mg bd. Toxicities were mainly gastrointestinal and mild, with little myelosuppression. 1 patient receiving 400mg bd had a dose limiting neurocognitive toxicity. In total 32 patients, the majority of whom were platinum resistant/refractory, were evaluable for response. All evaluable patients received treatment for at least 8 weeks (2 cycles) or progressed prior to completion of 2 cycles. 14 patients achieved a partial response, 13 meeting CA125 criteria and 10 meeting RECIST criteria. 7 patients maintained responses for ≥ 24 weeks. Stable disease (SD) was seen in additional 8 patients. Responses were seen at all dose levels from 100mg bd and higher. AZD2281 is well tolerated and demonstrated compelling activity in patients with BDOC. Responses were seen in all groups including platinum-resistant disease.

VEGF is over-expressed in human ovarian tumours and is associated with a poor prognosis. *Cediranib (AZD2171)* is a novel, orally-administered, highly potent inhibitor of VEGFR1, VEGFR2, VEGFR3, PDGFR and c-kit. (abs 5.521) A two-stage, multicentre phase 2 clinical trial was initiated to evaluate the activity of cediranib in patients with recurrent ovarian cancer. Prior chemotherapy up to one line was permitted. Due to toxicity, the initial starting dose of cediranib was reduced from 45mg orally daily to 30mg. This study was stratified into platinum-sensitive (pl-s) and platinum-resistant (pl-r). 60 patients were enrolled, with 26 being pl-s and 34 being pl-r. The most frequent adverse events (AE) were fatigue (85%), diarrhoea (80%), hypertension (72%) and anorexia (57%). Hypertension (33%) and fatigue (20%) were the most frequent grade 3+ AEs. Response rate and prolonged SD rate were 41% and 29% for pl- s and pl-r pts respectively. In the pl-s group, there were 2 confirmed PRs and 1 unconfirmed PR while one unconfirmed PR was observed in the pl-r arm. Cediranib is well tolerated at 30mg od and shows significant activity in recurrent ovarian cancer.

Sunitinib is a multi-targeted receptor tyrosine kinase (RTK) inhibitor with potent activity against a number of RTK targets that are implicated in EOC growth and metastasis, including vascular endothelial growth factor and platelet-derived growth factor receptors. A phase II study was designed to evaluate single agent activity of oral sunitinib in recurrent EOC. (abs 5.522) Primary endpoint was objective response by RECIST criteria. CA125 response was the secondary endpoint. Eligibility required measurable disease, 1-2 prior chemotherapy regimens, but no prior anti-VEGF therapy. Both platinum-sensitive and platinum-resistant patients were eligible. Patients were treated with sunitinib 50mg po daily for 4 out of 6 weeks, with response assessed after each cycle. 17 pts (16 eligible) were included in the study. Partial response was seen in 2 pts, stable disease was observed in 10 pts and progressive disease (PD) was seen in 4. By size criteria alone, 4 pts had a decrease of >30%, but two developed effusions and were therefore PD by RECIST. A further 9 pts had a decrease of <30% measurable disease. Of 11 pts evaluable for CA125 response, 6 were responders (3 confirmed, 3 unconfirmed), and 5 were non-responders. Common grade 1-3 AE were fatigue, mucositis, dysgeusia, hypertension, nausea and hand-foot reaction. There was one serious, unexpected drug-related AE (pulmonary embolism) but no GI perforation. Results demonstrate single-agent sunitinib activity and tolerability in advanced EOC.

Sorafenib is a tyrosine kinase inhibitor targeting RAF and other receptor kinases (VEGF-R, PDGF-R, Flt3, c-KIT). Sorafenib may have anti-angiogenic activity through inhibition of VEGF-R. (abs 5.537) A phase II study was conducted to assess the activity and tolerability of sorafenib in patients with recurrent EOC. Treatment consisted of sorafenib 400mg orally bid until disease progression. 73 patients were enrolled and 68 patients are evaluable for toxicity. Prior treatment consisted of 1 regimen in 40 and 2 regimens in 28 patients. Significant grade 3 and 4 toxicities included: rash (12), metabolic (10), gastrointestinal (3), cardiovascular (2), and pulmonary (2). No treatment related deaths were recorded. Only patients with measurable disease were used to assess efficacy. Among the 59 patients with measurable disease, 12 survived progression-free for at least 6 months. Three patients are yet to be determined. Two patients had partial responses; 20 had stable disease; 30 had progressive disease, and 7 could not have their tumor assessed. Preliminary results suggest that sorafenib is tolerated and active in patients with EOC.

The combination of carboplatin and PLD administration in patients with relapsed, platinum sensitive and

platinum semi-sensitive ovarian cancer was assessed in a phase II second line study. (abs 5.555) PLD at a dose of 50mg/m^2 was combined with carboplatin (AUC = 5) every 28 days, in patients with recurrent ovarian cancer with a disease free interval (DFI) greater than 6 months. Patients were divided into 2 groups: group 1 (G1) with a DFI of 6 months to 1 year (semisensitive disease), and group 2 (G2) with DFI longer than 1 year (sensitive disease). Forty pts were enrolled (G1= 19 pts and G2= 21 pts). A total of 27 pts responded to treatment (67.5%) There were 14 CR and 13 PR. In the G1 10/19 pts responded (52.6%) (6 pts (38.1%) attained a CR). Among the G2 pts, 17/21 responded to treatment; 80.95% (8 pts (38.1%) attained a CR). The median response duration among the 27 responders was 373 days (53-1,856 days). The median response duration for pts attaining a CR was 462 days (94- 1,856). Grade III and IV haematological toxicity includes anaemia (grade III: 4 pts), neutropenia (grade III: 15 pts; grade IV: 5 pts) and thrombocytopenia (grade III: 12 pts; grade IV: 1 pt). No renal toxicity was seen. The combination of PLD 50mg/m^2 with carboplatin is a safe and an active second line chemotherapy regimen for advanced platinum sensitive and semi-sensitive ovarian cancer.

Endometrium cancer

Pelvic external beam radiotherapy (EBRT) reduces the risk of vaginal and pelvic recurrence in stage I endometrial carcinoma (EC), without survival benefit. In the PORTEC1-trial, the 5-year risk of vaginal and pelvic recurrence for high-intermediate risk patients was 19% without further treatment, compared to 5% after EBRT. Most recurrences were located in the upper vagina. Phase II trials suggested *vaginal brachytherapy (VBT)* to be as effective as EBRT. PORTEC-2 is the first randomized trial comparing the efficacy of VBT and EBRT to determine which treatment provides optimal local control with the best quality of life. (abs 5.504) This multicenter phase-III trial accrued 427 patients. After surgery, patients were randomly allocated to pelvic EBRT (46 Gy in 23 fractions) or VBT (21 Gy HDR in 3 fractions, or 30 Gy LDR). Eligible patients had a high-intermediate risk EC: age > 60 and stage 1C grade 1-2 or stage 1B grade 3; any age and stage 2A grade 1-2 or grade 3 with < 50% invasion. Primary endpoint was vaginal relapse (VR), which was expected to be 2% at 3 yrs in the EBRT group. At a median follow-up of 34 months, 3-year actuarial rates of vaginal relapse were 0.9% in the VBT arm and 2.0% after EBRT (p=0.97). Three-year rates of PR were 3.6% and 0.7% (p=0.03). Three-year rates of vaginal, pelvic and distant relapse as first failure were 0%, 1.3% and 6.4% in the VBT group, and 1.6%, 0.7% and 6.0% in the EBRT group. There were no significant differences in 3-year OS (90.4% vs. 90.8% p=0.55) and RFS (89.5% vs. 89.1% p=0.38). Vaginal brachytherapy is effective in preventing vaginal recurrence. Despite the slightly but significantly increased pelvic failure rate in the VBT arm, rates of distant metastases, OS and RFS were similar. As patient reported quality of life after VBT was shown to be better than after EBRT, VBT should be the treatment of choice for patients with high-intermediate risk endometrial carcinoma.

RAD001 is an oral rapamycin analog that acts by selectively inhibiting mTOR. An open-labeled phase II study in patients with recurrent EC who have failed at least one and no more than 2 prior chemotherapeutic regimens, was performed. (abs 5.520) RAD001 was administered at a dose of 10mg PO daily for 28 day cycles. Twenty-nine patients were enrolled and 11 of 25 (44%) evaluable patients for response had CBRs. All of these patients had SD One patient achieving CBR is still on treatment. RAD001 shows encouraging single agent clinical benefit in pretreated patients with recurrent EC. Loss of PTEN may predict CBR. Future studies will evaluate this agent in combination with hormonal and/or cytotoxic therapy.

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Respiratory Oncology: ASCO 2008 Highlights

Early stage non-small cell lung cancer

1. In 8-year follow-up data from the IALT trial (surgery + adjuvant chemotherapy in resected stage I-IIIA NSCLC), the survival benefit in favour of the combined modality treatment was no longer significant, due to late non-cancer-related mortality after 5 years.
2. Preoperative induction chemotherapy in the Ch.E.S.T. (Chemotherapy in Early Stages Trial) trial resulted in a trend towards a 3-year disease free survival and overall survival in favour of induction chemotherapy.
3. A randomised trial observed significantly more avoidance of futile surgery when staging with fusion PET-CT was compared to conventional imaging.

Locally advanced non-small cell lung cancer

4. A randomised comparison of concurrent chemoradiotherapy with a 2nd generation cisplatin-doublet (with mitomycin and vindesine) versus a 3rd generation cisplatin-doublet (with docetaxel), showed a significantly better outcome for the latter.

Advanced non-small cell lung cancer

5. A large randomized phase III study concluded that the anti-Epidermal Growth Factor Receptor (EGFR) antibody cetuximab, when added to cisplatin-vinorelbine in patients with EGFR-IHC positive NSCLC, resulted in superior overall survival.
6. A large randomized trial compared pemetrexed plus BSC versus placebo plus BSC in patients achieving disease control after 4 cycles of platinum-based doublet chemotherapy. Progression-free survival was significantly better with pemetrexed maintenance.
7. With many strategies now focusing on non-squamous NSCLC, it was encouraging to see promising phase II randomized data in squamous cell lung cancer with Insulin Growth Factor 1 receptor blocking strategies.
8. While adding EGFR tyrosine kinase inhibitors to first-line chemotherapy did not improve outcome, phase II randomised data from Korea using erlotinib (compared to placebo) in intermittent dosing on day 15 till 28 in a q4w chemotherapy cycle, were promising.

Small cell lung cancer

9. A large phase III study, mimicking exactly the promising Japanese cisplatin-irinotecan schedule, reported no benefit in a comparison with standard cisplatin-etoposide.
10. Amrubicin showed further promises in two phase II randomised trials in patients with relapsed SCLC. This drug is currently in phase III testing versus topotecan.

Introduction

At the ASCO 2008 meeting, a total of 415 abstracts in the field of respiratory oncology were accepted. A total of 187 were accepted for publication only, while 210 were presented, either as poster display (n=144), at poster discussion sessions (n=48), or in oral sessions (n=18, one in plenary session). For this report, we mainly concentrated on randomized controlled trial (RCT) data relevant for the practicing clinician.

NSCLC – Early stages (I, II, selected IIIA)

Different prospective randomized trials and an individual patient data based meta-analysis established the role of adjuvant cisplatin-based chemotherapy in completely resected stages (IB), II and IIIA NSCLC.

Long-term follow-up data of the IALT trial for completely resected stage I-IIIA NSCLC were reported (*Figure 1*). At 8-year follow-up the survival benefit

Figure 1: Abstract #7507: Long-term follow-up in the IALT adjuvant study.

Patient setting

Completely resected stage I-IIIA NSCLC.

Randomisation

Surgery, adjuvant cisplatin chemotherapy

versus

Surgery alone.

Outcome

Primary: 5Y overall survival: HR 0.86 (P=0.01), but at 8 years HR 0.91 (P=0.10).

At 8 years less local and distant recurrences, no differences in second primaries.

Conclusion

Possible late adjuvant chemo-related mortality underscores the need for long-term FU in adjuvant setting.

Figure 2: Abstract #7508 : Phase III Chemotherapy in Early Stages Trial (Ch.E.S.T).
Patient setting
Operable stage IB-IIIA NSCLC.
Randomisation
Three cycles cisplatin-gemcitabine, surgery
versus
Surgery alone.
Outcome
Primary: Progression-free survival at 3 years 53% versus 48% (P=0.11).
Other: 3-year overall survival 67% versus 60% (P=0.053).
Conclusion
Overall trend in favour of induction cisplatin-gemcitabine, significant in stages IIB and selected IIIA.

Figure 3: Abstract #7502 : ELPET, randomised study on fusion PET-CT for staging.
Patient setting
Potentially resectable stage I-IIIA NSCLC.
Randomisation
PET-CT plus cranial imaging
versus
Conventional imaging (CT and bone scan).

Outcome
Primary: correct upstaging avoiding futile surgery 14% versus 7% (P=0.046).

Conclusion
PET/CT can replace conventional imaging, as it spared more patients from inappropriate surgery.

in favour of the combined modality treatment was no longer significant. However, in terms of disease control there were still significantly less local and/or distant relapses in the chemotherapy arm. It was observed that adjuvant chemotherapy proved to be harmful after 5-year follow-up (HR=1.45), possibly caused by non-cancer chemotherapy-related mortality after 5 years of follow-up. This observation was not made in the ANITA trial and therefore could be attributed to the 2nd cytotoxic agent added to cisplatin, which was mainly (57%) etoposide in the IALT trial.
As compliance with postoperative cisplatin-based chemotherapy is far from optimal, the alternative of preoperative induction chemotherapy has been a focus of interest. The results of the Ch.E.S.T. (Chemotherapy in Early Stages Trial) trial in operable stages IB-IIIA(cT3cN1) NSCLC have been presented (*Figure 2*). Despite the lack of statistical significance (the trial was prematurely stopped at 270/700 inclusions when adjuvant chemotherapy became clinical routine in 2004), a trend for a 3-year disease free survival (DFS +5%) and overall survival (OS +7%) in favour of induction chemotherapy was observed. Looking at patient subgroups stratified for at randomisation (stage IB-IIA vs. stage IIB-selected IIIA), it is observed that only the latter group had a significant benefit of induction chemotherapy.
At present, how does preoperative compares to postoperative chemotherapy in patients with resectable early stage NSCLC? The beneficial effect on survival seems similar (HR about 0.80 for both strategies), but the power of the data, expressed in the width of the 95% CI and the *P*-value, is still strongly in favour of adjuvant trials.
Accurate staging of potentially resectable patients is of utmost importance to select those patients who can benefit from the surgical resection. A randomized trial (*Figure 3)* using a fusion PET-CT (plus cranial imaging) in this setting, observed significantly more avoidance of surgery (+7%) when a fusion PET-CT is performed compared to conventional imaging (CT abdomen + bone scan + cranial imaging). Therefore, after having detected a lung tumor on spiral CT thorax, PET-CT can replace conventional imaging in staging resectable stage I-IIIA NSCLC.

NSCLC – Locally advanced stages

Based on three positive phase III trials comparing concurrent to sequential chemoradiotherapy, the concurrent approach is considered the standard practice of care for inoperable stage III NSCLC.
A phase III study (*Figure 4*) compared a 3rd generation cisplatin-doublet (with docetaxel) to a 2nd generation cisplatin-doublet (with mitomycin and vindesine). The 3rd generation group had a significantly better outcome and an acceptable toxicity.
Moreover, several phase 2 trials are including targeted agents (erlotinib, bevacizumab, cetuximab) within a concurrent approach. A concurrent approach using a higher radiation dose and carboplatin-

Figure 4: Abstract #7515 : Phase III 3rd versus 2nd generation chemoradiotherapy.
Patient setting
Stage III unresectable NSCLC.
Randomisation
cisplatin-docetaxel based chemoradiotherapy
versus
mitomycinC-vinblastine-cisplatin based chemoradiotherapy.
Outcome
Primary: 2-year overall survival 60% versus 48% (P=0.02).
Less haematological AEs but more oesophagitis and pneumonitis with 3rd generation.
Conclusion
Cisplatin-docetaxel superior to MVP with concurrent RT: improved survival and less febrile neutropenia.

Figure 5: Abstract #3 : Phase III adding cetuximab to cisplatin-vinorelbine.
Patient setting
Advanced NSCLC with EGFR expression on immunohistochemistry.
Randomisation
Cisplatin-vinorelbine + cetuximab, cetuximab maintenance
versus
Cisplatin-vinorelbine.
Outcome
Primary: overall survival 11.3 versus 10.1 months (P=0.04).
Other: effect more prominent in Caucasians (P=0.0025). High rate of febrile neutropenia in both arms.
Conclusion
First study with survival benefit for chemotherapy + EGFR strategy in 1st line treatment.

pemetrexed with or without cetuximab, as well as platin-based consolidation therapy with or without cetuximab showed promising feasibility and tolerability but survival data are still awaited.

NSCLC – Advanced stages

Modern platinum doublets remain the standard of care for patients with good performance status, with docetaxel, pemetrexed and erlotinib being the registered compounds for relapse treatment.

One large randomized phase III study, powered to demonstrate superior OS was presented in the plenary session (*Figure 5*). Cetuximab administration resulted in superior overall survival (HR 0.87; *P*=0.044) when added to cisplatin-vinorelbine in patients with EGFR-IHC positive NSCLC. Side effects appeared manageable, with acne-like rash as most common cetuximab related toxicity. The presenter concluded that cetuximab added to platinum-based chemotherapy sets a new standard for the 1st line treatment of patients with advanced NSCLC.

In his discussion, *Dr. Lynch* raised his concern about the febrile neutropenia rate of 22% (cetuximab arm) and 15% (standard arm). However, as this was high in the standard arm as well, this may be attributed to the choice of chemotherapy. From a safety point of view, cetuximab can be combined with other doublets, as there are other randomized phase II or III data on carboplatin-gemcitabine, cisplatin-gemcitabine, carboplatin-paclitaxel and carboplatin-docetaxel.

Remarkably, progression-free survival (PFS) was not significantly different across arms. This was not due to the differences in post-study treatment (well balanced across arms), but may be due to study dynamics (very frequent visits (q week) may lead to an earlier detection of progression than on planned CT-scans, while OS may be improved because frequent visits lead to better overall care). Moreover, PFS is an imperfect endpoint in open-label studies, and OS remains the most important. One could wonder why RCT combining gefitinib or erlotinib with platinum doublets were negative. Possible explanations may be the immune actions of cetuximab (ADCC, receptor internalisation), the fact that cetuximab may act on signals not dependent on intracellular kinase, and the selectivity of the FLEX trial (limited, as a few EGFR-IHC+ cells was enough, but perhaps nonetheless relevant to exclude those who don't benefit). Cost was raised in the discussion as a major concern, and it is hoped that other biomarkers than EGFR-IHC, such as K-ras mutation or EGFR gene amplification (FISH) may further improve the selection of candidates for this therapy.

Another way to improve results of 1st line therapy that recently gained a lot of attention, is maintenance therapy after platinum doublet therapy. In 2007, a study with early versus late docetaxel was presented, and now the

Figure 6: Abstract #8011 : Phase III pemetrexed maintenance therapy.
Patient setting
Advanced NSCLC in disease control (response, stable) after 4 cycles of platinum doublet.
Randomisation
Maintenance pemetrexed q3w
versus
Maintenance placebo q3w.
Outcome
Primary: progression-free survival 4.0 versus 2.0 months (P<0.0001).
Other: effect mainly in non-squamous histology. Overall survival data immature but promising.
Conclusion
Post-doublet maintenance with pemetrexed is well tolerated and gives better progression-free survival.

Figure 7: Abstract #8015 : Phase II Insulin Growth Factor Receptor 1 (IGFR1) antibody.
Patient setting
Advanced NSCLC 1st line treatment.
Randomisation
Carboplatin-paclitaxel plus CP-751871 antibody
versus
Carboplatin-paclitaxel
Outcome
Primary: Response rate 51% versus 36% (P<0.001).
Other: striking response rate in squamous cell carcinoma.
Conclusion
Further study in squamous cell lung cancer needed.

large study comparing pemetrexed plus BSC versus placebo plus BSC was reported (*Figure 6*). The study was powered for superior PFS, and this endpoint was highly significant. OS data are not yet mature, but preliminary data were promising, certainly in the patients with non-squamous histology. It is clear that this is a positive study, and that the strategy works, but the question is if this is truly maintenance, as pemetrexed was never part of the initial doublet chemotherapy. So in a way, this is also direct vs. delayed 2nd line treatment, or one could even see it as a comparison of "2-drug treatment " vs. "3-drug treatment in a sequential way". Important data in the future will be the mature OS data, the effect on symptom control, and perhaps proof that pemetrexed maintenance also improves outcome when given after pemetrexed containing initial doublet therapy.

With many strategies now focusing on non-squamous tumours, it was encouraging to see an abstract with a strategy that may be particularly active in squamous cell carcinoma (*Figure 7*). The Insulin Growth Factor 1 receptor pathway is the target of several new compounds, of which CP-751871 is the most advanced in clinical development. In the phase II randomized trial reported here, promising signals of activity were reported, with a remarkable response in squamous cell lung cancer.

As mentioned above, adding EGFR tyrosine kinase inhibitors (TKIs) to first-line chemotherapy did not improve outcome, which was thought to be due to antagonism (G1 cell cycle arrest) when chemotherapy and EGFR-TKIs are given together. An interesting abstract from Korea reported on a phase II randomized study with erlotinib (compared to placebo) given in intermittent dosing on day 15 till 28 in a q4w chemotherapy administration (*Figure 8*). The primary endpoint was not met, but PFS pointed at a promising strategy.

Figure 8: Abstract #8031 : Phase II 1st line chemotherapy and intermittent erlotinib.
Patient setting
Advanced NSCLC 1st line treatment.
Randomisation
Platinum-gemcitabine q4w schedule + erlotinib 150 mg/d days 15-28, erlotinib
versus
Platinum-gemcitabine q4w schedule + placebo 150 mg/d days 15-28, placebo.
Outcome
Primary: progression-free rate at 2 months: 80% versus 77% (NS).
Other: median progression-free survival 7.2 versus 5.5 months (P=0.005).
Conclusion
Sequential administration of chemo and EGFR-TKI is promising.

Figure 9: Abstract #7512 : Phase III role of irinotecan in extensive SCLC.
Patient setting
Extensive disease SCLC.
Randomisation
Cisplatin-irinotecan (Noda schedule)
versus
Cisplatin-etoposide.
Outcome
Primary: overall survival similar (9.9 versus 9.1 months, NS).
Conclusion
Large trial in Western population failed to confirm the Japanese findings.

Figure 10: Abstract #8042 : Phase II randomised data on amrubicin relapse treatment.
Patient setting
Extensive SCLC with relapse (both sensitive and refractory).
Randomisation
Amrubicin 40 mg/m2 q3w
versus
Topotecan standard i.v. schedule.
Outcome
Primary: Response rate 38% versus 13%.
Other: in refractory patients 21% versus 0%.
Conclusion
Acceptable toxicity – activity in refractory patients.

SCLC

The main progress in recent years was the better integration of CT and RT, including prophylactic cranial irradiation (PCI). The chemotherapy itself did not substantially improve over the last 20 years, with platinum and etoposide still being the standard of care.

Since the positive data in a prematurely closed trial from Japan published in 2002, platinum plus irinotecan has been studied as a potentially better choice than platinum plus etoposide. A North-American study, mimicking exactly the same irinotecan schedule as in the Japanese trial was reported (*Figure 9*). There was no difference in outcome. Toxicity was different, with more haematological side-effects in the etoposide arm and more gastro-intestinal adverse events in the irinotecan arm.

Another phase III trial compared standard cisplatin-etoposide with cisplatin and topotecan i.v. days 1-5, both every 3 weeks. (abstract 7.513) There was no benefit in survival, and the topotecan arm had significantly more haematological toxicity. Another failure was the comparison of carboplatin-pemetrexed with carboplatin-etoposide, a study which had to be stopped prematurely due to inferiority of the new arm.

More promising was the news on relapse treatment with *amrubicin*. In a Western phase II randomized study in patients with sensitive relapse (i.e. >90 days post previous therapy), amrubicin was superior in terms of PFS and haematological toxicity. Another phase II randomized study from Asia demonstrated superior response rate in both sensitive and refractory patients (*Figure 10*). At present, amrubicin is in phase III testing versus topotecan.

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