Annual meeting of the American Society of Clinical Oncology (ASCO) 2010 - Part 1

Highlights of the 46th Annual ASCO meeting, June 4-8 Chicago, Illinois, United States

From June 4-8, 2010, the 46th annual meeting of the American Society of Clinical Oncology (ASCO) was held in Chicago, Illinois. The ASCO meeting attracted over 30,000 attenders and again proved to be the premier educational and scientific event in the oncology community. Due to the vast amount of data presented at ASCO it is impossible to address everything in this congress report. Therefore, the report aims at summarizing the important take-home messages in the different fields of oncology presented at the meeting. This report is based on the 13th post-ASCO meeting held in Genval on the 19th of June 2010. This first part of the report focuses on gastrointestinal cancer, head and neck cancer, supportive care and new agents emerging from the lab into the clinic. The second part of the ASCO report, to be published in the October issue of the BJMO, will address novelties in breast, lung and urogenital cancer. All abstracts referred to in this report can be consulted at the ASCO website (www.asco.org).

(Belg J Med Oncol 2010;4:173-88)

Gastrointestinal cancer

2010 was not a grand cru year in gastrointestinal (GI) cancer at ASCO, but was a very rich year in new information: it was a year of consolidation and of an improved understanding of several aspects. Highlights in 2010 include: the new treatment options for pancreatic neuroendocrine tumours, the further unravelling of the molecular characteristics of colon cancer and of the role of BRAF mutations, the lack of benefit of cetuximab in the adjuvant treatment of stage III colon cancer, the small but not significant benefit of bevacizumab in advanced gastric cancer and the demonstration of a significant benefit of FOLFIRINOX in metastatic pancreatic adenocarcinoma at the expense of toxicity.

Colorectal cancer

Metastatic colorectal cancer

The Spanish TTD group evaluated the role of maintenance treatment of bevacizumab in the primary therapy of metastatic colorectal cancer (mCRC; #3501). Patients treated with 6 cycles of XELOX/bevacizumab were randomized between continuation of the same regimen or bevacizumab as monotherapy. Although the study formally did not show a non-inferiority of bevacizumab, the authors concluded that bevacizumab maintenance is an option. However, the study did not have an fluoropyrimidine plus bevacizumab arm. The French Optimox study's earlier data indeed suggest that fluoropyrimidine as a maintenance

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Conflict of interest:he authors have nothing to disclose and indicate no conflicts of interest.

Key words: gastrointestinal cancer, bench to bedside, head and neck cancer, supportive care

treatment prolongs progression-free survival (PFS) compared to a drug holiday. Therefore, further studies have to be carried out with a combination of fluoropyrimidine and bevacizumab. The clinical take-home message is, that maintenance treatment is appropriate after a more intensive treatment episode. However, the optimal maintenance treatment strategy still needs to be determined: whether this would be fluoropyrimidine, a biological targeted agent or a combination of both. At the moment, an individualized approach is recommended, taking into account the goals of the treatment, the toxicity and the patient's wishes. Several important analyses of the role of cetuximab in the primary treatment of mCRC were presented.

The complexity of the UK COIN Study was criticized (#3502); this study, comparing fluoropyrimidine/oxaliplatin +/- cetuximab, was negative. However, a subgroup analysis showed the benefit of FOLFOX/cetuximab (and not capecitabine/oxaliplatin/cetuximab) in good performance *KRAS* wild type mCRC with limited disease (one metastatic site). The COIN study also showed a shorter survival for all patients than is generally found in other studies.

The updated analyses of the Crystal and Opus study showed not only a significant benefit of PFS and response rate, but also a significant survival benefit of a cytotoxic doublet (FOLFIRI/FOLFOX) plus cetuximab in *KRAS* wild type patients compared to the cytotoxic backbone alone (#3506 and #3570), with longer follow-up and with more tumour samples available for *KRAS* analysis. The new data confirmed the importance of *KRAS* mutation status as predictive marker for resistance to cetuximab. The role of *BRAF* mutations was analysed: *BRAF* mutations occur in 6-10% of mCRC and are related to a poor prognosis in mCRC. However, a predictive role for the lack of benefit was not proven. The clinical data of the primary and secondary studies of panitumumab were reanalyzed, and confirmed that the activity of panitumumab was also confined to KRAS wild type patients. These studies also confirmed the correlation between the degree of rash and activity (#3528 and #3529). The EORTC randomized phase II study in patients with non-resectable liver-limited metastases showed that chemotherapy (FOLFOX +/- bevacizumab) plus radiofrequency ablation (RFA) prolonged the PFS compared to the chemotherapy backbone alone, but did not have any impact on survival (#3526). The benefit of RFA may consist of reduction of bulky metastases that will "progress" sooner, but the clinical significance of this is unclear. Preliminary data of new classes of agents under development have been presented, including drugs interfering with the hedgehog pathway inhibitors (GDC-0449) (#3530), BRAF inhibitors (PLX4032) (#3534), AKT inhibitors (perifosine) (#3531) and Src inhibitors (#3536) and show hope for potential new treatment options in the future.

Adjuvant treatment

The US NO147 study evaluated the role of cetuximab in a large-scale study in stage III colon cancer. No benefit was found in adding cetuximab to FOLFOX compared to just FOLFOX in KRAS wild type patients; however, a higher degree of toxicity was found (#3507). Moreover a deleterious effect in KRAS mutant patients has been shown (#3508). The results of the PETACC-8 study with a similar design are still awaited.

Several presentations focused on the molecular events in adjuvant colon cancer studies and looked at prognostic and predictive markers. Although extremely important, they do not yet change practice today, but may well do so in the future.

Key messages

- Data presented of 4 large-scale adjuvant studies by 0'Connell showed that stage II and III colon cancer are remarkably similar in the expression of the 375 cancer-related genes tested. The significance of the few genes (such as MMR) differing between stage II and III colon cancer is not clear (#3503). A 12 gene signature under development in stage II colon cancer is under further evaluation. It is however not yet 'mature' for clinical practice.
- Data from the PETACC-3 study showed that, whereas BRAF status and tumour site were not prognostic for relapse-free survival of stage II and III colon cancer, BRAF status, tumour site and time to tumour recurrence (TTR) are highly prognostic for colon cancer survival after relapse

of colon cancer (#3504).

- A gene signature analysis of the PETACC-3 study showed that BRAF mutant colon cancers have a characteristic gene expression pattern (#3505). This is true for BRAF mutations occuring in microsatellite stable (MSS) tumours, but not in microsatellite instable (MSI) tumours. BRAF mutant MSS tumour had a clearly worse outcome compared to BRAF mutant MSI tumours. This may have clinical implications in the future in view of the development of specific BRAF inhibitors. The first data with the specific BRAF inhibitor PLX4032 showed signs of activity, although less impressive than in BRAF mutant melanoma (#3534).

Non-colorectal cancer

Oesophagogastric cancer

Two randomized studies focused on the neoadjuvant therapy of oesophageal and GE junction cancers. A Dutch study in more advanced oesophageal and GEJ cancers (adeno- or squamous histology; N1 or >T2) suggested a survival benefit of a neoadjuvant carboplatin/paclitaxel based chemoradiotherapy compared to just surgery without increasing the postoperative morbidity (#4004). A French randomized study in early oesophageal and GEJ cancers (adeno- or squamous histology; T1-2N0-1 or T3N0) with preoperative 5-FU/cisplatin based chemoradiotherapy did not show any benefit to the combined modality treatment compared to just surgery and showed an increased postoperative mortality (#4005). These studies show the need for a multidisciplinary discussion of every patient and the need for better treatments strategies, including the targeted agents.

The most important message in advanced cancer includes the failure of bevacizumab in advanced gastric cancer and the increasing data on the feasibility and activity of the modified DCF (docetaxel/cisplatin/5FU) regimens. A large intercontinental study (AVAGAST) showed no significant survival benefit in adding bevacizumab to capecitabine/cisplatin 6 in the primary treatment of advanced gastric cancer compared to just capecitabine/cisplatin, although the secondary endpoints were met: PFS and responses were improved with the addition of bevacizumab to chemotherapy backbone (#LBA4007). Interestingly, the lack of significant survival benefit was at least partly due to the lack of survival benefit in Asian patients, while there was a survival difference in the subgroups of European and American patients. The reasons for these differences are unclear. Hopefully, ongoing molecular analysis can clarify some of these findings.

Pancreatic adenocarcinoma

The French randomized Prodige 4-ACCORD 11/0402 trial, presented by T. Conroy was the highlight in pancreatic cancer. A total of 342 metastatic patients were randomized between gemcitabine and the FOLFIRINOX regimen. The median survival improved from 6.8 to 11.1 months and the 1-year survival from 20 to 48% (HR 0.57; $p<0.0001$). The PFS improved from 3.3 to 6.4 months (HR 0.46) and the response rate from 9 to 31% ($p<0.0001$), always in favour of the FOLFIRINOX regimen (#4010). Although the French group presented this as the new standard in metastatic pancreatic cancer, the discussant Dr Tempero stressed the selection of the patients in this study and the toxicity of this regimen (grade 3/4 fatigue and haematological toxicity and the systematic need for growth factors). These data endorse the knowledge that combination chemotherapy is an appropriate option for fit patients with metastatic pancreatic cancer: e.g. gemcitabine or 5-FU plus a platinum.

Pancreatic neuroendocrine tumours

In a clinical science symposium, new data were presented on the role of sunitinib in pancreatic neuroendocrine tumours (PNET): the randomized study of sunitinib versus placebo in PNET was stopped prematurely because of great efficacy: a statistically and clinical relevant difference in PFS (11.4 versus 5.5 months; HR 0.418; $p<0.0001$) had been reported previously. New data also showed a significant survival benefit (HR 0,409 (95% CI 0.187; 0.894; $p=0.0204$) and without a detrimental effect on quality of life (#4000 and #4003).

A few days prior to the ASCO, a press release also announced a significant benefit of everolimus compared to best supportive care (BSC) in PNET

in a large phase III study. These results were not yet presented during the ASCO meeting.
Interesting phase 2 results of pazopanib and of the combination bevacizumab plus erlotinib were shown in PNET (#4001 and #4002) at the clinical science symposium. The challenge will be to determine the optimal strategy and selection of patients for the new targeted biologicals, as well as for PRRT (radionucleide therapy) and to determine the activity and role of these agents in small bowel and other NET.

From the lab to the clinic

ASCO 2010 was characterised by numerous reports on newly emerging drugs that target pathways not yet exploited in the routine clinic, and new information on targeted drugs that are in early clinical development. Many phase I studies, including the first one in human studies, succeeded at a variable level in enriching the study population either phenotypically or genomically (based on known activation of the targeted pathway). The most robust activation of a pathway is when a gene implicated in the pathway is mutated (point mutations, rearrangements, intragenic deletions, increased copy number et cetera.) The major targets receiving prime attention were some growth factor receptors (for example the IGF1R; MET), the PI3Kinase-Akt pathway, RAS pathway (MEK), stemcell pathways (Hedgehog (Hhg) and Notch), DNA repair (in particular PARP-1) and the mitotic apparatus (Aurora kinase) and the death receptor pathway (TRAIL). The abstracts discussed, mainly involve phase I studies, and therefore the responses mentioned for the sake of interest are only preliminary evidence of potential activity that needs further confirmation in phase II studies.

Growth factor receptors

Insulin growth factor receptor 1 (IGF1R)

The insulin growth factor receptor 1 (IGF1R) has been under therapeutic investigation for many years, in cancer and other diseases. Both small molecule inhibitors and antibodies have been developed. In Ewing sarcoma and small round cell tumours ligand expression is driven by the fusion protein encoded by the rearranged ETS gene. In that disease, a modest single agent activity (10% PR) with receptor antibodies is observed and no predictive marker is available for identification of the patients likely to respond (#10000; #10001, #9538). In other cancers, no important constitutive activation of the receptor (some low level amplification or polysomy in small cell lung cancer) might make it worthwhile to investigate its activity for example in a genomically enriched SCLC population (#10584). Nevertheless, the receptor is thought to be of potential therapeutic value because of its importance in cell growth, cell metabolism and cell survival and some hope that combining IGF1R inhibition might enhance the activity of other targeted therapies or chemotherapy. Many such combinatorial options are explored, but a clear rationale for developing this strategy is not available as yet. Promising preclinical work and even promising phase II data have not yet lead to further validation of that strategy. Figitumumab (#7500), a monoclonal antibody against IGFR1 failed to improve the efficacy of carboplatinum plus paclitaxel in NSCLC, but lead rather to increased toxicity. The drug also failed in combination with erlotinib in NSCLC and, tested as single agent in head and neck cancer, failed to produce efficacy (#5500). When administered preoperatively in prostate cancer, the drug produced PSA responses (#4662) and partial responses in a breast cancer patient and an endometrial cancer patient (#3018). However, the clinical relevance of this finding is unclear as yet, and predictive markers are missing. One may wonder where efforts combining IGF1R with other agents are going: AMG 479 combined with conatumumab, a human DR5 agonist (#3102); combining figitumumab with a pan HER inhibitor (#3026); AMG 479 combined with erlotinib or sorafenib (#3018) in the absence of single agent activity and/or any patient enrichment. It is even more unclear for "dirty" targeted agents, for example XL228 a multitargeted inhibitor of IGF1R, the AURORA kinases, FGFR1-3, ABL, ALK, and SRC family kinases) (#3105).

Hepatocyte growth factor receptor (c-MET)

Amplification of c-MET is one of the leading mechanisms of resistance to EGFR inhibitors in lung cancer. Trials with c-MET small molecule

inhibitors (e.g. ARQ197, LBA7502; A3024; A4137; TPS215) or antibodies to the ligand , HGF, (#2525) are underway both as single agent testing in phase 1/2 as in combination with other targeted agents (because of preclinical synergy with EGFR inhibitors and cisplatinum) but always in unselected patient populations. They might have some efficacy in *KRAS* mutant lung cancers (#ARQ197, #LBA7502). In that study, patients were not selected for *EGFR* genomic status and therefore the results possibly only reflect the impact of just the MET inhibitor.

A more rational strategy would involve developing these agents in patients selected on the presence of c-MET amplification or mutation in their tumours; this might be a complex effort as both gene amplification and activating mutations have been found and amplification seems heterogeneous (primary versus met) in lung cancer.

Pi3kinase and mTOR

There are different classes of inhibitors: isoform-specific, promiscuous inhibitors and dual mTOR–Pi3kinase inhibitors. They consist of differential toxicities, depending on whether they target only Pi3kinase or are dual inhibitors of Pi43 kinase and mTOR kinase (TORC1/2). These drugs are generally well tolerated. An important dose-limiting toxicity follows from their inhibition of the insulin receptor signal transduction (hyperglycemia) that may or may not be compensated by increased insuline production (C-peptide) and, if not compensated, leads to hyperglycemia; this is a toxicity as well for more downstream inhibitors such as mTOR (rapamycin or kinase inhibitors). Those molecules crossing the blood brain barrier also generate central nervous system toxicity. In addition, many cause diarrhoea and rash. These toxicities limit the achievement of their maximal efficacy potential and in many of the early studies more often disease stabilization than objective response (but which may be important) are observed. Another limit to their efficacy is posed by negative feedback loops that lead to upstream receptor and pathway activation. Pharmacodynamic (PD) endpoints in phase 1 studies are PET (because the drugs inhibit glucose uptake; a PET response is thus not synonymous with a tumour response; although the absence of a PET response can be considered a lack of efficacy). Other PD endpoints are C-peptide, Ki67, pS6 inhibition, pERk, p4EBP, pAkt or other downstream mediators.

BKM120 (#3003) is a selective Pi3kinase inhibitor that has important toxicities: mood alterations (depression and anxiety) (crosses BB; involvement of psychiatrists necessary), rash, hyperglycemia. The drug produced a PR in a K-Ras mutant BC (Ras mutant cancer cells can be sensitive to Pi3 kinase inhibition).

XL147 (#3004, #3078) does not lead to hyperglycemia because it does not block the p110b Pi3kinase subunit; the drug might therefore also be less efficient. Responses (including in a NSCLC) were observed. The drug is also investigated in combinations with erlotinib (#3070), chemotherapy (#3078) and letrozole (cancer cells become sensitive to Pi3kinase inhibition when E deprived).

BEZ235 is an inhibitor of Pi3kinase and mTOR (Torc1/2) and causes fatigue, diarrhea, but is generally very tolerable. In a study with maximal pathway characterization, responses were noted in a PTEN deficient lung cancer and breast cancer and many SD in a wide variety of cancers. Interestingly, activity was twice as frequent in cancers with documented pathway activation. The maximum tolerated dose (MTD) was not yet reached.

mTOR

Current inhibition of mTOR has limited clinical activity and there is no predictive biomarker that would allow selecting patients with an increased clinical benefit. Current mTOR inhibtors are mTOR or TORC1 inhibitors. Novel mTOR inhibitors are being developed such as OSI-027, a dual TORC1 and 2 inhibitor (#3006). Dual IGF1R-mTOR ridaforolimus in combination with the IGF-1R antibody dalotozumab (#3008) and temsirolimus with cixutumumab (#3007) to overcome resistance (countering the effect of the feedback loop). There is some promising activity, unfortunately currently without a clear correlation with pathway activation.

Akt

Akt inhibitors are in early development. An important rationale is the amplification of Akt in cancer (for example 20% in pancreatic cancer). A second rationale is that when mTOR is pharmacologically

inhibited a negative feedback loop upstream is removed, leading to growth factor activation, e.g. IGF1R, which then in turn activates Akt. Very nicely done study with MK2206 (#3009) included extensive pharmacodynamic markers and genomic markers so that the activation status of the pathway canbe correlated with the clinical activity.

Ras-Raf pathway

This pathway is one of the most frequently activated in human cancer, by Ras (many cancers) or BRAF (lung, melanoma papillary thyroid) mutation. There is also significant cross-talk with the pi3kinase pathway. Ras itself has been elusive as a direct therapeutic target despite extensive efforts with varied approaches.

BRAF inhibitors are in more advanced clinical development. MEK is downstream on this pathway. Early compounds aborted because of poor tolerability or poor pharmacokinetic properties. An advantage of MEK inhibitors is that they also can work in KRAS mutant cancers in contrast to BRAF inhibitors, if they can be sufficiently dosed. A limit to Raf inhibition is that it activates wild-type Raf kinase. Concomitant mutation of the Pi3kinase pathway (e.g. PTEN inactivation) also diminishes the effect of BRAF inhibition. A class effect of MEK inhibitors is retinal vein occlusion and ophthalmologic monitoring is needed. In phase I studies clinical efficacy of MEK inhibition is especially found in BRAF mutant tumours (40% RR, including CRs) (GSK112, #2503) but occasional responses are also seen in BRAF wildtype tumours. Toxicities include acneiform rash similar to EGFR inhibition, diarrhoea and retinopathy. The activity found with this compound in a nicely designed trial seems superior to the activity of AZD6244 that as single agent earlier only gave a RR of 11% in BRAF mutant melanoma but now in combination with chemo a 56% RR (#8501). AS703 (#2504) produced PR only in melanoma, but the dose limiting toxicity was not reached in this early study. Again, there are limits to efficacy of MEK inhibiton as it leads to Akt upregulation and therefore there is a rationale for combining with Pi3kinase pathway inhibitors.

Hedgehog and Notch

Several therapeutic agents targeting these stem cell pathways are being developed. The Hedgehog (Hhg) and Notch pathways cross-talk. Transgenic animals with Ptch mutations develop medulloblastoma and activating mutations can be found in basal cell cancer and medulloblastoma. An oral Smo antagonist (LDE225, #2500) (before topical in basal cell cancer) produced short partial remissions in medulloblastoma (secondary mutations are a mechanism of resistance), in contrast to basal cell cancers that can remain in remission for years. BMS-833923 (XL139) produced a response in a NSCLC patient (#2501). In T-ALL, notch mutations are common (56%). Notch signalling is complex with many receptors and ligands: drugs in development are gamma secretase inhibitors or monoclonal antibodies against the receptors. Prior reports on notch inhibitors revealed important DLT (extreme diarrhoea through goblet cell) and no responses. Current drugs have no such prohibitive toxicity (MK0752, #9502 and RO4929097, #2502 and #8546). It is to be awaited whether receptor antibodies could be more efficient.

DNA repair: PARP inhibition

This was a hot topic at ASCO 2010. PARP1 and PARP2 are enzymes important for base excision repair (BER). It is possible that also other PARP family members are involved. When PARP is pharmacologically blocked, ssDNA damage turns into dsDNA breaks that need to be repaired by homologous recombination (HR). It has been proven very elegantly in preclinical experiments that cells that are HR defective (such as BRCA1/2 null cancer cells in BRCA1/2 mutation carriers) undergo apoptosis when treated with a PARP1 inhibitor, whereas wild-type cells or hemizygyous cells in mutations carriers are virtually insensitive to this effect. This is called synthetic lethality and has been validated in the clinic in ovarian cancer as a very effective treatment, with high response rates in pretreated ovarian cancers. Serous ovarian cancer and triple negative breast cancer can have a BRCA-like phenotype ("BRCA-ness") caused by epigenetic silencing of BRCA1/2. Olaparib was highly active in high grade serous OVCA (24% RR in BRCA1/2 wt disease vs 41% in BRCA1/2 carriers) (#3002). In contrast, and disappointingly, no RECIST activity was found in BC, mutant (some minor responses) or wild-type. There are therefore unknown elements

that make this drug less active in breast cancer as opposed to ovarian cancer. This group is now moving forward in trying to identify why some tumours do or do not respond. Known mechanisms of resistance are secondary mutations in BRCA1, restoring the reading frame and HR function; another is PgP overexpression. They aim to identify the specific genetic context underlying resistance versus sensitivity by looking for mutations that overlap between sensitive cancers, but differ with resistant tumours in a genome wide sequencing effort on both pre- and posttreatment tumour samples.

A second development of PARP inhibitors is in combination with DNA damaging chemotherapy in order to potentialize the DNA damage of chemotherapy: ABT-888 (velaparib with cyclofosfamide and other drugs) (#3000). The exact scheduling of such combinations needs to be further optimalized. So far the combination is quite tolerable and an MTD was not reached. Increased myelosuppression is observed as expected. MK-4827 (#3001) in a first-in human phase 1 study lead to multiple responses in breast and ovarian cancer and also long SD and one PR in lung cancers. Thrombocytopenia differentiates this drug from other PARP inhibitors.

A large number of PARPi are in development (at least 11) and they have all different biochemical and target properties. In combination with DNA damaging chemotherapy they might become a relevant part of the treatment for a significant proportion of all cancers (if combined toxicity is manageable, #2015 and #3027). It is remarkable that there is no therapeutic synergy with anthracyclines. The optimal for further development would be to have a highly selective PARP1 inhibitor with no off target activity.

Death receptor

Targeting the apoptotic machinery of malignant cells is an attractive concept to combat cancer, which is currently exploited for the proapoptotic members of the TNF ligand family at various stages of preclinical and clinical development. The death receptors of TNF, CD95L, and TRAIL mediate extrinsic induced cell death and is actively investigated especially in combination with other treatments such as chemotherapy since there is no notable single agent activity. The death receptors can be targeted by means of its cognate protein ligands, receptor specific antibodies, and gene therapeutic approaches.

A negative randomized phase II study in which mapatumumab was combined with carbotaxol in lung cancer (#LBA7501) highlights the difficult translation from lab to clinic. This monoclonal antibody, already in study for several years has an agonistic effect on death receptor 4 (DR4). Whereas all this works well in cell lines that do possess the receptor, in real live tumour biopsies reveal the presence of the receptor only in a minority proportion of malignant cells and only in a minority of lung cancers. So, there is an important deficit in the translational aspects of this development. If this is further pursued, studies should absolutely be performed in preselected enriched patient populations.

With Conatumumab, a DR5 agonist antibody, a weak therapeutic effect was observed when combined with gemcitabine compared to placebo in a randomized phase II study in pancreatic cancer (#4035)

Mitotic inhibitors

Aurora kinase inhibitors (#3010, #3011) and other inhibitors of the cell division machinery (#3012) give occasional responses in phase 1 studies and they are generally well tolerated, but the absence of any predictive biomarker is a serious impediment to their development.

Rational drug development

Many new drugs are tested in phase 1/2 in unselected patient populations, at best enriched for potential mutation carrying phenotypes. From all the presentations it became apparent that we need a new algorithm for drug development with genomic selection of patients, already in the phase 1 and 2 context. Targeted therapy only really works in cancers in which the targeted pathway and preferentially the target itself are constitutively activated by a genomic mutation (see for example EGFR inhibition in lung cancer). Enrichment for potentially sensitive patients will maximize early identification of active drugs, especially when many compounds are developed simultaneously for a single target and early insight in potential efficacy differences and accelerate drug development. To accomplish this, infrastructure needs to be generated that allows extensive genomic

characterization of cancers. Massive parallel sequencing (Illumina and other platforms) can now be achieved in a couple of weeks at 1OK $ and >40x coverage and uncover all pathogenic mutations in a specific cancer. This is currently a very powerful method for discovery of cancer genes. The tricky part is in the interpretation of the mutations with regard to their pathogenicity and their hierarchical importance in the pathogenesis of the disease and demands huge computational power to compare mutants to germline mutations and to known polymorphisms. What is now more generally affordable is sequencing of arrays of predefined genes for which targeted drugs are available or in development. This strategy will also allow rare tumours exposure to drug development.

Head and Neck cancer

This year's ASCO was clearly focusing on prognostic and predictive factors. Of all the 101 abstracts dealing with head and neck cancer this topic comprised 28 abstracts. Interestingly, this year also thyroid cancer got serious attention, in particular medullary thyroid cancer (MTC), now that tyrosine kinase inhibitors (TKIs) have shown interesting results. Interesting topics in the "other topics" section included:

Human papillomavirus (HPV), showing in the California Cancer Registry an increase only in the non-Hispanic white males and a decrease in the low socio-economic non-Hispanic black males when looking over the period 1988 to 2007 (#5526). Data from the M.D. Anderson Cancer Center indicated that there is a high rate of transmission and 100% HPV-genotype concordance between patients and their sexual partners (#5527).

Treatment-related consequences, showing that consequences are different in patients treated with surgery followed by radiotherapy (RT) from those treated exclusively with chemoradiation (CRT). In a study from Airoldi et al, it was shown that dysphagia and taste impairment occurred more frequently in patients treated exclusively with CRT, while patients with severe dysphagia and taste impairment showed higher levels of anxiety ($p<0.05$), which had consequences for quality of life, fatigue and physical-social functioning (#5575). No differences were found in stress and depression in patients who had been curatively treated with either surgery or RT, when participating in a chemoprevention trial (#5597). Earlier studies have shown that patient-reported outcomes with quality of life instruments are predictive of survival. The M.D. Anderson Cancer Center showed that 46% of the patients treated with RT or CRT were symptomatic before treatment. The top symptoms at presentation were fatigue, emotional distress, pain, disturbed sleep, drowsiness and sadness. Mostly they were mild in severity. Patients with high pretreatment symptom burden had poorer outcomes, and the combination of performance status and symptom burden proved to be a better predictor than either alone (#5600).

Competing mortality (CM) is a common event in patients with head and neck cancer that complicates the interpretation of treatment effects. Rose et al. analysed 22,729 patients diagnosed with advanced nonmetastatic head and neck cancer between 1993 and 2004 using SEER data and identified factors associated with cancer-specific mortality (CSM) and CM. The median follow-up of the surviving patients was 59 months. The 5-year cumulative incidence of all-cause mortality (ACM), CSM and CM was 57%, 45% and 12%, respectively. Risk factors for increasing CM were male sex, black race, low socio-economic status, age, being unmarried, grade 1-2 tumour, larynx subsite and nonsurgical treatment. The 5-year cumulative incidence of CM for patients with low, medium and high risk was 9%, 11% and 17%, respectively, and suggests that competing risk methods should be considered for power calculation in head and neck clinical trials.

LRA-SCCHN

The standard approach for patients with LRA-SCCHN is the concomitant use of platinum-based concurrent CRT, i.e. for patients with resectable disease (postoperatively in case of high-risk factors in the pathology specimen), for patients with nonresectable disease as primary nonsurgical treatment and for those treated for larynx preservation (LP). However, recently bioradiation with cetuximab (Bonner et al, 2006) has come forward as an alternative for concurrent CRT (but never reported to be equally efficacious in a direct comparison). Moreover, docetaxel, cisplatin, 5-fluorouracil (TPF) has replaced PF as the standard

induction regimen for those patients who are considered to be candidates to receive induction chemotherapy (ICT) (Posner et al, 2007, Vermorken et al, 2007, Pointreau et al, 2009). Priority studies nowadays are those comparing ICT followed by concurrent CRT *vs* concurrent CRT alone and the integration of targeted drugs in this complexity of treatment approaches.

The long-term results from TAX324 were presented again at this ASCO, now in the poster discussion session after the data had been presented already at ECCO/ESMO last year. The study showed that there was a sustained survival advantage of induction with TPF at 5 years, and now also for patients with oropharyngeal cancer (OPC) only. There was also a sustained reduction in the risk of progression or death for patients with hypopharyngeal and laryngeal disease. There were no significant differences in toxicities at 3 and 5 years (#5512). From the same group and study, another poster showed unprecedented 5-year survival data for HPV+ patients with OPC (82% in HPV+ vs 35% in HPV- patients, with PFS being 78% vs 28%, respectively). Posner et al. concluded that these data support the notion that different therapeutic approaches are to be developed for HPV+ and HPV- OPC patients. They suggested that it may be possible to reduce the long-term morbidity in HPV+ patients and preserve survival by reducing RT intensity in the context of this sequential treatment (ST: ICT→CRT) and that we might best approach HPV- disease with more aggressive ST and/or CRT. This was, but in a different manner, supported in the discussion of Dr. Rischin on the three posters on ICT→CRT +/– cetuximab (see below).

As mentioned above, bioradiation with cetuximab has shown promising results in combination with RT and the Hazard Ratios (HR) for survival in the Bonner trial vs RT alone were comparable with those from the meta-analysis with concurrent CRT vs RT but with better compliance and without a significant increase in late toxicity compared to those who received RT alone (Bonner et al, 2006). Preclinical studies have indicated that a further enhancement of the RT effect can be obtained by giving cetuximab not only during RT but also for some time thereafter. Mesia et al. performed a prospective randomized multicenter phase II trial evaluating the efficacy and safety of cetuximab maintenance therapy following definitive RT with concomitant cetuximab in patients with locally advanced OPC. Group A (n=45) received concomitant boost RT (69.9 Gy in 28 days) + cetuximab (400 mg/m^2 1 week before RT and 250 mg/m^2/wk during RT) and group B (n=46) an additional 12 consecutive weeks of cetuximab. CR at 12 weeks was 55.6% and 69.9% in group A and B, respectively, and the local control rate (primary endpoint) at 1 year was 56.8% and 60.5% in group A and B, respectively. This approach needs further study.

There were 3 posters at ASCO 2010 addressing the addition of cetuximab to ST in the poster discussion section, i.e. ECOG 2303 (#5513), a German study (#5514) and a follow-up of ASCO #6002 presented at ASCO 2008 by the Pittsburgh group (#5515). Cetuximab was used during ICT and CRT in 2 studies and only during CRT after ICT in the third study. It was clear that cetuximab can be combined with ICT using lower dosages and/or less drugs than in standard TPF. Moreover, it became clear that it was feasible to add cetuximab to weekly low dose cisplatin following ICT. However, the three studies do not allow a firm conclusion on whether the addition of cetuximab to ICT or to CRT might be superior to standard TPF sequential regimens.

A fourth abstract concerned the use of nimotuzumab in an open-label, randomized, study in patients with LRA-SCCHN. Nimotuzumab is a humanized IgG1 monoclonal antibody against EGFR, but with a different affinity to the receptor, therefore leading to less skin toxicity. It concerned a small study (113 patients), in which bioradiation was compared with RT or CRT and the authors suggested a better outcome with the use of nimotuzumab. However, the study sample size did not allow firm conclusions (#5530).

The role of EGFR TKIs in SCCHN in the LRA-SCCHN disease setting has been so far less promising. The UK study, presented by Dr. Harrington was no exception to this. In this small study (n=67), lapatinib (1,500 mg daily) or placebo was combined with RT locally advanced, unresected SCCHN. CR rates and HRs for PFS and OS were considered promising but evidently nonconclusive. The combination was well tolerated. Nevertheless, the question was raised what to do next? Were the data sufficiently promising to go for

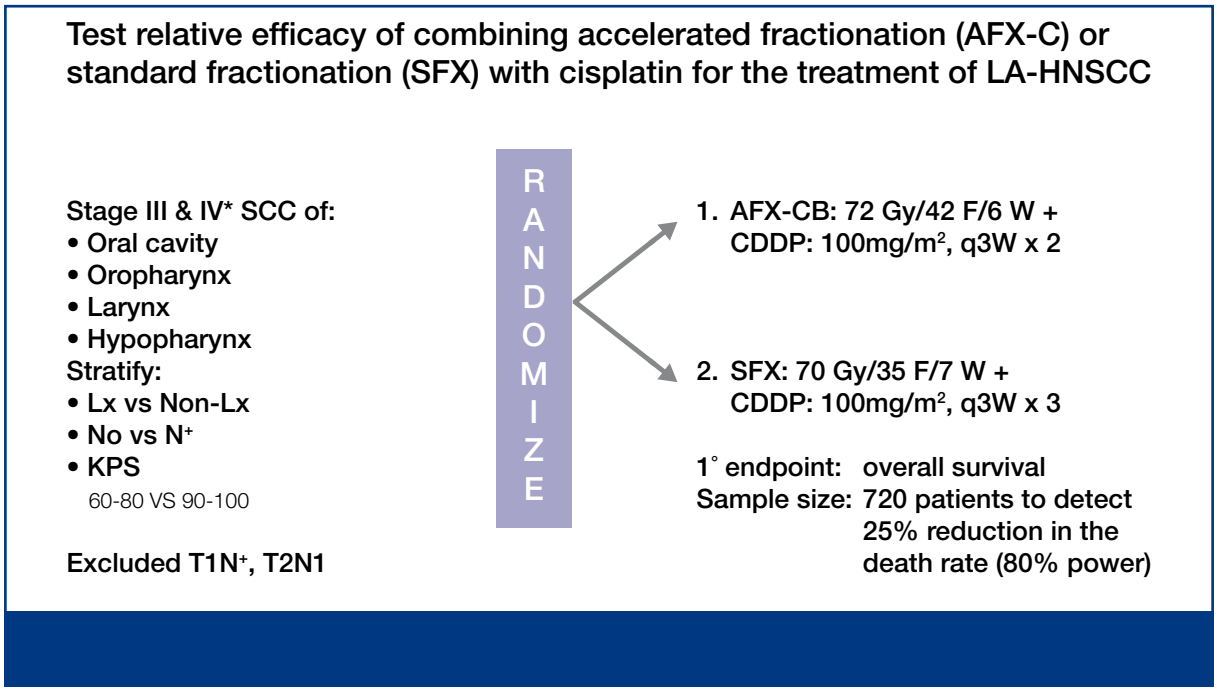

Figure 1. RTOG 0129: objective and study design.

a phase III study?

There were 2 interesting presentations on RT. The first concerned postoperative accelerated RT (POPART in 5 weeks) versus conventional postoperative RT (CPORT in 7 weeks), a multicenter prospective randomized trial of the Dutch Head and Neck Cooperative study group. Included were patients treated with curative surgery and with high-risk factors for locoregional recurrence (positive margins and/or extranodal spread). The study stopped early due to poor accrual and from December 2004 to October 2008 only 148 patients entered the study. No significant differences were noted with regard to acute and late toxicity. At 3 years, the locoregional control rate was 77% after POPART and 76% after CPORT. The 3-year OS was 71% with POPART and 63% with CPORT. The power with this sample size made the study nonclonclusive. The second trial concerned a secondary analysis looking for the relative impact of tumour, patient and therapy variables in the RTOG 0129 study (*Figure 1*). In this secondary analysis patients had to meet the following criteria: alive >3 months without disease progression, received therapy per protocol or with minor variations, i.e. 1-3 cycles of cisplatin, >63 Gy RT dose (≥90% of prescription) and ≤9 week overall RT duration. The primary endpoint of the study (OS) showed no difference between the 2 arms of the study. The secondary analysis showed that locoregional relapse (LRR) was the main cause of cancer mortality and that HPV status was the strongest prognostic factor. Moreover, receiving only 1 cisplatin cycle was associated with significantly worse OS, PFS and LRR rates. The third cisplatin cycle had no significant impact on OS or PFS rate but was associated with a higher LRR rate. Within the range of 64-76 Gy, a trend for dose-response relationship was detected for grade 3-4 late morbidity ($p=0.063$) but not for OS or other endpoints. Two to 3 weeks of RT prolongation correlated with poorer OS but not with other endpoints. Only N-category and HPV status were found to have significant impact on the distant metastases rate.

R/M-SCCHN

Treatment policy in R/M-SCCHN has changed recently with the positive outcome of the EXTREME trial in the first-line setting, showing that the addition of cetuximab during and after platinum/5-FU has significant impact on survival, response and disease control without a negative influence on quality of life (Vermorken et al, 2008). The outcome of a similar trial with panitumumab (SPECTRUM) is expected to be presented in 2010. Cetuximab is now approved for this indication in Europe and in the US, while in the US cetuximab is also

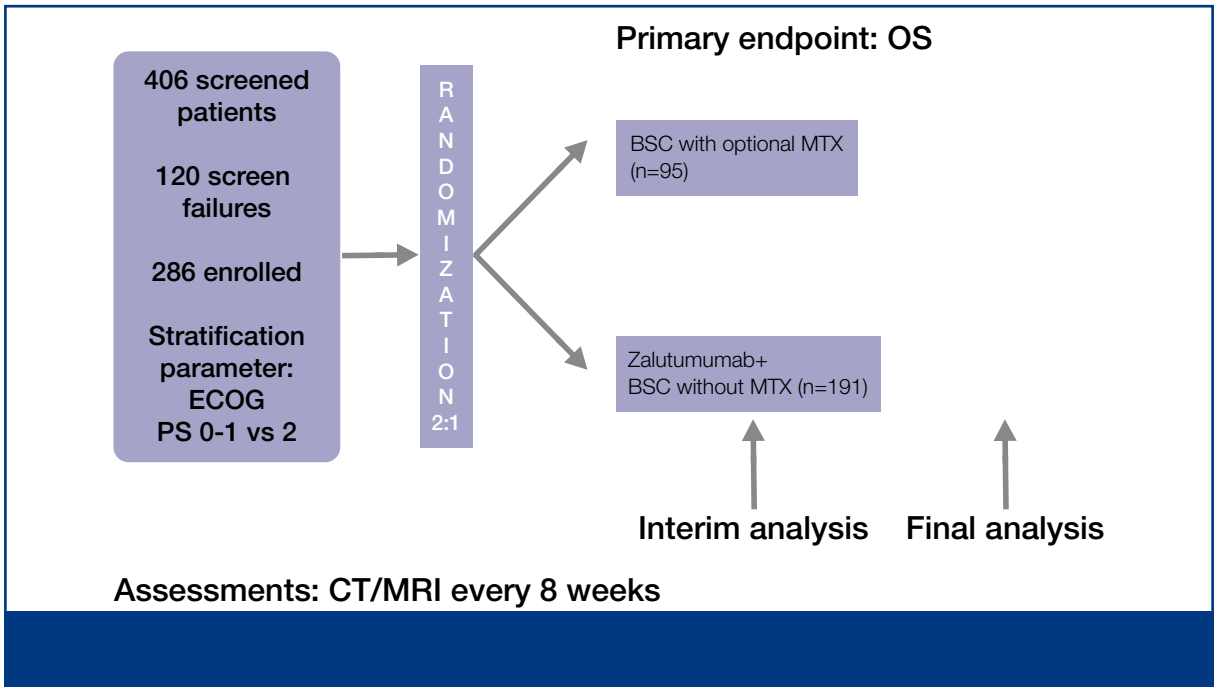

Figure 2. Hx-EGFr-202: study schema.

approved for treatment in the second line setting. The latter indication is only based on several phase II studies showing a response rate of approximately 10% and a disease control rate of about 50%. The zalutumumab trial presented by dr. Machiels is an important contribution, which gives further support to the idea that anti-EGFR MoAbs are of benefit also in second-line R/M-SCCHN after platinum failure (*Figure 2*) (#LBA5506). Patients with noncurable SCCHN with an ECOG performance status of 0-2 and centrally documented radiographic progressive disease within 6 months after platinum-based therapy were randomized between zalutumumab monotherapy and BSC in a 2:1 ratio. Methotrexate was allowed in the BSC arm only. Individual dose-titration of zalutumumab was applied (max. exposure 16 mg/kg). Primary endpoint was OS with PFS as the only secondary endpoint to be compared between groups. The primary endpoint was not reached (HR 0.77, 97.06% CI 0.57-1.05, p=0.065), with median survival 6.7 months vs 5.2 months with BSC, 6 months survival rates were 57% vs 42%, respectively. The HR for PFS was 0.62 (95% CI: 0.47-0.83, p=0.001) with a median PFS of 9.9 weeks with zalutumumab vs 8.4 weeks with BSC and a 6 months PFS rate of 20% vs 7.3%, respectively. Response rate was 6% vs 1% and the disease control rate 48% vs 27%, respectively.

Dr. Colevas in his discussion pointed out that cost-effectiveness with this treatment was unfavorable (709,738 USD per life year gained).

A very interesting presentation was given by dr. Seiwert on a randomized, open-label phase II study of BIBW 2992 vs. cetuximab in patients with R/M-SCCHN after failure of platinum-containing therapy with a cross-over period for progressing patients (*Figure 3*, page 184) (#5501). BIBW 2992 is a highly potent inhibitor of EGFR/erbB1 and erbB2. It retains activity for EGFRvIII mutation and provides a sustained blockage of receptors and inhibition of tumour cell proliferation. Primary endpoint was tumour shrinkage of target lesions before cross-over. Diarrhea, dehydration, epistaxis and asthenia occurred more frequently with BIBW 2992, but also tumour shrinkage occurred more frequently with BIBW 2992 than with cetuximab (objective response 21.7% vs. 13.3%). Disease control was similar (56.7% vs. 61.7%). Median PFS with BIBW 2992 was 16 weeks (95% CI 10-19) and 10 weeks (95% CI 8-17) with cetuximab. BIBW 2992 is the first TKI to demonstrate antitumour activity in SCCHN that appears to be at least comparable to cetuximab. The data on response compare favorably versus all the other EGFRIs tested (*Table 1*, page 185).

Prognostic/predictive factors

It is important to distinguish prognostic from

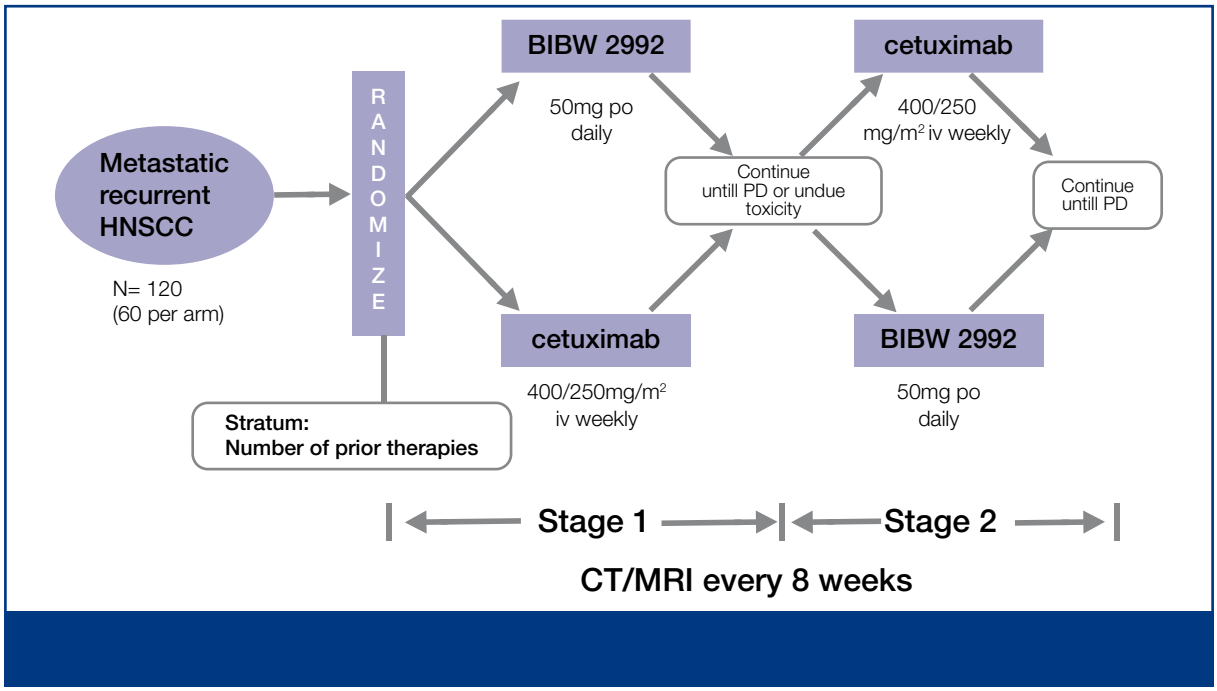

Figure 3. Study design of a randomized, open-label phase II study of BIBW 2992 vs. cetuximab in patients with R/M-SCCHN.

predictive factors. Prognostic factors inform about disease outcome and predictive factors inform about treatment/intervention. Many biomarkers have overlapping qualities (e.g. K-Ras mutation, HER2 amplification, EGFR TKI mutations). Important is whether these markers help us in making treatment decisions. Dr. Rischin gave a presentation on the prognostic significance of interleukin-8 (IL-8) and hepatocyte growth factor (HGF) in patients with SCCHN treated with CRT on a phase III trial (#5509). HGF is a hypoxia induced protein that binds to its receptor MET to regulate expression of a variety of molecules including the cytokine IL-8. Both markers are associated with angiogenesis, tumour growth, invasion and metastases. High plasma IL-8 levels and to a lesser extent high HGF levels are associated with an adverse prognosis in patients with LRA-SCCHN. Subgroup analysis in OPC with HPV-/p16- tumours showed that those with low levels of both plasma IL-8 and HGF had a better prognosis. P16 and tobacco pack-years were of influence in RTOG 0129. Gillison et al. looked back in a trial that was executed a decade ago, RTOG 9003, a 4-arm study of different forms of RT. The relative hazards of death or progression for p16+ vs. p16- patients and for pack-years of tobacco smoking appeared independent of treatment by either RT or CRT. The absolute rates for OS, PFS and second primary tumours may be compromised in part by higher cumulative pack-years of tobacco smoking in patients enrolled a decade before those in RTOG 0129 (*Figure 4*).

Snietura et al (#5519) presented data on the tumour suppressor gene PTEN, which is known to control a variety of processes related to cell proliferation, survival and growth. Patients were treated in a randomized clinical trial with RT in the postoperative setting, receiving conventional fractionation (CF) or a 7-days-a-week postop RT (p-CAIR). Out of the 279 patients enrolled 147 paraffin blocks were available for IHC assessment of PTEN (73 CF, 74 p-CAIR). High PTEN staining was of prognostic value in terms of gain in local control from p-CAIR (5-year LCTR 93% vs. 69%; RR=0.25, p=0.014). In contrast, tumours with a low intensity of PTEN did not gain from p-CAIR (5-year LCTR 56% vs. 47%, p=0.14, RR=0.94). Intensity of PTEN highly affected LCTR in the whole group of 147 patients (5-year LCTR 80% vs 52% for high vs. low PTEN, p=0.0005, RR=0.32). In a multivariate analysis PTEN seemed to outperform other variables such as neck node involvement, EGFR and nm23.

Other markers reported on are the following: neck nodes (#5517), HPV (#5525, #5537, #5544 and #5546), antibodies to HPV proteome (#5545), EGFR and p16 (#5528, #5537, #5546),

Table 1. EGFR inhibitor response rates in SCCHN

Drug	Phase	Reference	Response rate
Cetuximab	II	Vermorken, JCO, 2007	13%
Erlotinib	II	Soulieres, JCO, 2004	4.3%
Gefitinib	II	Cohen, JCO 2003	10.6%
	II	Cohen, CCR, 2005	1.8%
	II	Kirby, BJC, 2006	8.5%
	III	Stewart (IMEX study)	7.9%
		JCO, 2009	MTX 3.9%
Lapatinib	II	Abidoye, ASCO 2006	0%
Cetuximab	II	ASCO 2010	13.3%
BIBW 2992	II	ASCO 2010	21.7%

EGFRvIII, ERCC1 (#5537, #5538, #5539, #5540, #5541, #5551), angiopoietin-1 and -2 (#5542), haptoglobin (#5543), TIL (#5547), HIF-1a (#5548), ALDH1-A1 (#5549), STAT3 protein (#5550), Gli, E-cadherin,beta-cadherin (#5552) and epithilitis during RT plus cetuximab (#5594).

Medullary thyroid cancer (MTC)

Conventional options for advanced MTC are chemotherapy (doxorubicin, dacarbazine/5-FU, dacarbazine/5-FU+doxorubicin/streptozotocin, doxorubicin/dacarbazine/vincristine/cyclophosphamide, capecitabine, thalidomide) leading to response rates of 10-20%. Moreover, octreotide or lantreotide are sometimes given for symptoms and also Yttrium-90-labeled somatostatin analogs (response rate 9%). Several TKIs have shown to induce response in MTC. The ZETA trial is the first randomized controlled trial showing a significant improvement in PFS with Vadetanib (#5503). Activity was also presented during this ASCO for XL184 (targeting RET, VEGFR2, MET, KIT, TIE2) in a phase I study (#5502; response rate 29%, disease control rate 68%) and with sunitinib (targeting PDGFR, KIT, VEGFR, RET, FLT3) in a phase II study (abstract#5504; response rate 35%, disease control rate 91%).

Take-home messages

LRA-SCCHN

- Concurrent CRT is still the treatment of choice for the majority of patients with locoregionally advanced SCCHN.
- Anti-EGFR therapies can be combined with CRT, but it is presently unkown whether this leads to better outcome in the clinic.
- Anti-EGFR therapies can also be combined with ICT when chemotherapy regimens are adapted in terms of dose or composition (full TPF dose + full cetuximab dose is not feasible).
- HPV status is the strongest prognostic factor in OPC and separate trials in HPV+ and HPV- patients are needed in R/M SCCHN.
- Platinum/5-FU (PF) plus cetuximab is the new standard approach for patients who can tolerate PF.
- The zalutumumab trial supports the idea that anti-EGFR moAb may be of benefit in 2nd-line after platinum failure, however the cost-benefit ratio is questionable.
- BIBW 2992 is the first TKI to demonstrate

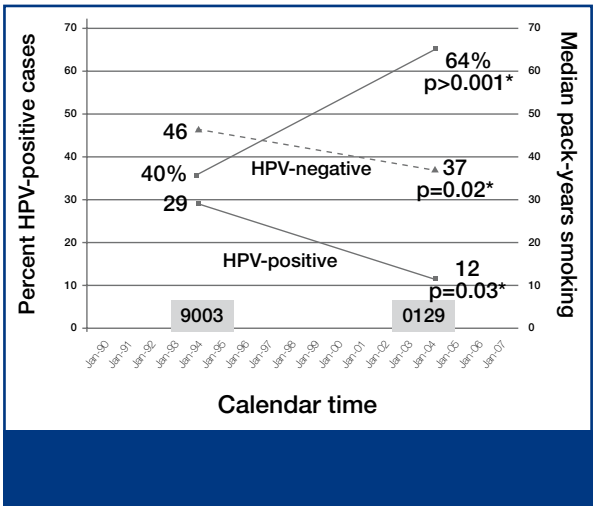

Figure 4. HPV status and tobacco use in RTOG9003 and RTOG0129.

antitumour activity in SCCHN that appears to be at least comparable to cetuximab.

Thyroid cancer (MTC)

- Tumour shrinkage and extent of PFS can be obtained with Vandetabin. Unclear if this is clinically meaningful.
- Vandetanib, motesanib and XL184 are all promising, butsorafenib and sunitinib are available now in some countries.

Supportive care

At the 2010 ASCO meeting, supportive care was embedded in the broad section "Patient and Survivor Care", which contained besides the classical supportive care also palliative care, end-of-live care, cancer-related complications, quality of live management, cancer in older patients and the all-embracing item "others". This report will limit this section to the more classical supportive care. The following topics will be discussed: cancer-related fatigue, pain therapy, emesis, treatment/prevention of bone metastasis, and an overview of what is usually called "miscellaneous".

Cancer-related fatigue

Up to 80-90% of patients under or after cancer therapy experience cancer related fatigue (CRF). The classical treatment or prevention of CRF is based on nonpharmacological interventions such as physical activity, in all possible formats, and psychological support, or pharmacological therapy.

Yoga was the trendy physical activity this year (#9013, #9089). Methylphenidate (Rilatine(R) in Belgium) was the most popular drug in the interventional studies. Despite earlier results and a still ongoing study from the group of Bruera (#TPS321), in a placebo-controlled phase III study, including 148 patients, the addition of long-acting methylphenidate (54 mg/day) was not effective in reducing the burden of CRF. Only patients with advanced disease seemed to have some benefit of this drug (#9004, #9005). Another myth that passed away was the use of coenzyme Q10 in this situation: in a large (236 patients) placebocontrolled study in women with early breast cancer experiencing moderate to serious fatigue, the addition of coenzyme Q10 to vit. E did not alter the CRF, even after 24 weeks of therapy (#9006).

But maybe a new myth is born: guarana, a roasted seed extract from a South-American plant (Paullinia cupana). It was given as a 50 mg extract BID, and proved to have a positive effect in a crossover study (21 days treatment, 8 days wash-out period), even if the study population was rather small (32 patients starting with the extract and 43 placebo-starters) and the effect of short duration (only significant after the first 3 weeks) (#9007). The effect is probably due to a caffeine-like substance: tetra methylxanthine. There were no abstracts this year about modafinil another psychostimulant frequently used in this setting.

Another interesting study reported the positive effect of a SARM (selective androgen receptor modulator) on body mass, muscle function and quality of life in patients with cancer cachexia. GTx-024 (Ostarine(R)) was tested at two dosages in a group of nonprostate cancer patients against placebo and was able to reverse the progression of cachexia (#9147).

Pain therapy

Breakthrough cancer pain (BTCP) is a very unpleasant situation for a lot of cancer patients already under opoid therapy for their cancer pain. It is usually relieved with oral morphine, but this has a rather slow action and sometimes there is even a spontaneous relief before the morphine works. Fentanyl pectin nasal spray is a new, easily applicable formulation of this classical pain medication, best known in its transdermal form. In a randomized double blind study versus immediate-release morphine sulphate tablets (84 patients, 740 episodes of BTCP) this way of pain therapy proved to be faster (almost 60% of the patients noted an improvement after 5 min) and also more efficacious (95% of patients had some relief after 30 min) (#9016). Another study demonstrated the long-term safety and patient satisfaction of this formulation (#9094).

A somewhat different approach to neuropathic pain was reported in a phase I study in 22 patients suffering from chemotherapy (mostly oxaliplatin) induced neuropathic pain. In these patients a 1% topical menthol cream (BID) was applied to the skin of the painful areas. After 2 weeks 1 out of 3 was pain free, and this increased to 50% after 6 weeks. Two out of 3 patients had some relief after the 6

weeks study period (#9129).
C-GSF induced bone pain can be disturbing for patients and some surveys indicate that this is the case for about 60-80%. A large (510 patients) placebo controlled phase III study reported the preventive effect of 500 mg naproxen (BID, 5-8 days) on this type of pain: both intensity and duration of the bone pain was reduced, but the effect was limited to moderate pain and less efficacious on severe pain (#9014).

Chemotherapy induced nausea and vomiting (CINV)
It was evident that there were no real breakthrough studies presented this year in the field of CINV. A large (2322 patients) randomized study compared the classical 3 day regimen of aprepitant to the intravenous formulation fosaprepitant given on day 1 alone (both regimens in combination with dexamethasone and ondansetron) in highly emetogenic chemotherapy (#9021). The results showed complete equivalence of both arms and confirms the hypothesis that the action of an NK1 antagonist is probably due to a longstanding binding of the drug to its receptors, as was previously demonstrated with L-758.298 and casopitant. A maybe more unexpected result was the equivalence of olanzapine (Zyprexa(R)) to aprepitant, both in combination with palonosetron and dexamethasone, in a small randomized study in a group of 50 patients treated with highly emetogenic chemotherapy (#9020). Even if the anti-emetic activity of olanzapine is known for about 10 years, until know no large randomized study has been done with this anti-psychotic drug, and hence its exact position in CINV prevention remains unclear.

Treatment/prevention of bone metastasis
The treatment and/or prevention of bone metastasis has been discussed in several abstracts and presentations. The comparison between bisphosphonates (zoledronic acid, ZA) and anti-RANKL antibodies (denosumab, DM) was studied in different types of tumours and was finally pooled for a meta-analysis.
One study compared 4 mg ZA IV every 4 weeks to 120 mg DM SC every 4 weeks in a double blind double dummy way, in 2,046 breast cancer patients with bone metastasis (#1024). Fifty one percent of patients had no of mild pain due to their bonemetastasis (n=1,042) and this subgroup had a statistical difference in delay for experiencing moderate/severe pain in favour of DM: 176 vs. 295 days (p=0.0024). This effect was not demonstrated in the moderate/severe group. During the whole observation period (73 weeks) less patients with no/mild pain on DM shifted to the worse category (NS). On the other hand time to improve pain was similar in both arms (DM: 82 days vs ZA: 85 days, p=0.72). The same patient population was also analysed for effect on quality of life (Qol) (#1025). Fallowfield reported the evolution in QoL of 1,808 patients (88.3% of the included patients). An improvement of 5 points on a scale of 108 (mean starting point: about 73/108) was noted in 37.1% on DM versus 31.4 on ZA (p=0.02) at week 25, but there was no difference in the percentage of patients remaining stable, or worsening or better plus stable. At the end of the study (73 weeks) only 3.2% (CI: 1-7%) more patients on DM had an improved Qol.
Fizazi et al. reported the comparative study of DM versus ZA in prostate cancer patients with at least one bone metastasis (#LBA4507). The same method of treatment was applied and 1,901patients were included. DM significantly delayed the time to first skeletal related event (SRE) with 3.6 months (20.7 vs. 17.1 months, HR: 0.82, p=0.008) and also to subsequent SREs, but with no impact on disease progression or survival. A none statistical difference in percentage of osteonecrosis of the jaw (DM: 2.3 vs. ZA: 1.3%) and hypocalcemia (13 vs. 6%) was noted, maybe in correlation with the greater suppression of bone turnover markers. Henry et al. presented a poster (#9133) on a subanalysis of a study (with the same design) in patients with advanced cancer (1,597 patients), excluding breast and prostate cancer and for this analysis also the patients with multiple myeloma. The same delay in time to first SRE was noted (HR 0.85; CI 0.72–1.00; p<0.05) but also no effect on disease progression or overal survival. Side effects ware similar in both arms including nephrotoxicity (DM: 7.1%, ZA: 10.3%), acute phase reactions (DM: 4.4%, ZA 1.1%) and osteonecrosis of the jaw (DM: 08%, ZA: 1.1%).
A re-analysis (#9042) of the previously reported study of Henry et al. focussed on time to first SRE and time to radiation in a cohort of 1,766 patients, this time including the multiple myeloma patients. The

difference in time to first SRE was 4.6 months (19.0 vs. 14.4 months) in favor of DM, which was also translated in a difference in time to radiotherapeutic intervention. This study was then also analysed looking at painscores (#9043) and confirmed the gain in delay of worsening of pain (26-32 days in favor of DM).
Finally two of these studies were pooled for a meta-analysis (#9015) and confirmed that DM was superior to ZA in delaying the time to first on-study SRE by 17% (HR 0.8), that the median time to first on-study SRE was 21.1 months for ZA and not reached for DM, that DM was also superior to ZA in delaying the time to first and subsequent on-study SRE (multiple event analysis) by 18% and that DM reduced the mean skeletal morbidity rate (SREs/year) vs ZA (0.64 vs 0.80). Overall rates of disease progression, survival and serious adverse events (53% denosumab, 56% ZA) were similar in both groups. Osteonecrosis of the jaw occurred in 30 (1.6%) denosumab patients and 25 (1.3%) ZA patients.
Gnant et al (#533) updated the results of the ABCSG-12 trial, adding ZA to endocrine therapy in early breast cancer. The study has now 62 months follow-up and looked in a randomized study at the effect of ZA addition to tamoxifen or anastrazole in 1,803 patients. ZA reduced the DFS with 32% and the OS with 34%, confirming the initial findings that ZA has an impact not only on SRE but also on the disease itself. An analogous study was reported in multiple myeloma where in a randomized study the impact of ZA in 1,970 patients resulted in a benefit of 5.5 months of OS and 2 months of PFS (#8021). Furthermore ZA proved to be cost-effective in prostate cancer patients (429 patients), based on the reduction of SREs in this group (#4679).

Miscellaneous
Hot flashes used to be a hot topic but has lost attention at ASCO 2010: only 4 posters looked at the impact of a specific intervention. One study confirmed the effect of gabapentin (900 mg or less) in prostate cancer patients under androgen deprivation (#9139), another revelad that women preferred venlafaxine over gabapentin, even if efficacy was equal (#9023), and a third one studied the effect of a stellate ganglion block (#9104), again resulting in an acceptable control in about half of the patients. Maybe a less expensive measure is oral magnesium which in a small study (29 patients) confirmed the classical outcome of this type of studies: about 50-60% control during a few months.
Hematological support is also out of the spotlights. Nevertheless J.-L. Canon reported a study where the risk for transfusion was explored in relation to the baseline hemoglobin level of starting darbepoetin (#9077). It was evident from this study that initiating darbepoetin close to 10 g/dl Hb reduced the need for subsequent transfusions, and that the ultimate goal of achieving a non-anemic status was easier to reach if starting up the darbepoetin was not delayed. This study also revealed that the nummer of deaths in the group (705 patients) increased with lower baseline Hb levels, without any difference in incidence of venous thrombosis events (4.4-6.8%).
The effect of the newer targeted therapies on the risk of anemia is rather unknown. A meta-analysis including 6,455 patients revealed that bevacizumab reduced the risk for anemia with about 38 % (HR: 0.72, p=0.005) compared to the same chemotherapy without this drug. The effect was not dependent of type of chemotherapy or type of tumour or of the dose of bevacisumab (2.5 vs. 5 mg/kg/week) (#9136).
An expected result was described in a study where ALD518, an anti-IL6 antibody was studied for its effect on CRF. In 38 out of 93 pts with anemia this resulted in an increase of 2 g/dl Hb level after about 12 weeks (#7631).
Overdose of 5-FU is not so frequent but in a poster it was stated that at least 1,300 patients per year died in the US due to this fact, and that another 8,250 people had life-threatening toxicities. In this poster the case reports of 24 patients overdosed were studied: only 3 survived. These historical data were reported to prove that if uridine triacetate was given as an antidote (2,100-10,000 mg) most of them should have recovered (34 patients treated, no deaths) (#9084).
Last item to remember is the confirmation that warfarin is inferior in the prevention of cancer related venous thromboembolism (VTE) and low molecular weight heparin is the first choice of therapy (#9115), and furthermore that 19% of patients with pancreatic cancer do have a VTE (6,780 patients studied) at one or another moment of their shortened life (#4062).