45th annual meeting of the American Society of Clinical Oncology

Highlights of the 45th annual ASCO meeting, May 29 – June 2 2008, Orange County Convention Center, Orlando, Florida, USA

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Summary

From the 29th of May until the 2nd of June, the 45th annual meeting of the American Society of Clinical Oncology (ASCO) was held at the Orange county convention center in Orlando, Florida. The ASCO meeting attracted more than 30,000 attendees and again proved to be the premier educational and scientific event in the oncology community. Only 49% of the attendees were domestic, demonstrating the international character of the meeting. 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 three 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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Head and neck cancer

The oral presentation session on head and neck cancer held during 2009 annual ASCO meeting revealed some interesting and useful results of recent clinical trials.

Biomarkers in head and neck cancer

Dr. Gillison presented outcomes by tumor human papillomavirus (HPV) status in stage III-IV oropharyngeal cancer in the RTOG 0129 trial (*Abstract #6003*). In general, more and more data are suggesting the favourable prognosis for HPV-positive oropharyngeal cancers. In this randomised phase III trial comparing standard fractionation radiotherapy (RT) and cisplatin (100 mg/m² day 1,22,43) to accelerated fractionation RT and cisplatin (100 mg/m² day 1,22), a correlative study was performed to evaluate the association of tumor HPV status and survival. Sixty point six percent of the evaluable cases (209 patients) were HPV16-positive. Tumor HPV status was strongly associated with overal survival (OS) and progression free survival (PFS) among oropharyngeal cancer patients receiving standard of care chemo-radiation. HPV status should be a stratification factor for all clinical trials including oropharyngeal cases. Moreover separate trials on tumor HPV status should be considered.

Another HPV evaluation was presented by *Dr. Rischin* (*Abstract #6004*). In this trial, patients with stage III or IV head and neck squamous cell carcinoma were randomised to receive definitive RT with cisplatin or cisplatin plus tirapazamine (an experimental anticancer drug that is activated to a toxic radical only at very low levels of oxygen). HPV16/18 status was detected using in situ hybridization while p16 expression was analysed using immunohistochemistry. A total of 384 patients was evaluble for this analysis. The prognostic significance of tumor HPV status was confirmed. It seemed that HPV negative / p16 positive population had a better prognosis compared to patients with HPV negative / p16negative tumors.

Furthermore, *Dr. Licitra* (*Abstract #6005*) showed

that the EGFR gene copy number, as determined by FISH, was not a predictive biomarker for Cetuximab efficacy in relapsed and/or metastatic squamous cell carcinoma of the head and neck as investigated in the *EXTREME* study.

Radiotherapy modifiers

In his presentation, *Dr. Overgaard* discussed the results of the *DAHANCA10 trial* (*Abstract #6007*). This study aimed at evaluating the correction of low haemoglobin levels by means of darbopoetin alpha during radiotherapy and the influence on survival in patients with squamous cell carcinoma of the head and neck. Corrections of the haemoglobin level with darbopoetin in this patient population resulted in a significantly poorer tumor control after radiotherapy.

Chemotherapy clinical trials in head and neck cancer

A phase III randomised, placebo controlled trial of docetaxel with or without gefitinib in recurrent or metastatic squamous cell carcinoma of the head and neck was discussed by *Dr. Argiris* (*Abstract #6011*). Results showed that the addition of gefitinib to docetaxel was well tolerated and improved the time to progression (2 versus 3.5 months) in previously treated patients. However, no effect was seen on survival.

The preliminary results of the phase II *TREMPLIN study* were presented by *Dr. Lefebvre* (*Abstract #6010*). This study reports on sequential chemoradiotherapy for larynx preservation.

According to *Dr. Lefebvre*, 2 validated options are present for larynx preservation to date: chemoradiotherapy based on cisplatin and induction chemotherapy with docetaxel, cisplatin and 5FU (TPF) followed by RT in good responders. However, none of these approaches has improved survival so far. The *TREMPLIN trial* was initiated to answer the following question: is it possible to combine both approaches and is induction TPF followed by RT with Cetuximab able to improve efficacy and tolerability? Previously untreated patients with squamous cell carcinoma of the larynx or hypopharynx who were suitable for total laryngectomy were included in the trial. All patients initiated 3 cycles of TPF. If less than PR, total laryngectomy was performed, if more than PR, patients were randomised between RT 70 Gy + cisplatin (100 mg/m² d1,22,43) and RT 70 Gy + Cetuximab weekly. After TPF induction chemotherapy, the objective response rate was as expected 85% allowing continuation of the larynx preservation protocol. TPF-induced toxicity precluded further cisplatin in some cases. The overall toxicity of TPF followed by RT + cisplatin was substantial. Due to a better overall toxicity profile, TPF followed by RT-cetuximab improved compliance to treatment and was more manageable. No final results of the trial could be presented yet.

The results of the randomised phase III trial comparing induction chemotherapy with cisplatin/5FU(PF) or docetaxel/cisplatin/5FU (TPF) followed by chemoradiotherapy versus chemoradiotherapy alone as first-line treatment of unresectable locally advanced head and neck cancer were eagerly awaited. The data of this trial were presented by *Dr. Hitt* (*Abstract #6009*). Chemoradiotherapy remains the current standard of care for patients with unresectable locally advanced head and neck cancer. Moreover, induction chemotherapy with docetaxel improves survival versus induction chemotherapy with PF. A phase II trial conducted by *Paccagnella et al* (in press) showed that induction chemotherapy with TPF plus chemoradiotherapy significantly improved response rate versus chemoradiotherapy alone. Patients with unresectable locally advanced tumors of the oral cavity, oropharynx, hypopharynx and larynx were included in this trial. Patients were randomised between chemoradiotherapy (with cisplatin 100 mg/m² d1,22,43), 3 cycles of PF followed by the same chemoradiotherapy and 3 cycles of TPF followed by chemoradiotherapy. Primary endpoint of the trial was time to treatment failure (TTF). Of the 439 patients enrolled, 155 patients received TPF, 156 received PF and only 128 patients received chemoradiotherapy alone. Only patients that received at least 1 cycle were evaluated. *Dr. Hitt* stated that patients who received induction chemotherapy had a TTF of 12.5 months while patients treated with chemoradiotherapy alone reached a TTF of only 4.9 months meaning that induction chemotherapy followed by chemoradiation should be considered standard treatment. *Prof. Vermorken* and the audience discussed the trial extensively after the presentation by *Dr. Hitt*. The results shown on the slides of *Dr. Hitt* demonstrate hazard ratios for the PF arm as effective as the TPF arm. *Dr. Hitt* stated that the most important objective of the trial was to compare induction chemotherapy followed by chemoradiotherapy with chemoradiotherapy alone. His slides discussing TTF and time to progression showed only 2 curves (induction chemotherapy versus no induction chemotherapy). It can be considered a problem that there was an interim analysis done that was reported at ASCO 2006 while the study was still running. In 2006, 3 arms were reported which showed a benefit for the TPF arm over the other 2 arms and in the slides presented at the 2009

meeting, the audience was confronted with a 2-arm asessment. The discussion revealed the fact that based on this trial, we cannot conclude that we have a new standard mainly because of the fact that there were unexplained patients excluded from the efficacy analysis. Therefore, an intention to treat analysis is needed.

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Breast cancer

Although ASCO 2009 did not include the presentation of practice-changing clinical trials, there were a number of important key messages for clinical practice were reported.

The "BRCAness" phenotype emerges as a exciting therapeutic target

Triple negative breast cancer (TNBC) is characterized by an aggressive clinical course without established targeted therapies. The 2009 Annual Meeting established "BRCAness", or traits that certain sporadic breast cancers share with BRCA1/2 mutated breast cancer, as an exciting therapeutic target for TNBC. The hallmark of BRCA1/2 mutation associated cancers is dysfunction in the homologous recombination pathway of DNA repair. Preclinical experiments have shown that inhibition of an alternative pathway of DNA repair with a poly(ADP-ribose) polymerase inhibitor (PARPi) in BRCA1/2 mutated BC models can selectively kill breast cancer cells while sparing non-cancerous host cells. During the plenary session, *Dr. O'Shaughnessy* presented the preliminary results from the first randomized phase II trial with a PARPi (BSI-201) (*Abstract #3*). In this study, 113 patients with advanced TNBC and unknown BRCA1/2-mutation status were randomized to a regimen of weekly Carboplatin (AUC 2) / Gemcitabine alone or in combination with BSI-201. This platinum-based chemotherapy regimen was selected to induce DNA damage and synergize with the PARPi. Remarkably, the addition of BSI-201 increased the overall response rate to 48% from 16% (p= 0.002) and the clinical benefit rate to 62% from 21% (p= 0.0002) in this heavily pre-treated population. The BSI-201 arm experienced significantly improved progression free survival (HR= 0.342, median PFS 6.9 vs 3.3 months, p< 0.0001) and overall survival (HR= 0.348, median OS 9.2 vs 5.7 months, p= 0.0005) with a similar incidence of treatment-related toxicity. *Dr. Tutt* also reported the results of a phase II trial with two dosing cohorts of an alternative PARPi alone (AZD2281, olparib) in known BRCA1/2-mutated advanced breast cancer (*Abstract #CRA501*). The observed response rate in the higher dose (400mg BID continuously) cohort (N= 27) was 41% as compared with 22% in the lower dose (100mg BID continuously) cohort (N= 27). Olparib was well-tolerated, although there was a higher incidence of fatigue, nausea, and vomiting in the 400mg BID cohort.

Bevacizumab prolongs PFS but does not improve survival for advanced disease

In the *RIBBON-1* study 1,237 women were randomized in a 2:1 manner to bevacizumab or placebo combined with chemotherapy across two cohorts (*Abstract #1005*). The first cohort included capecitabine chemotherapy (cohort 1) and the second either anthracycline or taxane therapy (cohort 2). Similar to the *E2100* and *AVADO studies*, *RIBBON-1* demonstrated an improvement in PFS (cohort 1: HR= 0.69; median PFS 8.6 months vs. 5.7 months; p= 0.0002; cohort 2: HR= 0.64; median PFS 9.2 months vs. 8.0 months; p< 0.0001) but no difference in OS (cohort 1: HR= 0.85; median OS 29.0 months vs. 21.2 months; p= 0.27; cohort 2: HR= 1.03; median OS 25.3 months vs. 23.8 months; p= 0.83). An increase in bevacizumab-related toxicities, namely hypertension, proteinuria, and bleeding events, similar to prior trials was seen in the bevacizumab arm. These results confirm that the activity of bevacizumab as first-line therapy for metastatic disease is not chemotherapy

specific, but do not provide a compelling rationale to routinely use bevacizumab in daily clinical practice.

Conflicting results regarding the influence of CYP2D6 in tamoxifen-related outcome

Conflicting results from two similarly designed studies were presented regarding the outcome of women treated with adjuvant tamoxifen who were co-prescribed medications known to inhibit cytochrome P450 2D6 (CYP2D6). Tamoxifen is metabolized primarily by the CYP2D6 system to yield endoxifen, a potent metabolite believed to be responsible for the anti-cancer activity of tamoxifen. Over the past five years, numerous retrospective studies have suggested that genetic variants of CYP2D6 associated with reduced enzymatic activity and co-administration of CYP2D6 inhibitors may lead to poorer outcomes with tamoxifen therapy. Using an American medical and pharmacy claims database, *Dr. Aubert* reported that concomitant use of tamoxifen and a moderate/potent CYP2D6 inhibitor was associated with an 1.92 increased risk of breast cancer recurrence (14.0% with inhibitor vs. 7.5% without inhibitor, p< 0.0001) (*Abstract #CRA 508*). In contrast, *Dr. Dezentje* reported that concurrent CYP2D6 inhibitor use with tamoxifen was not associated with an increased risk of recurrence (HR= 0.95; p=0.73) (*Abstract #CRA 509*). It is difficult to resolve how two similarly designed studies could report such conflicting findings. There may have been systematic differences in methodology that may account for these differences.

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Lung cancer

JMEN trial: pemetrexed as maintenance therapy

In the *JMEN trial* patients who did not progress on four cycles of non-pemetrexed containing platinum-based chemotherapy, were randomized to maintenance with pemetrexed (N= 441) or placebo (N= 222) (Abstract #CRA8000). Patients treated with pemetrexed had a clinically and statistically significant improvement in overall survival (OS) (HR= 0.79; p= 0.012). Tumor histology was predictive for the beneficial effect of pemetrexed maintenance: in the nonsquamous subgroup median OS was 15.5 months in the pemetrexed-arm compared with 10.3 months in the placebo-arm (HR= 0.70; p= 0.002), while patients with the squamous histology did not benefit (9.9 months vs. 10.8 months; HR= 1.07). The administration of pemetrexed in the maintenance setting is fairly well tolerated and devoid of any cumulative toxicity (3% grade 3 / 4 neutropenia and no drug-related deaths).

SATURN trial: erlotinib as maintenance therapy

The *SATURN trial* (N= 889) explored the effect on progression-free survival (PFS) of erlotinib given immediately following four cycles of 1st-line treatment to non-progressing patients (Abstrcat #8001). The PFS was significantly improved for all patients receiving erlotinib (6 months PFS rate: 32% vs. 18%; HR= 0.69; p< 0.001) and this survival benefit was seen in all "clinical subgroups" (i.e. irrespective of gender, histology, race, or smoking status). The biomarker analysis showed that a significant PFS benefit was seen in both EGFR-wild type and EGFR mutant patients, but the effect was significantly larger in the EGFR mutant patients (HR= 0.78 in wild type EGFR vs. HR= 0.10 in mutant EGFR).

ZODIAC trial: vandetanib in 2nd line treatment

In the *ZODIAC trial* 1,391 patients were randomized to 2nd-line treatment with either docetaxel + vandetanib (an oral TKI of VEGFR, EGFR, and RET signaling), or docetaxel + placebo (Abstract #CRA8003). Adding vandetanib resulted in a significant prolongation of the PFS (6-month PFS 28% vs. 22%; HR= 0.79; p< 0.001). Both the overall response rate (17% vs. 10%; p< 0.001) and the time to deterioration of symptoms were also significantly improved for patients receiving vandetanib (HR= 0.77; p< 0.001). The survival benefit was seen irrespective of gender, histology, race or biomarker status. The overall survival showed a non-significant trend in favor of the vandetanib arm (HR= 0.91; p= 0.196; 1-yr OS 45%

vs. 41%). However, the OS data are immature as over 40% of patients were censored at the time of analysis and may be influenced by subsequent therapy.

NATCH trial: role of adjuvant or induction chemotherapy in early stage NSCLC

In the *NATCH trial*, 624 patients with clinical stage I (> 2 cm), II, T3N1 were randomized to surgery alone, or surgery followed by adjuvant chemotherapy, or induction chemotherapy followed by surgery (Abstract #7500). In the induction chemotherapy arm 93% of the patients received all 3 planned chemotherapy cycles, while in the adjuvant arm this was only 65%. The study was powered to detect a 15% absolute improvement in 5-year disease-free survival (DFS). Given the fact that 77% of patients had clinical stage I disease, it is not surprising that the DFS was not significantly different between the different study arms. However, in the patients with clinical stage II or T3N1 disease (N= 154) a trend towards longer DFS in favor of induction chemotherapy was observed (5-yr DFS 25% surgery vs. 31% adjuvant chemotherapy vs. 37% induction chemotherapy; HR= 0.81, p= 0.07).

Molecular and clinical predictors of outcome from the FLEX trial

The biomarker analyses showed that the EGFR-related markers (IHC, FISH or mutation analysis) and the KRAS mutation are not predictive for cetuximab-efficacy in NSCLC. However the occurrence of early acne-like rash of any grade was associated with better outcome in patients treated with platinum-based chemotherapy plus cetuximab (median OS 15.0 m *vs.* 8.8 m; HR 0,63; *P* <0.001). *[Abstract #8007]*

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