Annual meeting of the American Society of Clinical Oncology (ASCO) 2010 - Part 2

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

From the 4th until the 8th of June, the 46th annual meeting of the American Society of clinical oncology (ASCO) was held in Chicago, Illinois. The ASCO meeting attracted over 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 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. The first part of the report, published in the August issue of the BJMO, focussed on gastrointestinal cancer, head and neck cancer, supportive care and new agents emerging from the lab into the clinic. This second part of the ASCO report addresses novelties in breast, lung and urogenital cancer. All abstracts referred to in this report can be consulted at the ASCO website (www.asco.org)

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Urogenital cancer

This year, a total 176 abstracts were devoted to genitourinary cancers, dispatched in 5 sessions. This summary will primarily address data that are likely to impact on practice within the next year. Phase I/II with new agents and "trial in progress" abstracts were not selected. When relevant to the discussion, historical data were reported and referenced.

Prostate cancer, a vintage year?

Treatment of high-risk locally-advanced hormone-naïve prostate cancer (PCa): emphasis on the role of local control.

Androgen deprivation therapy (ADT) is very often used as a the sole treatment of locally advanced PCa (stage T3-4; N1-2), although the EORTC Study 30891 already demonstrated that ADT confers only a marginal benefit in survival. The SPCG-7 study, published in 2009, was the first to demonstrate that the combination of ADT and external beam radiotherapy (EBRT) was better than ADT alone in term of PCa specific and overall survival. This study, however, was conducted with the antiandrogen flutamide only, which may have weakened the effect of ADT. Two pivotal trials confirm that hypothesis. *Warde et al.* have reported on intergroup phase III trial comparing ADT + EBRT *vs.* ADT in 1205 locally advanced PCa

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(#CRA4504). ADT was administered by bilateral orchiectomy or lifelong LHRH agonist. The addition of EBRT to ADT significantly increased overall survival (OS) (HR: 0.77, p=0.033) and PCa specific survival (HR: 0.57; p=0.001); 10-year PCa death rates being 15% with ADT/EBRT and 23% with ADT alone. Grade ≥2 late gastrointestinal toxicity rates were similar in both arms. Concomitantly, *N. Mottet et al.* reported the results a French trial on 263 patients, comparing ADT to ADT + EBRT, with ADT being administered for a fixed period of 3 years only (#4505). The 5 years progression free survival (PFS), including PSA, was 60,9% for ADT/EBRT *vs.* 8,5% for ADT (p<0,001). The 5-year clinical PFS (excluding PSA) was 88,7% for ADT/EBRT *vs.* 62,3% for ADT (p<0.001). Although the latter study is not mature yet for survival results, these data confirm that in locally advanced (T3-4 N1-2 M0) PCa, local treatment should never be omitted, since ADT alone only moderately increases survival. In addition, the French trial suggests that the duration of ADT could be significantly shortened when ADT is combined to EBRT.

Treatment of castration resistant prostate cancer (CRPC): new drugs and new promises

Until 2004, the treatment of PCa was limited to ADT, and options for CRPC were limited to purely palliative care. Two seminal trials, published in 2004, have changed the management of metastatic CRCP: the TAX327 and SWOG9916 studies have demonstrated that tri-weekly docetaxel extends survival of patients by almost 3 months and the publication of the long-term results of the zoledronic acid trial demonstrated that zoledronic acid delayed the induction of skeletal related events (SRE) by 4 months. These studies have impacted on the everyday management of PCa, not only because of the activity of these two drugs but more importantly because it motivated collaboration between urologists and medical oncologists. Despite an intensive search for successor drugs, that field was left empty until now. 2010 will indeed be the new vintage year, with three new drugs soon to be approved: sipuleucel T, the first ever registered vaccine therapy in PCa, the new taxane cabazitaxel, that extends survival by 3 months in docetaxel treated patients, and the Rank-L inhibitor denosumab, that may extend the time to SRE by 3 months.

J.S De Bono has reported on the updated results of study with the novel taxane cabazitaxel (Cbz) in 755 mCRPC previously treated with docetaxel (#4508). Cbz 25mg/m2 was compared to mitoxantrone 12mg/m2 (M), both combined to 10mg/day prednisone. CbzP confers a statistically significantly longer OS (15.1 months) compared with MP (12.7 months) (HR:0.70; p<0.0001). PFS, response rates, and time to progression (TTP) are also significantly better with Cbz. Most frequent grade ≥ 3 toxicity was neutropenia (81.7% for Cbz *vs.* 58.0% for M), including febrile neutropenia (7.5% for Cbz *vs.* 1.3% for M). This study was commented by *I. Tannock*, who highlighted a 5,1% toxic dead rate in the Cbz treated patients and the lack of robust data on quality of life. Whether the former results from a poor management of side effects in some European centers (the death rate is 1,5% in US) or just reflects the toxicity of a high dose of Cbz for a heavily pretreated population of old men, is not clear yet. Parallel to that study, *Fizazi K et al.* released the results of the phase III trial comparing the Rank-L inhibitor denosumab (Dmab; 120mg SC q4w) to zoledronic acid (ZA; 4mg IV q4w) in 1,901 patients with bone metastases from mCRPC (#LBA4507). The RANKL/RANK pathways is central in the tropism of PCa cells to the bone microenvironment and controls the local "vicious circle" allowing bone metastasis to develop and interfere with the normal bone remodeling. Dmab significantly delayed the time to first on-study SRE by 3.6 months compared with ZA. The median time to first on-study SRE was 20.7 months for Dmab *vs.* 17.1 months for ZA (HR:0.82; p= 0.008). Overall, adverse event rate was similar for both drugs. However, osteonecrosis of the jaw occurred in 2.3% of the patients receiving Dmab and in 1.3% of the patients treated with ZA patients (p= 0.09). OS and TTP were similar between treatment arms. Noteworthy, a large number of SRE were asymptomatic fractures that were unveiled by the extensive X-Ray study work-up, thus questioning the true relevance of the observed benefit.

Sipuleucel-T is an investigational autologous active cellular immunotherapy that was recently approved by the FDA for the treatment of CRPC6. The drug was approved on the pooled results of 2 trials and concerns have been raised that the observed survival

benefit of sipuleucel-T resulted from subsequent treatment with docetaxel. To verify that hypothesis, *D. Petrylak et al* have analyzed the effects of post-randomization docetaxel on OS. Across the 3 studies that were included in the analysis, sipuleucel-T treatment was associated with a 26.5% reduction in risk of death (HR: 0.735, p< 0.001). Treatment with docetaxel was reported in 363 patients (49%). Patients with subsequent docetaxel had better OS compared to those without, but when entered as a time-dependent covariate, docetaxel was not a significant predictor of OS (HR: 0.941, p= 0.54), and the sipuleucel-T effect remained significant (HR: 0.736, p< 0.001).

In contrast with these promising developments, it is worth noticing the final negative results of the ASCENT 2 trial that compared docetaxel (D) plus high-dose calcitriol (DN-101) versus D plus prednisone (P) for CRCP patients (#4509). This trial conducted in 953 men showed an inverted benefit on its primary endpoint of OS, the combination of docetaxel and DN-101 being associated with a shorter survival (HR: 1.33; p= 0.019) of 3 months. Interestingly, the docetaxel regimen was different in the two arms; 36mg/m2 weekly in combination with DN-101 *vs.* a standard dose of 75mg/m2 D every 3 weeks in the docetaxel alone arm. This to some extent may explain why the study failed.

Integration of anti angiogenesis agents, still a question

The significance of angiogenesis in PCa is well established. Many studies have demonstrated its direct correlation with Gleason score, tumor stage, progression, metastasis and survival, providing an excellent rationale for anti-angiogenic therapies. Preclinical and early phase II studies have confirmed the activity of vascular endothelial growth factor (VEGF) blockade and tyrosine kinase inhibition (TKI). Unfortunately, final confirmation of clinical impact is still awaited. *Kelly et al.* have reported the results of the CALGB 90401A phase III trial comparing bevacizumab (BDP) 15mg/kg q3w) to placebo (DP) in combination with docetaxel (75mg/m2 q3w) and prednisone (5mg BID) (#LBA4511). The study enrolled 1,050 patients with chemotherapy naïve metastatic CRPC. Despite an improvement in PFS (9.9 months for BDP *vs.* 7.5 months for DP; p<0,0001) and post-therapy PSA decline ≥ 50% (70% for BDP *vs.* 58% for DP; p=0,0002), the addition of bevacizumab to docetaxel did not improve OS (22.6 months for BDP *vs.* 21.5 months for DP; p=0,181), and was associated with more grade ≥ 3 toxicity (74.8% for BDP *vs.* 55,3% for DP; p<0,001). The earlier results of the competitive trial assessing the efficacy of VEGF-Trap in combination with docetaxel are expected for next year.

Renal cell carcinoma (RCC), evolving standard of care

After five years of incredible developments, there has been no major breakout reported during the meeting. As a result, this was a good opportunity to pause and try to design a rational approach for this disease. This was the challenge taken by *C. Ryan* from the Oregon Health and Science University. In 2010, physicians treating RCC will have access to 8 registered drugs: IFα, IL2, sunitinib, sorafenib, bevacizumab, everolimus, temsirolimus, and the last kid on the block pazopanib. All these treatment, except everolimus, were approved as first line therapy based on PFS improvement. OS data were not clinically significant, most probably because of a high rate of crossover from one treatment to another resulting in a washout of the survival data. A fierce competition has emerged between companies, resulting in confusing recommendation. Interestingly, *C. Ryan* managed to extract important messages from the current cacophony:

- To the question "what is the best first line treatment?", he provokingly answered "Choose any agent, but use it at the highest dose for the longest duration". As a main argument, he repeated that there are no comparative data and that many inclusion criteria were chosen arbitrarily for strategic rather than scientific reasons. In addition, there is little evidence that the risk group stratifications used to promote one drug over another are relevant to biological activity. He reminded that in a well-selected population of low-burden metastatic disease in patients in very good condition, high dose IL-2 was the only treatment providing long-term remission. *Donskov et al.* have confirmed that observation in a retrospective review of 422 consecutive patients treated by IL-2 between 1999 and 2008 (#4591). At a median follow-up of 76 months, 9% of patients showed no evidence of disease. The 10-year survival rate

was 10%. Similarly, *McDermott et al.* reported new data on high dose IL-2 (#4514). 121 RCC patients (71% MSKCC intermediate risk, 96% clear cell histology) were treated with 600,000 IU/kg IL-2 IV q8h for 5 days, starting on day 1 and 15 every 12 weeks, maximum 28 doses. Response rate (RR) was 29% (7 CR, 28 PR), thus significantly greater than the historical RR (95% CI: 21%-38%, p<0.0009).

- Regarding the role of sequencing, *C.Ryan* first acknowledged that sequencing has become de facto standard of care although there is no clear demonstration that it prolongs survival. The only indirect evidence is the comparison of the survival reported in the historical MSKCC model to contemporary model that *Heng et al.* validated for trials with VEGF-targeted agents. Doing so, it appears that for each of the risk categories there is an apparent increase in OS. This observation is contradicted by the epidemiological survey of *D. Shek et al.* that have analyzed 28,252 RCC patients from the California Cancer Registry and compared the pre targeted therapy (1998-2003) and the targeted therapy (2004-2007) eras (#4598). They have observed that the RCC frequency has increased but they could not detect a significant trend in OS and cancer specific (CSS) survival. 3 year cause-specific survival for distant stage was 19.6% and 20.5% before and after introduction of targeted therapies. The author concludes that the OS benefit from targeted therapies has not yet translated into the general RCC patient population. This confirms *Ryan's* observation that overemphasis on sequential PFS benefit is distracting from the fact that comparison should be performed only on OS and quality of life.
- Finally, *Ryan* addressed the emerging field of combination to conclude that so far only combinations with an immunomodulating agent were proven to be acceptable in term of toxicity. *Escudier et al.* investigated the combination of temsirolimus and bevacizumab (N=88) (#4516). The combination was stopped in 43% of patients and resulted in 36% G3/4 toxicity. In addition, there was no evidence of a synergistic/additive efficacy of this combination. *Ryan et al.* tested the combination of sunitinib and erlotinib in 37 patients and made similar conclusions (#4528). There was 22% G3/4 rash and 11% diarrhea, and the 8-month PFS rate of 39% (95% CI: 22-55) did not suggest improvement over a monotherapy with sunitinib. In contrast, *Dandamudi et al.* tested a combination of bevacizumab and high-dose IL-2 (600,000 IU/kg q8h, 2 X 5-day courses on day 15 and 29 of each 84 day, max 28 doses) (#4530). Median PFS was 9.0 months (90% CI: 5.7 -13.0) and 2 year PFS was 15% (90% CI: 5-24%), while toxicities appeared to be no different from single agent IL-2 or bevacizumab alone. Of note, *Plimack et al.* demonstrated that Sunitib treatment was ineffective in RCC with papillary histology. In a series of 23 papillary RCC, sunitinib yielded no major responses and short PFS (median 1.6 months) and OS (median 10 months) (#4604)

Testis cancer: confirming the role of active surveillance in stage I germ cell cancers (GCC)

This year the Belgian National College of Oncology, in collaboration with the KCE, will release the second version of the guidelines on germ cell cancer (GCC) of the testis. Annexed to the guidelines, there will be a set of clinical indicators developed to monitor compliance to the guidelines and variations in practice pattern. Physicians involved in the treatment of testis cancer may question that attitude, usually considering that the treatment of testis cancer is well documented and straightforward, as well as compliance to the guidelines. At least, this is no longer what our French colleagues believe. *Culine et al.* conducted a survey evaluating the management of GCC in France and compliance with national guidelines (#4580). The charts from 256 patients with seminoma (SGCC) and 197 with non-seminoma (NSGCC) were analyzed, including 69% stage I, 16% stage II, and 16% stage III. Globally, only 10% of patients with SGCC and 12% with NSGSS were managed in line with the guidelines; treatments recommendations were followed for 44% of NSGCC and 28% of SGCC.

The clearest trend seen in testis cancer was the emerging role of active surveillance for stage I GCC. This trend is fueled by accumulating reports on long-term toxicity, especially regarding the risk of secondary cancer and cardiovascular disease (CVD). *Leung et al.* have reviewed the charts of 764 Canadian stage I SGCC patients, treated between 1981 and 2004 (484 surveillance and 280 adjuvant RT) (#4534). First relapse on surveillance was

managed by EBRT alone, then by chemotherapy. OS at 5 and 10 years was 98% and 95%, respectively. Only 15% of the patients in the surveillance group received treatment. Only 4% of both group received salvage chemotherapy, allowing the author to conclude that active surveillance of stage I SGCC allows to significantly reduce the overall burden of treatment. *Nichols et al.* analyzed the data of 2 large testis cancer programs in British Columbia and Oregon (#4536). A total of 649 pts were managed from 1999-2008, including 545 stage I. They have observed a dramatic decrease in the utilization of prophylactic radiation (from 48% in 2000 to 7% in 2008), and increased use of active surveillance (from 46% in 2000 to 75% in 2008). No cancer related deaths were reported in the stage I SGCC treated with surveillance with median follow-up of 39 months. These results resonate better in light of the reported data on toxicity. *Lewinshtein et al.* investigated the risk of secondary malignancy in 8,590 SGCC patients from the US SEER database treated with radiation therapy between 1973 and 2006 (#4537). The rate of lymphoma and leukemia was 61.01 cases per 100,000 persons/year; thus 44% higher than the NCI published rate for a similar population. The rate of bladder cancer was 4.0 cases per 100,000 persons/year, 19% higher than national averages. *Horwich A et al.* reported similar results on a cohort of 2,703 long-term survivors of SGCC patients treated with radiotherapy in the UK and Norway (#4538). The excess of second cancers in long-term survivors was statistically significant (standard incidence ratio (SIR) 1.31; 95% CI 1.19-1.45); especially as regard to stomach (SIR 1.63), pancreas (SIR 2.35), and bladder cancers (SIR 2.14). *Haugnes et al.* investigated cardiovascular disease (CVD) in 990 long-term Norwegian GCC cancer survivors and matched their results to 990 male controls from the general population (#4533). Over a median observation period of 19 years, 9.9% of the GCC survivors experienced CVD events. Increased risks for CVD were observed after any non-surgical treatment: HR for radiation therapy (RT): 2.3, for chemotherapy: 2.4, and for RT/chemo: 5.2. This data should accelerate the trend toward an expectant management of stage I GCC.

On the other extreme of the disease, there is clearly an attempt to improve the management of poor prognosis GCC. *G. Daugaard* reported the result of intergroup trial EORTC 30974 standard dose BEP with sequential high-dose cisplatin, etoposide, ifosfamide (VIP) plus stem cell support in men with poor prognosis germ cell cancer (GCC) (#4512). The study failed to recruit the 222 preplanned patients, and the present analysis, performed on 137 patients, failed to show any benefit from the high-dose chemotherapy (HD-CT). Complete response rates (CRR), failure-free survival (FFS), and OS did not differ between groups, while toxicity was more severe in pts on HD-CT.

Breast cancer

During the 2010 ASCO meeting several presentations of practice–changing clinical trials as well as some interesting data related to disease biology were presented

Practice–changing clinical trials

The large and mature NSABP-B32 trial enrolled over 5,000 clinically node-negative patients and randomized them to sentinel lymph node (SLN) dissection with or without axillary lymph node dissection (ALND) in case of a negative SLN by routine pathological examination (N= 3,989 pts). The trial, powered to detect a 2% difference in overall survival, shows no difference at a median follow-up of 95 months and provides definitive evidence that ALND on top of SLN does not provide clinical benefit. This is also true for locoregional control (axillary relapses 0.3 *vs.* 0.1%!) (#LBA505)

The ACOSOG Z0011 trial asked a similar question but this time for clinically node negative patients having 1 or maximum 2 positive SLN (by H&E) (#CRA506). Closed early with only half of its anticipated patient population recruited (N= 891/1,900), the trial shows no difference in locoregional control at a median follow-up of 6.3 years (2.8% locoregional regional relapses for SLN dissection only and 4.1% for ALND). A negative impact on OS (which was the primary endpoint with the need to show a difference <3%) is very unlikely given the loco-regional results and therefore this trial does not support routine use of ALND in this particular group of patients (#CRA506).

The Intergroup CALGB 9343 trial randomized 631 clinically node-negative elderly women with small (≤2 cm) endocrine responsive tumors to tamoxifen with or

without breast radiotherapy. At 12 year median follow-up, the only clinical benefit of RT is a slight reduction in "in breast" relapses (from 9% to 2%) without a significant increase in secondary mastectomies (4% *vs.* 2%). All other outcomes are similar and it must be noted that only 3% of these women die from breast cancer (46% die from other causes). With today's use of aromatase inhibitors, the benefit of RT in these women is likely to be even less (#507).

Practice–influencing results

For medical oncologists, 3 lines of data are likely to influence clinical practice:

- The ABCSG–12 trial, which randomized 1803 premenopausal women with endocrine responsive tumors to receive goserelin + tamoxifen vs. goserelin + anastrozole, each with or without zoledronic acid (ZA) was updated at 62 months median follow-up and sub-analyzed according to BMI. While the ZA beneficial effect on disease recurrence was maintained in both arms (HR: 0.68, p=0.009), a slightly worse OS emerges for goserelin + anastrozole (#533). Moreover, overweight women (e.g. with a BMI ≥25kg/m2) on anastrozole did much worse than on tamoxifen, with almost a doubling in the rate of distant metastases (9% *vs.* 5%) (#512). Although caution must be raised regarding this unplanned subgroup analysis, the use of LHRH agonist with an aromatase inhibitor as adjuvant endocrine therapy should be avoided at the present time.
- A pessimistic attitude towards metastatic breast cancer is no longer permitted: the new antimicrotubule agent, Eribulin, shows a positive impact on survival of heavily pretreated women in a phase III trial of 762 patients *vs.* chemotherapy of physician's choice. The gain of 2.5 months in median survival was larger than the 1.5 month gain in median PFS. Of importance, the safety profile was favourable with dose-limiting neutropenia and only 8% of grade 3 neurotoxicity (#CRA10014).
- Discordant results between tissue analysis of metastatic lesions versus primary tumor have been reported for several years, but all these studies were small, retrospective and based on pathology reports. This year, an elegant prospective UK + Canadian study was reported, with detailed re-analysis of ER, PgR and HER2 on 271 primaries having generated metastases accessible to biopsies. ER receptor loss *vs.* gain was reported in 12 and 14% respectively. HER2 amplification loss vs gain was reported in 12.5 and 4.6% respectively. Importantly, a change in clinical management of the patients occurred in 15% (#1007). Two other studies, one from Italy and one from Sweden, although retrospective in nature, essentially confirmed these results in 255 and 477 patients respectively (#1008, #1009). These data, much stronger than those generated in the past, are an incentive for clinicians to biopsy breast cancer at relapse (with the added benefit that in some cases another malignancy, or even a benign lesion, will be discovered). The possible explanations behind the above discordant findings may include: tissue fixation differences (with more quality in general for the metastatic biopsy); genomic heterogeneity in the primary tumor; selection of a subpopulation of cancer cells through adjuvant medical therapy.

Other selected results of interest to researchers and/or clinicians

- The large (N=5,210), multicentric, prospective ACOSOG Z0010 trial, looking at the prognosis of positive SLN and bone marrow by H&E or IHC, shows no added benefit for routine IHC analysis of SLN at 5y median follow-up (no worsering in DFS or OS for SLN negative by H&E but positive by IHC). It confirms the worse outcome of positive SLN by H&E (92.8% 5y OS *vs.* 95.6%) and the worse outcome of positive bone marrow by IHC (90.2% *vs.* 95.1% 5y OS). Interestingly, positivity of BM is not correlated to positivity in SLN (#CRA 504).
- There is continuing interest in integrating molecular profiling with standard pathology in clinical practice. The "RSPC index" which combines the oncotype-DX recurrence score with pathology and clinical information supplies more powerful prognostic information for early ER positive disease in the context of 2 clinical trials (#509).
- The pharmacogenetics of tamoxifen remains complex! In the Dutch substudy of the TEAM trial (N= 747) CYP2D6 variants are not correlated with DFS in contrast to UGT2B15* 2 (a tam metabolic enzyme) and ESR1 variants (#510).
- Two further randomized clinical trials of sunitinib, in metastatic BC, turn out to be negative, namely

Figure 1. phase III trial on invasive mediastinal staging (ASTER). (#7000).

Patient setting

Resectable stage I-III (suspected) NSCLC requiring invasive mediastinal staging.

Randomization

Endosonography (EUS-FNA+EBUS-TBNA) followed by surgical staging if ES negative (n=123)

vs.

Surgical staging alone (n=118)

Outcome

Primary: detection of N2/3 disease : 50% *vs*. 35% (P=0.02) sensitivity for N2/3 : 94% (95%CI 85-98) *vs*. 80% (95%CI 68-89) (P=0.04).

Other: significantly less futile thoracotomies in strategy starting with endosonography.

Safety

similar complication rates between both arms.

Conclusion

Invasive mediastinal nodal staging of lung cancer should start with endosonography.

the trial of docetaxel (100 mg/sqm) *vs*. docetaxel (75) + sunitinib in 593 patients and the trial of capecitabine (2500mg/sqm) *vs*. capecitabine (2,000mg/sqm) + sunitinib in 442 patients (#LBA1010, #1011). They bring the total number of patients enrolled in "negative" randomized sunitinib trials to 2029 (2 previous trials included 482 patients treated with capecitabine vs sunitinib and 485 allocated to paclitaxel +/- sunitinib).

Respiratory oncology

At the ASCO 2010 meeting, a total of 240 abstracts in the field of respiratory oncology were presented (314 in 2009), 175 posters, 41 poster discussion items, and 17 oral presentations (including two in the plenary session). For this reports, we classified studies as *RCT* (large randomized controlled trial, i.e. >100 patients per arm), *RCT-small* (often phase 2 RCTs), *RCT-sec* (secondary analyses of previously presented RCTs), or *others* (phase 2 studies, retrospective analyses, surveys, etc.). This report concentrates on randomized data relevant for the practicing clinician.

NSCLC – Early stages (stage I-III)

The ASTER study is a randomized trial comparing surgical mediastinal staging alone *vs*. endosonography (ES) followed by surgical staging (only in case of a negative staging with ES) in an unselected patient population with resectable (suspected) NSCLC (#7000) (*Figure 1*). ES is the combination of esophageal ultrasonography (EUS) and endobronchial ultrasonography (EBUS) The prevalence of malignancy in mediastinal nodes was 49%, without a significant difference in prevalence between both study arms. Starting with ES thus significantly improves the detection of mediastinal nodal metastases. The number of patients having to undergo an additional surgical staging procedure in the ES arm in order to identify an additional patient with mediastinal nodal metastasis was 11. Moreover, although the complication rates were identical between the two study arms, only one complication was attributable to the ES procedure (pneumothorax due to EBUSTBNA).

A phase III randomized chemoprevention trial of selenium (Se) supplementation in resected stage I NSCLC failed to show an effect on the prevention of second primary cancers or overall second cancers. (#7004) (*Figure 2*). Smoking cessation thus remains the only effective prevention action which should be undertaken after curative resection of lung cancer.

Adjuvant chemotherapy trials already addressed the possible late chemotherapy-related effects (IALT at ASCO 2008; BR.10 at ASCO 2009). The BR.10 adjuvant chemotherapy trial showed a durable 11% long-term survival benefit without late chemotherapy-related toxicities, but the IALT data raised concerns about late chemotherapy-related toxicities. At ASCO 2010, the long-term survival of the French randomized trial comparing neo-adjuvant chemotherapy versus surgery alone was reported (#7003) (*Figure 3*). Thus, in concordance with the BR.10 adjuvant trial, the French neo-adjuvant chemotherapy trial did not observe any

Figure 2. Phase III chemoprevention trial in resected stage I NSCLC. (#7004).

Patient setting

Resected stage I NSCLC.

Randomization

Selenium yeast 200µg daily PO for 4 years (n=1041)

vs.

Placebo yeast daily PO for 4 years (n=520)

Outcome

Primary: second primary tumor incidence: 1.91 cases *vs*. 1.36 cases per 100 person years (P=0.15)

Other: PFS at 5yrs 72% *vs*. 78% (NS) and OS at 5yrs 75% *vs*. 80% (NS)

Conclusion

Selenium had no effect on the prevention of second primary lung cancer

Figure 3. phase III neo-adjuvant chemotherapy trial in tage IB-IIIA (#7003).

Patient setting

Operable stage IB-IIIA NSCLC.

Randomization

Neo-adjuvant 2 cycles MIC surgery à adjuvant 2 cycles MIC if response (n=179)

vs.

Surgery alone (n=176)

Outcome

Primary: OS at 10y follow-up : 29% *vs*. 21% (HR 0.82; P=0.12).

Other: PFS at 10y follow up: 25% *vs*. 16% (HR 0.78; P=0.03). Second primary cancers were not significantly different between both arms.

Conclusion

Although statistically NS, neo-adjuvant chemotherapy was associated with a long-term survival benefit of 8% at 10 years, the magnitude observed at 5 years was maintained.

Figure 4. phase III adjuvant Gefitinib trial (NCIC CTG BR.19) (#7005).

Patient setting

Completely resected stage IB-IIIA NSCLC.

Randomization

Surgery à adjuvant Gefitinib 250mg daily PO for 2 years (n=251)

vs.

Surgery alone à adjuvant placebo 0mg daily PO for 2 years (n=252)

Outcome

Primary: OS: HR 1.23 [0.94-1.64], P=0.136, median 5.1 years *vs*. not reached.

Other: DFS : HR 1.22, P=0.15. KRAS and EGFR mutation status were neither prognostic nor predictive of survival.

Conclusion

Adjuvant Gefitinib did not improve survival in completely resected NSCLC.

increase in 10-year non-cancer related death rate nor any difference in second primary cancers between both arms. The occurrence of brain metastases did not differ between both arms, but the rate of bone metastases significantly decreased after neo-adjuvant chemotherapy (5 *vs*. 13%; p=0.004).

In 2002, in the absence of positive adjuvant data for chemotherapy, a trial in completely resected NSCLC with the EGFR-TKI Gefitinib was initiated (#7005) (*Figure 4*). In 2005, accrual was stopped

Figure 5. Explorative subgroup analysis of CALGB 9633 (#7008).

Patient setting

77% tumor resection specimens available of completely resected stage IB patients.

Randomization

Surgery à adjuvant Carboplatin-Paclitaxel (n=139/173)

vs.

Surgery alone (n=128/171)

Outcome

KRAS not prognostic, but maybe predictive, especially in tumors ≥4.0 cm.

Conclusion

KRAS mutant patients may have less benefit from adjuvant chemotherapy

Figure 6. Phase III doublet versus single-agent chemotherapy in the elderly NSCLC patients (#2).

Patient setting

Advanced NSCLC, elderly (>70 years) with PS 0-2.

Randomization

Carboplatin AUC=6 every 4 weeks with Paclitaxel 90 mg/m2 on days 1, 8, and 15 (n=225)

vs.

Single agent chemotherapy (Gemcitabine 1150 mg/m2 or Vinorelbine 30 mg/m2, both days 1 and 8 every 3 weeks) (n=226).

Outcome

Primary: OS: HR 0.60 [0.46-0.78], P=0.0001, median 10.4 *vs*. 6.2 months.

Other: PFS HR 0.55 [0.44-0.70], P<0.0001, median 6.3 *vs*. 3.2 months. Safety: hematological toxicity significantly more common, 54.1% *vs*. 17.9%.

Conclusion

Doublet provides a significantly longer survival, making it a new treatment paradigm for PS 0-2 patients above the age of 70.

Figure 7. Phase II extension study with PF-02341066 in ALK positive NSCLC (#3).

Patient setting

Advanced NSCLC, FISH+ for EML4-ALK fusion oncogene, irrespective of previous therapy

Randomization

None, open phase II study with PF-02341066, an oral TKI acting on the ALK and MET/HGF receptor tyrosine kinases, in a dose of 250 mg twice daily.

Outcome

Primary: disease control rate at 8 weeks of 90% in 50 evaluable patients.

Other: response rate 64%. Safety: mainly (mild) gastro-intestinal toxicity (nausea, vomiting).

Conclusion

A new example of how molecularly targeted treatment results in very high disease control rate.

early with 503/1160 patients enrolled as Gefitinib demonstrated compared to placebo (1) no significant improvement in survival in advanced disease (ISEL; second line Gefitinib) and (2) worse survival in locally advanced disease (SWOG0023; maintenance Gefitinib after chemoradiotherapy). Exploratory subgroup analyses showed that (1) the presence of an EGFR activating mutation in the placebo arm was not associated with a prolonged survival (HR 1.06; P=0.66), and (2) a trend for worse OS (HR 1.58; P=0.16) in the EGFR mutant patients with Gefitinib compared to placebo. The results of the RADIANT trial (adjuvant Erlotinib in resected stage IB-IIIA NSCLC) are still awaited.

Currently, clinical 'high risk' predictive markers are used to decide upon adjuvant chemotherapy in early

Figure 8. Phase III on sequencing of chemotherapy and EGFR-TKI (TORCH) (#7508)

Patient setting

Advanced NSCLC.

Randomization

1st line Erlotinib 150 mg/day followed at progression by Cisplatin-Gemcitabine (n=380)

vs.

1st line Cisplatin-Gemcitabine followed at progression by Erlotinib 150 mg/day (n=380).

Outcome

Primary: OS ad interim analysis was inferior, HR 1.40 [1.13-1.73], P=0.002, median 10.1 *vs*. 7.7 months. Study was stopped by monitoring committee, ongoing Erlotinib patients were crossed over to chemotherapy.

Safety: no new findings, known toxicities for both treatments.

Conclusion

First-line chemotherapy remains the standard of care in unselected NSCLC patients.

Figure 9. Phase III on 1st line Erlotinib for poor PS patients (#7504).

Patient setting

Advanced NSCLC in poor PS (2-3) or PS 0-1 unfit for chemotherapy.

Randomization

BSC + 1st line Erlotinib 150 mg/day until PD (n=350)

vs.

BSC + 1st line Placebo until PD (n=320).

Outcome

Primary: OS: HR 0.98 [0.82-1.15], P=0.77.

Other: PFS HR 0.86 [0.74-1.01], P=0.07. Pre-specified subgroup analyses showed significantly longer OS for females only: HR 0.75 [0.57-0.99], P=0.04, median 5.3 *vs*. 4.3 months.

Safety: as expected, increased grade 3/4 rash and diarrhea with Erlotinib.

Conclusion

Overall, Erlotinib did not improve OS, but there was a clear effect for females.

Figure 10. phase III continuation of Gemcitabine after Carboplatin-Gemcitabine.(#7506).

Patient setting

Advanced NSCLC in disease control (response, stable) after 4 cycles of Carboplatin-Gemcitabine.

Randomization

BSC + continuation Gemcitabine 1000 mg/m2 days 1-8 every 3 weeks (n=128)

vs.

BSC alone (n=127).

Outcome

Primary: OS: HR=0.97 [0.72-1.30], P =0.84, median 8.0 (Gem) *vs*. 9.3 months (BSC alone).

Other: PFS median 3.9 (Gem) *vs*. 3.8 months (BSC).

Safety: well tolerated, more hematological toxicity.

Conclusion

Gemcitabine continuation failed to improve OS.

stage NSCLC (e.g. presence of hilar lymph nodes, or presence of a primary tumor ≥4.0). However, upon these 'high-risk' patients, we want to address who should not receive adjuvant chemotherapy. To address this question, an exploratory analysis on the impact of KRAS mutations was performed for stage IB patients with ≥4.0 tumors in CALGB 9633 (#7008) (*Figure 5*). KRAS mutant and wild

Figure 11. phase III Gemcitabine continuation or Erlotinib consolidation (#7507).

Patient setting

Advanced NSCLC in disease control (response, stable) after 4 cycles of Cisplatin-Gemcitabine.

Randomization

BSC + continuation Gemcitabine 1250 mg/m2 days 1-8 every 3 weeks (n=154)

vs.

BSC + consolidation Erlotinib 150 mg/day (n=155)

vs.

BSC alone (n=155).

Outcome

Primary: PFS for Gemcitabine: HR 0.51 [0.39-0.66], median 3.7 *vs*. 2.1 months

PFS for Erlotinib: HR 0.83 [0.73-0.94], median 2.8 *vs*. 2.1 months.

Other: 2nd line therapy well balanced with Pemetrexed in 60%/63%/76% of the patients. OS data are still immature, but at present not significant.

Safety: grade 3/4 adverse events more common with Gem (27%) / Erlo (14%) *vs*. observation (2%).

Conclusion

Primary endpoint of progression-free survival was met in both arms. Effect with Gemcitabine was mainly seen in responders to 1st line.

Figure 12. Phase III comparing Vandetanib to Placebo (#7525).

Patient setting

Advanced NSCLC with progression after one/two chemotherapies and EGFR-TKI.

Randomization

(2:1) Vandetanib 300 mg/d until progression (n=617)

vs.

Placebo until progression (n=307).

Outcome

Primary: OS: HR 0.95 [0.81-1.11], P=0.527, median 8.5 *vs*.7.8 months.

Other: response rate 2.6% *vs*. 0.7% (P=0.028). Disease control rate at 6 weeks 30% *vs*. 16% (P<0.0001). PFS HR 0.63 [0.54-0.74] (P<0.0001).

Safety: diarrhea (46% *vs*. 11%), rash (42% *vs*. 11%) and hypertension (26% *vs*. 3%).

Conclusion

Primary endpoint of OS not reached, but better disease control and PFS with Vandetanib.

type patients had a similar OS on the observation arm (HR: 1.28; p=0.47). The OS per treatment arm showed that KRAS mutant patients did significantly worse on adjuvant chemotherapy compared to KRAS wild type patients (HR: 2.15; p=0.02). Overall, this observation suggests that KRAS mutant stage IB patients with a primary tumor ≥4.0cm might less benefit from adjuvant chemotherapy. A meta-analysis is under way to further address this observation.

NSCLC – Advanced stage - First-line therapy

Classical options in fit patients are (Cis)platin-based doublets, with Pemetrexed superior to Gemcitabine in non-squamous histology. Adding a monoclonal antibody (Bevacizumab, Cetuximab) results in slight improvements in outcome. First-line Gefitinib can be considered for patients with EGFR mutant tumors. In so-called special populations, a distinction should be made between elderly but otherwise fit patients, who in general will have the same treatment, versus patients with major co-morbidity and/or low performance status, where an adaptation of the choice is often needed.

In the plenary session, a French Intergroup study in this setting was presented (#2) (*Figure 6*). Based on the OS difference, the study was stopped at the 2nd interim analysis, with 451 of the planned 522 patients. About three quarters of the patients

Figure 13. Phase III comparing Picoplatin to Best Supportive Care (#7002).

Patient setting

SCLC non-responsive or relapsing less than 6 months after platinum 1st line therapy.

Randomization

(2:1) Picoplatin 150 mg/m2 every 3 weeks (n=268)

vs.

Best Supportive Care alone (n=133).

Outcome

Primary: OS: HR 0.80, P=0.09, median 21 *vs.* 20 weeks.

Subanalysis refractory patients: HR 0.72 [0.54-0.95], P=0.017, median 21 *vs.* 18 weeks.

Other: PFS HR 0.80 (P=0.03), median 9 *vs.* 7 weeks.

Safety: mild, grade 3/4 AEs were 10%, mostly thrombocytopenia (44%), anemia (29%), neutropenia (18%), asthenia (11%), Febrile neutropenia occurred in 1%.

Conclusion

Primary endpoint of OS not met. On subanalysis, refractory patients had significant improvement in survival with Picoplatin.

had a PS 0-1. The survival difference thus was not truly a surprise, as several studies and e.g. a European Consensus meeting published in 2005 already stated "platinum-based chemotherapy a viable option for fit patients. This study adds to the evidence that age alone is not a reason to withhold the optimal treatment for NSCLC patients.

The other lung presentation in the plenary session was on targeted treatment for tumors harboring the EML4-ALK fusion oncogene (#3) (*Figure 7*). Based on the exciting findings with this drug in this niche of NSCLC patients (4% of total, in general never-smokers with adenocarcinoma and wild-type EGFR status), a phase III study is started.

Some other presentations focused on the use of the EGFR-TKI Erlotinib as 1st line treatment in non-molecularly selected patients, one in fit patients (#7508) (*Figure 8*), and one in patients unfit for chemotherapy (#7504) (*Figure 9*). These phase III trials were based on phase II studies that suggested that 1st line treatment with Erlotinib might be a valid alternative to chemotherapy. This study was designed to prove non-inferiority, but failed to do so, and was stopped after inclusion of 760 of the planned 900 patients. The data thus confirm with Erlotinib what has been learned from the IPASS study: EGFR-TKI is not an option for 1st line therapy in unselected NSCLC patients. Another study on the 1st line use of EGFR-TKI in special populations was reported from the UK (#7504) (*Figure 9*). The gender driven effect in this study is not easy to understand. In the Forest plot, gender had a significant interaction test for OS activity, and this was independent from histology or even EGFR status. Whether 1st line Erlotinib should now be considered in females in this setting remains a question, and in relation with the clinical relevance of the one month median survival difference in this study.

In two phase III trials, new platinum doublets were compared with Carboplatin-Paclitaxel. No outcome improvement was documented, just differences in toxicity, unlikely to have impact in European settings:

- Carboplatin + S1 (an oral prodrug of 5-FU mainly developed in Japan) (#7530).
- Carboplatin + nab-Paclitaxel (#7511).

Several initially promising agents did not fulfill expectations in further testing:

- Figitumumab (CP-751871, a monoclonal antibody targeting the IGF-IR) in a phase III in combination with Carboplatin-Paclitaxel: study stopped for futility (#7500).
- Mapatumumab (apoptosis agent, agonist monoclonal antibody for TRAIL-R1) in a phase II randomized study with Carboplatin-Paclitaxel (#7501).
- NOV-002 (a glutathione pathway regulator) did not give any benefit when combined with Carboplatin-Paclitaxel (#7007).

Interesting early findings were reported on agents that may be useful in EGFR-mutation positive patients experiencing disease progression while on Gefitinib or Erlotinib. PF299804 (an irreversible EGFR/HER2/HER4 TKI) resulted in better PFS than Erlotinib in a phase II comparison relapsing

NSCLC (#7523). ARQ 197-209 (a C-MET TKI) added to Erlotinib did the same in comparison with Erlotinib alone (#7502).

NSCLC – Advanced stage – Maintenance therapy

The classical approach to patients achieving disease control after four to six cycles of 1st line platinum doublet based chemotherapy is close follow-up with indication of relapse therapy at the time of progression. Recent important "maintenance" studies at ASCO 2008-2009, one with consolidation Pemetrexed, and one with consolidation Erlotinib have challenged this treatment paradigm. Three presentations at ASCO 2010 were presented. One was the OS outcome in the ATLAS study (maintenance Erlotinib *vs.* Placebo after doublet chemotherapy with Bevacizumab), it was negative, HR 0.90 [0.74-1.09], P=0.27 (#7526). One new result looked at continuation of Gemcitabine after Carboplatin-Gemcitabine as primary therapy (#7506) (*Figure 10*).

A very nicely designed study from France looked at maintenance with either Gemcitabine or Erlotinib (#7507) (*Figure 11*). Its original aspect was that the well predefined relapse therapy with Pemetrexed at the time of progression (one of the caveats in the previous studies). It should be understood that it was a 3-arm study designed to compare each maintenance arm with the standard, not for comparison between the two different drugs.

NSCLC – Advanced stage – Relapse therapy

Classical options are Docetaxel or Pemetrexed single agent chemotherapy (the latter only for patients with non-squamous histology), or Erlotinib (based on a phase III study where Erlotinib was better than placebo in 3rd line therapy or in 2nd line patients unfit for chemotherapy). Despite one global phase III trial that showed that Gefitinib was non-inferior to Docetaxel in the overall 2nd line population, this drug did got approval for targeted use in patients with EGFR activating mutations only. Several trials looked at combination therapy to improve outcome in this setting, until now with limited results. At ASCO 2009, two large phase III trials with Vandetanib (oral tyrosine kinase inhibitor active in the EGFR and VEGF axis) were reported, one in combination with Docetaxel (ZODIAC), and one in combination with Pemetrexed (ZEAL). The primary endpoint (PFS) was positive in ZODIAC only, and significant benefits in response rate and symptom control were reported for both trials.

At ASCO 2010, the biomarker data on 570 samples of the ZODIAC study were reported (#7516). Analyses were EGFR protein expression by immunohistochemistry (EGFR-IHC, 88% positive), EGFR gene copy number by fluorescent in situ hybridization (EGFR-FISH, 35% positive), and EGFR and KRAS gene mutation by ARMS assay (EGFR-MUT 14%; KRAS-MUT 13%). Consistent trends towards improved PFS, OS, and RR were seen for patients with positive EGFR-FISH or EGFR-MUT, with no difference for EGFR-IHC or KRAS-MUT.

Additionally, the phase III study with Vandetanib in patients failing after prior chemotherapy and EGFR-TKI was presented (#7525) (*Figure 12*). The study did not meet its primary objective of demonstrating an OS benefit with Vandetanib *vs.* Placebo in patients with advanced NSCLC who had previously failed chemotherapy and received treatment with an EGFR TKI, although PFS was better with Vandetanib *vs.* Placebo.

New strategies for better combination treatment for relapsing patients are eagerly awaited, and the use of Vandetanib seems to be a small step in that direction. Whether the overall data with this agent will suffice for registration remains uncertain.

Other tumors (SCLC – mesothelioma)

The standard primary chemotherapy for SCLC is a platinum compound plus Etoposide. For the relapse treatment of this disease, a distinction is often made between refractory patients (i.e. PD during platinum), resistant relapse (i.e. 2-3 months after stopping 1st line), or sensitive relapse (>2-3 months) For sensitive relapse, both Topotecan as well rechallenge with the initial regimen are options. The others are difficult to treat, Topotecan can be an option, while Amrubicin is in clinical development in that setting. The only phase III presentation at this ASCO was on the use of Picoplatin in relapsed patients (#5002) (*Figure 13*). Picoplatin is a new platinum compound designed to overcome platinum resistance, with less neurotoxicity/nephrotoxicity than other platinum agents. The study was heavily criticized by the discussant, as "best supportive care" is not an appropriate comparator arm in patients relapsing <6 months after the end of their initial treatment.