Plenary Session

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Adjuvant chemotherapy improves overall and disease-free survival in non-small cell lung cancer (NSCLC): results of the randomized international adjuvant lung cancer trial (IALT)

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Background: We recently reported (ASCO 2003) the results of a large international adjuvant lung cancer trial (IALT) which was designed to question the role of 3 to 4 cycles of adjuvant cisplatin-based Ct after complete resection of NSCLC.

Material and Methods: Each center predetermined cisplatin dose (total 300-400 mg/m*), combined drug (etoposide or a vinca-alkaloid) and radiotherapy policy. Tests were two-sided. Analyses were adjusted on center, type of surgery and pathological stage with Cox models.

Results: From 1995 to 2000, 1867 patients were randomized in 148 centers from 33 countries. On September 1st, 2002, median follow-up was 56 months and more than 98% of patients had a follow-up up to date. There were 935 patients in the Ct arm and 932 patients in the control arm. Overall survival was significantly different between the two arms: 5-yr survival rate was 45% in the Ct arm vs 40% in the control arm (RR=0.86 [0.76-0.98], $p<0.03$). Disease-free survival was also significantly different: 39% in the Ct arm vs 34% in the control arm at 5 yrs (RR=0.83 [0.74-0.94], $p<0.003$). Incidence of local recurrence was significantly different between the two arms: 5-yr rate was 24% in the Ct arm vs 29% in the control arm ($p<0.003$). Incidence of distant metastasis was significantly different between the two arms: 5-yr rate was 41% in the Ct arm vs 44% in the control arm ($p<0.03$). Incidence of brain metastasis was not significantly different between the two arms: 5-yr rate was 16% in the Ct arm and 14% in the control arm (p=0.64). Incidence of other metastasis was significantly different between the two arms: 5-yr rate was 29% in the Ct arm vs 35% in the control arm ($p<0.003$). Incidence of second cancer was not significantly different between the two arms: 5-yr rate was 6% in the Ct arm and 7% in the control arm (p=0.64).

Conclusion: Adjuvant Cisplatin based Ct in resected NSCLC significantly improves overall and disease-free survival. It decreases both local and distant recurrences and should become part of the standard management of operable NSCLC.

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Randomised trial of paclitaxel in combination with platinum chemotherapy versus platinum-based chemotherapy in the treatment of relapsed ovarian cancer (ICON4 / OVAR 2.2)

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Ovarian cancer is the sixth most common cause of cancer in women worldwide, and accounts for the greatest number of deaths from gynaecological malignancy in Europe and North America. There is no agreed second-line treatment for patients relapsing with ovarian cancer; patients (pts) who relapse > 6 months after platinum-based therapy are generally retreated with platinum-based chemotherapy. ICON4 (co-ordinated by MRC and Mario Negri Institute (IRFMN)) and OVAR 2.2 (co-ordinated by Arbeitsgemeinschaft Gynaekologische Onkologie (AGO)) were parallel randomised trials comparing 6 cycles of platinum chemotherapy (Plat) versus paclitaxel plus Plat (Pac-Plat) in pts relapsing with a treatment-free interval of > 6 months (MRC/AGO), or > 12 months (IRFMN). Protocol doses were: paclitaxel, 175mg/m^2 or 185mg/m^2; carboplatin, minimum AUC 5; single agent cisplatin, 75 mg/m^2; cisplatin in combination, 50mg/m^2. ICON4 / OVAR2.2 was a collaboration between groups in UK, Italy, Norway, Germany and Switzerland (SIAK); 802 patients were randomised between 01/96 and 03/02. Data were analysed as a single trial stratified by randomising group (MRC, IRFMN, AGO). Pt characteristics were similar both across the randomising groups and treatment arms. Median age was 60 and 8% pts had more than one previous line of chemotherapy. Previous chemotherapies received were: carboplatin (34%), cisplatin (30%), and platinum plus taxane (36%); 25% pts had relapsed $\leq$ 12 months after completing previous chemotherapy. By 10/02, with a median follow-up of 34 months, 674 (84%) pts had progressed or died, with a hazard ratio (HR) of 0.77 in favour of Pac-Plat (p=0.006). This translates into an absolute improvement in 1-year progression-free survival (PFS) of 9% (40% to 49%; 95% confidence interval (CI) 4%-15%). 463 (58%) pts have died; HR ratio is 0.77 in favour of Pac-Plat (p=0.006), which translates into an absolute improvement in 2-year survival of 9% (50% to 59%; 95% CI 3%-14%). Exploratory analyses revealed no evidence that the effect of Pac-Plat is larger or smaller in any subgroups (randomising group, time to relapse, number of previous lines of chemotherapy, use of taxanes first-line, age and performance status). These results suggest that Pac-Plat improves survival and PFS in pts with platinum-sensitive' relapsed ovarian cancer.

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Breast and prostate cancer: 10-year survival gains in the hormonal adjuvant treatment trials

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Worldwide collaborative meta-analyses of the randomised trials of hormonal treatments for early breast cancer and for non-metastatic prostate cancer both show substantial, and highly significant ($P<0.00001$) reductions in 10-year mortality from the index cancer, with little effect on mortality from other causes. Hence, both for breast and for prostate cancer, there were highly significant improvements in overall 10-year survival. These meta-analyses included 8000 women with estrogen-receptor-positive (ER+) breast cancer in the trials of immediate versus deferred hormonal treatment with about 5 years of tamoxifen versus control, and 3000 men with non-metastatic (M-) prostate cancer in the trials of immediate versus deferred hormonal treatment with orchiectomy or an LHRH antagonist.

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RNA interference (RNAi): the immune system of the genome

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All isolates of C. elegans contain multiple transposable elements in their genome. These elements jump around freely in somatic cells, but transposition is fully silenced in the germline. In investigating the mechanism of transposon silencing, we found that it was mechanistically linked to another phenomenon: RNAi or RNA interference. This is the experimental silencing of gene expression by administration of double-stranded RNA.

Mutants have been isolated that were defective in transposon silencing and/or in RNA interference. Several of these mutants have now been identified at the molecular level, thus defining essential components of the silencing machinery. The first biochemical analysis of the mechanism of silencing has also been initiated.

RNA interference is an experimental procedure that takes advantage of a mechanism that was probably meant for other purposes: the defense of the genome against the invasion of viruses and transposable elements. The human genome consists of approximately 50% repetitive DNA, derived from previous invasions by transposons and viruses. It is *a priori* to be expected that complex organisms must have "virus protection software", to limit such invasions to a minimum. This software must somehow be able to recognize the difference between *self* and *non-self* at the molecular level.