Table 1. Hazard Ratios for the 3 Experimental Doublet Regimens Relative to the Reference Arm of Cisplatin Plus Paclitaxel.

	Cisplatin + Gemcitabine	Cisplatin + Topotecan	Cisplatin + Vinorelbine
OS	1.322	1.255	1.147
PFS	1.394	1.268	1.357

The overall objective response rate (complete plus partial) according to RECIST criteria was 25%. The response rate was highest for cisplatin plus paclitaxel (29.1%) and lowest for cisplatin plus gemcitabine (22.3%). "This difference was not statistically significant but might be clinically important," said Dr. Monk. The rate was 25.9% for cisplatin plus vinorelbine and 23.4% for cisplatin plus topotecan.

Dr. Monk noted that the toxicities of the regimens were similar, except for a lower frequency of leukopenia and neutropenia in the cisplatin plus gemcitabine arm and a higher frequency of alopecia in the cisplatin plus paclitaxel arm.

Adjuvant Gemcitabine Extends Overall Survival in Patients with Resected Pancreatic Cancer

If their disease is caught early enough, patients with pancreatic cancer (PC) may undergo a resection of the diseased organ; this procedure, though intended to be curative, most often results in only a modest increase in overall survival (OS). As with other cancers, it is possible that adjuvant chemotherapy may improve long-term outcome, but there is no approved or accepted therapeutic in this setting. For patients with advanced PC, treatment with gemcitabine (GEM) is the standard of care, making it the logical choice for investigative use after resection of the pancreas.

To date, there has not been enough evidence to warrant the standardization of this approach. However, data presented by Ulf Neumann, MD, Charité Universitatsmedizin Berlin, Berlin, Germany, added to the position that adjuvant treatment with gemcitabine should be seriously considered (Abstract #LBA 4504. ASCO 2008).

This phase 3, randomized, multicenter investigation (CONKO-001) looked at the adjuvant use of gemcitabine versus observation in patients with complete PC resection (R0 or R1; n=368). Patients were first stratified by resection status, nodal tumor involvement, and tumor stage and then randomized to observation or treatment with GEM 1000 mg/m2 on Days 1, 8, and 15 every 4 weeks for a total of 6 months. The primary endpoint of the study was disease-free survival (DFS) with secondary endpoints that included OS and the parameters of toxicity.

"We already demonstrated safety data and efficacy for adjuvant treatment with gemcitabine in patients with resected pancreatic cancer 3 years ago," (Abstract #4014. ASCO 2007; Oettle et al. *JAMA* 2007) said Dr. Neumann. This final analysis, performed in March, incorporated data up to December 1, 2007, with 303 events in DFS (86.6%) and 293 events for OS (82.8%).

Results showed a median DFS of 13.4 months for GEM versus 6.9 months for observation (p=0.001). The proportion of patients with DFS at 5 years was 16% for GEM versus 6.5% for the observation arm. "Additionally, an unplanned subpopulation analysis showed the beneficial effect of gemcitabine in R0, R1, node-positive, node-negative, T1-2, and T3-4 tumors... all significant."

Perhaps what was most interesting was the significant improvement of OS in the final analysis, which in the preliminary report of this investigation had not reached significance. In this final analysis, median OS was 22.8 months for GEM as compared with 20.2 months for observation (p=0.005). This benefit was maintained out to 5 years, at which point a survival rate of 21% was recorded for the treatment arm versus 9% for observation.

Sequential Therapy with Gefitinib for Advanced Non-Small Cell Lung Cancer

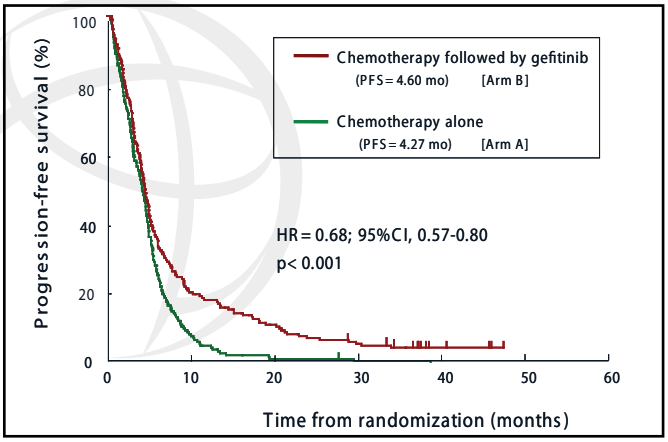
In previous studies, gefitinib combined with chemotherapy has provided no survival gain compared with chemotherapy alone for patients with advanced non-small cell lung cancer (NSCLC). However, a phase 3 trial has shown that sequential therapy with gefitinib may offer clinical benefit after platinum-based doublet chemotherapy in this setting.

The West Japan Thoracic Oncology Group trial (WJTOG 0203) (NCT00144066) involved patients who were randomly assigned to 3-6 cycles of chemotherapy alone (298 patients) or to 3 cycles of chemotherapy followed by daily gefitinib until disease progression (300 patients). The chemotherapy regimens consisted of cisplatin or carboplatin in combination with irinotecan, docetaxel,

paclitaxel, vinorelbine, or gemcitabine. Most patients had adenocarcinoma (78% in the chemotherapy alone arm and 79% in the chemotherapy plus gefitinib arm), and most patients (82% overall) had stage IV disease.

Toyoaki Hida, MD, PhD, Aichi Cancer Center, Nagoya, Japan, presented the findings on behalf of the WJTOG investigators. Dr. Hida reported that there was no significant difference between the two arms with respect to the primary endpoint of overall survival (OS). The mean survival was 13.68 months for the chemotherapy plus gefitinib arm and 12.89 months for the chemotherapy alone arm (p=0.10). However, progression-free survival (PFS; a secondary endpoint) was significantly longer for patients who received gefitinib (Figure 1).

Figure 1. Sequential Therapy With Gefitinib After Platinum-Based Doublet Chemotherapy Led to a Significantly Longer PFS Than Chemotherapy Alone for Patients With Advanced NSCLC.



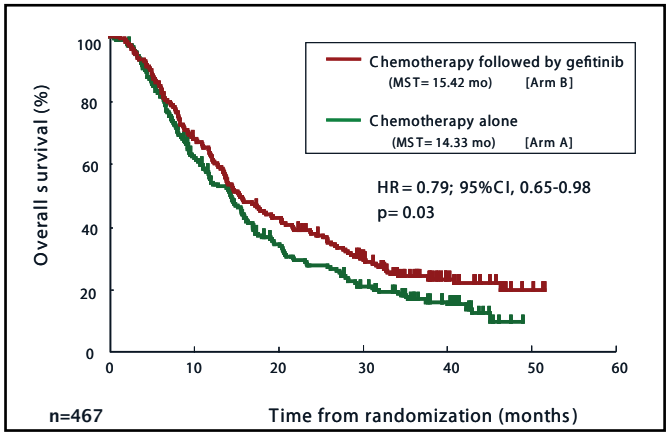
Dr. Hida added that a preplanned subset analysis showed that a platinum-based doublet followed by gefitinib was associated with a significantly superior OS for patients who had adenocarcinoma histology (Figure 2).

Chemotherapy followed by gefitinib was safe, with lower rates of adverse events than chemotherapy alone. Dr. Hida noted that the frequency of grade 3-4 anemia was significantly higher for the chemotherapy alone arm (21.8% vs 13.3%; p=0.006). All other toxicities were similar for the 2 arms. Among patients who received gefitinib, the 2 most common toxicities were elevated serum levels of liver enzymes (11.0%) and rash (4.1%).

Subgroup analysis showed that the hazard ratios (HRs) for death all favored sequential therapy with gefitinib except for non-adenocarcinoma histology (HR=1.24; 95% CI, 0.85-1.79) and stage IIIb disease (HR=0.99; 95% CI, 0.64-1.52).

Dr. Hida stated that in exploratory subgroup analyses, the mean survival was found to be longest for patients who had never smoked, with a slightly longer survival for patients in the chemotherapy alone arm (23.51 months vs 21.65 months; p=0.72). Among smokers, gefitinib led to significantly better survival (11.67 months vs 10.03 months; p=0.03); survival was further improved among smokers with adenocarcinoma histology (13.64 months vs 10.03 months; p=0.003).

Figure 2. Gefitinib was Associated With Significantly Better OS Only for Patients With Advanced NSCLC of Adenocarcinoma Histology.



A Randomized Phase 3 Trial of Intraperitoneal Cisplatin and Early Mitomycin C Plus Long-Term Doxifluridine Plus Cisplatin Versus Mitomycin C Plus Short-Term Doxifluridine

In patients with grossly serosa-positive advanced gastric cancer (AGC), postoperative adjuvant chemotherapy with intraperitoneal cisplatin and early mitomycin C (M) plus long-term doxifluridine plus cisplatin (iceMFP) improved recurrence-free and overall survival (OS). The comparator regimen in the phase 3 trial (AMC 0101) was M plus short-term doxifluridine (Mf), according to Yoon-Koo Kang, MD, Asan Medical Center, Seoul, Korea.

Dr. Kang noted that small but significant benefit for adjuvant chemotherapy in AGC has been demonstrated in meta-analyses and that a meta-analysis of M-based adjuvant chemotherapy studies from the 1960s-1980s in Japan (Nakajima et al. *Gan To Kagakis Ryoho* 1994)