Conclusion: Cisplatin plus S-1 chemotherapy is well tolerated, and our analysis suggests that the risk–benefit profile of this regimen is unaffected by patient age.

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Phase II trial of S-1 with bi-weekly docetaxel for non-small-cell lung cancer previously treated with platinum-based chemotherapy: a North Japan Lung Cancer Study Group (NJLCG0701)

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Background: S-1, a novel oral fluorouracil derivative, is active against non-small-cell lung cancer (NSCLC). A preclinical study showed the synergistic effect of docetaxel and S-1 *in vivo*. On the basis of the findings of the dose-escalation study of bi-weekly administered docetaxel and S-1, we conducted a phase II study to evaluate the efficacy and toxicity of this combination as a second-line treatment for patients (pts) with previously treated NSCLC.
Methods: Pts with NSCLC that was previously treated with one regimen of platinum-based chemotherapy were included. Gefitinib and/or prior surgery followed by adjuvant chemotherapy in addition to first-line treatment were acceptable. Other eligibility criteria were an Eastern Cooperative Oncology Group performance status (PS) of 0/1 and measurable lesions. Pts received S-1 (80 mg/m^2) on days 1−14 and docetaxel (25 mg/m^2) on days 1 and 15 of each 28-day cycle. The primary endpoint was the overall response rate (ORR), and secondary endpoints were progression-free survival (PFS), overall survival, and the toxicity profile. Assuming that 20% ORR in eligible pts indicated potential usefulness and 5% ORR is the lower limit of interest, along with alpha and beta values of 0.05 and 0.10, respectively, the estimated accrual was 34 pts.
Results: We enrolled 35 pts from 7 institutions (Feb. 2007−Sep. 2008). Patient characteristics: male/female, 23/12; median age, 64 years (43−74 years); and PS, 0/1 (17/18). The median number of treatment cycles was 3 (1−7). The objective responses were CR 0; PR 9; SD 14; PD 10; and NE 2, resulting in an ORR of 26% (95% confidence interval (CI), 11−40). The overall disease control rate was 66% (95% CI, 50−81); median PFS, 4.1 months; and overall survival time will be presented. Haematologic grade 3/4 toxicity included neutropenia (31%) and anemia (11%). No febrile neutropenia was observed. Non-haematologic grade 3 toxicity included diarrhoea (17%), infection (8.6%), anorexia (5.7%), rash (5.7%), elevation of serum aspartate aminotransferase (AST) (5.7%). No grade 4 non-haematologic toxicity was observed. There was 1 possible treatment-related death due to pneumonitis and infection after the first chemotherapy cycle.
Conclusion: The combination of S-1 and bi-weekly docetaxel is an active regimen with a tolerable toxicity profile for previously treated NSCLC. Further evaluation of this regimen as compared to the administration of docetaxel alone or pemetrexed is warranted.

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A phase II study of S-1 monotherapy as first-line treatment for elderly patients with advanced non-small cell lung cancer, the Central Japan Lung Study Group trial 0404

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Background: S-1 is an orally active combination of tegafur (a prodrug converted by cells to fluorouracil), gimeracil (an inhibitor of dihydropyrimidine dehydrogenase, which degrades fluorouracil), and oteracil (which inhibits the phosphorylation of fluorouracil in the gastrointestinal tract, thereby reducing its gastrointestinal toxic effects) in a molar ratio of 1:0.4:1. The rate of response to treatment with S-1 was reported to be 22% in patients with advanced non-small cell lung cancer (NSCLC). However, the activity of this drug in elderly patients remains unclear. This study evaluated the efficacy and safety of S-1 as first-line treatment in elderly patients with advanced NSCLC.
Materials and Methods: Elderly chemotherapy-naïve patients (age $\geqslant$70 years) with advanced NSCLC, an ECOG PS of 0−1, and adequate organ functions received oral S-1 for 14 consecutive days, followed by 7 days of no chemotherapy. S-1 was prescribed according to body surface area (BSA) to provide a dose approximately equivalent to 80 mg/m^2/day as follows: BSA < 1.25 m^2, 80 mg daily; BSA $\geqslant$1.25 m^2 but <1.5 m^2, 100 mg daily; and BSA $\geqslant$ 1.5m^2, 120 mg daily. This 3-week cycle was repeated until confirmation of progressive disease or intolerable toxicity. The primary objective of this study was to determine the objective response rate (RR). Secondary endpoints were tolerability, progression-free survival (PFS), and overall survival (OS).
Results: Thirty patients were enrolled, among whom 29 were eligible. Median age was 78 (range, 70−85) years. Twenty-two patients were men (75.9%), and 7 were women (24.1%). Eighteen patients had adenocarcinoma (62.1%), 7 had squamous cell carcinoma (24.1%), and 4 had others (13.8%). The median number of administered cycles was 3 (range, 1−19). Among the 29 patients, there were no complete responses and 8 partial responses for an overall response rate of 27.6% (95% CI, 11.3−43.9%). The median PFS and the median OS time have not yet been reached. Hematologic toxicities of grade 3 was anemia (6.9%). Nonhematologic toxicities of grade 3 consisted of anorexia (3.4%), nausea (3.4%), diarrhea (3.4%), and pneumonia (6.9%). No hematologic and nonhematologic toxicities of grade 4 were observed.
Conclusion: S-1 monotherapy is effective and well tolerated as first-line treatment in elderly patients with advanced NSCLC. The results of the present study warrant further investigations of this regimen, including a randomized controlled trial.

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Phase II study of amrubicin (AMR) in patients (pts) with non-small cell lung cancer (NSCLC) previously treated with platinum-based chemotherapy, a further analysis on adverse effect: WJTOG0401

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Background: AMR is a totally synthetic 9-aminoanthracycline and a novel topoisomerase II inhibitor. AMR has shown promising clinical activity for advanced NSCLC as well as SCLC. This trial was conducted to evaluate the efficacy and safety of AMR for pts with NSCLC previously treated with platinum-based chemotherapy.
Methods: Eligible Pts had a performance status 0 to 1, previous treatment with one platinum-based chemotherapy for advanced NSCLC, and adequate organ function. Pts received AMR 40 mg/m^2 intravenously on days 1−3 every 3 weeks. The primary endpoint was the objective response rate, which determined the sample size based on an optimal two-stage design. With the target activity level of 18% and the lowest response rate of interest set at 5%, 60 eligible patients were required with a 90% power to accept the hypothesis and a 5% significance level to reject the hypothesis.
Results: Sixty-one pts (median age, 63 years; range 51−74 years) were enrolled. The median treatment cycles were 2 (range, 1−15). No complete responses and 7 partial responses were observed, giving an overall response rate of 11.5% (95% CI, 4.7−22.2%). Twenty patients (32.8%) had stable disease and 34 patients (55.7%) had progressive disease as the best response. The overall disease control rate (complete response + partial response + stable disease) was thus 44.3% (95% CI, 31.5−57.6%). The median overall survival and 1-year survival rate were 8.5 months and 32.0%, respectively. Grade 3/4 hematological toxicities were neutropenia (82%), anemia (27.9%) and thrombocytopenia (24.6%). Serious neutropenia was observed in elderly patients. Grade 3/4 non-hematological toxicities were anorexia (9.8%), febrile neutropenia (29.5%) and pneumonitis (1.6%). One case of treatment-related death due to sepsis was observed.

Conclusions: AMR exhibits significant activity with manageable toxicities as second-line therapy for advanced NSCLC.

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Pemetrexed (PEM) safety and pharmacokinetics (PK) in patients (pts) with third-space fluid (TSF): final results of a phase II study

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Background: PEM is established as a first-line treatment with cisplatin for malignant pleural mesothelioma and advanced nonsquamous non-small cell lung cancer (NSCLC) and as a single-agent second-line treatment for nonsquamous NSCLC. Since PEM structure and PK are similar to methotrexate, which is associated with severe toxicity in pts with TSF, we evaluated PEM in pts with TSF.
Materials and Methods: Pts with TSF (pleural effusions or ascites) and either relapsed, stage III/IV NSCLC or malignant pleural/peritoneal mesothelioma were enrolled in this multicenter study. PEM (500 mg/m^2) was administered on day 1 of a 21-day cycle with folic acid and vitamin B_{12} as per label. TSF was checked prior to each cycle and drained only if clinically indicated. Plasma samples were collected during cycles 1 and 2 for comparison of PEM concentration with reference data from pts without TSF and evaluation using population PK methods.
Results: Thirty-one pts (87% male, 74% NSCLC) with TSF (small amount: 15 pts; medium: 14 pts; large: 2 pts) were enrolled and received a median of 4 cycles/pt (range, 1−11). Mean dose intensity was 97%, with 1 pt requiring 1 dose reduction for asthenia. Of the 123 doses administered, 7 were delayed due to adverse events (6%) in 4 pts (13%). One pt each had these possibly drug-related grade 3/4 events: febrile neutropenia, neutropenia, leukopenia, thrombocytopenia (requiring platelet transfusion). Five pts received $\geqslant$1 red blood cell transfusion for grade 2 anemia, with anemia as a pre-existing condition in 2 pts. One pt each had these investigator-reported, possibly drug-related grade 3/4 events: pulmonary pain, pleural effusion, ascites. Two pts died on study, one each from non-drug-related pneumonia and respiratory failure. There was no correlation between TSF amount and the type, number, and severity of toxicities. PEM plasma concentrations were within the range of those seen previously in pts without TSF. PEM CL (clearance), V1 (central volume of distribution) and V3 (peripheral volume) were not statistically different between patients with TSF and the reference population; V2 (peripheral volume) was 16% (95% CI: 2−31%) greater in patients with TSF.
Conclusions: No clinically relevant alterations of PEM PK occurred in pts with TSF. PEM was well tolerated; toxicities were expected, manageable, and consistent with the known PEM safety profile. No additional safety concerns were identified in these patients.

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Pattern of use of second-line treatment for NSCLC in the Nordic countries

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Background: SELECTTION is a pan-European, observational, multicentre, prospective cohort study to assess the standard use of 2nd-line treatment in locally advanced/metastatic NSCLC.
Methods: This report consists of analysis of the Nordic baseline data including patient and disease characteristics, treatment history and planned 2nd-line treatments. The primary objective of SELECTTION is to assess the time from initiation of 2nd-line treatment to treatment discontinuation. Treatment cohorts were constructed based on the distribution of patients across 2nd-line treatments by physician decision (pemetrexed, docetaxel, erlotinib and other treatments).
Results: From the Nordic countries (Denmark [DK], Finland [FI] and Sweden [SE]), a total of 179 patients was included between January 2007 to January 2008, of which 175 are available for analysis. There was a difference between the 3 countries with respect to the planned second line treatment. In FI and SE, newer drugs like erlotinib and pemetrexed were more often selected than in DK. Especially in FI, erlotinib was more frequently selected (32%) compared to SE (14%) and DK (9%). Pemetrexed was planned equally in FI and SE (42%) but less so in DK (11%). The majority of Danish patients were planned with docetaxel in 2nd-line (78%), while in SE and FI the use of this drug was modest (26% and 15% respectively). Most patients were in PS 0 or 1. Only 28 patients of total (N = 175) were in PS 2 or 3. In patients with low PS, erlotinib is selected more frequently. With respect to histology, the majority of patients had non-squamous NSCLC (130 out of 175 patients). Histology appeared to have no influence on the planned therapy with pemetrexed and docetaxel, while 33 out of 36 patients selected for erlotinib were non-squamous patients. Patients with stable disease or better as response to 1st-line therapy was more often planned with pemetrexed or erlotinib compared to docetaxel.
Conclusions: The planned use of 2nd-line treatment for NSCLC in the Nordic countries is not identical. The difference may be due to differences in institutional guidelines, or selection of patients to this study as only patients who were not enrolled in clinical trials were eligible for SELECTTION. Erlotinib was primarily selected in subgroups of patients which are previously shown to have a better chance of effect. For pemetrexed, newer data on better efficacy in non-squamous NSCLC did not greatly affect the planned use during the period that SELECTTION was active.

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Phase I study of the combination of docetaxel (D) and pemetrexed (P) in patients with advanced unresectable or metastatic non small cell lung cancer (NSCLC)

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Background: D and P are effective in the treatment of NSCLC either as monotherapy for the 2nd line treatment of NSCLC or in combination with other drugs (e.g cisplatin) in the 1st line. We designed a phase I study of the combination of D/P to determine the dose limiting toxicities (DLT) and the maximum tolerated dose (MTD) in patients with NSCLC.
Methods: Eligible were patients with confirmed NSCLC. 8 dose levels were explored of D (1h infusion, d1) and P (10min infusion, d1) every 21d, in a 3+3 escalation design after supplementation with B12 and oral folate. DLT was defined as gr4 neutropenia, thrombocytopenia and gr3 or 4 febrile neutropenia and non- hematological toxicity, in cycle 1.
Results: 39 patients were enrolled; male/female: 32/7; median age 60 years (42−80); PS 0/1/2: 15/20/4; stage IIIb/IV: 3/36; 21 patients were chemotherapy- naïve, 18 patients had received one prior chemotherapy regimen. 8 patients had squamous cell pathology, 25 adenocarcinoma and 6 other pathologic types. Median number of cycles was 3 (range, 1−9). With a median follow up of 16.5 months, the median TTP was 2.4 months (95% CI, 1.5−3.2) and the median OS was 10.3 months (95% CI, 9.3−11.2). In an intention- to- treat analysis the ORR was 18.4% (1CR, 6PR), whereas SD was15.8% (6 patients) among 38 eligible for response patients. No non- hematological DLT was observed. DLTs are shown in the table 1. The MTD was not reached. The most common toxicities in all dose levels and cycles were neutropenia (gr2/3/4: 13/12/10), febrile neutropenia (gr3: 3), nausea/vomiting (gr2: 8), diarrhea (gr2/3/4: 5/3/1) and fatigue (gr2/3: 20/3). 3 more patients have been enrolled at the 8th dose level but they have not been evaluated till now.
Conclusion: The combination of D/P regimen seems to be active, tolerable, feasible with easy manageable toxicity even in doses which exceed the recommended doses for each one in monotherapy setting. Though the MTD was not reached, we have already planned a phase II study with D at 75 mg/m^2 and P at 500 mg/m^2 which are the recommended doses for each drug as single agent therapy.

Level/no of pts	Doses of D	Doses of P	DLTs/ no of pts
1st/3	65	400	
2nd/6	65	450	neutropenia Gr4 = 1, febrile neutropenia Gr3 = 1
3rd/6	70	450	thrombocytopenia Gr4 = 1
4th/6	70	500	neutropenia Gr4 = 2
5th/3	75	500	
6th/6	80	500	neutropenia Gr4 = 1
7th/6	80	550	neutropenia Gr4 = 1
8th/3 pts out of 6	85	500	neutropenia Gr4 = 1