PL-4 **Phase III study of concurrent chemotherapy and full course radiotherapy (CT/RT) versus CT/RT induction followed by surgical resection for stage IIIA(pN2) non-small cell lung cancer (NSCLC): First outcome analysis of North American Intergroup trial 0139 (RTOG 93-09)**

Kathy S. Albain[1], Charles B. Scott[2], Valerie R. Rusch[3], Andrew T. Turrisi[4], Shepherd A. Shepherd[5], Colum Smith[6], David R. Gandara[7], David Johnson[8], Mark R. Green[9], Robert C. Miller[10]. *[1] Loyola University Chicago Medical Center, Maywood, USA; [2] Radiation Therapy Oncology Group, Philadelphia, USA; [3] Memorial Sloan-Kettering Cancer Center, New York, USA; [4] III, Medical University of South Carolina, Charleston, USA; [5] Princess Margaret Hospital/University of Toronto, Toronto, Canada; [6] Tom Baker Cancer Center, Calgary, Canada; [7] UC Davis Cancer Center, Sacramento, USA; [8] Vanderbilt-Ingram Cancer Center, Nashville, USA; [9] Cancer and Leukemia Group B, Charleston, USA; [10] Mayo Clinic, Rochester, USA*

Purpose: The role of surgery is controversial in pts with stage IIIA NSCLC and pathologically confirmed N2 nodes (pN2), so CT/RT alone is standard of care. Phase II studies suggest improved outcomes with concurrent CT/RT followed by resection. INT 0139 was designed to test the value of resection after induction CT/RT vs full course CT/RT. Endpoints were progression-free and overall survival (PFS, OS) and patterns of failure.

Methods: Pts with PS 0-1 and T1-3, pN2, M0 tumors were eligible if resection was technically feasible at randomization. All pts had induction with cisplatin 50 mg/m^2 d1,8 and etoposide 50 mg/m^2 d1-5 (PE) X2 and daily RT to 45 Gy starting day 1. Arm 1 underwent resection if no progression (PD), followed by PE X2; Arm 2 received uninterrupted RT to 61 Gy and PE X2.

Results: The trial was closed with sufficient events over the accrual period. 429 pts were randomized 3/94-11/01 (4% ineligible). 392 pts are evaluable for this report (201, Arm 1; 191, Arm 2). Induction CT/RT compliance was excellent (95%). PE 3 and 4 were not received in 42%, Arm 1 and 21%, Arm 2 (p<0.0001). RT was per protocol in 97%, Arm 1 and 82%, Arm 2 (p=.002). Most common grade 3/4 toxicities from CT/RT were neutropenia, emesis and esophagitis (9% Arm 1, 20% Arm 2, p=.001). Arm 1 had 14 deaths from treatment (6.9%), most of which were ARDS (postop, 4; during/after consolidation,10). In Arm 2, 3 deaths (1.6%) occurred with/after consolidation. Patterns of failure were similar. The pCR rate was 36% in Arm 1. The PFS is superior on Arm 1 (p=.02): median, 14.0 vs 11.7 mos; 3-year 29% vs 19%. The median S for each arm is 22 mos (OS p=.51). There were more early non-cancer deaths in Arm 1, but OS curves cross at the median so that by year 3, the OS is 15% better on Arm 1 (absolute: 38% vs 33%). Thus, more pts died without PD on Arm 1 (p=.004), but more are alive without PD on Arm 1 (p=.003).

Conclusions: 1) Both approaches yield median and 3-year survivals much better than predicted from phase II data, 2) more treatment-related deaths occur on the surgical arm, 3) the pathologic CR rate is significantly higher than previous trials, 4) CT/RT followed by surgery results in superior PFS, and 5) longer follow-up will determine if surgery significantly prolongs survival in stage IIIA(pN2) NSCLC.

PL-5 **A Phase III Study of Pemetrexed vs. Docetaxel in Patients with Advanced Non-Small-Cell Lung Cancer (NSCLC) who were Previously Treated with Chemotherapy**

Frances A. Shepherd[1], Jose R. Pereira[2], Joachim Von Pawel[3], Ulrich Gatzemeier[4], Thomas Chang Yao Tsao[5], Nasser Hanna[6], Rafael Rosell[7], Paolo Paoletti[8], Sofia Paul[8], Paul A. Bunn[9], Lawrence Einhorn[6]. *[1] Princess Margaret Hospital, Toronto, Canada; [2] Instituto Arnaldo Vieira De Carvalho, Sao Paolo, Brazil; [3] Asklepios Fachkliniken Munchen-Gauting, Munich, Germany; [4] Krankenhaus Grosshansdorf, Grosshansdorf, Germany; [5] Chang Gung Memorial Hospital, Kwei-Shan, Taiwan; [6] Indiana University Medical Center, Indianapolis, USA; [7] Hospital De Badalona Germans Trias I Pujol, Barcelona, Spain; [8] Eli Lilly and Company, Indianapolis, USA; [9] University of Colorado Cancer Center, Denver, USA*

Docetaxel is standard second-line treatment for NSCLC based on randomized phase III studies. Pemetrexed has shown clinical activity against NSCLC in phase II studies, as initial or second-line therapy. We report results of a multicenter, randomized, phase III comparison of pemetrexed vs docetaxel in previously treated patients with advanced NSCLC. 571 patients were randomized from 3/01 to 2/02, to receive either pemetrexed (500 mg/m^2 IV infusion), supplemented with vitamin B12 injections, folic acid and dexamethasone or docetaxel (75 mg/m^2 IV infusion) with dexamethasone on day 1 of 21-day cycles. The primary objective compared overall survival and secondary endpoints included time to event measures, response rate and toxicity. There were 411 males, 160 females, median age 58 years (range 22-87), ECOG PS 0-1 (88%), recurrent stage IV disease (75%). 94% had 1 prior chemotherapy regimen and 6% had 2 regimens. 91% had prior platinum therapy and 27% had prior taxanes. Patient and disease characteristics were evenly distributed between the two arms. Total cycles delivered were 1164 cycles (median 4, range 1-20) for pemetrexed and 1085 cycles (median 4, range 1-14) for docetaxel. Fewer drug-related deaths occurred with pemetrexed therapy relative to docetaxel, and drug-related SAE's were significantly lower for pemetrexed therapy (10%) compared to docetaxel (24%).

Efficacy	Pemetrexed (n=283)	Docetaxil (n=288)
Median survival	8.3 months (7, 9.4)	7.9 moths (6.3, 9.2)
HR (95%CI)	0.99 (0.8, 1.2)	
Time to progressive disease	2.9 months (2.4, 3.1)	2.9 months (2.7, 3.4)
HR (95%CI)	0.97 (0.8, 1.2)	
Response rate (CR/PR/PRNM)	9.1%	8.8%

Grade 3/4 Toxicities (CTC V.2)	Pemetrexed (n=285)	Docetaxil (n=276)	P value
Neutropenia	5%	40%	<.0001
Neutropenic Fever (F/N)	2%	13%	<.0001
Thrombocytopenia	2%	<1%	.116
Infection w/Gr3/4 Neutropenia	0	3%	.004
ALT	2%	0	.028
Diarrhea	<1%	3%	.069
Neuropathy Gr 2-4	3%	8%	.014
Hospitalizations due to F/N	29 days	192 days	-
Incidence	4 (2%)	43 (16%)	<.001

Survival, TTPD and response rates were similar in both treatment arms, but pemetrexed therapy produced a significantly more favorable toxicity profile with less bone marrow suppression and hospitalizations due to F/N. In conclusion, pemetrexed demonstrated a significantly better risk/benefit profile relative to docetaxel.

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Chemotherapy NSCLC Second-line Chemotherapy

O-1 **A phase III trial comparing weekly and three weekly docetaxel in second line treatment of patients with advanced non small cell lung cancer (NSCLC)**

Wolfgang Schuette[1], Sylke Nagel[2], C. Lautenschlaeger[3], Monika Serke[4], Bettina Wollschlaeger[5]. *[1] Martha-Maria-Hospital, Dept. of Internal Medicine, Halle, Germany; [2] Martha-Maria Hospital Dept. of Internal Medicine, Halle, Germany; [3] Martin-Luther-University Halle-Wittenberg Dept. of Biometric, Halle, Germany; [4] Lunghospital Heckeshorn Dept. of Internal Medicine, Berlin, Germany; [5] Martin-Luther-University Halle-Wittenberg Dep. of Internal Medicine II, Halle, Germany*

Docetaxel has proven significant activity in second line therapy of advanced or metastatic NSCLC. In order to improve tolerability of the three weekly regimen a phase III study has been initiated to compare a three weekly with a weekly administration. The patients are randomised either to treatment arm A (docetaxel 75 mg/m^2, d1, q3w) or to arm B (docetaxel 35 mg/m^2, d1,8,15, q4w). A total of 179 (215 planned) patients has been recruited with a median age of 63 years (range: 41- 78). 110 patients are evaluable for toxicity and tumor response. Data are not yet unblinded. 41/46/13% of the patients had ECOG performance status 0/1/2 and 58% had tumor stage IV. 24,5% had prior chemotherapy including paclitaxel. A median number of 3 cylces (range: 1-8) in arm A and 2 cycles in arm B (1-6) have been administered. A clinical benefit has been observed in 37,3% of the patients (efficacy: complete remission: 0,9%; partial remission: 8,2%; disease stabilisation: 29,1%). Grade 3 and 4 hematologic and non-hematologic toxicities were mild and occurred infrequent in both treatment arms. 21% of the patients in arm A and no patient in arm B experienced grade 3 and 4 leucopenia. Alopecia (21 vs. 9,3%), pain (15,1 vs. 9,3%), pulmonary symptoms (9,4 vs. 5,4%) and fluid retention (7,5 vs. 1,9%) have been observed as the main non-hematologic side effects. Both docetaxel regimen are well tolerated in second line setting and could be safely administrated on an outpatient basis. Weekly docetaxel seems to be an attractive treatment option because of significant lower grade 3 and 4 toxicities. Updated data will be present for the meeting.