

NON SMALL CELL LUNG CANCER

NON SMALL CELL LUNG CANCER – MOLECULAR BIOLOGY

W Franklin et al (Sem Oncol 2002;29:3-14) Séquence events in lung carcinogenesis: Normal (LOH 3p, 9p) hyperplasia (growth factors), Squamous metaplasia (loss of apoptosis via PI3K, Akt; proliferation myc, jun, ras), Dysplasia (p53), Ca in situ, Invasive carcinoma. Role for methyl p16, O6MGMT, RARB promoters...

J Brabender et al (Clin Ca Res 2001;7:1850-5) EGFR overexpression 33%, HER2 overexpression 34%, both 16%. Correlated with poor prognosis in surgically resected patients.

R Bremmes et al (JCO 2002;20:2417-28). E Cadherin and catenin (a, b & g) correlate with dedifferentiation, invasion and metastases leading to a reduced survival.

**A Maeshima et al (Cancer 2002;95:2546-54). Scar grade in small peripheral adenocarcinoma of the lung: Grade 1: no desmoplasia (with/out collapse) 10 y OS 100%; Grade 2: sparse desmolastic reaction (83%); Grade 3: Dense desmoplastic reaction of <10mm diameter (52%); and Grade 4: Dense desmoplastic > 10 mm diameter (37.5%).

***K Yanagisawa et al (Lancet 2003;362:433-9). Proteomic patterns identified by MALDI-TOF MS with profile of proteins up to 50 kDa. Used in 50 tumors distinguished squamous form adenocarcinoma and tumor vs normal lung with a sensitivity of 100% and predicted 5 y OS groups OF 50% AND <5% after surgical resection (50% cases).

H Endon et al (JCO 2004;22:811-9). Selected 8 genes out of 44 detected as prognostic markers of adenocarcinoma (Garber et al PNAS USA 98;13784-9, 2001 and Bhattachorjee et al PNAS USA 98;13790-5, 2001): PTK 7 (HR 0.5), CIT (HR 0.6), SCNNIA (HR 1.7), PGES (HR 2.2), EST-LB4D (HR 1.9), ERO 11 (HR 0.2), EST-AA434256 (HR 0.4) and ZWINT (HR 2.3). Low risk group had a 85% 5 y OS and high risk 40% 5 y OS.

H Ren et al (JCO 2004;22:3230-7). Hepatoma derived growth factor (HDGF) present in NSCLC. IN Stage I patients t5hose above the mean (185±41) had 5 y OS 26 vs 82% and 5 y DFS 42% vs 92%...

*****C French et al (JCO 2004;22:4135-9). Midline carcinoma of children and young adults (median age 32 yo) present with NUT oncogene fusion t(15;19), single chromosomal translocation. Poor prognosis in 50%. Should be considered a new entity with primaries in H&N, thymus, lung.

***S Kobayashi et al (NEJM 2005;352:786-92). Most common mutation of EGFR is L858R or a small deletion 747-750. After 2 y CR to Iressa progression is associated to a second mutation structurally equivalent of Gleevec bcr-abl mutation which abrogated a CR in CML: Threonine to methionine change at 790 EGFR position. An analog CL-387.785 has been identified to overcome this resistance in the T790M mutation. Brilliant.

A Shigematsu et al (JNCI 2005;97:339-46). EGFR mutation found in 130/617 NSCLC (21%) in an international study: mutations were: in frame in exon 19, single missense mutation in exon 21, in frame duplication/mutation in exon 20. K-ras mutations found in 8% (50/617) and none of them had EGFR mutation. EGFR mutations related to never smokers (51% vs 10%), adenocarcinoma (40% vs 3%), East Asians (ancestry also important since Asians in Australia and USA had higher frequency) (30% vs 8%), and females (42% vs 14%), and were not associated with age, stage, bronchioalveolar histology or OS.

***W Pao et al (JCO 2005;23:2556-68). Up to Novc 04 detected 192 EGFR mutations 85% in two spots: 55.8% LREA 19 del and 44.2% L858R exon 21 point mutation. Activation leads to oncogene addiction by continuous growth stimulation. PCR based assays are available.

***F Cappuzzo et al (JNCI 2005;97:643-5). High EGFR gene copy identified by FISH correlates with response to Gefitinib better than mutation of EGFR. EGFR amplification is related also to OR 36% vs 3%, disease control rate 67% vs 26%, TTP 9 mo vs 2.5 mo, and OS 18.7 mo vs 7 mo. Mutation of EGFR correlated with OR and TTP but not OS.

TW Generts et al (Clin Ca Res 2005;11:6608-14). Criteria to distinguish second lung primary vs metastatic head and neck cancer are base on stage of H&N cancer at presentation, central or peripheral location of lung mass & single or multiple nodules, and finally time interval more or less than 3 years. In a series of N=44, according to classical clinical criteria 38 were mets and 6 primaries. By PCR LOHP analysis 24 were concordant (mets) and 18 were primaries. Interest in surgery...

S Singhal et al (Clin Ca Res 2005; 11:3974-86). Favorable prognosis related to p16, p21 & p27. Unfavorable prognostic factors cyclin B1, cyclin E, surviving, VEGF, collagen XVIII. Rb failed and Cyclin D1 and Bcl2 were equivocal.

F Capuzzo et al (JCO 2005;23:5007-18). HER2 increase measured by FISH present in 22.8% correlated with OR 34.8% compared to normal HER2 only 6.4%, and had better disease control rate (56.5% vs 33%), MTTP 9.05 mo vs 2.7 mo, and OS 20.8 mo vs 8.4 mo. When HER2 associated with EGFR mutation had better outcome...

M Spinola et al (JCO 2006;24:1672-8). Rs1862214 single nucleotide polymorphism (GG or CG, compared to the common genotype CC) of PDCD5

gene (programmed cell death 5) increased lung cancer risk in smokers (HR 1.9) and presented with worst clinical stage (HR 1.8).

RK Thomas et al (Clin Ca Res 2006;12:4384S-91S). EGFR mutations: 45% 19del, 40% L858R, very sensitive to Iressa, 5% G719S.

S Toyooka et al (Ca Res 2006;66:1371-5). N=164 adenocarcinoma. Two pathways: First type characterized by EGFR lower expression in p16/CDH13 methylation cases and viceversa less methylation in EGFR mutation cases; and second type with k-ras mutation in p16 methylation cases.

RS Heist et al (Clin Ca Res 2006;12:5448-53). Matrix metalloproteinase variant G allele MMP-2 1082 A/G associated with poor survival in stage I NSCLC (HR 1.94 for OS).

DN Hayes et al (JCO 2006;24:5079-90). Gene expresión by DNA microarrays in lung adenocarcinoma distinguished 3 groups (bronchoid, squamoid and magnoid) with distinct clinical characteristics (BAC, epidermoir and large cell variants).

HY Chen et al National Taiwan Univ Hosp-7 (NEJM 2007;356:11-20). Microarray analysis identified a 5 gene signature (DUSP6, MMD, STAT1, ERB-B3, LCK) for RT-PCR decision tree analysis in operable lung cancer (no adjuvancy). Low risk 2 y OS 95% vs 50% in high risk signature in stage I, and 70% vs 30% in stage II. MST 40 vs 20 mo, MRFS 29 mo vs 13 mo.

NON SMALL CELL LUNG CANCER -PREVENTION

AV Peterson et al (JNCI 2000;92:1979-91). Hutchinson smoking prevention project of 40 high school districts was a well designed intervention trial, contrained 15 essential elements developed by the NCI and was well implemented, well measured and prolonged (grades 3-12). It showed no effect of intervention, no evidence that shool based social influences approach is effective...

G Goodman et al (JNCI 2004;96:1743-50). Beta carotene 30 mg + Retinyl palmitate 25.000 iu q d. N=18.314 high risk tobacco/asbestos. Adverse side effects prompted early discontinuation. Excess risk of lung cancer 1.12 and cardiovascular death 1.08 at 6 y. Negative study.

NON SMALL CELL LUNG CANCER -SCREENING

M Melamed (Cancer 2000;89:2356-62). NCI-NY Study with 10.000 male (MSKCC, JHUH Baltimore and Mayo Clinic), > 45 yo, smoking, 2 y F up:

Randomized to Cytology q 4 mo + Chest XR q 1 y (Initial lung cancer 30 –9 only cytology- and later 175 cases) and only chest XR (initial 23 AND LATER 175). Stage I 40%, 5 y OS 35% (historically USA Series 13%). Recommended.

C Henschke et al (Cancer 2001;92:153-9). Follow-up repeat screening of the initial 1000 high risk individuals. Initial findings 2.7% malignant tumors (83% not visible in the chest X.Ray), 2.3% Stage I. Follow up CT positive 2.5%: 2 deaths, 12 resolved, 16 no growth, 8 documented growth (6 NSCLC: 5 Stage IA, 1 Stage IIIA & 1 SCLC; median size 8 mm), and another 2 patients had further studies showing 1 NSCLC Stage IIB and 1 SCLC limited disease. Recommend annual CT study.

G Strauss (JCO 2002; 21: 1973-83) Mayo Clinic Project Cohort, N=9192. Mortality was increased in experimental group (screen with chest XR/cytology) due to increased cancer incidence (HR 1.3). Early diagnosis lead to a 50% cure rate due to resection. Survival was then improved in the screening group 5 y OS 29% vs 13% (plateau). Survival rather than mortality provided an unbiased surrogate for cure.

U Pastorino et al INT Milano (Lancet 2003;362:593-7). N=1035, >50 yo, 20 y/pack, annual CT±PET x 5 y & lesions < 5 mm repeat at 1 y. On second year: 22 lung cancer (11 base line and 11 at year 2). 29% participants had lung lesions (440 lesions/298 participants). PET + in 18/20 cancer cases. 6 false positive with benign diagnosis (6% of recalls and 22% of surgery cases). Complete resection 95%; stage I 77%, mean size 18 mm. Lesions < 5 mm can be delayed.

G Bepler et al (CANCER control 2003;10:306). CT screening of interest in > 60 y o with moderate smoking and without other medical problems. Pathologic CT 23.3%, cancer 2.7%.

*****International Early Lung Cancer Screening C Henschke et al (NEJM 2006;355:1763-71) N=31.567. First round 320 and second round screen 55. Stage I 412 (85%); 10 y OS 88% (operated first month 92%, and 8 patients without therapy, none survived 5 y). High risk >60 yo, former/current smokers give a 1.3% baseline & 0.3 annual screening (better than breast in >40 yo, with a 0.6-1% baseline & 0.2-0.4% second screen). Cost effective.

NON SMALL CELL LUNG – BRONCHIOLOALVEOLAR CANCER

J Zell et al (JCO 2005;23:8396-405). New definition by WHO in May 1999 restricted BAC to tumors without invasion, only bronchioloalveolar growth. End results changed with MOS improving from 32 to > 53 mo, while there were no changes in the other adenocarcinoma types. Adenocarcinoma with BAC features without foal invasion is excluded from BAC.

DJ Rag et al (Clin Ca Res 2006;12:3698-704). BAC surgery 5 y OS 50-70%, local recurrence 50%. Differences in gene expression were: Pure BAC Survivin +++, A Catenin ++, E Cadherin +++, Laminin -, k ras + p 53 +; Mixed BAC Laminin +, A catenin ++, E cadherin \pm , p53 +; Mucinous BAC p53 -, k ras +++; Adenocarcinoma p 53 ++, kras +.

L West et al (JCO 2006;24:1807-13). Gefitinib 500 mg qd. N=136. M age 68 yo, 71% female, 89% PSK 0-1. OR 17%, 6% CR untreated (N=69); OR 9%, 0 CR treated (N=22). MST 13 mo, 3 y OS 23%. 2% dead due to interstitial lung disease.

NSCLC – LOCALIZED COMBINED THERAPY

NK Altorki et al (JCO 2003;21:2645-50). Neoadjuvant treatment in stages IB-III A. TXL + CBDCA + Celecoxib 400 mg bid. OR 65% (CR 17%), 28/29 surgery, 24% minimal disease. PGE2 levels decreased in the tumor. Results suggested increase in CR.

International Adjuvant Lung Cancer Trial Group (NEJM 2004;350:351-60). Complete resected patients N=1867, 36% Stage I, 39% stage III, M F up 56 mo. Randomized to CDDP based ChX (5 y OS 44.5%, 5 y DFS 39.4%) vs Observation (5 y OS 40.4%, 5 y DFS 34.3%). New standard of care.

K Hotta et al (JCO 2004;22:3860-7). Meta-analysis of Adjuvant ChX in resected NSCLC, 11 trials, N=5716 patients. HR 0.872, CDDP based HR 0.891, Uracil-Tegafur based HR 0.799.

K Pisters, T Le Chevalier (JCO 2005;23:3270-8). Review prior trials and 7 recent ones on >4000 patients with adjuvant platinum based and recent doublet combinations, showing a 5 y increase in OS 5-18%, representing a new standard of care for Pt based chemotherapy.

B Jeremic et al (JCO 2005;23:1144-51). N=64, stage III. Treatment: TXL 30 mg/m² d1, Then Hyperfractionated RT 1.3 Gy bid up to 67.6 Gy, & daily CBDCA 25 mg/m² + TXL 10 mg/m² between XR doses. OR 83%, CR 42% + PR 41% + NC 16% + PD 2%, MST 28 mo, 3 y OOS 37%, 5 y OS 26%, MTTP 25 mo, 5 y Distant-Mets-DFS 31%.

J Bradley et al RTOG 9705 (JCO 2005;23:3480-7). Adjuvant postoperative treatment 8 wk after surgery, stage II-III A. TXL 135 mg/m² + CBDCA AUC 5-6 q 3 wk x 4 + RT 50 .4 GY (28F)/6 wk. Results: 93% completed RT, 86% completed ChX. MOS 56.3 mo, 3 y OS 61%, 3 y PFS 50%, local failure 15%. Improved historical series.

BE Lally et al (JCO 2006;24:2998-3006). Postoperative RT according to SEER Database: N=7465, M F up 3.5 y. N2: survival HR 0.855, N0 HR 1.17, N1 HR 1.09.

P De Leyn et al (JCO 2006;24:3333-9). N=30, Stage IIIA, N2, mediastinoscopy +. Neoadjuvant Rx then restage with PET-CT and mediastinoscopy. At thoracotomy 17 had N2+. PET-CT sensitivity 77%, specificity 92%, accuracy 83% and remediastinoscopy sensitivity 29%, specificity 100% and accuracy 60%.

T Seiwert et al (Clin Ca Res 2007;13:515-22). N=30. Alimta 500 mg/m² + CBDCA AUC 5-6 + RT 40-66 Gy. 4 CR + 8 PR. Esophagitis, myelotoxicity.

NON SMALL CELL LUNG CANCER -CHEMOTHERAPY

C Kosuras et al (Cancer 2000;89:774-82). N=50, Phase II. TXL 175 mg/m² + IFX 5 g/m² + CDDP 100 mg/m². OR 64% (4CR), QOL improvement 74%, MDR 7 mo, MTTP 8 mo, 1 y OS 53%.

J Schiller et al ECOG (NEJM 2002;346:92-8). N=1155, >80% stage IV, med age 62 yo. Randomize to CDDP+TXL (2 y OS 10%) vs CDDP + TXT (11%), vs CDDP+GEM (13), vs CBDCA+TXL (11%). No differences. Very slight improvement in 2 y OS. MST 7.8 to 8.1 mo.

J Hainsworth et al (JCO 2002;20: 2937-42). N=321, M F up 58 mo. Phase II CDDP+TXL and a third agent VNR or GEM. MOS 8.6 mo, 2 y OS 19%. No differences according to third agent.

M Socinski et al (Cancer 2002;95:1520-7). N=40. CPT 100 mg/m²+ TXL 175 mg/m² + CBDCA AUC 5. OR 32%, MTTP 5.3 mo. 2 y OS 21%.

Iressa ZD1839, **FDA approval** (accelerated approval as monotherapy in failures to CDP+TXT NSCLC) **on May 5th, 2003**. Second line IDEAL 1 & 2 TRIALS: OR 10-20% NC 30%, MST 6.5 –7.6 mo. OR better for females (17.5% vs 5.1%) and non smokers (28.6%), 75% had adenocarcinoma, MRD 250 mg/d. Diarrhea 50%, rash 50%, pulmonary interstitial fibrosis <1%. INTACT TRIALS no first line OR/MST improvement in combination with CDDP-GEM or CBDCA-TXL. (J Baselga JCO 2004;22:759-61, need of preclinical and early clinical results before large randomized studies).

N Akerley et al CALGB (Cancer 2003;97:2480-6). N=38, No prior RX. TXL 150 mg/m² in 3 h iv wkly x 6 q 8 wk (high dose). Neurotoxicity >50%, Hematologic toxicity 39%. PR 42%, MST 12.6 mo, 2 y OS 26%.

NK Altorki et al (JCO 2003;21:2645-50). N=29, stage IB-IIIa. Celecoxib 400 mg bid qd + TXL 225 mg/m² + CBDCA AUC 6 q 3 wk x 2 then operation: Operated and resected 28/29. No pCR found, 24% micro residual tumor, down staged 13/29. OR 65% (CR 17%). Toxicity hematol 67%. Celecoxib increased OR. Patients showed normal PGE₂ levels. Confirmatory trial on going...

Ch Belani et al (JCO 2003;21:2933-9). N=401, Stage IIIB-IV. Randomized to TXL 100 mg/m² wkly + CBDCA AUC 6 d 1 (OR 32%, MTTP 30 wk, MST 49 wk, 1 y OS 47%) vs TXL 100 mg/m² + CBDCA AUC 2 wkly x 3 q 4 wk (OR 24%, MTTP 21 wk, MST 31 wk, 1 y OS 31%) vs TXL 150 mg/m² 1st cycle and then 150 mg/m² cycle 2 + CBDCA AUC 2 wkly x 6 q 8 wk (OR 18%, MTTP 27 wk, MST 40 wk, 1 y OS 41%). At wk 16 maintenance randomized to TXL 70 mg/m² wkly x 3 q 4 or no RX. First arm best therapeutic index...

***JG Paez et al DFCI (Science 2004;304:1497). Mutation of EGFR 15/58 Japanese tumors and 1/61 USA tumors. Gefitinib response only in mutated cases 5/5 responders when mutation in TK domain and 0/5 responses when no mutation found.

***T Lynch et al MGH (NEJM 2004;350:2129-39). Identified TK domain mutation of EGFR gene in 8/9 patients with Gefitinib responses and in 0/7 non responders.

**V Miller et al MSKCC (JCO 2004;22:1103-9). N=139 on Gefitinib. OR 15%. Prognostic factors of the response: Adenocarcinoma 19% vs 0%, Bronchioloalveolar 38% vs 14%, non smoker 36% vs 8%, and KPS>80 22% vs 8%.

**D Johnson et al (JCO 2004;22:2184-91). N=99, Phase II. Randomized to TXL 200 mg/m² + CBDCA AUC 6 + BV 15 mg/kg (OR 31.5%, MTTP 7.4 mo, OS 17.7 mo) vs CBDCA + TXL (OR 18.8%, MTTP 4.2 mo, OS 14.9 mo). Toxicity minor mucocutaneous hemorrhage and major hemoptysis in squamous cell ca with necrosis and cavitation. Favorable in non squamous cell carcinoma.

**N Hanna et al (JCO 2004;22:1589-97). N=571, second line therapy. Randomized to Alimta 500 mg/m² d 1 + Vit B12 + FA + DXMTS q 3 wk (OR 9.1%, MOS 8.3 mo, 1 y OS 29.7%) vs TXT 75 mg/m² + DXMTS d 1 q 3 wk (OR 8.8%, MOS 7.9 mo, 1 y OS 29.7%). Equivalent.

C Monnerat et al (Clin Ca Res 2004;10:5439-46). N=60, Untreated, stage III-IV. GEM 1250 mg/m² d 1 & 8 + Alimta 500 mg/m² d 8 + FA + Vit B12. OR 15.5%, NC 50%. MOS 10.1 mo, 2 y OS 18.5%, MPFS 5 mo.

H Hotta et al (JCO 2004;22:3852-9). Meta-analysis comparing CCDP vs CBDCA based chemotherapy. 8 trials, 2948 patients. CDDP best OR but survival was equal (HR 1.05). Two drugs better survival HR 1.1 (11% benefit) than CBDCA with same combination agents.

Y Ichinose et al (Clin Ca Res 2004;10:7860-4). S1 40 mg/m² bid x 21 d + CDP 60 mg/m² d 8 q 5 wk. N=56. 1 CR + 25 PR (OR 47%), MST 11 mo, 1 y OS 45%.

N Hanna et al (JCO 2004;22:1589-97). N=571. Second line ChX randomized to Alimta, 500 mg/m² + Vits q 3 wk (OR 9.1%, MPFS 2.9 mo, MST 8.3 mo) vs TXT 75 mg/m² q 3 wk (OR 8.8%. MPFS 2.9 mo, MST 7.9 mo). Less toxic, no alopecia.

**** D H Johnson et al (JCO 2004;22:2184-91). N=99. Randomized study CBDCA AUC 6 + TXL 200 q 3wk + BV 15 mg/kg (OR 31.5%, TTP 7.4mo, MOS 17.7 mo) vs CBDCA + TXL (OR 18.8%, TTP 4.2 mo, MOS 14.9 mo). Major hemophthisis in squamous cell, cavitated, tumor necrosis and tumor invading major blood vessels...

***T Hoang et al ECOG DATA (JCO 2005;23:175-83). Prediction of OS with third generation regimens. Stage II (effusion) or IV: OR 20%, MST 8.2 mo, 1 y OS 33%, 2 y OS 11%. Factors: Skin mets (HR 1.88) score 66, Lower KPS (HR 1.46) score 43, Loss appetite (HR 1.62) score 38, liver mets (HR 1.32) score 35, >4 bone mets (HR 1.2) score 19, and no prior surgery (HR 1.16) score 15. Adding scores define a four risk groups: Low risk score <40 (1 y OS 40%, 2 y OS 15%); low intermediate score 40-60 (1 y OS 34%, 2 y OS 10%); high intermediate score 60-80 (1 y OS 27%, 2 y OS 6%); high score 80-120 (1 y OS 14%, 2 y OS 2%).

R Herbst et al (JCO 2005;23:2544-55). Erlotinib 150 mg/d po + BV 15 mg/kg q 3 wk. N=40 non squamous cell after prior ChX. OR 20% + NC 65%, MOS 12.6 mo, MPFS 6.2 mo.

****MS Tsao et al NCIC BR.21 (NEJM 2005;353:123-32). Double blind randomized trial second line Erlotinib vs Placebo. N=731, 49% prior Rx, 93% prior Pt ChX. OR 8.9% vs <1%, MDR 7.9 mo vs 3.7 mo, PFS 2.2 mo vs 1.8 mo, OS 6.7 mo vs 4.7 mo. ***** (NEJM 2005;353:133-44). OR to Tarceva related to mutation in EGFR (exon 19 del, and L858R exon 20) Number of copies non related to OR to Tarceva. OR not related to survival benefit...

T Takano et al (JCO 2005;23:6829-37). N=66 . Relapsed after surgery. 39/66 (59%) had EGFR mutation (20 with del 19, and 17 L858R as well as others, and had OR 32/39 (82%) to Gefitinib as compared with only 3/27 without EGFR mutation. MTTP 126 mo vs 1.7 mo, MOS 20.4 mo vs 6.9 mo. Another 29/66 (44%) had increased EGFR copies (>3/cell) and presented OR 72% (21/29) (no overexpression 38% (14/37), MTTP 9.4 vs 2.6 mo.

F Hirsch et al SWOG (JCO 2005;23:561-9). N=81 BAC. Treatment with Iressa 500 mg/d. EGFR+ by FISH (MOS 18+ mo, MPFS 9 mo, OR 63%) while EGFR- by FISH (MOS 8 mo, MPFS 4 mo, and OR 39%). T Mukohara et al (JNCI 2005;97:1185-94). Cell lines with EGFR mutation. Compared Gefitinib and

Cetuximab indicating better Gefitinib and suggesting a different mechanism of action for Cetuximab.

RL Yanch et al (Clin Ca Res 2005;11:8686-98). Multiarray study indicated that NSCLC cell lines showing epithelioid to mesenchymal transition presented resistance to Erlotinib, and E cadherin/ catenin correlated with Erlotinib sensitive cell lines

JY Han et al (Cancer 2005;104:2759-65). CPT 90 mg/m² d 1 & 8 + XEL 1000 mg/m² bid d 1-14 q 3 wk. OR 41.5%, MOS 14.6 mo. Non toxic.

***KL Reckamp et al (Clin Ca Res 2006;12:3381-8). Celecoxib optimal biological dose 600 mg bid (maximal urinary decrease of PGE-M without toxicity) + Erlotinib 150 mg qd. N=22, OR 7PR (33%) + 5NC (24%), Rash 86%. Decrease PGE-M in 8 wk. 5/17 EGFR mutation all had OR. COX2 inhibitors synergistic with EGFR pathway inhibition.

****K Olanssen et al (NEJM 2006;355:983-91). Reviewed ERCC1 by IHC (8FI, Neomarkers) in tumor biopsies after IALT study indicated CDDP adjuvant therapy improved survival in Stage I-III after surgery in NSCLC. ERCC1 + in 44% (N=335) and negative in 56% (N=426). CDDP OS improved only in ERCC1 negative (HR 0.65), but ERCC1 + patients without CDDP had a better survival (HR 0.66). In ERCC1 negative 5 y OS 47% vs 39%, MST 56 mo vs 42 mo. There was no difference for ERCC1+ due to ChX. 5 yOS for ChX 44% and control 42%.

S Niho et al Chiba Japan (JCO 2006;24:64-9). First line Gefitinib in Japan. N=42. OR 30%. Acne 50%, diarrhea 18%, liver toxicity 8%, fatal pulmonary interstitial disease 10%. MST 13.9 mo, 1 y OS 55%. EGFR mutation detected in 4/13 patients and all had a response.

A Paccagnella et al (JCO 2006;24:681-7). N=324. Randomized study of TXL 200 + CBDCA AUC6 + GEM 1000 d 1 & 8 (OR 46%, MTTP 7.6 mo, MOS 10.8 mo, 1 y OS 45%) vs TXL + CBDCA (OR 20%, MTTP 5.1 mo, MOS 8.3 mo, 1 y OS 34%).

****H Yasuda et al (JCO 2006;24:688-94). N=120 advanced IIIB & IV. Randomized to NITROGLYCERIN patches 25 mg/d x 5 starting d-3 + NVB 25 mg/m² d 1 & 8 + CDDP 80 mg/m² d 1 (OR 72%, TTP 327 d, MOS 413 d) vs NVB + CDDP (OR 42%, TTP 185d, MOS 289d... What about Radiotherapy?...

R Ramblan et al (JCO 2006;24:2800-7). N=829, IIIBand IV, PS>2, only one prior ChX. Randomized to TPTC 2.3 mg/m² d 1-5 po (1 y OS 25.1%, TTP 11.3 wk, OR 5%) vs TXT 75 mg/m² d 1 (1 y OS 28.7%, TTP 13.1 wk, OR 5%).

*****M Ando et al (JCO 2006;24:2549-56). Interstitial lung disease in Japan. Gefitinib series of 1967 patients in 84 centers. 70 cases, 31 deaths.

Incidence 3.5%, mortality 1.6%, correlated with smoking, male gender and interstitial pneumonia.

R Petty et al (JCO 2006;24:1729-44). Serpin B3 elevation correlated with Platinum response in SCC (HR 0.43) and paradoxically in adenocarcinoma (HR 2.09).

Z Zheng et al (NEJM 2007;356:800-8). ICH determination of RRM1 protein (involved in nucleotide excision repair) and ERCC1 (involved in DNA excision repair complex) in N=187 operated early stage NSCLC demonstrated positivity in both genes in 30%, identified as a group with excellent prognosis and 5y OS >80%. Since ERCC1 indicate resistance to CDDP and GEM it is difficult to explain the good prognosis but certainly indicated no need of adjuvant chemotherapy.

A Sandler et al ECOG (NEJM 2006;355:2542-50). N=878, stages IIIB & IV, no CNS, hemoptysis, low ECOG and organ disease, excluding squamous cell histology (hemorrhage). Randomized to TXL 200 mg/m² + CBDCA AUC 6 + BV 15 mg/kg q 3 wk (MST 12.3 mo, MPFS 6.2 mo, OR 35%, Bleeding 4.4%, MOS 11.7 mo, Females 13.3%) vs TXL + CBDCA ((MST 10.3 mo, MPFS 4.5 mo, OR 15%, Bleeding 0.74%, MOS 8.7 mo, Females 13.1%).

*R Lilienbaum et al (JCO 2006;24:4825-32). N=133, second line ChX, prior Pt based Rx. Randomized to CPT 60 mg/m² + TXT 35 mg/m² d 1 & 8 q 3 wk + Celecoxib 400 mg bid vs CPT 100 mg/m² + GEM 1000 mg/m² d 1 & 8 q 3 wk. Arm with Celecoxib had decreased 1 y OS 22% vs 36%. OR < 5%.

***G Giaccone et al (Clin Ca Res 2006;12:6049-55). First line Erlotinib 150 mg qd in NSCLC. N=53. OR 6/24 adenocarcinoma + 4/6 BAC + 2/8 SCC + 0/9 LCC + 0/6 other types (OR 27%), MDR 333 d. MST >1y. Compared favorably with ChX.

**D Jackman et al (JCO 2007;25:760-6). N=80. Elderly untreated patients treated with Erlotinib 150 mg qd. OR 10/ + NC 41%. MST 3.5 mo, MST 10.9 mo, 2 y OS 19%.

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J Y Pawel et al (JCO 2001;19:1743-9). Relapsed sclc. Randomized to TPTC oral 2.3 mg/m²/d x 5 q 3 wk (MST 32 wk, OR 32%, Myelotoxicity 35.5%) and TPTC iv 1.5 mg/m²/d x 5 q 3 wk (MST 25 wk, OR 15%, Myelotoxicity 67.3%).

K Noda et al (NEJM 2001;346:85-91). M=154. Randomized to CPT 60 mg/m² d 1, 8 & 15 + CDDP 60 mg/m² d1 (2 y OS 19.5%, CR 2.6%, PR 84.4%) vs CDDP 80 mg/m² d 1 + VP 100 mg/m²/d x 3 (2 y OS 5%, MST 9.4 mo, CR 9.1%, PR 67.5%). MST gain remarkable.

J Jett et al (Cancer 2003;97:2498-503). CDDP 30 mg/m²/d x 3 + VP 100 mg/m²/d x 3, cycles 1, 3 & 5; TPTC 1 mg/m²/d x 5 + TXL 200 mg/m² d 5 + GCSF, cycles 2, 4 & 6. N=44. ED. Hematologic toxicity with ANC 70%, Plat 23%; OR 77%, MTTP 6.9 mo, MST 10.5 mo, 2 y OS 12%.

A Ardizzoni et al (JCO 2002;20:3947-55). N=244, M F up 54 mo. Randomized study comparing CPA 1 g/m² + DOX 45 mg/m² + VP 100 mg/m² x 3 q 3 wk (Hematol toxicity grade IV 50%, OR 79%, MST 54 wk, 2 y OS 15%) vs **higher dose** CPA 1250 mg/m² + DOX 55 mg/m² + VP 125mg/m² x 3 + GCSF repeated q 2 wk (Hematol tox 79%, OR 84%, MST 52 wk, 2 y OS 18%). DI doubled sine benefit.

A Ardizzoni et al (Clin Ca Res 2003;9:143-50). N=110 resistant. CDDP 60 mg/m² + TPTC 0.75 mg/m²/d x 5 q 3 wk. Hematologic toxicity ANC 50-62%, Plat 44-54%. OR 30%, MST 6.4 mo.

M Reck et al (JNCI 2003;95:1118-27). N=614, stage IV. Randomized to TXL 175 mg/m² + VP 125-100 mg/m² x 3 + CBDCA AUC 5 q 3 wk (OR 72.1%, MST 12.7mo, 2 y OS 17%, 3 y OS 17%) vs VCR 2 mg + VP 125-160 mg/m² x 3 + CBDCA AUC 5 (OR 69.4%, MST 11.7, 2 y OS 16%, 3 y OS 9%).

*****R Kowaki et al MDACC (Sem Oncol 2003;30:56-70. Review. Work up: Cognitive evaluation done at diagnosis demonstrate 83% LD patients have deficiencies. When LDH is elevated BM aspiration biopsy should be carried out. Thoracocentesis when pleural effusion is present. PET. Prognostic factors are: age and gender, stage, continuing smoking, LDH, Na, Phosphatase alkaline. ChX: CAV-PE-IFX/TXL addition; CPT+CDDP>PE; Higher dose >lower dose (Arriagada, NEJM 1993; 329: 1848-52, indicating CDDP 100/CPA 300/DOX 40/VP 75 is better than CDDP 80/CPA225/DOX40/VP75 with a 2 y DFS 28% vs 8%; and Hainsworth, JCO 1997; 15; 3464-70), indicating that TXL 200/PE/RT is better than TXL 135/rest equal with CR 71% vs 40%. Combined ChX + RT increase 2 y OS from 10-15% to 25-30%, with still intrathoracic recurrences. Local control improves 25% & 2 y OS 5.4%. Also early thoracic irradiation with bid fractionation (1.5 Gy), 45 GY in the thorax improve local control from 40% to 55% and 2 y OS from 20% to 45%. Future improvements in dose elevation up to 65 Gy, and volume of thoracic irradiation in the postchemotherapy volume.

*****D Fried et al (JCO 2004;22:4785-93). Randomized trials timing thoracic RT in LD: Benefit for early RT (RR 1.17 2 y OS and RR1.13 3 y OS); Benefit for hyperfractionation (RR 1.44 2 y OS and 1.39 for 3y OS); No differences for once or twice daily fractionation; Benefit for CDDP based ChX (no diff for non CDDP based ChX) (RR 1.3 2 y OS, RR 1.35 3 y OS).

C Rudin et al (JCO 2004;22:1110-7). G3139, Oblimersen sodium (bcl2 antisense oligonucleotide). N=16. Oblimersen Na 5 mg/kg/d (escalated to 7 mg/kg) from d1-8 q 3 wk + CBDCA AUC 6 on d6 + VP 80 mg/m² d 6-8. OR 12/16 (86%), NC 2/16. MTTP 5.9 mo.

JY Han et al (JCO 2005;23:3488-94). N=35 LD. CPT 80 mg/m² + CDDP 40 mg/m² wkly x 3 q 4 x 2 induction, then RT bid 45 Gy + concurrent CDP 60 mg/m² + VP 100 mg/M²/d x 3 x 2 cycles. OR 97% after induction and 100% after RT. MF up 26.5 mo, MOS 25 mo, 2 y OS 54%, MPFS 12.9 mo, 2 y PFS 36.1%.

M Socinski et al (Sem Oncol 2005;32:1-4). First line randomization. CDDP 75 mg/m² + Alimta 500 mg/m² q 3 wk (N=35, OR76%) vs CBDCA AUC 5 + Aslimta (N=33, OR 58%).

**H Bozcuk et al (Cancer 2005;104:2650-7). Meta-analysis of maintenance ChX (14 trials, 2,550 patients), indicated improvement in 1 y OS 9% and 2 y OS 1%.

A Brau % I Tannock (JCO 2006;24:1020-2). Meta-analysis of early vs late RT showed a 1.8% decrease in OS per week delay over 3wk after the start of ChX. Hypothesis is repopulation resistance.

JR Eckardt et al (JCO 2006;24:2044-51). N=784, ED. Randomized to TPTC 1.7 mg/m² qd x 5 + CDDP 60 mg/m² d 5 q 3 wk (OS 39.3 wk, 1 y OS 31%, OR 63%, TTP 124.1 wk) vs VP 100 mg/m² qd x 3 + CDDP 80mg/ m² d 1 (OS 40.3 wk, 1 y OS 31%, OR 69%, TTP 25.1 wk. Similar results.

S Onoda et al (JCO 2006;24:5441-7). N=60, refractory. Amrubicin 40 mg/M² qd x 3 q 3 wk. OR 50%, PFS 2.6 mo, OS 11.6 mo. Active.

SJ Antonia et al (Clin Ca Res 2006;12:878-87). N=29. Patients with progression after conventional ChX treated with DC transfected with adenovirus carrying wild type p53, and 57% presented p53-T cell specific response without response: OR 1 PR + 7 NC + 21 PD. Subsequent chemotherapy on 23 patients showed 3 CR + 10 PR + 4 NC (third line), MOS 11.8 mo. It appears that specific vaccination improved second line ChX response.mm