PD-039 A phase II study of cetuximab (C225) in combination with chemoradiation (CRT) in patients (PTS) with stage IIIA/B non-small cell lung cancer (NSCLC): An interim overall toxicity report of the RTOG 0324 trial

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Background: Cetuximab (C225) is a chimerized monoclonal antibody that targets the epidermal growth factor receptor (EGFR). NSCLC commonly expresses the EGFR, which is associated with aggressive tumor behavior and poor clinical outcome. Preclinical model systems demonstrate radiosensitization following molecular inhibition of EGFR signaling. An ongoing Phase II trial is testing cetuximab, with CRT, in unresectable stage III NSCLC.
Methods: Eligibility criteria include Zubrod performance status (PS) ≤1, weight loss ≤5% over past 3 months, FEV_1 ≥1.2 l, adequate hematologic, hepatic, and renal function. PTS start an initial dose of C225 (400 mg/m^2) on day 1 of week 1, then weekly doses of C225 (250 mg/m^2) until completion of therapy (weeks 2–17). During week 2, patients receive CRT (63 Gy/35 fractions) with weekly carboplatin (C) AUC 2 and paclitaxel (P) 45 mg/m^2 x 6 doses followed by C (AUC 6) and P (200 mg/m^2) x 2 cycles (weeks 12–17). Interim monitoring for severe (grade ≥3) or excessive non-hematological toxicities will occur after PTS have been treated and followed for at least 90 days after RT. Endpoints include safety and compliance of concurrent C225 and CRT.
Results: 41 PTS have been entered to date with toxicity data available on 22. PTS characteristics (n = 33): 67% male, median age 68 years (range 42–84), 48% PS 0, 48% stage IIIA. Data on adverse events related to treatment (n = 22): 1 PTS with grade 3 thrombocytopenia, 5 PTS with grade 3 leukopenia and 1 PTS with grade 4 leukopenia. Number of grade 3 non-hematological toxicities: Metabolic/laboratory (4), fatigue (2), pulmonary (2), dermatologic (1), anorexia (1), pain (1), and allergy (1). There have been no grade 4 non-hematologic toxicities.
Conclusions: Patient accrual is ongoing. This regimen appears to be well tolerated. Updated toxicities will be reported.

PD-040 Efficacy and morbidity of a novel induction treatment for locally advanced NSCLC

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Background: The disappointing results of surgical therapy in patients with locally advanced non small cell lung cancer (NSCLC) have led to the investigation of induction treatments. Of these, phase II trials studies have shown that chemo-radiotherapy administered before surgery yields a down-staging with a significant complete pathological response amount. These results are often linked to enhanced surgical toxicities and impact on survival is not clear.
The aim of this study was to assess the efficacy and morbidity of a novel chemo-radiotherapy regimen followed by surgery in patients with locally advanced NSCLC.
Methods: From October 2000 to October 2004, 92 patients (age: 34–76 y, median 59 y; PS 0–1) with locally advanced NSCLC (12 IIB, 22 IIIA, 47 IIIB, 11 IV) were proposed induction chemo-radiotherapy. Chemotherapy consisted of 3 cycles of cisplatin 80–100 mg/m^2 + ifosfamide 3–4.5 g/m^2 + vinorelbine 25 mg/m^2 (3x) and was administrated on days 1–2–8–15 (1st cycle), 29–30–36–43 (2nd cycle) and daily from day 59 to 64 (3rd cycle). Concurrent thoracic irradiation (40Gy) was given from day 36 to 64. Three-dimensional dosimetry was performed using CT scan and ISIS treatment planning.
At the end of the induction treatment, 37 (initial staging: 9 IIB, 12 IIIA, 14 IIIB, 2 IV) of these 92 patients (40%) demonstrated objective clinical down-staging, had a good general status and were submitted to surgical resection (lobectomy: 16, pneumonectomy:15 left and 6 right). For these 37 patients, mean (SD) planning treatment volume was 656 (368) cm^3, V20 and V30 were 17 (5) and 14 (5) %, respectively. Mean (SD) fraction of oesophagus and heart receiving 40 Gy were 49 (18) and 14 (13) % respectively.
Results: Complete pathological response was found in 12/37 patients (32%). Median follow-up of these 37 patients was 14 months (3–51) and projected 2 years survival is 66%. Main side effects of induction treatment included grade ≥3 oesophagitis and febrile neutropenia in 50 and 12% of the patients, respectively. Three patients (all left pneumonectomies) died post-operatively from ARDS: 2 early after massive haemorrhage and transfusion and 1 at day 15 without bleeding or infection. Otherwise, no infection or bronchopleural fistula was noted.
Conclusions: This preliminary study demonstrates that induction chemotherapy with cisplatin, ifosfamide, vinorelbine combined with thoracic irradiation can convert 40% of inoperable locally advanced NSCLC patients to candidates for surgical resection. Early results promise improvement in survival with high but tolerable toxicity.

PD-041 Phase II trial on neoadjuvant chemoradiation with paclitaxel/carboplatin in stage III NSCLC

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Background: To test efficacy of a weekly schedule of paclitaxel and carboplatin in combination with hyperfractionated/accelerated radiotherapy (HFX-RT) in the neoadjuvant setting in locally advanced NSCLC.
Methods: Patients (>17 to <70 years, KPS > 70%) with stage III NSCLC (staging: CT-thorax/abdomen/cranium, PET, and mediastinoscopy) without supraclavicular lymph node involvment were qualified for the study. Paclitaxel 100 mg/sqm and carboplatin AUC 2 were administered at day 1, 8, 15, and 22 followed by HFX-RT starting at day 43 (2 x 1.5 Gy/day, 5x/week to 45 Gy) with simultaneous paclitaxel (50 mg/sqm) and carboplatin (AUC 2) at day 44, 51, and 58. After complete restaging, resections were planned 4–6 weeks after completion of the neoadjuvant therapy.
Results: 120 patients have been treated and complete data are available (30 IIIA, 88 IIIB; 2 IV). Grad III and IV toxicity occurred in 40 and 4 patients. Significant downstaging, no change, and progressive disease was observed in 60%, 34%, and 6% of the cases. R0 resections could be achieved in 62 (52%) patients. 15 (12.5%) patients had postoperative complete remission of the primary tumor and 31 (26%) patients complete remission of mediastinal nodes. After a median follow up of 41 months, 61 relapses have been observed. Median survival was 14 months, 5 year overall survival 29%. Median survival and 5 year overall survival was 64 months and 56% in complete resected patients and 9 months 0% in unresected patients ($p < 0.0001$).
Conclusions: In conclusion the tested neoadjuvant regimen exhibits tolerable toxicity, considerable activity and a promising 5 year survival of 56% for complete resected patients in advanced stage III lung cancer.

PD-042 Induction (I) or consolidation (C) chemotherapy with docetaxel (D) and gemcitabine (G) plus concomitant chemoradiotherapy (CT/TRT) with docetaxel and carboplatin (Cb) for unresectable stage III non-small cell lung cancer (NSCLC) patients (p). Initial report of the randomized phase II trial SLCG 0008

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Background: Standard treatment for unresectable stage III NSCLC p includes CT and XRT but the optimal sequence and the integration of new CT agents in the concurrent approach are not well defined yet.
Methods: P with unresectable stage III NSCLC with IK ≥70 and weight loss <5% were initially randomized to sequential treatment (arm A), concurrent CT/TRT followed by consolidation CT (arm B) or induction CT followed by CT/TRT (arm C). Based on RTOG 9410 results, arm A was removed and the study continues with two concomitant arms (B, C). All p receive 2 cycles of D 40 mg/m^2 d1, 8 plus G 1200 mg/m d1, 8 as I or C therapy. Concomitant treatment includes D 20 mg/m and Cb AUC 2 weekly plus 60 Gy TRT.
Results: From May 01 to Dec 04 102 p were included. An interim analysis was provided when a half of p were recruited (N: 70). Preliminary data of these p (arm A: 18, arm B: 27, arm C: 28) are available although only results of both concomitant arm are presented. All groups are well-matched for baseline disease characteristics. Toxicity grade 3–4 by CTC and RTOG criteria (27 p arm B / 28 p arm C) was: esophagitis 22% (arm B) and 20% (arm C); neumonitis 3.7% (arm B) and 10% (arm C). Neutropenia during I or C therapy: 22% (18 p, arm B) and 7% (28 p, arm C). Trombocytopenia 11% (arm B) and 7% (arm C). Neutropenia during concomitant therapy: 3.7% (27 p, arm B) and 5% (20 p, arm C). No thrombocytopenia or anemia severe were found during CT/TRT. The reduction rate was superior in consolidation (39%) than in induction (7%) CT. The preliminary response rate were 66.7% (arm B, 18 p analyzed) and 50% (arm C, 20 p analyzed). Nine p (13.6%) withdrawn the study due to toxicity and there were two treatment related deaths.
Conclusions: Concomitant TRT with weekly Docetaxel and Carboplatin is feasible without increasing toxicity. Non-platinum CT can be used as induction