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Health-related quality of life (HRQOL) with sunitinib (SU) as maintenance therapy following carboplatin (C) and paclitaxel (P) treatment for locally advanced or metastatic non-small cell lung cancer (NSCLC)

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Background: SU is an oral, multitargeted tyrosine kinase inhibitor of VEGFRs, PDGFRs, KIT, FLT3, CSF-1R, and RET. An open-label, multicenter, phase II trial was conducted to study SU as maintenance therapy following first-line treatment with C/P in patients (pts) with stage IIIB/IV NSCLC. We report HRQOL data during C/P treatment and the SU maintenance period from this trial [NCT00113516: Pfizer].
Materials and Methods: Pts received P (175−225 mg/m^2) plus C (AUC = 6 mg·min/mL) for 4 cycles followed by SU maintenance monotherapy (50 mg/d in 6-wk cycles: 4 wks on treatment, 2 wks off). HRQOL was assessed using EORTC QLQ-C30 and QLQ-LC13. Questionnaires were completed on day 1 of each C/P treatment cycle and days 1 and 28 of each 6-wk SU cycle. The long-term effect of C/P and SU on global quality of life (GQL), functioning, and symptom scales were examined with longitudinal models to compare difference in mean changes from baseline between C/P and SU treatment during corresponding cycles. The short-term effect of SU was examined with paired t-tests to compare mean change on-treatment versus off-treatment periods at cycle 1.
Results: A total of 84 pts received C/P, and 66 pts received SU maintenance therapy. Long- and short-term data were available for 36 and 29 pts, respectively. Relative to C/P, SU following C/P was suggestive of long-term improvements in emotional functioning (cycle 4, +14.2 points, $p = 0.08$), social functioning (cycle 4, +20.3 points, $p = 0.07$), fatigue (cycle 3, −13.9 points, $p = 0.06$; cycle 4, −21.3 points, $p = 0.04$), dyspnea item in C30 (cycle 4, −15.1 points, $p = 0.09$) and dyspnea scale in LC13 (cycle 4, −20.6 points, $p = 0.03$). Long-term worsening symptoms included diarrhea (cycle 1, +7.8 points, $p = 0.06$; cycle 2, +24.5 points, $p < 0.01$) and sore mouth (cycle 1, +10 points, $p = 0.04$). Statistically significant improvements ($p < 0.04$) were observed for peripheral neuropathy and alopecia due to cessation of C/P in nearly all visits. Short-term worsening in HRQOL at cycle 1 of SU treatment included fatigue (+7.4 points) and sore mouth (+13.3 points) while improvements included cognitive functioning (+6.1 points) and arm and shoulder pain (−8.0 points); all $p < 0.05$.
Conclusions: While there were increases in some treatment-related symptoms, this study found that SU maintenance treatment after C/P may also lead to some long-term improvements in HRQOL and functioning. SU maintenance therapy may be a feasible treatment option for pts with advanced NSCLC.

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Cetuximab in combination with gemcitabine/docetaxel or carboplatin/gemcitabine in chemonaïve patients with advanced non-small cell lung cancer: toxicity data from an ongoing Phase II/III trial (GemTax IV)

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Background: The EGFR-targeting antibody cetuximab has been shown to be effective in lung cancer. Our randomized trial assesses the safety profile of cetuximab in combination with two different chemotherapy regimens.
Methods: Patients with histologically confirmed stage IIIB or IV NSCLC, WHO PS 0−2, and no prior chemotherapy received cetuximab with 400 mg/m^2 as starting dose followed by 250 mg/m^2 weekly either combined with gemcitabine 1000 mg/m^2 at days 1 and 8 for 2 cycles (3qw) followed by docetaxel 75 mg/m^2 at day 1 for 2 cycles (q3w) (arm A) or carboplatin AUC5 at day 1 combined with gemcitabine 1200 mg/m^2 at days 1+8 for 4 cycles (q3w) (arm B). Maintenance cetuximab therapy was administered weekly until disease progression or unacceptable toxicity.
Results: 273 evaluable patients received 2255 cetuximab infusions combined with chemotherapy and 1591 infusions of maintenance cetuximab. Patient characteristics were balanced between treatment arms with 73% male patients of median age 64 years (range 36−80), 37% of WHO PS 0 and 56% of PS 1, and 84% had tumor stage IV. 49 patients in arm A received 1−26 cycles of maintenance cetuximab (8 patients >10 cycles); 61 patients in arm B received 1−23 cycles (7 patients >10 cycles). Grade 1 or 2 skin 0reactions related to study medication occurred in 83% of patients in arm A and 77% in arm B. In general, hematological toxicity was more common in patients receiving carboplatin; leukopenia and neutropenia occurred in more than 30% of patients, pneumonia and fever occurred in ~10% of patients; thrombopenia without intervention in 40% of patients, and allergic reactions in 5% of patients. Toxicities requiring clinical intervention are shown below.

	Arm A		Arm B	Maintenance
	Cetuximab plus gemcitabine (n = 136)	Cetuximab plus docetaxel (2nd part of the sequence) (n = 82)	Cetuximab plus gemcitabine/ carboplatin (n = 137)	Cetuximab maintenance (n = 110)
Total number of cycles	241	141	428	565
Median number of cycles	2	2	4	3
Grade 3/4 anemia + ⩾ 1 blood transfusion during treatment cycle (%)	<1	1	2	
Grade 3/4 thrombocytopenia + ⩾ 1 platelet transfusion during treatment cycle (%)	<1		6	
Grade 3/4 febrile neutropenia + IV antibiotics during treatment cycle (%)	<1	4	1	
Skin rash any (severe) (%)	56 (5)	21 (5)	38 (5)	8 (<1)

Conclusions: Cetuximab does not increase chemotherapy toxicity in the induction phase, and is well tolerated in the maintenance phase. Skin rash developed in about 80% of patients, and occurred early during treatment in most cases.

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Bevacizumab (B), cisplatin and vinorelbine in chemo-naïve patients (P) with non squamous non small cell lung cancer (NSCLC): a galician lung cancer group phase II study

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Background: Bevacizumab, an anti-VEGF monoclonal antibody, improves response rates and prolongs survival in p with non squamous NSCLC when combined with carboplatin-paclitaxel or cisplatin-gemcitabine. This single-arm, open-labeled phase II trial aims to evaluate the efficacy and safety profile of B in combination with another widely used chemotherapy doublet for NSCLC: cisplatin and vinorelbine.
Methods: Chemotherapy-naïve p diagnosed with stage IIIB or IV non squamous NSCLC received cisplatin (80 mg/m^2), vinorelbine (25 mg/m^2 IV days 1 and 8) and B (15 mg/kg IV) on day 1 every 3 weeks for up to 6 cycles followed by B 15 mg/kg alone every 3 weeks until disease progression. Main eligibility criteria were: PS 0−1, no brain metastases, no history of hemoptysis, stable cardiac condition and no full dose anticoagulation Primary endpoint was progression-free survival and secondary endpoints were RR, duration of response, OS, 1-year survival and safety profile of the combination.
Results: 49 p have been enrolled in the study and data of 27 p have been included in this analysis. P characteristics were: male 66.7%; median age 57 years (range 41−74); ECOG PS 0/1 (%) 33.3/66.7; adenocarcinoma/other (%) 74.1/25.9; stage IIIB/IV (%) 25.9/74.1. Median number of cycles for B/cisplatin/vinorelbine was 4.0 (range 1−6) and median number of cycles for B maintenance was 2 (range 1−4). 17 p were

evaluable for response according to RECIST criteria: PR 29.4% and SD 41.2%. With a median follow-up of 3.9 months (range 0.7−11.1), median PFS was 4.6 months (95% CI: 2.6−6.6) and median OS has not been reached yet. Hematological toxicities were: 1 p gr. 3 anemia; 2 p gr. 3 and 2 p gr. 4 leucopenia; 10 p gr. 3, 1 p gr. 4 neutropenia and 3 p febrile neutropenia. Most common grade 3/4 non hematological toxicities were: vomiting (1p gr. 4), high blood pressure, asthenia and hyperglycemia. 1 p experienced gr. 4 abdominal pain, 1 p. gr. 4 constipation, 1 p. gr. 4 nausea and 1 p gr. 4 respiratory infection. No grade 3/4 hemoptysis were reported.
Conclusions: This interim analysis shows that B in combination with cisplatin and vinorelbine is safe and well tolerated and has a promising activity in chemo-naïve p with non squamous NSCLC. Survival data will be updated.

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Long term benefit from erlotinib treatment is independent of prognostic factors and therapeutic response

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Background: Erlotinib (Tarceva®) is an orally-active targeted inhibitor of the epidermal growth factor receptor. In the TRUST study, a single arm open-label phase IV trial assessing Erlotinib treatment in over 7,000 patients with advanced non small-cell lung cancer (NSCLC), the median progression-free survival was 14.3 weeks. 20% of the TRUST study patient population had a progression free survival of more than 12 months. Based on these findings we have initiated this retrospective study, performed in Germany, in order to analyze the profile of long term survivors, thus optimizing the selection of NSCLC patients which will benefit the most from Erlotinib treatment.
Materials and Methods: Questionnaires were retrospectively filled in by attending physicians of patients surviving over one year from the TRUST cohort in Germany. Information of patients' demographics, disease and treatment characteristics were evaluated.
Results: Data from 301 patients were collected. The average age of long term survivors was 66 years (range 23−87). 75% of patients were in good or moderately restricted conditions (Eastern Cooperative Oncology Group score 0 or 1). 50% of the patients received Erlotinib as second line therapy; 52% had been treated with Erlotinib for at least 18 months, and 25% were treated for over 24 months. 43% of patients were male, 14% were smokers and 33% were past smokers. Histology type was adenocarcinoma and squamous cell in 67% and 15% of patients, respectively. 56% of patients had a stable disease over the course of treatment, while 44% had partial or full response. Although 78% of patients developed a typical skin reaction, the tolerability of Erlotinib was considered good or very good by 80% of treating physicians.
Conclusions: The long-term benefit of this target-oriented therapy, which was predominantly very well or well tolerated, was not limited to groups with good prognostic characteristics By contrast to conventional chemotherapy, long-term therapeutic success with Erlotinib was not restricted to patients in which complete or partial remission was induced. In summary, these data confirm Erlotinib to be effective in the long term treatment of NSCLC.

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Bevacizumab and erlotinib as first-line therapy in advanced (stage IIIB/IV) non-squamous non-small-cell lung cancer (NSCLC) followed by platinum-based chemotherapy (CT) at disease progression - a multicenter phase II trial of SAKK

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Background: Standard platinum-based CT for the treatment of advanced NSCLC is toxic and yields unsatisfactory results. This phase II trial aimed at evaluating the feasibility and efficacy of a first-line combination of two targeted therapies (TT), Bevacizumab (B) and Erlotinib (E), followed by standard platinum-based CT.
Methods: Inoperable patients (pts) with confirmed non-squamous stage IIIB or stage IV NSCLC, WHO performance status (PS) 0−1, without immediate need of CT, without large, centrally located tumors, pre-existing tumor cavitations and brain metastases were eligible. B was given at 15 mg/kg i.v. on day 1 of each 21-day cycle and E 150 mg p.o. daily until PD or unacceptable toxicity. Upon PD, patients received standard CT: gemcitabine 1250 mg/m^2 i.v. on days 1 and 8 q3w and either cisplatin 80 mg/m^2 or carboplatin AUC 5 i.v. on day 1 for a maximum of six cycles or until PD. Primary endpoint is disease stabilization (CR + PR + SD) at 12 weeks under B+E. Secondary endpoints are OS, RR, TTP, disease stabilization at 6 and 18 weeks, safety and QoL, response to subsequent CT and gene expression analysis.
Results: 101 eligible pts were accrued from January 9, 2006 to April 1, 2009. Median age 61y, 52.5% females, 85% stage IV, 49% PS 1, 29% never smokers. Among the 79 pts having stopped B+E, 70% continued to CT. Among 95 patients, the most frequent worst G3 toxicities during B+E were rash (3), acne (2), pruritus (2), hypertension (2), dyspnea (2, incl. one fatal) and diarrhea (2). There were 2 fatal hemorrhages and 1 cardiac failure. The median OS is 13.4 months (95% CI: 10.5−19.4 m) at a median follow-up of 17.5 m. Up to now, tumor assessments are available for 92 patients during B+E and for 53 during CT. Corresponding best RECIST-responses to first line B+E were 17.4% PR, 55.4% SD, 26.1% PD, and 1.1% early death. Best responses to 2nd line CT were 11.3% PR, 47.2% SD, 22.6% PD, and 18.9% not assessable.
Conclusions: Combined TT in first-line non-squamous NSCLC is feasible with acceptable toxicity and very good median OS. As the last patient was recruited on April 1, 2009, mature results of the primary endpoint and specific secondary endpoints will be available at the 2009 ESMO/ECCO meeting.

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Phase 1 study of the toll-like receptor 9 (TLR9) agonist, IMO-2055, combined with erlotinib (E) and bevacizumab (B) in patients (pts) with advanced or metastatic non-small cell lung cancer (NSCLC)

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Introduction: IMO-2055, a novel synthetic TLR9 agonist, induces Th-1 type immune responses and has shown promise in providing a potential means to control tumor growth. IMO-2055 has shown additive or synergistic antitumor activity in a number of tumor models in combination with cytotoxics, targeted therapies and monoclonal antibodies, including in lung cancer xenograft studies of IMO-2055, E, and B in triple combination. Clinical trials have shown IMO-2055 monotherapy is generally well tolerated given weekly for > 1 year. We report initial results of an open label 3+3 dose finding study of the combination of IMO-2055 with E and B.
Methods: IMO-2055 SC is given on days (d) 1, 8, and 15 of a 3-week (w) cycle. Dosages range from 0.08 to 0.48 mg/kg/w. B is given as 15 mg/kg IV on d1 and E as 150 mg PO daily. Pts have AJCC stage 3−4 histologically proven NSCLC not amenable to curative therapy, progression during or after 1st-line treatment, with ECOG score <2. Pts with intrathoracic