prior therapies, and 5 patients had more than two prior therapies. Median number of metastatic sites were 2 (range 1–5). Six patients were entered at dose level 0 and 6 patient entered at dose level 1 (Table).
Results: 9 of 12 patients have completed 12 weeks of therapy. Two partial responses have been observed. Six patients had stable disease. One patient has had progressive disease. The remaining patients are too early for evaluation. Non-hematologic toxicity was generally well tolerated. Hematologic toxicity at dose level 0 consisted of 3 patients with Grade 3/4 neutropenia and 1 patient with Grade 3 thrombocytopenia. Hematologic toxicity at dose level 1 consisted of 2 patients with Grade 2/3 neutropenia.
Conclusion: The completion of our phase I experience will determine an MTD.

Study design:

Protocol stage	Dose level	No. of patients	Interferon dosage	Thalidomide dosage	Capecitabine dosage (days 1–14, Wks 1+2)	Gemcitabine dose levels (Day 1, Wk 1 and Day 8, Wk 2)
1	−1	3	1 mlu bid	200 to 400 mg	1000 mg/m^2	200
1	0	3	1 mlu bid	200 to 400 mg	1000 mg/m^2	400

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Analysis of c-kit expression in small cell lung cancer patients and its clinical implications

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Background: c-Kit is a growth factor receptor with tyrosine kinase activity that play an important role in the biology of cancer and its expression has been documented in several malignancies. The aim of this study was to determine the incidence and role of CD117 overexpression as a predictive or prognostic marker in patients with small cell lung cancer (SCLC).
Patients and Methods: We performed a retrospective study with 51 patients diagnosed of SCLC between January 2000 to July 2003. Relevant clinical patient information was obtained from extensive chart review (age at diagnosis, performance status – PS, weight loss, tumor stage and response to therapy). c-kit expression was analysed in paraffin-embedded tumor tissues immunohistochemically with commercial antibodies and we obtain successful results in 40 patients (39 males and 1 female) with a mean age of 62.4 years.
Results: Positive c-kit expression was observed in 32.5% patients. At the time of diagnosis 27 patients presented extended disease (ED) while 13 patients limited disease (LD). c-kit expression was observed in 46.2% in LD and 25.9% in EE although this difference was not significant (p=0.21). Patients with a PS between 0–2 represented 85.7% of the c-kit positive group and 90% in the c-kit negative one. All patients were formers o actual smokers. Weight loss was present in 52.3% of the patients at diagnosis.
36 patients received as a median 4 cycles of chemotherapy as first-line treatment (78.6% vs 83.3% in c-kit positive and negative group). The most used schedule was platinum-salts + etopiside and the most common second-line agent was topotecan. Radiotherapy of the primary tumor was administered in 42.9% of the patients in the c-kit positive group and in 30% in the negative one.
Comparing the c-kit positive group vs the negative one, was observed Complete Response in 30.8% vs 7.4% of the patients while Partial Response in 15.4% vs 11.1% (with 7.7% vs 11.1% of patients who achieved PR>80%). Stable Disease was observed in 15.4% vs 14.8% and Disease Progression in 30.8% vs 51.9% of the patients. In patients with c-kit expression, the median survival was 16.01 months vs 7.6 months in the c-kit-negative population (p=0.093).
Conclusions: c-Kit is expressed in one third of the patients with SCLC. Our findings do not suggest a significant association between c-kit expression and survival. However more studies are needed to define its possible prognostic value.

Monoclonal antibodies and targeted toxins/nuclides

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Immunoassay and mass spectrometry analysis of specific EGFr phospho-tyrosines; effects of panitumumab (ABX: EGF), a fully humanized anti-EGFr monoclonal antibody, and the kinase inhibitor AG1478

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Background: There is a clinical need to verify and stratify patient response rate with bio- and surrogate markers. Over expression of the epidermal growth factor receptor (EGFr/ErbB1/HER1) and its ligands have been correlated with aggressiveness and poor prognosis in various tumors such as colon, breast and prostate cancer and treatment with antagonists of this receptor have been beneficial to some patients. We have previously shown, using mass spectrometry, seven ligand induced EGFr phosphorylation sites (J Am Soc Mass Spectrom. **14**:1022–1031) and quantified their phosphate content upon ligand (EGF, TGFα (and inhibitor (AG1478) addition. We have extended these results to include inhibition by panitumumab, a high affinity (KD=5×10^{-11}) fully human monoclonal antibody to EGFr. In addition, we report the development of an immunoassay platform to measure specific phosphotyrosines of the EGFr.
Material and Methods: Proliferating cell cultures of A-431, SK-MES, H1299, H2126, or xenografts (A431 or SK-MES) were pretreated with inhibitors before addition of ligand (EGF or TGFα (. Thereafter cells or xenograft tissue were immunoassayed using a BioVeris (Igen) platform. For LC tandem mass spectrometry, EGFr was immunoprecipitated and isolated by SDS-PAGE before analysis.
Results: The phosphate content of eight sites (T669, Y992, Y1045, Y1068, Y1086, S1142, Y1148, and Y1173) was measured by mass spectrometry upon ligand addition. Some sites exhibit large dynamic ranges (Y1045, Y1068, Y1086, Y1173) in their phosphate content, while other sites reach a plateau (Y992, S1142, Y1148). Decreases in phosphate content were seen with the addition of the EGFr inhibitor panitumumab similar to what was reported for the kinase inhibitor AG1478. The measurement of the phosphate content at several Tyr residues was adapted to a BioVeris immunoassay platform. Using this high through-put methodology we were able to detect increases in phosphate content with ligand addition and decreases in phosphate content upon inhibitor (panitumumab, AG1478) treatment of cells and xenograft tumors. An immunoassay using only monoclonal antibodies was also developed measuring phosphate content at Y1068.
Conclusion: We have identified specific Tyr residues that may serve as potential markers of the EGFr responsiveness to panitumumab administration. Phosphorylation induced by ligands or a decrease in phosphorylation by inhibitors (panitumumab, AG1478) can be monitored by measuring phosphate content at these ligand induced sites using a high through-put immunoassay. These experiments will allow us to investigate more precisely, the mechanism of action of anti-EGFr therapy in patients.

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Correlation of acne rash and tumor response with cetuximab monotherapy in patients with colorectal cancer refractory to both irinotecan and oxaliplatin

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Background: Cetuximab (Erbitux™), an IgG1 monoclonal antibody, has demonstrated activity in patients with epidermal growth factor receptor (EGFR)-expressing colorectal cancer (CRC) both as a single agent and in combination with irinotecan. Cetuximab binds specifically to the EGFR preventing homo- and heterodimerization and signal transduction. This large phase II study was designed to explore the activity of cetuximab in patients with metastatic CRC, with no clear treatment alternative.
Methods: Patients with metastatic EGFR+ CRC were eligible to enroll in this study if they have failed at least two prior chemotherapy regimens, containing irinotecan, oxaliplatin and a fluoropyrimidine. Patients were to receive cetuximab monotherapy at an initial dose of 400 mg/m^2, followed