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ABSTRACTS

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average of 4.6 (range 1–16) cycles of CMP, there were 1 complete remission (CR) and 7 partial remissions (PR) for an overall response rate of 21% and an overall clinical benefit (CR+PR+stable disease > 8weeks) of 68%. There were no major toxicities except 2 grade 3 leucopenias and 1 grade 3 fatigue. Significant hair loss occurred only in 7%. Time to progression was evaluable in 32 patients and averaged 4.8 (range 1–16) months. Time to progression was not evaluable in 8 patients: 2 were taken off therapy early due to toxicity (hair loss, fatigue), 2 receive currently CMP (one PR, one stable disease), 4 patients (1 CR, 3 PR) remain progression free on aromatase inhibitors (3) or MPA (1) for 11, 22, 30 and 43 months. The median survival time from the onset of metastatic disease is 4.1 (range 1.2–10) years. **Conclusion:** Oral CMP is an effective, very well tolerated and cost efficient regimen (approx. 50.- Ü/cycle) for the treatment of patients with metastatic breast cancer.

P932

An approach to standardize the detection circulating tumor cells comparing different methods for analysis in peripheral blood and bone marrow

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We have compared different methods for analysis of circulating tumor cells in blood and bone marrow in order to get closer to a standardized procedure to timely monitor the numbers of circulating tumour cells and their response to therapeutic regimen. There are already vast differences in the preanalytic treatment of the samples which may lead to differing results. Red blood cell lysis was compared to separation over density gradients, revealing that, unlike breast cancer cell line cells, most circulating epithelial cells from breast cancer patients sediment with the granulocytes and the red blood cells in ficoll gradients and are lost from the mononuclear fraction. Different magnetic bead enrichment procedures were also compared and the yield in epithelial antigen positive cells compared per volume of the initial sample. Whereas Miltenyi beads yielded highly pure populations of epithelial-antigen positive cells retained in the columns, however with a simultaneous high loss of positive cells into the washing buffer, the purification was low with Labsoft beads but with a much higher yield. Thus depending on the problem to be solved beads with higher potential in purification or in yield should be used. Analysis can be performed either by immunocytochemistry or by immunfluorescence. Intracellular antigens, such as cytokeratin stained by indirect methods will result in much more intense staining than analysis of surface antigens using direct staining. There is, however still no good correlation between the results from different investigators even in exchange analyses and it is difficult to discriminate between unspecific and specific staining. In addition, in fixed cells it is not possible to distinguish between dead and live cells. Immunofluorimetry of surface antigen staining, in contrast has the advantage of unequivocally recognizing live and using Laser Scanning Cytometry allows for quantification of epithelial-antigen positive cells per volume and per white blood cellsin unenriched and enriched smples. Using thei method breast cancer patients are now routinely evaluated for their response to adjuvant chemotherapy. Thus this method allows to determine therapy response of tumour cells in vivo and hopefully will enable individual tailoring of chemotherapy in cancer patients before development of metastases.

Poster session: New drugs

P933

Phase I study with the dolastatin-10-analogue TZT-1027 in patients with solid tumors

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TZT-1027 is a semisynthetic dolastatin-10 analogue derived from Dolabella auricularia with antineoplastic properties in various preclinical models. The present study evaluated the safety, toxicity, activity and pharmacokinetics of TZT-1027 given as a 1h-iv. infusion q3w in pts with solid tumors. Pts had histologically verified measurable disease, were at least 18 yrs old, had an ECOG PS <2 and adequate bone marrow, liver, and renal function. Dose limiting toxicity (DLT) was defined for haematological and non-haematological toxicities. The MTD was defined as <2/6 pts experiencing DLT. Over 12 months, 21 fully eligible and evaluable pts (19 male, 2 female) were enrolled in this single institution trial. The median age was 56 yrs (range 39–68) and the median no. of previous regimens 4 (range 1–12). Colorectal (11), renal ca. (3) and soft tissue sarcoma (3) tumors were the most common tumor types. All patients had previously received chemotherapy. Dose levels of TZT-1027 ranged from 1.35–3.0 mg/m^2. The median no. of cycles was 2 (range 1–4). DLTs were observed in 4 pts at the 3.0 mg/m^2 dose level, including neutropenia, fatigue, and a short-lasting, reversible neurotoxic syndrome of mandibular cramps, pain of arms/legs, paresthesias, insomnia and agitation. The most common non-hematological toxicities in cycle 1 were alopecia (8 pts), constipation (5), appetite loss (4), fatigue (4), nausea (4), anorexia (3), abdominal pain (3), pain of neck and mandibule (3), and taste irritation (3). Hypernatremia (6), GPT increase (4), hypochloremia (4), creatinine increase (3), GOT elevation (2), and hyperbilirubinemia (2) were seen. Hematologic events were mainly neutropenia (10) and leukopenia (7). The best response (RECIST criteria) was stable disease in 2 renal cell ca. pts, lasting for 2 and 4 cycles. There was no evidence of early metabolic response on serial 18FDG-PET scans according to EORTC criteria. PK evaluation revealed a t1/2 of approximately 7 hrs and linear kinetics. The recommended dose for further clinical trials with TZT-1027 is 2.7 mg/m^2 q3w.

P934

The new somatostatin analogue SOM230: A potent inhibitor of the GH/IGF-1 axis

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Somatostatin is expressed in many tissues throughout the body including the CNS, the gastrointestinal (GI) tract and the pancreas. Somatostatin exerts effects on target cells via activation of 5 SRIF receptors (sst1 to sst5) and inhibits effectively growth hormone and insulin-like growth factor-I (IGF-I) release. Natural somatostatins (SRIF 14 or 28) bind with high affinity to all sst receptors, however their use is limited by the rapid proteolytic degradation in plasma (t1/3 3min). The octapeptide Sandostatin (SMS 201–995) is successfully used in 2/3 of acromegaly patients and patients with gastroenteropancreatic (GEP) tumors, although desensitization of the inhibitory response occurs in GEP tumor patients after prolonged treatment. SOM230 is a new SRIF analog which binds with nanomolar affinity to sst1–3 and sst5.

In short term (1 h) rat experiments SOM230 and SMS 201–995 inhibit GH release with similar potency; however, the inhibitory effect of SOM230 on GH release was 4-fold more potent at 6 h post injection than SMS 201–995, indicating its increased metabolic stability. In fact, PK studies in rats demonstrated a plasma half-life of SOM230 of 23 h, as compared to 2 h for SMS 201–995. The improved metabolic stability of SOM230 was confirmed in monkeys and humans. Continuous treatment of rats with SOM230 at 10 "g/kg/h, decreased IGF-1 plasma levels on day 2 by 90% while under SMS 201–995 treatment plasma IGF-1 levels decreased only by 49%. After a 2-week infusion of somatostatin analogue in rats the suppression of GH and IGF-1 levels by SOM230 was still pronounced, while the response to SMS 201–995 was largely lost. This enhanced effect of SOM230 on IGF-1 plasma levels was confirmed in an 8-week study where both analogs were infused at the high dose of 50 "g/kg/h in rats. The marked suppression of plasma IGF-1 levels corresponded with potent inhibition of body weight gain of rats. In acute studies in Rhesus monkey, SOM230 and SMS 201–995 treatment resulted in GH inhibition at 1h with ID50 values of 0.5 and 0.4 "g/kg respectively, but plasma IGF-1 levels were only lowered by SOM230 at this early time point (-53% at 24h post injection). In Cynomolgus monkeys a 2-week infusion of SOM230, but to a much lesser extent SMS 201–995, lowered plasma GH levels significantly (from 16.3 to 1.8 ng/ml).

In conclusion, SOM230 has a unique structure, binds almost universally to human sst s and inhibits potently the GH/IGF-1 axis in various species. SOM230 is currently being evaluated in healthy volunteers and acromegalic patients.