Methods: JNJ-26481585 was administered orally, once daily (QD) in 3-weekly cycles to advanced cancer patients (pts) using a 2-stage accelerated titration design. Due to poor tolerance of the QD dosing, three intermittent schedules were explored: 1) 4 days on, 3 days off; 2) every Mon, Wed, Fri (MWF); and 3) every Mon, Thurs (M-Th). Primary objectives were safety, maximum tolerated dose (MTD) and pharmacokinetics (PK). Secondary objectives were pharmacodynamic (PD) effects in normal and tumour tissues (acetylated Histone 3, Ki67), PK food effect and anti-tumour activity.
Results: 78 patients (40 M, median age 56 yr, ECOG PS 0/1/2: 29/44/2, 3 pts NA) received JNJ-26481585. The number of pts, dose-limiting toxicities (DLTs) and MTD for each cohort and schedule are summarised in Table 1. Common grade 1−2 toxicities were: fatigue, anorexia and nausea. PK showed rapid absorption, high volume of distribution, dose-proportionality (range 2−19 mg) and no clinically meaningful food effect. From the 8 mg dose level onward increased acetylated Histone 3 and reduced Ki67 in tumour and skin biopsies were observed independent of the schedule. A partial response lasting 5 months (mo.) was seen in one patient with melanoma. Stable disease was seen in 8 pts (range 4–10.5 mo. tumour types included melanoma, NSCLC, CRPC, nasopharyngeal cancer, cholangiocarcinom and Bartholin's gland carcinoma).
Conclusions: The adverse event profile of JNJ-26481585 is comparable to other HDACi. Intermittent administration is better tolerated than QD. The recommended dose for phase 2 trials is 12 mg on the MWF schedule based on tolerability; further safety, anti-tumour activity, PK predictions and PD activity are being explored in an expanded patient cohort.

Table 1

Schedule	2 mg	4 mg	6 mg	8 mg	10 mg	12 mg	15 mg	16 mg	19 mg
QD	N = 2	N = 2	N = 6 1 DLT (*bilirubin rise*)	N = 8 1 DLT (*NSVT**) **MTD**	–	N = 2 2 DLTs (*NSVT*, fatigue*)	–	–	–
4 days on, 3days off	–	–	N = 3	N = 3	N = 6 0 DLTs **MTD**	N = 7 2 DLTs (*NSVT*, infection*)	–	–	–
MWF	–	–	N = 3	N = 3	–	N = 7+5 1 DLT (*hypertension + troponin rise*) **MTD**	–	N = 6 0 DLTs***	–
M-Th	–	–	–	N = 3	–	N = 3	N = 6 0 DLTs **MTD**	–	N = 3 2 DLTs (*T-wave inversion, SVT***)

*non-sustained ventricular tachycardia; **supraventricular tachycardia; ***palpitations + increased ventricular ectopics in 2 pts in Cycle 2.

1235 POSTER

Moguntinones − New Selective Inhibitors for Treating Human Gastrointestinal Tumours

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Background: Moguntinones are new innovative synthetic designed small molecules which are molecules with structural features of 3 natural products. They have been invented and patent-protected as tyrosine kinase inhibitors by the Institute of Pharmacy in cooperation with the I. and III. Dept. of Medicine, Mainz. Moguntinones display a new generation of inhibitors for tumur progression, angiogenesis and tumour cell resistance. Our aim was to analyse their antineoplastic effects in vitro and in vivo in human gastrointestinal cancers.
Methods: To establish their mode of action, firstly Moguntinones were analysed in the HET-CAM assay and characterized using IC50 values of kinase assays. Secondly. the human colon cancer HT-29, DLD-1, SW480 and gastric cancer MKN-45, AGS cells were analysed in vitro and in vivo after incubation with Moguntinones, for their interference with signalling pathways by RNA and protein levels (RT-PCR, Western, ELISA, FACS). Additionally, different viability and apoptosis assays were analysed after Moguntinones were combined with or without cytostatic drugs. The *in vitro* data were then verified in a human xenograft NOD/SCID mouse models.
Results: The first generation of Moguntinones showed clear antiangiogenic effects in HET-CAM assays and different spectra of activity in the kinase kinome, most commonly acting on VEGFR 1−3, PDGFR and FLT-3 receptor. Retaining the essential pharmacophore little structural changes lead to better biological antineoplastic and antiangiogenic effects. Moguntinones alone induced apoptosis only in higher micromolar concentrations. Furthermore, we observed strong synergistic effects for induction of apoptosis in lower concentrations of Moguntinones and combinations with cytostatic drugs, especially topoisomerase inhibitors such as irinotecan. In *in vivo* mouse models, similar reductions of tumour growth and tumour weight were seen with no limitation of treatment effects, even in KRAS-, BRAF-or PI3K-mutated colon and gastric cancer cells. Here, signalling pathways of Stat, GSK3b and FAK where inhibited. The antineoplastic effects could not be shown on normal epithelial HUVEC cells.
Conclusions: Our *in vitro* and *in vivo* data clearly support significant pro-apoptotic, anti-angiogenic and antiproliferative effects of Moguntinones in the combination with cytotoxic agents. The data argue for a high effectiveness of Moguntinones to complement standard therapies and to overcome tumour resistance. Our groups aim to bring these substances into a clinical phase I study.

1236 POSTER

Phase I Study to Assess the Safety, Tolerability and Pharmacokinetics of the Multikinase Inhibitor Regorafenib (BAY 73–4506) in Japanese Patients With Advanced Solid Tumours

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Background: Regorafenib (BAY 73–4506) is a novel, broad-acting tumour deactivating agent that inhibits angiogenic (VEGFR1−3, TIE2), stromal (PDGFR, FGFR), and oncogenic kinases (KIT, RET, RAF). In preclinical models, regorafenib has shown a broad spectrum of antitumour activity. Regorafenib 160 mg once daily (o.d.) in repeating cycles of 21 days on/ 7 days off was determined as recommended dose for phase II/ III in the US and EU countries. The aim of this study was to assess the safety, tolerability, pharmacokinetics (PK) and antitumour activity of regorafenib in Japanese patients (pts) with advanced solid tumours (ClinicalTrials.gov ID: NCT00960258). This trial is sponsored by Bayer and has completed enrollment.
Methods: Regorafenib 160 mg o.d. was administered orally in repeating cycles of 21 days on/7 days off until discontinuation due to toxicity or tumour progression. PK was evaluated after a single dose of 160 mg prior to the start of multiple dosing and after 21 days of multiple dosing in Cycle 1. Adverse events (AEs) were graded by NCI CTCAE v 3.0. Efficacy was evaluated using RECIST v 1.0.
Results: Fifteen pts were treated (pancreatic cancer 6 pts, neuroendocrine tumour 3 pts, other tumour types 6 pts). Commonly reported drug-related AEs of all grades included diarrhea (67%), hand-foot skin reaction (HFSR) (67%), hypophosphatemia (53%) and AST elevation (53%). Grade 3 or 4 drug-related AEs included hypophosphatemia (27%), lymphopenia (27%), HFSR (13%), AST/ ALT elevations (13%) and hepatobiliary related event (13%). Dose reduction in Cycle 1 occurred in 2 pts (hypertension, neutropenia); another pt had a dose reduction in Cycle 2 (AST/ ALT elevations). PK results of regorafenib on Day 21 of Cycle 1 showed that mean C_{max} and AUC(0−24) were 2512 mg/L and 32980 mg*h/L respectively. Terminal half life and t_{max} on Day 21 of Cycle 1 were not changed from the day of first dosing. A substantial accumulation was observed between a single dose and Day 21. Fifteen pts were evaluable for efficacy. Partial response was observed in 1 pt, who is ongoing in Cycle 14. Six pts had stable disease, two of whom are still ongoing in Cycles 12 and 20.
Conclusions: Regorafenib 160 mg o.d. given in 21 days on/7 days off repeating cycles was well-tolerated and demonstrated antitumour activity in Japanese pts with advanced solid tumours. The safety profile and PK parameters observed in the Japanese pts were comparable to those observed in Phase I studies in Caucasian pts.

1237 POSTER

WIN55,212−2 as a Potential Treatment for Estrogen-receptor Negative Breast Cancer

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Approximately 30% of all breast cancers are estrogen-receptor (ER) negative, which are often of poorer prognosis and more aggressive behavior compared to ER positive breast cancer cases. While estrogen receptor antagonists have been successfully used for the treatment of ER positive tumours, there have been no specific treatment options for triple negative breast cancers. Our study focused on anticancer potential of a synthetic cannabinoid, WIN55,212−2, in human ER negative breast cancer cells both *in vitro* and *in vivo*. Results demonstrated that WIN55,212−2 produced cytotoxicity toward MDA-MB-231 and MDA-MB-468 cells with

EC50 values of 4.3 μM and 2.6 μM, respectively, and time-course studies showed that WIN55,212−2 (6 μM) exhibited significant cytotoxicity 24 h after treatment and decreased cell numbers by 3% and 20% of control, respectively. Flow cytometry experiments demonstrated that WIN55,212−2 (6 μM) increased the proportion of apoptotic cells by 11 and 5.5 fold compared to control in MDA-MB-231 and MDA-MB-468 cells, respectively. WIN55,212−2 (6 μM) also significantly increased the proportion of MDA-MB-231 and MDA-MB-468 cells in G1 phase at 36 h by 114% and 115% of control. Western blotting showed the expression of CB1 and CB2 receptors in both the cell lines. *In vivo*, mice treated with WIN55,212−2 (25 μg/day i.p. for 10 weeks) showed a 74% reduction in tumour volume and 59% reduction in tumour weight compared to vehicle treament. This effect was reversed by CB2 antagonist AM630. Moreover, CB1 expression in tumours of WIN55,212−2 treated mice was higher than the vehicle group. In conclusion, the results demonstrated antiproliferative effects of WIN55,212−2 both *in vitro* and *in vivo* and suggested a relationship between these effects and G1-phase cell cycle arrest, apoptosis induction, and CB1 and CB2 receptor expression.

1238 POSTER

Phase 1 Clinical Trial of Oral PPAR − Agonist Efatutazone (CS-7017) in Japanese Patients With Metastatic Solid Tumours

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Background: Peroxisome proliferator-activated receptor gamma (PPARg) agonists are potent anticancer agents in preclinical models. Efatutazone is a novel, third-generation thiazolidinedione (TZD) showing higher potency over second-generation TZDs, such as pioglitazone. Now, phase 2 clinical trials of efatutazone in patients with metastatic non-small cell lung cancer and colorectal cancer at doses of 0.50 mg twice-daily (BID) are ongoing in the USA and Europe.
Material and Methods: This phase 1 dose-escalation study using a 3+3 design was initiated in Japanese patients with metastatic solid tumours. Patients with preexisting severe fluid retention were excluded. Efatutazone was administered orally BID starting at a dose of 0.25 mg. Pharmacodynamic (PD) and pharmacokinetic (PK) samples were collected on Day 1 and Day 22. Archived tumour specimens were used for immunohistochemistry. Primary objectives of this study were to assess safety profile and PK. All subjects provided written informed consent.
Results: A total of 13 patients were enrolled (8 male and 5 female; age range 45−73 years), and received treatment at doses 0.25 mg BID (n = 4), 0.50 mg BID (n = 6) and 0.75 mg BID (n = 3). Efatutazone was tolerated. Dose-limiting toxicity (DLT) was not observed, but one grade 3 edema, unresponsive to therapy, occurred after DLT evaluation period (Day 27). The maximum tolerated dose (MTD) was not reached. Observed common adverse events were edema, weight increase, hemoglobin decrease, creatinine increase, and malaise. Particularly, creatinine increase was shown in patients previously treated with cisplatin. All patients were evaluable for response. No objective response was observed, and 5 out of 13 patients showed stable disease. Two of them (thymic cancer and pleural mesothelioma) showed tumour decrease. Efatutazone increased plasma adiponectin levels. Plasma concentration of efatutazone and adiponectin had a tendency to be saturated in the 0.50 mg cohort.
Conclusions: Efatutazone is a novel anticancer therapy, which is tolerated and demonstrates evidence of antitumour activity and disease stabilization. Although the MTD was not reached, 0.50 mg BID, corresponding to the global recommended dose, was selected as the recommended phase 2 dose. Full safety data and clinical activity data will be presented.
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1239 POSTER

Novel Glycan Based Antibodies Highly Selective for Cancer Cells

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Background: Aberrant glycosylation occurs in essentially all types of human cancers, as has been reported in the last decades. Many glycosyl epitopes constitute tumour-associated antigens. Recent studies indicate that some aberrant glycosylation is a result of initial oncogenic transformation, as well as a key event in the induction of metastasis. Therefore, it is expected that cancer cells will express different glycan epitopes on their surface, compared to non-cancerous cells. Lectins are plant-derived proteins, which recognize and bind structures or carbohydrate sequence features of glycans. The current research utilized lectins to isolate antibodies that bind specifically to cancer cells.
Materials and Methods: Lectins that bind specifically to cancer cells were selected by staining of Non Small Cell Lung Cancer (NSCLC) cell line (A549) and cancer vs. normal tissue specimens.
The most selective lectins were used to isolate human antibodies from phage display library of single chains fragments (scFv) with the same binding properties as the lectins. The proprietary screening method led to isolation of five human scFvs out of $1x10^9$ different fragments, expressed on a phage display library. The specificity and selectivity of these scFvs were tested in two types of Adenocarcinomas: NSCLC and Colon cancer. The binding of each scFv was tested on cancerous and normal (dermal fibroblasts) cell lines and on 30 & 25 lung and colon cancer paraffin-embedded tissue specimens, respectively and their normal adjacent tissues by immunohistochemisry.
Results: The selectivity and specificity were demonstrated in both cell lines and paraffin-embedded tissues. In the cell line model, all scFvs showed binding to the cancer cells and none bound to the control cell line. In the paraffin-embedded tissue cohort, each scFvs was able to bind 53−92% of the tested cancer tissues and with lower intensity to 20−25% of the normal adjacent tissues. Furthermore, the combination of all scFvs resulted in 94% binding of the lung tumour tissues.
Conclusions: These results indicate that the selected scFv molecules, directed to glycan epitopes, have an impressive selectivity and specificity in binding to NSCLC and Colon cancer cells. Preliminary experiments using these scFvs in mice models of colon cancer demonstrated their capability to detect tumours in-vivo. Therefore, these molecules have huge potential in cancer therapy and diagnostics and are expected to evolve to breakthrough in cancer management.

1240 POSTER

Proprotein Convertases as Novel Targets for Treatment of Rhabdomyosarcoma

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Many who survive childhood cancer experience treatment complications as adults. One of the biggest challenges of treating children with cancer is achieving complete remission, while ensuring that they will be able to lead normal, productive life in adulthood.
To improve therapies for embryonal pediatric tumours such as rhabdomyosarcoma (RMS), the most common soft tissue sarcoma in children, we have selected peptides that bind to RMS with high specificity and are able to increase drug delivery to the tumour site. We have identified proprotein convertases (PC), a family of ten serine proteases which convert inactive proprotein into their active form, as targets RMS binding peptides (Hajdin et al. PLoS ONE 2010). In particular we have shown that coupling of Doxorubicin to the RMS targeting peptide RMS-P3 considerably increases its therapeutic impact in a mouse model for RMS.
Now we aim at elucidating the function of the proprotein convertases which we found highly expressed in RMS tumours: furin and PC7. In particular, our study should determine if these PCs might offer an additional therapeutic option based on their inhibition, which might be combined with targeted drug delivery.
To assess the functional role of furin and PC7 in RMS we have generated cell lines overexpressing furin, overexpressing a specific intrinsic PC inhibitor called α1 PDX, as well as cell lines were expression of furin or PC7 has been stably blocked by shRNA. These cells have been tested for their growth, migration and invasion potential in vitro as well as for their growth in vivo as subcutaneous xenografts. Histological analysis of tumour sections, in particular of microvessel density and angiogenesis has been performed to reveal if PC activity correlates with RMS progression.
Our results confirm a strong correlation between PCs activity and RMS growth in vivo and suggest furin and/or PC7 as viable target for therapeutic intervention and warrant further studies in the development of novel specific inhibitors of PCs protease activity. Moreover, the knowledge that furin/PC7 are valuable targets for RMS therapy reinforce the notion that furin targeting peptides must be considered for the development of novel targeted therapies and imaging approaches.