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.

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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