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Inhibition of prostate xenograft growth by two novel orally bioavailable microtubule disruptors

S.P. Newman[1], J.M. Day[1], Y. Ho[1], P.G. Kasprzyk[2], M.P. Leese[3], B.V.L. Potter[3], M.J. Reed[1], A. Purohit[1]. [1]*Imperial College London, Endocrinology and Metabolic Medicine, London, United Kingdom;* [2]*IPSEN-Biomeasure, Experimental Oncology Research, Boston, USA;* [3]*Bath University, Pharmacy and Pharmacology, Bath, United Kingdom*

Background: Treatment options for hormone independent prostate cancer remain limited, with only the taxanes offering some benefit to patients with advanced disease. 2-Methoxyestradiol-3,17-O,O-bis-sulfamate (2-MeOE2bisMATE) and 2-ethylestradiol-3,17,O,O-bis-sulfamate (2-EtE2bisMATE) are novel compounds which possess anti-tumor and anti-angiogenic activities.
Materials and Methods: Proliferation was quantified in vitro by MTS 96 well plate assays. FACS analysis was used to study both cell cycle arrest and to quantify apoptosis. Hif-1 alpha and Cyclin B1 expression was determined by immunoblotting of nuclear and whole cell extracts respectively. To assess in vivo efficacy, mice bearing PC-3 and DU-145 xenografts (80–100 mm^3) were treated for up to 60 days. The microtubule disruptors, Taxotere and Vinorelbine, and the anti-angiogenic agents 2-MeOE2 and Avastin were included in the study for comparison.
Results: In vitro studies demonstrated that both 2-MeOE2bisMATE and 2-EtE2bisMATE inhibited proliferation of PC-3 and DU-145 cells. These compounds induced cell cycle arrest and subsequent apoptosis in the prostate cell lines. Furthermore, there was decreased expression of Hif-1 alpha protein. In vivo both compounds are efficacious by daily oral administration, with 22 mg/kg 2-MeOE2bisMATE and 50 mg/kg 2-EtE2bisMATE causing significant regression in the PC-3 model. In contrast, the DU-145 tumours were more resistant to all the therapies studied, especially taxotere (30 mg/kg i.v.). 2-EtE2bisMATE (50 mg/kg p.o.) was more potent than 2-MeOE2bisMATE (22 mg/kg p.o.) in these tumors. 2-EtE2bisMATE (50 mg/kg p.o.) was equipotent to navelbine (80 mg/kg i.v.) but without the associated toxicity. Avastin (5 mg/kg i.v.) was only efficacious in the DU-145 model, indicating that VEGF may play an important role in this cell line.
Discussion: Here we describe and characterise two novel compounds, which combine anti-tumor and anti-angiogenic activities in one orally bioavailable molecule. Both compounds directly target the tumor by causing cell cycle arrest and apoptosis. The previously described anti-angiogenic activity of these compounds may, in part, be explained by the down-regulation of Hif-1 alpha protein expression. These properties may translate into a significant clinical improvement over existing agents used to treat advanced prostate cancer, such as the taxanes.

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Comparative antiproliferative activities and cellular distribution of the third-generation epothilone ZK-EPO and taxanes

J. Hoffman, S. Winsel, S. Hammer, K. Mittelstaedt, B. Buchmann, W. Schwede, W. Skuballa, G. Siemeister, K. Bosslet, U. Klar. *Schering AG, Corporate Research Oncology, Berlin, Germany*

Background: ZK-EPO, a synthetic third-generation epothilone in Phase II clinical trials, is a microtubule stabilizer that induces cell-cycle arrest in G2/M. Preclinical data indicate more potent antitumor activity than taxanes (eg paclitaxel) and second-generation epothilones such as ixabepilone (BMS-247550). ZK-EPO eludes the cellular efflux pumps normally responsible for multidrug resistance (MDR) and has activity against both taxane-resistant and taxane-sensitive tumor models. We compared the subcellular distribution of ZK-EPO and paclitaxel to assess the efficiency of cellular uptake and binding to subcellular compartments.
Materials and Methods: A panel of cultured human breast and lung tumor cells (including taxane-sensitive and -resistant models) was treated with ZK-EPO or other tubulin-binding agents, at a range of concentrations, to determine antitumor activity and uptake/distribution characteristics. Cells were incubated with tritiated ZK-EPO or paclitaxel, and radioactivity measured in the whole cell and in the subcellular fractions. For immunofluorescence (IF) studies, cultures were exposed to agents prior to fixation and stained with antibodies for tubulin isotypes.
Results: ZK-EPO was significantly more active than paclitaxel against breast and lung tumor cell proliferation in all cell lines examined. Activity against MCF7 cells was high for ZK-EPO (IC_{50} < 1 nM) compared with paclitaxel or ixabepilone (IC_{50} > 3 nM). Against MDR NCI/ADR cells, ZK-EPO also had subnanomolar potency, unlike epothilone B (IC_{50} > 1 nM), paclitaxel or ixabepilone (IC_{50} > 1 μM). In radiolabeling experiments, ZK-EPO almost completely localized to the nuclear/cytoskeletal fraction compared with the cytosolic fraction. In contrast, a majority of the tritiated paclitaxel was detected in the cytosolic fraction in all cell types examined. In MaTu/ADR and NCI/ADR cells, total cellular uptake of ZK-EPO was 7.5 and 290 times greater than uptake of paclitaxel, respectively, suggesting that ZK-EPO is not recognized by MDR mechanisms in taxane-resistant cells. IF studies showed that ZK-EPO induces microtubulin polymerization.
Conclusions: ZK-EPO displays a rapid cellular uptake compared with paclitaxel, and preferentially accumulates in the nucleus in a range of tumour cell types. ZK-EPO uptake may be unaffected by MDR-pump activity, suggesting efficient maintenance within tumor cells. ZK-EPO may be clinically effective as an alternative to taxanes.

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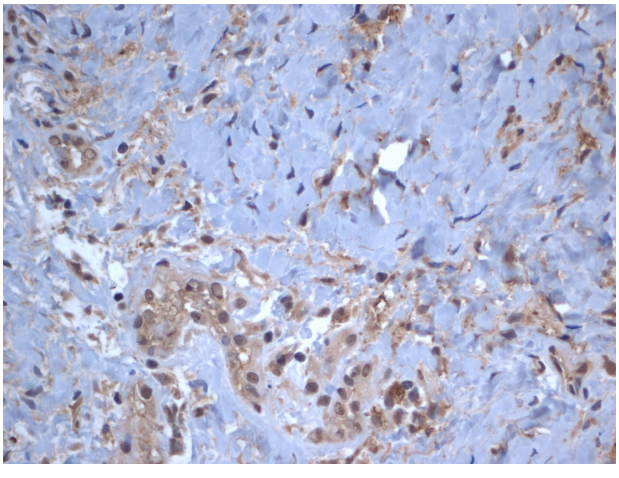
Randomized phase II study of BMS-247550 (NSC 710428) given daily X 5 days or weekly in patients with metastatic or recurrent squamous cell cancer of the head and neck: E2301

B. Burtness[1], J. Manola[2], A. Argiris[3], D. Altieri[4], R. Axelrod[5], A. Forastiere[6]. [1]*Fox Chase Cancer Center, Medical Oncology, Philadelphia, USA;* [2]*Eastern Cooperative Oncology Group, Statistical Center, Boston, USA;* [3]*University of Pittsburgh, Medical Oncology, Pittsburgh, USA;* [4]*University of Massachusetts, Medical Oncology, Worcester, USA;* [5]*Jefferson School of Medicine, Medical Oncology, Philadelphia, USA;* [6]*Johns Hopkins Medical Institute, Medical Oncology, Baltimore, USA*

Background: Ixabepilone is a novel tubulin-polymerizing agent, with potential activity in SCCHN.
Methods: Patients (pts) were eligible who had incurable, measurable SCCHN. ⩽2 prior regimens for metastatic/recurrent disease were permitted, including taxanes. ECOG PS 0 or 1, ANC > 1500/ml and adequate renal/hepatic function were required. Pts were randomized to ixabepilone 6 mg/m^2/d 60 minute (min) infusion × 5 days (d) q 21 d [Arm A], or 20 mg/m^2 60 min infusion d 1, 8, and 15 q 28 d [Arm B], with diphenhydramine premedication. Tumor assessment was q 6 weeks. Each arm accrued taxane-naive (Tax-N) and -exposed (Tax-E) patients as separate strata, in a 2-stage design. The primary endpoint was response. 16 pts entered each group in the first stage. If 1 response was observed in any group, it continued to 32 pts.



Results: 84 eligible pts entered. Male 68, ECOG PS (1) 57, metastatic disease 65. 15 Tax-E and 17 Tax-N eligible pts entered stage 1 of Arm A. There was 1 response (6.7%) among the Tax-E pts and none among the Tax-N with this dose and schedule. 34 eligible Tax-N pts were accrued to Arm B and 5 had partial responses (14.7%, 90% CI: 6.1%, 28.8%), 11 stable and 9 progressive disease. 9 in this group were inevaluable (5 died before restaging, 2 never treated). 18 eligible Tax-E pts entered Arm B and none responded. On Arm A, 2/16 Tax-N pts developed grade (gd) 3/4 anemia (13%), and 4/16 (25%) developed gd 3 fatigue. Other gd 3/4 toxicities occurred in <8% of pts on Arm A. On Arm B, 9/33 (27%) Tax-N pts experienced gd 3/4 leukopenia, 3/33 (9%) gd 3/4 anemia, 7 gd 3/4 fatigue (21%), 4 gd 3 nausea (12%), 9 (27%) gd 3 sensory and 2 (6%) gd 3 motor neuropathy. 2/21 Tax-E pts on Arm B experienced gd 4 neutropenia (10%), 6 gd 3 fatigue (29%), 3 gd 3 motor (14%) and 2 gd 3 sensory neuropathy (10%). Median follow up for eligible pts is 31.7 months (mo). 77 have died. Median progression-free survival for Arm A Tax-N is 1.5 mo, Arm A Tax-E is 1.8 mo, Arm B Tax-N 1.9 mo, Arm B Tax-E 1.6 mo. Median survival for Arm A Tax-N is 5.62 mo (CI 4.0, 10.0); for Arm A Tax-E is 6.5 mo (CI 2.7, 8.8); for Arm B Tax-N is 7.8 mo (CI 3.8, 9.9) and Arm B Tax-E is 6.8 mo (CI 2.0, 11.3). Baseline tissue is stained for survivin and