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An Open-Label, Multicenter, Single Arm QT Interval Prolongation Study of Eribulin Mesylate in Patients With Advanced Solid Tumours

J. Edeline[1], H. Lena[2], F.C. Cvitkovic[3], N. Penel[4], L. Reyderman[5], G. Edwards[6], K. Law[6], J.P.D. Delord[7], T.L. Lesimple[8]. [1]*Centre Eugène Marquis, Assistant Hospitalo-Universitaire Oncologie Médicale, Rennes,* [2]*CHU Pontchaillou, Service de Pneumologie, Rennes,* [3]*Centre René Huguenin, Service d' Oncologie Médicale, Saint Cloud,* [4]*Centre Oscar Lambret, Département de Cancérologie Générale, Lille Cedex, France;* [5]*Eisai Inc, Clinical Pharmacology & Translational Medicine Oncology, New Jersey, USA;* [6]*Eisai Ltd, Oncology PCU, Hatfield, United Kingdom;* [7]*Institut Claudius Regaud, Département de Medecine, Toulouse,* [8]*Centre Eugène Marquis, Service d'Oncologie, Rennes, France*

Background: The non-taxane microtubule dynamics inhibitor eribulin mesylate (Halaven™) exhibits clinical activity in breast cancer and other solid tumours. This uncontrolled, open-label, multicenter, single-arm Phase I study (NCT01106248 [completed]; sponsored by Eisai Ltd) assessed (i) effect of eribulin on cardiac repolarization (QT/QTc interval) and (ii) pharmacokinetic-pharmacodynamic (PK-PD) profile in patients with advanced solid tumours that progressed after standard therapy or for which none existed.
Methods: Patients (⩾18 years) received eribulin mesylate 1.4 mg/m^2 2−5 min IV bolus injection on Days 1 and 8 of a 21-day cycle. Repeat continuous ECG digital Holter recordings and triplicate 12-lead ECGs were obtained on these days. Blood samples were collected pre- and post-infusion, concurrent with ECG measurements. Cardiac repolarization was measured by comparing baseline and post-dose ECGs; QT was corrected for heart rate (HR) using Fridericia's methods (QTcF). Mean change of QTc from time-matched baseline was calculated and correlation between QTcF and plasma concentration modeled.
Results: Of the 26 patients that received eribulin, 6 had arterial hypertension, 3 had hypothyroidism and 2 had diabetes mellitus. No differences in mean change of QTcF from baseline were observed on Day 1. Time-matched mean pre-dose QTcF was 4 msec and greatest mean baseline-adjusted QTcF was 2 msec at 15 mins post-dose. On Day 8, there was an upward shift in QTcF values; the largest observed mean QTcF change from baseline was 11 msec. There was no QTc change ⩾20 msec at any timepoint on Day 8. On Days 1 and 8, eribulin exposure was comparable with no relationship between mean baseline-adjusted QTcF and eribulin concentrations. When an individualized HR correction algorithm was applied, the QTc increase from Day 1 to 8 was smaller than with QTcF, 5 vs 11 msec; no patient had a QTc interval value >500 msec on either day. Subgroup analyses on Day 8 showed greater differences in mean QTcF change from baseline in women (n = 13; 9−18 ms) compared with men (n = 13; −2−7 ms) although low patient numbers preclude conclusions. On Days 1 and 8, HR was reduced up to 1.5h post-dosing but returned to baseline. No adverse events related to ECG and eribulin were reported.
Conclusions: Eribulin did not cause QT prolongation on Day 1. QT prolongation observed on Day 8 was independent of eribulin concentration and is not expected to be of clinical concern in this patient population.

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Phase I Dose-escalation Study of the Oral Selective C-Met Inhibitor EMD 1204831 in Patients With Advanced Solid Tumours

G.S. Falchook[1], S. Fu[1], H.M. Amin[2], A.M. Tsimberdiou[1], D.S. Hong[1], A. Naing[1], M.B. Klevesath[3], M.R. Mattiacci[4], A. Johne[3], R. Kurzrock[1]. [1]*The University of Texas MD Anderson Cancer Center, Department of Investigational Cancer Therapeutics, Phase I Clinical Trials Program, Houston,* [2]*The University of Texas MD Anderson Cancer Center, Department of Hematopathology, Houston, USA;* [3]*Merck KGaA, Darmstadt, Germany;* [4]*Merck Serono International SA, Geneva, Switzerland*

Background: The cell surface receptor tyrosine kinase c-Met and its ligand, the hepatocyte growth factor (HGF), are implicated in pleiotropic effects, including tumour cell migration, invasion, survival and proliferation. C-Met signalling has been associated with numerous tumour types and appears to represent a suitable therapeutic approach for treating these tumours. EMD 1204831 is a novel potent and highly selective reversible and ATP-competitive c-Met inhibitor. In pre-clinical models, EMD 1204831 inhibits tumour growth and induces regression of HGF-dependent and HGF-independent tumours.
Methods: This is a phase I, first-time-in-human (FIH), clinical trial with escalating oral doses of EMD 1204831 (clinicaltrials.gov identifier NCT01110083). The primary objective is to determine the MTD, and secondary objectives include evaluating the safety profile, characterizing pharmacokinetics, and assessing anti-tumour effects and pharmacodynamics (Pd). Eligible patients had advanced solid tumours not amenable to standard therapies. Following a classical 3+3 dose escalation scheme, successive cohorts of patients were treated with twice daily (BID) oral EMD 1204831 in 21-day cycles. Pd markers were evaluated in plasma samples and paired tumour biopsies (phospho-c-Met).
Results: Until 15 February 2011, a total of 17 patients had been enrolled and treated. The dose has been escalated in four successive cohorts from a starting dose of 50 mg BID up to 400 mg BID. One DLT of grade 3 pancreatitis was observed at 400 mg BID. Other treatment-related AEs included G2 abdominal pain (n = 2), G2 dyspepsia (n = 1), G1 nausea (n = 2), G1 anorexia (n = 1), G1 fatigue (n = 1), G1 nyctalopia (n = 1), G1 somnolence (n = 1), and G1 thrombocytopenia (n = 1). Fourteen patients (82%) had no drug-related toxicity greater than grade 1. Variability of interindividual PK parameters was low to moderate. Mean Cmax and AUC0−12 values increased with dose, and the estimated apparent terminal half-life after multiple dosing is approximately 6.5 hours. Preliminary anti-tumour activity has been observed, including stable disease lasting at least 4 months in two patients.
Conclusions: The MTD has not yet been reached, and dose escalation of EMD1204831 continues. Updated results of this FIH study, including Pd analysis of phospho-c-Met, will be presented.

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A Phase I Dose-escalation Study of EMD 1214063, an Oral Selective C-Met Inhibitor, in Patients With Advanced Solid Tumours

G.S. Falchook[1], S. Fu[1], H.M. Amin[2], S.A. Piha-Paul[1], D.S. Hong[1], A. Naing[1], M.B. Klevesath[3], M.R. Mattiacci[4], A. Di Cara[4], R. Kurzrock[1]. [1]*The University of Texas MD Anderson Cancer Center, Department of Investigational Cancer Therapeutics, Phase I Clinical Trials Program, Houston,* [2]*The University of Texas MD Anderson Cancer Center, Department of Hematopathology, Houston, USA;* [3]*Merck KGaA, Darmstadt, Germany;* [4]*Merck Serono International SA, Geneva, Switzerland*

Background: The cell surface receptor tyrosine kinase c-Met and its ligand, the hepatocyte growth factor (HGF), mediate pleiotropic effects, including cell migration, survival and proliferation. C-Met is expressed in numerous tumour types and represents a suitable target for drug development. EMD 1214063 is a novel potent and highly selective reversible and ATP-competitive c-Met inhibitor. In pre-clinical models, EMD 1214063 causes growth inhibition and induces regression of HGF-dependent and HGF-independent tumours.
Methods: This is a first in human (FIH) dose-escalation study with a primary objective of establishing the MTD and secondary objectives of evaluating the safety, pharmacokinetics, anti-tumour effect and pharmacodynamics (Pd) of EMD 1214063 (clinicaltrials.gov identifier NCT01014936). Eligible patients had advanced solid tumours not amenable to standard therapies. Following a classical 3+3 dose escalation scheme, successive cohorts of patients were treated with once daily oral EMD 1214063 according to two 21-day-cycle schedules, either days 1−14 followed by a 7-day rest (regimen 1, [R1]), or continuous three times weekly administration (regimen 2, [R2]). Pd markers were evaluated in serial plasma samples and paired tumour biopsies (phospho-c-Met).
Results: Until February 15th, 2011, a total of 38 patients had been enrolled, 21 in R1 and 17 in R2. The dose was escalated from 30 mg/day to 115 mg/day in R2 and to 230 mg/day in R1. One DLT was reported in R1 at 115 mg/day, a grade 3 lipase and amylase elevation. The remaining treatment-related AEs were grade 1 or 2 and included nausea (n = 1), vomiting (n = 1), anorexia (n = 1), diarrhea (n = 1), oncholysis (n = 1), skin hyperpigmentation (n = 1), fatigue (n = 2), arthralgia (n = 1), and skin exfoliation (n = 1) in R1, and rash (n = 2), myopathy (n = 1), anemia (n = 1), peripheral edema (n = 1), transaminitis (n = 1), paraesthesia (n = 1), thrombocytopenia (n = 1), neutropenia (n = 2), leukopenia (n = 1), PPE (n = 1), and temperature intolerance (n = 1) in R2. 34 patients (89%) had no drug-related toxicity greater than grade 1. Preliminary antitumour activity has been observed, including an unconfirmed PR in one patient and stable disease lasting at least 4 months in 5 patients.
Conclusions: The MTD has not yet been reached and dose escalation of EMD 1214063 continues. Updated results of this FIH study, including Pd analysis of phospho-c-Met, will be presented.