age was 68 (29−77), 13 (75.5%) were male, 11 (64.7%) were Caucasian, 4 had prior systemic therapy, and 6 pts had prior TACE. Of the 13 pts evaluable for response, 5 SD at 16 wks (38% PFS; 2/5 showed tumor shrinkage <20%), 3 have confirmed PRs, 2 SD at 8 weeks continuing on therapy; 2 pts SD at 8 wks but removed for toxicity; 1 PD. 3 pts not yet evaluable, 1 pt withdrew consent. 8 pts with SD showed radiographic evidence of decreased tumor vascularity (Fig. 1). One pt with 20% tumor shrinkage and improved portal vein involvement was removed from the study and underwent surgical resection. Generally B+E are well tolerated; the most common Gr 1 and 2 toxicities are folliculitis, anorexia, diarrhea, dry skin, and epistaxis. Gr3 toxicities experienced by 4 pts were TA elevation, diarrhea, fatigue, hyperkalemia, hypertension, and proteinuria. No Gr4 toxicities have been encountered.
Conclusions: The trial will continue to full accrual of 40 patients. Based on these early encouraging results and the favorable side effect profile, the combination of B+E warrants further study in HCC.

35 POSTER

A Phase I trial of a combination of the mTOR Inhibitor Everolimus (RAD001) and two schedules of the vascular endothelial growth factor (VEGF) receptor tyrosine kinase inhibitor Vatalanib (PTK787/ZK 222584) in patients (pts) with advanced solid tumors

G. Dy, G. Croghan, A. Furth, J. Reid, L. Hanson, M. Roos, A. Tan, A. Adjei. *Mayo Clinic, Rochester, USA*

Background: Preclinical studies demonstrate synergistic antitumor effects of mTOR inhibitors in combination with anti-angiogenesis agents.
Materials and Methods: A phase I study was performed to define the maximum tolerated dose (MTD), toxicities and clinical activity of escalating single daily doses of vatalanib in combination with RAD001, followed by determination of the MTD of twice daily doses of vatalanib in combination with RAD001 (see table), in pts with advanced cancers. A cycle length was 28 days. Once the optimal dose and schedule of the combination is defined, the study will expand to evaluate pharmacokinetics (PK), and temporal changes in functional imaging and in molecular markers of VEGF inhibition (sVEGFR, VEGF levels) and mTOR inhibition (4EBP, eIF4E, p70S6 kinase activity).
Results: 29 pts received 106 cycles of treatment through 5 dose levels. The most common toxicities were fatigue, hyperlipidemia, transaminitis, nausea, stomatitis and hypertension. NCI CTC grade3+ treatment-related toxicities (cumulative events in all cycles, CTC grade) included transaminitis (3 grade 3 ALT elevation; 1 grade 3 AST elevation), diarrhea (3 grade 3), hypercholesterolemia (1 grade 3), hypertriglyceridemia (2 grade 3), thrombosis (1 grade 3), pancreatitis (1 grade 3), and muscle spasms (1 grade 3). DLTs were grade 3 ALT elevation, muscle spasms and diarrhea. Partial responses were seen in 2 patients (chemo-refractory neuroendocrine pancreatic cancer at dose level 0, treatment-naïve clear cell renal cell cancer at dose level 3). Stable disease (4+ cycles) occurred in 8 pts. Dose level 2 (10 mg RAD001 and 1250 mg vatalanib) is the MTD for the single daily dose schedule. Dose level 4 (10 mg RAD001 and 1000 mg vatalanib) is the MTD for the twice daily dose schedule of vatalanib.

Table 1. Treatment data

Dose level	RAD001 (mg, daily)	Vatalanib (mg)	No. pts (No. replaced)	No. cycles	No. DLTs
0*	5	1000 QD	3 (3)	32	0
1	10	1000 QD	3	14	0
2	10	1250 QD	6	21	1
3	10	750 BID	6 (1)	26	1
4	10	1000 BID	5 (2)	13	1

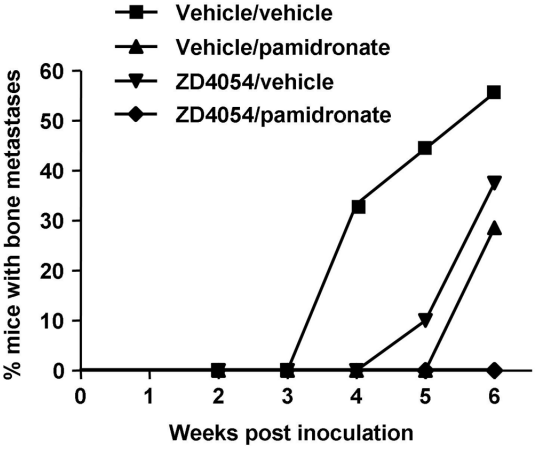
Conclusions: The combination of RAD001 and vatalanib is effective and well-tolerated. We recommend the twice-daily schedule of vatalanib in combination with RAD001 for future evaluation in phase II studies, based on a higher dose intensity and tolerability. Results of PK and pharmacodynamic studies in the expanded cohort will be presented.

36 POSTER

The combination of a specific endothelin A receptor antagonist ZD4054 and submaximal bisphosphonate pamidronate prevents bone metastasis

E.D. Williams[1], E.W. Thompson[2], D. Sreedharan[2], N. Brooks[3]. *[1]Bernard O'Brien Institute of Microsurgery, Prostate Cancer Metastasis Laboratory, Fitzroy, Australia; [2]University of Melbourne, Department of Surgery (St Vincent's Hospital), Melbourne, Australia; [3]AstraZeneca, Alderley Park, Macclesfield, United Kingdom*

Bone metastases cause significant morbidity for people with cancer due to bone pain, fractures, and nerve compression. Bone metastases are most commonly osteolytic, but some tumour types, most notably prostate cancer, typically form osteoblastic metastases. Nevertheless, many overtly osteolytic metastases have an osteoblastic component, which has been attributed to the ability of bone-synthesising osteoblasts to increase osteoclast function (as osteoblasts are the main regulators of osteoclasts). Tumour secreted endothelin-1 is thought to be a key factor stimulating the osteoblastic phenotype. Clinically approved bisphosphonates prevent bone resorption by osteoclastic mechanisms and reduce the release of bone growth factors, resulting in fewer skeletal-related events.
We have investigated the interaction between the specific endothelin A receptor antagonist ZD4054 and the bisphosphonate pamidronate on the formation of mixed osteoblastic/osteolytic metastases following systemic inoculation of the metastasis-selected B1 subline of the TSU-Pr1 human bladder carcinoma cell line.
Male SCID mice (n = 7–10/group) were randomly allocated to 4 experimental arms: (i) vehicle (oral gavage, daily)/vehicle (s.c., twice weekly), (ii) vehicle/pamidronate (4 mg/kg s.c., twice weekly), (iii) ZD4054 (25 mg/kg, oral gavage, daily)/vehicle, and (iv) ZD4054/pamidronate. Treatment was initiated the day prior to intracardiac inoculation of TSU-Pr1-B1 cells. Mice were X-rayed weekly, and tissues collected for histological analysis and measurement of human DNA at the conclusion of the experiment (6 weeks following inoculation of tumour cells). Treatment with either ZD4054 or pamidronate significantly delayed the formation of bone metastases. In the mice receiving both agents, no bone metastases were detected using high resolution X-ray.
Endothelin A receptors are found both on osteoblasts and on many types of tumour cells, including the majority of invasive bladder carcinomas. Bisphosphonates act on bone cells (predominantly osteoclasts) rather than tumor cells. These data suggest that combined therapy targeting tumour cells and the bone environment by a combination of anti-osteoblastic and anti-osteolytic treatments may provide maximal inhibition of bone metastasis.



37 POSTER

VEGFRs inhibitor E7080 inhibits lymph node metastasis of human breast carcinoma, by preventing murine lymphatic endothelial cells from lymphangiogenesis

M. Junji[1], A. Tsuruoka[1], K. Morimoto[2], T. Uenaka[1], Y. Yamamoto[1], T. Watanabe[3], M. Okada[2], S. Abe[1], T. Wakabayashi[1], M. Asada[1]. *[1]Discovery Research Laboratories II, Eisai Co., Ltd., Ibaraki, Japan; [2]KAN Research Institute, Kyoto, Japan; [3]New Product Development, Clinical Research Center, Eisai Co., Ltd., Tokyo, Japan*

The spread of tumor cells into regional lymph nodes through the lymphatic system correlates with poor prognosis in breast, lung and