

- 28 Wilhelm SM, Carter C, Tang L *et al*. BAY 43-9006 exhibits broad spectrum oral antitumor activity and targets the RAF/MEK/ERK pathway and receptor tyrosine kinases involved in tumor progression and angiogenesis. *Cancer Res* 2004; **64**: 7099–109.
- 29 Mendel DB, Laird AD, Xin X *et al*. *In vivo* antitumor activity of SU11248, a novel tyrosine kinase inhibitor targeting vascular endothelial growth factor and platelet-derived growth factor receptors: determination of a pharmacokinetic/pharmacodynamic relationship. *Clin Cancer Res* 2003; **9**: 327–37.
- 30 Faivre SJ, Raymond E, Douillard JBE *et al*. Assessment of safety and drug-induced tumor necrosis with sunitinib in patients (pts) with unresectable hepatocellular carcinoma (HCC). *J Clin Oncol* 2007; **25** (18S): 3546.
- 31 Wood JM, Bold G, Buchdunger E *et al*. PTK787/ZK 222584, a novel and potent inhibitor of vascular endothelial growth factor receptor tyrosine kinases, impairs vascular endothelial growth factor-induced responses and tumor growth after oral administration. *Cancer Res* 2000; **60**: 2178–89.
- 32 Liu Y, Poon RT, Li Q, Kok TW, Lau C, Fan ST. Both antiangiogenesis- and angiogenesis-independent effects are responsible for hepatocellular carcinoma growth arrest by tyrosine kinase inhibitor PTK787/ZK222584. *Cancer Res* 2005; **65**: 3691–9.
- 33 Koch I, Baron A, Roberts S *et al*. Influence of hepatic dysfunction on safety, tolerability, and pharmacokinetics of PTK787/ZK 222584 in patients with unresectable hepatocellular carcinoma (HCC). *J Clin Oncol* 2005; **23** (16S): 4134.
- 34 Wedge SR, Kendrew J, Hennequin LF *et al*. AZD2171: a highly potent, orally bioavailable, vascular endothelial growth factor receptor-2 tyrosine kinase inhibitor for the treatment of cancer. *Cancer Res* 2005; **65**: 4389–400.
- 35 Alberts SR, Morlan BW, Kim GP *et al*. NCCTG phase II trial (N044J) of AZD2171 for patients with hepatocellular carcinoma (HCC)—interim review of toxicity. 2007 Gastrointestinal Cancer Symposium; 19–21 Jan 2007, Orlando, FL, USA. Abstract 186.
- 36 Laird AD, Vajkoczy P, Shawver LK *et al*. SU6668 is a potent antiangiogenic and antitumor agent that induces regression of established tumors. *Cancer Res* 2000; **60**: 4152–60.
- 37 Kanai F, Yoshida H, Teratani T *et al*. New feasibility study design with hepatocellular carcinoma: A phase III study of TSU-68, an oral angiogenesis inhibitor. *J Clin Oncol* 2006; **24** (18S): 4145.
- 38 Hurwitz H, Fehrenbacher L, Novotny W *et al*. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med* 2004; **350**: 2335–42.
- 39 Jain RK. Normalization of tumor vasculature: an emerging concept in antiangiogenic therapy. *Science* 2005; **307**: 58–62.
- 40 Schwartz JD, Schwartz M, Lehrer D *et al*. Bevacizumab in unresectable hepatocellular carcinoma (HCC) for patients without metastasis and without invasion of the portal vein. *J Clin Oncol* 2006; **24** (18S): 4144.
- 41 Malka D, Dromain C, Farace F *et al*. Bevacizumab in patients (pts) with advanced hepatocellular carcinoma (HCC): preliminary results of a phase II study with circulating endothelial cell (CEC) monitoring. *J Clin Oncol* 2007; **25** (18S): 4570.
- 42 Zhu AX, Blaszkowsky LS, Ryan DP *et al*. Phase II study of gemcitabine and oxaliplatin in combination with bevacizumab in patients with advanced hepatocellular carcinoma. *J Clin Oncol* 2006; **24**: 1898–903.
- 43 Normanno N, De Luca A, Bianco C *et al*. Epidermal growth factor receptor (EGFR) signaling in cancer. *Gene* 2006; **366**: 2–16.
- 44 Yamaguchi R, Yano H, Iemura A, Ogasawara S, Haramaki M, Kojiro M. Expression of vascular endothelial growth factor in human hepatocellular carcinoma. *Hepatology* 1998; **28**: 68–77.
- 45 Couzin J. Cancer drugs. Smart weapons prove tough to design. *Science* 2002; **298**: 522–5.
- 46 Paez JG, Jänne PA, Lee JC *et al*. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. *Science* 2004; **304**: 1497–5.
- 47 Lynch TJ, Bell DW, Sordella R *et al*. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. *N Engl J Med* 2004; **350**: 2129–39.
- 48 O'Dwyer PJ, Giantonio BJ, Levy DE, Kauh JS, Fitzgerald DB, Benson AB III. Gefitinib in advanced unresectable hepatocellular carcinoma: results from the Eastern Cooperative Oncology Group's Study E1203. *J Clin Oncol* 2006; **24** (18S): 4143.
- 49 Moyer JD, Barbacci EG, Iwata KK *et al*. Induction of apoptosis and cell cycle arrest by CP-358,774, an inhibitor of epidermal growth factor receptor tyrosine kinase. *Cancer Res* 1997; **57**: 4838–48.
- 50 Philip PA, Mahoney MR, Allmer C *et al*. Phase II study of Erlotinib (OSI-774) in patients with advanced hepatocellular cancer. *J Clin Oncol* 2005; **23**: 6657–63.
- 51 Thomas MB, Chadha R, Glover K *et al*. Phase 2 study of erlotinib in patients with unresectable hepatocellular carcinoma. *Cancer* 2007; **110**: 1059–67.
- 52 Ramanathan RK, Belani CP, Singh DA *et al*. Phase II study of lapatinib, a dual inhibitor of epidermal growth factor receptor (EGFR) tyrosine kinase 1 and 2 (Her2/Neu) in patients (pts) with advanced biliary tree cancer (BTC) or hepatocellular cancer (HCC). A California Consortium (CCC-P) Trial. *J Clin Oncol* 2006; **24** (18S): 4010.
- 53 Prewett M, Rockwell P, Rockwell RF *et al*. The biologic effects of C225, a chimeric monoclonal antibody to the EGFR, on human prostate carcinoma. *J Immunother Emphasis Tumor Immunol* 1996; **19**: 419–27.
- 54 Lièvre A, Bachet JB, Boige V *et al*. KRAS mutations as an independent prognostic factor in patients with advanced colorectal cancer treated with cetuximab. *J Clin Oncol* 2008; **26**: 374–9.
- 55 Zhu AX, Stuart K, Blaszkowsky LS *et al*. Phase 2 study of cetuximab in patients with advanced hepatocellular carcinoma. *Cancer* 2007; **110**: 581–589.
- 56 Gruenewald V, Wilkens L, Gebel M *et al*. A phase II open-label study of cetuximab in unresectable hepatocellular carcinoma: final results. *J Clin Oncol* 2007; **25** (18S): 4598.
- 57 Louafi S, Hebbar M, Rosmorduc O *et al*. Gemcitabine, oxaliplatin (GEMOX) and cetuximab for treatment of hepatocellular carcinoma (HCC): results of the phase II study ERGO. *J Clin Oncol* 2007; **25** (18S): 4594.
- 58 Sachdev D, Yee D. Disrupting insulin-like growth factor signaling as a potential cancer therapy. *Mol Cancer Ther* 2007; **6**: 1–12.
- 59 Scharf JG, Braulke T. The role of the IGF axis in hepatocarcinogenesis. *Horm Metab Res* 2003; **35**: 685–93.
- 60 Tanaka S, Ito T, Wands JR. Neoplastic transformation induced by insulin receptor substrate-1 overexpression requires an interaction with Grb2 and Syp signaling molecules. *J Biol Chem* 1996; **271**: 14 610–16.
- 61 Tanaka S, Smidt EV, Mohr L, Sugimachi K, Wands JR. Biological effects of human insulin receptor substrate-1 overexpression in hepatocytes. *Hepatology* 1997; **26**: 598–604.
- 62 Tanaka S, Wands JR. A carboxy-terminal truncated IRS-1 dominant negative protein reverses the human hepatocellular carcinoma malignant phenotype. *J Clin Invest* 1996; **98**: 2100–8.
- 63 Tanaka S, Wands JR. Insulin receptor substrate-1 overexpression in human hepatocellular carcinoma cells prevents transforming growth factor- β 1 induced apoptosis. *Cancer Res* 1996; **56**: 3391–4.
- 64 Hotamisligil GS, Peraldi P, Budavari A, Ellis R, White MF, Spiegelman BM. IRS-1-mediated inhibition of insulin RTK activity in TNF- α - and obesity-induced insulin resistance. *Science* 1996; **271**: 665–8.
- 65 Feng Y, Zhu Z, Xiao X, Choudhry V, Barrett JC, Dimitrov DS. Novel human monoclonal antibodies to insulin-like growth factor (IGF)-II that potently inhibit the IGF receptor type I signal transduction function. *Mol Cancer Ther* 2006; **5**: 114–20.
- 66 Burtrum D, Zhu Z, Lu D *et al*. A fully human monoclonal antibody to the insulin-like growth factor I receptor blocks ligand-dependent signaling and inhibits human tumor growth *in vivo*. *Cancer Res* 2003; **63**: 8912–21.
- 67 Garber K. IGF-1: old growth factor shines as new drug target. *J Natl Cancer Inst* 2005; **97**: 790–2.
- 68 Desbois-Mouthon C, Cacheux W, Blivet-Van Eggelpeel MJ *et al*. Impact of IGF-1R/EGFR cross-talks on hepatoma cell sensitivity to gefitinib. *Int J Cancer* 2006; **119**: 2557–66.
- 69 Pawson T. Specificity in signal transduction: from phosphotyrosine-SH2 domain interactions to complex cellular systems. *Cell* 2004; **116**: 191–203.
- 70 Macdonald JS, McCoy S, Whitehead RP *et al*. A phase II study of farnesyl transferase inhibitor R115777 in pancreatic cancer: a Southwest oncology group (SWOG 9924) study. *Invest New Drugs* 2005; **23**: 485–7.
- 71 Schagdarsurengin U, Wilkens L, Steinemann D *et al*. Frequent epigenetic inactivation of the RASSF1A gene in hepatocellular carcinoma. *Oncogene* 2003; **22**: 1866–71.
- 72 Farazi PA, DePinho RA. Hepatocellular carcinoma pathogenesis: from genes to environment. *Nat Rev Cancer* 2006; **6**: 674–87.
- 73 Luo J, Manning BD, Cantley LC. Targeting the PI3K–Akt pathway in human cancer: rationale and promise. *Cancer Cell* 2003; **4**: 257–62.
- 74 Chiang GG, Abraham RT. Targeting the mTOR signaling network in cancer. *Trends Mol Med* 2007; **13**: 433–42.
- 75 Frost P, Shi Y, Hoang B, Lichtenstein A. AKT activity regulates the ability of mTOR inhibitors to prevent angiogenesis and VEGF expression in multiple myeloma cells. *Oncogene* 2007; **26**: 2255–62.
- 76 Raymond E, Alexandre J, Faivre S *et al*. Safety and pharmacokinetics of escalated doses of weekly intravenous infusion of CCI-779, a novel mTOR inhibitor, in patients with cancer. *J Clin Oncol* 2004; **22**: 2336–47.
- 77 Beuvink I, Boulay A, Fumagalli S *et al*. The mTOR inhibitor RAD001 sensitizes tumor cells to DNA-damaged induced apoptosis through inhibition of p21 translation. *Cell* 2005; **120**: 747–59.
- 78 Luo JL, Kamata H, Karin M. IKK/NF- κ B signaling: balancing life and death – a new approach to cancer therapy. *J Clin Invest* 2005; **115**: 2625–32.
- 79 Maeda S, Kamata H, Luo JL, Leffert H, Karin M. IKK β couples hepatocyte death to cytokine-driven compensatory proliferation that promotes chemical hepatocarcinogenesis. *Cell* 2005; **121**: 977–90.
- 80 Rajkumar SV, Richardson PG, Hideshima T, Anderson KC. Proteasome inhibition as a novel therapeutic target in human cancer. *J Clin Oncol* 2005; **23**: 630–9.
- 81 Teicher BA, Ara G, Herbst R, Palombella VJ, Adams J. The proteasome inhibitor PS-341 in cancer therapy. *Clin Cancer Res* 1999; **5**: 2638–45.

- 82 Hegewisch-Becker S, Sterneck M, Schubert U *et al.* Phase I/II trial of botezomib in patients with unresectable hepatocellular carcinoma. *J Clin Oncol* 2004; **22** (15S): 4089.
- 83 Malumbres M, Barbacid M. Cell cycle kinases in cancer. *Curr Opin Genet Dev* 2007; **17**: 60–5.
- 84 Keen N, Taylor S. Aurora-kinase inhibitors as anticancer agents. *Nat Rev Cancer* 2004; **4**: 927–36.
- 85 Lee CY, Andersen RO, Cabernard C *et al.* *Drosophila* Aurora-A kinase inhibits neuroblast self-renewal by regulating aPKC/Numb cortical polarity and spindle orientation. *Genes Dev* 2006; **20**: 3464–74.
- 86 Ruchaud S, Carmena M, Earnshaw WC. Chromosomal passengers: conducting cell division. *Nat Rev Mol Cell Biol* 2007; **8**: 798–812.
- 87 Tanaka S, Noguchi N, Ochiai T *et al.* Outcomes and recurrence of initially resection of hepatocellular carcinoma meeting Milan criteria: Rationale for partial hepatectomy as first strategy. *J Am Coll Surg* 2007; **204**: 1–6.
- 88 Tanaka S, Arai S, Yasen M *et al.* Aurora kinase B is a predictive factor for the aggressive recurrence of hepatocellular carcinoma after curative hepatectomy. *Br J Surg* 2008; **95**: 611–19.
- 89 Gadea BB, Ruderman JV. Aurora kinase inhibitor ZM447439 blocks chromosome-induced spindle assembly, the completion of chromosome condensation, and the establishment of the spindle integrity checkpoint in *Xenopus* egg extracts. *Mol Biol Cell* 2005; **16**: 1305–18.
- 90 Hauf S, Cole RW, LaTerra S *et al.* The small molecule Hesperadin reveals a role for Aurora B in correcting kinetochore–microtubule attachment and in maintaining the spindle assembly checkpoint. *J Cell Biol* 2003; **161**: 281–94.
- 91 Harrington EA, Bebbington D, Moore J *et al.* VX-680, a potent and selective small-molecule inhibitor of the Aurora kinases, suppresses tumor growth *in vivo*. *Nat Med* 2004; **10**: 262–7.
- 92 Soncini C, Carpinelli P, Gianellini L *et al.* PHA-680632, a novel Aurora kinase inhibitor with potent antitumoral activity. *Clin Cancer Res* 2006; **12**: 4080–9.
- 93 Hoar K, Chakravarty A, Rabino C *et al.* MLN8054, a small-molecule inhibitor of Aurora A, causes spindle pole and chromosome congression defects leading to aneuploidy. *Mol Cell Biol* 2007; **27**: 4513–25.
- 94 Wilkinson RW, Odedra R, Heaton SP *et al.* AZD1152, a selective inhibitor of Aurora B kinase, inhibits human tumor xenograft growth by inducing apoptosis. *Clin Cancer Res* 2007; **13**: 3682–8.
- 95 Girdler F, Gascoigne KE, Evers PA *et al.* Validating Aurora B as an anti-cancer drug target. *J Cell Sci* 2006; **119**: 3664–75.
- 96 Vakifahmetoglu V, Olsson M, Zhivotovsky B. Death through a tragedy: mitotic catastrophe. *Cell Death Differ* 2008; **15**: 1153–62.

