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Meeting report

Farnesyl transferase inhibitors: a major breakthrough in anticancer therapy? Naples, 12 April 2002

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An international meeting focused on farnesyl transferase inhibitors (FTIs) was held in Naples on 12 April 2002 and represented an excellent occasion to gather most of the clinicians who are involved in clinical trials with this class of new compounds. Oncogene mutations of the *ras* gene occur in approximately 30% of all human cancers and may have prognostic significance. Ras protein is normally synthesized as pro-Ras, which undergoes a number of post-translational modifications, among which farnesylation. Processed Ras proteins localize to the inner surface of the plasma membrane, and function as a molecular switch that cycles between an inactive and an active form. When in its active form, either because of the binding of an external ligand or because of its constitutive activation, Ras activates several downstream effectors, such as Raf-1, Rac, Rho and phospahtidylinositol-3 kinase, which mediate important cellular functions, such as proliferation, cytoskeletal organization and others. Interruption of the Ras signaling pathway can be basically achieved in three ways, i.e. inhibition of Ras protein expression through antisense oligonucleotides, prevention of Ras membrane localization and inhibition of Ras downstream effectors. SCH 66336 (lonafarnib; Sarasar), a tricyclic orally active FTI, has been the first of these compounds to undergo clinical development. The toxicity profile observed in all completed phase I/II trials has been fairly similar, since gastrointestinal tract toxicity (nausea, vomiting and diarrhea) and fatigue have generally qualified as dose-limiting toxicity (DLT). One objective response in a patient with pretreated non-small cell lung cancer (NSCLC) was observed. Based on preclinical evidence of synergism between lonafarnib and other anticancer agents, combination studies have been started. In particular, lonafarnib has been combined both with gemcitabine and with paclitaxel in phase I studies. Nausea, vomiting, diarrhea and myelosuppression represented DLTs in these studies, in which an encouraging clinical activity was observed, in particular in pancreatic carcinoma (lonafarnib plus gemcitabine) and in NSCLC (lonafarnib plus paclitaxel). R115777 (Zarnestra) is another novel orally active FT competitive inhibitor in clinical development. Single-agent phase I/II studies have shown that myelotoxicity and neurotoxicity are DLTs, intermittent schedule is probably better tolerated and antitumor activity is observed particularly in breast cancer. A number of combination studies with R115777 have been carried out; taken as a whole, they show that the drug can be easily combined with several anticancer agents and phase III trials exploring the potential benefit from incorporation of R115777 into active chemotherapy regimens are indicated. Two other FTIs are in an earlier stage of clinical development. BMS-214662 has the main advantage of being cytotoxic in nature, rather than cytostatic; in particular, potent *in vivo* antitumor activity in human tumor xenografts of different histologies has been reported. A major drawback for BMS-214662 is its severe gastrointestinal and liver toxicities, which prevent the achievement of adequate systemic exposures following the oral route. L-778,123 has been stopped in its clinical development due to its severe and unexpected toxicity, i.e. grade 4 thrombocytopenia and significant Q–T prolongation. [© 2002 Lippincott Williams & Wilkins.]

Key words: Anticancer therapy, farnesyl transferase inhibitors, *ras* oncogene.

Introduction

Oncogenic mutations of the *ras* gene occur in approximately 30% of all human cancers, and the *ras* signaling pathway has attracted considerable attention as a target for anticancer therapy due to its important role in carcinogenesis.[1] Several studies, mainly focused on hematologic malignancies, and pancreatic, colorectal and non-small cell lung cancer (NSCLC), have evaluated the prognostic importance of *ras* mutation in human tumors and conflicting results have been reported.[2,3] Ras protein is normally synthesized as pro-Ras, which undergoes a number of post-translational modifications, the first and most important of which is farnesylation, which acts by rendering Ras protein more hydrophobic and thus better capable of linking to the inner surface of the plasma membrane.[4] Farnesyl transferase (FT), the

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enzyme which catalyzes this reaction, is the target of a few drugs under clinical development. A meeting focused on preclinical and clinical studies with this class of compounds was held in Naples on 12 April 2002.

ras oncogene as a target for therapeutic intervention

Professor Alex Adjei (Mayo Clinic, Rochester, MN) gave the main lecture, in which he summarized the ways to target *ras* oncogene for therapeutic intervention. Processed Ras proteins localize to the inner surface of the plasma membrane, and function as a molecular switch that cycles between an inactive, guanosine 5′-diphosphate (GDP)-bound form and an active, guanosine 5′-triphosphate (GTP)-bound form. When in its active form, either because of the binding of an external ligand or because of its constitutive activation, *ras* activates several downstream effectors, such as Raf-1, Rac, Rho and phospahtidylinositol-3 kinase (PI3 K), which mediate important cellular functions, such as proliferation, cytoskeletal organization and others.[5] Raf-1 is a serine-threonine kinase, which is recruited by Ras–GTP to the plasma membrane, where it is activated by a yet unknown factor. Once activated, Raf triggers the mitogen-activated protein (MAP) kinase cascade, which is involved in transmitting membrane signals to the cell nucleus. The critical nuclear target of the above kinase cascade is the transcription factor Fos. Ras-mediated activation of the kinase pathway increases cellular levels of cyclin 1, which in turn promotes the progression of cells through the G_1 checkpoint and into S phase, leading to proliferation. Rac and Rho are two G-proteins, which cycle between GDP- and GTP-bound forms, and are activated by Ras–GTP. Rac and Rho are critical in cellular processes, such as formation of focal adhesions, stress fibers and membrane ruffling, all of which are important for the regulation of the active cytoskeleton and are important for the invasive phenotype of transformed cells. PI3 K is another Ras downstream effector, which is involved in important cellular processes for oncogenic transformation, such as prevention of apoptosis, increase in cell motility and invasiveness. The serine-threonine kinase AKT is a downstream effector of PI3 K and, in turn, modulates intracellular factors, which can be either survival or death factors. Professor Adjei has underlined that interruption of the *ras* signaling pathway can be basically achieved in three ways, i.e. inhibition of Ras protein expression through antisense oligonucleotides, prevention of Ras membrane localization and inhibition of Ras downstream effectors.

The antisense approach involves targeting specific RNA sequences to block translation of the RNA message into protein. Oligonucleotides, which are complementary to mRNA transcripts of the activated *ras* oncogene, have been utilized to decrease Ras protein expression. In particular, ISIS 2503, a phosphorothioate antisense oligodeoxynucleotide, is in clinical trials. Phase I studies with this compound have been completed, and they have shown that 6 mg/kg administered as a 14-day continuous infusion every 21 days, is a tolerable dose/schedule, moderate thrombocytopenia and fatigue representing the only adverse events.[6] Hints of antitumor activity observed in the above phase I study have prompted both phase II studies and phase I combination studies. Inhibitors of Ras membrane localization mainly include FTIs, which Professor Adjei deliberately overlooked, not to create an overlap with further speakers, and geranylgeranyl transferase (GGT) inhibitors, whose access to clinical trials has thus far been denied mainly by preclinical evidence of effects on cell signaling in normal cells, which induce cell cycle arrest and apoptosis.[7] Interruption of signaling pathways downstream of *ras* primarily involves the use of Raf kinase inhibitors. ISIS 5132 is a phosphorothiorate antisense oligonucleotide which inhibits Raf kinase. Phase I studies using different schedules have been completed in the absence of significant side effects,[8] and phase II studies are underway in colorectal, prostate and ovarian cancer. Raf kinase inhibition can be achieved also with orally active compounds, the first of which to enter clinical trials was BAY43-9006. Professor Adjei underlined that MEK inhibitors represent a promising, non-cytotoxic approach to the interruption of the Ras/MAP kinase pathway for cancer therapy and he focused on his ongoing clinical trial with CI-1040, an oral, highly selective small molecule inhibitor of the dual-specificity kinases, MEK 1 and MEK 2, which prevents phosphorylation and subsequent activation of mitogen-activated protein kinase (MAPK). A phase I trial of CI-1040, administered for 21 consecutive days every 4 weeks in patients with advanced cancer, is ongoing. Fatigue, skin toxicity and diarrhea have qualified as main toxicities in this trial, in which a partial response in a patient with pancreatic cancer, plus a huge number of stable diseases, was achieved. Pharmacodynamic effects were evaluated in this trial by inhibition of phosphorylation of MAPK in peripheral blood mononuclear cells and a dose of 800 mg twice a day to be

administered with food was considered as recommendable for phase II studies in order to achieve plasma concentrations necessary to inhibit the activation of MAPK in peripheral blood mononuclear cells.

FTIs in clinical development: SCH 66336

SCH 66336 (lonafarnib-Sarasar), a tricyclic FTI, was the first of these compounds to undergo clinical development. This compound is quite specific for its target enzyme, is rapidly absorbed following oral administration and has a linear pharmacokinetics. Early clinical trials with Sarasar monotherapy have been discussed by Dr Ferry Eskens (Rotterdam Cancer Institute and University Hospital). Four single-agent phase I trials, two of which are already published as full papers[9,10] have been carried out with this agent, using four different schedules (twice a day on days 1–7 every 21, twice a day on days 1–14 every 28, twice a day continuously and once a day continuously).

The toxicity profile observed in all different trials has been fairly similar, since gastrointestinal tract toxicity (nausea, vomiting and diarrhea) and fatigue have generally qualified as dose-limiting toxicity (DLT). Myelosuppression was not generally observed at the doses which were recommended for phase II. Since farnesylation is a crucial reaction for photoreceptor synthesis, concern was placed on ocular function in all these trials, but no abnormalities were ever recorded. One objective response was observed in the American study using the 1–7 every 21 days schedule.[9] In this study, which had the additional value of highlighting the importance of prelamin A accumulation in buccal mucosal smears as a biologic endpoint for *in vivo* evaluation of FT inhibition, a patient with pretreated NSCLC achieved a confirmed partial response. A number of disease stabilizations were observed in all of the four studies. Since a continuous exposure to a competitive inhibitor is the best way to achieve target enzyme inhibition, the continuous schedule has been chosen to be taken forward for further trials with this compound. A few phase II studies have already been carried out with Sarasar. In particular, a phase II randomized study of Sarasar and gemcitabine in metastatic pancreatic cancer has already been concluded, and it has shown no statistically significant differences between the two treatment arms in terms of objective responses, 3-month progression-free survival and median overall survival.[11] Sarasar has also been used in second-line treatment of bladder carcinoma, but little activity and an unfavorable toxicity profile emerged in this study. Although it is likely that most of the future efforts with Sarasar will be carried out in combination studies, a broad phase II program, including studies in melanoma and colorectal cancer, is planned/ongoing in order to identify the most chemosensitive diseases to which direct further efforts.

Dr Francesco Caponigro (National Tumor Institute of Naples) summarized preclinical and clinical studies of Sarasar in combination with other compounds. Sarasar strongly synergizes *in vitro* with paclitaxel and *in vivo* evidence of synergistic interaction has been also observed, both in NCI 460 human lung carcinoma xenografts and in the *wap–ras* (paclitaxel-resistant) transgenic mouse model.[12] Additive interaction has been observed between Sarasar and gemcitabine in four human tumor cell lines and in *in vivo* models. Sarasar has been combined *in vitro* with cisplatin as well and a cell line-specific, sequence-dependent interaction between the two drugs has been demonstrated.[13] Very recent data show that Sarasar synergizes with Glivec in acute Philadelphia-positive chronic myeloid leukemia and the combination of the two compounds might be able to reverse acquired Glivec resistance in the acute phase of the disease.[14] Based on the above preclinical observations, a few combination clinical trials with Sarasar have been started. In particular, Sarasar has been combined with gemcitabine in a phase I study.[15] Nausea, vomiting, diarrhea and myelosuppression represented DLTs in this study, in which an encouraging clinical activity was observed, in particular in pancreatic carcinoma (two partial responses and one minimal response), while a high percentage of patients achieved a long-lasting stable disease. The encouraging results of the phase I study have led to a number of phase II studies of the combination of Sarasar and gemcitabine, among which a study in second-line advanced bladder carcinoma, which has now completed its accrual and whose results will be communicated shortly. Paclitaxel has been studied in combination with Sarasar in a phase I study.[16] Myelosuppression has qualified as a DLT in this study and the response data have been particularly encouraging in the subset of patients with NSCLC, thus justifying an extension of this study to the subset of patients with taxane-refractory/resistant NSCLC. Responses and disease stabilizations have been observed also in this group of poor prognosis patients.[17] The clinical program for Sarasar includes studies in combination with weekly paclitaxel, docetaxel, Glivec, herceptin,

cisplatin–gemcitabine and carboplatin–paclitaxel, and most of these studies are ongoing. A pivotal program in NSCLC is being launched, with a phase III combination study of carboplatin–paclitaxel with or without Sarasar.

FTIs in clinical development: R115777

R115777 (Zarnestra) is another novel orally active FT competitive inhibitor in clinical development. A summary of clinical trials with single-agent R115777 was presented by Dr Stephen Johnston (Royal Mardsen Hospital, London). The first phase I study tested R115777 with an intermittent schedule (5 days every 2 weeks). Neurotoxicity and fatigue qualified as DLTs in this study, and a patient with metastatic colorectal cancer treated at the recommended dose for phase II had a 46% decrease in tumor marker level, improvement in cough and radiographically stable disease for 5 months.[18] Dr Johnston mainly focused on his phase II study in pretreated breast cancer, in which Zarnestra was administered at the dose of 300 mg twice a day via the oral route on a continuous basis.[19] Four out of 41 patients achieved a partial response, which lasted 4–12 months, while six patients had a long-lasting (6–12 months) stable disease; clinical activity was related neither to *ras* mutational status nor to HER2 positivity. Hematologic toxicity was the main toxicity in this study, since grade 3–4 neutropenia was recorded in 43% of patients and grade 3–4 thrombocytopenia was observed in 23% of patients. Neurotoxicity and fatigue/lethargy were the main non-hematologic toxicities. Dr Johnston treated a second cohort of patients with an intermittent schedule (21 days of treatment, followed by 7 days of rest), reporting similar clinical efficacy, with a better toxicity profile.

Key messages that come up from single-agent Zarnestra studies are the following: the recommended dose for phase II is 300 mg twice a day; the optimal schedule is still under investigation (intermittent schedule is possibly less neurotoxic); DLTs are myelosuppression and neurotoxicity; and hints of antitumor activity mainly in breast cancer and acute myeloid leukemia have been observed. A huge combination study program is being carried out for Zarnestra. These ongoing studies were presented and discussed by Dr Ahmad Awada (Institute Jules Bordet, Bruxelles), who focused mainly on his own phase I study of Zarnestra plus docetaxel.[20] Thirty-two patients were accrued in this study, the majority of whom with breast cancer. Hematologic toxicity qualified as DLT in this study, while non-hematologic toxicities were moderate, since less than 16% of patients had grade 3 toxicity, which consisted of fatigue, vomiting, diarrhea, anorexia, skin toxicity and stomatitis. One complete response in a patient with breast cancer and liver metastases was observed; furthermore, seven patients (four with breast cancer) had a partial response and six patients had a stable disease. No significant pharmacokinetic interaction between the two drugs was observed and two different schedules were judged as feasible because of the low incidence or absence of DLT following the first cycle: Zarnestra 200 mg twice a day for 14 days every 21 plus docetaxel 75 mg/m^2 or Zarnestra 300 mg twice a day for 14 days every 21 plus docetaxel 60 mg/m^2. Zarnestra has also been combined with other compounds, such as leucovorin-modulated 5-fluorouracil (5-FU), capecitabine, irinotecan, topotecan, gemcitabine and herceptin. In the phase I combination study of Zarnestra + 5-FU/leucovorin (administered according to De Gramont schedule), DLT was neutropenia, maximum tolerated dose (MTD) was 200 mg twice a day for 21 days every 28. Neutropenia, along with hand–foot syndrome and diarrhea, was DLT also in the phase I combination study of Zarnestra and capecitabine, in which MTDs were 400 mg twice a day and 2000 mg/m^2, respectively, for 14 days every 21. Myelosuppression and diarrhea were, as expected, DLTs in the phase I combination study of Zarnestra plus irinotecan; in this study, MTDs were 300 mg twice a day for 14 days every 21 for Zarnestra and 350 mg/m^2 every 3 weeks for irinotecan. The phase I combination study of Zarnestra plus topotecan has been interrupted prematurely because of inability to escalate the doses as a consequence of severe myelosuppression. Myelosuppression also represented DLT in the phase I study of Zarnestra plus gemcitabine, in which MTDs were 200 mg twice a day on a continuous basis for Zarnestra and 1000 mg/m^2/week for gemcitabine. In all of the above-mentioned phase I combination studies with Zarnestra, no pharmacokinetic interaction between the tested compounds was observed. Zarnestra has already been combined with combinations of cytotoxics, such as cisplatin–gemcitabine. This study has demonstrated that the combination is well tolerated, DLT is neutropenia, and MTDs were 300 mg twice a day for Zarnestra, 1000 mg/m^2 for gemcitabine and 75 mg/m^2 for cisplatin. The combination showed significant antitumor activity, since 10 objective responses were observed, five of which were in NSCLC patients. Zarnestra is also being tested in combination with Herceptin. A sound rationale for testing this combination exists, since

signal transduction pathways including Ras/Raf mediate neoplastic proliferation from HER2 and other ErbB family members, and since the majority of patients who over-express HER2 will not respond to single-agent herceptin, suggesting either incomplete inhibition or alternative cell signaling pathways. Only toxicity data are available for the study at this stage and they show that myelotoxicity is dose limiting. The conclusion of Dr Awada's thorough review were that Zarnestra can be safely combined with several highly active anticancer drugs, DLT being mostly myelosuppression; phase III trials exploring the potential benefit from incorporation of Zarnestra into active chemotherapy regimens are indicated. Dr Awada completed his presentation reminding us that interference with the *ras* oncogene pathway can also be obtained acting downstream, i.e. interfering with Raf kinase. A single-agent phase I study with BAY 43-006, a novel, potent, orally active inhibitor of Raf kinase, with a 3 out of 4 weeks schedule, is being conducted at the Jules Bordet Institute. This drug looks particularly interesting, since it works in K-*ras* mutant and wild *ras* models, and causes G_1 arrest by down-regulation of cyclin D_1, cyclin D_3 cdk4 and p21. Combination studies of BAY 43-006 with cytotoxic agents, such as docetaxel and gemcitabine, are planned.

Other FTIs in clinical development

Two other FTIs have entered clinical trials, i.e. BMS-214662 and L-778,123. Professor Alex Adjei summarized preclinical findings and ongoing/completed trials with these two compounds. BMS-214662 is a lead compound in the tetrahydrobenzodiazepine class of FTIs discovered at Bristol-Myers Squibb and is presently being evaluated in phase I clinical trials, both alone and in combination. As compared to other classes of FTIs, enzyme inhibitory potencies and cell activities are comparable. In fact, in many cell types, low micromolar concentrations of these inhibitors block Ras farnesylation to near completion and BMS-214662, like other FTIs, is more than 1000-fold selective for FT over GGT. However, unlike most of other FTIs, which are known to be non-toxic at high micromolar concentrations, BMS-214662 is cytotoxic at 2–10 μM concentrations and this prompts possible additional mechanisms of action besides FT inhibition. *In vitro* apoptosis was particularly evident in HCT-116 human colon cancer cells, when cells were exposed to BMS-214662 for more than 24 h. Consistent with its potent apoptotic activity, BMS-214662 demonstrated potent *in vitro* cytotoxicity against a wide cell line panel. Particularly sensitive to BMS-214662 were human tumor lines OVCAR-3 ovarian carcinoma, HCT-116 colon carcinoma, A431 squamous cell carcinoma and HL60 leukemia.[21] Potent *in vivo* antitumor activity in human tumor xenografts of different histologies has been observed with both orally and parenterally administered BMS-214662, regardless of the presence of *ras* mutation in the responding tumor lines. These results obtained with BMS-214662 sharply differ from those obtained with other FTIs. In particular, curative activity against well-established tumors, retained also against a multidrug resistant tumor subline, appears to be a peculiar feature of this compound.[21] A major drawback for BMS-214662, which has come up from the phase I program, is its severe gastrointestinal and liver toxicities, which prevent the achievement of adequate systemic exposures following the oral route. Therefore, it needs parenteral administration (1 or 24 h weekly infusion), which is a major disadvantage for a drug to be used on a long-term basis. Professor Adjei then mentioned his ongoing study, in which BMS-214662 is being tested in combination with paclitaxel and carboplatin in a phase I study in patients with advanced cancers. Myelotoxicity, peripheral neuropathy, nausea, fatigue and diarrhea have emerged as main toxicities in this study, in which objective responses were observed even in patients that had failed prior treatment including paclitaxel and carboplatin. L-778,123 is a peptidomimetic FTI, which has been tested in a phase I study using a continuous infusion schedule.[22] This drug has been stopped in its clinical development due to its severe and unexpected toxicity. In particular, severe thrombocytopenia, a significant and possibly life-threatening Q–T prolongation and profound fatigue represented the main toxicities. This study had the considerable merit of validating the importance of serial analyses of HDJ2, a chaperone protein that undergoes farnesylation, in peripheral blood mononuclear cells, as a pharmacodynamic marker of protein prenylation that might be useful in optimizing the development of drugs targeting FT.[22] L-778,123 is the only FTI which has been tested in combination with radiation therapy up to now. The ability of the *ras* oncogene to lead to radioresistance has been indicated through several independent lines of experimentation and PI3 K has been identified as the likely downstream mediator of *ras*-induced radioresistance.[23] FTIs, which block the processing of Ras, result in radiosensitization and one of the possible mechanisms for that is the

FTI-induced reduction of hypoxia in tumors with H-*ras* mutation.[24] Combination studies of FTIs and radiation therapy represent a well worth pursuing field for further trials.

Ongoing preclinical work at National Tumor Institute of Naples

Two short presentations summarizing ongoing preclinical work, which is being carried out in Naples, concluded the meeting. Dr Anna Maria D'Alessandro presented interesting data showing aminobiphosphonate (pamidronate or zoledronate)-induced growth inhibition and apoptosis in human epidermoid cancer KB cells.[25] Aminobiphosphonates abolished the proliferative stimulus induced by epidermal growth factor (EGF); furthermore, a strong decrease of *ras* activity and of its stimulation by EGF, plus a strong reduction of *raf*-1 expression (probably due to increased ubiquitination), were observed. Finally, synergism between pamidronate or zoledronate and R115777 in inducing apoptosis in KB cells was observed. Similar experiments are being carried out in other cell lines and the achieved results may help in the design of new therapeutic strategies. Dr Giovanni Santelli has synthesized a series of H-Cys-Val-Phe-Met-OH analogs in which the phenylalanine residue is replaced by unconventional amino acids. These synthetic compounds inhibit FT with different potencies; however, none of these compounds showed a significant antiproliferative activity, probably because of charged C-terminus which prevented them from crossing the cell membrane (unpublished observations).

References

1. Bos JL. Ras oncogenes in human cancer: a review. *Cancer Res* 1989; **49**: 4682–9.
2. Beaupre DM, Kurzrock R. RAS and leukemia: from basic mechanisms to gene-directed therapy. *J Clin Oncol* 1999; **17**: 1071–9.
3. Field JK, Spandidos DA. The role of *ras* and *myc* oncogenes in human solid tumours and their relevance in diagnosis and prognosis [Review]. *Anticancer Res* 1990; **10**: 1–22.
4. Rowinsky EK, Windle JJ, Von Hoff D. Ras protein farnesyltransferase: a strategic target for anticancer therapeutic development. *J Clin Oncol* 1999; **17**: 3631–52.
5. Adjei AA. Blocking oncogenic *ras* signaling for cancer therapy. *J Natl Cancer Inst* 2001; **93**: 1062–74.
6. Dorr A, Bruce J, Monia B, *et al.* Phase I and pharmacokinetic trial of ISIS 2503, a 20-mer antisense oligonucleotide against H-RAS by 14-day continuous infusion in patients with advanced cancer. *Proc Am Soc Clin Oncol* 1999; **18**: 157a (abstr 603).
7. Sebti SM, Hamilton AD. Inhibition of *ras* prenylation: a novel approach to cancer chemotherapy. *Pharmacol Ther* 1997; **74**: 103–14.
8. Holmlund JT, Rudin CM, Mani S, *et al.* Phase I trial of ISIS 5132/ODN 698A, a 20-mer phosphorothioate antisense oligonucleotide inhibitor of C-RAF kinase, administered by a 24-hour weekly intravenous infusion to patients with advanced cancer. *Proc Am Soc Clin Oncol* 1999; **18**: 157a (abstr 605).
9. Adjei AA, Erlichman C, Davis JN, *et al.* A phase I trial of the farnesyl transferase inhibitor SCH 66336: evidence for biological and clinical activity. *Cancer Res* 2000; **60**: 1871–7.
10. Eskens FALM, Awada A, Cutler DL, *et al.* Phase I and pharmacokinetic study of the oral farnesyl transferase inhibitor SCH 66336 given twice daily to patients with advanced solid tumors. *J Clin Oncol* 2001; **19**: 1167–75.
11. Lersch C, Van Cutsem E, Amado R, *et al.* Randomized phase II study of SCH 66336 and gemcitabine in the treatment of metastatic adenocarcinoma of the pancreas. *Proc Am Soc Clin Oncol* 2001; **20**: 153a (abstr 608).
12. Shi B, Yaremko B, Hajiam G, *et al.* The farnesyl protein transferase inhibitor SCH 66336 synergizes with taxanes *in vitro* and enhances their antitumor activity *in vivo*. *Cancer Chemother Pharmacol* 2000; **46**: 387–93.
13. Adjei AA, Davis JN, Bruzek LM, *et al.* Synergy of the protein transferase inhibitor SCH 66336 and cisplatin in human cancer cell lines. *Clin Cancer Res* 2001; **7**: 1438–45.
14. Nakajima A, Tauchi T, Sumi M, *et al.* Efficacy of SCH 66336, the farnesyl transferase inhibitor, against Glivec-resistant BCR–ABL-positive cells. *Proc Am Ass Cancer Res* 2002; **43**: 855 (abstr 4235).
15. Hurwitz HI, Amado R, Prager D, *et al.* Phase I pharmacokinetic trial of the farnesyl transferase inhibitor SCH 66336 plus gemcitabine in advanced cancer. *Proc Am Soc Clin Oncol* 2000; **19**: 185a (abstr 717).
16. Kim ES, Glisson BS, Meyers ML, *et al.* A phase I/II study of the farnesyl transferase inhibitor (FTI) SCH 66336 with paclitaxel in patients with solid tumors. *Proc Am Ass Cancer Res* 2001; **42**: 488 (abstr 2629).
17. Kim ES, Kies MS, Fossella FV, *et al.* A phase I/II study of the farnesyl transferase inhibitor (FTI) SCH 66336 (lonafarnib) with paclitaxel in taxane refractory/resistant patients with non-small cell lung cancer (NSCLC): final report. *Proc Am Ass Cancer Res* 2002; **43**: 550 (abstr 2735).
18. Zujewski J, Horak ID, Bol CJ, *et al.* Phase I and pharmacokinetic study of farnesyl protein transferase inhibitor R115777 in advanced cancer. *J Clin Oncol* 2000; **18**: 927–41.
19. Johnston SR, Ellis PA, Houston S, *et al.* A phase II study of the farnesyl transferase inhibitor R115777 in patients with advanced breast cancer. *Proc Am Soc Clin Oncol* 2000; **19**: 83a (abstr 318).

20. Piccart-Gebhart MJ, Branle F, de Valeriola D, *et al.* A phase I clinical and pharmacokinetic trial of the farnesyl transferase inhibitor R115777 + docetaxel: a promising combination in patients with solid tumors. *Proc Am Soc Clin Oncol* 2001; **20**: 80a (abstr 316).
21. Rose WC, Lee FYF, Fairchild CR, *et al.* Preclinical antitumor activity of BMS-214662, a highly apoptotic and novel farnesyl transferase inhibitor. *Cancer Res* 2001; **61**: 7507–17.
22. Britten CD, Rowinsky EK, Soignet S, *et al.* A phase I and pharmacological study of the farnesyl protein transferase inhibitor L-778,123 in patients with solid malignancies. *Clin Cancer Res* 2001; **7**: 3894–903.
23. Cohen-Jonathan E, Evans SM, Koch CJ, *et al.* The farnesyl transferase inhibitor L 744, 832 reduces hypoxia in tumors expressing activated H-*ras*. *Cancer Res* 2001; **61**: 2289–93.
24. Gupta AK, Bakanauskas VJ, Cerniglia GJ, *et al.* The *ras* radiation resistance pathway. *Cancer Res* 2001; **61**: 4278–82.
25. Caraglia M, D'Alessandro AM, Addeo R, *et al.* Aminobiphosphonates induce apoptosis dependent form *ras* disruption and synergize with farnesyl transferase inhibitors in human epidermoid cancer cells. *Proc Am Ass Cancer Res* 2002; **43**: 942 (abstr 4664).