Cancer Therapy: Clinical

A Phase I Study of PF-04929113 (SNX-5422), an Orally Bioavailable Heat Shock Protein 90 Inhibitor, in Patients with Refractory Solid Tumor Malignancies and Lymphomas


Abstract

Purpose: To determine the maximum tolerated dose (MTD), toxicities, and pharmacokinetic/pharmacodynamic profile of the Hsp90 inhibitor PF-04929113 (SNX-5422) in patients with advanced solid tumors and lymphomas.

Methods: This was a single-institution, phase I, dose-escalation study of PF-04929113 administered twice weekly. Endpoints included determination of dose-limiting toxicities (DLT), MTD, the safety profile of PF-04929113, pharmacodynamic assessment of PF-04929113 on Hsp70 induction, pharmacokinetic analysis of PF-04928473 (SNX-2112) and its prodrug PF-04929113, and assessment of response.

Results: Thirty-three patients with advanced malignancies were treated. Dose escalation was continued up to 177 mg/m² administered orally twice a week. One DLT (nonseptic arthritis) was noted. No grade 4 drug-related adverse events were seen; grade 3 adverse events included diarrhea (9%), nonseptic arthritis (3%), aspartate aminotransferase elevation (3%), and thrombocytopenia (3%). No objective responses were seen in 32 evaluable patients. Fifteen patients (47%) had stable disease; 17 patients (53%) had progressive disease. Pharmacokinetic data revealed rapid absorption, hepatic, and extrahepatic clearance, extensive tissue binding, and almost linear pharmacokinetics of the active drug PF-04928473. Pharmacodynamic studies confirmed inhibition of Hsp90 and a linear correlation between pharmacokinetic parameters and Hsp70 induction.

Conclusions: PF-04929113 administered orally twice a week is well tolerated and inhibits its intended target Hsp90. No objective responses were seen, but long-lasting stabilizations were obtained. Although no clinically significant drug-related ocular toxicity was seen in this study, the development of PF-04929113 has been discontinued because of ocular toxicity seen in animal models and in a separate phase I study.

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Introduction

Hsp90 belongs to a family of highly conserved proteins that play an integral role within cells acting as molecular chaperones to numerous biologically important client proteins essential for constitutive cell signaling and adaptive response to stress (1, 2). Cancer cells use the Hsp90 chaperone machinery to protect an array of mutated and overexpressed oncoproteins from misfolding and degradation (3). Many potential partner proteins in the Hsp90 interactome have been identified including protein kinases [e.g., epidermal growth factor receptor (EGFR), HER2, Src, Akt, BRAF, and BCR-ABL], steroid receptors (e.g., ER, PR, and AR), telomerase reverse transcriptase, nitric oxide synthase, and transcription factors (e.g., hypoxia-inducible factor 1, alpha subunit, aryl hydrocarbon receptor, p53, and STAT3), many of which are dysregulated in human cancer (4). Preclinical data show that Hsp90 inhibitors can abrogate the oncogenic switch that is frequently induced as a resistance mechanism to tyrosine kinase inhibitors. Interestingly, most of the induced and/or mutated kinases that have been identified (HER2, BRAF, MET, and ALK) are Hsp90 clients and remain sensitive to Hsp90 inhibition (5). Similarly, the development of secondary mutations (e.g., T790M) that provide resistance to EGFR tyrosine kinase inhibitors also remain sensitive to Hsp90 inhibition.
Translational Relevance

Hsp90 serves as a molecular chaperone to multiple oncoproteins and biologically important protein kinases. Although many clinical trials have been done to evaluate Hsp90 inhibitors, the development of ocular toxicity in animal models and clinical trials has raised concerns about further development of these compounds. We believe our study is the first to incorporate comprehensive ophthalmologic evaluation to assess ocular toxicity that is associated with these drugs. Although no clinically significant drug-related ocular toxicity was seen in this study, the occurrence of ocular complaints in a separate phase I study of PF-04929113 using a different schedule of administration suggests an association between schedule of administration and development of ocular toxicity. Unless the cause of these ocular symptoms is determined and resolved satisfactorily, it is likely to have a significant impact on further clinical development of Hsp90 inhibitors. In addition, to the best of our knowledge this is the first study to describe a linear correlation between a pharmacodynamic endpoint as illustrated by Hsp70 induction and pharmacokinetic parameters across dose levels.

Targeting Hsp90 is potentially a powerful strategy in cancer therapeutics due to the central role this protein plays in many simultaneous oncological signaling pathways (8). PF-04929113 (SNX-5422) is a water-soluble and orally bioavailable prodrug of PF-04928473 (SNX-2112), a potent and highly selective small-molecule inhibitor of Hsp90 (9, 10). PF-04928473 competitively binds to the N-terminal ATP pocket of Hsp90 family members (Hsp90α, Hsp90β, Grp94, and Trap-1) and is highly potent against various cancers in vitro and in vivo (9–11). On the basis of these results, a single-institution phase I study was conducted to evaluate the maximum tolerated dose (MTD) and safety profile of PF-04929113 when administered twice weekly every 28 days via a continuous dosing schedule.

Patients and Methods

Patients

Eligibility criteria included histologically documented solid tumors and lymphoid malignancies (lymphoma and CLL) refractory to or for whom there is no standard therapy, measurable or evaluable disease, age older than 18 years, Eastern Cooperative Oncology Group (ECOG) performance status 2 or less, life expectancy of more than 3 months, adequate organ and bone marrow function, and the ability to understand and willingness to sign informed consent. Patients were not permitted to have major surgery, radiation therapy, chemotherapy, or biological therapy within 4 weeks before entering the study and any toxicity related to previous therapy had to have recovered to at least grade 1. Patients with symptomatic brain metastases or HIV infection on antiretroviral therapy were also excluded.

The primary endpoints for this phase I study were to determine the MTD, safety, and toxicity of PF-04929113 when administered twice weekly for 28 days. Secondary objectives included investigation of the effects of PF-04929113 on engagement of the Hsp90 target by pharmacodynamic assessment of Hsp70 levels, assessment of response using the National Cancer Institute Response Evaluation Criteria in Solid Tumors (RECIST 1.0) for solid tumors (12) and standardized lymphoma criteria (13) for lymphomas and determining the pharmacokinetic profile of the active drug PF-04928473 (SNX-2112) in humans.

Study design

Cohorts of 3 to 6 patients were enrolled at each dose level. The dose level at which 2 patients experienced dose-limiting toxicity (DLT) was considered to have exceeded the MTD. The next lower dose level at which no more than one out of six patients experienced DLTs was considered the MTD. DLTs were defined as adverse events possibly, probably, or definitely related to administration of PF-04929113 and fulfilling any of the following criteria: grade 4 nonhematologic and hematologic toxicities with the exception of grade 4 neutropenia lasting less than 5 days without fever or infection; and grade 3 nonhematologic toxicities with the following exceptions: grade 3 nausea, vomiting, diarrhea, and electrolyte abnormalities if refractory to treatment, grade 3 creatinine if not correctable to grade 1 or less after 2 L of intravenous fluids within 48 hours, and grade 3 elevation in liver transaminases and/or bilirubin if they did not return to baseline after a maximum of 2 dropped doses (not to exceed 10 days) within a cycle or 15 days between cycles.

The starting dose of PF-04929113 was 4 mg/m² per dose. The dose-escalation schema and the number of patients treated are depicted in Supplementary Table S1. Intrapatient dose escalation was permitted per protocol if (i) there was no greater than grade 1 drug-related toxicity after 1 course at the initial dose level, (ii) the higher dose level had been completed by all patients in that cohort and no patients experienced a DLT, and (iii) disease had not progressed. Patients self-administered the assigned dose of PF-04929113 with 225 mL of water twice a week continuously in a 28-day cycle. Food was held 2 hours before and 1 hour after ingestion of the study drug. Treatment was continued until disease progression or development of intolerable toxicity. Dose modifications were done if patients developed severe toxicities based on predefined criteria, according to the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. Intrapatient dose escalation up to the last evaluated dose not associated with a DLT was permitted if there was no greater than grade 1 drug-related toxicity after 1 cycle at the initial dose level, the higher dose level had been completed by all patients in that cohort with no DLTs observed, and there was no evidence of disease progression.

Studies conducted for baseline assessment and on-study evaluation are presented in Supplementary Material.
On-study evaluation included an electrocardiograph (ECG) obtained on day 1 of each cycle starting with cycle 2. To examine the relationship between plasma concentrations of PF-04929113 and its effect on the corrected QT (QTc) interval, the study was amended in May 2009 to include continuous ECG monitoring beginning 1 hour predose and continuing for 23 hours postdose on day 1 and day 15 of cycle 1. In July 2010, because of findings from animal studies that showed the potential of PF-04929113 to induce irreversible retinal damage, the study was further amended to include a comprehensive ophthalmologic evaluation including visual acuity and visual field assessment, ophthalmoscopy, dark-adaptation testing, Ganzfeld electroretinography (ERG), and optical coherence tomography if these tests had not been conducted earlier or if new visual symptoms developed while a patient was on study.

**Pharmacokinetic analysis**

Blood was drawn on day 1 and days 15/18 of cycle 1 at the following time points: predose and postdose at 20 and 40 minutes and at 1, 2, 3, 4, 6, 8, 10, 12, 24, 36, and 48 hours. During subsequent cycles, blood was drawn before dosing on day 1 only. Details of sample processing are presented in Supplementary Material. Samples were analyzed by a validated liquid chromatography/tandem mass spectrometry (LC/MS-MS) method (14). Pharmacokinetic parameters, including area under the curve (AUC0–48), apparent clearance (CL/Fm), volume of distribution (Vz/Fm), maximum concentration (Cmax), time to reach maximum concentration (tmax), and half-life for PF-04928473, were calculated by noncompartmental analysis with WinNonlin professional software version 5.0 (Pharsight Corporation).

**Pharmacodynamic analysis**

The analysis of Hsp70 induction in peripheral blood was conducted by Western blotting. Details of sample processing and analysis are presented in Supplementary Material.

**Statistical analysis**

The dose-dependent linearity in pharmacokinetics of PF-04928473 was determined on the basis of the slope of the following power model: AUC = intercept × (dose)^slope. If 90% confidence interval (CI) on slope contained 1, pharmacokinetics was considered linear (i.e., dose proportional). Statistical comparisons between Hsp70 induction, dose of PF-04929113, and pharmacokinetic parameters were carried out by the nonparametric Mann-Whitney U test. All tests were 2 tailed and statistical analysis software GraphPad Prism v5.0c was used. Spearman correlation analyses were conducted with GraphPad Prism software to correlate Hsp70 induction with pharmacokinetic parameters (mean Cmax and AUCinf of each cohort) measured on day 1 of cycle 1. Other secondary evaluations were done in a descriptive manner. Results from secondary analyses are exploratory in nature, and P values are presented without correction for multiple comparisons.

**Results**

Between March 2008 and October 2009, a total of 33 patients were enrolled. Patient characteristics are summarized in Table 1. Intrapatient dose escalation was carried out in 4 patients: from 4 to 16 mg/m² in 1 patient, from 8 to 16 mg/m² in 2 patients, and from 8 to 33 mg/m² in 1 patient.

**Toxicity**

PF-04929113 was well tolerated. A DLT was noted in 1 patient in the form of nonseptic arthritis at a dose of 16 mg/
m² per dose 18 days after initiation of cycle 3 of treatment. Although this adverse event arose beyond the period for evaluation of toxicity at a given dose level (defined as 28 days after 3 evaluable patients in a dose cohort receive the last dose in cycle 1), the cohort that was enrolling when this adverse event occurred (cohort 5 at 44 mg/m² on which 2 patients had enrolled) was expanded to 6 patients and no further DLTs were seen. However, dose escalation was stopped at a dose of 177 mg/m² per dose because of reports of irreversible retinal damage observed in a canine model after 4 of 20 patients on another phase I study evaluating PF-04929113 had visual symptoms of nictalopia and blurred vision.

In addition to the grade 3 nonseptic arthritis, another patient being treated at a dose of 16 mg/m² experienced joint swelling and stiffness possibly related to the study drug. Further workup in both cases did not reveal any other cause to account for these symptoms.

Most adverse events that could be possibly attributed to the study drug were grade 1 or 2 in severity (Table 2). Grade 3 adverse events possibly related to the drug included diarrhea, nonseptic arthritis (described earlier), aspartate aminotransferase elevation, and thrombocytopenia (Table 3). Grade 3 diarrhea was seen in 3 patients; 2 treated at dose level 8 (100 mg/m²) and 1 patient treated at dose level 10 (177 mg/m²). It was not considered a DLT because it lasted less than 48 hours and was not refractory

### Table 2. Adverse events possibly, probably, or definitely attributed to treatment with PF-04929113

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
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<tr>
<td>Nausea</td>
<td>8 (24)</td>
<td>1 (3)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Emesis</td>
<td>2 (6)</td>
<td>1 (3)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Anorexia</td>
<td>2 (6)</td>
<td>1 (3)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4 (12)</td>
<td>0</td>
<td>3 (9)</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td>1 (3)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>1 (3)</td>
<td>1 (3)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>1 (3)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>1 (3)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Weight loss</td>
<td>1 (3)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>4 (12)</td>
<td>2 (6)</td>
<td>0</td>
<td>0</td>
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<td>Joint pain</td>
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</tr>
<tr>
<td>Arthritis (nonseptic)</td>
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<td>1 (3)</td>
<td>0</td>
</tr>
<tr>
<td>Muscle pain</td>
<td>0</td>
<td>1 (3)</td>
<td>0</td>
<td>0</td>
</tr>
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<td>Influenza-like symptoms</td>
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<td>0</td>
<td>0</td>
<td>0</td>
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<td>Edema</td>
<td>0</td>
<td>1 (3)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cough</td>
<td>1 (3)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>AST elevation</td>
<td>3 (9)</td>
<td>2 (6)</td>
<td>1 (3)</td>
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</tr>
<tr>
<td>ALT elevation</td>
<td>5 (15)</td>
<td>1 (3)</td>
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<td>0</td>
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<td>Alkaline phosphatase elevation</td>
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<td>Hypophosphatemia</td>
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<td>0</td>
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<td>6 (18)</td>
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<td>0</td>
</tr>
<tr>
<td>Anemia</td>
<td>2 (6)</td>
<td>3 (9)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>4 (12)</td>
<td>0</td>
<td>1 (3)</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.

### Table 3. Relationship between grade 3 adverse events at least possibly related to PF-04929113 and dose level

<table>
<thead>
<tr>
<th>Grade 3 adverse event</th>
<th>Cohort</th>
<th>Dose level, mg/m²</th>
</tr>
</thead>
<tbody>
<tr>
<td>AST elevation</td>
<td>7</td>
<td>77</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>8</td>
<td>100</td>
</tr>
<tr>
<td>8</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>177</td>
<td></td>
</tr>
<tr>
<td>Nonseptic arthritis</td>
<td>3</td>
<td>16</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>10</td>
<td>177</td>
</tr>
</tbody>
</table>

Abbreviation: AST, aspartate aminotransferase.
to treatment. Grade 3 aspartate aminotransferase elevation possibly related to the investigational agent was seen in 1 patient at dose level 7 (77 mg/m²). It was not considered a DLT because it resolved within 4 days. Grade 3 thrombocytopenia was seen in 1 patient at dose level 10 (177 mg/m²).

Continuous ECG monitoring did not reveal any effect of PF-04929113 on the QTc interval. No drug-related grade 4 adverse events or deaths were seen.

Because of the potential impact of PF-04929113 on visual function, a protocol amendment was implemented requiring patients to undergo a comprehensive ocular examination (see earlier). Three patients who were actively being treated at dose levels of 77, 133, and 177 mg/m² were evaluated. One patient requested to come off study after 10 cycles prior to ocular assessment. She was initially treated at a DLT because it resolved within 4 days. Grade 3 thrombocytopenia was seen in 1 patient at dose level 10 (177 mg/m²).

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Discussion

This phase I study shows that treatment with PF-04929113 administered orally twice a week via a continuous dosing schedule is well tolerated. Drug-related adverse events were generally mild, with the most common being nausea, fatigue, and diarrhea. The toxicity profile observed is similar to that reported with other Hsp90 inhibitors in phase I studies (15, 16). Schedule of administration of Hsp90 inhibitors has been shown to have a significant effect on drug tolerability (17–19). PF-04929113 has been evaluated in 2 separate phase I studies using different schedules of administration; every other day for 21 days of a 28-day cycle and every day for 21 of 28 days continuously (later amended to daily continuous administration) The most frequent adverse events were nausea, vomiting, fatigue, and diarrhea. DLTs with daily administration included 3 cases of grade 3 diarrhea, 1 case of grade 2 dehydration and grade 3 gastrointestinal hemorrhage, and 1 case of grade 3 visual disturbance and grade 3 diarrhea. Four of 20 patients who were receiving PF-04929113 daily complained of visual symptoms at doses ranging from 50 to 89 mg/m²/d. Three patients complained of nictalopia, and 1 patient complained of
blurred vision. These patients had grade 1 visual changes, which were reported as mild darkening of vision. In most cases, the onset of the event was within 2 weeks of beginning the drug, and all cases recovered within a few days from stopping treatment. Although no similar unexplained ocular symptoms were noted in our study, ocular examination did reveal a slightly prolonged cone–rod break in 1 patient (data not shown). Preclinical data have shown that geldanamycin and 17-allylamino-17-demethoxygeldanamycin (17-AAG) generate cytostaticity and cytotoxicity in cultured human retinal pigment epithelial cells which are essential for physiologic function of adjacent photoreceptors, possibly by downregulating AKT- and ERK1/2-mediated signaling activities (20). In a phase I study of the Hsp90 inhibitor AUY922, administered intravenously at doses of 2 to 70 mg/m² over 1 hour once weekly, night blindness was reported in 19 of 96 patients treated (20%). Other visual symptoms that were generally grade 1 and 2 and mostly reversible started at 40 mg/m² and included blurred vision, flashing, and delayed dark and light accommodation that increased in frequency or severity with dose. Grade 3 darkening of vision at a dose of 70 mg/m² was listed as a DLT in this study (21). Given these findings, we believe it is critical to carry out a comprehensive ocular assessment in future trials evaluating Hsp90 inhibitors, because this may represent a class side effect. Dose escalation of our study was terminated on the basis of the ocular findings in preclinical and clinical studies of this and other Hsp90 inhibitors. Further understanding of the ocular toxicity observed in a separate phase I study is warranted to continue with the development of PF-04929113. On the basis of the clinical and preclinical safety observations, and despite the preliminary observation of antitumor activity, PF-04929113 has been withdrawn from clinical testing. PF-04929113 and a structurally different backup compound show evidence of retinal toxicity by a yet unknown mechanism. These data indicate that Hsp90 is a critical component of retinal function and that its prolonged inhibition can lead to irreversible retinal damage with photoreceptor death. Further evaluation is
warranted to better understand whether this is a class/target-mediated effect of Hsp90 inhibition. Although, no objective tumor responses were seen in our study, 15 of 32 patients (47%) evaluable for response achieved disease stabilization. This is worth noting in a cohort of heavily pretreated patients who had progressive disease at enrollment after multiple lines of systemic therapy (median number of prior systemic therapies was 4). Disease stabilization was seen across all dose levels. Supplementary Table S5 shows the underlying tumor type in patients who had stable disease on treatment and the duration of disease stabilization in each case.

Our efficacy results are similar to those seen with other Hsp90 inhibitors in patients with advanced solid tumors, where responses are rarely reported (22–24). In a phase II study of IPI-504, a total of 76 patients with NSCLC were enrolled and 5 patients (7%) had an objective response including 4 with EGFR wild-type tumors and 1 with EGFR mutation. Interestingly, among 3 patients with ALK rearrangements, there were 2 partial responses and 1 prolonged stable disease (16). These results suggest benefit among patients with certain solid tumors. The next step would be to determine the biological underpinnings of responses in these patients and potential for patient selection in future trials based on the presence of a tumor that is primarily driven by an Hsp90 client protein.

In our study, pharmacokinetic analysis did not reveal any drug accumulation after the administration of multiple doses via a twice-weekly schedule. Pharmacodynamic analysis showed induction of Hsp70 in PBMCs. Hsp70 levels increase as a result of Hsp90 inhibitor–induced activation of heat shock factor 1 (HSF1), which then enters the nucleus and activates Hsp70 gene expression. An increase in Hsp70 levels was seen in all patients treated at or above a dose of 33 mg/m^2/d. Furthermore, the increase in Hsp70 levels at 24 hours compared with baseline showed a linear correlation when plotted against the mean C_{max} and AUC_{inf} of each cohort (Fig. 3). This is the first study that has shown a correlation between pharmacokinetics and Hsp70 induction across dose levels. Because Hsp70 induction is seen at dose levels as low as 33 mg/m^2/d, PF-04929113 could be combined at relatively low doses with other systemic therapy in future studies while retaining the ability to inhibit Hsp90. Hsp70 has, however, been identified as an anti-apoptotic protein and it may play a role in Hsp90 resistance. Ongoing strategies to overcome this problem include direct inhibition of Hsp70 activity (25, 26) and inhibition of the transcriptional induction of Hsp70 by HSF1, which has been identified to have potent oncogenic activity (27). The complexity of chaperone biology is further highlighted by reports suggesting that Hsp70 induction may have beneficial neuroprotective activity when an Hsp90 inhibitor is combined with bortezomib (28).

One drawback of this study is that PBMCs were used as a surrogate tissue for Hsp70 analysis. The data thus far suggest that Hsp90 exists in a high-affinity state for pharmacologic inhibitors in tumor tissue compared with normal tissues (29). Coincident with this observation, Hsp90 inhibitors tend to accumulate in tumor tissues as compared with normal tissues.

For the first 8 years of clinical development, the only Hsp90 inhibitors in clinical trial were the natural product ansamycins, which had major drawbacks in insolubility and formulation. The data reported here are the first full report of a second-generation Hsp90 inhibitor that is fully synthetic and orally available.

In conclusion, our study shows that PF-04929113 administered twice weekly via a continuous dosing schedule is well tolerated with mild adverse events but modest antitumor activity when used as a single agent. The recommended phase II dose has not been determined; further evaluation including a better understanding of the mechanism of ocular toxicity, relationship between ocular toxicity and plasma levels, and implementation of appropriate testing to evaluate ocular toxicity of PF-04929113 in patients would be needed to define the recommended phase II dose.
However, on the basis of pharmacodynamic data from our study, the lowest biologically effective dose seems to be 33 mg/m² administered orally twice a week; at or above this dose induction of Hsp70 was observed in all cases. Clearly, drug scheduling is an extremely important issue. Hsp90 inhibitors given on a daily basis may enhance toxicity where no identifiable clinical benefit can be observed. A deeper understanding of proteins that interact with Hsp90 and further insights gained into molecular aberrations in recurrent or refractory tumors by comprehensive molecular profiling may help in the development of novel combinations of Hsp90 inhibitors such as PF-04929113.

Disclosure of Potential Conflicts of Interest

N. Brega, B.E. Houk, and M. Shnaidman have employment other than primary affiliations [e.g., consulting] and ownership interest (including patents). No potential conflicts of interest were disclosed by the other authors.

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References


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