The HSP90 Inhibitor NVP-AUY922 Potently Inhibits Non–Small Cell Lung Cancer Growth

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Abstract

Heat shock protein 90 (HSP90) is involved in protein folding and functions as a chaperone for numerous client proteins, many of which are important in non–small cell lung cancer (NSCLC) pathogenesis. We sought to define preclinical effects of the HSP90 inhibitor NVP-AUY922 and identify predictors of response. We assessed in vitro effects of NVP-AUY922 on proliferation and protein expression in NSCLC cell lines. We evaluated gene expression changes induced by NVP-AUY922 exposure. Xenograft models were evaluated for tumor control and biological effects. NVP-AUY922 potently inhibited in vitro growth in all 41 NSCLC cell lines evaluated with IC50 < 100 nmol/L. IC100 (complete inhibition of proliferation) < 40 nmol/L was seen in 36 of 41 lines. Consistent gene expression changes after NVP-AUY922 exposure involved a wide range of cellular functions, including consistently decreased dihydrofolate reductase after exposure. NVP-AUY922 slowed growth of A549 (KRAS-mutant) xenografts and achieved tumor stability and decreased EGF receptor (EGFR) protein expression in H1975 xenografts, a model harboring a sensitizing and a resistance mutation for EGFR–tyrosine kinase inhibitors in the EGFR gene. These data will help inform the evaluation of correlative data from a recently completed phase II NSCLC trial and a planned phase IB trial of NVP-AUY922 in combination with pemetrexed in NSCLCs. Mol Cancer Ther; 12(6); 890–900. ©2013 AACR.

Introduction

Heat shock proteins (including HSP90) serve as molecular chaperones required for stability, posttranslation modification, and function of multiple client proteins (1). Expression of heat shock proteins (HSP) is increased at times of physiologic stress, and these effects are believed to support cell survival. Preclinical data indicate that malignant cells have increased levels of active HSP90, and mutated oncogenic proteins are more reliant on HSP90 function (1). Increased HSP90 expression has been linked to worse prognosis in patients with non–small cell lung cancer (NSCLC; ref. 2). On the basis of these data, as well as a long list of client proteins important in malignancy (3), HSP90 has emerged a promising therapeutic target (1).

HSP90 operates in an ATP-dependent manner with several co-chaperones. HSP90 inhibitors developed to date block the N-terminal ATP-binding pocket, altering normal HSP90 function and leading to release of client proteins with eventual destruction via the ubiquitin–proteasome pathway (1). Inhibition of HSP90 releases heat shock factor 1 (HSF1), a transcription factor that controls HSP expression (4). This response increases expression of other family members, including HSP70 and HSP72, limiting the biologic effects of HSP90 inhibition (4). Induction of this response is a pharmacodynamic endpoint to evaluate target inhibition by HSP90 inhibitors. On the basis of the wide range of client proteins, HSP90 inhibitors are expected to have diverse molecular effects.

Naturally occurring HSP90 inhibitors include the geldanamycin class, of which 17-AAG has been most extensively evaluated. Phase I and II trials evaluating 17-AAG show evidence of activity (5–9). Other synthetic inhibitors have been developed, including NVP-AUY922, a novel isoxazole-based inhibitor (Fig. 1; ref. 10). The compound inhibits HSP90α and β subunits at low nanomolar concentrations, whereas the other 2 HSP90 family members Grp 94 and Trap-1 are inhibited at 25- to 40-fold higher concentrations (11, 12). A phase I trial of NVP-AUY922 showed tolerability with prolonged disease stabilization in some patients (13).
It is now recognized that NSCLC arises as a result of several driver mutations (14). EGF receptor (EGFR) mutations, particularly deletions in exon 19 or a point mutation in exon 21 (L858R), are seen in approximately 10% of NSCLCs and are associated with a favorable prognosis (15–18) and radiographic response to EGFR-tyrosine kinase inhibitors (TKI; refs. 19–21). Cell lines with activating EGFR mutations are reliant on HSP90 function for protein stabilization and undergo growth inhibition when HSP90 function is inhibited (22, 23). HSP90 inhibition can overcome the T790M secondary mutation, which confers resistance to EGFR-TKIs in preclinical models (23, 24). Other important proteins considered relevant in EGFR-mutant NSCLCs are HSP90 clients (25, 26). c-RAF is an HSP90 client protein, and this has been hypothesized as an explanation of sensitivity among ras-mutant NSCLC models (27, 28). ALK gene rearrangements have emerged as an explanation of sensitivity among other types of NSCLC (A549, H1155, H1435, H1793, H1975, H2172, H23, and HCC827) were evaluated at baseline and after exposure (1, 24, and in some cases 48 hours) to NVP-AUY922 at different concentrations (10, 50, and 100 nmol/L). In each case, RNA from a cell line before treatment (GSE 43567) and cell line profiles were exported to Excel (Microsoft) for additional analysis of the distribution of gene expression changes across the various subtypes and the individual cell line response data. Baseline (GSE 43568) array data have been submitted and accepted in the Gene Expression Omnibus (GEO) repository.

Statistical methods

Baseline gene expression analyses. Cell lines were separated into “sensitive” and “resistant” groups based on IC_{50} values. Only probes with greater than 2-fold change in expression and a P < 0.01 in at least one experiment were analyzed. Multiple probes identifying a single gene were reported as a single gene. For correlations between expression of protein levels and NVP-AUY922 sensitivity, Pearson χ² test was conducted.
Pre versus posttreatment expression analysis (two types of analyses were performed).

(1) To determine effects of NVP-AUY922 on global gene expression, a direct comparison was conducted by hybridizing RNA from exposed and unexposed lines to the same array. Changes in gene expression were considered significant if the fold change was greater than 2 with a multistep corrected (Benjamini–Hochberg) 

\[ P < 0.01. \]

(2) To identify genes for which mean expression intensity differed between 2 conditions on separate arrays (e.g., differences between sensitive and resistant cell lines at 24 hours), we conducted a one-way ANOVA with multistep correction using the Benjamini–Hochberg false discovery rate (FDR) with a corrected \( P \) value cutoff of 0.05.

Proliferation assays

Cells were seeded in duplicate at 5,000 to 10,000 cells per well. The day after plating (day 1), NVP-AUY922 was added at 1 \( \mu \text{mol/L} \) and 2-fold dilutions over 12 concentrations. Data were compared with untreated controls. Cells were counted on the day drug was added and 5 days later and these 2 counts were compared. Cells were harvested by trypsinization and counted immediately using a Coulter Z2 particle counter (Beckman Coulter Inc.). Percentage of growth inhibition, defined as 100 - \( \frac{N}{C} \times 100 \) was determined. Experiments were carried out in duplicate. Error bars represent SE for each experiment. Nonlinear curve fitting was conducted by fitting curves to data points using the Proc NLMIXED function in SAS (SAS Institute, Inc.) using a basic 4-parameter sigmoid model. \( IC_{50} \) (concentration needed to prevent 50% of cell population doublings) and \( IC_{100} \) (complete inhibition of proliferation) were the summary outcome measures interpolated from the resulting curves.

Western blots

The same subset of 8 cell lines evaluated for pre- and postexposure gene expression (A549, H23, H1435, H2127, HCC827, H1155, H1793, and H1975) growing in log phase were exposed to media with or without 50 and 100 \( \mu \text{mol/L} \) NVP-AUY922 for 30 minutes, 18 and 24 hours before cell lysis [the only exception being dihydrofolate reductase (DHFR), which was exposed to 50 \( \mu \text{mol/L} \) NVP-AUY922 for 1, 24, and 48 hours] after cell lysis (the only exception being dihydrofolate reductase, which was exposed to 50 \( \mu \text{mol/L} \) NVP-AUY922 for 30 minutes, 18 and 24 hours before cell lysis) was determined. Experiments were carried out in duplicate. Error bars represent SE for each experiment. Nonlinear curve fitting was conducted by fitting curves to data points using the Proc NLMIXED function in SAS (SAS Institute, Inc.) using a basic 4-parameter sigmoid model. \( IC_{50} \) (concentration needed to prevent 50% of cell population doublings) and \( IC_{100} \) (complete inhibition of proliferation) were the summary outcome measures interpolated from the resulting curves.

To establish tumor xenografts, A549 (10^7) or H1975 (5 \times 10^6) cells were injected in 200 \( \mu \text{L} \) HBSS subcutaneously in the right flank. Fragments from established H1975 tumors (~30 mm^3) were serially transplanted subcutaneously onto recipient mice, which were used for efficacy studies. When tumors reached a size of 100 to 200 mm^3, animals were randomized into treatment groups \( n = 8 \) and intravenous NVP-AUY922 was initiated weekly (qw) or thrice weekly (3 qw). Tumor volumes (measured manually with calipers) and body weights were measured 2 to 3 times/wk and presented as means for each group. Error bars represent the SEM. Tumor volume was estimated using the formula: \( L \times W^2 \times \pi/6 \), where width \( (W) \) and length \( (L) \) are the 2 largest diameters. Tumor and body weight were analyzed by one-way ANOVA with post hoc Dunnett test for comparison of treatment (T) versus control (C) group. The post hoc Tukey test was used for intragroup comparison. Statistical analysis was conducted using GraphPad Prism 5 (GraphPad Software). As a measure of efficacy, the % T/C value is calculated at the end of the experiment according to (Atumor volume_treated/Atumor volume_control × 100), where Atumor volumes represent the mean tumor volume on the evaluation day minus the mean tumor volume at the start of the experiment. Invasive procedures were conducted under Forene anesthesia. All experiments were carried out using female Harlan Hsd:Npa athymic nude-nu mice that were obtained from Novartis internal breeding stocks (Laboratory Animal Services, Novartis Pharma AG). Animals were kept under optimized hygienic conditions with a 12-hour dark, 12-hour light cycle. Animals were fed food and water ad libitum. All animal experiments were carried out in adherence to the Swiss law for animal protection. The experimental protocols were...
approved by the Swiss Kantonal Veterinary Office of Basel Stadt, Basel, Switz.

Results

**NVP-AUY922 potently inhibits NSCLC growth in vitro**

All 41 cell lines were sensitive to the antiproliferative effects of NVP-AUY922, with IC₅₀ < 100 nmol/L (Fig. 2A). In contrast to near-uniformity in sensitivity, relative differences were seen with regard to IC₁₀₀ (complete inhibition of proliferation) among cell lines (Fig. 2B). Thirty-six cell lines had an IC₁₀₀ < 40 nmol/L whereas 5 had an IC₁₀₀ > 200 nmol/L.

**Western blot analysis of NSCLC cell lines demonstrates that differences in protein expression correlate with in vitro sensitivity to NVP-AUY922**

To assess the biochemical effects of NVP-AUY922 and predictors of in vitro sensitivity, Western blot analyses were conducted to assess HSP70, total and phospho-ERK (pERK), and total and phospho-AKT (pAKT; serine 308 or 473) at baseline and after 50 and 100 nmol/L NVP-AUY922 exposure for 30 minutes, 18, and 24 hours (Fig. 3). Eight cell lines were selected for this analysis based on NVP-AUY922 sensitivity and molecular characteristics. Three harbored KRAS mutations (A549, H23, and H1155) and 2 harbored EGFR mutations, HCC827, which is sensitive to EGFR-TKIs, and H1975, which is resistant. Evaluated lines included 3 with IC₅₀ < 5 nmol/L and IC₁₀₀ < 40 nmol/L (Fig. 3A), 2 with IC₅₀ > 5 nmol/L and IC₁₀₀ < 40 nmol/L (Fig. 3B), and 3 with IC₁₀₀ > 200 nmol/L (Fig. 3C). Little change in protein levels was seen 30 minutes after exposure, but HSP70 was reliably increased in all evaluated cell lines after 18 hours. After NVP-AUY922 exposure, pERK and pAKT were inhibited to a high degree in cell lines with IC₁₀₀ < 40 nmol/L (Fig. 3A and 3B). Among cell lines with IC₁₀₀ > 200 nmol/L, pAKT and pERK inhibition was more variable (Fig. 3C).

**NVP-AUY922 induces stereotyped changes in gene expression**

Changes in gene expression after NVP-AUY922 exposure were evaluated in the 8 cell lines described in the preceding section and over a range of exposure times...

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**Figure 2.** In vitro sensitivity to NVP-AUY922. Forty-one cell lines with IC₅₀ (A) represented in nmol/L and IC₁₀₀ (B) represented in nmol/L. Error bars represent SE based on multiple experiments.
(1, 24, and in some lines 48 hours) and concentrations (10, 50, and 100 nmol/L). For each cell line, exposed and unexposed samples were compared on a single microarray with the unexposed sample serving as the control. Time-dependent gene expression changes were evaluated. Eighty-six genes were more than 2-fold changed in expression with unadjusted \( P < 0.01 \) in at least one experiment after 1 hour of 100 nmol/L NVP-AUY922 exposure.
(data not shown), including increases in HSP family members HSPA1A (HSP70 protein A1) and HSPA6 (HSP70B). However, these results did not meet the cutoff for statistical significance (FDR ≤ 0.01). More significant changes in gene expression occurred by 24 hours, and changes at 24 hours correlated well with 48 hours with slightly more pronounced changes after longer exposure (data not shown).

Concentration-dependent gene expression changes were less pronounced. Changes in response to 10 nmol/L of NVP-AUY922 generally mirrored those at higher concentrations but were less pronounced (data not shown). Changes in response to 50 and 100 nmol/L NVP-AUY922 were very similar (correlation > 0.9 for each cell line). Thus, data from 50 and 100 nmol/L experiments were pooled for analysis. After a 24-hour exposure to 50 or 100 nmol/L NVP-AUY922, 7,078 genes showed at least 2-fold change in expression and a P < 0.01 in at least one cell line without FDR (Fig. 4).

Western blot analysis confirms decreased DHFR expression in many cell lines after exposure to NVP-AUY922, particularly at 24 hours

To evaluate whether the decreased DHFR expression seen in the microarray experiments led to decreased DHFR protein levels, the 8 cell lines evaluated in the microarray experiments were exposed to 50 nmol/L of NVP-AUY922 at the same time points (1, 24, and 48 hour) as the microarray experiment. Western blot analyses were conducted to assess DHFR compared with an α-tubulin control (Fig. 5). Three of the cell lines showed levels of DHFR less than 40% of baseline when compared with a tubulin control after 48 hours of NVP-AUY922 exposure (Fig. 5A). The other 5 cell lines did not show as significant reductions in DHFR levels after NVP-AUY922 exposure (Fig. 5B). DHFR levels did not predict sensitivity among the cell lines.

Baseline gene expression predicts NVP-AUY922 sensitivity

To identify genes associated with NVP-AUY922 sensitivity, baseline gene expression was compared between all 5 resistant lines (IC100 > 200 nmol/L) and the 29 sensitive lines (IC100 < 40 nmol/L) for which baseline gene expression data were available. For each baseline array, cell line–specific RNA was compared with a control reference mixture of pooled NSCLC cell line RNA. Probes with a greater than 2-fold deviation from control and P < 0.01 were considered significant and used in the ANOVA analysis comparing sensitive and resistant cell lines. Five hundred and twenty-one genes were identified (P < 0.01 without FDR; Fig. 6). When the same analysis was repeated using FDR multitest correction, 4 probes retained significance (increased expression of KIAA1324L and decreased expression of THC1923177, DSG3 and PI3 in sensitive lines as compared with resistant lines), but relevance to sensitivity after NVP-AUY922 exposure is not clear.

Figure 4. Heatmaps from microarray analyses of gene expression changes after exposure to NVP-AUY922. Heatmap showing hierarchical clustering of 8 cell lines after 24-hour exposure to either 50 or 100 nmol/L of NVP-AUY922 using 7,078 genes that showed greater than 2-fold expression change at P < 0.01 in at one experiment.
Gene expression changes in response to NVP-AUY922 correlate with sensitivity

To assess the difference in gene expression after NVP-AUY922 exposure between sensitive and resistant cell lines, the 8 cell lines with posttreatment gene expression data were evaluated using ANOVA comparing the 5 sensitive and 3 resistant cell lines (with and without FDR correction). After 1 hour of 100 nmol/L NVP-AUY922 exposure, 4 probes were differentially expressed on the basis of sensitivity before FDR adjustment. In the sensitive lines, A_32_P150802 and PRAM1 expression increased with drug exposure, and LIN37 and CLCA3 expression

Figure 5. Immunoblot evaluation of DHFR in response to NVP-AUY922 exposure. Immunoblot evaluation for DHFR as compared with \(\alpha\)-tubulin after exposure to 50 nmol/L of NVP-AUY922 for 1, 24, and 48 hours as compared with controls (C). The 8 cell lines evaluated by microarray experiments are shown, including 3 cell lines with DHFR levels less than 40% of baseline when compared with a tubulin control at 48 hours (A) and 5 cell lines with less or no decrease in DHFR expression after exposure (B).

Figure 6. Heatmap showing baseline gene expression differences based on NVP-AUY922 sensitivity. Heatmap showing hierarchical clustering of 34 cell lines using 521 genes associated with NVP-AUY922 sensitivity. Genes were identified using ANOVA comparing baseline arrays of 5 resistant (IC\(_{100}\) > 200 nmol/L; listed on the top of the heatmap) with 29 sensitive cell lines (IC\(_{100}\) < 40 nmol/L).
decreased compared with resistant lines (data not shown). After 24 hours of 50 or 100 nmol/L NVP-AUY922 exposure, 1,982 genes were associated with sensitivity, of which 127 remained significant after FDR correction (Supplementary Fig. S2). Genes identified among these 127 were AHSA1, the gene coding the HSP90 co-chaperone AHA1 as well as HSP10 (HSPE1) and HSP60 (HSPD1). All 3 genes increased in response to NVP-AUY922 exposure but had significantly higher expression in resistant lines.

**In vivo effects of NVP-AUY922**

Effects of NVP-AUY922 were assessed in xenograft models. The A549 and H1975 cell lines were injected subcutaneously in nude mice. For each line, 32 mice were randomized to 1 of 4 arms, 3 active treatment arms and a control arm. The A549 cell line, which is relatively resistant in vitro, showed a dose-dependent reduction in tumor growth rates at doses of 25 mg/kg weekly, 50 mg/kg weekly, and 50 mg/kg thrice weekly (Fig. 7A). All 3 dosing schemes were tolerable, but the thrice weekly schedule led to a reduction in animal weight (Supplementary Table S1). The H1975 cell line, which harbors an activating and resistance EGFR mutation for EGFR-TKIs and was relatively sensitive to NVP-AUY922 in vitro, grew more quickly than the A549 xenografts, and the animals needed to be sacrificed after 27 days, as opposed to 48 days in A549 xenografts (Fig. 7A). In H1975 xenografts, all dosing schemes were tolerable, without reduction in body weight at 50 mg/kg weekly, 75 mg/kg weekly, and 50 mg/kg thrice weekly. Tumor growth inhibition was again dose-dependent, with essential stabilization of tumor size in the 50 mg/kg thrice weekly group (Supplementary Table S1). These results are in contrast to the A549 xenografts in which no difference was seen between tumors in treated and control mice after 27 days. To evaluate effects of HSP90 inhibition on the pathway driving H1975 proliferation, EGFR and pAKT levels were evaluated 6 hours after the final dose (Fig. 7B) compared with tAKT and tubulin controls. EGFR levels decreased in a dose- and dose frequency–dependent manner, whereas pAKT levels were highly suppressed with all schedules.

**Discussion**

HSP90 has emerged as an attractive target for therapy in a broad range of malignancies. We evaluated a novel synthetic diarylisoxazol resorcinol HSP90 inhibitor, NVP-AUY922, across a broad range of NSCLC models. We showed potent growth inhibition across a broad sample of NSCLC cell lines with maximum IC50 < 100 nmol/L. Evaluated cell lines harbored KRAS mutations (H23, H1944, A549, H1155, H1385, H2122, H358, SHP77, SKLU1), EGFR-TKI sensitizing, and resistant EGFR mutations (HCC827 and H1975, respectively), HER2

![Figure 7](https://www.aacrjournals.org/doi/figure/10.1158/1535-7163.MCT-12-0998)
amplification (Calu-3), BRAF mutations (H1755), PI3KCA mutations (H1975, H1563), NRAS mutations (H1299, H2135), and PTEN loss (H1155). In general, these findings are similar to those seen in vitro by others (39). However, there are some differences in the observed results, and these may be secondary to our proliferation assay, in which calculations are based on changes in generations over time rather than cell counts remaining at the end of the experiment. Our results also differ somewhat compared with other HSP90 inhibitors (40), but as differences in clinical activity have also been seen (33, 34), it is very possible that the spectrum of activity differs among compounds.

Changes we describe in gene expression following NVP-AUY922 exposure are consistent with those observed by others, without alteration of known HSP90 client proteins (41, 42). Our evaluation confirms increased HSP family member expression, which we see as early as 1 hour after NVP-AUY922 exposure. Additional changes were seen across a broad range of cellular activities, reflecting the diverse action of HSP90. Many of the genes for which expression changed in all or most exposed cell lines were HSPs, including HSP70, which is known to increase in response to HSP90 inhibition, but also HSP90, potentially in an effort to maintain effective levels in the setting of functional inhibition. Changes in genes involved in cell cycle could correspond with the profound inhibitory effect of NVP-AUY922.

In our study, many changes seen, such as those seen in pERK after NVP-AUY922 exposure, were felt to be downstream effects of pathways disrupted by HSP90 inhibition. Decreased DHFR expression after NVP-AUY922 exposure was seen in some sensitive cell lines, and this observation has potential implications for treatment with pemetrexed, a standard chemotherapeutic used in NSCLCs. DHFR is inhibited by pemetrexed, and reduction in DHFR expression may serve as a marker for pemetrexed responsiveness (43), whereas increased DHFR has been associated with development of pemetrexed resistance (44). Therefore, combination of NVP-AUY922 with pemetrexed-based therapy is a potential area for future investigation, and a clinical trial in that setting is planned. At this time, we are exploring the dynamics of the changes in DHFR as well as evaluating potential sequencing of the 2 agents to support the planned clinical trial.

To identify baseline molecular characteristics of cell lines that were most sensitive to NVP-AUY922, cell lines were separated on the basis of IC_{100} into a sensitive (IC_{100} < 40 nmol/L) and resistant group (IC_{100} > 200 nmol/L). Genes differentiating these cell lines at baseline represent diverse molecular pathways. On the basis of the relatively smaller number of resistant cell lines, the relevance of this gene set is considered exploratory and will require validation in ongoing trials. Although 4 probes were differentially expressed on the basis of sensitivity to NVP-AUY922 after 1 hour of exposure, one does not code a known gene, whereas the other 3 code proteins for which testing is not commonly conducted, making them poor candidates for biomarkers. In nearly 2,000 genes, expression differed after 24 hours of NVP-AUY922 exposure in 5 sensitive and 3 resistant cell lines (based on IC_{100}). These genes again represent a wide range of pathways, and many changes were likely related to greater growth inhibition in sensitive cell lines. One intriguing gene identified was AHA1, activator of heat shock 90-KD protein ATPase, also called AHA1. AHA1 binds HSP90 and stimulates the activity of it ATPase (45). AHA1 is upregulated by exposure to the HSP90 inhibitor 17-AAG, and it was one of the genes upregulated in our treatment experiments (46). siRNA knockdown of AHA1 induced increased sensitivity to HSP90 inhibition with 17-AAG (46). HSP10 and HSP60 also increased disproportionately after NVP-AUY922 exposure in resistant cell lines. These 2 genes are located head to head, separated by a bidirectional promoter (47), and increased expression of these genes represents another potential resistance mechanism. We are planning further experiments to evaluate these genes as potential resistance mechanisms.

Our in vivo findings corroborate the in vitro findings although they were in general less profound, with the H1975 cell line inhibited with thrice weekly NVP-AUY922 and relative resistance for the A549 line. The H1975 xenograft model mimics a common clinical scenario of patients with known EGFR mutations who develop a secondary mutation and experience clinical progression with EGFR-TKI therapy. Although pAKT was inhibited at low doses in tumors, the clinical stabilization of disease correlated with EGFR inhibition with thrice weekly dosing as shown by Western blotting. Clinical data with NVP-AUY922 now shows a 20% response rate in patients with EGFR-mutant tumors after EGFR-TKI progression (33). On the basis of these laboratory and clinical data, secondary resistance in patients with EGFR mutations will be evaluated in an expansion cohort of an ongoing clinical trial, and in some patients, biopsies during treatment will be obtained to correlate EGFR mutations and expression with clinical response to NVP-AUY922 (33). In patients harboring an EGFR mutation, a study of NVP-AUY922 versus chemotherapy after progression on an EGFR-TKI is planned, and an ongoing study is evaluating NVP-AUY922 along with erlotinib (48, 49).

In summary, our evaluation shows that NVP-AUY922 is an extremely potent inhibitor of NSCLC cell lines. Although consistent patterns of gene expression changes are seen in response to exposure, these effects span a large number of pathways. The finding of a decrease in DHFR after NVP-AUY922 exposure in some cell lines has implications for therapy with pemetrexed, and a study of pemetrexed plus NVP-AUY922 is planned. As a result of the high degree of sensitivity and the diverse set of pathways involved, clinical development of NVP-AUY922 initially has been in a broad subset of patients with NSCLCs. The data in the setting of EGFR-TKI-resistant
EGFR-mutant NSCLCs justify a particular focus in that setting.

Disclosure of Potential Conflicts of Interest
E.B. Garon received research funding from Novartis. R.S. Finn and D.J. Slamon are on the Consultant/Advisory Board of Novartis. S. Ide, E. Avsar, M.R. Jensen, C. Quadt, and M. Liu are full-time employees of Novartis. No potential conflicts of interest were disclosed by the other authors.

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Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): E.B. Garon, R.S. Finn, H. Hamidi, J. Dering, A.J. Desai, W. Hosmer, E. Avsar, M. Liu, D.J. Slamon

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