Biomarkers Predict $p53$ Gene Therapy Efficacy in Recurrent Squamous Cell Carcinoma of the Head and Neck

John Nemunaitis,$^1$ Gary Clayman,$^2$ Sanjiv S. Agarwala,$^4$ William Hrushesky,$^5$ James R. Wells,$^5$ Charles Moore,$^6$ John Hamm,$^7$ George Yoo,$^8$ Jose Baselga,$^9$ Barbara A. Murphy,$^{10}$ Kerstin A. Menander,$^3$ Laura L. Licato,$^3$ Sunil Chada,$^3$ Robert D. Gibbons,$^{11}$ Magali Olivier,$^{12}$ Pierre Hainaut,$^{12}$ Jack A. Roth,$^2$ Robert E. Sobol,$^3$ and W. Jarrard Goodwin$^{13}$

Abstract

Purpose: Most recurrent squamous cell carcinomas of the head and neck have a dysfunctional $p53$ tumor suppressor pathway contributing to treatment resistance. We hypothesized that tumor $p53$ biomarkers may predict the efficacy of normal $p53$ delivered by gene therapy in these patients. Experimental Design: Tumor $p53$ biomarkers were evaluated in 116 patients, including 29 treated with methotrexate in a phase III randomized controlled trial. Profiles favorable for $p53$ gene therapy efficacy were hypothesized to have either normal $p53$ gene sequences or low-level $p53$ protein expression, whereas unfavorable $p53$ inhibitor profiles were predicted to have high-level expression of mutated $p53$ that can inhibit normal $p53$ protein function. Results: A statistically significant increase in tumor responses was observed for patients with favorable $p53$ efficacy profiles compared with those with unfavorable $p53$ inhibitor profiles (phase I/II trials: favorable [34 of 46, 74%] versus unfavorable [1 of 5, 20%], $P = 0.0290$; phase III trial: favorable [17 of 24, 71%] versus unfavorable [2 of 11, 18%], $P = 0.0088$). In the phase III trial, there was statistically significant increased time to progression (TTP) and survival following $p53$ gene therapy in patients with favorable $p53$ profiles compared with unfavorable $p53$ inhibitor profiles (median TTP, 2.7 months versus 1.4 months, $P = 0.0121$; median survival, 7.2 months versus 2.7 months, $P < 0.0001$). In contrast, the biomarker profiles predictive of $p53$ gene therapy efficacy did not predict methotrexate response, TTP, or survival outcomes. Conclusions: These results indicate that tumor $p53$ biomarker profiles may predict $p53$ gene therapy efficacy in recurrent squamous cell carcinoma of the head and neck. (Clin Cancer Res 2009;15(24):7719–25)

Recurrent, late-stage squamous cell carcinoma of the head and neck (SCCHN) is typically incurable. The vast majority of patients do not respond to standard therapies, which may result in toxicity (1–3). In addition, conventional treatments provide median survivals of only 4 to 6 months and there is a clear need for novel therapies (1–3).

The $p53$ tumor suppressor pathway is dysfunctional in virtually all cases of recurrent SCCHN (4–7). Hence, $p53$ gene therapy to restore $p53$ function is a logical targeted treatment for this disease (8, 9). Adenoviral $p53$ gene therapy (Advexin) uses a replication-defective adenovirus to deliver and express normal $p53$ following local intratumoral administration (8, 9).
Knowledge of the mechanisms tumors use to inhibit p53 (8–13) supported the development of p53 biomarker profiles to predict the efficacy of p53 gene therapy. Before analysis, we hypothesized that tumor p53 profiles favorable for gene therapy efficacy would have wild-type p53 gene configurations where additional normal p53 may overcome p53 inhibition caused by upregulation of the p53 inhibitors HDM2 and HDM4. We further hypothesized that tumor p53 profiles unfavorable for p53 gene therapy may be characterized by high-level expression of mutated p53 proteins that are associated with “dominant-negative” p53-inhibitory effects, which may inactivate the normal p53 delivered by gene therapy.

The National Cancer Institute and the Food and Drug Administration proposed the Oncology Biomarker Qualification Initiative to accelerate cancer drug development and to guide patient care by identifying biomarkers that define patient populations most likely to benefit from a specific therapy (14, 15). Biomarkers predictive of therapeutic efficacy are particularly important for patients with short life expectancies, as the limited time for empirical selection may result in the failure to administer a beneficial therapy.

These considerations lead to the incorporation of predictive p53 biomarkers in clinical trials to evaluate the benefit of p53 gene therapy in patients with recurrent SCCHN. The results of these trials indicate the utility of tumor p53 biomarkers to identify patients most likely to benefit from p53 gene therapy.

Materials and Methods

Study design. Tumor p53 biomarker profiles were evaluated in 116 patients enrolled in adenoviral p53 gene therapy clinical trials. The training tumor p53 biomarker data set involved 51 patients evaluated for tumor response who were treated in trials INT-002 (phase I/II) and T201 (phase II) as described (9). The validation set of 65 patients was evaluated in a multicenter, multinational, open-label, prospectively randomized, phase III study of adenoviral p53 gene therapy (Advexin) and methotrexate (control agent) in recurrent SCCHN patients who had previously been exposed to platinum or taxane therapy in the recurrent disease setting. Eligible patients in the phase III trial had histologically-confirmed SCCHN with cytologically confirmed recurrence after first-line therapy administered with curative intent (at least 50 Gy radiotherapy and/or surgery with or without initial chemotherapy). All patients were required to have had at least one prior platinum or taxane chemotherapy regimen.

All human investigations were done after approval by a local Human Investigations Committee and in accordance with assurances approved by required regulatory agencies. In the phase III trial, patients were randomly assigned to receive either adenoviral p53 gene therapy administered intratumorally on days 1 and 3 of each week at a daily dose of \(2 \times 10^{12}\) viral particles or methotrexate administered i.v. once weekly at a starting dose of 40 mg/m². Each treatment cycle was 3 wk (21 d). The primary efficacy end point was survival and the secondary efficacy end point was tumor growth control response based on comparisons of pretreatment and posttreatment computerized tomography or magnetic resonance imaging scans of treated lesions. Response was defined as either stable disease or tumor size reduction by Southwest Oncology Group criteria (16) that were assessed following two cycles of treatment. In the phase III biomarker study, one patient in each of the p53 gene therapy and methotrexate treatment groups was not evaluable for treatment response. For agents such as adenoviral p53 that are known to induce cell cycle arrest and senescence, tumor response definitions based on tumor growth control are more appropriate for defining tumor responses predictive of increased survival than response definitions based solely on reduction in tumor size (17, 18).

Tumor p53 biomarker evaluations. The p53 biomarker profiles predictive of p53 gene therapy effects were based on mechanisms of tumor...
p53 inactivation (4, 9–13). p53 biomarker profiling involved determination of mutation by p53 gene sequencing and p53 protein expression by immunohistochemistry (9). The tumor p53 profiles favorable and unfavorable for p53 gene therapy efficacy are summarized in Table 1. Tumor p53 profiles were determined in a blinded manner without knowledge of the clinical results. Mutational p53 gene sequence analysis was done by BRT Laboratories, Inc. Genomic DNA preparation was carried out using the QIAamp kit (Qiagen, Inc.) for frozen tumor tissue samples or by standard phenol/chloroform extraction for paraffin-embedded tissues. Mutational screening was carried out by amplification of all samples using Multiplex primers (Affymetrix, Inc.). The resultant PCR products were analyzed using the Affymetrix p53 GeneChip, which encompasses all coding exons, 2 to 11, as well as immediate flanking regions. Confirmation of the results was carried out by sequencing of the particular locations indicated by gene chip screening analysis or all exons in the cases where no mutation was detected using the gene chip.

Immunohistochemical staining was done at QualTek Molecular Laboratories following Good Laboratory Practices. The DO-7 monoclonal antibody (Lab Vision Corp.) was used for p53 detection. This antibody binds at the NH2 terminus of p53 and thus can be used to detect both wild-type and mutant protein. The characteristics of the monoclonal antibodies specific for HDM2 and HDM4 have been described previously (4). Criteria for positive p53 overexpression were nuclear staining in ≥20% of tumor cells, whereas the criteria for HDM2 and HDM4 positivity were >10% as described (4). Samples from patients in trial INT-002 were analyzed as reported (9). The criteria for immunohistochemistry positivity were consistent with previously published studies (4, 9) and the prospectively defined values developed for the phase III registration clinical trial. In the majority of positive cases, >50% of the tumor cells expressed the biomarker.

Comparison of the study patients’ p53 tumor profile characteristics was made with the IARC TP53 database for European and North American patients with SCCHN (19).

Statistical analysis. All statistical analyses were prospectively specified. Time to progression (TTP) and survival curves were generated using the Kaplan-Meier method (19). Comparisons between treatment arms were made with the log-rank test (20). Cox regression analysis was used to evaluate the interactions of treatment and tumor p53 biomarker profiles in terms of survival (21). Fisher’s exact test was used to compare overall tumor response rates, and logistic regression analysis was used to evaluate the interactions of treatment and p53 biomarker profiles in terms of tumor response (21). A Cox proportional hazards regression model was used to assess the prognostic ability of treatment while adjusting for the effect of important covariates (21, 22).

Results

Patient demographic and clinical characteristics. The demographic and clinical characteristics of the 116 patients evaluated for tumor p53 profiles in comparison with the intent to treat populations are listed in Supplementary Tables S1 to S4. There were no statistically significant differences in the demographic and clinical characteristics between patients with and without tumor p53 profile data (Supplementary Tables S1-S4). The phase III trial was initiated on April 24, 2001 and closed to enrollment on April 30, 2008.

Table 1. p53 biomarker profiles predictive of p53 gene therapy efficacy

<table>
<thead>
<tr>
<th>p53 gene therapy efficacy</th>
<th>p53 sequence</th>
<th>p53 immunohistology</th>
<th>Resumed mechanisms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favorable</td>
<td>Wild-type</td>
<td>Negative (low normal p53 expression)</td>
<td>p53 treatment reverses HDM2/HDM4 inhibition</td>
</tr>
<tr>
<td>Favorable</td>
<td>Wild-type</td>
<td>Positive (high normal p53 expression)</td>
<td>Excess normal p53 restores mutated p53 function</td>
</tr>
<tr>
<td>Favorable</td>
<td>Mutated</td>
<td>Negative (low mutated p53 expression)</td>
<td>Normal p53 inhibited by dominant-negative effects of high-level mutated p53 expression</td>
</tr>
<tr>
<td>Unfavorable</td>
<td>Mutated</td>
<td>Positive (high mutated p53 expression)</td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Tumor responses and p53 biomarkers predictive of p53 gene therapy efficacy

<table>
<thead>
<tr>
<th>Study/treatment population</th>
<th>Tumor p53 profile for p53 gene therapy efficacy</th>
<th>% Tumor growth control*</th>
<th>P1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase I/II trials</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p53 gene therapy</td>
<td>Favorable</td>
<td>74% (34/46)</td>
<td>0.0290</td>
</tr>
<tr>
<td></td>
<td>Unfavorable</td>
<td>20% (1/5)</td>
<td></td>
</tr>
<tr>
<td>Phase III trial†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p53 gene therapy</td>
<td>Favorable</td>
<td>71% (17/24)</td>
<td>0.0088</td>
</tr>
<tr>
<td></td>
<td>Unfavorable</td>
<td>18% (2/11)</td>
<td></td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Favorable</td>
<td>50% (11/22)</td>
<td>0.1965</td>
</tr>
<tr>
<td></td>
<td>Unfavorable</td>
<td>83% (5/6)</td>
<td></td>
</tr>
</tbody>
</table>

*All patients with reductions in tumor size had favorable p53 profiles. Of the phase III trial patients who received p53 gene therapy, one had a complete response, five patients had >50% tumor reduction, eight patients had tumor reductions ranging between >10% and <50%, and five patients had stable disease. In the methotrexate-treated group, two patients had >50% tumor reduction, two patients had tumor reductions ranging between >10% and <50%, and 12 patients had stable disease.

†Fisher’s exact test.

Logistic regression analysis of the phase III response data revealed a statistically significant interaction of tumor response, treatment, and p53 biomarker profiles (P = 0.0069).


p53 tumor biomarker profiles and expression of the p53 inhibitors HDM2 and HDM4. Tumor samples were evaluated for p53 gene sequence and for expression of p53 and the p53-inhibitory proteins HDM2 and HDM4 (also known as mdm2 and mdm4). The vast majority of cases (>90%) had evidence for inhibited p53 either by the presence of a mutated p53 genotype or by overexpression of the p53 inhibitors HDM2 or HDM4. Elevated levels of HDM2 or HDM4 were observed in >90% of patients with either normal or mutated p53 gene sequences. The majority of cases (72%) had tumor p53 profiles favorable for p53 gene therapy efficacy, which were characterized by either wild-type p53 genotypes or low-level expression of mutated p53 by immunohistochemical staining. The remaining patients had tumor p53 inhibitor profiles unfavorable for p53 gene therapy efficacy characterized by high-level expression of mutated p53.

p53 tumor biomarker profiles and tumor response. Tumor p53 biomarker analysis in the training data set involved patients receiving p53 gene therapy in phase I/II clinical trials and revealed a statistically significant increase in tumor responses for patients with favorable p53 biomarker profiles compared with unfavorable profiles (Table 2). Tumor responses were observed in 74% (34 of 46) of p53 gene therapy–treated patients with favorable tumor p53 profiles compared with only 20% (1 of 5) of patients with unfavorable profiles (P = 0.0290, Fisher’s exact test).

The tumor response results for p53 gene therapy–treated patients were validated in the phase III trial. Tumor growth control response following p53 therapy was retained as an independent prognostic factor for survival in Cox proportional hazards multivariate analysis of known prognostic variables, with a significantly decreased risk of death for patients with tumor growth control responses compared with nonresponders [hazard ratio (HR), 0.17; 95% confidence interval (95% CI), 0.08-0.36; P < 0.0001]. There was a statistically significant increase in tumor responses for patients with favorable p53 efficacy profiles compared with those with unfavorable profiles [favorable (17 of 24, 71%) versus unfavorable (2 of 11, 18%); P = 0.0088; Table 2]. In contrast, the p53 profiles predictive of p53 gene therapy efficacy did not predict methotrexate response outcomes. Opposite to p53 gene therapy, methotrexate responders had a lower percentage of p53 profiles favorable for p53 gene therapy efficacy and a higher proportion of responders with unfavorable p53 profiles, although the difference was not statistically significant [favorable (11 of 22, 50%) versus unfavorable (5 of 6, 83%); P = 0.1965; ref. 2]. The treatment by p53 biomarker profile interaction was statistically significant by logistic regression analysis (P = 0.0069) and indicates that p53 gene therapy and methotrexate tumor responses were associated with different and complimentary groups of recurrent SCCHN patients (Table 2).
p53 tumor biomarker profiles, TTP, and survival. Consistent with the tumor response results presented above, the favorable p53 biomarker profiles associated with increased tumor responses were also significantly related to increased TTP and survival following p53 gene therapy. There was a statistically significant increased TTP following p53 gene therapy for patients with p53 favorable profiles compared with those with unfavorable p53 inhibitor profiles (median TTP, 2.7 months versus 1.4 months; \( P = 0.0121 \); Fig. 1A). There was a statistically significant increased survival following p53 gene therapy for patients with p53 favorable profiles compared with those with unfavorable profiles (median survival, 7.2 months versus 2.7 months; \( P < 0.0001 \), log-rank test; Fig. 2A). The p53 profiles predictive of p53 gene therapy treatment effects were retained as an independent prognostic factor for survival in Cox proportional hazards multivariate analysis of known prognostic variables, with a significantly decreased risk of death for patients with favorable Advexin efficacy profiles (HR, 0.15; 95% CI, 0.06-0.39; \( P = 0.0001 \)) compared with patients with unfavorable profiles.

In contrast and consistent with the tumor response results, the p53 profiles predictive of p53 gene therapy efficacy did not predict methotrexate TTP or survival outcomes. There was no statistical difference between the median TTP or median survival of methotrexate-treated patients with favorable versus unfavorable tumor p53 profiles for p53 gene therapy efficacy (median TTP, 2.3 months versus 2.5 months, \( P = 0.3819 \); median survival, 4.3 months versus 5.9 months, \( P = 0.5701 \); Fig. 1B). Comparison of the intent to treat population without consideration of tumor p53 biomarker profile status revealed no statistically significant difference in the survival between the p53 gene therapy and methotrexate-treated patients (median survival, 4.4 versus 6.1 months; \( P = 0.236 \)).

However, as shown in Table 3, there was a statistically significant difference in survival outcomes by Cox regression analysis for patients treated with p53 gene therapy versus methotrexate based on p53 biomarker profiles. There was a statistically significant treatment effect by tumor p53 profile interaction in terms of overall survival (\( P = 0.0215 \)). Specifically for overall survival, the HR for the interaction was 0.249 (95% CI, 0.076-0.815), indicating that for patients with a favorable tumor p53 profile, there was significantly increased survival for treatment with p53 gene therapy. The HR for the effect of treatment (2.941; 95% CI, 1.057-8.183) revealed that for patients with an unfavorable tumor p53 profile, there was increased survival for methotrexate (\( P = 0.0388 \)). These findings were consistent with the p53 biomarker tumor response results and indicate that p53 gene therapy and methotrexate survival benefits were associated with different and complimentary groups of recurrent SCCHN patients (Table 3).

Fig. 2. A, tumor p53 biomarker efficacy profiles predict p53 gene therapy survival benefit in recurrent SCCHN. B, p53 biomarker profiles favorable and unfavorable for p53 gene therapy efficacy do not predict methotrexate outcome in recurrent SCCHN.
Knowledge of the genetic defects responsible for cancer pathology provides the opportunity to develop targeted molecular treatments with specific therapeutic advantages. In addition to permitting the design of rational therapy addressing a fundamental molecular pathway, targeted treatments also allow development of companion predictive diagnostic biomarkers to guide the appropriate application of these therapies. These principles were exemplified in the present study describing the development of p53 gene therapy for the treatment of patients with recurrent SCCHN characterized by a high frequency of inhibited p53 function.

The results presented in this report indicate that tumor p53 biomarker profiles can identify recurrent, refractory SCCHN patients most likely to benefit from targeted p53 gene therapy with statistically significant increased tumor responses, TTP, and survival. These p53 profiles were based on knowledge of the mechanisms tumors use to block p53 activity. In tumors with normal p53 gene sequences, p53 may be inactivated by upregulation of the p53 inhibitors HD2 and/or HDM4 as shown in our study and reported by other investigators (4, 10). The combination of normal p53 delivered by gene therapy and endogenous wild-type p53 produced by these tumors seems sufficient to overcome this form of p53 inhibition, and tumors with wild-type p53 gene profiles were found to be favorable for p53 gene therapy efficacy.

Another major mechanism of p53 inactivation is through gene mutations that result in the loss of p53 function. A similar frequency of favorable p53 profiles (64.4%) was observed in the IARC TP53 database for SCCHN cancers from Europe and Northern America with both p53 immunohistochemistry and gene sequence information (14). Consistent with the IARC TP53 database (19), the vast majority of p53 mutations in our study (88%) were found in the DNA binding domain (exons 5-8), which may be associated with dominant-negative activity that can inhibit normal p53 (10-13). The majority of missense mutations observed in our study population are defective for transactivation (21 of 25, 84%) according to classification available in the IARC TP53 database, and the majority of base substitutions were G>T or from A:T bases (18 of 25, 72%), which is a pattern of mutation typical of tobacco and alcohol exposure (19). Several studies have shown a correlation between the concentration of mutant p53 molecules and decreased p53 transcriptional activity of normal p53 (10, 12, 13). These observations predict that tumors with low and high levels, respectively, of mutated p53 protein expression would have favorable and unfavorable profiles for p53 gene therapy efficacy. In our study, tumor p53 profiles with high-level expression of mutated p53 were unfavorable for p53 gene therapy efficacy and patients with these unfavorable tumor p53 inhibitor profiles had statistically significant decreased tumor responses, TTP, and survival compared with patients with favorable tumor p53 profiles. The ability of these molecular biomarkers to direct targeted p53 gene therapy was supported by consistent results among several types of efficacy parameters and statistical analyses reproduced in two sets of data from independently done clinical trials. Our study patients had at least one lesion amenable to intratumoral injection and seemed to share similar p53 characteristics representative of the recurrent SCCHN population based on comparison with the IARC TP53 database for European and North American patients with SCCHN (19).

The tumor p53 profiles predictive of p53 gene therapy effects did not similarly predict methotrexate efficacy outcomes, and there was no statistical difference between tumor responses, TTP, or survival of methotrexate-treated patients with p53 tumor profiles favorable or unfavorable for p53 gene therapy efficacy. Hence, the p53 tumor profiles used in the study are not general prognostic markers. This result is not surprising for the methotrexate-treated patients, as these predictive biomarkers were developed based on known mechanisms of expected p53 gene therapy efficacy.

Hence, our findings showed the ability of molecular biomarkers to direct efficacy of the p53 therapy to which they are targeted. However, our results also illustrate the unexpected utility of targeted biomarkers to guide the clinically beneficial application of other treatments. Patients with p53 profiles unfavorable for gene therapy efficacy had a statistically significant increase in tumor growth control and survival when treated with methotrexate. It was uncertain from previous clinical studies whether methotrexate efficacy was affected by p53 functional status (23). Our findings are consistent with in vitro studies showing therapeutic activity of methotrexate in tumors with p53 mutations (24). The clinical results of our study extend these observations and indicate that p53 gene therapy and methotrexate are efficacious in different and complementary groups of recurrent head and neck cancer patients that can be identified by tumor p53 biomarker profiles.

The results of our study encourage the identification of predictive molecular markers to guide cancer patient management (14, 15). The survival outcomes comparing p53 gene therapy and methotrexate in the overall intent to treat populations were not statistically significant. An important result of our study is that traditional trial designs without predictive biomarkers for target-specific therapeutics may fail to identify clinically beneficial therapies when the efficacy of the compared treatments occurs in different patient populations. Our findings also show that molecular biomarkers of targeted therapies may also prove useful in guiding the application of other treatments, which have efficacy in patient populations.

<table>
<thead>
<tr>
<th>Phase III trial treatment</th>
<th>Tumor p53 profile for p53 gene therapy efficacy</th>
<th>Median survival (mo)</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>p53 gene therapy</td>
<td>Favorable</td>
<td>7.2</td>
<td>0.249 (0.076-0.815)</td>
<td>Overall survival</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Favorable</td>
<td>4.3</td>
<td></td>
<td>P = 0.0215</td>
</tr>
<tr>
<td>p53 gene therapy</td>
<td>Unfavorable</td>
<td>2.7</td>
<td>2.941 (1.057-8.183)</td>
<td></td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Unfavorable</td>
<td>5.9</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 3. Interaction of treatment and tumor p53 profiles in terms of survival by Cox regression analysis.
where the targeted treatment is not efficacious. As illustrated by our findings, pairing of treatments for comparison in clinical trials with different mechanisms of action combined with the performance of predictive biomarkers may result in the ability to direct potentially efficacious individualized treatment for both therapies. These results show useful principles and the benefits of incorporating molecular biomarkers in the design of cancer clinical trials.

In conclusion, the results of this study have implications for the treatment of patients with recurrent SCCHN. The data suggest that p53 gene therapy is efficacious for tumors with favorable p53 biomarker profiles and that p53 gene therapy may represent a new treatment option for patients whose tumors are refractory to standard therapies. In addition, the p53 biomarker analyses of survival and tumor response indicate that p53 gene therapy and methotrexate have therapeutic efficacy in different and complementary groups of recurrent SCCHN patients refractory to platinum or taxanes. Hence, these p53 biomarker profiles permit the personalized selection of potentially efficacious p53 gene therapy or methotrexate treatment for recurrent SCCHN patients. Further studies will be required to determine if the tumor p53 biomarker profiles predictive of p53 gene therapy efficacy in recurrent SCCHN will also be useful to guide p53 gene therapy of other tumors that are known to have similar p53 molecular abnormalities.

Disclosure of Potential Conflicts of Interest

J. Nemunaitis, G. Clayton, W. Hrushesky, J. Wells, C. Moore, J. Hamm, G. Yoo, J. Baselga, J.A. Roth, B.A. Murphy, and W.J. Goodwin have received research funding from Introgen Therapeutics; K.A. Menander, L.L. Licato, S. Chada, and R.E. Sobol hold employment or leadership positions with, as well as stock in, Introgen Therapeutics; R.D. Gibbons, J.A. Roth, and R.E. Sobol are consultants for Introgen Therapeutics.

Acknowledgments

We thank Drs. Arlene Forastiere, Carol Prives, David Sidransky, Bert Vogelstein, and Everett Vokes for helpful suggestions; Susan Mill, Tresha Goldsmith, and Marthe French for their assistance in preparing the manuscript; and Sara Koehler, Wesley Gage, Dr. Hector Battifora, and Dr. Frank Lynch for assistance with the immunohistochemistry studies.

References

15. FDA. New health initiative to improve cancer treatments: Oncology Biomarker Qualification Initiative. FDA Consumer Magazine 2006; 40.
Biomarkers Predict $p53$ Gene Therapy Efficacy in Recurrent Squamous Cell Carcinoma of the Head and Neck


Updated version
Access the most recent version of this article at:
doi:10.1158/1078-0432.CCR-09-1044

Cited articles
This article cites 21 articles, 9 of which you can access for free at:
http://clincancerres.aacrjournals.org/content/15/24/7719.full#ref-list-1

Citing articles
This article has been cited by 6 HighWire-hosted articles. Access the articles at:
http://clincancerres.aacrjournals.org/content/15/24/7719.full#related-urfs

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.