Impact of an Interactive On-line Tool on Therapeutic Decision-Making for Patients with Advanced Non–Small-Cell Lung Cancer

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Background: Treatment guidelines provide recommendations but cannot account for the wide variability in patient-tumor characteristics in individual patients. We developed an on-line interactive decision tool to provide expert recommendations for specific patient scenarios in the first-line and maintenance settings for advanced non–small-cell lung cancer. We sought to determine how providing expert feedback would influence clinical decision-making.

Method: Five lung cancer experts selected treatment for 96 different patient cases based on patient and/or tumor-specific features. These data were used to develop an on-line decision tool. Participant physicians entered variables for their patient scenario with treatment choices, and then received expert treatment recommendations for that scenario. To determine the impact on decision-making, users were asked whether the expert feedback impacted their original plan.

Results: A total of 442 individual physicians, of which 88% were from outside the United States, entered 653 cases, with report on impact in 389 cases. Expert feedback affected treatment choice in 73% of cases (23% changed and 50% confirmed decisions). For cases with epidermal growth factor receptor (EGFR) mutation or anaplastic lymphoma kinase (ALK) fusion, all experts selected targeted therapy whereas 51% and 58% of participants did not. Greater variability was seen between experts and participants for cases involving EGFR or ALK wild-type tumors. Participants were 2.5-fold more likely to change to expert recommended therapy for ALK fusions than for EGFR mutations ($p = 0.017$).

Conclusion: This online tool for treatment decision-making resulted in a positive influence on clinician's decisions. This approach offers opportunities for improving quality of care and meets an educational need in application of new therapeutic paradigms.

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The transition from empiric to evidence-based medicine has accelerated in recent years. In the case of advanced stage non-small cell lung cancer (NSCLC), a number of treatment guidelines have been published, both within the United States and internationally, which are increasingly utilized by not only practitioners, but also institutions, governments, and third-party payers. These guidelines provide lists of multiple options for first-line and maintenance therapy for broad groups of patients with advanced stage NSCLC. However, guidelines are less useful for selecting first-line or maintenance therapy for individual patients, where many variables must be considered, including both tumor and patient-specific characteristics.

The importance of performance status (PS) and gender as prognostic and predictive factors for therapeutic outcome in NSCLC is well established.[1] Within the last decade, specific histologic subtypes of NSCLC, particularly nonsquamous cancers, have been recognized as useful to select for treatment with chemotherapy, such as pemetrexed, and targeted therapy, such as bevacizumab.[2] Most recently, knowledge of the specific molecular genotype of NSCLC, specifically activating mutations of the epidermal growth factor receptor (EGFR) gene and rearrangements of the anaplastic lymphoma kinase (ALK) gene, has become essential to optimizing therapy.[2] Even with these distinctions, there are often several reasonable therapeutic options available. Thus, integration of these clinical, histologic, and molecular features into therapeutic decision-making is essential to optimize therapy.

To assist clinical oncologists in making informed treatment decisions, we developed an on-line tool—an interactive interface designed to provide expert guidance on treatment choices in multiple defined patient case scenarios. This educational tool, based on 96 different patient case variations for first-line and maintenance therapy in advanced NSCLC, also explored and captured the variability in treatment decisions by practicing physicians in this disease setting and provided an interactive forum for comparison of expert and participant treatment choices. The interactive tool was constructed

to survey both experts and practicing oncologists about treatment recommendations, using a panel of expert opinions as a comparator, and to serve as an educational tool for therapeutic decision-making. Here, we report results from 389 participant evaluations from a total of 653 case interactions captured with this on-line tool.

PATIENTS AND METHODS

This interactive program was designed to be accessed on-line (http://www.clinicaloptions.com/Oncology/Treatment%20Updates/Advanced%20NSCLC%202012/Interactive%20Tool/NSCLC.aspx) by participants who provide clinical care to patients with advanced NSCLC. The primary objective of the tool was to provide an interactive mechanism for assessing practitioner therapeutic decision-making in a wide variety of patient case scenarios and to compare practitioner choices with those of an expert panel. Both experts and participants were instructed to assume that all choices were available in all case scenarios.

Five experts made first and second treatment recommendations for 96 patient cases that varied based on permutations of six characteristics, namely tumor histology, tumor mutational status (EGFR or ALK), age, PS, smoking history, and patient goals (Table 1). Age of ≥70 years was selected as an age threshold because of its typical use as a definition of "elderly" in clinical trials of lung cancer and the fact that age 70 years represents the approximate median age of NSCLC patients.[3] Expert decision-making was based on individual knowledge and experience rather than adherence to published guidelines. Treatment choices were integrated into an interactive decision support tool. All five experts addressed each of the 96 case scenarios independently, blinded from each other. The goal was to obtain their independent recommendations, not to reach consensus. There was no attempt to reconcile differences of opinion because one of the goals was to display both concurrence and differences opinion between experts. The table of cases and expert treatment selections was entered into Site core, a Microsoft.NET-based web content management system. The content drove a custom-built workflow engine that leverages HTML and JavaScript to dynamically guide users through the process of supplying patient-tumor characteristics and proposed treatment options. On the basis of the options chosen, users were presented with appropriate recommendations from experts.

The on-line tool began with a disclaimer statement stating its purpose and limitations. After acknowledging the disclaimer, participants were able to enter specific information related to six major clinical elements important for making therapeutic decisions using pull-down menus. Participants addressed case scenarios of their choosing in a tree-based format, in which the on-line clinical tool populated details of the corresponding clinical case based on the algorithm. Users of the tool entered specific patient characteristics, such as tumor histologic subtype and primary patient goals on a case-by-case basis, and then selected their therapeutic choice. All treatment choices were available to all participants, regardless of country of origin. Subsequently, expert recommendations for a case that specifically matched the user's case were displayed. Users were then asked if those recommendations impacted their treatment decision. Expert and participant responses were subsequently analyzed.

Case Variations for First-Line and Maintenance Therapy

A total of 96 individual case variations were available in the on-line tool, based on matching characteristics from six categories, as described above and summarized in Table 1. Therapeutic options were divided among (a) targeted therapy, (b) platinum-based chemotherapy, (c) non-platinum-based chemotherapy, (d) unsure, and (e) none. Options under targeted therapy were bevacizumab, cetuximab, erlotinib, crizotinib, unsure, and none. Platinum chemotherapy were cisplatin versus carboplatin (paired with a non-platinum drug to form a chemotherapy doublet), unsure, or none. Non-platinum chemotherapy options were paclitaxel, docetaxel, gemcitabine, vinorelbine, pemetrexed, and etoposide, unsure or none.

Statistical Analysis

Physician characteristics were summarized descriptively as number and proportion from outside United States, both overall and for participants who provided one or more evaluations of the on-line tool. A generalized Kappa statistics method was employed to calculate agreement among experts, compared with that expected by chance, across the 96 patient-description combinations as recommended by Agresti,[4] implemented in SAS. Case characteristics were summarized descriptively as observed case-wise frequencies and proportions. We estimated population probability of changing treatment plan with 95% confidence interval (CI) adjusted for within-physician clustering of patients. We examined whether the odds of modifying the care plan for a case were affected by patient, physician, or tumor characteristics, using a generalized linear model approach with logistic link and binomial error structure, adjusted for within-physician clustering. All analyses were carried out in SAS.

TABLE 1. Case Scenario Variable

Tumor Histology	Mutation Status	Age (years)	Zubrod PS	Smoking History	Desired Outcome
Non–squamous	EGFR+/ALK−	<70	0, 1	No/former light smoker	Response/survival
Squamous	EGFR−/ALK+	≥70	2	Former heavy/current smoker	QoL/low risk of AEs
	EGFR−/ALK−				

Ninety-six case variations created based on these variables.
PS, performance status;EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; AEs, toxicities from therapy.

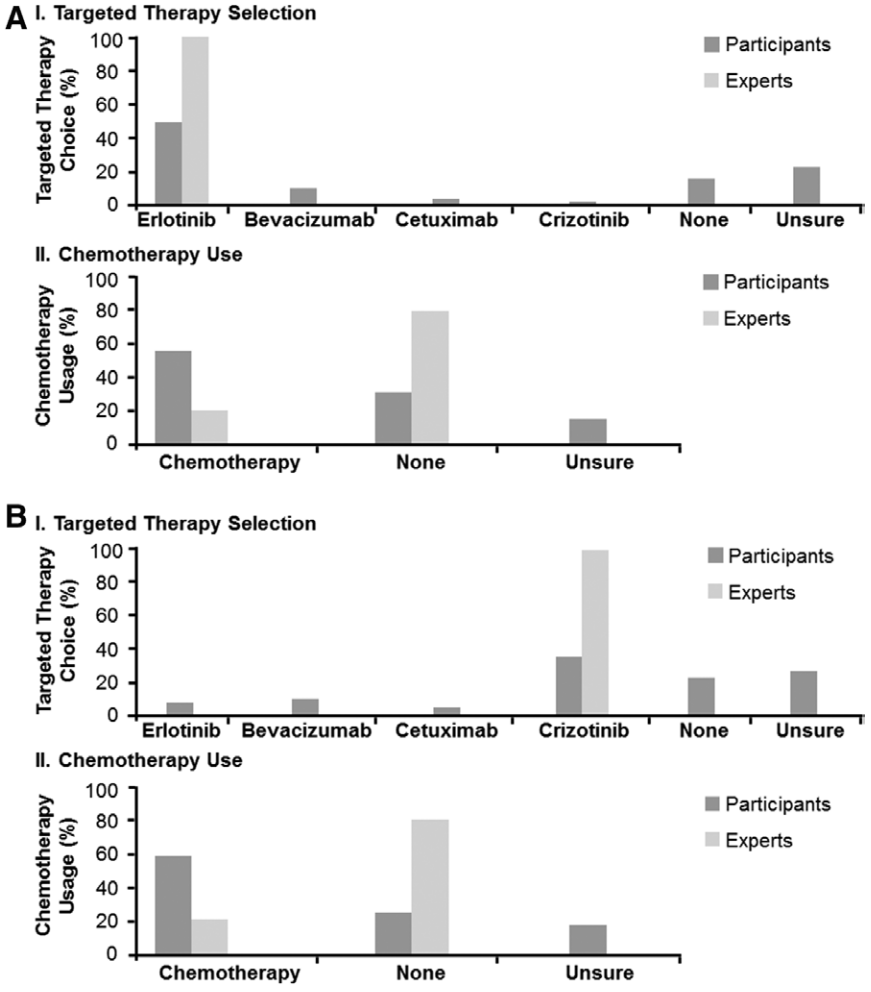

FIGURE 1. Choice of first-line therapy: (*A*) nonsquamous (EGFR–/ALK–) and (*B*) squamous (EGFR–/ALK–).

Validation of Expert Recommendations

Expert recommendations consisted not only of a treat/do-not-treat for each component of first-line and maintenance treatment, but also of a choice for specific drugs. An agreement algorithm was constructed as follows: we characterized agreement for each of the six questions as perfect consensus (all five experts recommended exactly the same choice), near-perfect consensus (four of the five recommended exactly the same choice), good consensus (at least four of the five recommended that class of treatment but there was disagreement on the specific therapy), or disagreement (the experts had a 3–2 split on treatment). The six questions pertain to expert recommendations in selecting either targeted therapy, platinum chemotherapy, or non-platinum based chemotherapy as first-line treatment and maintenance treatment.

RESULTS

Demographics of Participants

A total of 442 physicians entered 653 cases from between March 2012 and July 2012 with the majority of cases entered within 1 month of on-line posting of the tool; 273 participants also recorded whether the on-line tool influenced their decision, for a total of 389 cases. Overall, 12% of the participating physicians were from the United States, whereas 88% were practitioners outside the United States. Of the participants, 82% recorded influence of the on-line tool in their decision-making.

The overall distribution of the clinical characteristics of the 653 unique cases is summarized in Table 2. The majority of case scenarios entered (74%) were for non–squamous histology. The distribution of the oncogene status of the physician-entered cases was 31% for EGFR mutation only, 9% for ALK-fusion only, and 59% without these alterations (i.e., were wild type for both EGFR and ALK). A majority of the cases (79%) were for patients younger than 70 years old. A similar distribution of entered cases was seen for Zubrod PS with 86% having a PS of 0 and 1 and 14% of the cases having a PS of 2. Nonsmokers or former light smokers comprised 43% of the cases versus 57% reported as former heavy or current smokers. Finally, the desired outcome and goals of treatment in most cases (76%) were improved tumor response rate or survival, with 24% favoring a better quality of life (QoL) or fewer treatment-related adverse events. Percentages were similar for the subset of cases for which physicians reported the influence of the on-line tool (Table 2).

TABLE 2. Characteristics of Patient Cases Entered by Physician Participants

Case Characteristic	Number (%) of 653 Total Cases	Number (%) of 389 Cases in Evaluation Subsample
Tumor histology		
Non–squamous	483 (74)	293 (75)
Squamous	170 (26)	96 (25)
Mutational status		
EGFR+/ALK−	204 (31)	125 (32)
EGFR−/ALK+	62 (9)	33 (8)
EGFR−/ALK−	387 (59)	231(59)
Age		
<70 yrs	519 (79)	311 (80)
≥70 yrs	134 (21)	78 (20)
Zubrod PS		
0 or 1	562 (86)	332 (85)
2	91 (14)	57 (15)
Smoking history		
No/former light	281 (43)	174 (45)
Former heavy/current	372 (57)	215 (55)
Treatment goals		
Improved RR, survival	486 (76)	296 (76)
Better QOL	167 (24)	93 (24)

PS, performance status; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; RR, response rate; QoL, quality of life.

Experts' Responses

First-line therapy

Five thoracic medical oncology experts participated in the process, each completing treatment selections for all 96 possible case scenarios, and each blinded from the opinions of the other experts. The experts were largely in agreement for cases that had actionable genetic alterations in the tumor. In EGFR mutation-positive cases, all of the experts (100%) agreed with using erlotinib-based therapy in the frontline setting. Four of five of the experts (80%) agreed on using first-line therapy with erlotinib alone, whereas three of five (60%) agreed with maintenance therapy with single-agent erlotinib. This recommendation was independent of tumor histology, age, PS, smoking history, or desired outcome. One of the experts chose erlotinib plus doublet chemotherapy as first-line treatment and maintenance therapy with erlotinib plus chemotherapy, depending on the specific case scenario for tumor histology, PS, and desired outcome. Similarly, in ALK fusion-positive cases, all experts (100%) chose crizotinib-based therapy in the frontline setting with four of five experts choosing single-agent crizotinib as both first-line therapy and maintenance therapy independent of patient characteristics. One expert chose crizotinib plus chemotherapy as both first-line and maintenance therapy in nonsquamous cell tumor histology and PS 0 and 1 patients. There was greater variability in regimens selected by the experts for patients with cancers without an EGFR mutation or ALK fusion, where factors such as PS, age, and patient desired outcomes changed the choice of treatment between various experts (Fig. 1*A* and *B*).

Maintenance therapy

When experts offered maintenance chemotherapy, it tended to associate closely with age, PS, and primary patient objective. Experts tended to offer maintenance therapy for patients whose desired outcome was higher response rate and increased chance of survival in the nonsquamous and EGFR mutation/ALK fusion negative cases with four of five experts recommending maintenance therapy in patients <70 years of age regardless of PS or in patients ≥70 with a PS of 2. Only two of five experts offered maintenance therapy for patients with squamous cancers (EGFR mutation and ALK fusion negative) independent of age, PS, and patient objective/desired outcome.

Validation of experts' advice

There was generally excellent agreement among the experts for all six questions pertaining to treatment selection using targeted, platinum, and non-platinum therapy in both first-line and maintenance therapy. Either perfect agreement among experts or near-perfect consensus (four of the five agreeing exactly) was observed for 81–100% of the 96 case scenarios, with greatest agreement on recommendation for first-line targeted therapy and lowest for platinum-based therapy either for first-line or maintenance. In almost all the remaining cases, at least four of the five agreed on the decision to treat or not to treat, with some disagreement on which treatment to choose. In 10 cases, there was a 3:2 split on the question of whether to use non-platinum-based maintenance therapy, but general consensus on the other questions. For two cases, there was a 3:2 split not only on non-platinum-based maintenance therapy but also on whether to use targeted therapy, both first-line and maintenance.

Thus, overall there was consensus among experts in 94 of the 96 case scenarios for all treatment questions except for platinum maintenance therapy, with an average of 90% having perfect agreement or near-perfect agreement (four or five of five experts). For non-platinum maintenance therapy, agreement was excellent (perfect and near perfect) in 82 of the 96 cases.

Generalized Kappa statistics showed agreement exceeding chance alone for all components of frontline and maintenance therapy, with the best agreement for whether targeted therapy should be used (0.86 frontline, 0.81 maintenance) and platinum (0.61 frontline, 1.0 maintenance.) Experts agreed more than by chance on non-platinum based chemotherapy, but less strikingly (0.39 frontline, 0.37 maintenance)

Physician Participants' Responses

Choice of first-line therapy in regard to the EGFR mutation/ALK fusion status

Physician participants entered 189 EGFR mutation-positive cases. For these patients, participants varied considerably in selection of frontline EGFR tyrosine kinase inhibitor-based therapy, in contrast to the expert panel (49% of participants vs. 100% of experts chose erlotinib; Fig. 2*A*). Moreover, participants more frequently selected frontline chemotherapy for

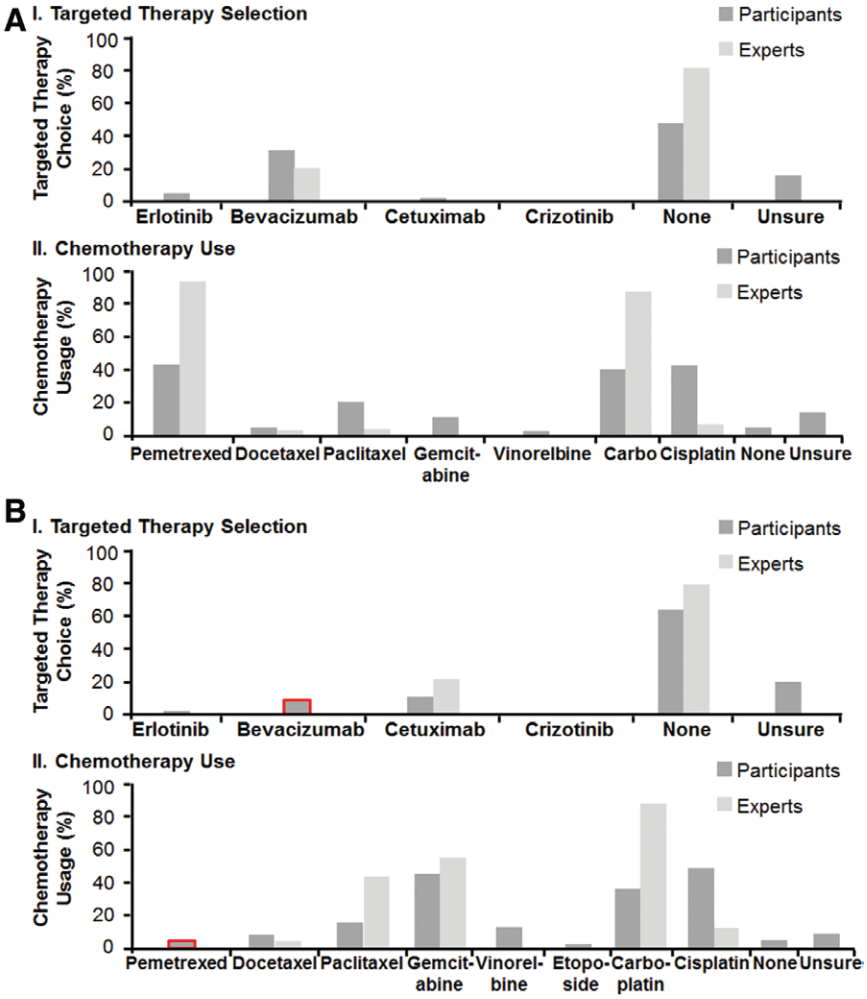

FIGURE 2. Choice of first-line therapy: (*A*) EGFR mutation positive and (*B*) ALK fusion positive.

this group of patients (56% of participants vs. 20% of experts; Fig. 2A). Another 21% of the participating physicians were initially unsure of what targeted therapy to choose, and 14% were unsure about the use of chemotherapy in the setting of EGFR mutation-positive cases.

Physician participants entered 55 ALK fusion-positive case scenarios. Fewer participants (42%) selected crizotinib when compared with the experts who all selected crizotinib (100%; Fig. 2*B*). Again, in these patient scenarios, participants selected chemotherapy more often as first-line treatment (68% vs. 20%; Fig. 2*B*). Similar to the results seen with EGFR mutation-positive cases, 24% of the participating physicians were initially unsure of what targeted therapy to choose, and 16% were unsure about the use of chemotherapy in the setting of ALK fusion-positive cases. Among the 96 case scenarios, 81% of the non-US participants chose to proceed with treatment selection. Among this group, approximately 42% of participants elected targeted therapy using crizotinib.

In the 244 case scenarios with nonsquamous histology (EGFR and ALK wild type), participants tended to use a broader range of first-line targeted therapy and chemotherapy compared with the experts (Fig. 1*A*): 32% used bevacizumab and 5% used erlotinib, whereas 16% were unsure about the use of targeted therapy for this group of patients. In contrast, 80% of the experts did not use targeted therapy and showed a large preference for chemotherapy with pemetrexed (94%) and carboplatin (88%) in this setting. Lastly, 121 case scenarios fell into the squamous histology category (also EGFR and ALK wild type; Fig. 1B). In this setting, there was also a diversity of first-line targeted therapy and chemotherapy selected by the participating physicians with 19% and 8% being unsure about the choice of targeted therapy and chemotherapy, respectively. Notably, participants rarely selected contraindicated agents for squamous histology (such as bevacizumab [7%] or pemetrexed [3%]) with a predilection to use a cisplatin-based regimen.

Impact on ultimate treatment choice

Data from 273 physicians who reported impact of expert feedback on a total of 389 cases showed that treatment decision was changed in to reflect expert opinion in 23% of cases (95% CI, 19–27%, adjusted for multiple cases per physician), reflecting a positive influence on clinician treatment decision-making. An additional 50% agreed initially and reported that experts confirmed their treatment choices. Physician responses were summarized descriptively by calculating the

proportion of cases with specific characteristics and the proportion of cases for which the on-line tool led to a change, confirmation, or disagreement by the physician user (Fig. 3). We further examined what features of the case were most likely to be associated with a change in treatment to conform with expert opinion, and found that ALK mutations were 2.5-fold more likely than EGFR mutations to be associated with a change to recommended therapy (95% CI, 1.18–5.49 fold, $p = 0.017$), whereas wild-type tumors were no more likely than EGFR+ to lead to treatment changes. Tumor histology, treatment goal, age and PS status of patient, smoking history, and nationality of physician participant were not associated with differences in likelihood of changing treatment (Table 3). The self-reported responses to expert opinion on treatment for ALK-positive tumors were very similar for foreign and US physicians. Although the numbers of US physicians were small, the observed frequencies were very similar between the two groups, suggesting that the absence of statistical significance was not simply a result of sample size.

DISCUSSION

Significant advances in the treatment of advanced stage NSCLC have been made, driven by availability of new drugs, recognition of drug-specific implications of histologic subtyping, and even more importantly, by discovery of molecular subsets of NSCLC, currently best defined by EGFR mutation and ALK fusion.[5–8] Contraindications in patients with squamous cell cancers for bevacizumab because of toxicity issues and for pemetrexed because of reduced efficacy, stand as prime examples for the importance of histology-directed therapy in advanced NSCLC. Although initial data support the increased efficacy of EGFR tyrosine kinase inhibitors in patients with adenocarcinomas, the discovery of EGFR activating mutations in 2004 provides an underlying biologic explanation for histology-divergent activity of these agents.[5] Moreover, trials, such as IPASS, have shown that clinical-pathologic characteristics such as younger age, never-smoking status, and adenocarcinoma subtype are insufficient for treatment decision-making when compared with mutation status.[6–8]

More recently, patients with cancers positive for the EML4-ALK rearrangement, observed almost exclusively in the adenocarcinoma subtype of NSCLC, have been found to be highly responsive to crizotinib,[9] a potent and relatively specific ALK inhibitor.[5,10] Thus, with increasing recognition of the molecular heterogeneity of NSCLC and the emergence of personalized therapy for patients with advanced disease, molecular and genomic testing in addition to conventional pathology has become a central focus.[11] The recent guidelines from International Association for the Study of Lung Cancer reinforce the importance of testing for EGFR mutations and ALK fusions to guide patient selection for therapy with an EGFR or ALK inhibitor, respectively, in patients with advanced stage adenocarcinoma, regardless of sex, race, smoking history, or other clinical risk factors, and to prioritize EGFR and ALK testing over other molecular predictive tests.

Further complicating therapeutic decision-making in advanced stage NSCLC is the advent of maintenance therapy. In particular, pemetrexed has been demonstrated to improve progression-free survival and overall survival, when employed after first-line platinum-based chemotherapy in patients with initial response or disease control. Other agents, such as docetaxel and gemcitabine, have shown activity in this setting as well.[2,12,13]

How to interpret the large number of recent clinical trials in first-line therapy/maintenance therapy of advanced NSCLC, including the increasingly complex landscape created by molecular testing, is a daunting task for the practicing oncologist, especially when placed into context for an individual patient. Thus, there continues to be a need for new and easily accessible educational tools to assist in this transition from empiric to histology and molecular-based therapy. We postulate that integrating expert opinion into this educational process using a relatively simple interactive tool could be of additional assistance in understanding various case scenarios and formulating treatment plans.

Here, we report results of an interactive on-line tool that matched expert opinion with participant responses with respect to specific NSCLC case scenarios. This analysis highlights clinical practice gaps between experts and participants that were present during the time of the on-line tool's implementation in 2012. This gap existed irrespective of whether the participants were US-based or not (Fig. 3), reflecting the value of this tool in identifying areas of focus for continuing medical education and quality improvement initiatives on an international basis.

Furthermore, this on-line tool can be adapted as needed to help clinicians in continuous acquisition of knowledge essential to understanding and applying many consensus guidelines currently in place.[14] However, in this era of genomic and molecular profiling, it is increasingly difficult to translate guidelines into individual patient care. Often, the patient sitting in the oncologist's office just does not fit into the guidelines because of a myriad of patient and tumor-related variables. In addition to examining ways of streamlining guidelines themselves, interactive tools can serve both an educational purpose and a more practical one by translating

Impact, %	US Cases (n = 59)	Non-US Cases (n = 330)	Total Cases (n = 389)
Yes, confirmed my choice	44	52	50
Yes, changed my choice	27	22	23
No, did not follow expert guidance	29	27	27

This optional question had a response in 389 of 653 physician-submitted cases

FIGURE 3. Physician Responses: did this tool affect (change) your treatment choice? This optional question had a response in 389 of 653 physician-submitted cases.

TABLE 3. Estimated Impact of Tumor, Patient, and Physician Characteristics on the Odds of Changing Treatment Plan to Follow Expert Advice

Predictor	Estimated Fold Effect on Odds of Change in Treatment	95% Confidence Interval	*P* Value
Histology = squamous	0.56	0.30–1.03	0.062
Mutational status			
EGFR+/ALK− (reference)	2.54	1.18–5.49	0.017
EGFR−/ALK+	1.13	0.67–1.92	0.65
Treatment goal = QOL	1.09	0.52–1.61	0.77
Patient age 70 or older	0.63	0.33–1.21	0.16
Zubrod PS = 2	0.90	0.45–1.78	0.76
Current or former heavy smoker	1.08	0.61–1.67	0.88
Participant has US origin	1.33	0.71–2.51	0.37

Based on generalized linear models for 273 physicians reporting on 389 cases, one predictor at a time.
PS, performance status; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; QoL, quality of life.

guidelines into direct patient care.[15] Equally importantly, the other intent of this interactive tool was to survey both experts and practicing physicians about treatment recommendation. Clinical parameters were selected in part to see if there was bias in some scenarios, such as altering recommendations based on smoking status or age. The fact that there were few differences in recommendations was accurately reflected in the survey results. Finally, such a tool has the potential for use in "performance improvement continuing medical education" modules that attempt to measure the impact of an educational intervention on actual physician practice and patient outcomes.

The on-line tool is not designed to provide an expected prognosis, and potential risk associated with each regimen can affect the selection of the participant physicians. However, unlike adjuvant on-line for breast cancer for example, which is used to support in to selecting whether to recommend cytotoxic treatment or not, the on-line tool for advance NSCLC, serves as an education tool for the participant physicians in providing expert guidance to choosing the most optimal regimen for patients and promoting personalized cancer therapy. In this on-line tool, the expected prognosis and potential risks to each treatment modality were not incorporated and not intended as the purpose of the on-line tool.

This work has several limitations, however. First, it is sensitive to selection bias: participants may be those who are less informed of the current status of care and are therefore seeking guidance from the on-line tool. In addition, the expert panel is small and therefore may not be representative of a broader group of experts in the treatment of patients with advanced NSCLC. Second, inasmuch as82% of the participants were international, it is possible that variations in regional drug availability at the time of participation or reimbursement issues may have influenced participants' responses on a regional basis, leading to divergence from the expert panel's recommendations. The impact of country of origin of the experts was considered in regression models, and there was no impact on likelihood of changing recommendation. The number of cases for specific scenarios was too small to assess whether likelihood of changing varied in a specific scenario or case type according to country of origin of the physician. Nevertheless, the tool was designed such that all treatment choices were available to all experts and participants, regardless of country of origin. Third, the use of physician self-report in this interactive tool is a limitation and is subjective to response bias, which can have a large impact on the validity of the tool. Nevertheless, prior studies have reported that the effect of response bias in this context is actually very small, thus likely having little to no impact toward changing the responses of participants[16,17] and does not undermine the benefit of the interactive tool, which was primarily designed to serve both a survey purpose and an educational purpose.

Discordance between experts and participants' use of crizotinib in the front-line setting was notable. The US Food and Drug Administration granted approval of crizotinib in August 2011 based on the phases I and II trial data from PROFILE 1005.[18] In Europe, European Medicines Agency approved crizotinib for ALK-positive patients in 2012, without specifying the type of test used for determining the positivity. In chemotherapy-pretreated patients with metastatic NSCLC and ALK positivity by an FDA-approved test, crizotinib was nevertheless approved without restriction to line of therapy (first, second, third, etc.) in the United States. On the contrary, in Europe, crizotinib was approved only in chemotherapy-pretreated patients.[19] Because both experts and participants were instructed to assume that all options were available in all case scenarios, the expert panel was perhaps more proactive in early adoption of crizotinib in the first-line setting.

Despite a large number of treatment options provided by the tool, there was consensus among the experts in for 94 of the 96 case scenarios, with an average of 90% having perfect agreement or near-perfect agreement (four or five of five experts). On a similar note, agreement among the expert panel was excellent (perfect and near perfect) in 82 of the 96 cases seen for non-platinum maintenance therapy. This degree of agreement among the experts' recommendations provides support for the kappa statistical analysis. The expert results were presented both individually and as summary of the five opinions in a blinded fashion with the goal of displaying both concurrence and differences of opinion. There was no attempt

made to resolve disagreements among the experts or reach a consensus. The intent of this interactive tool was to survey practice patterns of experts and practicing physician and to serve an educational purpose rather than to determine adherence to guidelines and evidence based recommendations.

Another point worthy of discussion is that changing the smoking status or age of the patient had almost no effect on expert recommendations. This is in agreement with current guidelines that elderly fit patients and smokers can still benefit from standard of care therapies for NSCLC, and that therapeutic options should not be curtailed. Indeed, guidelines recommend molecular testing in all patients with an adenocarcinoma component, regardless of age or smoking status. By comparison, PS and co-morbidities are typically of greater importance in therapeutic decision-making. Thus, our findings are generally in agreement with current guidelines. Likewise, patient desire for QOL by itself does not necessarily change therapeutic recommendations, because some therapies are documented to improve QOL. For example, meta-analyses published on nine randomized clinical trials assessing QOL with chemotherapy in NSCLC[20,21] demonstrate that some components of QoL improve with chemotherapy, reflecting therapeutic efficacy.[20,21] This is again consistent and accurately reflected in the survey results.

This on-line tool provided potential treatment choices for 96 different scenarios, without restriction to experts or participants based on prognosis, cost or potential toxicity of each regimen. Thus, it is of interest that experts tended to select carboplatin over cisplatin in many scenarios, as seen in Figure 1*A* and *B*. This is likely due to its more favorable toxicity profile and ease of administration in these palliative settings. Two North American phase III trials have compared carboplatin plus paclitaxel with cisplatin-based combinations and demonstrated similar efficacy but lower rates of nausea, leukopenia, and nephrotoxicity with the use of carboplatin[22,23] in the first-line treatment of patients with metastatic NSCLC. In addition, three meta-analyses have addressed the question of whether carboplatin based chemotherapy is as effective as cisplatin based,[24–26] which collectively confirm that cisplatin based regimens are associated with a slightly higher response rate than carboplatin regimens, with no definite survival difference.

Future iteration of the tool may be enhanced by including brief comments from the expert panelists regarding their choices. This is currently not a part of the tool but has the potential to enhance its utility. For example, based on the large comparative Elderly Lung Cancer Vinorelbine Italian Study, vinorelbine as a single agent is effective in elderly patients with advanced NSCLC and is associated with improved survival and at least a trend toward improved QoL parameters compared with best supportive care alone.[27] On the other hand, one can also justify using modified combination chemotherapy in the elderly population based on the chemotherapy French Intergroup study (IFCT-0501) to a combination of carboplatin plus paclitaxel or to single agent therapy with either gemcitabine or vinorelbine. Both overall survival and progression-free survival are significantly prolonged with combination chemotherapy compared with single agent with therapy and overall generally well tolerated in both arms.[28] Patients in the study were aged 70 to 89 years and approximately 30% of these were PS 2. This demonstrated that chemotherapy can provide substantial clinical benefits, including improved overall survival, for older patients and those with Eastern Cooperative Oncology Group PS 2. Because guidelines have not been firmly established in the setting of PS2 patients does not mean that oncologists do not have to make day-to-day treatment decisions for this category of patients. In such situations, providing commentary from the expert panel regarding why certain choices were made may enhance the educational aspect of this tool.

Another enhancement of the on-line interactive tool could be citing direct evidence to support treatment decisions in each case scenario. However, this tool was designed to incorporate expert opinion, not adherence to guidelines. As such, expert opinion is valuable both when direct evidence is not available and for interpretation of nuances not covered within guidelines. Other considerations to expand the utility of the on-line interactive tool include specifying parameters on restrictions for usage of certain drugs based on pre-existing end organ damage and providing potential risks associated with each treatment regimen, thus assisting participant physicians in tailoring therapeutic decision-making.

In conclusion, our study shows the feasibility of utilizing an interactive on-line tool to assess practice patterns, to aid in therapeutic decision-making and to serve an educational mission by providing comparisons between practitioner choices and those of an expert panel. To the best of our knowledge, this is the first study demonstrating quantitative variability in expert versus practicing physician using such an on-line interactive tool. Further studies utilizing such web-based applications are warranted.

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