harbored HER2 amplifications and HER2 mutations, respectively. These results are mostly consistent with those of Yoshimasu et al.

Importantly, our study data also suggested that the sensitivity to cisplatin depended not only on EGFR mutations but also on other driver mutations the tumor harbored and on the epithelial-mesenchymal transition phenotype. For example, the EGFR mutant H1975, with some features of EMT,[5] was relatively sensitive to cisplatin. Five cell lines with MET amplifications or HER2 abnormalities, all with high levels of E-cadherin mRNA, showed IC50 values similar to those of EGFR mutants. It was also of interest that KRAS-mutated cells with low levels of E-cadherin mRNA were more sensitive to cisplatin, while KRAS-mutated cells with high levels of E-cadherin mRNA were highly resistant to cisplatin (Figure 1). We did not find any correlations between ERCC1 and beta III tubulin expressions and sensitivities to cisplatin and paclitaxel, respectively (data not shown).

In light of our results, it would be more informative to analyze genetic abnormalities other than EGFR, as well as histologic features and E-cadherin expression, in the study by Yoshimasu et al. We would like to stress that EGFR wild-type tumors are actually heterogeneous tumors with regard to driver mutations, such as the KRAS mutation, HER2 mutation, ALK rearrangement, etc., and the EMT phenotype, and the proportion of these heterogeneous tumors may differ in different ethnic groups. Therefore, the results comparing the EGFR-mutant and EGFR wild-type tumors must be interpreted with caution.

In summary, we appreciate the work by Yoshimasu et al. regarding EGFR mutations and chemosensitivities, but we believe that genetic profiles other than the EGFR mutation and EMT phenotype need to be considered when analyzing sensitivities to chemotherapeutic agents, especially cisplatin.

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In Response:

We thank Dr. Matsubara and coworkers for their interest in our article and presenting their informative data. It is known that epidermal growth factor receptor (EGFR) mutation-positive and -negative tumors have different characteristics. Therefore, we consider that chemosensitivity profiles for anticancer agents are not identical between EGFR mutation-positive and -negative tumors.

As Dr. Matsubara mentioned in his letter, EGFR mutation-negative tumors are heterogenous. Tumors with various driver mutations are included in this group. We also agree that tumors with different driver mutations have the possibility of showing different chemosensitivity profiles. Their data clearly provide evidence for this issue.[1]

It is also important to be aware that these genetic alterations probably do not directly regulate chemosensitivity for anticancer agents, unlike ERCC1 and class-III β-tubulin.[2,3] We surmise that the EGFR gene does not directly regulate chemosensitivity for docetaxel. Our data, as well as Dr. Matsubara's data, may only show that different cancers have different chemosensitivity profiles.

The prognosis of patients with advanced non–small-cell lung cancer (NSCLC) highly depends on their EGFR mutation status. Therefore, the EGFR mutation status is now routinely tested in patients with NSCLC in clinical practice. This can be useful if the EGFR mutation status also provides some more information regarding chemosensitivity for cytotoxic anticancer agents. Our article has provided such data.

To investigate predictive markers for cancer chemotherapy, established cell lines are useful and powerful tools. However, this involves some limitations. Cell lines cannot be established from all lung-cancer specimens. Usually they originate from a highly malignant subgroup, and then they involve a certain selection bias.[4] Our approach, based on the histoculture drug response assay, is a solution to reduce this selection bias.

It is unknown whether some driver mutations in NSCLC directly regulate chemotherapy responses. Our histoculture drug response assay–based approach does not seem to be suitable for investigating this problem. Further investigation by Dr. Matsubara's research group using an established cell-line panel might be helpful.

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KRAS Mutation Spectrum Notably Diverges between Non-small Cell Lung and Colorectal Carcinomas

To the Editor:

We read the article entitled "A systematic review and Canadian consensus recommendations on the use of biomarkers in the treatment of non-small cell lung cancer" by Ellis et al.[1] with major interest and would like to address comment on it. Since 2008, clinical research studies on non-small cell lung cancer (NSCLC) have allowed the transfer of *EGFR* gene mutations testing to the routine analysis for predicting the response to tyrosine kinase inhibitors (TKI) such as gefitinib or erlotinib. Therefore, interest in individualizing patient treatment to maximize clinical benefit has become a focus of scientific investigation. The presence of a translocation involving the anaplastic lymphoma kinase (*ALK*) gene with *EML4* is now admitted to confer a remarkable sensitivity to crizotinib, a specific ALK TKI. In contrast, mutations activating the *KRAS* oncogene are generally reported as associated with a lack of response to EGFR TKI in several studies, but the mechanism remains unclear and controversial thus insufficient to adopt *KRAS* mutation detection as a consensual tool for therapeutic decision.[2–5]

When entering into details of *KRAS* somatic mutations, their predictive value in stage IV colorectal cancer (CRC) patients for treatment with EGFR monoclonal antibodies has been established. *RAS* mutations are found in 40 to 45% of metastatic colorectal adenocarcinomas, and the mutation spectrum has been extensively studied, mutations involving codon 12 or 13 of *KRAS* being found in 40% of cases and the remaining 5% being spread over *KRAS* codons 61 and 146 or *NRAS*. On *KRAS* codons 12 and 13, seven mutations have been recognized as the most frequent, leading to the development of commercial kits focusing on these seven mutations. The use of these kits has been extended to other tumor types, in particular NSCLC, as able to predict the absence of EGFR mutation or ALK translocation as these events have been reported as mutually exclusive, instead of predicting a specific resistance to EGFR TKI. Also, the strategy of drug development moves toward the ability of specifically targeting the RAS pathway.

Involved in somatic mutations detection in our Cancer Institute, we evaluated the possibility to use those kits targeted on the seven most frequent *KRAS* mutations that are less expensive and time consuming when compared with nonselective techniques like sequencing. From June 2006 to September 2011, a consecutive series of 1642 histologic samples of metastatic CRC patients has been referred to the bio-pathologic department for sequencing the *KRAS* codons 12 and 13 mutation status before enrolling patients in cetuximab-based protocols, and 633 mutations were recorded (39%). Since January 2009, an additional 762 samples from patients affected by NSCLC was screened using the same approach, leading to the identification of 186 mutations (24.4%) (Table 1). When comparing the mutation spectra of these two tumor types, no major difference in frequencies is observed except for c.37G>T and for delins mutations that are found in 15 of CRC, i.e., 2.3% of mutated samples, and 27 of NSCLC, i.e., 14.5% of mutated samples. These mutations are not precisely or unreliably detected using the commercial kits. If the proportion of missed mutations is quite low in CRC, it is much higher in NSCLC and cannot be neglected. In those cases, there is a risk to treat with an ineffective therapy, and in the future these patients could lack chance of having a *RAS*-targeted therapy.

In summary, meta-analyses on molecular biomarkers usually put together results derived from clinical studies based on heterogeneous molecular approaches, and subsequent conflicting results lead to preclude the use of potential markers in medical practice. When transferring new molecular markers in routine testing, we would like to recommend a scrupulous consideration when choosing the detection technique.

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