BIOMARKERS

Select Biomarkers Possibly Ready for Primetime: *EGFR*, HER2, and K-*ras*

By Tatiana Spicakova and Richard Wagner

Undoubtedly, biomarkers represent the new frontier in medicine, but a major question looms ahead: Are there limits to their potential impact? Despite the unprecedented technological advancements and explosion of biomarker research over the past few years, the low success rate of bench-to-clinic translation leaves oncologists struggling with basic questions of cancer management, such as: Who to treat; when to treat; how aggressively, and with what agent?

Several presentations at the 2009 American Society of Clinical Oncology's (ASCO) 45th Annual Meeting, held in Orlando, Florida, again highlighted the potential of biomarkers to change the way oncology is practiced, and most would agree that *EGFR* mutation, along with HER2 overexpression and K-*ras* mutation, are ready for primetime.

Moreover, two themes emerged from this year's ASCO regarding biomarker advancement—biomarker information must be actionable to impact cancer management practices; and biomarkers do not easily leapfrog across distinct tumor types, further complicating the emergence of a new biomarker-based molecular taxonomy of tumors.

EGFR Mutations—The New NSCLC Treatment Paradigm

Much like K-*ras* mutations in colorectal cancer were the big story at last year's ASCO, *EGFR* mutations in patients with non–small-cell lung cancer (NSCLC) made the headlines this year. In the first-line setting, Masahiro Fukuoka, MD, Kinki University School of Medicine, Osaka, Japan, presented the results of the IPASS trial (Iressa Pan-Asia Study), which compared the activity of Iressa [gefitinib; AstraZeneca] against standard chemotherapy in clinically selected Asian patients—those who were light or non-smokers and had adenocarcinoma NSCLC.

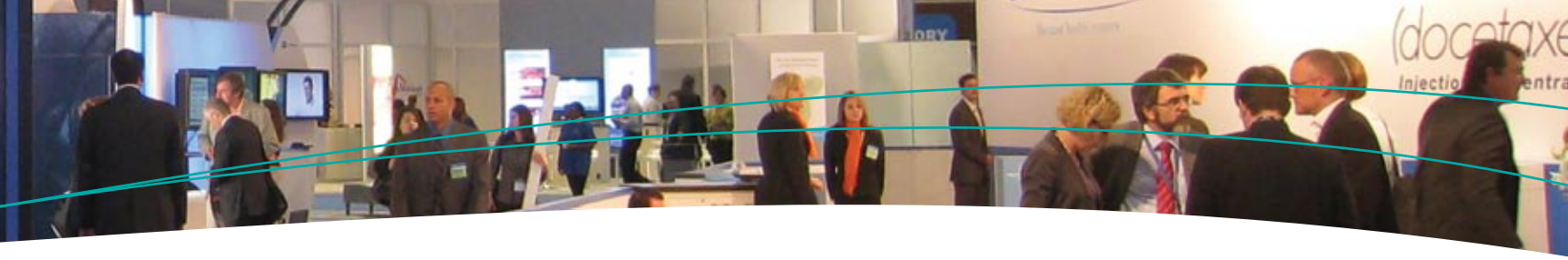
The results revealed markedly different, statistically significant outcomes based on *EGFR* mutation status. For patients with *EGFR* mutations who received Iressa treatment, progression-free survival (PFS) of 9.5 months was achieved compared with 6.3 months in patients in the chemotherapy arm. In contrast, for patients with the *EGFR* wild-type gene, Iressa was inferior compared with chemotherapy, achieving PFS of only 1.5 months compared with 5.5 months, respectively.

The impressive results of the IPASS trial were confirmed in a separate Phase 3 trial in Japanese patients. Although this trial also compared Iressa with chemotherapy in the first-line setting, the key difference was that only patients with *EGFR* mutations were eligible for enrollment to overcome the drawbacks associated with subset analyses.

The results, presented by Kunihiko Kobayashi, MD, PhD, Saitama Medical School, Saitama, Japan, showed an even more dramatic five month PFS benefit for Iressa versus chemotherapy (10.5 mo vs. 5.3 mo, respectively). The benefit was based on less than 100 patients per arm, highlighting the fact that if the biomarker guides the selection of patients, registration-enabling trials could be conducted with substantially fewer patients compared with the costly Phase 3 trials enrolling unselected patients.

The IPASS study also evaluated the impact of a different biomarker—*EGFR* gene copy number—on response to Iressa. The statistically significant result showed that patients with a high *EGFR* gene copy number benefited from improved PFS whereas patients with a low *EGFR* copy gene number did not.

At first glance, it may appear that gene amplification represents an additional predictive biomarker of response to Iressa, but further analysis of the data stresses the



importance of caution when interpreting biomarker data. It was found that a high *EGFR* gene copy number was only predictive if mutations in the gene were also present. Like the clinical characteristics that shaped the IPASS population, *EGFR* copy number is informative only because it increases the chance that a mutation is present. Mutations are the real driver of response to Iressa.

Can Biomarkers Bridge Different Tumor Types?

It is too early to conclude which predictive biomarkers will apply to a variety of tumor types and which will be confined to unique tumor types, but what is clear thus far from the following two presentations, is that each biomarker must be individually validated for each new tumor type.

PROTEOMICS-BASED BIOMARKER IN HEAD AND NECK CANCER

Biodesix has successfully translated a proteomics-based biomarker into a diagnostic blood test called VeriStrat® that identifies NSCLC patients likely to benefit from *EGFR*-targeted therapies, regardless of mechanism of action. But can the biomarker predict benefit from *EGFR*-targeted therapies across different tumor types? The results presented by Christine H. Chung, MD, Vanderbilt University, Nashville, TN, seem to suggest that the predictive value of VeriStrat holds true—at least for squamous cell carcinoma of the head and neck.

In the study, the biomarker was able to predict an overall survival benefit for head and neck cancer patients treated with *EGFR*-targeted therapies, but not for chemotherapy-treated patients. Although a positive result, one must be cautious about making the general conclusion that any biomarkers will be predictive of response across different tumor types.

For example, K-*ras* mutations were the lead story of last year's ASCO as biomarkers of resistance to Erbitux [cetuximab; Bristol-Myers Squibb/Merck/ImClone] in colorectal cancer—naturally setting the expectation that the same would apply to NSCLC where K-*ras* mutations also occur with a relatively high frequency. However, two studies presented at this year's meeting seem to challenge this expectation.

First, Philip C. Mack, PhD, UC Davis Cancer Center, Sacramento, CA, presented the results of a retrospective analysis of two Southwest Oncology Group studies, where the K-*ras* mutation did not predict resistance to Erbitux. The same conclusion was reached by Shirin Khambata-Ford, PhD, Bristol-Myers Squibb, Princeton, NJ, during his presentation on the retrospective biomarker analysis of the BMS099 trial that evaluated Erbitux in the first-line NSCLC setting.

HER2 EXPRESSION IN GASTRIC CANCER

HER2 overexpression is a biomarker that defines a group of breast cancer patients with poorer outcomes who might benefit from treatment with Herceptin [trastuzumab; Genentech/Roche]. But does HER2 expression identify a Herceptin-sensitive patient population across distinct tumor types? Based on the presentation of the ToGa trial presented by Eric Van Cutsem, MD, PhD, University Hospital Gasthuisberg, Leuven, Belgium, the answer seems to be "yes" at least for gastric cancer.

Much like pancreatic and NSCLC, metastatic gastric cancer is notoriously difficult to treat, as well as challenging to improve outcomes. However, the ToGa trial results demonstrated that when the patients are selected for expression of HER2, the addition of Herceptin to standard chemotherapy prolongs overall survival by more than 2 months compared with chemotherapy alone.

Are Biomarkers Actionable?

A biomarker will have a practice-changing impact only if physicians are able to act upon the information to improve clinical outcomes for their patients. Thus, biomarker actionability is a hurdle that must also be cont. on pg 18 >>

>>OBR DAILY ASCO NEWS COVERAGE

OncoGenex Pharmaceuticals' cancer drug OGX-011 extended the survival of patients with advanced prostate cancer by almost seven months, according to results from a randomized Phase 2 study presented at ASCO. *(TheStreet.com, 5/30/09)*

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overcome by investigators, as exemplified by the following two studies presented at ASCO.

CA125 BIOMARKER IN OVARIAN CANCER

CA125 has become one of the most utilized protein biomarkers in ovarian cancer to detect tumor recurrence before the emergence of clinical symptoms. But should CA125 levels alone be used to guide the timing of second-line chemotherapy? The results of a large clinical trial presented by Gordon J. Rustin, MD, Mount Vernon Cancer Centre, Middlesex, United Kingdom, in a plenary session seem to suggest "no".

The study was designed to compare overall survival between patients receiving early second-line chemotherapy based on elevated CA125 levels alone versus delayed chemotherapy also based on symptoms of clinical progression. Surprisingly, there was absolutely no difference between the two arms.

This finding undermines the clinical value of CA125 measurement—though foreshadowing cancer recurrence, it did not improve outcomes when used to guide the timing of treatment. Essentially "inactionable" to the physician, CA125 monitoring may still persist given its deeply embedded importance among the ovarian cancer patient population.

GENE EXPRESSION PROFILE IN BREAST CANCER

Agendia's MammaPrint™ is a 70-gene expression profile assay that stratifies women with early-stage breast cancer into two groups: low versus high risk of developing distant metastases. But can the prognostic profile become actionable by also predicting benefit from adjuvant chemotherapy? Based on the results of pooled analysis of seven clinical studies presented by Richard A. Bender, MD, FACP, Agendia Inc, the answer seems to be "yes".

In the presented study, both low- and high-risk women were treated with either endocrine therapy alone or in combination with chemotherapy. The results showed that addition of chemotherapy provided statistically significant 12% increase in metastasis-free survival for the high-risk women, whereas there was no chemotherapy benefit for the low-risk subpopulation. To confirm these results in a prospective manner, the predictive value of MammaPrint is currently being evaluated in a randomized clinical trial (MINDACT).

Biomarkers on the Horizon

Although it is beyond the scope of this article to cover all of the emerging biomarkers presented at ASCO this year, two biomarkers seemed to generate much excitement because of their pairing with novel targeted agents: *EML4-ALK* fusion as a predictor of response to ALK inhibitors such as PF-02341066 (Pfizer) and BRAF V600E mutation as a predictor of response to BRAF V600E inhibitors such as PLX4032 (Plexxikon/Roche).

The results of a Phase 1 trial presented by Eunice L. Kwak, MD, PhD, Massachusetts General Hospital Cancer Center, Boston, MA, showed a striking 56% partial response rate to PF-02341066 for NSCLC subpopulation harboring the *ALK* fusion. Similarly dramatic response was observed in the Phase 1 study presented by Keith Flaherty, MD, University of Pennsylvania, Hematology/Oncology, Philadelphia, PA, where 60% of melanoma patients harboring the BRAF V600E mutation achieved partial response to PLX4032.

The reason why these results spurred a lot of excitement is that Phase 1 studies typically only evaluate safety, with sample sizes too small for efficacy conclusions. The fact that over half of patients achieved partial response to both PF-02341066 and PLX4032 is, therefore, quite dramatic, highlighting again the striking outcomes that can come when selecting molecularly defined populations for clinical trials of targeted agents.

Concluding Thoughts

The theme of this year's ASCO was Personalizing Cancer Care; however, despite major scientific advances oncologists continue to struggle with basic questions of cancer management such as who to treat, when, how aggressively and with what agent? Most will agree that biomarkers have the potential to bring personalized cancer care into

the mainstream of oncology by enabling physicians to identify therapy-sensitive patients *a priori*.

Several presentations at the meeting again highlighted the potential of biomarkers to change the way oncology is practiced, and most would agree that *EGFR* mutations will have a practice-changing impact. The magnitude of the benefit that *EGFR* mutations offer to patients is quite dramatic, illustrating the importance of adopting a new drug development paradigm of pairing an active targeted agent with a biomarker-defined patient subpopulation. TS RW

About the Contributors of This Article

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>>OBR DAILY ASCO NEWS COVERAGE

Data presented at ASCO found that using a peptide vaccine with the immunotherapy drug Interleukin-2 improved response rates and progression-free survival in advanced melanoma patients—researchers said it was the first Phase 3 trial to show a clinical benefit in a vaccine for melanoma. *(U.S. News & World Report, 5/30/09)*

>>OBR DAILY ASCO NEWS COVERAGE

BiovaxID®, a custom-made treatment vaccine—made with proteins from a patient's own tumor—delayed relapses in some lymphoma patients by 14 months researchers announced at ASCO. *(USA Today, 5/31/09)*

>>OBR DAILY ASCO NEWS COVERAGE

GlaxoSmithKline's experimental cancer pill pazopanib reduced the risk of tumor progression or death by 54 percent in advanced kidney cancer patients compared to placebo in trial results announced at ASCO. *(Reuters, 6/1/09)*

ABSTRACTS

For further information on any of the ASCO studies discussed in this article visit: http://www.asco.org/ASCOv2/Meetings/Abstracts

ABSTRACT	TITLE
8006	Biomarker analyses from a phase III, randomized, open-label, first-line study of gefitinib (G) versus carboplatin/paclitaxel (C/P) in clinically selected patients (pts) with advanced non-small cell lung cancer (NSCLC) in Asia (IPASS) **First Author:** Masahiro Fukuoka
8016	First-line gefitinib versus first-line chemotherapy by carboplatin (CBDCA) plus paclitaxel (TXL) in non-small cell lung cancer (NSCLC) patients (pts) with EGFR mutations: A phase III study (002) by North East Japan Gefitinib Study Group **First Author:** Kunihiro Kobayashi
6000	Mass spectrometry profile as a predictor of overall survival benefit after treatment with epidermal growth factor receptor inhibitors in head and neck squamous cell carcinoma. **First Author:** Christine H. Chung
8022	KRAS mutation analysis in cetuximab-treated advanced stage non-small cell lung cancer (NSCLC): SWOG experience with S0342 and S0536 **First Author:** Philip C. Mack
8021	K-Ras mutation (mut), EGFR-related, and exploratory markers as response predictors of cetuximab in first-line advanced NSCLC: Retrospective analyses of the BMS099 trial **First Author:** Shirin Khambata-Ford
LBA4059	Efficacy results from the ToGA trial: A phase III study of trastuzumab added to standard chemotherapy (CT) in first-line human epidermal growth factor receptor 2 (HER2)-positive advanced gastric cancer (GC) **First Author:** Eric Van Cutsem
1	A randomized trial in ovarian cancer (OC) of early treatment of relapse based on CA125 level alone versus delayed treatment based on conventional clinical indicators (MRC OV05/EORTC 55955 trials) **First Author:** Gordon J Rustin
512	The 70-gene profile and chemotherapy benefit in 1,600 breast cancer patients **First Author:** Richard A. Bender
3509	Clinical activity observed in a phase I dose escalation trial of an oral c-met and ALK inhibitor, PF-02341066 **First Author:** Eunice L. Kwak
9000	Phase I study of PLX4032: Proof of concept for V600E BRAF mutation as a therapeutic target in human cancer **First Author:** Keith Flaherty