SUMMARY MINUTES

IMMUNOLOGY DEVICES PANEL MEETING

November 16, 2006

Gaithersburg Holiday Inn
Gaithersburg, MD.

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Attendees:

Chairman:

Clive R. Taylor, MD, PhD
University of Southern California

Industry Representative:

W. Jeffrey Allard, MS, PhD
Fujirebio Diagnostics, Inc.

Consumer Representative:

Joan London, MA
Media Works

Members:

Suzanne Gollin, PhD
University of Pittsburg

James L. Gulley, MD, PhD
National Cancer Institute, NIH

Terry R. Lichtor, MD. PhD
Rush University

Marc S. Ernstoff, MD
Dartmouth-Hitchcock Medical Center

Patricia A. Thoms, MD
University of Kansas

Deputized Voting Members:

Marilyn Leitch, MD
University of Texas

M. Margaret Kemeny, MD
Mt. Sinai Cervices/Queens Hospital Center

George J. Netto, MD

Johns Hopkins University

Gene P. Siegal, MD, PhD
University of Alabama

Elbert B. Whorton, Jr, MS
University of Texas

Colin B. Begg, PhD
Memorial Sloan-Kettering Center

Executive Secretary:

Rufina Carlos, BS

FDA Staff:

Don St. Pierre, BS

CALL TO ORDER

The Chairman called the meeting to order at 8:03 a.m., noted the presence of a quorum, and had the members introduce themselves. Executive Secretary Carlos read the conflict of interest statement and deputization of temporary voting members Dr. Leitch, Dr. Kemeny, Dr. Netto, Dr. Siegal, Dr. Whorton, and Dr. Begg. She then read the conflict of interest statement. All members were in compliance, and no waivers were issued. The Chairman opened the floor to comment from the public. Seeing none, he called for the sponsor's presentation.

SPONSOR PRESENTATION

Lubna Syed, manager of regulatory affairs for Veridex LLC, started the presentation. Veridex is a Johnson&Johnson company that makes cancer diagnostic products. The GeneSearch breast lymph node assay is a qualitative in vitro test for the rapid detection of clinically relevant (greater than 0.2 mm) metastasises in lymph node tissue removed from breast cancer patients. Results from the assay can be used to guide the decision to excise additional lymph nodes and to aid in patient staging.

During surgery, the sentinel lymph node is excised from the patient and taken to the lab, where it can be dissected and have its RNA extracted. GeneSearch reverse transcribes and amplifies the RNA, which is used in a Cepheid Smart Cycler II. The result can be relayed to the surgeon before the surgery is finished so the surgeon can decide whether to complete the surgery or remove axillary nodes.

The benefits of the GeneSearch BLN assay are many. For the patient, there is reduced probability of a second surgery for nodal positive patients. A greater proportion

of the removed node is being assayed with GeneSearch than with histology. Patients will not have to undergo the inconvenience, stress, and risks associated with additional surgery and more invasive lymphatic excision. For the pathologist, there's improved support of surgeons implementing state-of-the-art commercial grade tests. The surgeon is providing improved patient care with reduction in the number of second surgeries potentially for breast cancer patients, and the oncologist is getting more thorough staging information of the lymph node itself.

Dr. Vargo, Veridex's director of clinical affairs, further described the product and its performance. The presence or absence of metastasises in the sentinel lymph node is over 95 percent accurate in predicting axillary lymph node status. If the sentinel node tests negative, that spares the patient an unnecessary complete axillary lymph node dissection (ALND). If the sentinel nodes are positive for metastasizes, the surgeon would remove the rest of the nodes in the axillary basin. The data would aid the oncologist in choosing a therapy and would provide important prognostic information.

The current standard of care in diagnosing those sentinel lymph nodes is two-fold. Some labs use some intraoperative histology methods that give fast but sometimes inaccurate results. The most accurate is permanent section histology, which takes one to two days. The problems with the current standard of care are that there is no rapid test with high sensitivity, the limited amount of node tissue that can be sampled, and the subjective nature of histology. GeneSearch is designed to use over half of the node tissue to quickly give objective, standardized, and reproducible, highly sensitive results. Up to six patient samples can be run at once, with an average turnaround time of 30-46 minutes. The results are reported as negative or positive.

There are two analyte markers for the assay: cytokeratin 19 (CK19) which is expressed in epithelial cells, and mammoglobin (MG) which is expressed in breast tissue. Both have a cutoff to correlate with 0.2 mm metastasises, 31 for MG, 30 for CK19. If either or both of the markers are positive, the result is positive. To ensure accuracy, there is an internal control, porphobillnogen deaminase (PBGD), which is positive when the cancer markers are negative and negative when the cancer markers are positive. External controls serve as a negative control for positive PBGD and a positive control for negative PBGD. For the run to be valid, all marker and control results must be valid. The results are highly reproducible. A 2-day, 3 site, 6 operator, reproducibility study that tested 4 different samples showed 100 percent agreement.

A validation study was held with an independent patient set with pre-determined cutoffs. The objective was to evaluate assay clinical sensitivity and specificity against permanent sectional histology. A histology was positive if metastasises greater than 0.2 mm were identified and confirmed by 2 out of 3 pathologists. This was a prospective, multi-center blinded study with assay testing performed by site personnel.

Different samples of the same node were used for the experiment and the control, so there would not be 100 percent agreement. Metastasises may not be distributed through the node evenly, so some results may be incorrectly called false positives and false negatives. To minimize that, the two tests were performed on alternating slices of the node. When confirmation was needed, the sections were taken very near each other on the same face of the tissue. In performance evaluations, the cuttings that were done were all taken from one face of the tissue, for practical reasons.

There was a 29 percent positivity rate from permanent section histology results. For the assay, sensitivity was 87.6 percent, specificity 94.2 percent. The overall agreement between histology and the assay was 92.3 percent. For the purpose of the study, tests yielding no results were considered negative. A similar study in Belgium showed similar results. The rate of assay failure was 8.1 percent, but failure decreases as operators gain experience. External control failure rates drop dramatically with experience. New training programs used at site 14 and in the Belgium study showed much lower failure rates. In the pivotal study, the assay was 97.9 percent sensitive for macrometastases (larger than 2 mm). For micrometastases (0.2 mm to 2 mm), the assay was 56.5 percent sensitive, due to size and distribution.

In centers where frozen section or touch prep were standard care, the BLN assay was compared to these methods. Permanent section histology remained the gold standard against which all methods were compared. The assay out-performed frozen section 95.6 percent to 85.6 in sensitivity, but the frozen section was more specific: 97.8 percent to 94.3. In the pivotal study, the assay was 100 percent sensitive for macrometastases, 81.8 percent for micrometastases, compared to 90.8 and 54.5 for frozen section. In invasive lobular patients, the BLN assay was 100 percent sensitive and 93.5 percent specific, compared to 64.3 and 96.8 percent for frozen section. The assay agreed with permanent section histology 88.5 percent of the time on the number of positive nodes. The results of the pivotal studies were comparable to the results of the cutoff study.

Due to the limitations of the clinical study, the sponsor believes that the assay's 87.6 percent sensitivity, 94.2 percent specificity, and 5.8 percent false positive rate are underestimations of the assay's performance. There was a 25 percent chance that one

pathologist would find nothing on a slide if another found micromets, a fifty percent chance of agreeing, and a 25 percent chance of saying it was macromet. The assay was compared against an imperfect gold standard. There was also the matter of sampling differences. Part of the node can be positive and another part negative. The assay's sensitivity is an improvement over current intraoperatives and comparable in specificity to histological testing. He concluded that the data support the use of the assay as a stand-alone intraoperative decision-maker for ALND.

Dr. Donald Berry gave a statistical analysis of the results. For the study, specificity was defined as the probability that the assay would match the control when the control was negative. Sensitivity was the probability that the assay would be positive when the histology was positive. There were interim analyses planned so that if there was a 98.5 percent likelihood of success, specificity greater than 90 percent and sensitivity above 70 percent, success could be declared and the study ended early. There was a futility function also built in to declare the study a failure when the probability of success dropped below 0.5, which was the Type I error rate. The first interim analysis was at 412 cases. Sensitivity was 89 percent, specificity 94 percent. The odds of success were greater than 99 percent, so the trial was stopped. The final analysis included 416 cases. Observed sensitivity was 87.6 percent, specificity 94.2 percent. The probability of both measures being higher than the target exceeded 99 percent.

Dr. Barry pointed out that the histology test is not perfect, so some false positives in the context of the study are actually not false positives. The study results understate the assay's value. The total error rate for BLN is 5.4 percent, compared to 5.6 percent for frozen section.

Dr. Thomas Julian of Allegheny General Hospital reported on practice of medicine and clinical utility. Due to public awareness and screening, there is increased early detection of breast cancer. The average tumor is detected at 1 to 1.5 cm. At the earlier stages, there are fewer lymph nodes involved, so the metastatic rate is lower and the metastases are smaller.

The sentinel mode concept is based on the belief that metastatic disease to the lymph nodes is not a random event, that there is an orderly progression of tumor cells within the lymphatic system. The primary draining or sentinel nodes are the first to contain metastatic deposits. Biopsy of the sentinel node can predict axillary involvement. Surgeons, oncologists, and pathologists look at sentinel lymph nodes for prognosis, local control, and treatment planning. Axillary lymph node status is the most prognostic factor in early stage breast cancer. Even molecular ray tumor analysis requires node status to be known. Recurrence rates following an axillary lymph node dissection (ALND) is 2-3 percent. However, ALND increases the risk of pain, lymphedema, paresthesia, and arm weakness. Whether chemo, hormonal, regional radiation, or Herceptin therapy is used and dose is partly dependent upon node status and the number of positive nodes.

The sentinel node procedure is performed by injecting radioactive dye into the breast before surgery. A gamma detector is then used to find the sentinel node. Sentinel Node Biopsy (SNB) is between 70 and 100 percent sensitive for detection of ALN involvement, with false negative rates between 0 and 29 percent. In the NSABP B-32 Study, the identification rate was 97 percent. The accuracy was 98 percent, the positive node rate was 26 percent, and our false negative rate was 9.8 percent. American Society for Clinical Oncology (ASCO) guidelines and several consensus panels and societies

support SNB. The benefits of SNB is that there are fewer complications than ALND, decreased catheter drainage, and less axillary web syndrome. The risks are an increased risk of missing metastases due to false negatives and a rare allergic reaction to the dye. Intra-operative SN analysis allows the surgeon to perform an ALND if it is necessary, avoiding a second surgery and the related risks. In the past, intraoperative analysis has had a high false negative rate.

The GeneSearch Assay is a real-time, rapid, reproducible, and robust analysis. It permits an objective evaluation of a large amount of the SLN, reducing the likelihood of false negatives. The assay has detection limits that are appropriately matched to the histologic criteria, so they can be utilized for an intraoperative decision to be carried out, as per established guidelines.

Dr. Juan Palazzo of Thomas Jefferson University spoke on current standards of care. The predictors of axillary metastasis are primary tumors larger than 2 cm, vascular invasion in the primary tumor, SLN metastases larger than 0.2 mm, more than one positive SLN, and extranodal extension in the SLN. The incidence of further axillary metastasis is predicted by the size of the metastasises in the SLN. Macromets predict a 45-79 percent chance of further metastases, micromets 10 to 25 percent, and sub-micromets 7-25 percent. The pathologist can measure the metastases with an ocular micrometer or a ruler.

The AJCC cancer staging manual recommends the lymph node should be regarded as pN1 it's positive by H&E (haematoxylon and eosin stain slice) during frozen section or in permanent section. The node is pN0 when they are negative by H&E, pN01(i+) when the pathologist does immuno-cyto-chemistry and the result is positive.

Immuno-histo-chemistry is the use of an antibody against a cytokeratin that will identify these cells in the lymph nodes. And pN0(i-) are those that are negative by H&E, and IHC. AJCC recommends reporting PCR negative nodes as pN0(mol-) and as pN0(mol+) those that are positive by the same method.

SLN are approached three ways by surgical pathologists: permanent section histology with no intraoperative test, touch prep, or the frozen section. If the intraoperative tests are positive, ALND is performed. The lymph node is embedded and H&E is done, and ALND is performed if the result is positive. The introduction of the BLN Assay would allow the practitioner to know whether or not there are micrometastasises present larger than .2 mm. The remaining LN can be studied with H&E, IHC, or both. H&E can determine the tumor size.

One challenge of dealing with sentinel node assays is false negatives, due to limited sampling and heterogeneous metastasises distribution, lobular metastasises, and the relative expertise of the pathologist. Another is false positives due to benign nevic cells, macrophages, and the relative experience of the pathologist. Third, results are obtained one or two days after the lymph node is fixed and cut for permanent sections.

Intra-operative histology is limited is that frozen section only evaluates 2 to 3 percent of the lymph node. As a result, intraopertaive histologic evaluation has low sensitivity and high specificity. It is also not standardized. The sections can be of poor quality and difficult to interpret. Permanent section histology evaluates 2 to 5 percent of the lymph node, more if IHC is done. However, 10 to 15 percent of clinically relevant mets will be missed. How and where the node is cut and where the mets are is important to how useful a given test is. Even for advanced pathologists, the evaluation is difficult.

The assay is rapid, allows fewer second surgeries, is objective and standardized, and it uses more of the lymph node for a more representative sample, resulting in fewer false negatives. It also reduces the lab workload by better utilizing resources. He concluded by saying that the test was not intended to replace the surgical pathologist but that it was an additional tool for better assessment and staging.

Debra Rasmussin of Veridex concluded the presentation by reiterating the intended use of the assay, the benefits, the clinical utility, safety, and effectiveness.

FDA PRESENTATION

The Chairman called for the FDA presentation. Dr. James P. Reeves, the lead reviewer, gave the introduction. GeneSearch BLN assay's development and evaluation have been oriented toward intraoperative use after sentinel lymph node dissection, but the intended use does not limit its use to that setting and did not address use of the assay with other diagnostic methods. The FDA especially sought the panel's advice concerning the clinical validity and clinical utility of the GeneSearch BLN Assay. The FDA believes that several characteristics of the device will require special attention: safety and effectiveness; that its use without histology will impact medical practice, since the analytical target combines tumor staging categories that are currently separate; the device's being more sensitive than frozen section consultation, but less specific; that about 8 percent of the assays yielded no reportable results; and that no data was submitted to establish the time needed to perform the study.

Dr. Roxolana Horbowyj presented on sentinel lymph node dissection. Current tumor node metastasises staging for cancer nodal status is based on clinical and

histological evaluations. Surgical staging of the axilla is the most important predictor of clinical outcome. The size of the metastasises determines the additional treatment. The likelihood of axillary lymph node involvement is related to tumor size and location, histologic rating, and the presence of a lymphatic invasion.

Current options for primary tumor management include mastectomy, mastectomy plus reconstruction, and breast-conserving surgery plus radiation therapy. Selection is based on patient preference and suitability for breast conservation, and survival rates are equivalent for all of these options. Breast conserving surgery consists of a lumpectomy to remove the tumor and a margin of normal tissue. Additionally axillary staging is performed. Axillary lymph node dissection (ALND) aims to remove level 1 and 2 lymph nodes, preserving level 3 nodes unless gross disease is present. Sentinel lymph node dissection (SLND) aims to remove the sentinel lymph node, which is the first node cancer is likely to spread to. Patients have a ten year higher survival rate with axillary surgery than without, 85 percent, compared to 66 percent; however, ALND carries the risks of lymphedema, injury to or thrombosis of the axillary vein, seroma formation, impairment of shoulder movement, damage to the brachial plexus with chronic pain and varying degrees of decreased grip strength, as well as chest wall pain.

SLND is an approach to decrease morbidity, while maintaining accurate axillary staging assessment of the sentinel lymph node in patients with clinically negative axillary lymph nodes. SLND is performed during the same surgery as the lumpectomy, but earlier in the surgery. If the SLN had metastises on pathological assessment, ALND is performed. Outcomes for effects on tumor recurrence or patient survival are pending. The ALMANAC trial, a prospective study of 1.031 node negative patients were

randomized for SLND and ALND. At one year after surgery, quality of life was better in the SLND group, as well as arm function and return to daily activities. The NSABP-32 trial found that for long term control of regional disease, SLND alone is equivalent and shows less morbidity compared to SLND followed by ALND. An American College of Surgeons Oncology Group Study on micrometastases in the sentinel node is ongoing.

There are risks associated both with false negatives and false positives. False positives will lead to unnecessary ALNDs. False negatives will lead to under-staging, under-treatment, and decreased survival, unless the false negative is identified by histologic evaluation.

Dr. Max Robinowitz presented on the surgical pathology of SLN biopsies, which Veridex used as the comparator to their test kit. Cancer cells are first trapped in the subcapsular space, so it must be sampled to detect metastatic cancer cells. In current practice, the directions for the pathologists are that all submitted lymph nodes should be counted and measured, the color noted (especially for blue dye) and to record the relative radioactivity uptake for each node detected by the surgeon. It is the responsibility of the pathologist to systematically quantify and characterize the tumor burden in each SLN and all other nodes that are submitted. This is important because the pathologic examination of axillary lymph nodes is a requirement for consistent categoric reporting using the AJCC/UICC cancer staging system.

Macrometasises usually show histologic evidence of metastatic activity, such as proliferation, stromal reaction, penetration of vascular or lymphatic sinus walls. If any node metastasises is larger than 2 millimeters, the total number of tumor positive nodes determines the N category. Micrometasises are usually detected by

immunohistochemistry or molecular methods but can be verified by H&E. They can be single foci, multi-focal, or diffuse, especially with lobular carcinoma. Isolated tumor cells must be distinguished from mimics, such as macrophages and nevic cells. It is also possible for them to be introduced to the SLN by iatrogenic causes, such as needle biopsy.

The Veridex LN sectioning plan is very different from the ASCO sectioning plan, cutting different sizes of slabs along a different axis. The choices for intraoperative examination in the ASCO guideline are gross inspection of the cut surfaces of the node, cytology of node imprints or cell smears, and frozen section histopathology. Permanent section histopathology is considered the definitive pathologic diagnosis. Frozen sections are more sensitive than cytology, but the preparations are seldom as good as permanent sections.

The ASCO guideline estimates that for every 100 patients considered for sentinel node biopsy 25 percent will be positive by permanent H&E. Of that 25 percent, 16 to 17 of the 25 will be positive by frozen section, and 8 to 9 of the 25 will be false negative by the frozen section. When the frozen section is negative or suspicious, the recommendation is that the finding should be reported as not diagnostic for tumor and deferred for paraffin section. Frozen section is 80 percent sensitive for macrometastases, and false positives are rare.

IHC analysis is not recommended as a routine method by the ASCO guidance because of insufficient evidence, particularly for isolated tumor cells, or micrometastasises. ASCO guidelines recognize that molecular approaches are highly sensitive and may permit evaluation of relatively large amounts of tissue, but it is

considered investigational. Additionally, the tissues examined by this method are destroyed, making it impossible to identify the cells that triggered the tumor marker.

Dr. Reeves reported on the Veridex GeneSearch BLN assay. He noted that the sponsor used a controversial definition for metastasizes in the intended use and did not mention intraoperative use or use of the assay as a substitute for or addition to other assessment procedures.

In the assay, the instrument fluorescent signal is converted to cycle threshold values using the Cepheid Smart Cycler instrument. CT values of the external positive and negative controls are compared with an acceptable range of values for each of the three markers using assay-specific software in the Smart Cycler. An assay run is only considered valid if the external positive and negative controls are within the acceptable range. The result is considered positive if the CT value for either marker is below the cutoff. If the CT value of both markers and the internal control are above the cutoff, the specimen is negative. The result is considered invalid if the CT value of all three markers is above the cutoff.

In the clinical study, 34 of 421 subjects, 8.1 percent, had failures of the external controls or internal control gene. Assay results from these subjects were classified assay negative for purpose of performance calculations, and the sponsor included those results in the "intent to diagnose" population. Exclusion of invalid assay results does not create a statistically significant change in the sensitivity and specificity results. The sponsor did not say how an invalid result should be treated clinically, immediate retesting or deferral of a decision until a permanent section histology can be performed. Although technician experience significantly lowers the failure rate initially, the improvement levels off at

around 20 runs, and the error rate remains between 4 and 8 percent. Even highly trained technicians have a failure rate of about 6 percent.

Although the sponsor indicated that the assay is designed to be completed in about 30 minutes, no data has been supplied as to actual times, so there is no way to know if the assay completion time set the sponsor's expectation, and no information was given on the trending of external positive and negative controls among sites and overall.

The study was performed in a clinical setting of sentinel lymph node biopsy on breast cancer patients who qualified for sentinel lymph node biopsy. The population was breast cancer patients 18 years or older who had a diagnosis of invasive breast cancer and were scheduled for sentinel lymph node biopsy. Since the assay is designed for intraoperative use, positive results suggest immediate intraoperative followup with full axillary node dissection in the absence of any other intraoperative histology results. Negative assay results suggest no further dissection of axillary lymph nodes. Use of the assay in conjunction with other current intraoperative histological procedures was not evaluated in the study.

The objective of the study was to gather data necessary to support safety, defined by a low percentage of false negatives, and effectiveness of the assay in the end user's hands and to determine specificity and sensitivity compared to H&E staining and immunohistochemistry. The hypothesis was that sensitivity would be 70 percent or better and specificity would be 90 percent or better for the lower 95 percent confidence limit. A secondary objective, for which no data has yet been submitted, was to collect long-term clinical outcome data for use in evaluating the assay and other marker sets as prognostic or diagnostic indicators.

The study was a prospective study at five or more clinical sites (ultimately 11) with patients with previously diagnosed invasive breast cancer who were scheduled for sentinel lymph node dissection. The extracted sentinel node was sectioned perpendicular to the long axis of the node and in a more rigorous manner than that in ASCO guidelines. Each site used the H&E evaluation criteria for patient management decisions.

Sentinel lymph node tissue identified by standard locating techniques was removed. Each removed node was cut as described in the node cutting scheme, and the clinical site used alternating tissue slabs for histology and the assay. Patient tissue for the proposed assay was pooled and processed intraoperatively. Permanent section histopathology was evaluated by site pathologists and by a panel of three independent, blinded pathologists: a site pathologist, a central pathologist, and a tiebreaker. A histology was deemed valid if two of the three pathologists agreed, so a third pathologist was not consulted in that case. It was deemed invalid when the two disagreed and no third pathologist was consulted. The frozen section results were handled separately; they were considered positive if the metastasis were over 0.2 mm.

H&E histology categorization was compared to final histology categorization from H&E plus immunohistochemical evaluations, and the agreement was 95.2 percent; only one of the 421 subjects had results significantly changed by ICH. From this, it was concluded that H&E alone is representative of final histology.

Agreement between the site and central pathologists was 91 percent, with a 86.7 to 95.4 percent confidence interval. The assay was found to be 87.6 percent sensitive with a 95 percent confidence interval and 94.2 percent specific with a 95 percent confidence interval. The risk of absence of detectable cancer metastases when the assay

is positive is 13.8 to 21.2 percent. The risk of detectable cancer metastases being present when the test is negative is 5.1 to 8.3 percent. The consequence of assay false positives is overtreatment and the associated morbidity. The consequence of a false negative is a delayed ALND and a second operation. False information can lead to misstaging, and the assay does not distinguish micrometastatic disease from macrometastatic. For staging purposes, the assay should be used in conjunction with histology.

Dr. Gene Pennello gave the statistical report. The study consisted of the cutoff and the pivotal studies. The study designs were identical and conducted at the same sites. A Baysian analysis was designed, though no prior information was added to the analysis. The cut-off study was to be concluded when there was a 98.5 percent probability of the assay's meeting or exceeding 70 percent sensitivity and 90 percent specificity. There were 412 patients at the first interim analysis, when the sensitivity and specificity hypotheses were met.

The prevalence of disease involving metastases of over .2 mm increases from 29.1 percent in the sample population to 86.2 percent in patients with a positive assay test. That is the positive predictive value, and it also means that 13.8 percent of test positive subjects may undergo an unnecessary ALND, 4.1 percent of all subjects. The number of ALNDs would increase from 29.1 percent to 33.2 percent. The negative predictive value is that the 70.9 percent prevalence of nondisease would increase to 94.9 percent, meaning 5.1 percent of patients would not be referred to needed surgeries, unless the disease is detected in the permanent sections.

Frozen section and the BLN assay appear to operating at different points on the same ROC curve. Frozen section is 3.5 percentage points higher in specificity but 10 percentage points lower in sensitivity.

The Chairman opened the floor to questions. Dr. Gollin asked if the assay was supposed to be used with or instead of frozen section testing or replace it. Dr. Reeves said it could do either.

PANEL DISCUSSION

The Chairman called for Dr. Reeves to present the questions to the panel.

Question 1) Is the inability of this test to distinguish size of metastasizes (micro versus macro) relevant to the safe and effective use of the test? If so, how should this issue be addressed?

Dr. Netto said it was an important matter, since the findings guide therapy, and wondered if the assay could be used as a stand-alone for that reason. Dr. Leitch said that both axillary dissection and systemic therapy are issues in the matter. If the node was treated as it was in the study, permanent section histology remains an option. Dr, Kemeny pointed out that frozen section after sentinel lymph node biopsies is not standard of care.

Question 2) The BLN assay detects histological metastases >0.2 mm with the following performance characteristics:

--Sensitivity 87.6% (CI 80.4% to 92.9%)

--Specificity 94.2% (CI 90.9% to 96.6%)

For Prevalence of 29.1% node-positive patients, 8% invalid results (treated as negative) estimated time of 30 minutes:

--Predictive value of a positive result is 86.2% (CI 78.8% to 91.7%)--point estimate of false positive results in any individual tested is 14%

--Predictive value of a negative result is 94.4% (CI 91.7% to 97.1%)—point estimate of false negative results in any individual patient tested is 5%

Given the performance above, is this device safe and effective for use as a stand-alone addition for intraoperative testing in settings that currently do not use intra-operative testing to determine disease status?

Dr. Leitch said that the answer would depend on what was meant by stand-alone and whether there would still be a sample left for permanent slide histology. Dr. Netto agreed and added that it was unknown what to do in case of a conflict between assay and histology results. Dr. Gollin advocated using the assay as an adjunct to permanent section histology. Dr. Becker clarified that the FDA meant stand-alone to mean only as an intraoperative test; the designation makes no reference to a later permanent section. Dr. Thomas doubted the assay would be performed quickly enough. Dr. Gollin said that the labeling should define that and whether or not the whole node is used.

Question 3) The BLN assay to detect histological metastases >0.2 mm, and frozen section consultation performed in parallel have the following performance characteristics:

BLN Sens 95.6% (CI 89.0% to 98.8%) FS Sens 85.5% (CI 76.6% to 92.1%)

BLN Spec 94.3% (CI 90.5% to 96.9%) FS Spec 97.8% (95.0% to 99.3%)

For Prevalence of the 29.1 % node-positive patients, 8% invalid results (treated as negative), estimated test time of 30 minutes; Predictive values of BLN and FS are:

BLN PPV 86.9% (CI 78.6% to 92.8%) FS PPV 93.9% (CI 86.3% to 98.0%)

BLN NPV 98.2% (CI 95.4% to 99.5%) FS NPV 94.5% (CI 90.8% to 97.1%)

This comparison was not a planned analysis in the pivotal trial. The frozen section specificity here differs from that reported in the literature. Estimates are statistically different between molecular and frozen section testing for NPV and are borderline significant for PPV.

Given the performance above, is this device safe and effective for use as a stand-alone replacement for frozen section consultation to determine disease status?

The Chairman pointed out that there was a subtle difference between questions two and three. He asked how a device could be both stand-alone and an addition, as in question two. Dr. Becker explained that the two questions differ in that the second question asks about BLN assay being added when there is no intraoperative procedure in place. The third question asks if it would be safe and effective to replace frozen section, if it is already in place. Dr. Netto commented that a center adopting the assay would have to deal with the 14 percent positivity, which may be false. Dr. Siegel said that the answer would depend upon the standard of care in the institution and on the third party payer. Dr. Leitch said that in the question both frozen section and BLN assay would not be done, though they may both be used clinically. In the context of the question, informing the patient of the high positive rate is important. Dr. Ernstoff pointed out that H&E has false negatives, but that is not discussed with the patients. Dr. Kemeny said that she does explain the sentinel lymph node biopsy to patients because there is a chance of inaccuracy. Dr. Leitch said that informing the patient is important because there are so

many unknowns. Followup studies are being done, and more data will come. She explains the false negative rate of sentinel node and the state of the current science. If an intraoperative assay will be used, it is important that the patient have input on the decision the doctor will make while the patient is on the table. Of course, there is no option of intraoperative informed consent.

Question 4) Are there sufficient data to establish safe and effective use of the test for any aspect of tumor staging in breast cancer patients?

Dr. Thomas noted that the assay does not give size information, and size is a factor in staging. Dr. Ernstoff agreed that the kind of adjuvant therapy a patient has is impacted by size. It would be beneficial to have a quantitative assay. Dr. Becker clarified that the question is general, just asking if data from the assay can assist in establishing the stage of disease. Dr. Vargo said that the device could fit into NNM as a molecular plus and that the data supports making the node N1. Dr. Ernstoff said that not only is size lost but capsular spread and mitotic rate, as well. Dr. Leitch said that the AJCC would be unlikely to accept the present data as sufficient to describe the nodes as prognostically positive. Dr. Vargo said that when a touch prep is positive and the permanent section negative, the node is positive. Dr. Leitch disagreed, saying a positive touch prep means more data was needed through a frozen section or permanent slide for further documentation. Dr. Julian said that conflicting results should be discussed with the patient. Reactions to positive touch preps vary by practitioner and center. Dr. Whitworth said the question of clinically useful information is for the AJCC.

Dr. Siegel asked the FDA if the assay is an all or none test or if a practitioner could use portions of it. Dr. Becker said that the test would be sold as a unit but that

clinicians may make adaptations. The FDA does not regulate medical practice and does not control off-label use.

OPEN PUBLIC HEARING

The Chairman opened the public session. Dr. Pat Whitworth and Peter Blumencrantz, both principal investigators in the study and consultants to the sponsor, presented.

Dr. Whitworth said that the assay is more sensitive than frozen section and offers two advantages: it avoids misleading the patient with a false negative and reduces second surgeries. Additionally, the assay reduces the burden on pathology laboratories and reduces inter-institutional variation in results. If the assay is more accurate than permanent slide, the gold standard, it will lead to more effective treatment and better survival rates. Still, it is important to preserve tissue to allow for histology when necessary. The concerns with the assay have to do with whether the false positives are false or not. If they are truly positive, then the test is better than the gold standard. If they are reference misses, they still provide valuable information. The gold standard only tests a portion of the node, resulting in false negatives.

Dr. Blumencranzt said that no test is 100 percent accurate, but clinicians do rely on them. He said that the device should not be considered MOL relative to IHC. The assay was designed to be conservative so that when patients were declared positive by the test the tumor burden in the node would exceed normal ITC.

CONCLUDING REMARKS

The FDA had no closing remarks. Dr. Vargo spoke for the sponsor, saying that using the assay for intraoperative result, the false positive rate is 5.8 percent but reminding the panel to compare that to the 10 percent false negative rate under current practice. Properly diagnosing positives gives a patient a better chance of survival.

Dr. Allard, industry representative, congratulated the sponsor on a well-constructed test for a stand-alone device. He said that the clinical performance was good, the device performance impressive, and that following the Bayesian statistical plan could have made approval easier for the sponsor, but the sponsor chose a higher statistical standard. He said that the volume of tissue used should be clarified in the labeling.

Ms. London, the consumer representative, said that the assay will help many people in the future.

PANEL DELIBERATIONS AND VOTE

Ms. Carlos read the panel recommendation options. **Dr. Gollin moved that the proposed assay be approvable with conditions. Dr. Thomas seconded the motion.**

As the first condition, Dr. Siegel moved that there be a post-market analysis as to whether or not lymphoma or other tumors interfere with the reliability of the assay. Dr. Thomas seconded the motion. Dr. Ernstoff offered an amendment that there be statistical advice from the FDA on the number of specimens to be analyzed. Dr. Gollin offered a further amendment that the information from the analysis be incorporated into the labeling once the study is complete. Dr. Siegel accepted both as friendly amendments and **the motion carried unanimously.**

Dr. Gollin moved that the labeling state that the assay be performed on a segmented lymph node so that there is residual lymph node that would be submitted for H&E permanent section evaluation. Dr. Gulley seconded the motion. Dr. Leitch commented that in the future the sponsor may want to use the whole node; she suggested follow-up on the question on whether or not the assay is more accurate than permanent section. Dr. Gollin said that would be better addressed in a separate motion. Dr. Ernstoff added that the FDA and sponsor should discuss how the node should be sectioned, if it is large enough. Dr. Netto said that if there is not enough tissue for both, the permanent section should take precedence until the long-term data is in. The Chairman called the question of the condition that the assay be performed on a segmented lymph node, that there be sufficient remaining tissue for H&E permanent, and that the assay be compared to the permanent section evaluation, which would be addressed in a subsequent condition. **The motion carried unanimously.** The Chairman noted that Dr. Siegel had left before the vote but that a quorum was still present.

Dr. Gollin moved that user training and more detailed precautions against PCR contamination in the operating room and the pathology lab be specified in the labeling. Dr. Ernstoff seconded the motion, and it carried unanimously.

Dr. Ernstoff moved that there be clinical followup data collected in relationship to how patients are treated with this information, their participation in adjuvant therapies, and how there would be interaction with participation in clinical trials. Dr. Leitch seconded the motion. Dr. Leitch offered the amendment that the outcomes of axillary dissection from nodes judged positive by the assay be included to determine whether the dissection was necessary or not. Mr. St. Pierre said that each

aspect of the followup study did not need to be part of the motion, since the FDA would review the discussion and work out the study with the sponsors. Dr. Gollin recommended that a long-term followup study of the assay positive histology negative cases be included in that study. Dr. Netto commented that if the panel was requiring a separate study the right vote might be to not approve. Mr. St. Pierre said that follow-up can be a condition, so long as there is sufficient data to approve the device; if certain results of a new study are a condition of approval, the device is not approvable, since the decision must be based on available data, not future data. Dr. Gollin withdrew the request for a study. Dr. Erstoff clarified that his motion was for a follow-up database, not a study. Dr. Netto said that it would be difficult to approve the device without long-term outcome data on false positivity. The Chairman suggested revisiting the three conditions already voted upon but first called the question on this condition. **The motion carried unanimously.**

Dr. Leitch moved that the inclusion of clear information in the labeling about the false positive rate be made a condition of approval. Dr. Netto seconded the motion. Dr. Whorton offered an amendment requiring that the upper and lower confidence limit and the margin of error be included with the information. **The motion carried unanimously.**

Dr. Thomas moved that the labeling make clear that the device being stand-alone means that it can replace frozen section and stand alone as an intraoperative procedure. It does not replace permanent section. Dr. Netto seconded the motion. There was discussion as to whether or not the second condition said the same thing. **The motion carried 9:1 with Dr. Netto dissenting.**

The Chairman called for any other conditions. Hearing none, he **called the question of approval with the conditions that had been voted upon. The motion carried 9:1 with Dr. Netto dissenting.**

The Chairman polled the members on why they voted as they had. Those voting in favor of the motion spoke of the quality of the data, the promise of the assay, the benefit to patients and practitioners, and the conditions being prudent. Some concerns remained: the false positives, the circumstances of use, and informed consent. Dr. Netto said he voted against the motion because he had no way of knowing the conditions would have the intended results. Since approval comes before the conditions are carried out and the post-approval data may be detrimental, he felt that FDA lost a lot of enforcement power by approving before the data is in. The vote was not a no-confidence vote on the assay itself.

ADJOURNMENT

The Chairman thanked the sponsor for its presentation, commenting that standardized and reproducible tests are the future of pathology and that he looked forward to the post-approval data. The meeting adjourned at 4:08 p.m.

I certify that I attended this meeting of the Immunology Devices Panel on November 16, 2006 and that these minutes accurately reflect what transpired.

Rufina Carlos
Executive Secretary

I approve the minutes of this meeting as recorded in this summary.

Clive R. Taylor, MD, PhD
Chairman

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