APPENDIX A

Correlation of Ki-67 Immunohistochemistry with Oncotech Extreme Drug Resistance Assay Profiles in Melanoma (Abstract)

Title: Correlation of Ki-67 Immunohistochemistry with Oncotech Extreme Drug Resistance Assay Profiles in Melanoma

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Background: Toward the goal of personalized medicine, in vitro drug sensitivity assays have been developed to help clinicians tailor specific treatment regimens. The “Extreme Drug Resistance (EDR) Assay” offered by Oncotech Inc. (Tustin, CA) exposes the patient’s cancer cells to extreme levels of chemotherapeutic drug, and assesses proliferation by 3H-thymidine incorporation. Ki-67 has been used as a mechanism to assess proliferation rate and thus, aggressiveness of tumors. We hypothesize that Ki-67 expression will be correlated with extreme drug resistance. Here we test this hypothesis and determine the relationship between EDR and initial recurrence in a cohort of 100 malignant melanoma specimens.

Design: Fresh samples from 100 specimens seen in the Yale University Department of Pathology between 1995 and 2002 were tested for drug resistance by the EDR assay. The formalin-fixed, paraffin-embedded melanoma blocks from each specimen were collected to produce a tissue microarray (0.6 mm cores, twofold redundancy). The majority of cases were metastatic (92), followed by local recurrences (7), and a primary (1). Data from the Oncotech EDR Assay was available for the following drugs: 5FU (69), 5FU+Leucovorin (70), Carmustine (83), Cisplatin (83), Dacarbazine (76), Doxorubicin (70), Etoposide (65), Mitomycin C (65), Vinblastine (72). Immunohistochemistry was performed on the tissue microarray slide with a purified mouse anti-human monoclonal antibody to Ki-67 (Clone B56, BD Pharmingen, San Jose, CA). The slide was then scored for percent positive nuclei by two independent observers (M.H. and A.B.). Statistical analyses were performed using JMP 5.0.1 (SAS Institute Inc., Cary, NC).

Results: Ninety-three percent of the histospots were scoreable. The distribution of Ki-67 scores was bimodal so nominal classes were constructed dividing the population into high and low level Ki-67 expression. Scores for the EDR assay are provided in 3 groupings (extreme, intermediate, and low drug resistance). Neither the EDR Assay results, nor the Ki-67 score, were able to distinguish aggressive from non-aggressive primary melanomas (i.e., time to first recurrence after initial diagnosis). The survival curve for the 5FU+Leucovorin EDR assay showed a significant correlation with primary tumor aggressiveness (p=0.0088), though cohort numbers were small (EDR=1, IDR=11, LDR=25). Only the assay for the combination regimen 5FU+Leucovorin correlated with Ki-67 expression (p=0.02).

Conclusion: Although Ki-67 and EDR are both predictors of aggressive tumors, no correlation was found between Ki-67 and drug resistance in eight of nine drug assays tested. Furthermore, no relationship was found between Ki-67 expression and primary tumor aggressiveness or EDR and primary tumor aggressiveness. However, the specimens examined were predominantly metastatic tumors where high levels of Ki-67 expression are more common. Finally, the absence of a relationship between either Ki-67 and EDR and the time to first recurrence may be overshadowed by the value of either test to predict response to therapy. Future studies will include this analysis upon collection of treatment and outcome data.
APPENDIX B

Concise Tabulated Oncotech EDR Results Data

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<th>IDR</th>
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Extreme Drug Resistance (EDR)

Extreme Drug Resistance (EDR) indicates that tumor cell growth was virtually unaffected by the high chemotherapeutic agent exposure. Data published in the April 1990 edition of the Journal of the National Cancer Institute (JNCI) and other published data show that patients had less than 1% chance of responding to EDR agents.

Intermediate Drug Resistance (IDR) indicates moderate tumor growth. In published studies, patients treated with agents in the IDR category had response rates that were about half of the rates reported in the medical literature.

Low Drug Resistance

Low Drug Resistance (LDR) indicates that tumor cell proliferation was inhibited by the tested agent and that tumor cells demonstrated less than median growth. Patients treated with agents in the LDR category had response rates that were approximately 1 1/2 to 2-fold greater than the literature reported rates in published studies.

**Literature Response Rate**

Determined from an extensive review of clinical trials in which each drug was administered as single agent therapy to specific tumor type.

**Assay Predicted Response Probability**

Derived from an algorithm involving in vitro tumor cell proliferation, literature response rate, patient treatment status, and a comparison with a growing database of over 80,000 in vitro assays, in accordance with the Bayesian mathematical model.

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**EDR® Assay Features and Benefits**

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<th>Description</th>
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<td>Accurate</td>
<td>- Over 99% accuracy for identifying ineffective (resistant) agents&lt;br&gt;- Independent of host factors</td>
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<td>Cost Effective</td>
<td>- Avoids direct costs of ineffective therapies&lt;br&gt;- Avoids costs of managing treatment related morbidity</td>
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<td>Humane</td>
<td>- Spares patients unnecessary toxicity&lt;br&gt;- Saves valuable treatment time</td>
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<tr>
<td>Reliable</td>
<td>- Avoids the potential of inducing cross resistance to other effective agents&lt;br&gt;- Approximately 90% of tumor specimens submitted yield successful assay results</td>
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<td>Fast</td>
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### APPENDIX D Formatted Melanoma Patient Data

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Assay Specimen Preparation Guidelines

Solid Tumor (including Lymphoma)

- Obtain fresh biopsy specimen. Do not mince, fix or freeze specimen.
- Rinse specimen in sterile saline or lactated Ringer’s solution.
- Immediately place sample into the inner specimen transport vial which contains Oncotech transport media.
- In the absence of Oncotech transport media, use sterile lactated Ringer’s solution or RPMI 1640.
- Place specimen vial into center of Oncotech box. Place ice pack on top of vial assembly. Enclose completed requisition form.
- Place closed box into Federal Express Diagnostic Pack for shipment.
- Call 1-800-ONCOTECH for specimen pick up.

Important Reminders:

- Refrigerate transport vial until use.
- Freeze Oncotech transport box at least 24 hours before use.
- Patients must not have had chemotherapy or radiation therapy within 3 weeks of specimen collection.

Selected Oncotech EDR® Assay Standard Test Panels*

**BREAST**
1. Doxorubicin
2. Cyclophosphamide
3. Taxol
4. Fluorouracil
5. Neovastine
6. Taxotere
7. Gemcitabine
8. Cisplatin

**COLON**
1. Fluorouracil
2. Mitomycin
3. 5 FU + Leucovorin
4. 5 FU + Irinotecan
5. Oxaliplatin
6. Topotecan
7. Mitomycin C

**ENDOMETRIAL**
1. Cisplatin
2. Taxotere
3. Doxorubicin
4. Ifosfamide
5. Etoposide
6. Cyclophosphamide
7. Topotecan

**KIDNEY**
1. Interferon 2
2. Alpha Interferon
3. Fluorouracil
4. Gemcitabine
5. Doxil
6. Vinblastine
7. Interferon + Vinblastine
8. Mitomycin C
9. Cyclophosphamide

**LUNG (Non-Small Cell)**
1. Carboplatin
2. Taxol
3. Neovastine
4. Etoposide
5. Gemcitabine
6. Topotecan
7. Cisplatin
8. Taxotere

**LUNG (Small Cell)**
1. Cisplatin
2. Taxol
3. Gemcitabine
4. Etoposide
5. Topotecan
6. Doxorubicin
7. Neovastine
8. Irinotecan

**MELANOMA**
1. Cisplatin
2. Temazolomide
3. Vinblastine
4. Taxol
5. Gemcitabine
6. Topotecan
7. Neovastine + Etoposide
8. Alpha Interferon
9. Carmustine

**OVARIAN**
1. Carboplatin
2. Taxol
3. Topotecan
4. Etoposide
5. Gemcitabine
6. Taxol
7. Taxotere
8. Cyclophosphamide
9. Cisplatin
10. Cisplatin + Gemcitabine

**SARCOMA (Soft Tissue)**
1. Doxorubicin
2. Ifosfamide
3. Temazolomide
4. Cisplatin
5. Taxotere
6. Gemcitabine
7. Topotecan

**SQUAMOUS (Cervix)**
1. Ifosfamide
2. Vinblastine
3. Cisplatin
4. Taxol
5. Fluorouracil
6. Mitomycin C
7. Topotecan

**STOMACH**
1. Fluorouracil
2. Mitomycin C
3. Doxorubicin
4. Cisplatin
5. Etoposide
6. Gemcitabine
7. Taxol

**UNKNOWN PRIMARY**
1. Cisplatin
2. Doxorubicin
3. Fluorouracil
4. Cyclophosphamide
5. Taxol
6. Topotecan
7. Etoposide

*Updated October 2002*
References


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regional lymph nodes in patients with melanoma of the trunk: A randomized

3645-3646.

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management of melanoma in situ: a survey of US dermatologists.” Archives in
Dermatology 141: 723-729.

1997. “Automated and quantitative immunocytochemical assays of Bcl-2 protein

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induced apoptosis in gastric cancer cell line BGC-9823.” International Journal of
Molecular Medicine 16: 741-745.


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