Improving the Quality of Cancer Clinical Trials
National Cancer Policy Forum – Screening for Predictive Markers

Daniel D. Von Hoff, M.D., F.A.C.P.

Physician-in-Chief, Senior Investigator
Translational Genomics Research Institute (TGen)
and
Clinical Professor of Medicine
University of Arizona, Arizona Cancer Center
and
Chief Scientific Officer
Scottsdale Healthcare and US Oncology Research
Thank You to the Organizers for the Invitation

John Mendelsohn, MD

Hal Moses, MD

Sharyl Nass, PhD
Study Director
It is a privilege to represent our Research Teams here today
The orientation of the Research Teams I represent here today is “Improving a Patient’s Chance of Benefiting from Early Clinical Trials”

Translational Genomics Research Institute - TGen

TGen Clinical Research Service – Scottsdale Healthcare – Home of the Arizona Cancer Center, Phoenix Arizona

US Oncology Research
- 660 community medical oncologists
- 145 radiation oncologists
- 33 gynecological oncologists
- Sees > 17% of all patients with cancer in the US
- A spectacular group of colleagues very devoted to clinical research
Previous sessions of the conference have discussed “targeting multiple pathways with multiple drugs”

Roy Herbst, MD, PhD
The Phase I Risk/Benefit Study Report

1. 11,935 participants in 460 phase I trials of single new agents and combinations of a new agent plus at least one agent approved by FDA

   • overall toxic death rate = 0.19%
   • overall response rate = 10.6%
     - new agent + established agent = 17.8%
     - Classic single agent phase I = 4.4%
     - an additional 34% of patients had stable disease or <PR

Horstmann, BA, McCabe, MS, Grochow, L, Yamamoto, S, Rubinstein, L, Budd, T et al. NEJM 352: 895-904, 2005
More of Our New Agents Are Being Used in Combinations (with pivotal trials using combination regimens)

1.

![Image of original article](image)

2. Patients HER2-positive metastatic breast cancer

<table>
<thead>
<tr>
<th>Combination</th>
<th>Med. Time to Prog.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cape + latap</td>
<td>8.4 months</td>
</tr>
<tr>
<td>cape</td>
<td>4.4 months</td>
</tr>
</tbody>
</table>

Geyer and colleagues NEJM 355: 2733-2743, 2006
Our Team Has Found A Phase I Clinical Trial Design which introduces combinations early, which provides more patient benefit and speeds the drug development process

The Complete Phase Ib Clinical Trial: A Method To Accelerate New Agent Development
Carmel D. Von Hoff 1,2, Jeffrey A. Nieves 2, Linde K. Vocila 1, Steven O. Wellman 1,3, Estelian Cytovac 5,6
1 Translational Genomics Research Institute (TGen), and Scottsdale Healthcare Clinical Research Institute, Phoenix and Scottsdale, AZ; 2 US Oncology Research, Translational Oncology Program, Houston, TX; 3 Institute for Drug Development, San Antonio, TX; 6 ARIAD Oncology, 4427 Le Klein Blvd, Bedford, France.

Abstract #2662

Background
- Tremendous use of combinations in clinical practice
- Response rates in first combinations in Phase I studies are nearly 10-fold greater (17.2% vs 1.6%) than for monotherapy regimens
- Need for rapid development of combinations
- Usually study combinations as separate studies
- Problems with serial development
- Problems with timing
- Problems with expense
- New study design could be beneficial

Methods
- Named Complete Phase Ib study
- All combinations are assessed in one trial
- Randomize for combination agents
- Pre-clinical data
- Clinical judgment
- Use full dose of standard agent
- Start at 1/3 MTWD of new agent then 2/3 MTWD, then MTWD of other agent
- 3:1 design

Results (cont)
- Noteworthy findings (cont)
- A majority of patients presenting to clinic are eligible for arm of the study
- Patients with no prior therapy are eligible
- Much greater chance of seeing antitumor activity for patients
- Parallel non-rational drug development
- Robust response (p≤5%)
- Timeline goals achieved

Conclusion
The Complete Phase Ib study conceptually a viable new option for developing drugs intended for use in combination.

References
1. Rostmann, E, et al. NEJM, 2006;352:556-60

Acknowledgement
We would like to thank the members of the US Oncology Translational Oncology Program (TO-P) for their dedication and perseverance in making this study design a success.

Von Hoff, DD, Nieves J, Vocila, L, and colleagues J Clin Onc (suppl) 25: no 18s, 112s, 2007
We Proposed the Complete Phase Ib Trial – All Combinations In One Trial

1. Begins when the phase I with the single new agent (NA) is just nearing completion

2. Trial design (combinations and sequencing based on preclinical, theoretical or clinical judgment)

   - New agent + docetaxel
   - New agent + gemcitabine
   - New Agent + bevacizumab
   - New Agent + sunitinib
   - New Agent + carbo + taxol
   - New Agent + new agent

Patients with advanced cancer goes on most appropriate therapy
The Complete Phase I Trial (cont’d.)

3. Specifics
   • Full dose of standard agent or completed phase I of new agent
   • Start at 1/3 MTD of new agent, then 2/3 MTD then MTD
   • 3 patients/level

4. Benefits
   • Parallel (not serial drug development)
   • Almost every patient walking into the clinic is eligible for an arm
   • Patients do not have as much prior treatment
   • Much greater chance of seeing antitumor activity for the patient

Speeds the development process
Our US Oncology Research Team Has Had A Very Favorable Experience With This Complete Phase Ib Approach

<table>
<thead>
<tr>
<th>Type of Agent</th>
<th>Number of Combinations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polyamine biosynthesis inhibitor</td>
<td>6</td>
</tr>
<tr>
<td>Cell adhesion inhibitor</td>
<td>3</td>
</tr>
<tr>
<td>Angiokinase inhibitor</td>
<td>2</td>
</tr>
<tr>
<td>Survivin inhibitor</td>
<td>4</td>
</tr>
<tr>
<td>DNA – minor groove binder</td>
<td>5</td>
</tr>
</tbody>
</table>

We have several more complete phase Ib trials lined up
Now What About the Topic Today?

“Screening for predictive markers”

Gordon Mills, MD, PhD
“Screening for Predictive Markers” is going to take a while

1. We need to help the patient with refractory cancer who is sitting in front of us now
2. The work on biomarkers is complicated
3. Our clinical research teams are focused on applying what we already know (mutations, deletions, etc.)
   - That is an important policy
   - This can do a lot of good - now
The Operating Principle (hypothesis) for Our Research Team

There is a clinical and/or genomic vulnerability which we can exploit now to improve a patient’s chance of benefiting from a particular therapy

• and we need to put a system in place to take advantage of that hypothesis–find that vulnerability – find the addictions of these tumors*

To Try to Ensure a Patient’s Chance for Clinical Benefit in our Phase I Clinic We Have Changed our Workup

1. The workup
   - history
   - Physical exam
   - Lab results
   - path; blood studies; x-rays and scans
   - Check performance status
   - Select treatment

2. We have rigorously added one additional step to our workup before recommending anything
   - Check for a Context of Vulnerability
   - Not just take the next agent to come along
The Oncologists’ Sixth Vital Sign Project

A research method using molecular medicine and bioinformatics to select the best therapy for an individual patient with advanced cancer.
Context of Vulnerability

1. Concept conceived/named by Dr. Spyro Mousses

2. Think of the context of vulnerability as the 6th vital sign which should be measured by oncologists

   - BP
   - Resp
   - pulse
   - performance status
   - temp
   - context of vulnerability

3. There are 2 different kinds of contexts of vulnerability

   • Clinical context of vulnerability
   • Genomic context of vulnerability

Von Hoff, Gray and Dragovitch Pursuing Therapeutics Targets That Are And Are Not There: A Tumor’s Context of Vulnerability, Seminars in Oncology 33: 367-368, 2007
Examples of Clinical Contexts of Vulnerability – To Help Select A Therapy

1. A man with non-seminomatous testicular cancer - curable

2. A patient with CML

3. Asian non-smoking woman with broncoalveolar carcinoma

4. 81 year old patient smoked for 72 years –his tumor can repair almost any DNA damage


A Terrific Example of a Genomic Context of Vulnerability – To Help Select a Therapy

EGFR Mutations in Lung Cancer: Correlation with Clinical Response to Gefitinib Therapy

J. Guillermo Paez,1,2* Pasi A. Jänne,1,2* Jefffrey C. Lee,1,2* Sean Tracy,1 Heidi Groesz,1,2 Stacey Gabriel,1 Paula Herman,1 Frederic J. Kaye,3 Neal Lindeman,1 Titus J. Boggong,1,2 Katsuhiko Naoki,1 Hidefumi Sasaki,1 Yoshitaka Fujii,2 Michael J. Eck,1,3 William R. Sellers,1,2,4 Bruce E. Johnson,1,2,4 Matthew Meyerson1,2,4

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*These authors contributed equally to this work.

Paez and colleagues Science 304: 1497-1500, 2004

Activating Mutations in the Epidermal Growth Factor Receptor Underlying Responsiveness of Non–Small-Cell Lung Cancer to Gefitinib

Thomas J. Lynch, M.D., Daphne W. Bell, Ph.D., Raffaella Sordella, Ph.D., Sarada Gurubhagavatula, M.D., Ross A. Okimoto, B.S., Brian W. Brannigan, B.A., Patricia L. Harris, M.S., Sara M. Hasserlat, B.A., Jeffrey G. Supko, Ph.D., Frank G. Haluska, M.D., Ph.D., David N. Louis, M.D., David C. Christiani, M.D., Jeff Settleman, Ph.D., and Daniel A. Haber, M.D., Ph.D.

Lynch and colleagues NEJM 350: 2129-2139, 2004
An Example of the 6th Vital Sign Approach

• using what we already know to help an individual patient
It’s 4:30pm On A Friday Afternoon

1. A new patient arrives for consultation and treatment recommendations
   - 24th patient of the day
   - You are the only partner in the office
   - Everyone wants to call it a day
   - You muster up your concentration skills, grab a diet coke and “go in”
1. A 31 year old man

2. Noted abdominal distention - CT scan showed a huge mass in the abdominal cavity – arising from the retroperitoneum
   - Invasion of right kidney, abdominal wall, small bowel - unresectable

3. Needle biopsy = myxoid liposarcoma

4. “What is your recommendation Doc?”
Patient’s Cat Scan
Pathology For This Patient
Now It’s Friday Afternoon – at 6PM – And It Is Very Appropriate To Invoke

The Oncologists’ 6th Vital Sign – A Context of Vulnerability

And not just start doxorubicin + dacarbazine (NCCN practice guidelines)
What Is The Context of Vulnerability For Our Patient With Myxoid Liposarcoma?

It is a genomic context of vulnerability.

Efficacy of trabectedin (ecteinascidin-743) in advanced pretreated myxoid liposarcomas: a retrospective study

Fedrica Grosso, Robin I. Jones, George D Demetri, Ian R Judson, Jean-Yves Blay, Axel Le Cesne, Roberta Sarafilippo, Paolo Casieri, Paolo Collini, Falmira Dileo, Carlo Sopravfico, Silvia Stacchioni, Elena Tamborini, Juan Carlos Tercero, Jose Jimeno, Maurizio D'incalci, Alessandro Granchi, Jonathan A Fletcher, Silvana Pilotti, Paolo G Casali

Summary

Background Previous studies have suggested that trabectedin (ecteinascidin-743) could have antitumour activity in soft-tissue sarcoma. We aimed to study the usefulness of trabectedin in the treatment of patients with myxoid liposarcomas, a subtype of liposarcoma that is associated with specific chromosomal translocations t(12;16)(q13;p11) or t(12;22)(q13;q12) that result in the formation of DDIT3-FUS or DDIT3-EWSR1 fusion proteins.

Methods 51 patients with advanced pretreated myxoid liposarcoma who started treatment with trabectedin between April 4, 2001, and Sept 18, 2006 at five institutions in a compassionate-use programme were analysed retrospectively.

Centralised radiological and pathological reviews were done for most patients. Trabectedin was given either as a 24-h continuous infusion or as a 3 h infusion, every 21 days, at 1–1.5 mg/m². 558 courses of trabectedin were given in total, with a median of ten courses for each patient (range 1–23). The primary endpoints were response rate and progression-free survival, and the secondary endpoint was overall survival.

Findings According to Response Evaluation Criteria in Solid Tumors (RECIST), after a median follow-up of 14.0 months (IQR 8.7–20.0), two patients had complete responses (CR) and 24 patients had partial responses (PR); the overall response was 51% (95% CI 36–65). Five patients had early progressive disease. In 17 of the 23 patients who achieved PR or CR as defined by RECIST and who had centralised radiological review, tissue-density changes, consisting of a decrease in tumour density on CT scan or a decrease in contrast enhancement on MRI (or both), preceded tumour shrinkage. Median progression-free survival was 14.0 months (13.1–21.0), and progression-free survival at 6 months was 88% (79–95).

Interpretation Trabectedin was associated with antitumour activity in this series of patients with myxoid liposarcoma.

The noted patterns of tumour response were such that tissue density changes occurred before tumour shrinkage in several patients. In some patients, tissue-density changes only were seen. Longlasting tumour control was noted in responsive patients. The compassionate-use programme is still ongoing. This analysis has resulted in the initiation of two prospective studies to assess the role of trabectedin in the treatment of patients with myxoid liposarcoma in preoperative and metastatic settings. Furthermore, the selective mechanism of action for trabectedin in this translocation-related sarcoma is being studied.
For Our Patient - An Incredible Context of Vulnerability

- Myxoid liposarcoma – the worst sarcoma (12-16 chromosomal translocations) t(12;16)

- ET743 – trabectedin; Yondelis*
  works in only 7% of all patients with sarcoma overall but in 97% of patients with myxoid liposarcoma

* Made by PharmaMar – approved by EMEA 4 weeks ago
0 \rightarrow +3c

Courtesy of Drs. Paolo Casali, Frederica Grosso and Jose Jimeno and *Lancet* published online June 21st 2007
Courtesy of Drs. Paolo Casali, Frederica Grosso and Jose Jimeno and *Lancet* published online June 21st 2007
Now You Know What You Must Get For This Patient:

ET743 (trabectedin; Yondelis) because it hits the patients’ tumors context of vulnerability

We have to get it for this patient
### Other Emerging (Incredible) Contexts of Vulnerability – Common In Sarcoma

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>Target</th>
<th>Agent(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ewings Sarcoma</td>
<td>IGFR 1</td>
<td>AMG479; CP751, 871</td>
</tr>
<tr>
<td>Ewings Sarcoma</td>
<td>PI3K (IGFR 1)</td>
<td>SF1126</td>
</tr>
<tr>
<td>Synovial cell sarcoma</td>
<td>T (x, 18) EGFR</td>
<td>Iressa/Tarceva</td>
</tr>
<tr>
<td>Chondrosarcoma</td>
<td>TRAIL</td>
<td>Trail interactive agent</td>
</tr>
</tbody>
</table>
## Other Vulnerabilities We Know About

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>Vulnerability</th>
<th>“go to agent”</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alveolar soft part sarcoma</td>
<td>Translocation (X;17)(p11.2;q25) results in ASPL/TFE3 gene fusion (same as papillary renal)</td>
<td>C-met inhibitor</td>
</tr>
<tr>
<td>Osteogenic sarcoma</td>
<td>C-met abnormalities</td>
<td>C-met inhibitor</td>
</tr>
<tr>
<td>Small blue round cell tumors – Ewing’s, osteosarcoma, neuroblastoma, desmoplastic small round cell, synovial</td>
<td>PDGFRα</td>
<td>PDGFR inhibitor</td>
</tr>
<tr>
<td>CML</td>
<td>Bcr-abl fusion protein</td>
<td>Gleevec</td>
</tr>
<tr>
<td>ALL</td>
<td>Bcr-abl fusion protein</td>
<td>Gleevec</td>
</tr>
<tr>
<td>CNL (chronic neutrophilic leukemia)</td>
<td>Bcr-able fusion protein</td>
<td>Gleevec</td>
</tr>
</tbody>
</table>
### Other Vulnerabilities We Know About (cont’d.)

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>Vulnerability</th>
<th>“go to agent”</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypereosinophilic syndrome</td>
<td>Mutation in PDGFRα and PDGFRβ</td>
<td>Gleevec</td>
</tr>
<tr>
<td>medulloblastoma</td>
<td>PDGFRβ, patched</td>
<td>Gleevec, hedgehog</td>
</tr>
<tr>
<td>GIST</td>
<td>C-kit receptor mutation</td>
<td>Gleevec, Sunitinib</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>TMPRSS2-ERG fusion gene (fused androgen receptor with ERG)</td>
<td>HDAC inhibitor reversing the phenotype</td>
</tr>
<tr>
<td>Castleman’s disease</td>
<td>Increased IL-6</td>
<td>CNTO 328</td>
</tr>
</tbody>
</table>

There is no place where these vulnerabilities are written down for access by busy clinicians
Improvement in Castleman’s disease by humanized anti-interleukin-6 receptor antibody therapy

Norihiro Nishimoto, Mitsuko Sasai, Yoshihito Shima, Masashi Nakagawa, Tomoshige Matsumoto, Toshikazu Shirai, Tadamitsu Kishimoto, and Kazuyuki Yoshizaki

Castleman’s disease, an atypical lymphoproliferative disorder, can be classified into 2 types: hyaline-vascular and plasma cell types according to the histologic features of the affected lymph nodes. The plasma cell type is frequently associated with systemic manifestations and is often refractory to systemic therapy including corticosteroids and chemotherapy, particularly in multicentric form. Dysregulated overproduction of interleukin-6 (IL-6) from affected lymph nodes is thought to be responsible for the systemic manifestations of this disease. Therefore, interference with IL-6 signal transduction may constitute a new therapeutic strategy for this disease. We used humanized anti-IL-6 receptor antibody (rhPM-1) to treat 7 patients with multicentric plasma cell or mixed type Castleman’s disease. All patients had systemic manifestations including secondary amyloidosis in 3. With the approval of our institution’s ethics committee and the consent of the patients, they were treated with 50 to 100 mg rhPM-1 either once or twice weekly. Immediately after administration of rhPM-1, fever and fatigue disappeared, and anemia as well as serum levels of C-reactive protein (CRP), fibrinogen, and albumin started to improve. After 3 months of treatment, hypergammaglobulinemia and lymphadenopathy were remarkably alleviated, as were renal function abnormalities in patients with amyloidosis. Treatment was well tolerated with only transient leukopenia. Histopathologic examination revealed reduced follicular hyperplasia and vascularity after rhPM-1 treatment. The pathophysiologic significance of IL-6 in Castleman’s disease was thus confirmed, and blockade of the IL-6 signal by rhPM-1 is thought to have potential as a new therapy based on the pathophysiologic mechanism of multicentric Castleman’s disease. (Blood. 2000;95:56-61)

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Molecular Cancer Therapeutics Has A New Section on Clinical/Genomic Contexts of Vulnerability

We are looking for contributions!

Dr. Razelle Kurzrock
Senior Editor

Spotlight on Clinical Response

p53 therapy in a patient with Li-Fraumeni syndrome

Neil Senzer,1,2 John Nemunaitis,1,2 Michael Nemunaitis,1,2 Jeffrey Lamont,2 Martin Gore,3 Hani Gabra,4 Rosalind Eales,5 Nayanta Sodha,5 Frank J. Lynch,5 Louis A. Zunzwein,7 Keratin D. Menander,7 Robert E. Sobol,7 and Sunil Chada7

1Mary Crowley Medical Research Center; 2Sammons Cancer Center, Baylor University Medical Center, Dallas, Texas; 3The Royal Marsden Hospital NHS Foundation Trust; 4Imperial College London Hammarassth Campus, London, United Kingdom; 5Institute of Cancer Research, Sutton, United Kingdom; 6Qualtek, Inc., Newton, Pennsylvania; and 7Inogen Therapeutics, Inc., Houston, Texas

molecular markers may prove useful in guiding future application of p53 tumor suppressor therapy. [Mol Cancer Ther 2007;6(5):1478–82]

Introduction

Li-Fraumeni syndrome is an inherited genetic disorder characterized by familial clustering of multiple malignancies predominantly including sarcomas, breast cancers, brain tumors, and other diverse neoplasms (1–3). In this syndrome, patients often develop multiple primary cancers typically with initial occurrence at a young age. The genetic basis of this syndrome is a germ-line mutation in the p53 gene (2, 4). In addition to pathogenesis, defects in p53-mediated apoptotic pathways contribute to the resistance of
It Is the Duty of Our Research Teams (National Cancer Policy Forum)

1. To identify and catalog and get the contexts of vulnerability (addictions) as rapidly as possible – a central database

2. To provide a place to measure a patient’s tumor for that context of vulnerability
   - a clearinghouse for characterization of a patient’s tumor (more on this later)

3. To obtain the agent which will work for the patient (if we have time)

So practices’ teams where > 80% of patients are seen can offer this special, intense, highly individualized therapy
Our Research Team’s Philosophy On Finding New Biomarkers

To find biomarkers – have to make it simpler

• find deletions/mutations which give genomic contexts of vulnerability
  - what are their addictions?
• Biomarker patterns etc. are great – will take longer
A tremendous number of these genomic contexts of vulnerability will be deletions or mutations
First, We Have to Keep Our Eyes and Ears Open to Add to Our List of 6th Vital Signs (Clinical/Genomic Contexts of Vulnerability)

**Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy**

Hannah Farmer1,2,*, Nuala McCabe1,2,*, Christopher J. Lord1,*, Andrew N. J. Tutt1,*, Damian A. Johnson1, Tobias B. Richardson1, Manuela Santarosa1,*, Krystyna J. Dillon1, Ian Hickson1, Charlotte Knights1, Niall M. B. Martin1, Stephen P. Jackson1,3, Graeme C. M. Smith1 & Alan Ashworth1,2

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3Guy’s Hospital, St Thomas’ Street, London SE1 9RT, UK
4RaDOS Pharmaceuticals Ltd, Cambridge Science Park, Cambridge CB4 0WG, UK
5Wellcome Trust and Cancer Research UK, Garden Institute of Cancer and Developmental Biology, and Department of Zoology, University of Cambridge, Tennis Court Road, Cambridge CB2 1QH, UK

*These authors contributed equally to this work.

Present address: Division of Experimental Oncology, ICG-IRCCS, Aviano 33081 PN, Italy

BRCA1 and BRCA2 are important for DNA double-strand break repair by homologous recombination1, and mutations in these genes predispose to breast and other cancers2. Poly(ADP-ribose) polymerase (PARP) is an enzyme involved in base excision repair, a key pathway in the repair of DNA single-strand breaks3. We show here that BRCA1 or BRCA2 dysfunction unexpectedly and profoundly sensitizes cells to the inhibition of PARP enzymatic activity, resulting in chromosomal instability, cell cycle arrest and subsequent apoptosis. This seems to be because the inhibition of PARP leads to the persistence of DNA lesions normally repaired by homologous recombination. These results illustrate how different pathways cooperate to repair damage, and suggest that the targeted inhibition of particular DNA repair pathways may allow the design of specific and less toxic therapies for cancer.

Farmer et al. Nature 434: 917-921, 2005
I Think the Most Important Abstract at ASCO This Year Was

1. Orally active PARP1 and PARP2 inhibitor KU-0059436
   - Inhibits base excision repair – a key pathway in repair of DNA single strand breaks

2. Remarkable responses in patients with BRCA1 and BRCA2 ovarian and breast cancer

3. The PARP inhibitor, which we currently have in clinical trials, INNO probably will work too!

Yap and colleagues  J. Clin Oncol (suppl) 25: No.18s, p145s Part I of II, 2007
### If A Person Is BRCA1 Mutation Carrier

<table>
<thead>
<tr>
<th>Sex</th>
<th>Type of cancer</th>
<th>% cumulative risk at age 70</th>
<th>Fold increase compared to overall population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>Breast</td>
<td>78</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Ovarian</td>
<td>50</td>
<td>29</td>
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<tr>
<td></td>
<td>Uterine</td>
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<tr>
<td></td>
<td>Fallopian tube</td>
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<td>All other cancer</td>
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<tr>
<td>Male</td>
<td>Breast</td>
<td>6</td>
<td>58</td>
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<tr>
<td></td>
<td>Prostate</td>
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<td>All other cancer</td>
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<tr>
<td>Female and Male</td>
<td>Colon</td>
<td>11</td>
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<tr>
<td></td>
<td>Pancreatic</td>
<td>4</td>
<td>3</td>
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<td></td>
<td>Lung</td>
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<td>Melanoma</td>
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<td></td>
<td>Gastric</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>All other cancers</td>
<td>14</td>
<td>--</td>
</tr>
</tbody>
</table>

Brose and colleagues *JNCI* 94: 1365-1372, 2002
Two Recent Science Discoveries at TGen

A transforming mutation in the pleckstrin homology domain of AKT1 in cancer

John D. Carpten1, Andrew L. Faber2, Candice Horns3, Gregory P. Denicola4, Stephen L. Briggs5, Christiane M. Robbins6, Gailen Horbitter7, Sophie Boguslawski8, Tracy Y. Moses9, Stephanie Savage10, Mark Uhlik11, Amin Lin6, Jian Du12, Yue-Wei Gian7, Douglas J. Zeckner13, Greg Tucker-Kolbog14, Jeffrey Touchman15, Ketan Patel16, Spiro Mouskos17, Michael Bittner18, Richard Schevitz19, Mei-Huei T. Lai20, Kerry L. Blanchard21 & James E. Thomas21

Although AKT1 (v-akt murine thymoma viral oncogene homologue 1) kinase is a central member of possibly the most frequently activated proliferation and survival pathway in cancer, mutation of AKT1 has not been widely reported. Here we report the identification of a somatic mutation in human breast, colorectal and ovarian cancers that results in a glutamic acid to lysine substitution at amino acid 17 (E17K) in the lipid-binding pocket of AKT1. Lys 17 alters the electrostatic interactions of the pocket and forms new hydrogen bonds with a phosphoinositide ligand. This mutation activates AKT1 by means of pathologic localization to the plasma membrane, stimulates downstream signaling, transforms cells and induces leukemia in mice. This mechanism indicates a direct role of AKT1 in human cancer and adds to the known genetic alterations that promote oncogenesis through the phosphatidylinositol-3-OH kinase/AKT pathway. Furthermore, the E17K substitution decreases the sensitivity to an allosteric kinase inhibitor, so this mutation may have important clinical utility for AKT drug development.

John Carpten, PhD

• AKT 1 kinase – a central member of the most frequently activated proliferation and survival pathway in cancer

• Identified a somatic mutation in human breast (5/61-5%), colorectal(13/51-6%) and ovarian cancer (1/50-2%)

- glutamic acid→lysine substitution at amino acid 17 (E17k) in the lipid binding pocket of AKT1 (not in catalytic domains)

- the mutation activates AKT1 by making it have a pathologic localization to the plasma membrane. Stimulates downstream signaling, transforms cells, induces leukemia in mice

- allosteric inhibitors are being designed – we are ready

Carpten et al. Nature (published on line)1-7, July 2007
A TGen Investigator Has:

1. Discovered an activating mutation for FGFR in endometrial cancer
   • Very low IC_{50} s for FGFR kinase inhibitor

2. FGFR inhibitors
   - BIBF1120
   - MP470
   - TKI258
   - others
Pancreatic Cancer is a Tumor With Multiple Genomic Vulnerabilities – The Second Project in Our P01 Grant is Predicated On:

The Genomic Contexts of Vulnerability include:

• Deletions
• Mutations
• Amplification
• Rearrangement (translocations)
• Aberrant methylation patterns
• Other genetic abnormalities

### List of Genes Deleted or Mutated in Pancreatic Cancer

<table>
<thead>
<tr>
<th>Genes</th>
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<th>Genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPC4*</td>
<td>MKK 4</td>
<td>PTEN</td>
</tr>
<tr>
<td>ras</td>
<td>MKP-3</td>
<td>MLH1</td>
</tr>
<tr>
<td>p16</td>
<td>Rb</td>
<td>FHIT</td>
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<tr>
<td>p53</td>
<td>ERCCB</td>
<td>others</td>
</tr>
<tr>
<td>MKD-3</td>
<td></td>
<td></td>
</tr>
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</table>

* Deleted in 54% of patients’ tumors
We Have Been Using Synthetic Lethal Screening Will Yield Agents Which Will Selectively Kill Tumor Cells With Specific Deletions/Mutations
Jim’s Flies (synthetic lethal screening) Will Yield Agents Which Will Selectively Kill Tumor Cells With Specific Deletions/Mutations
A Second Technique (Easier More Targeted) To Determine How To “Take Out” Pancreatic Cancer Cells With Deletions of DPC4

1. Small interference RNA (SiRNA)

2. Use Isogenic pair of BxPC3 pancreatic cell lines (one line with DPC4 deleted and one line with DPC4 replaced)

3. Use 19,000 different SiRNA’s to knockdown specific genes in both cell lines
   • determine which specific gene knockdown(s) kill DPC4 deleted pancreatic cancer cells
An Automated and Integrated Robotic System for High Throughput siRNA Transfections

Robotic Liquid Handling, Robotic Plate Management, 37C 5% CO₂ Incubation, Plate Reading, Q-RT-PCR, Scheduling Software
Requires Super Quality Control

Confirmation of siRNA Silencing of Genes in HeLa cells using Western Blot Analysis

<table>
<thead>
<tr>
<th>Cyclin D1 siRNA</th>
<th>GFP siRNA</th>
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<tr>
<td>No siRNA</td>
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<tr>
<td>5 nM siRNA</td>
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<td>50 nM siRNA</td>
</tr>
<tr>
<td>150 nM siRNA</td>
<td>150 nM siRNA</td>
</tr>
</tbody>
</table>

- Tubulin
- Cyclin D1
- GFP
Contexts: Two variants of the same cell line (BxPC3) with TWO states for DPC4 function

BxPC3/BxPC3_DPC4 siRNA Druggable Genome Screen

- DPC4/BxPC3 Ratio >1.5 Fold
- DPC4/BxPC3 Ratio >2.0 Fold

BXPC3-DPC4- +/-
What Is Of Incredible Interest As We “Map” How These SiRNA Gene Knockdowns Functionally Interact

It is encouraging that the lethal knockdowns are frequently in a master pathway (which could give us a unified method for “taking out” cells with the deleted DPC4 context of vulnerability)

This is the way to “screen for predictive markers”
Design of an Agent to “Take Out” Pancreatic Cancer Cells With Deletions (50% of Pancreatic Cancer)

1. Identification of an Agent Selectively Targeting DPC4 (Deleted in Pancreatic Cancer Locus 4)–Deficient Pancreatic Cancer Cells

H. Wang, H. Han, and D. D. Von Hoff

The Translational Genomics Research Institute, Phoenix, Arizona

2. Structure of UA62007

We Also Now Have A Drug to ATTACK Tumor Cells With Deleted or Mutated Ras

1. PRLX 93936 – A compound similar to erastin
   - Substantial activity in 23 of 27 tumor cell lines with activating mutations/deletions in ras pathway
   - No activity in any cell without genomic mutations/deletions in ras

RAS–RAF–MEK-dependent oxidative cell death involving voltage-dependent anion channels

Nicholas Yagoda1,*, Moritz von Rechenberg3,*, Elma Zašcanjor1,*, Andras J. Bauer1, Wan Seok Yang1, Daniel J. Fridman1, Adam J. Wolpaw1, Inese Smukste1, John M. Peltier1, J. Jay Boniface1, Richard Smith1, Stephen L. Lessnick2,*, Sudhir Sahasrabudhe1* & Brent R. Stockwell3,2

Therapeutics that discriminate between the genetic makeup of normal cells and tumour cells are valuable for treating and understanding cancer. Small molecules with oncogene-selective lethality may reveal novel functions of oncoproteins and enable the creation of more selective drugs. Here we describe the mechanism of action of the selective anti-tumour agent erastin, involving the RAS–RAF–MEK signalling pathway functioning in cell proliferation, differentiation and survival. Erastin exhibits greater lethality in human tumour cells harbouring mutations in the oncopogenes HNRAS, KRAS or BRAF. Using affinity purification and mass spectrometry, we discovered that erastin acts through mitochondrial voltage-dependent anion channels (VDACs)—a novel target for anti-cancer drugs. We show that treatment of cells harbouring oncogenic RAS causes the appearance of oxidative species and subsequent death through an oxidative, non-apoptotic mechanism. RNA-interference-mediated knockdown of VDAC2 or VDAC3 caused resistance to erastin, implicating these two VDAC isoforms in the mechanism of action of erastin. Moreover, using purified mitochondria expressing a single VDAC isoform, we found that erastin alters the permeability of the outer mitochondrial membrane. Finally, using a radio-labelled analogue and a filter-binding assay, we show that erastin binds directly to VDAC2. These results demonstrate that ligands to VDAC proteins can induce non-apoptotic cell death selectively in some tumour cells harbouring activating mutations in the RAS–RAF–MEK pathway. Two compounds (nos 21,000 and 24,000, respectively) identified on the basis of their affinity for purified mitochondrial two-pronged approach to define the mechanism, involving, first, a suppressor screen to identify annotated compounds that prevent erastin-induced cell death and, second, an affinity purification approach to identify proteins that mediate the activity of erastin. First, we performed a suppressor screen using a library of about 2,000 biologically active compounds7 and found that antioxidants (α-tocopherol, butylated hydroxytoluene and β-carotene) prevent erastin-induced death (Fig. 1d, Supplementary Fig. 3). Moreover, we detected generation of an oxidizing species in response to erastin treatment in BJ-TERT/LT5ST/RAS12 cells, but not in isogenic BJ-TERT cells (Fig. 1e, Supplementary Fig. 4). Finally, we found that erastin-induced death in the HT-1080 fibrosarcoma cell line was also suppressed by antioxidants (Supplementary Fig. 5).

To characterize the mode of erastin-induced cell death, we looked for features of well characterized death pathways. We determined that the oxidizing species generated in BJ-TERT/LT5ST/RAS12 cells in the presence of erastin emanate from mitochondria (see Supplementary Discussion), consistent with the perturbation in mitochondrial morphology. We discovered that the oxidizing species do not cause poly(ADP-ribose) polymerase 1 (PARP1) cleavage (Fig. 1f, Supplementary Fig. 6), cytochrome c release from mitochondria (Fig. 1g), or pro-caspase-3 cleavage (Fig. 1h)7,8—all of which are hallmarks of apoptosis, a stereotypical form of cell death activated by many antitumour agents5,9,10 as well as by staurosporine (Fig. 1f–h). Moreover, we looked for these hallmarks in four different cell lines sensitive to erastin—namely, shown activation of these proteins (Fig. 1h). Other

Erastin takes out KRAS mutated cell by acting through mitochondrial voltage dependent anion channel (VDAC) – a novel target – causes the appearance of oxidative species and subsequent cell death through an oxidative non-apoptotic mechanism
Finally the Ultimate In A Context of Vulnerability – An Incredible Target for Patients With This Tumor

Note: Loss of *patched* function or gain of *smoothened* function is common in basal cell carcinoma (basal cell nevus syndrome [Gorlin’s Syndrome])
An Antagonist of Hedgehog Signaling Pathway Which Came Our Way – Involved In Development of Structures – Could Be Active Against Basal Cell Carcinoma

Pancreas, breast, brain, lung, colon, gastric, prostate, and in stem cell, others.
We Have All Been Waiting for Hedgehog Antagonists
Control the Situation

Instead of “screening for predictive markers”

• get the markers (e.g. DPC4 deletion, mutated ras)

• then design the drug to take out cells with the marker
Now It Is the Duty

1. To identify and catalog and get the contexts of vulnerability as rapidly as possible
   - Oncologists’ 6th vital sign

2. To provide a place to measure a patient’s tumor for that context of vulnerability
   - a clearinghouse for characterization of a patient’s tumor
However “Houston We Have a Problem”

There is absolutely no place in this country or any other country for a patient’s tumor to be sent

• for assessment of all possible targets in their tumor for which we already have a therapeutic against their tumor (e.g. ER, CD25, etc)

• to assess for targets for which we have a promising new agent (e.g. HSP90, Chk1)

[note these targets might be quite rare 1-2 percent of patients – have to screen a great number of patients] - e.g. 1-2% of patients will go on to a particular phase I trial
What we really need to be developing for our patients is a central place or places to have their tumors sent to have them assayed

• clearinghouses for targets, patterns, etc.
• patients’ tumors can be sent to clearinghouse for that service
• give patients an opportunity to enroll on Phase I or Phase II trials requiring enriched populations

In US Oncology Research we have set up such a clearinghouse
We Now Have a Central Place In Phoenix to Have
our Patients’ Tumors Sent to have them Assayed (a
clearing house for targets)

1. Tumors assayed for all targets
   for which we have new therapeutics
2. The Tissue Banking and Analysis Center (TBAC)

US Oncology and Molecular Profiling Institute Enter Venture to Accelerate the
Development of Personalized Cancer Treatments

By: US Oncology Corporate Communications

(Houston and Phoenix, August 4, 2006) US Oncology, a leading national cancer treatment and research
network, has entered into a venture with the Molecular Profiling Institute, Inc. (Molecular Profiling), a
laboratory respected for its genomic and proteomic profiling, to create the Tissue
Banking and Analysis Center, Inc. (TBAC).
The US Oncology Research Team

- 660 community medical oncologists
- 145 radiation oncologists
- 33 gynecological oncologists

- Sees > 17% of all patients with cancer in the US
- A spectacular group of colleagues very devoted to clinical research

We have special targeted phase I and Phase II trials – we needed a central place to measure targets – to give patients option of participating in targeted trials – have their tumors assayed for multiple targets – e.g. ZAP70 in CLL
Multiple such clearinghouses need to be established – in the world – the need will be great

1. USA

John Niederhuber, MD, NCI

2. World

Andrew Von Eschenbach, MD, FDA

Should also be talking with Dr. Janet Woodcock

3. Someone please get such a clearinghouses up and running!
Having This TBAC Clearinghouse Has Allowed Us to Reach One More of Our USON Research Goals

To conduct a clinical trial which will be a model for approval of a new agent for a target in a patient’s tumor rather than for a particular histologic type of cancer
New Clinical Trial Design for Evaluating an Agent Against a Target Rather Than Against a Tumor Type

1250 patients with endometrial, pancreas, NSCLC, colon, bladder, etc. evaluated for specific FGFR mutations

250 patients positive for specific FGFR mutation

All treated with new agent

CR and PR (continue agent)

Stable x 4 months

continue agent

Progression – off study

D/C

Such trials are ongoing
Finally, Present Some Ongoing Work

To try to improve a patient’s chance of responding to an agent

- Perhaps one can use currently available molecular techniques (profiling) to find a tumor’s genomic context of vulnerability
Again Everything Begins with our Individual Patients

1. Our patient
   - 51 year old patient with adenoid cystic cancer of the head and neck area

2. Prior therapy
   - surgery, radiation therapy, multiple chemotherapy regimens

3. Refractory metastatic disease in lung

4. Since there is no standard therapy option for this patient
   - best supportive care
     (take care of pain, dyspnea)
   - a new agent in a phase I trial

5. Patient wanted to keep fighting her disease (like she had been doing)

What could we offer to give her a chance for clinical benefit — fix what is bothering her
To Improve a Patient With Refractory Cancer Chances of Responding to an Agent, Our Phase I Effort Has Evolved Into:

Trying to determine whether or not molecular profiling of a patient’s tumor might help provide some clinical benefit for individual patients referred to our phase I clinical trial program

Would we see genomic contexts of vulnerability?
Our Approach to Test the Hypothesis That We Can Do Better By Profiling Patients’ Tumors – 2 Sequential Studies

1. Performed a pilot trial to see how often targets are present in patients referred for phase I studies whose tumors have progressed on all standard therapies (logistics, sample size etc.)

- Target Now

2. Performing a prospective clinical trial – Bisgrove Trial
To Try to Address This Hypothesis – Fortunate to Have

Translational Genomics Research Institute (TGen)

Clinical Arm of TGen – Scottsdale Healthcare– Home of the Arizona Cancer Center Greater Phoenix Area
Utilizing Every Approach We Have To Find Individual Targets In Individual Patient’s Tumors (through CLIA certified lab pathologist directed)

1. Immunohistochemistry

2. Microarray

3. CGH Array
Methods for the First “Target Now” Study

1. 112 patients who were being referred for phase I studies (had exhausted conventional chemotherapy options and were undergoing procedures for a cancer-related matter (e.g. ascites, obstruction)

2. Patients tissues submitted for molecular profiling in 2 formats
   - Recently obtained paraffin embedded tumor samples submitted for immunohistochemistry (IHC)
   - Frozen tumor samples processed for oligonucleotide microarray (OMA)
1. IHC evaluated 13 possible targets for which we had potential therapies

- Androgen Receptor
- BCL-2
- CD20
- CD25
- CD52
- c-Kit
- Cox-2
- cyclin D1
- EGFR (not sequenced)
- ER
- Her2/neu
- PDGFR
- PR

- A positive was assessed based on ≥ 2+ strong which was pervasive (≥ 30% of tumor cells stained)
2. Oligonucleotide microarray

- Tumor samples not microdissected
- 2 color oligonucleotide microarray with 17,089 unique probes with attention to the 51 probes for which we had a potential therapeutic agent
  - same targets as for IHC
  - VDR
  - GARFT
  - VEGFR
  - ADA
  - ZAP70
  - ERCC1
  - VHL
  - Asparagine synthase
  - Etc

- A gene expression was judged to be significantly different from its normal reference tissue based on change in the level of $p \leq 0.001$
The Target Now Study

Frequency of Potential Therapeutic Targets Identified by Immunohistochemistry (IHC) and DNA Microarray (DMA) in Tumors from Patients who have progressed on multiple therapeutic agents

Michael Bittner, PhD, Robert Penny, MD, PhD, Johanna Gardner, CTR, Sondsoles Shack, BS, Liz Campbell, OCN, RN, Darin Taverna, PhD, Mitesh Borad, MD, Richard Love, NSE, Jeffrey Trent, PhD, and Daniel D. Von Hoff, MD

Translational Genomics Research Institute (TGen), Phoenix, Arizona; Scottsdale Healthcare Clinical Research Institute, Scottsdale, Arizona; and Molecular Profiling Institute (MPI), Phoenix, Arizona

Abstract # 3071

An important question that arises while treating patients enrolled in phase I clinical trials is: If one enrolls that patient's tumor carefully enough, would there be enough information on which to base decisions regarding a potential new drug that might be better than trying the phase I agent? To address this issue, we have performed IHC assays for up to 10 target antigens (VHL, HER2, ER, Cdk 4, CD31, CD34, CD117, CD68, Ki-67, and PD-L1) on all patient tumors in the phase I clinical trials at the TGRN and the DCCG. Immunohistochemistry (IHC) data were analyzed for determination of target antigen expression using a panel of validated antibodies and image analysis software. These data provide insight into the frequency of targeted tumors that might benefit from specific immunotherapeutic or targeted therapies.

Results Summary

A. A central processing of patient/tumor by IHC and DMA can be accomplished with excellent quality. IHC
B. One can combine both types for potential targets in tumors to provide new progression or therapeutic options
C. This approach has potential for identifying targets in patient tumors who are enrolled for phase I clinical trials
D. Whether this methodology will improve patient outcomes of having clinical benefit from a protocol approach remains to be addressed by a prospective intervention study.

Methods

IHC
- Over 100 patients and tumors from the phase I clinical trials were analyzed
- The large TGen tumor repository includes over 10,000 patients

Results
- Overall, the frequency of tumors with high expression levels of specific target antigens varies widely
- For example, HER2 is expressed in approximately 10% of tumors, while VHL is expressed in over 50% of tumors

IHC Results

Microarray Results

Background

The Target Now Study

Surprising Results from the Target Now Study (in patients referred for new agent phase I trials)

1. 112 patients tumors submitted (all had good RNA)

2. On IHC
   - An average of 1.6 targets/patient (range 0-5) for which a conventional therapeutic agent was available
   - 74% of patients had at least one potential target identified

3. On microarray
   - An average of 11 targets/patient (range 0-14)
   - 99% of patients had at least one potential target identified (for a potential therapeutic agent)

Note: we basically always find a potential target in every patients’ tumor
Although Not a Specific Aim of the Study of course the Profiling Results Were Made Available to the Patients and their Physicians – normally would go on a phase I agent but tried a standard agent first

1. The patients treatment was not systemically based on results from “Target Now”

2. Several examples of feedback from patients’ physicians

   • Patient with advanced ovarian cancer progressed on 4 prior regimens
     - ER found as target and patient treated with tamoxifen

   • Patient with advanced metastatic ovarian cancer previously on 4 prior regimens
     - PDGFR found as a target and patient treated with imatinib

   • Patient with advanced adenoid cystic cancer of head and neck
     - GARFT as a target (patient treated with pemetrexed)
The Results for Dr. Stephenson’s Patient

Before Pemetrexed

After Pemetrexed

After Pemetrexed
Multiple Patients In Which We Had No Idea What to Try For Them – and They Have Had Very Remarkable Responses

1. Dr. Charles (Terry) S. White – Dallas – patient with inflammatory myofibroblastic tumor responded to imatinib

2. Dr. Lon Smith - San Antonio – patient with chordoma a remarkable response to sunitinib

3. Multiple others

These are anecdotes, but they have been remarkable to those taking care of these individual patients
But There Have Also Been Some Dramatic Failure Anecdotes

48 year old woman with advanced previously treated colorectal cancer whose tumor had progressed on multiple prior therapies. Biopsy demonstrated PDGFR as a target both by IHC and microarray – treated with sunitinib

Baseline 11/5/16

Post treatment 2/16/07

The patients and their tumors have complex contexts of vulnerability
<table>
<thead>
<tr>
<th>Targets that are there</th>
<th>Targets that “are not there” (deleted or mutated) may sensitize to an agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estrogen receptor</td>
<td>ERCC1</td>
</tr>
<tr>
<td>Progesterone receptor</td>
<td>Asparagine synthase</td>
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<tr>
<td>Her2/neu</td>
<td>MGMT</td>
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<td>EGFR</td>
<td>MLH1/MSH2</td>
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<td>CD52</td>
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<td>ERCC3</td>
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<td>MTAP</td>
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<td>TOP2B</td>
<td>Fanc1A</td>
</tr>
<tr>
<td>VEGF</td>
<td>BRCA1/2*</td>
</tr>
<tr>
<td>Others</td>
<td>Others</td>
</tr>
</tbody>
</table>

Yap and colleagues, J. Clin. Oncol. 25: No18s, pg 145s, 2007
In Summary, A Key Finding from the “Target Now” Study

1. Even patients with a history of extensive prior treatment have tumors which can harbor targets for which we have conventional agents

2. Therefore we could say that for future patients who are candidates for phase I studies we should make more of an all out effort to assay for targets in these patients’ tumors before contemplating offering them a phase I trial – look at the 6th vital sign – context of vulnerability

   - but we needed a prospective trial before suggesting something so radical
A Study Utilizing Molecular Profiling of Patients’ Tumors to Find Potential Targets and Select Treatment for their Refractory Cancers

The Bisgrove Trial
May Debi Rest in Peace but Her Determination Continue

Debi Bisgrove, 54, leaves a legacy of humanity that will carry on her memory for generations to come. For those who knew her, Debi's passing on January 3, 2007, following a courageous battle with colon cancer, leaves an absence that cannot be filled. She will be remembered for her vivacious character, sincere and warm personality, and gentle and compassionate outlook on life.

Debi approached life with outstretched arms and a ready hug for everyone from every walk of life. She was a woman of tremendous dignity and a woman to be admired--an angel walking among us, a princess of compassion, an adoring "Mama Babe" to her son, a source of endless maternal inspiration to her daughters, and a loving "Mimi" to her seven grandchildren. She was many things to many people yet she had only one hero, her husband, Jerry.

For 20 years, they have been the perfect complement, a true bringing together of hearts and souls.

Debi has been a champion for many causes and described as an "essence of humanity." Together with Jerry, many organizations benefited from their generous contributions. They also were graced by her enthusiasm for stepping into blue jeans and strapping on a tool belt so she could use her hands and her heart to make a difference.

In recent years, she was most passionate and involved with the ASU Foundation, Arizona Humane Society, the Debi and Jerry Bisgrove Cancer Research Pavilion at Scottsdale Healthcare, the Southwest Autism Research & Resource Center, The Bisgrove Clinical Trials, The Wellness Center, Translational Genomics Research Institute, Woman in Philanthropy and the Valley of the Sun United Way.

Her unbridled passion for family and friends and her philanthropic commitment are legacies she left in the physical life and will carry on in the spiritual. Debi, born December 9, 1952, is survived by her husband, Jerry; four children, Niki Cocuzza and Kris Wall of Scottsdale, Christy Holdofehr of Allendale, NJ, and Megan Bisgrove of Ridgewood, NJ; and seven grandchildren.
<table>
<thead>
<tr>
<th>Institution</th>
<th>Site</th>
<th>Investigator(s)</th>
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<tbody>
<tr>
<td>Scottsdale Clinical Research Institute</td>
<td>Scottsdale, AZ</td>
<td>Mitesh Borad, MD</td>
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<tr>
<td>Cancer Centers of the Carolinas</td>
<td>Greenville, SC</td>
<td>Joe Stephenson, MD</td>
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<td>Peter Rosen, MD</td>
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<td>Oncology Specialties</td>
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<td>Jeremey Hon, MD</td>
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<td>South Texas Hem/Onc</td>
<td>San Antonio, TX</td>
<td>Lon Smith, MD</td>
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<tr>
<td>Mayo Clinic-Scottsdale</td>
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<td>Tom Fitch, MD</td>
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<td>Central Indiana Cancer Centers-South</td>
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<td>David Loesch, MD</td>
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<tr>
<td>Cedars Sinai</td>
<td>Los Angeles, CA</td>
<td>David Agus, MD</td>
</tr>
<tr>
<td>Tyler Cancer Center</td>
<td>Tyler, TX</td>
<td>Don Richards, MD, PhD</td>
</tr>
</tbody>
</table>
Primary Study Objective

To compare the time on therapy (TOT) using a treatment regimen selected by molecular profiling versus TOT for the most recent regimen the patient had just progressed on

- Use 2 molecular profiling methods
  - IHC – 14 targets
  - oligomicroarray – 58 targets
- algorithms are more complicated than originally thought
Study Schema

Patient with advanced refractory cancer, progression on at least two previous treatment regimens

After informed consent, biopsy tumor

Microarray and IHC analysis

Target Found? [Diamond]

YES

Treatment based on target found

Follow-up every eight weeks

Primary Endpoint: Time patient is on therapy (compared to time patient was on therapy on which their tumor had just progressed).

NO

Treatment based on empirical basis

Follow-up every eight weeks
Details On Endpoint for Bisgrove Trial

1. Usually the period of time a patient is on successive therapies is progressively shorter

2. | Period A-TOT | Period B-TOT |
   | just prior therapy | therapy selected by molecular profiling |

3. If period B is greater than period A, the profiling-selected therapy has changed the natural history of the patient’s disease

4. If 30% of patients on this Bisgrove trial have period B longer than period A = molecular profiling helps

Robert Temple - A regulatory authority’s opinion about surrogate endpoints. Clinical measurement in drug evaluation. Edited by Ws. Ninano and G.T. Thicker John Wiley and Sons Ltd. 1995. - an “n” of one

Von Hoff, D.D., There are no bad antitumor agents only bad clinical trial designs. Clin Can Res. 4: 1079-1086, 1998
1. 184 patients

2. Started November 2006
   • Patients on study as of 9/14/07 (n=69)

Note: A terrific prospectively collected data set – a model in which to study biomarkers
The Bisgrove Trial is Looking for Targets In Patients’ Tumors for Which We Already Have Standard Anticancer Agents

If the results from this trial are promising

- we will have to rethink the eligibility criteria for a patient entering a particular phase I trial
- Can we improve patients’ chances of getting something that will help them more by profiling their tumor?
In Conclusion

1. Discovery and use of biomarkers is tough in drug development
   - But we should not be paralyzed by that because there are already described contexts of vulnerability

2. We should focus on contexts of vulnerability that are deletions/mutations/translocations
   - Probably easier to find with CGH, SiRNA
   - Probably more dramatic results
   - Possibly smaller trials
   - Better control of the situation
     - have a known genetic abnormality (predictive marker) then we find the drug
3. It is very feasible to molecular profile nearly all patients’ tumors who are candidates for phase I trials
   • Perhaps this approach will find a genomic context of vulnerability for them (this is under prospective study)

4. We need clearinghouses where patient tumors can be sent
   • To assay patients tumors for their context of vulnerability
Thank You Again for Inviting Me to Give This Presentation

Always remember the Oncologists’ 6th Vital Sign - Context of Vulnerability
ACCELERATING ONCOLOGY CLINICAL TRIAL ENROLLMENT IN COMMUNITY-BASED PRACTICES: JUST-IN-TIME APPROACH

ABSTRACT

Background: ACCONTs (approved clinical oncology trial enrollment) is a key bottleneck in the achievement of new cancer treatments. This is due to the need for site activation and onboarding, which can require several months. The Just-in-Time (JIT) approach to clinical trial site activation is a promising solution to this problem. JIT aims to reduce the time and resources needed to activate sites by focusing on the most critical activities.

OBJECTIVES

- To evaluate the implementation of JIT in community-based practices
- To compare enrollment rates between traditional site activation and JIT approach

METHOD: TRADITIONAL SITE ACTIVATION

- Protocol review, feasibility, and budget
- Regulatory documents, contract, budget
- Site Initiation Visit
- Study material shipment
- Consent, access, enroll patients

METHOD: JUST-IN-TIME SITE ACTIVATION

- Protocol review, feasibility, JIT protocol
- Regulatory documents, contract, JIT budget
- Site Initiation Visit
- Study material shipment
- Consent, access, enroll patients

RESULTS

<table>
<thead>
<tr>
<th>Traditional</th>
<th>JIT</th>
</tr>
</thead>
<tbody>
<tr>
<td># of Oncology practices approached with protocol</td>
<td>66</td>
</tr>
<tr>
<td># of sites JIT trained &amp; pre-identifying potential subjects</td>
<td>38</td>
</tr>
<tr>
<td># of sites opened with IRB</td>
<td>8</td>
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<tr>
<td>Business days (avg.) from patient ID to IRB approval</td>
<td>2.75</td>
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<tr>
<td>Business days (avg.) from IRB approval to patient enrolled</td>
<td>3</td>
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<tr>
<td>Weeks from project start to last patient enrolled</td>
<td>46</td>
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<tr>
<td>Weeks from project start to last JIT (50%) patient enrolled</td>
<td>34</td>
</tr>
</tbody>
</table>

DISCUSSION

To test the JIT approach, Pharmatech applied it to a study targeting an advanced stage of a rare cancer. The results showed a significant decrease in the time needed to activate sites and enroll patients compared to traditional approaches.

CONCLUSIONS

- Increased site activation efficiency:
  - Minimized need for enrollment feasibility assessment
  - Increased number of patients enrolled
  - Increased site activation rate
  - Increased site activation within the specified timeframe
  - Reduced site activation costs
- Increased patient enrollment:
  - Increased site enrollment rate
  - Increased patient accrual

The JIT approach was found to be effective in accelerating clinical trial site activation and enrollment, leading to faster patient recruitment and reduced costs.