Thirty First Annual Symposium
August 27-28, 2010

This Activity is jointly sponsored by Wake Forest University School of Medicine and the Piedmont Oncology Association

2011 Meeting Dates

March 25, 2011– Spring POA Meeting
Grandover Resort and Conference Center, Greensboro, North Carolina

September 16-17, 2011
Marina Inn at Grande Dunes, Myrtle Beach, South Carolina
The Piedmont Oncology Association
31st Annual Symposium

Grove Park Inn
Asheville, North Carolina

August 27-28, 2010

CREDIT

CME
The Wake Forest University School of Medicine designates this educational activity for a maximum of 8 AMA PRA Category 1 Credit(s)™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

CNE
This meeting is approved for a maximum of 8 contact hours. Each participant should claim only those credits that he/she actually spent in the activity.

ACCREDITATION STATEMENTS

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education through the joint sponsorship of Wake Forest University School of Medicine and the Piedmont Oncology Association. The Wake Forest University School of Medicine is accredited by the ACCME to provide continuing medical education for physicians.

The Section on Hematology and Oncology, Comprehensive Cancer Center of Wake Forest University is an approved provider of continuing nursing education by North Carolina Nurses Association, an accredited approver by the American Nurses Credentialing Center's Commission on Accreditation.
Piedmont Oncology Association 31st Annual Symposium

August 27-28, 2010

Faculty List

Kenneth Anderson, MD
Kraft Family Professor of Medicine
Dana Farber Cancer Institute

Sage Bolte, PhD, LCSW, OSW-C
Oncology Counselor, Life with Cancer
Inova Cancer Services

Leslie Ellis, MD
Assistant Professor
Section on Hematology and Oncology
Wake Forest University Baptist Medical Center

Matthew Farber
Director
Provider Economics & Public Policy, Association of Community Cancer Centers

Matthew Galsky, MD
Director
Genitourinary Medical Oncology Program
Mt. Sinai Medical Center/Trish Cancer Institute

John Owen, MD
Professor
Section on Hematology and Oncology
Wake Forest University Baptist Medical Center

David Lawson, MD
Associate Professor
Hematology and Oncology
Emory University Hospital

Rogerio Lilenbaum, MD
Director
Thoracic Oncology Program
Mt. Sinai Comprehensive Cancer Center

Kathleen Wesa, MD
Assistant Attending Physician
Integrative Medicine Services
Memorial Sloan-Kettering Cancer Center

Planning Committee

Bayard L. Powell, MD
Chair

Antonius Miller, MD
Program Chair

Lisa Hodges, RN, BSN, OCN
Nursing and CRA Subcommittee Chair

Debbie Olson
POA Administrator
Faculty and Planning Committee Disclosure

As an accredited CME provider, Wake Forest University School of Medicine requires that its speakers comply with the ACCME Standards for Commercial Support of CME. All speakers have been asked to disclose any significant financial interest or relationship that they may have with the manufacturer(s) of any commercial product/service that is discussed as part of their presentation. Their responses are listed below. The commercial support standards also require that their presentation be free of commercial bias and that any information regarding commercial products or services be based on scientific methods generally accepted by the medical community. When discussing therapeutic options, they have been asked to use only generic names. If it is necessary to use a trade name, than those of several companies are to be used. Further, should their presentation include discussion of any unlabeled/investigational use of a commercial product, they are required to disclose that information to the audience.

In the spirit of full disclosure, the following information is provided to all attendees:

Dr. Kenneth Anderson has research activities funded by Celgene, Novartis, and Millennium. He also serves on the following speaker's bureaus: Celgene and Millennium.

Ms. Sage Bolte has research activities funded by the American Cancer Society. She also serves on the following speaker's bureau: Genentech.

Dr Leslie Ellis serves on the following speaker's bureau: Genentech.

Mr Matthew Farber has nothing to disclose.

Dr Matthew Galsky has research activities funded by Pfizer and Novartis. He also serves on the following speaker's bureaus: Novartis and Myriad.

Dr David Lawson serves as a consultant for Genzyme.

Dr Rogerio Lilienbaum serves as a consultant for Genentech and Abraxis.

Dr John Owen has nothing to disclose.

Dr. Kathleen Wesa has nothing to disclose.

Dr. Bayard Powell has research activities funded by Celgene, Novartis, Wyeth, Genzyme Oncology, Amgen, Cell Therapeutics, Millennium, Xanthus, and Structural Genomixs. Dr Powell has received honorarium from Genzyme and Cephalon.

Dr. Antonius Miller has nothing to disclose.

Lisa Hodges, RN, BSN, OCN serves on the following speaker's bureau: Cephalon, Novartis and Millennium.

Debbie Olson has nothing to disclose.
The registration fees for this Meeting have continued to remain low. This is possible due to the support provided by our pharmaceutical and home care company representatives through educational grants and exhibitor fees.

**Educational Grants**

Celgene  
Cephalon  
Genzyme  
Bristol Myers Squibb Oncology  
ICU Medical

We invite and encourage you to visit these representatives and their displays located in Grand Ballroom A

Abraxis Oncology
Allos Therapeutics, Inc  
Amgen  
AstraZeneca Pharmaceuticals  
Bayer Pharmaceuticals  
Biogen Idec  
Biologics  
Bristol-Myers Squibb Oncology  
Celgene  
Centocor Ortho Biotech  
Cephalon  
Eisai, Inc  
Genentech, Inc  
Genomic Health  
Genzyme  
GlaxoSmithKline  
ICU Medical  
Lilly Oncology  
Merck Oncology  
Millennium  
Novartis Pharmaceuticals Hematology Division  
Novartis Pharmaceuticals  
OSI Pharmaceuticals  
Pfizer  
Sanofi-Aventis  
Sirtex Medical  
Spectrum Pharmaceuticals
Friday, August 27, 2010

7:15 AM  
SCCC Annual Meeting Breakfast  
Coolidge DE

7:15 AM  
Continental Breakfast and Exhibits  
Grand Ballroom A

Session I  
Eisenhower FG

8:00 AM  
Welcome & Remarks  
Bayard Powell, MD

8:10 AM  
Prostate Cancer Update  
Matthew Galsky, MD

9:10 AM  
Healthcare Reform and Regulatory Trends  
Matthew Farber

10:10 AM  
Break and Exhibits  
Grand Ballroom A

Session II  
Grand Ballroom B

8:00 AM  
Welcome & Remarks  
Lisa Hodges, RN, BSN, OCN

8:10 AM  
The Sexual Self of Cancer Survivors: Assessing and Addressing Sexuality in Persons with Cancer  
Sage Bolte, PhD, LCSW, OSW-C

10:10 AM  
Break and Exhibits  
Grand Ballroom A

General Session  
Grand Ballroom B

10:40 AM  
Fundamentals of Coagulation  
John Owen, MD

11:40 AM  
Update in Myeloma Therapy  
Kenneth Anderson, MD

12:40 PM  
Adjourn

6:30 PM  
Sport’s Night Dinner and DJ  
Skyline Mountain View Terrace
Agenda

Saturday, August 28, 2010

7:00 AM  SCCC Community Leaders’ Breakfast Meeting
          Eisenhower FG

7:15 AM  Breakfast and Exhibits
          Grand Ballroom A

General Session
          Grand Ballroom B

7:50 AM  Welcome And Remarks
          Bayard Powell, MD

8:00 AM  Individualized Management of Advanced Non-Small Cell Lung Cancer Patients
          Rogerio Lilenbaum, MD

9:00 AM  Management Strategies for the Metastatic Melanoma Patient
          David Lawson, MD

10:00 AM Break and Exhibits
          Grand Ballroom A

10:30 AM POA Business Meeting

10:45 AM Chronic Lymphocytic Leukemia: Novel Agents and Available Chemotherapy Regimens
          Leslie Ellis, MD

11:45 AM Integrative Oncology-Complementary Therapies During and After Cancer Treatment
          Kathleen Wesa, MD
Prostate Cancer Update

Matthew D. Galsky, MD
Director, Genitourinary Medical Oncology Program
Tisch Cancer Institute
Mount Sinai School of Medicine

Demographics

<table>
<thead>
<tr>
<th>Incidence</th>
<th>Cause of Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melanoma of Skin</td>
<td>Esophagus</td>
</tr>
<tr>
<td>Oral Cavity &amp; Pharynx</td>
<td>Lung &amp; Bronchus</td>
</tr>
<tr>
<td>Lung &amp; Bronchus</td>
<td>Pancreas</td>
</tr>
<tr>
<td>Pancreas</td>
<td>Stomach</td>
</tr>
<tr>
<td>Colon &amp; Rectum</td>
<td>Liver &amp; Bile Duct</td>
</tr>
<tr>
<td>Kidney &amp; Renal Pelvis</td>
<td>Colon &amp; Rectum</td>
</tr>
<tr>
<td>Prostate</td>
<td>Prostate</td>
</tr>
<tr>
<td>Urinary Bladder</td>
<td>Urinary Bladder</td>
</tr>
<tr>
<td>Leukemia</td>
<td>Leukemia</td>
</tr>
<tr>
<td>Non-Hodgkin's Lymphoma</td>
<td>Non-Hodgkin's Lymphoma</td>
</tr>
<tr>
<td>All Other Sites</td>
<td>All Other Sites</td>
</tr>
</tbody>
</table>

Prostate Cancer: Clinical States

Androgen signaling in prostate cancer

Studies on Prostatic Cancer
1. The Effects of Carcinoestrogens on Endometrial Carcinoma. A Preliminary Report
   Charles R. Kistler, M.D., and C. E. van der Waal
   (From the Department of Surgery, the University of Michigan, Ann Arbor, Mich.)
   (Presented at the Annual Meeting of the American Society for Clinical Investigation, Chicago, Ill., April 1947)

Androgen Receptor Signaling

Androstenedione
DHEAS
DHEA
Testosterone
Estradiol

Protein Synthesis

AR
DHT
5-Alpha reductase

Flutamide
Bicalutamide
Nilutamide
MDV-3100

Ketoconazole
Aminogluthemide
Abiraterone
TAK-700

Leuprolide
Goserelin
Abarelix
Orchiectomy
Adrenalectomy
ACTH
Ketoconazole
Aminogluthemide
Abiraterone
TAK-700

Androstenedione
Testosterone (T)
Estradiol
SHBG

What is hormone-refractory?

CRPC is NOT Hormone Refractory Cancer, but is frequently Hormone Ultra-Sensitive

What is hormone-refractory?

Anti-androgen Withdrawal

Mechanism of action:
- Increased in SHBG levels
- Decrease in DHEA-S levels
- More profound decrease in testosterone levels
- T Direct cytotoxic effects

Estrogens and Prostate Cancer

Mechanism of action:
- Increased in SHBG levels
- Decrease in DHEA-S levels
- More profound decrease in testosterone levels
- T Direct cytotoxic effects

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- Increased in SHBG levels
- Decrease in DHEA-S levels
- More profound decrease in testosterone levels
- T Direct cytotoxic effects

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Oh et al, JCO, 2004

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Oh et al, JCO, 2004

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- More profound decrease in testosterone levels
- T Direct cytotoxic effects

Oh et al, JCO, 2004
Ketoconazole: Phase III Clinical Trial Results

• 20-30%: prolonged PFS / Survival > 24 months.

Small et al, Journal of Clinical Oncology 2004

Observation #1: Adrenal Androgens Increase on Progression

Androgen Resurgence at Progression on Keto

<table>
<thead>
<tr>
<th>Androgen</th>
<th>Odds Ratio for Response to Keto (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Androstenedione</td>
<td>5.09 (1.05-24.6)</td>
<td>0.043</td>
</tr>
<tr>
<td>DHEA</td>
<td>2.18 (0.84-5.65)</td>
<td>0.11</td>
</tr>
<tr>
<td>DHEAS</td>
<td>0.87(0.87-0.87)</td>
<td>0.64</td>
</tr>
<tr>
<td>Testosterone</td>
<td>4.14 (2.7-7.4)</td>
<td>0.75</td>
</tr>
</tbody>
</table>

Androgens have prognostic significance in "Androgen Independent" disease

Ryan, Halabi et al, Clinical Cancer Research 2007
How does prostate cancer become castration-resistant?

- Intra-tumoral androgen levels are often not "castrate".
  - Intratumor androgen production/conversion/sequestration
  - Persistent serum androgens (e.g. adrenal)
- AR gene amplification (~30%).
- AR point mutations
- Increased expression of AR co-activators.
- Ligand-independent (or alternative ligand) AR activation

**Abiraterone (CYP-17 Inhibitor)**

- Phase I Trial of Abiraterone
  - 21 patients enrolled
  - Dose escalation to 2000 mg daily
  - No treatment-related grade 3 or 4 toxicities

Attard, JCO, 2008
Pre-docetaxel Phase I/II (n = 54): Maximal PSA Decrements After Abiraterone Monotherapy


Relationship of Prior Ketoconazole Response to Abiraterone Response


Cougar Biotechnology: Schematic of Phase III Trial Design (Trial 302)

Progressive Prostate Cancer WITHOUT prior Docetaxel based chemotherapy

ENDPOINTS - PFS, Overall Survival

Arm A
• Abiraterone plus Prednisone

Arm B
Placebo plus Prednisone
MDV3100: A Second-Generation Antiandrogen

- Engineered for activity in prostate cancer cells that overexpress the androgen receptor (AR).
- Binds the AR more potently than bicalutamide.
- Unlike bicalutamide, MDV3100 inhibits nuclear translocation of the AR and its binding to DNA.
- Induces apoptosis in prostate cancer cells.

Tran et al, Science, 2009

Phase I/II Trial of MDV3100 in Castration Resistant Prostate Cancer

Escalations were permitted after 28 days of continuous therapy, if no significant adverse events were observed in a pre-specified number of patients.

MDV3100: Adverse Events

Scher et al, Lancet, 2010
MDV3100: PK and PD

Scher et al, Lancet, 2010

MDV3100: PSA Responses

Medivation: Schematic of Phase III Trial Design

- Progressive Prostate Cancer after Docetaxel based chemotherapy
- No prior ketoconazole

2:1 Randomization
Primary Endpoint - Overall Survival
Secondary aims – PFS and Pain control
Conclusions - I

- AR signaling remains a key target in CRMPC
- Additional “hormonal manipulations” may provide clinical benefit to men with CRMPC
- Novel rationally designed “hormonal” agents have demonstrated significant activity in CRMPC and have rapidly moved forward to phase III testing.

Sipuleucel-T: Proposed Mechanism of Action

Sipuleucel-T: Logistics

COMPLETE COURSE OF THERAPY: Weeks 0, 2, 4
Randomized Phase 3 IMPACT Trial

Asymptomatic or Minimally Symptomatic Metastatic Castration Resistant Prostate Cancer (N=512)

Sipuleucel-T Q 2 weeks x 3

Primary Endpoint: Overall Survival
Secondary Endpoint: Objective Disease Progression

Adverse Events More Commonly Reported in Sipuleucel-T Group

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Sipuleucel-T N = 338 %</th>
<th>Placebo N = 168 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chills</td>
<td>54.1</td>
<td>12.5</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>29.3</td>
<td>13.7</td>
</tr>
<tr>
<td>Headache</td>
<td>16.0</td>
<td>4.8</td>
</tr>
<tr>
<td>Influenza-Like Illness</td>
<td>9.8</td>
<td>3.6</td>
</tr>
<tr>
<td>Myalgia</td>
<td>9.8</td>
<td>4.8</td>
</tr>
<tr>
<td>Hypertension</td>
<td>7.4</td>
<td>3.0</td>
</tr>
<tr>
<td>Hyperhidrosis</td>
<td>5.3</td>
<td>0.6</td>
</tr>
<tr>
<td>Groin Pain</td>
<td>5.0</td>
<td>2.4</td>
</tr>
</tbody>
</table>

1 Reported by ≥ 5% of sipuleucel-T patients and having a ≥ 2-fold difference from placebo.

The majority of the most common AEs were mild or moderate in severity.

Serious Adverse Events

<table>
<thead>
<tr>
<th>SAE Preferred Term</th>
<th>Sipuleucel-T N = 338 %</th>
<th>Placebo N = 168 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any SAE</td>
<td>24.3</td>
<td>23.8</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>1.8</td>
<td>0.6</td>
</tr>
<tr>
<td>Cerebrovascular Accident</td>
<td>1.8</td>
<td>1.8</td>
</tr>
<tr>
<td>Pulmonary Embolism</td>
<td>1.2</td>
<td>0.0</td>
</tr>
<tr>
<td>Spinal Cord Compression</td>
<td>1.2</td>
<td>1.2</td>
</tr>
<tr>
<td>Nausea</td>
<td>0.9</td>
<td>1.2</td>
</tr>
<tr>
<td>Atrial Fibrillation</td>
<td>0.9</td>
<td>0.6</td>
</tr>
<tr>
<td>Dehydration</td>
<td>0.9</td>
<td>0.6</td>
</tr>
<tr>
<td>Cardiac Failure Congestive</td>
<td>0.6</td>
<td>1.2</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>0.6</td>
<td>1.2</td>
</tr>
<tr>
<td>Hematuria</td>
<td>0.6</td>
<td>1.2</td>
</tr>
<tr>
<td>Deep Vein Thrombosis</td>
<td>0.3</td>
<td>1.8</td>
</tr>
<tr>
<td>Renal Failure Acute</td>
<td>0.3</td>
<td>2.4</td>
</tr>
</tbody>
</table>
IMPACT Overall Survival
Final Analysis (349 events)

Survival Results Across 3 Randomized Sipuleucel-T Studies

Conclusions - II
Docetaxel is Standard First Line Cytotoxic Therapy for CRPC

Median Survival
Dq3 = 19.2 mos (95% CI 17.5–21.3)
Dq1 = 17.8 mos (95% CI 16.2–19.2)
M+P = 16.3 mos (95% CI 14.3–17.9)


Targeting the Tumor and Its Microenvironment

Recent “Negative” Phase III Trials

<table>
<thead>
<tr>
<th>Sponsor</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Novacea</td>
<td>Docetaxel ± DN101</td>
</tr>
<tr>
<td>CALGB</td>
<td>Docetaxel ± bevacizumab</td>
</tr>
<tr>
<td>Cell Genesys</td>
<td>Docetaxel vs. GVAX</td>
</tr>
<tr>
<td>Cell Genesys</td>
<td>Docetaxel ± GVAX</td>
</tr>
</tbody>
</table>
Some failures due to schedule/steroids??

- **VITAL-2**
  - Docetaxel + GVAX versus Docetaxel + Prednisone
  - Halted after interim analysis revealed imbalance of deaths on the immunotherapy arm (67 vs 47)
  - Lack of prednisone?
- **ASCENT2**
  - Docetaxel (weekly) + DN101 versus Docetaxel (q3weeks)
  - Halted early after increased deaths on the DN101 arm (10% on control arm versus 17% on DN101)
  - Weekly versus q3week schedule?

Multivariate model of plasma VEGF levels predicting survival time among 197 patients

<table>
<thead>
<tr>
<th>Factor</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>VEGF (&gt;$260$ vs $\leq 260$)</td>
<td>2.42 (1.29–4.54)</td>
<td>.006</td>
</tr>
<tr>
<td>Measurable disease (Y vs N)</td>
<td>2.01 (1.36–3.00)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Alkaline phosphatase (&gt;170 vs $\leq 170$)</td>
<td>1.60 (1.05–2.44)</td>
<td>.030</td>
</tr>
<tr>
<td>Baseline PSA (&gt;150 vs $\leq 150$)</td>
<td>1.48 (1.00–2.20)</td>
<td>.050</td>
</tr>
</tbody>
</table>


CALGB 90410: Treatment Schema

- **Arm 1**
  - Dexamethasone 8 mg po x 3 doses
  - Docetaxel 75 mg/m² on day 1 q 21 days
  - Prednisone 10 mg po daily
  - Bevacizumab

- **Arm 2**
  - Dexamethasone 8 mg po x 3 doses
  - Docetaxel 75 mg/m² on day 1 q 21 days
  - Prednisone 10 mg po daily
  - Placebo

*ASA 325 mg encouraged in all patients that can tolerate
1In the event of intolerable toxicity to Docetaxel the Bevacizumab/placebo may be continued alone until POD*
CALGB 90410: Statistical Considerations

- Power Calculations: Randomized double blinded phase III of 1050 men with CRPC
- 86% power to detect a hazard ratio (HR) of 1.26
- Assume an increase in median OS from 19 in DP months to 24 months in DP+B
- Primary analysis: Stratified log rank test adjusting for the stratification factors

Significant Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>ARM 1 DP+B Grade 3+</th>
<th>ARM 2 DP Grade 3+</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukocytes</td>
<td>69 (17%)</td>
<td>6 (13%)</td>
<td>0.091</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>152 (30%)</td>
<td>120 (24%)</td>
<td>0.028</td>
</tr>
<tr>
<td>Febrile Neutropenia</td>
<td>36 (7%)</td>
<td>21 (4%)</td>
<td>0.055</td>
</tr>
<tr>
<td>Hypertension</td>
<td>36 (7%)</td>
<td>7 (1%)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Thrombosis/embolism</td>
<td>20 (4%)</td>
<td>33 (7%)</td>
<td>0.068</td>
</tr>
<tr>
<td>Fatigue</td>
<td>89 (18%)</td>
<td>51 (10%)</td>
<td>0.0006</td>
</tr>
<tr>
<td>GI, Perforation</td>
<td>18 (4%)</td>
<td>0 (0%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Mucositis/stomatitis</td>
<td>14 (3%)</td>
<td>1 (0%)</td>
<td>0.0007</td>
</tr>
<tr>
<td>Hemorrhage, GI</td>
<td>30 (6%)</td>
<td>12 (2%)</td>
<td>0.007</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>10 (2%)</td>
<td>2 (0%)</td>
<td>0.038</td>
</tr>
</tbody>
</table>

Secondary Endpoints: Objective Response and 50% Decline in PSA

<table>
<thead>
<tr>
<th>Clinical Endpoint</th>
<th>Arm 1 DP+B (N=524)</th>
<th>Arm 2 DP (N=526)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥50% decline in PSA (95% CI)</td>
<td>69.5% (65.2-73.5)</td>
<td>57.9% (53.3-62.3)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Objective Response (95% CI) (# with measurable disease)</td>
<td>53.2% (46.8-59.6) (248)</td>
<td>42.1% (36.2-48.2) (273)</td>
<td>0.0113</td>
</tr>
</tbody>
</table>
Kaplan-Meier PFS Curves by Treatment Arm

Placebo+Docetaxel vs Bev+Docetaxel, log-rank p<0.0001
Median DP = 7.5 (6.7-8.0)
Median DPB=9.9 (9.1-10.6)
HR= 0.77 (0.68-0.88)

Number of Patients at Risk
Placebo+Docetaxel 526 303 134 75 34 8 4 0
Bev+Docetaxel 524 384 134 97 44 11 5 1

Kaplan-Meier Overall Survival Curves by Treatment Arm

Placebo+Docetaxel vs Bev+Docetaxel, log-rank p=0.181
Median DP = 21.5 (20.0-22.0)
Median DPB=22.6 (21.1-24.0)
HR= 0.91 (0.78-1.05)

Number of Patients at Risk
Placebo+Docetaxel 526 480 390 303 199 100 44 2
Bev+Docetaxel 524 484 417 327 217 117 52 23

Ongoing Phase III Docetaxel Combination Trials

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>SWOG</td>
<td>Docetaxel ± Atrasentan</td>
</tr>
<tr>
<td>AZ</td>
<td>Docetaxel ± Zibotentan</td>
</tr>
<tr>
<td>BMS</td>
<td>Docetaxel ± Dasatinib</td>
</tr>
<tr>
<td>Sanofi</td>
<td>Docetaxel ± Afilbercept</td>
</tr>
<tr>
<td>Celgene</td>
<td>Docetaxel ± Lenalidomide</td>
</tr>
</tbody>
</table>
Conclusions - III

- Several docetaxel combination trials have failed to demonstrate improvements in outcomes in phase III trials.
- The imbalance of steroids and the use of weekly docetaxel may have contributed to some of these “negative” trials.
- Ongoing phase III combination trials are targeting angiogenesis and the bone microenvironment.

Satraplatin

- Oral platinum compound
- Activity against cell lines resistant to taxanes, anthracyclines and other platinum compounds
- Activity in early prostate cancer trials

EORTC 30972: Progression-Free Survival

Median:
- Satraplatin + Pred 5.2 months (95% CI: 2.8 – 13.7)
- Prednisone 2.5 months (95% CI: 2.1 – 4.7)
- HR: 0.50 (95% CI: 0.28 – 0.92)

Log Rank, p=0.023

Patients (%)

0 10 20 30 40 50 60 70 80 90 100

0 3 6 9 12 15 18 21 24 27

Satraplatin + Pred
Prednisone

2.5 months

O’Hara CN, Oncol. 2005; 68:2-9
Endpoints

Primary
- Progression Free Survival (PFS)
- Overall Survival (OS)
  - 700 events needed to detect HR of 0.77 with 90% power

Secondary
- Time to Pain Progression (TPP)

Other Pre-specified Endpoints
- Pain response
- Tumor response
- PSA response

Baseline Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Satraplatin n=635</th>
<th>Placebo n=315</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prior Chemotherapy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Docetaxel</td>
<td>51.5%</td>
<td>50.8%</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>2.7%</td>
<td>2.9%</td>
</tr>
<tr>
<td>Mitoxantrone</td>
<td>20.2%</td>
<td>20.3%</td>
</tr>
<tr>
<td>Others</td>
<td>25.6%</td>
<td>26.0%</td>
</tr>
<tr>
<td><strong>Bisphosphonates</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Progression Free Survival
ITT Population (per IRC)

33% Improvement in PFS

Satraplatin + Prednisone

Placebo + Prednisone

No. at Risk
Satraplatin 635 363 229 143 90 63 43 24 14 12
Placebo 315 140 63 37 24 11 5 5 1 0

S 11.1
P 0.7
Median (wks) 12.5
HR: 0.67 (95% CI: 0.57 - 0.77)
Log-Rank P = 0.0000003
Hematologic Toxicity

<table>
<thead>
<tr>
<th></th>
<th>Satraplatin, % (n=629)</th>
<th>Placebo, % (n=313)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3/4</td>
<td>13.7</td>
<td>0.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Grade 4</td>
<td>1.0</td>
<td>0.0</td>
<td>NS</td>
</tr>
<tr>
<td>Neutrophils</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3/4</td>
<td>21.1</td>
<td>0.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Grade 4</td>
<td>4.1</td>
<td>0.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>0.6</td>
<td>0.0</td>
<td>NS</td>
</tr>
<tr>
<td>Platelets</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3/4</td>
<td>21.1</td>
<td>1.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Grade 4</td>
<td>0.2</td>
<td>0.0</td>
<td>NS</td>
</tr>
<tr>
<td>Hb</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3/4</td>
<td>9.4</td>
<td>3.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Grade 4</td>
<td>1.6</td>
<td>0.6</td>
<td>NS</td>
</tr>
</tbody>
</table>

Non Hematologic Adverse Events
Grade 3/4

<table>
<thead>
<tr>
<th></th>
<th>Satraplatin, % (n=629)</th>
<th>Placebo, % (n=313)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilirubin</td>
<td>0.5</td>
<td>0.0</td>
<td>ns</td>
</tr>
<tr>
<td>Serum Creatinine</td>
<td>0.8</td>
<td>0.3</td>
<td>ns</td>
</tr>
<tr>
<td>Nausea</td>
<td>1.3</td>
<td>0.3</td>
<td>ns</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1.6</td>
<td>0.0</td>
<td>0.036</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2.1</td>
<td>0.0</td>
<td>0.007</td>
</tr>
<tr>
<td>Constipation</td>
<td>2.1</td>
<td>1.0</td>
<td>ns</td>
</tr>
<tr>
<td>Fatigue/Asthema</td>
<td>4.9</td>
<td>2.6</td>
<td>ns</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>0.3</td>
<td>0.3</td>
<td>ns</td>
</tr>
<tr>
<td>DVT</td>
<td>0.6</td>
<td>0.0</td>
<td>ns</td>
</tr>
</tbody>
</table>

Satraplatin was discontinued in 2.5% vs. placebo in 0.6%

Satraplatin

- 33% reduction in the risk of disease progression
- 36% reduction in risk of pain progression
- A significant improvement in pain, tumor and PSA response rates
- Well tolerated in this elderly population
- Not approved by the FDA based on lack of overall survival benefit
**Cabazitaxel**

- New semi-synthetic taxane
  - May overcome taxane resistance
- Preclinical data
  - As potent as docetaxel against sensitive cell lines and tumor models
  - Activity against tumors resistant to currently available taxanes
- Clinical data
  - Phase I trial DLT neutropenia

Mita Clin Can Res 2009

**TROPIC**

- mCRPC patients who progressed during and after treatment with a docetaxel-based regimen (n=755)
  - ECOG PS (0, 1 vs. 2) • Measurable vs. non-measurable disease
  - Cabazitaxel 25 mg/m² q 3 wk + prednisone* for 10 cycles (n=378)
  - Mitoxantrone 12 mg/m² q 3 wk + prednisone* for 10 cycles (n=377)

*Oral prednisone/prednisolone: 10 mg daily.

Primary endpoint: OS
Secondary endpoints: Progression-free survival (PFS), response rate, and safety

Inclusion: Patients with measurable disease must have progressed by RECIST; otherwise must have had new lesions or PSA progression

**Pre-Protocol Treatments**

<table>
<thead>
<tr>
<th>MP (n=377)</th>
<th>CBZP (n=378)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total prior docetaxel dose (mg/m²)</td>
<td>529.2</td>
</tr>
<tr>
<td>Months from last docetaxel dose to progression</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>0.70</td>
</tr>
<tr>
<td>Number of patients progressed (%)</td>
<td></td>
</tr>
<tr>
<td>During last docetaxel treatment</td>
<td>27.6</td>
</tr>
<tr>
<td>≤3 months since last docetaxel dose</td>
<td>48.6</td>
</tr>
<tr>
<td>≥3 months since last docetaxel dose</td>
<td>24.0</td>
</tr>
<tr>
<td>Radiation (%)</td>
<td></td>
</tr>
<tr>
<td>Curative</td>
<td>26.7</td>
</tr>
<tr>
<td>Palliative</td>
<td>93.3</td>
</tr>
<tr>
<td>Chemotherapy (%)</td>
<td></td>
</tr>
<tr>
<td>1 regimen</td>
<td>71.1</td>
</tr>
<tr>
<td>≥2 regimens</td>
<td>28.9</td>
</tr>
<tr>
<td>≥3 regimens</td>
<td>8.0</td>
</tr>
</tbody>
</table>
Overall Survival (ITT)

<table>
<thead>
<tr>
<th></th>
<th>MP (n=377)</th>
<th>CBZP (n=371)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All grades (%)</td>
<td>Grade ≥3 (%)</td>
</tr>
<tr>
<td>Any adverse event</td>
<td>88.4</td>
<td>39.4</td>
</tr>
<tr>
<td>Fever</td>
<td>1.3</td>
<td>1.3</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>10.5</td>
<td>0.3</td>
</tr>
<tr>
<td>Fatigue</td>
<td>27.5</td>
<td>3</td>
</tr>
<tr>
<td>Asthenia</td>
<td>12.4</td>
<td>2.4</td>
</tr>
<tr>
<td>Back pain</td>
<td>12.1</td>
<td>3</td>
</tr>
<tr>
<td>Nausea</td>
<td>22.9</td>
<td>0.3</td>
</tr>
<tr>
<td>Vomiting</td>
<td>10.2</td>
<td>0</td>
</tr>
<tr>
<td>Hematuria</td>
<td>0.4</td>
<td>0.5</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>3.5</td>
<td>0</td>
</tr>
</tbody>
</table>

*Sorted by decreasing frequency of events grade ≥3 in the CBZP arm.

Grade ≥3 SAEs

Conclusions – IV

- Satraplatin did not extend survival in patients previously treated with docetaxel compared with placebo
- Cabazitaxel had significant improvement in survival compared with mitoxantrone in patients previously treated with docetaxel
  - 30% risk reduction of death (HR = 0.70, P < .0001)
  - Median OS improvement: 15.1 vs 12.7 months
  - OS benefit was consistent across subgroups
- Cabazitaxel was approved by the FDA 6/2010
**Cabazitaxel Summary**

- Cabazitaxel had significant improvement in survival compared with mitoxantrone
  - 30% risk reduction of death (HR = 0.70, \( P<.0001 \))
  - Median OS improvement: 15.1 vs 12.7 months
  - OS benefit was consistent across subgroups
- Toxicity
  - Febrile neutropenia: 7.5% vs 1.9%
- Is it better than more docetaxel?
Healthcare Reform & Regulatory Trends

Piedmont Oncology Association
31st Annual Symposium
August 27, 2010

Matthew Farber
Director, Provider Economics & Public Policy
Association of Community Cancer Centers

Regulatory and Legislative Overview

- SGR
- Meaningful Use and EHR
- Health Care Reform
- 2011 Proposed Physician Fee Schedule
  - Physician Quality Reporting Initiatives
- 2011 Proposed Hospital Outpatient Prospective Payment System (HOPPS)
  - Minor Update to Physician Supervision
  - Pharmacy Overhead Pool
- Recovery Audit Contractors (RACs)

Sustainable Growth Rate (SGR)

- Congress stepped in to halt the projected 21.3% cut in June, 2010 for 6 months, through Nov. 30
  - Also provided a 2.2% increase during this time
- Every few months, a “band-aid” fix is implemented
- Hopefully we will see a long term fix but unlikely this year
  - Was not part of Health Care reform
  - Senate voted to exclude 5 year fix from pay-go rules in debt ceiling extension bill, but that did not lead to a long term fix
  - CMS will pull drugs from formula for future
- Will lessen future cuts
- Without Congressional action before 11/30, we will be faced with the same 21% cut plus even more
  - Projected 6.1% cut in 2011
Relative Increase in Part B Expenditures vs. per Capita GDP 1996-2008


Electronic Health Record Payment Year Requirements

<table>
<thead>
<tr>
<th>First Payment Year</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
<th>2015+</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011</td>
<td>Stage 1</td>
<td>Stage 1</td>
<td>Stage 2</td>
<td>Stage 2</td>
<td>Stage 3</td>
</tr>
<tr>
<td>2012</td>
<td>Stage 1</td>
<td>Stage 1</td>
<td>Stage 2</td>
<td>Stage 2</td>
<td>Stage 3</td>
</tr>
<tr>
<td>2013</td>
<td>Stage 1</td>
<td>Stage 2</td>
<td>Stage 2</td>
<td>Stage 3</td>
<td></td>
</tr>
<tr>
<td>2014</td>
<td>Stage 1</td>
<td>Stage 3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2015+</td>
<td>Stage 3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Meaningful Use

- Proposal had set out a robust set of requirements
  - ACCC and many others commented that they were asking too much too soon
  - CMS has estimated that over 50% of providers will face penalties in 2015 for failing to meet criteria
- Issues included:
  - E-Rx
  - Electronic reminders, records and charts to patients
  - Quality reporting
Final Meaningful Use Provision

- CMS released final version July 13, 2010
- Many of the concerns that we voiced were addressed:
  - To introduce more flexibility, EPs will be required to report 15 core objectives, and 5 out of 10 Menu objectives
  - EP could begin meaningful use of their certified EHR technology as late as October 1, 2011 and still qualify for calendar year (CY) 2011 incentive payments

### Meaningful Use: Required

<table>
<thead>
<tr>
<th>Core Set</th>
<th>Measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Record patient demographics</td>
<td>More than 50% of demographic data recorded</td>
</tr>
<tr>
<td>Record vital signs and chart changes</td>
<td>More than 50% of patients 2 years of age or older with height, weight, bp</td>
</tr>
<tr>
<td>Maintain up to date problem list of current diagnoses</td>
<td>More than 80% of patients have at least one entry recorded</td>
</tr>
<tr>
<td>Maintain active medication list</td>
<td>More than 80% of patients have at least one entry recorded</td>
</tr>
<tr>
<td>Maintain active allergy list</td>
<td>More than 80% of patients have at least one entry recorded</td>
</tr>
<tr>
<td>Record Smoking status over 13 y.o.</td>
<td>More than 50% of patients 13 or older have status recorded</td>
</tr>
<tr>
<td>Provide patients with clinical summaries for each office visit</td>
<td>Clinical summaries provided for more than 50% within 3 business days</td>
</tr>
<tr>
<td>On request, provide patients with electronic copy of health info.</td>
<td>More than 50% of requesting patients receive copy within 3 business days</td>
</tr>
<tr>
<td>Generate and transmit permissible prescriptions electronically</td>
<td>More than 40% transmitted electronically</td>
</tr>
<tr>
<td>Computer Provider Order Entry (CPOE) for medication errors</td>
<td>More than 30% of patients with at least 1 med in list have at least one med. Ordered through CPOE</td>
</tr>
</tbody>
</table>
## Meaningful Use: Required

<table>
<thead>
<tr>
<th>Core Set</th>
<th>Measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Implement drug-drug and drug-allergy checks</td>
<td>Functionality enabled for reporting period</td>
</tr>
<tr>
<td>Implement capability to electronically exchange key clinical info among patient-approved entities</td>
<td>Perform at least one test of EHR’s capacity to electronically exchange data</td>
</tr>
<tr>
<td>Implement one clinical decision support rule and ability to track compliance with rule</td>
<td>One clinical decision support rule implemented</td>
</tr>
<tr>
<td>Implement systems to protect privacy and security of patient data in EHR</td>
<td>Conduct a security risk analysis, implement updates as necessary</td>
</tr>
<tr>
<td>Report clinical quality measures to CMS</td>
<td>Provide aggregate numerator and denominator through attestation</td>
</tr>
</tbody>
</table>

## Meaningful use: Menu Set
EPs choose 5 of 10

<table>
<thead>
<tr>
<th>Menu Set</th>
<th>Measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Implement drug formulary checks</td>
<td>Drug formulary check system is implemented and has access to at least one internal or external formulary</td>
</tr>
<tr>
<td>Incorporate clinical lab test results into EHRs</td>
<td>More than 40% lab test results incorporated into EHR</td>
</tr>
<tr>
<td>Generate lists of patients by conditions to use for quality improvement, research, outreach</td>
<td>Generate at least one listing of patients with specific condition</td>
</tr>
<tr>
<td>Use EHR to identify patient-specific education resources and provide to patient</td>
<td>More than 10% of patients are provided patient-specific education</td>
</tr>
<tr>
<td>Perform medication reconciliation between care settings</td>
<td>Medication reconciliation performed more than 50% of transitions of care</td>
</tr>
</tbody>
</table>

## Meaningful use: Menu Set
EPs choose 5 of 10

<table>
<thead>
<tr>
<th>Menu Set</th>
<th>Measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Provide summary of care record for patients referred or transitioned</td>
<td>Summary of care for more than 50% of patient transitions or referrals</td>
</tr>
<tr>
<td>Submit electronic immunization data to registries or info. Systems</td>
<td>Perform at least one test of data submission and follow-up submission</td>
</tr>
<tr>
<td>Submit electronic syndromic surveillance data to public health agency</td>
<td>Perform at least one test of data submission and follow-up submission</td>
</tr>
<tr>
<td>(For EPs) Send reminders to patients for preventative or follow-up care</td>
<td>More than 20% sent appropriate reminders</td>
</tr>
<tr>
<td>(For EPs) Provide patients with timely electronic access to their health information</td>
<td>More than 10% provided access within 4 days of being updated in EHR</td>
</tr>
</tbody>
</table>
HIT Bonus Payments

- For Physician Offices (money is per physician):
  - 1st Year: $18,000 (if 2011 or 2012), $15,000 if later
  - 2nd year: $12,000
  - 3rd year: $8,000
  - 4th year: $4,000
  - 5th year: $2,000
  - 6th year and beyond: 0

- If in a Secretary-designated health professional shortage area, may be increased by 10%

These numbers are based on Medicare bonus; Medicaid bonus is different

Data on HIT can be found at: http://www.cms.hhs.gov/Recovery/11_HealthIT.asp

HIT bonus: Hospitals

- Sample, courtesy of eHealth Initiative
- Assume the following:
  - 20,000 discharges
  - 34,000 Medicare bed-days
  - 100,000 total bed-days
  - 1,000,000,000 in hospital charges
  - 200,000,000 in charity care

  *Formula 1: 2,000,000 + ((20,000 - 1,150) x 200) = $5,770,000
  *Formula 2: 34,000 / (100,000 x ((1,000,000,000 - 200,000,000) / 1,000,000,000 = 0.425

Bonus Sample cont.

- First Year Payment: $5,770,000 x 0.425 = $2,452,250
- In succeeding years, a transition factor would be introduced that would reduce this number to 3/4, then 1/2, then 1/4
- Second Year: $1,839,188
- Third Year: $1,226,125
- Fourth Year: $613,063
- Total Payments: $6,130,626
Health Care Reform

- Has Everyone enjoyed the Civics lesson that Congress has given the entire country this year?

Environment prior to reform: Costs

- High Costs
  - Healthcare costs make up roughly 17% of GDP with that only expected to grow to at least 20% in near future
  - Cancer care amounts to roughly 5% of that number, or nearly 1% of GDP
  - Medicare trust fund was expected to run out of money by 2017

Medicare Spending per Beneficiary
Health Care as part of GDP

Environment Prior to Reform: Coverage
• Nearly 50 million uninsured by the latest count
• The number has increased in recent years as more people have lost coverage due to unemployment or work no longer offering coverage

Goal of Reform: Bend the curve
• You probably heard many times, “we need to bend the curve of health care spending.”
• The current buy and bill or fee-for-service model incentivizes more procedures, drugs, devices, etc
• Congress has been looking at new payment models to pay for quality, not quantity
• Going back to PQRI, E-Rx, HIT, and now aspects of new law
• Care coordination, comparative effectiveness research, etc
How Best to do that?

- Depends on who you ask
- Liberals feel a single-payer model would accomplish this
- Conservatives favor greater cost-sharing; consumer informed choice
- Law falls somewhere in the middle, with quality focus and state-run insurance exchanges

Key Aspects of Health Care Law

<table>
<thead>
<tr>
<th>Cost</th>
<th>$940 Billion ($70B more than Senate version)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coverage</td>
<td>95% of legal US Residents</td>
</tr>
<tr>
<td>Coverage Method</td>
<td>No Public Plan; 50 State Exchanges; increased subsidies to buy into Medicaid; mandates</td>
</tr>
<tr>
<td>When?</td>
<td>Most provisions take effect in 2014; some insurance reforms sooner</td>
</tr>
<tr>
<td>Effect on Debt</td>
<td>$138 Billion reduction over 10 years (may be slightly lower)</td>
</tr>
</tbody>
</table>

Changes to Medicaid

- Expanded to cover a family up to 133% of federal poverty level
- Federal government will pay 100% of Medicaid expansion from 2011-2016
- The special deal for Nebraska was removed
- In 2013-2014, Primary Care will be reimbursed at Medicare rates
Changes to Medicare

<table>
<thead>
<tr>
<th>The Good...</th>
<th>The Not so Good...</th>
<th>The Other...</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donut Hole would eventually be closed, with greater brand drug discount, and $250 this year</td>
<td>$500 Billion in cuts over 10 years; nearly $130B from MA plans</td>
<td>Established a Center for Comparative Effectiveness Research</td>
</tr>
<tr>
<td>Expansion of PQRI</td>
<td>“Super MedPAC”: new independent advisory board tasked with reducing spending by $125 Billion</td>
<td>Voluntary participation in Accountable Care Organizations</td>
</tr>
<tr>
<td>Insurance Reforms</td>
<td>No fix to SGR</td>
<td>CMS Innovation Center</td>
</tr>
<tr>
<td>No co-pay on Preventative services</td>
<td>Disclose of alternative locations for referrals</td>
<td></td>
</tr>
</tbody>
</table>

How do we Pay for all this?

Taxes

- Cuts to Medicare will only cover about half the cost
- New Taxes: In 2013 Medicare payroll tax will increase to 2.35% from 1.45% for people making more than $200,000, or $250,000 for families
- Additional tax on Capital Gains, dividends for same bracket
- Cadillac Tax: Starting in 2018, a tax will be levied on plans worth $10,000 for individuals and $27,500 for families

How do we pay for this?

Fees from Mandates

<table>
<thead>
<tr>
<th>Employer</th>
<th>Individual</th>
</tr>
</thead>
<tbody>
<tr>
<td>For companies with more than 50 employees and that do not offer coverage, employers would have to pay $2,000 per FTE (first 30 deducted)</td>
<td>Fees are phased in over 7 years: 2014: $95/year or 1% of income 2015: $125/year or 2% of income 2016: $195/year or 2.5% of income</td>
</tr>
<tr>
<td>This provision is expected to raise $52 Billion</td>
<td>Exemptions for people with financial hardships, below the tax-filing threshold, American Indians, religious objections,</td>
</tr>
<tr>
<td>Some questions over how much this will raise</td>
<td></td>
</tr>
</tbody>
</table>
How do we pay for this?

Industry Fees

<table>
<thead>
<tr>
<th>Drug Companies</th>
<th>Device Makers</th>
<th>Insurers</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011: $2.5 Billion</td>
<td>2.9% excise tax on devices sold, excluding: hearing aids, contact lenses and eyeglasses</td>
<td>2011: $2 Billion and gradually increase to $10 Billion in 2017</td>
</tr>
<tr>
<td>2012-2016: $5 Billion</td>
<td>2017: $3.5 Billion</td>
<td>2018: $4.2 Billion</td>
</tr>
<tr>
<td>2019: $2.8 Billion</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Much of this is already covered when we spoke about the Donut Hole in Part D

It is possible that these fees may be passed onto the providers and patients in some way

Insurance Reforms

- Insurers will no longer be able to:
  - Drop coverage or not offer coverage due to pre-existing conditions
  - Deny coverage due to annual or life-time caps on coverage
  - Use premium disparities based on gender or health status
- Insurers must put 85% of premiums toward actual health services (80% in small & individual markets)

Exchanges

- Exchanges to be established by State, in order to increase competition and hopefully lower cost in the individual and small insurance market
- Government will provide subsidies:
  - Available for families earning up to 400% of FPL on a sliding scale
  - Illegal immigrants would not be able to participate in exchanges
  - Government subsidies cannot go toward the coverage of abortions: people must pay separately
Other Reforms

• Coverage of Clinical Trials
  • Insurance companies will be required to cover routine costs associated with the trial
  • Grandfathering clause
• Unfortunately, no reimbursement was included for care planning
• Increase in the utilization rate for MRI and CT to 75%

HCR Today

• Some aspects have been implemented to date:
  ▫ High risk pools set up
    • Premiums range from $459–$773/month depending on where you live
  ▫ Expanded coverage
    • Young adults to age 26, children with pre-existing conditions
  ▫ Donut Hole Rebate
    • Many Seniors were already mailed $250 rebate check

Where do we stand?

• How did oncology make out?
  • A mixed bag

<table>
<thead>
<tr>
<th>Clinical trials coverage</th>
<th>Cuts to Medicare</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insurance reforms</td>
<td>More Medicaid patients</td>
</tr>
<tr>
<td>No direct cuts to oncology reimbursement rates</td>
<td>Questions surrounding ACOs and new payment models</td>
</tr>
<tr>
<td>More of premiums to be spent on actual care</td>
<td>Closing of the Donut Hole</td>
</tr>
</tbody>
</table>
Proposed Updates to 2010 Physician Fee Schedule

- **E/M Services**
  - Evaluation & Management Codes: mixed: some codes up, some down

- **Drug Administration**
  - All codes related to Chemo admin. saw increase
  - Overall reimbursement for Med Onc will decrease by ~1%
  - Cuts from previous rule in year 2 of 4 year phase in; cuts would be ~2% if not for rebasing of Medicare Economic Index (MEI)
  - Radiation Oncology will not face cuts this year: +2%
  - Mainly due to rebasing of MEI (increase in PE)
  - Utilization rate increase to 75% for diagnostics over $1 million (from HCR)
  - All figures assume Congress will halt 21% cut from this year and 6.1% cut in 2011 due to SGR

- **Drug Reimbursement**
  - Average Sales Price (ASP)+6%

---

Final Admin Rates

<table>
<thead>
<tr>
<th>Physician Fee Schedule Drug Administration Rates</th>
<th>2010</th>
<th>2011</th>
<th>% change</th>
</tr>
</thead>
<tbody>
<tr>
<td>96360 Hydration iv infusion, init</td>
<td>$54.94</td>
<td>$56.03</td>
<td>2.0%</td>
</tr>
<tr>
<td>96361 Hydrate iv infusion, add-on</td>
<td>$15.49</td>
<td>$15.28</td>
<td>-1.3%</td>
</tr>
<tr>
<td>96365 Ther/proph/diag iv inf, init</td>
<td>$67.48</td>
<td>$69.62</td>
<td>3.2%</td>
</tr>
<tr>
<td>96366 Ther/proph/diag iv inf, add-on</td>
<td>$21.02</td>
<td>$21.39</td>
<td>1.8%</td>
</tr>
<tr>
<td>96367 Tx/proph/diag add seq iv inf</td>
<td>$32.82</td>
<td>$32.60</td>
<td>-0.7%</td>
</tr>
<tr>
<td>96368 Ther/diag concurrent inf</td>
<td>$19.54</td>
<td>$19.36</td>
<td>-0.9%</td>
</tr>
<tr>
<td>96369 Sc ther infusion, up to 1 hr</td>
<td>$148.60</td>
<td>$167.42</td>
<td>12.7%</td>
</tr>
<tr>
<td>96370 Sc ther infusion, addl hr</td>
<td>$15.12</td>
<td>$15.28</td>
<td>1.1%</td>
</tr>
<tr>
<td>96371 Sc ther infusion, reset pump</td>
<td>$76.70</td>
<td>$78.45</td>
<td>2.3%</td>
</tr>
</tbody>
</table>

---

<table>
<thead>
<tr>
<th>Drug Administration Rates</th>
<th>2010</th>
<th>2011</th>
<th>% change</th>
</tr>
</thead>
<tbody>
<tr>
<td>96372 Ther/proph/diag inj, sc/im</td>
<td>$21.76</td>
<td>$22.75</td>
<td>4.6%</td>
</tr>
<tr>
<td>96373 Ther/proph/diag inj, ia</td>
<td>$18.44</td>
<td>$18.68</td>
<td>1.3%</td>
</tr>
<tr>
<td>96374 Ther/proph/diag inj, iv push</td>
<td>$53.83</td>
<td>$54.68</td>
<td>1.6%</td>
</tr>
<tr>
<td>96375 Ther/proph/diag inj add-on</td>
<td>$22.49</td>
<td>$22.41</td>
<td>-0.4%</td>
</tr>
<tr>
<td>96401 Chemo, anti-neopl, sq/im</td>
<td>$68.95</td>
<td>$71.32</td>
<td>3.4%</td>
</tr>
<tr>
<td>96402 Chemo hormone antimetopl sq/im</td>
<td>$35.77</td>
<td>$34.64</td>
<td>-3.2%</td>
</tr>
<tr>
<td>96405 Chemo intrales’l, up to 7</td>
<td>$83.70</td>
<td>$84.90</td>
<td>1.4%</td>
</tr>
<tr>
<td>96406 Chemo intrales’l over 7</td>
<td>$116.52</td>
<td>$116.48</td>
<td>0.0%</td>
</tr>
<tr>
<td>96409 Chemo, iv push, sqnl drug</td>
<td>$109.51</td>
<td>$111.05</td>
<td>1.4%</td>
</tr>
<tr>
<td>96411 Chemo, iv push, addl drug</td>
<td>$61.58</td>
<td>$62.15</td>
<td>0.9%</td>
</tr>
<tr>
<td>96413 Chemo, iv infusion, 1 hr</td>
<td>$143.07</td>
<td>$144.33</td>
<td>0.9%</td>
</tr>
<tr>
<td>96415 Chemo, iv infusion, addl hr</td>
<td>$30.97</td>
<td>$30.56</td>
<td>-1.3%</td>
</tr>
</tbody>
</table>
### Table: Chemo Procedures and Costs

<table>
<thead>
<tr>
<th></th>
<th>Description</th>
<th>Current</th>
<th>Previous</th>
<th>Percentage Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>96416</td>
<td>Chemo prolong infuse w/pump</td>
<td>$156.71</td>
<td>$158.25</td>
<td>1.0%</td>
</tr>
<tr>
<td>96417</td>
<td>Chemo iv infus each addl seq</td>
<td>$70.80</td>
<td>$70.98</td>
<td>0.3%</td>
</tr>
<tr>
<td>96420</td>
<td>Chemo, ia, push technique</td>
<td>$105.82</td>
<td>$106.97</td>
<td>1.1%</td>
</tr>
<tr>
<td>96422</td>
<td>Chemo ia infusion up to 1hr</td>
<td>$169.98</td>
<td>$172.18</td>
<td>1.3%</td>
</tr>
<tr>
<td>96423</td>
<td>Chemo ia infuse each addl hr</td>
<td>$77.06</td>
<td>$78.45</td>
<td>1.8%</td>
</tr>
<tr>
<td>96425</td>
<td>Chemotherapy, infusion method</td>
<td>$170.72</td>
<td>$176.25</td>
<td>3.2%</td>
</tr>
<tr>
<td>96440</td>
<td>Chemotherapy, intracavitary</td>
<td>$666.66</td>
<td>$716.21</td>
<td>7.4%</td>
</tr>
<tr>
<td>96445</td>
<td>Chemotherapy, intracavitary</td>
<td>$283.55</td>
<td>$282.21</td>
<td>-0.5%</td>
</tr>
<tr>
<td>96450</td>
<td>Chemotherapy, into CNS</td>
<td>$202.43</td>
<td>$195.61</td>
<td>-3.4%</td>
</tr>
<tr>
<td>96521</td>
<td>Refill/maint, portable pump</td>
<td>$126.11</td>
<td>$131.09</td>
<td>3.9%</td>
</tr>
<tr>
<td>96522</td>
<td>Refill/maint pump/resvr syst</td>
<td>$106.93</td>
<td>$109.35</td>
<td>2.3%</td>
</tr>
<tr>
<td>96523</td>
<td>Irrig drug delivery device</td>
<td>$24.70</td>
<td>$25.13</td>
<td>1.7%</td>
</tr>
<tr>
<td>96542</td>
<td>Chemotherapy injection</td>
<td>$128.69</td>
<td>$125.31</td>
<td>-2.6%</td>
</tr>
</tbody>
</table>

---

**Physician Quality Reporting Initiative (PQRI)**

- Bonus payment will be 1% in 2011, 0.5% 2012-2014
  - This due to PPACA
- Starting in 2015, it will become a penalty based system
  - 1.5% in 2015 and 2% in subsequent years
- More ways to participate included in proposal
  - New group practice reporting option
  - Reduce reporting requirements from 80% to 50%
- CMS implemented a new Help Desk for PQRI
  - Call 866-288-8912 or email qnetsupport@sdps.org with questions
- CMS must provide timely feedback
  - Reports to be issued starting in 2011
- Creates informal appeals process as well

---

**E-Rx**

- 1% bonus payment for proper reporting in 2011
- CMS made reporting easier in 2010, and through Meaningful Use provision
- Cannot qualify for both E-Rx and HIT bonus
Other provisions mandated by HCR

- Overfill
- Multiple Procedure Payment Reduction (MPPR) expanded
  - Increases reduction from 25% to 50%
  - Would apply to CT and CTA, MRI and MRA, and ultrasound procedures services furnished to the same patient in the same session, regardless of the imaging modality, and not limited to contiguous body areas.
  - Would add 4 new CT CPT codes

Proposed Updates to Hospital Outpatient Payment Rule for 2011

- Payments for drugs below $70 are bundled into the drug administration payment
- Drugs increase to ASP+6%; Likely to decrease to 5% in final rule
- Pharmacy services and overhead costs continue to be recognized, but still inadequately reimbursed
  - Recognizes that some pharmacy overhead for separately paid drugs is being included in packaged drugs
  - $438 million pool, of which, CMS proposed to move $150 (+$50 million) million to cover pharmacy, thus bringing overall reimbursement to ASP+6%
  - Without this, drug reimbursement would be at ASP+0%

2011 Proposed Rule

- Assumes that 1/3 to 1/2 of the total pharmacy overhead cost currently associated with packaged drugs is appropriate to reallocate to separately paid drugs
  - This is a conservative number, and CMS continues to say may not be the best process
  - Reallocated $200 million in pharmacy overhead cost from packaged drugs to separately payable drugs
  - Listened to comments from ACCC that more needs to be moved due to mis-reported codes
  - Calculates a payment rate for separately payable drugs at ASP +6%
  - Possibly due in part to better reporting of all drugs
- The claims data for 340B hospitals will remain in the drug payment calculation and that 340B hospitals be paid the same amounts for separately payable drugs as non-340B hospitals

**DSH Hospital Site Participation Growth in 340B Program**

Numbers Provided by HRSA, Source 340B Database October 2008

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
<th>2009</th>
<th>2010</th>
<th>% Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>96360</td>
<td>Hydration iv infusion, init</td>
<td>$75.50</td>
<td>$76.16</td>
<td>0.9%</td>
</tr>
<tr>
<td>96361</td>
<td>Hydrate iv infusion, add-on</td>
<td>$25.61</td>
<td>$26.30</td>
<td>2.7%</td>
</tr>
<tr>
<td>96365</td>
<td>Ther/proph/diag iv inf, init</td>
<td>$126.47</td>
<td>$126.28</td>
<td>-0.2%</td>
</tr>
<tr>
<td>96366</td>
<td>Ther/proph/diag iv inf, add-on</td>
<td>$25.61</td>
<td>$26.30</td>
<td>2.7%</td>
</tr>
<tr>
<td>96367</td>
<td>Tx/proph/diag add seq iv inf</td>
<td>$37.35</td>
<td>$37.49</td>
<td>0.4%</td>
</tr>
<tr>
<td>96369</td>
<td>Sc ther infusion, up to 1 hr</td>
<td>$126.47</td>
<td>$126.28</td>
<td>-0.2%</td>
</tr>
<tr>
<td>96370</td>
<td>Sc ther infusion, add hr</td>
<td>$37.35</td>
<td>$37.49</td>
<td>0.4%</td>
</tr>
<tr>
<td>96371</td>
<td>Sc ther infusion, reset pump</td>
<td>$25.61</td>
<td>$26.30</td>
<td>2.7%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>APC</th>
<th>Description</th>
<th>2009 Rate</th>
<th>Final 2010 Rate</th>
<th>% Change 2009-2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>300</td>
<td>Level II Rad. Therapy</td>
<td>$92.55</td>
<td>$98.43</td>
<td>6.4%</td>
</tr>
<tr>
<td>301</td>
<td>Treatment Device Construction</td>
<td>$154.86</td>
<td>$162.07</td>
<td>4.7%</td>
</tr>
<tr>
<td>303</td>
<td></td>
<td>$191.15</td>
<td>$198.12</td>
<td>4.2%</td>
</tr>
<tr>
<td>304</td>
<td>Level I Therapeutic Rad. Treatment Prep</td>
<td>$102.68</td>
<td>$105.14</td>
<td>2.4%</td>
</tr>
<tr>
<td>305</td>
<td>Level II Therapeutic Rad. Treatment Prep</td>
<td>$256.67</td>
<td>$278.27</td>
<td>4.7%</td>
</tr>
<tr>
<td>310</td>
<td>Level III Therapeutic Rad. Treatment Prep</td>
<td>$925.07</td>
<td>$926.05</td>
<td>0.1%</td>
</tr>
<tr>
<td>312</td>
<td>Radioelement Applications</td>
<td>$301.55</td>
<td>$348.00</td>
<td>15.4%</td>
</tr>
</tbody>
</table>

Supervision from 2010

Non-physician practitioners specifically:
- physician assistants,
- nurse practitioners,
- clinical nurse specialists,
- certified nurse-midwives,
- social workers

May directly supervise all HOPD therapeutic services that they may perform themselves in accordance with their State law and scope of practice and hospital-granted privileges, provided that they continue to meet all additional requirements.

Supervision changes for 2011

- Only minor changes for 2011
- Identifies set of non-surgical services that may go on for extended period of time
  - Initiation of these services must be directly supervised, but may be under general supervision for remainder
  - This change will NOT apply to chemotherapy of blood transfusions

Recovery Audit Contractors (RACs)

- CMS is using RACs to identify under and overpayments nation-wide
- RAC program has been started with all contractors in place
- Complex reviews have begun
  - List of complex reviews available on RAC and CMS websites
  - We suggest you review audits in all RAC regions on regular basis
RAC Contractors

- Diversified Collection Services, Inc. of Livermore, California, in Region A
- CGI Technologies and Solutions, Inc. of Fairfax, Virginia, in Region B
- Connolly Consulting Associates, Inc. of Wilton, Connecticut, in Region C
- HealthDataInsights, Inc. of Las Vegas, Nevada, in Region D

Grassroots
Questions

Go to ACCC’s website at http://www.accc-cancer.org/

Matthew Farber
mfarber@accc-cancer.org
(301) 984-9496 ext. 221

Thank you
The Sexual Self of Cancer Survivors: Assessing and Addressing Sexuality in Persons with Cancer
Sage Bolte, PhD, LCSW, OSW-C
The Sexual Self of Cancer Survivors: Addressing and Assessing Sexuality in Person’s with Cancer

Sage Bolte, PhD, LCSW, OSW-C
sage.bolte@inova.org
sagebolte@gmail.com

Why Are We Here?

“Sexuality is part of life. It reflects and affects an individual’s physical and emotional well-being, which in turn shapes one’s sense of health. Physicians should ask about their patient’s sexual functioning... Knowing about patients’ sexuality and sexual functioning enhances the delivery of integrated health care.”


Objectives

- Define sexuality and intimacy
- Identify the impact of cancer and its treatment on sexuality and intimacy
- Define the PLISSIT model
- Understand how to integrate the PLISSIT model into biopsychosocial-sexual assessments
What do we know?

- Person’s diagnosed with cancer are already 15% – 25% more likely to experience significant distress than the general population

Zabora et al., 2001

Common Areas of Distress

- Sleep disturbance
- Somatic Complaints: Fatigue, Nausea, Pain
- Depression
- Anxiety
- Fertility
- Sexual Function?
- Relationship stress?
- Self Esteem / Sexual Esteem?

“I guess, side effects of post-treatment like my specific case is, I had a bone marrow transplant [3 years ago] and I have transplant rejection issues called Graft-versus-Host. And it’s – I’m being treated for that, so that’s – it’s also introducing a lot of physical limitations in terms of flexibility and skin – my skin is very tight. I mean, just – like, I have trouble bending down on my knees. So, you know, I mean, just trying to bend in certain positions sometimes is impossible or my skin feels like it's going to rip. So, I mean, that – I mean, I'm talking – like I said, I'm talking physical limitations [around sexual health] is basically the main thing that cancer introduced for me. But that's not – it also introduced, I suppose, some mental limitations...Well, obviously the physical limitations are, you know, hammering down on my mental state of mind because, okay, I can't perform, you know, because of this, this and this. And so, I mean, it's bogging me down like emotionally sometimes I just don't – I don't even feel like trying.” (Bolte, 2010)
What is the Sexual Self?

1. Information or Event: External events that affect sexual function or affect aspects of sexuality (e.g., disfigurement, positive sexual experiences, etc.)

2. Sexual Esteem: Cognitive, attitudes, Sexual Schemata


4. Sexual Behavior and Function:

Sexual Dysfunction

Effects can be multi-factorial:

- Physical / Biological
- Psychological
- Social

- Desire
- Arousal
- Orgasm
- Resolution

- Intimacy

• Does not discriminate among age
• Resuming sexual function can be one way of feeling that life is ‘normal’

Sexuality and Intimacy are not Life or Death Issues but are very real Quality of Life Issues
Understanding the Problem
Assessment and Evaluation of Sexual Problems

Prevalence of Sexual Dysfunction

10.5 Million Cancer Survivors

10% – 100% of these patients experience sexual problems

Derogatis, L. & Kourtesis SM., 1981; Schover, 2002

Long Term Sexual Dysfunction

- 70% of prostate cancer survivors
- 50% of breast cancer survivors
- 50% of gyn oncology survivors
- 25% of Hodgkin’s disease survivors
- 25% of testicular cancer survivors
- Other cancers? colorectal, bladder, lung, renal, head and neck...

http://www.cancer.gov/cancertopics/pdq/supportivecare/sexuality/HealthProfessional
**Perceived Barriers**

- Lack of privacy & lack of time
- Belief that patient does not need information or someone else will provide it
- Patients often sick - perception that information is not applicable
- If they want the information they will ask for it
- Lack of resources to screen patients sexual concerns/needs
- If they don’t have cancer of a sexual organ and fertility is not perceived to an issue, then it doesn’t need to be addressed

**Survivorship**

- Assume they either have the information or they aren’t experiencing any problems
- Are we really following them long enough to identify when the concerns arise?

---

**Effects of Cancer Treatments on Sexuality**

- Radiation
- Chemotherapy
- Transplant
- Surgery

---

**Side Effects of Treatment: Radiation**

- Fatigue
- Vaginal Dryness
- Skin discomfort, irritation and discoloring
- Vaginal Stenosis
- Infertility
- Erection difficulties
- Bowel & Bladder problems
- Respiratory & Cardiac Problems
- Mouth problems
- Damage to microvasculature
Side Effects of Treatment: Chemotherapy

- "Chemo Brain"
- Hormone changes: POF, Menopausal symptoms, Hot flashes, Libido change
- Hair Loss
- Weight Loss / Weight Gain
- Nausea / Smell Sensitivity
- Vaginal Dryness
- Peripheral neuropathy
- Mucositis / Mouth / Taste problems
- Infertility
- Cardiac and Respiratory Problems
- Neutropenia / Thrombocytopenia
- "The Thalidomide Promise" (Myeloma)

Bone Marrow / Stem Cell Transplant

- Present a higher risk of infertility
- Isolation
- Fear of getting sick or being infected
- Withdrawal - both emotional and physical
- Fatigue
- Can impact integrity of erection
- Neutropenia / Thrombocytopenia
- GVH can cause loss of vaginal depth
- Often requires hormone replacement therapy (young adult)

Impact of Cancer on Sexual Response

- Impaired sexual arousal
  - Erectile dysfunction in men
  - Lack of lubrication or dryness and vaginal discomfort in women
  - Lack of subjective pleasure
- Orgasmic dysfunction
  - Delayed ejaculation or anorgasmia in men
  - Difficulty reaching orgasm or anorgasmia in women
  - Alteration in orgasmic intensity
Impact of Cancer on Sexual Response

- Painful intercourse, including vaginismus and stenosis
- Sexual aversion
- Treatments can also interfere with the sexual response cycle
  - Antihypertensives - lowered libido and possible temporary impotence
  - Psychotropics - desire and arousal and can interfere with orgasm
  - Surgical treatments such as prostatectomy can interfere with arousal and orgasm

Commonly used medications that may impair sexual function

- Benzodiazepines
- β-Blockers
- Calcium-channel blockers
- Cimetidine
- Digoxin
- Lipid-lowering agents
- Lithium
- Monoamine oxidase inhibitors (MAO1's)
- Neurotoxic cancer chemotherapies
- Oestrogens
- Opiates, including synthetic opiates
- Phenytoin
- Progesternes
- Thiazide diuretics
- Tricyclic antidepressants
- Selective serotonin reuptake inhibitors (SSRI's)

PsychoSocial Effects & Sexuality

- The “asexual” myth (and patients not knowing who to turn to to ask questions)
- Health care providers regard decline of sexual functioning as consequence of aging process
- Chronic illness can impair sexual functioning long before a person reaches puberty
- Individuals who are single, divorced, mentally ill or elderly are often overlooked
- Intimate and social relationships can be greatly impacted
- Loss: Fertility, role changes, body changes
“So, I totally know about that cycle about the physical discomfort affecting my mental state especially when entering a new sexual relationship with somebody that I wasn't already comfortable with. And then, of course, once the emotions get into it, that makes the – that affects the physical part of it. So, it was like a cycle where, you know, I – it was really something that was difficult to get over. And, in fact, I’m not sure I have and now I keep going to my doctor – my trustee doctor for the Cialis prescription. So, that’s something I’m still dealing with now”. (Bolte, 2010)

The under-recognized in the under-served on sexual health

The Young Adult Survivor: The Adolescent / Pediatric Patient
-Delayed menses
-Social Isolation
-Possible Infertility
-Pubertal process stunted / Underdevelopment
-Early menopause or POF (noted mostly in girls with blood disorders in their early 20's)
-Skin changes and weight changes
-“Chemo Brain” and other possible learning disabilities/delays
-May not know what “normal” or “healthy” sexual function is like
The Young Adult Patient

- Dating / Relationship Fears
- Fertility concerns
- Identity and Appearance Changes
- Social Isolation / Withdrawal
- Intimacy with children, friends, family
- Sexual function change
  - Libido may change from body to head to head response, along with spontaneity being challenged

The Single Patient

- Fears of “never being wanted” or “being alone”
- Myth that sexuality concerns / side effects don't apply
- Often overlooked in sexual discussions (dilators, safe sex, masturbation)
- Age heightens providers dismissal of discussion
- Friendships and intimacy extremely important
- Fear of being a burden to friends and family

The Elderly Patient

- More likely to be overlooked by health care providers
- Impact of the normal aging process may be heightened and exacerbated by cancer treatments
  - Intercourse may be less, but sexual confidence or expression may not be altered
  - The generational and cultural differences of this population need attention, sexual function may be significantly important to some elderly patients
  - Reasons for decreased sexual function
    - Negative body image
    - Physical limitations
    - Physiological/Biological process of aging: vaginal dryness, flattening of the vaginal epithelium, decreased erections
  - Intimacy and closeness are found to impact sexual activity however, when intimacy was high couples adjusted to the lack of sex easier (Ginsberg et al., 2005)
The Advanced Disease Patient

- Heightened recognition of losses
- Fear of incontinence
- Fear of pain
- Less "alone" time and/or setting not conducive to much privacy
- Not provided with information due to providers assumptions
- Redefine sexual contact and intimacy

Laughter quotation:

"It appears your HMO will only allow 2 prescriptions: 1. Childhood trauma, and 3. Flashbacks per visit."

So, Now What?
What does the research say?

Effect of sexual satisfaction on self esteem and psychological impact:
- 1,196 individuals
  - 748 physically disabled
  - 448 able bodied
- Findings:
  - Sexual esteem, body esteem and sexual satisfaction were strong predictors of self esteem.
  - If people with disability were sexually satisfied and felt good about their sexuality and their body, they were more likely to have high levels of self-esteem.

Prior to Assessment

It is the health care provider's responsibility to have an awareness and sensitivity to cultural and religious norms.
- Remember to address sexuality with the patient fully clothed (not in gown) if possible.
- Is it appropriate to discuss sex or sexuality with patient? With partner in the room?
- What is acceptable behavior? Masturbation or pursuing sex for the enjoyment of sex may be taboo.
- What importance is placed on fertility?
- Does a guardian need to be in the room for this discussion?

Integrating Sexuality into Daily Practice Assessments

- Building a Referral Network (suggestions listed in handout section)
- Routine Quality-of-Life Screening
  - Interview and assessment (i.e. PLASSIT model)
  - Questionnaires:
    - Cancer Rehabilitation and Evaluation System (CARES)
    - Functional Assessment of Cancer Therapy (FACT)
    - Derogatis Inventory of Sexual Functioning (DISF)
    - Satisfaction with Life Domains Scale for Cancer (SLDS-C), etc.
    - Depression Anxiety and Stress Scale, short form (DASS)
    - Body Esteem Scale
    - International Index of Erectile Function (for men)
    - Brief Index of Sexual Functioning for Women
    - Female Sexual Function Index (FSFI)
    - Create your own Likert scale with a question inquiring about sexual satisfaction (i.e. “Over the past three months, how sexually satisfied do you feel overall?”)
This questionnaire may be used as part of the review of systems with patients. The clinician might begin, "I need to ask a few short questions about your sexual health in order to be thorough in providing your medical care."

Adapted with permission from the Program in Human Sexuality, Department of Family Practice and Community Health, University of Minnesota Medical School, 11/25/03. Thanks also to Harold S. Levine of Levine & Co., NY, NY.

Brief Sex History Questionnaire

Patient name: __________________________
Birthdate: __________________________
Chart number: __________________________

1. Are you sexually active? __________________________
2. If so, when was the last time you engaged in sexual activity? __________________________
3. If you are sexually active, are you sexual with men, women, or both? __________________________
Men               women               both
4. How many people have you been sexual with in the past year? __________________________
   0          1           2-3           4-10          more than 10
5. What, if anything, do you do to protect yourself from getting a sexually transmitted disease, (including HIV)? Have you ever had a sexually transmitted disease? __________________________
6. If applicable: What do you do to protect yourself or your partner from unplanned pregnancy? __________________________
7. For males: Do you have any problems with sexual functioning, for example, getting aroused, getting or maintaining an erection, or problems with ejaculation or orgasm? __________________________
8. For females: Do you have any problems with sexual functioning, for example, getting aroused, becoming lubricated, experiencing pain during sexual activity, or problems with orgasm? __________________________
9. Is there anything else that I need to know about your sexuality in order to provide you with good medical care? __________________________

PLISSIT

• Permission (Assessment)
• Limited
• Information (Education)
• Specific
• Suggestions (Counseling)
• Intensive
• Therapy (Referral)

Permission: Assessment

• Obtaining Permission from patient to initiate sexual discussion and legitimize sexual concerns.
  • Use Generalization, Statistics, Normalize, Routine Questioning
    ▪ Has this illness affected the way you feel about yourself as a man/woman?
    ▪ Has this condition interfered with your being a husband/wife/father/partner?
    ▪ Often times individuals find that cancer treatments impact ones ability to perform sexually? What happens when you and your partner try to make love?

Woods assessment questions:
Penson, Gallagher, Gawika et al.2000
Permission
Examples of questions broaching the subject of sex

Routine questioning
"I always ask whether patients are having any relationship or sexual problems. Your sexual health is an important part of your life. Sometimes an illness or medication can affect your sexuality. How has your relationship been going lately?"

Generalizing
"People with chronic renal failure often experience sexual difficulties, such as loss of desire or problems with enjoyment. How have you been affected?"
McInnes, Rosemary MJA 2003; 179: 263–266

Permission

Normalizing
"When a woman receives a diagnosis of breast cancer it’s normal for her to be concerned about how treatment might affect her sex life. What worries have you had?"

Using statistics
"Over (80% of men with peripheral vascular disease, prostate cancer, etc) report problems with sex, such as difficulty gaining and keeping an erection. What changes have you noticed?"
McInnes, Rosemary MJA 2003; 179: 263–266

Limited Information: Education

Providing Limited Information needed to function sexually

- "Yes, I find that a lot of patients I work with...  
  - experience anxiety around performance,  
  - have a lot of questions about fertility,  
  - experience vaginal dryness  
  ...from cancer and its treatments"
Limited Information

- As simple as giving each patient:
  - Create a Resource List
    - Books/Pamphlets, Lubricants, Contraception, Information on Safety issues/positions
    - Other disease specific resources/websites
  - Provide a referral list of
    - PT who know pelvic floor exercises
    - GYN/Endocrinologist/Urologist who is willing to discuss sexual concerns
    - Sex Therapist (www.aasect.org)
    - Oncology Social Worker or Counselor who specializes in cancer or chronic illness
    - Websites or information that has reliable sexual health information

Specific Suggestions: Counseling

- Giving Specific Suggestions for the individual/couple to proceed with sexual relations and/or intimacy
  - Reinforce that an Orgasm does not need to be present to have an enjoyable sexual experience
  - Understand their definitions of sexuality/intimacy/sex and the impact of their cultural and religious values
  - Address in further detail common areas of concern, i.e.:
    - Partner’s reaction, concerns about attractiveness
    - Performance anxiety
    - Fear of pain
    - “When do I disclose?”
    - Safety Concerns
    - Loss of desire

Specific Suggestions: Pain & Fatigue

- Plan for time of day pain is weakest and when most refreshed
- Take pain medication one hour prior to intercourse
- Coital Positions: position self most comfortably (i.e. avoid weight bearing positions, use pillows to protect joints, etc.)
- Use lubricants and vaginal dilators if indicated
- Practice deep breathing or relaxation techniques
- Encourage foreplay and/or massage prior to intercourse
- Use silk sheets, they help with easier movement
- Exercise combats fatigue and helps relax and warm muscles
- Assess for depression
Specific Suggestions:
Loss of Desire and Performance Enhancers

**Men**
- Viagra, Levitra, Cialis
- MUSE or Caverject
- Penile pumps or Penile Implants
- Viagra 50-100 mg 1 hr prior to intercourse

**Women**
- Estradiol-releasing vaginal ring (Estring), Vagifem, Premarin (for non-estrogen sensitive cancers)
- Eros-C, Vibrator, Dilators, Personal Lubricants
- Clitoral sensitivity creams

**Both**
- Bupropion (Wellbutrin) 75 - 150 mg prior to sex
  - For patients that are on antidepressants and experiencing erection problems or delayed ejaculation, possibly for lowered orgasmic response
  - Mathias et al., 2006 reported improvement in female survivors’ sexual function at 150mg
- Buspirone (Buspar) 40-50mg QD

Specific Suggestions:
Loss of Desire

- Assess for depression & anxiety (Depression is 15% - 25% more prevalent in cancer patients)
  - If anxious – Sensate focus exercises, medication
  - If depressed – medication, self-esteem building exercises
- Assess patient/partner’s expectations for sexual activity and intimacy
- Encourage activities that do not involve sexual intercourse
- Assess for fatigue and interventions
- Normalize the loss of desire experience, changes in body image, etc.
- Recognize the need for “desire” to become a “mind thing” vs. a “body thing” (esp. for women)

Specific Suggestions:
Testosterone levels may decrease in both sexes as a result of cancer treatments or the use of opioids

- Testosterone replacement by injection or patch is often effective in restoring normal sexual function in men who have clinically low levels of serum testosterone (who have not had prostate cancer). Has not yet been proven to be clinically effective in women; however, many women report improvement with testosterone/progesterone creams.

- 200mg of testosterone enanthate or cypionate intramuscularly every 2 weeks (McKee, Schover 2001)
Pharmacologic Interventions for Patients on SSRI’s

- **Antidepressants**
  - May experience delayed orgasm or anorgasmia (especially with SSRIs)
  - May benefit from dose reduction or medication change
- **Dosage recommendations along with SSRI from NCI literature on ‘Sexuality and Cancer’, 2004**
  - Cyproheptadine (Periactin) 4-16 mg/day or 4-6mg 2hrs prior to intercourse
  - Viagra 50-100 mg 1 hr prior to intercourse
  - Buspirone (Buspar) 40-50mg QD


Specific Suggestions: Performance Anxiety/ Fear of Rejection

- Exploration of self perception and exercises for self esteem
- Providing specific suggestions on common overlooked effects that impact sexual health
  - Pain & Fatigue
  - Ostomy or stoma information/suggestions
  - Odor or mouth problems
  - Instruction on bowel and bladder management
- Reminding the patient, that often it is not about them and there may be some underlying communication problems or fears on the partner’s part

Body Image Exercises

- Identify negative thoughts and try to replace with positive thoughts and affirmations
- Practice Positive Affirmations
  - "I accept my body I will do everything I can to love and help it heal"
  - "My body supports my healing process"
- Focus on the things that haven’t changed or that other people compliment you on (find three things you like about yourself)
- Meditation and Relaxation
- Celebrate the person you are and the body you have
Specific Suggestions: Dating and Disclosure

Dating and disclosure concerns are often the same as before cancer, but AMPLIFIED. Encourage patient to know him/her self first.

- The unknown – “the illusion of control”
- Fear of being rejected
- Disclosure:
  - How, what, and when do I tell?
  - “Who would want me now?”
- Differences in sex drive or sexual performance
- Falling in love and being hurt
- Know your treatment, risks, late effects, etc

Specific Suggestions: Performance Anxiety/ Fear of Rejection

- Orgasm:
  - Sensate focus exercises (see handout)
  - Re-explore pleasurable body experiences alone
  - Kegel exercises
- Disclosure:
  - Role play with a friend
  - Discuss story in multiple settings
  - Patient should educate self on implications of treatment on sexuality & fertility
  - Identify intimate relationships in which they would feel comfortable asking questions, sharing their story, showing their scars, etc.

Specific Suggestions: Stomas

- Wear an opaque pouch or pouch cover
- If ostomy requires irrigation, complete before sexual activity and empty prior
  - wear a closed-end pouch, a minipouch or stoma cap during sexual activity
- If patient has worry about the bulk of the appliance
  - Use a fancy cover
  - Crotchless panties for women
  - Tuck it into a cummerbund, belt, sash or fancy slip
  - Make sure appliance fits well
  - Tape it down carefully during activity
  - Find a sexual position that does not put weight on the device
- Educate around safety issues of stoma
- www.cmmostomysupply.com
Specific Suggestions: Mouth & Odor Problems

- Keep your mouth moist, always have water with you
- Clean your mouth, tongue, and gums
- Clean your dentures often and make sure they are a good fit
- Chew sugar free gum to manage odor
- Kissing may not be an option due to mucositis, lack of control, breathlessness, pain or dry mouth
- Be creative:
  - Minimize activities around food if it makes you uncomfortable
  - Touch, cuddle, caress instead of kissing
  - Change coital positions (side by side position) or find other enjoyable activities that provide you with intimacy
  - Partner can put lavender oil under nose

Vaginal Dilators

- Use during and after radiation to pelvis, cervix, vagina and reconstruction surgery
- Assists in learning to relax vaginal muscles
- Even if patient is not sexually active, it is important to maintain patency for exam comfort
- Scar tissue may form during healing process and possibly years after XRT
- Must be used early in treatment to maximize efficacy

Specific Suggestions: Performance Enhancement

- Artificial lubrication: Astroglide, Albolene, Gyne-Moistrin, K-Y Personal Lubricants, Replens, Vitamin-E oil, Plain yogurt
- Deep breathing & Relaxation techniques
- Enhancement aids (clitoral warming creams, Eros-C, candles, setting the stage, etc.)
- Mutual masturbation
- Changing coital positions
- Fantasy and erotica
- Oral sex (use dental dams for ‘safe sex’)
- Use pillows for support and protection
- Take a warm bath or shower before sex
Specific Suggestion

“I provide my patients with actual prescriptions for dildos for vaginal conditioning. It helps them overcome their embarrassment when they go to sex shops or feminist stores to purchase these items.”—Marisa Weiss, M.D.

Could we do the same for penile pumps, lubricants, or other sexual health items that may carry stigmas for some our patients?

Specific Suggestions:
Fertility Preservation

Females
- Egg Freezing
- Ovarian tissue freezing
- Ovarian shielding / transposition
- Radical trachelectomy
- Embryo freezing (ethical considerations)
  - Gonadotropin-releasing hormones (GnRH)

Males
- Sperm banking
- Testicular tissue freezing
- Radiation shielding
- Intracytoplasmic sperm injection (ICSI)

Specific Suggestions:
Fertility

- Surrogacy (not legal in all states)
- Adoption (some require a 5 year “cancer free” letter)
- Refer to Infertility Clinics
- Fertile Hope - www.fertilehope.org
Specific Suggestions: Maintaining Sexual and Intimate Moments

- Redefine “normal”
- Can have a good intimate relationship without sex, focus on shared interests and pleasurable activities
- Find other ways to be sexual: sometimes being naked together is the most intimate experience
- Go slowly at first (allow time to get used to the scars, spend time touching, etc)
- Ask for more foreplay
- Find ways to feel more sexual and sensual
- Adapt social life to meet needs

Specific Suggestions: Maintaining Sexual and Intimate Moments

Specific Suggestions:
- Maintaining intimacy with children
- Maintaining intimacy with partner
- Maintaining intimacy with friends / family

Specific Suggestions: End of Life

For the couple:
- Clearly outline what self-care activities can be done independently, which require assistance from the partner and which require professional help
- Set clear boundaries between caregiving time and couple time
- If cognitive ability is affected, capacity for intimacy may be lost and they must develop a new relationship
- Encourage partner to lie in bed with person with cancer, hold hands, give foot massage, read a book
- Sometimes the most private things, such as helping with self care, can be the most intimate connection

Esmail, Esmail & Munro. 2001. Sexuality and Disability 19:4
Specific Suggestions:
End of Life

- Find other ways of connecting intimately with friends, family or children
- If inpatient
  - Allow the patient to dictate to you whom he/she would like to see and if they would like you to create privacy
  - Provide opportunities for privacy – do we need to be interrupting?
  - Get creative if there are non-private rooms
    - Can the roommate be taken for a walk? Is there a family room? Can the roommate wear headphones to watch TV or listen to music?

Intensive Therapy:
Referral

- Providing Intensive Therapy surrounding the issues of sexuality for that patient/caregiver
  - Know your limits and skills
  - Refer to trusted network
  - Provide support and compassion

PLISSIT

- Permission (Assessment)
- Limited
- Information (Education)
- Specific
- Suggestions (Counseling)
- Intensive
- Therapy (Referral)

Can work in any health care setting
“Today, the physician [nurse, PT, social worker] who treats oncologic diseases should no longer join the collusion of silence about sexuality any more than he should join the collusion of silence about death. Sexuality [and intimacy] is part of life and, hence, a part of cancer patients and their families.”


Biological Effects

- Effects and side effects of medications
- Sexuality or sexual desire may be altered through interference with hormonal activity
- Vascular and neural integrity of genitalia
- Reduced cardiovascular and pulmonary function (causing fatigue & shortness of breath)
- Surgical procedures and medical treatments that may alter appearance and function
- Joint and muscle problems/pain (Fibromyalgia, Lupus, Parkinson’s)

McInnes, Rosemary  MJA 2003; 179: 263–266

“Safe” Sex: preventing infection

- Urinate after sex (prevent yeast infection)
- Wash hands before and after sexual contact and after using the bathroom
- Avoid sexual contact with people who may have infections and transmissible diseases like colds, flu, or cold sores
- Clean the rectum thoroughly after bowel movements
- Remember to take caution with oral sex as well
- Use birth control (condoms usually best option)

Sensate Focus Exercise

Phase 1: Each partner takes a turn touching and being touched. Try many types of touching, varying light stroking and a firmer touch, as in a massage.
- One partner lies face down on the bed, allowing the other partner to touch the entire back, from toes to scalp
- Turn over (after ~15 min) so the front of the body can be touched
- While being touched pay attention to your own feelings
- When you are doing the touching, enjoy the shape and texture of your partner’s body
- The first touching session should avoid genitals and breasts. Your goals are to feel relaxed and to experience sensual pleasure. It is not important to get sexually excited.
Sensate Focus Exercise

Phase 2: If you both feel relaxed during the first touching session, you can add some genital touching the next time

- Over several sessions, partners can slowly spend more time on genital touching, until each one can reach an orgasm
- Stroking with a hand or through oral sex, if that is comfortable for both of you. Penetration not necessary or recommended for several sessions, if at all.

Specific Suggestions: Stomas

- Worry about gas or watery discharge
  - Check and empty pouch just before sexual activity
  - Avoid food that may cause strong odor or gas
  - Use other intimacy suggestions to manage anxiety
- Choose a position for sexual intercourse that protects your ostomy to keep weight off pouch
- Assure your partner that the stoma will not get hurt during sexual activity to lower anxiety
- Make sure your partner and you remember that gas is natural - with or without a stoma!!

Pharmacologic Interventions for Patients on SSRI’s

- Antidepressants
  - May experience delayed orgasm or anorgasmia (especially with SSRI’s)
  - May benefit from dose reduction or medication change
- Dosage recommendations along with SSRI from NCI literature on ‘Sexuality and Cancer’, 2004
  - Cyproheptadine (Periactin) 4-16 mg/day or 4-6 mg 2 hrs prior to intercourse
  - Viagra 50-100 mg 1 hr prior to intercourse
  - Buspirone (Buspar) 40-50 mg QD

Resources

- The American Medical Association has developed a workshop curriculum to train physicians to talk about sex and sexuality with patients, [http://www.ama-assn.org](http://www.ama-assn.org)
- The American Cancer Society, [http://www.cancer.org](http://www.cancer.org)
- The American Association of Sex Educators, Counselors and Therapists, [http://www.aasect.org](http://www.aasect.org)

Resources:

- [www.fertilehope.org](http://www.fertilehope.org): fertility information
- [www.cancer.org](http://www.cancer.org): sexuality, fertility, managing side effects
- [www.gayhealth.com](http://www.gayhealth.com): LGBT resources
- [www.faceit.org](http://www.faceit.org): resource for people affected by facial disfigurement
- [www.cmostomysupply.com](http://www.cmostomysupply.com): Ostomy covers and resources
- [www.planetcancer.org](http://www.planetcancer.org): Young Adults with Cancer
- [www.ulmanfund.org](http://www.ulmanfund.org): Young Adults with Cancer
- [www.lls.org](http://www.lls.org): Leukemia and Lymphoma Society
  Fact Sheets on Sexuality and Intimacy and Fertility
- [www.y-me.org](http://www.y-me.org): Colon Cancer Alliance
- [www.cmmostomysupply.com](http://www.cmmostomysupply.com): CM Ostomy Supply
- [www.y-me.org](http://www.y-me.org)
**Resources for AYA**

- [http://www.youngwomenshealth.org/cancer.html](http://www.youngwomenshealth.org/cancer.html)
- [http://www.planetcancer.org](http://www.planetcancer.org)
- [http://fertilehope.org](http://fertilehope.org)

**Additional References**

- Meston Laboratory at the University of Texas: [http://homepage.psy.utexas.edu/homepage/group/MestonLAB/resources_sexuality.htm](http://homepage.psy.utexas.edu/homepage/group/MestonLAB/resources_sexuality.htm)
Sexuality and Illness
This information is not written or provided as a treatment guideline but rather suggestions for your sexual health. Please consult with your health care professional if you have concerns or questions.
Compiled by Sage Bolte, PhD, LCSW. OSW-C. Life with Cancer ®. Fairfax, VA, sage.bolte@inova.org

Suggested Lubricants:

Adequate lubrication is an important part of positive sexual interaction. Below are listed lubrications that are widely available in pharmacies over the counter. This does not attempt to be a complete list and lubrications are not contraceptives.

Vaseline and other petroleum-based gels are not recommended because they are not water-soluble. They also weaken latex and can cause condom tears.

Astroglide
K-Y Personal Lubricants
Replens gel
Replens: Inserted by applicator.
Lubrin: A suppository (good for women post radiation). Most post-menopausal women find this is a helpful lubricant because it lasts longer.
Femigel: Natural product from tea trees. For vaginal dryness. Order on web www.gardenco.uk/
Sylk: Natural product from kiwi fruit vine and purified water. Marketed through Whole Foods. Call 1-888-853-4773 or email them at genevausa@aol.com
Wet: Often only found in adult erotica stores. Very little residue and is not as sticky as some.
Vitamin E oil: Available in health food stores. Get as oil and make sure it is only vitamin E for no irritation. Long lasting. (Not to be used as a lubricant with sexual activity, but as one to help with dryness and help improve elasticity of vagina)
Albolene - This is not sold as a lubricant, it's actually a makeup remover. It is made up of petrolatum, mineral oil, cerasin, and paraffin. This is oil-based, so do not use with latex condoms. Can also be used as a massage agent.

Plain yogurt – This can be used to both help with maintaining the PH balance of the vagina as well as help with moisture. Apply internally daily with either a dilator, applicator or finger.

Vaginal Dilators and Periometers:
Ask your Dr. for a referral to the local physical therapist or gynecologist who specializes in Women’s health

Syracuse Medical Devices, Inc
315-637-9275

Cooper Surgical - Milex Dilators 800-621-1278

PMTx Periometer 888-442-4689

Pure Romance – www.pureromance.com
Websites:

Information & Support (Fertility and Sexuality, Chat Rooms, Blogs, Resources)

- [http://www.faceit.org](http://www.faceit.org) Resource for people affected by facial disfigurement:
- [www.sexualhealth.com](http://www.sexualhealth.com)
- [www.ulmanfund.org](http://www.ulmanfund.org) A resource for young adults with cancer
- [www.planetcancer.org](http://www.planetcancer.org) A resource for young adults with cancer
- [www.i2y.org](http://www.i2y.org) A resource for young adults with cancer
- [www.youngsurvival.org](http://www.youngsurvival.org) A resource for young women with breast cancer
- [www.cancerbackup.org](http://www.cancerbackup.org)
- [www.fertilehope.org](http://www.fertilehope.org) A resource on fertility information and support
- [http://www.plannedparenthood.org](http://www.plannedparenthood.org)

Variety of discussion, chat and resources for multiple 'disabilities', including the LGBT community: [http://sexsupport.org/index.html](http://sexsupport.org/index.html)

Sexuality and Disability Webliography (videos, devices, books, etc).
- [http://www.bccpd.bc.ca/i/pdf/WDI/Sex_DisabilityWebliog.pdf](http://www.bccpd.bc.ca/i/pdf/WDI/Sex_DisabilityWebliog.pdf)

Finding a Sex Therapist: The American Association of Sex Educators, Counselors and Therapists, [http://www.aasect.org](http://www.aasect.org)

Enhancement Aids and Information
- [www.goodvibes.com](http://www.goodvibes.com)
- [www.babeland.com](http://www.babeland.com)
- [www.libida.com](http://www.libida.com)
- [www.slumberparties.com](http://www.slumberparties.com)
- [www.bettersex.com](http://www.bettersex.com)
- [www.pureromance.com](http://www.pureromance.com) – has a survivorship section on their website

Books


Fundamentals of Coagulation

or
DIC in three easy pieces

Points to Ponder

- Hemophilia A and B are major bleeding disorders
- John Hageman died of a massive pulmonary embolus
- Homozygous Factor VII deletion is an embryonic lethal condition

Hemostasis

- The Biochemical Pathways
  - Coagulation
  - Natural anticoagulation
  - Fibrinolysis
A Model of Blood Coagulation

http://www.icsi.berkeley.edu/~snarayan/clot.pdf

Blood Coagulation

Trigger

Magic

Fibrin Clot

Tissue Factor is the Trigger

- Transmembrane protein
- Found everywhere
  - Except in the bloodstream
  - Deletion is lethal
- Cofactor for Factor VIIa activity
  - Factor X activation – static system
  - Factor IX activation – flowing system
- TF-VIIa is rapidly inhibited by TFPI
Blood Coagulation

Tissue Factor

Magic

Fibrin Clot

Fibrin Clot Formation

- Requires thrombin
  - Major coagulation effector enzyme
  - Converts Fibrinogen to Fibrin
  - Activates Factor XIII
    - FXIIIa crosslinks Fibrin
  - Activates Platelets
Fibrin and Fibrinogen

- Fibrinogen
  - Soluble, digested by plasmin
- Fibrin
  - Weak clot, easily digested by plasmin
- Gamma crosslinked Fibrin
  - Strong clot, can be digested by plasmin
- Alpha crosslinked Fibrin
  - Strong clot, resists plasmin digestion

Blood Coagulation

Tissue Factor

Magic

Fibrin Clot

Magic

Tissue Factor (TF) - VIIa - FIXA - FX - FXa - Thrombin
Natural Anticoagulation

- Antithrombin 3
  - a.k.a. Heparin Cofactor
  - a.k.a. antithrombin

- Protein C System
  - Protein S
  - Thrombomodulin

Heparin Cofactor Activity

Blood Coagulation

- Tissue Factor
  - Coagulation Cascade
    - Crosslinked Fibrin Clot
    - Thrombin
Protein C System

Blood Coagulation

Fibrinolysis

- Triggered by aPC
- Plasmin is the effector enzyme
- Relatively non-specific serine protease
- Fibrin specificity is conferred by activation mechanism
Fibrinolytic System

Hemostatic System

Defective Hemostasis

- Decreased thrombin/plasmin ratio
  - Severe deficiency of a single factor
    - Hemophilia
    - Immune inhibitors
  - Combined deficiency of many factors
    - Vitamin K deficiency
    - Liver disease
  - Anticoagulation
    - Warfarin
    - Heparin
  - Angiotensin, Refrulan, Angiomax
  - Excess Fibrinolysis
    - Liver disease
    - Thrombolytic therapy

- Severe deficiency of a single factor
  - Hemophilia
  - Immune inhibitors
- Combined deficiency of many factors
  - Vitamin K deficiency
  - Liver disease
- Anticoagulation
  - Warfarin
  - Heparin
- Angiotensin, Refrulan, Angiomax
- Excess Fibrinolysis
  - Liver disease
  - Thrombolytic therapy
Coagulation

It’s how you look at it that matters

Three Stages of DIC

- Stage 1 - Prothrombotic
- Stage 2 - Defective hemostasis
- Stage 3 - Hemorrhagic

Coagulation Cascade

- Tissue factor is the trigger
- TF:VIIa activates factor IX
- Low baseline activity
- Antithrombin III is the major control
Intrinsic and Extrinsic Pathways

- Biochemical construct to explain clotting in a test tube.
- In static blood FVIIA/TF activates FX
  - Does not explain why hemophiliacs bleed
- In flowing blood FVIIa/TF activates FIX
  - Does explain why hemophiliacs bleed

Procoagulant System

- Dependent on thrombin (IIa)
- Activates factors V and VIII
- Causes more than 10,000 fold amplification
- Positive feedback loops

Stage 1 - Prothrombotic

- The hypercoagulable state
- Common in association with cancer
- Due to tissue factor exposure
  - Perhaps on microparticles
- Role of the cancer procoagulant ??
**Stage 1 - Prothrombotic**

- Excess fluid phase thrombin
- Consumption of ATIII
- Activation of FV and FVIII
  - short aPTT
- Activation of platelets
  - thrombocytopenia
- Treat with low dose heparin

**Anticoagulant System**

- Protein C is activated by thrombin (IIa) with thrombomodulin
- Protein S is an obligate cofactor for PCa
- Factor Va is the critical target of PCa
- Negative feedback loops

**Stage 2 - Defective Hemostasis**

- Mild or Early DIC
- Classic "consumption" coagulopathy
- Prolonged PT and aPTT
- Low factor V and Factor VIII
- Thrombocytopenia
- Generalized easy bleeding
Stage 2 - Defective Hemostasis

- Excess fluid phase PCa
- Destruction of Va and of VIIIa by PCa
- Consumption of protein C inhibitor
- Further consumption of antithrombin III
- Treat by replacing missing factors
  - Cryoprecipitate, platelets, AT3, plasma

Fibrinolytic System

- Basis for Genentech’s success
- Fibrin is both cofactor and target
- Plasmin is NOT very specific
- Excess plasmin destroys all clotting factors

Stage 3 - Hemorrhagic

- Late or Severe DIC
- Marked prolongation of PT and aPTT
- All clotting factors decreased
- Marked reduction in antithrombin III, protein C and protein C inhibitor
- Marked hypofibrinogenemia
- Spontaneous rebleeding from old wounds
Stage 3 - Hemorrhagic

- Excess fluid phase plasmin
- Fibrinolysis, fibrinogenolysis and generalized proteolysis
- Dissolution of hemostatic plugs
- Destruction of platelet receptors
- Treatment requires an antifibrinolytic agent, factor replacement and possibly heparin

Causes of DIC in Cancer

- Sepsis induced monocyte tissue factor
- Tumor expressing tissue factor
- Necrotic tissue exposing tissue factor
- Cancer procoagulant activating factor X

Treatment of DIC in Cancer

- Remove the cause
- Inhibit the active factors
  - low dose heparin
  - activated protein C, hirudin
  - Tick anticoagulant peptide, Draculin
- Replace the missing factors
  - cryoppt, F IX complex, platelets, ATIII
  - plasma, need not be fresh frozen
Diagnosis of Stage 1 DIC

- High index of suspicion
- Unexplained thrombocytopenia
- No response to transfused platelets
- Short aPTT with normal fibrinogen
- Require some elevation of D-dimer

Diagnosis of Stage 2 DIC

- New onset bleeding
- Prolonged PT and aPTT
- Thrombocytopenia
- Low fibrinogen, high level of D-dimer
- Low factor V and factor VIII, other factors normal
- Decreased level of ATIII

Diagnosis of Stage 3 DIC

- Rebleeding from old wounds
- Markedly prolonged PT and aPTT
- Severe thrombocytopenia
- Very low fibrinogen, and very high level of D-dimer
- Low levels of all clotting factors
- Marked decreased level of ATIII
Treatment of DIC

- Stage 1  Heparin
- Stage 2  Cryoprecipitate and platelets
  - Antithrombin III
- Stage 3  Antifibrinolytic after heparin
  - Cryoprecipitate, platelets,
  - FIX complex, Antithrombin III

Coagulation

It’s how you look at it that matters

From my Point of View
The DIC Paradigm

Stage 0
- Heparin

Stage 1
- Thrombin
- Factor VIII and platelets
- Antithrombin III

Stage 2
- Antifibrinolytic agent
- All clotting factors

Stage 3
- PCa
- Plasmin

Time
- Depletion of ATIII
- Ongoing stimulus

Thrombin
- PCa
- Plasmin
Update in Myeloma Therapy

Kenneth C. Anderson, MD
Jerome Lipper Multiple Myeloma Center
Dana-Farber Cancer Institute
Harvard Medical School

Disclosures: Consultant and Research Support from Celgene, Millennium, and Novartis

Historical Perspective of Multiple Myeloma

Integration of Novel Therapy Into Myeloma Management

Bortezomib, Lenalidomide, Thalidomide, Doxil

Target MM in the BM microenvironment to overcome conventional drug resistance in vitro and in vivo
Effective in Relapsed/Refractory MM
Effective as Induction/First-line Therapy in Combination
Prevention/Transplant Consolidation/Maintenance
Outcome of Novel Therapy In Myeloma Management

Six FDA/EMEA Drug Approvals in Last Five Years

Median survival prolonged from 3-7 years (especially in younger patients)

Three phase III trials of novel agents ongoing for FDA approval

Multiple Myeloma NCCN Practice Guidelines (2009)

Criteria for Diagnosis of Myeloma

Lenalidomide 25 mg/daily during 21 d every 28 d

Dexamethasone 20 mg D1-D4 and D12-D15 every 28 d

Therapeutic Abstention

Induction:
Nine 4-wks cycles

Median TTP in control arm: 19 months
16 out of 47 pts in control arm progressed, 10 with bone lesions
No progressions in treatment arm

High-Risk Smoldering MM

Treatment arm

Lenalidomide 25 mg/daily during 21 d every 28 d

Dexamethasone 20 mg D1-D4 and D12-D15 every 28 d

Therapeutic Abstention

Control arm

Lenalidomide 10 mg/daily during 21 d every 2 months

Therapeutic Abstention

MP vs MPT in Newly Diagnosed or Transplant-Ineligible Myeloma

• Meta-analysis of 5 prospective randomized clinical trials (N = 1571) of MPT vs MP
  – Rationale: unclear whether adding thalidomide to MP improves PFS and OS, conflicting results in previous studies

• Addition of thalidomide to MP improved response rates, PFS, and OS vs MP alone
  – Odds ratio for PR with MP vs MPT: 0.307 (P < .001), indicating MP worse than MPT
  – HR for PFS: 1.59 (P < .001) in favor of MPT
  – HR for OS: 1.34 (P = .006) in favor of MPT


Secondary Comparison

MPR-R vs. MPR
Addition of MPR arm per EMEA advice

MP
M: 0.18 mg/kg, days 1-4
P: 2 mg/kg, days 1-4
R: 10 mg/day po, days 1-21
PBO: days 1-21

Primary Comparison

MPR-R vs. MP

MPR
M: 0.18 mg/kg, days 1-4
P: 2 mg/kg, days 1-4
R: 10 mg/day po, days 1-21
Placebo

Phase III Study Schema

N=459, 82 centers in Europe, Australia and Israel

Stratified by age (≤ 75 vs. > 75 years) and stage (ISS 1,2 vs. 3)

Palumbo et al, ASH 2009
Best Response

<table>
<thead>
<tr>
<th></th>
<th>MPR-R</th>
<th>MPR</th>
<th>MP</th>
<th>P Value (MPR-R vs. MP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>77%</td>
<td>67%</td>
<td>49%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CR</td>
<td>18%</td>
<td>13%</td>
<td>5%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥ VGPR</td>
<td>32%</td>
<td>33%</td>
<td>11%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PR</td>
<td>45%</td>
<td>34%</td>
<td>37%</td>
<td>---</td>
</tr>
<tr>
<td>Progressive Disease</td>
<td>0%</td>
<td>1%</td>
<td>0%</td>
<td>---</td>
</tr>
<tr>
<td>Median time to first response, months</td>
<td>1.9</td>
<td>1.9</td>
<td>2.8</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

a. As measured using EBMT criteria
b. Immunofixation negative with or without bone marrow confirmation
c. VGPR: >90% reduction in M protein


Palumbo et al, ASH 2009

Time to Next Treatment

63% Reduced Risk for Next Treatment

HR 0.369
95% CI [0.243, 0.559]
Logrank P<0.001

MPR-R vs. MPR

47% Reduced Risk in PFS

HR 0.530
95% CI [0.335, 0.832]
Logrank P<0.002

Palumbo et al, ASH 2009
MPR-R vs. MPR
Landmark PFS Analysis After Cycle 9
75% Reduced Risk in PFS

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>MPR-R</th>
<th>MPR</th>
</tr>
</thead>
<tbody>
<tr>
<td>75</td>
<td>40</td>
<td>17</td>
</tr>
<tr>
<td>61</td>
<td>21</td>
<td>8</td>
</tr>
</tbody>
</table>

HR 0.245
95% CI [0.126, 0.476]
Logrank P<0.001

- G-CSF administration (49% MPR-R vs. 29% MP)
- Platelet transfusion (6% MPR-R vs. 5% MP)

Grade 3/4 Hematologic Adverse Events

VISTA: VELCADE as Initial Standard Therapy in multiple myeloma: Assessment with melphalan and prednisone

- Randomized, international, phase III trial of VMP vs MP in previously untreated MM patients who were not candidates for HDT-ASCT
- Patients: Symptomatic multiple myeloma/end organ damage with measurable disease
  - ≥65 yrs or <65 yrs and not transplant-eligible; KPS ≥60%

- Primary Endpoint: TTP
- Secondary Endpoints: CR rate, ORR, TTR, DOR, PFS, TNT, OS, QoL (PRO)

VMP
- Cycles 1-4: Bortezomib 1.3 mg/m² IV: days 1,4,8,11,22,25,29,32, Melphalan 9 mg/m² and prednisone 40 mg/m² days 1-4
- Cycles 5-9: Bortezomib 1.3 mg/m² IV: days 1,8,15,22,29, Melphalan 9 mg/m² and prednisone 40 mg/m² days 1-4

MP
- 9 x 6-week cycles (54 weeks) in both arms
- Cycles 1-9: Melphalan 90 mg/m² and prednisone 40 mg/m² days 1-4
VISTA: VMP vs MP Updated Follow-Up and Results of Subsequent Therapy

- Conclusions:
  - Updated data with over 3-year follow-up confirm that VMP results in significantly longer OS vs MP
  - OS benefit seen overall and in analysis of subsequent therapy
  - Pts received VMP derived greater clinical benefit (TNT, TFI) than pts receiving MP
  - Subsequent salvage therapies were similarly effective in pts from both arms, demonstrating that use of bortezomib does not preclude use of novel agents at relapse
  - Retreatment with bortezomib-based therapies resulted in a 47% ORR

VMP versus VMPT in Elderly Newly Diagnosed Patients

- 393 patients (older than 65 years) randomized from 58 Italian centers
- Patients: Symptomatic multiple myeloma/end organ damage with measurable disease
  - ≥65 yrs or <65 yrs and not transplant-eligible; creatinine ≤ 2.5 mg/dL

### Response to Treatment

<table>
<thead>
<tr>
<th></th>
<th>VMP (N=253)</th>
<th>VMPT→VT (N=250)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>24%</td>
<td>38%</td>
<td>0.0008</td>
</tr>
<tr>
<td>TTNT @ 3 years</td>
<td>60%</td>
<td>75%</td>
<td>0.0029</td>
</tr>
<tr>
<td>PFS @ 3 years</td>
<td>42%</td>
<td>60%</td>
<td>0.007</td>
</tr>
<tr>
<td>OS @ 3 years</td>
<td>89%</td>
<td>89%</td>
<td>0.96</td>
</tr>
</tbody>
</table>
**Efficacy and Toxicity by Bortezomib Schedule**

Palumbo et al. ASH 2009

<table>
<thead>
<tr>
<th></th>
<th>VMP* (VISTA)</th>
<th>VMP weekly N=62*</th>
<th>once weekly N=190*</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>30%</td>
<td>25%</td>
<td>23%</td>
</tr>
<tr>
<td>PFS @ 2 years</td>
<td>48%</td>
<td>56%</td>
<td>58%</td>
</tr>
<tr>
<td>Sensory PN</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any grade</td>
<td>44%</td>
<td>43%</td>
<td>21%</td>
</tr>
<tr>
<td>Grade 3-4</td>
<td>13%</td>
<td>14%</td>
<td>2%</td>
</tr>
<tr>
<td>PN discontinuation</td>
<td>NA</td>
<td>16%</td>
<td>4%</td>
</tr>
<tr>
<td>Total planned dose</td>
<td>67.6 mg/m²</td>
<td>67.6 mg/m²</td>
<td>46.8 mg/m²</td>
</tr>
<tr>
<td>Total delivered dose</td>
<td>NA</td>
<td>41 mg/m²</td>
<td>40 mg/m²</td>
</tr>
</tbody>
</table>

*San Miguel JF et al. New Eng J Med 2008; 359: 906-17; †3 patients in twice weekly and 1 patient in once weekly group did not receive bortezomib because they never started therapy.
PN: peripheral neuropathy.

---

**Multicenter, Two-stage Randomized Trial in Newly Diagnosed MM Patients Older than 65 Years**

Mateos et al. ASH 2009

**Induction**

- Bort/Mel/Pred (VMP)
- Bort/Thal/Pred (VTP)

**Maintenance**

- Bort/Thal (VT)
- Bort/Pred (VP)

---

**Efficacy: Response Rate After Induction Therapy**

(ITT analysis in 260 patients)

Mateos et al. ASH 2009

**ORR: 80% vs 81%**

*EBMT criteria

- Responses to VMP/VTP were rapid: Median time to achieve first response: 1.6 m
- Prolonged therapy improves the quality of response: Median time to achieve CR: VMP: 4.4 m, VTP: 4.9 m
Efficacy: Response Rate to Maintenance Therapy

(N=178)

CR (IF-) increased from 23% (after induction) up to 42% (maintenance)

CR/nCR: 59% vs 55%

VT = 91
VP = 87

Outcome of the four different cohorts (n: 178)

Cox regression analysis of PFS and OS with inverse probability weighting (p=0.8 for the interaction term)

Len High Dose Dex versus Len Low Dose Dex-ECOG Schema

445 pts

@ 4 months Pts can go off study

Rajkumar et al, ASH 2008
Results of Primary Therapy beyond 4 cycles with Rd

<table>
<thead>
<tr>
<th>“Primary Rd”</th>
<th>(n=140)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Response Rate</td>
<td>91%</td>
</tr>
<tr>
<td>CR* (IF-)</td>
<td>22%</td>
</tr>
<tr>
<td>CR + VGPR</td>
<td>57%</td>
</tr>
<tr>
<td>Grade ≥3 non-heme toxicity**</td>
<td>26%</td>
</tr>
</tbody>
</table>

*measured in serum or urine
**92% with Rd

Rajkumar et al, ASH 2008

Vel/Dex versus VAD Induction Pre Transplant

Primary analysis: post-induction response in VAD (A1+A2) vs Vel-Dex (B1+B2)

Randomization
stratified by β2-microglobulin level (>3mg/L vs ≤3mg/L) and presence of chromosome 13 abnormalities (by FISH analysis)

VAD x 4 | VAD x 4 | Induction | Vel-Dex x 4 | Vel-Dex x 4

DCEP x 2 | DCEP x 2 | Consolidation

Melphalan 200mg/m² + ASCT | Melphalan 200mg/m² + ASCT | Transplant 1 | Melphalan 200mg/m² + ASCT | Melphalan 200mg/m² + ASCT 

Second ASCT or RIC allo if <VGPR

Harousseau et al, ASH 2008

Response To Induction

Evaluable Patients

<table>
<thead>
<tr>
<th>VAD (A1+A2)</th>
<th>N=210</th>
<th>Vel-Dex (B1+B2)</th>
<th>N=214</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>1.4%</td>
<td>6.1%</td>
<td>0.0109</td>
<td></td>
</tr>
<tr>
<td>CR+nCR</td>
<td>6.7%</td>
<td>15%</td>
<td>0.0035</td>
<td></td>
</tr>
<tr>
<td>≥ VGPR</td>
<td>16%</td>
<td>39%</td>
<td>&lt; 0.0001</td>
<td></td>
</tr>
<tr>
<td>≥ PR</td>
<td>65%</td>
<td>82%</td>
<td>&lt;.0001</td>
<td></td>
</tr>
<tr>
<td>MR+SD</td>
<td>28%</td>
<td>13%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PD</td>
<td>4.3%</td>
<td>4.7%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>2.9%</td>
<td>0.5%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Response by IRC assessment

Harousseau et al, ASH 2008
### Response to First ASCT

**Evaluable Patients**

<table>
<thead>
<tr>
<th></th>
<th>VAD</th>
<th>Vel-Dex</th>
</tr>
</thead>
<tbody>
<tr>
<td>(A1+A2) N=213</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>9%</td>
<td>17%</td>
</tr>
<tr>
<td>CR + nCR</td>
<td>19%</td>
<td>37%</td>
</tr>
<tr>
<td>≥ VGPR</td>
<td>38%</td>
<td>57%</td>
</tr>
<tr>
<td>≥ PR</td>
<td>79%</td>
<td>84%</td>
</tr>
<tr>
<td>MR/SD/PD</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>No ASCT</td>
<td>17%</td>
<td>13%</td>
</tr>
</tbody>
</table>

**P value**

- 0.016
- <0.0001
- 0.0003
- NS

Harousseau et al, ASH 2008

### Bort/Dex in Young Newly Diagnosed Myeloma Patients with Poor Cytogenetics

- Analysis of 507 patients in IFM-2005-01 treated with VD + 1-2 courses MEL200
  - Median PFS with vs without t(4;14): 2.32 yrs vs 2.90 yrs (P < .02)
  - 3-year OS with vs without t(4;14): 81% vs 91% (P = .002)
- Results suggest VD induction can partially overcome poor prognosis of t(4;14), but not del(17p)

Avet-Loiseau H, et al. ASH 2009

### CALGB 100104 Schema

- 3-D Stage 1-3, <70 years
- 2 cycles of induction
- Attained SD or better
- ≤ 1 yr from start of therapy
- 2 x 10^6 CD34 cells/kg

Stratification based on diagnostic β2M and thalidomide and lenalidomide use during Induction

McCarthy et al, ASCO 2010
Results

• TTP was defined as disease progression or death due to any cause
• TTP was calculated from day 0 of ASCT
• Of 210 lenalidomide pts, 29 have experienced an event (progression or death)
• Of 208 placebo pts, 58 have experienced an event (p < 0.0001)
• Estimated hazard ratio of 0.42, thus a 58% reduction in the risk of disease progression with lenalidomide

McCarthy et al, ASCO 2010

Median Follow up from ASCT is 12 months

McCarthy et al, ASCO 2010

There is not long enough follow up to determine if there is a difference in OS; 11 deaths in lenalidomide arm and 17 deaths in the placebo arm (p=0.2)
IFM 2005-02: Study design

Phase III randomized, placebo-controlled trial
N=614 patients, from 78 centers, enrolled between 7/2006 and 8/2008

Patients < 65 years, with non-progressive disease, < 6 months after ASCT in first line
Randomization: stratified according to Beta-2m, del13, VGPR

Arm A:
Placebo (N=307) until relapse

Arm B:
Lenalidomide (N=307) 10-15 mg/d until relapse

Consolidation:
Lenalidomide alone 25 mg/day p.o. days 1-21 of every 28 days for 2 months

Atal et al, ASCO 2010

IFM 2005-02: Response* during consolidation (n=572)

<table>
<thead>
<tr>
<th></th>
<th>PRE</th>
<th>POST</th>
<th>p value b</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR (IF -)</td>
<td>13 %</td>
<td>19 %</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>≥ VGPR</td>
<td>58 %</td>
<td>68 %</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Atal et al, ASCO 2010

IFM 2005-02: PFS from randomization

<table>
<thead>
<tr>
<th></th>
<th>Arm A N=307</th>
<th>Arm B N=307</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progression or Death</td>
<td>143 (47%)</td>
<td>77 (25%)</td>
<td></td>
</tr>
<tr>
<td>Median PFS (m)</td>
<td>24 (21-27)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>3-year post rando PFS</td>
<td>34%</td>
<td>68%</td>
<td></td>
</tr>
<tr>
<td>Hazard Ratio</td>
<td>1</td>
<td>0.46</td>
<td>&lt;10^-6</td>
</tr>
</tbody>
</table>

Atal et al, ASCO 2010
**IFM 2005-02 : PFS from randomization**

[Graph showing PFS from randomization with Placebo and Revlimid lines, p<10^-7]

**IFM 2005-02 : OS from randomization**

<table>
<thead>
<tr>
<th></th>
<th>Arm A N=307</th>
<th>Arm B N=307</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths</td>
<td>27</td>
<td>24</td>
</tr>
<tr>
<td>3-year post Rando OS</td>
<td>80%</td>
<td>88%</td>
</tr>
<tr>
<td>Hazard Ratio</td>
<td>1</td>
<td>0.88</td>
</tr>
</tbody>
</table>

**Bortezomib Consolidation Following High-Dose Melphalan: Phase III Study (N=330)**

- **Bortezomib 1.3 mg/m² given twice weekly Q3W in cycles 1 and 2, then weekly Q4W in cycles 3-6**
- **CR/nCR rate at 9 months after ASCT significantly higher (49%) with bortezomib vs control (33%) (P = .01)**
- **Significantly less progression with bortezomib (6%) vs control (12%) (P = .08)**
- **Grade 3/4 toxicities in bortezomib-treated patients**
  - Neutropenia (22%), thrombocytopenia (9%), neurologic pain (5%)

Phase II Study of Lenalidomide, Bortezomib, and Dex (RVD) in Newly Diagnosed MM

Richardson et al, Blood 2010

• Response:
  - ORR (PR or better): 100%
  - CR/nCR: 52%
  - VGPR or better: 74%
  - No effect from adverse cytogenetics on RR, or PFS

• At 19 mos follow up, TTP, PFS, and OS not reached

• Toxicity:
  - Grade > 3 PN in 1 pt only
  - VTE in 2 pts
  - No treatment-related mortality

• Stem cell collection (15/35 pts)
  - Median collection 4.4 x 10^6 CD34+ cells/kg

IFM/DFCI 2009 Study
Newly Diagnosed MM Pts (SCT Candidates)

Randomize

Induction

Collection

Consolidation

Maintenance

Revlimid 18 mos

SCT at relapse

Treatment schedule

• 402 patients (younger than 65 years) randomized from 62 centers
• Patients: Symptomatic disease, organ damage, measurable disease

Rd

Rd* four 28-day courses
- 40 mg/m² days 1-21
- 40 mg/m² days 1-21

MPR

Three 28-day courses
- 0.18 mg/kg/d, days 1-4
- 2 mg/m²/d, days 14
- 10 mg/m², days 1-21

MEL 200

Two courses
- 200 mg/m² day 0
- Stem cell support day 0

Rd

Rd four 28-day courses
- 25 mg/d, days 1-21
- 40 mg/d, days 1, 8, 15, 22

Rd

Rd four 28-day courses
- 25 mg/d, days 1-21
- 40 mg/d, days 1, 8, 15, 22

*Thromboprophylaxis randomization: aspirin vs low molecular weight heparin
R, lenalidomide; M, melphalan; d, dexamethasone; P, prednisone
Palumbo et al, ASCO 2010
Patient Characteristics

Palumbo et al, ASCO 2010

<table>
<thead>
<tr>
<th></th>
<th>MPR (N=202)</th>
<th>MEL200 (N=200)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (median)</td>
<td>58</td>
<td>58</td>
</tr>
<tr>
<td>&lt; 60 years</td>
<td>24%</td>
<td>29%</td>
</tr>
<tr>
<td>ISS (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I + II</td>
<td>76</td>
<td>76</td>
</tr>
<tr>
<td>III</td>
<td>25</td>
<td>24</td>
</tr>
<tr>
<td>del 13 (pos %)</td>
<td>57</td>
<td>47</td>
</tr>
<tr>
<td>del 17 (pos %)</td>
<td>17</td>
<td>13</td>
</tr>
<tr>
<td>t(4;14) (pos %)</td>
<td>16</td>
<td>13</td>
</tr>
</tbody>
</table>

MPR vs MEL200:
Response rate

MPR=117
After 3 cycles

CR  VGPR  PR  SD  PD
13  42  36  7  1

MEL200=122
After 1 cycle

CR  VGPR  PR  SD  PD
16  27  38  5  0

* p=0.82

MPR vs MEL200:
Progression Free Survival

Median follow-up 14.07 months

MPR: PFS @ 12 months = 91%
MEL200: PFS @ 12 months = 91%
P=0.77
MPR vs MEL200:
Overall survival
Median follow-up 14.07 months

MPR: OS @ 12 months = 97%
MEL200: OS @ 12 months = 98%
P=0.27

MPR vs MEL200
Grade 3–4 Adverse Events

MPR (n=117) MEL200 (n=122)

P<0.001
P<0.001
P<0.001
P<0.001

Phase II: Evolution Study

• Eligible patients could undergo ASCT after 4 cycles

Kumar et al ASH 2009
Conclusions

- VDCR, VDR, and VDC (initial and modified) are highly active and generally well-tolerated regimens in previously untreated MM
- Overall rates of most hematologic AEs also appear similar between arms
- Early responses in the VDC-mod arm, especially CRs and VGPRs are encouraging
- Long term follow up required to assess the MRD status and durability of response

Kumar et al ASH 2009

Therapies for Relapsed/Refractory Multiple Myeloma

Approved Therapies:
- Bortezomib (Dex)
- Lenalidomide/Dex
- Bortezomib/Doxil

Proteasome: Present and Future Therapies

Deubiquitylating Enzymes DUBs
P0031 target USP-7

Potential Therapeutic Targets

ATPas/Cal-68

Immunoproasome

Bortezomib, Carfilzomib, CEP-18770
NPI-0052: g5, g1, g2

Free E6 for re-cycling

Degraded protein

265 PROTEASOME
Carfilzomib: A Novel, Selective Proteasome Inhibitor

- Novel chemical class with highly selective and irreversible proteasome binding
  - Potent target inhibition
  - Minimal off target activity
- Improved antitumor activity with consecutive day dosing
  - In vivo, prolonged proteasome inhibition by carfilzomib improved antitumor activity
- No neurotoxicity in animals
  - No histological or behavioral neurotoxicity in animals was observed with chronic dosing

*Oren et al. (2007), Cancer Research, 67:6383
*Yerk et al. (2008) Blood, 112: 2765

PX-171-004 Study Design

Study Population
- Relapsed and/or refractory MM following 1-3 prior treatment regimens

Primary endpoint: Overall response rate (CR+PR) (IMWG criteria)
Secondary endpoints: Duration of response, PFS, TTP, OS, safety

Vij et al ASCO 2010

Single-Agent Anti-tumor Activity BTZ-treated cohort

<table>
<thead>
<tr>
<th>Response rate</th>
<th>Cohort 1 20 mg/m² (N=34)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>0%</td>
</tr>
<tr>
<td>VGPR</td>
<td>9%</td>
</tr>
<tr>
<td>PR</td>
<td>12%</td>
</tr>
<tr>
<td>MR</td>
<td>12%</td>
</tr>
<tr>
<td>SD</td>
<td>35%</td>
</tr>
<tr>
<td>PD</td>
<td>32%</td>
</tr>
</tbody>
</table>

Vij et al ASCO 2010
Time to Progression
BTZ-treated N= 34*

<table>
<thead>
<tr>
<th>Months</th>
<th>0</th>
<th>3</th>
<th>6</th>
<th>9</th>
<th>12</th>
<th>15</th>
<th>18</th>
</tr>
</thead>
<tbody>
<tr>
<td>% history free</td>
<td>100</td>
<td>75</td>
<td>50</td>
<td>25</td>
<td>10</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Vij et al ASCO 2010

Single-Agent Anti-tumor Activity
BTZ-naïve patients*

<table>
<thead>
<tr>
<th>Response Rate</th>
<th>Cohort 1</th>
<th>Cohort 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>20 mg/m²</td>
<td>20/27 mg/m²</td>
</tr>
<tr>
<td>(N=53)*</td>
<td></td>
<td>(N=53)*</td>
</tr>
<tr>
<td>CR</td>
<td>2%</td>
<td>0%</td>
</tr>
<tr>
<td>VGPR</td>
<td>13%</td>
<td>17%</td>
</tr>
<tr>
<td>PR</td>
<td>30%</td>
<td>38%</td>
</tr>
<tr>
<td>MR</td>
<td>13%</td>
<td>8%</td>
</tr>
<tr>
<td>SD</td>
<td>9%</td>
<td>26%</td>
</tr>
<tr>
<td>PD</td>
<td></td>
<td>11%</td>
</tr>
</tbody>
</table>

ORR
45%

CBR
58%
55%
62%

Vij et al ASCO 2010

Time to Progression
BTZ-naïve patients

<table>
<thead>
<tr>
<th>Months</th>
<th>0</th>
<th>3</th>
<th>6</th>
<th>9</th>
<th>12</th>
<th>15</th>
<th>18</th>
</tr>
</thead>
<tbody>
<tr>
<td>% history free</td>
<td>100</td>
<td>75</td>
<td>50</td>
<td>25</td>
<td>10</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Vij et al ASCO 2010
Treatment-Emergent Neuropathy was Infrequent and Not Treatment Limiting

<table>
<thead>
<tr>
<th></th>
<th>Cohort 1 (N=36)</th>
<th>Cohort 2 (N=40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BTZ-treated</td>
<td>20 mg/m²</td>
<td>20/27 mg/m²</td>
</tr>
<tr>
<td>Active Grade 1/2 peripheral neuropathy at baseline*, %</td>
<td>50</td>
<td>42</td>
</tr>
<tr>
<td>Treatment-emergent neuropathy, %</td>
<td>8.6 2.9 0</td>
<td>11.9 0 0</td>
</tr>
<tr>
<td>Grade 1/2</td>
<td>Grade 3</td>
<td>Grade 4</td>
</tr>
<tr>
<td>Treatment discontinuations due to peripheral neuropathy, %</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Vj et al ASCO 2010

Novel Proteasome Inhibitor NPI-0052 Inhibits Human MM Cell Growth and Prolongs Survival in a Murine Model

Phase I clinical trial in myeloma 11/06 Chauhan et al, Cancer Cell, 2005.

NPI-0052: Novel Proteasome Inhibitor

- NPI-0052: second-generation 20S proteasome inhibitor
- Phase I, open-label, dose-escalation study in relapsed and relapsed/refractory myeloma (N = 32)
  - Best response (paraprotein; EBMT criteria): SD in 18 (58%)
  - SD > 6 mo: 9 (38%)
  - Recommended phase II dose: 0.7 mg/m²
- Generally well tolerated
  - Common AEs: fatigue, nausea/vomiting, dizziness, headache
  - No neuropathy, neutropenia, thrombocytopenia

**Pomalidomide in Myeloma**

- MM cells
- Bone Marrow Stromal Cells
- IL-6
- TNFa
- IL-1b
- Bone Marrow Vessels
- ICAM-1
- VEGF
- bFGF
- Dendritic Cells
- NK Cells
- CD8+ T Cells
- Bone Marrow Vessels

**Pomalidomide Efficacy Across Several Trials In Relapsed/Refractory Myeloma**

<table>
<thead>
<tr>
<th>Lacy Pom + dex 1-3 Prior Therapies</th>
<th>Lacy Pom + dex Lenalidomide refractory</th>
<th>Richardson Pom+/- dex MM-002 Ph1</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ PR</td>
<td>63%</td>
<td>32%</td>
</tr>
<tr>
<td>≥ MR</td>
<td>82%*</td>
<td>47%</td>
</tr>
<tr>
<td>Median 3 prior regimens</td>
<td></td>
<td>Median 4-6 prior regimens</td>
</tr>
<tr>
<td>≥ MR</td>
<td>52%</td>
<td></td>
</tr>
</tbody>
</table>

**Adverse Events**

- Most common hematologic AEs seen across all MM studies are neutropenia, thrombocytopenia and anemia
- Most common non-hematologic AEs seen across all MM studies are fatigue, rash
- Incidence of peripheral neuropathy and VTEs infrequent
Rationally Based Combination Therapies

- Bortezomib and Hsp 90 inhibitor
- Bortezomib and doxil
- Bortezomib and NPI-0052
- Bortezomib and perifosine
- Bortezomib and LBH 589
- Bortezomib and Smac peptides
- Bortezomib and Bcl 2 inhibitor
- Bortezomib and p38 MAPK inhibitor
- Bortezomib and HuLuc63
- Lenalidomide and mTOR inhibitor
- Lenalidomide and Anti-CD40 antibody
- Lenalidomide and doxil
- Lenalidomide and HuLuc63
- Lenalidomide and LBH 589
- Lenalidomide and perifosine
- Lenalidomide and Bevacizumab
- Lenalidomide and Vaccine

Phase II Study of Bortezomib and mTOR Inhibitor CCI-779 in Relapsed Refractory MM

- Phase I study established MTD
  - Bortezomib 1.6 mg/m² days 1, 8, 15, and 22 every 35 days
  - CCI-779 25 mg IV days 1, 8, 15, 22, and 29
- 27 pts enrolled
- Responses:
  - MR or better: 79%
    - CR 5%, VGPR 16%, PR 26%, MR 26%
- Toxicity
  - Grade 4 hematologic – thrombocytopenia, anemia, and neutropenia
  - Other: diarrhea, pulmonary toxicity (pneumonitis, DAH)

Ghobrial et al. ASH 2009

Akt Inhibitor Perifosine Enhances Bortezomib-Induced Cytotoxicity in MM Cells

Hideshima et al. Blood 2006; 107: 4053-52
Perifosine/Bortezomib ± Dexamethasone in Relapsed/Refractory Myeloma: Phase I/II

- Long-term follow-up results of phase I/II study (N = 73)

<table>
<thead>
<tr>
<th>Patients</th>
<th>ORR, %</th>
<th>Median TTP, mo (range)</th>
<th>Median OS, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>38</td>
<td>6.4 (5.3-7.1)</td>
<td>&gt; 22.5</td>
</tr>
<tr>
<td>Bort relapsed</td>
<td>55</td>
<td>8.8 (6.3-11.2)</td>
<td>&gt; 25</td>
</tr>
<tr>
<td>Bort refractory</td>
<td>32</td>
<td>5.7 (4.3-6.4)</td>
<td>16</td>
</tr>
</tbody>
</table>

- Grade 3/4 AEs in ≥ 5%: thrombocytopenia, neutropenia, anemia
  Clinical trial of Bortezomib and perifosine versus Bortezomib in relapsed MM ongoing for FDA approval

Richardson P, et al. ASH 2009

Blockade of Ubiquinated Protein Catabolism

Hideshima et al, Clin Cancer Res; 2005; 11: 8530

Panobinostat Bortezomib in Rel or Rel & Ref MM pts
SanMiguel et al, ASCO 2010

- 3 week cycles
- Week 1
  - PAN, TIW QW
  - BTZ
  - Dex
- Week 2
  - PAN, TIW QW
  - BTZ
  - Dex
- Week 3
  - PAN, TIW QW
  - BTZ
  - Dex

TIW QW: three times a week, every week
- Drug dose levels used in dose escalation phase
  - PAN: 10 mg, 20 mg, 25 mg, and 30 mg
  - BTZ: 1.0 mg/m², 1.3 mg/m²
  - (Dex: 20 mg fixed dose added at Cycle 2 in suboptimal responders)
- Pts with MM relapsed after ≥ 1 line of therapy, or relapsed and refractory, and suitable for treatment with BTZ
Panobinostat + Bortezomib Efficacy
San Miguel et al, ASCO 2010

Response Rate (%)

0 10 20 30 40 50 60 70 80 90 100
All (N = 47) BTZ refractory (n = 15)

MR PR VGR CR

Vorinostat-Bortezomib
Webber et al ASH 2008
Effective for treatment of relapsed/refractory MM
Overall response (PR + CR) ~38-43%
SD ~90%
Effective despite prior bortezomib therapy
Overall response ~29-35%
SD ~41-53%
Overall response refractory pts ≥ PR ~29-38%
SD refractory pts ~42-50%
Well Tolerated Fatigue, Diarrhea, thrombocytopenia
Phase III trial of Bortezomib and SAHA versus Bortezomib in relapsed MM ongoing for FDA approval

Anti-CS-1 Mab Elotuzumab Induces Specific MM Cell Lysis

Single agent and combination trials (lenalidamide or bortezomib) ongoing

HuLuc63, μg/ml

CS1

MMR MMIR U266 CD19+ B cells CD19+ B cells
**Conclusions and Future Directions**

1. All patients should receive novel therapies included in initial therapies to improve OR, CR, EFS and OS.

2. The role of high dose therapy in the context of novel therapies is under evaluation.

3. Novel proteasome inhibitors and immunomodulatory drugs offer promise in relapsed disease.

4. Molecularly based rationally designed combination therapies are under evaluation in phase III clinical trials (ie bortezomib with hsp 90 inhibitor, Akt inhibitor, and HDAC inhibitor).
Individualized Management of Advanced Non-Small Cell Lung Cancer Patients
Rogerio Lilenbaum, MD
Current Topics in Clinical Research

- Adjuvant Chemotherapy
  - BR-19 and Metagene CALGB Trial
- New Targets and Agents
  - New Inhibitors
- Patient subsets
  - Elderly and PS 2-3

ADJUVANT CHEMOTHERAPY

WHO SHOULD GET IT?
WHO BENEFITS?
### Overall Survival by trial

<table>
<thead>
<tr>
<th>Trial</th>
<th>No. Deaths / No. Entered</th>
<th>Hazard ratio (Chemotherapy / Control)</th>
<th>HR [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALPI</td>
<td>569 / 1088</td>
<td>0.95</td>
<td>0.81;1.12</td>
</tr>
<tr>
<td>ANITA</td>
<td>458 / 840</td>
<td>0.82</td>
<td>0.68;0.96</td>
</tr>
<tr>
<td>BLT</td>
<td>152 / 307</td>
<td>1.00</td>
<td>0.72;1.38</td>
</tr>
<tr>
<td>IALT</td>
<td>980 / 1867</td>
<td>0.91</td>
<td>0.80;1.03</td>
</tr>
<tr>
<td>JBR10</td>
<td>197 / 482</td>
<td>0.71</td>
<td>0.54;0.94</td>
</tr>
<tr>
<td>Total</td>
<td>2356 / 4584</td>
<td>0.89</td>
<td>0.62;0.96</td>
</tr>
</tbody>
</table>

Test for heterogeneity: p = 0.34

Chemotherapy effect: p = 0.004

---

### ADJUVANT CHEMOTHERAPY

- Adjuvant cisplatin-based chemotherapy improves survival for stage II and III NSCLC
- Issues for further clinical research:
  - Stage-dependent benefit
  - Age and PS-dependent benefit
  - Long term morbidity/mortality
  - Molecular-based selection

---

### CT effect & stage

<table>
<thead>
<tr>
<th>Category</th>
<th>No. Deaths / No. Entered</th>
<th>Hazard ratio (Chemotherapy / Control)</th>
<th>HR [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage IA</td>
<td>102 / 347</td>
<td>1.41</td>
<td>0.96;2.09</td>
</tr>
<tr>
<td>Stage IB</td>
<td>509 / 1371</td>
<td>0.92</td>
<td>0.78;1.10</td>
</tr>
<tr>
<td>Stage II</td>
<td>880 / 1616</td>
<td>0.83</td>
<td>0.73;0.95</td>
</tr>
<tr>
<td>Stage III</td>
<td>865 / 1247</td>
<td>0.83</td>
<td>0.73;0.95</td>
</tr>
</tbody>
</table>

Test for trend: p = 0.051

CT may be detrimental for stage IA, but stage IA patients were generally not given cisplatin+vinorelbine (13% of stage IA patients versus ~43% for other stages)
## Clinical Trial Patients vs. Real World Clinical Population

<table>
<thead>
<tr>
<th>Study</th>
<th>Median Age (2 arms)</th>
<th>Pts PS2</th>
</tr>
</thead>
<tbody>
<tr>
<td>IALT</td>
<td>59</td>
<td>7</td>
</tr>
<tr>
<td>BR.10</td>
<td>61</td>
<td>0</td>
</tr>
<tr>
<td>CALGB 9633</td>
<td>61-62</td>
<td>1</td>
</tr>
<tr>
<td>ANITA</td>
<td>59</td>
<td>3</td>
</tr>
<tr>
<td>ChEST</td>
<td>61-63</td>
<td>0</td>
</tr>
<tr>
<td>US Population</td>
<td>70</td>
<td>34-48%*</td>
</tr>
</tbody>
</table>

*Lilenbaum et al, JTO 2008

## LACE Meta-Analysis: Late Deaths Among Adjuvant Chemotherapy Recipients

5 trials, 4584 patients

- Excess non-cancer deaths (1.4%) on pooled chemo arm after 5 years
- A wide range of causes: PEs, MIs, infections, and “other”

Pignon, J Clin Oncol 2008

## IALT: Cisplatin + a Vinca or Etoposide

2008 Update: 7.5-Year Median Follow-up

<table>
<thead>
<tr>
<th>Cause of Death (First 5 Years / After 5 Years)</th>
<th>Chemotherapy</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>495 / 83</td>
<td>534 / 56</td>
</tr>
<tr>
<td>Death with lung cancer</td>
<td>390 / 48</td>
<td>443 / 37</td>
</tr>
<tr>
<td>Noncancer death*</td>
<td>82 / 25</td>
<td>62 / 10</td>
</tr>
<tr>
<td>Death of unknown cause</td>
<td>23 / 10</td>
<td>29 / 9</td>
</tr>
</tbody>
</table>

*HR 1.34 for chemotherapy vs control, P = 0.06 (not related to increased second malignancy, P = 0.54).

Adjuvant Chemotherapy for NSCLC
Molecular Profiling: Breast and Colon

Oncotype DX: Considerations for Patient Selection
- Stage I: PT1.N0
- Stage II: PT3.N0
- Stage III: PT1,3, N1

Adjuvant Chemotherapy for NSCLC
Molecular Profiling: ERCC1 and Survival in IALT

Results persist at 7.5-year follow-up:
ERCC1 negative HR 0.76 [0.59 - 0.98], ERCC1 positive HR 1.2 [0.91 - 1.59]


Adjuvant Chemotherapy for NSCLC
Molecular Profiling: ERCC1 and Survival in IALT

ERCC Negative
ERCC Positive

Adjuvant Chemotherapy for NSCLC
Chemotherapy Benefits BR.10 High Risk but Not Low Risk Patients: 15 Gene Signature

Tsao, PASCO 2008, A47510
Adjuvant Chemotherapy for NSCLC
Metagene Model: Prediction


Resected tumors 2 cm-6 cm

Adjuvant Chemotherapy for NSCLC
Molecular Profiling: CALGB 30506

Observation
Chemotherapy

Adjuvant Chemotherapy for NSCLC
Molecular Profiling: CALGB 30506

Duke Scientist Suspended Over Rhodes Scholar Claims
New York Times: July 20, 2010

In this week’s letter to Dr. Harold E. Varmus, the director of the National Cancer Institute, more than two dozen biostatisticians and oncology researchers from academic institutions recommended ending the studies pending further outside review. “Recently, published and peer-reviewed re-analyses of the work done by Potti and Nevins revealed serious errors that questioned the validity of the prediction models upon which these ongoing clinical trials are based”

TEMPORARY SUSPENSION OF CALGB 30506
07/21/2010
Pts with completely resected stage IB, II, and IIA NSCLC
Stratified by
- stage
- histology
- post-op RT
- sex
- adjuvant chemotherapy

BR.19 - Schema

Gefitinib
250 mg po
daily x 2 yrs

Placebo
0 mg po
daily x 2 yrs

Randomized 1:1

BR.19 - Disease Free Survival

HR: 1.22 (95% CI 0.93-1.61)
p=0.152*
Median survival: Gefitinib - 4.2 yrs
Placebo - N.E.

BR.19 - Overall Survival

HR: 1.23 (95% CI 0.94-1.64)
p=0.136*
Median survival: Gefitinib - 5.1 yrs
Placebo - N.E.

*Stratified Log Rank
Overall Survival by EGFR Mutation Status and Treatment

**Wild type**
- Placebo
- Gefitinib

**Sensitizing mutation**
- Placebo
- Gefitinib

HR Gef/Placebo: 1.21 (0.84, 1.73)
Log Rank: p=0.301
Median (95% C.I.)
- Placebo: Not reached (5.1, inf.)
- Gefitinib: 5.0 (4.3, inf.)

HR Gef/Placebo: 1.58 (0.83, 3.00)
Log Rank: p=0.160
Median (95% C.I.)
- Placebo: 5.1 (4.4, inf.)
- Gefitinib: 3.7 (2.6, inf.)

Randomized Double-blind trial in Adjuvant NSCLC with TARCEVA [RADIANT]

Eligibility:
- Stage IB – IIA NSCLC
- EGFR + (IHC and/or FISH)
- Complete Surgical Resection
- No Chemotherapy or up to 4 cycles of standard platinum-based, adjuvant chemotherapy

Follow up visit 0-6 months X 5 years, then yearly

IB - IIA Resectable NSCLC: E1505

Eligibility (proposed)
- Resected IB (>4 cm) - R0 - 2 lobectomy
- No previous chemotherapy
- No planned XRT
- No CVA/TIA
- No ATE in 12 months

N = 1500

Specified regimens
- Cisplatin and docetaxel
- Cisplatin and vinorelbine
- Cisplatin and gemcitabine

Primary end point: overall survival
Secondary end points: disease-free survival, safety [bleeding and arterial thromboembolic events (ATEs)]
Current Topics in Clinical Research

• Adjuvant Chemotherapy
  – BR-19 and Metagene CALGB Trial
• New Targets and Agents
  – New Inhibitors
• Patient subsets
  – Elderly and PS 2-3

Molecular Targets in NSCLC

Potential Oncogenic “Drivers” in Non-small Cell Lung Cancer (NSCLC)

Adenocarcinoma

ALK = anaplastic lymphoma kinase, EGFR = epidermal growth factor receptor, HER2 = human epidermal growth factor receptor 2, PIK3CA = phosphoinositide-3-kinase, catalytic, alpha polypeptide
Randomization: Equal → Adaptive

Primary end point: 8 week Disease Control (DC)

ES Kim, AACR Plenary Lecture, Annual Meeting, LBA

BATTLE Schema

Umbrella Protocol

Core Biopsy

EGFR VEGF KRAS BRAF

Randomization: Equal → Adaptive

EGFR and KRAS Mutations: Novel Discovery Findings

Achieved 8 week DC (%)

N = 45 13 67

Erlotinib 29% 23%
Vandetanib 64%
Erlotinib + Bexarotene 71%
Sorafenib

N = 43 18 62

Erlotinib 37% 22%
Sorafenib 66%
Erlotinib + Bexarotene 61%
Sorafenib

BATTLE Implications

- A step towards personalizing medicine
- New research paradigm
  - Real-time tumor profiling of “current” disease status
  - Novel adaptive clinical trial design
- Discovery of new biomarkers
- BATTLE paves the way forward for our next study
**Phase III Study of Carboplatin + Paclitaxel +/- Figitumumab in 1st Line NSCLC of non-adenocarcinoma histology**

<table>
<thead>
<tr>
<th>Trial Design</th>
<th>Endpoints</th>
<th>Stratification</th>
<th>Study Sites</th>
<th>FSFV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multi-center</td>
<td>Primary: OS</td>
<td>Gender</td>
<td>Global</td>
<td>2Q08</td>
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<tr>
<td>randomized,</td>
<td>Secondary: PFS, ORR,</td>
<td></td>
<td></td>
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<tr>
<td>open-label</td>
<td>Safety, QoL,</td>
<td></td>
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<tr>
<td></td>
<td>biomarkers,</td>
<td></td>
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<tr>
<td></td>
<td>pharmacoeconomics</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Key Entry Criteria**
- Other than Adenoca
- Brain mets allowed
- Adjuvant > 12 month prior

**Overall Survival**

- PC: mOS = 10.3 mo
- PCF: mOS = 8.5 mo

HR (95%CI): 1.23 (1.0, 1.5), p=0.051

**Crizotinib: First-in-human/Patient Trial**

- Part 1: Dose escalation
  - Cohort 1 (n=3): 50 mg QD
  - Cohort 2 (n=6): 100 mg QD
  - Cohort 3 (n=8): 200 mg QD
  - Cohort 4 (n=7): 200 mg QD
  - Cohort 5 (n=6): 250 mg QD

- Part 2: Molecularly enriched cohorts (ALK and c-MET)
  - Enrolling patients with ALK-positive NSCLC after preliminary observation of impressive activity in a few patients

ALT = alanine aminotransferase
Clinical and Demographic Features of Patients with ALK-positive NSCLC

<table>
<thead>
<tr>
<th>Feature</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (range) age, years</td>
<td>51 (25–78)</td>
</tr>
<tr>
<td>Gender, male/female</td>
<td>43/39</td>
</tr>
<tr>
<td>Performance status*</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>24 (29)</td>
</tr>
<tr>
<td>1</td>
<td>44 (54)</td>
</tr>
<tr>
<td>2</td>
<td>13 (16)</td>
</tr>
<tr>
<td>3</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>46 (56)</td>
</tr>
<tr>
<td>Asian</td>
<td>29 (35)</td>
</tr>
<tr>
<td>Smoking history</td>
<td></td>
</tr>
<tr>
<td>Never smoker</td>
<td>62 (76)</td>
</tr>
<tr>
<td>Former smoker</td>
<td>19 (23)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>79 (96)</td>
</tr>
<tr>
<td>Squamous</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Prior treatment regimens</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>5 (6)</td>
</tr>
<tr>
<td>1</td>
<td>27 (33)</td>
</tr>
<tr>
<td>2</td>
<td>15 (18)</td>
</tr>
<tr>
<td>≥3</td>
<td>34 (41)</td>
</tr>
</tbody>
</table>

Clinical Activity of Crizotinib in Patients with ALK-positive NSCLC

- Objective response rate (ORR): 57% (95% CI: 46, 68%)
  - 63% including 5 as yet unconfirmed PRs
  - 57% (8/14) for patients with performance status 2 or 3

<table>
<thead>
<tr>
<th>No. prior</th>
<th>ORR % (n/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>80 (4/5)</td>
</tr>
<tr>
<td>1</td>
<td>52 (14/27)</td>
</tr>
<tr>
<td>2</td>
<td>67 (10/15)</td>
</tr>
<tr>
<td>≥3</td>
<td>56 (19/34)</td>
</tr>
</tbody>
</table>

- Response duration: 1 to 15 months
- DCR† (CR/PR/SD at 8 weeks): 87% (95% CI: 77, 93%)

†Disease control rate

Current Crizotinib Clinical Trials

PROFILE 1007: NCT00932893; PROFILE 1005: NCT00932451

Key entry criteria
- Positive for ALK by central laboratory
- 1 prior chemotherapy (platinum-based)

Crizotinib 250 mg BID (n=159) administered on a continuous dosing schedule
Pemetrexed 500 mg/m² or docetaxel 75 mg/m² (n=159) infused on day 1 of a 21-day cycle

PROFILE 1005

Key entry criteria
- Progressive disease in Arm B of study A8081007
- 1 prior chemotherapy

Crizotinib 250 mg BID (n=259) administered on a continuous dosing schedule

PROFILE 1007: NCT00932893; PROFILE 1005: NCT00932451
A Phase II study of BIBW 2992 in patients with adenocarcinoma of the lung and activating EGFR mutations (LUX-Lung 2)

Chih-Hsin Yang1, Jin-Yuan Shih1, Wu-Chou Su2, Te-Chun Hsia3, Ching-Liang Tsai4, Sai-Hong Ignatius Ou5, Roser Calvo6, Xiuyu Julie Cong6, Mehdi Shahidi7, Vincent A. Miller8, on behalf of the LUX-Lung 2 Clinical Study Team

1National Taiwan University Hospital, Taipei, Taiwan; 2National Cheng Kung University Hospital, Tainan, Taiwan; 3National Taiwan University Hospital, Taipei, Taiwan; 4Veterans General Hospital, Taipei, Taiwan; 5Masonic Chao Family Comprehensive Cancer Center, University of California Irvine Medical Center, Orange, CA; 6Boehringer Ingelheim, Ridgefield, CT, USA; 7Boehringer Ingelheim, Bracknell, Berkshire, UK; 8Memorial Sloan-Kettering Cancer Center, New York, NY, USA

BIBW 2992 - Efficacy

<table>
<thead>
<tr>
<th>Overall Response Rate</th>
<th>1st line</th>
<th>Independent review</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigator</td>
<td>37/61 (61%)</td>
<td>35/61 (57%)</td>
</tr>
<tr>
<td>2nd line</td>
<td>41/68 (60%)</td>
<td>38/68 (56%)</td>
</tr>
<tr>
<td>Total</td>
<td>78/129 (60%)</td>
<td>73/129 (57%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Median duration of response * (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st line</td>
</tr>
<tr>
<td>2nd line</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disease Control Rate (CR/PR + SD) **</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st line</td>
</tr>
<tr>
<td>2nd line</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>

* Longest duration of treatment for both 1st line and 2nd Line: 28 months

Overall Survival by trial

<table>
<thead>
<tr>
<th>Trial</th>
<th>No. Deaths / No. Entered</th>
<th>Hazard ratio (Chemotherapy / Control)</th>
<th>HR [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALPI</td>
<td>569 / 1088</td>
<td>0.95 [0.81;1.12]</td>
<td></td>
</tr>
<tr>
<td>ANITA</td>
<td>458 / 840</td>
<td>0.82 [0.68;0.96]</td>
<td></td>
</tr>
<tr>
<td>BLT</td>
<td>152 / 307</td>
<td>1.00 [0.72;1.38]</td>
<td></td>
</tr>
<tr>
<td>IALT</td>
<td>980 / 1867</td>
<td>0.91 [0.80;1.03]</td>
<td></td>
</tr>
<tr>
<td>JBR10</td>
<td>197 / 482</td>
<td>0.71 [0.54;0.94]</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>2356 / 4584</td>
<td>0.89 [0.82;0.96]</td>
<td></td>
</tr>
</tbody>
</table>

Chemotherapy better | Control better

Test for heterogeneity: p = 0.34
Chemotherapy effect: \( p = 0.004 \)

Trials (Associated drug(s)):

- ALPI (MTC+VDS)
- ANITA (NVB)
- BLT (NVB / VDS / MTC+VDS / MTC+IFM)
- JBR10 (NVB)
- IALT (NVB / VDS / VLB / VP16)
Efficacy and Safety of PF299804 Versus Erlotinib: A Randomized Phase 2 Trial in Patients with Advanced Non-small Cell Lung Cancer After Failure of Chemotherapy

M Boyer, F Blackhall, K Park, C Barrios, M Krzakowski, I Taylor, J Liang, L Denis, J O’Connell, S Ramalingam

1 Sydney Cancer Centre, Camperdown, Australia; 2 The Christie NHS Foundation Trust, Manchester, UK; 3 Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; 4 PUCRS School of Medicine, Porto Alegre, Brazil; 5 The Maria Sklodowska-Curie Memorial Cancer Center Institute of Oncology, Warsaw, Poland; 6 Pfizer Oncology, New London, CT, USA; 7 Emory University, Atlanta, GA, USA
Table 3. Objective Tumor Response

<table>
<thead>
<tr>
<th></th>
<th>PF299804 45 mg (n=94)</th>
<th>Erlotinib 150 mg (n=94)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response, n (%)</td>
<td>1 (1.1)</td>
<td>0</td>
</tr>
<tr>
<td>Partial response, n (%)</td>
<td>15 (16.0)</td>
<td>4 (4.3)</td>
</tr>
<tr>
<td>Stable disease, n (%)</td>
<td>33 (35.1)</td>
<td>38 (40.4)</td>
</tr>
<tr>
<td>Progressive disease, n (%)</td>
<td>28 (29.8)</td>
<td>48 (51.1)</td>
</tr>
<tr>
<td>Non-evaluable,* n (%)</td>
<td>17 (18.1)</td>
<td>4 (4.3)</td>
</tr>
<tr>
<td>Objective response rate (CR + PR), n (%) [95% CI]</td>
<td>16 (17.0) [10.1, 26.2]</td>
<td>4 (4.3) [1.2, 10.5]</td>
</tr>
<tr>
<td>Clinical benefit response rate (CR + PR + SD ≥24 weeks), n (%) [95% CI]</td>
<td>26 (27.7) [18.9, 37.8]</td>
<td>13 (13.8) [7.6, 22.5]</td>
</tr>
</tbody>
</table>

*Post-baseline tumor assessments were initiated at week 8 and conducted every 4 weeks thereafter.

CI = confidence interval; EGFR = epidermal growth factor receptor; wt = wild type
ARQ 197-209: Study Design
Randomized, placebo-controlled, double-blind clinical trial

- **NSCLC**
  - Inoperable locally adv/metastatic dz.
  - ≥ 1 prior chemo
  - (no prior EGFR TKI)

Endpoints
- 1° PFS
- 2° ORR, OS
- Subset analyses
- Crossover: ORR

ARQ 197/erlotinib vs. placebo/erlotinib
28-day cycle

**Endpoints**
- 1° PFS
- 2° ORR, OS
- Subset analyses
- Crossover: ORR

NSCLC
- Inoperable locally adv/metastatic dz.
- ≥ 1 prior chemo
- (no prior EGFR TKI)

Randomization stratified by prognostic factors
- incl. sex, age, smoking, histology, performance status, prior therapy and best response, and geography (U.S. vs. ex-U.S.)

**Endpoints**
- 1° PFS
- 2° ORR, OS
- Subset analyses
- Crossover: ORR

ARQ 197-209: Progression-Free Survival (ITT Population)

* Cox regression model
  - PFS also measured by independent radiographic review:
    - Median 15.6 vs. 8.4 weeks
    - unadjusted/adjusted HR= 0.74/0.51

**ARQ 197-209: PFS in Histologic and Molecular Subgroups**

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>ARQ197/erlotinib</th>
<th>Placebo/erlotinib</th>
<th>Unadjusted HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Squamous Cell</td>
<td>26 / 24</td>
<td>13.7 (8.5-18.1)</td>
<td>8.4 (7.3-21.0)</td>
</tr>
<tr>
<td>Non-Squamous Cell</td>
<td>58 / 59</td>
<td>18.5 (15.0-31.1)</td>
<td>9.7 (6.0-16.0)</td>
</tr>
<tr>
<td>c-MET/FISH +4</td>
<td>19 / 18</td>
<td>15.4 (8.1-24.4)</td>
<td>15.3 (7.1-31.6)</td>
</tr>
<tr>
<td>c-MET/FISH +5</td>
<td>8 / 11</td>
<td>24.1 (16.3-NE)</td>
<td>19.6 (7.9-31.4)</td>
</tr>
<tr>
<td>EGFR mutant</td>
<td>6 / 11</td>
<td>24.1 (8.5-32.1)</td>
<td>21.0 (6.1-36.0)</td>
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<tr>
<td>KRAS wt</td>
<td>51 / 48</td>
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</tr>
</tbody>
</table>
Current Topics in Clinical Research

- Adjuvant Chemotherapy
  - BR-19 and Metagene CALGB Trial
- New Targets and Agents
  - New Inhibitors
- Patient subsets
  - Elderly and PS 2-3

Weekly paclitaxel combined with monthly carboplatin versus single agent therapy in patients aged 70 to 89: IFCT-0501 Randomized Phase III Study in Advanced NSCLC

NSCLC
Stage III-IV
Age 70-89 years
PS 0-2
n = 451

Vinorelbine or Gemcitabine

Carboplatin + paclitaxel

Stratification by centre, PS 0-1 vs. 2, age ≤80 vs. >80 and stage III vs. IV

*Choice of the center at the beginning of the study
**In case of PD or excessive toxicity

Response rate at 6 weeks (ITT)

<table>
<thead>
<tr>
<th></th>
<th>Single Agent Arm A (n = 211)</th>
<th>Doublet Arm B (n = 210)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR</td>
<td>23 (10.9%)</td>
<td>61 (29.05%)</td>
<td>&lt;10^-6</td>
</tr>
<tr>
<td>ST</td>
<td>96 (45.5%)</td>
<td>61 (38.57%)</td>
<td>0.18</td>
</tr>
<tr>
<td>DCR (PR + ST)</td>
<td>119 (56.4%)</td>
<td>142 (67.82%)</td>
<td>0.02</td>
</tr>
<tr>
<td>PD</td>
<td>46 (21.8%)</td>
<td>15 (7.14%)</td>
<td>&lt;10^-4</td>
</tr>
<tr>
<td>Not reported</td>
<td>15 (7.11%)</td>
<td>20 (9.53%)</td>
<td>0.47</td>
</tr>
<tr>
<td>Withdrawal before 1st evaluation*</td>
<td>31 (14.7%)</td>
<td>33 (15.7%)</td>
<td>0.68</td>
</tr>
</tbody>
</table>

*Main causes: deaths (20 in arm A and 23 in arm B), reduced general condition (respectively 7 and 4), toxicity 0 and 4 cases respectively and withdrawal of consent (6 cases)
**PFS (ITT)**

- Median: 6.1 months (95% CI 5.5-6.9)
  - 1-year PFS: 15.4% (95% CI 10.8-20.8)

- Median: 3.0 months (95% CI 2.6-3.9)
  - 1-year PFS: 2.3% (95% CI 0.8-5.3)

- p <10^{-6}

**Overall survival (ITT)**

- MST = 10.3 months (95% CI 8.3-13.3)
  - 1-year survival: 45.1% (95% CI 38.2-51.8)

- MST = 6.2 months (95% CI 5.3-7.4)
  - 1-year survival: 28.9% (95% CI 21-33.1)

- p < 0.00004

**Exploratory Sub-group analysis**
Conclusions

Dear Dr Lilenbaum, thank you for your kind mail. I must say that your work was a motivation for me to perform this randomized trial. Here are the slides, please use them as you like! With my best regards, Elisabeth Quoix

TOPICAL study design

Inclusion criteria
- Histologically or cytologically confirmed NSCLC
- Measurable stage IIIB/IV disease and ≥ 18 yrs
- Chemo-naïve and unsuitable for chemotherapy
  - ECOG PS 2
  - 3 or
  - PS 0
  - EC (E) ≥60 ml/min
- Life expectancy ≥8 weeks

Endpoints
- Primary
  - Overall survival (OS)
- Secondary
  - Progression-free survival (PFS)
  - Objective response rate
  - Quality of life (QoL)
  - Disease-related symptoms
  - Safety and tolerability

Translational
- Biomarker analyses
  - EGFR mutation
  - Proteomic/genomic markers

Endpoints

Progression-free survival (PFS)

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>Erlotinib</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>2</td>
<td>80</td>
<td>80</td>
</tr>
<tr>
<td>4</td>
<td>60</td>
<td>60</td>
</tr>
<tr>
<td>6</td>
<td>40</td>
<td>40</td>
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<tr>
<td>8</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>12</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

HR=0.85 (0.72–0.99); p=0.038

Median PFS, months 2.6 2.7

PFS at 6 months, % 22 13

PFS at 12 months, % 9 4
PFS by gender

**Male**
- Median PFS, months: 2.4 vs. 2.5 (p=0.83)
- PFS at 6 months, %: 14 vs. 12
- PFS at 12 months, %: 5 vs. 3

**Female**
- Median PFS, months: 3.4 vs. 2.8 (p=0.008)
- PFS at 6 months, %: 35 vs. 13
- PFS at 12 months, %: 15 vs. 5

**OS by gender**

**Male**
- Median OS, months: 3.1 vs. 3.3 (p=0.32)
- OS at 6 months, %: 29 vs. 32
- OS at 12 months, %: 12 vs. 15

**Female**
- Median OS, months: 5 vs. 4.3 (p=0.025)
- OS at 6 months, %: 49 vs. 34
- OS at 12 months, %: 24 vs. 18

**SUMMARY**

- Clinical research efforts are appropriately focused on selecting patients, in different settings, who are likely to benefit with acceptable risk.
- Random trials of EGFR inhibitors in unselected patients are no longer justified.
- New EGFR inhibitors have shown promise and may replace current agents for mutated patients.
- Agents that address secondary resistance to EGFR inhibitors are an important research subject.
- For "special population patients", paradigm questions are still in need of definitive answer.
ADJUVANT THERAPY

- Radiation Therapy
- Interferon
- GM-CSF

Is There A Role for Radiation Therapy in the Adjuvant Treatment of Melanoma?
Clinical Data

- 250 pts, 217 evaluable, 109 XRT, 108 obs; all had palpable nodes
- High risk defined as:
  - Extracapsular extension; OR
  - # of nodes:
    - parotid >/= 1
    - neck/axilla >/= 2
    - groin >/= 3; OR
  - Size of nodes:
    - parotid/neck/axilla > 3cm
    - groin > 4cm

Lymph Node Field Relapse following Lymphadenectomy

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>5 yr Nodal Field Relapses</th>
<th>5 yr Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Risk</td>
<td>1-2 positive nodes</td>
<td>5-10%</td>
</tr>
<tr>
<td></td>
<td>Minimal extra nodal spread</td>
<td></td>
</tr>
<tr>
<td>Intermediate Risk</td>
<td>3-5 positive nodes</td>
<td>25-30%</td>
</tr>
<tr>
<td></td>
<td>Max node size 30-60mm</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Extra nodal spread</td>
<td></td>
</tr>
<tr>
<td>High Risk</td>
<td>&gt;5 positive nodes</td>
<td>50%</td>
</tr>
<tr>
<td></td>
<td>Mattled nodes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Max node size &gt;60mm</td>
<td></td>
</tr>
<tr>
<td></td>
<td>“close” margins</td>
<td></td>
</tr>
</tbody>
</table>
Trial Schema
Surgery for Lymph Node Field Recurrent Melanoma

Main Eligibility Criteria
- Completely resected, palpable, nodal metastatic melanoma
- No previous or concurrent local, in-transit or distant metastatic relapse
- At significant risk for lymph node field relapse

Stratification
- Institution
- Lymph node field site
- Number of positive nodes
- Metastatic node diameter
- Extent of extra-nodal spread

RANDOMISATION

Adjuvant Radiotherapy
Observation
RT for isolated lymph node field relapse

Trial Endpoints

• Primary Endpoint:
  - Lymph Node Field Relapse
  (as a first relapse)

• Secondary Endpoints:
  - Overall survival
  - Relapse-free survival
  - Patterns of relapse
  - Adverse events
  - Quality of life

Eligibility Criteria

Standard Surgical Procedure
Minimum lymph node numbers harvested:
- Parotid & Neck: 7 - 25 (Level(s) of dissection)
- Axilla: 10
- Groin: 6

Increased risk of lymph node field relapse
- Extra-nodal spread, OR
- No of positive lymph nodes, OR
  - Parotid: ≥ 1
  - Neck, axilla: ≥ 2
  - Groin: ≥ 3
- Maximum positive lymph node size
  - Parotid, Neck, Axilla: ≥ 10 mm
  - Groin: > 40 mm
Overall Outcome

- 161 relapses (74%)
- 62 relapses in nodes (28%) (with or without distant metastases)
- 120 deaths (55%), all but 2 from melanoma

Adjuvant Radiation Reduced Frequency of Nodal Recurrence

- HR 0.47, with 95% confidence intervals 0.28 – 0.81
- 2 year recurrences
  - Radiation: 20%
  - Observation: 35%

P=0.005
Adjuvant Radiation Therapy had no Effect on Overall Recurrence Rate

- HR 0.9, with confidence intervals 0.66 – 1.22
- 2 year RFS
  - Radiation: 44%
  - Observation: 38%

P=0.53
Adjuvant Radiation had no Significant Effect on OS

- HR 1.33, with Confidence Intervals 0.93 – 1.9
- 2 year OS:
  - Radiation: 55%
  - Observation: 67%

P = 0.14

Toxicity of Radiation to Nodal Basin

- Except for head and neck, mostly lymphedema
- Worse as you go from head and neck to axilla to groin
- Obesity increases the risk
CONCLUSIONS and QUESTIONS

Post-op radiation given in this way reduces risk of recurrence in the nodal basin by about 15%.
There is clearly no beneficial effect on survival.
Whether other radiation dosing (e.g., MD Anderson plan for head and neck melanomas) would yield superior results is not known.

What is the Role of Interferon in Adjuvant Therapy of Melanoma?

- Generally accepted that IFN can prolong DFS, but effect on OS controversial.
- Not clear which preparation/dose/route/duration is optimal.
- Since last meta-analysis 2 RCTs published with 1700 pts, leading to an updated meta-analysis (JNCI 102 (7): 493, April 7, 2010).

Meta-Analysis

- 14 met authors' criteria for inclusion.
- 8,122 pts, 4,362 of whom got IFN.
- Included T2-T4 and/or node +.
- 17 comparisons from these 14 trials, usually with observation.
Effect of IFN on DFS

- IFN improved DFS in 10/17 comparisons
- In the meta-analysis, the overall HR was 0.82, with 95% CI 0.77-0.87, p<0.001

Effect of IFN on OS

- IFN significantly improved OS in only 4/14 comparisons
- In the meta-analysis, however, the overall HR was 0.89, with 95% CI 0.83-0.96, p=0.002
Effect of Dose, Duration, Pt Subset

- No optimal dose (high 20 MIU/M2, intermediate 10 MIU/M2, low 1-3 MIU/M2)
- No optimal duration (4 months – 5 years)
- No optimal subset (node – vs node +)

CONCLUSION

- Interferon in the newest meta-analysis improves relapse free survival by up to 18% and may improve overall survival by as much as 11%
- There is no clearly superior dose, route of administration, duration (4mos to 5yrs), or preparation, and no clearly defined group for whom it is more or less efficacious (eg, node + vs node -)
QUESTIONS ABOUT INTERFERON
- Should we continue the high dose month?
  This is the FDA approved regimen
  Theoretical reasons why it may be important
- Is the high dose month enough?
  Still no data to prove or disprove this;
  E1697 ongoing
- Should we expand the indications?

Suggestions for Dosing Now
- Continue the high dose month and ask patients to complete it without interruption if possible
- During the subcutaneous phase dose reduce, hold treatments, etc, in order to keep performance status 1

Interferon Toxicity
- Depression: pretreatment helps
- Hepatic toxicity can be fatal: Hold for SGOT > 5x normal
- Adjustments for marrow toxicity NOT like chemo: No need to hold until AGC < 500
- No steroids
Is There a Role for GMCSF in Adjuvant Treatment of Melanoma?

Abstract 8504:
E4697: Phase III Cooperative Group Study of Yeast Derived GM-CSF vs Placebo as Adjuvant Treatment of Patients with Completely Resected Stage III-IV Melanoma

DH Lawson, SJ Lee, AA Tarhini, KA Margolin, MS Ernstoff, JM Kirkwood
Winship Cancer Institute of Emory University, Dana Farber Cancer Institute, University of Pittsburgh Cancer Institute, University of Washington, Dartmouth Hitchcock Medical Center
Eligibility for E4697: Stage III
- Intransit metastases including local recurrence
- Gross extracapsular extension
- Recurrence in previously resected nodal basin
- Four or more involved nodes
- Ulcerated primary with any clinically involved nodes
- Locoregional recurrence after IFN or S0008

Eligibility for E4697
- Resected locoregional mucosal melanoma
- Completely resected stage IV melanoma, – Cutaneous, mucosal, ocular, and unknown 1°

Treatment Plan
- GM-CSF 250 mcg SC 14 days of 28 for one year (13 cycles)
- Patients with resectable recurrences encouraged to continue 6 months past recurrence or for one year, whichever is longer
- Disease assessments every 3 mos
Statistical Considerations

- 800 patients gives 80% power to detect a 33% increase in median survival from 40 to 53 months with 2-sided type 1 error rate of 0.05
- 80% power to detect 24% increase in DFS from 11 to 13.6 months
- Placebo controlled to enhance validity of the DFS endpoint

DFS by GM-CSF (n=743)

- Placebo: 9.2 mos, 95% CI (7.68, 12.46)
- GM-CSF: 11.6 mos, 95% CI (9.72, 13.48)

OS by GM-CSF Treatment Status

- Placebo: 62.4 mos, 95% CI (45.6, -)
- GM-CSF: 69.6 mos, 95% CI (59.4, -)
Subset Analysis of Effect of GMCSF on OS and DFS by Stage

- Stage III B and III C: 374 pts
- Stage IV: 258 pts

Stage III Melanoma

DFS

OS

Stage IV Melanoma

DFS

OS
ADJUVANT TRIALS

- DERMA trial evaluating a vaccine for patients whose tumors express MAGE-A3 antigen
- Proposed: Cooperative group study comparing ipilimumab with interferon. Similar study already underway in Europe

Conclusions

- Neither GMCSF nor peptide vaccination achieved OS and DFS objectives
- There is a suggestion of favorable effect of GMCSF on DFS
- Subset analysis suggests effects of GMCSF on DFS and OS are largest among Stage IV subjects

Conclusions

- Further study of adjuvant GMCSF is warranted (patients, dose, duration)
- Use of GMCSF in the adjuvant setting is worthy of discussion (IFN failures, resected stage IV)
- Laboratory immunologic responses in relation to clinical outcome are under investigation
What is the Role of Surgery in Stage IV Melanoma?

21st Century Surgical Results, all Multiple Sites of Metastases
Sondak, et al, SWOG  
Morton, et al, JWCI

- N= 62  
- Median OS: 21 mos  
- 5-yr OS: 25%

- N= 496  
- Median OS: 35 months  
- 5-yr OS: 40%

Adapted from Morton, DL.

What are the “Limits” on Resectability?

- No more than 6 lesions  
- No more than 3 involved visceral organ sites  
- ECOG 0-1  
- Life expectancy otherwise 5 yrs  
- Exclude brain and multiple bone metastases

Eligibility criteria for proposed international study of resection of metastatic melanoma (Morton). In practice brain and bone metastases are also resectable.
Surgery vs Best Medical Care

- Eligible patients randomized:
  - Best medical care vs Surgery vs Surgery plus BCG

At relapse patients receive best salvage as determined by treating physician, which may include crossover

Therapy of Unresectable Melanoma

- Ipilimumab
- Carboplatin + Paclitaxel
- Targeted Therapy
  - BRAF
  - CKIT
- Anti-angiogenesis
- Intralesional injection with Oncolytic Viruses or Rose Bengal
Ipilimumab: Mechanism of Action

- T-cell activation
- T-cell inhibition
- T-cell potentiation

Ipilimumab: Phase II Experience

- Ipilimumab monotherapy
  - 20–30% durable disease control and 2-year survival¹,²
- Mechanism-based side effects
  - Immune-related Adverse Events (irAEs)
  - Onset predominantly in first 12 weeks
  - Management with vigilant follow-up and early steroids required
- Ipilimumab + vaccine combinations explored


gp100 Vaccine Control

- HLA-A*0201 restricted
- T-cell specific immune responses
- Rare objective clinical response
- Combination with IL-2 in metastatic melanoma (ASCO, 2009)
  - Improved Response Rate, PFS
- Active control arm for present study
MDX010-20: Patient Eligibility

- Inclusion
  - Pre-treated stage III or IV melanoma
  - HLA-A*0201 positive
  - Pre-treated CNS metastases allowed
  - Any LDH level

- Exclusion
  - No autoimmune disease
  - No prior therapy with anti-CTLA-4 antibody
  - No prior therapy with anti-cancer vaccine

MDX010-20: Study Design

Randomize

Pre-treated Metastatic Melanoma (N=476)

- Ipilimumab + gp100 (N=403)
- Ipilimumab + placebo (N=137)
- gp100 + placebo (N=136)

MDX010-20: Study Design Details

  - 125 Centers in 13 Countries
- Randomized (3:1:1), Double-Blind
- Stratified for M-Stage and prior IL-2
- Induction
  - Ipilimumab: 3 mg/kg q 3 weeks X 4 doses
  - gp100: 1mg q 3 weeks X 4 doses
- Re-induction (same regimen) in eligible patients
Statistical Considerations

- **Primary Endpoint**
  - Original: BORR (N=750)
  - Changed to OS (Jan. 2009) before unblinding

- **Primary Comparison**
  - Ipilimumab + gp100 vs gp100 (3:1)
  - 385 events required
  - 90% power to detect: 10.8 vs 8.6 months OS

- **Secondary Comparison**
  - Ipilimumab vs gp100 (1:1)
  - 219 observed events
  - 80% power

Balanced Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Ipil + gp100 N=403</th>
<th>Ipil + pbo N=137</th>
<th>gp100 + pbo N=136</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>65.6</td>
<td>58.8</td>
<td>67.4</td>
</tr>
<tr>
<td>Gender (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>61</td>
<td>59</td>
<td>54</td>
</tr>
<tr>
<td>Female</td>
<td>39</td>
<td>41</td>
<td>46</td>
</tr>
<tr>
<td>M Stage (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M0</td>
<td>1</td>
<td>0.7</td>
<td>3</td>
</tr>
<tr>
<td>M1a</td>
<td>9</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>M1b</td>
<td>19</td>
<td>16</td>
<td>17</td>
</tr>
<tr>
<td>M1c</td>
<td>71</td>
<td>73</td>
<td>72</td>
</tr>
</tbody>
</table>

Kaplan-Meier Analysis of Survival

<table>
<thead>
<tr>
<th>Survival Rate</th>
<th>Ipil + gp100 N=403</th>
<th>Ipil + pbo N=137</th>
<th>gp100 + pbo N=136</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 year</td>
<td>44%</td>
<td>46%</td>
<td>25%</td>
</tr>
<tr>
<td>2 year</td>
<td>22%</td>
<td>24%</td>
<td>14%</td>
</tr>
</tbody>
</table>
CONCLUSION

Ipilimumab may be the next drug to get FDA approval for Stage IV melanoma
Available now through Expanded Access Program
What is the Role of Carboplatin plus Paclitaxel in Treatment of Unresectable Melanoma?

E2603: a randomized phase III trial comparing sorafenib, carboplatin & paclitaxel to carboplatin & paclitaxel in metastatic melanoma

Keith T. Flaherty, M.D.
Massachusetts General Hospital
on behalf of ECOG & CTSU-registered investigators

Eligibility

- Metastatic or unresectable melanoma
  - No selection BRAF/NRAS mutation
- No prior chemotherapy, but prior immunotherapy (approved or investigational) & other investigational agents (not MAP kinase pathway inhibitors) permitted
- ECOG PS 0 or 1
- No brain metastases (baseline MRI required)
- No ocular melanoma
**E2603 efficacy**

<table>
<thead>
<tr>
<th></th>
<th>Carboplatin-paclitaxel</th>
<th>Carboplatin-paclitaxel &amp; sorafenib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall survival</td>
<td>11.3 mo.</td>
<td>11.1 mo.</td>
</tr>
<tr>
<td>Progression-free survival</td>
<td>4.1 mo.</td>
<td>4.9 mo.</td>
</tr>
<tr>
<td>Response rate</td>
<td>16%</td>
<td>18%</td>
</tr>
</tbody>
</table>

*p < 0.05 for all comparisons*

Two arms combined:
- 1 yr OS rate: 47% 95% CI (43-50%)
- 6-mo PFS rate: 39% 95% CI (36-42%)

---

**E2603 toxicity**

<table>
<thead>
<tr>
<th></th>
<th>Carboplatin-paclitaxel</th>
<th>Carboplatin-paclitaxel &amp; sorafenib</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 390</td>
<td>n = 384</td>
<td></td>
</tr>
<tr>
<td>Leukopenia</td>
<td>16/5</td>
<td>16/6</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>13/31</td>
<td>14/30</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>4/1 (1 focal case)</td>
<td>5/1</td>
</tr>
<tr>
<td>Anemia</td>
<td>5/1</td>
<td>7/1</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>6/3</td>
<td>13/8</td>
</tr>
<tr>
<td>Neutropathy</td>
<td>13/1</td>
<td>18/1</td>
</tr>
<tr>
<td>Fatigue</td>
<td>12/1</td>
<td>13/1</td>
</tr>
<tr>
<td>Rash</td>
<td>2/9</td>
<td>14/1</td>
</tr>
<tr>
<td>Myalgia</td>
<td>6/4/1</td>
<td>4/0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4/4/1</td>
<td>7/0</td>
</tr>
</tbody>
</table>

*p < 0.001*

10 on-study deaths thought to be treatment related (both arms)
CONCLUSION

- Carboplatin plus paclitaxel appears to have activity in patients with unresectable melanoma
- Whether it should replace DTIC as front line or be used in second line is not clear
- Enrollment in clinical trials is still to be preferred
Targeted Therapy for Melanoma- the Path Towards Combination Therapy

Grant McArthur MBBS FRACP PhD
Peter MacCallum Cancer Centre Australia

BRAF-inhibitors evolution of selectivity

- Sorafenib: class II inhibitor displaying limited capacity to inhibit BRAF containing the most common mutation V600E (Strumberg JCO 2005)
- XL-261 / BMS-908662: broadly active inhibitor more potent than sorafenib (Schwartz ASCO 2009)
- PLX-4032 / RO6185426: class I inhibitor active against BRAF in its active conformation V600E, V600K, (Flaherty ASCO 2009)
- GSK2118436: class I inhibitor with clinical activity against V600E, V600K & V600G (Keffer 2010)
### BRAF-inhibitors evolution of selectivity: Efficacy

<table>
<thead>
<tr>
<th>Class</th>
<th>Response Rate</th>
<th>Early FDG-PET Response</th>
<th>Inhibition of pERK at MTD in melanoma</th>
<th>PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sorafenib</td>
<td>II</td>
<td>&lt;5%</td>
<td>No</td>
<td>±</td>
</tr>
<tr>
<td>XL281</td>
<td></td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>PLX4032</td>
<td>I</td>
<td>~70-80%</td>
<td>~100%</td>
<td>Yes</td>
</tr>
<tr>
<td>GSK2118436</td>
<td>I</td>
<td>~60-70%</td>
<td>~90%</td>
<td>Yes*</td>
</tr>
</tbody>
</table>

GSK2118436 shows activity against cerebral metastases. No MTD defined to date.

---

### BRAF-inhibitors evolution of selectivity: Safety

<table>
<thead>
<tr>
<th>MTD</th>
<th>DLTs</th>
<th>KA / SCC</th>
<th>Activation of ERK in RAS mutant Cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sorafenib</td>
<td>400mg bid</td>
<td>Diarrhea</td>
<td>Fatigue ~7%</td>
</tr>
<tr>
<td>XL-281</td>
<td>150mg daily</td>
<td>Nausea/Vomiting</td>
<td>Fatigue, Diarrhea, Nausea, Vomiting</td>
</tr>
<tr>
<td>PLX4032</td>
<td>960mg bid</td>
<td>Rash</td>
<td>Arthralgia 20%</td>
</tr>
<tr>
<td>GSK2118436</td>
<td>TBD</td>
<td>Pyrexia 25%</td>
<td></td>
</tr>
</tbody>
</table>

---

### BRAF-inhibitors evolution of selectivity: Safety

- The induction of keratoacanthoma / squamous cell carcinoma with class I and II inhibitors indicates pharmacological inhibition of RAF kinases can induce cell proliferation clinically.
- Cell proliferation induced by BRAF-inhibitors is now well studied in preclinical models and surprisingly is associated with upstream activation of RAF kinases.
- Causes of pyrexia with GSK2118436 uncertain but may be off-target or relate to tumor response.
Current Trials of Inhibitors of Mutated BRAF

- RO5185426 (PLX4032, Plexxikon) vs DTIC is underway
- GSK 1120212 vs DTIC soon to open
- Other BRAF inhibitors in development

Inhibitors of Mutated CKIT

- Several potentially druggable mutations of CKIT exist
- Mutations apparently much less common than BRAF mutations (10-20% acral and mucosal, less in others)
- Dastatinib (E2607), Imatinib, and other newer agents are in trial

CONCLUSIONS/COMMENTS

- Drugs against mutations in BRAF and CKIT may be of value
- Some of these trials require no prior treatment
- Some of these trials prefer no prior testing for mutations
Anti-angiogenic Therapy for Patients with Advanced Melanoma: Abstracts 8518-8522

David F. McDermott
Beth Israel Deaconess Medical Center
Assistant Professor of Medicine
Harvard Medical School

BEAM Study Schema

O'Day, Kim et al., ECCO 2009

BEAM Trial: Phase II Carbo/paclitaxel +/- Bev:
OS KM plots (36% censored at time of analysis)

O'Day, Kim et al., ECCO 2009
BEAM Trial: Phase II Carbo/paclitaxel +/- Bev: Exploratory OS analysis in poor prognosis patients

BEAM Study: Conclusions

- Encouraging data reported from this Phase 2, randomized, placebo-controlled trial in metastatic melanoma patients
- Consistent benefit across all endpoints (PFS, OS, ORR)
- Benefits also seen in worst prognosis patients (M1c and elevated LDH)
- CPS was well tolerated and safety profile was consistent with other bevacizumab combination chemotherapy trials
- Further investigation in a larger Phase 3 trial is warranted

VEGF Pathway Inhibition in Advanced Melanoma

- Single agents
  - VEGF receptor inhibitors
    - Sorafenib – limited to no activity
    - Axitinib – more encouraging
- Combination with chemotherapy – extending clinical benefit
  - 1st generation VEGF receptor inhibitors (e.g. sorafenib)
    - Encouraging Phase II data in combination with DTIC and TMZ (McDermott et al, JCO 2008, Amaravadi et al, CCR 2009)
    - No additional benefit in combination with Carboplatin/paclitaxel (PRISMA, E3663)
  - VEGF Ligand inhibitors (e.g. bevacizumab)
    - Encouraging randomized phase II data in combination with carboplatin
      - (O’Day et al, ECCO 2009)
CONCLUSION

- Antiangiogenic agents have not been proven to be of value in melanoma, but trials are ongoing

Intralesional Injections

- Uncontrolled studies of injections of BCG, GMCSF, Interferon, IL-2
- Recent trial of injections of Rose Bengal
- Ongoing randomized trial of intralesional injections of an oncolytic herpesvirus engineered to secrete GMCSF vs GMCSF alone (Oncovex)

Can Genetic Profiling Help with Prognostication in Uveal Melanoma?

- Gene Expression Microarray Analysis on 25 enucleated melanomas
- Sets of 3 genes could differentiate 2 classes of melanoma
- Second group of 25 more patients confirmed
- Class 1: 1 death, 92 month survival 95%
- Class 2: 8 deaths, 92 month survival 31%
  - P=0.01  Harbour Ca Res 64:7205, 10/15/04

Harbour Ca Res 64:7205, 10/15/04
Genetic Profiling vs Conventional Clinical Staging

- Class 1 corresponded to low grade spindle cell melanomas, whereas class 2 corresponded with higher grade epithelioid melanomas
- Outperformed monosomy chromosome 3, a previously used test
- Can be done with FNA

SAMPLE LIST OF ONGOING AND PROPOSED TRIALS
ADJUVANT
- DERMA trial evaluating a vaccine for patients whose tumors express MAGE-A3 antigen
- Proposed: Cooperative group study comparing ipilimumab with interferon. Similar study already underway in Europe

Stage IV
- Dr. Morton has opened a trial comparing surgical therapy of up to 6 metastases to best medical care

Stage IV Unresectable
- Expanded Access to Ipilimumab
- ABI-007 (Abraxane) vs DTIC
- RO5185426 (PLX4032, Plexxikon) vs DTIC for patients whose tumors have the V600E BRAF mutation
- AMNN107 vs DTIC for patients whose tumors have a CKIT mutation
- Intratumoral Oncovex (oncolytic herpesvirus secreting GMCSF) vs GMCSF
Other Targeted Therapy

- GSK 1120212 and E 7080 (Eisai) are BRAF inhibitors earlier in development
- Imatinib and Dasatinib (ECOG 2607) are also being studied in patients whose tumors have CKIT mutations
- Other CKIT inhibitors are under development
- ECOG 2602 is a phase II trial evaluating PEG-Interferon in patients who excrete large quantities of bFGF

Other Approaches

- Cellular Therapy
- Vaccines
- Oncolytic Viruses
- Intratumoral Rose Bengal
- Denileukin difitox to deplete Tregs
- Combinations

CONCLUSION

- THE TREATMENT OF CHOICE FOR A MELANOMA PATIENT IS A CLINICAL TRIAL
Chronic Lymphocytic Leukemia

- Leuko-: white; -emia: in blood
- Ann Arbor Staging System does not apply
- Many patients diagnosed incidentally and are asymptomatic from their disease
- 10,000 new diagnoses each year in US
- Only 4600 deaths per year in US
- Median age 72 years
Normal B Cell Development

- Primary follicles
  - Naïve B cells
- Secondary follicles
  - B cells that are proliferating after encountering an antigen
  - Naïve B cells in secondary follicles get pushed to periphery and form the mantle zone
  - Have germinal centers
    - Dark zone: centroblasts
    - Light zone: centrocytes
    - Tingible body macrophages: destroy B cells with “wrong” antibodies

CLL: Pathophysiology

- Centroblasts are where the B cells normally undergo somatic hypermutation in their V genes
  - More mature
- A sequence that differs from germline by 2% or more is considered mutated
- If CLL cells have 2% or more mutations in their IgVH sequence, this is associated with a more indolent course of disease

CLL: Pathophysiology

- IgV\textsubscript{H} somatic mutations
  - Indolent
    - Median OS 25 years
  - Unmutated IgV\textsubscript{H} genes
    - More aggressive
    - Median OS 8 years
- Replaces prior notion that CLL cells are stuck in \textit{G\textsubscript{0}}
- ~50% of patients with CLL will have unmutated IgVH
CLL: Pathophysiology

- **CD 38:**
  - expressed when B cells are activated to allow for interaction with other cells
  - amplifies signaling of B cell receptors and inhibits apoptosis through the Src pathway
  - >30% expression is considered unfavorable
- **ZAP-70 (zeta chain associated protein 70):**
  - serves a similar function on normal T cells
  - aberrantly expressed on CLL cells
  - exact cutoff unclear
  - lab reproducibility is poor

CLL: Prognostic Factors

- **Favorable:**
  - >2% mutation in IgVH
  - <30% CD38 expression
  - No ZAP-70 expression

- **Cytogenetics:**

CLL: Cytogenetics

- **Not diagnostic**
- **Abnormalities detected in over 80% of CLL patients**

---


CLL: Prognostic Factors

- Favorable:
  - >2% mutation in IgVH
  - <30% CD38 expression
  - ZAP-70 expression
  - del 13q

- Cytogenetics

References:

CLL: Diagnosis

- (+) CD5, CD19, CD23
- (+/-) CD20 (weak expression)
- (+/-) surface immunoglobulin
- Light chain restriction
- (-) for cyclin D1 and CD10
- Do not need a bone marrow for diagnosis
**CLL: Criteria for Diagnosis**

<table>
<thead>
<tr>
<th>Criteria</th>
<th>NCI-WG 1996*</th>
</tr>
</thead>
<tbody>
<tr>
<td>PB Lymphocytes</td>
<td>&gt; 5 x 10^9/L</td>
</tr>
<tr>
<td>Morphology</td>
<td>Not specified</td>
</tr>
</tbody>
</table>
| Immunophenotype           | 1. > 1 B cell marker (CD19, CD20, or CD23), absence of other pan-T cell markers  
2. Monoclonal expression of K or λ chain  
3. Low density surface Ig |
| Atypical cells (prolymphocytes) | <55% and/or 15 x 10^9/L |
| Duration of lymphocytosis | >4 weeks     |
| Bone marrow lymphocytes   | >30%         |

* Updated in 2008


**Risk Rai Stage Location Median Overall Survival**

<table>
<thead>
<tr>
<th>Risk</th>
<th>Rai Stage</th>
<th>Location Description</th>
<th>Median Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>0</td>
<td>Lymphocytosis only</td>
<td>&gt; 10 years</td>
</tr>
<tr>
<td></td>
<td>I</td>
<td>Lymphocytosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lymphadenoathpy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>Lymphocytosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Splenomegaly</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>III</td>
<td>Lymphocytosis</td>
<td>8-12 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hb &lt; 11.0 due to progression of CLL in the marrow</td>
<td></td>
</tr>
<tr>
<td></td>
<td>IV</td>
<td>Lymphocytosis</td>
<td>8-12 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Plts &lt; 100K due to progression of CLL in the marrow</td>
<td></td>
</tr>
</tbody>
</table>

**CLL: Indications for Treatment**

- Significant B symptoms
- Recurrent infections
- Symptomatic lymphadenopathy
- Symptomatic splenomegaly
- "Symptomatic" bone marrow involvement
  - Stage III or IV disease
- Note that the absolute white cell count is NOT an indication to treat!
  - Doubling time of < 6 months
  - Increase of > 50% over 2 months

Image courtesy of Dr. Cruz


• **Immune dysregulation**
  • **Insufficient immune system:**
    - Difficult to fight infection
    - Often need prolonged courses of antibiotics
  • **Hypogammaglobulinemic**
    - Quantitative immunoglobulins often reveal patients to be pan-hypoglobulinemic
    - If patients have persistent infections or infections severe enough to require hospitalization, will treat with IVIG

• **Overactive immune system**
  • Inappropriate destruction of “self” cells
    - Autoimmune hemolytic anemia
    - Immune thrombocytopenic purpura
  • Labs for AIHA are the same as with any other:
    - Elevated LDH, bilirubin
    - Low Hb, haptoglobin
    - Can be Coombs positive
    - Generally treat with steroids
    - Don’t need a bone marrow to make this diagnosis

• How can we tell if a CLL patient’s thrombocytopenia is from ITP or stage IV disease?
How can we tell if a CLL patient’s thrombocytopenia is from ITP or stage IV disease?
- Do a bone marrow

Richter’s transformation
- Development of diffuse large B cell lymphoma arising from one CLL clone
- May have B symptoms, one area of lymphadenopathy out of proportion to others
- PET scan will show transformed sites
  - CLL is not PET avid
  - DLBCL is very PET avid
- Must document with biopsy to prove transformed disease
- Treat with DLBCL regimen such as R-CHOP
  - CLL chemo is ineffective
  - Pts are still left with underlying CLL after treatment complete
• Transformation to prolymphocytic leukemia
• >55% prolymphocytes
• Treatment is different from standard CLL treatment

• CLL treatment:
  • Chemotherapy
  • Purine analog based
    • Fludarabine based
    • Pentostatin based
  • Patients are at significant risk for tumor lysis syndrome with the first cycle of treatment
  • Hydration and frequent lab monitoring is important

CLL: Treatment
• Purine analog-based
• FCR x 6 cycles
  – Fludarabine 25 mg/m² IV days 1-3
  – Cyclophosphamide 250 mg/m² days 1-3
  – Rituximab 375 mg/m² with cycle 1, 500 mg/m² in cycles 2-6
• Repeat bone marrow three months after last cycle
• 95% ORR, 70% CR
• Median TTP:
  – 80 months for CR
  – 80 months for nPR
  – 27 months for PR
• Presented 5 year follow up data at ASCO 2006 and this was durable

Keating MJ et al, JCO 2005
Tam CS et al, JCO abstr 2007
FDA Approved 2/18/10
CLL: FCR Treatment

- **Prophylaxis:**
  - Tumor lysis:
    - Allopurinol 300 mg daily
    - Hold rituximab with first cycle; split dose if WCC still >20K
  - Infection:
    - TMP-SMX DS one tablet bid q M, W, F
    - Acyclovir 400 mg bid
    - Antibiotics if became neutropenic
    - Growth factors if needed
  - Anti-emetic

- **FCR Downsides:**
  - Cytopenias persist for up to a year after completion of treatment
  - Multi-day regimen
  - Can be tough on patients
  - Fludarabine is associated with an autoimmune hemolytic anemia

Keating MJ et al. JCO 2005
Tam CS et al. JCO abstr 2007

CLL: PCR Treatment

- **Pentostatin**
  - Purine analog
  - Pentostatin 2 mg/m^2 vs 4 mg/m^2 on day 1
  - Cyclophosphamide 600 mg/m^2 on day 1
  - Rituximab 375 mg/m^2 on day 1
  - Supportive med:
    - 1500 cc NS on day of treatment
    - Anti-emetic
    - Tumor lysis prophylaxis
    - Infectious prophylaxis

- **Front line data:**
  - ORR 95%
  - CR 70%
  - 69% of patients were treatment failure free at 4 years
  - Much better tolerated – better choice for older patients
  - Treatment completed in one day
  - Far less risk for AIHA
  - No prolonged cytopenias

Kay NE et al Blood 2007

CLL: Treatment

- **Alemtuzumab (Campath)**
  - Anti-CD52 monoclonal antibody
  - FDA approved for front line use on 9/17/07
  - Compared to chlorambucil with similar OS rates
  - Allowed for crossover
  - CMV reactivation
    - Ganciclovir is more effective than acyclovir


**Table 1**

<table>
<thead>
<tr>
<th>Guidelines for Prophylactic Treatment (WHO Recommendations)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with high risk disease stage or treated for CMV infection by allopurinol 3 mg/day.</td>
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<tr>
<td>Patients with high risk disease stage or treated for CMV infection by allopurinol 3 mg/day.</td>
</tr>
<tr>
<td>CMV testing is not routinely employed; physicians should treat in cases of low risk infection with acyclovir or a prophylactic regimen.</td>
</tr>
</tbody>
</table>

CLL: Treatment

• Chlorambucil
  – Alkylator
  – Oral
  – Increases risk of secondary AML
  – ORR ~40%
  – CR 2%
  – Is the “standard arm” for many randomized controlled trials in CLL.


CLL: Treatment

• Bendamustine
  – Combination purine analog/alkylating agent
  – FDA approved for single agent use in CLL on 3/20/08
  – Randomized controlled trial:
    • 301 untreated, symptomatic patients with CLL
    • Bendamustine 100 mg/m2 IV on days 1, 2 q 28 days x 6 cycles
    • Chlorambucil 0.8 mg/kg/day po on days 1 and 15 q 28 days x 6 cycles
    • ORR 59% for bendamustine; 26% for chlorambucil
    • CR 8% for bendamustine; >1% for chlorambucil
    • Median PFS for bendamustine 18 months; 6 months for chlorambucil

Knauf WU, et al JCO 2009

Lenalidomide

• Similar to thalidomide
• Immunomodulator
  – Inhibits secretion of pro-inflammatory cytokines (TNF-alpha)
• Anti-angiogenic
• “Anti-neoplastic”
• CLL cells produce and express cell surface receptors for pro-survival cytokines
  – TNF-alpha
  – VEGF
• Creates an autocrine loop that leads to prolonged survival

Kay NE Leuk Res 2004
Kay NE et al, Leukemia 2002

**Lenalidomide in CLL**

- Phase II non-randomized study
- 45 patients with relapsed or refractory CLL
  - 51% were refractory to fludarabine
- Lenalidomide 25 mg po days 1-21 of a 28 day cycle
- Rituximab was added upon disease progression
- ORR 47%; 9% CR

*Chanan-Khan A, et al. JCO 2006*

**CC-5013-CCL-001 (CCCWFU 27106)**

- Phase 2/3 parallel group study
- Comparing 2 dose regimens of lenalidomide in relapsed or refractory CLL patients
  - 10 mg po qd x 28 days q 28 days
  - 25 mg po qd x 21 days q 28 days
- Plan was to enroll 310 patients
- After 18 patients enrolled
  - Marked activity noted (decreased ALC)
  - Temporary suspension:
    - 4 cases of tumor lysis syndrome
    - 2 associated with renal failure and tumor flare reaction
    - 2 fatalities

**Lenalidomide**

- Redesigned to phase I study only
  - ie: determine maximum tolerated dose level
- Separate protocol generated for phase 2:
  - After MTD in CLL patients is identified,
  - Evaluate cyclic vs. continuous dosing in a gentle stepwise dose escalation
- CC-5013-CCL-009…. 
CC-5013-CLL-009 (CCCWFU 27109)

• Relapsed or refractory CLL
• Randomized to 3 different arms:
  – 5 mg po qd x 28 days → 10 mg → 15 mg → 20 mg → 25 mg (or highest dose tolerated)
  – 10 mg po qd x 28 days → 15 mg → 20 mg → 25 mg (or highest dose tolerated)
  – 15 mg po qd x 28 days → 20 mg → 25 mg (or highest dose tolerated)

CC-5013-CLL-009 (CCCWFU 27109)

• Inclusion criteria:
  – ≥ 18 yo
  – Relapsed or refractory to 1 to 3 regimens
    • At least one must be a purine analog
    • Meet criteria for needing treatment

CC-5013-CLL-002 (CCCWFU 27209)

• Phase 3 randomized controlled trial evaluating lenalidomide as maintenance therapy after second line chemotherapy
• Lenalidomide 2.5 mg po qd x 28 days (vs. placebo) → 5 mg po qd x 28 days x 5 cycles → 10 mg po qd x 28 days
CC-5013-CLL-002 (CCCWFU 27209)

- Inclusion criteria:
  - 18 yo or older
  - Must have been treated with a purine analog-containing regimen in the first and/or second line treatment
  - Must have a minimum response of PR after completion of their second line therapy prior to randomization
  - Last cycle of second line treatment must have been completed between 8 and 16 weeks prior to randomization
  - ECOG 0-2

Ofatumumab

- Fully human monoclonal antibody to CD20
  - Results in cell lysis, through CDC and ADCC
- Binds to a different epitope (small loop) than rituximab
- Slower off-rate; more stable binding
  - In vitro studies show that rituximab-resistant cells will still lyse with ofatumumab


Ofatumumab

- Phase I/II study was performed in 33 patients with relapsed or refractory CLL
- Dose escalation performed; MTD not reached
  - A: 100 mg then 500 mg IV qwk x 4 total doses
    • 3 patients
  - B: 300 mg then 1000 mg IV qwk x 4 total doses
    • 3 patients
  - C: 500 mg then 2000 mg IV qwk x 4 total doses
    • 27 patients

Ofatumumab

- Adverse events:
  - Infusional reactions
  - Cytopenias
  - Infection

- FDA approved 10/28/09


Integrative Oncology - Complementary Therapies During and After Cancer Treatment

Piedmont Oncology Association 31st Annual Fall Symposium
August 28, 2010

Kathleen Wesa, MD
Integrative Medicine Service
Memorial Sloan-Kettering Cancer Center
New York, USA

Outline

1- Integrative Oncology
2- Physical Fitness
3- Nutrition
4- Botanicals & Supplements
5- Acupuncture
6- Mind-Body Interventions

Alternative vs Complementary

Alternative Therapies
• Promoted for use instead of mainstream treatment for cancer & other serious illnesses
• Usually biologically invasive
• Costly; potentially harmful

Complementary Therapies
• Used WITH mainstream care for serious illnesses
• Non-invasive
• Inexpensive; safe; evidence-based
Integrative Oncology

Combines the best of complementary and mainstream care

Complementary Therapies control many symptoms experienced by patients and by people generally

- Pain
- Hot flashes
- Sexual dysfunction
- Urinary problems
- Fatigue
- Xerostomia
- Anxiety, depression, stress
- Osteoarthritis

2-Fitness/Physical Activity

Essential per data on activity and cancer outcome
Obesity Trends* Among U.S. Adults


(*BMI ≥30, or about 30 lbs. overweight for 5’4” person)

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>&lt;10%</td>
<td>No Data</td>
<td>&lt;10%</td>
<td>10%–14%</td>
</tr>
<tr>
<td>15%–19%</td>
<td>15%–14%</td>
<td>15%–19%</td>
<td>20%–24%</td>
</tr>
<tr>
<td>25%–29%</td>
<td>25%–24%</td>
<td>25%–29%</td>
<td>30%–34%</td>
</tr>
</tbody>
</table>

Exercise Increases Survival

• Studies involving breast, colon, lung, prostate cancer all show survival benefit
• 50-60% increase in survivorship seen with regular physical fitness
• Greatest benefit from walking 3-5 hrs/wk
• Combination of aerobic, resistance and stretching activities recommended


Summary of Exercise-Induced Changes

INCREASED
• Muscle mass, strength & power
• CV fitness
• Max walk distance
• Immune system capacity
• Physical functional ability
• Flexibility
• QOL
• Hemoglobin

DECREASED
• Nausea
• Body fat
• Fatigue
• Symptom Experience
• Duration of hospitalization
• HR
• SBP
• Psychological & emotional stress
• Depression & anxiety
**Hormonal Treatment Changes in Prostate Cancer**

- 10% increase in whole body fat, lean muscle loss
- Increased girth at waistline - risk for metabolic syndrome, diabetes, cardiovascular disease
- Osteoporosis risk similar to post-menopausal women
- These problems are preventable via fitness

---

**Aging and Musculoskeletal fitness**

---

**ACS/ASCM Physical Activity Recommendations for Cancer Survivors**

- 30+ minutes of moderate to vigorous physical activity, above usual activities, on 5+ days/ wk
- 45 to 60 minutes physical activity is preferable
- If sedentary, begin with 10 minutes fitness and add 10-15% each wk, total 30 min continuous/5 days per wk

*ACSMB New Guidelines Presented at ASCO June 6, 2010*
3-Nutrition Recommendations

Nutrition Counseling

Diet is very important, but NO DIET can cure cancer

WCRF/AICR Recommendations

1- Be as lean as possible w/o being underweight
2- Limit consumption of energy-dense foods
   • Avoid sugary drinks
3- Plant Foods
   • 5+ servings of non-starchy veg and fruits every day
4- Animal Foods
   • Limit intake of red meat and avoid processed meat
5- Alcoholic Drinks
   • ≤ 2 drinks/day for men and ≤ 1/day for women
6- Preservation, Processing, Preparation
   • Limit salt, avoid moldy cereals
7- Dietary Supplements
   • Meet nutritional needs through diet alone
   • Dietary Supplements not recommended for cancer prevention
Mediterranean Diet

• 3-5 servings of fruits/day
• 3-5 servings of vegetables/day
• 2+ protein meals (legumes, nuts, soy, etc)
• WHOLE GRAINS: whole wheat, brown rice
• Extra Virgin Olive Oil rather than (NOT in addition to) butter/margarine
• Calcium 1000-1200 mg/day
• Vitamin D 1000-2000 IU daily


Epidemiology

• Vitamin D deficiency is pandemic (70-90%)
• Colorectal, Lung, Breast cancers and Lymphoma association between Vitamin D levels and survival
• Anti-inflammatory, apoptosis, antiangiogenic, calcium homeostasis, blood pressure & glucose regulation
• Muscle weakness, falls, depression, fatigue, pain
• Normal >30-32 ng/ml; 75 nmol/l


2 main forms of Vitamin D supplements

• Vitamin D2 Ergocalciferol (Drisdol)
  – Vegetarian source, derived primarily from yeast, mushrooms also used
• Vitamin D3 Cholecalciferol
  – Animal source, derived primarily from lanolin (sheep) occasionally from salmon
• Typical daily requirements are 1000-2000 IU daily
  if starting from normal vit D level
• Repletion regimens vary; 50,000 IU weekly x 8 wks to 50,000 IU 3 times/wk for 4-6 weeks (most effective in reaching normal levels)
**Vitamin D safety**

- Doses of 10,000 IU daily long-term are safe
- Typically no adverse side-effects until serum level > 150 ng/ml
- Calcium renal stones; Sarcoid; hypercalcemia
- Constipation, Nausea, muscle weakness, metastatic calcification are possible with repletion
- Follow serial 25-OH vit D levels until stable 3-4 values
- Wait for DEXA scans until vit D replete!

**Supplements?**
4- Botanicals and Nutritional Supplements

• 23+ BILLION dollars are spent each year in the USA on vitamins and nutritional supplements
• Antioxidants are highly marketed and are of uncertain benefit
• Wheat grass, Gogi, Noni, AÇAI, Pomegranate, Mangostin, EGCG/green tea, resveratrol, Vitamin A, C and E, selenium

Herbs and Dietary Supplements

• Herbal remedies are the most commonly used CAM therapies in cancer patients in Europe with >20% using herbs or medicinal teas (Molassiotis A. Annals of Oncology 2005)
• Other studies show more than 50% cancer patients worldwide use herbs (Powell C. 2002, Hyodo I. 2005, Molassiotis 2006)

Cancer Patients Use Herbs For

• Symptom control
  • Pain, N/V, fatigue, sexual dysfunction
• Treatment of active diseases
  • As cytotoxic agents
• Prevention of cancer or metastasis
  • Enhance immune system
• General health and tradition
  • Tonic
Herbs and Other Botanicals
Benefits and Problems

• Faulty Assumptions
  Natural = safe; Long-term use = effective
• Botanicals are unrefined pharmaceuticals
• OK for general public, probably not for cancer patients
• Concerns: contamination, toxicity, standardization, bioavailability, proper doses, and herb-drug interactions

Antioxidants

• Primary prevention- decrease DNA oxidative damage
• Radiation and some chemotherapy agents act solely though production of reactive oxygen species (ROS)
  – Anthracyclines (doxorubicin)
  – Platinum containing complexes
  – Alkylating agents (cyclophosphamide, ifosfamide)
  – Cytotoxic antibiotics (bleomycin, mitomycin-C)

Antioxidants- 2

• Antioxidants are controversial in cancer patients- vitamin C, SELECT trial, Physicians Health Study vit C/E
• Chemotherapy + antioxidant use: 16 Randomized Controlled Trials; 6 had placebo control
• None powered to show any decrease in tumor response rates or survival rates, most had <50 pts; requires >2000 pts to detect 5% difference in survival
• 6 recent authoritative reviews do not recommend concurrent use of antioxidants during chemotherapy/radiation; 1 review concluded antioxidants were safe
Nutritional Adequacy in Adult Lymphoma Patients

- Adequacy of folate, vitamin A, iron, selenium and calcium are required for cancer prevention
- Excess amounts of vitamin A, folate and iron may promote cancer
- Cross-sectional survey of 144 patients with Hodgkin Lymphoma or B-cell type Non-Hodgkin Lymphoma
- Age 20-64; completed initial Rx within past 1-3 years; excluded those with BMT or Stem Cell Transplant

Nutritional Adequacy in Adult Lymphoma Patients-2

- Food frequency questionnaires, supplement questionnaire on vitamin use
  - Supplement use “fairly regular” 94 (67% of 141)
  - 26 (18%) Herbal/other supplements + vitamins/minerals
  - 6 (4%) Herbs but not vitamins
- 75 (53%) reported healthy dietary changes
- 44 (31%) consumed 5+ fruits/veg/day
- 132 (94%) were consuming either excess or inadequate amounts of these nutrients

Anticancer Supplements?

- Supplements promoted to cancer patients but have no proven clinical benefits
  - Laetrile (Amygdalin, Vit B17)
  - Essiac (Flor-Essence)
- Herbs with promising anticancer effects
  - Turmeric, maitake, green tea
No Herbs during Cancer Treatment

• Antiplatelet activity
• Adverse interactions with corticosteroids, CNS depressant meds
• GI problems, liver & kidney toxicity
• Additive effects when used with opioid analgesics

Interactions with Anticoagulants

• Anticoagulant Properties
  – Vitamin E (Comigel 1979)
  – Garlic (Browne et al. 1986, Ross et al. 1986, Burnett et al. 1988)
  – Asian ginseng
  – St. John’s wort, Dong Gui etc.
  – Monitor INR and caution patients when taken
    • with Rx anticoagulants
    • before surgery
• Procoagulant Properties
  – Coenzyme Q10, and any supplement that inhibits warfarin

Interactions with Hormonal Therapies

• Certain breast and ovarian cancers are sensitive to hormones
• Some botanicals have estrogenic effects
  • Soy, Dong Gui, Red clover, Wild yam, Kudzu,
    Cinnamon, Flax seeds, grapefruit seed extract
  • May stimulate proliferation of cancer cells
  • May affect the action of tamoxifen
  • Avoid in patients with hormone-sensitive cancers

Genistein
Estradiol
Alternative Medicine in Leukemia cells

- Ex vivo testing of 3 botanical agents popularly used as alternative treatments in cancer pts
  - Viscum album (misteltoe); Uncaria tomentosa (cat’s claw); Croton Lechleri (Dragon’s blood)
- 53 children with leukemia, 8 healthy controls, 4 leukemic cell lines used
- MTT assay; cell-cycle analysis; annexin-V binding assay

USP Dietary Supplement Verification Program

- Contains the ingredients and amount stated
- Tested for bioavailability
- Screened for harmful contaminants
- Manufactured using safe, sanitary and well-controlled procedures

ConsumerLab

- Product met CL’s standards.
- CL is independent and consumer-focused.
- This specific ingredient was tested.
- Product was laboratory-tested by experts.
- This seal is a registered certification mark.
- Product was tested for ingredient quality.
- You can learn more about this product, ingredient, and testing at our website.
Web site about herbs, botanicals, vitamins, etc.

www.mskcc.org/aboutherbs

Website
250+ monographs; each contains
- Clinical Summary
- Scientific Name
- Also Known As
- Patient Use
- Constituents
- Mechanism of Action
- Warnings/Adverse Reactions
- Drug Interactions
- Dosage
- Literature Summary and Critique
- References
Traditional Chinese Medicine (TCM)
- Acupuncture
- Herbs
- Exercise (Qi Gong)
- Manipulation
- Moxabustion
- Cupping

Common Indications for Acupuncture
- Pain
- Stress
- Insomnia, anxiety
- Addiction
- Asthma and allergies
- Gastrointestinal tract dysfunction
- Hypertension
- Endocrine disturbance

Application in Cancer Patients
- Pain
- Xerostomia
- Neuropathy
- Nausea
- Fatigue
- Hot flashes
- Stress/Depression
- Bowel Irregularity
- Lymphedema?
Acupuncture Needles

25 gauge needle
acupuncture "stilts"
(indwelling needle)

Acupoints and Meridians

• No unique anatomic structures
• Coincide with trigger points, nerves, blood vessels and myofascial planes
• Appear rich in nerve endings
Is Acupuncture Analgesia a Placebo Effect?

- Seen in animals
- Seen in children
- Higher than the expected 20-30% placebo effects in chronic pain
- Seen in randomized placebo controlled clinical trials


Xerostomia

- 58 pts randomized to acupuncture vs usual care
- Decreased pain & dysfunction, improved xerostomia symptoms of dryness, hoarseness, improved taste
- May be delayed response, tissue regeneration
- 39% acupuncture group clinically significant improvements in pain/dysfunction compared 7% in control group

Acupuncture Safety

- Administered by a certified practitioner, licensed, carries insurance
- Graduate of Accreditation Commission for Acupuncture and Oriental Medicine (ACAOM) accredited school
- Licensed through state regulatory agency recognized by the Federation of Acupuncture and Oriental Medicine Regulatory Agencies (FAOMRA)

Acupuncture Safety-2

- Physicians practicing medical acupuncture may come under different regulatory agencies- The American Association of Medical Acupuncture
- Very important acupuncturists receive additional training in Oncology before working with Cancer patients

Acupuncture Safety-3

- Significant adverse events are very rare >0.55 per 10,000 individuals
- Even less common with single use needles
- Deep needle insertion avoided if low platelets, but 40-50,000/µl very safe
- Low ANC not contraindication to aseptic procedure
- Avoid needling in irradiated field
6- Mind-Body Interventions

• Meditation - includes mantra, mindfulness and relaxation techniques
• Yoga
• Tai Chi and Qi-Gong
• Hypnosis
• Guided Imagery
• Breath Awareness

RCT of Presurgical Hypnosis

• Objectives: to determine whether brief, presurgery hypnosis decreases intraoperative anesthesia or post-op analgesic use; reduces side-effects; is cost-effective

• 200 patients scheduled for excisional breast biopsy or lumpectomy randomized to 15-minute presurgery hypnosis session or nondirective empathic listening


Hypnosis RCT, Results

Intraoperative analgesia use-
Hypnosis group required less propofol 64.01 vs 96.64 µg [3.95-61.3] and less lidocaine 24.23 vs 31.09 mL [3.05-10.68]

Pain intensity-
Hypnosis group reported less pain intensity 22.43 vs 47.83 [9.92-25.80]; pain unpleasantness 21.29 vs 39.05 [9.92-25.80]; nausea 6.57 vs 25.49 [12.98-24.87]; discomfort 23.01 vs 43.20 [12.36-28.02]

Cost effectiveness-
The hypnosis group cost $772.71 less per patient compared with controls
Complementary Medicine at the NIH

• Website for Office of Cancer Complementary and Alternative Medicine  www.cancer.gov/cam

• National Center for Complementary and Alternative Medicine  http://nccam.nih.gov

Summary

Eat food
Not too much
Mostly plants
Be physically active every day
Discuss all botanical/supplement use
Supplements are not recommended for cancer prevention
Acupuncture can benefit many symptoms
Don’t forget the Mind-body interventions
Beware of Online Cancer Fraud

While health fraud is a cruel form of greed, fraud involving cancer treatments can be particularly heartless—especially because fraudulent information can travel around the Web in an instant.

“Anyone who suffers from cancer, or knows someone who does, understands the fear and desperation that can set in,” says Gary Coody, R.Ph., the National Health Fraud Coordinator and a Consumer Safety Officer with the Food and Drug Administration’s (FDA) Office of Regulatory Affairs. “There can be a great temptation to jump at anything that appears to offer a chance for a cure.”

Medicinal products and devices intended to treat cancer must gain FDA approval before they are marketed. The agency’s review process helps ensure that these products are safe and effective.

Nevertheless, it’s always possible to find someone or some company hawking bogus cancer “treatments.” Such “treatments” come in many forms, including pills, tonics, and creams. “They’re frequently offered as natural treatments and ‘dietary supplements,’” says Coody. Many of these fraudulent cancer products even appear completely harmless, but may cause indirect harm by delaying or interfering with proven, beneficial treatments.

Advertisements and other promotional materials touting bogus cancer ‘cures’ have probably been around as long as the printing press,” says Coody. “However, the Internet has compounded the problem by providing the peddlers of these often dangerous products a whole new outlet.”

Unproven ‘Remedies,’ False Promises
Coody cites black salves as one of the fake cancer “remedies” that indeed have proven to be harmful. “Although it is illegal to market these salves as a cancer treatment, they are readily available online,” he says. The salves are sold with false promises that they will cure cancer by “drawing out” the disease from beneath the skin. “However, there is no scientific evidence that black salves are effective,” says Janet Woodcock, Director of FDA’s Center for Drug Evaluation and Research (CDER). “Even worse, black salves can cause direct harm to the patient.”

Public Beware!

WARNING AGAINST THE HOSSEY CANCER TREATMENT

Sufferers from cancer, their families, physicians, and all concerned with the care of cancer patients are hereby advised and warned that the Hossey treatment for cancer has been found worthless by the Federal courts. The Hossey treatment costs $600, plus $50 in additional fees—expenditures which will yield nothing of value in the case of cancer. It may cause potentially fatal disease which are worthless for treating cancer. The Food and Drug Administration has condemned as fraudulent the use of any of the Hossey treatment and the salves which were claimed to be needed. That a single method of cancer cure has been found.

Those afflicted with cancer are warned not to be misled by the false promise that the Hossey cancer treatment will cure or alleviate their condition. Cancer can be cured only through surgery or radiation. Death from cancer is inevitable when cancer patients fail to obtain prompt medical treatment because of the lure of a worthless cure “without the use of surgery, x-ray, or radium” as claimed by Hossey.

Anyone planning to try this treatment should get the facts about it.

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

FDA Press Release
www.fda.gov/bbs/topics/NEWS/2008/NEW01852.html

125 Fake Cancer ‘Cures’ Consumers Should Avoid
www.fda.gov/bbs/topics/factsheets/fakecancercures.html

CDER: Fake Cancer Cures
www.fda.gov/cder/news/fakecancercures.htm
The corrosive, oily salves “essentially burn off layers of the skin and surrounding normal tissue,” says Woodcock. “This is not a simple, painless process. There are documented cases of these salves destroying large parts of people’s skin and underlying tissue, leaving terrible scars.”

Another unproven “remedy” that has been hawked for decades is an herbal regimen known as the Hoxsey Cancer Treatment. “FDA has taken regulatory and enforcement action against this discredited course of therapy beginning in the 1950s,” says Coody. “There is no scientific evidence that it has any value to treat cancer,” he adds. “Yet consumers can go online right now and find all sorts of false claims that Hoxsey treatment is effective against the disease.”

Red Flags

Coody says that firms engaged in cancer treatment or prevention fraud often use exaggerated and bogus claims to promote these products. He adds that consumers should recognize the following phrases as red flags:

- “Treats all forms of cancer”
- “Skin cancers disappear”
- “Shrinks malignant tumors”
- “Non-toxic”
- “Doesn’t make you sick”
- “Avoid painful surgery, radiotherapy, chemotherapy, or other conventional treatments”
- “Treat Non Melanoma Skin Cancers easily and safely”

“Unproven claims are also found in unverified testimonials, research results, or even in product and website names,” says Coody. He offers important points that consumers seeking cancer treatments should keep in mind:

- Always consult with your health care professional before starting a new treatment or adding one to existing therapies. “Some products may interact with your medicines or keep them from working the way they are supposed to,” says Coody.
- Understand the difference between fraudulent drug products and what FDA calls “investigational drugs.” Investigational drugs undergo clinical testing to determine if they are safe and effective for their intended uses. Fraudulent products, on the other hand, are unapproved and typically have never been clinically tested or reviewed by FDA for safety and effectiveness. Marketing them is a violation of federal law.

“There are legal ways for patients to access investigational drugs,” says Coody. “The most common way is by taking part in clinical trials. But patients can also receive investigational drugs outside of clinical trials in some cases.” For more details on this, visit www.fda.gov/oashi/speedaccess.html.

Signs of Health Fraud

All consumers seeking information about any health product or medical treatment should be familiar with the following signs of health fraud:

- Statements that the product is a quick and effective cure-all or a diagnostic tool for a wide variety of ailments.
- Suggestions that a product can treat or cure serious or incurable diseases.
- Claims such as “scientific breakthrough,” “miraculous cure,” “secret ingredient,” and “ancient remedy.”
- Impressive-sounding terms, such as “hunger stimulation point” and “thermogenesis” for a weight loss product.
- Claims that the product is safe because it is “natural.”
- Undocumented case histories or personal testimonials by consumers or doctors claiming amazing results.
- Claims of limited availability and advance payment requirements.
- Promises of no-risk, money-back guarantees.
- Promises of an “easy” fix for problems like excess weight, hair loss, or impotency.

For More Information

FDA Press Release
www.fda.gov/bbs/topics/NEWS/2008/NEW01852.html

FDA: Cracking Down on Health Fraud
www.fda.gov/fdac/features/2006/606_fraud.html

FDA’s Cancer Liaison Program
www.fda.gov/oashi/cancer/cancer.html

National Cancer Institute: Clinical Trials
www.cancer.gov/clinicaltrials

Competition Bureau Canada’s Project False Hope
www.competitionbureau.gc.ca/epic/site/cb-bc.nsf/en/02614e.html
Heterocyclic Amines in Cooked Meats

Research has shown that cooking certain meats at high temperatures creates chemicals that are not present in uncooked meats. A few of these chemicals may increase cancer risk. For example, heterocyclic amines (HCAs) are the carcinogenic chemicals formed from the cooking of muscle meats such as beef, pork, fowl, and fish. HCAs form when amino acids (the building blocks of proteins) and creatine (a chemical found in muscles) react at high cooking temperatures. Researchers have identified 17 different HCAs resulting from the cooking of muscle meats that may pose human cancer risk.

Research conducted by the National Cancer Institute (NCI) as well as by Japanese and European scientists indicates that heterocyclic amines are created within muscle meats during most types of high temperature cooking.

Recent studies have further evaluated the relationship associated with methods of cooking meat and the development of specific types of cancer. One study conducted by researchers from NCI’s Division of Cancer Epidemiology and Genetics found a link between individuals with stomach cancer and the consumption of cooked meats. The researchers assessed the diets and cooking habits of 176 people diagnosed with stomach cancer and 503 people without cancer. The researchers found that those who ate their beef medium-well or well-done had more than three times the risk of stomach cancer than those who ate their beef rare or medium-rare. They also found that people who ate beef four or more times a week had more
than twice the risk of stomach cancer than those consuming beef less frequently. Additional studies have shown that an increased risk of developing colorectal, pancreatic, and breast cancer is associated with high intakes of well-done, fried, or barbequed meats.

Four factors influence HCA formation: type of food, cooking method, temperature, and time. HCAs are found in cooked muscle meats; other sources of protein (milk, eggs, tofu, and organ meats such as liver) have very little or no HCA content naturally or when cooked. Temperature is the most important factor in the formation of HCAs. Frying, broiling, and barbecuing produce the largest amounts of HCAs because the meats are cooked at very high temperatures. One study conducted by researchers showed a threefold increase in the content of HCAs when the cooking temperature was increased from 200° to 250°C (392° to 482°F). Oven roasting and baking are done at lower temperatures, so lower levels of HCAs are likely to form, however, gravy made from meat drippings does contain substantial amounts of HCAs. Stewing, boiling, or poaching are done at or below 100°C (212°F); cooking at this low temperature creates negligible amounts of the chemicals. Foods cooked a long time (“well-done” instead of “medium”) by other methods will also form slightly more of the chemicals.

Meats that are partially cooked in the microwave oven before cooking by other methods also have lower levels of HCAs. Studies have shown that microwaving meat prior to cooking helps to decrease mutagens by removing the precursors. Meats that were microwaved for 2 minutes prior to cooking had a 90-percent decrease in HCA content. In addition, if the liquid that forms during microwaving is poured off before further cooking, the final quantity of HCAs is reduced.

One study has evaluated the content of HCAs in fast food restaurants. After evaluating five kinds of meat products from various fast food restaurant chains, the study concluded that
there were low levels of HCAs found in fast food meat products due to factors such as cooking temperature and time. The study suggested that greater exposure to HCAs stems from home cooking and cooking in non-fast-food restaurants where food may be cooked to order and where a larger amount of meat is consumed.

Studies are being conducted to assess the amount of HCAs in the average American diet, but at present the maximum daily intake of HCAs in food has not been established. At the moment, no Federal agency monitors the HCA content of cooked meats (how much a person could be eating), there is no good measure of how much HCAs would have to be eaten to increase cancer risk, and there are no guidelines concerning consumption of foods with HCAs. Further research is needed before such recommendations can be made.

However, concerned individuals can reduce their exposure to HCAs by varying methods of cooking meats; microwaving meats more often, especially before frying, broiling, or barbecuing; and refraining from making gravy from meat drippings.

References


###

**Related Resources**


- *Cancer and the Environment: What You Need To Know, What You Can Do*
- *What You Need To Know About™ Cancer*

**National Cancer Institute (NCI) Resources**

**Cancer Information Service (toll-free)**

Telephone: 1–800–4–CANCER (1–800–422–6237)

TTY: 1–800–332–8615

**Online**


*LiveHelp*, NCI’s live online assistance:


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**This fact sheet was reviewed on 9/15/04**
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<th>Role</th>
<th>Name</th>
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<tr>
<td>CHAIR</td>
<td>Bayard L. Powell, MD</td>
<td>336/716-7970</td>
<td>336/713-0061</td>
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<tr>
<td>PROGRAM CHAIR</td>
<td>Antonius Miller, MD</td>
<td>336/713-4392</td>
<td>336/716-5687</td>
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<tr>
<td>CHAIR, NURSING/</td>
<td>Lisa Hodges, RN, BSN, OCN</td>
<td>336/713-6842</td>
<td>336/713-5464</td>
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<tr>
<td>ADMINISTRATOR</td>
<td>Debbie Olson</td>
<td>336/716-0457</td>
<td>336/713-0061</td>
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<td>WFUSM STUDY COORDINATORS</td>
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<tr>
<td>CCCWFU</td>
<td>Edward Shaw, MD</td>
<td>336/713-6506</td>
<td>336/713-6512</td>
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<td>CALGB</td>
<td>David D. Hurd, MD</td>
<td>336/716-7972</td>
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<td>GOG</td>
<td>Samuel Lentz, MD</td>
<td>336/716-6673</td>
<td>336/716-6961</td>
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<tr>
<td>ABTC (formerly NABTT)</td>
<td>Glenn Lesser, MD</td>
<td>336/716-9527</td>
<td>336/716-6961</td>
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<tr>
<td>NSABP / ACOSOG</td>
<td>Edward Levine, MD</td>
<td>336/716-4276</td>
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<td>COG</td>
<td>Thomas McLean, MD</td>
<td>336/716-2563</td>
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<td>RTOG</td>
<td>Kathryn Greven, MD</td>
<td>336/716-4981</td>
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<td>BIOSTATISTICS</td>
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<tr>
<td>DIRECTOR</td>
<td>Ralph D'Agostino, PhD</td>
<td>336/716-9410</td>
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<td></td>
<td>James Lovato, MS</td>
<td>336/713-4172</td>
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<td>Thomas McCoy, MS</td>
<td>336/716-3483</td>
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<td>Greg Russell, MS</td>
<td>336/716-5449</td>
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<td>Janet Tooze, PhD</td>
<td>336/716-3833</td>
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<td>Scott Isom, MS</td>
<td>336/716-0758</td>
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<td></td>
<td>Doug Case, PhD</td>
<td>336/716-1048</td>
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<td>CLINICAL RESEARCH MANAGEMENT</td>
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<tr>
<td>DIRECTOR</td>
<td>Audrey Bell-Farrow, MBA, MHA</td>
<td>336/716-6910</td>
<td>336/713-6773</td>
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<tr>
<td>Protocol &amp; Grant Writer</td>
<td>Megan Whelen, MPH</td>
<td>336/716-7298</td>
<td>336/716-5687</td>
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<tr>
<td>QA Specialist</td>
<td>Amy Landon, BS, CCRP</td>
<td>336/716-1656</td>
<td>336/716-4128</td>
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<tr>
<td>Physician Assistant</td>
<td>Thomas Freeman, II, MMS, PA-C</td>
<td>336/713-6914</td>
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<td>ASSISTANT PROJECT MANAGERS</td>
<td>Kimberly Sweat, AAS, CCRP</td>
<td>336/713-6771</td>
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<tr>
<td>(Protocol Communications)</td>
<td>Megan Brown, BS</td>
<td>336/713-6913</td>
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<td>Sara Vaughan, BA</td>
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<td>CLINICAL RESEARCH ASSOCIATES</td>
<td>Lisa Dixon</td>
<td>336/713-6767</td>
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<td>Julie Turner, BS, MS, MS (SurgOnc)</td>
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<td>Cynthia Bowman-Joyce, (GOG)</td>
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<td>Margie Hauser (secretary)</td>
<td>336/713-6909</td>
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<td>RESEARCH NURSES</td>
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<td>Tammy Carter, RN,</td>
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<td>Michelle Harmon, RN, BSN</td>
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<td>Joyce Fenstermaker, RN, OCN(surgery)</td>
<td>336/713-3155</td>
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<td>Melissa Swain, RN (Gynonc)</td>
<td>336/716-9097</td>
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<td>Rebecca Bishop, RN (Radonc)</td>
<td>336/713-6518</td>
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<td>Margaret Crowley, LPN (Radonc)</td>
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<td>Sharon McFadden</td>
<td>336/713-6931</td>
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| HEMATOLOGY AND ONCOLOGY                        |                |              |
| INDUSTRY STUDIES                                |                |              |

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<td>Karen Craver, MT, MHA, CCRP</td>
<td>336/713-4394</td>
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<td>336/716-9342</td>
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<td>Carolyn Mobley, CCN, CCRP</td>
<td>336/713-6850</td>
<td>336/713-3541</td>
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<tr>
<td>Brenda Taylor, CCRP</td>
<td>336/713-3531</td>
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<td>Lee Jones, LPN (BMT)</td>
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<td>Scarlett Hutchens, RN, BSN, OCN</td>
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<td>Jennifer Maclean, BS, RN, OCN</td>
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## New Protocol Openings

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<td>27109</td>
<td>D</td>
<td>A Phase II, Multi-Ctr, Rand, Double-Blind, Parallel-Group Study of the Safety and Efficacy of Different Lenalidomide (Revlimid) Dose Regimens in Subjects with Relapsed or Refractory B-Cell Chronic Lymphocytic Leukemia</td>
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