“The whole business Case from a patients view”

Prof. Jelle Barentsz
Prostate MR Reference/Expert Center Nijmegen
One of the Dancing Doctors
Cost-effectiveness

- More effective & higher costs
- More effective & lower costs
- Less effective & higher costs
- Less effective & lower costs

△ Effectiveness (QALYs) → △ Costs

- More effective & lower costs (AUS)
- Cost-effective
- NL

US
“MRI has improved in recent years, and urologists are learning to make better use of it. We are coming around to the idea that MRI is the best first step.”
Nano (Combidex) MRI
Nano (Combidex) MRI
Nano-MRI is very accurate!

QUADAS-2 criteria

Specificity  93%
Sensitivity  88%
1.5 mm LN metastase
1.5 mm LN metastase
1.5 mm LN metastase
All Cancers
MS-activity better detected with Combidex-MRI

Gd- (normal) MRI contrast

V. Dousset, AJNR 2006
Vulnerable plaque can be identified with Nano (Combidx) MRI

Degnan, Cerebrovasc Dis. 2012
Ushman, Nanomedicine 2015
MS-activity better detected with Combidex-MRI

V. Dousset, AJNR 2006
Best Research Evidence

Oncology Drugs Advisory Committee (ODAC) March 3, 2005.
The FDA and Its Firing Squad (Combidex Part 3)

BY RALPH BLUM

After interviewing several staff members at Ad Mag, I became very aware of the financial reality. Contrast agents are not economically viable. Subjected to all the same requirements as a drug, a contrast agent like Combidex can cost over $100 million to develop, and the likelihood of FDA approval is increased by having a narrow indication. But here's the irony: the narrower the indication, the less chance the company will ever recoup its money.
WHEN ARTIFICIAL INTELLIGENCE GOES WRONG.

PREY

MAY 2012
Old laptops
No “cross-hairs”
High inter-reader variability

EMA 2009
Suboptimal design off-center centralised reading
Combidex vs Feraheme

ftol = ferumoxytol; f10 = ferumoxtran-10; R = reference region; M = metastasized; N = normal

Debats, Peer J 2016
Rebirth of Combidex 2014

Combidx Technology Sale Opens Door to a Revolution in Diagnostic Cancer Imaging

Improved cancer diagnostic imaging is one step closer to reality with the sale of Combidex® by an American pharmaceutical company to a Dutch university that intends to launch global trials, reports the International Strategic Cancer Alliance. Combidex® is a nanoparticle fluid used with magnetic resonance imaging (MRI) that can visualize cancer metastases with pinpoint accuracy in lymph nodes as small as 2 - 3 millimeters, compared to conventional CT imaging, which can only visualize malignant nodes that are larger than 8 millimeters.

Kennett Sq., PA (PRWEB) April 08, 2013

The exclusive technology and development rights to Combidex® (Saccharin-10), a contrast agent showing great potential in the field of diagnostic imaging, have been sold by the U.S. pharmaceutical company AMAG Pharmaceuticals, Inc. to a Dutch University Medical center. The new owner of the technology package is Radboud University Nijmegen Medical Center (RUNMC), a part of Stichting Katholieke Universiteit, a non-profit foundation in The Netherlands. Under the direction of noted radiologist Jeroen Baranzitz, M.D., RUNMC will continue research and development of Combidex®, to include global clinical trials advancing towards regulatory application, a commercialized product and widespread patient access.

The sale agreement was negotiated with the assistance of Örn Adalsteinsson, Ph.D., President and CEO of the International Strategic Cancer Alliance, a cancer research organization based in Kennett Square, PA.

Combidex® is an injectable nanoparticle fluid used in conjunction with magnetic resonance imaging (MRI). Clinical cancer studies have demonstrated Combidex’s capability in visualizing malignant lesions in lymph nodes as small as 2.3 millimeters. By comparison, state-of-the-art CT imaging can only visualize malignant nodes that are larger than 8 millimeters. The potential of Combidex technology includes earlier, more specific lymph node cancer detection, resulting in more appropriate and effective therapy with reduced side effects and improved patient outcomes.

The details of upcoming clinical trials will be announced
Acceptable safety profile (>2000 p)
<table>
<thead>
<tr>
<th>Type of adverse event all were Grade 1</th>
<th>Number of patients (n= 7/310) 2%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor back pain</td>
<td>2 (contrast related)</td>
</tr>
<tr>
<td>Minor nausea</td>
<td>1 (contrast related)</td>
</tr>
<tr>
<td>Flushing/feeling hot</td>
<td>1 (contrast related)</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>3 (possibly contrast related)</td>
</tr>
</tbody>
</table>
## Table 4

### Comparison of MR Lymphography and PLND Strategies

<table>
<thead>
<tr>
<th>Category</th>
<th>MR Lymphography</th>
<th>PLND</th>
</tr>
</thead>
<tbody>
<tr>
<td>Expected cost per patient, per strategy ($)</td>
<td>8652</td>
<td>9789</td>
</tr>
<tr>
<td>Expected no. of life-years gained per strategy</td>
<td>. . .</td>
<td>. . .</td>
</tr>
<tr>
<td>Expected no. of QALYs per strategy</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Health care costs per QALY ($)</td>
<td>888</td>
<td>1014</td>
</tr>
<tr>
<td>Incremental costs per QALY</td>
<td>. . .</td>
<td>Dominated</td>
</tr>
</tbody>
</table>

Hovels, Radiology 2009
Combidex

Sensitivity 88%
Specificity 93%

Saves $2000 pp
The Benefits and Harms of Different Extents of Lymph Node Dissection During Radical Prostatectomy for Prostate Cancer: A Systematic Review

Nicola Fossati\textsuperscript{a,1}, Peter-Paul M. Willemse\textsuperscript{b,1}, Roderick C.N. van den Bergh\textsuperscript{c}, Thomas Van den Broeck\textsuperscript{d}, Cathy Yuhong Yuan\textsuperscript{e}, Erik Briers\textsuperscript{f}, Joaquim Bellmunt\textsuperscript{g,h}, Michel Bolla\textsuperscript{i}, Philip Cornford\textsuperscript{j}, Maria De Santis\textsuperscript{k}, Ekelechi MacPepple\textsuperscript{l}, Ann M. Henry\textsuperscript{m}, Malcolm D. Mason\textsuperscript{n}, Vsevolod B. Matveev\textsuperscript{o}, Henk G. van der Poel\textsuperscript{p}, Theo H. van der Kwast\textsuperscript{q}, Olivier Rouvière\textsuperscript{r}, Ivo G. Schoots\textsuperscript{s,t}, Thomas Wiegel\textsuperscript{u}, Thomas B. Lam\textsuperscript{v,w}, Nicolas Mottet\textsuperscript{x}, Steven Joniau\textsuperscript{d,*}
PLND and e-PLND

Worse intra- and peri-operative outcome

Direct therapeutic effect is still not evident

Has staging benefit
Combidex-MRI can solve this problem
We need resources to help patients, and do research within those 4 years.