Strategies For Meaningful Biomarkers in Neoadjuvant Trials

Federico Innocenti, MD, PhD
University of North Carolina
Chapel Hill, NC, USA
Clonal selection

- Genomic heterogeneity within individual tumors
- Result of clonal evolution during progression

Bain GH and Petty RD, The Oncologist 2010
Biomarker discovery

A DROP IN THE OCEAN
Few of the numerous biomarkers so far discovered have made it to the clinic.

Estimated number of papers documenting thousands of claimed biomarkers
150,000

Estimated number of biomarkers routinely used in the clinic
100

Poste G, Nature 2011
Potential of molecular biomarkers to predict histopathological response

Table 4. Studies demonstrating the potential of molecular markers to predict histopathological response/survival of patients with GEJ adenocarcinoma given neoadjuvant treatment.

<table>
<thead>
<tr>
<th>Type of cellular pathway/factor</th>
<th>Marker/type of change</th>
<th>Timing of measurement</th>
<th>Sample size</th>
<th>Tumor type</th>
<th>Tumor site</th>
<th>Neoadjuvant treatment</th>
<th>Methods</th>
<th>Histopathological response score</th>
<th>Outcome</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transcription factors</td>
<td><strong>NF-κB</strong> -ve</td>
<td>Pretreatment</td>
<td>58</td>
<td>A</td>
<td>Esophagus</td>
<td>CRT</td>
<td>Electroblot mobility shift assay, western blot, IHC</td>
<td>PathR ↑ (p = .001); survival ↑ (p &lt; .05)</td>
<td>Abdul-Latif et al. (2004) [47]</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>NF-κB</strong> +ve</td>
<td>Pretreatment</td>
<td>37</td>
<td>ASCC</td>
<td>Esophagus and GEJ</td>
<td>CRT</td>
<td>IHC</td>
<td>Other</td>
<td>PathR ↓ (p = .05); OS ↓ (p = .06)</td>
<td>Izzo et al. (2006) [48]</td>
</tr>
<tr>
<td></td>
<td><strong>NF-κB</strong> +ve</td>
<td>Pretreatment</td>
<td>75</td>
<td>ASCC</td>
<td>Esophagus and GEJ</td>
<td>CRT</td>
<td>IHC</td>
<td>Other</td>
<td>PathR ↑ (p = .005); OS ↑ (p &lt; .001); OS ↓ (p = .009)</td>
<td>Izzo et al. (2006) [49]</td>
</tr>
<tr>
<td>Growth factor receptors</td>
<td>EGFR ↓</td>
<td>Pretreatment</td>
<td>54</td>
<td>ASCC</td>
<td>Esophagus and GEJ</td>
<td>CRT</td>
<td>IHC</td>
<td>Other</td>
<td>OS ↑ (p = .009)</td>
<td>Gibson et al. (2003) [50]</td>
</tr>
<tr>
<td></td>
<td>EGFR ↑</td>
<td>Pretreatment to resection</td>
<td>22</td>
<td>ASCC</td>
<td>Esophagus</td>
<td>CRT</td>
<td>PCR</td>
<td>Junker</td>
<td>PathR ↑ (p = .014)</td>
<td>Schreiber et al. (2005) [51]</td>
</tr>
<tr>
<td></td>
<td>HER-2 ↓</td>
<td>Pretreatment</td>
<td>36</td>
<td>ASCC</td>
<td>Esophagus</td>
<td>CRT</td>
<td>PCR</td>
<td>Junker</td>
<td>PathR ↑ (p = .015)</td>
<td>Miki et al. (2004) [52]</td>
</tr>
<tr>
<td>Angiogenic factors</td>
<td>Vascular endothelial growth factor ↓</td>
<td>Pretreatment</td>
<td>56</td>
<td>ASCC</td>
<td>Esophagus</td>
<td>CRT</td>
<td>IHC</td>
<td>Other</td>
<td>PathR ↑ (p = .05); survival ↑ (p = .021)</td>
<td>Indolfi et al. (2002) [53]</td>
</tr>
<tr>
<td>Tumour suppressor genes</td>
<td>p53 mutation</td>
<td>Pretreatment</td>
<td>46</td>
<td>ASCC</td>
<td>Esophagus and GEJ</td>
<td>CRT</td>
<td>PCR, DNA sequencing</td>
<td>Other</td>
<td>OS ↑ (p = .051)</td>
<td>Gibson et al. (2001) [54]</td>
</tr>
<tr>
<td></td>
<td>p53 + ve</td>
<td>Pretreatment</td>
<td>48</td>
<td>ASCC</td>
<td>Esophagus and GEJ</td>
<td>CRT</td>
<td>Chemotherapy</td>
<td>IHC</td>
<td>Other</td>
<td>PathR ↓ (p = .04)</td>
</tr>
<tr>
<td></td>
<td>p53 + to -ve</td>
<td>Pretreatment to resection</td>
<td>23</td>
<td>A</td>
<td>Esophagus and GEJ</td>
<td>CRT</td>
<td>Chemotherapy</td>
<td>IHC</td>
<td>Other</td>
<td>PathR ↑ (p = .035); OS ↓ (p = .036)</td>
</tr>
<tr>
<td>Cell cycle regulators</td>
<td>Cyclin E ↑</td>
<td>Pretreatment to resection</td>
<td>23</td>
<td>A</td>
<td>Esophagus and GEJ</td>
<td>Chemotherapy</td>
<td>IHC</td>
<td>Other</td>
<td>PathR ↑ (p = .003); OS ↑ (p = .056)</td>
<td>Heron et al. (2004) [57]</td>
</tr>
<tr>
<td>Nucleotide excision repair pathway</td>
<td><strong>ERCC1</strong> ↓</td>
<td>Pretreatment</td>
<td>36</td>
<td>ASCC</td>
<td>Esophagus</td>
<td>CRT</td>
<td>PCR</td>
<td>Junker</td>
<td>PathR ↑ (p &lt; .001)</td>
<td>Warnecke-Schroeer et al. (2006) [58]</td>
</tr>
<tr>
<td></td>
<td><strong>ERCC1</strong> ↑</td>
<td>Pretreatment</td>
<td>84</td>
<td>ASCC</td>
<td>Esophagus</td>
<td>CRT</td>
<td>PCR</td>
<td>Other</td>
<td>Survival ↓ (p = .071)</td>
<td>Josh et al. (2005) [59]</td>
</tr>
<tr>
<td>Apoptotic factors</td>
<td>Survivin ↑</td>
<td>Pretreatment</td>
<td>51</td>
<td>ASCC</td>
<td>Esophagus</td>
<td>CRT</td>
<td>PCR</td>
<td>Junker</td>
<td>PathR + OS (p &lt; .003)</td>
<td>Wimsche-Schroeer et al. (2007) [60]</td>
</tr>
<tr>
<td>Chemotherapy associated edenoses</td>
<td><strong>TS</strong> ↑</td>
<td>Pretreatment</td>
<td>69</td>
<td>ASCC</td>
<td>Esophagus</td>
<td>CRT</td>
<td>PCR</td>
<td>Other</td>
<td>PathR ↓ (p &lt; .001); survival ↓ (p &lt; .001)</td>
<td>Josh et al. (2005) [61]</td>
</tr>
<tr>
<td></td>
<td><strong>TS</strong> +ve</td>
<td>Pretreatment</td>
<td>118</td>
<td>ASCC</td>
<td>Esophagus</td>
<td>CRT</td>
<td>IHC</td>
<td>Other</td>
<td>Survival ↓ (p = .04)</td>
<td>Haysley et al. (2001) [62]</td>
</tr>
<tr>
<td></td>
<td><strong>TS</strong> ↓</td>
<td>Pretreatment to resection</td>
<td>21</td>
<td>A</td>
<td>Esophagus</td>
<td>Chemotherapy</td>
<td>PCR</td>
<td>Becker</td>
<td>PathR ↑ (p = .013)</td>
<td>Langer et al. (2007) [63]</td>
</tr>
<tr>
<td></td>
<td>Thymidine phosphotransferase ↓</td>
<td>Pretreatment</td>
<td>21</td>
<td>A</td>
<td>Esophagus</td>
<td>Chemotherapy</td>
<td>PCR</td>
<td>Becker</td>
<td>PathR ↑ (p = .013)</td>
<td>Langer et al. (2007) [64]</td>
</tr>
<tr>
<td></td>
<td>Dihydropyrimidinucleotide dehydrogenase ↓</td>
<td>Pretreatment</td>
<td>21</td>
<td>A</td>
<td>Esophagus</td>
<td>Chemotherapy</td>
<td>PCR</td>
<td>Becker</td>
<td>PathR ↑ (p = .021)</td>
<td>Langer et al. (2007) [65]</td>
</tr>
</tbody>
</table>

continued
Different settings in GI

- GEJ
- Pancreas
- Colon
- Rectal
Variable Clonal Repopulation Dynamics Influence Chemotherapy Response in Colorectal Cancer

Antonija Kreso,1,2∗ Catherine A. O’Brien,1,3∗ Peter van Galen,1 Olga I. Gan,1 Faiyaz Notta,1,2 Andrew M. K. Brown,4 Karen Ng,4 Jing Ma,5 Erno Wienholds,1 Cyrille Dunant,6 Aaron Pollett,7 Steven Gallinger,8 John McPherson,4 Charles G. Mullighan,5 Darryl Shibata,9 John E. Dick1,2†

SCIENCE VOL 339 1 FEBRUARY 2013
Adjuvant therapy, clonal selection, and mCRC

- Adjuvant FOLFOX and improved OS in FOLFIRI/bevacizumab

- CALGB 80405 (not on FOLFOX+targeted, Venook et al., ASCO 2014)

- TRIBE (not in FOLFOXIRI/bevacizumab) (Loupakis et al., NEJM 2014)

- FIRE-3 (Heinemann et al., ESMO 2014)
Neo-Adjuvant therapy, clonal selection, and mCRC
Serial FDG-PET in GEJ adenocarcinoma

• During the course on neoadj

• Early metabolic response and correlation with
  – decrease in tumor size
  – higher rate of curative resections
  – histopathological regression
  – survival
Serial FDG-PET in GEJ adenocarcinoma

• High NPV
• Limited PPV

• Optimization of time and point repeat, plus standardization of protocols

• IMAGE trial
Borderline resectable PDAC

• Node involvement and marginal status predict relapse

• Neoadj (CRT)
  – might improve R0 resection rates
  – select out patients

• Studies not adequately powered
• Utility not fully established yet
Precision Cancer Medicine
Exceptional Responders

Barbara A. Conley, MD
Associate Director, Cancer Diagnosis Program,
DCTD

Mullard A, Nature Reviews Drug Discovery
13, 803 (2014) Published online 31 October 2014
NCI Exceptional Responders Initiative

• To understand the molecular underpinnings of exceptional responses to chemotherapy

• Cancer Therapy Evaluation Program phase II trial database over a period of 10 years (2002-2012)

• 100 cases were identified
Definitions of an “exceptional responder”

• Achieved either a complete response or a partial response for >6 months, as defined by RECIST

• Received a treatment in which <10% of patients had either a complete response or partial response for >6 months
NCI Exceptional Responders Initiative

- DNA and RNA will be isolated from tissues submitted to the NCI

- Exome sequencing and/or mRNA sequencing from 100 cases (up to 300 possibly)
Opportunities – neoadj in PDAC

- Ultrasound and FNAs for diagnosis – pre-sample unlikely to be available
- Use of circulating tumor cells
- Stroma predominates in core biopsies
Vitamin D Receptor-Mediated Stromal Reprogramming Suppresses Pancreatitis and Enhances Pancreatic Cancer Therapy

Mara H. Sherman,1 Ruth T. Yu,1 Dannielle D. Engle,2 Ning Ding,1 Annette R. Atkins,1 Herve Tiriac,2 Eric A. Collisson,3 Frances Connor,4 Terry Van Dyke,5 Serguei Kozlov,6 Philip Martin,9 Tiffany W. Tseng,1 David W. Dawson,7 Timothy R. Donahue,7 Atsushi Masamune,8 Tooru Shimosegawa,8 Minoti V. Apte,9 Jeremy S. Wilson,9 Beverly Ng,10,11 Sue Lynn Lau,10,12,13 Jenny E. Gunton,10,11,12,13 Geoffrey M. Wahl,1 Tony Hunter,14 Jeffrey A. DREBIN,15 Peter J. O'DWYER,16 Christopher Liddle,17 David A. Tuveson,2 Michael Downes,1,* and Ronald M. Evans1,18,*

Cell 159, 80–93, September 25, 2014 ©2014 Elsevier Inc.

- VDR activation reprograms reactive stroma and reduces inflammation
- Increased gemcitabine concentration
- Reduced tumor volume
Opportunities – neoadj in PDAC

• Rather than stromal ablation or inhibition

• Modality of reprogramming the stromal function

• Prospective testing

• Pre- and post-evaluations of molecular biomarkers
New York Times
Sidestepping the Biopsy With New Tools to Spot Cancer,
Pollack A, April 7th, 2014
Building a better mouse
New animal models guide the fight against cancer pp. 24 & 28