Tumor markers and biology in gastric and esophageal cancers

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Disclosure slide

Matthias Ebert
• no conflicts of interest to declare

Manfred Lutz
• advisory board / speaker
  Bayer
  Celgene
  Clovis
  Merck
  Sanofi-Aventis
Targeted Therapy in the Management of Advanced Gastric Cancer: Are We Making Progress in the Era of Personalized Medicine?

Wong H, Yau T. Review in *The Oncologist* 2012
Alterations in critical pathways

Published evidence
- HER pathway
- Angiogenesis
- PI3K/Akt/mTor
Disappointing results of recent trials

Table 4. Ongoing phase III trials of targeted agents in the systemic treatment of advanced gastric cancer

<table>
<thead>
<tr>
<th>Clinical trial</th>
<th>Targeted agent</th>
<th>Chemotherapy</th>
<th>Line of treatment</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>ToGA, Bang et al. (2011) [109]</td>
<td>Trastuzumab</td>
<td>FP or XP</td>
<td>First</td>
<td>Completed</td>
</tr>
<tr>
<td>AVAGAST, Kang et al. (2010) [107]</td>
<td>Bevacizumab</td>
<td>XP</td>
<td>First</td>
<td>Completed</td>
</tr>
<tr>
<td>EXPAND [50]</td>
<td>Cetuximab</td>
<td>XP</td>
<td>First</td>
<td>Ongoing</td>
</tr>
<tr>
<td>REAL-3 [55]</td>
<td>Panitumumab</td>
<td>EOX</td>
<td>First</td>
<td>Ongoing</td>
</tr>
<tr>
<td>LoGIC [66]</td>
<td>Lapatinib</td>
<td>OX</td>
<td>First</td>
<td>Ongoing</td>
</tr>
<tr>
<td>TYTAN, Satoh et al. (2010) [67]</td>
<td>Lapatinib</td>
<td>T</td>
<td>Second</td>
<td>Ongoing</td>
</tr>
<tr>
<td>GRANITE-1 [82]</td>
<td>Everolimus</td>
<td>--</td>
<td>Second or third</td>
<td>Ongoing</td>
</tr>
</tbody>
</table>

COG ESMO 2012

Gefitinib -- second Fail Fail Fail Fail

Success Fail Fail Fail Fail
Targeted Therapy in the Management of Advanced Gastric Cancer:

Why Are We Not Making Progress in the Era of Personalized Medicine?
Tumor markers and biology

- Druggable Targets
- Overcoming resistance in targeted therapy
Phase III study of trastuzumab added to standard chemotherapy in first-line HER2-positive advanced gastric cancer

3807 Gastric Cancer
\[\downarrow\]
810 HER2+
\[\downarrow\]
- advanced gastric cancer
- HER2 +
- (IHC2+/FISH+ oder IHC3+)

\[R\]
\[\downarrow\]
(n=294)

XP/5FUP or 5FUP

XP/5FUP + Herceptin

(n=290)

Primary EP: OS
Sekundary EP: PFS, TTP, ORR, Benefit

Bang, Lancet 2010
Phase III study of trastuzumab added to standard chemotherapy in first-line HER2-positive advanced gastric cancer

![Graph showing survival analysis with median overall survival times and HR (95% CI) values.]

- **Trastuzumab plus chemotherapy**: 167 events, 13.8 months, 0.046 (95% CI 0.046-0.91)
- **Chemotherapy alone**: 182 events, 11.1 months

**Number at risk**
- Trastuzumab plus chemotherapy: 294, 277, 246, 209, 173, 147, 113, 90, 71, 56, 43, 30, 21, 13, 12, 6, 4, 1, 0
- Chemotherapy alone: 290, 256, 223, 185, 143, 117, 90, 64, 47, 32, 24, 16, 14, 7, 6, 5, 0, 0, 0

Bang, Lancet 2010
ALK, anaplastic lymphoma kinase

Non-small-cell lung cancer

Patient cohort appropriate for ALK-targeted therapy

Neuroblastoma

Crizotinib

Anaplastic large-cell lymphoma

Genomically activated ALK

McDermott U, JCO 2009
Her2/neu

Patient cohort appropriate for Her2/neu therapy
Druggable Targets

Breast Ca

HER2-

HER2+
MALDI Spectroscopic Imaging

Matrix spotted section

Laser

TOF MS

Stained tissue section

Average mass spectrum

5 mm
Differential Expression

* P value < 0.05

m/z: mass-to-charge
Visualisation Peak m/z 8404

A

H&E | MALDI image | MALDI image | IHC for HER2

B

m/z 4969: cancer | m/z 6225 | m/z 4969 | m/z 8404 | HER2 positive

m/z 4969: cancer | m/z 6225 | m/z 4969 | m/z 8404 | HER2 negative

Rauser et al., J Proteome Research 2010; 9: 1854
Druggable Targets

Breast Ca

HER2-  HER2+  

Gastric Ca

HER2+  HER2-
### Table 3. Classification Results for Training Set–Test Set Lineups A–D*

<table>
<thead>
<tr>
<th>Setting</th>
<th>Random Forest</th>
<th>Support Vector Machine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>sensitivity</td>
<td>specificity</td>
</tr>
<tr>
<td>A</td>
<td>Mean</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>CI-95%</td>
<td>±0%</td>
</tr>
<tr>
<td>B</td>
<td>Mean</td>
<td>28%</td>
</tr>
<tr>
<td></td>
<td>CI-95%</td>
<td>±9%</td>
</tr>
<tr>
<td>C</td>
<td>Mean</td>
<td>50%</td>
</tr>
<tr>
<td></td>
<td>CI-95%</td>
<td>±7%</td>
</tr>
<tr>
<td>D</td>
<td>Mean</td>
<td>70%</td>
</tr>
<tr>
<td></td>
<td>CI-95%</td>
<td>±3%</td>
</tr>
</tbody>
</table>

*Prediction performances of the two classification algorithms—Random Forest and Support Vector Machine—were evaluated according to their sensitivity, specificity, and accuracy within their 95% confidence intervals (CI) for each setting as described in Table 2.

<table>
<thead>
<tr>
<th>Setting</th>
<th>Training set</th>
<th>Test set</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Gastric</td>
<td>Gastric</td>
</tr>
<tr>
<td>B</td>
<td>Breast</td>
<td>Gastric</td>
</tr>
<tr>
<td>C</td>
<td>Gastric + Breast</td>
<td>Gastric</td>
</tr>
<tr>
<td>D</td>
<td>Gastric + Breast</td>
<td>Gastric + Breast</td>
</tr>
</tbody>
</table>
Druggable Targets

Breast Ca

- HER2-
- HER2+

Gastric Ca

- HER2+
- HER2-

!
Druggable Targets

Ca
HER2-
RAS
pAKT

HER2+
RASmut
pAKT-

HER2+
RASmut
pAKT-

HER2-
RAS
pAKT
Tumor markers and biology

- Druggable Targets

- Overcoming resistance in targeted therapy
  - only ~ 50% of patients respond to trastuzumab in the TOGA trial
Combating trastuzumab resistance by targeting SRC, a common node downstream of multiple resistance pathways

Siyuan Zhang, Wen-Chien Huang, Ping Li, Hua Guo, Say-Bee Poh, Samuel W Brady, Yan Xiong, Ling-Ming Tseng, Shau-Hsuan Li, Zhaoxi Ding, Aysegul A Sahin, Francisco J Esteva, Gabriel N Hortobagyi & Dihua Yu

Transfection with activated SRC decreases trastuzumab activity

Y527F Src mutant active, K295R Src mutant dead

Nature Medicine 2011;4:461
Combating trastuzumab resistance by targeting SRC, a common node downstream of multiple resistance pathways

Siyuan Zhang¹, Wen-Chien Huang¹, Ping Li¹, Hua Guo¹, Say-Bee Poh¹, Samuel W Brady¹,², Yan Xiong¹, Ling-Ming Tseng¹, Shau-Hsuan Li¹, Zhaoxi Ding¹, Aysegul A Sahin³, Francisco J Esteva¹,²,⁴, Gabriel N Hortobagyi⁴ & Dihua Yu¹,²

BT474 orthotopic xenograft tumors
Correlation of responses and survival with phospho-SRC-Y416 (pSRC) expression in breast cancer patients treated with trastuzumab 1st line
Therapy: Inhibition of Src with saracatinib reverses trastuzumab-resistance
1. Primary resistance
2. Trastuzumab induced resistance
Conclusions

• Targeted therapies and improved treatment regimens are advancing in GI cancers
• Early identification of „Druggable Targets“ will improve individualisation of therapy and treatment results
• However, novel resistance mechanisms in targeted therapies are also evolving and present a major challenge for the future