When to consider mid-course changes of therapy based on early response?

Gunter von Minckwitz, M.D., Ph.D., German Breast Group
Topics

Early response:

• As predictor of pathologic response
• As predictor of long-term outcome
• As a decision aid to switch therapy
• To identify patients who might (not) benefit from a switch
Royal Marsden Hospital  
n = 198 pts. with operable b.c.

<table>
<thead>
<tr>
<th>Predictors of pCR/pINV</th>
<th>univariate p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1/T2 tumors</td>
<td>0.004</td>
</tr>
<tr>
<td>Young age</td>
<td>0.008</td>
</tr>
<tr>
<td>Response after 2\textsuperscript{nd} cycle</td>
<td>0.001*</td>
</tr>
</tbody>
</table>

*best predictor in multi-variate analysis

Prediction of pCR by response evaluation after 2-4 cycles

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>N pts.</th>
<th>pCR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>R pts.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>R</td>
<td>NR</td>
</tr>
<tr>
<td>• GeparDuo</td>
<td>ddAT</td>
<td>350</td>
<td>348</td>
</tr>
<tr>
<td>• GeparDuo</td>
<td>AC-T</td>
<td>300</td>
<td>148</td>
</tr>
<tr>
<td>• GeparTrio</td>
<td>TAC</td>
<td>1390</td>
<td>622</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>2040</td>
<td>1118</td>
</tr>
</tbody>
</table>

(65%) (35%) p<0.001

R=Responder (cCR or cPR); NR=Non-responder (cNC); dd=dose-dense; T=Docetaxel
### Multivariate analysis for pCR in GeparTrio (N=2190)

<table>
<thead>
<tr>
<th>Group with Highest Chance for pathCR</th>
<th>All</th>
<th>Responder</th>
<th>Non-Responder</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 40 yrs</td>
<td>2.0</td>
<td>-</td>
<td>6.3</td>
</tr>
<tr>
<td>High grade</td>
<td>2.7</td>
<td>2.2</td>
<td>-</td>
</tr>
<tr>
<td>ductal</td>
<td>2.2</td>
<td>2.1</td>
<td>-</td>
</tr>
<tr>
<td>ER/PR neg</td>
<td>3.7</td>
<td>4.3</td>
<td>2.5</td>
</tr>
<tr>
<td>Complete Response after 2 cycles</td>
<td>10.4</td>
<td>2.3</td>
<td>n.a.</td>
</tr>
</tbody>
</table>

*Odds ratio* against group with lowest pCR rate
Predictors of pCR in GeparTrio

Response after 2 cycles

% pCR

ER/PR (P<0.00000)

- / - (N=629)
+ / - (N=266)
+ / + (N=900)

CR (N=108) PR (N=1257) NC (N=627) PD (N=12)
N=1500

Stratified acc. to Early Response

Epirubicin 90 mg/m²
Cyclophosphamide 600 mg/m²
Docetaxel 100 mg/m² (A)
75 mg/m² (B,C)
Capecitabine 1800 mg/m²
If Her2 pos: Trastuzumab 6 mg/kg q3w 1y
If endocrine responsive Tam/AIs
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• As predictor of pathologic response
• As **predictor of long-term outcome**
• As a decision aid to switch therapy
• To identify patients who might (not) benefit from a switch
Long Term Prognosis according to Early Response to 4xAC(+Tam)

<table>
<thead>
<tr>
<th>Response to 4x AC(+Tam)</th>
<th>N Pts.</th>
<th>Event rate at 78 months (after nil or Docetaxelx4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>cCR</td>
<td>906</td>
<td>24.7%</td>
</tr>
<tr>
<td>cPR</td>
<td>1079</td>
<td>35.1%</td>
</tr>
<tr>
<td>cNC</td>
<td>324</td>
<td>49.1%</td>
</tr>
</tbody>
</table>

p<0.0001

Bear D, NSABP B-27, JCO 2006
GeparDuo
425 Pts. receiving AC-Doc

1st measurement after 4xAC
2nd measurement after 4xDoc

Logrank p=0.0098
Topics

Early response:

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02SR 86 French Phase II Trial
n = 272 Patients Stage I-IIIB

VTMFA: Vinblastin Thiotepa MTX 5-Fu Doxorubicin

VTMFA x 3

Evaluation

cCR/cPR VTMAP 82%
cNC PEFM±A 67%

5yrs OS

D. Khayat, ASCO 2001 Educational Book
02SR 86 French Phase II Trial
n = 272 Patients Stage I-IIIb

D. Khayat, ASCO 2001 Educational Book
Aberdeen Trial
n = 133 Patients T>3cm or IIIB

CVAP x 4

Evaluation

cCR/cPR (n=97) cNC (n=45)

R

CVAP x 4 T x 4 T x 4

16% 34% 2%
pCR

CVAP:
- Cyclophosphamide
- Vincristine
- Doxorubicin
- Prednisolone

Progression-free Survival in the Aberdeen-Study (median F-up: 104 wks)

Heys SD, Clin Breast Cancer 2002
Core biopsy: uni/bilateral cT2-4 cN0-3 size \( \geq 2 \text{ cm} \)

Docetaxel
Adriamycin
Cyclophosphamide + G-CSF

NC
Palpation / sonography

R

CR/ PR

TAC

OP

TAC x 8

NX

Vinorelbine
Capecitabine

TAC
Docetaxel
Adriamycin
Cyclophosphamide + G-CSF

Von Minckwitz, SABCS 2006
pCR Rates in GeparTrio Study

Responder
N=1344
P=0.27  P=0.08

Non-Responder
N=604
P=0.73  P=0.17

TAC x 6
TAC x 8
TAC x 6
TAC-NX

21.0
23.5
5.8
1.7

7.6
9.7
5.3
6.0

Path CR
ypTis or ypT0, ypN+

40%
Topics

Early response:

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### Predictive Factors in GeparTrio for pCR by Therapy

<table>
<thead>
<tr>
<th>%path CR</th>
<th>Responder</th>
<th>Non-Responder</th>
</tr>
</thead>
<tbody>
<tr>
<td>TACx6</td>
<td>11.7</td>
<td>9.5</td>
</tr>
<tr>
<td>TACx8</td>
<td>18.3</td>
<td>2.5</td>
</tr>
<tr>
<td>P=0.03</td>
<td>P=0.01</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ER+ and PR+</th>
<th>TACx6</th>
<th>TACx8</th>
<th>TAC/Nx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partial Response after 2 cycles</td>
<td>25.5</td>
<td>31.4</td>
<td>n.a.</td>
</tr>
<tr>
<td>P=0.02</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Adding a Taxan to FAC
*(Experience from 7 MD Anderson Trials)*

<table>
<thead>
<tr>
<th></th>
<th>pCR (%)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Taxane</td>
<td>Taxane</td>
</tr>
<tr>
<td>ER neg</td>
<td>15</td>
<td>29</td>
</tr>
<tr>
<td>ER pos</td>
<td>2</td>
<td>9</td>
</tr>
</tbody>
</table>

Mazouni C, Ann Oncol 2007
Patients with a Partial Response after AC might benefit from Preop Doc

Bear D, NSABP B-27, JCO 2006
Her2 negative – Non-Responding Patients

N=540 Her 2 neg. Non-responder

Pw = weekly Paclitaxel
R = Rad 001

Pw
Surgery

NC
R

Surgery

Repeat Core

EC+/-B

Core biopsy

Sonography

continue responder part
Decision Tree

N=2500

In/Exclusion criteria fulfilled

yes

Her-2 Status positive

no

N=1900

Her2- Setting:
EC vs EC + Bevacizumab

yes

N=600

Her2+ Setting:
EC-Doc/Cap Trastuzumab vs. Lapatinib

no

Response after 4xEC+/-B

N=540

Non-Responder Setting:
Pw +/- RAD 001

yes

N=1360

Continue Doc/Cap +/- Bev.
Conclusion

• Early response is an independent predictor of pCR and long term outcome (CR>PR>NC>PD).
• Benefit of a late response after switching of treatment is unclear.
• Patients with an early cCR might not need further treatment intensification.
• Patients with an early cPR (incomplete chemoresistance due to e.g. ER+) might benefit from more intense treatment.
• Patients with an early cNC or cPD are at high medical need for new treatment options.