Targeted agents in cervical cancer

So far, 2 promising targets in clinical studies

EGFR
VEGF

with sound molecular, biological and preclinical data
EGFR in cervical cancer

Overexpressed in up to 85% of cases

EGFR expression associated with higher stage and poor prognosis

Anti EGFR synergistic with DDP/doxo in vivo and additive with RT

EGFR and pEGFR independent predictors of response to (chemo) radiation

Expression of EGFR and pEGFR predictor of poor response to (chemo) RT and survival

- IHC on pretreatment TMA of 375 pts treated with (chemo) RT
- EGFR, pEGFR, PTEN, AKT, pAKT, ERK, pERK

<table>
<thead>
<tr>
<th>Response to (chemo)RT</th>
<th>P</th>
<th>Disease specific death</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respondees</td>
<td></td>
<td></td>
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<tr>
<td>EGFR pEGFR</td>
<td>1.84 (1.20-2.82)</td>
<td>0.005</td>
<td>1.54 (1.09-2.17)</td>
</tr>
<tr>
<td></td>
<td>1.71 (1.11-2.66)</td>
<td>0.016</td>
<td></td>
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<tr>
<td>No responders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EGFR pEGFR</td>
<td>6.08 (2.39-15.47)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4.06 (1.58-10.43)</td>
<td>0.004</td>
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</tbody>
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Noordhuis, CCR, 2009
Cetuximab in advanced cervical cancer

- Single agent in recurrent disease (GOG-022 7E)
- In combination with RT in early disease (GOG-9918)
- In combination with CisPt in recurrent disease (GOG-0076 DD)
- In combination with CisPt and topotecan: effective but too toxic

Erlotinib in advanced cervical cancer

- Single agent in recurrent disease (GOG-0227D)
- In combination with cisPt and RT in locally advanced disease (NCT00428194)
VEGF in cervical cancer

Higher MVD (by CD31 staining) independent prognostic marker

p53 mutation and increased angiogenic potential

correlation between serum VEGF expression and stage

Bevacizumab in advanced cervical cancer

• Single agent in recurrent disease (GOG-227 C)

• Four arm study in recurrent disease (GOG-0240)
  paclitaxel + CisPt ± BEV
  paclitaxel + Topotecan ± BEV : OS and toxicity
Phase II trial of Bevacizumab in persistent/recurrent squamous cell carcinoma of the cervix - a GOG study

- 46 pts, all with prior CT, prior RT in 56%
- BEV 15 mg/kg q3wks
- Hypertension 15%
- TE 11%
- PR 11%

Median PFS 3.4 mo
OS 7.3 mo

JCO, 2009

PFS of non randomized GOG studies in cervical cancer

Bevacizumab in advanced cervical cancer

- Single agent in recurrent disease (GOG-227 C)
- Four arm study in recurrent disease (GOG-0240)
  paclitaxel + CisPt ± BEV
  paclitaxel + Topotecan ± BEV : OS and toxicity
## Developing targeted treatments in cervical cancer

<table>
<thead>
<tr>
<th>Strengths</th>
<th>Opportunities</th>
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<tbody>
<tr>
<td><strong>Geographical factors</strong></td>
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<tr>
<td>Local/regional recurrences (main problem)</td>
<td>Feasibility of repeated biopsies</td>
</tr>
<tr>
<td>Tumor accessible and visible</td>
<td>Pre-post treatment tissues available</td>
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<tr>
<td><strong>Biological factors</strong></td>
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<tr>
<td>Role of viral infections</td>
<td>Combined and/or sequential approach</td>
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<tr>
<td>Angiogenesis</td>
<td>Dissect role of different factors</td>
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<td>Radiosensitivity</td>
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### Objective
Define predictors of response