Recent advances in Germ cell tumors and Colorectal cancer: Role models for oncology?

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University Cancer Center Hamburg (UCCH)
University Hospital Hamburg-Eppendorf, Hamburg, Germany
# Cancer Incidence in Germany

<table>
<thead>
<tr>
<th>Cancer Site</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>25.7</td>
<td></td>
</tr>
<tr>
<td>Colon and rectum</td>
<td>14.3</td>
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<tr>
<td>Lung</td>
<td>13.8</td>
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<tr>
<td>Bladder</td>
<td>4.6</td>
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<tr>
<td>Oral cavity and pharynx</td>
<td>3.9</td>
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<tr>
<td>Stomach</td>
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<tr>
<td>Kidney</td>
<td>3.6</td>
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<tr>
<td>Malignant melanoma of the skin</td>
<td>3.6</td>
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<tr>
<td>Pancreas</td>
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<tr>
<td>Non-Hodgkin lymphomas</td>
<td>2.9</td>
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</tr>
<tr>
<td>Leukaemias</td>
<td>2.6</td>
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<tr>
<td>Liver</td>
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<tr>
<td>Oesophagus</td>
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<tr>
<td>Testis</td>
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<tr>
<td>Central nervous system</td>
<td>1.5</td>
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<tr>
<td>Larynx</td>
<td>1.5</td>
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</tr>
<tr>
<td>Multiple myeloma</td>
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<tr>
<td>Gallbladder and biliary tract</td>
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<td>Thyroid gland</td>
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<td>Hodgkin's lymphoma</td>
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<tr>
<td>Breast</td>
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<td>Ovaries</td>
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<tr>
<td>Pancreas</td>
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<td>3.4</td>
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<td>2.5</td>
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<tr>
<td>Leukaemias</td>
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<td>2.3</td>
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<tr>
<td>Cervix</td>
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<td>2.2</td>
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<tr>
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<td>2.0</td>
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<tr>
<td>Thyroid gland</td>
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</table>

- **2nd place**: 62,000 cases
- **14ths place**: 4,000 cases
Testicular germ cell cancer

1-2% of all tumors in men are germ cell cancers

→ Rare disease in young patient population

Example for interdisciplinary team approach

→ Urologists, medical oncologists and radiation oncologists

High cure rate due to exceptional sensitivity to antineoplastic therapy

→ Individualized treatment: „risk-adapted strategy“
Cisplatin

40ths Anniversary

1974: First trial of PVB in germ cell cancer started at Indiana University, USA

Celebration tomorrow!

Italian Pharmacy around 1500
Effect of cisplatin on survival of patients with metastatic germ cell cancer: From palliation to cure

GCT treatment – A role model in oncology?

- From palliative to curative treatment by one effective, but toxic drug:
  - progress from several well designed clinical trials
  - individual treatment intensity based on prognostic factors: more intensive for poor risk pts and less toxic for good risk patients
- High cure rate makes late toxicities relevant: frequency / types investigated → basis for survivorship plans
- Treatment of refractory disease: progress translated from the lab to the patient
- Rare disease with even rarer patient subgroups (e.g. CNS mets, bone mets): Questions can only be answered by international worldwide collaboration
Reducing toxicity in metastatic seminoma: Cisplatin-based Ctx more effective than single agent Carboplatin

- European meta-analysis of two randomized trials
- Carboplatin inferior: Standard of care remain 3-4 cycles PEB

Bokemeyer, et al BJC 2004
More intensive treatment in poor prognosis pts:
Sequential HD-VIP with PBSC + G-CSF
(German multi-center phase II study)

GTCSG 1992 – 2000:
221 pts in 23 centers
5-Year OS 75 %
A randomized phase III study comparing standard dose BEP with sequential high-dose cisplatin, etoposide, and ifosfamide (VIP) plus stem-cell support in males with poor-prognosis germ-cell cancer. An intergroup study of EORTC, GTCSG, and Grupo Germinal (EORTC 30974)


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Randomized trial of HD VIP vs SD PEB:
Failure-free survival borderline but overall survival not significantly different

Only 140 of 240 planned pts recruited → difficulty of trials in this disease

Focus on treatment failures

Treatment failure occurs in 20-30% of metastatic GCTs

Classic relapse:
1-2 years after response to first line therapy

Platinum-refractory disease:
PD under or immediately after therapy or failure after HD-salvage therapy

poor prognosis - experimental therapy
Retrospective multicenter study of 1600 pts:

- Histology
- Primary Site
- Response to 1° Line
- Progression-free Interval
- AFP at Salvage
- HCG at Salvage
- Bone, Brain Metastases

(worldwide collaboration lead by the GTCSG, A. Lorch)
HD Ctx is superior to SD Ctx as first salvage therapy

2-year PFS: 50% vs 29%
3-year OS: 55% vs 46%

A randomized trial planned to define the optimal salvage strategy
(Tiger Study: worldwide G3 consortium)
Sequential HD CTX is superior to a single course HD CTx as first salvage treatment: A randomized trial

Lorch A, Bokemeyer C, JCO 2012
From the Lab to the Clinic and back:
Translational research on cisplatin resistance in GCTs
Microsatellite instability (MSI) and/or BRAF V600E mutations predict chemotherapy resistance in GCT

1/100 (1%) in unselected GCTs
9/35 (26%) in cisplatin-resistant cases (p<0.0001)

Honecker, Bokemeyer JCO 2009
### Activity of single agents in platinum refractory GCTs

<table>
<thead>
<tr>
<th>Substance</th>
<th>RR</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gemcitabine</td>
<td>15-19%</td>
<td>Bokemeyer JCO 1999, Einhorn JCO 1999</td>
</tr>
<tr>
<td>Oxaliplatin</td>
<td>15%-19%</td>
<td>Kollmannsberger JCO 2002</td>
</tr>
</tbody>
</table>
Gemcitabin, Oxaliplatin and Paclitaxel (GOP) in pts with refractory GCT

Response rate CR/ PRm - 16/41 pts (39%)

Ongoing remission / NED in 6 patients (15%) > 1 year

→ Currently most effective regimen for pts with platinum-refractory GCT

→ Outcome Research German Centers 2010-2013: similar results for GOP achieved in > 80 pts treated as routine care


to be presented by K. Oechsle, DGHO 2014
Molecular targeted therapy in GCT?

Sunitinib in patients with multiply relapsed or cisplatin-refractory germ cell cancer

Phase II trial: **33 pts: only 3 PRs (9%)**

Oechsle, Bokemeyer, Honecker Ann Oncol 2011

Everolimus in patients with multiply relapsed or cisplatin-refractory germ cell cancer

Phase II trial: **34 pts: minor activity**

Fenner, Bokemeyer, Oechsle submitted

NGS of 10 refractory pts (44 gene panel):

only 6 mutations in 4 pts found

Oing, Bokemeyer ASCO 2014
European Phase II Trial of Cabazitaxel in refractory GCT

Cabazitaxel effective after taxane pretreatment
High activity in cisplatin refractory GCT cell line models

Gerwing, Honecker, Bokemeyer et al. unpublished data

European trial starts beginning of 2015 (EORTC)

→ it still remains chemotherapy in GCT?
Late toxicity following treatment of testicular cancer

- Young patients with excellent prognosis
- Normal life expectancy after curative treatment
- Importance of long term toxicities
  (second cancers, platinum toxicities, metabolic changes…)

- Risk - benefit analysis for treatment strategies
- Survivorship care plans
Maintaining success, reducing treatment burden, focusing on survivorship: highlights from the third European consensus conference on diagnosis and treatment of germ-cell cancer
High burden of mCRC globally and in Europe

Globally each year
- New CRC cases: 1,234,000
- Deaths: 608,000

In Europe each year
- New CRC cases: 450,000
- Deaths: 232,000

About half of all patients with mCRC are in a palliative situation

1. GLOBOCAN Cancer fact sheets: colorectal cancer. 2008
2. WHO. Available at: http://www.euro.who.int/en/.
mCRC treatment – A role model in oncology?

- Frequent disease in an elderly patient population
- From palliative care to extended (chronic) treatment:
  - stepwise progress from well designed clinical trials
  - individual treatment based on patient characteristics and aim of treatment
- Introduction of new drug (example used: EGFR- antibodies) lead to molecular identification of pts for treatment selection
- Progress translated from the lab to the patient
- Speed of new developments entering the clinic and the size of trials necessary to demonstrate further benefits require international collaboration
### Increased options for systemic treatment of mCRC

<table>
<thead>
<tr>
<th>Single agent chemotherapy</th>
<th>Combinations infusional</th>
<th>“Biologicals”</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-FU/LV</td>
<td>FOLFOX</td>
<td>Bevacizumab</td>
</tr>
<tr>
<td>Capecitabine/UFT</td>
<td>FOLFIRI</td>
<td>Aflibercept</td>
</tr>
<tr>
<td>Irinotecan (Oxaliplatin)</td>
<td>oral</td>
<td>Cetuximab</td>
</tr>
<tr>
<td></td>
<td>CAPOX</td>
<td>Panitumumab</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Regorafinib</td>
</tr>
</tbody>
</table>

5-FU=fluorouracil
LV=leucovorin
UFT= tegafur-uracil
FOLFOX=fluorouracil+leucovorin
FOLFIRI=fluorouracil+irinotecan
CAPOX=XELOX=capecitabine+oxaliplatin
EGF-Receptor and KRAS signaling

# 10 Years of EGFR Antibodies in Metastatic CRC

<table>
<thead>
<tr>
<th>1st line</th>
<th>OPUS (randomized) phase II FOLFOX ± cetuximab</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CRYSTAL: FOLFIRI ± cetuximab</td>
</tr>
<tr>
<td></td>
<td>PACCE: chemo/bevacizumab ± panitumumab</td>
</tr>
<tr>
<td></td>
<td>CAIRO2: Xelox/bevacizumab ± cetuximab</td>
</tr>
<tr>
<td></td>
<td>COIN: FOLFOX ± cetuximab (5FU given cont. or intermittent)</td>
</tr>
<tr>
<td></td>
<td>PRIME: FOLFOX ± panitumumab</td>
</tr>
<tr>
<td></td>
<td>NORDIC VII: FLOX ± cetuximab</td>
</tr>
<tr>
<td></td>
<td>CALGB: FOLFOX/FOLFIRI + bevacizumab / cetuximab (2014)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2nd line</th>
<th>Cetuximab ± irinotecan</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Irinotecan ± cetuximab</td>
</tr>
<tr>
<td></td>
<td>FOLFIRI ± panitumumab</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3rd line</th>
<th>Cetuximab ± irinotecan (2004)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cetuximab vs BSC</td>
</tr>
<tr>
<td></td>
<td>Panitumumab vs BSC</td>
</tr>
</tbody>
</table>

(2014)
Improved Survival with Ctx plus Cetuximab (Opus/Crystal pooled analysis) for pts with KRAS wt tumors

**KRAS wt**

HR: 0.81 [0.69–0.94]  p=0.0062

FOLFIRI / FOLFOX4 + cetuximab: (n=398) med 23.5 mo

FOLFIRI / FOLFOX4: (n=447) median 19.5 mo

Difference med. OS 4 months

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>CT + cetuximab</th>
<th>CT</th>
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</thead>
<tbody>
<tr>
<td>0</td>
<td>398</td>
<td>447</td>
</tr>
<tr>
<td>6</td>
<td>356</td>
<td>395</td>
</tr>
<tr>
<td>12</td>
<td>296</td>
<td>313</td>
</tr>
<tr>
<td>18</td>
<td>246</td>
<td>227</td>
</tr>
<tr>
<td>24</td>
<td>177</td>
<td>159</td>
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<td>30</td>
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<td>48</td>
<td>21</td>
<td>18</td>
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<td>54</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>60</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Bokemeyer et al EJC 2012
Distribution of RAS mutations in mCRC

Any RAS mt: ‘New’ RAS mt or KRAS mt (exon 2)

‘New’ RAS mt:  
- KRAS mutations (exons 3, 4)
- NRAS mutations (exons 2, 3, 4)

New RAS mt ~10%*

KRAS mt (exon 2) ~40%

RAS wt ~50%

OPUS trial in 1st-line mCRC

Primary endpoint
- Overall confirmed response rate

Secondary endpoints
- PFS time
- OS time
- Safety

Cetuximab + FOLFOX4
- Cetuximab (400 mg/m² initial IV infusion on day 1 then 250 mg/m² weekly)
  + oxaliplatin 85 mg/m² + 5-FU/FA, every 2 weeks

FOLFOX4
- Oxaliplatin 85 mg/m² + 5-FU/FA every 2 weeks

S Tejpar ASCO GI 2014; C. Bokemeyer ASCO 2014
OPUS-Study: PFS and OS
RAS wt pts

**Progression-free survival**

<table>
<thead>
<tr>
<th>Events, n</th>
<th>Median, months</th>
<th>95%CI</th>
<th>HR [95% CI]</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FOLFOX4</td>
<td>28</td>
<td>5.8</td>
<td>4.5 – 7.5</td>
<td>0.43 (0.21 – 0.88)</td>
</tr>
<tr>
<td>FOLFOX4 / cetuximab</td>
<td>11</td>
<td>12.0</td>
<td>7.7 – NR</td>
<td>0.83 (0.49 – 1.41)</td>
</tr>
</tbody>
</table>

**Overall survival**

<table>
<thead>
<tr>
<th>Events, n</th>
<th>Median, months</th>
<th>95%CI</th>
<th>HR [95% CI]</th>
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<tr>
<td>FOLFOX4</td>
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<td>17.8</td>
<td>12.4 – 23.9</td>
<td>0.83 (0.49 – 1.41)</td>
</tr>
<tr>
<td>FOLFOX4 / cetuximab</td>
<td>25</td>
<td>20.7</td>
<td>18.3 – 26.8</td>
<td>0.497</td>
</tr>
</tbody>
</table>

Tejpar S, et al. ASCO GI 2014 (Abstract no. LBA444
Bokemeyer C, ASCO 2014)
**OPUS-Study: PFS and OS**

**RAS mut pts**

**Progression-free survival**

- **FOLFOX4**
  - Events, n: 44
  - Median, months: 7.8
  - 95%CI: 6.7 – 9.3
  - HR [95% CI]: 1.59 (1.08 – 2.36)
  - p-value: 0.018

- **FOLFOX4 / cetuximab**
  - Events, n: 68
  - Median, months: 5.6
  - 95%CI: 4.4 – 7.4
  - HR [95% CI]: 1.35 (0.95 – 1.92)
  - p-value: 0.089

**Overall survival**

- **FOLFOX4**
  - Events, n: 57
  - Median, months: 17.8
  - 95%CI: 15.9 – 24.8
  - HR [95% CI]: 1.35 (0.95 – 1.92)
  - p-value: 0.089

- **FOLFOX4 / cetuximab**
  - Events, n: 74
  - Median, months: 13.4
  - 95%CI: 11.1 – 17.7
  - HR [95% CI]: 1.35 (0.95 – 1.92)
  - p-value: 0.089

**Patients at risk**

- **FOLFOX4**
  - 78
  - 66
  - 37
  - 15
  - 3
  - 0
  - 67
  - 34
  - 12
  - 4
  - 0

- **FOLFOX4 / cetuximab**
  - 94
  - 79
  - 73
  - 60
  - 54
  - 41
  - 32
  - 26
  - 22
  - 20
  - 18
  - 8
  - 2
  - 0

*Tejpar S, et al. ASCO GI 2014 (Abstract no. LBA444)*

*Bokemeyer C, ASCO 2014*
Resistance under selective pressure of EGFR antibodies

- EGFR mutations detectable in circulating DNA
- Frequency 20% after therapy with Panitumumab / Cetuximab
- Mutations are specific for the antibody used

CETUXIMAB

Voigt, Binder, Bokemeyer Neoplasia 2012
PANITUMUMAB

GXXXR
unpublished data

S492R

Tyrosin Kinase Domain
# Improvements in OS in mCRC over the past decade

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Overall survival (months)</th>
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</thead>
<tbody>
<tr>
<td>Saltz¹, 2000</td>
<td>5-FU/LV bolus</td>
<td>12.6</td>
</tr>
<tr>
<td>Douillard², 2000</td>
<td>5-FU/LV infusion</td>
<td>14.1</td>
</tr>
<tr>
<td>Saltz¹, 2000</td>
<td>IFL</td>
<td>14.8</td>
</tr>
<tr>
<td>Douillard², 2000</td>
<td>FOLFIRI (de Gramont or AIO)</td>
<td>17.4</td>
</tr>
<tr>
<td>Goldberg³, 2004</td>
<td>FOLFOX</td>
<td>19.5</td>
</tr>
<tr>
<td>Hurwitz⁴, 2004</td>
<td>IFL + bevacizumab</td>
<td>20.3</td>
</tr>
<tr>
<td>Saltz⁵, 2008</td>
<td>XELOX/FOLFOX + bevacizumab</td>
<td>21.3</td>
</tr>
<tr>
<td>Falcone⁶, 2007</td>
<td>FOLFOXIRI</td>
<td>22.6</td>
</tr>
<tr>
<td>Van Cutsem⁷, 2011</td>
<td>FOLFIRI + cetuximab</td>
<td>23.5</td>
</tr>
<tr>
<td>Douillard⁹, 2013</td>
<td>FOLFOX + panitumumab (all ras wt)</td>
<td>26.0</td>
</tr>
<tr>
<td>Falcone¹⁰, 2013</td>
<td>FOLFOXIRI - bevacizumab</td>
<td>31.0</td>
</tr>
<tr>
<td>Heineman⁸, 2013</td>
<td>FOLFiFIRI + cetuximab (all ras wt)</td>
<td>33.1*</td>
</tr>
</tbody>
</table>

Informal comparison as these are not head-to-head clinical trials; *WT KRAS; #WT RAS, WT in KRAS & NRAS exons 2/3/4

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GCT and mCRC as models in Oncology today: More than ever...

- Are well conducted trials the basis for progress in oncology
- Do clinicians need to understand tumor biology to ask the right questions to the lab and to understand how to use new experimental findings in the clinic
- Will treating patients be the “Art of Oncology” by integrating all scientific knowledge into empathic individual care
- Will international collaboration in oncology be necessary to answer the upcoming questions
- Will education be extremely important to maintain high standards of patient care in a world of rapidly expanding knowledge and ESMO is a great platform to provide this
Thanks to the Hamburg Testis Cancer Group:


Thanks to many co-operation partners (selected)

L. Loojienga and W. Oosterhuis, LEPO, Erasmus University, Rotterdam
F. Mayer, J Hartmann, Tübingen; Ch Kollmannsberger, Vancouver,
F. Honecker, St. Gallen, J. Beyer, Zürich, A. Lorch, Düsseldorf and the German
speaking testicular cancer study group

The world of testis cancer collaborators (G3 consortium)

S. Tajpar, E. van Cutsem, Belgium; H. Koehne, Oldenburg, U. Vanhoefer, A. Stein,
M. Binder, Hamburg and the German AIO Group for Medical Oncology

Thanks to many important former teachers and mentors (selected):

H.-J. Schmoll, A. Harstrick, H. Poliwoda, HJ Wilke,
M. Freund, HJ Illiger, DK Hossfeld, Pierre Alberto, M. Andreeff, L. Kanz

Thanks for support of funding organisations and partners in the
pharmaceutical industry

Thanks to my family