Standard of care for anal squamous cell carcinoma

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Disclosure

- Advisory Board: Eli-Lilly, Bristol Meyers Squibb, MSD, Bayer, Roche, Merck-Serono, Astra-Zeneca
- Research funding: Eli-Lilly, Janssen-Cilag, Sanofi Oncology, Merck-Serono
- Honorarium: Eli-Lilly, Five Prime Therapeutics
SEER epidemiology for anal cancer: incidence, time trend and survival

Accessed 16 November 2018
Increasing incidence over time in various countries

Approximately 2-fold ↑ in incidence ↑: Female > male¹

In the US, SEER database suggests rates for new anal cancer cases ↑ on average 2.2% each year over the last 10 years. Death rates ↑ on average 2.9% each year over 2006-2015²

Table 1: Age-adjusted incidence rates of anal cancer and changes over time in anal cancer incidence by country, gender and period

<table>
<thead>
<tr>
<th>Country</th>
<th>Diagnosis</th>
<th>Age-adjusted incidence rates per 100,000 per year/period</th>
<th>Annual percentage change per period (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA¹,²</td>
<td>All histological types of cancer of the anus, anal canal and anorectum (ICD-10 C21.8)</td>
<td>1.75 (2005-2009)</td>
<td>1.75 (2005-2009)</td>
</tr>
<tr>
<td></td>
<td>Female: 0.8</td>
<td>1.5 (2005-2009)</td>
<td>2.2²</td>
</tr>
<tr>
<td></td>
<td>Male: 0.7</td>
<td>1.4 (2005-2009)</td>
<td>2.9²</td>
</tr>
<tr>
<td>Canada (Quebec)³</td>
<td>Squamous cell carcinoma of the anus, anal canal and anorectum (ICD-10 C21.8)</td>
<td>2.84 (1986-1990)</td>
<td>2.84 (1986-1990)</td>
</tr>
<tr>
<td></td>
<td>Total: -</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Female: 0.4</td>
<td>0.7 (1986-1990)</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Male: 0.3</td>
<td>0.4 (1986-1990)</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Female: 0.45</td>
<td>0.83 (2005-2009)</td>
<td>0.83 (2005-2009)</td>
</tr>
<tr>
<td></td>
<td>Male: 0.49</td>
<td>0.81 (2005-2009)</td>
<td>0.81 (2005-2009)</td>
</tr>
<tr>
<td></td>
<td>Female: 0.5</td>
<td>1.10 (2000-2004)</td>
<td>1.10 (2000-2004)</td>
</tr>
<tr>
<td>Scotland⁶</td>
<td>Squamous cell carcinoma of the anus, anal canal and anorectum (ICD-10 C21.8)</td>
<td>late 1970⁶, 1998-2002</td>
<td>-</td>
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<tr>
<td></td>
<td>Total: -</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Female: 0.23-0.27</td>
<td>0.57 (1998-2002)</td>
<td>0.57 (1998-2002)</td>
</tr>
<tr>
<td></td>
<td>Male: 0.14-0.17</td>
<td>0.37 (1998-2002)</td>
<td>0.37 (1998-2002)</td>
</tr>
<tr>
<td>Denmark⁷</td>
<td>All histological types of cancer of the anus, anal canal and anorectum (ICD-10 C21.8)</td>
<td>1.94 (1984-1987)</td>
<td>1.94 (1984-1987)</td>
</tr>
<tr>
<td></td>
<td>Female: 0.25</td>
<td>0.74 (1984-1987)</td>
<td>0.74 (1984-1987)</td>
</tr>
<tr>
<td></td>
<td>Male: 0.60</td>
<td>0.38 (1984-1987)</td>
<td>0.38 (1984-1987)</td>
</tr>
<tr>
<td>Australia⁸</td>
<td>All histological types of cancer of the anus, anal canal and anorectum (ICD-10 C21.8)</td>
<td>1.68 (2000-2005)</td>
<td>1.68 (2000-2005)</td>
</tr>
<tr>
<td></td>
<td>Female: 0.68</td>
<td>1.48 (2000-2005)</td>
<td>1.48 (2000-2005)</td>
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<tr>
<td></td>
<td>Male: 0.45</td>
<td>0.80 (2000-2005)</td>
<td>0.80 (2000-2005)</td>
</tr>
<tr>
<td></td>
<td>Squamous cell carcinoma of the anus, anal canal and anorectum (ICD-10 C21.8)</td>
<td>1.00 (2000-2005)</td>
<td>1.00 (2000-2005)</td>
</tr>
<tr>
<td></td>
<td>Female: 0.78</td>
<td>1.10 (2000-2005)</td>
<td>1.10 (2000-2005)</td>
</tr>
<tr>
<td></td>
<td>Male: 0.48</td>
<td>0.88 (2000-2005)</td>
<td>0.88 (2000-2005)</td>
</tr>
</tbody>
</table>

¹Van der Zee et al Neth J Med 2013;
Accessed 16 November 2018
N=496
88.3% of anal cancer was positive for HPV DNA

Alemany et al Int J Cancer 2015
**TNM staging for anal cancer**

**T categories for anal cancer**  
**TX:** Primary tumour cannot be assessed  
**T0:** No evidence of primary tumour  
**Tis:** The cancer is only in the mucosa  
This is also known as *carcinoma in situ* (CIS).  
**T1:** The tumour is $\leq 2$ cm  
**T2:** Tumour is $>2$ cm but $<5$ cm  
**T3:** Tumour $\geq 5$ cm across  
**T4:** Tumour of any size that is growing into nearby organ(s), such as the vagina, urethra, prostate gland, or bladder

**N categories for anal cancer**  
**NX:** Regional lymph nodes cannot be assessed  
**N0:** No spread to nearby lymph nodes  
**N1:** Spread to lymph nodes near the rectum  
**N2:** Spread to lymph nodes on one side of the groin and/or pelvis  
**N3:** Spread to lymph nodes near the rectum and in the groin or pelvis, or to both sides of the groin or pelvis

**M categories for anal cancer**  
**M0:** No distant spread  
**M1:** Distant spread to internal organs or lymph nodes of the abdomen
Pivotal randomised phase III trials in squamous cell cancer of anus

- **RT**: MMC/5-FU
  - **ACT 1**: n=585
  - **EORTC 22861**: n=110
  - **ACT II**: n=940
  - **Cisplatin / 5-FU**: RT ±
    - **Post CRT Cisplatin/5-FU**: ± Pre-CRT
      - **Cisplatin / 5-FU**: RT

- **5-FU RT**: RTOG 87-04 n=291
  - **Pre-CRT Cisplatin/5-FU**: → Cisplatin / 5-FU
    - **RT boost dose**: 15Gy → 20-25Gy

- **ACCORD 03**: n=307
## ACT II 2×2 factorial trial design

<table>
<thead>
<tr>
<th>MMC/5FU + RT</th>
<th>Maintenance Cisplatin/5FU × 2 cycles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin/5FU + RT</td>
<td>No Maintenance</td>
</tr>
</tbody>
</table>

**Primary endpoints:**
- MMC vs. Cisplatin CRT - complete response @ 26 weeks and acute toxicities
- Maintenance vs. no maintenance – progression free survival

James et al Lancet Oncol 2013
ACT II response assessment

Chemoradiation 50.4 Gy in 25 fractions over 38 days

Response assessment 1
Digital rectal examination with or without examination under anaesthetic

Response assessment 2
Digital rectal examination with or without examination under anaesthetic

Response assessment 3
Digital rectal examination with or without examination under anaesthetic and CT mandated

James et al Lancet Oncol 2013; Glynne-Jones Lancet Oncol 2017
Primary tumour response @26 weeks

<table>
<thead>
<tr>
<th></th>
<th>MMC</th>
<th>Cisplatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>432</td>
<td>431</td>
</tr>
<tr>
<td>CR</td>
<td>90.5%</td>
<td>89.6%</td>
</tr>
<tr>
<td>PR</td>
<td>3.2%</td>
<td>5.6%</td>
</tr>
<tr>
<td>SD</td>
<td>1.2%</td>
<td>1.4%</td>
</tr>
<tr>
<td>PD</td>
<td>5.1%</td>
<td>3.5%</td>
</tr>
</tbody>
</table>

Absolute $\Delta$ of CR rate = 0.9% (95%CI: -4.9 to 3.1%; $p=0.64$)

James et al Lancet Oncol 2013
ACT 2 Progression free survival

Maintenance comparison

4-arms comparison

James et al Lancet Oncol 2013
## Timing of CR Assessment

(691 pts with data at all 3 time-points)

<table>
<thead>
<tr>
<th>Wk</th>
<th>Total patients with CR (%)</th>
<th>CR (%) MMC</th>
<th>CR (%) Cisplatin</th>
<th>(\chi^2)</th>
<th>HR (95% CI) (CR vs not CR)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>PFS</td>
<td>OS</td>
<td>p</td>
<td>PFS</td>
</tr>
<tr>
<td>11</td>
<td>441 (64)</td>
<td>231 (67)</td>
<td>210 (61)</td>
<td>p=0.09</td>
<td>0.59 (0.45, 0.78)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>p=0.0002</td>
<td>p=0.0002</td>
</tr>
<tr>
<td>18</td>
<td>556 (80)</td>
<td>273 (79)</td>
<td>283 (82)</td>
<td>p=0.38</td>
<td>0.37 (0.28, 0.49)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>p&lt;0.0001</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>26</td>
<td>590 (85)</td>
<td>292 (85)</td>
<td>298 (86)</td>
<td>p=0.58</td>
<td>0.16 (0.12, 0.21)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>p&lt;0.0001</td>
<td>p&lt;0.0001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Glynn-Jones et al Lancet Oncol 2017
Progression free survival (CR vs. non-CR)

Assessment 1: ~ 11 weeks
Assessment 2: ~ 18 weeks
Assessment 3: ~ 26 weeks

Glynn-Jones et al Lancet Oncol 2017
Overall survival (CR vs. non-CR)

Assessment 1: ~ 11 weeks
Assessment 2: ~ 18 weeks
Assessment 3: ~ 26 weeks

Glynn-Jones et al Lancet Oncol 2017
ESMO Anal Cancer Practice Guideline

Chemoradiation schedule and assessment used in the ACT II trial

Chemoradiation
- 5FU 1000 mg/m2 days 1–4 (week 1) and 29–32 (week 5) by continuous 24 h IV infusion.
- MITOMYCIN 12 mg/m2 IV bolus on day 1 (maximum single dose 20 mg)
- RADIOTHERAPY*: Total dose 50.4 Gy delivered in 28 daily fractions starting on Day 1.

Assessment of tumour response
- Digital examination at 11, 18 and 26 weeks from the start of the treatment.
- Abdominopelvic CT at week 26.
- Confirm residual or recurrent disease by biopsy (routine biopsies not recommended).

Complete response
- Follow-up

Persistent / recurrent disease
- Surgery
NCCN guidelines flow diagram

NCCN Clinical Practice Guidelines in Oncology
Anal Carcinoma version 2.2017
MRI surveillance anal cancer

Dec 2010 T3N3
Newly diagnosed HIV positive

Jun 2011
Post CRT

- MRI reserved to specialist radiologist
- Multidisciplinary input
- CT Chest and Abdomen
  ?restricted to annually for 3 years

Mar 2012
Surveillance
MRI surveillance anal cancer

Jan 2007 T3N1 Baseline

May 2007 Post CRT
Oct 2007 → Residual SCC
Nov 2007 AP resection

Jan 2009 Surveillance

Jun 2009 Massive pelvic recurrence
Unanswered questions in anal cancer treatment

• Optimal radiotherapy dose
  – More advanced T3/T4 tumours/ nodal metastases (RT dose escalation)
  – Earlier stage (RT dose de-escalation)

• Role of IMRT to reduce toxicities

• CT/MRI/PET planning for RT

• Incidental anal cancer
PLATO Trial Design

**ACT3**

**Low-risk disease**
ECOG PS 0-2
T1 N0/X Anal margin
Local excision

**Question:**
Does a low-dose CRT treatment strategy based on tumour margins post local excision result in acceptably low rates of LRF?

**Observation**
(margin >1mm)
vs
Reduced-dose CRT
(margin ≤1mm)

**ACT4**

**Intermediate-risk disease**
ECOG PS 0-1
T1-2 ≤4cm N0/X Anal canal, or
T2 ≤4cm N0/X Anal margin

**Question:**
Can we reduce radiotherapy dose in early stage disease?

Standard-dose CRT
vs
Reduced-dose CRT using IMRT with elective nodal RT

**ACT5**

**High-risk disease**
ECOG PS 0-1
T2N1-3 or T3-4 Nany
Anal margin or canal

**Question:**
Can radiotherapy dose escalation reduce locoregional failure with acceptable toxicity?

Standard-dose CRT
vs
SIB dose-escalated CRT using IMRT with elective nodal RT
Trial Design

Low-risk disease

ACT3

- Margin ≤1mm
- Obs^n
- 41.4Gy 23F
- MMC & CAP

Non-randomised Phase II trial
n=90
3 year recruitment

Intermediate-risk disease

ACT4

- Randomised 1:2
- 50.4Gy 23F
- 41.4Gy 23F
- MMC & CAP
- MMC & CAP

Phase II trial
n=162
2 year recruitment

High-risk disease

ACT5

- Randomised 1:1:1
- 53.2Gy 28F
- 58.8Gy 28F
- 61.6Gy 28F
- Pilot
n=60
Ph II
n=80
Ph III
n=500
- MMC & CAP or MMC & 5FU
- 5 year recruitment
PLATO Endpoints

**Primary**
- Locoregional failure (LRF) at 3 years post close of recruitment

**Secondary**
- Acute and late toxicities
- Treatment compliance
- Clinical response rate (ACT4 & 5)
- Disease-free survival
- Colostomy-free survival
- Progression-free survival
- Overall survival
- Patient Reported Outcome Measures
(Non) - Standard of care for locally recurrent and metastatic anal squamous cell carcinoma
Locally recurrent and metastatic disease flow diagram

- Local relapse post-CRT is still potentially amenable to cure with salvage APR
- Distant metastases following curative treatments occur in 10-20% of patients
- According to the latest SEER figures, 5-years OS of patients with recurrent/metastatic disease is 29.8%
- Chemotherapy is the standard treatment for patients with inoperable locally recurrent/metastatic disease
- Platinum-Fluoropyrimidine is the regimen most commonly used

NCCN Clinical Practice Guidelines in Oncology
Anal Carcinoma version 2.2017;
# Chemotherapy in anal cancer: available evidence

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>N</th>
<th>Agents</th>
<th>Response Rate N/N (%)</th>
<th>mPFS (months)</th>
<th>mOS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wilking, 1985</td>
<td>15</td>
<td>Vincristine-Bleomycin-HD methotraxate</td>
<td>3/12 (25)</td>
<td>2</td>
<td>NA</td>
</tr>
<tr>
<td>Ajani, 1989</td>
<td>3</td>
<td>Cisplatin-5FU</td>
<td>NA</td>
<td>17</td>
<td>NA</td>
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<tr>
<td>Faivre, 1999</td>
<td>19</td>
<td>Cisplatin-5FU</td>
<td>12/18 (66)</td>
<td>NA</td>
<td>34.5</td>
</tr>
<tr>
<td>Hainsworth, 2001</td>
<td>7</td>
<td>Paclitaxel-carboplatin-CI 5FU</td>
<td>4/7 (57)</td>
<td>26</td>
<td>NA</td>
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<tr>
<td>Abbas, 2001</td>
<td>7</td>
<td>Paclitaxel (2nd line)</td>
<td>4/7 (57)</td>
<td>4</td>
<td>7</td>
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<tr>
<td>Jhawer, 2006</td>
<td>20</td>
<td>Mytomycin C-adriamycin-cisplatin-bleomycin-lomustine</td>
<td>12/20 (60)</td>
<td>8</td>
<td>15</td>
</tr>
<tr>
<td>Alcindor, 2008</td>
<td>5</td>
<td>Paclitaxel (1st and 2nd line)</td>
<td>3/5 (60)</td>
<td>3.8</td>
<td>4-20</td>
</tr>
<tr>
<td>Kim, 2013</td>
<td>8</td>
<td>Docetaxel-cisplatin-5-FU</td>
<td>4/8 (50)</td>
<td>19-88</td>
<td>NA</td>
</tr>
<tr>
<td>Byer, 2013</td>
<td>13</td>
<td>Carboplatin-Paclitaxel (1st and 2nd line)</td>
<td>8/13 (62)</td>
<td>4.6</td>
<td>10.5</td>
</tr>
<tr>
<td>Eng, 2014</td>
<td>42</td>
<td>Cisplatin-5FU</td>
<td>24/42 (57)</td>
<td>8</td>
<td>NA</td>
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<tr>
<td></td>
<td>24</td>
<td>Carboplatin-Paclitaxel</td>
<td>8/24 (33)</td>
<td>4</td>
<td>NA</td>
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<tr>
<td></td>
<td>11</td>
<td>Other</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>
RMH experience in advanced anal cancer

• N=64 (managed between 1997-2014)
  – inoperable locally advanced n=16
  – metastatic n=48

• Treatment used
  – 51 (80%) received ≥1 line of chemotherapy
  – 75% received platinum + fluoropyrimidine
  – Paclitaxel based chemo used in 15 patients

Sclafani et al Oncologist 2017
ORR and PFS

First line therapy

- N=51
- ORR: 34%
- Median PFS = 5.8 months

Second line therapy

- N=21
- ORR: 33.3%
- Median PFS = 3.2 months

Sclafani et al Oncologist 2017
Overall survival

N=51
Median follow up : 71.9 months
Median OS = 14.1 months
Median OS for second line chemotherapy: 14.9 months
5-year OS: 15%

Sclafani et al Oncologist 2017
Epitopes – HPV02: multicentre French non-randomised phase 2 trial of DCF in advanced anal SCC

Non-randomised R = registered

Metastatic or locally recurrent anal SCC
No prior taxanes
CF given as part of CRT regimen permitted

n=36

Classical DCF*
Docetaxel 75mg/m² D1
Cisplatin 75mg/m² D1
5-FU 750mg/m²/day D1-5 every 3 weeks

Modified DCF*
Docetaxel 40mg/m² D1
Cisplatin 40mg/m² D1
5-FU 1200mg/m²/day D1-2 every 2 weeks

(n=30)

Primary endpoint: Progression free survival

*Investigators’ choice of DCF

Kim et al Lancet Oncol 2018
## Epitopes – HPV02: multicentre French non-randomised phase 2 trial of DCF in advanced anal SCC

<table>
<thead>
<tr>
<th></th>
<th>ITT</th>
<th>Classical DCF</th>
<th>Modified DCF</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>66</td>
<td>36</td>
<td>30</td>
</tr>
<tr>
<td>ORR</td>
<td>86%</td>
<td>89%</td>
<td>83%</td>
</tr>
<tr>
<td>mPFS</td>
<td>11 months</td>
<td>10.7 months</td>
<td>11 months</td>
</tr>
<tr>
<td>12-month OS</td>
<td>83.1%</td>
<td>83.3%</td>
<td>82.7%</td>
</tr>
</tbody>
</table>

### Progression free survival

<table>
<thead>
<tr>
<th>Number at risk (number censored)</th>
<th>Standard DCF</th>
<th>Modified DCF</th>
</tr>
</thead>
<tbody>
<tr>
<td>36 (0)</td>
<td>36 (0)</td>
<td>30 (0)</td>
</tr>
<tr>
<td>36 (0)</td>
<td>30 (0)</td>
<td>28 (0)</td>
</tr>
<tr>
<td>30 (0)</td>
<td>22 (1)</td>
<td>24 (0)</td>
</tr>
<tr>
<td>24 (0)</td>
<td>18 (1)</td>
<td>15 (1)</td>
</tr>
<tr>
<td>15 (1)</td>
<td>7 (7)</td>
<td>14 (3)</td>
</tr>
<tr>
<td>14 (3)</td>
<td>3 (13)</td>
<td>11 (4)</td>
</tr>
</tbody>
</table>

### Overall survival

<table>
<thead>
<tr>
<th>Number at risk (number censored)</th>
<th>Standard DCF</th>
<th>Modified DCF</th>
</tr>
</thead>
<tbody>
<tr>
<td>36 (0)</td>
<td>36 (0)</td>
<td>30 (0)</td>
</tr>
<tr>
<td>36 (0)</td>
<td>30 (0)</td>
<td>27 (1)</td>
</tr>
<tr>
<td>30 (0)</td>
<td>24 (0)</td>
<td>17 (3)</td>
</tr>
<tr>
<td>24 (0)</td>
<td>10 (14)</td>
<td>3 (17)</td>
</tr>
<tr>
<td>17 (3)</td>
<td>6 (12)</td>
<td>5 (14)</td>
</tr>
<tr>
<td>10 (14)</td>
<td>3 (17)</td>
<td>3 (10)</td>
</tr>
</tbody>
</table>

Kim et al. Lancet Oncol 2018
InterAACT trial

Multicentre, international, open label, randomised phase II trial

First line treatment for advanced SCCA

Mar 2014 ➣ Oct 2017

Cisplatin 60 mg/mq d1 q21
5-FU 1000 mg/mq d1-4 q21
Carboplatin AUC5 d1 q28
Paclitaxel 80 mg/mq d1,8,15 q28

24 weeks of treatment
(untill PD/unacceptable toxicity upon investigators discretion)

Stratification factors:
- Region (Europe vs North America vs Australia)
- ECOG PS (0-1 vs 2)
- HIV + (yes vs no)
- Inoperable locally recurrent vs metastatic

Statistical considerations:
- Sample Size: 90 patients 36 patients to be recruited to each arm in order to detect 10% difference in response rates between the experimental arms with 80% power (20% withdrawal rate taken into account)
- If no difference in response rate then the least toxic regimen will be selected
### InterAAACT objective response rate

<table>
<thead>
<tr>
<th>Response (RECIST)</th>
<th>Carboplatin-Paclitaxel N=39</th>
<th>Cisplatin-5FU N=35</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (%) CI</td>
<td>N (%)</td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>5 12.8 5 14.3</td>
<td></td>
</tr>
<tr>
<td>PR</td>
<td>18 46.2 15 42.9</td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>10 25.6 7 20.0</td>
<td></td>
</tr>
<tr>
<td>PD</td>
<td>6 15.4 8 22.9</td>
<td></td>
</tr>
<tr>
<td>CR/PR</td>
<td>23 59 20 57</td>
<td></td>
</tr>
</tbody>
</table>

95% CI: [42.1-74.4] [39.4-73.7]

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Rao et al ESMO 2018
### Selected grade ≥3 adverse events

<table>
<thead>
<tr>
<th>Toxicity ≥ Grade 3</th>
<th>Carboplatin Paclitaxel</th>
<th>Cisplatin-5FU</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=42</td>
<td>N=42</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>Anaemia</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Fatigue</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Mucositis</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Thromboembolism</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Overall</td>
<td>30</td>
<td>71</td>
</tr>
<tr>
<td>SAEs</td>
<td>15</td>
<td>36</td>
</tr>
</tbody>
</table>

Rao et al ESMO 2018
InterAACT progression free survival

Median follow up
25.3 mths

Carbo/PAC  Cis/5FU
mPFS 8.1 months 5.7 months
p=0.375

Rao et al ESMO 2018
InterAACT overall survival

Median follow up 25.3 mths

Carbo/PAC Cis/5FU
mOS 20.0 months 12.3 months
p=0.014

Rao et al ESMO 2018
InterAACT conclusions

• This is the first reported randomised clinical trial in advanced anal cancer
• Using a pragmatic randomised phase II pick the winner design, we successfully demonstrated feasibility of international collaboration in a rare cancer
• No difference in objective response rate was observed between arms
• Carboplatin/ paclitaxel demonstrated less toxicity therefore is declared the winner
  • In addition carboplatin/ paclitaxel demonstrated improved OS and can now be considered a new standard of care for treatment naïve advanced anal cancer

Carboplatin/ paclitaxel should be the cytotoxic platform for future combination trials
Molecular characterisation of anal SCC

<table>
<thead>
<tr>
<th>Gene</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>PIK3CA</td>
<td>29%–40%</td>
</tr>
<tr>
<td>MLL3</td>
<td>32%</td>
</tr>
<tr>
<td>MLL2</td>
<td>22%</td>
</tr>
<tr>
<td>EP300</td>
<td>22%</td>
</tr>
<tr>
<td>p53</td>
<td>15%–20%</td>
</tr>
<tr>
<td>FBXW7</td>
<td>13%–14%</td>
</tr>
<tr>
<td>PTEN</td>
<td>2%–14%</td>
</tr>
<tr>
<td>BRCA1</td>
<td>1%–12%</td>
</tr>
<tr>
<td>BRCA2</td>
<td>3%–12%</td>
</tr>
<tr>
<td>AKT1</td>
<td>3%–7%</td>
</tr>
<tr>
<td>EGFR</td>
<td>0%–5%</td>
</tr>
<tr>
<td>BRAF</td>
<td>0%–5%</td>
</tr>
<tr>
<td>KRAS</td>
<td>0%–4%</td>
</tr>
<tr>
<td>NRAS</td>
<td>0%–2%</td>
</tr>
</tbody>
</table>

Table 1. Frequency of the most commonly occurring mutations in SCCA.

Jacome et al Expert Opin Investig Drugs 2018
Molecular profile of metastatic SCC anus (n=41)

- Whole exome sequence in 24 tumours
- 20/24 (88%) had activating mutation ± gene amplification of PIK3CA

Activating mutation analysis

Copy number analysis

Morris et al Mol Cancer Res 2017
Molecular profile of metastatic SCC anus (n=45)

- MSK-IMPACT sequencing in 45 tumours
- 44% genomic alterations involving the PI3K pathway

Mondaca et al Clin Colorectal cancer 2018
Preclinical validation of drug target against PI3 kinase

Xenograft model established from a patient with metastatic anal SCC treated with a PI3K inhibitor (A) or with an anti-EGFR antibody (B).

Morris et al Mol Cancer Res 2017
Mutation load of SCC anus vs. other primary sites

Morris et al Mol Cancer Res 2017
**NCI9673 Nivolumab for previously treated advanced anal cancer**

Phase 2 multicenter, open-label, single-arm study to evaluate the efficacy and safety of nivolumab in anal cancer patients who have failed standard chemotherapies.

**Key Eligibility Criteria:**
- Squamous cell carcinoma of anus
- ECOG PS 0 or 1
- Surgically unresectable or metastatic disease
- At least 1 previous therapy

**Nivolumab 3 mg/kg Q2W**

- **Tumor response assessment**
  - Response of CR, ORR, or ≤SD
  - PD or unacceptable toxicity
  - Observe 4 weeks later
  - 6 weeks, repeated cycle

**Primary Outcome Measure:** ORR using RECIST v1.1

**Secondary Outcome Measures:** OS, PFS, duration of response, depth of response, safety, immune biomarkers

- The population was comprised only of 37 US patients with advanced anal squamous cell carcinoma

Morris et al Lancet Oncol 2017
# NCI9673: objective response

<table>
<thead>
<tr>
<th>Best Overall Response/ORR</th>
<th>Investigator</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
</tr>
<tr>
<td>Complete response (CR)</td>
<td>2</td>
</tr>
<tr>
<td>Partial response (PR)</td>
<td>7</td>
</tr>
<tr>
<td>Stable disease (SD)</td>
<td>15</td>
</tr>
<tr>
<td>Progressive disease (PD)</td>
<td>10</td>
</tr>
<tr>
<td>NE</td>
<td>3</td>
</tr>
<tr>
<td>ORR (CR+PR)</td>
<td>9</td>
</tr>
</tbody>
</table>

- **Depth of response:** 
  - Median 70% (IQR: 57-90%)
- **Duration of Response**
  - Median 5.8 months (IQR: 3.9-8.1)

[Image of graphs]

Morris et al Lancet Oncol 2017
NCI9673: Survival

Progression free survival

Median PFS = 4.1 months
6-month PFS: 38%

Overall survival

Median OS = 11.5 months
1-year OS: 48%

Morris et al Lancet Oncol 2017
NCI9673: immune profiling in pre-treatment biopsies between responders and non-responders

Immunohistochemistry

Flow cytometry

Morris et al Lancet Oncol 2017
**Proposed InterAACT II trial**

Multicentre, international, open label, randomised phase II-III trial

First line treatment for advanced SCCA

- Doublet chemotherapy (i.e., winner regimen of the InterAACT trial*) × 24 week

Stratification factors:
- Region (Europe vs Australia)
- ECOG PS (0-1 vs 2)
- HIV + (yes vs no)
- Inoperable locally recurrent vs metastatic

Doublet chemotherapy (i.e., winner regimen of the InterAACT trial*) + checkpoint inhibitor × 24 week

Observe or further chemo (clinician’s choice)

Checkpoint inhibitor till PD

* Cisplatin plus 5FU or Carboplatin plus Paclitaxel
Acknowledgement

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