Standard of care for anal squamous cell carcinoma

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Disclosure

• Advisory Board: Sanofi Oncology, Eli-Lilly, Bristol Meyers Squibb, MSD, Bayer, Roche, Five Prime Therapeutics

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• Honorarium: Taiho, Pfizer, Amgen, Eli-Lilly
SEER epidemiology for anal cancer: incidence, time trend and survival

Estimated New Cases in 2017: 8,200
% of All New Cancer Cases: 0.5%
Estimated Deaths in 2017: 1,100
% of All Cancer Deaths: 0.2%

Number of New Cases and Deaths per 100,000: The number of new cases of anal cancer was 1.8 per 100,000 men and women per year. The number of deaths was 0.2 per 100,000 men and women per year. These rates are age-adjusted and based on 2010-2014 cases and deaths.

Lifetime Risk of Developing Cancer: Approximately 0.2 percent of men and women will be diagnosed with anal cancer at some point during their lifetime, based on 2012-2014 data.

Accessed 31 October 2017
Increasing incidence over time in various countries

Van der Zee et al Neth J Med 2013

Approximately 2-fold ↑ in incidence
↑: Female > male
Aetiology of anal cancer

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 ≤2 cm
- **T2:** Tumour is >2 cm but <5 cm
- **T3:** Tumour ≥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

ACT I n=585
EORTC 22861 n=110

MMC/5-FU

RT

EORTC 22861 n=110

ACT II n=940

Cisplatin/5-FU

RT ±

Pre-CRT Cisplatin/5-FU

→ Cisplatin/5-FU

Cisplatin/5-FU

RT ± Pre-CRT

Post CRT Cisplatin/5-FU

ACCORD 03 n=307

Pre-CRT Cisplatin/5-FU

→ Cisplatin/5-FU

RTOG 87-04 n=291

5-FU RT

RTOG 98-11 n=644

Cisplatin/5-FU

15Gy → 20-25Gy
# 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

- 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

Chemoradiation: 50.4 Gy in 25 fractions over 38 days

Maintenance chemotherapy

Week: 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26

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 Δ 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 (%)</th>
<th>χ²</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(CR vs not CR)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MMC</td>
<td>Cisplatin</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>
</tr>
<tr>
<td>18</td>
<td>556 (80)</td>
<td>273 (79)</td>
<td>283 (82)</td>
<td>p=0.38</td>
</tr>
<tr>
<td>26</td>
<td>590 (85)</td>
<td>292 (85)</td>
<td>298 (86)</td>
<td>p=0.58</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

5-yearOS
CCR 83%
Non-CCR 72%

5-yearOS
CCR 84%
Non-CCR 59%

5-yearOS
CCR 87%
Non-CCR 46%

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**

Glynn-Jones et al Ann Oncol 2014
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

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**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
    - Non-randomised
    - Phase II trial
      - n=90
      - 3 year recruitment
  - 41.4Gy 23F
  - MMC & CAP

**Intermediate-risk disease**

- ACT4
  - Randomised 1:2
    - 50.4Gy 28F
    - MMC & CAP
    - 41.4Gy 23F
    - MMC & CAP

**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

- Phase II trial
  - n=182
  - 2 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 29.6%
- 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</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>
</tr>
<tr>
<td>Abbas, 2001</td>
<td>7</td>
<td>Paclitaxel (2nd line)</td>
<td>4/7 (57)</td>
<td>4</td>
<td>7</td>
</tr>
<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>
</tr>
<tr>
<td></td>
<td>24</td>
<td>Carboplatin-Paclitaxel</td>
<td>8/24 (33)</td>
<td>4</td>
<td>NA</td>
</tr>
<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
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
24 weeks of treatment
(untill PD/unacceptable toxicity upon investigators discretion)

Carboplatin AUC5 d1 q28
Paclitaxel 80 mg/mq d1,8,15 q28

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: 80 patients (↑ to 90)
- 36 patients to be recruited to each arm in order to detect 10% difference in response rates between the experimental arms with 80% power (10% withdrawal rate taken into account)
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
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

- Anal cancer: Median 2.5
- HPV+ Head/neck cancer: Median 2.8
- Cervical cancer: Median 3.4
- Squamous cell lung cancer: Median 9.8

*P < 0.001

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

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)

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

First line treatment for advanced SCCA

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

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

Observe or further chemo (clinician’s choice)

Nivolumab till PD

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

* Cisplatin plus 5FU or Carboplatin plus Paclitaxel
Acknowledgement

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