Update on the treatment of squamous cell cancer of the anus

Rob Glynne-Jones
Mount Vernon Cancer Centre / Champalimaud Foundation
Disclosures

2019 BCUK have taken on responsibility for squamous cell cancer of the anus and rectum

www.bowelcanceruk.org.uk
Risk Factors

- Persistent HPV infection
- Previous HPV-related malignancy
- HIV infection
- Immune suppression/immunodeficiency
- Receptive anal intercourse (MSM)
- Tobacco Smoking

Age at Diagnosis

Median Age at Diagnosis: 62

New cases (%)

<table>
<thead>
<tr>
<th>Age</th>
<th>0</th>
<th>1.1</th>
<th>5.9</th>
<th>23.9</th>
<th>28.4</th>
<th>20.7</th>
<th>13.8</th>
<th>6.2</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;20</td>
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<tr>
<td>20-34</td>
<td>1.1</td>
<td></td>
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<tr>
<td>35-44</td>
<td>5.9</td>
<td></td>
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<tr>
<td>45-54</td>
<td>23.9</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>55-64</td>
<td>28.4</td>
<td></td>
<td></td>
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<tr>
<td>65-74</td>
<td>20.7</td>
<td></td>
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<tr>
<td>75-84</td>
<td>13.8</td>
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<tr>
<td>&gt;84</td>
<td>6.2</td>
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</tbody>
</table>

The culprit - Human papillomavirus (HPV)

- The HPV virus is highly contagious from sexual intercourse both vaginally and anally
- virtually endemic in many countries
- 90%-95% of cases of SCCA in UK associated with HPV16 and HPV 18
- as in SCCHN modified by smoking
- HPV negative cancers fare badly
### Prognostic Relevance of HPV and p16

<table>
<thead>
<tr>
<th>Author</th>
<th>Patients (n)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Körber</td>
<td>105</td>
<td>increased local control, PFS, OS</td>
</tr>
<tr>
<td>Mai</td>
<td>106</td>
<td>increased 5 years local control/trend to</td>
</tr>
<tr>
<td></td>
<td></td>
<td>increased OS</td>
</tr>
<tr>
<td>Rödel</td>
<td>95</td>
<td>improved local control, CSS and OS</td>
</tr>
<tr>
<td>Serup-Hansen</td>
<td>143</td>
<td>improved DSS and OS</td>
</tr>
<tr>
<td>Baricevic</td>
<td>110</td>
<td>improved relapse-free survival and OS</td>
</tr>
</tbody>
</table>

**HPV and p16 positivity associated with a More favourable clinical response and increased survival**

Overview

A Systematic Review and Meta-Analysis of Prognostic Biomarkers in Anal Squamous Cell Carcinoma Treated With Primary Chemoradiotherapy

I. Parwaiz, T.A. MacCabe, M.G. Thomas, D.E. Messenger

Department of Coloproctology, University Hospitals Bristol NHS Foundation Trust, Bristol, UK

Received 20 February 2019; received in revised form 15 May 2019; accepted 21 May 2019

Abstract

Recent studies suggest that the treatment response and survival from head and neck tumours can be stratified according to biomarker status, particularly human papillomavirus (HPV) status and p16 expression, but the evidence for predictive biomarkers in anal squamous cell carcinoma (ASCC) remains limited.

HPV-positive tumours were associated with reduced LRR hazard ratio = 0.27 [95% confidence interval 0.16-0.48]; P < 0.001),

Likewise, p16-positive tumours were associated with reduced LRR (hazard ratio = 0.26 [0.13-0.52]; P < 0.001),
Martin D et al., 2017 The immune microenvironment and HPV in anal cancer: Rationale to complement chemoradiation with immunotherapy

Very complex!!
<table>
<thead>
<tr>
<th>Author</th>
<th>Patients (n)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grabenbauer</td>
<td>38</td>
<td>CD3/CD4: decreased 3 years NED</td>
</tr>
<tr>
<td>Rubio</td>
<td>277</td>
<td>CD3/CD8: increased 15 years survival</td>
</tr>
<tr>
<td>Hu</td>
<td>40</td>
<td>intratumoral CD8: increased DFS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>peritumoral CD8: increased OS</td>
</tr>
<tr>
<td>Gilbert</td>
<td>153</td>
<td>increased relapse-free survival</td>
</tr>
</tbody>
</table>

High levels of TILs, especially CD8(+) cells, are associated with a favourable clinical response and survival

Resolution involves

- Either viral clearance over time and local host memory
- Or a transition to a chronic infectious state
- Very slow (if any) systemic antibodies in most people

- (chronic viruses can persist in a semi-stable relationship within their host, generating antigenic stimulation for decades)
Gut microbiota from high-risk men who have sex with men drive immune activation in gnotobiotic mice and in vitro HIV infection

Sam X. Li, Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – original draft,¹ Sharon Sen, Formal analysis, Investigation, Methodology, Validation,¹ Jennifer M. Schneider, Data
Importance of Smoking/Tobacco abuse

Anal microbiome altered by

- Anal sex (fructose/citric acid/lipids in semen)
- Local immuno-suppressive effects of smoking in the anal canal

- Smoking also increases the mutational load mediated by tobacco associated carcinogens
E6 and E7 viral oncogenes

- Rapid inactivation of suppressor genes
- Inactivating mutations at TP53
- Inhibition of apoptosis
- Hijacks immune response

Longstanding immune selection for loss of HLA

E5 and E7 viral oncogene down-regulates / reduces MHC/HLA class I expression

Loss of HLA class 1
NK cells restrict metastases

Loco-regional invasion into Lymph nodes

HPV infection \(\rightarrow\) HPV persistence \(\rightarrow\) HPV entrenched

Aided by
- Immunosuppression (HIV, transplants etc.)
- Tobacco
- Multiple partners
- Anal sex
- ?anal microbiome

T-cell exhaustion, inhibition of T-cell proliferation, and cell cycle arrest

downregulates chemokine CXCL14 (NK killer cells in lymph nodes) to allow nodal extension
Preventive against the 9 most common HPV subtypes (HPV16, 18, 31, 4, 11, 33, 45, 52, and 58).

when administered to boys and girls prior to the onset of sexual activity, should effectively prevent anal cancer
Population-level impact and herd effects following the introduction of human papillomavirus vaccination programmes: updated systematic review and meta-analysis

Mélanie Drolet, PhD  Élodie Bénard, MSc  Norma Pérez, MSc  Prof Marc Brisson, PhD  
on behalf of the HPV Vaccination Impact Study Group

Published: June 26, 2019  DOI: https://doi.org/10.1016/S0140-6736(19)30298-3
In the past eight years, the number of Australian women who contracted HPV fell by 92%.

Precancerous cervical lesions reduced by 70% for those under 20 years of age and by 50% in women aged 20 to 24.
"It is, however, too soon to see reductions in cervical cancers - but our results strongly suggest that cervical cancer will decrease since both the cause — HPV infections — and precancerous cervical lesions, are significantly declining."
2074 patients with anal intraepithelial neoplasia (AIN) III

- 4 year follow-up
- 171 patients (8.2%) developed anal cancer
- Median time from AIN III to SCCA was 2.7 years (interquartile range, 1.1–4.5 y)
- 52 patients (30.4%) who developed anal carcinoma were staged T2 or higher.
- Ablative therapies for initial AIN III associated with a reduction in the risk of anal cancer (OR = 0.3 (95% CI, 0.1–0.7); p = 0.004).

Squamous Cell Anal Cancer

Low tumour mutational burden (TMB) (even in non HPV driven cancers)
Mean number of 2.5 to 3.5 somatic mutations/Mb

Figure 1. Comprehensive genomic profiling of 70 ASCC patients. Recurrent alterations in PI3K/AKT/mTOR pathway genes were observed commonly. Long tail demonstrates low-frequency alterations in multiple cancer-related genes.
Still no particular clonal somatic mutations
Still no validated biomarkers (HPV negative commonly have disruptive TP53 mutations [Meulendijks 2015])

have been reported to date to predict response to chemoradiation (CRT)
STAGING OF ANAL CANCER

The 8th edition of the AJCC classification

Tis  carcinoma in situ
T1  Tumor ≤2 cm in diameter
T2  Tumor >2 cm, but <5 cm in diameter
T3  Tumor ≥5 cm in diameter
T4  Tumor infiltration into neighboring organs

N0: No regional lymph node metastasis
N1: Metastasis in inguinal, mesorectal, internal iliac or external iliac nodes
  - N1a: Metastasis in inguinal, mesorectal or internal iliac nodes
  - N1b: Metastasis in external iliac lymph nodes
  - N1c: Metastasis in external iliac with any N1a nodes
SCC of Anus  Nigro et al 1983

- Preop chemoradiation to primary tumour, pelvic and inguinal nodes
- Radiotherapy  2 fields 30 Gy /15/21 days
- Chemotherapy  5FU 1000mg/m²
  Days 1-4,  29-32
- Mitomycin C 15mg/m²
  Day 1
We have managed to perform 6 major randomised trials

<table>
<thead>
<tr>
<th>Date</th>
<th>Trial protocol</th>
<th>Pt number</th>
<th>RT dose (Gy)</th>
<th>Chemo</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>UKCCCR/ACT 1 1996</td>
<td>RT vs CRT</td>
<td>577</td>
<td>45/25 + boost if response after 6 weeks</td>
<td>MMC + 5FU</td>
<td>CRT better RT boost after gap no advantage</td>
</tr>
<tr>
<td>EORTC 22861 1997</td>
<td>RT vs CRT</td>
<td>110</td>
<td>45/25 + boost after 6 weeks (15 – 20)</td>
<td>MMC + 5FU</td>
<td>CRT better RT boost after gap no advantage</td>
</tr>
<tr>
<td>RTOG 8704</td>
<td>CRT FU vs FU/MMC</td>
<td>310</td>
<td>Median 48Gy</td>
<td>5FU vs 5FU/MMC</td>
<td>Better DFS 51% vs 73% p=0.003</td>
</tr>
<tr>
<td>RTOG 9811</td>
<td>CRT vs CRT</td>
<td>682</td>
<td>30.6 + 14.4 + more if residual disease</td>
<td>MMC + 5FU Vs CP + 5FU</td>
<td>MMC + 5FU better</td>
</tr>
<tr>
<td>ACT2</td>
<td>CRT vs CRT +/- maintenance chemo</td>
<td>940</td>
<td>50.4 Gy</td>
<td>MMC + 5FU Vs CP + 5FU + maintenance</td>
<td>MMC + 5FU = Cisp + 5FU Maintenance no better</td>
</tr>
<tr>
<td>Accord 03</td>
<td>CRT +/- Ind chemo +/- HD Boost</td>
<td>307</td>
<td>45/25 +/- 20 Gy</td>
<td>MMC + 5FU</td>
<td>No advantage to either intervention</td>
</tr>
</tbody>
</table>
# Outcomes according to more advanced TNM stage

<table>
<thead>
<tr>
<th>TNM stage</th>
<th>RTOG 9811</th>
<th>ACT-2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RT up to 59.4 Gy</td>
<td>RT up to 50.4 Gy</td>
</tr>
<tr>
<td><strong>DFS (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T3-4Nany</td>
<td>53%*</td>
<td>63%*</td>
</tr>
<tr>
<td>N0</td>
<td>72%*; 64%**</td>
<td>76%*</td>
</tr>
<tr>
<td>N+</td>
<td>42%*; 35%**</td>
<td>62%*</td>
</tr>
<tr>
<td><strong>PFS (%)</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*3-year DFS (or PFS)

**5-year DFS (or PFS)


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7.5 ANTIBIOTIC COVER

It is recommended that all patients receive prophylactic antibiotics (e.g. ciprofloxacin - 250 mg bd.) during chemoradiation (~6 weeks in total) according to local practice.
Squamous carcinoma of the anus

- The standard of care is chemoradiation with 5FU and MMC
- Standard of care for radiation is now IMRT

- But disagreement regarding
  - Total Dose
  - Field sizes
  - Techniques (VMAT/IMRT/Brachytherapy)
### Site of relapse after CRT with 50.4Gy from ACT II (940 patients)

<table>
<thead>
<tr>
<th>Primary Inguinal/pelvic nodes Metastases/oligometastases</th>
<th>Number</th>
<th>% total relapses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pelvic - no metastases</td>
<td>133</td>
<td>64%</td>
</tr>
<tr>
<td>Pelvic - with metastases</td>
<td>30</td>
<td>14%</td>
</tr>
<tr>
<td>Distant metastases only</td>
<td>46</td>
<td>22%</td>
</tr>
<tr>
<td>Total crude pelvic failure (with or without metastases)</td>
<td>163</td>
<td>78%</td>
</tr>
<tr>
<td>Total relapses</td>
<td>209/940</td>
<td></td>
</tr>
</tbody>
</table>

Data from ACT II  Sebag-Montefiore D et al ASCO 2012
### Patterns and Predictors of Relapse Following Radical Chemoradiation Therapy Delivered Using Intensity Modulated Radiation Therapy With a Simultaneous Integrated Boost in Anal Squamous Cell Carcinoma

Shakir R et al 2019

<table>
<thead>
<tr>
<th>Site of recurrence</th>
<th>n (% of total failures)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Locoregional* (+/- distant)</td>
<td>63 (85.1)</td>
</tr>
<tr>
<td>Primary site</td>
<td>62 (83.4)</td>
</tr>
<tr>
<td>Pelvic nodes</td>
<td>7 (9.5)</td>
</tr>
<tr>
<td>Inguinal nodes</td>
<td>5 (6.8)</td>
</tr>
<tr>
<td>Perineum</td>
<td>1 (1.4)</td>
</tr>
</tbody>
</table>

385 patients treated with IMRT
Survivorship – late toxicity

• Grade 3 and above (classified as severe) up to 33.3%.
• The most commonly reported late toxicities were faecal incontinence (up to 44%), diarrhea (up to 26.7%), and ulceration (up to 22.6%)
• Intensity-modulated radiation therapy appears to reduce late toxicity.

IMRT vs 3D-CRT

- 70 women after the treatment
- 43% in the 3D-CRT group and 29% in the IMRT group reported a severe loss of QoL.

# Anal Cancer Specific Quality of Life Questionnaire

## The EORTC QLQ-ANL27

**EORTC QLQ-ANL27**

Phase I–III development of the EORTC QLQ-ANL27, a health-related quality of life questionnaire for anal cancer


## Conceptual Scale

<table>
<thead>
<tr>
<th>Conceptual Scale</th>
<th>Issues</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bowel</td>
<td>Flatulence, Bowel incontinence, Frequent defecation, Bowel urgency, Sensation of inability to effectively empty bowels</td>
</tr>
<tr>
<td>Pain/Discomfort</td>
<td>Pain or discomfort in the anus or anal opening, Pain while sitting Discomfort in certain positions (e.g. lying down), Soreness in treatment area, Itchy/irritated skin in treated areas</td>
</tr>
<tr>
<td>Stoma</td>
<td>Skin reaction around stoma site, Leakage of stools from stoma bag, Unintentional release of gas/flatulence from stoma bag</td>
</tr>
<tr>
<td>Sexual</td>
<td>General, Sexual interest, Affected sex life, Painful sexual intercourse, Male, Impotence, Female, Vaginal dryness, Vaginal narrowing, Vaginal pain</td>
</tr>
</tbody>
</table>

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*Sodergren, Radiother Oncol 2018*
Squamous cell carcinoma of the anus

• Usually localized with a low risk of metastases at presentation
• Metastases rare unless primary uncontrolled
• So local control ? more important than distant metastases.
• The majority 70-90% respond to CRT (depending on stage)
• But results for cT3/T4 less favourable
Best time to assess complete clinical response (cCR) after CRT in Anal-Cancer: ACT II data

- n=691 attended all three assessments
- cCR: 64%, 80% and 85% at assessments 1, 2 and 3, respectively
- 72%: no cCR at assessment 1; cCR by assessment 3
- 5-year OS (at assessment 3): cCR=87%; non-cCR=48%

Can take 6 months for tumor to completely regress
- Close follow-up with APR reserved for progression
## Overall survival following salvage surgery

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of deaths</th>
<th>Median OS (months)</th>
<th>Hazard Ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group A</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N=19 Surgery &lt; 6/12</td>
<td>15 (79)</td>
<td>9.6 (5.8 to 26.3)</td>
<td>1.00 (baseline)</td>
<td>-</td>
</tr>
<tr>
<td><strong>Group B</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N=36 Surgery 6-12 months</td>
<td>21 (58)</td>
<td>21.1 (11.7 to 118.1)</td>
<td>0.53 (0.27 to 1.03)</td>
<td>0.062</td>
</tr>
<tr>
<td><strong>Group C</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N=28 Surgery 24-12 months</td>
<td>12 (43)</td>
<td>47.7 (15.7 to NR)</td>
<td>0.33 (0.15 to 0.70)</td>
<td>0.004</td>
</tr>
<tr>
<td><strong>Group D</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N=18 Surgery &gt;24 months</td>
<td>5 (28)</td>
<td>NR</td>
<td>0.31 (0.11 to 0.85)</td>
<td>0.024</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N=101</td>
<td>53 (52)</td>
<td>30.3 (11.7 to 118.1)</td>
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</tr>
</tbody>
</table>
Impact of timing from salvage surgery until death
Impact of day 29 Chemo Compliance on PFS (n=862)

Initial GFR relevant

HR 1.63 (95% CI: 1.23 to 2.17)  
p=0.001
RT Compliance and PFS n=933

A. Per protocol – 50.4 Gy in 28F in 38 – 42 days

B. ≤40 Gy (includes X early deaths)

C. 40-48.6 Gy in 23-27F

D. 50.4 Gy in >42 days

E. >52.2Gy

Number at risk

<table>
<thead>
<tr>
<th>Group</th>
<th>Number at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td>786</td>
</tr>
<tr>
<td>Group B</td>
<td>18</td>
</tr>
<tr>
<td>Group C</td>
<td>21</td>
</tr>
<tr>
<td>Group D</td>
<td>93</td>
</tr>
<tr>
<td>Group E</td>
<td>15</td>
</tr>
</tbody>
</table>

Time since randomisation (years)

<table>
<thead>
<tr>
<th>Time (years)</th>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
<th>Group D</th>
<th>Group E</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>528</td>
<td>5</td>
<td>9</td>
<td>54</td>
<td>7</td>
</tr>
<tr>
<td>1</td>
<td>205</td>
<td>3</td>
<td>0</td>
<td>24</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>17</td>
<td>1</td>
<td>0</td>
<td>3</td>
<td>0</td>
</tr>
</tbody>
</table>
Colostomy outcomes: ACT II

- Median f/u = 5.1 yrs

- Majority of pre-treatment colostomies not reversed

- T3/T4 (vs. T1/T2) strongest predictor for colostomy (HR=2.5)

**Risk-adapted RT: the PLATO trial**

**Primary endpoint:** locoregional failure (LRF)
Plato design

- 5 Different doses (but within a range) 41.4Gy/50.4Gy/53.2Gy/58.8Gy/61.6Gy
- Allows current prognostic groups (p16+etc..)
- To be validated as predictive
60 centres in UK, Australia, Norway and US

**InterAACT Study Design**

**International multi-centre randomised phase II study**

**Advanced anal cancer**

- Carboplatin AUC5 D1
- Paclitaxel 80mg/m² D1,8,15 q=21 days

- Cisplatin 60mg/m² D1
- 5FU 1000mg/m² D1-4 q=28 days

Planned N=90 R1:1

- Stratified
  - PS-ECOG 0:1:2
  - HIV status +:-
  - Extent of disease LA:Met
  - Region UK:Aus:US:Europe

**End Points**
1. ORR
2. Feasibility of international study
3. Toxicity, PFS, OS, DCR, QOL
4. Exploratory biomarker analysis

*International Rare Cancers Initiative (IRCI)*
InterAACT: Secondary endpoints

Progression Free Survival

Overall Survival

Rao et al., ESMO 2018
Docetaxel, Cisplatin, and 5-fluorouracil (DCF) chemotherapy in the treatment of metastatic or unresectable locally recurrent anal squamous cell carcinoma: a phase II study of French interdisciplinary GERCOR and FFCD groups (Epitopes-HPV02 study)

PD-L1 INHIBITORS IN THE REFRACTORY SETTING

**Nivolumab - NCI9673 trial**

- Multicentre, single-arm, phase II study (n=37)
- Inoperable locally recurrent/metastatic disease, ECOG PS 0-1
- Pre-treated for M+ disease (median 2 lines of chemotherapy)
- Nivolumab 3 mg/kg every 2 weeks
- Primary endpoint: Objective response rate

- ORR: 24% (CR in 5%) as per local RR
- Median duration of response: 5.8 months
- Disease control rate: 72%
- Median PFS: 4.1 months
- Median OS: 11.5 months
- 2 HIV+ patients treated with no grade ≥3 AEs

*Eng, Lancet Oncol 2017*
Nivolumab for previously treated unresectable metastatic anal cancer

Phase II trial (NCT02314169)
- Inclusion: previously-treated metastatic patients
- Primary Endpoint: Tumor response (RECIST 1.1)

Results:
- Response in 9 of 37 patients (24%; CR in n=2)
- Median OS: 11.5 months; median PFS: 4.1 months
- Good toxicity profile, no SAEs

Higher immunogenicity → Better response

*Morris et al, Lancet Oncology 2017*
Identifying HPV ctDNA by droplet digital polymerase chain reaction (ddPCR) is highly sensitive and specific.

The detection of small tumors indicates that HPV16 and HPV33 ctDNA ddPCR could be readily used in early detection screening trials and in disease response monitoring, analogous to Epstein-Barr virus DNA.
residual ctDNA levels after CRT are associated with very poor outcome

Cabel L et al., Clin Cancer Res 2018; 24(22);5767–71
Prognostic Impact of Residual HPV ctDNA after chemoXRT in Locally Advanced Anal Cancer

FIG 1

33 patients with Stage II-III ASCC undergoing chemoradiotherapy

33 patients with blood samples at baseline

18 patients with matched blood samples before and after chemoradiotherapy

15 patients with blood samples only before chemoradiotherapy

3 metastatic relapses
1 locoregional relapse

1 metastatic relapse
3 locoregional relapses

FIG 3

HPV ctDNA copies/ml

0
10
100
1000
10000
100000

Baseline
After CRT
• CRT standard of care
• Compliance is essential for optimal outcomes
• Early and late toxicities induced by CRT substantial
• 10–20% of patients are not sensitive to CRT or relapse early after treatment.
• Once relapsed, only 30-40% of patients can be salvaged by abdominoperineal resection
• Carboplatin-paclitaxel is standard of care in recurrent or metastatic disease
• If refractory immunotherapy ORR of 24% and 17%, respectively.
Pre-register

High Risk Anal Cancer

5FU/Capecitabine+ Mitomycin or 5FU+CDDP and concurrent RT

Observation

Nivolumab q4 weeks x 6

Study PI's: L. Rajdev
Co-PI's: C. Eng and A. Benson
SWOG PI: V. Morris

Stratification Factors: Nodal status, HIV, RT dose

Primary endpoint: 2-yr DFS (Goal of 62.5% vs. 45%)
Secondary endpoints: CFS, OS, Toxicity

Started April 2018 - Estimated enrolment - 200 by 2020 (Enrolled 105 to date)
The future

• Need better CRT strategies for more advanced tumours
• Immune stratification for prognosis and prediction of response
• Immunotherapy strategies (checkpoint inhibition, vaccines, taxanes)
• Liquid biopsy to assess/readout HPVdna and CTCs and immune responses
• Long term follow up and proactive measures for immune competence
• Long term follow up and proactive measures for survivorship
Thank you
MDACC Genentech Rare Cancers Alliance: Phase II Study of Atezolizumab/Bevacizumab in Metastatic SCCA

Patients with metastatic squamous cell carcinoma of the anal canal
- Treated with at least one prior therapy for metastatic disease
- No prior immune therapies received as part of cancer treatment

20 patients treated initially with Atezo 1200 mg IV and bev 15 mg/kg q 3 weeks

Primary endpoint: RR

Patients will be followed for best response using RECIST criteria 1.1

- Clopper and Pearson Method phase II study
  - $H_0: p \leq 0.05$ and an alternative hypothesis $H_a: p \geq 0.30$,
  - $\alpha = 0.10$ and $\beta = 0.10$
(CoRInTH)

- TITLE: Phase 1b/II trial of Checkpoint Inhibitor (Pembrolizumab an anti PD-1 antibody) plus standard IMRT in HPV induced stage III/IV carcinoma of anus

- Due to start in UK in April 2019
Research

• In addition to non-coding RNAs (IncRNAs) and microRNAs (miRNAs), circular RNAs (circRNAs) are endogenous RNAs with various functions, which have recently become a research hotspot.

• CircRNAs are a kind of closed circular RNA molecule widely existing in transcriptomes. Due to lack of free ends, they are not easily cleaved by RNase R, thus avoiding degradation.