Neoplasie uroteliali
Posters & oral presentations

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OUTLINE

❖ Role of chemo-radiotherapy in bladder cancer

- Oral abstract #280: long terms outcomes of BC2001 (CRUK/01/004):
  A phase III trial of chemo-radiotherapy versus radiotherapy and standard RT versus reduced high-dose volume RT in muscle invasive bladder cancer

- Abstract #343: The impact of MRE11 in nuclear to cytoplasmic ratio on outcomes in muscle invasive bladder cancer an analysis of NRG/RTOG 8802, 8903, 9506, 9706, 9906, and 0233

- Abstract #292: Quality of life (QL) of patients (pts) treated for muscle invasive bladder cancer (MIBC) with radiotherapy (RT) +/- chemotherapy (CT) in the BC2001 trial (CRUK/01/004): Analysis of impact of treatment at an individual level

- Abstract #298: Outcome of BC2001 patients (CRUK/01/004) who received neoadjuvant chemotherapy prior to randomization to chemo-radiotherapy (cRT) versus radiotherapy (RT)

❖ Combining targeted therapy with immunocheckpoint inhibitors

- Abstract #293: A phase I study of cabozantinib plus nivolumab (CaboNivo) and ipilimumab (CaboNivoIpi) in patients (pts) with refractory metastatic urothelial carcinoma (mUC) and other genitourinary (GU) tumors
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BC2001 Trial design

Eligible patients had histologically confirmed T2-T4a N0 M0 MIBC, WHO performance status 0 to 2; GFR > 25ml/min. For radiotherapy (RT) comparison: single tumour at time of invasive disease diagnosis.
BC2001 Methods

Treatment
- Platinum based neoadjuvant CT permitted – see abstract 298 / poster E11
- 3D conformal RT (55Gy/20 fractions/4 weeks or 64Gy/32 fractions/6.5 weeks)
- Reduced high dose volume RT: 80% RT dose to uninvolved bladder
- Chemotherapy: intravesical MMC (12mg/m2) d1 of RT and 5-FU as a continuous infusion at 500mg/m2/24 hours for 5 days corresponding to RT fractions 1-5 and 16-20

Key assessments
- Follow up for disease control and late toxicity (RTOG & LENT/SOM scales) at 6, 9 & 12 months after randomization and annually thereafter
- QoL: Functional Assessment of Cancer Therapy-Bladder (FACT-BL) questionnaires at baseline, end of treatment (EoT), 6, 12, 24, 36, 48 & 60 months (m) post RT – see abstract 292 / poster E5
### Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>% patients (N=458)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years) at randomisation</strong> Median (IQR)</td>
<td>72.9 (65.5, 77.6)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
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<tr>
<td>Male</td>
<td>80.8%</td>
</tr>
<tr>
<td>Female</td>
<td>19.2%</td>
</tr>
<tr>
<td><strong>Pathological stage</strong></td>
<td></td>
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<tr>
<td>T1</td>
<td>0.2%</td>
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<tr>
<td>T2</td>
<td>83.3%</td>
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<tr>
<td>T3a</td>
<td>6.6%</td>
</tr>
<tr>
<td>T3b</td>
<td>6.6%</td>
</tr>
<tr>
<td>T4a</td>
<td>3.3%</td>
</tr>
<tr>
<td><strong>Residual mass post resection</strong></td>
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</tr>
<tr>
<td>Yes</td>
<td>29.2%</td>
</tr>
<tr>
<td>No</td>
<td>70.8%</td>
</tr>
<tr>
<td><strong>Neoadjuvant chemotherapy planned</strong></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>29.7%</td>
</tr>
<tr>
<td>No</td>
<td>70.3%</td>
</tr>
<tr>
<td><strong>Planned radiotherapy schedule</strong></td>
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</tr>
<tr>
<td>55Gy/20F</td>
<td>38.8%</td>
</tr>
<tr>
<td>64Gy/32F</td>
<td>61.2%</td>
</tr>
</tbody>
</table>
Updated results - CT comparison

Loco-Regional Control (LRC)

- HR (95% CI) = 0.61 (0.43-0.86), p1=0.004
- Adj. HR (95% CI) = 0.59 (0.41-0.83), p2=0.003

Invasive Loco-Regional Control (ILRC)

- HR (95% CI) = 0.55 (0.36-0.84), p1=0.006
- Adj. HR (95% CI) = 0.52 (0.33-0.81), p2=0.004

Snapshot of data: July 2016, N=360, median FUP 117.1 m

Presented By Emma Hall at 2017 Genitourinary Cancers Symposium
Borderline significant improvement in metastasis free survival
Conclusions:

- Data continues to support the use of chemoradiotherapy (robust improvement in bladder cancer specific survival)

- 5Fu/MMC is a standard of care

Snapshot of data: July 2016, N=360, median FUP 117.1 m
Updated results - CT comparison

**Salvage Cystectomy Rate**

HR (95% CI) = 0.54 (0.31-0.95), p1 = 0.03

<table>
<thead>
<tr>
<th>N at risk (events)</th>
<th>Months since randomization</th>
</tr>
</thead>
<tbody>
<tr>
<td>cRT 182 (15)</td>
<td>24 98 (3) 79 (1) 51 (0)</td>
</tr>
<tr>
<td>RT 178 (25)</td>
<td>24 95 (3) 64 (4) 49 (1)</td>
</tr>
</tbody>
</table>

**Reason for salvage cystectomy**

<table>
<thead>
<tr>
<th>Reason for salvage cystectomy</th>
<th>cRT+RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>53</td>
</tr>
<tr>
<td>Recurrence</td>
<td>43</td>
</tr>
<tr>
<td>Late RT toxicity</td>
<td>5</td>
</tr>
<tr>
<td>Other / unknown</td>
<td>5</td>
</tr>
</tbody>
</table>

Snapshot of data: July 2016, N=360, median FUP 117.1 m

Presented By Emma Hall at 2017 Genitourinary Cancers Symposium
Radiotherapy volume:

- No significant difference in long-term toxicity depending on radiotherapy field size

- No difference in loco-regional control based on radiotherapy field size
But...the conclusions of the discussant are different:

- Data continues to support the use of chemoradiotherapy as an option for these pts

- 5FU/MMC is a standard of care regardless of cisplatin eligibility

- Cannot draw conclusions on dose volume

- Other options for chemosensitization:
  → cisplatin eligible: 5FU and cisplatin or cisplatin single agent
  → cisplatin ineligible: low-dose gemcitabine (lower level evidence)
We need to...

- Predictive biomarkers for chemo-RT in bladder cancer
- Novel approaches—moving beyond chemotherapy (integration of immunotherapy with radiation therapy)
Predictive biomarkers for chemo-RT response

- Radiotherapy mechanism of action is via DNA damage
  - Direct ionization of DNA leading to double strand breaks
  - Indirect by ionization of water molecules producing free radicals which then damage DNA
- DNA repair mechanisms could be important as predictive biomarkers
MRE11 and radiation response

- MRE11 is part of the MRN complex with RAD50 and NBS1
  - Detects DNA breaks
  - Involved in homologous recombination, non-homologous end-joining, and telomere maintenance
- MRE11 expression is regulated at the post-transcriptional level
- High MRE11 (rather than deficiency) associated with better outcomes
The impact of MRE11 in nuclear to cytoplasmic ratio on outcomes in muscle invasive bladder cancer an analysis of NRG/RTOG 8802, 8903, 9506, 9706, 9906, and 0233 – Abstract 343

NRG: MRE11 validation

- NRG/RTOG 8802, 8903, 9506, 9706, 9906, and 0233 (N=465 but 135 available for analysis)
- Archival tissue via TMA or unstained slides evaluated by AQUA analysis
- MRE11 divided into quartile cut points looking at N/C ratio
- Endpoint was disease-specific mortality
MRE11 lowest quartile associated with higher DSM

- HR = 2, 95% CI: 1.1, 3.8, p = 0.033
- 4-year DSM was 41% for pts with MRE11 lowest quartile vs. 21% for pts with MRE11 N/C > 1.49.
- MRE11 was not associated with OS or bladder intact survival

Conclusions abstract 343:
This adds further evidence of MRE11 as a potential RT response biomarker for selection of pts most likely to respond to bladder-sparing CRT

Presented By Jonathan Rosenberg at 2017 Genitourinary Cancers Symposium
Quality of life (QL) of patients (pts) treated for muscle invasive bladder cancer (MIBC) with radiotherapy (RT) +/- chemotherapy (CT) in the BC2001 trial (CRUK/01/004): Analysis of impact of treatment at an individual level – Abstract 292

**BC2001 quality of life substudy**

**Assessments:**
- Pts were asked to complete Functional Assessment of Cancer Therapy-Bladder (FACT-BL) questionnaires at baseline (bl), end of treatment (EoT), 6, 12 months (m) & 2, 3, 4 & 5 years post RT.
- FACT-BL includes 39 questions on 5 point Likert scale:
  - High scores represent better QoL
  - Five domains: Physical well-being (PWB), Social/family well-being (SWB), Emotional well-being (EWB), Functional well-being (FWB), Additional concerns (BLCS)
  - FACT-BL total score (TOTAL) = sum of all scores
  - Trial Outcome Index (TOI) = sum PWB, FWB & BLCS

**Endpoints**
- **Primary:** Change from baseline in BLCS - primary timepoint of interest: 12m
- **Secondary included:** Change from baseline in TOTAL FACT-BL and TOI
- **Exploratory:** Clinically relevant difference in BLCS, TOI and TOTAL

**Statistical considerations**
- Analysis conducted on intention to treat population for 1) **all patients** (N=458), 2) **CT comparison** (n=360) & 3) **RT comparison** (n=219).
- 5% significance was used at 1 year for BLCS, 1% was used for all other timepoints & endpoints (in view of multiple testing).
Conclusions:

- Following (chemio)RT a significant proportion of pts experience a decline in QoL at EoT but after 12m overall QL is similar to that at baseline.
- The addition of chemotherapy or modification of RT technique in this study had no significant impact on patient reported QoL.
Outcome of BC2001 patients (CRUK/01/004) who received neoadjuvant chemotherapy prior to randomization to chemo-radiotherapy (cRT) versus radiotherapy (RT) - Abstract 298

117 pts received neoadjuvant chemotherapy: 56 in the cRT group and 61 in the RT group

- Neoadjuvant treatment was: Gemcitabine plus cisplatin (69.2%) or plus carboplatin (4.3%), methotrexate/vinblastine/doxorubicin/cisplatin (MVAC, 13.6%), cisplatin/methotrexate/vinblastine (CMV 11.1%) or other (<2%).
- RT schedule: 59 patients (50.9%) received the 55Gy/20F and 15 patients (12.8%) received RHDVRT within the RT comparison of the trial.
- 92.3% cRT and 91.8% RT pts completed radiotherapy as planned.

Efficacy: cRT resulted in better loco-regional control in this group of patients, though the difference was not statistically significant.

Conclusions- 1:

The benefit in improved LRC of synchronous chemotherapy with 5FU/MMC was also found in the subgroup of BC2001 pts receiving neoadjuvant chemotherapy, with no significance increase in late toxicity.
Conclusions -2:

- No differences in OS or MFS between randomised groups were found. Median OS was 47 months and median MFS 68.5 months.

- Neoadjuvant chemotherapy did not compromise the delivery of radical curative treatment with RT or cRT.

- Median MFS was: cRT 118.5 vs RT 54.2 months.
- 5-year MFS rates were: cRT 54% vs RT 48%.
- No statistically significant differences in MFS were found.

- Median OS was: cRT 50.4 vs RT 46.7 months.
- 5-year OS rates were: cRT 48% vs RT 46%.
- No statistically significant differences in OS were found.

- No differences found in OS or MFS between different neoadjuvant regimes.

- Grade 3 or above adverse events during treatment occurred in 26.7% GC patients vs 29.0% non-GC patients. During follow-up, these occurred in 11.3% GC patients vs 4.8% non-GC (RTOG).
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A phase I study of cabozantinib plus nivolumab (CaboNivo) and ipilimumab (CaboNivoIpi) in patients (pts) with refractory metastatic urothelial carcinoma (mUC) and other genitourinary (GU) tumors – Abstract 293

Results:
48 pts enrolled
30 pts treated with CaboNivo combination
18 pts treated with CaboNivoIpi combination
Results:

ORR = 30%,
CabNivo = 38% (bladder 44%),
CaboNivoIpi 18% (bladder 29%)

Table 3: Summary of best response by tumor type and dose level

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Total N</th>
<th>Stable Disease % (N)</th>
<th>Partial Response % (N)</th>
<th>Complete Response % (N)</th>
<th>ORR % (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urothelial carcinoma</td>
<td>43</td>
<td>56 (24)</td>
<td>23 (10)</td>
<td>7 (3)</td>
<td>38 (13)</td>
</tr>
<tr>
<td>Urachal adenocarcinoma</td>
<td>16</td>
<td>56 (9)</td>
<td>25 (4)</td>
<td>6 (2)</td>
<td>38 (6)</td>
</tr>
<tr>
<td>Squamous cell carcinoma of the bladder</td>
<td>4</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>20 (1)</td>
</tr>
<tr>
<td>Castration-resistant prostate cancer</td>
<td>2</td>
<td>0</td>
<td>50 (1)</td>
<td>50 (1)</td>
<td>100 (2)</td>
</tr>
<tr>
<td>Renal cell carcinoma—sarcomatoid</td>
<td>9</td>
<td>66 (6)</td>
<td>11 (1)</td>
<td>0</td>
<td>11 (1)</td>
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<tr>
<td>Trophoblastic</td>
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<td>50 (1)</td>
<td>50 (1)</td>
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<td>50 (1)</td>
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<tr>
<td>Germ cell tumor</td>
<td>1</td>
<td>100 (1)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Soft tissue</td>
<td>1</td>
<td>100 (1)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Penile cancer</td>
<td>4</td>
<td>50 (2)</td>
<td>50 (2)</td>
<td>0</td>
<td>50 (2)</td>
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<tr>
<td>Combination</td>
<td>43</td>
<td>56 (24)</td>
<td>23 (10)</td>
<td>7 (3)</td>
<td>30 (13)</td>
</tr>
<tr>
<td>CaboNivo</td>
<td>26</td>
<td>46 (12)</td>
<td>31 (8)</td>
<td>8 (2)</td>
<td>38 (10)</td>
</tr>
<tr>
<td>CaboNivolpi</td>
<td>17</td>
<td>70 (12)</td>
<td>12 (2)</td>
<td>6 (1)</td>
<td>18 (3)</td>
</tr>
</tbody>
</table>

*Solid tumor in lung became cavitary (no solid component), but outline became larger; categorized as stable disease.
CRPC: castration-resistant prostate cancer; GCT: germ cell tumor; ORR: overall response rate; SCC: squamous cell carcinoma; urachal: urachal adenocarcinoma.
Conclusions:

- Both combinations are safe and well tolerated
- The recommended phase II dose for CaboNivo= cabo 40 mg + nivo 3 mg/kg
- The recommended phase II dose for CaboNivoIpi = cabo 40 mg + nivo 3 mg/kg + ipi 1 mg/kg
- The combination is active in GU tumors in particular urothelial carcinoma
- Rare tumors such as squamous cell carcinoma of the bladder, urachal adenocarcinoma and penile carcinoma demonstrated response to the combination
In conclusion:

1) Despite encouraging data of combined chemo-RT for treatment of bladder cancer...
   Today integrated treatment for bladder-sparing is reserved only for pts
   - who refuse radical cystectomy
   - unfit for comorbidities and age
   - who have unresectable disease

2) The efficacy of immunocheckpoint inhibitors in urothelial tumors is considerable, but we already expect data of combination with other treatments