**Outcomes in patients with muscle-invasive bladder cancer treated with neoadjuvant chemotherapy followed by (chemo) radiotherapy in the BC2001 trial**

**Supplementary material**

Table S1. Baseline characteristics for the main BC2001 trial population (n=360, chemotherapy randomisation), neoadjuvant and non-neoadjuvant cohorts

|  |  | **Total** | **Neoadjuvant received** | **No neoadjuvant received** | **p-value(1)** |
| --- | --- | --- | --- | --- | --- |
|  |  | **360 (100.0%)** | **117 (100.0%)** | **243 (100.0%)** |
| Sex  | Male | 289 (80.3%) | 100 (85.5%) | 189 (77.8%) | 0.086 |
|   | Female | 71 (19.7%) | 17 (14.5%) | 54 (22.2%) |   |
| Age (years) | N | 360 | 117 | 243 | <0.001 |
|   | Median (Q1-Q3) | 71.9 (64.1-76.2) | 65.7 (60.5-72.7) | 73.6 (67.9-77.6) |   |
|   | Min-Max | 40.2-88.6 | 50.5-83.9 | 40.2-88.6 |   |
| WHO Performance Status | 0 | 232 (64.4%) | 85 (72.6%) | 147 (60.5%) | 0.040\* |
| 1 | 117 (32.5%) | 31 (26.5%) | 86 (35.4%) |   |
|   | 2 | 11 (3.1%) | 1 (0.9%) | 10 (4.1%) |   |
| Pathological stage - primary tumour | 1§ | 1 (0.3%) | 0 (0.0%) | 1 (0.4%) | 0.339\* |
| 2 | 297 (82.5%) | 95 (81.2%) | 202 (83.1%) |   |
|   | 3a | 25 (6.9%) | 6 (5.1%) | 19 (7.8%) |   |
|   | 3b | 22 (6.1%) | 11 (9.4%) | 11 (4.5%) |   |
|   | 4a | 14 (3.9%) | 5 (4.3%) | 9 (3.7%) |   |
|   | Unknown | 1 (0.3%) | 0 (0.0%) | 1 (0.4%) |   |
| Grade primary tumour | 1 | 1 (0.3%) | 0 (0.0%) | 1 (0.4%) | 0.999\* |
|   | 2 | 46 (12.8%) | 15 (12.8%) | 31 (12.8%) |   |
|   | 3 | 309 (85.8%) | 102 (87.2%) | 207 (85.2%) |   |
|   | Unknown | 4 (1.1%) | 0 (0.0%) | 4 (1.6%) |   |
| TSCC |  Yes | 352 (97.8%) | 114 (97.4%) | 238 (97.9%) | 0.687\* |
| Multiple tumours | Yes | 70 (19.4%) | 22 (18.8%) | 48 (19.8%) | 0.803 |
|   | No | 288 (80.0%) | 95 (81.2%) | 193 (79.4%) |   |
|   | Unknown | 2 (0.6%) | 0 (0.0%) | 2 (0.8%) |   |
| Extent of tumour resection  | Not resected/Biopsy | 40 (11.1%) | 16 (13.7%) | 24 (9.9%) | 0.620\* |
| Complete Resection | 199 (55.3%) | 64 (54.7%) | 135 (55.6%) |   |
|   | Incomplete Resection | 115 (31.9%) | 36 (30.8%) | 79 (32.5%) |   |
|   | Resected (extent unknown) | 2 (0.6%) | 1 (0.9%) | 1 (0.4%) |   |
|   | Unknown | 4 (1.1%) | 0 (0.0%) | 4 (1.6%) |   |
| Tumour size group | <30mm | 73 (20.3%) | 26 (22.2%) | 47 (19.3%) | 0.738 |
|   | >30mm | 157 (43.6%) | 48 (41.0%) | 109 (44.9%) |   |
|   | Unknown | 130 (36.1%) | 43 (36.8%) | 87 (35.8%) |   |
| Residual mass post resection | Yes | 99 (27.5%) | 28 (23.9%) | 71 (29.2%) | 0.327 |
| No | 240 (66.7%) | 81 (69.2%) | 159 (65.4%) |   |
|   | Unknown | 21 (5.8%) | 8 (6.8%) | 13 (5.3%) |   |
| Chemotherapy randomisation | Chemoradiotherapy  | 182 (50.6%) | 56 (47.9%) | 126 (51.9%) | 0.478 |
| No Chemotherapy | 178 (49.4%) | 61 (52.1%) | 117 (48.1%) |   |
| Radiotherapy randomisation | stRT | 63 (17.5%) | 18 (15.4%) | 45 (18.5%) | 0.306 |
| RHDVRT | 58 (16.1%) | 15 (12.8%) | 43 (17.7%) |   |
|   | Elective stRT | 239 (66.4%) | 84 (71.8%) | 155 (63.8%) |   |
| Radiotherapy schedule | 55Gy/20F | 142 (39.4%) | 59 (50.4%) | 83 (34.2%) | 0.003 |
| 64Gy/32F | 217 (60.3%) | 58 (49.6%) | 159 (65.4%) |   |
|   | Unknown | 1 (0.3%) | 0 (0.0%) | 1 (0.4%) |   |

§ This tumour was deemed to be pathological stage T1, but radiologic staging confirmed the tumour as T3. Therefore, the patient was not considered to be ineligible for the trial
Q1: Lower quartile, 25% percentile, Q3: Upper quartile, 75% percentile
(1) P-value: for categorical variables, Chi-square test or Fisher test (\*) as appropriate, excludes missing category; for continuous variables, non-parametric Kruskall Wallis rank test
TSCC: Transitional cell carcinoma; stRT: standard whole bladder radiotherapy; RHDVRT: reduced high dose volume radiotherapy; Gy: gray, F: fractions

Table S2. Toxicity outcomes for chemoradiation vs radiotherapy alone, in the neoadjuvant cohort and main trial population (chemotherapy randomisation)

|  |  |  |
| --- | --- | --- |
|  **Worst Grade 3+** | **Neoadjuvant cohort (N=117)** | **Overall (N=360)\*** |
| **n/N** | **%** | **n/N** | **%** |
| **Acute toxicity (NCI-CTC)\*** |  |  |  |  |  |
| On treatment (overall) | cRT | 18/54 | 33.3% | 64/178 | 36.0% |
|   | RT alone | 14/63 | 22.2% | 50/182 | 27.5% |
| Genito-urinary | cRT | 8/54 | 14.2% | 38/178 | 21.3% |
|   | RT alone | 8/63 | 13.6% | 39/182 | 21.4% |
| Gastro-intestinal | cRT | 4/54 | 6.2% | 17/178 | 9.6% |
|   | RT alone | 3/63 | 5.1% | 5/182 | 2.7% |
| **Late toxicity (RTOG)** |  |  |  |  |  |
| At 1 year | cRT | 1/30 | 3.3% | 3/92 | 4.6% |
|   | RT alone | 0/30 | 0.0% | 1/78 | 1.3% |
| At 2 years | cRT | 1/19 | 5.3% | 3/65 | 4.6% |
|   | RT alone | 0/21 | 0.0% | 3/58 | 5.2% |
| Up to 5 years | cRT | 5/35 | 14.3% | 10/120 | 8.3% |
|   | RT alone | 2/39 | 5.1% | 17/108 | 15.7% |
| **Late toxicity (LENT/SOM)** |  |  |  |  |  |
| At 1 year | cRT | 9/27 | 33.3% | 29/77 | 37.7% |
|   | RT alone | 10/28 | 35.7% | 22/75 | 29.3% |
| At 2 years | cRT | 5/17 | 29.4% | 21/61 | 34.4% |
|   | RT alone | 6/19 | 31.6% | 19/53 | 35.8% |
| Up to 5 years | cRT | 21/35 | 60.0% | 63/117 | 53.8% |
|   | RT alone | 18/37 | 48.6% | 51/100 | 51.0% |

N: total patients returning toxicity forms; n=number of patients experiencing grade 3+ toxicity; cRT: chemoradiotherapy; RT: radiotherapy.
\*As reported in James at al (2012) NEJM 366;16

Table S3. Efficacy outcomes for chemoradiation vs radiotherapy alone, in the neoadjuvant cohort and main trial population (chemotherapy randomisation)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Endpoint** | **Treatment group** | **Type of event** | **Neoadjuvant cohort (N=117)** | **Overall (N=360)\*** |
| **N** | **5yr event-free rate %** | **95% CI** | **N** | **5yr event-free rate %** | **95% CI** |
| **Loco-Regional Control (LRC)** | cRT | Any LRC event | 18 | 62% | 49-77 | 55 | 63% | 54-71 |
|  | *Bladder non-muscle invasive* | *12* |  |  | *26* |  |  |
|  | *Bladder muscle invasive* | *4* |  |  | *20* |  |  |
|  | *Pelvis* | *2* |  |  | *9* |  |  |
|   | Censored | 38 |   |   | 127 |   |   |
| RT alone | Any LRC event | 31 | 46% | 32-59 | 84 | 49% | 41-57 |
|  | *Bladder non-muscle invasive* | *20* |  |  | *34* |  |  |
|  | *Bladder muscle invasive* | *6* |  |  | *37* |  |  |
|  | *Pelvis* | *5* |  |  | *13* |  |  |
|   | Censored | 30 |   |   | 94 |   |   |
| **Invasive Loco-Regional Control (ILRC)** | cRT | Any ILRC event | 8 | 86% | 72-94 | 33 | 79% | 72-85 |
|  | *Bladder muscle invasive* | *5* |  |  | *23* |  |  |
|  | *Pelvis* | *3* |  |  | *10* |  |  |
|   | Censored | 48 |   |   | 149 |   |   |
| RT alone | Any ILRC event | 14 | 74% | 59-84 | 58 | 64% | 55-71 |
|  | *Bladder muscle invasive* | *8* |  |  | *44* |  |  |
|  | *Pelvis* | *6* |  |  | *14* |  |  |
|  | Censored | 47 |  |  | *120* |  |  |
| **Metastasis-Free Survival (MFS)** | cRT | Any MFS event | 26 | 54% | 40-67 | 80 | 58% | 50-65 |
|  | *Distant recurrence* | *22* |  |  | *56* |  |  |
|  | *Bladder cancer death* | *4* |  |  | *24* |  |  |
|   | Censored | 30 |   |   | 102 |   |   |
| RT alone | Any MFS event | 32 | 48% | 35-61 | 98 | 43% | 35-51 |
|  | *Distant recurrence* | *21* |  |  | *59* |  |  |
|  | *Bladder cancer death* | *11* |  |  | *39* |  |  |
|   | Censored | 29 |   |   | 80 |   |   |
| **Overall Survival** | cRT | Death | 37 | 48% | 34-61 | 123 | 49% | 41-56 |
|  | Censored | 19 |  |   | 59 |  |   |
| RT alone | Death | 39 | 46% | 33-58 | 127 | 37% | 30-44 |
|   | Censored | 22 |   |   | 51 |   |   |
| **Salvage cystectomy rate** | cRT | Cystectomy | 11 | 21% | (11-37) | 20 | 14% | 9-21 |
|  | No cystectomy | 45 |  |  | 162 |  |  |
| RT alone | Cystectomy | 16 | 29% | (19-45) | 33 | 22% | 16-31 |
|  | No cystectomy | 45 |  |  | 145 |  |  |

N=number of patients experiencing an event at any time during trial follow-up (can be beyond 5 years); 95%CI: 95% confidence interval; cRT: chemoradiotherapy; RT: radiotherapy.

\*Updated current snapshot, as reported in Hall et al. Journal of Clinical Oncology. 2017;35(6\_suppl):280-280

Table S4. Quality of life outcomes (FACT-BL) for chemoradiation vs radiotherapy alone, in the neoadjuvant cohort and main trial population (chemotherapy randomisation)

|  |  |  |
| --- | --- | --- |
| **Baseline scores** | **Neoadjuvant subgroup (N=117)** | **Overall (N=360)\*** |
| **FACT-BL** | **Treatment** | **N** | **p50** | **p25** | **p75** | **N** | **p50** | **p25** | **p75** |
| BLCS | cRT | 53 | 33.6 | 30.0 | 39.6 | 169 | 33.6 | 30.0 | 38.4 |
|   | RT alone | 58 | 36.0 | 32.4 | 40.0 | 160 | 34.7 | 28.8 | 39.0 |
| TOI | cRT | 53 | 78.0 | 72.0 | 87.8 | 167 | 79.6 | 71.0 | 88.0 |
|   | RT alone | 58 | 82.1 | 68.6 | 89.0 | 160 | 81.2 | 68.7 | 88.0 |
| TOTAL | cRT | 53 | 124.7 | 111.8 | 134.8 | 168 | 123.8 | 108.0 | 134.0 |
|   | RT alone | 58 | 126.2 | 113.5 | 135.0 | 160 | 125.4 | 110.8 | 133.0 |
| **Change at 1 year** | **Neoadjuvant subgroup (N=117)** | **Overall (N=360)\*** |
| **Change from baseline at 1 yr** | **Difference cRT-RT§** | **Change from baseline at 1 yr** | **Difference cRT-RT§** |
| **FACT-BL** | **Treatment** | **N** | **Mean** | **99% CI** | **Mean†** | **99% CI** | **N** | **Mean** | **99% CI** | **Mean†** | **99% CI** |
| BLCS | cRT | 29 | -0.71 | (-4.40, 2.97) | -0.35 | (-4.41, 3.71) | 89 | -0.59 | (-2.42, 1.24) | 0.18 | (-1.60, 1.96) |
|  | RT alone | 31 | -0.16 | (-3.30, 2.99) |  |   | 88 | -0.42 | (-2.27, 1.44) |  |   |
| TOI | cRT | 29 | 1.11 | (-7.19, 9.41) | -4.73 | (-13.31, 3.85) | 88 | -0.5 | (-4.45, 3.45) | -1.07 | (-6.21, 4.07) |
|  | RT alone | 30 | 5.99 | (0.64, 11.33) |  |   | 86 | 0.94 | (-3.08, 4.96) |  |   |
| TOTAL | cRT | 29 | 1.16 | (-10.65, 12.98) | -6.27 | (-18.03, 5.50) | 89 | 0.67 | (-4.56, 5.89) | -1.79 | (-8.3, 4.72) |
|   | RT alone | 30 | 7.58 | (0.78, 14.38) |   |   | 86 | 2.67 | (-2.46, 7.80) |   |   |

§ Mean difference between groups, computed by ANCOVA and adjusted by alternate randomisation, radiotherapy fractionation schedule, and baseline score.

† Positive differences favour cRT group.

ANCOVA = analysis of variance; BLCS = bladder cancer subscale; CI = confidence interval; cRT = radiotherapy with chemotherapy; RT = radiotherapy without chemotherapy; TOI = Trial Outcome Index; TOTAL = FACT-BL total score.

\*As reported in Huddart et al Eur Urol. 2020;77(2):260-268