**Supplementary Data**

**Legends**

**Supplementary Table S1.** - Overview of previously reported associations and the current replication results for SNPs validated against recurrence risk in the overall NMIBC patient group of the NBCS.

**Supplementary Table S2.** - Overview of previously reported associations and the current replication results for SNPs validated against recurrence risk in TUR-only-treated NMIBC patients of the NBCS.

**Supplementary Table S3.** - Overview of previously reported associations and the current replication results for SNPs validated against recurrence risk in BCG-treated NMIBC patients of the NBCS.

**Supplementary Table S4.** - Overview of previously reported associations and the current replication results for SNPs validated against progression risk in the overall NMIBC patient group of the NBCS.

**Supplementary Table S5.** - Overview of previously reported associations and the current replication results for SNPs validated against progression risk in i.v. chemotherapy-treated NMIBC patients of the NBCS.

**Supplementary Table S6.** - Overview of previously reported associations and the current replication results for SNPs validated against overall survival in the MIBC patient group of the NBCS.

**Supplementary Table S7.** - Overview of previously reported SNP associations with outcome in (chemo-)radiotherapy-treated UBC.

**Supplementary Table S8.** - Overview of previously reported SNP associations with outcome in (platinum-based) systemic chemotherapy-treated UBC**.**

**Supplementary Table S9.** - Overview of current replication results for SNPs validated against progression risk in the overall NMIBC patient group of the NBCS using the original and alternative criterion for progression.

**Supplementary Table S1.** Overview of previously reported associations and the current replication results for SNPs validated against recurrence risk in the overall NMIBC patient group of the NBCS

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Original publication** | | | | | | **Replication in NBCS seriesa** | | | | | | | | |
| **Reference** | **Gene** | **SNP ID** | **N (n events)b** | **HR (95% CI), p** | **Val.** | **M/I** | **Info (NBCS1/ NBCS2)** | **A1c** | **A2** | **Genotype counts (A1A1/A1A2/A2A2)** | | **Additive model** | **Dominant model** | **Recessive model** |
| **Event** | **No event** | **HR (95% CI), p** | **HR (95% CI), p** | **HR (95% CI), p** |
| Andrew AS et al. BJU Int 2014 [1] | *ALDH2* | rs2238151 | 527 (279 R) NMIBC + MIBC | TC vs. TT:  1.08 (0.83-1.40), NP  CC vs. TT:  2.03 (1.41-2.91), NP;  Logrank P < 0.001 | N | I | 0.943/ 0.921 | T | C | 261/263/74 | 300/300/87 | 1.01 (0.90-1.14), 0.860 | 1.01 (0.86-1.20), 0.875 | 1.02 (0.79-1.31), 0.896 |
| *IGF1* | rs5742714 [G]: 9.9% | ? (? R)  (In total study: 476 NMIBC (? R)) | GC vs. GG:  1.61 (1.19-2.17), NP  CC vs. GG: NA;  Logrank P = 0.002 | N | I | 0.999/ 0.999 | C | G | 499/94/5 | 547/130/9 | 0.84 (0.69-1.02), 0.084 | 0.83 (0.67-1.03), 0.089 | 0.73 (0.30-1.78), 0.493 |
| Zhang K et al. Tumour Biol 2014 [2] | *NAMPT* | rs2505568d | 325 (95 R) NMIBC + MIBC | AT vs. TT:  0.30 (0.09-0.97), 0.03  AA vs. TT : NA | N | - | - | - | - | - | - | - | - | - |
| Lee EK et al. Cancer 2013 [3] | *RGS1* | rs1323291 | 421 (232 R) | DOM (AC/CC vs. AA):  1.60 (1.13-2.28), 0.0084 | IV | I | 0.939/ 0.941 | T | G | 481/111/6 | 545/127/14 | 0.95 (0.78-1.14), 0.553 | 0.98 (0.80-1.21), 0.873 | 0.52 (0.22-1.21), 0.128 |
| *RGS13* | rs3795617 | 421 (232 R) | ADD (AA vs. AG vs. GG):  0.79 (0.65-0.96), 0.0187 | IV | M | M | C | T | 136/318/144 | 204/335/147 | **1.13 (1.01-1.27), 0.033** | **1.26 (1.04-1.53), 0.016** | 1.10 (0.91-1.33), 0.308 |
| *RGS2* | rs16829458 | 421 (232 R) | DOM (AG/AA vs. GG):  0.63 (0.41-0.95), 0.0268 | IV | M | M | G | A | 500/94/4 | 589/96/1 | 1.07 (0.87-1.32), 0.512 | 1.05 (0.85-1.31), 0.640 | 1.89 (0.71-5.06), 0.204 |
| Ke HL et al. Carcinogenesis 2013 [4] | *DGRC8* | rs720012 | 421 (232 R) | REC (AA vs. AG/GG):  2.65 (1.38-5.08), 0.0034 | EV: F | I | 1/  1 | G | A | 472/120/6 | 524/145/17 | 1.15 (0.96-1.37), 0.122 | 0.89 (0.73-1.08), 0.241 | 0.50 (0.22-1.11), 0.087 |
| *DGRC8* | rs2073778 | 421 (232 R) | REC (TT vs. CT/CC):  2.63 (1.37-5.03), 0.0036 | EV: F | I | 1/  1 | C | T | 472/120/6 | 524/145/17 | 1.15 (0.96-1.37), 0.122 | 0.89 (0.73-1.08), 0.241 | 0.50 (0.22-1.11), 0.087 |
| Yang X et al. Int J Genomics 2013 [5] | *THBS1* | rs2169830 | 236 (78 R) NMIBC + MIBC | AG vs. AA:  1.68 (0.97-2.88), 0.062  GG vs. AA:  2.63 (1.43-4.83), 0.002  AG/GG vs. AA:  1.95 (1.20-3.19), 0.007  GG vs. AG/AA:  2.07 (1.23-3.49), 0.006 | N | I | 0.997/ 0.997 | T | C | 305/237/56 | 356/267/63 | 1.02 (0.90-1.15), 0.759 | 1.02 (0.87-1.20), 0.795 | 1.03 (0.79-1.36), 0.807 |
| Wang M et al. Cancer Res 2012 [6] | *MIR146A* | rs2910164 | 199 (74 R) | GC/CC vs GG:  0.58 (0.36-0.94), NP;  Logrank P = 0.016 | N | I | 0.998/ 0.990 | G | C | 335/224/39 | 397/248/41 | 1.04 (0.91-1.18), 0.577 | 1.05 (0.89-1.24), 0.541 | 1.03 (0.74-1.42), 0.870 |
| Wei H et al. PLoS One 2012 [7] | *NEIL2* | rs4639 | 399 (211 R) | REC (GG vs. AG/AA):  1.90 (1.39-2.59), 6x10-5 | N | I | 0.988/ 0.989 | A | G | 186/287/124 | 209/330/148 | 0.98 (0.87-1.10), 0.715 | 0.96 (0.81-1.15), 0.687 | 0.98 (0.80-1.20), 0.854 |
| *NEIL2* | rs804276 | 399 (211 R) | REC (GG vs. AG/AA):  1.89 (1.37-2.59), 9x10-5 | N | I | 0.986/ 0.974 | G | A | 199/282/117 | 217/325/144 | 0.96 (0.86-1.08), 0.495 | 0.95 (0.80-1.13), 0.545 | 0.95 (0.77-1.16), 0.607 |
| *NEIL2* | rs804256 | 399 (211 R) | REC (CC vs. CT/TT):  1.95 (1.34-2.84),5x10-4 | N | I | 0.975/ 0.978 | T | C | 244/271/83 | 264/323/98 | 0.97 (0.86-1.10), 0.645 | 0.95 (0.80-1.12), 0.537 | 0.99 (0.79-1.26), 0.966 |
| *NEIL2* | rs1874546 | 396 (208 R) | ADD (GG vs. CG vs. CC):  1.38 (1.12-1.70),2x10-3 | N | I | 0.986/ 0.988 | C | G | 380/192/26 | 441/214/30 | 1.02 (0.88-1.17), 0.828 | 1.01 (0.86-1.20), 0.887 | 1.06 (0.71-1.57), 0.780 |
| *NEIL2* | rs804267 | 399 (211 R) | REC (CC vs. CT/TT):  0.75 (0.46-1.22),3x10-3 | N | M | M | A | G | 288/246/64 | 313/295/78 | 0.95 (0.84-1.07), 0.392 | 0.92 (0.79-1.08), 0.324 | 0.97 (0.75-1.25), 0.793 |
| *TDG* | rs4135054 | 399 (211 R) | DOM (AG/AA vs. GG):  1.59 (1.15-2.20),5x10-3 | N | M | M | C | T | 480/112/6 | 532/143/11 | 0.89 (0.74-1.08), 0.240 | 0.90 (0.73-1.10), 0.282 | 0.73 (0.33-1.64), 0.447 |
| Wang M et al. Oncogene 2010 [8] | *XPF* | rs6498486 | 79 (38 R) | AC/CC vs. AA:  2.13 (1.04-4.40), NP;  Logrank P = 0.025 | N | I | 0.939/ 0.911 | A | C | 277/269/51 | 355/283/48 | 1.10 (0.97-1.25), 0.146 | 1.15 (0.97-1.36), 0.106 | 1.07 (0.79-1.45), 0.655 |
| Horikawa Y et al. Oncol Rep 2008 [9] | *TP53* | rs1042522 | 87 (49 R) Ta/T1 | Pro/Pro vs. Arg/Arg & Arg/Pro:  0.36 (0.14-0.93), 0.035 | N | I | 0.943/ 0.951 | C | G | 318/228/52 | 372/271/44 | 1.07 (0.94-1.22), 0.295 | 1.04 (0.89-1.23), 0.605 | 1.27 (0.94-1.70), 0.117 |
| Ahirwar D et al. Cancer Genet Cytogenet 2008 [10] | *IL6* | rs1800795 [C: 25.2%] | 113 (50 R) | GC vs. GG:  0.63 (0.27-1.44), 0.27  CC vs. GG:  0.41 (0.17-0.94), 0.03 | N | I | 0.991/ 0.984 | G | C | 244/259/95 | 245/348/93 | 0.95 (0.84-1.07), 0.396 | 0.86 (0.73-1.02), 0.082 | 1.09 (0.87-1.35), 0.467 |
| Mittal RD et al. Cancer Biol Ther 2008 [11] | *XRCC1* | rs25487 | 112 (55 R) | GA vs. GG:  1.13 (0.53-2.42), 0.74  AA vs. GG:  5.27 (1.00-27.65), 0.04 | N | I | 0.996/ 0.996 | C | T | 283/235/80 | 287/297/102 | 0.90 (0.81-1.02), 0.090 | 0.86 (0.73-1.01), 0.072 | 0.90 (0.71-1.14), 0.387 |
| Sanyal S et al. Acta Oncol 2007 [12] | *XRCC1* | rs25487 | 22 (? R) TaG2 treated with instillation therapy (BCG/ MMC) | GA/AA vs. GG:  0.4 (0.2-1.0), 0.05 | N | I | 0.996/ 0.996 | C | T | 283/235/80 | 287/297/102 | 0.90 (0.81-1.02), 0.090 | 0.86 (0.73-1.01), 0.072 | 0.90 (0.71-1.14), 0.387 |
| Lin J et al. Clin Genet 2006 [13] | *CDH1* | rs16260 | 274 (138 R) | CA/AA vs. CC:  0.68 (0.48-0.96), NP;  Logrank P = 0.04 | N | I | 0.966/ 0.966 | C | A | 302/245/51 | 322/289/75 | 0.91 (0.80-1.03), 0.119 | 0.91 (0.77-1.07), 0.236 | 0.80 (0.59-1.07), 0.137 |
| Gu J et al. Clin Cancer Res 2005 [14] | *ERCC6* | rs2228526 | 197 (120 R) | AG/GG vs. AA:  1.54 (1.02-2.33), NP | N | I | 1/  1 | T | C | 378/195/25 | 447/210/29 | 1.05 (0.91-1.21), 0.490 | 1.07 (0.91-1.27), 0.394 | 0.99 (0.66-1.47), 0.943 |
| Zhao H et al. Urology 2005 [15] | *GPX1* | rs1050450 | 200 (122 R) (in whites) | Pro/Leu & Leu/Leu vs. Pro/Pro:  0.63 (0.42-0.96), NP;  Logrank P = 0.036 | N | I | 0.968/ 0.981 | G | A | 297/256/45 | 343/280/63 | 0.96 (0.84-1.08), 0.483 | 0.98 (0.83-1.16), 0.828 | 0.82 (0.60-1.12), 0.222 |
| Kim EJ et al. Urology 2005 [16] | *OGG1* | rs1052133 | 93 (38 R) | Ser/Ser & Ser/Cys vs. Cys/Cys:  OR = 6.49 (1.25-33.33), 0.026 | N | I | 0.945/ 0.938 | C | G | 347/221/30 | 392/254/40 | 0.96 (0.83-1.10), 0.532 | 0.97 (0.82-1.14), 0.697 | 0.85 (0.58-1.25), 0.415 |

**Abbreviations:** SNP: single-nucleotide polymorphism; HR: hazard ratio; CI: confidence interval; M: measured (genotyped); I: imputed; NMIBC: non-muscle-invasive bladder cancer; MIBC: muscle-invasive bladder cancer; R: recurrence; BCG: bacillus Calmette-Guérin; MMC: mitomycin; Val.: validation; N: no validation; IV: internal validation; EV:F: external validation failed; NBCS: Nijmegen Bladder Cancer Study; OR: odds ratio; NP: not presented; DOM: dominant; REC: recessive; ADD: additive.

**a** N=1284 NMIBC patients (598 recurrence events; five-year Kaplan-Meier recurrence risk: 50.5 %).

**b** Patient numbercorresponds to the number of NMIBC patients included in the original study unless otherwise specified.

**c** A1: major/reference allele; A2: minor/predictive allele (both according to + strand orientation).

**d** This SNP is not measured or imputed in the NBCS.

**Supplementary Table S2.** Overview of previously reported associations and the current replication results for SNPs validated against recurrence risk in TUR-only-treated NMIBC patients of the NBCS

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Original publication** | | | | | | **Replication in NBCS seriesa** | | | | | | | | |
| **Reference** | **Gene** | **SNP ID** | **N (n events)** | **HR (95% CI), p** | **Val.** | **M/I** | **Info (NBCS1/ NBCS2)** | **A1b** | **A2** | **Genotype counts (A1A1/A1A2/A2A2)** | | **Additive model** | **Dominant model** | **Recessive model** |
| **Event** | **No event** | **HR (95% CI), p** | **HR (95% CI), p** | **HR (95% CI), p** |
| Ke HL et al. Carcinogenesis 2013 [4] | *DDX20* | rs197412 | 136 (91 R) TUR only | ADD (TT vs. CT vs. CC):  0.58 (0.40-0.82), 0.002  (pooled: 0.62 (0.48-0.81), 0.00077) | IV  EV: P | I | 0.999/ 0.998 | T | C | 74/122/47 | 75/111/34 | 1.10 (0.91-1.32), 0.323 | 1.08 (0.82-1.42), 0.592 | 1.20 (0.87-1.65), 0.256 |
| *DROSHA* | rs12186785 | 136 (91 R) TUR only | DOM (CT/CC vs. TT):  2.15 (1.25-3.68), 0.005 | IV  EV: F | I | 0.582/ 0.505 | T | C | 199/43/1 | 172/45/2 | 0.79 (0.53-1.18), 0.255 | 0.80 (0.52-1.22), 0.304 | 0.22 (0.01-4.59), 0.331 |
| Chen M et al. Cancer Prev Res (Phila) 2010 [17] | *GLI2* | rs11685068 | 141 (92 R) TUR only | DOM (AG/AA vs. GG):  2.19 (1.22-3.93), 0.01  (pooled: 2.07 (1.33-3.21), 1.3x10-3) | EV: P | I | 0.864/ 0.891 | C | T | 218/25/0 | 197/23/0 | 1.01 (0.64-1.58), 0.972 | 1.01 (0.64-1.59), 0.962 | NA |
| *SHH* | rs1233560 | 141 (92 R) TUR only | ADD (GG vs. AG vs. AA):  1.49 (1.07-2.07), 0.02  (pooled: 1.39 (1.14-1.70), 1.0x10-3) | EV: P | M | M | A | G | 56/125/62 | 65/114/41 | 1.18 (0.99-1.41), 0.071 | 1.26 (0.93-1.70), 0.130 | 1.23 (0.92-1.64), 0.157 |
| *GLI2* | rs7605011 | 141 (92 R) TUR only | DOM (AG/AA vs. GG):  2.03 (1.14-3.62), 0.02 | N | I | 0.776/ 0.810 | G | A | 212/31/0 | 193/27/0 | 1.06 (0.69-1.64), 0.780 | 1.08 (0.70-1.67), 0.739 | NA |
| *GLI3* | rs3801192 | 141 (92 R) TUR only | DOM (AG/AA vs. GG):  0.43 (0.21-0.88), 0.02 | N | I | 0.840/ 0.837 | C | T | 206/36/2 | 186/32/2 | 1.07 (0.75-1.53), 0.692 | 1.08 (0.74-1.58), 0.694 | 1.13 (0.21-6.22), 0.886 |
| *GLI3* | rs17172001 | 141 (92 R) TUR only | DOM (AG/AA vs. GG):  3.26 (1.48-7.19), 3x10-3 | EV: F | I | 0.841/ 0.819 | G | A | 221/20/2 | 206/14/0 | 1.13 (0.73-1.74), 0.589 | 1.08 (0.67-1.72), 0.761 | 2.94 (0.62-14.0), 0.176 |
| *GLI2* | rs10170242 | 141 (92 R) TUR only | ADD (GG vs. AG vs. AA):  1.58 (1.13-2.20), 0.01 | EV: F | M | M | A | G | 125/95/23 | 118/84/18 | 1.07 (0.89-1.30), 0.470 | 1.08 (0.84-1.39), 0.562 | 1.15 (0.75-1.77), 0.526 |
| *SMO* | rs2718107 | 141 (92 R) TUR only | ADD (CC vs. AC vs. AA):  0.71 (0.52-0.96), 0.03 | EV: F | M | M | A | C | 57/138/48 | 67/116/37 | 1.16 (0.97-1.40), 0.111 | 1.32 (0.98-1.77), 0.070 | 1.11 (0.81-1.53), 0.508 |
| *GLI2* | rs2310897 | 141 (92 R) TUR only | ADD (AA vs. AG vs. GG):  1.44 (1.01-2.06), 0.05 | EV: F | M | M | G | A | 180/56/7 | 148/65/7 | 0.79 (0.62-1.02), 0.070 | 0.75 (0.56-1.00), 0.052 | 0.84 (0.40-1.79), 0.654 |
| *SUFU* | rs11594179 | 141 (92 R) TUR only | DOM (AG/AA vs. GG):  1.57 (1.00-2.45), 0.05 | EV: F | M | M | C | T | 150/90/3 | 143/62/15 | 0.95 (0.76-1.18), 0.635 | 1.09 (0.84-1.42), 0.497 | **0.23 (0.07-0.72), 0.012** |
| Gangwar R et al. Mutat Res 2009 [18] | *OGG1* | rs1052133 | 66 (28 R) non-BCG treated | CG vs. CC:  0.89 (0.30-2.60), 0.83  GG vs. CC:  4.04 (1.33-12.1), 0.013 | N | I | 0.945/ 0.938 | C | G | 137/93/13 | 114/91/16 | 0.94 (0.76-1.17), 0.575 | 0.93 (0.71-1.20), 0.569 | 0.93 (0.51-1.69), 0.805 |
| Mittal RD et al. Cancer Biol Ther 2008 [11] | *XRCC1* | rs1799782 | 35 (19 R) non-BCG treated | CT vs. CC:  4.57 (1.10-18.97), 0.03  TT vs. CC: NA | N | I | 0.993/ 0.988 | G | A | 204/39/0 | 181/38/1 | 0.94 (0.67-1.31), 0.702 | 0.96 (0.68-1.35), 0.795 | NA |
| Leibovici D et al. J Clin Oncol 2005 [19] | *PPARG* | rs1801282 | 89 (60 R) non-BCG treated | CG/GG vs. CC:  0.41 (0.20-0.86), NP | N | I | 0.991/ 0.981 | C | G | 192/47/4 | 172/44/4 | 0.98 (0.74-1.29), 0.893 | 0.98 (0.72-1.34), 0.906 | 0.95 (0.35-2.57), 0.919 |

**Abbreviations:** SNP: single-nucleotide polymorphism; HR: hazard ratio; CI: confidence interval; M: measured (genotyped); I: imputed; NMIBC: non-muscle-invasive bladder cancer; R: recurrence; TUR: transurethral resection; BCG: bacillus Calmette-Guérin; Val.: validation; N: no validation; IV: internal validation; EV: F: external validation failed; EV: P: external validation passed; NBCS: Nijmegen Bladder Cancer Study; NP: not presented; NA: not assessed; DOM: dominant; ADD: additive.

**a** N=463 TUR-only treated patients (243 recurrence events; five-year Kaplan-Meier recurrence risk: 56.5 %).

**b** A1: major/reference allele; A2: minor/predictive allele (both according to + strand orientation).

**Supplementary Table S3.** Overview of previously reported associations and the current replication results for SNPs validated against recurrence risk in BCG-treated NMIBC

patients of the NBCS

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Original publication** | | | | | | **Replication in NBCS seriesa** | | | | | | | | |
| **Reference** | **Gene** | **SNP ID** | **N (n events)b** | **HR (95% CI), p** | **Val.** | **M/I** | **Info (NBCS1/ NBCS2)** | **A1c** | **A2** | **Genotype counts (A1A1/A1A2/A2A2)** | | **Additive model** | **Dominant model** | **Recessive model** |
| **Event** | **No event** | **HR (95% CI), p** | **HR (95% CI), p** | **HR (95% CI), p** |
| Lima L et al. BJU Int 2014 [20] | *ICAM1* | rs5498 | 204 (70 R) | GG vs. AA/AG:  1.76 (1.05-2.95), 0.032 | N | M | M | A | G | 28/37/8 | 39/57/23 | 0.83 (0.59-1.15), 0.256 | 0.89 (0.56-1.43), 0.632 | 0.57 (0.27-1.19), 0.137 |
| *IL2RA* | rs2104286 | 204 (70 R) | CT vs. TT :  2.01 (1.21-3.34), 0.007  CC vs. TT :  1.25 (0.48-3.26), 0.655 | N | I | 0.988/ 0.990 | T | C | 48/21/4 | 68/44/7 | 0.84 (0.56-1.26), 0.401 | 0.78 (0.48-1.28), 0.330 | 0.94 (0.33-2.68), 0.909 |
| *IL17A* | rs2275913 | 204 (70 R) | AA vs. GG/GA:  2.10 (1.12-3.93), 0.021 | N | M | M | G | A | 36/29/8 | 56/44/19 | 0.90 (0.65-1.25), 0.539 | 0.94 (0.59-1.49), 0.794 | 0.72 (0.35-1.50), 0.381 |
| *TNF* | rs1799964 | 204 (70 R) | CC vs. TT/TC:  2.43 (1.14-5.15), 0.021 | N | I | 0.998/ 0.998 | T | C | 43/24/6 | 78/32/9 | 1.19 (0.84-1.69), 0.333 | 1.28 (0.80-2.03), 0.308 | 1.20 (0.52-2.78), 0.662 |
| *CCR2* | rs391835 | 204 (70 R) | GA/AA vs. GG:  0.46 (0.23-0.89), 0.022 | N | I | 0.975/ 0.982 | G | A | 22/34/17 | 31/66/22 | 1.07 (0.76-1.51), 0.696 | 0.89 (0.54-1.48), 0.657 | 1.40 (0.81-2.44), 0.228 |
| *TNFRSF10A* | rs13278062 | 204 (70 R) | TG/GG vs. TT:  3.20 (1.37-7.43), 0.007 | N | I | 0.915/ 0.911 | T | G | 20/37/16 | 33/64/22 | 1.09 (0.76-1.55), 0.635 | 1.01 (0.59-1.74), 0.967 | 1.26 (0.70-2.27), 0.433 |
| *IL17RA* | rs4819554 | 204 (70 R) | GG vs. AA/AG:  2.89 (1.49-5.63), 0.002 | N | I | 0.985/ 0.991 | A | G | 47/26/0 | 78/36/5 | 0.89 (0.58-1.37), 0.596 | 0.99 (0.61-1.61), 0.983 | NA |
| *FASLG* | rs763110 | 204 (70 R) | CC vs. TT/TC:  1.70 (1.02-2.84), 0.042 | N | I | 0.931/ 0.905 | C | T | 27/36/10 | 46/58/15 | 1.06 (0.74-1.52), 0.757 | 1.07 (0.65-1.77), 0.795 | 1.10 (0.53-2.25), 0.803 |
| Andrew AS et al. BJU Int 2014 [1] | *VCAM1* | rs3176879d | ? ( ? R)  immuno-therapy  (In total study: 479 NMIBC (259 R)) | AG/GG vs. AA:  5.0 (1.89-13.17), NP | N | I | 0.388/ 0.406 | - | - | - | - | - | - | - |
| Lima L et al. Urol Oncol 2014 [21] | *FASLG* | rs763110 | 125 (48 R) | CC vs. TC/TT:  1.88 (1.04-3.40), 0.037 | N | I | 0.931/ 0.905 | C | T | 27/36/10 | 46/58/15 | 1.06 (0.74-1.52), 0.757 | 1.07 (0.65-1.77), 0.795 | 1.10 (0.53-2.25), 0.803 |
| Jaiswal PK et al. Gene 2013 [22] | *IL18* | rs187238  [C]: 28.8% | 78 (34 R) | GC vs. GG:  2.35 (1.09-5.10), 0.030  CC vs. GG:  2.43 (0.50-11.79), 0.269 | N | I | 0.999/ 0.998 | C | G | 35/28/10 | 65/48/6 | 1.38 (0.97-1.96), 0.073 | 1.25 (0.79-1.98), 0.340 | **2.35 (1.20-4.59), 0.013** |
| Srivastava P et al. Urol Oncol 2013 [23] | *MMP2* | rs243865 | 78 (34 R) | CT vs. CC:  4.32 (1.51-12.39), 0.006  TT vs. CC:  1.36 (0.32-5.76), 0.679  CT/TT vs. CC:  2.06 (1.01-4.18), 0.047 | N | I | 0.992/ 0.987 | C | T | 38/27/8 | 59/50/10 | 1.07 (0.75-1.53), 0.713 | 0.99 (0.63-1.58), 0.978 | 1.41 (0.67-2.97), 0.361 |
| Wei H et al. PLoS One  2012 [7] | *NEIL2* | rs804256 | 192 (110 R) | REC (CC vs. CT/TT):  4.58 (2.61-8.02), 1x10-7 | IV | I | 0.975/ 0.978 | T | C | 33/30/10 | 46/55/18 | 0.88 (0.63-1.23), 0.453 | 0.80 (0.50-1.28), 0.362 | 0.93 (0.47-1.81), 0.828 |
| *NEIL2* | rs804276 | 192 (110 R) | REC (GG vs. AG/AA):  2.71 (1.75-4.20), 9x10-6 | IV | I | 0.986/ 0.974 | G | A | 26/35/12 | 40/53/26 | 0.90 (0.65-1.24), 0.505 | 0.94 (0.58-1.53), 0.808 | 0.75 (0.40-1.39), 0.362 |
| *NEIL2* | rs4639 | 192 (110 R) | REC (GG vs. AG/AA):  2.60 (1.68-4.03),2x10-5 | IV | I | 0.988/ 0.989 | A | G | 25/33/14 | 38/57/24 | 0.96 (0.69-1.32), 0.786 | 0.92 (0.57-1.49), 0.733 | 0.97 (0.54-1.75), 0.931 |
| *SOD1* | rs2173962 | 192 (110 R) | DOM (AG/GG vs. AA):  2.45 (1.42-4.23), 1x10-3 | IV | I | 0.969/ 0.972 | T | C | 70/2/1 | 110/9/0 | 0.72 (0.27-1.91), 0.513 | 0.55 (0.17-1.79), 0.320 | 2.48 (0.34-17.9), 0.367 |
| *NEIL2* | rs804267 | 192 (110 R) | DOM (CT/CC vs. TT):  0.53 (0.36-0.78), 1x10-3 | IV | M | M | A | G | 32/30/11 | 57/49/13 | 1.13 (0.81-1.57), 0.472 | 1.12 (0.70-1.77), 0.638 | 1.29 (0.68-2.46), 0.431 |
| *NEIL2* | rs8191604 | 192 (110 R) | DOM (AC/CC vs. AA):  0.54 (0.36-0.81), 3x10-3 | IV | I | 0.980 / 0.983 | T | G | 35/30/9 | 66/44/9 | 1.22 (0.86-1.71), 0.263 | 1.24 (0.78-1.98), 0.370 | 1.44 (0.70-2.93), 0.321 |
| Jaiswal PK et al. Mol Biol Rep 2012 [24] | *BIRC5* | rs9904341 | 78 (34 R) | GC vs. GG:  0.35 (0.16-0.77), 0.009  CC vs. GG:  0.22 (0.05-0.95), 0.043 | N | I | 0.994/ 0.995 | G | C | 38/30/5 | 64/50/5 | 1.16 (0.79-1.71), 0.438 | 1.13 (0.71-1.80), 0.596 | 1.52 (0.61-3.76), 0.370 |
| Chiong E et al. Eur Urol 2011 [25] | *GPX1* | rs1050450 | 99 (31 R)  BCG +/ IFNα | CT vs. CC:  3.0 (1.04-8.6), 0.03  TT vs. CC: NA | N | I | 0.968/ 0.981 | G | A | 37/34/2 | 61/49/9 | 0.91 (0.62-1.33), 0.622 | 1.03 (0.65-1.65), 0.896 | 0.36 (0.09-1.51), 0.163 |
| *SLC11A1* | rs17235409 | 69 (23 R)  BCG no IFNα | GG vs. GA:  3.0 (1.03-8.9), 0.033  GG vs. AA: NA | N | I | 0.551/ 0.593 | G | A | 69/4/0 | 110/9/0 | 0.67 (0.20-2.21), 0.506 | 0.67 (0.20-2.22), 0.508 | NA |
| 99 (7 CSD)  BCG +/- IFNα | GG vs. GA:  44 (1.01-300), 0.036  GG vs. AA: NA |  |
| Mittal RD et al. Eur J Surg Oncol 2011 [26] | *CASP3* | rs4647603 | 78 (34 R) | AG vs. AA:  1.56 (0.57-4.27), 0.387  GG vs. AA:  5.20 (1.51-17.96), 0.009  AG/GG vs. AA:  2.05 (0.82-5.14), 0.124 | N | I | 0.866/ 0.858 | C | T | 52/18/2 | 81/36/2 | 0.94 (0.58-1.53), 0.813 | 0.88 (0.51-1.52), 0.647 | 1.63 (0.38-7.04), 0.516 |
| Gangwar R et al. Surgery 2011 [27] | *PTGS2* | rs20417 | 79 (35 R) | GC/CC vs. GG:  2.43 (0.34-1.85), 0.024 | N | I | 0.989/ 0.987 | C | G | 51/20/2 | 75/42/1 | 0.79 (0.49-1.28), 0.341 | 0.73 (0.44-1.21), 0.218 | 1.97 (0.45-8.66), 0.371 |
| Srivastava P et al. Cancer Biomark 2010-2011 [28] | *TP53* | rs1042522 | 78 (34 R) | GC vs. GG:  0.29 (0.11-0.84), 0.022  CC vs. GG:  3.36 (0.62-18.3), 0.161 | N | I | 0.943/ 0.951 | C | G | 40/27/6 | 57/54/9 | 0.85 (0.58-1.23), 0.386 | 0.77 (0.48-1.23), 0.278 | 0.98 (0.42-2.30), 0.959 |
| Chen M et al. Cancer Prev Res (Phila) 2010 [17] | *GLI3* | rs6463089 | 201 (118 R) | DOM (AG/AA vs. GG):  2.40 (1.50-3.84), 2x10-4 | IV | M | M | G | A | 61/11/1 | 88/30/1 | 0.66 (0.37-1.19), 0.167 | 0.61 (0.33-1.13), 0.115 | 2.00 (0.28-14.5), 0.492 |
| *GLI3* | rs3801192 | 200 (117 R) | DOM (AG/AA vs. GG):  2.54 (1.47-4.39), 9x10-4 | IV | I | 0.840/ 0.837 | C | T | 62/11/1 | 96/22/1 | 0.77 (0.40-1.50), 0.444 | 0.74 (0.37-1.49), 0.394 | 1.35 (0.09-20.8), 0.831 |
| Gangwar R et al. DNA Cell Biol 2010 [29] | *MDM2* | rs2279744 | 79 (36 R) | GT vs. TT:  1.35 (0.64-2.85), 0.422  GG vs. TT:  0.25 (0.08-0.80), 0.019 | N | I | 0.984/ 0.989 | T | G | 32/37/4 | 52/53/14 | 0.85 (0.59-1.22), 0.372 | 0.92 (0.58-1.47), 0.726 | 0.51 (0.18-1.39), 0.186 |
| Gangawar R et al. Med Oncol 2010 [30] | *ERCC2* | rs1799793 | 74 (35 R) | GA vs. GG:  0.64 (0.25-1.64), 0.356  AA vs. GG:  3.07 (1.22-7.68), 0.016  (Pc=0.048) | N | I | 0.927/ 0.904 | C | T | 27/31/15 | 49/62/8 | **1.49 (1.03-2.15), 0.033** | 1.21 (0.73-2.00), 0.462 | **2.76 (1.53-4.99), 7.88x10-4** |
| Gangwar R et al. J Cancer Res Clin Oncol 2010 [31] | *XPC* | rs2228001 | 77 (28 R) | AC vs. AA:  1.77 (0.65-4.81), 0.260  CC vs. AA:  3.21 (1.07-9.61), 0.036  AC/CC vs. AA:  3.98 (1.02-10.7), 0.031 | N | I | 0.982/ 0.981 | T | G | 29/28/16 | 40/59/20 | 0.96 (0.69-1.34), 0.831 | 0.78 (0.48-1.24), 0.292 | 1.29 (0.74-2.25), 0.366 |
| Ahirwar DK et al. Arch Med Res 2010 [32] | *IL8* | rs4073 | 71 (28 R) | TA vs. TT:  0.43 (0.16-1.09), 0.076  AA vs. TT:  0.12 (0.04-0.38), <0.001 | N | I | 0.989/ 0.984 | T | A | 21/40/12 | 34/61/24 | 0.89 (0.64-1.25), 0.509 | 0.96 (0.58-1.61), 0.886 | 0.73 (0.39-1.37), 0.334 |
| Vázquez-Lavista LG et al. Urology 2009 [33] | *CCL2* | rs1024611 | 33 (16 R/P) | GG vs. AG/AA:  associated with BCG  response, NP  (all non-responders have AA/AG genotype) | N | I | 0.991/ 0.995 | A | G | 37/32/4 | 65/48/7 | 1.03 (0.71-1.51), 0.868 | 1.07 (0.67-1.70), 0.772 | 0.91 (0.33-2.52), 0.853 |
| Gangwar R et al. Mutat Res 2009 [18] | *PRKDC* | rs7003908 | 79 (36 R) | TG vs. TT:  0.25 (0.09-0.65), 0.004  GG vs. TT:  0.44 (0.17-1.11), 0.084 | N | M | M | A | C | 33/37/3 | 50/58/11 | 0.87 (0.60-1.26), 0.446 | 0.95 (0.60-1.50), 0.817 | 0.47 (0.15-1.49), 0.197 |
| Ahirwar DK et al. BJU Int 2009 [34] | *TNF* | rs1799964 | 73 (31 R) | CT vs. TT:  1.27 (0.56-2.84), NP  CC vs. TT:  0.38 (0.14-0.98), 0.024  (Pc=0.048) | N | I | 0.998/ 0.998 | T | C | 43/24/6 | 78/32/9 | 1.19 (0.84-1.69), 0.333 | 1.28 (0.80-2.03), 0.308 | 1.20 (0.52-2.78), 0.662 |
| Gangwar R et al. Ann Surg Oncol 2009 [35] | *CASP9* | rs4645978 | 79 (36 R) | GA vs. AA:  0.46 (0.19-1.07), 0.074  GG vs. AA:  0.22 (0.75-0.62), 0.005 | N | I | 0.985/ 0.988 | T | C | 27/30/16 | 43/56/20 | 1.00 (0.72-1.38), 1.000 | 0.89 (0.55-1.43), 0.617 | 1.19 (0.68-2.09), 0.542 |
| Ahirwar DK et al. Biomarkers 2009 [36] | *TGFB1* | rs1800470 | 73 (30 R) | CT vs. CC:  0.68 (0.29-1.56), 0.364  TT vs. CC:  0.37 (0.14-0.98), 0.046  CT/TT vs. CC:  0.52 (0.24-1.13), 0.100 | N | I | 0.938/ 0.938 | A | G | 27/34/12 | 44/57/18 | 1.06 (0.75-1.48), 0.751 | 1.04 (0.64-1.70), 0.867 | 1.14 (0.60-2.17), 0.694 |
|  | *IFNG* | rs2430561 | 73 (30 R) | TA vs. TT:  2.80 (1.13-6.97), 0.024  AA vs. TT:  2.09 (0.77-5.66), 0.114  TA/AA vs. TT:  2.24 (1.06-5.80), 0.036 | N | I | 0.955/ 0.949 | T | A | 18/41/14 | 39/51/29 | 1.03 (0.75-1.42), 0.863 | 1.36 (0.78-2.37), 0.279 | 0.77 (0.42-1.39), 0.383 |
| Ahirwar D et al. Cancer Genet Cytogenet 2008 [10] | *IL6* | rs1800795 | 69 (28 R) | GC vs. GG:  0.96 (0.35-2.33), 0.94  CC vs. GG:  0.30 (0.09-0.91), 0.03 | N | I | 0.991/ 0.984 | G | C | 30/36/7 | 39/58/22 | 0.76 (0.54-1.07), 0.116 | 0.78 (0.49-1.25), 0.305 | 0.53 (0.24-1.15), 0.108 |
| Mittal RD et al Cancer Biol Ther 2008 [11] | *XRCC1* | rs25487 | 57 (25 R) | GA vs. GG:  1.63 (0.52-5.16), 0.40  AA vs. GG:  5.05 (1.34-19.01), 0.01 | N | I | 0.996/ 0.996 | C | T | 35/30/8 | 42/61/16 | 0.74 (0.52-1.06), 0.098 | 0.65 (0.41-1.02), 0.063 | 0.80 (0.38-1.66), 0.544 |
| Decobert M et al. J Urol 2006 [37] | *SLC11A1* | rs17235409 | 67 (51 R) | GA vs. GG:  5.74 (2.4-13.8), < 0.0001  AA vs. GG: NP | N | I | 0.551/ 0.593 | G | A | 69/4/0 | 110/9/0 | 0.67 (0.20-2.21), 0.506 | 0.67 (0.20-2.22), 0.508 | NA |
| Lin J et al. Clin Genet 2006 [13] | *CDH1* | rs16260 | 48 (18 R)  mBCG | CA/AA vs. CC:  0.21 (0.07-0.63), NP | N | I | 0.966/ 0.966 | C | A | 33/36/4 | 54/51/14 | 0.90 (0.63-1.29), 0.561 | 1.02 (0.64-1.63), 0.924 | 0.48 (0.17-1.35), 0.164 |
| Basturk B et al. Cytokine 2006 [38] | *TGFB1* | rs1800470 | 60 (14 R/P) | T allele:  OR = 7.5 (1.33-55.1), 0.006 | N | I | 0.938 0.938 | A | G | 27/34/12 | 44/57/18 | 1.06 (0.75-1.48), 0.751 | 1.04 (0.64-1.70), 0.867 | 1.14 (0.60-2.17), 0.694 |
| Leibovici D et al. J Clin Oncol 2005 [19] | *IL6* | rs1800795 | 33 (16 R)  mBCG | GC vs. GG:  4.31 (1.09-17.09), NP  CC vs. GG:  5.47 (1.05-28.44), NP  GC/CC vs. GG:  4.60 (1.24-17.09), NP | N | I | 0.991/ 0.984 | G | C | 30/36/7 | 39/58/22 | 0.76 (0.54-1.07), 0.116 | 0.78 (0.49-1.25), 0.305 | 0.53 (0.24-1.15), 0.108 |
| Gu J et al.Clin Cancer Res 2005 [14] | *ERCC6* | rs2228526 | 105 (61 R) | GG vs. AG vs. AA:  shorter RFS,  Logrank P= 0.022 | N | I | 1/  1 | T | C | 46/24/3 | 85/30/4 | 1.30 (0.88-1.91), 0.193 | 1.41 (0.87-2.26), 0.159 | 1.20 (0.38-3.83), 0.753 |

**Abbreviations:** SNP: single-nucleotide polymorphism; HR: hazard ratio; CI: confidence interval; M: measured (genotyped); I: imputed; NMIBC: non-muscle-invasive bladder cancer; R: recurrence; P: progression; CSD: cancer-specific death; RFS: recurrence-free survival; (m)BCG: (maintenance) bacillus Calmette-Guérin; IFN: interferon; Val.: validation; N: no validation; IV: internal validation; NBCS: Nijmegen Bladder Cancer Study; OR: odds ratio; NP: not presented; NA: not assessed; REC: recessive; dom: dominant.

**a** N=192 BCG treated NMIBC patients (≥6 instillations) (73 recurrence events; five-year Kaplan-Meier recurrence risk: 41.1 %).

**b** Patient numbercorresponds to the number of BCG treated NMIBC patients included in the original study unless otherwise specified.

**c** A1: major/reference allele; A2: minor/predictive allele (both according to + strand orientation).

**d** This SNP did not pass QC (info < 0.4).

**Supplementary Table S4.** Overview of previously reported associations and the current replication results for SNPs validated against progression risk in the overall NMIBC

patient group of the NBCS

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Original publication** | | | | | | **Replication in NBCS seriesa** | | | | | | | | |
| **Reference** | **Gene** | **SNP ID** | **N (n events)b** | **HR (95% CI), p** | **Val.** | **M/I** | **Info (NBCS1/ NBCS2)** | **A1c** | **A2** | **Genotype counts (A1A1/A1A2/A2A2)** | | **Additive model** | **Dominant model** | **Recessive model** |
| **Event** | **No event** | **HR (95% CI), p** | **HR (95% CI), p** | **HR (95% CI), p** |
| Lee EK et al. Cancer 2013 [3] | *RGS1* | rs1323291 | 421 (85 P) | DOM (AC/CC vs. AA):  2.14 (1.25-3.66), 0.0059 | IV | I | 0.939/ 0.941 | T | G | 159/35/3 | 867/202/18 | 0.96 (0.69-1.33), 0.792 | 0.97 (0.67-1.40), 0.861 | 0.77 (0.21-2.84), 0.698 |
| *RGS5* | rs10917690 | 421 (85 P) | ADD (GG vs. AG vs. AA):  0.58 (0.39-0.86), 0.0065 | IV | I | 0.714/ 0.707 | A | G | 108/79/10 | 566/439/81 | 0.83 (0.63-1.10), 0.194 | 0.85 (0.61-1.20), 0.365 | 0.49 (0.20-1.20), 0.119 |
| *RGS4* | rs6678136 | 421 (85 P) | DOM (AG/AA vs. GG):  2.07 (1.20-3.57), 0.0094 | IV | M | M | G | A | 55/105/37 | 389/506/192 | 1.18 (0.97-1.43), 0.103 | **1.39 (1.02-1.90), 0.038** | 1.08 (0.75-1.54), 0.677 |
| *RGS5* | rs11585883 | 421 (85 P) | DOM (AG/GG vs. AA):  1.93 (1.12-3.32), 0.018 | IV | I | 0.984/ 0.986 | T | C | 166/29/2 | 936/150/1 | 1.20 (0.83-1.75), 0.339 | 1.13 (0.76-1.66), 0.548 | **10.0 (2.47-40.6), 1.27x10-3** |
| Ke HL et al. Carcinogenesis 2013 [4] | *DGCR8* | rs2073778 | 401 (75 P) | REC (TT vs. CT/CC):  4.00 (1.53-10.46), 0.0047 | EV: F | M | M | C | T | 156/37/4 | 840/228/19 | 0.92 (0.68-1.25), 0.595 | 0.88 (0.63-1.24), 0.475 | 1.23 (0.46-3.31), 0.684 |
| *DGCR8* | rs720012 | 399 (75 P) | REC (AA vs. AG/GG):  3.97 (1.52-10.36), 0.0049 | EV: F | I | 1/  1 | G | A | 156/37/4 | 840/228/19 | 0.92 (0.68-1.25), 0.595 | 0.88 (0.63-1.24), 0.475 | 1.23 (0.46-3.31), 0.684 |
| Guirado M et al. Hum Immunol 2012 [39] | *TLR10* | rs4129009 | 275 (66 CSD)  NMIBC + MIBC | CT/CC vs. TT:  0.49 (0.27-0.90), 0.022 | N | I | 0.936/ 0.921 | T | C | 123/66/8 | 718/332/37 | 1.11 (0.86-1.43), 0.440 | 1.12 (0.83-1.51), 0.461 | 1.18 (0.56-2.52), 0.664 |
| *NOD2* | rs9302752 | 275 (66 CSD)  NMIBC + MIBC | GG vs. AA/AG:  3.19 (1.40-7.24), 0.006 | N | M | M | C | T | 106/76/15 | 623/411/53 | 1.18 (0.94-1.48), 0.163 | 1.14 (0.86-1.51), 0.351 | 1.56 (0.92-2.64), 0.098 |
| Wei H et al. PLoS One 2012 [7] | *UNG* | rs3890995 | 402 (75 P) | ADD (GG vs. AG vs. AA):  1.92 (1.33-2.77), 5x10-4 | IV | I | 0.995/ 0.995 | T | C | 138/51/8 | 731/320/36 | 0.95 (0.73-1.23), 0.691 | 0.90 (0.66-1.22), 0.493 | 1.24 (0.61-2.52), 0.556 |
| Ryk C et al. Scand J Urol Nephrol 2011 [40] | *NOS2* | rs2297518 | 320 (105 P)  NMIBC + MIBC | CT vs. CC:  1.09 (0.73-1.62), 0.690  TT vs. CC:  0.21 (0.05-0.87), 0.031 | N | M | M | G | A | 131/63/3 | 700/340/47 | 0.86 (0.66-1.11), 0.248 | 0.90 (0.67-1.22), 0.507 | 0.38 (0.12-1.19), 0.097 |
| Ryk C et al. J Urol 2010 [41] | *NOS2* | rs2301368 | 139 (29 CSD)  NMIBC + MIBC | CT vs. CC:  3.08 (1.29-7.36), 0.011  TT vs. CC:  0.34 (0.07-1.63), 0.176 | N | I | 0.923/ 0.926 | A | G | 72/98/27 | 347/543/197 | 1.19 (0.96-1.47), 0.108 | 1.39 (0.91-2.14), 0.132 | 1.20 (0.88-1.63), 0.240 |
| Horikawa Y et al. Oncol Rep 2008 [9] | *TP53* | rs1042522  [Pro]/[C]: 41.3% | 86 (26 CSD)  Cystectomy treated NMIBC + MIBC | Pro/Pro vs. Arg/Arg & Arg/Pro (CC vs. CG vs. GG):  2.76 (1.11-6.84), 0.028 | N | I | 0.943/ 0.951 | C | G | 101/76/20 | 589/423/75 | 1.17 (0.94-1.46), 0.157 | 1.14 (0.85-1.52), 0.390 | 1.54 (0.96-2.48), 0.072 |
| Sanyal S et al. Acta Oncol 2007 [12] | *HRAS* | rs12628 | 196 (? P)  Ta/T1  (In total study:  207 (22 P)) | TC/CC vs. TT:  0.3 (0.1-0.9), 0.03 | N | I | 0.907/ 0.910 | A | G | 85/94/17 | 500/454/133 | 0.97 (0.78-1.20), 0.784 | 1.10 (0.81-1.48), 0.540 | 0.66 (0.39-1.13), 0.127 |
| Sanyal S et al. Scand J Urol Nephrol 2007 [42] | *MTHFR* | rs1801133 | 264 (? CSD)  NMIBC + MIBC  (In total study: 311 (68 CSD)) | CT/TT vs. CC:  0.5 (0.3-0.9), 0.03 | N | M | M | G | A | 99/77/21 | 489/475/123 | 0.88 (0.71-1.09), 0.253 | 0.82 (0.62-1.08), 0.160 | 0.95 (0.61-1.50), 0.839 |
| Frey UH et al. Cancer Epidemiol Biomarkers Prev 2005 [43] | *GNAS* | rs7121 | 254 (? P)  NMIBC + MIBC | TC vs. TT:  1.48 (0.86-2.54), 0.160  CC vs. TT:  1.94 (1.11-3.38), 0.020 | N | I | 0.758/ 0.715 | C | T | 64/92/41 | 307/539/241 | 0.88 (0.70-1.11), 0.288 | 0.79 (0.56-1.12), 0.190 | 0.91 (0.60-1.38), 0.650 |
| 254 (? MT)  NMIBC + MIBC | TC vs. TT:  2.71 (1.13-6.48), 0.025  CC vs. TT:  3.49 (1.46-8.37), 0.005 | N |
| 254 (? CSD)  NMIBC + MIBC | TC vs. TT:  2.15 (0.95-4.84), 0.065  CC vs. TT:  2.49 (1.09-5.71), 0.031 | N |
| Eisenhardt A et al. World J Urol 2005 [44] | *GNB3* | rs5443 | 339 (88 MT)  NMIBC + MIBC | TT/TC vs. CC:  Shorter mean time to metastasis, 0.02 | N | I | 0.963/ 0.962 | C | T | 86/90/21 | 514/465/107 | 1.08 (0.87-1.33), 0.489 | 1.13 (0.84-1.50), 0.420 | 1.04 (0.65-1.67), 0.854 |
| 339 (169 P)  NMIBC + MIBC | TT/TC vs. CC:  Shorter mean time to progression, 0.042 | N |
| ? (70 CSD)  NMIBC + MIBC (non-smokers) | TT/TC vs. CC:  1.93 (1.04-3.20), NP;  Logrank P = 0.037 | N |
| Sakano S et al. Int J Cancer 2003 [45] | *CDKN2A* | rs3088440 | 211 (23 P)  Ta/T1 | CT/TT vs. CC:  2.5 (1.0-6.1), 0.043 | N | I | 0.965/ 0.969 | G | A | 159/37/1 | 917/158/12 | 1.21 (0.87-1.68), 0.260 | 1.28 (0.89-1.83), 0.182 | 0.71 (0.12-3.99), 0.694 |

**Abbreviations:** SNP: single-nucleotide polymorphism; HR: hazard ratio; CI: confidence interval; M: measured (genotyped); I: imputed; NMIBC: non-muscle-invasive bladder cancer; MIBC: muscle-invasive bladder cancer; P: progression; MT: metastasis; CSD: cancer-specific death; Val.: validation; N: no validation; IV: internal validation; EV:F: external validation failed; NBCS: Nijmegen Bladder Cancer Study; NP: not presented; DOM: dominant; ADD: additive; REC: recessive.

**a** N=1,284 NMIBC patients (197 progression events; five-year Kaplan-Meier progression risk: 17.2 %).

**b** Patient numbercorresponds to the number of NMIBC patients included in the original study unless otherwise specified.

**c** A1: major/reference allele; A2: minor/predictive allele (both according to + strand orientation).

**Supplementary Table S5.** Overview of previously reported associations and the current replication results for SNPs validated against progression risk in i.v. chemotherapy-

treated NMIBC patients of the NBCS.

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| **Original publication** | | | | | | **Replication in NBCS seriesa** | | | | | | | | |
| **Reference** | **Gene** | **SNP ID** | **N (n events)** | **HR (95% CI), p** | **Val.** | **M/I** | **Info (NBCS1/ NBCS2)** | **A1b** | **A2** | **Genotype counts (A1A1/A1A2/A2A2)** | | **Additive model** | **Dominant model** | **Recessive model** |
| **Event** | **No event** | **HR (95% CI), p** | **HR (95% CI), p** | **HR (95% CI), p** |
| Sacerdote C et al. Int J Cancer 2013 [46] | *XRCC1* | rs915927 | 114 (? CSD)  i.v. /syst. CT treated UBC  (In total study:  153 (45 CSD)) | Per allele G:  0.55 (0.32-0.94), 0.03 | N | I | 0.975/ 0.974 | T | C | 10/20/9 | 88/116/67 | 1.10 (0.72-1.67), 0.663 | 1.38 (0.67-2.86), 0.380 | 0.93 (0.44-1.96), 0.848 |
| *XRCC1* | rs762507 | 123 (? CSD)  i.v. /syst. CT treated UBC | Per allele A:  0.48 (0.27-0.84), 0.01 | N | I | 0.975/ 0.974 | C | T | 11/18/10 | 91/114/67 | 1.07 (0.71-1.62), 0.744 | 1.27 (0.63-2.57), 0.502 | 0.94 (0.45-1.98), 0.873 |
| *XRCC1* | rs2854501 | 120 (? CSD)  i.v. /syst. CT treated UBC | Per allele T:  0.25 (0.12-0.52), 0.001 | EV: F | I | 0.972/ 0.967 | G | A | 24/12/3 | 151/99/22 | 0.84 (0.50-1.40), 0.498 | 0.81 (0.42-1.54), 0.514 | 0.76 (0.21-2.71), 0.673 |
| *XRCC1* | rs2854509 | 122 (? CSD)  i.v. /syst. CT treated UBC | Per allele A:  0.21 (0.09-0.46), 0.001 | N | I | 0.991/ 0.989 | G | T | 26/11/2 | 156/95/20 | 0.74 (0.43-1.28), 0.285 | 0.69 (0.36-1.35), 0.283 | 0.67 (0.17-2.70), 0.571 |
| *XRCC1* | rs3213255 | 125 (? CSD)  i.v. /syst. CT treated UBC | Per allele C:  0.46 (0.26-0.80), 0.01 | EV: F | M | M | A | G | 12/18/9 | 88/121/63 | 1.01 (0.66-1.54), 0.965 | 1.06 (0.54-2.10), 0.861 | 0.96 (0.45-2.02), 0.908 |
| *ERCC2* | rs171140 | 121 (? CSD)  i.v. /syst. CT treated UBC | Per allele C:  2.07 (1.06-4.28), 0.03 | N | I | 0.990/ 0.990 | A | C | 17/16/6 | 87/132/53 | 0.75 (0.47-1.19), 0.221 | 0.63 (0.33-1.19), 0.157 | 0.80 (0.33-1.92), 0.619 |

**Abbreviations:** SNP: single-nucleotide polymorphism; HR: hazard ratio; CI: confidence interval; M: measured (genotyped); I: imputed; NMIBC: non-muscle-invasive bladder cancer; UBC: urinary bladder cancer; i.v.: intravesical; syst.: systemic; CT: chemotherapy; CSD: cancer-specific death; Val.: validation; N: no validation; EV:F: external validation failed; NBCS: Nijmegen Bladder Cancer Study.

**a** N=311 i.v. chemotherapy treated NMIBC patients (39 progression events; five-year Kaplan-Meier progression risk: 14.3 %).

**b** A1: major/reference allele; A2: minor/predictive allele (both according to + strand orientation).

**Supplementary Table S6.** Overview of previously reported associations and the current replication results for SNPs validated against overall survival in the MIBC patient

group of the NBCS

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| **Original publication** | | | | | | **Replication in NBCS seriesa** | | | | | | | | |
| **Reference** | **Gene** | **SNP ID** | **N (n events)b** | **HR (95% CI), p** | **Val.** | **M/I** | **Info (NBCS1/ NBCS2)** | **A1c** | **A2** | **Genotype counts (A1A1/A1A2/A2A2)** | | **Additive model** | **Dominant model** | **Recessive model** |
| **Event** | **No event** | **HR (95% CI), p** | **HR (95% CI), p** | **HR (95% CI), p** |
| Andrew AS et al. BJU Int 2014 [1] | *RB1CC1* | rs35402311 | 563 (230 OD)  NMIBC + MIBC | CT vs. CC:  2.29 (1.54-3.41), NP  TT vs. CC: NA;  Logrank P = 0.001 | N | I | 0.897/  0.874 | G | A | 84/3/0 | 175/13/0 | 0.47 (0.13-1.72), 0.253 | 0.46 (0.12-1.73), 0.252 | NA |
| Djukic TI et al. PLoS One 2013 [47] | *GSTO1* | rs4925 | 101 (62 CSD) | Asp/Asp vs Asp/Ala & Ala/Ala:  2.94 (1.16-7.43), 0.022 | N | M | M | C | A | 44/35/8 | 92/81/15 | 0.95 (0.69-1.32), 0.775 | 0.92 (0.60-1.40), 0.692 | 1.02 (0.49-2.10), 0.966 |
| *GSTO2* | rs156697 | 101 (62 CSD) | Asp/Asp vs Asp/Asn & Asn/Asn:  3.97 (1.76-8.94), 0.001 | N | M | M | A | G | 38/39/10 | 83/84/21 | 0.98 (0.72-1.34), 0.909 | 0.98 (0.64-1.50), 0.943 | 0.96 (0.50-1.85), 0.897 |
| Lee EK et al. Cancer 2013 [3] | *RGS5* | rs2344673 | 325 (144 OD) | ADD (AA vs. AG vs. GG):  1.55 (1.15-2.11), 0.0045 | IV | I | 0.764/ 0.774 | G | A | 69/16/2 | 132/53/3 | 0.67 (0.38-1.17), 0.159 | 0.59 (0.32-1.11), 0.100 | 1.28 (0.21-7.83), 0.789 |
| *RGS5* | rs10917690 | 325 (144 OD) | REC (GG vs. AG/AA):  1.88 (1.19-2.96), 0.0066 | IV | I | 0.714/ 0.707 | A | G | 46/39/3 | 105/74/9 | 1.02 (0.65-1.59), 0.932 | 1.12 (0.66-1.90), 0.680 | 0.45 (0.07-2.94), 0.401 |
| *RGS2* | rs1890398 | 325 (144 OD) | DOM (AG/AA vs. GG):  1.46 (1.03-2.08), 0.0353 | IV | I | 0.996/ 0.998 | C | T | 37/42/8 | 82/83/23 | 0.98 (0.71-1.34), 0.878 | 1.05 (0.68-1.60), 0.830 | 0.78 (0.38-1.62), 0.513 |
| *RGS3* | rs1051013 | 325 (144 OD) | REC (AA vs. AG/GG):  0.44 (0.20-0.95), 0.0362 | IV | I | 0.995/ 0.995 | C | T | 43/41/3 | 111/60/17 | 1.11 (0.81-1.54), 0.515 | 1.41 (0.93-2.15), 0.106 | 0.43 (0.14-1.37), 0.156 |
| *RGS5* | rs1395960 | 325 (144 OD) | DOM (AG/AA vs. GG):  0.53 (0.29-0.96), 0.0377 | IV | I | 0.999/ 0.999 | C | T | 60/25/2 | 143/43/2 | 1.33 (0.88-2.02), 0.173 | 1.32 (0.84-2.08), 0.232 | 2.16 (0.53-8.78), 0.282 |
| *RGS5* | rs12035879 | 325 (144 OD) | REC (AA vs. AG/GG):  1.65 (1.02-2.66), 0.0387 | IV | I | 0.619/ 0.607 | G | A | 23/44/20 | 62/101/24 | **1.72 (1.13-2.61), 0.011** | 1.76 (0.88-3.54), 0.110 | **2.79 (1.40-5.56), 3.47x10-3** |
| *RGS12* | rs762861 | 325 (144 OD) | DOM (CG/CC vs. GG):  0.69 (0.48-0.98), 0.0389 | IV | I | 0.837/ 0.828 | G | C | 46/36/5 | 94/84/10 | 0.93 (0.63-1.38), 0.723 | 0.90 (0.56-1.43), 0.652 | 1.05 (0.32-3.41), 0.936 |
| *RGS5* | rs10753605 | 325 (144 OD) | REC (GG vs. AG/AA):  1.88 (1.03-3.46), 0.0395 | IV | M | M | T | C | 42/42/3 | 88/81/19 | 0.84 (0.60-1.17), 0.294 | 0.94 (0.62-1.44), 0.787 | 0.35 (0.11-1.10), 0.072 |
| Kim EJ et al. Urol Oncol 2012 [48] | *OGG1* | rs1052133 | 113 (42 P) | Ser/Cys vs. Ser/Ser:  0.43 (0.21-0.91), 0.027  Cys/Cys vs. Ser/Ser:  0.28 (0.12-0.70), 0.006 | N | I | 0.945/ 0.938 | C | G | 46/36/5 | 112/66/10 | 1.18 (0.84-1.67), 0.341 | 1.30 (0.84-2.01), 0.236 | 0.98 (0.37-2.58), 0.962 |
| 113 (32 CSD) | Ser/Cys vs. Ser/Ser:  0.87 (0.35-2.17), 0.766  Cys/Cys vs. Ser/Ser:  0.31 (0.10-0.91), 0.033 | N |
| Guirado M et al. Hum Immunol 2012 [39] | *TLR10* | rs4129009 | 275 (66 CSD)  NMIBC + MIBC | CT/CC vs. TT:  0.49 (0.27-0.90), 0.022 | N | I | 0.936/ 0.921 | T | C | 68/16/3 | 129/52/7 | 0.73 (0.46-1.16), 0.180 | 0.65 (0.38-1.10), 0.109 | 1.04 (0.31-3.47), 0.948 |
| *NOD2* | rs9302752 | 275 (66 CSD)  NMIBC + MIBC | GG vs. AA/AG:  3.19 (1.40-7.24), 0.006 | N | M | M | C | T | 53/31/3 | 97/78/13 | 0.74 (0.51-1.06), 0.103 | 0.72 (0.47-1.11), 0.140 | 0.54 (0.17-1.69), 0.287 |
| Ha YS et al. Ann Surg Oncol 2011 [49] | *OGG1* | rs1052133 | 117 (41 P) | Ser/Cys vs. Ser/Ser:  0.62 (0.30-1.31), 0.214  Cys/Cys vs. Ser/Ser:  0.31 (0.12-0.84), 0.021 | N | I | 0.945/ 0.938 | C | G | 46/36/5 | 112/66/10 | 1.18 (0.84-1.67), 0.341 | 1.30 (0.84-2.01), 0.236 | 0.98 (0.37-2.58), 0.962 |
| Ryk C et al. Scand J Urol Nephrol 2011 [40] | *NOS2* | rs2297518 | 320 (105 P)  NMIBC + MIBC | CT vs. CC :  1.09 (0.73-1.62), 0.690  TT vs. CC :  0.21 (0.05-0.87), 0.031 | N | M | M | G | A | 65/20/2 | 129/55/4 | 0.83 (0.54-1.29), 0.412 | 0.79 (0.49-1.28), 0.333 | 1.15 (0.28-4.69), 0.843 |
| Chen M et al. Carcinogenesis 2010 [50] | *AKT2* | rs3730050 | 302 (125 OD) | wv vs. ww (AG vs. GG):  1.51 (1.02-2.23), 0.05  vv vs. ww (AA vs. GG):  2.99 (1.65-5.42), 2x10-4  ADD (AA vs. AG vs. GG):  NP, 4x10-4 | IV | M | M | C | T | 35/45/7 | 85/84/19 | 1.01 (0.73-1.39), 0.950 | 1.12 (0.73-1.72), 0.605 | 0.76 (0.35-1.64), 0.481 |
| *PIK3R1* | rs10515074 | 300 (125 OD) | wv vs. ww (AG vs. AA):  1.88 (1.27-2.78), 2x10-3  vv vs. ww (GG vs. AA):  1.37 (0.48-3.94), 0.56  DOM (AG/GG vs. AA):  1.83 (1.24-2.69), 2x10-3 | IV | M | M | A | G | 56/28/3 | 116/62/10 | 0.91 (0.63-1.32), 0.618 | 0.92 (0.59-1.43), 0.716 | 0.73 (0.23-2.31), 0.592 |
| *RPTOR* | rs9906827 | 299 (125 OD) | wv vs. ww (AG vs. GG):  0.55 (0.36-0.84), 6x10-3  vv vs. ww (AA vs. GG):  0.54 (0.34-0.88), 0.01  DOM (AG/AA vs. GG):  0.55 (0.37-0.81), 2x10-3 | IV | I | 0.997/ 0.996 | C | T | 28/30/29 | 59/88/41 | 1.15 (0.87-1.52), 0.339 | 0.96 (0.61-1.50), 0.854 | 1.52 (0.97-2.38), 0.065 |
| *RPTOR* | rs7208502 | 300 (125 OD) | wv vs. ww (AG vs. GG):  0.55 (0.36-0.84), 6x10-3  vv vs. ww (AA vs. GG):  0.54 (0.33-0.87), 0.01  DOM (AG/AA vs. GG):  0.54 (0.37-0.80), 2x10-3 | IV | M | M | C | T | 28/30/29 | 59/88/41 | 1.15 (0.87-1.53), 0.318 | 0.96 (0.62-1.51), 0.876 | 1.53 (0.98-2.40), 0.060 |
| Ryk C et al. J Urol 2010 [41] | *NOS2* | rs2301368 | 139 (29 CSD)  NMIBC + MIBC | CT vs. CC:  3.08 (1.29-7.36), 0.011  TT vs. CC:  0.34 (0.07-1.63), 0.176 | N | I | 0.923/ 0.926 | A | G | 30/38/19 | 53/96/38 | 1.12 (0.82-1.54), 0.476 | 0.92 (0.54-1.56), 0.749 | 1.39 (0.87-2.21), 0.163 |
| Mason RA et al. Carcinogenesis 2009 [51] | *EGFR* | rs2017000 | 577 (? OD)  NMIBC + MIBC | GG/AG vs. AA:  0.6 (0.3-1.0), NP | N | I | 0.994/ 0.994 | A | G | 56/25/6 | 100/75/13 | 0.80 (0.56-1.15), 0.225 | 0.70 (0.45-1.09), 0.119 | 1.04 (0.45-2.39), 0.922 |
| *EGFR* | rs2227983 | 515 (? OD)  NMIBC + MIBC | AA/AG vs. GG:  0.3 (0.1-0.9), NP | N | I | 0.994/  0.990 | G | A | 60/22/5 | 109/70/9 | 0.78 (0.53-1.14), 0.198 | 0.67 (0.43-1.06), 0.088 | 1.19 (0.48-2.95), 0.701 |
| *EGF* | rs971696 | ? (? OD)  NMIBC + MIBC | AT vs. TT:  1.5 (1.0-2.3), NP | N | I | 0.939/ 0.911 | A | T | 76/11/0 | 161/25/2 | 0.78 (0.41-1.47), 0.438 | 0.81 (0.41-1.59), 0.538 | NA |
| Castillejo A et al. Int J Cancer 2009 [52] | *TGFBR1* | rs868 | 225 (92 CSD) | AG vs. AA:  1.85 (1.15-2.97), NP  GG vs. AA:  3.00 (1.15-7.82), NP;  pLRT = 0.013, ptrend = 0.003 | N | I | 0.983/ 0.971 | A | G | 56/29/2 | 129/55/4 | 1.12 (0.76-1.67), 0.563 | 1.16 (0.74-1.81), 0.518 | 1.00 (0.24-4.08), 0.997 |
| *TGFBR1* | rs334358 | 227 (93 CSD) | GT vs. GG:  1.67 (1.05-2.68), NP  TT vs. GG:  2.83 (1.09-7.34), NP;  pLRT = 0.032, ptrend = 0.009 | N | I | 0.982/ 0.970 | G | T | 56/29/2 | 129/55/4 | 1.12 (0.76-1.67), 0.562 | 1.16 (0.74-1.81), 0.516 | 1.00 (0.24-4.08), 0.997 |
| Andrew AS et al. Hum Genet 2009 [53] | *CD80* | rs9282638 | 419 (171 OD)  NMIBC + MIBC | Het vs. wt (AG vs. GG):  1.9 (1.4-2.8), NP  Var vs. wt (AA vs. GG):  1.5 (0.2-10.9), NP  Any var (AG/AA vs. GG):  1.9 (1.4-2.7), NP;  Logrank P = 0.008 | N | I | 0.996/ 0.994 | T | C | 65/20/2 | 125/58/5 | 0.79 (0.51-1.22), 0.293 | 0.75 (0.46-1.22), 0.245 | 0.97 (0.24-3.94), 0.961 |
| *BCL2L1* | rs1994251 | 419 (169 OD)  NMIBC + MIBC | Het vs. wt (AC vs. AA):  1.5 (1.1-2.1), NP  Var vs. wt (CC vs. AA):  1.5 (0.7-3.3), NP  Any var (AC/CC vs. AA):  1.5 (1.1-2.1), NP;  Logrank P = 0.01 | N | I | 0.999/  1 | T | G | 51/29/7 | 115/64/9 | 1.09 (0.78-1.53), 0.617 | 1.05 (0.68-1.60), 0.836 | 1.40 (0.65-3.03), 0.395 |

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|  | *EPHX1* | rs2854461 | 419 (172 OD)  NMIBC + MIBC | Het vs wt (AC vs. AA):  0.8 (0.5-1.1) , NP  Var vs. wt (CC vs. AA):  0.5 (0.2-0.9) , NP  Any var (AC/CC vs. AA):  0.7 (0.5-1.0) , NP;  Logrank P = 0.02 | N | I | 0.973/ 0.975 | C | A | 31/47/9 | 85/81/22 | 1.16 (0.85-1.58), 0.357 | 1.40 (0.90-2.20), 0.136 | 0.88 (0.44-1.75), 0.710 |
| *ERCC4* | rs1800067 | 419 (172 OD)  NMIBC + MIBC | Het vs. wt (AG vs. GG):  1.7 (1.1-2.8)  Var vs. wt (AA vs. GG):  5.6 (1.4-23.4)  Any var (AG/AA vs. GG):  1.8 (1.2-2.9);  Logrank P = 0.1 | N | M | M | G | A | 75/12/0 | 158/29/1 | 0.83 (0.46-1.50), 0.537 | 0.85 (0.46-1.56), 0.595 | NA |
| *GATA3* | rs528778 | 419 (171 OD)  NMIBC + MIBC | Het vs. wt (CT vs. CC):  0.9 (0.67-1.3) , NP  Var vs. wt (TT vs. CC):  2.8 (1.6-5.0) , NP  Any var (CT/TT vs. CC):  1.1 (0.8-1.5) , NP; Logrank P < 0.001 | N | I | 0.933/ 0.944 | C | T | 54/30/3 | 110/70/9 | 0.87 (0.59-1.28), 0.475 | 0.86 (0.55-1.34), 0.501 | 0.77 (0.23-2.61), 0.677 |
| *CXCR2* | rs1126579 | 417 (172 OD)  NMIBC + MIBC | Het vs. wt (CT vs. TT):  1.7 (1.2-2.5) , NP  Var vs. wt (CC vs. TT):  1.7 (1.1-2.8) , NP  Any var (CT/CC vs. TT):  1.7 (1.2-2.5) , NP;  Logrank P = 0.003 | N | I | 0.998/ 0.997 | C | T | 22/49/16 | 45/95/48 | 0.86 (0.63-1.17), 0.342 | 0.92 (0.57-1.49), 0.736 | 0.72 (0.41-1.24), 0.230 |
| *UGT1A1* | rs1042640 | 415 (168 OD)  NMIBC + MIBC | Het vs. wt (CG vs. GG):  1.4 (1.0-2.0) , NP  Var vs. wt (CC vs. GG):  1.4 (0.6-3.1) , NP  Any var (CG/CC vs. GG):  1.4 (1.0-2.0) , NP;  Logrank P = 0.1 | N | I | 0.976/ 0.962 | C | G | 52/33/2 | 123/58/7 | 1.11 (0.76-1.60), 0.589 | 1.21 (0.78-1.87), 0.397 | 0.69 (0.18-2.63), 0.589 |

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|  | *PGR* | rs613120 | 418 (172 OD)  NMIBC + MIBC | Het vs. wt (CT vs. TT):  1.2 (0.8-1.9) , NP  Var vs. wt (CC vs. TT):  1.4 (0.9-2.3) , NP  Any var (CT/CC vs. TT):  1.3 (0.8-2.0) , NP; Logrank P = 0.005 | N | I | 0.994/ 0.995 | A | G | 19/44/24 | 60/90/38 | 1.33 (1.00-1.79), 0.053 | 1.62 (0.97-2.70), 0.066 | 1.37 (0.85-2.19), 0.194 |
| *AURKA* | rs6024840 | 314 (146 OD)  NMIBC + MIBC | Het vs. wt (CT vs. TT):  1.4 (1.0-2.1) , NP  Var vs. wt (CC vs. TT):  1.1 (0.5-2.5) , NP  Any var (CT/CC vs. TT):  1.4 (1.0-2.0) , NP;  Logrank P = 0.1 | N | I | 0.888/ 0.874 | A | G | 46/35/6 | 105/72/11 | 1.08 (0.75-1.55), 0.680 | 1.09 (0.69-1.71), 0.712 | 1.15 (0.45-2.94), 0.764 |
| *TERT* | rs2075786 | 410 (172 OD)  NMIBC + MIBC | Het vs. wt (CT vs. TT):  0.8 (0.6-1.1) , NP  Var vs. wt (CC vs. TT):  0.5 (0.3-1.0) , NP  Any var (CT/CC vs. TT):  0.8 (0.5-1.0) , NP;  Logrank P = 0.1 | N | I | 0.719/  0.721 | G | A | 34/36/17 | 81/86/21 | 1.27 (0.90-1.80), 0.171 | 1.18 (0.71-1.97), 0.527 | **1.93 (1.01-3.68), 0.045** |
| *CASP9* | rs1052576 | 410 (167 OD)  NMIBC + MIBC | Het vs. wt (AG vs. AA):  1.3 (0.9-2.0) , NP  Var vs. wt (GG vs. AA):  1.4 (0.8-2.4) , NP  Any var (AG/GG vs. AA):  1.3 (0.9-2.0) , NP;  Logrank P = 0.003 | N | I | 1/  1 | C | T | 25/44/18 | 64/87/37 | 1.10 (0.82-1.48), 0.516 | 1.21 (0.76-1.92), 0.429 | 1.06 (0.63-1.78), 0.819 |
| Horikawa Y et al. Oncol Rep  2008 [9] | *TP53* | rs1042522 | 86 (26 CSD)  Cystectomy treated NMIBC + MIBC | Pro/Pro vs. Arg/Arg & Arg/Pro (CC vs. CG vs. GG):  2.76 (1.11-6.84), 0.028 | N | I | 0.943/ 0.951 | C | G | 53/31/3 | 102/78/9 | 0.81 (0.55-1.19), 0.285 | 0.78 (0.50-1.22), 0.283 | 0.76 (0.21-2.67), 0.664 |
| Sanyal S et al. Acta Oncol 2007 [12] | *ERCC2* | rs13181 | 260 (? OD)  NMIBC + MIBC  (In total study: 272 (96 OD)) | AC/CC vs. AA:  0.6 (0.4-0.9), 0.008 | N | M | M | T | G | 42/33/12 | 86/73/29 | 0.93 (0.69-1.26), 0.655 | 0.92 (0.60-1.40), 0.689 | 0.90 (0.49-1.66), 0.735 |

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Sanyal S et al. Scand J Urol Nephrol 2007 [42] | *NQO1* | rs1131341 | 257 (? OD)  NMIBC + MIBC  (In total study: 311 (113 OD)) | CT/TT vs. CC:  1.8 (1.0-3.3), 0.05 | N | I | 0.883/ 0.900 | G | A | 79/8/0 | 180/8/0 | 1.96 (0.91-4.20), 0.083 | 1.96 (0.91-4.20), 0.083 | NA |
| *MTHFR* | rs1801133 | 264 (? CSD)  NMIBC + MIBC  (In total study: 311 (68 CSD)) | CT/TT vs. CC:  0.5 (0.3-0.9), 0.03 | N | M | M | G | A | 42/36/9 | 86/82/20 | 0.93 (0.67-1.28), 0.658 | 0.89 (0.58-1.36), 0.588 | 0.97 (0.49-1.94), 0.940 |
| Leibovici D et al. J Clin Oncol 2005 [19] | *IL6* | rs1800795 | 149 (? OD)  (In total study: 232 (68 OD)) | GC/CC vs. GG (wildtype):  0.43 (0.19-0.94), NP | N | I | 0.991/ 0.984 | G | C | 37/39/11 | 68/93/27 | 0.86 (0.62-1.18), 0.339 | 0.79 (0.51-1.21), 0.279 | 0.89 (0.47-1.68), 0.720 |
| 149 (? CSD)  (In total study: 232 (38 CSD)) | GC/CC vs. GG (wildtype):  0.39 (0.15-1.00), NP | N |
| *TNF* | rs1800629 | 156 (? OD)  (In total study: 232 (68 OD)) | GA/AA vs. GG (wildtype):  2.35 (1.07-5.16), NP | N | I | 0.997/ 0.999 | G | A | 58/25/4 | 128/53/7 | 1.07 (0.74-1.56), 0.711 | 1.06 (0.68-1.66), 0.801 | 1.26 (0.46-3.45), 0.647 |
| Frey UH et al. Cancer Epidemiol Biomarkers Prev 2005 [43] | *GNAS* | rs7121 | 254 (? P)  NMIBC + MIBC | TC vs. TT:  1.48 (0.86-2.54), 0.160  CC vs. TT:  1.94 (1.11-3.38), 0.020 | N | I | 0.758/ 0.715 | C | T | 22/45/21 | 53/89/46 | 1.03 (0.73-1.45), 0.872 | 1.19 (0.65-2.19), 0.573 | 0.92 (0.50-1.67), 0.773 |
| 254 (? MT)  NMIBC + MIBC | TC vs. TT:  2.71 (1.13-6.48), 0.025  CC vs. TT:  3.49 (1.46-8.37), 0.005 | N |
| 254 (? CSD)  NMIBC + MIBC | TC vs. TT:  2.15 (0.95-4.84), 0.065  CC vs. TT:  2.49 (1.09-5.71), 0.031 | N |
| Eisenhardt A et al. World J Urol 2005 [44] | *GNB3* | rs5443 | 339 (88 MT)  NMIBC + MIBC | TT/TC vs. CC:  Shorter mean time to metastasis, 0.02 | N | I | 0.963/ 0.962 | C | T | 44/35/8 | 85/83/20 | 0.87 (0.62-1.21), 0.406 | 0.85 (0.55-1.30), 0.443 | 0.80 (0.37-1.73), 0.575 |
| 339 (169 P)  NMIBC + MIBC | TT/TC vs. CC:  Shorter mean time to progression, 0.042 | N |
| ? (70 CSD)  NMIBC + MIBC (non-smokers) | TT/TC vs. CC:  1.93 (1.04-3.20), NP;  Logrank P = 0.037 | N |

**Abbreviations:** SNP: single-nucleotide polymorphism; HR: hazard ratio; CI: confidence interval; M: measured (genotyped); I: imputed; NMIBC: non-muscle-invasive bladder cancer; MIBC: muscle-invasive bladder cancer; OD: overall death; CSD: cancer-specific death; P: progression; MT: metastasis; Val.: validation; N: no validation; IV: internal validation; NBCS: Nijmegen Bladder Cancer Study; LRT: likelihood ratio test; NP: not presented; NA: not assessed; ADD: additive; DOM: dominant; REC: recessive; var (vv): homozygous variant; wt (ww): homozygous wildtype; het (wv): heterozygous variant.

**a** N=275 MIBC patients (87 deceased cases; five-year Kaplan-Meier overall mortality risk: 32.4 %).

**b** Patient numbercorresponds to the number of MIBC patients included in the original study unless otherwise specified.

**c** A1: major/reference allele; A2: minor/predictive allele (both according to + strand orientation).

**Supplementary Table S7.** Overview of previously reported SNP associations with outcome in (chemo-)radiotherapy-treated UBC

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Original publication** | | | | | |
| **Reference** | **Gene** | **SNP ID** | **N (n events)** | **HR (95% CI), p** | **Val.** |
|
| Teo MTW et al. Ann Oncol 2014 [54] | *MRE11A* | rs1805363 | 186 (70 CSD)  RT-treated MIBC | AG vs. GG:  1.49 (0.80-2.78), NP  AA vs. GG:  8.00 (2.93-21.90), NP  Per allele A:  2.10 (1.34-3.28), 0.001 | N |
| Teo MT et al. Carcinogenesis 2012 [55] | *RAD51* | rs7180135 | 189 (? CSD)  RT-treated MIBC | AG/GG vs. AA:  0.52 (0.31-0.87), 0.01 | N |
| Shinohara A et al. Cancer Sci 2009 [56] | *MDM2* | rs2279744 | 95 (19 CSD)  Platinum-based CRT treated T1G3/MIBC | TG/GG vs. TT:  0.57 (0.36-0.95), 0.031 | N |
| Sanyal S et al. Acta Oncol 2007 [12] | *XRCC1* | rs25487 | 11 (? CSD)  RT treated MIBC | GA/AA vs. GG:  0.1 (0.0-0.8), 0.03 | N |
| *OGG1* | rs1052133 | 10 (? CSD)  RT treated MIBC | CG/GG vs. CC:  10.8 (1.2-99.5), 0.04 | N |
| Sanyal S et al. Scand J Urol Nephrol 2007 [42] | *NQO1* | rs1800566 | 11 (? CSD)  RT treated MIBC | Variant allele carriers vs. non-carriers:  24.4 (1.5-409.0), 0.03 | N |
| Sakano S et al. Br J Cancer 2006 [57] | *XRCC1* | rs25487 | 35 (? CSD)  CRT treated T3/T4 patients | GA/AA vs. GG:  RR = 0.0004 (NA), 0.02  All CRT treated patients:  RR= 0.51 (0.20-0.98), 0.04 | N |

**Abbreviations:** SNP: single-nucleotide polymorphism; HR: hazard ratio; CI: confidence interval; MIBC: muscle-invasive bladder cancer; UBC: urinary bladder cancer; RT: radiotherapy; CRT: chemoradiotherapy; CSD: cancer-specific death; Val.: validation; N: no validation; RR: risk ratio; NP: not presented; NA: not assessed.

**Note:** These SNPs were not included in our replication study because of too low patient numbers in the specific MIBC treatment subgroup (*i.e.*, n=36 MIBC patients that received initial treatment with radiotherapy).

**Supplementary Table S8.** Overview of previously reported SNP associations with outcome in (platinum-based) systemic chemotherapy-treated UBC

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Original publication** | | | | | |
| **Reference** | **Gene** | **SNP ID** | **N (n events)** | **HR (95% CI), p** | **Val.** |
|
| Gallagher DJ et al. Ann Oncol 2013 [58] | *IL1B* | rs1143627 | 210 (98 response)  Platinum-based CT treated, advanced UC | CT vs. TT:  OR = 1.81 (0.96-3.44), NP  CC vs. TT:  OR = 3.38 (1.46-8.18), NP;  P = 0.01  Per allele C:  OR = 1.83 (1.23-2.77), 0.003 | N |
| *IL1B* | rs16944 | 209 (98 response)  Platinum-based CT treated, advanced UC | AG vs. GG:  OR = 1.89 (1.0-3.62), NP  AA vs. GG:  OR = 3.56 (1.53-8.69), NP;  P = 0.008  Per allele A:  OR = 1.89 (1.26-2.87),  0.002 | N |
| *-* | rs1520896 | 210 (98 response)  Platinum-based CT treated, advanced UC | CT vs. CC:  OR = 0.75 (0.39-1.42), NP  TT vs. CC:  OR = 0.18 (0.04-0.61), NP;  P = 0.02  Per allele T:  OR = 0.55 (0.34-0.88), 0.01 | N |
| *CCND1* | rs9344 | 207 (98 response)  Platinum-based CT treated, advanced UC | GA vs. GG:  OR = 1.71 (0.86-3.46), NP  AA vs. GG:  OR = 0.38 (0.16-0.89), NP;  P = 0.0005  Per allele A:  OR = 0.67 (0.44-1.0), 0.05 | N |
| *PARD6B* | rs6512670 | 208 (98 response)  Platinum-based CT treated, advanced UC | CT vs. CC:  OR = 1.22 (0.64-2.34), NP  TT vs. CC:  OR = 2.82 (1.21-6.84), NP;  P = 0.05  Per allele T:  OR = 1.6 (1.06-2.43), 0.03 | N |
| Sacerdote C et al. Int J Cancer 2013 [46] | *XRCC1* | rs915927 | 114 (? CSD)  i.v. /syst. CT treated UBC  (In total study:  153 (45 CSD)) | Per allele G:  0.55 (0.32-0.94), 0.03 | N |
| *XRCC1* | rs762507 | 123 (? CSD)  i.v. /syst. CT treated UBC | Per allele A:  0.48 (0.27-0.84), 0.01 | N |
| *XRCC1* | rs2854501 | 120 (? CSD)  i.v. /syst. CT treated UBC | Per allele T:  0.25 (0.12-0.52), 0.001 | EV: F |
| *XRCC1* | rs2854509 | 122 (? CSD)  i.v. /syst. CT treated UBC | Per allele A:  0.21 (0.09-0.46), 0.001 | N |
| *XRCC1* | rs3213255 | 125 (? CSD)  i.v. /syst. CT treated UBC | Per allele C:  0.46 (0.26-0.80), 0.01 | EV: F |
| *ERCC2* | rs171140 | 121 (? CSD)  i.v. /syst. CT treated UBC | Per allele C:  2.07 (1.06-4.28), 0.03 | N |
| Djukic TI et al. PLoS One 2013 [47] | *GSTO2* | rs156697 | 51 (? CSD)  Neo-adjuvant platinum-based CT treated MIBC | Asp/Asp vs Asp/Asn & Asn/Asn:  Shorter survival (19.4±3.4 months vs. 40.3±3.7 months)  Logrank P = 0.006 | N |
| Nikitas N et al. Pharmacogenomics 2012 [59] | *ERCC1* | rs11615 | 109 (65 CSD)  Platinum-based CT treated, advanced UC | TT vs. CC/CT:  Multivariable model 1:  0.49 (0.25-0.96), 0.037  Multivariable model 2:  0.42 (0.24-0.87), 0.026 | N |

**Abbreviations:** SNP: single-nucleotide polymorphism; HR: hazard ratio; CI: confidence interval; MIBC: muscle-invasive bladder cancer; UT: urothelial carcinoma; UBC: urinary bladder cancer; CT: chemotherapy; i.v.: intravesical; syst.: systemic; CSD: cancer-specific death; Val.: validation; N: no validation; IV: internal validation; EV:F: external validation failed; OR: odds ratio; NP: not presented.

**Note:** These SNPs were not included in our replication study because of too low patient numbers in the specific MIBC treatment subgroup (*i.e.*, n=43 MIBC patients that received initial treatment with systemic platinum-based chemotherapy).

**Supplementary Table S9.** Overview of previously reported associations and the current replication results for SNPs validated against progression risk in the overall NMIBC patient group of the NBCS using the original and alternative criterion for progression.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | | | | **Original definition progressiona** | | | | | **Alternative definition progressionb** | | | | | |
| **Gene** | **SNP ID** | **A1c** | **A2** | **Genotype counts**  **(A1A1/A1A2/A2A2)** | | **Additive model** | **Dominant model** | **Recessive model** | **Genotype counts**  **(A1A1/A1A2/A2A2)** | | **Additive model** | **Dominant model** | **Recessive model** |
| **Event** | **No event** | **HR (95% CI), p** | **HR (95% CI), p** | **HR (95% CI), p** | **Event** | **No event** | **HR (95% CI), p** | **HR (95% CI), p** | **HR (95% CI), p** |
| *RGS1* | rs1323291 | T | G | 159/35/3 | 867/202/18 | 0.96 (0.69-1.33), 0.792 | 0.97 (0.67-1.40), 0.861 | 0.77 (0.21-2.84), 0.698 | 45/15/1 | 981/223/19 | 1.40 (0.85-2.32), 0.186 | 1.51 (0.84-2.71), 0.164 | 1.34 (0.22-8.12), 0.751 |
| *RGS5* | rs10917690 | A | G | 108/79/10 | 566/439/81 | 0.83 (0.63-1.10), 0.194 | 0.85 (0.61-1.20), 0.365 | 0.49 (0.20-1.20), 0.119 | 32/25/4 | 642/493/87 | 0.98 (0.60-1.58), 0.919 | 0.99 (0.54-1.83), 0.987 | 0.85 (0.22-3.28), 0.814 |
| *RGS4* | rs6678136 | G | A | 55/105/37 | 389/506/192 | 1.18 (0.97-1.43), 0.103 | **1.39 (1.02-1.90), 0.038** | 1.08 (0.75-1.54), 0.677 | 17/36/8 | 427/575/221 | 1.05 (0.73-1.49), 0.805 | 1.38 (0.79-2.41) , 0.262 | 0.70 (0.33-1.47), 0.345 |
| *RGS5* | rs11585883 | T | C | 166/29/2 | 936/150/1 | 1.20 (0.83-1.75), 0.339 | 1.13 (0.76-1.66), 0.548 | **10.0 (2.47-40.6), 1.27x10-3** | 54/6/1 | 1048/173/2 | 0.93 (0.45-1.94), 0.851 | 0.81 (0.37-1.77), 0.599 | **11.79 (1.62-85.65), 0.015** |
| *DGCR8* | rs2073778 | C | T | 156/37/4 | 840/228/19 | 0.92 (0.68-1.25), 0.595 | 0.88 (0.63-1.24), 0.475 | 1.23 (0.46-3.31), 0.684 | 48/11/2 | 948/254/21 | 1.00 (0.59-1.72), 0.986 | 0.92 (0.50-1.69), 0.777 | 2.02 (0.49-8.25), 0.330 |
| *DGCR8* | rs720012 | G | A | 156/37/4 | 840/228/19 | 0.92 (0.68-1.25), 0.595 | 0.88 (0.63-1.24), 0.475 | 1.23 (0.46-3.31), 0.684 | 48/11/2 | 948/254/21 | 1.00 (0.59-1.72), 0.986 | 0.92 (0.50-1.69), 0.777 | 2.02 (0.49-8.25), 0.330 |
| *TLR10* | rs4129009 | T | C | 123/66/8 | 718/332/37 | 1.11 (0.86-1.43), 0.440 | 1.12 (0.83-1.51), 0.461 | 1.18 (0.56-2.52), 0.664 | 36/20/5 | 805/377/41 | 1.39 (0.90-2.14), 0.133 | 1.32 (0.78-2.25), 0.301 | 2.54 (0.95-6.82), 0.063 |
| *NOD2* | rs9302752 | C | T | 106/76/15 | 623/411/53 | 1.18 (0.94-1.48), 0.163 | 1.14 (0.86-1.51), 0.351 | 1.56 (0.92-2.64), 0.098 | 35/19/7 | 694/468/61 | 1.18 (0.79-1.78), 0.417 | 0.99 (0.59-1.64), 0.955 | **2.48 (1.13-5.44), 0.024** |
| *UNG* | rs3890995 | T | C | 138/51/8 | 731/320/36 | 0.95 (0.73-1.23), 0.691 | 0.90 (0.66-1.22), 0.493 | 1.24 (0.61-2.52), 0.556 | 42/15/4 | 827/356/40 | 1.08 (0.69-1.70), 0.744 | 0.95 (0.55-1.64), 0.865 | 2.09 (0.75-5.78), 0.157 |
| *NOS2* | rs2297518 | G | A | 131/63/3 | 700/340/47 | 0.86 (0.66-1.11), 0.248 | 0.90 (0.67-1.22), 0.507 | 0.38 (0.12-1.19), 0.097 | 45/15/1 | 786/388/49 | 0.66 (0.39-1.10), 0.109 | 0.64 (0.36-1.14), 0.128 | 0.42 (0.06-3.02), 0.387 |
| *NOS2* | rs2301368 | A | G | 72/98/27 | 347/543/197 | 1.19 (0.96-1.47), 0.108 | 1.39 (0.91-2.14), 0.132 | 1.20 (0.88-1.63), 0.240 | 20/27/14 | 399/614/210 | 1.15 (0.79-1.68), 0.454 | 1.02 (0.58-1.79), 0.9451 | 1.51 (0.81-2.81), 0.196 |
| *TP53* | rs1042522  [Pro]/[C]: 41.3% | C | G | 101/76/20 | 589/423/75 | 1.17 (0.94-1.46), 0.157 | 1.14 (0.85-1.52), 0.390 | 1.54 (0.96-2.48), 0.072 | 26/27/7 | 663/471/88 | **1.46 (1.00-2.14), 0.050** | 1.60 (0.95-2.70), 0.079 | 1.76 (0.79-3.95), 0.169 |
| *HRAS* | rs12628 | A | G | 85/94/17 | 500/454/133 | 0.97 (0.78-1.20), 0.784 | 1.10 (0.81-1.48), 0.540 | 0.66 (0.39-1.13), 0.127 | 25/31/5 | 560/518/145 | 1.03 (0.70-1.52), 0.878 | 1.22 (0.71-2.10), 0.468 | 0.68 (0.26-1.77), 0.425 |
| *MTHFR* | rs1801133 | G | A | 99/77/21 | 489/475/123 | 0.88 (0.71-1.09), 0.253 | 0.82 (0.62-1.08), 0.160 | 0.95 (0.61-1.50), 0.839 | 31/22/8 | 557/530/136 | 0.93 (0.64-1.36), 0.701 | 0.81 (0.49-1.34), 0.413 | 1.20 (0.57-2.52), 0.630 |
| *GNAS* | rs7121 | C | T | 64/92/41 | 307/539/241 | 0.88 (0.70-1.11), 0.288 | 0.79 (0.56-1.12), 0.190 | 0.91 (0.60-1.38), 0.650 | 19/31/11 | 353/600/270 | 0.89 (0.59-1.33), 0.557 | 0.91 (0.48-1.72), 0.766 | 0.75 (0.34-1.64), 0.465 |
| *GNB3* | rs5443 | C | T | 86/90/21 | 514/465/107 | 1.08 (0.87-1.33), 0.489 | 1.13 (0.84-1.50), 0.420 | 1.04 (0.65-1.67), 0.854 | 28/28/5 | 573/527/123 | 0.98 (0.66-1.44), 0.903 | 1.04 (0.62-1.74), 0.874 | 0.77 (0.30-2.00), 0.594 |
| *CDKN2A* | rs3088440 | G | A | 159/37/1 | 917/158/12 | 1.21 (0.87-1.68), 0.260 | 1.28 (0.89-1.83), 0.182 | 0.71 (0.12-3.99), 0.694 | 50/10/1 | 1026/185/12 | 1.19 (0.66-2.16), 0.560 | 1.18 (0.61-2.28), 0.629 | 1.81 (0.24-13.69), 0.563 |

**Abbreviations:** SNP: single-nucleotide polymorphism; HR: hazard ratio; CI: confidence interval; NMIBC: non-muscle-invasive bladder cancer; MIBC: muscle-invasive bladder cancer; NBCS: Nijmegen Bladder Cancer Study; DOM: dominant; ADD: additive; REC: recessive.

**a** progression defined as G1/2/2A/low-grade to G2B/3/high-grade; Ta/CIS to T1; T1 to ≥T2; NX/0 to ≥N1; MX/0 to M1

**b** progression defined as Ta/CIS/T1 to ≥T2

**c** A1: major/reference allele; A2: minor/predictive allele (both according to + strand orientation),

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