SUPPLEMENTARY MATERIAL AND METHODS

Multi Marker Methods (MMM)

Bayes A (BA) and Bayesian LASSO (BL) were coupled with the sequential threshold model developed by Albert and Chib [1] to handle the large *p* small *n* problem accounting for the time to event and censoring. It assumes that for an observation of a patient to be present at a given period of time, he/she must have survived through all previous time periods. Thus, the probability of not presenting the event of interest until interval *l*, conditional on the event that the *l*-th interval has been reached, is given by $\Pr(y_i = l \mid y_i \geq l-1, \boldsymbol{\gamma}, \boldsymbol{\theta}) = \Phi\left(\frac{\gamma_l - \mathbf{X}'\boldsymbol{\theta}}{\sigma_e^2}\right)$, where $\boldsymbol{\gamma}$ corresponds to unordered cutoff points corresponding to each time interval, $\mathbf{X}$ corresponds to the incidence matrix of effects ($\boldsymbol{\theta}$) affecting the liability to survive to the next interval given that the present interval has been reached and σ_e^2 is the residual variance, which was set to 1 for identification purposes [2]. Thus, the presence of the event of interest (first recurrence or progression) is checked in each interval, and the outcome in that interval is codified as 0 if present and 1 otherwise. If the data is not censored in that interval, then the patient has data in the next interval and the outcome in that interval is codified as 0 or 1 as before mentioned. If the data is censored in the first interval, then the individual does not have data in the subsequent intervals.

Intervals were defined according to the survival functions for each event (see Figures S2 and S3), considering a minimum of events for interval. For time to first recurrence, 9 follow-up intervals were defined: ≤ 3, 4-6, 7-9, 10-12, 13-18, 18-24, 24-36, 36-48 and > 48 months. Regarding time to progression, 4 intervals were defined (4 levels, (≤ 12 months, 13-24 months, 25-48 months and >48 months). When patients were stratified at

high/low risk, 4/3 intervals were defined: ≤ 6; 7-12; 13-24 and > 24 months; and ≤ 24; 25-48 and >48 months, respectively.

As in [3], markers were considered as associated with bladder cancer when both BA_t and BL_t identified them as associated with the outcome. Both BA and BL are characterized by thick-tailed priors, the scaled t and the double exponential (DE), respectively. These densities have higher mass at 0, which shrinks toward 0 the estimates of marker effects with small effects and induces less shrinkage (thicker tails) to markers with larger effects. The prior distributions were $\text{Inv}-\chi^2(4.01,0.016)$ (scaled *t* prior for marker effects) in BA and an exponential density (double exponential prior for marker effects, $\prod_{j=1}^{m} N\left(\beta_j\middle|0,\tau_j^2\sigma_\varepsilon^2\right)\times\prod_{j=1}^{m}\exp\left(\tau_j^2\middle|\lambda\right)$) in BL. Parameter λ in BL controls the shape of the prior distribution assigned to τ_j^{-2}, assigning more density to small values of τ_j than to large ones, and follows, a priori, a Gamma distribution $G\left(\lambda^2\middle|10,0.75\right)$. For each analysis, a unique Markov Chain Monte Carlo of 50,000 iterations was obtained using a Gibbs sampler. The first 20,000 iterations were discarded as burn-in and all the remaining iterations were retained to infer posterior marginal distributions of unknown parameters. Convergence of chains was assessed visually, applying the Geweke criterion [4] and running parallel chains with different initial values. A permutation within Markov Chain Monte Carlo approach [5] was used to determine the markers that were associated with the phenotype for both models. Markers were considered as associated to the trait if the $\max(a,1-a)>t$, where $a=\int_{-\infty}^{\hat{\beta}_p} p\left(\beta_p\middle|\mathbf{y}_{permu},\boldsymbol{\beta}_{-p}\right)d\beta_p$, $\hat{\beta}_p$ is the posterior mean of the SNP *p* after analyzing the original data, and $p\left(\beta_p\middle|\mathbf{y}_{permu}\right)$ is the posterior distribution of the marker effect given the permuted data ($\mathbf{y}_{permu}$).

When the existence of BCG*SNP interactions associated with time to progression were explored in the high-risk NMIBC subgroup, we also used MMMs, adding the interaction terms to the model including clinical-pathological parameters and SNPs.

REFERENCES

[1] Albert JH, Chib S. Sequential ordinal modeling with applications to survival data. Biometrics 2001;57:829-36.

[2] Sorensen D, Gianola D. Likelihood, Bayesian, and MCMC Methods in Quantitative Genetics. New York: Springer Science & Business Media; 2002.

[3] Lopez de Maturana E, Ibanez-Escriche N, Gonzalez-Recio O, Marenne G, Mehrban H, Chanock SJ, et al. Next generation modeling in GWAS: comparing different genetic architectures. Hum Genet 2014;133:1235-53.

[4] Geweke J. Bayesian Statistics 1992. p. 169-93.

[5] Che X, Xu S. Significance test and genome selection in bayesian shrinkage analysis. Int J Plant Genomics 2010;2010:893206.

Table S1: List of inflammation-related genes selected for the study.

ABCA1	CCR10	CXCR3	IL12A	MAP3K7	SOCS5
ABCA7	CCR2	CXCR4	IL12B	MAP3K7IP2	SOCS6
ABCC4	CCR3	CXCR7	IL13	MAPK14	STAT1
ABCF1	CCR4	EIF2AK2	IL15	MASP1	STAT3
ABO	CCR5	EPHX2	IL15RA	MBL2	TBK1
AICDA	CCR7	EXO1	IL16	MPO	TFF1
AIRE	CCR7	FADD	IL17A	MS4A1	TFF3
AKR1C3	CCR9	FAS	IL17C	MSH2	TGFB1
AKT1	CD14	FAS	IL18	MX1	TGFBR1
ALOX12	CD180	FASLG	IL1A	MYD88	TICAM1
ALOX15	CD2	FCGR2A	IL1B	NBS1	TIRAP
ALOX5	CD274	FOS	IL1RN	NCF2	TLR1
ANPEP	CD28	GATA3	IL2	NFKB1	TLR10
APOA2	CD3	GDF15	IL21	NFKBIA	TLR2
ARHGDIB	CD33	GSK3B	IL21R	NINJ1	TLR4
BCL10	CD4	H2AFX	IL22	NLRP12	TLR6
BCL3	CD40	HAVCR2	IL23	NOD2	TLR9
BCL6	CD45	HDAC5	IL2RA	NOS2A	TMED7
BIRC2	CD5	HDAC7A	IL3	OPRD1	TMEM189
BIRC3	CD68	HFE	IL4	OSCAR	TNF
BIRC5	CD8	HLA-A	IL4R	PARP4	TNFAIP3
BLNK	CD80	HLA-B	IL6	PPARG	TNFRSF10A
CARD15	CD81	HLA-C	IL6R	PRF1	TNFRSF1A
CARD4	CD86	HLA-E	IL7	PRG3	TNFRSF7
CASP1	CDH1	HLA-F	IL7R	PRKRA	TNFSF14
CASP3	CFH	HLA-G	IL8	PTGS1	TNIP1
CASP8	CFLAR	HLA-H	IL8RA	PTGS2	TOLLIP
CASP9	CGB	HSP90AA1	IL8RB	RAG1	TRADD
CBR1	CHKA	HSPA4	IRAK2	RELA	TRAF1
CCL13	CHUK	HSPB1	IRF1	RHOA	TRAF2
CCL17	COX2	HSPD1	IRF3	RIPK1	TRAF5
CCL17	CRP	ICAM1	JAG2	RIPK2	TRAF6
CCL19	CSF1R	ICBR	JAK1	ROCK1	TSLP
CCL2	CSF3	IFNAR2	JAK3	SARM1	UBE2N
CCL21	CTLA4	IFNG	LEPR	SCARB1	ULBP1
CCL22	CX3CL1	IFNGR1	LITAF	SELE	ULBP2
CCL22	CX3CR1	IFNGR2	LTA	SFTPD	ULBP3
CCL28	CXCL10	IKBKB	LY96	SIGIRR	VCAM1
CCL28	CXCL11	IKZF1	MAP2K3	SLAMF1	WWP1
CCL5	CXCL12	IL10	MAP2K4	SLC20A1	XBP1
CCND3	CXCL9	IL10RA	MAP3K14	SLC44A2	YY1
CCR1	CXCR1	IL11	MAP3K3	SOCS2	

Table S2: Variables used for adjustment in the single and multimarker models.

TFR	Area + gender + multiplicity[a] + TSG[b] + tumour size[c] + treatment[d]
TP	Area + age + multiplicity[a] + TSG[b] + number of recurrences[e] + treatment[f]

TFR = Time to first recurrence; TP= Time to progression : TSG = Tumour stage and grade

[a] Divided in 3 categories: 1= One tumour, 2= >1, and 3= missing data.

[b] Divided in 6 categories: 1= PUNLMP+TaG1, 2= TaG2, 3= TaG3, 4= T1G2, 5= T1G3 and 6=TiG2+TiG3.

[c] Divided in 3 categories: 1= < or equal 3 cm, 2= >3 cm and 3= missing data.

[d] Divided in 5 categories 1= TURB alone, 2= TURB+intravesical chemotherapy, 3= TURB +Bacillus Calmette Guerin (BCG), 4= TURB+intravesical chemotherapy+BCG and 5= Other treatments.

[e] Divided in 3 categories 1= 1 recurrence, 2= 2 recurrences, 3= 3 recurrences and 4= >3 previous recurrences.

[f] Divided in 6 categories as in [d] plus TURB+radical cystectomy.

Table S3: Treatment characteristics.

	Low Risk (N=538)	**High Risk (N=284)**
	N (%)	**N (%)**
TURB	274 (51)	78 (27.5)
TURB + IVC	134 (25)	46 (16.2)
TURB + BCG	111 (20.6)	134 (47.3)
TURB + IVC + BCG	12 (2.2)	9 (3.1)
TURB + Cystectomy	4 (0.7)	8 (2.8)
Others	3 (0.5)	9 (3.1)

TURB = Trans Urethral Resection of the Bladder; IVC= Intra-vesical chemotherapy; BCG = Bacillus Calmette et Guerin.

Table S4: The top 10 autosomal SNPs associated with NMIBC risk of first recurrence using multivariate Cox regression additive model.

GENE	SNP	HR	*p-value*	MAF
TNIP1	rs2277940	1.74	0.0001	0.07
CCL28	rs779850	0.61	0.0004	0.17
CCR9	rs2191031	0.62	0.0005	0.17
PPARG	rs3112395	1.73	0.0007	0.05
CCL2	rs10805673	0.75	0.0012	0.49
CARD4	rs10267377	0.71	0.0013	0.29
PTPRC	rs1036332	0.73	0.0029	0.27
RIPK1	rs6596945	0.70	0.0029	0.22
CD3Z	rs1554669	1.50	0.0044	0.07
CCR2	rs3138042	0.76	0.0046	0.34

Analyses were adjusted for: geographical area, gender, multiplicity, tumour stage&grade, tumour size, and treatment (See, Table S2).

Table S5: SNPs with a strong posterior probability (PP>80%) of being associated with time to first recurrence considering all NMIBC patients. Those with PP in both BA and BL >90% are bold-faced. The last column shows Cox regression results. SNPs in red were also among the top10 SNPs identified by Cox regression.

			BA		BL		Single marker Cox	
Gene	SNP	MAF	HR_{aa_A}	PP>80%	HR_{aa_A}	PP>80%	HR	*p*-value
JAK3	rs6523*	0.40	1.69	98	1.17	92	1.20	0.0488
CCL2	rs4497746	0.08	1.59	94	1.14	87	1.31	0.0641
ICEBERG	rs3736149	0.43	1.41	93	1.15	89	1.20	0.0349
CD180	rs5744463	0.11	1.52	93	1.13	86	1.23	0.1230
ICAM1	rs5030390	0.08	0.63	92	0.87	87	0.56	0.0053
CD274	rs7043593	0.23	1.44	92	1.10	81	1.09	0.3827
MAP3K14	rs3785803	0.14	0.67	91	0.88	87	0.68	0.0058
TNIP1	**rs2277940**	**0.07**	**1.50**	**91**	**1.24**	**94**	**1.74**	**0.0001**
CD5	**rs7104333**	**0.49**	**0.72**	**90**	**0.86**	**92**	**0.81**	**0.0126**

					0.84		**0.7**	**0.001**
CCL28	**rs10805673**	**0.49**	**0.73**	**90**		**94**	**5**	**2**
					1.16		1.2	0.009
BLNK	rs11188660	0.29	1.42	89		90	7	8
					1.11		1.1	0.062
SCARB1	rs3924313	0.33	1.29	89		84	8	8
					0.84		0.7	0.002
PTPRC	rs1036332	0.27	0.69	89		92	3	9
					0.88		0.8	0.069
BLNK	rs12772113	0.23	0.71	89		87	2	5
					0.84		0.6	0.000
CCR9	rs2191031	0.17	0.70	88		92	2	5
					0.89		0.8	0.017
CCL2	rs317325	0.37	0.74	88		87	0	9
					0.86		0.7	0.001
CARD4	rs10267377	0.29	0.75	88		90	1	3
RIPK1	rs6596945	0.22	0.74	88	0.86	90		
					1.10		1.1	0.236
CMKOR1	rs7556982	0.47	1.34	88		82	1	4
					0.90		0.8	0.154
IL18	rs11214093	0.43	0.75	87		85	8	1
					0.91		0.8	0.204
TNFRSF10A	rs2235126	0.29	0.77	87		81	8	3
					0.91		0.8	0.318
CX3CL1	rs2239354	0.10	0.71	87		81	6	7
					1.09		1.1	0.249
CD33	rs3865444	0.29	1.30	87		80	2	0

					1.13		1.2	0.056
IL6	rs13247988	0.25	1.35	86		86	0	1
					1.09		1.2	0.041
CD3Z	rs858553	0.39	1.30	86		81	0	9
					0.88		0.8	0.067
CD3D	rs2276424	0.30	0.75	86		88	3	5
					0.90		0.7	0.062
CD5	rs7342164	0.14	0.73	86		83	7	8
					1.10		1.2	0.026
CD8B1	rs13024609	0.20	1.34	85		82	5	8
					1.12		1.2	0.032
HAVCR2	rs919746	0.16	1.30	85		84	7	0
					0.89		0.7	0.004
CCR2	rs3138042	0.34	0.78	84		87	6	6
					0.88		0.8	0.012
CMKOR1	rs2720100	0.48	0.77	84		87	0	2
					0.87		0.6	0.000
CCL28	rs779850	0.17	0.77	84		89	1	4
					1.14		1.2	0.010
TNF	rs1799964	0.24	1.30	84		87	8	9
					0.91		0.6	0.009
IFNGR1	rs3799488	0.12	0.77	83		82	7	9
					0.91		0.8	0.195
CCL21	rs2812377	0.37	0.77	83		83	9	5
					1.11		1.3	0.018
CD80	rs9282638	0.16	1.28	83		83	0	0

					0.90		0.8	0.094
IFNGR2	rs1059293	0.44	0.81	83		85	6	8
					0.90		0.8	0.101
CXCR4	rs543721	0.45	0.77	82		84	6	8
					0.91		0.7	0.014
PRKRA	rs2059691	0.35	0.80	82		84	9	7
					1.12		1.7	0.000
PPARG	rs3112395	0.05	1.35	81		83	3	7
					1.12		1.2	0.005
IL23R	rs10489628	0.35	1.26	81		85	7	0
					1.10		1.2	0.081
ABCA1	rs4149313	0.18	1.23	80		83	1	7
					1.09	81	1.1	0.126
BLNK	rs11188661	0.34	1.23	80			4	3

* Previously as rs2286662. Analyses were adjusted for: geographical area, gender, multiplicity, tumour stage&grade, tumour size, and treatment (See, Table S2).

Table S6. SNPs with a strong posterior probability (PP>75%) of being associated with time to first progression considering high-risk NMIBC patients. The last column displays the Cox regression results for each SNP + covariates. SNPs in red were also among the top10 SNPs identified with Cox regression.

			BA		BL		Cox regression	
Gene	SNP	MAF	HR_{aa_AA}	PP>75%	HR_{aa_AA}	PP>75%	HR	*p*-value
TMEM189	rs2269217	0.23	1.31	80	1.10	80	2.41	0.0003
MAP2K3	rs9901404	0.48	1.27	77	1.10	80	1.86	0.0018
CARD4	rs2256023	0.44	1.27	79	1.09	79	1.68	0.0084

Analyses were adjusted for: geographical area, age, multiplicity, tumour stage&grade, number of recurrences, and treatment (See, Table S2).

Table S7: SNPs with a strong posterior probability (PP>75%) of being associated with time to first progression considering low-risk NMIBC patients. The last column displays the Cox regression results for each SNP + covariates. The SNP (in red) was also among the top10 SNPs identified with Cox regression.

			BA		BL		Cox regression	
Gene	SNP	MAF	HR_{aa_AA}	PP>75%	HR_{aa_AA}	PP>75%	HR	*p*-value
CD68	rs12942088	0.43			1.08	75	2.91	0.0006

Analyses were adjusted for: geographical area, age, multiplicity, tumour stage&grade, number of recurrences, and treatment (See, Table S2).

Table S8. Apparent and validated c-index using Bootstrap alone or 1000 bootstrap cross validation indicating the discriminatory ability of the models including the clinical variables (CV) and each of the SNPs showing an association with each outcome of interest.

	Apparent *c*-index	Bootstrap alone *c*-index	Bootstrap cross validation *c*-index
Recurrence ALL (N=268 events)			
CV + rs2277940[a]	64	61.3	59.8
CV + rs7104333[b]	63.2	60.6	59
CV + rs2286662[c]	63.3	60.5	58.9
CV + rs2277940 + rs7104333	64.5	61.8	60.3
CV + rs2277940 + rs2286662	64.3	61.7	60.1
CV + rs7104333 + rs2286662	63.7	61	59.4
Progression ALL (N=76 events)			
CV + rs698079 [d]	78.1	74.9	72.2
CV + rs941405 [e]	78.1	75.1	72.6
Progression HiR (N=52 events)			
CV + rs2256023	71.6	65.5	62
CV + rs9901404	71.9	65.7	62.1
CV + rs2269217	72.2	67	63.9
CV + rs2269217 + rs9901404	74.3	68.8	65.6
CV + rs9901404 + rs2256023	73.8	63.8	67.5
CV + rs2269217 + rs2256023	73.6	68	64.8

[a] *TNIP1*; [b] *CD5;* [c]*JAK3;* [d] *MASP1*; [e] *AIRE;* [f] *CARD4;* [g] *MAP2K3;* [h] *TMEM189*

Figure S1. Methodology used for statistical analyses. A Single Marker Method (SMM) consists of inclusion of each SNP individually while a Multi Marker Method (MMM) allows inclusion of all SNPs together in the model. Interest lies in mimicking the polygenic scenario that features bladder cancer prognosis.

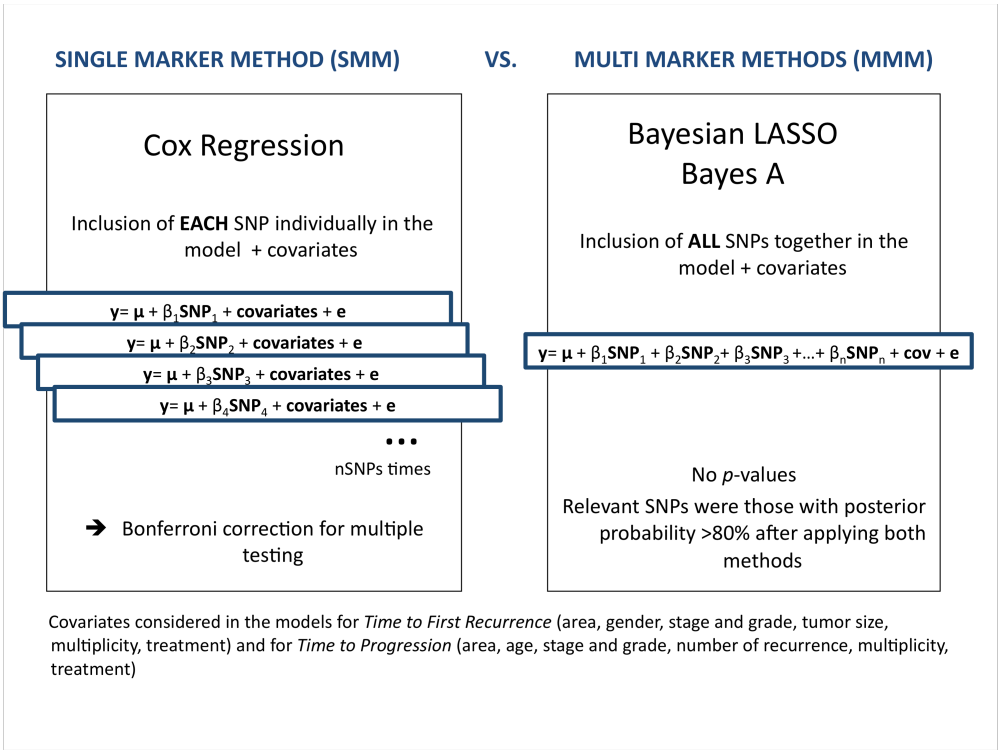

Figure S2. Survival curve for time to recurrence considering all of non-muscle invasive bladder cancer patients.

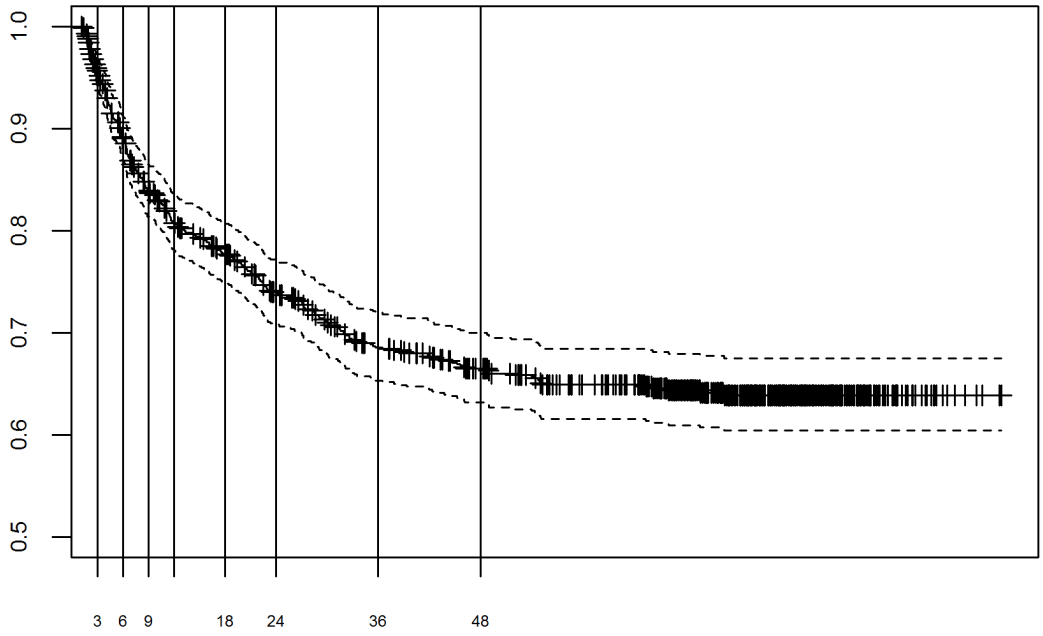

Figure S3. Survival curve for time to first progression considering all of non-muscle invasive bladder cancer patients.