Replication studies

Table S8. Characteristics and results of independent discovery and replication cohorts, studying genetic variants associated with treatment response in patients with osteosarcoma.

Author	Outcome	No. of patients	HR (95% CI)	P value	Ref
***ABCB1* rs10276036**					
Caronia *et al.,* 2011*	EFS	102	0.42 (0.29-0.81)	**0.0021**	(1)
Liu *et al.*, 2014	PFS	186	1.24 (0.79-1.93)	0.32	(2)
***ABCB1* rs1128503**					
Caronia *et al.,* 2011*	EFS	102	0.42 (0.29-0.81)	**0.0021**	(1)
Windsor *et al.,* 2012	PFS	58	N/S	ns	(3)
Yang *et al.*, 2013	DFS	208	3.74 (1.63-7.4)	**0.003**	(4)
Li *et al*., 2014	OS	162	3.17 (1.14-6.67)	**0.01**	(5)
Liu *et al.*, 2014	PFS	186	0.49 (0.31-0.76)	**<0.001**	(2)
Hattinger et al., 2016	EFS	126	N/S	ns	(6)
***ABCB1* rs4148737**					
Caronia *et al.,* 2011*	EFS	102	2.6 (1.24-3.22)	**0.00051**	(1)
Liu *et al.*, 2014	PFS	186	1.47 (0.93-2.33)	0.08	(2)
***ABCC2* rs2273697**					
Hattinger *et al.,* 2016*	EFS	126	N/S	**0.049**	(6)
Windsor *et al.,* 2012	PFS	58	N/S	ns	(3)
***ABCC2* rs717620**					
Windsor *et al.,* 2012*	Histological response	58	6.3 (1.4-28.5)[a]	**0.017**	(3)
Yang *et al.*, 2013	DFS	208	N/S	ns	(4)
Goričar *et al.*, 2014	OS	44	0.5 (0.14-1.75)	0.275	(7)
Hagleitner *et al.,* 2015	PFS	126	N/S	ns	(8)
Hattinger et al., 2016	EFS	126	N/S	ns	(6)
***ABCC3* rs4148416**					
Caronia *et al.,* 2011*	EFS	102	6.33 (1.79-12.7)	**0.00028**	(1)
Yang *et al.*, 2013	DFS	208	4.32 (1.75-15.65)	**0.006**	(4)
Liu *et al.*, 2014	PFS	186	2.73 (1.62-4.66)	**<0.001**	(2)
***ABCC5* rs939338**					
Hagleitner *et al.,* 2015*	PFS	126	1.86 (1.06-3.24)[a]	**0.03**	(8)
Hagleitner *et al.,* 2015	PFS	64	1.36 (0.62-2.98)[a]	0.44	(8)
Xu *et al.*, 2018	PFS	132	2.01 (1.2-3.37)[a]	**0.008**	(9)
***CASP3* rs2720376**					

Hagleitner *et al.,* 2015*	PFS	126	0.52 (0.3-0.9)[a]	**0.02**	(8)
Hagleitner *et al.,* 2015	PFS	64	0.68 (0.3-1.56)[a]	0.36	(8)
Xu *et al.*, 2018	PFS	132	1.02 (0.62-1.71)[a]	0.95	(9)
***CCND1* rs9344**					
Windsor *et al.,* 2012*	PFS	58	N/S	**0.018**	(3)
***CHST12* rs3735099**					
Bhuvaneshwar *et al.,* 2019*	OS and tumor necrosis	100	3.124 (N/S)	**0.04**	(10)
***CHST12* rs3735100**					
Bhuvaneshwar *et al.,* 2019*	OS and tumor necrosis	100	3.124 (N/S)	**0.04**	(10)
CYP2B6*6					
Hattinger *et al.,* 2016*	EFS	126	N/S	**0.039**	(6)
***CYP3A4* rs4646437**					
Hagleitner *et al.,* 2015*	PFS	126	0.34 (0.13-0.85)[a]	**0.02**	(8)
Hagleitner *et al.,* 2015	PFS	64	0.61 (0.19-1.94)[a]	0.4	(8)
Xu *et al.*, 2018	PFS	132	0.69 (0.39-1.26)[a]	0.24	(9)
***FasL* rs763110**					
Hagleitner *et al.,* 2015*	PFS	126	1.97 (1.04-3.73)[a]	**0.04**	(8)
Hagleitner *et al.,* 2015	PFS	64	1.5 (0.7-3.21)[a]	0.3	(8)
Xu *et al.*, 2018	PFS	132	2.26 (1.35-3.77)[a]	**0.002**	(9)
***GGH* rs11545078**					
Hattinger *et al.,* 2016*	EFS	126	N/S	**0.037**	(6)
***GLDC* rs3765555**					
Koster *et al.,* 2018*	OS	523	1.71 (1.34-2.18)	**1.60×10^{-5}**	(11)
Koster *et al.,* 2018	OS	109	2.12 (1.27-3.53)	**3.87×10^{-3}**	(11)
***GLDC* rs55933544**					
Koster *et al.,* 2018*	OS	523	1.91 (1.49-2.45)	**3.20×10^{-7}**	(11)
Koster *et al.,* 2018	OS	109	1.98 (1.16-3.38)	**0.012**	(11)
Lin *et al.*, 2020	OS	72	3.98 (1.87-4.96)[a]	**<0.001**	(12)
***GSTP1* rs1695**					
Windsor *et al.,* 2012*	Histological response	58	7.9 (1.5-42.5)[a]	**0.016**	(3)
Windsor *et al.,* 2012*	PFS	58	N/S	**0.025**	(3)
Yang *et al.*, 2012	OS	187	0.53 (0.24-1.16)	0.32	(13)
Zhang *et al.*, 2012	EFS	159	2.35 (1.13-4.85)	N/S	(14)
Teng *et al.*, 2013	OS	146	2.73 (1.05-7.45)	**<0.05**	(15)
Li *et al*., 2014	OS	162	3.86 (1.41-10.2)	**0.004**	(5)

Liu *et al.*, 2014	PFS	186	2.16 (1.38-3.38)	**<0.001**	(2)
Hattinger et al., 2016	EFS	126	N/S	ns	(6)
***GSTT1* null**					
Windsor *et al.,* 2012*	PFS	58	N/S	**0.006**	(3)
Yang *et al.*, 2012	OS	187	0.92 (0.57-1.76)	0.75	(13)
Zhang *et al.*, 2012	EFS	159	0.7 (0.39-1.33)	ns	(14)
Teng *et al.*, 2013	OS	146	1.43 (0.72-3.04)	0.31	(15)
Li *et al*., 2014	OS	162	1.26 (0.63-2.42)	0.66	(5)
Liu *et al.*, 2014	PFS	186	1.18 (0.64-2.18)	0.58	(2)
Hattinger et al., 2016	EFS	126	N/S	ns	(6)
***MSH2* rs4638843**					
Hagleitner *et al.,* 2015*	PFS	126	2.32 (1.02-5.27)[a]	**0.04**	(8)
Hagleitner *et al.,* 2015	PFS	64	3.86 (0.98-15.25)[a]	**0.05**	(8)
***MTHFD1* rs2236225**					
Windsor *et al.,* 2012*	Histological response	58	0.2 (0.05-0.9)[a]	**0.03**	(3)
Goričar *et al.*, 2014	OS	44	1.52 (0.54-4.27)	0.43	(7)
Hattinger et al., 2016	EFS	126	N/S	ns	(6)
***RFC1/SLC19A1* rs1051266**					
Windsor *et al.,* 2012*	PFS	58	N/S	**0.02**	(3)
Goričar *et al.*, 2014	OS	44	0.77 (0.29-2.07)	0.601	(7)
Jabeen *et al.*, 2015	OS	62	N/S	**0.046**	(16)
Hattinger et al., 2016	EFS	126	N/S	ns	(6)
***SLC22A1* rs4646272**					
Bhuvaneshwar *et al.,* 2019*	OS and tumor necrosis	100	3.723 (N/S)	**0.007**	(10)
***SLC22A8* rs2187384**					
Bhuvaneshwar *et al.,* 2019*	OS and tumor necrosis	100	3.161 (N/S)	**0.019**	(10)
***TP53* rs1642785**					
Hattinger *et al.,* 2016*	EFS	126	N/S	**0.01**	(6)
***UGT2B15* rs34073924**					
Bhuvaneshwar *et al.,* 2019*	OS and tumor necrosis	100	3.462 (N/S)	**0.024**	(10)

N/S, not specified; ns, not significant; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; EFS, event-free survival; DFS, disease-free survival

* discovery study that was identified in systematic literature search

[a] Odds ratio (95% CI)

Table S9. Characteristics and results of independent discovery and replication cohorts, studying genetic variants associated with doxorubicin-induced cardiotoxicity.

	Outcome	Patient cohort	Diagnosis	No. of patients	OR (95% CI)	P value	Ref.
***ATP2B1* rs17249754**							
Hildebrandt *et al.,* 2017*	EF 45–50% and symptoms; or FS ≤ 25% and/or EF ≤ 45%	Pediatric	Mixed cancer cohort	108	0.33 (0.12–0.92)	**0.034**	(17)
***CELF4* rs1786814**							
Wang *et al*., 2016*	FS ≤ 28% or LVEF ≤ 40% or symptoms	Pediatric	Mixed cancer cohort	331	10.16 (3.8-27.3)	**<0.001**	(18)
Wang *et al*., 2016	FS ≤ 28% or LVEF ≤ 40% or symptoms	Pediatric	Mixed cancer cohort	75	5.09 (1.03-25.23)	**0.046**	(18)
Leger *et al*., 2016	ICD codes of symptoms or self-reported through surveys	Adult	Hematopoietic cell transplantation survivors	576	22.2 (1.5-339.2)	**0.01**	(19)
***GPR35* rs12468485**							
Ruiz-Pinto *et al*., 2017*	FS ≤ 27%	Pediatric	Mixed cancer cohort	93	N/A	**7×10^{-6}**	(20)
***GSTP1* rs1695**							
Windsor *et al.,* 2012*	EF decrease with ≥1 CTCAE	Pediatric	Osteosarcoma	58	4.8 (1.4-16.4)	0.011	(3)
***HAS3* rs2232228**							
Wang *et al*., 2014*	FS ≤ 28% or LVEF ≤ 40% or symptoms	Pediatric	Mixed cancer cohort	401	8.9 (2.1-37.5)	**0.003**	(21)
Wang *et al*., 2014	FS ≤ 28% or LVEF ≤ 40% or symptoms	Pediatric	Mixed cancer cohort	76	4.5 (1.1-18.7)	**0.04**	(21)
Wang *et al*., 2016	FS ≤ 28% or LVEF ≤ 40% or symptoms	Pediatric	Mixed cancer cohort	331	N/S	0.6	(18)
Leger *et al*., 2016	ICD codes of symptoms or self-reported through surveys	Adult	Hematopoietic cell transplantation survivors	576	21.8 (1.2-386.4)	**0.02**	(19)
Sági *et al*., 2018	FS ≤ 28%	Pediatric	ALL and osteosarcoma	661	N/S	N/S, ns	(22)
***PLCE1* rs932764**							
Hildebrandt *et al.,* 2017*	EF 45–50% and symptoms; or FS ≤ 25% and/or EF ≤ 45%	Pediatric	Mixed cancer cohort	108	0.48 (0.27–0.85)	**0.012**	(17)
***RARG* rs2229774**							
Aminkeng *et al*., 2015*	FS ≤ 24% or symptoms requiring intervention in CTCAE v3	Pediatric	Mixed cancer cohort	280	7 (2.9-17)	**5.0×10^{-6}**	(23)
Aminkeng *et al*., 2015	FS ≤ 24% or symptoms requiring intervention in CTCAE v3	Pediatric	Mixed cancer cohort	80	N/A	**4.3×10^{-11}**	(23)
Aminkeng *et al*., 2015	FS ≤ 24% or symptoms requiring intervention in CTCAE v3	Pediatric	Mixed cancer cohort	96	4.1 (1.5-11.5)	**0.0043**	(23)
Serie *et al*., 2017	LVEF reduction > 10% or LVEF < 53%	Adult	HER2+ breast cancer	1191	2.39 (0.91-6.23)	0.076	(24)
Schneider *et al*., 2017	LVEF reduction > 20% or LVEF < 50%	Adult	Breast cancer	102	0.11 (N/S)	**0.0000041**	(25)
Sági *et al*., 2018	FS ≤ 28%	Pediatric	ALL and osteosarcoma	661	N/S	N/S, ns	(22)
Park *et al*., 2020	LVEF reduction > 10% or LVEF < 50%	Adult	Breast cancer	257	N/S	N/S, ns	(26)

***SLC22A17* rs4982753**							
Visscher *et al*., 2015*	FS ≤ 26% or symptoms requiring intervention in CTCAE v3	Pediatric	Mixed cancer cohort	335	0.52 (0.31-0.85)	**0.0078**	(27)
Visscher *et al*., 2015	FS ≤ 26% or symptoms requiring intervention in CTCAE v3	Pediatric	Mixed cancer cohort	185	0.39 (0.19-0.81)	**0.0071**	(27)
Schneider *et al*., 2017	LVEF reduction > 20% or LVEF < 50%	Adult	Breast cancer	102	N/S	N/S, ns	(25)
Ságі *et al*., 2018	FS ≤ 28%	Pediatric	ALL and osteosarcoma	661	N/S	N/S, ns	(22)
***SLC22A7* rs4149178**							
Visscher *et al*., 2015*	FS ≤ 26% or symptoms requiring intervention in CTCAE v3	Pediatric	Mixed cancer cohort	335	0.41 (0.21-0.77)	**0.0034**	(27)
Visscher *et al*., 2015	FS ≤ 26% or symptoms requiring intervention in CTCAE v3	Pediatric	Mixed cancer cohort	185	0.39 (0.14-1.05)	**0.047**	(27)
Schneider *et al*., 2017	LVEF reduction > 20% or LVEF < 50%	Adult	Breast cancer	102	N/S	N/S, ns	(25)
Ságі *et al*., 2018	FS ≤ 28%	Pediatric	ALL and osteosarcoma	661	N/S	N/S, ns	(22)
***SLC28A3* rs7853758**							
Visscher *et al*., 2012*	FS ≤ 26% or symptoms requiring intervention in CTCAE v3	Pediatric	Mixed cancer cohort	156	0.29 (0.11-0.81)	**0.0071**	(28)
Visscher *et al*., 2012	FS ≤ 26% or symptoms requiring intervention in CTCAE v3	Pediatric	Mixed cancer cohort	188	0.33 (0.13-0.8)	**0.0072**	(28)
Visscher *et al*., 2012	FS ≤ 26% or symptoms requiring intervention in CTCAE v3	Pediatric	Mixed cancer cohort	96	0.69 (N/S)	0.38	(28)
Visscher *et al*., 2013	FS ≤ 26% or symptoms requiring intervention in CTCAE v3	Pediatric	Mixed cancer cohort	177	0.46 (0.2-1.08)	0.058	(29)
Vulsteke *et al*., 2015	LVEF reduction > 10% or CTCAEv4 grade 3-5	Adult	Breast cancer	877	N/S	N/S, ns	(30)
Reichwagen *et al*., 2015	CTCAE v2 > grade 0	Adult	CD20+ B-cell lymphoma	450	1.4 (0.8-2.3)	0.27	(31)
Reichwagen *et al*., 2015	CTCAE v2 > grade 0	Adult	CD20+ B-cell lymphoma	634	1.4 (0.7-3)	0.39	(31)
Hertz *et al*., 2016	EF < 55%	Adult	Breast cancer	166	0.55 (0.16-1.91)	0.43	(32)
Ruiz-Pinto *et al*., 2017	FS ≤ 27%	Pediatric	Mixed cancer cohort	93	N/S	**<0.05**	(20)
Serie *et al*., 2017	LVEF reduction > 10% or LVEF < 53%	Adult	HER2+ breast cancer	1191	0.71 (0.25-2.02)	0.52	(24)
Ságі *et al*., 2018	FS ≤ 28%	Pediatric	ALL and osteosarcoma	661	9.837 (1.73-56.02)	**0.01**	(22)

N/S, not specified; N/A, not applicable; ns, not significant; FS, fractional shortening ;LVEF, left ventricular ejection fraction; EF, ejection fraction; CTCAE, Common Terminology Criteria for Adverse Events; ALL, acute lymphatic leukemia

* discovery study that was identified in systematic literature search

Table S10. Characteristics and results of independent discovery and replication cohorts, studying genetic variants associated with bone marrow- hepato- and nephrotoxicity after treatment with cisplatin, doxorubicin or methotrexate.

Author	Outcome	Induced by[a]	Patient cohort	Diagnosis	No. of patients	OR (95% CI)	p-value	Ref.
***ABCB1* rs1128503**	**Hepatotoxicity**							
Hattinger et al., 2016*	CTCAE v4 grade 4	MAP	Pediatric	Osteosarcoma	57	2.06 (1.16-3.66)	**0.014**	(6)
Hegyi et al., 2017	CTCAE v3 grade 3-4	MTX	Pediatric	Osteosarcoma	59	N/S	ns	(33)
Hurkmans et al., 2020	ALAT	MTX	Pediatric	Osteosarcoma	113	N/S	ns	(34)
***ABCC2* rs17222723**	**Leukopenia**							
Windsor et al., 2012*	CTCAE v3 grade 3-4	MTX	Pediatric	Osteosarcoma	58	5.2 (1.2-22.4)	**0.028**	(3)
Hurkmans et al., 2020	Leukocyte counts	MTX	Pediatric	Osteosarcoma	113	N/S	ns	(34)
***ABCC2* rs2273697**	**Hepatotoxicity**							
Windsor et al., 2012	CTCAE v3 grade 3-4	MAP	Pediatric	Osteosarcoma	58	N/S	ns	(3)
Sharifi et al., 2014	CTCAE v3 grade 1-4	MTX	Pediatric	ALL	65	0.55 (0.2-1.48)	0.32	(35)
Goričar et al., 2014	CTCAE v4 grade 3-4	MTX	Pediatric	Osteosarcoma	118	1.88 (0.1-3.49)	0.414	(7)
Hattinger et al., 2016*	CTCAE v4 grade 4	MAP	Pediatric	Osteosarcoma	57	1.96 (1.2-3.2)	**0.007**	(6)
Gervasini et al., 2017	CTCAE v4	MTX	Pediatric	ALL	41	N/S	ns	(36)
Hegyi et al., 2017	CTCAE v3 grade 3-4	MTX	Pediatric	Osteosarcoma	59	N/S	ns	(33)
Hurkmans et al., 2020	ALAT	MTX	Pediatric	Osteosarcoma	113	N/S	ns	(34)
***ABCC2* rs2273697**	**Leukopenia**							
Windsor et al., 2012	CTCAE v3 grade 3-4	MAP	Pediatric	Osteosarcoma	58	N/S	ns	(3)
Sharifi et al., 2014	CTCAE v3 grade 1-4	MTX	Pediatric	ALL	65	0.61 (0.13-2.97)	0.69	(35)
Hattinger et al., 2016*	CTCAE v4 grade 4	MAP	Pediatric	Osteosarcoma	57	13.16 (1.56-111.12)	**0.018**	(6)
Gervasini et al., 2017	CTCAE v4	MTX	Pediatric	ALL	41	N/S	ns	(36)
Hegyi et al., 2017*	CTCAE v3 grade 3-4	MTX	Pediatric	Osteosarcoma	59	3.3 (1.2-9.4)	**0.02**	(33)
Hurkmans et al., 2020	Leukocyte counts	MTX	Pediatric	Osteosarcoma	113	N/S	ns	(34)
***ABCC2* rs2273697**	**Thrombocytopenia**							
Windsor et al., 2012	CTCAE v3 grade 3-4	MAP	Pediatric	Osteosarcoma	58	N/S	ns	(3)
Sharifi et al., 2014	CTCAE v3 grade 1-4	MTX	Pediatric	ALL	65	2.5 (0.89-6.97)	0.12	(35)
Hattinger et al., 2016*	CTCAE v4 grade 4	MAP	Pediatric	Osteosarcoma	57	4.33 (1.2-15.63)	**0.025**	(6)
Gervasini et al., 2017	CTCAE v4	MTX	Pediatric	ALL	41	N/S	ns	(36)
Hurkmans et al., 2020	Thrombocyte counts	MTX	Pediatric	Osteosarcoma	113	N/S	ns	(34)
***ABCC2* rs3740066**	**Leukopenia**							
Hattinger et al., 2016	CTCAE v4 grade 4	MAP	Pediatric	Osteosarcoma	57	N/S	ns	(6)
Hegyi et al., 2017*	CTCAE v3 grade 3-4	MTX	Pediatric	Osteosarcoma	59	0.4 (0.2-0.9)	**0.02**	(33)

Hurkmans et al., 2020	Leukocyte counts	MTX	Pediatric	Osteosarcoma	113	N/S	ns	(34)
***CYBA* rs4673**	**Anemia**							
Windsor et al., 2012*	CTCAE v3 grade 3-4	Doxorubicin, cisplatin	Pediatric	Osteosarcoma	58	0.3 (0.09-0.9)	**0.038**	(3)
***CYP2B6* rs4803418**	**Thrombocytopenia**							
Hurkmans et al., 2020*	Thrombocyte counts	MTX	Pediatric	Osteosarcoma	113	-0.19 (-0.27--0.1) [b]	**0.00003**	(34)
***CYP2B6* rs4803419**	**Thrombocytopenia**							
Hurkmans et al., 2020*	Thrombocyte counts	MTX	Pediatric	Osteosarcoma	113	0.19 (0.1-0.29) [b]	**0.00006**	(34)
***CYP4F8* rs4808326**	**Thrombocytopenia**							
Hurkmans et al., 2020*	Thrombocyte counts	MTX	Pediatric	Osteosarcoma	113	-0.19 (-0.28--0.09) [b]	**0.00009**	(34)
***ERCC1* rs3212986**	**Leukopenia**							
Windsor et al., 2012*	CTCAE v3 grade 3-4	Doxorubicin	Pediatric	Osteosarcoma	58	5.4 (1.1-26)	**0.036**	(3)
Hattinger et al., 2016	CTCAE v4 grade 4	MAP	Pediatric	Osteosarcoma	57	N/S	ns	(6)
***ERCC2/XPD* rs13181**	**Nephrotoxicity**							
Khrunin et al., 2010	CTCAE grade 1-4	Cisplatin	Adult	Ovarian cancer	104	1.385 (0.526-3.644)	0.615	(37)
Khrunin et al., 2012	CTCAE v2 grade 1-4	Cisplatin	Adult	Ovarian cancer	87	N/S	ns	(38)
Windsor et al., 2012*	CTCAE v3 grade 3-4	MAP	Pediatric	Osteosarcoma	58	4.4 (1-18.8)	**0.044**	(3)
Lopes-Aguiar et al., 2017	CTCAE v4 grade 2-5	Cisplatin	Adult	Head and neck squamous cell carcinoma	90	3.55 (1.27-9.87)	**0.01**	(39)
Zazuli et al., 2019	CTCAE grade 1-4	Cisplatin	Adult	Testicular cancer	163	3.16 (1.17-8.58)	**0.02**	(40)
Garcia et al., 2020	GFR decline	Cisplatin	Adult	Testicular cancer	433	N/S	**0.03**	(41)
***ERCC2/XPD* rs1799793**	**Thrombocytopenia**							
Tibaldi et al., 2008	CTCAE v3 grade 3-4	Cisplatin, gemcitabine	Adult	Non-Small Cell Lung Cancer Patients	65	N/S	0.35	(42)
Khrunin et al., 2010	CTCAE grade 1-4	Cisplatin	Adult	Ovarian cancer	87	4.054 (1.21-13.583)	**0.027**	(37)
Hattinger et al., 2016*	CTCAE v4 grade 4	MAP	Pediatric	Osteosarcoma	57	5.59 (1.66-18.87)	**0.006**	(6)
Lopes-Aguiar et al., 2017	CTCAE v4 grade 1-4	Cisplatin	Adult	Head and neck squamous cell carcinoma	90	N/S	ns	(39)
***GGH* rs1800909[HW]**	**Hepatotoxicity**							
Hattinger et al., 2016*	CTCAE v4 grade 4	MAP	Pediatric	Osteosarcoma	57	2.87 (1.53-5.41)	**0.001**	(6)
***GSTP1* rs1695**	**Leukopenia**							
Windsor et al., 2012*	CTCAE v3 grade 3-4	Doxorubicin	Pediatric	Osteosarcoma	58	7.8 (1.3-47)	**0.024**	(3)
Aráoz et al., 2015	WHO grade 3-4	MTX	Pediatric	ALL	286	N/S	ns	(43)
Hattinger et al., 2016	CTCAE v4 grade 4	MAP	Pediatric	Osteosarcoma	57	N/S	ns	(6)

Hurkmans et al., 2020	Leukocyte counts	MTX	Pediatric	Osteosarcoma	113	N/S	ns	(34)
***MTHFD1* rs2236225**	**Anemia**							
Erculj et al., 2012	CTCAE grade 2-4	MTX	Pediatric	ALL	167	0.84 (0.37-1.91)	0.669	(44)
Windsor et al., 2012*	CTCAE v3 grade 3-4	MTX	Pediatric	Osteosarcoma	58	5.4 (1-27.5)	**0.044**	(3)
***MTHFR* rs1801131**	**Anemia**							
Huang et al., 2008	Requirement of red blood cell transfusions	MTX	Pediatric	ALL	81	N/S	**0.043**	(45)
Kantar et al., 2009	CTCAE grade 3-4	MTX	Pediatric	ALL and NHL	37	N/S	**0.02**	(46)
Karathanasis et al., 2011	CTCAE v4 grade 1-4	MTX	Pediatric	ALL	35	N/S	0.578	(47)
Liu et al., 2011	CTCAE v1 grade 2-4	MTX	Pediatric	ALL	181	0.52 (0.25-1.09)	0.081	(48)
Erculj et al., 2012	CTCAE grade 2-4	MTX	Pediatric	ALL	167	0.85 (0.38-1.88)	0.69	(44)
Windsor et al., 2012*	CTCAE v3 grade 3-4	MTX	Pediatric	Osteosarcoma	58	4.6 (1.1-19.2)	**0.038**	(3)
Aráoz et al., 2015	WHO grade 3-4	MTX	Pediatric	ALL	286	N/S	ns	(43)
Yousef et al., 2019	CTCAE v4.03 grade 3-4	MTX	Pediatric	ALL	64	N/S	0.25	(49)
***MTHFR* rs1801131**	**Leukopenia**							
Huang et al., 2008	White blood cell count	MTX	Pediatric	ALL	31	N/S	0.053	(45)
van Kooten et al., 2008	CTCAE v2 grade 3-4	MTX	Pediatric	ALL	88	N/S	ns	(50)
Kantar et al., 2009	CTCAE grade 3-4	MTX	Pediatric	ALL and NHL	37	N/S	0.09	(46)
Faganel Kotnik et al., 2011	Leukopenia ≥ grade 1	MTX	Pediatric	ALL and ML	64	0.14 (0.037-0.54)	**0.012**	(51)
Karathanasis et al., 2011	CTCAE v4 grade 1-4	MTX	Pediatric	ALL	35	N/S	0.464	(47)
Haase et al., 2012	CTCAE grade 3-4	MTX	Pediatric	ALL	34	N/S	ns	(52)
Suthandiram et al., 2014	CTCAE v2 grade 1-4	MTX	Adult	Hematological malignancies	71	0.92 (0.28-23.37)	0.9	(53)
Aráoz et al., 2015	WHO grade 3-4	MTX	Pediatric	ALL	286	N/S	ns	(43)
Hattinger et al., 2016*	CTCAE v4 grade 4	MAP	Pediatric	Osteosarcoma	57	4.15 (1.06-16.13)	**0.04**	(6)
Milosevic et al., 2019	Number of leukopenic episodes	6-MP, MTX	Pediatric	ALL	127	N/S	0.25	(54)
Yousef et al., 2019	CTCAE v4.03 grade 3-4	MTX	Pediatric	ALL	64	2.1 (0.91-5)	0.076	(49)
***MTHFR* rs1801133**	**Nephrotoxicity**							
Kantar et al., 2009	CTCAE grade 3-4	MTX	Pediatric	ALL and NHL	37	N/S	0.29	(46)
Karathanasis et al., 2011	CTCAE v4 grade 1-4	MTX	Pediatric	ALL	35	N/S	0.628	(47)
Windsor et al., 2012*	CTCAE v3 grade 3-4	MAP	Pediatric	Osteosarcoma	58	3.1 (0.9-11.6)	0.085 [c]	(3)
El Khodary et al., 2012	Serum alpha1-microglobulin, serum creatinin, GFR	MTX	Pediatric	ALL	40	N/S	**<0.0001**	(55)

Xu et al., 2018	CTCAE grade 3-4	MTX	Pediatric	Osteosarcoma	109	1.12 (0.61-2.01)	0.76	(56)
Chae et al., 2020	Nephrotoxicity	MTX	Pediatric	ALL	117	N/S	ns	(57)
***NR1I2/SXR/PXR* rs3732361**	**Hepatotoxicity**							
Hegyi et al., 2017*	CTCAE v3 grade 3-4	MTX	Pediatric	Osteosarcoma	59	0.1 (0.01-0.7)	**0.014**	(33)
***NR1I2/SXR/PXR* rs3732361**	**Leukopenia**							
Hegyi et al., 2017*	CTCAE v3 grade 3-4	MTX	Pediatric	Osteosarcoma	59	0.1 (0.01-0.7)	**0.013**	(33)
***NR1I2/SXR/PXR* rs3814058**	**Hepatotoxicity**							
Hegyi et al., 2017*	CTCAE v3 grade 3-4	MTX	Pediatric	Osteosarcoma	59	0.3 (0.1-0.7)	**0.007**	(33)
***NR1I2/SXR/PXR* rs3814058**	**Leukopenia**							
Hegyi et al., 2017*	CTCAE v3 grade 3-4	MTX	Pediatric	Osteosarcoma	59	0.3 (0.1-0.7)	**0.007**	(33)
***NR1I2/SXR/PXR* rs6785049**	**Hepatotoxicity**							
Hegyi et al., 2017*	CTCAE v3 grade 3-4	MTX	Pediatric	Osteosarcoma	59	0.1 (0.01-0.7)	**0.02**	(33)
Hurkmans et al., 2020	ALAT	MTX	Pediatric	Osteosarcoma	113	N/S	ns	(34)
***NR1I2/SXR/PXR* rs6785049**	**Leukopenia**							
Hegyi et al., 2017*	CTCAE v3 grade 3-4	MTX	Pediatric	Osteosarcoma	59	0.09 (0.01-0.7)	**0.01**	(33)
Hurkmans et al., 2020	Leukocyte counts	MTX	Pediatric	Osteosarcoma	113	N/S	ns	(34)
***XPC* rs2228001**	**Infection**							
Windsor et al., 2012*	CTCAE v3 grade 3-4	Doxorubicin	Pediatric	Osteosarcoma	58	0.2 (0.06-0.8)	**0.024**	(3)

N/S, not specified; OR, odds ratio; CTCAE, Common Terminology Criteria for Adverse Events; MAP, methotrexate, anthracycline (doxorubicin), cisplatin treatment regimen; MTX, methotrexate; ALAT, alanine aminotransferase; ALL, acute lymphatic leukemia; ML, malignant lymphoma; NHL, non-Hodgkin lymphoma

* discovery study that was identified in systematic literature search

[a] As reported by the authors

[b] Coefficient (95% CI)

[c] p=0.043 in t-test, but results from regression analysis are reported in the table for consistency

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