

# Clinical and germline risk factors for multiple treatment-related toxicities in pediatric acute lymphoblastic leukemia

## Authors

Marion K. Mateos,<sup>1-4</sup> Chelsea Mayoh,<sup>2,5</sup> Patricia Sullivan,<sup>2</sup> Pasquale M. Barbaro,<sup>6,7</sup> Michael C.J. Quinn,<sup>8,9</sup> Carly George,<sup>10</sup> Rosemary Sutton,<sup>2,3</sup> Tom Revesz,<sup>11,12</sup> Jodie E. Giles,<sup>2,3</sup> Draga Barbaric,<sup>1</sup> Frank Alvaro,<sup>13,14</sup> Rachel Conyers,<sup>15-17</sup> Daniel Catchpoole,<sup>18</sup> Stuart MacGregor,<sup>8</sup> Rishi S. Kotecha,<sup>10,19,20</sup> Luciano Dalla-Pozza,<sup>6,21,22</sup> Toby N. Trahair<sup>1-3#</sup> and Glenn M. Marshall<sup>1-3#</sup>

<sup>1</sup>Kids Cancer Center, Sydney Children's Hospital Randwick, Sydney, New South Wales, Australia; <sup>2</sup>Children's Cancer Institute, Lowy Cancer Research Center, UNSW, Sydney, New South Wales, Australia; <sup>3</sup>Discipline of Pediatrics and Child Health, School of Clinical Medicine, UNSW Medicine & Health, UNSW, Sydney, New South Wales, Australia; <sup>4</sup>Northern Institute for Cancer Research, Wolfson Childhood Cancer Research Center, Newcastle-Upon-Tyne, UK; <sup>5</sup>School of Clinical Medicine, UNSW Medicine & Health, UNSW Sydney, Kensington, New South Wales, Australia; <sup>6</sup>Children's Medical Research Institute, University of Sydney, Sydney, New South Wales, Australia; <sup>7</sup>Department of Hematology, Queensland Children's Hospital, Brisbane, Queensland, Australia; <sup>8</sup>QIMR Berghofer Medical Research Institute, Brisbane, Queensland, Australia; <sup>9</sup>Genetic Health Queensland, Royal Brisbane and Women's Hospital, Herston, Queensland, Australia; <sup>10</sup>Department of Clinical Hematology, Oncology, Blood and Marrow Transplantation, Perth Children's Hospital, Perth, Western Australia, Australia; <sup>11</sup>Department of Hematology and Oncology, Women's and Children's Hospital, North Adelaide, South Australia, Australia; <sup>12</sup>University of Adelaide, North Adelaide, South Australia, Australia; <sup>13</sup>John Hunter Children's Hospital, Newcastle, New South Wales, Australia;

<sup>14</sup>University of Newcastle, Newcastle, New South Wales, Australia;

<sup>15</sup>Children's Cancer Center, The Royal Children's Hospital, Melbourne, Victoria, Australia; <sup>16</sup>Department of Pediatrics, University of Melbourne, Carlton, Melbourne, Victoria, Australia;

<sup>17</sup>Pharmacogenomics Team, Stem Cell Medicine, Murdoch Children's Research Institute, Parkville, Melbourne, Victoria, Australia;

<sup>18</sup>Biospecimen Research Services, Children's Cancer Research Unit, The Children's Hospital at Westmead, Sydney, Australia;

<sup>19</sup>Leukaemia Translational Research Laboratory, Telethon Kids Cancer Center, Telethon Kids Institute, University of Western Australia, Perth, Western Australia, Australia; <sup>20</sup>Curtin Medical School, Curtin University, Perth, Western Australia, Australia;

<sup>21</sup>Cancer Center for Children, The Children's Hospital at Westmead, Sydney, New South Wales, Australia and <sup>22</sup>Children's Cancer Research Unit, The Children's Hospital at Westmead, Sydney, New South Wales, Australia

*#TNT and GMM contributed equally as senior authors.*

Correspondence:

T. TRAHAIR - Toby.Trahair@health.nsw.gov.au  
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# **Supplementary Information for Clinical and germline risk factors for multiple treatment related toxicities during pediatric acute lymphoblastic leukaemia therapy**

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**Supplementary References**

<b>Supplementary Table 1. Characteristics of the ERASE multiple toxicity cohort</b>		
<b>DIAGNOSTIC INFORMATION</b>	<b>NUMBER (n=1251)</b>	<b>% OF COHORT</b>
Male	696	55·6
<b>DIAGNOSIS</b>		
Pre-B ALL	1068	85·4
B-lymphoblastic lymphoma	14	1·1
T-ALL	110	8·8
T-lymphoblastic Lymphoma	39	3·1
Other (ALL/LL, not specified)	20	1·6
<b>TREATMENT PROTOCOL</b>		
<b>AIEOP-BFM-based protocols</b>	<b>(n=1033)</b>	
ANZCHOG Study 7	239	19·1
ANZCHOG Study 8	608	48·6
AIEOP-BFM-Study 9	40	3·2
BFM-95	125	10·0
COG A5971	21	1·7
<b>COG-based protocols</b>	<b>(n=218)</b>	
AALL0031	2	0·2
AALL0232	25	2
AALL0331	49	3·9
AALL0434	12	1·0
AALL08P1	2	0·2
AALL0932	17	1·4
AALL1131	4	0·3
CCG1882	1	0·1
CCG1952	16	1·3
CCG1961	36	2·9
CCG1991	54	4·3
<p>The ERASE cohort of 1251 patients was derived from analysing 1438 records of consecutive patients treated for ALL at 6 Australian hospitals. Patients excluded (n=187) included clinical information not available (n=31), treatment center (n=7), time period (n=1), protocol exclusion (n=9), age exclusion (n=4), relapsed ALL therapy (n=4), premorbid condition exclusion (n=3), early death from relapse (n=8), early death from treatment* (n=24), &lt; 18 months in CR1 and no toxicity (n=96) Patients without adequate clinical information to determine case or control status were excluded. *Early death from treatment: patients who experienced treatment-related mortality unrelated to target toxicities were excluded. Abbreviations: AIEOP: Associazione Italiana Ematologia Oncologia Pediatrica; ANZCHOG: Australian and New Zealand Children's Haematology &amp; Oncology Group; BFM: international Berlin-Frankfurt-Munster study group; CCG: Children's Cancer Group; COG: Children's Oncology Group</p>		

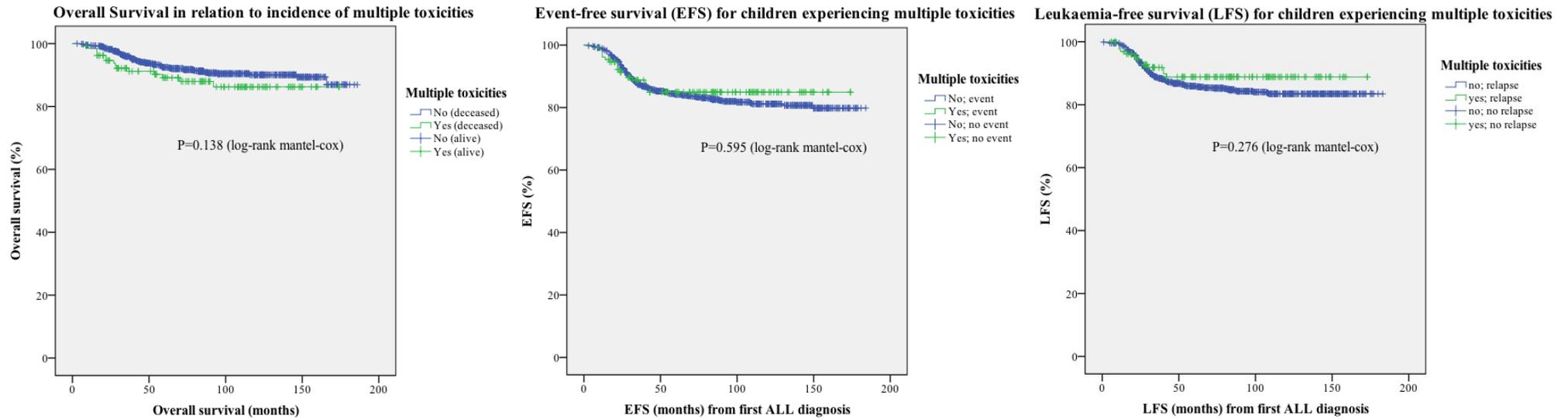
Supplementary Table 2: Overview of risk and response adapted risk classification systems used in patients participating in the ERASE study																							
Study	ALL-BFM-95 <sup>1</sup>			ANZCCSG Study VII <sup>2</sup>		ANZCHOG Study VIII <sup>3</sup>				AIEOP-BFM Study 9 <sup>4</sup>			COG stratification for ALL <sup>5</sup>										
Risk Group	Standard	Medium	High	Standard	High	Standard	Medium	High	Very High	Standard	Medium	High	Low	T	Average			High			Very High		
	No HR features	No HR features		No HR features		No HR features	No HR features			No HR features	No HR features			T cell low risk		T cell intermediate			T cell high				
<b>NCI Risk Group</b>	Not used	Not used	Not used	Not used	Not used	Not used	Not used	Not used	Not used	Not used	Not used	Not used	SR		SR		SR	SR	HR	HR	HR	HR (≥13y)	SR or HR
<b>Age</b>	1-6y	1-6y or older		1-10y	>10y	Not used	Not used	Not used	Not used				1-9-99	1-9-99	1-9-99	Any		1-9-99	>10-0	>10-0			
<b>White cell count</b>	<20x10 <sup>9</sup> /l	>20x10 <sup>9</sup> /l	-	<50x10 <sup>9</sup> /l	>50x10 <sup>9</sup> /l and ETV6::RUNX1 negative				≥100x10 <sup>9</sup> /l and PPR				<50	<50	<50	<50		<50	>50	>50			
<b>Immunophenotype</b>	B-ALL	T-ALL	B or T	B or T					T-ALL and PPR Pro-B ALL and PPR				B	T	B			B		B	B or T		
<b>ALL genetics</b>			BCR::ABL1 KMT2a::AFF1	ETV6::RUNX1	BCR::ABL1, KMT2a::AFF1, TCF3::PBX1 hypodiploidy			BCR::ABL1 KMT2a::AFF1	BCR::ABL1 KMT2a::AFF1			KMT2a::AFF1 hypodiploidy		No BCR::ABL		No BCR::ABL		KMT2a-r with RER		KMT2a-r with RER	BCR::ABL Hypodiploidy KMT2a-r with a SER		
<b>CNS Status</b>													1	1	2	1-3		CNS3		CNS3			
<b>Extramedullary disease</b>													No	No	No			No	No	Testicular			
<b>Steroid Pre-treatment</b>																		Yes	No	Yes			
<b>COG favourable genetics</b> Triple trisomy 4, 10, 17 OR ETV6::RUNX1													Yes		Yes		Yes	No	Any	No	Any	Any	Any

Supplementary Table 2: Overview of risk and response adapted risk classification systems used in patients participating in the ERASE study																							
Study	ALL-BFM-95 <sup>1</sup>			ANZCCSG Study VII <sup>2</sup>		ANZCHOG Study VIII <sup>3</sup>				AIEOP-BFM Study 9 <sup>4</sup>			COG stratification for ALL <sup>5</sup>										
Risk Group	Standard	Medium	High	Standard	High	Standard	Medium	High	Very High	Standard	Medium	High	Low	T	Average			High			Very High		
	No HR features	No HR features		No HR features		No HR features	No HR features			No HR features	No HR features			T cell low risk		T cell intermediate			T cell high				
<b>NCI Risk Group</b>	Not used	Not used	Not used	Not used	Not used	Not used	Not used	Not used	Not used	Not used	Not used	Not used	SR		SR		SR	SR	HR	HR	HR	HR (≥13y)	SR or HR
<b>COG unfavourable characteristics</b> CNS3, hypodiploidy, iAMP21, Induction failure or MLL rearrangement	Not used	Not used	Not used	Not used	Not used	Not used	Not used	Not used	Not used	Not used	Not used	Not used	No		No	No	No	No	No	No	No	Yes	
<b>Day 8 Prednisone response</b> Peripheral blasts <or> 1·0x10 <sup>9</sup> /l	PGR	PGR	PPR	Not used	Not used	PGR	PGR	PPR	PPR & immunophenotype or PPR	PGR	PGR	PPR											
<b>Day 8 peripheral blood MRD</b>													<0·01 %		≥0·01%	<1 %	Any	≥1%	Any	Any	Any	Any	
<b>Day 8 or 15 BM Response</b>					M3				M3 (HR ALL only)			≥10%	M1	M1	M1	M1-3		D15 M2/3	M1				
<b>End Induction Morphologic Response</b>	M1	M1	M2 or M3	M1	M2 or M3	M1	M1	M2 or M3	M2 or M3	M1	M1	M2 or M3	M1	M1	M1	M1		M2	M1	M2	M3 or M2		
<b>End induction MRD response</b>				Not used	Not used	MRD negative	low positive			MRD negative	MRD positive		<0·1%	<0·1%	<0·1%	<1 %	≥0·01 %	≥1%	<0·1%	≥1 %	≥1%	<0·01 %	Any

Supplementary Table 2: Overview of risk and response adapted risk classification systems used in patients participating in the ERASE study																							
Study	ALL-BFM-95 <sup>1</sup>			ANZCCSG Study VII <sup>2</sup>		ANZCHOG Study VIII <sup>3</sup>				AIEOP-BFM Study 9 <sup>4</sup>			COG stratification for ALL <sup>5</sup>										
Risk Group	Standard	Medium	High	Standard	High	Standard	Medium	High	Very High	Standard	Medium	High	Low	T	Average			High			Very High		
	No HR features	No HR features		No HR features		No HR features	No HR features			No HR features	No HR features			T cell low risk		T cell intermediate			T cell high				
<b>NCI Risk Group</b>	Not used	Not used	Not used	Not used	Not used	Not used	Not used	Not used	Not used	Not used	Not used	Not used	SR		SR		SR	SR	HR	HR	HR	HR (≥13y)	SR or HR
<b>Post consolidation MRD response</b>						MRD negative	<10 <sup>-3</sup>	Consolidation ≥10 <sup>-3</sup>		MRD negative	MRD<10 <sup>-3</sup>	MRD≥10 <sup>-3</sup> OR B-ALL with slow early response (End induction MRD ≥10 <sup>-3</sup> and consolidation MRD positive <10 <sup>-3</sup> )	Not used		Not used	Not used	Not used	M1 marrow and MRD <1%	Not used	M1 marrow & MRD <0-1%	M2/3 and/or MRD ≥1%	Not used	Not used

COG risk classification based on the AALL08B1 Classification System<sup>5</sup>. Patients on the ERASE study were treated on the following CCG and COG protocols: AALL0031<sup>6,7</sup>, AALL0232<sup>8</sup>, AALL0331<sup>9</sup>, AALL0434<sup>10</sup>, AALL08P1<sup>11</sup>, AALL0932<sup>12,13</sup>, AALL1131<sup>12</sup>, CCG1882<sup>14</sup>, CCG1952<sup>15</sup>, CCG1961<sup>16</sup> and CCG1991<sup>17</sup>.  
 BCR::ABL1 – not eligible· **Abbreviations:** NCI / Rome Consensus criteria for B-ALL: Standard risk: Age 1·0-9·99 years and WBC < 50,000/μl· High Risk: Age <1y OR ≥10y OR WBC ≥50,000/μl· MRD: measurable residual disease. RER: rapid early response· SER: slow early response

**Supplementary Figure 1: Overall, event-free and leukaemia-free survival in ALL patients in the ERASE cohort**



Overall, event-free and leukaemia-free survival in the ERASE cohort. Five-year OS for children who experienced multiple toxicities was  $89.1 \pm 2.9\%$  compared to  $92.5 \pm 0.9\%$  for children who did not experience multiple toxicity. Five-year EFS for children who experienced multiple toxicities was  $84.9 \pm 3.3\%$  compared to  $84.2 \pm 1.2\%$  for children who did not experience multiple toxicities. Five-year LFS for children who experienced multiple toxicity was  $88.8 \pm 2.9\%$  compared to  $85.9 \pm 1.1\%$ .

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