An international retrospective study for tolerability of 6-mercaptopurine on *NUDT15* bi-allelic variants in children with acute lymphoblastic leukemia

Yoichi Tanaka,[1] Allen Eng Juh Yeoh,[2] Takaya Moriyama,[3] Chi-Kong Li,[4] Ko Kudo,[5] Yuki Arakawa,[6] Jassada Buaboonnam,[7] Hui Zhang,[8] Hsi-Che Liu,[9] Hany Ariffin,[10] Zhiwei Chen,[2] Shirley K.Y. Kham,[2] Rina Nishii,[3] Daisuke Hasegawa,[11] Junya Fujimura,[12] Dai Keino,[13] Kensuke Kondoh,[13] Atsushi Sato,[14] Takahiro Ueda,[15] Masaki Yamamoto,[16] Yuichi Taneyama,[17] Moeko Hino,[18] Masatoshi Takagi,[19] Akira Ohara,[20] Etsuro Ito,[5] Katsuyoshi Koh,[7] Hiroki Hori,[21] Atsushi Manabe,[22] Jun J. Yang,[3] and Motohiro Kato,[23,24,25]

[1]Division of Medicinal Safety Science, National Institute of Health Sciences, Kawasaki, Japan; [2]VIVA-NUS Center of Translational Research in Acute Leukemia (Molecular), Department of Pediatrics, Yong Loo Lin School of Medicine, National University of Singapore, Singapore; [3]Department of Pharmaceutical Sciences, St. Jude Children's Research Hospital, Memphis, TN, USA; [4]Hong Kong Children's Hospital, The Chinese University of Hong Kong, Shatin, Hong Kong, Special Administrative Region, China; [5]Department of Pediatrics, Hirosaki University Graduate School of Medicine, Hirosaki, Japan; [6]Department of Hematology/Oncology, Saitama Children's Medical Center, Saitama, Japan; [7]Hematology/Oncology Division, Department of Pediatrics, Faculty of Medicine, Siriraj Hospital Mahidol University, Thailand; [8]Department of Hematology and Oncology, Women and Children's Medical Center, Guangzhou, China; [9]Division of Pediatric Hematology-Oncology, Mackay Children's Hospital and Mackay Memorial Hospital, Taipei, Taiwan; [10]Department of Pediatrics, University of Malaya Medical Center, Kuala Lumpur, Malaysia; [11]Department of Pediatrics, St. Luke's International Hospital, Tokyo, Japan; [12]Department of Pediatrics, Juntendo University, School of Medicine, Tokyo, Japan; [13]Department of Pediatrics, St. Marianna University School of Medicine Hospital, Kawasaki, Japan; [14]Department of Hematology and Oncology, Miyagi Children's Hospital, Sendai, Japan; [15]Department of Pediatrics, Nippon Medical School, Tokyo, Japan; [16]Department of Pediatrics, Sapporo Medical University School of Medicine, Sapporo, Japan; [17]Department of Hematology and Oncology, Chiba Children's Hospital, Chiba, Japan; [18]Department of Pediatrics, Chiba University Graduate School of Medicine, Chiba, Japan; [19]Department of Pediatrics, Tokyo Medical and Dental University, Tokyo, Japan; [20]Department of Pediatrics, Toho University School of Medicine, Tokyo, Japan; [21]Department of Pediatrics, Mie University, Tsu, Mie, Japan; [22]Department of Pediatrics, Hokkaido University Graduate School of Medicine, Sapporo, Japan; [23]Department of Transplantation and Cell Therapy, Children's Cancer Center, National Center for Child Health and Development, Tokyo, Japan; [24]Department of Pediatric Hematology and Oncology Research, National Center for Child Health and Development, Tokyo, Japan and [25]Department of Pediatrics, University of Tokyo, Tokyo, Japan.

Correspondence: MOTOHIRO KATO - katom-tky@umin.ac.jp

doi:10.3324/haematol.2020.266320

Supplementary Table 1. Standard 6-mercaptopurine dose in each protocol

Protocol	Country	Phase	6-MPdose (/day)
TCCSG L99-15	Japan	Intensification	60 mg/m^2
		Interim maintenance	60 mg/m^2
		Late intensification	60 mg/m^2
		Maintenance	40 mg/m^2
TCCSG L04-16	Japan	Early intensification-1 (SR, IR)	60 mg/m^2
		Interim maintenance (SR)	60 mg/m^2
		Reinduction (SR)	60 mg/m^2
		Late intensification-1 (IR)	60 mg/m^2
		Late intensification (HR)	60 mg/m^2
		Maintenance	40 mg/m^2
JPLSG ALL B12	Japan	Early intensification (IB)	60 mg/m^2
		Consolidation	25 mg/m^2
		Reinduction	60 mg/m^2
		Interim maintenance	50 mg/m^2
		Maintenance	50 mg/m^2
JPLSG ALL T11	Japan	Early intensification (IB)	60 mg/m^2
		Consolidation (SR)	25 mg/m^2
		Reinduction (SR, HR)	60 mg/m^2
		Interim maintenance (SR)	50 mg/m^2
		Maintenance	50 mg/m^2
Ma-Spore ALL 2003 Ma-Spore ALL 2010	Singapore	Induction (Phase IB)	50 mg/m^2
		Consolidation	25 mg/m^2
		Interim maintenance	50 mg/m^2
		Maintenance	50 mg/m^2
CCCG-ALL-2015	China	Induction	60 mg/m^2
		Interim maintenance	50 mg/m^2
		Maintenance	50 mg/m^2
ALL IC-BFM2002 (SR-2)	China (Hong Kong)	Induction2	60 mg/m^2
		Consolidation	25 mg/m^2
		Reinduction	60 mg/m^2
		Maintenance	50 mg/m^2
TPOG-ALL-2002-SRA	Taiwan	Consolidation #1	40 mg/m^2
		Consolidation #2	40 mg/m^2
		Interim maintenance	50 mg/m^2
		Maintenance	60 mg/m^2
COG base	Thailand	Consolidation	60 mg/m^2
		Reinduction	60 mg/m^2
		Maintenance	50 mg/m^2

6-MP, 6-mercaptopurine.

Supplementary Table 2. Tolerable 6-mercaptopurine dose for NUDT15 activity predicted by diplotype

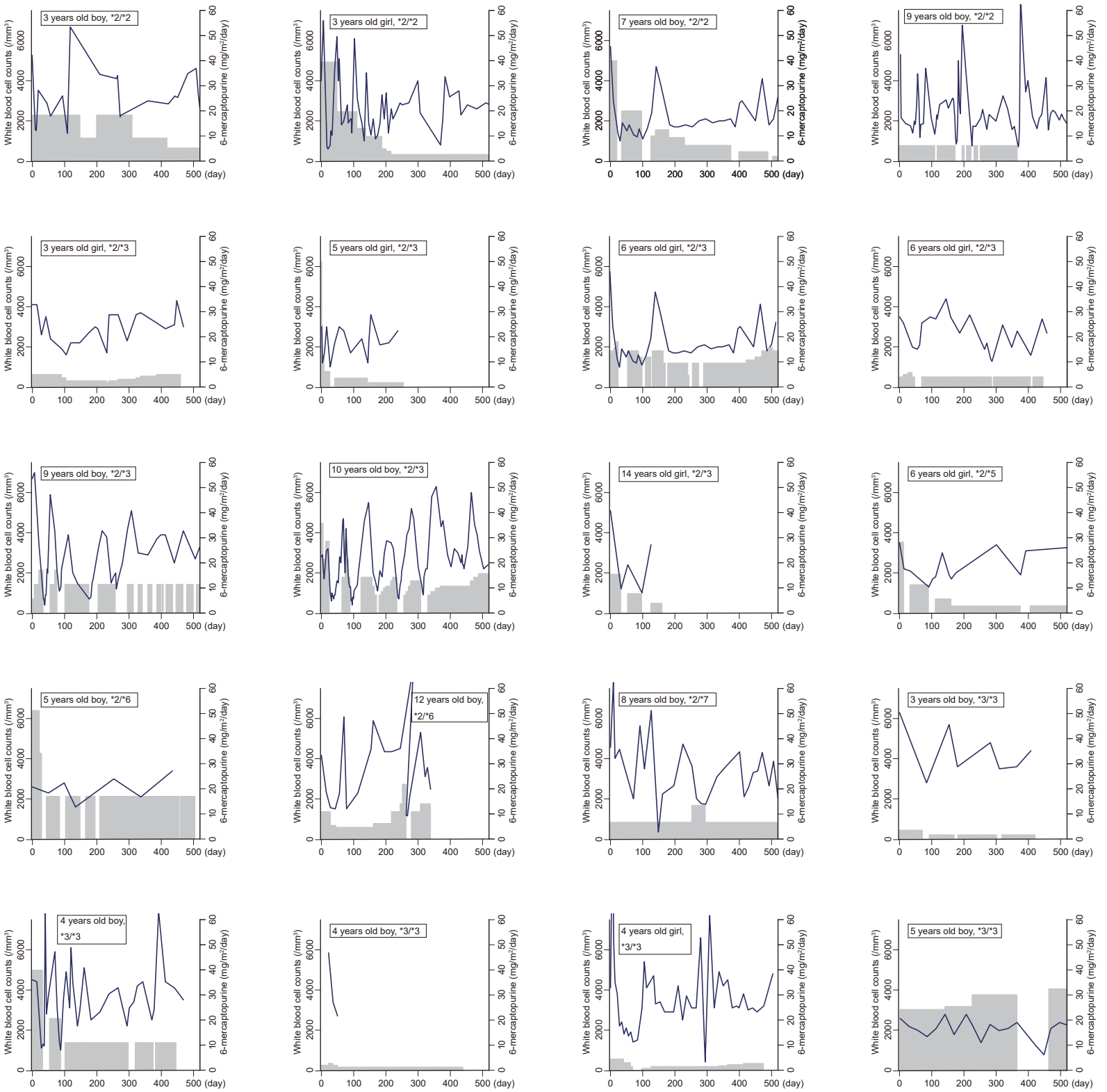
NUDT15 activity	N	6-MP dose (mg/m^2) median (range)	*P*-value
Poor metabolizer (*2/*2, *2/*3, *3/*3)	29	5.2 (1.1–25.6)	0.53*
Possible Intermediate metabolizer (*2/*5, *2/*6, *2/*7, *3/*5)	7	5.5 (1.2–16.7)	
Indeterminate (*5/*5)	1	18.3	

*Poor metabolizer vs. non-poor metabolizer

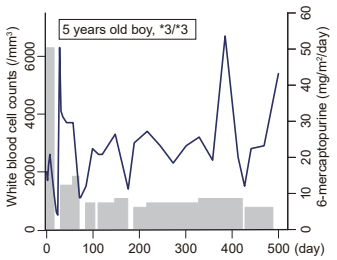
6-MP, 6-mercaptopurine.

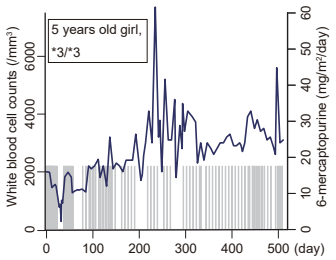
Supplementary Table 3. 6-mercaptopurine induced severe toxicities before maintenance therapy

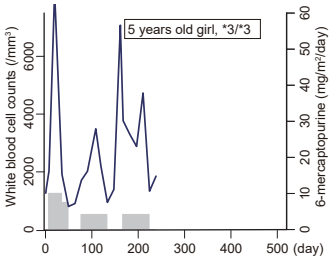
NUDT15 diplotype	White blood cells count < 2,000/μL or neutrophil count < 1,000/μL	ALT and/or AST > 200 IU
Total (N = 37)	21	5
*2/*2 (N = 4)	0	0
*2/*3 (N = 7)	6	0
*2/*5 (N = 1)	0	0
*2/*6 (N =2)	1	0
*2/*7 (N =1)	0	0
*3/*3 (N = 18)	12	4
*3/*5 (N = 3)	2	1
*5/*5 (N = 1)	0	0

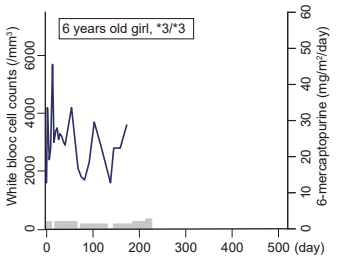


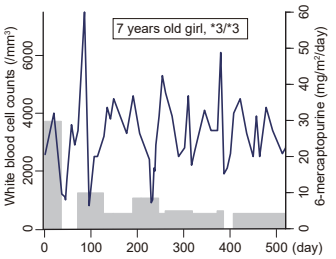
Supplementary Figure 1 Time course of 6-MP dose and white blood cell counts in each *NUDT15* bi-allelic patients.
Gray bar showed 6-MP dose, and blue line showed the value of white blood cell counts.

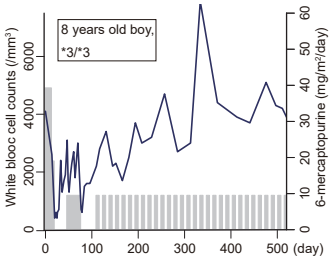


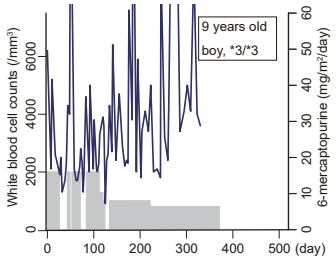


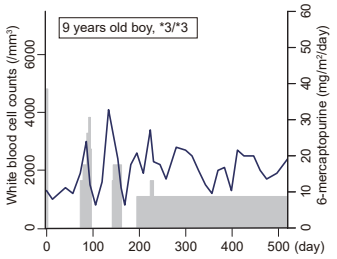


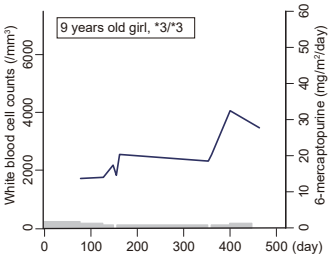


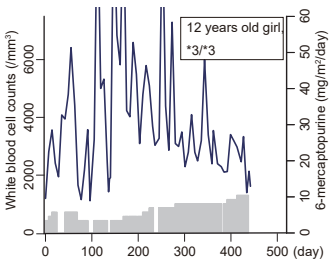


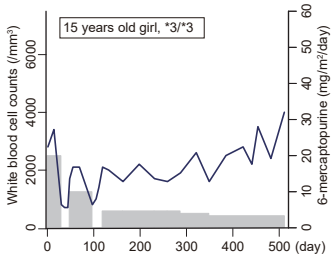


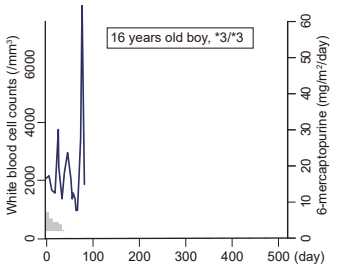


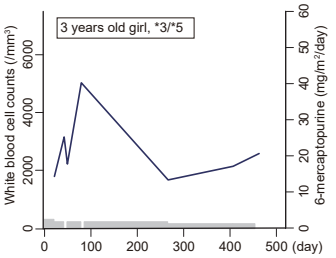


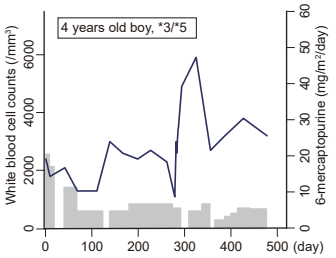


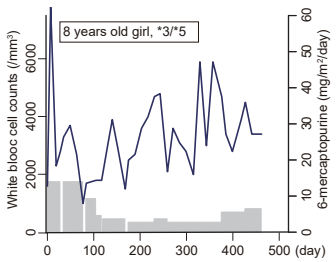


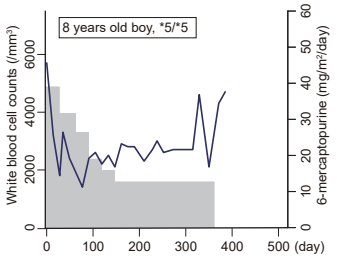




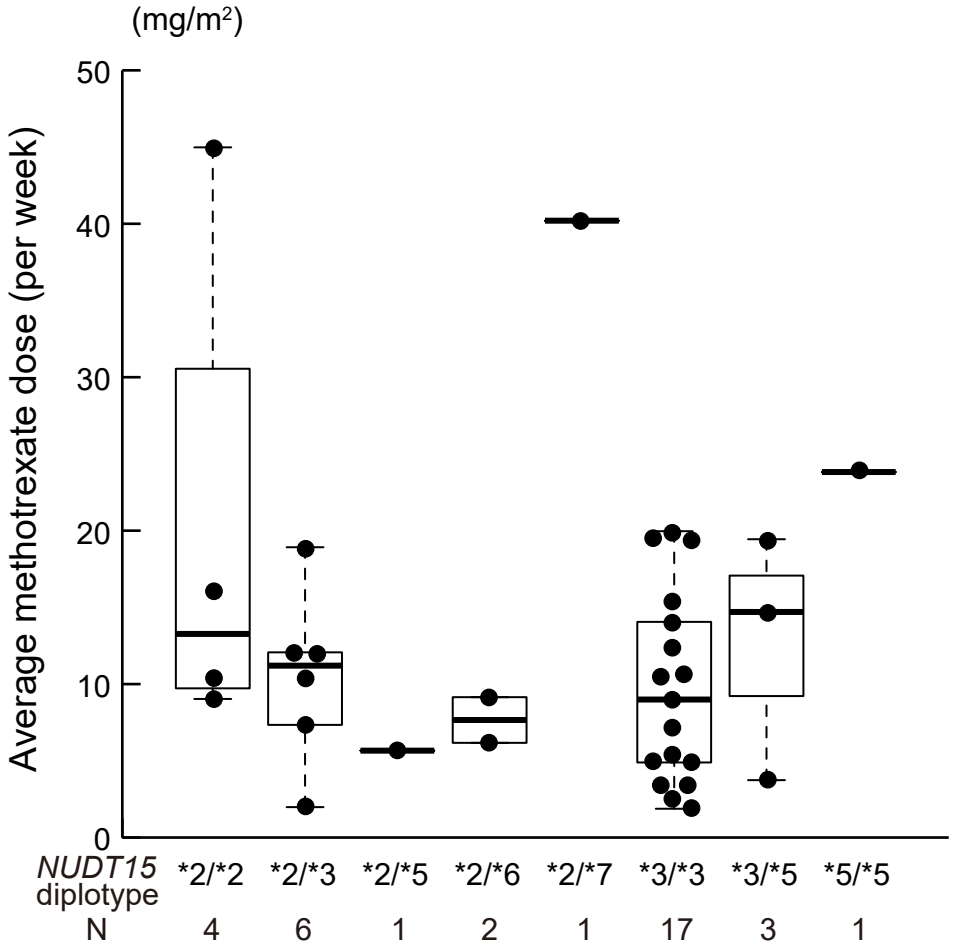




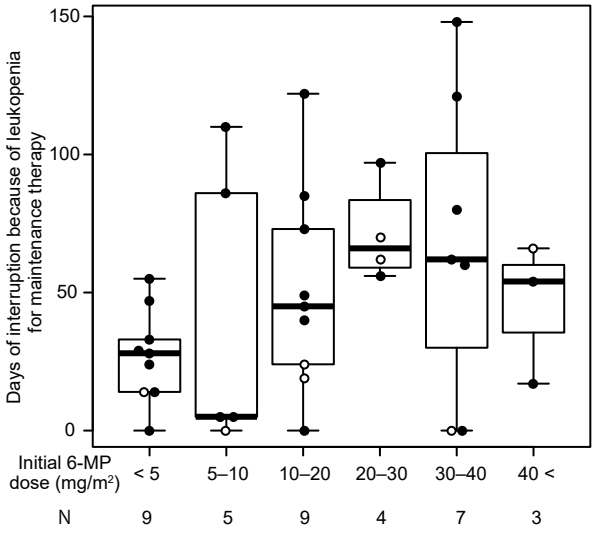




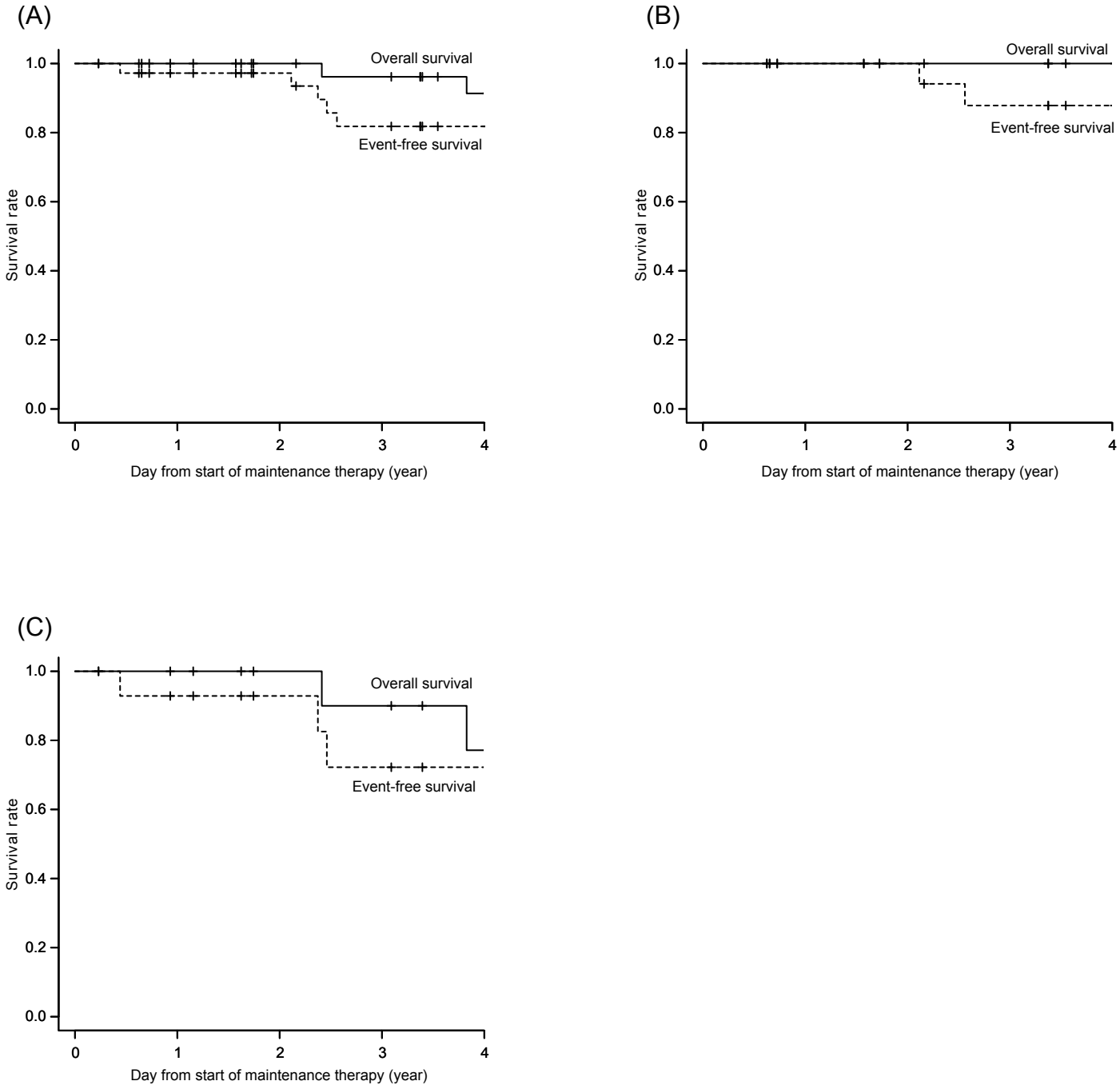
Supplementary Figure 1 (Continued)



Supplementary Figure 2 Average methotrexate dose in each *NUDT15* bi-allelic variant.
The two patients (*2/*3 and *3/*3) are not shown because they did not receive methotrexate.



Supplementary Figure 3 The association between initial 6-mercaptopurine dose and therapy interruption during entire maintenance therapy in patients with *NUDT15* bi-allelic variants. Black circles and white circles showed starting dose for patients with or without c.415C>T, respec-tively.



Supplementary Figure 4 Outcome of *NUDT15* homozygous patients.

Four-year overall survival and event-free survival in risk of National Cancer Institute/Rome criteria (N = 37). (A) all patients; (B) standard risk; (C) high risk.