Table S1. World Health Organization bleeding scale

	Grade 1	Grade 2	Grade 3
Oral and nasal	➢ Oropharyngeal bleeding – total duration of all episodes in previous 24 hours ≤ 30 minutes* ➢ Petechiae of oral mucosa ➢ Epistaxis – total duration of all episodes in previous 24 hours ≤ 30 minutes*	➢ Oropharyngeal bleeding – total duration of all episodes in previous 24 hours > 30 minutes* ➢ Epistaxis – total duration of all episodes in previous 24 hours > 30 minutes*	➢ Any bleeding requiring RBC transfusion over routine transfusion needs†
Skin, soft tissue, musculoskeletal	➢ Petechiae of skin ➢ Purpura ≤ 1 inch diameter ➢ One or more spontaneous hematomas in the soft tissue or muscle > 1 inch	➢ Purpura > 1 inch diameter ➢ Spontaneous hematoma in deeper tissues ➢ Joint bleeding (confirmed by aspiration, imaging study or other accepted technique)	➢ Any bleeding requiring RBC transfusion over routine transfusion needs†
Gastrointestinal	➢ Positive stool occult blood test‡	➢ Melanotic stool ➢ Hematochezia – visible red blood mixed in stool, not requiring a transfusion ➢ Hematemesis – grossly visible blood in emesis or in nasogastric drainage tube (not related or secondary to swallowed blood)	➢ Any bleeding requiring RBC transfusion over routine transfusion needs†
Genitourinary	➢ Any biochemical or microscopic Hb/RBCs without red urine‡ ➢ Abnormal vaginal bleeding (Unexpected bleeding out of normal cycle *or* bleeding heavier than normal *or* breakthrough bleeding (patient on hormonal therapy to prevent bleeding)) with spotting	➢ Gross/visible hematuria without need for transfusion ➢ Abnormal vaginal bleeding (Unexpected bleeding out of normal cycle *or* bleeding heavier than normal *or* breakthrough bleeding (patient on hormonal therapy to prevent bleeding)) more than spotting	➢ Any bleeding requiring RBC transfusion over routine transfusion needs†

Pulmonary		➢ Hemoptysis – visible blood ➢ Blood in broncho-pulmonary lavage, or blood tinged sputum (excluding those with nose or oropharyngeal bleeding)	➢ Any bleeding requiring RBC transfusion over routine transfusion needs†
Body cavity		➢ Visible blood in body cavity fluid (e.g. red cells apparent in fluid aspirate) short of criteria for Grade 3 or 4	➢ Grossly bloody body cavity fluids and organ dysfunction with symptoms, and/or need to intervene (e.g. to aspirate), and/or need for transfusion
Central nervous system		➢ Retinal bleeding without visual impairment ➢ Lumbar puncture with blood (>5 RBC/μL in CSF on microscopic analysis and non-traumatic tap), no symptoms and no visible red color	➢ Lumbar puncture with visible red color in absence of symptoms, and non-traumatic tap
Invasive sites		➢ Bleeding at invasive sites (venipuncture sites, intravenous lines or catheter exit sites): active oozing at site for a cumulative total of > 1 hour in the previous 24 hours	➢ Any bleeding requiring RBC transfusion over routine transfusion needs†
Hemodynamic instability			➢ Any bleeding associated with moderate hemodynamic instability (hypotension; >30mmHg fall or >30% decrease in either systolic or diastolic blood pressure) and requiring RBC transfusion over routine transfusion needs†

Grade 4:

- Any bleeding associated with severe hemodynamic instability (hypotension; >50mm/Hg fall or >50% decrease in either systolic or diastolic blood pressure, with associated tachycardia (heart rate increase of ≥ 20% for 20 minutes) and requiring RBC transfusion over routine transfusion needs
- Fatal bleeding from any source
- Retinal bleeding with visual impairment (Visual impairment is defined as a field deficit, and patients with suspected visual impairment require an ophthalmologic consult for documentation)
- CNS symptoms with non-traumatic bloody lumbar puncture
- CNS bleeding on imaging study with or without dysfunction

RBC indicates red blood cell; Hb, hemoglobin; CSF, cerebrospinal fluid; Hg, mercury; and CNS, central nervous system

* Count actual bleeding (i.e. “running out” or need for basin, Kleenex, towel, etc.) not minor bleeding

†Red cell transfusion must be specifically related to treatment of bleeding within 24 hours of onset of bleeding

‡Not assessed in PLADO

Table S2: Primary diagnosis by age group within disease treatment category

	0 - 5 years	6 - 12 years	13 - 18 years	19+ years	Total	P for overall comparison of the four age groups	Significant pairwise comparisons
Primary diagnoses for subjects with autologous or syngeneic stem cell transplant (number of patients)	29	12	12	376	429	<0.001	A, B, C, E, F
Acute lymphocytic leukemia	0 (0)	2 (17)	0 (0)	4 (1)	6 (1)		
Acute myelogenous leukemia	0 (0)	1 (8)	0 (0)	15 (4)	16 (4)		
Chronic lymphocytic leukemia	0 (0)	0 (0)	0 (0)	2 (1)	2 (<1)		
Non-Hodgkins lymphoma	0 (0)	2 (17)	3 (25)	136 (36)	141 (33)		
Hodgkins lymphoma	0 (0)	2 (17)	2 (17)	62 (16)	66 (15)		
Myelodysplastic syndromes	0 (0)	0 (0)	0 (0)	1 (<1)	1 (<1)		
Plasma cell disorders	0 (0)	0 (0)	0 (0)	148 (39)	148 (35)		
Non-hematopoietic solid tumor carcinoma	5 (17)	0 (0)	1 (8)	4 (1)	10 (2)		
Non-hematopoietic solid tumor sarcoma	0 (0)	0 (0)	1 (8)	1 (<1)	2 (<1)		
Non-hematologic solid tumor (non-sarcoma, non-carcinoma)	24 (83)	5 (42)	5 (42)	3 (1)	37 (9)		
Primary Diagnoses for Subjects with Allogeneic Stem Cell Transplant (number of patients)	27	45	39	412	523	<0.001	B, C, E, F
Acute lymphocytic leukemia	7 (26)	14 (31)	14 (36)	50 (12)	85 (16)		
Acute myelogenous leukemia	6 (22)	14 (31)	14 (36)	145 (35)	179 (34)		
Chronic myelogenous leukemia	1 (4)	2 (4)	6 (15)	42 (10)	51 (10)		
Chronic lymphocytic leukemia	0 (0)	0 (0)	0 (0)	18 (4)	18 (3)		
Chronic myelomonocytic leukemia	0 (0)	0 (0)	0 (0)	5 (1)	5 (1)		
Non-Hodgkins lymphoma	1 (4)	5 (11)	1 (3)	53 (13)	60 (11)		
Hodgkins lymphoma	0 (0)	0 (0)	0 (0)	12 (3)	12 (2)		
Myelodysplastic syndromes	0 (0)	0 (0)	0 (0)	69 (17)	69 (13)		
Plasma cell disorders	0 (0)	0 (0)	0 (0)	7 (2)	7 (1)		
Non-hematopoietic solid tumor carcinoma	1 (4)	0 (0)	0 (0)	0 (0)	1 (<1)		
Aplastic anemia congenital and acquired	5 (19)	7 (16)	3 (8)	9 (2)	24 (5)		
Other	6 (22)	3 (7)	1 (3)	2 (<1)	12 (2)		

Primary diagnoses for subjects with chemotherapy for hematologic malignancy (number of patients)	7	11	11	284	313	0.19	
Acute lymphocytic leukemia	2 (29)	3 (27)	0 (0)	20 (7)	25 (8)		
Acute myelogenous leukemia	5 (71)	7 (64)	11 (100)	251 (88)	274 (88)		
Chronic myelogenous leukemia	0 (0)	0 (0)	0 (0)	3 (1)	3 (1)		
Chronic lymphocytic leukemia	0 (0)	0 (0)	0 (0)	1 (<1)	1 (<1)		
Chronic myelomonocytic leukemia	0 (0)	0 (0)	0 (0)	1 (<1)	1 (<1)		
Non-hodgkins lymphoma	0 (0)	1 (9)	0 (0)	1 (<1)	2 (1)		
Hodgkins lymphoma	0 (0)	0 (0)	0 (0)	1 (<1)	1 (<1)		
Myelodysplastic syndromes	0 (0)	0 (0)	0 (0)	4 (1)	4 (1)		
Plasma cell disorders	0 (0)	0 (0)	0 (0)	2 (1)	2 (1)		
Primary diagnoses for subjects with chemotherapy for solid tumor (number of patients)	3	1	3	0	7	0.10	
Non-hodgkins lymphoma	0 (0)	0 (0)	1 (33)	0 (0)	1 (14)		
Non-hematopoietic solid tumor carcinoma	3 (100)	0 (0)	0 (0)	0 (0)	3 (43)		
Non-hematopoietic solid tumor sarcoma	0 (0)	1 (100)	2 (67)	0 (0)	3 (43)		

Values presented are n (%).

* A: 0-5 years vs. 6-12 years; B: 0-5 years vs. 13-18 years; C: 0-5 years vs. 19+ years; D: 6-12 years vs. 13-18 years; E: 6-12 years vs. 19+ years; F: 13-18 years vs. 19+ years

Table S3. Relationship between age group and organ systems with grade 2 or higher bleeding

Organ system	0 - 5 years	6 - 12 years	13 - 18 years	19+ years	Total	P for overall comparison of the four age groups	Significant pairwise comparisons*
No. of patients	66	69	65	1072	1272		
Oral and nasal	23 (35)	22 (32)	21 (32)	155 (14)	221 (17)	<0.001	C, E, F
Oropharyngeal bleeding, total duration more than 30 minutes	15 (23)	15 (22)	16 (25)	68 (6)	114 (9)	<0.001	C, E, F
Epistaxis, total duration more than 30 minutes	15 (23)	11 (16)	11 (17)	118 (11)	155 (12)	0.02	C
Skin. Soft Tissue, and Musculoskeletal	9 (14)	11 (16)	8 (12)	325 (30)	353 (28)	<0.001	C, E, F
Purpura greater than 1 inch diameter	7 (11)	7 (10)	8 (12)	306 (29)	328 (26)	<0.001	C, E, F
Spontaneous deep hematoma	4 (6)	1 (1)	0 (0)	13 (1)	18 (1)	0.04	C
Joint bleeding	2 (3)	4 (6)	0 (0)	21 (2)	27 (2)	0.09	
Gastrointestinal	47 (71)	42 (61)	37 (57)	334 (31)	460 (36)	<0.001	C, E, F
Melanotic stool	19 (29)	10 (14)	10 (15)	92 (9)	131 (10)	<0.001	C
Hematochezia	11 (17)	10 (14)	15 (23)	177 (17)	213 (17)	0.54	
Hematemesis	36 (55)	38 (55)	32 (49)	160 (15)	266 (21)	<0.001	C, E, F
Genitourinary	13 (20)	16 (23)	19 (29)	227 (21)	275 (22)	0.45	
Gross/visible hematuria	13 (20)	16 (23)	19 (29)	212 (20)	260 (20)	0.28	
Abnormal vaginal bleeding, more than spotting†	0 (0)	0 (0)	5 (26)	55 (13)	60 (12)	0.005	B, D, E

Pulmonary	12 (18)	12 (17)	23 (35)	189 (18)	236 (19)	0.01	B, D, F
Hemoptysis	4 (6)	5 (7)	11 (17)	97 (9)	117 (9)	0.16	
Blood in broncho-pulmonary lavage or blood tinged sputum	10 (15)	11 (16)	20 (31)	151 (14)	192 (15)	0.008	B, F
Body cavity - visible blood	1 (2)	0 (0)	5 (8)	26 (2)	32 (3)	0.0495	D, F
Central nervous system	4 (6)	4 (6)	6 (9)	29 (3)	43 (3)	0.009	F
Retinal bleeding	2 (3)	0 (0)	4 (6)	11 (1)	17 (1)	0.01	F
Microscopic or visible blood in lumbar puncture (non-traumatic tap) with or without symptoms	3 (5)	3 (4)	2 (3)	14 (1)	22 (2)	0.03	no pairwise significant at 0.05 level
CNS bleeding on imaging study	1 (2)	1 (1)	2 (3)	7 (1)	11 (1)	0.08	
Invasive sites	4 (6)	10 (14)	6 (9)	78 (7)	98 (8)	0.17	
Hemodynamic instability - moderate or severe	32 (48)	30 (43)	36 (55)	349 (33)	447 (35)	<0.001	C, F

Values are presented as n (%). The percentages were calculated from the patients with available data on each parameter.

For each type of bleeding, the table indicates the number of patients who had at least one day of Grade 2 or higher bleeding of the specified type. Some patients had bleeding in more than one organ system and/or more than one type of bleeding within an organ system. These patients are included in all applicable rows of Table 4. For example, 114 patients experienced oropharyngeal bleeding totaling at least 30 minutes duration in a single calendar day, and 155 patients experienced epistaxis totaling at least 30 minutes duration in a single calendar day. However, there was overlap between these groups; 221 patients experienced one or both types of oral/nasal bleeding while on study.

* A: 0-5 years vs. 6-12 years; B: 0-5 years vs. 13-18 years; C: 0-5 years vs. 19+ years; D: 6-12 years vs. 13-18 years; E: 6-12 years vs. 19+ years; F: 13-18 years vs. 19+ years

† Among female patients only