Supplementary Appendix

All Panelists

In each cell below, **the group rated the appropriateness of the treatment strategies** on a 1 to 9 scale, where:

1	← →	5	← →	9
highly inappropriate, risks outweigh the benefits		not sure (e.g., due to inadequate data) or the risks and benefits seem balanced		highly appropriate, benefits outweigh the risks

The following document presents the group's ratings median and range of ratings. Each cell is color coded. Cells in yellow are ones where the group disagreed (≥2 panelists gave that cell a rating of 1-3 and ≥2 panelists gave that cell a rating of 7-9); cells in blue are ones where the group agreed, with the darker blues representing higher medians, as shown in the key on the right.

Median (Range)
Yellow: Disagreement (≥2 ratings of 1-3 and ≥2 ratings of 7-9)
Blue 1: Median ≥7-9 without disagreement
Blue 2: Median ≥4-<7 without disagreement
Blue 3: Median 1-<4 without disagreement

Part I. Initial management

Table 1. First, imagine a patient in whom you have confirmed a diagnosis of acquired SAA (i.e., you have ruled out inherited SAA) who has not received any prior treatments. Consider the appropriateness of the following therapies **first-line** [8]. The columns and meta rows describe different types of patients. For example, the patient in cells A1-3 is a medically fit ≤20-year-old who has a matched related donor available.

Do your best to imagine a typical patient with these characteristics. For each patient, rate the appropriateness of the following therapies **first-line** on a 1 to 9 scale, where 1 is highly inappropriate and 9 is highly appropriate.				**Medically fit** [9] in the following age groups [10]			
				≤20 years old	21-40 years old	41-60 years old	>60 years old
				A	B	C	D
In a patient whose highest quality transplant is a	matched related [11] donor	HSCT	1	9.0 (9 - 9)	9.0 (7 - 9)	6.0 (4 - 9)	5.0 (2 - 8)
		Horse ATG + CsA + eltrombopag (triple IST)	2	5.0 (3 - 6)	6.0 (3 - 8)	8.0 (7 - 9)	9.0 (5 - 9)
		Horse ATG + CsA	3	6.0 (3 - 7)	4.0 (2 - 7)	5.0 (2 - 8)	6.0 (2 - 8)
	matched unrelated [12] donor	HSCT	4	7.0 (5 - 9)	7.0 (4 - 9)	5.0 (2 - 8)	4.0 (1 - 8)
		Horse ATG + CsA + eltrombopag (triple IST)	5	6.0 (3 - 9)	8.0 (5 - 9)	9.0 (7 - 9)	9.0 (5 - 9)
		Horse ATG + CsA	6	8.0 (6 - 9)	6.0 (2 - 8)	6.0 (2 - 9)	7.0 (2 - 9)
	haploidentical [13] donor	HSCT	7	6.0 (4 - 9)	6.0 (4 - 9)	5.0 (2 - 9)	4.0 (1 - 8)
		Horse ATG + CsA + eltrombopag (triple IST)	8	8.0 (3 - 9)	8.0 (5 - 9)	9.0 (7 - 9)	9.0 (5 - 9)
		Horse ATG + CsA	9	8.0 (6 - 9)	6.0 (2 - 9)	6.0 (2 - 8)	6.0 (2 - 8)
Unknown or no donor available		Horse ATG + CsA + eltrombopag (triple IST)	10	7.0 (5 - 9)	9.0 (7 - 9)	9.0 (7 - 9)	9.0 (8 - 9)
		Horse ATG + CsA	11	9.0 (6 - 9)	7.0 (2 - 9)	7.0 (2 - 9)	7.0 (2 - 8)

[8] Note that we are not asking you to consider CsA with or without eltrombopag in this table because we heard it is rare to recommend in medically fit patients
[9] ECOG ≤2 (0=Fully active, no performance restrictions; 1=Strenuous physical activity restricted, fully ambulatory and able to carry out light work; 2=Capable of all self-care but unable to carry out any work activities, up and about >50% of waking hours)
[10] Age categories based on Tichelli Haematologica 2020 (https://www.haematologica.org/article/view/9378)
[11] Matched sibling donor (MSD), may include matched family donor (MFD), a 10/10 match
[12] Includes matched unrelated (MUD), may also include cord blood, a 10/10 match
[13] A 5/10 match

Part II. Subsequent management

Table 2a. Next, imagine a patient who received **horse ATG + CsA + eltrombopag** (triple IST) first-line and was **refractory** [14] to this treatment. Consider the appropriateness of the following therapies **second-line** [15]. The columns and meta rows describe different types of patients. For example, the patient in cells A12-18 is a medically fit ≤20-year-old who has a matched related donor available.

Do your best to imagine a typical patient with these characteristics. For each patient, rate the appropriateness of the following therapies **second-line** on a 1 to 9 scale, where 1 is highly inappropriate and 9 is highly appropriate.					**Medically fit** [16] in the following age groups [17]			
					≤20 years old	21-40 years old	41-60 years old	>60 years old
					A	B	C	D
In a patient whose highest quality transplant is a	matched related [18] donor		HSCT	12	9.0 (9 - 9)	9.0 (8 - 9)	8.0 (7 - 9)	7.0 (4 - 8)
		High intensity therapy [19]	with eltrombopag	13	4.0 (3 - 6)	5.0 (3 - 6)	6.0 (3 - 7)	6.0 (3 - 7)
			with romiplostim	14	3.0 (2 - 6)	4.0 (3 - 6)	5.0 (3 - 8)	5.0 (3 - 8)
			without TPO-RAs	15	4.0 (1 - 5)	4.0 (1 - 6)	4.0 (1 - 6)	4.0 (1 - 6)
		Low intensity therapy [20]	with eltrombopag	16	3.0 (1 - 4)	3.0 (2 - 4)	4.0 (2 - 7)	4.0 (3 - 7)
			with romiplostim	17	3.0 (1 - 5)	3.0 (2 - 5)	4.0 (2 - 8)	5.0 (3 - 8)
			without TPO-RAs	18	2.0 (1 - 4)	2.0 (1 - 4)	3.0 (1 - 5)	3.0 (2 - 8)
	matched unrelated [21] donor		HSCT	19	9.0 (8 - 9)	9.0 (8 - 9)	7.0 (7 - 9)	6.0 (3 - 8)
		High intensity therapy	with eltrombopag	20	5.0 (3 - 7)	5.0 (3 - 8)	6.0 (3 - 9)	6.0 (2 - 9)
			with romiplostim	21	4.0 (3 - 6)	4.0 (3 - 6)	4.0 (3 - 8)	5.0 (3 - 8)
			without TPO-RAs	22	4.0 (1 - 8)	4.0 (2 - 8)	4.0 (2 - 8)	4.0 (2 - 8)
		Low intensity therapy	with eltrombopag	23	3.0 (1 - 4)	3.0 (1 - 8)	4.0 (1 - 8)	5.0 (1 - 8)
			with romiplostim	24	2.0 (1 - 5)	3.0 (2 - 7)	4.0 (2 - 8)	5.0 (3 - 9)
			without TPO-RAs	25	2.0 (1 - 4)	2.0 (1 - 4)	3.0 (2 - 6)	3.0 (2 - 8)
	haploidentical [22] donor		HSCT	26	8.0 (7 - 9)	8.0 (5 - 9)	7.0 (6 - 9)	5.0 (3 - 8)
		High intensity therapy	with eltrombopag	27	5.0 (3 - 7)	5.0 (3 - 8)	6.0 (3 - 9)	7.0 (2 - 9)
			with romiplostim	28	5.0 (3 - 6)	5.0 (3 - 6)	5.0 (3 - 8)	6.0 (3 - 8)
			without TPO-RAs	29	4.0 (1 - 8)	4.0 (1 - 8)	4.0 (1 - 8)	4.0 (1 - 8)
		Low intensity therapy	with eltrombopag	30	3.0 (1 - 5)	4.0 (2 - 8)	5.0 (2 - 8)	6.0 (3 - 8)
			with romiplostim	31	3.0 (1 - 5)	4.0 (2 - 7)	5.0 (2 - 8)	6.0 (4 - 9)
			without TPO-RAs	32	2.0 (1 - 4)	2.0 (1 - 4)	3.0 (2 - 6)	4.0 (2 - 8)

[14] Lack of response with persistent severe pancytopenia at 6 months after 1 course of IST and still meets criteria for SAA (https://pubmed.ncbi.nlm.nih.gov/22517900/)
[15] After confirming there is no evidence of clonal evolution (e.g., MDS, AML)
[16] ECOG ≤2 (0=Fully active, no performance restrictions; 1=Strenuous physical activity restricted, fully ambulatory and able to carry out light work; 2=Capable of all self-care but unable to carry out any work activities, up and about >50% of waking hours)
[17] Age categories based on Tichelli Haematologica 2020 (https://www.haematologica.org/article/view/9378)
[18] Matched sibling donor (MSD), may include matched family donor (MFD), a 10/10 match
[19] Includes a combination of agents or single agent cyclophosphamide or alemtuzumab (see examples in "Definitions and acronyms" section above)
[20] Includes single agents other than cyclophosphamide, alemtuzumab, or TPO-RAs (see examples in "Definitions and acronyms" section above)
[21] Includes matched unrelated (MUD), may also include cord blood, a 10/10 match
[22] A 5/10 match

Table 2b. Next, imagine a patient who received horse **ATG + CsA + eltrombopag** (triple IST) first-line, **relapsed** [23], and again meets the criteria for SAA. Assume the patient initially responded to treatment, is still on full dose CsA +/- eltrombopag (e.g., within <12 months since initiation of therapy), and this relapse is **not** a loss of response as a result of discontinuation of eltrombopag. Consider the appropriateness of the following therapies **second-line** [24]. The columns and meta rows describe different types of patients. For example, the patient in cells A33-40 is a medically fit ≤20-year-old who has a matched related donor available.

Do your best to imagine a typical patient with these characteristics. For each patient, rate the appropriateness of the following therapies **second-line** on a 1 to 9 scale, where 1 is highly inappropriate and 9 is highly appropriate.					**Medically fit** [25] in the following age groups [26]			
					≤20 years old	21-40 years old	41-60 years old	>60 years old
					A	B	C	D
In a patient whose highest quality transplant is a	matched related [27] donor		HSCT	33	9.0 (9 - 9)	9.0 (8 - 9)	8.0 (7 - 9)	6.0 (5 - 8)
		High intensity therapy [28]	with eltrombopag	34	6.0 (2 - 9)	6.0 (2 - 9)	6.0 (4 - 9)	7.0 (2 - 9)
			with romiplostim	35	4.0 (2 - 5)	4.0 (2 - 8)	5.0 (2 - 9)	5.0 (3 - 9)
			without TPO-RAs	36	4.0 (2 - 6)	3.0 (2 - 6)	3.0 (2 - 6)	3.0 (1 - 6)
		Low intensity therapy [29]	with eltrombopag	37	2.0 (2 - 6)	3.0 (2 - 6)	4.0 (2 - 6)	5.0 (2 - 7)
			with romiplostim	38	2.0 (2 - 5)	3.0 (2 - 8)	3.0 (2 - 8)	4.0 (2 - 8)
			without TPO-RAs	39	2.0 (1 - 3)	3.0 (1 - 5)	2.0 (2 - 6)	3.0 (2 - 6)
		Eltrombopag (single agent only)		40	2.0 (1 - 3)	2.0 (1 - 5)	4.0 (1 - 6)	5.0 (1 - 6)
	matched unrelated [30] donor		HSCT	41	9.0 (8 - 9)	9.0 (7 - 9)	7.0 (5 - 9)	6.0 (4 - 8)
		High intensity therapy	with eltrombopag	42	6.0 (2 - 9)	6.0 (2 - 9)	6.0 (4 - 9)	6.0 (1 - 9)
			with romiplostim	43	4.0 (2 - 6)	5.0 (2 - 8)	5.0 (3 - 9)	5.0 (1 - 9)
			without TPO-RAs	44	4.0 (2 - 7)	4.0 (2 - 6)	3.0 (2 - 6)	3.0 (1 - 6)
		Low intensity therapy	with eltrombopag	45	3.0 (2 - 6)	3.0 (2 - 7)	4.0 (2 - 7)	5.0 (2 - 7)
			with romiplostim	46	2.0 (2 - 5)	3.0 (2 - 8)	4.0 (2 - 8)	5.0 (2 - 8)
			without TPO-RAs	47	2.0 (1 - 3)	3.0 (1 - 5)	3.0 (2 - 7)	3.0 (2 - 6)
		Eltrombopag (single agent only)		48	2.0 (1 - 5)	2.0 (1 - 5)	3.0 (1 - 6)	5.0 (1 - 6)
	haploidentical [31] donor		HSCT	49	9.0 (3 - 9)	8.0 (7 - 9)	7.0 (4 - 9)	5.0 (3 - 8)
		High intensity therapy	with eltrombopag	50	6.0 (4 - 9)	7.0 (2 - 9)	7.0 (2 - 9)	7.0 (1 - 9)
			with romiplostim	51	4.0 (2 - 8)	5.0 (2 - 8)	5.0 (2 - 9)	5.0 (1 - 9)
			without TPO-RAs	52	5.0 (2 - 7)	4.0 (2 - 7)	3.0 (2 - 6)	3.0 (1 - 6)
		Low intensity therapy	with eltrombopag	53	4.0 (2 - 6)	4.0 (2 - 7)	4.0 (2 - 7)	4.0 (2 - 7)
			with romiplostim	54	3.0 (2 - 5)	3.0 (2 - 8)	4.0 (2 - 8)	4.0 (2 - 8)
			without TPO-RAs	55	2.0 (1 - 4)	3.0 (1 - 5)	3.0 (2 - 5)	3.0 (2 - 6)
		Eltrombopag (single agent only)		56	2.0 (1 - 6)	3.0 (1 - 6)	5.0 (1 - 6)	5.0 (1 - 6)

[23] Initially responded to treatment but requires a reintroduction to or escalation of immunosuppression for decreasing blood counts, usually but not always accompanying a reinstitution of transfusions (https://pubmed.ncbi.nlm.nih.gov/22517900/)
[24] After confirming there is no evidence of clonal evolution (e.g., MDS, AML)
[25] ECOG ≤2 (0=Fully active, no performance restrictions; 1=Strenuous physical activity restricted, fully ambulatory and able to carry out light work; 2=Capable of all self-care but unable to carry out any work activities, up and about >50% of waking hours)
[26] Age categories based on Tichelli Haematologica 2020 (https://www.haematologica.org/article/view/9378)
[27] Matched sibling donor (MSD), may include matched family donor (MFD), a 10/10 match
[28] Includes a combination of agents or single agent cyclophosphamide or alemtuzumab (see examples in "Definitions and acronyms" section above)
[29] Includes single agents other than cyclophosphamide, alemtuzumab, or TPO-RAs (see examples in "Definitions and acronyms" section above)
[30] Includes matched unrelated (MUD), may also include cord blood, a 10/10 match
[31] A 5/10 match

Table 2c. Next, imagine a patient who received horse **ATG + CsA + eltrombopag** (triple IST) first-line, **relapsed** [32], and again meets the criteria for SAA. Assume the patient had a complete response, is no longer on full dose CsA or eltrombopag (e.g., after ≥12 months since initiation of therapy), and this is **not** a gradual loss of response during a taper [33]. Consider the appropriateness of the following therapies **second-line** [34]. The columns and meta rows describe different types of patients. For example, the patient in cells A57-64 is a medically fit ≤20-year-old who has a matched related donor available.

Do your best to imagine a typical patient with these characteristics. For each patient, rate the appropriateness of the following therapies **second-line** on a 1 to 9 scale, where 1 is highly inappropriate and 9 is highly appropriate.					**Medically fit** [35] in the following age groups [36]			
					≤20 years old	21-40 years old	41-60 years old	>60 years old
					A	B	C	D
In a patient whose highest quality transplant is a	matched related [37] donor		HSCT	57	9.0 (7 - 9)	9.0 (7 - 9)	7.0 (4 - 9)	6.0 (4 - 8)
		High intensity therapy [38]	with eltrombopag	58	6.0 (5 - 8)	6.0 (5 - 8)	7.0 (5 - 9)	6.0 (5 - 8)
			with romiplostim	59	4.0 (2 - 7)	5.0 (2 - 8)	5.0 (4 - 8)	5.0 (3 - 8)
			without TPO-RAs	60	5.0 (2 - 7)	5.0 (2 - 7)	4.0 (3 - 8)	5.0 (3 - 8)
		Low intensity therapy [39]	with eltrombopag	61	5.0 (2 - 9)	5.0 (2 - 9)	6.0 (2 - 9)	5.0 (2 - 9)
			with romiplostim	62	3.0 (1 - 5)	4.0 (1 - 8)	5.0 (2 - 5)	5.0 (2 - 9)
			without TPO-RAs	63	3.0 (1 - 5)	3.0 (1 - 5)	4.0 (2 - 6)	4.0 (2 - 8)
		Eltrombopag (single agent only)		64	2.0 (1 - 4)	2.0 (1 - 5)	4.0 (1 - 6)	5.0 (1 - 7)
	matched unrelated [40] donor		HSCT	65	8.0 (7 - 9)	8.0 (7 - 9)	7.0 (4 - 9)	5.0 (4 - 7)
		High intensity therapy	with eltrombopag	66	6.0 (5 - 9)	6.0 (5 - 9)	7.0 (5 - 9)	6.0 (5 - 8)
			with romiplostim	67	4.0 (2 - 8)	5.0 (2 - 8)	6.0 (4 - 8)	5.0 (4 - 8)
			without TPO-RAs	68	5.0 (2 - 7)	5.0 (2 - 7)	5.0 (2 - 8)	5.0 (2 - 8)
		Low intensity therapy	with eltrombopag	69	5.0 (2 - 9)	5.0 (2 - 9)	6.0 (2 - 9)	6.0 (3 - 9)
			with romiplostim	70	3.0 (1 - 6)	4.0 (1 - 8)	5.0 (2 - 6)	5.0 (2 - 8)
			without TPO-RAs	71	3.0 (1 - 5)	4.0 (1 - 5)	5.0 (2 - 6)	4.0 (2 - 7)
		Eltrombopag (single agent only)		72	2.0 (1 - 4)	3.0 (1 - 6)	4.0 (1 - 6)	5.0 (1 - 6)
	haploidentical [41] donor		HSCT	73	8.0 (7 - 9)	8.0 (6 - 9)	7.0 (5 - 9)	5.0 (1 - 7)
		High intensity therapy	with eltrombopag	74	6.0 (5 - 9)	6.0 (5 - 9)	8.0 (4 - 9)	7.0 (5 - 8)
			with romiplostim	75	4.0 (2 - 8)	6.0 (2 - 8)	7.0 (4 - 8)	5.0 (4 - 8)
			without TPO-RAs	76	5.0 (2 - 7)	5.0 (2 - 7)	4.0 (3 - 8)	5.0 (3 - 8)
		Low intensity therapy	with eltrombopag	77	5.0 (2 - 9)	5.0 (2 - 9)	6.0 (2 - 9)	6.0 (2 - 9)
			with romiplostim	78	3.0 (1 - 6)	4.0 (1 - 8)	5.0 (2 - 7)	5.0 (2 - 7)
			without TPO-RAs	79	3.0 (1 - 6)	4.0 (1 - 6)	5.0 (2 - 6)	5.0 (2 - 6)
		Eltrombopag (single agent only)		80	2.0 (1 - 5)	4.0 (1 - 6)	4.0 (1 - 6)	5.0 (1 - 8)

[32] Initially responded to treatment but requires a reintroduction to or escalation of immunosuppression for decreasing blood counts, usually but not always accompanying a reinstitution of transfusions (https://pubmed.ncbi.nlm.nih.gov/22517900/)
[33] If the patient experienced a gradual loss of response during a medication taper (e.g., eltrombopag, CsA), treatment would include reverting back to the prior, higher dose of medication
[34] After confirming there is no evidence of clonal evolution (e.g., MDS, AML)
[35] ECOG ≤2 (0=Fully active, no performance restrictions; 1=Strenuous physical activity restricted, fully ambulatory and able to carry out light work; 2=Capable of all self-care but unable to carry out any work activities, up and about >50% of waking hours)
[36] Age categories based on Tichelli Haematologica 2020 (https://www.haematologica.org/article/view/9378)
[37] Matched sibling donor (MSD), may include matched family donor (MFD), a 10/10 match
[38] Includes a combination of agents or single agent cyclophosphamide or alemtuzumab (see examples in "Definitions and acronyms" section above)
[39] Includes single agents other than cyclophosphamide, alemtuzumab, or TPO-RAs (see examples in "Definitions and acronyms" section above)
[40] Includes matched unrelated (MUD), may also include cord blood, a 10/10 match
[41] A 5/10 match

Table 3a. Next, imagine a patient who received **horse ATG + CsA** (without eltrombopag) first-line and was **refractory** [42] to this treatment. Consider the appropriateness of the following therapies **second-line** [43]. The columns and meta rows describe different types of patients. For example, the patient in cells A81-88 is a medically fit ≤20-year-old who has a matched related donor available.

Do your best to imagine a typical patient with these characteristics. For each patient, rate the appropriateness of the following therapies **second-line** on a 1 to 9 scale, where 1 is highly inappropriate and 9 is highly appropriate.				**Medically fit** [44] in the following age groups [45]			
				≤20 years old	21-40 years old	41-60 years old	>60 years old
				A	B	C	D
In a patient whose highest quality transplant is a	matched related [46] donor		HSCT 81	9.0 (7 - 9)	9.0 (7 - 9)	8.0 (4 - 9)	7.0 (1 - 8)
		High intensity therapy [47]	with eltrombopag 82	5.0 (2 - 8)	5.0 (2 - 8)	6.0 (2 - 8)	6.0 (2 - 8)
			with romiplostim 83	4.0 (1 - 5)	4.0 (1 - 5)	4.0 (2 - 7)	5.0 (2 - 7)
			without TPO-RAs 84	3.0 (1 - 7)	3.0 (1 - 7)	4.0 (1 - 8)	5.0 (1 - 8)
		Low intensity therapy [48]	with eltrombopag 85	5.0 (2 - 8)	6.0 (4 - 8)	6.0 (4 - 8)	6.0 (4 - 8)
			with romiplostim 86	3.0 (3 - 7)	4.0 (3 - 7)	5.0 (3 - 8)	5.0 (3 - 8)
			without TPO-RAs 87	3.0 (2 - 4)	3.0 (2 - 4)	3.0 (2 - 5)	3.0 (2 - 5)
		Eltrombopag (single agent only) 88		3.0 (2 - 5)	5.0 (2 - 6)	6.0 (2 - 7)	6.0 (3 - 7)
	matched unrelated [49] donor		HSCT 89	9.0 (6 - 9)	9.0 (6 - 9)	7.0 (4 - 9)	6.0 (1 - 8)
		High intensity therapy	with eltrombopag 90	5.0 (2 - 8)	5.0 (2 - 8)	6.0 (4 - 9)	6.0 (4 - 9)
			with romiplostim 91	4.0 (1 - 5)	4.0 (1 - 5)	5.0 (4 - 7)	5.0 (3 - 7)
			without TPO-RAs 92	3.0 (1 - 7)	3.0 (1 - 7)	4.0 (1 - 8)	5.0 (1 - 8)
		Low intensity therapy	with eltrombopag 93	5.0 (2 - 8)	6.0 (2 - 8)	6.0 (2 - 8)	6.0 (4 - 8)
			with romiplostim 94	3.0 (2 - 7)	4.0 (2 - 7)	5.0 (2 - 8)	5.0 (3 - 8)
			without TPO-RAs 95	3.0 (2 - 4)	3.0 (2 - 4)	3.0 (2 - 5)	3.0 (2 - 5)
		Eltrombopag (single agent only) 96		3.0 (1 - 5)	5.0 (1 - 6)	6.0 (2 - 8)	6.0 (3 - 8)
	haploidentical [50] donor		HSCT 97	9.0 (6 - 9)	8.0 (6 - 9)	7.0 (3 - 9)	6.0 (1 - 8)
		High intensity therapy	with eltrombopag 98	6.0 (2 - 8)	6.0 (2 - 8)	7.0 (4 - 8)	7.0 (4 - 8)
			with romiplostim 99	5.0 (1 - 6)	5.0 (1 - 6)	5.0 (4 - 8)	5.0 (3 - 8)
			without TPO-RAs 100	3.0 (1 - 7)	3.0 (1 - 7)	4.0 (1 - 8)	5.0 (1 - 8)
		Low intensity therapy	with eltrombopag 101	6.0 (2 - 8)	6.0 (2 - 8)	6.0 (2 - 8)	7.0 (4 - 8)
			with romiplostim 102	3.0 (2 - 7)	5.0 (2 - 7)	5.0 (2 - 8)	5.0 (3 - 8)
			without TPO-RAs 103	3.0 (2 - 4)	3.0 (2 - 4)	3.0 (2 - 5)	3.0 (2 - 5)
		Eltrombopag (single agent only) 104		3.0 (1 - 6)	5.0 (1 - 6)	6.0 (2 - 8)	6.0 (3 - 8)

[42] Lack of response with persistent severe pancytopenia at 6 months after 1 course of IST and still meets criteria for SAA (https://pubmed.ncbi.nlm.nih.gov/22517900/)
[43] After confirming there is no evidence of clonal evolution (e.g., MDS, AML)
[44] ECOG ≤2 (0=Fully active, no performance restrictions; 1=Strenuous physical activity restricted, fully ambulatory and able to carry out light work; 2=Capable of all self-care but unable to carry out any work activities, up and about >50% of waking hours)
[45] Age categories based on Tichelli Haematologica 2020 (https://www.haematologica.org/article/view/9378)
[46] Matched sibling donor (MSD), may include matched family donor (MFD), a 10/10 match
[47] Includes a combination of agents or single agent cyclophosphamide or alemtuzumab (see examples in "Definitions and acronyms" section above)
[48] Includes single agents other than cyclophosphamide, alemtuzumab, or TPO-RAs (see examples in "Definitions and acronyms" section above)
[49] Includes matched unrelated (MUD), may also include cord blood, a 10/10 match
[50] A 5/10 match

Table 3b. Next, imagine a patient who received **horse ATG + CsA** (without eltrombopag) first-line, **relapsed** [51], and again meets the criteria for SAA. Assume the patient initially responded to treatment and is still on full dose CsA (e.g., within <12 months since initiation of therapy). Consider the appropriateness of the following therapies **second-line** [52]. The columns and meta rows describe different types of patients. For example, the patient in cells A105-112 is a medically fit ≤20-year-old who has a matched related donor available.

Do your best to imagine a typical patient with these characteristics. For each patient, rate the appropriateness of the following therapies **second-line** on a 1 to 9 scale, where 1 is highly inappropriate and 9 is highly appropriate.				**Medically fit** [53] in the following age groups [54]			
				≤20 years old	21-40 years old	41-60 years old	>60 years old
				A	B	C	D
In a patient whose highest quality transplant is a	matched related [55] donor		HSCT 105	9.0 (5 - 9)	9.0 (5 - 9)	7.0 (1 - 9)	7.0 (1 - 8)
		High intensity therapy [56]	with eltrombopag 106	5.0 (4 - 8)	6.0 (4 - 8)	6.0 (4 - 8)	6.0 (4 - 8)
			with romiplostim 107	4.0 (2 - 5)	4.0 (2 - 5)	4.0 (2 - 7)	5.0 (2 - 7)
			without TPO-RAs 108	3.0 (2 - 7)	3.0 (1 - 7)	3.0 (1 - 5)	3.0 (1 - 5)
		Low intensity therapy [57]	with eltrombopag 109	6.0 (2 - 7)	6.0 (4 - 7)	7.0 (4 - 9)	7.0 (4 - 9)
			with romiplostim 110	4.0 (2 - 7)	4.0 (2 - 7)	5.0 (2 - 8)	5.0 (2 - 8)
			without TPO-RAs 111	3.0 (1 - 4)	3.0 (1 - 4)	3.0 (1 - 7)	3.0 (1 - 7)
		Eltrombopag (single agent only) 112		3.0 (2 - 5)	3.0 (2 - 6)	5.0 (2 - 7)	5.0 (2 - 7)
	matched unrelated [58] donor		HSCT 113	9.0 (5 - 9)	9.0 (5 - 9)	7.0 (1 - 9)	6.0 (1 - 8)
		High intensity therapy	with eltrombopag 114	6.0 (4 - 9)	6.0 (4 - 9)	6.0 (4 - 8)	7.0 (4 - 8)
			with romiplostim 115	4.0 (2 - 8)	4.0 (2 - 8)	4.0 (2 - 7)	5.0 (2 - 7)
			without TPO-RAs 116	4.0 (1 - 7)	4.0 (1 - 7)	3.0 (1 - 5)	4.0 (1 - 5)
		Low intensity therapy	with eltrombopag 117	5.0 (2 - 7)	6.0 (4 - 7)	6.0 (4 - 9)	6.0 (4 - 9)
			with romiplostim 118	3.0 (2 - 7)	4.0 (2 - 7)	5.0 (2 - 8)	5.0 (2 - 8)
			without TPO-RAs 119	3.0 (1 - 5)	3.0 (1 - 5)	3.0 (1 - 7)	3.0 (1 - 7)
		Eltrombopag (single agent only) 120		3.0 (1 - 5)	3.0 (2 - 6)	5.0 (2 - 7)	5.0 (2 - 7)
	haploidentical [59] donor		HSCT 121	8.0 (7 - 9)	8.0 (7 - 9)	6.0 (6 - 9)	5.0 (2 - 8)
		High intensity therapy	with eltrombopag 122	6.0 (4 - 8)	6.0 (4 - 7)	7.0 (4 - 8)	7.0 (4 - 8)
			with romiplostim 123	4.0 (2 - 5)	4.0 (2 - 5)	5.0 (2 - 7)	5.0 (2 - 7)
			without TPO-RAs 124	3.0 (1 - 7)	3.0 (1 - 7)	4.0 (1 - 5)	4.0 (1 - 5)
		Low intensity therapy	with eltrombopag 125	5.0 (2 - 7)	5.0 (4 - 7)	6.0 (4 - 9)	7.0 (4 - 9)
			with romiplostim 126	4.0 (2 - 7)	4.0 (2 - 7)	5.0 (2 - 8)	5.0 (2 - 8)
			without TPO-RAs 127	3.0 (1 - 4)	3.0 (1 - 5)	3.0 (1 - 7)	3.0 (1 - 7)
		Eltrombopag (single agent only) 128		4.0 (1 - 5)	4.0 (2 - 6)	5.0 (2 - 7)	5.0 (2 - 7)

[51] Initially responded to treatment but requires a reintroduction to or escalation of immunosuppression for decreasing blood counts, usually but not always accompanying a reinstitution of transfusions (https://pubmed.ncbi.nlm.nih.gov/22517900/)
[52] After confirming there is no evidence of clonal evolution (e.g., MDS, AML)
[53] ECOG ≤2 (0=Fully active, no performance restrictions; 1=Strenuous physical activity restricted, fully ambulatory and able to carry out light work; 2=Capable of all self-care but unable to carry out any work activities, up and about >50% of waking hours)
[54] Age categories based on Tichelli Haematologica 2020 (https://www.haematologica.org/article/view/9378)
[55] Matched sibling donor (MSD), may include matched family donor (MFD), a 10/10 match
[56] Includes a combination of agents or single agent cyclophosphamide or alemtuzumab (see examples in "Definitions and acronyms" section above)
[57] Includes single agents other than cyclophosphamide, alemtuzumab, or TPO-RAs (see examples in "Definitions and acronyms" section above)
[58] Includes matched unrelated (MUD), may also include cord blood, a 10/10 match
[59] A 5/10 match

Table 3c. Next, imagine a patient who received **horse ATG + CsA** (without eltrombopag) first-line, **relapsed** [60], and again meets the criteria for SAA. Assume the patient had a complete response, is no longer on full dose CsA (e.g., after ≥12 months since initiation of therapy), and this is **not** a gradual loss of response during a taper [61]. Consider the appropriateness of the following therapies **second-line** [62]. The columns and meta rows describe different types of patients. For example, the patient in cells A129-136 is a medically fit ≤20-year-old who has a matched related donor available.

Do your best to imagine a typical patient with these characteristics. For each patient, rate the appropriateness of the following therapies **second-line** on a 1 to 9 scale, where 1 is highly inappropriate and 9 is highly appropriate.					**Medically fit** [63] in the following age groups [64]			
					≤20 years old	21-40 years old	41-60 years old	>60 years old
					A	B	C	D
In a patient whose highest quality transplant is a	matched related [65] donor		HSCT	129	9.0 (7 - 9)	9.0 (6 - 9)	7.0 (2 - 9)	6.0 (2 - 8)
		High intensity therapy [66]	with eltrombopag	130	6.0 (4 - 8)	6.0 (4 - 8)	7.0 (4 - 8)	8.0 (5 - 8)
			with romiplostim	131	5.0 (2 - 6)	5.0 (3 - 6)	5.0 (4 - 7)	5.0 (4 - 7)
			without TPO-RAs	132	4.0 (2 - 7)	4.0 (1 - 7)	3.0 (1 - 5)	4.0 (1 - 5)
		Low intensity therapy [67]	with eltrombopag	133	5.0 (2 - 7)	6.0 (4 - 7)	6.0 (4 - 7)	7.0 (4 - 8)
			with romiplostim	134	4.0 (3 - 9)	5.0 (3 - 9)	5.0 (3 - 9)	6.0 (3 - 8)
			without TPO-RAs	135	3.0 (2 - 8)	3.0 (2 - 8)	4.0 (2 - 8)	4.0 (2 - 8)
		Eltrombopag (single agent only)		136	3.0 (2 - 5)	4.0 (2 - 6)	5.0 (2 - 6)	5.0 (2 - 7)
	matched unrelated [68] donor		HSCT	137	9.0 (7 - 9)	9.0 (6 - 9)	7.0 (2 - 8)	6.0 (2 - 8)
		High intensity therapy	with eltrombopag	138	6.0 (4 - 8)	6.0 (4 - 8)	7.0 (4 - 8)	7.0 (5 - 8)
			with romiplostim	139	5.0 (2 - 6)	5.0 (3 - 6)	5.0 (4 - 7)	5.0 (4 - 7)
			without TPO-RAs	140	3.0 (1 - 7)	3.0 (1 - 7)	3.0 (1 - 5)	4.0 (1 - 5)
		Low intensity therapy	with eltrombopag	141	5.0 (2 - 7)	6.0 (4 - 7)	7.0 (4 - 7)	7.0 (4 - 8)
			with romiplostim	142	4.0 (2 - 7)	5.0 (3 - 7)	5.0 (3 - 8)	5.0 (3 - 8)
			without TPO-RAs	143	3.0 (2 - 8)	4.0 (2 - 8)	4.0 (2 - 8)	4.0 (2 - 8)
		Eltrombopag (single agent only)		144	3.0 (2 - 5)	4.0 (2 - 6)	5.0 (2 - 6)	5.0 (2 - 7)
	haploidentical [69] donor		HSCT	145	8.0 (6 - 9)	8.0 (6 - 9)	6.0 (2 - 8)	5.0 (2 - 8)
		High intensity therapy	with eltrombopag	146	6.0 (4 - 8)	6.0 (4 - 8)	7.0 (4 - 8)	7.0 (5 - 8)
			with romiplostim	147	5.0 (2 - 5)	5.0 (3 - 5)	5.0 (4 - 7)	5.0 (4 - 7)
			without TPO-RAs	148	3.0 (1 - 7)	3.0 (1 - 7)	3.0 (1 - 5)	4.0 (1 - 5)
		Low intensity therapy	with eltrombopag	149	5.0 (2 - 7)	6.0 (4 - 7)	6.0 (4 - 7)	7.0 (4 - 8)
			with romiplostim	150	4.0 (2 - 7)	5.0 (3 - 7)	5.0 (3 - 8)	5.0 (3 - 8)
			without TPO-RAs	151	3.0 (2 - 8)	4.0 (2 - 8)	4.0 (2 - 8)	4.0 (2 - 8)
		Eltrombopag (single agent only)		152	4.0 (2 - 5)	4.0 (2 - 6)	4.0 (2 - 7)	5.0 (2 - 7)

[60] Initially responded to treatment but requires a reintroduction to or escalation of immunosuppression for decreasing blood counts, usually but not always accompanying a reinstitution of transfusions (https://pubmed.ncbi.nlm.nih.gov/22517900/)
[61] If the patient experienced a gradual loss of response during a medication taper (e.g., eltrombopag, CsA), treatment would include reverting back to the prior, higher dose of medication
[62] After confirming there is no evidence of clonal evolution (e.g., MDS, AML)
[63] ECOG ≤2 (0=Fully active, no performance restrictions; 1=Strenuous physical activity restricted, fully ambulatory and able to carry out light work; 2=Capable of all self-care but unable to carry out any work activities, up and about >50% of waking hours)
[64] Age categories based on Tichelli Haematologica 2020 (https://www.haematologica.org/article/view/9378)
[65] Matched sibling donor (MSD), may include matched family donor (MFD), a 10/10 match
[66] Includes a combination of agents or single agent cyclophosphamide or alemtuzumab (see examples in "Definitions and acronyms" section above)
[67] Includes single agents other than cyclophosphamide, alemtuzumab, or TPO-RAs (see examples in "Definitions and acronyms" section above)
[68] Includes matched unrelated (MUD), may also include cord blood, a 10/10 match
[69] A 5/10 match

Part III. Medically unfit patients

Table 4. Now think about patients who are medically unfit, regardless of age. Rate the appropriateness of the following first- and second-line therapies in these patients. We have not asked you to consider transplant or donor availability in these patients since they would not be eligible for transplant.

Do your best to imagine a typical patient with these characteristics. Rate the appropriateness of the following therapies on a 1 to 9 scale, where 1 is highly inappropriate and 9 is highly appropriate.				**Medically unfit** [70] regardless of age
				A
First-line therapy				
No prior therapies (i.e., rate first-line therapy)		High intensity [71] therapy with eltrombopag	153	7.0 (2 - 9)
		High intensity therapy without eltrombopag	154	5.0 (1 - 8)
		Low intensity [72] therapy with eltrombopag	155	7.0 (6 - 9)
		Low intensity therapy without eltrombopag	156	6.0 (2 - 8)
Second-line therapy				
Received any IST [73] with eltrombopag first-line	and was refractory [74] to this therapy	Low intensity therapy [72] with eltrombopag	157	5.0 (3 - 8)
		Low intensity therapy [72] with romiplostim	158	6.0 (3 - 9)
		Low intensity therapy [72] without TPO-RAs	159	4.0 (2 - 9)
	and relapsed [75] without complete response	Low intensity therapy with eltrombopag	160	7.0 (5 - 8)
		Low intensity therapy with romiplostim	161	6.0 (5 - 9)
		Low intensity therapy without TPO-RAs	162	4.0 (2 - 9)
		Eltrombopag (single agent only)	163	6.0 (3 - 8)
	and relapsed after complete response [76]	Low intensity therapy with eltrombopag	164	8.0 (6 - 9)
		Low intensity therapy with romiplostim	165	6.0 (5 - 9)
		Low intensity therapy without TPO-RAs	166	4.0 (2 - 7)
		Eltrombopag (single agent only)	167	6.0 (3 - 8)
Received any IST without eltrombopag first-line	and was refractory to this therapy	Low intensity therapy with eltrombopag	168	8.0 (5 - 9)
		Low intensity therapy with romiplostim	169	6.0 (4 - 8)
		Low intensity therapy without TPO-RAs	170	4.0 (2 - 5)
		Eltrombopag (single agent only)	171	7.0 (3 - 9)
	and relapsed without complete response	Low intensity therapy with eltrombopag	172	8.0 (6 - 9)
		Low intensity therapy with romiplostim	173	6.0 (5 - 8)
		Low intensity therapy without TPO-RAs	174	4.0 (2 - 5)
		Eltrombopag (single agent only)	175	7.0 (3 - 9)
	and relapsed after complete response	Low intensity therapy with eltrombopag	176	8.0 (7 - 9)
		Low intensity therapy with romiplostim	177	6.0 (5 - 8)
		Low intensity therapy without TPO-RAs	178	4.0 (2 - 8)
		Eltrombopag (single agent only)	179	7.0 (3 - 8)

[70] ECOG >2 (3=Capable of only limited self-care, confined to bed or chair >50% of waking hours; 4=Completely disabled, cannot carry out any self-care, totally confined to bed or chair)
[71] Includes a combination of agents or single agent cyclophosphamide or alemtuzumab (see examples in "Definitions and acronyms" section above)
[72] Includes single agents other than cyclophosphamide, alemtuzumab, or TPO-RAs (see examples in "Definitions and acronyms" section above)
[73] Includes horse or rabbit ATG, CsA, or other non-CsA immunosuppressants (e.g., mycophenolate mofetil, sirolimus, tacrolimus, alemtuzumab) (see "Definitions and acronyms" section above)
[74] Lack of response with persistent severe pancytopenia at 6 months after 1 course of IST and still meets criteria for SAA (https://pubmed.ncbi.nlm.nih.gov/22517900/)
[75] Initially responded to treatment but requires a reintroduction to or escalation of immunosuppression for decreasing blood counts, usually but not always accompanying a reinstitution of transfusions (https://pubmed.ncbi.nlm.nih.gov/22517900/); meets criteria for SAA
[76] Assume the patient meets criteria for SAA

Part IV. Supportive care

Table 5. Now, we would like you to think about supportive care prior to and during first-line therapy, regardless of whether the patient received medical therapy or was transplanted. Rate the appropriateness of recommending the following supportive care.

Do your best to imagine a typical patient. Rate appropriateness on a 1 to 9 scale, where 1 is highly inappropriate and 9 is highly appropriate.			A
Leukoreduced, irradiated red blood cell and platelet transfusion	In patients with hemoglobin <7, platelets <10,000, or symptomatic	180	9.0 (9 - 9)
	In asymptomatic patients with higher counts than listed in row 180	181	4.0 (1 - 9)
Antibiotic prophylaxis for pneumocystis pneumonia [77] (e.g., Bactrim, pentamidine)		182	9.0 (5 - 9)
Antibiotic prophylaxis for gram negative coverage [77] (e.g., levofloxacin)		183	7.0 (3 - 9)
Antifungal prophylaxis [77] (e.g., voriconazole, fluconazole)		184	9.0 (4 - 9)
Antiviral prophylaxis [77] (e.g., acyclovir)		185	9.0 (3 - 9)

[77] In patients without an active infection

Part V. Ruling out inherited SAA

Table 6. Lastly, consider tests to **rule out inherited SAA** or **rule in acquired SAA** [78]. Many of these tests are available in NGS panels. Depending on the specific NGS panel, some may have to be ordered individually if not available.

Do your best to imagine a typical patient. Rate the appropriateness on a 1 to 9 scale, where 1 is highly inappropriate and 9 is highly appropriate.		Patient age			
		≤20 years old	21-40 years old	41-60 years old	>60 years old
		A	B	C	D
Tests to rule out inherited SAA					
Chromosome breakage analysis for Fanconi anemia	186	9.0 (9 - 9)	9.0 (8 - 9)	7.0 (3 - 9)	3.0 (2 - 7)
Telomere length analysis for Dyskeratosis congenita	187	9.0 (5 - 9)	9.0 (5 - 9)	7.0 (5 - 9)	5.0 (3 - 7)
Genetic testing for Dyskeratosis congenita	188	7.0 (5 - 9)	7.0 (4 - 9)	5.0 (1 - 7)	4.0 (1 - 5)
Genetic testing for germline RUNX1 mutation	189	6.0 (4 - 9)	6.0 (2 - 9)	5.0 (2 - 7)	4.0 (1 - 5)
Genetic testing for Shwachman-Bodian-Diamond syndrome	190	9.0 (2 - 9)	8.0 (1 - 9)	3.0 (1 - 6)	3.0 (1 - 5)
Genetic testing for Diamond-Blackfan anemia	191	9.0 (1 - 9)	7.0 (1 - 9)	4.0 (1 - 6)	3.0 (1 - 6)
Genetic testing for GATA2 deficiency	192	5.0 (1 - 9)	5.0 (1 - 9)	4.0 (1 - 6)	3.0 (1 - 5)
Genetic testing for germline c-MPL mutation	193	5.0 (2 - 9)	5.0 (1 - 7)	3.0 (1 - 6)	3.0 (1 - 5)
Genetic testing for germline MECOM mutation	194	5.0 (2 - 8)	5.0 (1 - 7)	3.0 (1 - 6)	3.0 (1 - 5)
Genetic testing for SAMD9/SAMD9L syndromes	195	6.0 (5 - 9)	5.0 (1 - 9)	5.0 (1 - 6)	3.0 (1 - 5)
Genetic testing for CTLA4 deficiency	196	5.0 (3 - 9)	4.0 (1 - 9)	4.0 (1 - 6)	3.0 (1 - 5)
Genetic testing for congenital neutropenia	197	4.0 (1 - 7)	4.0 (1 - 7)	3.0 (1 - 6)	2.0 (1 - 5)
Tests to rule in acquired SAA					
PNH flow cytometry [79]	198	9.0 (9 - 9)	9.0 (9 - 9)	9.0 (8 - 9)	9.0 (8 - 9)
Genetic testing for 6p CN-LOH clone [79]	199	9.0 (5 - 9)	9.0 (5 - 9)	7.0 (5 - 9)	7.0 (6 - 9)

[78] DeZern AE, Churpek JE. Approach to the diagnosis of aplastic anemia. Blood Adv. 2021 Jun 22;5(12):2660-71. https://doi.org/10.1182/bloodadvances.2021004345