Additional Materials

Additional Figure Legends

Additional Figure 1 Risk of bias summary

Review authors' judgements about each risk of bias item for each included study. Green "-" means low risk, and red "+" means high risk.

Additional Figure 2 Results for the network of early response and rescue treatment comparison

The summary effect estimate for risk ratio [RR] of **(A)** early response (Plt $\geq 50\times10^9$/L in 1 – 2 weeks from the initiation of the therapy, and **(B)** rescue treatment (including new treatment for ITP, increased dose of baseline treatment, platelet transfusion, intravenous immunoglobulin administration, and splenectomy) for each combination of treatments. RRs are indicated by dots, and 95% confidence intervals by bars.

Additional Figure 3 Results for the network of adverse events comparison

The summary effect estimate for risk ratio [RR] of thrombosis for each combination of treatments. RRs are indicated by dots, and 95% confidence intervals by bars.

Additional Figure 4 Funnel Plot of comparison

Risk ratio (RR) for overall response and standard error of each study are plotted.

Additional Tables

Additional Table 1 MEDLINE search strategy (via PubMed)

((((((((randomized controlled trial[pt]) OR controlled clinical trial[pt]) OR randomized[tiab]) OR clinical trials as topic[mesh:noexp]) OR randomly[tiab]) OR trial[ti])) NOT ((animals[mh]) NOT humans[mh])) AND ((((Purpura, Thrombocytopenic, Idiopathic[mh]) OR ITP) OR (purpura AND thrombocytop*)) OR ((autoimmun* OR immun*) AND thrombocytop*))

Additional Table 2 CENTRAL search strategy

#1	MeSH descriptor Purpura, Thrombocytopenic, Idiopathic explode all trees
#2	ITP
#3	purpura near thrombocytop*
#4	(autoimmun* or immun*) near thrombocytop*
#5	#1 or #2 or #3 or #4

Additional Table 3 Items in data extraction sheet

GENERAL INFORMATIONS
Study ID / Year
STUDY CHARACTERISTICS
Design
Country
Randomization
No. arm
No. pt randomized (each arm)
PATIENTS CHARACTERISTICS
No. of each gender (male / female)
Age (y; median / min / max)
Ethnicity
Diagnosis / Past tx history
Platelet count at dx
Bleeding score at dx
Other complications
COMPONENTS OF THE INTERVENTION
Intervention (dosage, duration, interval, total amounts, tapering)
Additional tx (type, dosage, interval)
OUTCOMES
Overall response (n; at 6wk – 1yr)
Early response (n; at 7 - 14d)
Rescue therapy (n)
Total No. Pt (AE measured)
Total No. of bleeding (n; all grade, clinically significant, severe)
Total No. of thrombosis (n)
Total No. Pt (AE measured)
Types of AE (n, grade)
RISK OF BIAS
Random sequence generation
Allocation concealment
Blinding of participants and personnel
Blinding of outcome assessment
Incomplete outcome data (efficacy / safety)
Selective reporting
Other RoB (definition / assessment)

Additional Table 4 Assessment form for risk of bias

RANDOM SEQUENCE GENERATION

Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence.

Criteria for a judgement of 'Low risk' of bias.	The investigators describe a random component in the sequence generation process such as: Referring to a random number table; Using a computer random number generator; Coin tossing; Shuffling cards or envelopes; Throwing dice; Drawing of lots; Minimization*. *Minimization may be implemented without a random element, and this is considered to be equivalent to being random.
Criteria for the judgement of 'High risk' of bias.	The investigators describe a non-random component in the sequence generation process. Usually, the description would involve some systematic, non-random approach, for example: Sequence generated by odd or even date of birth; Sequence generated by some rule based on date (or day) of admission; Sequence generated by some rule based on hospital or clinic record number. Other non-random approaches happen much less frequently than the systematic approaches mentioned above and tend to be obvious. They usually involve judgement or some method of non-random categorization of participants, for example: Allocation by judgement of the clinician; Allocation by preference of the participant; Allocation based on the results of a laboratory test or a series of tests; Allocation by availability of the intervention.
Criteria for the judgement of 'Unclear risk' of bias.	Insufficient information about the sequence generation process to permit judgement of 'Low risk' or 'High risk'.

ALLOCATION CONCEALMENT

Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment.

Criteria for a judgement of 'Low risk' of bias.	Participants and investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation: Central allocation (including telephone, web-based and pharmacy-controlled randomization); Sequentially numbered drug containers of identical appearance; Sequentially numbered, opaque, sealed envelopes.
Criteria for the judgement of 'High risk' of bias.	Participants or investigators enrolling participants could possibly foresee assignments and thus introduce selection bias, such as allocation based on: Using an open random allocation schedule (e.g. a list of random numbers); Assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or nonopaque or not sequentially numbered); Alternation or rotation;

	Date of birth; Case record number; Any other explicitly unconcealed procedure.
Criteria for the judgement of 'Unclear risk' of bias.	Insufficient information to permit judgement of 'Low risk' or 'High risk'. This is usually the case if the method of concealment is not described or not described in sufficient detail to allow a definite judgement – for example if the use of assignment envelopes is described, but it remains unclear whether envelopes were sequentially numbered, opaque and sealed.

BLINDING OF PARTICIPANTS AND PERSONNEL

Performance bias due to knowledge of the allocated interventions by participants and personnel during the study.

Criteria for a judgement of 'Low risk' of bias.	Any one of the following: No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.
Criteria for the judgement of 'High risk' of bias.	Any one of the following: No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.
Criteria for the judgement of 'Unclear risk' of bias.	Any one of the following: Insufficient information to permit judgement of 'Low risk' or 'High risk'; The study did not address this outcome.

BLINDING OF OUTCOME ASSESSMENT

Detection bias due to knowledge of the allocated interventions by outcome assessors.

Criteria for a judgement of 'Low risk' of bias.	Any one of the following: No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; Blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.
Criteria for the judgement of 'High risk' of bias.	Any one of the following: No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; Blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding.
Criteria for the judgement of 'Unclear risk' of bias.	Any one of the following: Insufficient information to permit judgement of 'Low risk' or 'High risk'; The study did not address this outcome.

INCOMPLETE OUTCOME DATA

Attrition bias due to amount, nature or handling of incomplete outcome data.

Criteria for a judgement of 'Low risk' of bias.	Any one of the following: No missing outcome data; Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias);

	Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; Missing data have been imputed using appropriate methods.
Criteria for the judgement of 'High risk' of bias.	Any one of the following: Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; 'As-treated' analysis done with substantial departure of the intervention received from that assigned at randomization; Potentially inappropriate application of simple imputation.
Criteria for the judgement of 'Unclear risk' of bias.	Any one of the following: Insufficient reporting of attrition/exclusions to permit judgement of 'Low risk' or 'High risk' (e.g. number randomized not stated, no reasons for missing data provided); The study did not address this outcome.

SELECTIVE REPORTING

Reporting bias due to selective outcome reporting.

Criteria for a judgement of 'Low risk' of bias.	Any of the following: The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).
Criteria for the judgement of 'High risk' of bias.	Any one of the following: Not all of the study's pre-specified primary outcomes have been reported; One or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified; One or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); One or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; The study report fails to include results for a key outcome that would be expected to have been reported for such a study.
Criteria for the judgement of 'Unclear risk' of bias.	Insufficient information to permit judgement of 'Low risk' or 'High risk'. It is likely that the majority of studies will fall into this category.

OTHER BIAS

Bias due to problems not covered elsewhere in the table.

Criteria for a judgement of 'Low risk' of bias.	The study appears to be free of other sources of bias.
Criteria for the judgement of 'High risk' of bias.	There is at least one important risk of bias. For example, the study: Had a potential source of bias related to the specific study design used (cluster-randomized trials and crossover randomized trials); or Had an inappropriate influence of funders due to industry-initiated protocols; or Has been claimed to have been fraudulent; or Had some other problem.
Criteria for the judgement of 'Unclear risk' of bias.	There may be a risk of bias, but there is either: Insufficient information to assess whether an important risk of bias exists; or Insufficient rationale or evidence that an identified problem will introduce bias.

Cited and Revised from *the Cochrane Handbook for Systematic Reviews of Interventions*.

Additional Table 5 Definition of overall response, and number of patients in total and those achieving overall response in each study

ID	*Definition of overall response Plt (×10^9/L)/ time-point*	Eltrombopag		Romiplostim		RTX		rhTPO+RTX		Avatrombopag		placebo	
		response	total	response	total	response	total	response	total	response	total	response	total
Bussel 2006	*50/6wk (>2×baseline)*			12	16							1	4
Bussel 2007	*50/6wk*	48	82									3	27
Bussel 2009	*50/6wk*	43	74									6	38
Bussel 2014	*50/4wk (increase>20)*									29	59	0	5
Cheng 2011	*50/6mo*	70	135									10	62
Ghanima 2015	*100/1.5yr (>2×baseline)*					28	55					21	54
Kuter 2008	*50/9mo*			69	83							3	42
Kuter 2010	*50/1yr*			127	157							26	77
Shirasugi 2011	*50/12wk*			13	22							0	12
Tomiyama 2012	*50/6wk*	9	15									0	8
Yang 2017	*50/6wk*	60	104									3	50
Zhou 2015	*100/3mo*					9	38	35	77				
Total		230	410	221	278	37	93	35	77	29	59	73	379
(response rate, %)			56.1		79.5		39.8		45.5		49.2		19.3

Abbreviations are shown in Table 1.

Additional Table 6 Number of patients in total and those causing clinically significant bleeding events in each study

	Eltrombopag		Romiplostim		RTX		rhTPO+RTX		placebo	
ID	event	total	event	total	event	total	event	total	event	total
Bussel 2006			1	16					1	4
Bussel 2009	5	76							7	38
Cheng 2011	10	135							10	62
Ghanima 2015					19	55			21	54
Kuter 2008			13	83					14	41
Kuter 2010			25	154					18	75
Shirasugi 2011			1	22					1	12
Yang 2017	6	104							4	50
Zhou 2015					13	38	24	77		

Abbreviations are shown in Table 1.

Additional Table 7 Number of patients in total and those causing severe adverse events in each study

	Eltrombopag		Romiplostim		RTX		placebo	
ID	event	total	event	total	event	total	event	total
Bussel 2006			1	16			2	4
Bussel 2007	2	88					4	29
Bussel 2009	2	76					1	38
Cheng 2011	20	135					7	62
Ghanima 2015					3	55	6	54
Kuter 2008			2	83			0	41
Kuter 2010			35	154			28	75
Shirasugi 2011			2	22			1	12
Tomiyama 2012	1	15					0	8
Yang 2017	5	104					5	50

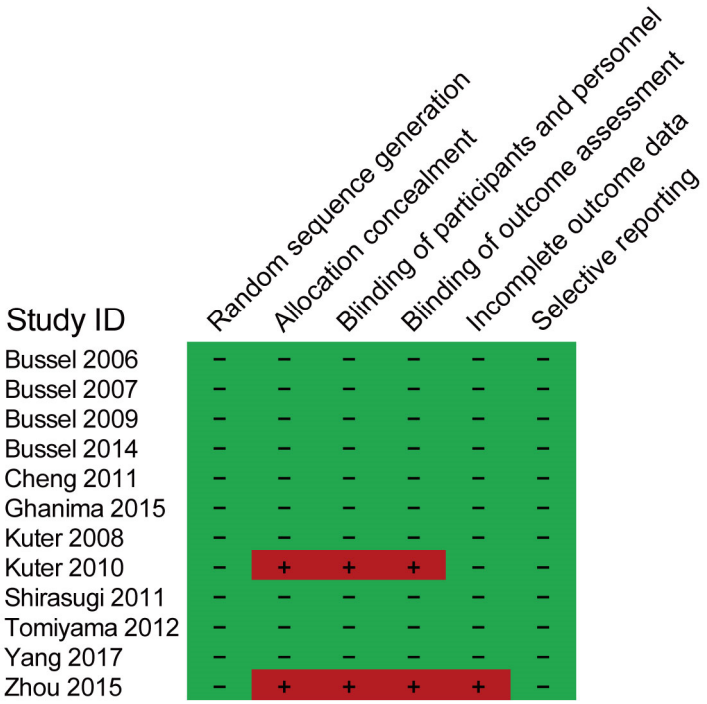
Abbreviations are shown in Table 1.

Additional Table 8 Description of severe adverse events in each study

ID	Intervention		Comparison	
	Regimen	Events (*N*)	Regimen	Events (*N*)
Bussel 2006	Romiplostim	vaginal bleeding(1)	placebo	asthma(1), intracranial hemorrhage/deep vein thrombosis(1)
Bussel 2007	Eltrombopag	leg pain (1), pneumonitis (1), rectal hemorrhage (1), herpes zoster (1), thrombocytopenia (1), pneumonia/hepatitis/renal failure/chronic obstructive pulmonary disease (1), trigger finger (1), menorrhagia (1), rash (1)	placebo	nausea/vomit/salmonella gastroenteritis (1), toxic hepatitis (1), varicose vein rupture (1), convulsion (1)
Bussel 2009	Eltrombopag	ND (2)	placebo	ND (1)
Bussel 2014	Avatrombopag	ND	placebo	ND
Cheng 2011	Eltrombopag	ND (20)	placebo	ND (7)
Ghanima 2015	RTX	pneumonia (1), appendicitis (1), back pain (1)	placebo	abdominal pain (2), pneumonia (1), back pain (1), ovarian cyst (2), pelvic pain (1)
Kuter 2008	Romiplostim	bone marrow reticulin increase (1), popliteal artery thrombosis (1)	placebo	0
Kuter 2010	Romiplostim	ND (35)	standard therapy	ND (28)
Shirasugi 2011	Romiplostim	ND (2)	placebo	ND (1)
Tomiyama 2012	Eltrombopag	ND (1)	placebo	0
Zhou 2015	rhTPO+RTX	ND	RTX	ND
Yang 2017	Eltrombopag	ND (5)	placebo	ND (5)

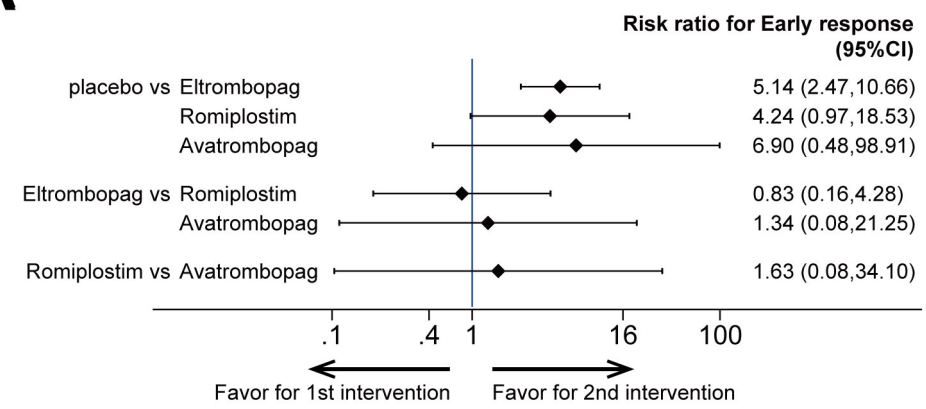
Abbreviations are shown in Table 1.

Supplemental Figure 1



Supplemental Figure 2

A



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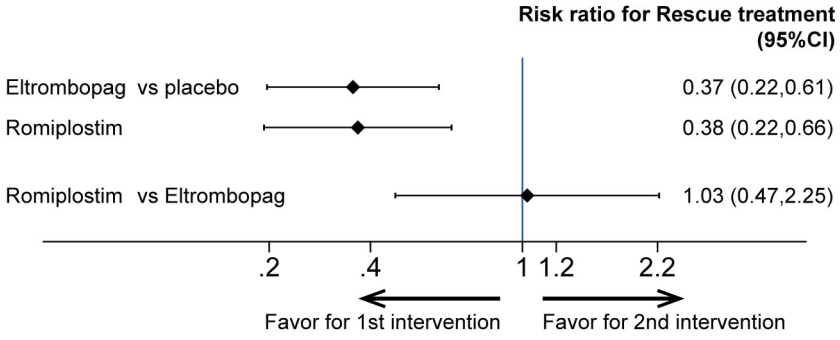
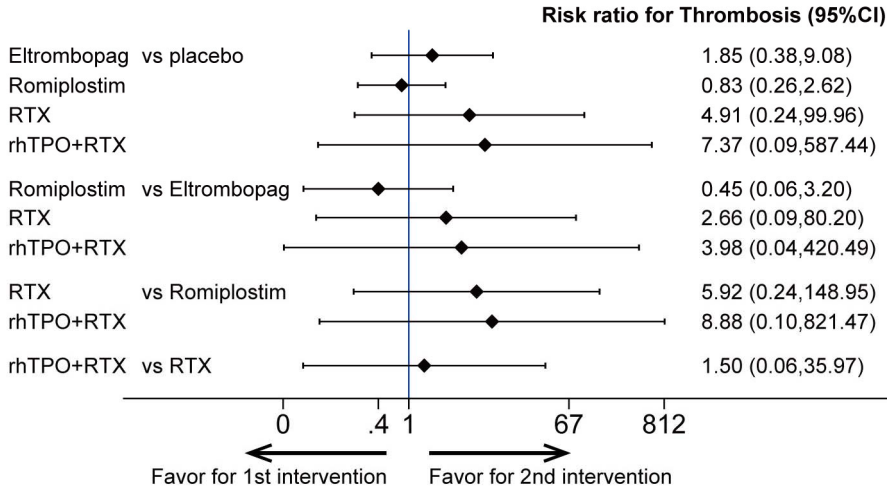


Supplemental Figure 3



Supplemental Figure 4