

Review

# Report of a 'consensus' on the lines of treatment for primary immune thrombocytopenia in adults, promoted by the Italian *Gruppo di Studio delle Piastrine*

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**Abstract:** Despite the publication in 2009 of a paper on 'terms and definitions of immune thrombocytopenia', (ITP) some unresolved issues remain and are reflected by the disagreement in the treatment suggested for primary ITP in adults. Considering that these disagreements could be ascribed to non-shared goals, a 'consensus' to classify the different lines of treatment for primary ITP in adults according to their indications and goals was proposed in October 2018 to the XIX annual meeting of the Italian *Gruppo di Studio delle Piastrine* (GSP), a non-profit platelet study group of scientists and physicians. Having approved the project, 60 potential co-authors and experts in the world were invited to take part to a consensus through e-Delphi method and nine of the 12 who initially accepted the invitation completed the work. Agreement was reached on a classification of four lines of treatment for primary ITP in adults based on their indications and goals. The consensus obtained regarded also the criteria, 'timing' included, to consider practicable elective splenectomy in these patients. In our opinion, the classification of the lines of treatment for primary ITP in adults here proposed could facilitate the realization of better shared evidence-based guidelines for the treatment of the disease.

**Keywords:** adult 1; classification 2; consensus 3; goal 4; guideline 5; immune thrombocytopenia 6; indication 7; ITP 8; therapy 9

## 1. Introduction

The publication of a paper on ‘terms and definitions of immune thrombocytopenia’ (ITP) by the International Working Group on ITP in 2009 (2009 IWG) [1] represented a fundamental step in the management of ITP. Nevertheless, some unresolved issues remain and are reflected by the disagreement in the suggested treatments for primary ITP in adults between the two guidelines that most influence the management of the disease, the 2010 International Consensus Report (ICR) [2] and the 2011 American Society of Hematology (ASH) [3] guidelines (Table 1) [1-27]. In the last years, the reasons for this disagreement [28], particularly evident for second-line therapy [16,25,28-30], has been attributed by George *et al.* [31] to differences in financial support [31,32] and methods of evidence evaluation [16,31].

Assuming that the existing disagreement in the proposed treatment for primary ITP in adults could be ascribed to non-shared goals, the constitution of an international working group of experts who gave their assent to participate was proposed in 2018 by the Italian *Gruppo di Studio delle Piastrine*, a non-profit platelet study group of scientists and physicians. Aim of the working group was to try and reach a consensus on terms, expressions and definitions that could help to classify the different lines of treatment for primary ITP in adult patients according to their indications and goals, thus favoring the development of better shared evidence-based guidelines. Particular conditions of ITP were not considered in our exercise, such as pregnancy-associated ITP [2,3,11,22] and secondary ITP [2,3,11,13,22] including *Helicobacter pylori*-related ITP [12,13,22,33].

## 2. Methods

The procedure used to reach a consensus consisted of the following consecutive steps, which are summarized in Table 2.

### 2.1. Proposal and approval of the consensus, choice of the method, and planning of the next steps

The issues on which to try to reach a possible consensus (Table 2), suggested by an already published proposed classification of the lines of treatment for primary ITP in adults [34], were presented to and approved by the XIX annual meeting of the Italian *Gruppo di Studio Piastrine* (GSP), held in Ostuni (BR), Italy, from October 7<sup>th</sup> – 9<sup>th</sup>, 2018. During the meeting, it was also suggested that the study/work should not be limited to a single country and that the individual members of the panel did not influence each other. Consequently, it was decided that the e-Delphi method would be used to reach the consensus, because of the inexpensiveness of the method, even in the case of considerable distances between the components of the study/work, and the possibility of maintaining anonymity among the panel members [35,36].

**Table 1. Denominations and proposed four lines of therapy of primary ITP in adults according to the 2010 ICR and the 2011 ASH guidelines.**

	First-line treatment <sup>1</sup>	Second-line treatment <sup>2</sup>	Third- (and further) line treatment <sup>3</sup>	Emergency treatment	
20 10 I C R	Denominator used	<i>“First-line treatment: initial treatment for newly diagnosed ITP”</i>	<i>“Second-line treatment”</i>	<i>“Treatment for patients failing first- and second-line therapies”</i>	<i>“Emergency treatment”</i>
	Proposed treatments	Anti-D <sup>4</sup> Corticosteroids: Dexamethasone <sup>5</sup> Methylprednisolone Prednisolone IVIg	Azathioprine Cyclosporin A Cyclophosphamide Danazol Dapsone Mycophenolate	Category A: treatments with sufficient data: TPO receptor agonists Category B: treatments with minimal data and	Combined first-line therapies such as prednisone and IVIg High-dose methylprednisolone (HDMP)

			mofetil RTX Splenectomy TPO-RA Vinca alkaloids	potential considerable toxicity: Campath-1H Combination of first-and second-line therapies Combination chemotherapy HSCT	Platelet transfusion with or without IVIg Emergency splenectomy Vinca alkaloids with or without other agents Antifibrinolytics General measures
20 11 A S H	Denominati on used	<i>"First-line treatment for newly diagnosed ITP"</i>	<i>"Treatment of patients who are unresponsive to or relapse after initial corticosteroid therapy"</i>	<i>"Treatment of refractory ITP after splenectomy"</i>	<i>"Emergency management of ITP"</i>
	Proposed treatments	Suggested: - Longer standard oral course of corticosteroids <sup>6</sup> to prefer over either high dose short courses of dexamethasone (HD-DXM) <sup>5</sup> or IVIg. - IVIg associated with corticosteroids when a more rapid increase in platelet count is required. - Either IVIg or anti-D (in appropriate patients) <sup>4</sup> if corticosteroids are contraindicated. If IVIg is used, the dose should initially be 1 g/Kg as one-time dose. This dosage may be repeated if necessary <sup>7</sup> .	Recommended: - Splenectomy. - TPO-RA for patients at risk of bleeding who relapse after splenectomy <sup>8</sup> or who have a contraindication to splenectomy and who have failed at least one other therapy. Suggested: - TPO-RA for patients at risk of bleeding who have failed one line of therapy such as corticosteroids or IVIg and who have not had splenectomy. - RTX for patients at risk of bleeding who have failed one line of therapy such as corticosteroids, IVIg, or splenectomy <sup>8</sup> .	Recommended: Against further treatment in asymptomatic patients after splenectomy who have platelet counts >30x10 <sup>9</sup> /L.	IVIg along with corticosteroids Platelet transfusion alone or in conjunction with IVIg (continual infusion) Recombinant factor VIIa (rfVIIa), considering the risk of thrombosis. Antifibrinolytics (unproven efficacy) Emergent splenectomy only as heroic given the dangers of unplanned surgery

2010 IRC indicates 2010 International Consensus Report on ITP [2]; 2011 ASH, 2011 guideline of the American Society of Hematology on ITP [3].

Anti-D indicates anti-Rh(D) immunoglobulin; HSCT, hematopoietic stem cell transplantation; IVIg, intravenous immunoglobulin; RTX, rituximab; TPO-RA, thrombopoietin receptor agonists.

<sup>1</sup> For 2010 ICR, treatment options are listed in alphabetic order, thus not implying a preferred treatment option [2,4,5]. For 2010 ASH 'longer courses of corticosteroids' are preferred to brief courses of both high-dose steroid or IVIg treatment, while IVIg associated with corticosteroids are suggested when a more rapid increase in platelet count is required, and IVIg or anti-D (in appropriate patients)<sup>4</sup> are utilized if corticosteroids are contraindicated [3,6].

<sup>2</sup> For 2010 IRC, treatment options are listed in alphabetic order, thus not implying a preferred treatment option [2,4,5,7]. For 2011 ASH, the preference for splenectomy as second-line therapy [7-10] is based on the fact that it '... remains the only treatment that provides sustained remission off all treatments at 1 year and beyond in a high proportion of patients with ITP', while 'sustained remission rates with rituximab are disappointing and the thrombopoietin receptor agonists produce off-treatment sustained remissions very infrequently' [3]. In a recent guideline [11], all the medical treatments, TPO-RA excluded, reported by 2010 ICR for this line, have been included in the treatment options for third- and not second-line therapy.

<sup>3</sup> The patients for whom this line is foreseen are the most difficult to treat and, for this reason, this line might include new treatments, particularly if significant bleeding and poor quality of life (QoL)

occur. In contrast, simple observation (a ‘wait-and-watch’ approach) and treatments which are low cost and/or have lower toxicity might be an alternative if bleeding is not significant. Third (and further)-line treatment is reserved for patients with ‘refractory’ (after splenectomy) ITP [1,5,9,12-19] and patients not eligible for splenectomy and not responsive to alternative second-line therapy [9,12,15-20]. This line of treatment also concerns patients with ‘multirefractory ITP’, who, more often affected by secondary ITP, are defined as ITP patients who fail to respond to splenectomy, rituximab and thrombopoietin [14]. The third-line treatments include accessory splenectomy which may be required for patients with ‘refractory’ ITP after splenectomy [9].

<sup>4</sup> For Rh(D)-positive, non-splenectomized patients, without autoimmune hemolytic anemia.

<sup>5</sup> For example, dexamethasone 40 mg orally for 4 days. With cumulative cortisol equivalent doses [21], a definitive advantage of HD-DXM over a standard-dose course of prednisone or prednisolone, in terms of response duration over 6-12 months, has not been demonstrated [4,22-27]. Nevertheless, HD-DXM may be preferred over prednisone for patients with severe ITP who require a more rapid rise in platelet count [22,24-27].

<sup>6</sup> For example, prednisone 1 mg/Kg orally for 21 days then tapered off.

<sup>7</sup> Patients who fail to respond to 1 g/Kg may respond to higher doses (e.g., 2 g/Kg) [3]. In older adults with impaired renal function a daily IVIg dose of 0.4-0.5 g/Kg is preferable [25].

<sup>8</sup> Patients who, due to the severity of their disease, need treatment after splenectomy are properly recognized as being affected by ‘refractory ITP’ [1,9,18] and the treatment required for them is categorized as a third-line treatment [4,19].

The plan was to submit a specifically designed questionnaire to the panel, in two consecutive rounds, with the forced closure of the study/work by the two co-chairmen (MC and LC) in the case of persistent disagreements at analysis of the results of the second round.

**Table 2. Steps of the study/work.**

a.	Proposal and approval of the consensus, choice of the method and planning of the next steps (October 7 <sup>th</sup> – 9 <sup>th</sup> , 2018).
b.	Invitation of potential participants (from October 15 <sup>th</sup> , 2018 to November 22 <sup>nd</sup> , 2018) and identification of the panel of experts (December 4 <sup>th</sup> , 2018).
c.	Systematic review of the literature (December 9 <sup>th</sup> , 2018) with selection (from January 30 <sup>th</sup> , 2019 to March 6 <sup>th</sup> , 2019) and distribution (from February 1 <sup>st</sup> , 2019 to March 24 <sup>th</sup> , 2019) of the relevant articles to all the components of the study/work.
d.	Conversion into simple questions of the issues identified and their submission to the panel with the first-round questionnaire (from February 18 <sup>th</sup> , 2019 to March 12 <sup>th</sup> , 2019).
e.	Receipt of the panel responses to the first-round questionnaire (from March 12 <sup>th</sup> , 2019 to April 30 <sup>th</sup> , 2019), their analysis (May 31 <sup>st</sup> , 2019) and approval of the changes suggested for the second (and final)-round questionnaire (June 15 <sup>th</sup> , 2019).
f.	Submission of the questionnaire of the second (and final) round (June 27 <sup>th</sup> , 2019), analysis (November 1 <sup>st</sup> , 2019) of the responses received (July 31 <sup>st</sup> , 2019) and conclusion of the study/work (November 15 <sup>th</sup> , 2019).
g.	Writing of the paper (from November 16 <sup>th</sup> , 2019 to January 19 <sup>th</sup> , 2020) with its approval for publication by all the components of the study/work (February 2 <sup>nd</sup> , 2020).

In the two consecutive rounds, each member of the panel would express his/her opinions regarding the appropriateness of each single question, through a graduated scale of scores from 1 to 9, those from 7 to 9 indicating ‘appropriateness’, those from 4 to 6 ‘uncertain appropriateness’, and those from 1 to 3 ‘inappropriateness’ of the single proposals. It was also established in advance that consensus for each single issue of the two consecutive rounds would be defined by the placing of the given answers in one of the three above mentioned scale groups in percentage of 70% or more.

## 2.2. Invitation to possible participants and creation of the panel

Between October 15<sup>th</sup>, 2018 and November 22<sup>nd</sup>, 2018, 60 researchers from 18 different countries in various continents (27 from Europe, 19 from North America, 8 from Asia, 4 from South America, 1 from North Africa, and 1 from Oceania) were contacted through e-mail by one of the two co-chairmen (LC) and formally invited to participate to the study/work as authors and members of the panel. The members of the panel would join the other components of the study/work who would have figured as co-authors of the study/work, but not as members of the panel. All of these individuals were Italians and internists with an interest in the field of ITP, and consisted of the two co-chairmen (MC and LC) and two other authors (GMP, and AMR),

On December 4<sup>th</sup>, 2018, 12 of the 60 researchers (3 from Europe, 5 from North America, 2 from Asia, 1 from South America, and 1 from North Africa), who accepted the conditions of the invitation, were identified as potential members of the panel.

**Table 3. Issues identified for the consensus and their conversion into simple questions.**

Issues identified ('Points')	Simple questions ('Indicators')
1. Classification of the 'lines of therapy' for primary ITP in adults based on their 'goals'	1. Classification of the 'lines of therapy'
2. Acceptance of the expression 'sequences of disease' in association with that of 'phases of disease' of the 2009' International working group (IWG)	2. Acceptance of the expression 'sequences of disease'
	3i. Practicability of splenectomy
	3ia. Acceptance of a 'timing for elective splenectomy of 3 months'
	3ib. Acceptance of a 'timing for elective splenectomy of 12 months'
	3ic. Acceptance of a 'timing for elective splenectomy of 6 months'
	3id. Acceptance of a 'timing for elective splenectomy of 6-12 months'
3. Practicability and verification of the most appropriate 'timing for elective splenectomy' in adults	4a. Goals of 'emergency therapy'
	4b. Goals of 'first-line therapy'
	4c. Goals of 'second-line therapy'
4. Agreement on the 'goals of the lines of therapy' of primary ITP in adults with verification of their present validity	4d. Goals of 'third (and further)-line therapy'

## 2.3. Systematic review of the literature with selection and distribution of the articles to read to all the components of the study/work

On December 9<sup>th</sup>, 2018, a systematic review of the literature of the last 10 years was completed separately by two authors (LC and GMP), through a Medline database search, using PubMed, after restrictions of language (English), age (>19 years), and species (human), with the following Medline Subject Heading (MeSH) and free text terms: "Purpura, Thrombocytopenic, Idiopathic" [Mesh] OR primary immune thrombocytopenic purpura OR primary immune thrombocytopenia OR idiopathic thrombocytopenic purpura.

The titles of the retrieved publications were subdivided into six groups, each of which was distributed, from December 11<sup>th</sup> 2018 to December 14<sup>th</sup> 2018, along with a detailed explanation of the different steps of the study/work, to two of the 12 potential members of the panel, who were also divided into six groups, each one composed of two members. The task required of the 12 potential members, for receiving the first round questionnaire and proceeding with the study/work, was the analysis and selection of the publications to read and their distribution, through one of the two co-chairmen (LC), to all the components of the study/work. In this way, each member of the panel and all the other components of the study/work would receive the whole body of the relevant literature to read and consult during the compilation of the questionnaire. Considering the scope of the study/work, the selected articles included not only reviews and trials but also editorials and/or comments. Only case reports were excluded from the search.

In the meantime, all the literature sent to the six groups of the potential components of the panel was also checked by two other authors (LC and AMR).

Once received (between January 30<sup>th</sup>, 2019 and March 6<sup>th</sup>, 2019) and having checked the titles of the articles selected by the six groups on the basis of the systematic literature search, the relevant articles were sent (between February 1<sup>st</sup> 2019 and March 24<sup>th</sup> 2019) to all the components of the study/work.

#### *2.4. Conversion of the issues identified into simple questions and their submission to the panel with the first-round questionnaire*

Table 3 reports the simple questions into which the issues initially identified for the study/work were converted.

Receipt of the selection of article, between January 30<sup>th</sup> 2019 and March 6<sup>th</sup> 2019, was considered confirmation of intention to continue the study/work by 9 of the 12 members of the panel. The first-round questionnaire was then submitted, between February 18<sup>th</sup> 2019 and March 12<sup>th</sup> 2019, for consensus.

#### *2.5. Receipt of the panel answers to the first-round questionnaire, their analysis and approval of the changes suggested for the second-round questionnaire*

On April 30<sup>th</sup> 2019, the first round was considered concluded because the first-round questionnaires had been completed and returned to the appointed co-chairman (between March 12<sup>th</sup> 2019 and April 30<sup>th</sup> 2019) by all nine members of the panel who continued the study/work. On May 31<sup>st</sup> 2019, an analysis of the responses to the questionnaire and observations made was reported to the panel together with the suggested changes to include in the second-round questionnaire for approval.

#### *2.6. Submission of the questionnaire for the second (and final) round, analysis and reporting of the answers obtained and conclusion of the study/work*

On June 27<sup>th</sup> 2019, with approval of the changes to include in the questionnaire for the second (and final) round (June 15<sup>th</sup> 2019), the amended questionnaire was submitted to the nine members of the panel who completed and returned it by July 31<sup>st</sup> 2019. On November 1<sup>st</sup> 2019 a report of the analysis of the answers to the second-round questionnaire, together with the changes suggested for the conclusions of the work, was sent to all the components of the study/work and on November 15<sup>th</sup>, with the approval of these changes by the panel, the work was considered concluded.

#### *2.7. Data analysis*

The data were analyzed using the PASW Statistics 18 software package.



3. Results

3.1. Panel composition

The nine researchers who completed the study/work as authors and members of the panel were of different nationalities (2 from Europe, 3 from North America, 2 from Asia, 1 from South America, and 1 from North Africa). Eight of them (88.9%) were hematologists or hemato-oncologists and one (11.1%) was an internist.

3.2. Publications identified during the literature analysis and data extraction

Initially, 1,397 titles were retrieved from the systematic analysis of the literature. Figure 1 reports the methods of selection and the number of articles that were examined from the systematic search and other sources.

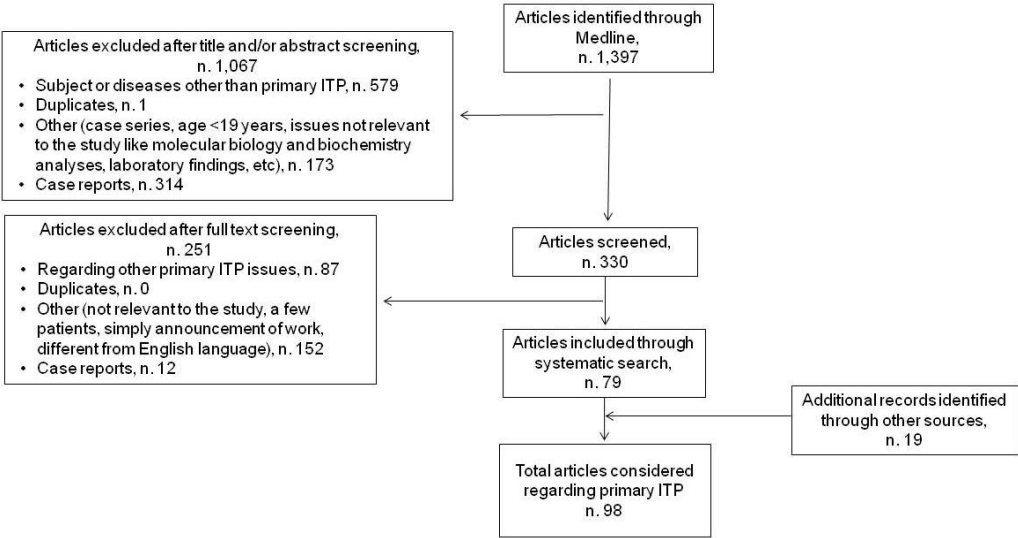


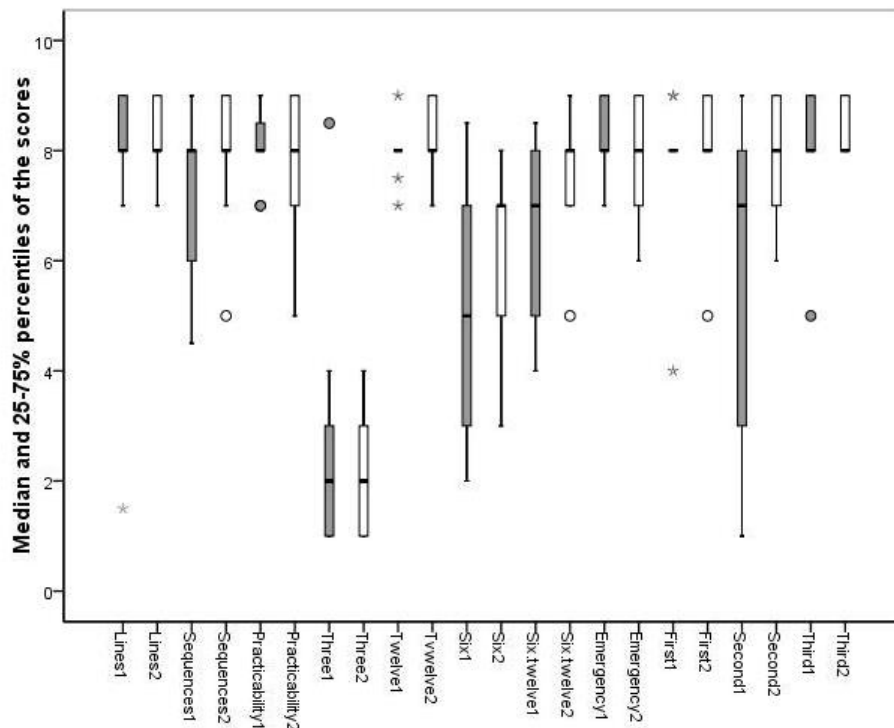
Figure 1. Total number of screened and selected articles on immune thrombocytopenia.

3.3. Responses to the first- and second-round questionnaires

Figure 2 shows a comparison of the medians and box-plots with the 25% and 75% percentiles of the scores obtained from the responses to each proposal of the first and the second rounds, while Figure 3 illustrates the agreement (percentage of 70% or more) on the appropriateness of the proposals in the two consecutive rounds. The results of the analysis of the scores of the second-round questionnaire, with the replies to the observations produced, are included in the backgrounds and final statements of the various indicators (see discussion).

3.4. Final purpose

Table 4 [1-5,9-13,15-20,22,25,26,29,30,32-34,37-96] reports the purpose of the classification of the four lines of treatments for primary ITP in adults which, based on their respective indications (or sequences of disease) and goals, was obtained by consensus.



**Figure 2.** Median and box-plots of the evaluations for the single proposals in the two consecutive rounds of the consensus procedure.

The grey boxes, labeled in the sub-titles by number 1, summarize the scores of the evaluations of the first round, while the white boxes, labeled in the sub-titles by number 2, summarize the scores of the evaluations of the second round of the consensus. The eleven questions submitted for consensus regarded the following indicators: 1. Classification of the (four) 'lines of therapy' (see 'Lines1' for the first round and 'Lines2' for the second round); 2. Acceptance of the expression 'sequences of disease' (see 'Sequences1' for the first round and 'Sequences2' for the second round); 3*a*. 'Practicability of splenectomy' (see 'Practicability1' for the first round and 'Practicability2' for the second round); 3*ia*. 'Timing for elective splenectomy of 3 months' (see 'Three1' for the first round and 'Three2' for the second round); 3*ib*. 'Timing for elective splenectomy of 12 months' (see 'Twelve1' for the first round and 'Twelve2' for the second round); 3*ic*. 'Timing for elective splenectomy of 6 months' (see 'Six1' for the first round and 'Six2' for the second round); 3*id*. 'Timing for elective splenectomy of 6-12 months' (see 'Six.twelve1' for the first round and 'Six.twelve2' for the second round); 4*a*. Goals of 'emergency therapy' (see 'Emergency1' for the first round and 'Emergency2' for the second round); 4*b*. Goals of 'first-line therapy' (see 'First1' for the first round and 'First2' for the second round); 4*c*. Goals of 'second-line therapy' (see 'Second1' for the first round and 'Second2' for the second round); 4*d*. Goals of 'third (and further)-line therapy' (see 'Third1' for the first round and 'Third2' for the second round).

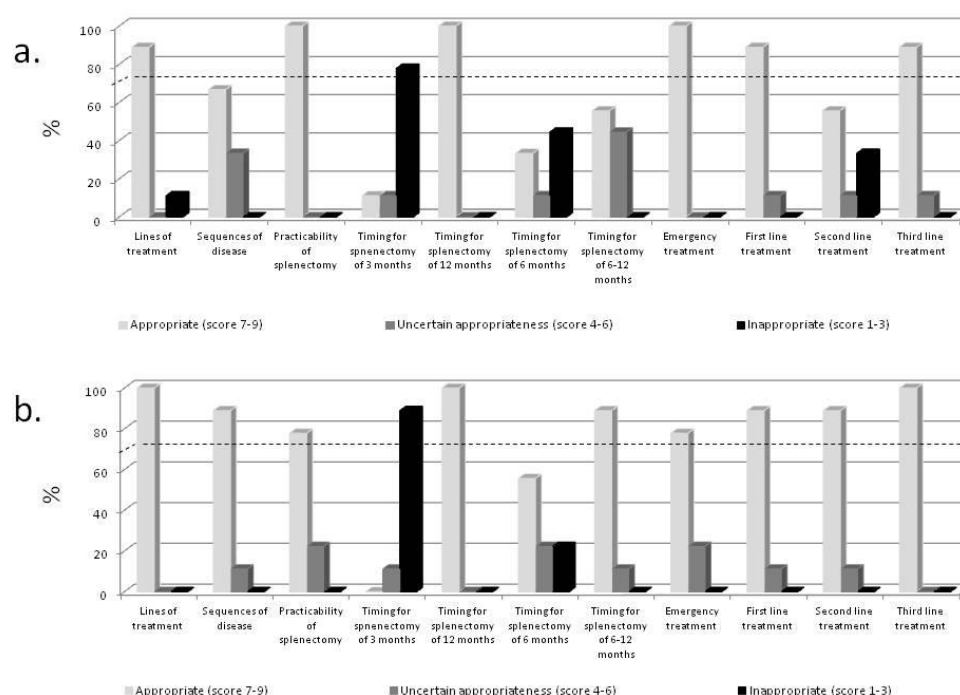
#### 4. Discussion

With the present work we report a classification of the lines of treatment for primary ITP in adults (Table 4) [1-5,9-13,15-20,22,25,26,29,30,32-34,37-96] which, based on their indications (or sequences of diseases) and goals, was obtained through consensus using a two-round e-Delphi method [35,36]. The consensus regarded the acceptance of the use of various terms, expressions and definitions that, already proposed [34], had been submitted to the XIX annual meeting of the Italian *Gruppo di Studio delle Piastrine* held in Ostuni (BR), Italy, from October 7<sup>th</sup> to 9<sup>th</sup>, 2018. The reason underlying the work was the



disagreement regarding suggested treatments for primary ITP in adults between the two guidelines that most influence the management of the disease, the 2010 ICR [2] and the 2011 ASH [3] guidelines (Table 1) [1-27].

Here we report the backgrounds and the final statements for the single points examined by the consensus.



**Figure 3.** Agreement ( $\geq 70\%$ ) on the appropriateness of the single assertions at the first (a.) and second (b.) rounds of the consensus procedure.

#### Point 1 - Indicator 1: Classification of the 'lines of therapy'

**Background** - Excluding specific conditions treated separately, such as pregnancy-related ITP and secondary ITP [2,3], for example *Helicobacter pylori*-related ITP [12,33], the 2010 ICR [2] and 2011 ASH guideline [3] describe, with some differences in their proposals, four lines of therapy for ITP in adults (Table 1) [1-27].

**Final statement** – The panel considers it useful to accept a classification of 'lines of therapy' for primary ITP in adults which distinguishes four lines of treatments, each defined by specific indications and goals (Table 4) [1-5,9-13,15-20,22,25,26,29,30,32-34,37-96]. Of these, the first three correspond approximately to the three consecutive lines of treatment described by the 2010 ICR [2] and the 2011 ASH guideline [3] and used by many authors [9,15-17,33,37,38,57]. The fourth line is represented by 'emergency treatment', which may be required at any time during the course of the disease [9,15,19,34,89] (median and 25% - 75% percentiles of the second-round scores = 8 and 8-9; agreement on appropriateness 100%).

#### Point 2 - Indicator 2: Acceptance of the expression 'sequences of disease'

**Background** - The expression 'phases of disease' proposed by the 2009 IWG report [1] corresponds to a chronological classification which, based on the time of progression of the disease since its diagnosis (i.e., 'newly diagnosed', 'persistent', and 'chronic ITP' for diseases present  $\leq 3$ , between  $>3$  and  $<12$ , and  $\geq 12$  months since diagnosis, respectively) [1,5,10,11,13,19,22,30,42,43,50,97], and the likelihood of spontaneous remission [16], is useful for helping to design and interpret novel trials [10,97]. Nevertheless, these phases of disease are not matched by specific lines of treatment for primary ITP in adults and this is

particularly true for the ‘persistent’ and ‘chronic’ phases of the disease, for which the most appropriate treatment is doubtful and is not specifically addressed in any guideline [16,29].

**Final statement** – As expressed above (see final statement for point 1), the panel considers it useful, for the clinical practice, to define the single lines of treatment for primary ITP in adults according to their indications and goals (Table 4) [1-5,9-13,15-20,22,25,26,29,30,32-34,37-96]. Moreover, since the indications for the different lines of treatment do not always match those for the ‘phases of disease’ [16,29], the panel proposes using the expression ‘sequences of disease’ to designate these indications [34]. So, noting the different meanings and usefulness of the two expressions, those regarding ‘phases of diseases’ being more useful to design and interpret novel trials [10,97], and those regarding ‘sequences of disease’ being more useful for clinical practice, the panel suggests their complementary use (*median and 25% -75% percentiles of the second-round scores = 8 and 7.5-9; agreement on appropriateness 88.9%*).

### **Point 3 – Practicability of splenectomy and verification of its most appropriate timing in adult patients with primary ITP**

**Background** – Once the only treatment approach for primary ITP, and, subsequently, the standard of care for patients with steroid-resistant ITP [9,10,13,16,19,22,32,33,42,73,78,82], splenectomy is now being used less frequently [9,11,13,32,50,73,82,91] and is often delayed until later in the disease course [9,16,32,37,58,82,86,91,92,98] because of the availability of alternative medical therapies, such as rituximab and the thrombopoietin receptor agonists [5,9-11,13,16,17,19,25,29,32,37,40-43,47,48,50-58,61,63-65,67-77,79-82,86,91,98,99], and of the increase in the mean age of the general population [25,58,99]. Due to demographic changes, ITP is now indeed frequently observed in elderly patients [12,25,41,85,99] who are at high risk of complications after surgery because of many associated diseases [13,22,25,58,91-93,99,100].

Despite these considerations and even if it is increasingly used as a third (and further)-line therapy for ITP [9,18,32,37,82], splenectomy provides high rates of durable remissions (50-70%) in comparison with other therapies [9-11,13,17,19,22,33,37,42,78,82,90,92], and does therefore remain a reasonable option for second-line therapy of ITP for many patients [9,11,13,17,19,32,33,42,73,78,82,90], including those with an active lifestyle who want to be free of protracted medical therapies and frequent monitoring [18,58,82,98] and those with fulminating ITP who respond poorly to medical treatment [18,58].

At present, there is a lack of evidence-based guidance on the optimal timing of splenectomy and, while there is agreement on the indications for and timing of splenectomy in children, this is not the case for adults.

**Table 4.** Lines of treatment for primary ITP in adults according to their indications (*sequences of disease*) and goals.

<b>Lines of treatment</b>	<b>Indications (<i>sequences of disease</i>)</b>	<b>Goals of therapy</b>
First-line	Patients requiring treatment for the first time [1-5,9,10,16,17,19,26,40-43] <sup>1</sup>	First-line therapy is not addressed at modifying the natural history of severe ITP in adults [44], but at rapidly achieving, ‘a safe platelet count to prevent or stop hemorrhages and to ensure an acceptable quality of life, avoiding as much possible treatment-related adverse effects’ [1,4,9,10,17,19,45] <sup>2,3</sup> .
Second-line	Patients who relapse after first-line therapy has been tapered and require treatment [5,9,10,17,19,42,43,53-56] <sup>4</sup>	The goal of this line of therapy is to obtain a long-term response with stabilization or improvement of health-related quality of life, while avoiding toxic treatments [1,2,10,17,20]. At present this goal can be achieved by multiple therapeutic regimens [1-5,10-13,16-19,20,25,29,30,40-43,47,48,51-81], even if splenectomy remains the choice that, despite the

		<p>inherent risks [9,11,16,25,40,61,70-72,82-85] and the difficulties in being accepted by patients and physicians as the preferred second-line therapy [10,29,40,47,59,61,62,70,72,73,82,86-89] is most likely to produce long-term remission [3,9,11,12,16,17,19,40,42,43,58,60-62,70-73,78,82,84,85,88-90].</p> <p>Regarding splenectomy, the choice to perform it may be influenced by some other factors, such as the duration of the disease since the diagnosis of ITP, the age of the patient [25,33,42,78,84,91,92], the presence or not of co-morbidities [16,17,25,33,42,71,89,92], cultural prejudices, such as contrariness to surgical removal of organs [82], and lifestyle [92]<sup>5</sup>. When splenectomy is considered, it should be performed 12 or more months after diagnosis [1,4,11,58,61]<sup>6</sup>, given the potential spontaneous resolution of the disease [1,11,50,67] or potential evidence of the secondary nature of the disease [94]. Consequently, when splenectomy is planned and the disease has been present for less than 12 months, the immediate goal of this line of treatment would be to control the disease, by using medical treatments until 12 months [1,4,13,58,95].</p>
Third (and further)-line	Patients failing first- and second-line therapies who require treatment [2,9,10,16-20] <sup>7</sup>	<i>'... the achievement of a platelet count sufficient to prevent clinically significant bleeding with the least toxicity. ... treatment should be evaluated for the potential to induce an acute response and also a long-lasting response with minimum side effects/toxicity'</i> [1,4,10,15].
Emergency	Serious bleeding or preparation for emergency surgery [2,3,5,9,15,89,96]	To reduce bleeding [5,9,12,22,25,39,89] and to increase the platelet count [22,89,96], thereby preventing life-threatening bleeding, in a time frame of 24-72 hours [22].

The descriptions reported here for the four lines of therapy for primary ITP in adults have been used by many authors [16,20,34,37,38,39]. In the panel's opinion, resort to the different lines of treatment should be based on the bleeding score [5,13,39] more than the platelet count, and on the choice of the lowest maintenance dose, when a response to therapy has been obtained and a medical maintenance treatment is required.

<sup>1</sup> The indication 'patients requiring treatment for the first time' has been preferred to that of 'newly diagnosed patients requiring therapy' of the 2009 IWG [1].

<sup>2</sup> Intensive therapy [46], such as rituximab [17,47,48], with relevant side effects and potential complications [13], are not presently acceptable as first-line therapy [4,13,26,49].

<sup>3</sup> Thrombopoietin-receptor agonist therapy [10,29,38,50-52], due to its high costs compared to corticosteroids, should be reserved only for patients unresponsive to standard first-line therapy and should not be used in all newly diagnosed patients [11,26,38].

<sup>4</sup> This line of treatment includes both patients who relapse after first-line therapy is tapered and those who fail to respond to first-line therapy, although treatment for these two conditions may differ [29].

<sup>5</sup> In the absence of important co-morbidities [25,32,33,37,60,71,89,92,93] old age is not an absolute contraindication to splenectomy [25,29].

<sup>6</sup> The panel assumes that a waiting time of 12 months is appropriate for elective splenectomy with some exceptions (see text) that can justify a shorter waiting time [5,25,58,60].

<sup>7</sup> Beginning with the therapies already described for this line by the 2010<sup>7</sup> ICR [2] (Table 1), some of which still require further investigation [16], the third (and further)-line of treatment for primary ITP in adults can also include conventional options of treatment of the first two lines of therapy, such as splenectomy or rituximab [70], if they were not previously considered.

The 2010 ICR [2] and 2011 ASH guideline [3], in accordance with the first ASH guideline published in 1996 [45], state that splenectomy is rarely indicated in children [11,13], and when it is really indicated, the 2011 ASH guideline proposes waiting at least 12 months [3], while no indication is given by the 2010 ICR [2].

As far as concerns adults the 2011 ASH guideline does not give an opinion regarding timing [3], while the 2010 ICR suggests to defer splenectomy for at least 6 months [2], a much longer period than the 6 weeks-3 months judged appropriate in the past by the 1996 ASH guideline (6 weeks for patients with a platelet count  $<10^9/L$  and no bleeding symptoms; 3 months for patients who, independently of the presence of bleeding complications, had a transient or incomplete response to primary treatment, and a platelet count  $<30 \times 10^9/L$ ) [45].

Before the 2010 ICR [2] and 2011 ASH guideline [3], the 2009 IWG report, which did not clearly distinguish between adults and children, suggested deferral of splenectomy for at least 12 months [1]. This opinion, based on the fact that for patients whose disease lasts between 3 and 12 months since diagnosis '*chances of spontaneous remission are still significant*' [1], is still shared by many clinicians [4,11,58,61,97]. An obvious exception to the proposed waiting time of 6 or 12 months is emergency splenectomy; although this is less frequently required nowadays than in the past, it can be necessary when disease control is particularly difficult to obtain [2,3,11,42,79,96].

### **Indicator 3: Practicability of splenectomy**

**Final statement** - The panel believes that it is important to state in advance that, at present, there are no widely available or accepted predictors of splenectomy success to guarantee that in a specific patient splenectomy will be successful [11,22]. Given the foregoing, a patient may undergo elective splenectomy when, together with his or her acceptance of the risks of the intervention and the recommended strategies to prevent them, some specific objective conditions are satisfied [58]. These include: (i) exclusion of secondary forms of ITP [11,13], including drug-induced ITP [11,13], which could contraindicate splenectomy and/or require treatment of the primary cause of the disease [5,11,13,22,40]; (ii) optimal timing for splenectomy (see indicators 3<sub>1a</sub>-3<sub>1d</sub>); (iii) good general conditions of the patient (young age and/or absence of associated diseases contraindicating surgery) [13]; and (iv) the patient's capacity to understand the potential risks of splenectomy and to accept the recommended strategies to prevent them [58].

When all these conditions are satisfied, other factors that need to be taken into account include: (i) the patient's preferences, related to personal motivations such as the desire to avoid drug therapy or close medical monitoring because of participation in contact sports or high-risk activities and/or plans, including, for those women of child-bearing age, to have children, and (ii) the availability, (iii) costs and (iv) efficacy of splenectomy in comparison with other treatments [58]. Furthermore, although splenectomy is not contraindicated in some forms of secondary ITP, it is essential to exclude underlying immunological disorders, such as an autoimmune lymphoproliferative disorder, before splenectomy [11,13] given the increased risk of overwhelming sepsis and death in patients with such conditions [13] (*median and 25% - 75% percentiles of the scores = 8 and 6-9; agreement on appropriateness 77.8%*).

### **Indicators 3<sub>1a</sub>-3<sub>1d</sub>: 'Timing of elective splenectomy'**

**Final statement** - The panel agrees fully on the waiting time of 12 months (indicator 3<sub>1b</sub>) suggested by the 2009 IWG [1] and utilized by many authors [4,11,25,33,58,61,68,97]. This waiting time appears to some members of the panel particularly useful in elderly patients, who can have increased surgical morbidity because of their higher probability of co-morbidities [13,22,25,58,91-93,99,100] and lower rates of response [58] (*median and 25% - 75% percentiles of the scores = 8 and 8-9; agreement on appropriateness 100%*). Nevertheless, the panel considers that some exceptions can justify a waiting time of 6-12 months (indicator 3<sub>1d</sub>) [13,25,29,34,50,58,86,89]. These exceptions are the following: patients who, requiring treatment, strongly prefer splenectomy for particular and motivated reasons and patients

who, at high risk of bleeding or with poor quality of life because of the bleeding manifestations, do not tolerate medical therapy [25,58] (*median and 25% -75% percentiles of the scores = 8 and 7-8; agreement on appropriateness 88.9%*).

No agreement was reached by the panel, even with the above reported exceptions [25,58], on the waiting time of 6 months (indicator 3<sub>ic</sub>) suggested by the 2010 ICR [2,5,13] (*median and 25% -75% percentiles of the scores = 7 and 4-7.5; agreement on appropriateness 55.6%*). The panel did reach an agreement on a waiting time of 3 months (indicator 3<sub>ia</sub>), suggested by the 1996 ASH guideline [45], but in this case the agreement was on its 'inappropriateness' (*median and 25% -75% percentiles of the scores = 2 and 1-3; agreement on inappropriateness 88.9%*). Observations made by many members of the panel about the best timing for elective splenectomy in adults with primary ITP regarded the availability and efficacy of treatments not previously utilized, such as thrombopoietin and rituximab [5,11, 13,16,25,29,32,37,40,47,50,57,58,61,63-65,67-73,82,86,91,98,99], the potential spontaneous resolution of the disease [1,11,50] and the discovery of its secondary nature in the first 12 months after diagnosis [94].

Point 4 - Agreement on the 'goals of the lines of therapy' of primary ITP in adults with verification of their present validity

#### **Indicator 4a: Goals of 'emergency therapy'**

**Final statement** – For the panel the goals of emergency therapy are to reduce bleeding [5,9,12,22,25,39,89] and to increase the platelet count [22,89,96], thereby preventing life-threatening bleeding, in a time frame of 24-72 hours [22] (*median and 25% -75% percentiles of the scores = 8 and 6.5-9; agreement on appropriateness 77.8%*).

#### **Indicator 4b: Goals of 'first-line therapy'**

**Final statement** – For the panel, first-line therapy is not addressed at modifying the natural history of severe ITP in adults [44], but at rapidly achieving, 'a safe platelet count to prevent or stop hemorrhage and to ensure an acceptable quality of life, avoiding as much possible treatment-related adverse effects' [1,4,9,10,17,19,45]. This fact and the lack of evidence that intensive medical therapy administered early in the disease course may improve or even cure ITP [46] mean that some treatments, including rituximab [17,47,48], in part because of their side effects and complications [13] are not, presently, acceptable as first-line therapy [4,13,26,49]. Thrombopoietin receptor agonist therapy [10,29,38,50-52], given its prohibitive cost in comparison with the relatively low cost of corticosteroids, should be reserved only for patients unresponsive to standard first-line therapy and should not be used in all newly diagnosed patients [11,26,38] (*median and 25% -75% percentiles of the scores = 8 and 8-9; agreement on appropriateness 88.9%*).

#### **Indicator 4c: Goals of 'second-line therapy'**

**Final statement** – The panel believes that the *goal* of this line of therapy is to obtain a long-term response with stabilization or improvement of health-related quality of life, while avoiding toxic treatments [1,2,10,17,20].

At present this goal can be achieved by multiple therapeutic regimens [1-5,10-13,16-19,20,25,29,30,40-43,47,48,51-81], even if splenectomy remains the choice that, despite the inherent risks [9,11,16,25,40,61,70-72,82-85] and the difficulties in being accepted by patients and physicians as the preferred second-line therapy [10,29,40,47,59, 61,62,70,72,73,82,86-89], is most likely to produce long-term remission [3,9,11,12,16,17, 19,40,42,43,58,60-62,70-73,78,82,84,85,88-90].

The choice to perform splenectomy may be influenced by some other factors, such as the duration of the disease since the diagnosis of ITP, the age of the patient [25,33,42,78,84,91,92], the presence or not of co-morbidities [16,17,25,33,42,71,89,92], cultural prejudices, such as contrariness to surgical removal of organs [82], and lifestyle [92]. In this regard, the panel considers it useful to specify that in the absence of important co-morbidities [25,32,33,37,60,71,89,92,93], and with the disease present for 12 or more months [1,4,11,58,61], the old age of a patient is not an absolute contraindication to splenectomy [25,29].



When splenectomy is considered, it should be performed 12 or more months after diagnosis [1,4,11,58,61], given the potential spontaneous resolution of the disease [1,11,50,67] or potential evidence of the secondary nature of the disease [94]. Consequently, when splenectomy is planned and the disease has been present for less than 12 months, the immediate goal of this line of treatment would be to control the disease, using medical treatments, until 12 months [1,4,13,58,95].

A waiting time of 6-12 months for elective splenectomy can be accepted for the exceptions described for indicator 3<sub>ld</sub> ('Timing for elective splenectomy of 6-12 months': 'patients who, requiring treatment, strongly prefer splenectomy for particular and motivated reasons, and patients who, at high risk of bleeding or with poor quality of life because of the bleeding manifestations, do not tolerate medical therapy') [25]. The waiting time for splenectomy of 12 (or even of 6-12 months for the exceptions above mentioned), together with the classification into lines of treatments here reported, that is a classification independent of the duration of the disease from diagnosis, actually helps to make splenectomy more a third (or further)-line than a second-line intervention [16,32,37,82] (*median and 25% - 75% percentiles of the score = 8 and 8-9; agreement on appropriateness 88.9%*).

#### **Indicator 4a: Goals of 'third-line therapy'**

**Final statement** – The panel strongly agrees on '... the achievement of a platelet count sufficient to prevent clinically significant bleeding with the least toxicity. ... treatment should be evaluated for the potential to induce an acute response and also a long-lasting response with minimum side effects/toxicity' [1,4,10,15] (*median and 25% - 75% percentiles of the scores = 8 and 8-9; agreement on appropriateness 100%*).

## **5. Conclusions**

Through the agreement obtained by the consensus procedure, we obtained the classification of the four lines of treatment for primary ITP in adults based on their respective indications (or sequences of disease) and goals (Table 4) [1-5,9-13,15-20,22,25, 26,29,30,32-34,37-96]. We propose this classification with the hope that it can facilitate the achievement of better shared evidence-based guidelines on the use of the various treatments available for adults with primary ITP. At this regard, the issue, on November 2019, of the new ASH guideline on ITP does not appear to reduce at the present time the validity of our work.

## **6. Patents**

**Author Contributions:** LC proposed the study/work and realized it initially with MC and GMP and subsequently with AMR and the members of the panel, represented in alphabetic order by EA, JMD, ME, AH, TK, MPL, SRL, KRM, and JWL. The literature search was made by LC and GMP, while its selection was conducted by the members of the panel and checked by LC and AMR. LC, MC, and GMP planned the study/work. The two co-chairmen (LC and MC) with the help of GMP and AMR prepared the questionnaires for the two rounds that were submitted to the panel, processed the respective replies and wrote the work, which was reviewed, shared and accepted by all the other authors.

**Funding:** This work did not receive external funding.

**Acknowledgments:** The Authors thank Alessia D'Introno, MD at the Operative Unit of Medicine of Ostuni Hospital, ASL BR, Italy, for her secretarial contribution.

**Conflicts of Interest:** EA: receipt of several grants from different laboratories: (Novartis, BMS, Pfizer, Léo Pharma, Boehringer, Ferring, Chugai, Amgen, and Servier); MPL: consultancy (CSL, Behring, Amgen, Bayer, Novartis, Shiongi, Kedrion, Sysmex), advisory boards (Amgen, Bayer, Novartis), and research funding (Astra Zeneca, PDSA, Novartis, Rigel); KRM: advisory board (Dova, Sanofi, Rigel); JMD: not provided; all other authors: no conflicts of interest.

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