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Expert opinion: criteria for second-line treatment failure in patients with multiple sclerosis

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ABSTRACT

Objectives
In the management of multiple sclerosis (MS), defining criteria for identification of suboptimal therapy responses and switching treatment is essential to avoid worsening. Despite the lack of a standardised definition, criteria for first-line treatment are well documented in the literature, based on clinical measures or magnetic resonance imaging (MRI) (gadolinium enhancing [Gd⁺] lesions or new/enlarging T2 lesions) assessed during the first 6–18 months after treatment initiation. However, it is unknown whether the same criteria can be used for second-line treatment failure.

Methods
Five regional boards involving 36 French MS experts were convened to discuss published literature regarding criteria for first- and second-line treatment failure, and to identify differences in local therapeutic practices. A national board of 11 experts was subsequently conducted to identify convergences and differences between regions, and to propose second-line criteria for the definition of therapeutic failure.

Results
Published information is lacking regarding second-line treatment failure criteria. In light of this, regional differences in current therapeutic practices are justifiable. Due to the risk-benefit ratio of these treatments and limited options for third-line treatments, the authors recommend a different therapeutic approach when assessing second-line treatment failure. The treatment switch for second-line treatment should be informed by confirmed disease progression, after 6 months, or combined clinical and MRI outcomes, but only after at least 1 year of treatment.

Conclusions
Experts compared therapeutic attitudes and practices regarding second-line treatment failure between French regions. They identified convergences that were used to propose a national agreement on second-line treatment failure criteria, which should be evaluated in real-life prospective cohorts.
1. INTRODUCTION

Multiple sclerosis (MS) is a complex disease characterised by periods of relapsing–remitting and progressive disease that are unpredictable and vary widely in individual patients [1–4]. Current therapies aim to reduce the risk of relapses, and slow disability progression [5,6] with disease-modifying therapies (DMTs), which remain the mainstay of chronic treatment for patients with MS [5]. Increasing treatment options offers the opportunity to individualise treatment [6,7]; however, understanding the complex treatment landscape remains challenging [7]. While guidance regarding choice of individual therapies is relatively limited [7], current European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS)/European Academy of Neurology (EAN) and American Academy of Neurology (AAN) treatment guidelines recommend early initiation of DMT in patients with active, relapsing–remitting multiple sclerosis (RRMS), defined as the presence of relapses and/or activity documented by magnetic resonance imaging (MRI) [6–8].

Guidelines also recommend ongoing clinical and MRI assessment for monitoring the disease progression and treatment effectiveness.

Since relapses or new MRI-detected lesions may develop before a newly initiated treatment becomes effective, and because DMTs reduce but do not eliminate relapses and MRI activity [8], deciding if treatment is effective and whether a treatment switch is warranted can be challenging. Moreover, guidance regarding switching between therapies is limited [6–8]. Conversely, criteria for first-line treatment failure are well documented [9–16]. Several studies corroborated that the combination of MRI for presence of new lesions and clinical assessment allow the evaluation of disease worsening. Indeed, clinical trials have demonstrated significant correlations between MRI activities and the presence of relapses or disabilities progression or both, in RRMS IFN-β treated patients, after a follow-up
of 2, 3 [17] and 15 years [12]. These observations have led to the publication of several expert opinions. Indeed, the importance of performing an annual MRI and/or clinical evaluation for a better disease control was recommended by Lublin et al. publications initially [14] then reiterated by Montalban et al.,[6]. Sormani and colleagues redefined the Rio score for greater accommodation of T2 lesion evaluation [13]. First-line failure criteria thus rely on either clinical activity or MRI findings. These studies further established that the combination of clinical relapses and MRI activity significantly increases the risk of disease progression and treatment failure [14,16]. Beside these studies, another criteria endpoint allowing the definition of first-line failure criteria has emerged. “No Evidence of Disease Activity”, also named NEDA, was originally described in a post-hoc analysis of the placebo-controlled, two-year Phase III pivotal trial for natalizumab [18]. It is defined by the composite measure of the absence of confirmed disability worsening (as measured by the Expanded Disability Status Scale (EDSS)) and of clinical and MRI measures of disease activity in relapsing multiple sclerosis (RMS). NEDA has since been widely used in analyses of other DMT and adopted as an outcome measure in RMS clinical trials [19–22].

Nevertheless, information regarding criteria [19] for failure of second-line therapy is lacking. This work reviews the therapeutic approaches of French MS experts for failure criteria of second-line treatment and highlights the convergences, which are used as the basis to inform therapeutic decisions.

2. METHODS

Because heterogeneous MS therapeutic strategies were observed in France, collegiate boards were runned in order to align practices. A 2-phase approach was set up. Five regional boards comprising of a total of 36 French MS experts (Auvergne-Rhône Alpes [n=9],
were conducted between November 2016 and February 2018 (Table 1). The participating experts provided a good representation of practices throughout each region, including university hospitals, regional hospitals, general hospitals and private practices. The experts identified and explained therapeutic practices for the management of MS patients in their region.

Subsequently, a national board involving 11 experts was conducted on March 28, 2018. This national board was composed of an expert from each of the regional boards, as well as invited practitioners and professional society representatives from different regions selected for their expertise in the field. The experts examined and discussed available literature on the monitoring of and failure criteria for the first- and second-line treatments for MS patients, with the aim of identifying second-line treatment failure criteria. The literature review was based on a search of Pubmed, congress presentations covering the previous 10 years and included publications relating to first- or second-line treatment failure criteria. Third-line therapies were also discussed. In addition, the experts discussed collated results from the regional boards. The experts worked in two sub-groups (using a majority consensus methodology), assessing study practices in each region, and identifying convergences and differences. Following discussion of the data, expert opinion was provided to define the criteria for second-line treatment failure.

3. RESULTS

3.1. Literature review analysis

Published data describes the role of clinical and MRI activity as criteria to define non-responders to first-line treatments (Table 2), mainly interferons. But, it is unknown whether
these criteria can be directly applied to second-line treatment failure [9–16]. Data from the literature for first-line treatments (interferons, teriflunomide, glatiramer acetate) converge, with criteria proposed for the prompt identification of a suboptimal response to first-line therapies based on clinical evaluation or MRI assessed during the first 6–18 months after treatment initiation. Detection of disease activity is defined as either a clinical relapse or Gd⁺ lesions or new/enlarging T2 lesions on follow-up compared with baseline scans [9–16].

Noteworthy publications include the work of Sormani and colleagues [13], with simplification of previously reported Rio criteria [17], validated in patients receiving first-line IFNβ-1a in the extension phase of the PRISMS study. The predictive value of the original Rio score, which is based on a combination of MRI (>2 active T2 lesions plus Gd⁺ lesions), relapse and Expanded Disability Status Scale (EDSS) criteria, was improved by using only MRI (>5 new T2 lesions) and relapse criteria [13]. The modified Rio score, assessed after one year of IFN therapy, defines 3 scores depending on both the number of relapses and new MRI lesions. This score is then correlated to the risk of disability progression in the subsequent 3 years [13,16].

In addition, Sormani and colleagues showed that the modified Rio score can be successfully applied to patients treated in first line with teriflunomide [15]. In this analysis, patients with RRMS who received teriflunomide (n=552) in the 108-week randomised, double-blind, placebo-controlled, phase 3 TEMSO study, where categorised as 0, 1, or 2/3 according to the modified Rio score and compared with those who received placebo (n=286). Similarly to patients treated with IFNβ-1a, MRI flares and lesions in the first 12 months of first-line teriflunomide in clinically stable patients predicted progression of disability [15].
A similar study confirmed the importance of MRI monitoring of patients, but concluded that particular attention should be paid to early Gd+ lesions while receiving first-line IFNβ, as their presence strongly correlates with severe disability 15 years later [12]. This observational study examined data in 136 patients with RRMS who received intramuscular IFNβ-1a in the pivotal, 2-year MSCRG study. Relationships between the worst disability at 15 years (i.e., median change in EDSS score from a baseline of 5) and Gd+ lesions, T2 lesions or relapses during the 2-year trial were explored. MRI activity had high specificity for predicting poor long-term outcomes in IFNβ-1a-treated patients (Gd+ lesions, odds ratio [OR] 8.96; p<0.001; new T2 lesions, OR 2.90; p=0.080). Moreover, several clinical studies showed the number of patients who had reached clinical NEDA was higher in treatment groups, as compared to placebo, during a 5-years long follow-up [20–22].

Recommendations for criteria for failure of second-line treatments are lacking in the literature, with only three studies exploring the subject [23–25]. Bates et al. first suggested that for second-line natalizumab therapy, disease activity reflected by MRI might not be predictive of clinical activity [23]. The study examined data from the pivotal AFFIRM and SENTINEL studies, which examined the use of natalizumab versus placebo and natalizumab ± IFNβ, respectively, in patients with RRMS [23]. Results showed a reduced annualised relapse rate (p=0.004) despite the presence of Gd+ lesions (p=0.008) or new or enlarging T2 hyperintense lesions (each p<0.0001), leading the authors to conclude that MRI findings alone may not mandate a switch from natalizumab [23]. Also, of note, before observing the full effectiveness of natalizumab treatment, new early T2 lesions could appear, due to MR imaging at the time. Thus, it is recommended to perform a rebaseline MRI at least 12 months after treatment initiation, regardless of treatment line or to adjust the timing of both MRIs according to treatment speed of action or disease activity [6].
Sormani and colleagues [24] examined data from 1,370 patients treated with fingolimod in the FREEDOMS and FREEDOMS II studies to assess whether the addition of brain volume loss to modified Rio criteria improved prediction of disability progression. The one-year measurements allowed the estimation of a 4-year risk of confirmed disease progression (4-year roCDP) of patients, stratified according to their modified Rio score. Independent of the inclusion of brain volume loss, this work successfully used the modified Rio score to predict disease progression (progression free survival) of patients treated with fingolimod [24].

Finally, the work of Signoriello and colleagues showed that Gd⁺ lesions occurring in patients on second-line fingolimod treatment were significantly more likely to be asymptomatic than those that appeared during first-line IFNβ-1a (88% vs. 30.9%; p≤0.025) [25]. This retrospective study assessed the annualised relapse rate (ARR), EDSS and the number of new brain and spinal Gd⁺ and T2 lesions in 103 patients with RRMS switching from IFNβ-1a to fingolimod [25]. Lesions appearing in patients on fingolimod (especially Gd⁺ lesions) did not necessarily result in an increase in disability, and Gd⁺ lesions did not have the same impact on clinical expression when they appeared with IFNβ-1a compared with fingolimod [25]. The authors suggested that conventional MRI as a surrogate measure of response provides only part of the information associated with both new and active lesions during treatment with fingolimod [25].

Thus, given the lack of data, it is not clear whether it is possible to extrapolate a predictive value of an MRI lesion on disability in a patient treated in first line, to a patient receiving second-line therapy.

3.2. Analyses of regional group practices
Discussions conducted during the regional board meetings highlighted the complexity of care of patients treated in second line, as well as a disparity of practices according to each region (Table 2).

3.2.1. Regional differences

Differences between regions in the methods used for evaluating progression were highlighted. In addition to EDSS, treatment failure was assessed using a variety of measures; including the annual Symbol Digit Modalities Test (SDMT), the 9-Hole Peg Test (9-HPT), the Timed 25-Foot Walk (T25-FW); decreased walking distance despite unchanged EDSS and low-contrast visual acuity.

Moreover, the decision-making regarding the next therapeutic strategy may vary between centres, depending on their level of confidence in unique MRI activity results and a unique relapse. Some regions placed the cut-off at 2 or 3 new T2 lesions, and some regions consider that the decision to change second-line treatment or not could generally be influenced by the clinical symptoms of the relapse (i.e. sensitive versus motor) and by the location of the new lesion (spinal cord or posterior fossa versus supratentorial).

3.2.2. Regional similarities

The board identified points of convergence between the regions in the follow-up of patients receiving second-line treatments and failure criteria (Figure 1), with various parameters to be evaluated. The response evaluation should be based on disease progression, MRI activity and clinical relapses. Disease progression assessment is based on an annual EDSS. The experts also agreed on the need to develop and validate new tools for the evaluation of disease progression. The most useful tools to be considered are those
used in many clinical trials, such as the Shared-Decision-Making questionnaire (SDM), the 9-HPT and the SDMT, the latter highlighting the need to incorporate a cognitive screening test. Any confirmed progression at 6 months defines a therapeutic failure. Otherwise, following the benefit-risk ratio, the decision-making regarding a treatment switch could be discussed after one year of treatment with the multidisciplinary meeting, as explained in Figure 1. Brain and spinal cord MRI are recommended at 6 months, followed by encephalic MRI alone once a year for up to 5 years. Evidence of brain atrophy is not considered to be clinically relevant. A spinal cord MRI as control can be prescribed in case of clinical activity.

In addition, all regions agreed that "failure" does not mean "inefficacy" or "therapeutic discontinuation or switch" and that confounding factors such as non-compliance or the presence of anti-treatment antibodies and poor prognostic factors (e.g. high baseline EDSS, age, immunosenescence, ethnicity and comorbidities) should be considered when the therapeutic decision is made. Failure criteria are not considered to be valid after 3 years of treatment.

3.3. Proposed criteria for second-line treatment failure

The recommendations made here are proposals from a group of experts. While some of the regional boards date back to 2016 and 2017, expert’s medical practices are not considered to have changed significantly in that time. All experts considered that treatment failure with second-line treatments are mainly due to disability progression and a significant proportion switching to secondary progressive multiple sclerosis (SPMS). Thus, based on current practices and expert opinion, the following criteria have been proposed for evaluation and for treatment failure in second line. Compared with first-line failure criteria, it is necessary to be less restrictive with the criteria for second-line treatment failure due to
the rather limited third-line therapeutic options as well as the lack of experience concerning outcomes after the switch from second-line to third-line treatments or lateral switch. As opposed to first-line treatment failure criteria, it is recommended that second-line therapeutic failure should be based on both clinical relapses and MRI activity. Disability progression is an essential indicator of second-line treatment response, even if clinical relapses and MRI activity are to be considered.

Second-line treatment failure criteria are thus defined by either a confirmed progression at 6 months or a clinical relapse combined with MRI activity after one year of treatment. Mainly due to the high frequency of pseudo relapses and associated permanent sequela with second-line therapy [8], a relapse only or an MRI activity alone should not lead to a treatment switch. Further investigation and development of new tools are required to better evaluate disease progression. A lateral switch is systematic in the event of tolerance issues. Failure criteria are valid for up to 3 years of treatment.

Evaluation of the current proposals in real-life prospective cohorts would help provide data useful for defining second-line treatment failure criteria in the future.
4. DISCUSSION

In general, ECTRIMS/EAN and AAN guidelines recommend switching to a more effective drug in patients with evidence of disease activity; however, no distinction is made between lines of therapy [6,8]. Disease activity is defined as the appearance of new or unequivocally enlarging T2 lesions measured by brain MRI within 6 months of starting treatment (baseline) and repeated 12 months after treatment initiation [6,8]. In addition, monitoring of gadolinium-enhancing (Gd⁺) lesions is also recommended for assessment of treatment response [6].

While criteria for first-line treatment failure included the appearance of Gd⁺ lesions [12,13], results with second-line therapies were not as clear, with two of the three identified studies showing that the appearance of new Gd⁺ lesions and/or T2 lesions did not correlate with relapses/disability with fingolimod or natalizumab ± INFβ [23,25]. The experts believe that there are too few data with second-line treatments and that first-line treatment data are not applicable. Several study have documented a tissue accumulation of gadolinium, thus raising the possibility of toxicity issues as well as the development of neurodegenerative diseases in the long term, particularly with linear agents [26–29]. The use of gadolinium have been discussed leading to new guidelines for limitation of routine gadolinium injections to specific clinical situations, which will be detailed in next OFSEP’s publications.

The counting of T2 lesions is more challenging than Gd⁺ lesions. Detection of active T2 lesions in patients with MS can be made more difficult by a high burden of inactive T2 lesions, the presence of small and confluent lesions, inadequate repositioning, and high interobserver variability [30,31]. However, measurement of new and/or enlarged T2 lesions
should be encouraged. Automatic counting of MRI lesions might help in this respect. Automatic methods appear to be fast and accurate, and avoid the variability introduced by manual analyses [32–34].

Regarding clinical relapses with second-line therapies, progression of disability (as measured by the EDSS) is essential; however, it was agreed that it is necessary to develop and validate tools for evaluating disease progression, in addition to EDSS. An important consideration is that, while the impact of relapses during the first 5 years of the disease is known [9–11,13,15,16], data after this period are lacking and it is during this time that second-line treatment is typically initiated. Paradoxically, it seems that treatment is more permissive in patients receiving second-line therapy than in those receiving first-line, whereas second-line treatment is supposed to be more effective. In our opinion, the concept of first- and second-line MS therapies is artificial, being mainly related to the marketing authorisation process. For example, the SENTINEL [35], TRANSFORMS [36,37] and FREEDOMS trials [38,39] were designed to obtain a first-line marketing authorisation, but natalizumab and fingolimod were instead granted second-line marketing authorisations due to a lack of data regarding their long-term safety [40,41]. There was general agreement that long-term monitoring data for second-line treatments are lacking.

It is also important to consider that criteria for second-line failure must take into account the existence of alternatives to treatment: the reduced number of therapeutic alternatives in third line and the accumulation of treatment lines limit a more clear and direct approach. The availability of multiple treatments complicates the treatment choice, and, as mentioned previously, specific guidance is lacking. Guidelines recommend individualised therapy based on factors such as: patient characteristics, disease severity, the
presence of comorbidities and likelihood of adherence to treatment, as well as the mechanism of action, efficacy, availability and safety of individual therapies [6,7]. In practice, the experts agreed that natalizumab or fingolimod are most commonly used (for approximately 85% of patients in France) after first-line treatments failure. The best treatment options after second-line natalizumab or fingolimod are unknown, but relief of symptoms and improvement in quality of life are important factors to consider when choosing a third-line therapy. Furthermore, the lack of long-term data regarding the efficacy or tolerability of third-line treatments, after a switch from fingolimod or natalizumab, complicates the choice when switching from a second-line to a third-line treatment.

Finally, is it necessary to differentiate between patients with slow-worsening MS, with therapeutic escalation over several years, and those with rapidly worsening MS who are naïve to treatment. Catastrophic MS forms exist either from the outset or occur during evolution and are associated with a rapid increase in EDSS. They require a very fast-acting treatment capable of significantly reducing immune cells. But there is a possibility of a rebound effect with some treatments [42] and an accumulation of side effects between second- and third-line treatments. It is important to consider efficacy, tolerance, the place in therapeutic succession and patient’s profile.

The authors believe that the differences in therapeutic practices between regions highlighted in this report are currently justifiable given the absence of published data.
5. CONCLUSIONS

Convergences and differences between regions in France in terms of therapeutic attitudes and practices for second-line treatment failure were identified. These differences were justified in the absence of published recommendations. The authors agreed that criteria for second-line treatment failure must consider either disease progression (according to EDSS) confirmed at 6 months, or clinical relapses and MRI findings (new or increasing T2 and/or Gd\+ lesions) but only after at least 1 year of treatment. The development of new tools is necessary to improve the evaluation of disease progression. These proposals should be evaluated in real-life prospective cohorts.
Author’s contributions

Among all co-authors, PV, JDS, PC, FDD, EM, TM, AT and PL participated in the discussion during a regional board to share therapeutic practices for the management of MS patients in their respective region. All co-authors participated to the national board. Finally, PV, JDS and PL mainly were involved in the writing and review process of the manuscript.

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References


[41] Novartis Europharm Ltd. Gilenya 0.5 mg hard capsules: Summary of product characteristics. 2018.


**Tables and Figure**

**Table 1.** Disease-modifying therapies available for the treatment of MS in Europe [5,41,43–55]

<table>
<thead>
<tr>
<th>Drug name (brand name)</th>
<th>Indication</th>
<th>Route of administration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First-line therapies</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interferon β-1b (Betaferon®)</td>
<td>RMS</td>
<td>SC injection</td>
</tr>
<tr>
<td>Interferon β-1a (Rebif®)</td>
<td>RMS</td>
<td>SC injection</td>
</tr>
<tr>
<td>Interferon β-1a (Avonex®)</td>
<td>RRMS</td>
<td>IM injection</td>
</tr>
<tr>
<td>Glatiramer acetate (Copaxone®)</td>
<td>RRMS</td>
<td>SC injection</td>
</tr>
<tr>
<td>Interferon β-1b (Extavia®)</td>
<td>RMS</td>
<td>SC injection</td>
</tr>
<tr>
<td>Pegylated interferon β-1a (Plegridy®)</td>
<td>RRMS</td>
<td>SC injection</td>
</tr>
<tr>
<td>Teriflunomide (Aubagio®)</td>
<td>RRMS</td>
<td>Oral</td>
</tr>
<tr>
<td>Dimethyl fumarate (Tecfidera®)</td>
<td>RRMS</td>
<td>Oral</td>
</tr>
<tr>
<td>Ocrelizumab (Ocrevus®)</td>
<td>PPMS</td>
<td>IV</td>
</tr>
<tr>
<td><strong>Second-line therapies</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Natalizumab (Tysabri®)</td>
<td>HA RRMS, RES RRMS</td>
<td>IV</td>
</tr>
<tr>
<td>Fingolimod (Gileny®)</td>
<td>HA RRMS, RES RRMS</td>
<td>Oral</td>
</tr>
<tr>
<td>Mitoxantrone (Novantrone®)</td>
<td>HA RRMS, RES RRMS</td>
<td>IV</td>
</tr>
<tr>
<td><strong>Others</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ocrelizumab (Ocrevus®)</td>
<td>RMS</td>
<td>IV</td>
</tr>
</tbody>
</table>
Cladribine (Mavenclad®) | HA RMS | Oral  
--- | --- | ---  
Alemtuzumab (Lemtrada®)\(^{a}\) | active RRMS, | IV  

\(^{a}\) Difficult access in some countries in Europe. Indications restriction.

**Abbreviations:** HA, highly active; IM, intramuscular; IV intravenous; PPMS, primary progressive multiple sclerosis; RES, rapidly evolving severe; RMS, relapsing multiple sclerosis; RRMS, relapsing/remitting multiple sclerosis; SC, subcutaneous.

### Table 2. Summary of outcomes from the individual boards

<table>
<thead>
<tr>
<th>Board</th>
<th>Outcomes</th>
</tr>
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</table>
| Auvergne-Rhône Alpes | • The criteria of Sormani [13] (i.e., modified Rio criteria) are not transferable to second-line therapy.  
• There is a need for a stratified medicine.  
• Therapeutic switch from the second- to third-line treatment if progression or relapse with sequelae.  
• Switch also on the sole basis of MRI, but there was hesitation in the working group about a switch based exclusively on combined clinical and radiological criteria (MRI + relapse). |
| Grand-Est | • Therapeutic approaches are more permissive with second-line therapy because of a lack of third-line possibilities.  
• Change of treatment if true relapse (beware of pseudo-flares that can cause exacerbations without lesions).  
• Change of treatment if radiological evolution alone after one year of second-line treatment. |
<table>
<thead>
<tr>
<th>Region</th>
<th>Details</th>
</tr>
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</table>
| Languedoc-Roussillon  | • A switch from second- to the third-line treatment is systematically discussed in a multidisciplinary meeting.  
|                       | • A treatment change can be made on the basis of combined clinical and radiological criteria at one year of treatment:  
|                       |   o Gd⁺ lesion and relapse;  
|                       |   o Gd⁺ lesion and worsening EDSS;  
|                       |   o Gd⁺ lesion, relapse and worsening EDSS.                           |
| Ile de France         | • A switch from second- to third-line treatment is systematically discussed in a multidisciplinary meeting.  
|                       | • Less strict criteria of second-line treatment failure than for first-line treatment because of a lack of third-line possibilities.  
|                       | • Changing the treatment must be discussed after 1 year of treatment.  
|                       | • Criteria are EDSS, relapse and radiological activity, but without cut-off like Rio Score. |
| Nord Pas de Calais    | • Maintenance of second-line treatment if the patient has a single flare or radiological activity alone.  
|                       | • There is lack of clarity regarding third-line treatment options; there is no consensus, only suggestions. |
Figure 1. Expert consensus for failure criteria for second-line treatments