

## REVIEW

## IMWG consensus on risk stratification in multiple myeloma

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Multiple myeloma is characterized by underlying clinical and biological heterogeneity, which translates to variable response to treatment and outcome. With the recent increase in treatment armamentarium and the projected further increase in approved therapeutic agents in the coming years, the issue of having some mechanism to dissect this heterogeneity and rationally apply treatment is coming to the fore. A number of robustly validated prognostic markers have been identified and the use of these markers in stratifying patients into different risk groups has been proposed. In this consensus statement, the International Myeloma Working Group propose well-defined and easily applicable risk categories based on current available information and suggests the use of this set of prognostic factors as gold standards in all clinical trials and form the basis of subsequent development of more complex prognostic system or better prognostic factors. At the same time, these risk categories serve as a framework to rationalize the use of therapies.

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## INTRODUCTION

Multiple Myeloma (MM) is a malignancy characterized by the infiltration of clonal plasma cells in the bone marrow that secrete a monoclonal protein in the majority of patients. Several new therapies have been approved for the treatment of myeloma in the last decade, with a resultant improvement in outcome. However, considerable heterogeneity exists in the survival outcomes among patients diagnosed with MM. Although a large number of prognostic markers have been described in MM, none of them completely explain the heterogeneity seen in this disease and attempts have been made to develop systems using several of these prognostic factors to better risk stratify patients with MM. To complicate matters further, some of the new treatment appears to overcome the high-risk defined by one or more of these prognostic factors. With the increased treatment options, the ability of some treatment to overcome certain risk factors and the availability of markers to define risk categories, the question of risk stratification in the management of myeloma is becoming an important issue. Development of a uniform risk stratification system will also allow better comparison of patient groups across different trials, given the heterogeneity seen in the outcomes. During the International Myeloma Working Group (IMWG) Meeting in London in 2011 June, a group was convened to discuss issues around risk stratification in MM. In particular, the following were discussed in the context of evolving treatment paradigms and prognostic factors:

- (1) What defines high-risk and low-risk patients?
- (2) What should we use to define the risk groups?
- (3) Can risk-adapted therapy be recommended at this time?
- (4) What are the best trial designs for risk stratification?

In the following sections, we shall discuss current evidence and arguments for risk stratification in myeloma based on the above questions and discussions. We will then present our consensus recommendations at the end. Some of these recommendations will be applicable clinically, whereas others will be for research and design of clinical trials as we continue to optimize management of myeloma patients.

## CURRENT TREATMENT LANDSCAPE

In recent years, the treatment landscape of myeloma has evolved considerably. Three effective novel agents have been approved for myeloma treatment and incorporated into the treatment armamentarium in the last decades. This includes thalidomide and lenalidomide, so-called immunomodulatory drugs (Imids), and bortezomib, the first in class proteasome inhibitor.<sup>1</sup> More recently, Carfilzomib, the second-generation proteasome inhibitor, as well as Pomalidomide, a third-generation Imids has also been approved by the US Food and Drug Administration for the treatment of relapse myeloma. The incorporation of these drugs in combination with steroid and/or alkylating agents at different

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phases of myeloma treatment (induction phase, consolidation phase and maintenance phase) has significantly improved response rates and overall survival.<sup>2,3</sup>

### PREDICTIVE VERSUS PROGNOSTIC MARKERS

With increase therapeutic choices, and improved outcomes, the issue of risk stratification is becoming important as we could potentially tailor treatment for different groups of patients.

In this regard, the concept of predictive versus prognostic markers should be distinguished. Prognostic markers provide information about the outcome, whereas predictive markers provide information specifically about different drugs or regimen and the likelihood of good response and the outcome with them. A marker can be either prognostic or predictive or both. For example, 17p13 deletion is a poor prognostic marker but not predictive of response or outcome to any specific drugs. TRAF3 deletion or mutation may predict response to bortezomib but is not itself a prognostic factor.<sup>4</sup> Cereblon expression may predict resistance to immunomodulatory drugs but is itself not a prognostic factor.<sup>5</sup> In myeloma, we have a number of markers associated with prognosis but few predictive markers.

The predictive markers are useful for individualizing treatment, whereas the prognostic markers are useful in risk stratification. Although we do not yet have robust predictive markers for selecting treatment, treatment doses should be individualized according to host factors such as age and renal function. The European Myeloma Network has recently proposed useful dose reduction guidelines according to patient's constitution.<sup>6</sup>

### WHAT ARE THE PROGNOSTIC MARKERS?

A large number of prognostic biomarkers has been identified over the years. These markers may reflect host factors and hence fitness to receive therapy, tumor-related factors which reflect tumor biology, tumor stage and disease burden and tumor response to treatment. It is important to note that most of these prognostic factors are derived from patient cohorts treated with alkylator-based and/or transplant-based treatment in the era before novel agents. Nevertheless, many of them are still relevant in the era of novel agents and are used to assess how treatment with the novel agents can modify the patient's risk. Several markers have been more widely validated and utilized in prognostication.

#### Host factors

The most important host factor is age. There is an incremental shortening of survival in every increasing 10-year age band in a large cohort from Europe, United States and Japan treated with both conventional and novel agents.<sup>7</sup> Furthermore, in a recent Francophone Myeloma Intergroup (IFM) analysis to identify factors associated with long survival, young age was one such independent factor.<sup>8</sup>

#### Tumor characteristics

Tumor-related factors include proliferation as measured by the plasma cell labeling index,<sup>9</sup> presence of circulating plasma cells<sup>10</sup> and plasmablastic morphology.<sup>11</sup> However, these are either not widely adopted or not easily reproducible. The most important tumor factors are genetic aberrations and gene expression profiles. A number of genetic aberrations have been shown to be associated with poor survival consistently across studies. These includes t(4;14) and 17p13 deletion.<sup>12–14</sup> The data for t(14;16) are mixed with the Mayo Clinic and MRC (Medical Research Council) group showing that it is associated with poorer outcome, whereas this was not the case in the IFM studies.<sup>15–17</sup> Another factor where data are conflicting is chromosome 1q21 amplification (1q21+). Some reports have shown 1q21+ to be an independent

prognostic factor,<sup>17,18</sup> whereas others have not.<sup>19,20</sup> Although its role as a poor prognostic factor is controversial, the lack of 1q21+ may be useful in identifying patients with very good prognosis.<sup>8</sup> More recently, the deletion of 1p has also been shown to be independent prognostic factors associated with shorter survival.<sup>21–23</sup> The prognostic importance of 1p deletion and the locus of relevance (1p21 or 1p32; although the latter is common to all studies) need to be further confirmed. t(4;14) and t(14;16) can only be detected by fluorescent *in situ* hybridization (FISH) as these translocations are not detectable by conventional cytogenetics. 17p13 deletion and 1q21 gain can be detected by both FISH and conventional cytogenetics and is associated with poor outcome when detected by either method although most of the studies used FISH as the detection method.

However, even within groups with these genetic prognostic factors, there may be further heterogeneity. For example, the IFM group showed that among the patients with t(4;14), those with a hemoglobin greater than 10 g/l and beta-2 microglobulin less than 4 mg/l had significantly longer survival compared to those without.<sup>24</sup> At the same time, a recent analysis showed that patients with high-risk genetic changes have significantly different survival depending on the presence or absence of trisomies.<sup>25</sup> These results suggest that with the current state of knowledge about myeloma genetics, genetics alone may be suboptimal as prognostic factors. Combining information about genetic abnormalities with other parameters may further improve their prognostic value.

A number of prognostic gene expression signatures have been reported. Some of these are derived directly as a measure of poor survival, whereas others were derived to reflect underlying biology and subsequently found to be prognostic (Table 1). Several of these have been validated in a number of independent data sets as independent prognostic factors. The prognostic utility of some of these gene expression profiling (GEP) signatures are currently being prospectively evaluated in the EMN02 trials and IFM/USA trials.

The technology of gene expression microarray is now mature and robust, with good inter-laboratory agreement.<sup>26</sup> However, there are still three major hindrances to its clinical application: (1) there is not yet one standard recognized GEP-signature; and (2) the perception of a lack of reproducibility as so many different signatures exists. The lack of overlap in the genes constituting the different prognostic signatures is a function of the different ways in which these signatures are generated. Different signatures may signify different aspects of myeloma biology. In this context, a combination of signatures may be better than individual signatures. To this end, the International Myeloma Working Group is conducting a study to unify the GEP prognostic signatures using prognostic modeling. Lastly, the lack of ability of most myeloma physicians to analyze and interpret GEP data leads to the perception that it is still a research tool and not clinically applicable. To move GEP toward the clinic, it is critical that we create user-friendly platforms. Dedicated chips can be created (for example, Mammarray (Agendia Inc, Irvine, CA, USA) for breast cancer and MyPRS (Signal Genetics AR, New York, NY, USA) for MM) or automated analytical algorithm that generates reports on results and interpretation can be incorporated to laboratory workflow. The feasibility of one such attempt has been demonstrated.<sup>27</sup> The parallel resolution of these issues should make clinical application of GEP in myeloma a reality in next few years.

#### Tumor burden/stage

The Durie-Salmon staging system was the first commonly used staging system largely reflecting tumor burden.<sup>28</sup> It has been superseded by the International staging system (ISS)<sup>29</sup> which is based on two simple and routine laboratory tests, serum albumin and beta-2 microglobulin, that is widely available. The ISS therefore combines factors that relates to the host (albumin)

**Table 1.** GEP-based prognostic signatures

<i>GEP signatures</i>	<i>Methods</i>	<i>Ref</i>
UAMS 70-gene <sup>60</sup>	Comparing the expression profiles of patients with top and bottom quartile of survival treatment on Total Therapy II	Blood 2006; 109: 2276–2284 <sup>60</sup>
IFM signature <sup>61</sup>	Model derived from iterative process of univariate cox analysis, resampling analysis and then principle component analysis	J Clin Oncol 2008; 26: 4798–4805 <sup>61</sup>
Centrosome index <sup>62</sup>	Based on expression of genes encoding components of the centrosome	Blood 2008; 111: 1603–1609 <sup>62</sup>
HZD cell death signature <sup>63</sup>	Signature derived from genes homozygously deleted in myeloma as detected by array comparative genomic hybridization	Clin Cancer Res 2010; 16: 1856–1864 <sup>63</sup>
IL6-HMCL signature <sup>64</sup>	13 Genes signature build from genes accounted for heterogeneity in human myeloma cells lines upon IL6 stimulation	Haematologica 2011; 96: 574–582 <sup>64</sup>
Proliferation index <sup>65</sup>	Based on proliferation genes	Haematologica 2011; 96: 87–95 <sup>65</sup>
EMC 92-gene signature <sup>66</sup>	Generated by supervised component analysis with simulated annealing	Leukemia 2012; 26: 2406–2413 <sup>66</sup>
Chromosome instability genomic event count (CINGEC) signature <sup>67</sup>	Genes differentially expression between patients with the top quartile and bottom quartile of genomic complexity based on the number of aCGH defined abnormalities including both DNA gains and losses and breaks.	PLoS One 2013; 8: e66361 <sup>67</sup>

Abbreviations: EMC, Erasmus Medical Center; GEP, gene expression profiling; HMCL, human myeloma cell lines; HZD, homozygous deletion; IFM, immunofluorescence microscopy.

and the disease activity (beta-2 microglobulin). The ISS is robustly derived and validated and applicable across geographical areas. During the derivation of the ISS, traditional prognostic factors such as blood counts, renal function, hypercalcaemia, M-protein levels, percentage of bone marrow involvement and immunoglobulin isotypes were not significant in the multivariate analysis. However, genetic abnormalities were not included in the derivation of the ISS. It was subsequently shown by the IFM group that high-risk cytogenetics have prognostic impact independent of the ISS,<sup>20</sup> suggesting that the integration of both ISS and genetics produces a more robust model. Recently, it was shown that the extent of disease detected by magnetic resonance imaging and positron emission tomography-computed tomography correlated with tumor burden and has prognostic utility.<sup>30</sup> These results require further confirmation before clinical implementation.

#### Combined genetics-ISS model

Indeed a recent analysis by IMWG incorporating data from the international community demonstrated that a combined model could segregate patients into three risk groups. High-risk patients with either ISS II or III and the presence of either t(4;14) and/or 17p13 deletion detected by FISH have a median survival of about 2 years, whereas low-risk patients with ISS I or II and absence of these high-risk genetics have 5- and 10-year overall survival rates of 70% and 51%, respectively.<sup>31</sup> Similar results were seen in an independent German study<sup>32</sup> and an independent MRC study<sup>17</sup> (Table 2). The best outcomes were seen in the German study, most likely because it included only transplant patients and it was a more recent study, making it more likely that a higher percentage of patients had access to novel therapies.

#### Tumor responsiveness to treatment

There is substantial data showing the association of depth of response and outcome. Most, but not all, studies showed that achieving complete remission (CR) is an important surrogate for improved OS.<sup>33</sup> There are studies that suggest that CR is not needed for prolonged survival of patients with low-risk disease based on gene expression profile.<sup>34</sup> In addition, the Arkansas group has shown that it is not the achievement of CR but the ability to sustain the CR that is important for overall survival.<sup>35,36</sup> Further, the IFM group have shown in their trials that very good partial response is associated with good outcome,<sup>37,38</sup> although it is important to note that the consideration of all patients who

achieve at least very good partial response will include a substantial proportion of patients who actually achieve CR. In two large series of patients treated in Spanish<sup>33</sup> and Italian trials,<sup>39</sup> respectively, the achievement of CR has a significant impact on survival when compared with very good partial response only. Furthermore, there are a number of studies showing that the achievement of immunophenotypic remission, where abnormal plasma cells are no longer detectable by flow cytometry, is associated with longer survival than CR.<sup>40,41</sup> There are also data suggesting that achieving a molecular CR with no detectable clones by PCR is better than CR.<sup>42,43</sup> On the other hand, the detection of disease by magnetic resonance imaging<sup>44</sup> or positron emission tomography-computed tomography<sup>45</sup> after treatment is associated with high-risk of relapse. There are therefore ample evidence suggesting that for a given treatment strategy, a deeper response is associated with better outcome. However, this does not suggest that strategies producing greater depth of response are inherently better. Which treatment strategy is better will need to be assessed in the setting of randomized studies.

What is the best measure of response is at present still not clear. There are potential limitations with each technology and some technologies are still evolving. It is conceivable that a combination of these methods would be needed to define the deepest response.

Counter intuitively, patients with identifiable high-risk genetic findings have response rates that are comparable to those with favorable genetics. What distinguishes these high-risk patients is their inability to stay in response. Not achieving partial response or very good partial response among patients with apparently favorable genetics is another surrogate for adverse biology, and should be considered *post hoc* as a risk factor. Early relapse, however, is a far worse prognostic factor.<sup>46</sup>

#### WHY SHOULD WE RISK STRATIFY?

##### Patient counseling

One of the main reasons for assigning risk to each patient with a disease is to inform the patient of his prognosis. This is and still remains a very important reason for risk categorization and provides a framework for patient counseling, providing the answer to one of the most commonly ask question of 'How long do I have to live?', after someone is told of their diagnosis of cancer. This is no different for myeloma patients.

**Table 2.** Comparison of studies using combined prognostic models of ISS and FISH

	IMWG <sup>31</sup>	MRC <sup>17</sup>	German <sup>32</sup>
Treatment	Include both young patients (transplant) and older patients (chemotherapy only)	Young (intensive) and old patients (non-intensive) with thalidomide-based combination at induction and thalidomide maintenance on MRC IX trials	Chemo-based induction followed by HD Mel ASCT and maintenance
N	2637	629	315
<i>Low-risk</i>			
Parameter	ISS <sup>a</sup> I/II with no adverse FISH <sup>b</sup>	ISS I/II with no adverse FISH <sup>c</sup> or ISS I with 1 adverse FISH lesions	ISS I with no adverse FISH <sup>b</sup>
% Patients	51%	38%	42%
OS	76% at 4 years	Median 67.8 months	72% at 5 years
<i>Int risk</i>			
Parameter	ISS III with no adverse FISH or ISS I and t(4;14)/17p13 del	ISS I with > 1 adverse FISH lesions or ISS II/III with 1 adverse FISH lesions or ISS III and no adverse FISH	ISS II/III with no adverse FISH or ISS I and t(4;14)/17p13 del
% Patients	29%	48%	44%
OS	45% at 4 years	Median 41.3 months	62% at 5 years
<i>High-risk</i>			
Parameter	ISS II/III and t(4;14)/17p13 del	ISS II/III with > 1 adverse FISH lesions	ISS II/III and t(4;14)/17p13 del
% Patients	20%	14%	14%
OS	33% at 4 years	Median 19.4 months	41% at 5 years

Abbreviations: HD Mel ASCT, high-dose Melphalan Autologous stem cell transplantation; FISH, fluorescent *in situ* hybridization; IMWG, International Myeloma Working Group; ISS, International staging system; MRC, Medical Research Council; OS, overall survival. <sup>a</sup>ISS stage I, Beta-2 microglobulin <3.5 mg/l and albumin <3.5 g/dl; ISS stage III, Beta-2 microglobulin ≥5.5 mg/l; ISS stage II, not ISS I or ISS III. <sup>b</sup>Adverse FISH here refers to t(4;14) and/or 17p13 del. <sup>c</sup>Adverse FISH here refers to adverse IgH translocations (t(4;14) or t(14;16) or t(14;20)), 17p13 del and/or 1q21 gain.

#### Minimize toxicity and maximize outcome

Risk-adapted therapy is not new in hematologic malignancy and is routinely used in the management of acute leukemias and Hodgkin's lymphoma. In these diseases, low-risk patients may get away with less intensive treatment and still be cured, whereas high-risk patients will require more intensive treatment to achieve long-term remission. Risk stratification, in principle, allows the reduction in treatment toxicity and optimizing outcome. It may also allow the better optimization of therapeutic resources to prevent over-treatment in subgroups of patients. The risk of this approach is that some patients may be under-treated.

In myeloma, there is a strong argument that this concept does not apply as we still view the disease as incurable. In this situation, all patients should receive the most optimal treatment tested in phase III clinical trials and currently available to achieve the best outcome. Certainly in recent published trials using novel agents, the benefits are seen across the risk categories, often benefiting the non-high-risk patients more.<sup>47–49</sup> Therefore, by treating low-risk patients with less, we may potentially undertreat these patients. However, the recent description of factors—absence of t(4;14), del(17p), and 1q gain and b2-microglobulin less than 5.5 mg/l—that could identify the patients who have greater than 50% chance of surviving more than 10 years may start to challenge this concept.<sup>8</sup> It is therefore important that future clinical trials should take the different risk groups into consideration when asking the therapeutic questions.

#### Research

Perhaps more importantly, risk stratification sets the framework to identify continuing area of clinical needs and to allow the continuous optimization of treatment. For the very high-risk patients, such as those with 17p13 deletion, who have generally poor outcome with current treatment strategies, alternative strategies should be considered. For the low-risk patients that have a more than 50% chance of surviving more than 10 years perhaps treatment strategies without stem cell transplantation

and even maintenance can be tested (Table 3). Therefore, risk stratification provides the framework for testing these therapeutic strategies in clinical trials and also to identify new and more effective treatment for high-risk patients.

#### WHAT DEFINES HIGH-RISK AND LOW-RISK PATIENTS?

The panel agrees that a reasonable benchmark to define high-risk patients will be an overall survival of 2 years or less despite the use of novel agents. Conversely, low-risk patients will be those that survive more than 10 years.

#### WHAT SHOULD WE USE TO DEFINE THE RISK GROUPS?

On the basis of existing laboratory tests, there are already good and robust markers for risk stratification. These include serum albumin and beta-2 microglobulin for ISS staging, and FISH for t(4;14), deletion 17p13 and 1q21 gain. Using these markers that can be applied to more than 90% of all myeloma patients, a high-risk group of patients can be defined by ISS stage II/III and the presence of either t(4;14) or 17p13.<sup>31</sup> At the same time, a low-risk group can be defined by age less than 55 years, ISS stage I or II and normal results for the three FISH markers.<sup>8</sup> These can be applied today and it is felt that this risk stratification should form the current standard to which future prognostic markers should be compared and be the platform upon which new prognostic markers can be integrated. This schema also fits in with the Mayo stratification of myeloma and risk-adapted therapy (mSMART) risk categories proposed by the Mayo Clinic<sup>50</sup> and provides further refinement through the addition of a low-risk group of patients. In the mSMART schema, t(4;14) is considered to have intermediate risk as its risk can be modulated by bortezomib treatment.

Prognostic markers may evolve with new understanding of disease, new treatments and new technologies. However, new prognostic makers should be assessed against a baseline standard.



**Table 3.** Risk stratification and possible therapeutic questions within each risk categories

	High-risk	Standard-risk	Low-risk
Parameters	ISS II/III and t(4;14) <sup>a</sup> or 17p13 del	Others	ISS I/II and absence of t(4;14), 17p13 del and + 1q21 and age <55 years
Median OS	2 years	7 years	> 10 years
% Patients	20%	60%	20%
Therapeutic questions	There is a need for novel therapeutic approaches e.g. Allogeneic stem cell transplant or immune therapy approaches		Do these patients benefit from maintenance therapy? Is VGPR a good enough response in these patients, as they may revert to an MGUS state

Abbreviations: ISS, International staging system; MGUS, monoclonal gammopathy of undetermined significance; OS, overall survival; VGPR, very good partial response. <sup>a</sup>Survival of t(4;14) patients is improved with the use of velcade-based therapy.

Currently, different studies may utilize different standards for risk stratification and the prognostic impact of new markers is not always compared with the same standards. There is a strong argument that the assessment of a standard set of prognostic markers should be mandated for all studies and that any new prognostic markers should always be compared with this standard. This will make the interpretation of data easier and more consistent, and facilitate more rapid adoption of new prognostic markers. We therefore propose the use of the IWMG combined ISS-genetic prognostic system as the new standard to define high-risk disease (Table 3).

#### CAN RISK-ADAPTED THERAPY BE RECOMMENDED AT THIS TIME?

It was felt that at the present time, although we have the markers to stratify patients into different risk groups, we are still not in a position to recommend different treatments for patients in the different risk groups. The only possible exception is that bortezomib-based treatment for induction and maintenance should be recommended for patients with t(4;14), as results from different trials have consistently showed that bortezomib-based treatment improved outcome of these patients.<sup>51</sup> Some studies suggest that the poor risk of t(4;14) is completely negated,<sup>47,48</sup> whereas others suggest that the risk is attenuated but not completely abrogated.<sup>49,52</sup> Two reports utilizing bortezomib combinations before and after autologous stem cell transplantation appear to be able to overcome the poor prognosis conferred by 17p13 deletion.<sup>53,54</sup> In the University of Arkansas for Medical Sciences (UAMS) study, this benefit with bortezomib was seen in the GEP defined high-risk but not low-risk patients.<sup>53</sup> However, the number of patients with 17p13 deletions in these studies is relatively small and current strategies await further confirmation. On the other hand, it is clear that thalidomide maintenance is detrimental to patients with 17p13 deletions.<sup>55</sup> In fact, there is no clear evidence till now that maintenance therapy, with any agents, benefits patients with very high-risk disease such as patients with 17p13 deletions.

Although it is true that there are little data from randomized studies to suggest the benefit of specific treatments for patients in different risk groups, the risk stratification schema is nevertheless a useful framework for rational selection of treatment taking into consideration the cost of drugs, toxicities and efficacies. For high-risk patients, the threshold for using more expensive and potent treatment with potentially greater toxicity could be lower, whereas for low-risk patients, this threshold will be much higher with a preference for less toxic and less costly regimen albeit with slight compromise on efficacy. These thresholds varies according to the inclinations of the treating physicians, and are determined to a large extent based on the dichotomy in treatment philosophies that currently exist in myeloma; one of cure (adopting a more aggressive approach) versus control (adopting a less aggressive approach with focus on quality of life).<sup>56</sup>

#### WHAT ARE THE BEST TRIAL DESIGNS FOR RISK STRATIFICATION?

It was unanimously agreed that information on risk assignment should be prospectively collected in all trials in a standard manner so that results can be compared across trials. It is also agreed that samples should be prospectively collected from large clinical trials so that GEP can be performed and GEP prognostic signatures applied. This will facilitate the creation of repositories of good quality prospectively collected material from patients who entered into clinical trials that can be retrospective analyzed to either validate or generate new prognostic markers/signatures.

In terms of trial design, there can be two general approaches. One is where risk stratified treatment is not applied and not the focus of study, but markers used for risk stratification are prospectively collected so that *post hoc* analysis looking at the impact of treatment in relation to the different risk factors can be analyzed. This is particularly important for trials involving new drugs and new combinations and will allow the assessment of how the impact of risk factors can be modified by new treatments.

The other approach is to apply risk stratification in the trial design in order to specifically answer questions on treatment within each risk group. This may be appropriate for testing different approaches to treat patients in different risk groups. For example, as the high-risk patients have poor outcome with current treatment strategies, novel treatment approaches may be tested such as the incorporation of allogeneic transplantation following reduced intensity conditioning or the incorporation of immune-based therapy for consolidation compared with current approach. On the other hand, with the identification of low-risk patients who can survive for more than 10 years, it may be appropriate to ask the questions of whether maintenance therapy is required for these patients.

#### FUTURE PERSPECTIVE

The biology of myeloma is increasingly being unraveled and will only escalate as the results of ongoing whole-genome sequencing efforts in myeloma starts to emerge.<sup>57,58</sup> The multitude of molecular abnormalities and their different combinations in different patients underlie the tremendous heterogeneity in myeloma. It would be elegant if the current risk groups can be further refined by the underlying biological heterogeneity as many of these molecular pathways may be targeted for treatment. Although this remains an important goal of ongoing research, it will remain a challenge for some years. Coupled with the clear demonstration of clonal heterogeneity in individual patients,<sup>59</sup> it is unlikely that biology-based individualized treatment can be delivered to large number of myeloma patients in the near future. Until that becomes clinically feasible on a large scale, our current proposed risk categorization provides a practical approach to defining clinically relevant heterogeneity in patients, which can be used as a framework to study issues regarding treatment

strategies. It also acts as a foundation that can be built upon and refined as biological heterogeneity become better define through current genomic initiatives.

## SUMMARY OF IMWG CONSENSUS RECOMMENDATIONS

### Recommendations for clinical practice

- (1) Combination of ISS and FISH should be used for risk stratification. This includes the following makers: Serum Beta-2 microglobulin, serum albumin, t(4;14), 17p13 and 1q21 by FISH. Using this combination, high-risk patients will survive less than 2 years despite novel agents, and low-risk patients can survive for more than 10 years (Table 3).
- (2) This risk stratification system should be adopted into clinical practice and used as the standard for comparison in all future studies looking at prognostic markers and also in clinical trials.
- (3) There is no evidence so far to suggest altering treatment based on risk groups with the exception that prolonged proteasome inhibitor-based treatment should be given to patients with t(4;14) and possibly 17p13 deletion.<sup>54</sup>

### Recommendations for clinical trials

- (1) Clinical trials testing different treatment strategies for specific risk group should be considered especially for high-risk myeloma patients who have short survival with current treatment.
- (2) Even if risk stratification is not incorporated into the trial design, factors needed for risk stratification, including samples for GEP, should be prospectively collected so that *post hoc* analysis of impact of treatment on the outcome of risk groups can be assessed. In the context of GEP, this would be important for the validation of GEP models that is required for eventual implementation.
- (3) In the design of these trials, consideration should be given to adequate sample size to adequately assess the impact of risk factors and to provide as much molecular testing as possible (including GEP when feasible) to gather the best correlative data.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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