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Risk factors and their contributions to prognosis in multiple myeloma

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Data-sharing statement

The data that support the findings of this study are available from the corresponding author upon request.

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Authorship Contributions

T.-H.C. and W.J.C. conceptualized the study; T.-H.C. and T.K.T. processed data; T.-H.C. and J.G.C. analyzed data; T.-H.C., J.G.C., W.J.C. interpreted data and wrote manuscript; W.J.C. supervised the study; and all authors approved the manuscript.

T.-H.C. and J.G.C. contributed equally to this study.

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Key Points.

1. Though IMS/IMWG high risk (HR) criteria are an important step forward, additional risk factors are required for better risk assessment of MM patients.
2. Risk factors like EMC92 can add significantly to prognostic power and help better manage HR MM patients.

Abstract

Despite improvements in clinical outcomes for multiple myeloma (MM), some patients still experience short survival, and identifying high-risk (HR) MM patients early remains a substantial challenge. In this study, we collected recently published International Myeloma Society (IMS) / International Myeloma Working Group (IMWG) recommendation and four additional risk factors of diverse nature (APOBEC mutational activity, chromothripsis, EMC92 gene expression signature, proliferation index (PR)) and examined their predictive utility on CoMMpass data. All factors were highly associated with survival even when the treatment heterogeneity in CoMMpass data was adjusted. 27% of the patients harbored the IMS/IMWG lesion, but only 21% of them were implicated uniquely by it. As a whole, 68% of the patients harbored HR lesions, 62% of them with multiple lesions. “Multi-hit" effect was profound with median survival reduced drastically while the hazard ratio (HzR) increased sharply from single to quadruple-or-more HR factor inflicted groups compared with those without any HR lesions. The concordance, *C*-statistic, of patient’s risk prediction starting from a baseline model with patient age and sex (*C*=0.63) increased slightly to *C*=0.65 with IMS/IMWG factor only but improved further to *C*=0.72 with additional HR factors. Interestingly, EMC92 turned out essential in the reliable prediction of a patient’s risk of overall survival. Most functional high risk (FHR) patients also harbored additional HR lesions although a quarter of them were free of other lesions but still had very poor outcomes. These results provide a solid rationale for expanding HR factors beyond IMS/IMWG recommendation utilizing diverse genomic technologies.

Key words: multiple myeloma, risk prediction, IMS/IMWG, EMC92, FHR

Introduction

Recent expansion in therapeutic options for MM patients has led to significant improvement in clinical outcomes, lengthening median survival approximately 3-fold over recent two decades and reducing death rate from 3.8 deaths out of 100,000 in 2002 to 2.9 deaths in 2022.[1, 2] Despite these improvements, a non-negligible group of patients still survive less than 3-4 years after diagnosis, benefitting little from therapeutic advancements and remaining as a group with unmet medical needs.

Early identification of HR patients to implement tailored therapeutic programs has emerged as an issue of pivotal urgency in MM.[3, 4] A wide spectrum of parameters have been recognized as risk factors to facilitate the determination of HR MM patients.[5] They range from clinical factors like age, β2-microglobulin (β2M) and serum albumin, the latter two forming International Staging System (ISS), to genomic factors like translocations of IgH locus including t(4;14) and t(14;16), copy number aberrations involving chromosomes 1q gain, 1p deletion, 17p deletion, and mutations of genes like TP53. Moreover, "multi-hits" of those risk factors have been found to capture HR patients.[6, 7] Recently, these have been incorporated into the IMS/IMWG definition of HR MM and validated in a large independent study.[8, 9]

With the advance of technologies, a few more genomic risk factors have been proposed.[10-14] Gene expression signatures have emerged to be strong factors. Using gene expression microarray data of transplant-eligible newly diagnosed MM (NDMM) patients enrolled in HOVON-65/GMMG-HD4 clinical trial, researchers produced a highly effective signature with 92 probe sets, EMC92, that was additionally validated in independent datasets composed of NDMM and relapsed patients.[10] Similarly, HR signatures were also derived from total therapy studies.[15, 16] Proliferation index (PR) was identified as another risk factor of MM,

with high PR correlated with 1q gain and LOF of RB1 or MAX.[12, 17] Intriguingly, however, there is little overlap in member genes, suggesting possible recruitment of diverse mechanisms while rendering MM patients HR.

Mutational signatures and a severe form of genomic rearrangement events were also indicated. The activity of APOBEC mutation signatures observed in approximately 4% of MM patients were noted as another HR factor, linked to increased mutational burden and translocation-mediated deregulation of MAF and MAFB.[14] It was further suggested to show positive correlation with disease progression from MGUS through MM and beyond.[18] Chromothripsis, an extreme event of genomic aberration resulting in a complex rearrangement of genomic segments in confined regions of one or a few chromosomes, turned out to be another risk factor in univariate and multi-variate survival analyses involving APOBEC mutational activity and gain/amplification of 1q21.[11]

Finally, though it cannot be classified exactly as a risk factor, FHR MM is an entity of a particular interest. Proposed as a clinical phenotype of suboptimal response to induction therapy or early relapse, FHR MM appeared as an indicator of HR MM[13] with a higher risk than those with standard genomic risk factors in the CoMMpass dataset.[19] However, the fact that it cannot be identified at the time of diagnosis rendered it ill-suited to the consideration as a risk factor although a way to replicate its utility with the help of measurements available at diagnosis is urgently required. The multiplicity of complementary risk factors could suggest a practical solution for it.

The proliferation of HR factors led to several important questions that need to be addressed. For instance, it is unclear if these factors are truly independent or how much they overlap with each other. It is also unclear how much they can be useful for the purpose of

predicting patient's risk of early death. The possibility that these HR factors or their combinations help to identify the FHR patients upfront is intriguing but unclear as well. Finally, in the presence of multiple risk factors, it is unclear how to construct the best performing predictive model of patient's risk with them. This prompts ramifications of further questions such as the framework with which to measure the performance of predictive models and each factor's contribution to models' performances, the optimal number and subsequent combination of risk factors that form the best performing model, etc.

In this study, we examined to what extent additional risk factors would supplement IMS/IMWG recommendation in distinguishing HR MM patients through patient survival modeling in CoMMpass dataset. Tested factors complementing IMS/IMWG recommendation encompass DNA mutational spectrum, structural variation, and RNA transcriptional activity.[20] Establishing each risk factor's efficacy in differentiating HR MM from baseline risk MM individually, we examined its improvement through two approaches. We first performed survival modeling with patient groups defined by the number of inflicting risk factors per patient. We then examined all possible combinations of risk factors exhaustively and assessed their predictive power, through which we could produce an essential set of risk factors that should be included in constructing survival models of MM. Significant survival association results were further examined with treatment heterogeneity variables to adjust impacts due to immense treatment heterogeneity in CoMMpass data.

Methods

The CoMMpass dataset

We used the CoMMpass (Relating Clinical Outcomes in MM to Personal Assessment of Genetic Profile) trial (NCT01454297) data of Multiple Myeloma Research Foundation (MMRF) in this study.[21]

IMS/IMWG HR MM

IMS/IMWG HR signatures are composed of four criteria: (1) del(17p) and/or TP53 mutation, (2) one of these translocations—t(4;14) or t(14;16) or t(14;20)—co-occurring with +1q and/or del(1p32), (3) monoallelic del(1p32) along with +1q, or biallelic del(1p32), (4) high β2M (>5.5 mg/dL) with normal creatinine (<1.2 mg/dL).[8] We reformulated the four criteria into 15 sub-criteria, and examined each of them as described in **Supplementary Methods**.

PR and EMC92 HR MM

Top 31% of the proliferative index in patients' clinical information of CoMMpass data were regarded as HR MM of PR. EMC92 signature index was estimated using signatures in **Supplementary Table 1** as outlined in Chng WJ *et al.*[22] Patients in top 35% were considered as HR MM. (**Supplementary Methods**)

APOBEC activity HR MM

We flagged 252 out of 993 patients (25.4%) as APOBEC HR MM based on the APOBEC activity of SBS2 and SBS13 obtained by applying SigProfiler[23] on CoMMpass (IA21) whole exome variant call. (**Supplementary Methods**)

Chromothripsis HR MM

We utilized ShatterSeek[11, 24-26] to infer chromothripsis from both structural variant calls and copy number variation calls. 71 out of 906 patients (7.8%) were classified as HR MM. (**Supplementary Methods**)

FHR MM

FHR MM was assigned as described in Soekojo *et al.*[19] with a slight modification: patients with suboptimal response to induction therapy or disease progressed within 18 months, a 6-month extension of progression threshold from original definition. This was intended to include both transplant eligible and non-eligible patients.[13] (**Supplementary Methods**)

"Multi-hit" and combination effects of HR factors

We grouped patients by the number of inflicting HR factors and performed Cox proportional hazard (CPH) test with the patient grouping to examine "multi-hit" effect using five HR factors. (**Supplementary Methods**)

Full potential of HR factors' predictive utility was examined through the exhaustive search of their possible combinations. Using age + sex as the baseline model, we performed multivariate CPH test by first adding each of five risk factors, then each of 2-factor combinations, 3-factor combinations, …, until the whole five factors were included, and the *C*-statistic[27, 28] of each individual survival model was obtained. (**Supplementary Methods**)

Adjustment of treatment heterogeneity

To adjust treatment heterogeneity in survival analyses using CoMMpass data, we introduced three variables, the number of therapy lines (line count), the categorical profile of lifetime drug exposure (drug profile), and prioritized induction line drug combinations (induction combo), for each patient and used them for survival analyses (line count and drug profile for OS and induction combo for PFS, respectively). (**Supplementary Methods**)

Results

Characteristics of IMS/IMWG HR MM in CoMMpass

While the IMS/IMWG criteria represent an important progress, it remains unclear how much the four criteria that were reformulated into 15 sub-criteria overlap with each other and

what are their respective contributions to prognosis. We first examined the incidence (**Supplementary Table 2**), member overlap (**Supplementary Figure 2**), and survival association (**Supplementary Table 3** and **Supplementary Figures 3-8**) of IMS/IMWG HR MM in CoMMpass data. Interestingly, criterion 1, the union of del(17p) and TP53 mutation with respective prevalences of 7.8% (90/892) and 4.8% (46/958) each in CoMMpass data, had the largest prevalence of HR MM (10.4%, 92/882), and other three criteria had similar prevalences, criteria 2 (7.8%, 70/900), 3 (7.1%, 63/892), and 4 (7.8%, 88/1,125), respectively. When combined, 29.2% (244/836) of patients were HR in IMS/IMWG (**Table 1**, **Supplementary Table 2**).

Patients satisfying multiple criteria were not frequent, and only 8.1% (64/794) of patients where all IMS/IMWG information is available or only 5.8% (66/1,143) of patients where some IMS/IMWG information is missing harbored multiple IMS/IMWG HR MM lesions (**Supplementary Figure 2**).

Interestingly, sub-criterion 2b, t(4;14) & del(1p32), exhibited the strongest association with OS (HzR=4.37, 95% confidence interval (CI)=[2.32-8.21], p=4.74×10^{-6}, C=0.515) and PFS (HzR=2.74, CI=[1.51-4.99], p=0.000939, C=0.509) in terms of HzR, followed by sub-criterion 3b, bidel(1p32), (HzR=3.22, CI=[1.76-5.89], p=0.000151, C=0.516 for OS; HzR=2.78, CI=[1.60-4.84], p=0.000281, C=0.511 for PFS, respectively), 3a, monoallelic del(1p32) & +1q, (HzR=2.82, CI=[1.88-4.22], p=4.72×10^{-7}, C=0.529 for OS; HzR=1.87, CI=[1.30-2.70], p=0.000729, C=0.515 for PFS, respectively), and 1c, del(17p) and TP53 mutation, (HzR=2.47, CI=[1.47-4.16], p=0.000627, C=0.514 for OS; HzR=1.95, CI=[1.24-3.09], p=0.00419, C=0.509 for PFS, respectively; **Supplementary Table 3** and **Supplementary Figure 8**). We confirmed the final IMS/IMWG HR criterion was highly associated with both OS (HzR=2.08, CI=[1.64-

2.63], p=1.03×10^{-9}, C=0.581, **Figure 2(a)**) and PFS (HzR=1.65, CI=[1.36-1.99], p=3.39×10^{-7}, C=0.561, **Supplementary Figure 7(b)**). Association between IMS/IMWG HR criteria and OS/PFS remained significant even when we took treatment heterogeneity in CoMMpass data into account (**Supplementary Table 4**). When patients were stratified into those who underwent autologous stem cell transplant (ASCT; 53.5%, 612/1143) and those not (Non-ASCT; 46.5%, 531/1143), final IMS/IMWG criterion was still statistically significant in both ASCT (OS: HzR=2.48, CI=[1.72-3.59], p=1.39×10^{-6}, C=0.599; PFS: HzR=1.90, CI=[1.46-2.49], p=2.46×10^{-6}, C=0.575) and Non-ASCT (OS: HzR=2.07, CI=[1.52-2.82], p=3.62×10^{-6}, C=0.587; PFS: HzR=1.52, CI=[1.15-2.00], p=0.00286, C=0.565), respectively (**Supplementary Table 3**).

Characteristics of other HR factors

The prevalences of other HR factors in CoMMpass are displayed in **Table 1**. As shown in **Methods**, 25% (252/993), 33% (266/806), 31% (187/601) of patients were assigned as HR for APOBEC, EMC92, and PR signatures, respectively. For chromothripsis, 7.8% (71/906) of patients were assigned to HR class. In comparison, 16.8% (86/512) of patients were in HR class for the clinical phenotype FHR.

When we examined the occurrence of HR cases over the ideal cohort composed of patients without any missing data in all factors, only 36.9% (182/493) carried no HR lesion while 63.1% (311/493) carried at least one HR lesion (**Figure 1**). Of patients with at least one HR lesion, as much as 56.6% (176/311) were implicated by more than one HR lesions. Numbers and percentages from all patients roughly followed the trend (**Supplementary Figure 9**). The percentage of uniquely inflicted patients for each HR lesion ranged in 16~27% with IMS/IMWG the highest percentage (26.7%) and chromothripsis the lowest percentage (16.2%), indicating that HR MM patients are frequently inflicted by multiple HR lesions. Prevalent co-existence of

multiple HR lesions on HR MM patients suggests that most HR factors may phenotypically overlap with one another, possibly due to shared biological mechanisms, potentially confounding survival analysis using them.

As expected, all HR factors were associated with survival in CoMMpass (**Table 1, Figure 2, Supplementary Table 5, Supplementary Figures 10-14**). EMC92 had the strongest impact on patient prognosis (HzR=3.23, p=2.48×10^{-22}), followed by PR (HzR=2.22, p=1.21×10^{-9}), chromothripsis (HzR=2.13, p=6.96×10^{-6}), IMS/IMWG (HzR=2.08, p=1.21×10^{-11}) with similar impact, and APOBEC (HzR=1.60, p=8.16×10^{-5}) had the lowest impact. For PFS, the order was slightly different, with EMC92 most significant (p=2.46×10^{-18}), followed by IMS/IMWG (p=2.34×10^{-9}), PR (p=6.27×10^{-8}), APOBEC (p=7.32×10^{-8}), and chromothripsis (p=8.86×10^{-5}). All factors remained significant when treatment heterogeneity was considered (**Supplementary Table 6**). In terms of univariate analysis *C*-statistic, they ordered as EMC92 (*C*=0.642, 0.600), PR (*C*=0.594, 0.567), IMS/IMWG (*C*=0.587, 0.562), APOBEC (*C*=0.542, 0.545), chromothripsis (*C*=0.541, 0.530) for both OS and PFS.

Most HR factors remained significant even when assessed separately in ASCT and non-ASCT cohorts, except for chromothripsis in ASCT for OS/PFS or APOBEC in Non-ASCT for OS (**Table 1**, **Supplementary Table 5**).

"Multi-hit" effect on patient prognosis

Patients who harbor multiple HR lesions are expected to show worse prognosis than those with fewer or no lesions. We first examined the "multi-hit" effect of HR factors for OS and indeed observed a profound impact: median survival (MS) time of 96.0, 63.5, 33.9, and 25.9 months, and HzR of 1.77 (p=0.00800), 3.19 (p=7.72x10^{-8}), 6.04 (p=9.88x10^{-16}), 6.02 (p=1.95x10^{-11}) for single-, double-, triple-, and quadruple-or-more-factor inflicted patients,

respectively, compared with those without HR lesions (**Table 2(a)** and **Figure 3(a)**). Results for PFS revealed a parallel trend in terms of MS (36.3, 26.7, 15.9, 16.9 months for 1, 2, 3, 4+ lesions group, respectively) and survival association (HzR=1.66 (p=0.000602), 2.58 (2.03×10^{-9}), 4.52 (1.24×10^{-16}), 3.67 (6.19×10^{-9}) for 1, 2, 3, 4+ lesions groups, respectively; **Supplementary Table 7**). These results remained intact for both OS and PFS when treatment heterogeneity was adjusted (**Supplementary Table 8**).

When we further subdivided single-factor inflicted patient group into individual inflicting factor groups, only EMC92 still remained significant for OS (HzR=2.82, p=0.000368) with the shortest MS (78.1 months) even with substantially reduced number of cases while other four lost significance (**Table 2(b**) and **Figure 3(b)**). For PFS, three HR factors APOBEC (MS=26.9 months, HzR=2.45, p=0.000104), chromothripsis (MS=29.2 months, HzR=2.85, p=0.0130), and EMC92 (MS=32.4 months, HzR=1.95, p=0.00319) remained significant (**Supplementary Table 7**).

Multi-factor combination and predictive capacity improvement

Finally, we assessed the utility of individual HR factors as predictors of MM patients' prognostic risks and sought to identify factors essential to achieve the best discrimination. We evaluated multivariate CPH models by adding one, two, ... up to full five individual HR factors using age + sex as the baseline model and obtained C-statistic and p-value from each model (**Figure 4** and **Supplementary Tables 9-10**). Baseline models using age alone and age + sex produced C=0.619 ($p=1.21 \times 10^{-9}$) and 0.633 ($p=1.65 \times 10^{-10}$) for OS and C=0.579 ($p=3.16 \times 10^{-6}$) and 0.585 ($p=3.10 \times 10^{-6}$) for PFS, respectively. In general, C-statistic improved when more HR factors were added, reaching the maximum with a model using all HR factors (OS: C=0.724, $p=1.55 \times 10^{-27}$; PFS: C=0.666, $p=2.54 \times 10^{-22}$). The pronounced separation of peaks and troughs

observed in the *C*-statistic and *p*-value profiles in **Figure 4** suggests the separation of HR factors that provide significant or marginal impact on the improvement of *C*-statistics and *p*-values. In particular, the prominent peaks in single- or double-factor models and the pronounced dips in three- or four-factor models strongly indicate the existence of a HR factor that provides a strong impact on the performance. Lists of HR factors involved in the top performing models of OS/PFS from single- to quadruple-factor models shown in **Table 3** indicate EMC92 integral for best performing models of CoMMpass. This suggests the existence of biological mechanisms unique to EMC92 that are not shared with other factors.

The summary of survival analysis of a minimal model composed of core factors age, sex, IMS/IMWG, and EMC92 over ideal cohort patients is described in **Table 4**. All factors were significant in OS, but sex and IMS/IMWG were not in PFS. In particular, EMC92 contributed a solid impact (OS: HzR=3.04, p=8.73x10^{-14}; PFS: HzR=2.35, p=1.69x10^{-13}) on patient survival. Results over all patients were similar (**Supplementary Table 11**) except that sex was also significant but IMS/IMWG was marginally significant for PFS. These results remained intact when treatment heterogeneity was adjusted (**Supplementary Tables 12-13**).

Stratification of clinical phenotype FHR

Stratification of clinical phenotype FHR with HR MM factors can bring a fruitful insight on the interplay between FHR and HR MM factors examined in this study, and the possibility of utilizing HR MM factors in place of FHR. In CoMMpass data where 16.8% (86/512) in complete FHR cohort, patients with missing data in HR MM factors but not in FHR phenotype, or 18.6% (71/381) in ideal cohort were of FHR phenotype, FHR indeed had significantly poorer OS (HzR=2.70, p=2.58×10^{-9}; **Supplementary Table 14**, **Supplementary Figure 17**) than baseline risk group and remained significant in ASCT (HzR=3.10, p=2.57×10^{-5}) and non-ASCT

(HzR=1.83, *p*=0.00456) cohorts as well as when treatment heterogeneity was adjusted. When stratified with HR MM factors, 74.6% (53/71) of FHR patients in ideal cohort or 72.1% (62/86) of FHR patients in complete FHR cohort harbored either individual or various combinations of HR lesions (**Supplementary Figure 18**). Unfortunately, a high percentage (25.4% (18/71) of ideal cohort or 27.9% (24/86) of complete FHR cohort) of FHR did not have any of the HR lesions. Of note, these FHR patients without any HR lesions still had very poor outcomes (**Supplementary Table 16**, **Supplementary Figure 19**).

Discussion

Prognostic systems for MM have gradually evolved over time along the advances in technology, knowledge on myeloma biology, and therapeutic options. While the R-ISS has been widely used clinically due to the simplicity and easy accessibility of component tests, there are clear inadequacies due to evolving environments. Factors like p53 mutations, 1p deletion and combinations of genetic factors including so-called “double-hit” myeloma have emerged also important. In this sense, recently published IMS/IMWG HR MM definition represents a valuable step forward.

However, as this study clearly shows, this should serve as a foundation while we continue to improve, taking advantage of developments like genomic sequencing for prognostication. Indeed, several transcriptome-based signatures have shown prognostic capacity in numerous studies despite limited presence in this study. Moreover, prospective risk factors can bring about an unanticipated change of myeloma management. For instance, phenotypes based on liquid biopsy techniques like circulating tumor cells/DNA or on whole-body (WB) MRI can open a new era of a continuous non-invasive risk monitoring and dynamic response paradigm, a

monumental shift from a current static risk stratification and pre-determined therapeutic intervention course strategy once the association to patient prognosis is established.[29-31] In this sense, efforts to examine other risk factors in relation to IMS/IMWG criteria like this study is crucial in refining non-redundant factors for patient prognostication since patients frequently harbor multiple HR factors, and the main prognostic impact seems to be delivered through the "multi-hit" effect. When isolated, individual HR factors do not seem to bear a significant impact on patient survival, except for particular ones like EMC92, which may be crucial in constructing high performing prognostic models.

All of these have several significant implications. If we stick to only IMS/IMWG factor, ~4% of all patients where IMS/IMWG factor exists in isolation may be identified as HR MM despite outcomes similar to standard risk myeloma while missing out many true HR MM (**Figures 1** and **3**). Considering standard risk MM patients' superb outcome with quadruplet treatments today, this could be an important consideration if we are to subject HR MM patients to alternative treatments that may be more toxic or novel. In complementing IMS/IMWG HR platform, risk factors like EMC92 where a commercial assay (SKY92) is available can be convenient for a routine practice. The combination of IMS/IMWG with EMC92 will reduce the identification of HR patients with outcomes similar to baseline risk patients (**Supplementary Table 17** and **Supplementary Figure 20**). The IMS/IMWG recommendation already alluded to the need to incorporate sequencing in clinical prognostication tools. Unfortunately, there is currently no standardized NGS panel for clinical use although efforts are currently ongoing.

FHR MM has received significant interest in recent years as this group of patients undergo very poor outcome even with current therapeutic settings. Our study confirms that this group bears a significant priority to identify clinically. While adding additional HR factors will

reduce the number of patients uniquely inflicted with FHR alone, this still retains the highest percentage (25%) among all the HR factors studied (**Supplementary Figure 18**). Not only that this patient group is difficult to identify early but also they exhibited prognosis worse than those with one or two HR lesions (**Supplementary Table 16**, **Supplementary Figure 19**). A recent study addressing the issue of predicting the treatment response using WB MRI is particularly intriguing in the perspective of elucidating the FHR MM cases unaccounted for with the help of HR factors included in this study.[32] Fortunately, only ~5% of patients were single-hit FHR patients (24/512 in complete FHR cohort or 18/381 in ideal cohort), which is consistent with a recent publication claiming that FHR is rather infrequent.[33]

One important caveat of describing FHR MM in an observational cohort such as CoMMpass is that we do not have full information on the treatment compliance of the participating patients. This can obscure the real cause of patients' early progression if it is due to the non-compliant haphazard adherence to the treatment program or to the underlying biology despite strict compliance. However, if the early progression is dominantly due to poor treatment compliance rather than MM biology, it is unlikely that they have such poor overall survival despite subsequent therapies.

The current criterion in the IMW/IMWG HR classification that designates patients with high level β2M and normal level creatinine as HR MM deserves some consideration. According to our analysis, patients stratified using two-parameter combinations of β2M and creatinine such as normal β2M-normal creatinine (NBNC), normal β2M-high creatinine (NBHC), high β2M-normal creatinine (HBNC), high β2M-high creatinine (HBHC) has distinct survival risks in a descending order of prognostic risk as follows: HBHC (HR=3.08, CI=[2.44-3.89], p=4.6×10^{-21}), HBNC (HR=2.53, CI=[1.77-3.62], p=3.91×10^{-7}), NBHC (HR=1.72, CI=[1.28-2.32],

p=0.000341) for OS compared to NBNC, respectively (**Auxiliary Table 4** and **Auxiliary Figure 3** in **Supplementary Results**). The intention of this criterion in IMS/IMWG recommendation is to include a factor reflecting tumor burden, not confounded by renal function. However, our analysis shows that HBHC is much worse than HBNC in OS and encompasses a larger fraction of patients (21.6%, 221/1108) than HBNC (7.9%, 88/1108) in CoMMpass (IA21) (**Auxiliary Table 3** in **Supplementary Results**). It is worthwhile to assess this criterion in more datasets.

Conclusion

In this study, we examined five genomics-based risk factors including newly defined IMS/IMWG HR criteria on the CoMMpass dataset and investigated the possibility of utilizing them in predicting MM patient's prognostic risk. We noticed that only 37% of NDMM patients were free of any HR lesions, and similar 36% already harbored two or more HR lesions, putting them in a greater risk than the baseline risk group. As such, supplying additional risk factors could improve the performance of patient's risk prediction. In particular, the addition of factors like EMC92 that added most substantially to patient's prognosis and is already available through a commercial platform to the IMS/IMWG criteria could be strongly advised. We also found phenotypes like FHR MM that does very poorly could be mostly covered with risk factors albeit a fraction of them, about a quarter for the case of FHR MM in CoMMpass data for instance, could not be identified by any of the factors unfortunately.

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Tables

Table 1. Proportions of baseline and HR cases of each HR factor and univariate survival analysis *p*-values and *C*-statistics of HR factors. Results over all patients as well as ASCT and non-ASCT cohorts are shown together.

Factor	Baseline[1]	HR[1]	Overall	ASCT	Non-ASCT
IMS/IMWG	592 (70.8%) 280 (73.5%)	244 (29.2%) 101 (26.5%)	$P_{OS}=1.03\times10^{-9}$ (C=0.581) $P_{PFS}=3.39\times10^{-7}$ (C=0.561)	$P_{OS}=1.39\times10^{-6}$ (C=0.599) $P_{PFS}=2.46\times10^{-6}$ (C=0.575)	$P_{OS}=3.62\times10^{-6}$ (C=0.587) $P_{PFS}=0.00286$ (C=0.565)
APOBEC	741 (74.6%) 292 (76.6%)	252 (25.4%) 89 (23.4%)	$P_{OS}=8.16\times10^{-5}$ (C=0.542) $P_{PFS}=7.32\times10^{-8}$ (C=0.545)	$P_{OS}=6.81\times10^{-5}$ (C=0.58) $P_{PFS}=1.36\times10^{-7}$ (C=0.566)	$P_{OS}=0.0582$ (C=0.524) $P_{PFS}=0.00787$ (C=0.534)
Chromothripsis	835 (92.2%) 354 (92.9%)	71 (7.8%) 27 (7.1%)	$P_{OS}=6.96\times10^{-6}$ (C=0.541) $P_{PFS}=8.86\times10^{-5}$ (C=0.53)	$P_{OS}=0.126$ (C=0.519) $P_{PFS}=0.0975$ (C=0.513)	$P_{OS}=0.00058$ (C=0.546) $P_{PFS}=0.00135$ (C=0.542)
EMC92	540 (67%) 245 (64.3%)	266 (33%) 136 (35.7%)	$P_{OS}= 2.48\times10^{-22}$ (C=0.642) $P_{PFS}=2.46\times10^{-18}$ (C=0.6)	$P_{OS}=3.97\times10^{-16}$ (C=0.693) $P_{PFS}=3.02\times10^{-12}$ (C=0.615)	$P_{OS}=8.41\times10^{-9}$ (C=0.619) $P_{PFS}=3.77\times10^{-8}$ (C=0.593)
PR	414 (68.9%) 260 (68.2%)	187 (31.1%) 121 (31.8%)	$P_{OS}=1.21\times10^{-9}$ (C=0.594) $P_{PFS}=6.27\times10^{-8}$ (C=0.567)	$P_{OS}=2.66\times10^{-7}$ (C=0.624) $P_{PFS}=8.74\times10^{-5}$ (C=0.575)	$P_{OS}=0.000202$ (C=0.579) $P_{PFS}=9.76\times10^{-5}$ (C=0.561)

[1]Numbers on top represent patient counts and percentages over all patients. Numbers at bottom represent patient counts and percentages over the ideal cohort (381 patients without any missing data on all HR factors).

Table 2. "Multi-hit" effect of HR factors in the ideal cohort of CoMMpass for OS. (a) CPH test results over patient groupings by the number of implicating HR factors. (b) The same results with (a) except for the detailed stratification of count = 1 cases into specific implicating HR factors. HzR = hazard ratio. CI = 95% confidence interval.

(a)

Factor	Median Survival (mth)	HzR [CI]	P-value
Count=0	-	-	-
Count=1	**96.0 [86.6-∞]**	**1.77 [1.16-2.70]**	**0.00800**
Count=2	**63.5 [47.4-∞]**	**3.19 [2.09-4.87]**	**7.72×10^{-8}**
Count=3	**33.9 [25.7-58.7]**	**6.04 [3.89-9.36]**	**9.88×10^{-16}**
Count≥4	**25.9 [17.4-63.0]**	**6.02 [3.56-10.17]**	**1.95×10^{-11}**
Log-rank test	$P=1.29\times10^{-21}$ (C=0.676)		

(b)

Factor		Median Survival (mth)	HzR [CI]	P-value
Count=0		-	-	-
Count=1	APOBEC	- [58.4-∞]	1.60 [0.77-3.30]	0.206
	Chromothripsis	80.9 [13.3-∞]	2.52 [0.78-8.15]	0.124
	EMC92	**78.1 [46.0-∞]**	**2.82 [1.59-4.98]**	**0.000368**
	IMS/IMWG	96.0 [85.0-∞]	1.42 [0.71-2.84]	0.325
	PR	- [78.5-∞]	1.25 [0.61-2.59]	0.539
Count=2		**63.5 [47.4-∞]**	**3.19 [2.09-4.87]**	**7.68×10^{-8}**
Count=3		**33.9 [25.7-58.7]**	**6.04 [3.89-9.37]**	**9.75×10^{-16}**
Count≥4		**25.9 [17.4-63.0]**	**6.02 [3.56-10.17]**	**1.94×10^{-11}**
Log-rank test		$P=6.46\times10^{-20}$ (C=0.682)		

Table 3. Participating HR MM factors and *C*-statistics of best performing survival models when grouped by the number of HR MM factors for OS and PFS.

N	Top (OS)
1	**EMC92** (*C*=0.710)
2	**EMC92**|PR (*C*=0.715)
3	**EMC92**|IMS/IMWG |PR (*C*=0.720)
4	Chromothripsis|**EMC92**|IMS/IMWG|PR (*C*=0.723)
N	**Top (PFS)**
1	**EMC92** (*C*=0.648)
2	APOBEC|**EMC92** (*C*=0.658)
3	APOBEC|Chromothripsis|**EMC92** (*C*=0.662)
4	APOBEC|Chromothripsis|**EMC92**|PR (*C*=0.665)

Table 4. Summary of multivariate CPH test results using core factors age, sex, EMC92, and IMS/IMWG factor over ideal cohort patients of CoMMpass data.

Factor	OS		PFS	
	HzR [CI]	*P*	HzR [CI]	*P*
Age	**1.04 [1.03-1.06]**	**2.88×10^{-8}**	**1.03 [1.01-1.04]**	**7.04×10^{-6}**
Sex	**0.70 [0.52-0.94]**	**0.0192**	0.84 [0.67-1.05]	0.123
EMC92	**3.04 [2.27-4.07]**	**8.73×10^{-14}**	**2.35 [1.87-2.95]**	**1.69×10^{-13}**
IMS/IMWG	**1.41 [1.05-1.90]**	**0.0234**	1.21 [0.95-1.54]	0.131
Log-rank	$P=7.35\times10^{-27}$ (C=0.715)		$P=1.27\times10^{-19}$ (C=0.652)	

Figure Legends

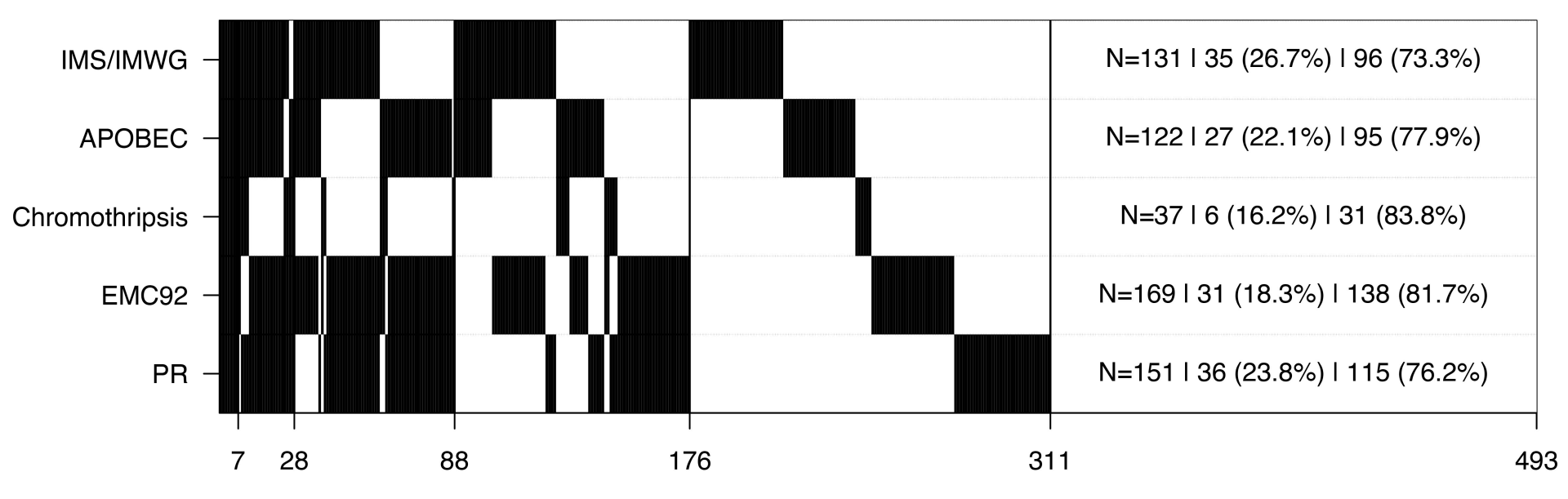
Figure 1. Overlap of HR factors in CoMMpass data. Patients arranged along the horizontal axis are ordered according to the number of inflicting HR factors in a descending order, and HR factors are arranged along the vertical axis. HR MM patients are marked in black, and baseline risk patients are left in white. Patients from 1 to 311 harbored at least one inflicting HR lesion while the rest 182 patients did not harbor any inflicting HR lesions. For each HR factor, total number of HR MM patients, the number (percentage) of HR MM patients inflicted by the HR factor alone, and the number (percentage) of HR MM patients inflicted by the HR factor and additional ones are indicated.

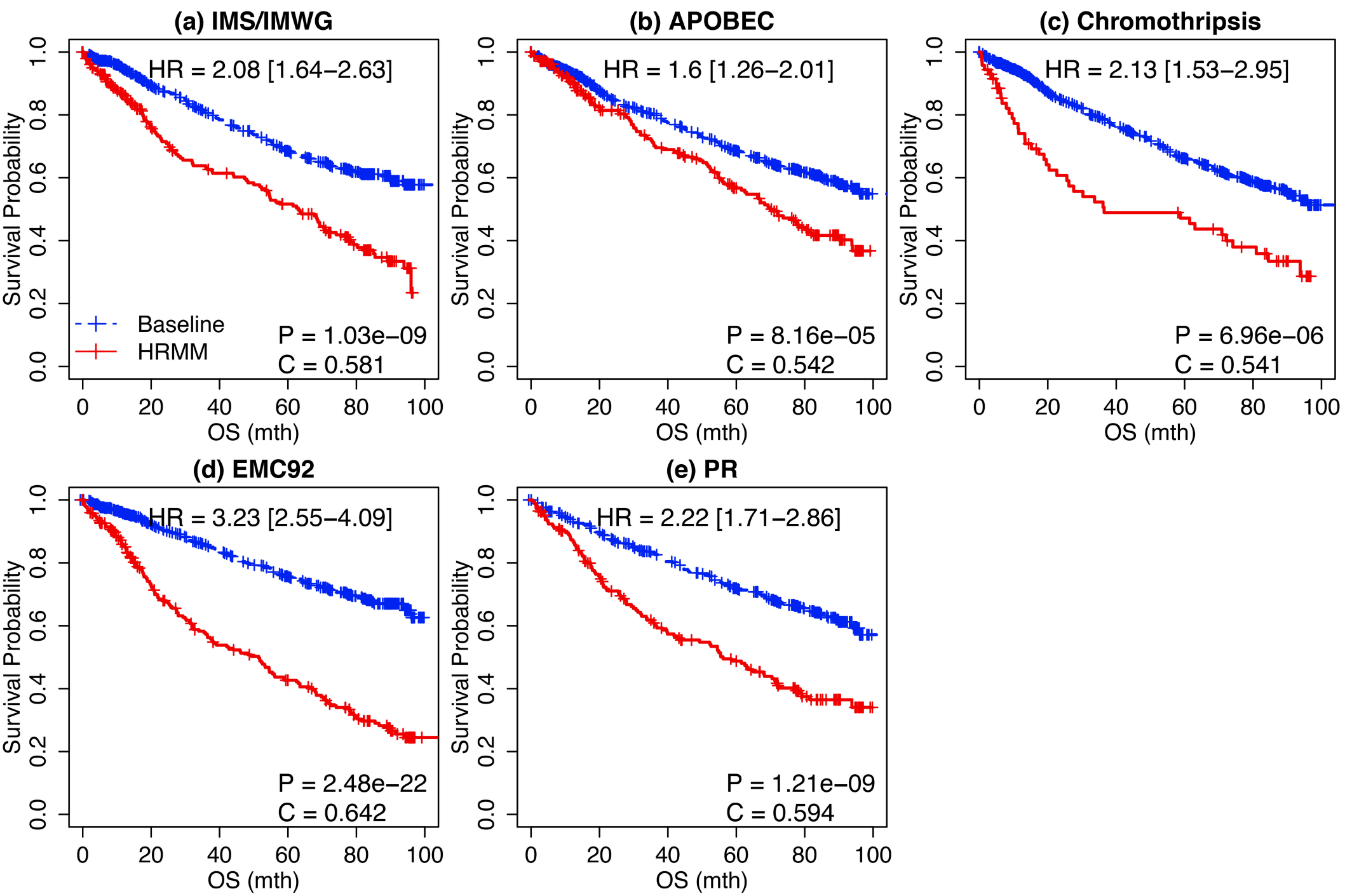
Figure 2. Survival curves of HR factors. Survival curves of (a) IMW/IMWG, (b) APOBEC, (c) Chromothripsis, (d) EMC92, (e) PR factors are shown. CPH test result and *C*-statistic of each factor are shown at the top and the bottom, respectively. For each HR factor, the blue curve indicates the survival of baseline risk group while the red curve indicates that of HR group, respectively.

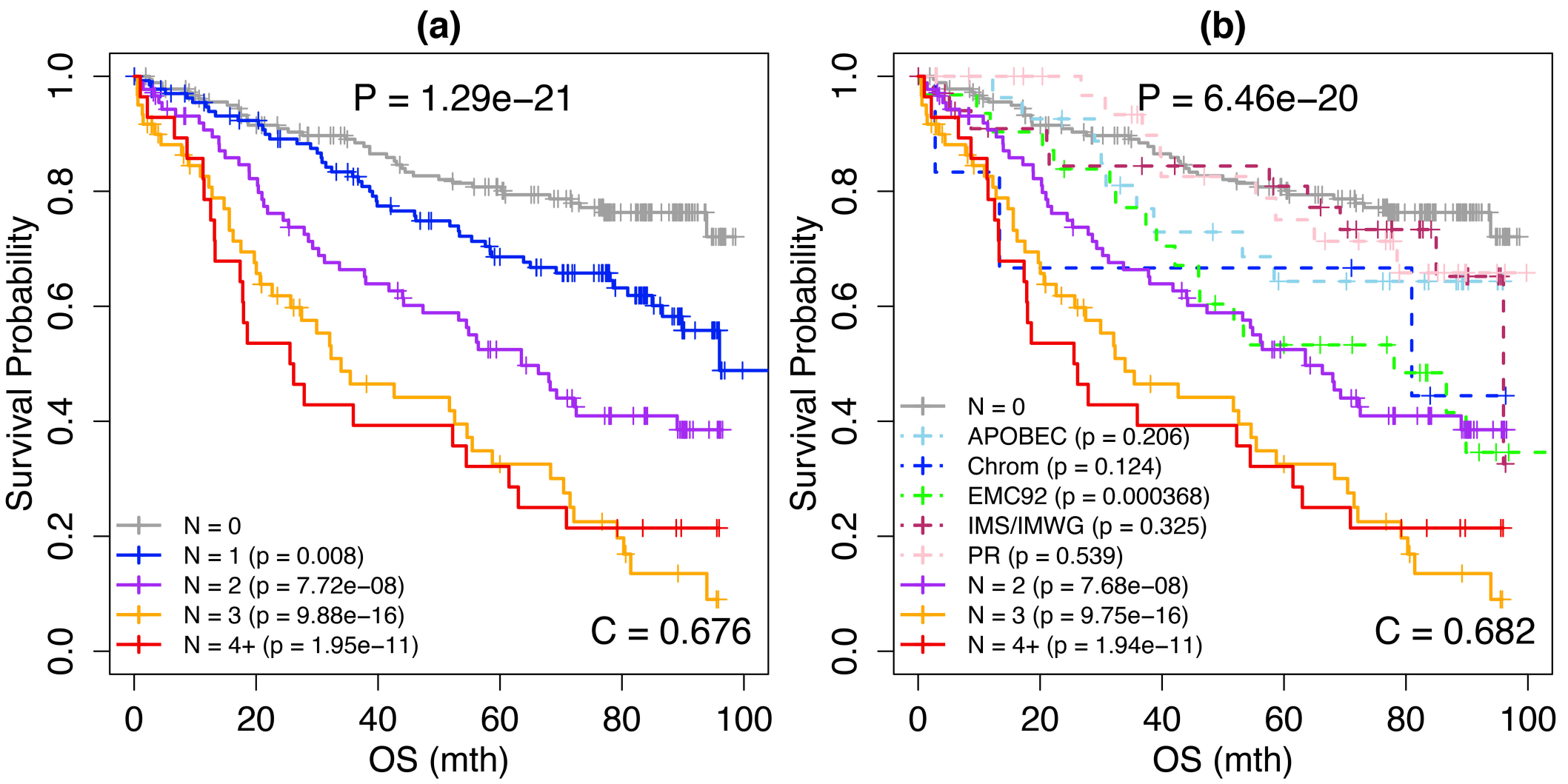
Figure 3. Multi-hit effect of HR factors. (a) Survival curves of patients grouped by the number of implicating HR lesions for OS are shown. (b) The survival curve of single HR lesion group in (a) was further stratified into groups of respective implicating HR factors for OS. Only EMC92 remained significant after the stratification.

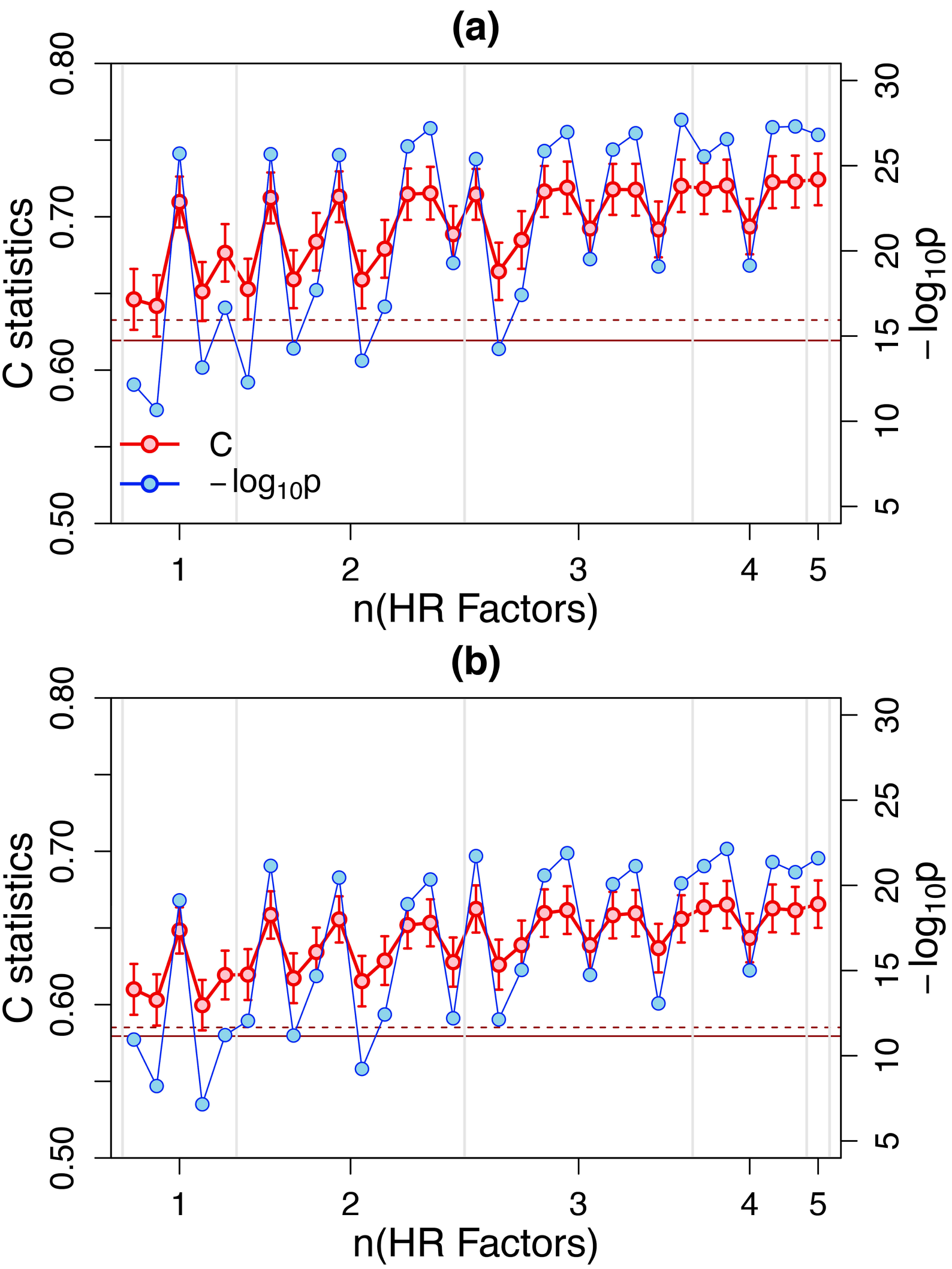
Figure 4. Combination effect of HR factors. *C*-statistic and *p*-value profiles of survival models for exhaustive combinations of HR factors for (a) OS and (b) PFS. Starting from each of HR factors, 2, 3, …, full factor combinations were separately added besides the baseline model (age + sex), and *C*-statistic and *p*-value were retrieved from each survival model. Horizontal full and

broken lines indicate *C*-statistics from the survival model of age alone and age + sex, respectively.


IMS/IMWG
APOBEC
Chromothripsis
EMC92
PR
N=131 I 35 (26.7%) I 96 (73.3%)
N=122 I 27 (22.1%) I 95 (77.9%)
N=37 I 6 (16.2%) I 31 (83.8%)
N=169 I 31 (18.3%) I 138 (81.7%)
N=151 I 36 (23.8%) I 115 (76.2%)
7
28
88
176
311
493


(a) IMS/IMWG
HR = 2.08 [1.64–2.63]
Baseline
HRMM
P = 1.03e−09
C = 0.581
(b) APOBEC
HR = 1.6 [1.26–2.01]
P = 8.16e−05
C = 0.542
(c) Chromothripsis
HR = 2.13 [1.53–2.95]
P = 6.96e−06
C = 0.541
(d) EMC92
HR = 3.23 [2.55–4.09]
P = 2.48e−22
C = 0.642
(e) PR
HR = 2.22 [1.71–2.86]
P = 1.21e−09
C = 0.594
Survival Probability
0.0
0.2
0.4
0.6
0.8
1.0
0
20
40
60
80
100
OS (mth)


(a)
P = 1.29e−21
Survival Probability
1.0
0.8
0.6
0.4
0.2
0.0
N = 0
N = 1 (p = 0.008)
N = 2 (p = 7.72e−08)
N = 3 (p = 9.88e−16)
N = 4+ (p = 1.95e−11)
C = 0.676
0
20
40
60
80
100
OS (mth)
(b)
P = 6.46e−20
Survival Probability
1.0
0.8
0.6
0.4
0.2
0.0
N = 0
APOBEC (p = 0.206)
Chrom (p = 0.124)
EMC92 (p = 0.000368)
IMS/IMWG (p = 0.325)
PR (p = 0.539)
N = 2 (p = 7.68e−08)
N = 3 (p = 9.75e−16)
N = 4+ (p = 1.94e−11)
C = 0.682
0
20
40
60
80
100
OS (mth)


(a)
C statistics
0.50
0.60
0.70
0.80
C
$-\log_{10}p$
1
2
3
4
5
n(HR Factors)
$-\log_{10}p$
5
10
15
20
25
30
(b)
C statistics
0.50
0.60
0.70
0.80
1
2
3
4
5
n(HR Factors)
$-\log_{10}p$
5
10
15
20
25
30

SUPPLEMENTARY INFORMATION

Supplementary Results

Survival association of high β2M and high creatinine (HBHC) patients

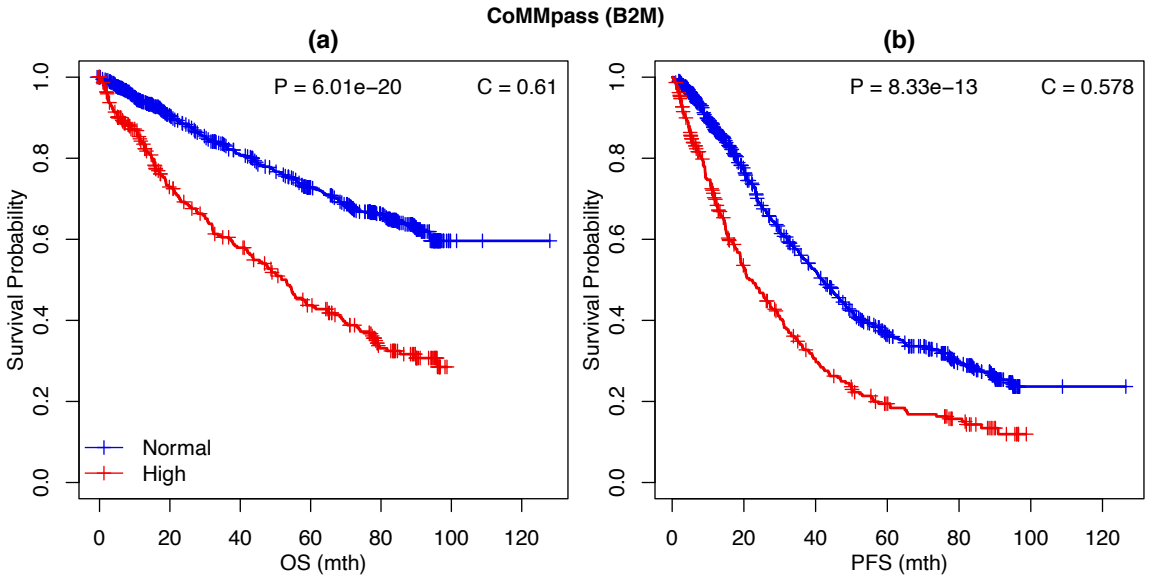
Criterion 4 of IMS/IMWG recommendation decides MM patients with high β2M and normal creatinine (HBNC), representing patients with high tumor burden, as HRMM. This makes the effect of interaction between β2M and creatinine on MM patients' survival an interesting question. Here, we briefly describe the results of the interaction on CoMMpass data (IA21).

β2M in CoMMpass data

Summary of serum β2M concentration status in CoMMpass data is provided in **Auxiliary Table 1**. Of 1,113 patients with β2M record, 802 (72.1%) and 311 (27.9%) were in normal and high concentration state respectively while 30 (2.6%, out of 1,143) did not have relevant information. In univariate survival analysis, patients with high β2M were significantly riskier than those with normal β2M (OS: HzR=2.57, CI=[2.1-3.15], p=6.01×10^{-20}, C=0.61; PFS: HzR=1.81, CI=[1.54-2.14], p=8.33×10^{-13}, C=0.58) as shown in **Auxiliary Figure 1**.

Normal	High	Total	Missing	N
802 (72.1%)	311 (27.9%)	1,113 (100%)	30 (2.6%)	1,143

Auxiliary Table 1. Summary statistics of β2M status.



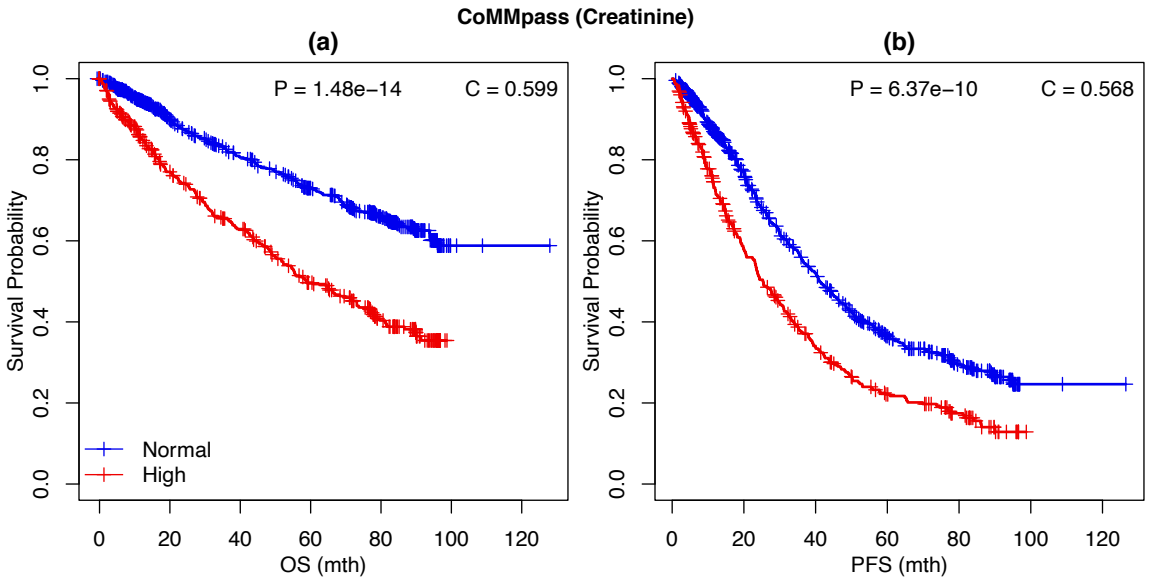
Auxiliary Figure 1. Survival curves of high and normal β2m patient groups.

Creatinine in CoMMpass data

Summary of serum creatinine concentration status in CoMMpass data is provided in **Auxiliary Table 2**. Of 1,138 patients with creatinine record, 753 (66.2%) and 385 (33.8%) were in normal and high concentration state respectively while 5 (0.4%, out of 1,143) did not have relevant information. In univariate survival analysis, patients with high creatinine were significantly riskier than those with normal creatinine (OS: HR=2.17, CI=[1.78-2.65], p=1.48×10^{-14}, C=0.6; PFS: HR=1.63, CI=[1.4-1.9], p=6.37×10^{-10}, C=0.57) as shown in **Auxiliary Figure 2**.

Normal	High	Total	Missing	N
753 (66.2%)	385 (33.8%)	1,138 (100%)	5 (0.4%)	1,143

Auxiliary Table 2. Summary statistics of creatinine status.



Auxiliary Figure 2. Survival curves of high and normal creatinine patient groups.

β2M × creatinine in CoMMpass data

Summary statistics of serum β2M concentration and serum creatinine concentration cross-tabulation in CoMMpass data are shown in **Auxiliary Table 3**. Of the 1,108 patients with both β2M and creatinine information available, 649 (58.4%) and 221 (21.6%) patients were in normal β2M-normal creatinine (NBNC) and high β2M-high creatinine (HBHC) states, respectively, while 150 (12%) and 88 (7.9%) patients were in normal β2M-high creatinine (NBHC) and high β2M-normal creatinine (HBNC) states, respectively. During this, we had to ignore 35 patients due to missing information in either β2M or creatinine, or both information unfortunately.

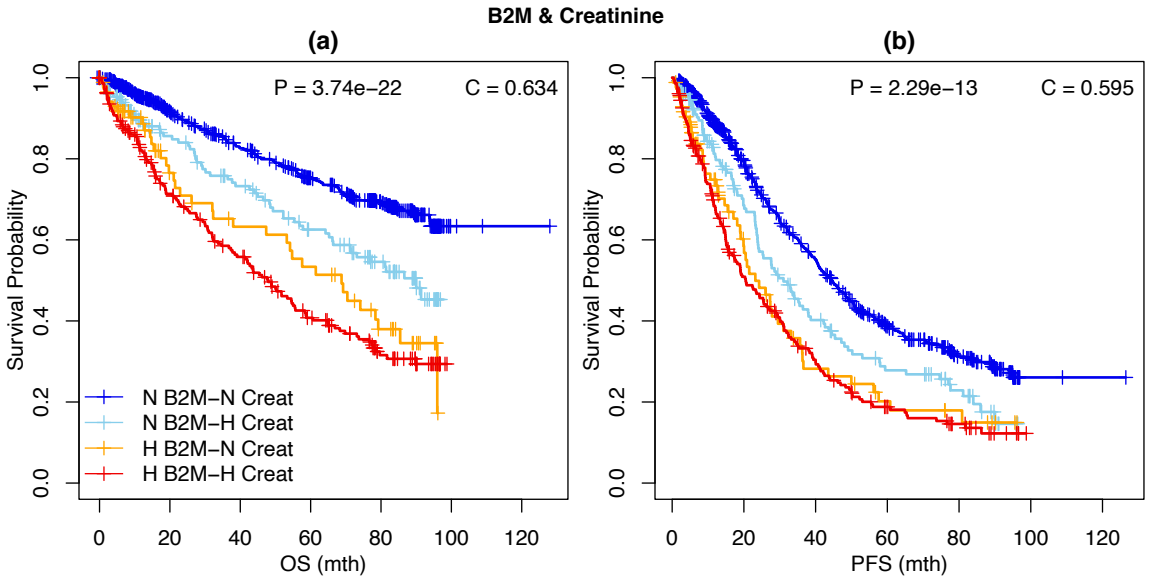
		Creatinine		N
		Normal	**High**	
β2M	**Normal**	**649 (58.4%)**	**150 (12%)**	**799 (72.1%)**
	High	**88 (7.9%)**	**221 (21.6%)**	**309 (27.9%)**
N		**737 (66.5%)**	**371 (33.5%)**	**1,108 (100%)**

Auxiliary Table 3. Cross-tabulation of serum β2m and creatinine concentration states in CoMMpass data.

Survival analysis results of combined β2M-creatinine groups are shown in **Auxiliary Table 4** and **Auxiliary Figure 3** with NBNC group as the baseline risk group. NBHC, HBNC, HBHC groups were all significantly riskier than the NBNC group for both OS and PFS. More importantly, HBHC group was much riskier than HBNC group, HR MM group in IMS/IMWG criterion 4 for OS though they mostly overlap for PFS in survival curves shown in **Auxiliary Figure 3**. Interestingly, high β2M produced more noticeable impact on patient survival than high creatinine as is easily noticed from the clear separation of survival curves of HB•• vs NB•• groups than the mixture of survival curves corresponding to ••HC vs ••NC groups in **Auxiliary Figure 3**. We cannot ignore creatinine completely, though, considering the clear separation of survival curves due to high and low creatinine groups in high β2M group (HBHC vs HBNC) or in low β2M group (NBHC vs NBNC).

Group	OS		PFS	
	HR [CI]	P	HR [CI]	P
NBNC	-	-	-	-
NBHC	1.72 [1.28-2.32]	P=0.000341	1.41 [1.13-1.77]	P=0.00275
HBNC	2.53 [1.77-3.62]	$P=3.91\times10^{-7}$	1.84 [1.37-2.46]	$P=4.63\times10^{-5}$
HBHC	3.08 [2.44-3.89]	$P=4.6\times10^{-21}$	2 [1.66-2.41]	$P=3.55\times10^{-13}$
Log-rank	$P=3.74\times10^{-22}$ (C=0.634)		$P=2.29\times10^{-13}$ (C=0.595)	

Auxiliary Table 4. Summary of survival analyses of combined b2M-creatinine groups.



Auxiliary Figure 3. Survival curves of combined b2M-creatinine patient groups.

Consideration of treatment heterogeneity of CoMMpass data and adjustment of survival analyses of risk factors.

Therapy line counts

All patients in CoMMpass cohort underwent multiple lines of therapy with a variety of drug combinations for each therapy line. The number of therapy lines a patient experienced that ranged from single to 6 rounds (**Auxiliary Table 5**) itself was associated with OS by itself (HzR=1.08, CI=[1.01-1.16], p=0.0172; **Auxiliary Table 6**). Interestingly, HzR > 1 for the number of therapy lines, which means that the more a patient experienced therapy lines, the riskier the patient was and the shorter the patient's OS. In this sense, the number of therapy lines a patient experienced in CoMMpass data indicates how resistant the patient was to treatments in general and hence reflects the patient's risk of early death.

Line	1	2	3	4	5	6
N	649 (57.7%)	240 (21%)	117 (10.2%)	62 (5.4%)	28 (2.4%)	37 (3.2%)

Auxiliary Table 5. Summary statistics of the number of therapy lines a patient experienced in CoMMpass (IA21).

Therapy line drug combination and lifetime drug exposure variables

The number of therapy lines is too brief to faithfully reflect the immense heterogeneity of treatment spectrum in CoMMpass data. To compensate for this, we introduced two new variables, drug combination regimen classes of induction therapy (line 1 drug combo) and lifetime drug exposure profile (drug profile). (See **Supplementary Methods** for details.) After discarding regimen classes utilized less than 20 times during the induction therapy (IMID/Alk/Glu-triplet, PI/IMID/Alk-triplet, PI/IMID-doublet, PI/Alk-doublet, Other), we retained the following 5 classes: Quadruplet (PI/IMID/Alk/Glu; 21.8%, 242/1,110), PI/IMID/Glue-triplet (39.5%, 439/1,110), PI/Alk/Glu-triplet (23.1%, 256/1,110), PI/Glu-doublet (9.8%, 109/1,110), IMID/Glu-doublet (5.8%, 64/1,110). When used for survival analysis of PFS, different drug combination regimens were found to exhibit different efficacy as expected (**Auxiliary Table 6**). Compared with IMID/Glu-doublet group patients, those in quadruplet or PI/IMID/Glu-triplet class exhibited much subdued risk of disease progression indicating much delayed time to disease progression although those in PI/Alk/Glu-triplet or in PI/Glu-doublet classes exhibited similar risk indicating no difference in time to disease progression.

Group	Prevalence	PFS		
		HR	CI	P
Quadruplet	**242 (21.8%)**	**0.56**	**0.39-0.80**	**0.00145**
PI/IMID/Glu-triplet	**439 (39.5%)**	**0.64**	**0.47-0.88**	**0.00533**
PI/Alk/Glu-triplet	256 (23.1%)	0.90	0.65-1.25	0.545
PI/Glu-doublet	109 (9.8%)	1.14	0.80-1.64	0.472
IMID/Glu-doublet	64 (5.8%)	-	-	-
PI/IMID/Alk-triplet	4			
IMID/Alk/Glu-triplet	6			
PI/IMID-doublet	5			
PI/Alk-doublet	5			
Other	13			

Auxiliary Table 6. Prevalence and PFS survival analysis results for line 1 drug combo variable. Drug combo groups with the size < 20 were shaded off and removed from the survival analysis. The percentages in the prevalence column were calculated using groups with the size ≥ 20 only. In the PFS survival analysis, IMS-doublet group was used as the baseline.

Compared with the simple configuration for line 1 drug combo variable, drug profile variable projected a more complicated picture with 23 different lifetime drug exposure profiles as a whole, which was reduced to only 11 profiles after removing those with size < 20 (**Auxiliary Table 7**). We used the remaining 11 ones for survival analysis of OS. We found that they had different efficacy on OS as expected. For instance, patients treated with only one PI class drugs along the course of treatment history showed comparable OS with those treated with only one IMID class drugs, but most other patients who experienced drugs of heterogeneous classes exhibited subdued risk of earlier death compared to those treated with only one IMID class drugs except for two profiles PI(1)-IMID(2) and PI(2)-IMID(2). The reason for this unexpected behavior for the two profiles seemed to require more elaborate analysis, which was beyond the scope of this study.

Group	Prevalence	OS		
		HR	CI	P
IMID(1)	44 (4.0%)	-	-	-
PI(1)	168 (15.4%)	1.45	0.90-2.32	0.126
PI(1)-IMID(1)	**491 (44.9%)**	**0.32**	**0.20-0.50**	**7.14×10^{-7}**
PI(1)-IMID(1)-Dara	**36 (3.3%)**	**0.33**	**0.17-0.65**	**0.00136**
PI(1)-IMID(2)	37 (3.4%)	0.81	0.45-1.45	0.468
PI(1)-IMID(2)-Dara	**46 (4.2%)**	**0.14**	**0.06-0.31**	**1.64×10^{-6}**
PI(2)-IMID(1)	**91 (8.3%)**	**0.43**	**0.25-0.72**	**0.00140**
PI(2)-IMID(1)-Dara	**24 (2.2%)**	**0.41**	**0.20-0.85**	**0.0158**
PI(2)-IMID(2)	47 (4.3%)	0.89	0.52-1.53	0.680
PI(2)-IMID(2)-Dara	**83 (7.6%)**	**0.46**	**0.27-0.76**	**0.00262**
PI(3)-IMID(2)-Dara	**27 (2.5%)**	**0.34**	**0.16-0.69**	**0.00317**
IMID(1)-Dara	2			
PI(1)- Dara	5			
PI(1)-IMID(3)	2			

PI(1)-IMID(3)-Dara	2	
PI(2)	8	
PI(2)-Dara	2	
PI(2)-IMID(3)	3	
PI(2)-IMID(3)-Dara	5	
PI(3)-IMID)1)	6	
PI(3)-IMID(1)-Dara	3	
PI(3)-IMID(2)	7	
PI(3)-IMID(3)-Dara	4	

Auxiliary Table 7. Prevalence and OS survival analysis results for drug profile variable. Drug profile groups with the size < 20 were shaded off and removed from the survival analysis. The percentages in the prevalence column were calculated using groups with the size ≥ 20 only. In the survival analysis, PI(0)-IMID(1) group was used as the baseline.

Supplementary Methods

The CoMMpass dataset

CoMMpass trial releases cumulative collections of whole genome/exome sequencing, copy number and structural variation, and RNA-seq data of 1,143 patient pool regularly as different versions on an ad hoc basis. Interchangeable utilization of diverse versions enabled us to exploit information discontinued or only available at earlier/later times, enriching the repertoire of possible analysis and patient characterization.

IMS/IMWG HR MM

We took the definition of IMS/IMWG new genetic HR signatures summarized in Avet-Loisau, *et al.*(7). It is composed of four criteria: (1) del(17p) and/or TP53 mutation, (2) one of these translocations—t(4;14) or t(14;16) or t(14;20)—co-occurring with +1q and/or del(1p32), (3) monoallelic del(1p32) along with +1q, or biallelic del(1p32), (4) high β2M (>5.5 mg/dL) with normal creatinine (<1.2 mg/dL). These four cryptic criteria were unfolded into the following 15 sub-criteria: (1a) del(17p), (1b) TP53 mutation, (1c) del(17p) & TP53 mutation, (2a) t(4;14) & +1q, (2b) t(4;14) & del(1p32), (2c) t(4;14) & (+1q or del(1p32)), (2d) t(14;16) & +1q, (2e) t(14;16) & del(1p32), (2f) t(14;16) & (+1q or del(1p32)), (2g) t(14;20) & +1q, (2h) t(14;20) & del(1p32), (2i) t(14;20) & (+1q or del(1p32)), (3a) monoallelic del(1p32) & +1q, (3b) bidel(1p32), (4) high β2M with normal creatinine. For this signature, we used CoMMpass (IA13a) where IgH translocation partner information (MMSET/WHSC1/NSD2 or FGFR3 for t(4;14), MAF for t(14;16), MAFB for t(14;20), and MAFA) was provided specifically (file "MMRF_CoMMpass_IA13a_RNAseq_Canonical_Ig_Translocations.txt.gz"). For the copy number variation (CNV) calls for +1q, del(1p32), del(17p), we followed the steps outlined in Soekojo, *et al.*(17). Briefly, after determining segment-wise CNV status by applying CNV level cutoffs chosen by analyzing segments' average levels, we decided CNV status of a specific chromosomal region if a specific CNV covered more than half of the region. For the TP53 mutation, we only considered non-synonymous mutations. We supplemented the absence of specific information on high β2M level in CoMMpass data with the equivalent information ISS stage III. Finally, we considered patients who met any of the eight sub-criteria ((1a-c), (2a-b), (3a-b), (4)) as HR MM. Sub-criteria (2c), (2e-i) were excluded since too little patients were stratified as HR MM group, and their

association with patient survival could not be examined faithfully. Sub-criterion (2d) was excluded since it was not associated with patient survival in univariate analysis. (**Supplementary Table 3**)

PR and EMC92 HR MM

PR signature was taken from the proliferative index of CoMMpass data. In this study, we took patients in top 31% of it as HR MM. (Please refer to the section **Determination of cutoff value** below.)

EMC92 signature was originally defined using 92 probe sets of HG-U133 Plus 2 platform microarray. We first mapped these probe sets to gene symbols or NCBI GenBank id using platform's own annotation, and they were mapped to Ensembl gene id (Ensembl version 111). Interestingly, 92 original probe sets were collapsed into 91 gene symbols/GenBank ids, and one of the GenBank ids could not be mapped. Remaining 90 Ensembl gene ids were used to construct the EMC92 signature (**Supplementary Table 1**). The estimation of EMC92 signature index was executed as outlined in Chng WJ, *et al.*(20). In actual computing, we put +1/-1 instead of positive/negative weights. Finally, patients in top 35% EMC92 signature index were considered as HR MM. (Please refer to the section **Determination of cutoff value** below.)

APOBEC activity HR MM

We ran SigProfiler(21) tool of COSMIC database on CoMMpass (IA21) whole exome variant call files constructed from accumulated variant calls ("MMRF_CoMMpass_IA21_combined_vcfmerger2_All_Canonical_Variants.tsv") of 993 NDMM patients to obtain activity levels of 86 single-base substitution (SBS) signatures.(22) The APOBEC activity is estimated as the sum of two SBS signatures, SBS2 and SBS13.(16) We flagged 252 out of 993 patients (25.4%) as APOBEC HR MM. (Please refer to **Determination of cutoff value** section below.)

Determination of HR thresholds for PR, EMC92, and APOBEC signatures

Contrary to genetic or genomic risk factors that are inherently discrete valued entities, PR, EMC92, and APOBEC signatures are continuous valued entities, and threshold values to delineate HR MM and baseline risk group (Baseline) patients should be introduced. To determine optimal threshold values for them, we designed a small scale simulation study for each of them where the threshold value was reduced like 90, 89, 88, …, 51, 50 percentiles of each of them, and survival analysis was performed between upper percentile simulated HR MM group and lower percentile

simulated Baseline group at each threshold value. (For the case of APOBEC signature, however, threshold simulation range could not be reduced all the way down to 50 percentile since there was a limit below which no APOBEC activity was observed. In this case, the simulation was conducted within the limited range naturally.)

Respective adequacy of a threshold value was assessed by examining the survival analysis *p*-value and *C*-statistics together. The survival test *p*-value represents the degree of survival trend separation between HRMM and Baseline groups while the *C*-statistics represents the predictive utility of the HR MM-Baseline group separation. Specifically, *C*-statistics is the probability where, for any choice of a pair of patients one from HR MM and the other from Baseline, the patient from HR MM experienced outcome while the patient from Baseline did not. Since our purpose of considering diverse risk factors is to utilize them for modeling patients' prognosis in the end, we put more emphasis on *C*-statistics in deciding the optimal thresholds for PR, EMC92, and APOBEC signatures unless the survival difference between HR MM and Baseline is severely compromised.

Simulation survey results are shown in **Supplementary Figure 1** where results of PR in (a), (b), EMC92 in (c), (d), and APOBEC in (e), (f) are gathered. Interestingly, survey results of PR and EMC92 signatures exhibit similar patterns for both L_p (= $-log_{10} p$) and *C*-statistics. For instance, L_p that started high at the top threshold (90 percentile) was reduced as a whole when we lowered the threshold parameter down to 50 percentile, revealing an intermediate local peak in between. To the contrary, however, *C*-statistics that started low at the top threshold was increased and then decreased as we lowered the threshold down to 50 percentile, leaving an intermediate global peak in between. (L_p profile for APOBEC was rather opposite to the other two. It rose steadily as the threshold parameter was lowered from 90 percentile, which was also the case with *C*-statistics profile.) Interestingly, the threshold where the intermediate local peak of L_p appeared coincided with the threshold where the intermediate global peak of *C*-statistics appeared for all three risk factors. This threshold where the L_p peak and *C*-statistics peak appeared simultaneously was 69 percentile for PR, 67 percentile for EMC92, and 75 percentile for APOBEC, respectively.

Chromothripsis HR MM

While some studies had relied on copy number signatures alone(9, 22, 23), we utilized ShatterSeek(24) algorithm to infer chromothripsis from both structural variant calls ("MMRF_CoMMpass_IA21_genome_manta.tsv") and genome-wide copy number variation calls ("MMRF_CoMMpass_IA21_genome_ichorCNA.seg"). We followed the criteria recommended by

the official ShatterSeek tutorial to call high confidence chromothripsis.(25) A *p*-value threshold of 0.05 was used to determine the significance of all statistical tests, namely the fragment joins test, chromosomal enrichment of breakpoints test, and random distribution of breakpoints test. 71 (7.8%) out of 906 patients who carried high confidence chromothripsis events in at least one chromosome were classified as HR MM.

Adjustment of treatment heterogeneity

All patients in CoMMpass study were actively treated with diverse combinations regimens, and the immense treatment heterogeneity of CoMMpass data demands proper adjustment of it in survival modeling. We introduced three variables. We first selected the number of therapy lines each patient had to undergo (**line count**) as an indirect signature for treatment heterogeneity since the more lines of therapy a patient had to experience, the worse the patient responded to therapies and hence prognosis the patient might present.

Then, based on treatment regimens recorded in CoMMpass data and knowledge of main drug classes commonly prescribed to MM patients, we produced the following 12 drug combination regimen classes where combinations of four main drug classes, proteasome inhibitors (PI: bortezomib, carfilzomib, ixazomib), immunomodulatory drugs (IMID: thalidomide, lenalidomide, pomalidomide), alkylating agents (Alk: cyclophosphamide, melphalan), and glucocorticoids (Glu: prednisone, dexamethasone) were categorically classified as (1) Quadruplet regimen ([PI]-[IMID]-[Alk]-[Glu]), (2) PI-IMID-Alkylator triplet regimen ([PI]-[IMID]-[Alk]), (3) PI-IMID-Glucocorticoid triplet regimen ([PI]-[IMID]-[Glu]), (4) PI-Alkylator-Glucocorticoid triplet regimen ([PI]-[Alk]-[Glu]), (5) IMID-Alkylator-Glucocorticoid triplet regimen ([IMID]-[Alk]-[Glu]), (6) PI-IMID doublet regimen ([PI]-[IMID]), (7) PI-Alkylator doublet regimen ([PI]-[Alk]), (8) IMID-Alkylator doublet regimen ([PI]-[Alk]), (9) PI-Glucocorticoid doublet regimen ([PI]-[Glu]), (10) IMID-Glucocorticoid doublet regimen ([IMID]-[Glu]), (11) Alkylator-Glucocorticoid doublet regimen ([Alk]-[Glu]) and (12) Other. Here, a drug class enclosed by square brackets indicates one or sporadically two different drugs of the specified drug class (for instance "bortezomib" or "carfilzomib" or "bortezomib/carfilzomib" as [PI] and "thalidomide" or "lenalidomide" or "lenalidomide/pomalidomide" for [IMID], etc). Moreover, drug combination regimens could contain additional supportive agents that do not belong to any of the main drug classes. (For instance, PI-IMID-Alkylator triplet regimen can include regimens like "bortezomib-lenalidomide-dexamethasone" as well as "bortezomib-lenalidomide-dexamethasone-doxorubicin" or

"bortezomib-carfilzomib-lenalidomide-dexamethasone"). Also note that the last "Other" class is a heterogeneous class incorporating all singlet regimens of main drug classes ([PI], [IMID], [Alk], [Glu]) as well as combinations of miscellaneous drugs. Finally, treatments using multiple drug combination regimens in induction therapy were resolved by prioritizing classes along the order they are presented here and utilized in the analysis of PFS (**line 1 drug combo**).

For the case of OS, however, utilizing drug combination regimen classes was impractical since 42.3% (454/1,143) of patients underwent multiple lines of therapy (maximum up to 6 lines of therapy), and resolving the heterogeneity of a patient's lifetime treatment history by the simple prioritization scheme could be overly simplistic. Instead, we produced each patient's drug exposure profile over the course treatment history (**drug profile**) where numbers of different drugs each patient was exposed to between the PI and IMID classes plus the utilization of daratumumab over the course of treatment history were symbolically annotated like "PI(2)-IMID(1)-Dara" which means the patient was exposed to 2 PI agents, 1 IMID agent, and daratumumab possibly with other supportive agents over the course of treatment history.

In survival modeling of this study, we used line count and drug profile for OS and line 1 drug combo for PFS. For variables drug profile and line 1 drug combo, groups with less than 20 records were discarded.

Multi-hit effect of HR factors

Establishing each HR factor's survival association individually, we assessed the "multi-hit" effect of HR factors. We divided patients by the number of implicating HR factors and performed Cox's proportional hazard (CPH) test with the patient grouping. We first tried this using four criteria of IMS/IMWG recommendation only and then expanded to pools of HR factors. All six HR factors were used for OS but five HR factors omitting FHR were used for PFS to avoid confounding effects. To ensure enough members and events for each factor-count group, patients implicated by 2 or more factors were pooled together in IMS/IMWG recommendation investigation and 4 or more factors in full HR factors investigation. Then, in full factors investigation, the singly implicated patient group was further split into individual HR factor groups, and resultant patient groupings were subjected to CPH test again. In all CPH test, the patient group without any implicating factor was used as Baseline.

Combination effect of HR factors

Full potential of HR factors' predictive utility was finally examined using the framework of multivariate CPH test through exhaustive search of their possible combinations. Using age + sex as the baseline model, we added each of six risk factors, then each of 2-factor combinations, 3-factor combinations, …, until the whole six factors were included besides it in the modeling, and the *C*-statistics of each individual survival model was computed.

For this study, we used 'survival' package (version 3.8-3) and R system (version 4.4.2).

Supplementary Tables

Supplementary Table 1. Mapping of EMC92 probe ids.

Symbol	ENSG	WEIGHT	PROBE
-	ENSG00000157168	-0.0493	208232_x_at
ACVR2A	ENSG00000121989	-0.0778	228416_at
AIMP1	ENSG00000164022	0.087	202542_s_at
AK2	ENSG00000004455	0.0113	208967_s_at
ANGEL2	ENSG00000174606	0.02	221826_at
ARL8B	ENSG00000134108	0.0008	217852_s_at
ARPC5	ENSG00000162704	0.0303	211963_s_at
ATP6V0E1	ENSG00000113732	-0.0349	214150_x_at
ATPBD4	ENSG00000134146	0.049	238662_at
BCS1L	ENSG00000074582	0.0746	207618_s_at
BIRC5	ENSG00000089685	0.0175	210334_x_at
C11orf85	ENSG00000168070	0.0093	231210_at
C15orf38	ENSG00000242498	-0.0423	217548_at
C18orf10	ENSG00000134779	0.0384	212055_at
C1S	ENSG00000182326	-0.0874	208747_s_at
CCRL1	ENSG00000129048	0.042	220351_at
CDH22	ENSG00000149654	-0.0342	215181_at
CENPE	ENSG00000138778	0.0087	205046_at
DARS2	ENSG00000117593	0.0035	218365_s_at
DHFR	ENSG00000228716	-0.0006	202532_s_at
DHRS9	ENSG00000073737	-0.052	224009_x_at
DNAJB9	ENSG00000128590	-0.0626	202842_s_at
DONSON	ENSG00000159147	0.0126	221677_s_at
DTL	ENSG00000143476	0.0205	222680_s_at
DUX4	ENSG00000260596	-0.0576	216473_x_at
DYNLRB2	ENSG00000168589	0.0661	238116_at
EHBP1L1	ENSG00000173442	0.0396	221755_at
ESPL1	ENSG00000135476	0.0423	38158_at
EST/BE568408	--	0.0407	243018_at
EST/BX647543	ENSG00000120457	-0.0529	238780_s_at
FAM49A	ENSG00000197872	-0.0561	209683_at
FANCF	ENSG00000183161	0.0278	222713_s_at
FANCI	ENSG00000140525	-0.0106	213007_at
FGFR3	ENSG00000068078	0.0594	204379_s_at
FTL	ENSG00000087086	-0.0164	212788_x_at

GABRA4	ENSG00000109158	0.0446	233437_at
GGPS1	ENSG00000152904	0.0129	202322_s_at
GRB14	ENSG00000115290	0.0477	206204_at
HMGB3	ENSG00000029993	0.075	225601_at
HMGN5	ENSG00000198157	0.0208	221606_s_at
HNRNPK	ENSG00000165119	0.0163	200775_s_at
IL7R	ENSG00000168685	-0.0644	226218_at
ITGA6	ENSG00000091409	-0.0768	215177_s_at
ITM2B	ENSG00000136156	-0.0252	217732_s_at
KIF4A	ENSG00000090889	0.0116	218355_at
LBR	ENSG00000143815	0.0067	201795_at
LOC100271836	ENSG00000180747	0.073	231989_s_at
LTBP1	ENSG00000049323	-0.1105	202728_s_at
MAGEA6	ENSG00000197172	0.0496	214612_x_at
MARCKS	ENSG00000277443	-0.0418	213002_at
MCM2	ENSG00000073111	0.0225	202107_s_at
MCM3	ENSG00000112118	-0.0052	201555_at
MCM6	ENSG00000076003	-0.009	201930_at
MRPL41	ENSG00000182154	-0.033	230034_x_at
NCAPG	ENSG00000109805	-0.0176	218662_s_at
NCUBE1	ENSG00000198833	-0.0041	217824_at
NOP56	ENSG00000101361	0.0437	200875_s_at
NPC2	ENSG00000119655	-0.021	200701_at
NUF2	ENSG00000143228	-0.007	223381_at
PCDHB7	ENSG00000113212	0.0686	231738_at
PFKL	ENSG00000141959	0.0349	201102_s_at
PGM2	ENSG00000169299	0.014	225366_at
POLQ	ENSG00000051341	-0.0097	219510_at
PPP2R1B	ENSG00000137713	0.0714	202884_s_at
RAB2A	ENSG00000104388	-0.0618	208732_at
ROBO3	ENSG00000154134	0.0559	219550_at
RPS11	ENSG00000142534	0.0056	213350_at
RPS28	ENSG00000233927	-0.0334	208904_s_at
RPS4X	ENSG00000198034	-0.0323	200933_x_at
S100A6	ENSG00000197956	0.0773	217728_at
SAR1B	ENSG00000152700	-0.0345	226742_at
SEC62	ENSG00000008952	-0.0997	208942_s_at
SEPT11	ENSG00000138758	0.0165	201307_at
SFMBT1	ENSG00000163935	-0.1088	239054_at
SLC17A5	ENSG00000119899	-0.052	221041_s_at
SLC30A7	ENSG00000162695	-0.0319	226217_at

SPAG5	ENSG00000076382	-0.0002	203145_at
SPATS2L	ENSG00000196141	0.0154	222154_s_at
ST13	ENSG00000100380	-0.039	208667_s_at
STAT1	ENSG00000115415	0.0525	AFFX-HUMISGF3A/M97935_MA_at
GET4/SUN1	ENSG00000239857	0.0556	223811_s_at
SYF2	ENSG00000117614	0.0054	202553_s_at
TARBP1	ENSG00000059588	0.0548	202813_at
TMEM97	ENSG00000109084	0.053	212282_at
TOP2A	ENSG00000131747	-0.0372	201292_at
TRAM1	ENSG00000067167	-0.0254	201398_s_at
TSPAN16	ENSG00000130167	-0.0585	242180_at
TUBB	ENSG00000196230	0.0238	209026_x_at|211714_x_at
ZBTB25	ENSG00000089775	0.0861	214482_at
ZNF252	ENSG00000196922	-0.0184	233399_x_at
ZWINT	ENSG00000122952	0.0046	204026_s_at

Supplementary Table 2. IMS/IMWG HR MM in CoMMpass data.

IMS/IMWG consensus recommendation is composed of four criteria that can be reconstructed into 15 sub-criteria: (1a) del(17p), (1b) TP53 mutation, (1c) del(17p) & TP53 mutation, (2a) t(4;14) & +1q, (2b) t(4;14) & del(1p32), (2c) t(4;14) & (+1q or del(1p32)), (2d) t(14;16) & +1q, (2e) t(14;16) & del(1p32), (2f) t(14;16) & (+1q or del(1p32)), (2g) t(14;20) & +1q, (2h) t(14;20) & del(1p32), (2i) t(14;20) & (+1q or del(1p32)), (3a) monoallelic del(1p32) & +1q, (3b) bidel(1p32), (4) high β2M with normal creatinine. Final IMS/IMWG HR MM group is patients who have any lesions of the following eight sub-criteria: (1a), (1b), (1c), (2a), (2b), (3a), (3b), (4). Sub-criteria omitted from the final risk assessment were either insufficient HR MM group (<1% of patient pool) or insignificant association with survival.

Criterion	Sub-criterion	Negative[1]	Positive[1]	Total	Missing[2]	N
1	(1a) del(17p)	822 (92.2)	70 (7.8)	892	-	892
	(1a) ⋂ ASCT[4]	442 (91.9)	39 (8.1)	481	-	481
	(1a) ⋂ Non-ASCT[5]	380 (92.5)	31 (7.5)	411	-	411
	(1b) TP53 mutation	912 (95.2)	46 (4.8)	958	-	958
	(1b) ⋂ ASCT[4]	485 (93.6)	33 (6.4)	518	-	518
	(1b) ⋂ Non-ASCT[5]	427 (97)	13 (3)	440	-	440
	(1c)[3] = (1a) ⋂ (1b)	944 (97.5)	24 (2.5)	968	2 (0.2)	970
	(1c) ⋂ ASCT[4]	507 (96.9)	16 (3.1)	523	-	523
	(1c) ⋂ Non-ASCT[5]	437 (98.2)	8 (1.8)	445	2 (0.4)	447
	(1) = (1a) ⋃ (1b) ⋃ (1c)	790 (89.6)	92 (10.4)	882	88 (9.1)	970
	(1) ⋂ ASCT[4]	420 (88.2)	56 (11.8)	476	47 (9)	523
	(2) ⋂ Non-ASCT[5]	370 (91.1)	36 (8.9)	406	41 (9.2)	447
2	(A) t(4;14)	685 (86.2)	110 (13.8)	795	-	795
	(B) t(14;16)	757 (95.2)	38 (4.8)	795	-	795
	(C) t(14;20)	785 (98.7)	10 (1.3)	795	-	795
	(D) gain(1q)	619 (69.4)	273 (30.6)	892	-	892
	(E) del(1p32)	774 (86.8)	118 (13.2)	892	-	892
	(2a) = (A) ⋂ (D)	883 (95.5)	42 (4.5)	925	72 (7.2)	997
	(2a) ⋂ ASCT[4]	473 (94.6)	27 (5.4)	500	35 (6.5)	535
	(2a) ⋂ Non-ASCT[5]	410 (96.5)	15 (3.5)	425	37 (8)	462
	(2b) = (A) ⋂ (E)	940 (98.5)	14 (1.5)	954	43 (4.3)	997
	(2b) ⋂ ASCT[4]	504 (98.2)	9 (1.8)	513	22 (4.1)	535
	(2b) ⋂ Non-ASCT[5]	436 (98.9)	5 (1.1)	441	21 (4.5)	462
	(2c) = (A) ⋂ (D) ⋂ (E)	963 (99.1)	9 (0.9)	972	25 (2.5)	997
	(2c) ⋂ ASCT[4]	518 (98.9)	6 (1.1)	524	11 (2.1)	535
	(2c) ⋂ Non-ASCT[5]	445 (99.3)	3 (0.7)	448	14 (3)	462
	(2d) = (B) ⋂ (D)	918 (98.3)	16 (1.7)	934	63 (6.3)	997

	(2d) ⋂ ASCT[4]	493 (98.2)	9 (1.8)	502	33 (6.2)	535
	(2d) ⋂ Non-ASCT[5]	425 (98.4)	7 (1.6)	432	30 (6.5)	462
	(2e) = (B) ⋂ (E)	958 (99.5)	5 (0.5)	963	34 (3.4)	997
	(2e) ⋂ ASCT[4]	512 (99.4)	3 (0.6)	515	20 (3.7)	535
	(2e) ⋂ Non-ASCT[5]	446 (99.6)	2 (0.4)	448	14 (3)	462
	(2f) = (B) ⋂ (D) ⋂ (E)	979 (99.8)	2 (0.2)	981	16 (1.6)	997
	(2f) ⋂ ASCT[4]	525 (99.8)	1 (0.2)	526	9 (1.7)	535
	(2f) ⋂ Non-ASCT[5]	454 (99.8)	1 (0.2)	455	7 (1.5)	462
	(2g) = (C) ⋂ (D)	934 (99.3)	7 (0.7)	941	56 (5.6)	997
	(2g) ⋂ ASCT[4]	505 (99.6)	2 (0.4)	507	28 (5.2)	535
	(2g) ⋂ Non-ASCT[5]	429 (98.8)	5 (1.2)	434	28 (6.1)	462
	(2h) = (C) ⋂ (E)	968 (99.8)	2 (0.2)	970	27 (2.7)	997
	(2h) ⋂ ASCT[4]	520 (100)	0 (0)	520	15 (2.8)	535
	(2h) ⋂ Non-ASCT[5]	448 (99.6)	2 (0.4)	450	12 (2.6)	462
	(2i) = (C) ⋂ (D) ⋂ (E)	986 (99.8)	2 (0.2)	988	9 (0.9)	997
	(2i) ⋂ ASCT[4]	531 (100)	0 (0)	531	4 (0.7)	535
	(2i) ⋂ Non-ASCT[5]	455 (99.6)	2 (0.4)	457	5 (1.1)	462
	(2)[6]	830 (92.2)	70 (7.8)	900	97 (9.7)	997
	(2) ⋂ ASCT[4]	444 (91.7)	40 (8.3)	484	51 (9.5)	535
	(2) ⋂ Non-ASCT[5]	386 (92.8)	30 (7.2)	416	46 (11)	462
3	(F) mono del(1p32)	794 (89)	98 (11)	892	-	892
	(3a) = (D) ⋂ (F)	849 (95.2)	43 (4.8)	892	-	892
	(3a) ⋂ ASCT[4]	463 (96.3)	18 (3.7)	481	-	481
	(3a) ⋂ Non-ASCT[5]	386 (93.9)	25 (6.1)	411	-	411
	(3b) bidel(1p32)	872 (97.8)	20 (2.2)	892	-	892
	(3b) ⋂ ASCT[4]	471 (97.9)	10 (2.1)	481	-	481
	(3b) ⋂ Non-ASCT[5]	401 (97.6)	10 (2.4)	411	-	411
	(3) = (3a) ⋃ (3b)	829 (92.9)	63 (7.1)	892	-	892
	(3) ⋂ ASCT[4]	453 (94.2)	28 (5.8)	481	-	481
	(3) ⋂ Non-ASCT[5]	376 (91.5)	35 (8.5)	411	-	411
4	(G) ISS = 3	802 (72.1)	311 (27.9)	1,113	30 (2.6)	1,143
	(H) Creatinine ≤ 106.08	385 (33.8)	753(66.2)	1,138	5 (0.4)	1,143
	(4) = (G) ⋂ (H)	1,037 (92.2)	88 (7.8)	1,125	18 (1.6)	1,143
	(4) ⋂ ASCT[4]	561 (93)	42 (7)	603	9 (1.5)	612
	(4) ⋂ Non-ASCT[5]	476 (91.2)	46 (8.8)	522	9 (1.7)	531
Final	(5)[7]	592 (70.8)	244 (29.2)	836	307 (26.9)	1,143
	(5) ⋂ ASCT[4]	318 (70.8)	131 (29.2)	449	163 (26.6)	612
	(5) ⋂ Non-ASCT[5]	274 (70.8)	113 (29.2)	387	144 (27.1)	531

[1]Numbers in parentheses represent percentages over "Total" (= "Positive" + "Negative"). [2]Numbers in parentheses represent percentages over "N". [3]Results over all patients with information on (1) del(17p) or (2) TP53 mutation. [4]Results over patients who underwent autologous stem cell transplant (ASCT). [5]Results over patients who did not undergo ASCT. [6](2)=(2a)⋃(2b)⋃(2c)⋃(2d)⋃(2e)⋃(2f)⋃(2g)⋃(2h)⋃(2i). [7](5)=(1a)⋃(1b)⋃(1c)⋃(2a)⋃(2b)⋃(3a)⋃(3b)⋃(4).

Supplementary Table 3. Univariate survival association results of IMS/IMWG criteria.

Univariate CPH survival test results of IMS/IMWG HR MM in CoMMpass data. Of six sub-categories of criterion 2, only those in which at least 1% of patients were in HR MM group (2a, 2b, 2d) were examined. Results over all patients as well as ASCT and non-ASCT cohorts are shown together. Criteria whose multiple comparison adjusted *p*-values ≤ 0.05 are marked in boldface. Multiple comparison adjustment was performed using Bonferroni's method as adjusted *p*-value = min(1, 10×*p*-value).

Criterion		Patient group	OS[1]	PFS[1]
1	1a	**Overall**	**HzR=1.75 [1.23-2.50], *p*=0.00204 (0.0204), *C*=0.523**	HzR=1.31 [0.96-1.80], *p*=0.0865 (0.865), *C*=0.515
		ASCT	**HzR=2.36 [1.41-3.93], *p*=0.00106 (0.0106), *C*=0.541**	HzR=1.61 [1.06-2.46], *p*=0.0264 (0.264), *C*=0.523
		Non-ASCT	HzR=1.49 [0.90-2.45], *p*=0.118 (1), *C*=0.518	HzR=1.10 [0.69-1.75], *p*=0.696 (1), *C*=0.513
	1b	**Overall**	**HzR=1.89 [1.28-2.81], *p*=0.00155 (0.0155), *C*=0.516**	HzR=1.45 [1.03-2.05], *p*=0.0325 (0.325), *C*=0.508
		ASCT	**HzR=2.96 [1.79-4.88], *p*=2.16×10^{-5} (0.000216), *C*=0.543**	HzR=1.82 [1.20-2.77], *p*=0.00524 (0.0524), *C*=0.521
		Non-ASCT	HzR=1.69 [0.87-3.30], *p*=0.124 (1), *C*=0.509	HzR=1.42 [0.78-2.60], *p*=0.253 (1), *C*=0.505
	1c	**Overall**	**HzR=2.47 [1.47-4.16], *p*=0.000627 (0.00627), *C*=0.514**	**HzR=1.95 [1.24-3.09], *p*=0.00419 (0.0419), *C*=0.509**
		ASCT	**HzR=3.45 [1.69-7.08], *p*=0.000705 (0.00705), *C*=0.526**	**HzR=2.49 [1.36-4.57], *p*=0.00315 (0.0315), *C*=0.514**
		Non-ASCT	HzR=2.29 [1.08-4.88], *p*=0.0312 (0.312), *C*=0.51	HzR=1.78 [0.88-3.59], *p*=0.11 (1), *C*=0.507
2	2a	**Overall**	**HzR=1.89 [1.26-2.85], *p*=0.00224 (0.0224), *C*=0.516**	**HzR=1.76 [1.24-2.51], *p*=0.0016 (0.016), *C*=0.512**
		ASCT	HzR=1.79 [0.99-3.24], *p*=0.0553 (0.553), *C*=0.517	HzR=1.81 [1.15-2.86], *p*=0.0105 (0.105), *C*=0.516
		Non-ASCT	**HzR=2.89 [1.64-5.09], *p*=0.000241 (0.00241), *C*=0.52**	**HzR=2.41 [1.37-4.24], *p*=0.00218 (0.0218), *C*=0.513**
	2b	**Overall**	**HzR=4.37 [2.32-8.21], *p*=4.74×10^{-6} (4.74×10^{-5}), *C*=0.515**	**HzR=2.74 [1.51-4.99], *p*=0.000939 (0.00939), *C*=0.509**
		ASCT	**HzR=4.41 [1.80-10.79], *p*=0.00115 (0.0115), *C*=0.517**	HzR=2.35 [1.05-5.29], *p*=0.0382 (0.382), *C*=0.508

		Non-ASCT	**HzR=9.51 [3.81-23.7], p=1.43×10^{-6} (1.43×10^{-5}), C=0.516**	**HzR=5.98 [2.42-14.8], p=0.000104 (0.00104), C=0.511**
	2d	Overall	HzR=1.21 [0.50-2.92], p=0.675 (1), C=0.502	HzR=1.53 [0.82-2.86], p=0.185 (1), C=0.502
		ASCT	HzR=1.51 [0.48-4.75], p=0.48 (1), C=0.504	HzR=1.72 [0.76-3.87], p=0.191 (1), C=0.503
		Non-ASCT	HzR=1.30 [0.32-5.26], p=0.712 (1), C=0.502	HzR=1.72 [0.64-4.63], p=0.284 (1), C=0.504
3	3a	**Overall**	**HzR=2.82 [1.88-4.22], p=4.72×10^{-7} (4.72×10^{-6}), C=0.529**	**HzR=1.87 [1.30-2.70], p=0.000729 (0.00729), C=0.515**
		ASCT	**HzR=4.83 [2.59-9.00], p=7.05×10^{-7} (7.05×10^{-6}), C=0.541**	**HzR=2.49 [1.45-4.28], p=0.000918 (0.00918), C=0.519**
		Non-ASCT	HzR=1.66 [0.98-2.81], p=0.0612 (0.612), C=0.516	HzR=1.29 [0.79-2.11], p=0.314 (1), C=0.508
	3b	**Overall**	**HzR=3.22 [1.76-5.89], p=0.000151 (0.00151), C=0.516**	**HzR=2.78 [1.60-4.84], p=0.000281 (0.00281), C=0.511**
		ASCT	HzR=2.57 [0.95-7.00], p=0.0643 (0.643), C=0.511	HzR=2.44 [1.08-5.49], p=0.0312 (0.312), C=0.508
		Non-ASCT	**HzR=5.13 [2.37-11.07], p=3.19×10^{-5} (0.000319), C=0.521**	**HzR=4.20 [1.96-8.99], p=0.000222 (0.00222), C=0.517**
4		**Overall**	**HzR=1.69 [1.20-2.38], p=0.00251 (0.0251), C=0.517**	HzR=1.48 [1.11-1.96], p=0.00718 (0.0718), C=0.516
		ASCT	HzR=1.54 [0.87-2.71], p=0.137 (1), C=0.51	HzR=1.48 [0.98-2.25], p=0.063 (0.63), C=0.514
		Non-ASCT	HzR=1.76 [1.15-2.69], p=0.00867 (0.0867), C=0.521	HzR=1.48 [1.00-2.18], p=0.0481 (0.481), C=0.52
Final		**Overall**	**HzR=2.08 [1.64-2.63], p=1.03×10^{-9} (1.03×10^{-8}), C=0.581**	**HzR=1.65 [1.36-1.99], p=3.39×10^{-7} (3.39×10^{-6}), C=0.561**
		ASCT	**HzR=2.48 [1.72-3.59], p=1.39×10^{-6} (1.39×10^{-5}), C=0.599**	**HzR=1.90 [1.46-2.49], p=2.46×10^{-6} (2.46×10^{-5}), C=0.575**
		Non-ASCT	**HzR=2.07 [1.52-2.82], p=3.62×10^{-6} (3.62×10^{-5}), C=0.587**	**HzR=1.52 [1.15-2.00], p=0.00286 (0.0286), C=0.565**

[1]Values are presented as "HzR [CI lower limit-CI higher limit], raw p-value (adjusted p-value), C-statistic" format. HzR (hazard ratio), CI (95% confidence interval).

Supplementary Table 4. Treatment heterogeneity adjusted survival association results of IMS/IMWG criteria.

CPH survival test results of IMS/IMWG HR MM in CoMMpass data with treatment heterogeneity adjustments using the lifetime number of therapy lines and drug exposure profile variable for OS and prioritized drug combination in induction line therapy variable for PFS. Baseline levels were exposure to single IMID agent (IMID(1)) over the course of treatment history for OS and IMID-Glu-Doublet for PFS. Results over all patients as well as ASCT and non-ASCT cohorts are shown together.

Survival		OS			PFS			Survival	
Factor		HzR	CI	P	HzR	CI	P	Factor	
IMS/IMWG-1a (del(17p), Overall)									
IMS/IMWG-1a		**2.09**	**1.42-3.07**	**0.00176**	**1.84**	**1.27-2.68**	**0.00138**	**IMS/IMWG-1a**	
Therapy line count		**1.35**	**1.18-1.56**	**2.5×10^{-5}**	-	-	-	IMID-Glu Doublet	**Line 1 drug combo**
Drug profile	IMID(1)	-	-	-	0.82	0.52-1.29	0.383	PI-Alk-Glu Triplet	
	PI(1)	1.39	0.80-2.42	0.238	1.02	0.62-1.68	0.937	PI-Glu Doublet	
	PI(1)-IMID(1)	**0.31**	**0.18-0.52**	**1.18×10^{-5}**	**0.49**	**0.32-0.77**	**0.00196**	**PI-IMID-Glu Triplet**	
	PI(1)-IMID(1)-Dara	**0.21**	**0.10-0.47**	**0.000111**	**0.36**	**0.22-0.62**	**0.000184**	**Quadruplet**	
	PI(1)-IMID(2)	0.63	0.30-1.33	0.225					
	PI(1)-IMID(2)-Dara	**0.08**	**0.03-0.20**	**8.97×10^{-8}**					
	PI(2)-IMID(1)	**0.36**	**0.20-0.66**	**0.000881**					
	PI(2)-IMID(1)-Dara	**0.17**	**0.07-0.43**	**0.000146**					
	PI(2)-IMID(2)	**0.45**	**0.22-0.91**	**0.0267**					
	PI(2)-IMID(2)-Dara	**0.17**	**0.08-0.37**	**5.56×10^{-6}**					
	PI(3)-IMID(2)-Dara	**0.11**	**0.04-0.29**	**1.14×10^{-5}**					
IMS/IMWG-1a (del(17p), ASCT)									
IMS/IMWG-1a		**3.10**	**1.77-5.43**	**7.19×10^{-5}**	**1.61**	**1.04-2.51**	**0.0345**	**IMS/IMWG-1a**	
Therapy line count		**1.22**	**1.00-1.48**	**0.0462**	-	-	-	IMID-Glu Doublet	Line 1 drug combo
Drug profile	IMID(1)	-	-	-	0.55	0.23-1.28	0.166	PI-Alk-Glu Triplet	
	PI(1)	0.61	0.07-5.46	0.656	0.90	0.36-2.42	0.819	PI-Glu Doublet	
	PI(1)-IMID(1)	0.27	0.04-1.97	0.196	0.52	0.23-1.17	0.114	PI-IMID-Glu Triplet	
	PI(1)-IMID(1)-Dara	0.25	0.03-2.25	0.215	0.61	0.26-1.43	0.258	Quadruplet	
	PI(1)-IMID(2)	0.90	0.11-7.71	0.926					

	PI(1)-IMID(2)-Dara	**0.07**	**0.01-0.68**	**0.022**					
	PI(2)-IMID(1)	0.35	0.05-2.73	0.318					
	PI(2)-IMID(1)-Dara	0.12	0.01-1.38	0.0886					
	PI(2)-IMID(2)	0.74	0.09-5.95	0.777					
	PI(2)-IMID(2)-Dara	0.41	0.05-3.36	0.404					
	PI(3)-IMID(2)-Dara	0.32	0.03-3.00	0.319					
IMS/IMWG-1a (del(17p), Non-ASCT)									
IMS/IMWG-1a		**1.81**	**1.05-3.10**	**0.0325**	1.05	0.65-1.71	0.84	IMS/IMWG-1a	
Therapy line count		**1.24**	**1.01-1.51**	**0.0351**	-	-	-	IMID-Glu Doublet	**Line 1 drug combo**
Drug profile	IMID(1)	-	-	-	**1.55**	**1.01-2.38**	**0.046**	**PI-Alk-Glu Triplet**	
	PI(1)	**1.88**	**1.06-3.33**	**0.0298**	1.32	0.82-2.10	0.251	PI-Glu Doublet	
	PI(1)-IMID(1)	0.58	0.33-1.01	0.055	1.20	0.78-1.84	0.408	PI-IMID-Glu Triplet	
	PI(1)-IMID(1)-Dara	**0.35**	**0.14-0.89**	**0.0274**	0.69	0.39-1.22	0.2	Quadruplet	
	PI(1)-IMID(2)	0.92	0.38-2.23	0.855					
	PI(1)-IMID(2)-Dara	0.34	0.10-1.17	0.0874					
	PI(2)-IMID(1)	0.75	0.37-1.50	0.412					
	PI(2)-IMID(1)-Dara	**0.35**	**0.13-1.00**	**0.0499**					
	PI(2)-IMID(2)	0.70	0.29-1.70	0.431					
	PI(2)-IMID(2)-Dara	**0.17**	**0.05-0.53**	**0.00234**					
	PI(3)-IMID(2)-Dara	**0.06**	**0.01-0.56**	**0.0129**					
IMS/IMWG-1b (mut(TP53), Overall)									
IMS/IMWG-1b		**2.02**	**1.32-3.11**	**0.00131**	1.43	0.99-2.06	0.0552	IMS/IMWG-1b	
Therapy line count		**1.44**	**1.25-1.65**	**2.84×10^{-7}**	-	-	-	IMID-Glu Doublet	**Line 1 drug combo**
Drug profile	IMID(1)	-	-	-	0.92	0.65-1.32	0.653	PI-Alk-Glu Triplet	
	PI(1)	1.34	0.78-2.31	0.281	1.16	0.78-1.72	0.468	PI-Glu Doublet	
	PI(1)-IMID(1)	**0.31**	**0.18-0.51**	**4.93×10^{-6}**	**0.66**	**0.47-0.93**	**0.0164**	**PI-IMID-Glu Triplet**	
	PI(1)-IMID(1)-Dara	**0.20**	**0.09-0.43**	**4.2×10^{-5}**	**0.63**	**0.43-0.92**	**0.0175**	**Quadruplet**	
	PI(1)-IMID(2)	**0.44**	**0.22-0.90**	**0.0249**					
	PI(1)-IMID(2)-Dara	**0.08**	**0.03-0.19**	**1.69×10^{-8}**					
	PI(2)-IMID(1)	**0.30**	**0.17-0.55**	**9.25×10^{-5}**					
	PI(2)-IMID(1)-Dara	**0.18**	**0.08-0.43**	**0.000106**					
	PI(2)-IMID(2)	**0.41**	**0.21-0.80**	**0.0092**					
	PI(2)-IMID(2)-Dara	**0.13**	**0.06-0.28**	**1.2×10^{-7}**					

	PI(3)-IMID(2)-Dara	**0.08**	**0.03-0.20**	**2.71×10^{-7}**					
IMS/IMWG-1b (mut(TP53), ASCT)									
IMS/IMWG-1b		**2.82**	**1.62-4.9**	**0.000246**	**1.90**	**1.20-3.01**	**0.00622**	**IMS/IMWG-1b**	
Therapy line count		**1.37**	**1.13-1.67**	**0.00159**	-	-	-	IMID-Glu Doublet	Line 1 drug combo
Drug profile	IMID(1)	-	-	-	0.63	0.27-1.49	0.292	PI-Alk-Glu Triplet	
	PI(1)	0.57	0.06-5.10	0.613	1.10	0.44-2.76	0.845	PI-Glu Doublet	
	PI(1)-IMID(1)	0.26	0.03-1.89	0.181	0.59	0.26-1.35	0.211	PI-IMID-Glu Triplet	
	PI(1)-IMID(1)-Dara	0.20	0.02-1.82	0.153	0.72	0.31-1.70	0.454	Quadruplet	
	PI(1)-IMID(2)	0.50	0.06-4.25	0.523					
	PI(1)-IMID(2)-Dara	**0.08**	**0.01-0.75**	**0.0273**					
	PI(2)-IMID(1)	0.28	0.04-2.18	0.225					
	PI(2)-IMID(1)-Dara	0.17	0.02-1.75	0.138					
	PI(2)-IMID(2)	0.58	0.07-4.57	0.602					
	PI(2)-IMID(2)-Dara	0.25	0.03-2.11	0.203					
	PI(3)-IMID(2)-Dara	0.13	0.01-1.29	0.082					
IMS/IMWG-1b (mut(TP53), Non-ASCT)									
IMS/IMWG-1b		1.64	0.78-3.47	0.195	1.29	0.68-2.45	0.431	IMS/IMWG-1b	
Therapy line count		**1.28**	**1.05-1.56**	**0.0135**	-	-	-	IMID-Glu Doublet	Line 1 drug combo
Drug profile	IMID(1)	-	-	-	1.46	0.98-2.19	0.0649	PI-Alk-Glu Triplet	
	PI(1)	**1.83**	**1.05-3.20**	**0.0339**	1.28	0.81-2.01	0.29	PI-Glu Doublet	
	PI(1)-IMID(1)	0.58	0.34-1.00	0.0509	1.11	0.74-1.66	0.626	PI-IMID-Glu Triplet	
	PI(1)-IMID(1)-Dara	**0.34**	**0.14-0.87**	**0.0238**	0.69	0.40-1.17	0.17	Quadruplet	
	PI(1)-IMID(2)	0.68	0.29-1.57	0.368					
	PI(1)-IMID(2)-Dara	**0.23**	**0.07-0.78**	**0.0177**					
	PI(2)-IMID(1)	0.64	0.32-1.28	0.207					
	PI(2)-IMID(1)-Dara	**0.34**	**0.12-0.96**	**0.0421**					
	PI(2)-IMID(2)	0.73	0.30-1.78	0.488					
	PI(2)-IMID(2)-Dara	**0.13**	**0.04-0.41**	**0.000519**					
	PI(3)-IMID(2)-Dara	**0.10**	**0.02-0.54**	**0.00755**					
IMS/IMWG-1c (del(17p) & mut(TP53), Overall)									
IMS/IMWG-1c		**2.07**	**1.17-3.68**	**0.0129**	**1.85**	**1.12-3.05**	**0.0155**	**IMS/IMWG-1c**	
Therapy line count		**1.41**	**1.23-1.62**	**8.93×10^{-7}**	-	-	-	IMID/Glu Doublet	

Drug profile	IMID(1)	-	-	-	0.93	0.65-1.32	0.671	PI-Alk-Glu Triplet	**Line 1 drug combo**
	PI(1)	1.42	0.83-2.44	0.198	1.13	0.76-1.69	0.538	PI-Glu Doublet	
	PI(1)-IMID(1)	**0.32**	**0.20-0.54**	**1.3×10^{-5}**	**0.66**	**0.47-0.94**	**0.0197**	**PI-IMID-Glu Triplet**	
	PI(1)-IMID(1)-Dara	**0.21**	**0.09-0.45**	**6.27×10^{-5}**	**0.63**	**0.43-0.93**	**0.0195**	**Quadruplet**	
	PI(1)-IMID(2)	**0.49**	**0.24-0.99**	**0.0483**					
	PI(1)-IMID(2)-Dara	**0.09**	**0.04-0.21**	**6.18×10^{-8}**					
	PI(2)-IMID(1)	**0.34**	**0.19-0.61**	**0.000295**					
	PI(2)-IMID(1)-Dara	**0.20**	**0.08-0.47**	**0.000238**					
	PI(2)-IMID(2)	**0.44**	**0.22-0.86**	**0.0163**					
	PI(2)-IMID(2)-Dara	**0.15**	**0.07-0.31**	**5.92×10^{-7}**					
	PI(3)-IMID(2)-Dara	**0.10**	**0.04-0.26**	**2.21×10^{-6}**					
IMS/IMWG-1c (del(17p) & mut(TP53), ASCT)									
IMS/IMWG-1c		**3.43**	**1.55-7.59**	**0.00228**	**2.61**	**1.34-5.11**	**0.00503**	**IMS/IMWG-1c**	
Therapy line count		**1.33**	**1.10-1.61**	**0.00342**	-	-	-	IMID/Glue Doublet	Line 1 drug combo
Drug profile	IMID(1)	-	-	-	0.55	0.24-1.29	0.169	PI-Alk-Glu Triplet	
	PI(1)	0.57	0.06-5.15	0.619	0.97	0.39-2.40	0.949	PI-Glu Doublet	
	PI(1)-IMID(1)	0.28	0.04-2.02	0.205	0.52	0.23-1.17	0.115	PI-IMID-Glu Triplet	
	PI(1)-IMID(1)-Dara	0.20	0.02-1.84	0.156	0.61	0.26-1.42	0.255	Quadruplet	
	PI(1)-IMID(2)	0.60	0.07-5.11	0.641					
	PI(1)-IMID(2)-Dara	**0.09**	**0.01-0.8**	**0.0314**					
	PI(2)-IMID(1)	0.33	0.04-2.55	0.288					
	PI(2)-IMID(1)-Dara	0.18	0.02-1.79	0.142					
	PI(2)-IMID(2)	0.61	0.08-4.84	0.641					
	PI(2)-IMID(2)-Dara	0.30	0.04-2.51	0.268					
	PI(3)-IMID(2)-Dara	0.20	0.02-1.91	0.163					
IMS/IMWG-1c (del(17p) & mut(TP53), Non-ASCT)									
IMS/IMWG-1c		1.62	0.69-3.8	0.268	1.53	0.72-3.26	0.149	IMS/IMWG-1c	
Therapy line count		**1.27**	**1.04-1.54**	**0.0193**	-	-	-	IMID-Glu Doublet	**Line 1 drug combo**
Drug profile	IMID(1)	-	-	-	1.49	0.99-2.24	0.212	PI-Alk-Glu Triplet	
	PI(1)	**1.95**	**1.12-3.40**	**0.0183**	1.25	0.79-1.97	0.157	PI-Glu Doublet	
	PI(1)-IMID(1)	0.61	0.35-1.04	0.0716	**1.12**	**0.74-1.69**	**0.0119**	**PI-IMID-Glu Triplet**	
	PI(1)-IMID(1)-Dara	**0.36**	**0.14-0.92**	**0.0319**	0.72	0.42-1.22	0.484	Quadruplet	
	PI(1)-IMID(2)	0.71	0.31-1.65	0.428					

	PI(1)-IMID(2)-Dara	**0.30**	**0.09-0.98**	**0.0467**					
	PI(2)-IMID(1)	0.67	0.34-1.34	0.259					
	PI(2)-IMID(1)-Dara	0.38	0.14-1.06	0.0643					
	PI(2)-IMID(2)	0.77	0.32-1.88	0.571					
	PI(2)-IMID(2)-Dara	**0.14**	**0.04-0.44**	**0.000802**					
	PI(3)-IMID(2)-Dara	**0.11**	**0.02-0.60**	**0.0102**					
IMS/IMWG-2a (t(4;14) & +1q, Overall)									
IMS/IMWG-2a		**1.85**	**1.20-2.85**	**0.00525**	**1.79**	**1.25-2.55**	**0.00131**	**IMS/IMWG-2a**	
Therapy line count		**1.39**	**1.21-1.59**	**3.65×10^{-6}**	-	-	-	IMID-Glu Doublet	**Line 1 drug combo**
Drug profile	IMID(1)	-	-	-	0.88	0.61-1.26	0.487	PI-Alk-Glu Triplet	
	PI(1)	1.26	0.74-2.16	0.394	0.93	0.62-1.39	0.723	PI-Glu Doublet	
	PI(1)-IMID(1)	**0.30**	**0.18-0.50**	**3.96×10^{-6}**	**0.62**	**0.44-0.87**	**0.00606**	**PI-IMID-Glu Triplet**	
	PI(1)-IMID(1)-Dara	**0.21**	**0.09-0.46**	**0.000121**	**0.57**	**0.39-0.85**	**0.00501**	**Quadruplet**	
	PI(1)-IMID(2)	**0.42**	**0.20-0.86**	**0.0174**					
	PI(1)-IMID(2)-Dara	**0.08**	**0.03-0.19**	**1.69×10^{-8}**					
	PI(2)-IMID(1)	**0.31**	**0.17-0.56**	**0.000105**					
	PI(2)-IMID(1)-Dara	**0.22**	**0.09-0.53**	**0.000677**					
	PI(2)-IMID(2)	**0.42**	**0.22-0.82**	**0.0116**					
	PI(2)-IMID(2)-Dara	**0.17**	**0.08-0.35**	**1.53×10^{-6}**					
	PI(3)-IMID(2)-Dara	**0.10**	**0.04-0.26**	**2.74×10^{-6}**					
IMS/IMWG-2a (t(4;14) & +1q, ASCT)									
IMS/IMWG-2a		1.57	0.84-2.94	0.158	**1.85**	**1.17-2.92**	**0.00837**	**IMS/IMWG-2a**	
Therapy line count		**1.33**	**1.10-1.60**	**0.00299**	-	-	-	IMID-Glu Doublet	Line 1 drug combo
Drug profile	IMID(1)	-	-	-	0.57	0.25-1.33	0.195	PI-Alk-Glu Triplet	
	PI(1)	0.47	0.05-4.22	0.5	0.68	0.27-1.72	0.418	PI-Glu Doublet	
	PI(1)-IMID(1)	0.29	0.04-2.14	0.226	0.52	0.23-1.19	0.122	PI-IMID-Glu Triplet	
	PI(1)-IMID(1)-Dara	0.26	0.03-2.35	0.23	0.58	0.25-1.35	0.207	Quadruplet	
	PI(1)-IMID(2)	0.55	0.06-4.72	0.584					
	PI(1)-IMID(2)-Dara	**0.09**	**0.01-0.84**	**0.0346**					
	PI(2)-IMID(1)	0.31	0.04-2.39	0.259					
	PI(2)-IMID(1)-Dara	0.17	0.01-1.90	0.149					
	PI(2)-IMID(2)	0.76	0.10-5.95	0.79					
	PI(2)-IMID(2)-Dara	0.36	0.04-2.92	0.338					

	PI(3)-IMID(2)-Dara	0.19	0.02-1.82	0.151					
IMS/IMWG-2a (t(4;14) & +1q, Non-ASCT)									
IMS/IMWG-2a		**2.62**	**1.42-4.82**	**0.002**	**2.32**	**1.30-4.14**	**0.00428**	**IMS/IMWG-2a**	
Therapy line count		1.22	0.99-1.49	0.0555	-	-	-	IMID/Glu Doublet	Line 1 drug combo
Drug profile	IMID(1)	-	-	-	1.41	0.94-2.12	0.0998	PI-Alk-Glu Triplet	
	PI(1)	**1.82**	**1.04-3.17**	**0.0348**	1.06	0.67-1.68	0.791	PI-Glu Doublet	
	PI(1)-IMID(1)	**0.55**	**0.32-0.96**	**0.0344**	1.00	0.66-1.52	0.982	PI-IMID-Glu Triplet	
	PI(1)-IMID(1)-Dara	**0.33**	**0.12-0.88**	**0.027**	0.66	0.39-1.12	0.12	Quadruplet	
	PI(1)-IMID(2)	0.66	0.29-1.53	0.337					
	PI(1)-IMID(2)-Dara	**0.24**	**0.07-0.79**	**0.0195**					
	PI(2)-IMID(1)	0.61	0.31-1.22	0.164					
	PI(2)-IMID(1)-Dara	0.48	0.18-1.32	0.154					
	PI(2)-IMID(2)	0.60	0.24-1.49	0.273					
	PI(2)-IMID(2)-Dara	**0.16**	**0.05-0.52**	**0.00213**					
	PI(3)-IMID(2)-Dara	0.19	0.03-1.00	0.0506					
IMS/IMWG-2b (t(4;14) & del(1p32), Overall)									
IMS/IMWG-2b		**4.03**	**2.12-7.69**	**2.25×10^{-5}**	**2.91**	**1.60-5.31**	**0.000492**	**IMS/IMWG-2b**	
Therapy line count		1.39	1.21-1.60	3.23×10^{-6}	-	-	-	IMID/Glu Doublet	**Line 1 drug combo**
Drug profile	IMID(1)	-	-	-	0.95	0.67-1.36	0.788	PI-Alk-Glu Triplet	
	PI(1)	1.36	0.80-2.34	0.26	1.04	0.70-1.54	0.853	PI-Glu Doublet	
	PI(1)-IMID(1)	**0.34**	**0.20-0.56**	**2.4×10^{-5}**	**0.68**	**0.48-0.95**	**0.0236**	**PI-IMID-Glu Triplet**	
	PI(1)-IMID(1)-Dara	**0.22**	**0.10-0.48**	**0.000137**	**0.61**	**0.41-0.90**	**0.0128**	**Quadruplet**	
	PI(1)-IMID(2)	0.50	0.24-1.00	0.053					
	PI(1)-IMID(2)-Dara	**0.09**	**0.04-0.21**	**7.17×10^{-8}**					
	PI(2)-IMID(1)	**0.33**	**0.18-0.61**	**0.000317**					
	PI(2)-IMID(1)-Dara	**0.26**	**0.11-0.60**	**0.00161**					
	PI(2)-IMID(2)	**0.50**	**0.25-0.98**	**0.0428**					
	PI(2)-IMID(2)-Dara	**0.16**	**0.07-0.33**	**1.42×10^{-6}**					
	PI(3)-IMID(2)-Dara	**0.10**	**0.04-0.28**	**5.88×10^{-6}**					
IMS/IMWG-2b (t(4;14) & del(1p32), ASCT)									
IMS/IMWG-2b		**3.61**	**1.44-9.09**	**0.00633**	**2.44**	**1.08-5.52**	**0.000492**	**IMS/IMWG-2b**	
Therapy line count		**1.30**	**1.07-1.56**	**0.00708**	-	-	-	IMID-Glu Doublet	

Drug profile	IMID(1)	-	-	-	0.57	0.25-1.33	0.788	PI-Alk-Glu Triplet	Line 1 drug combo
	PI(1)	0.46	0.05-4.16	0.492	0.78	0.32-1.94	0.853	PI-Glu Doublet	
	PI(1)-IMID(1)	0.29	0.04-2.16	0.228	0.53	0.23-1.20	0.0236	PI-IMID-Glu Triplet	
	PI(1)-IMID(1)-Dara	0.23	0.03-2.10	0.192	0.59	0.25-1.38	0.0128	Quadruplet	
	PI(1)-IMID(2)	0.64	0.08-5.40	0.679					
	PI(1)-IMID(2)-Dara	**0.10**	**0.01-0.90**	**0.0399**					
	PI(2)-IMID(1)	0.32	0.04-2.45	0.271					
	PI(2)-IMID(1)-Dara	0.24	0.02-2.43	0.229					
	PI(2)-IMID(2)	0.85	0.11-6.70	0.877					
	PI(2)-IMID(2)-Dara	0.32	0.04-2.68	0.296					
	PI(3)-IMID(2)-Dara	0.22	0.02-2.07	0.186					
IMS/IMWG-2b (t(4;14) & del(1p32), Non-ASCT)									
IMS/IMWG-2b		**6.31**	**2.47-16.10**	**0.000119**	**6.76**	**2.72-16.8**	**4×10^{-5}**	**IMS/IMWG-2b**	
Therapy line count		**1.28**	**1.05-1.57**	**0.0155**	-	-	-	IMID-Glu Doublet	**Line 1 drug combo**
Drug profile	IMID(1)	-	-	-	**1.52**	**1.02-2.27**	**0.039**	**PI-Alk-Glu Triplet**	
	PI(1)	**1.93**	**1.11-3.38**	**0.0208**	1.19	0.76-1.87	0.438	PI-Glu Doublet	
	PI(1)-IMID(1)	0.62	0.36-1.07	0.0877	1.13	0.76-1.68	0.555	PI-IMID-Glu Triplet	
	PI(1)-IMID(1)-Dara	**0.37**	**0.15-0.93**	**0.0349**	0.65	0.38-1.12	0.119	Quadruplet	
	PI(1)-IMID(2)	0.64	0.27-1.48	0.297					
	PI(1)-IMID(2)-Dara	**0.23**	**0.07-0.76**	**0.0163**					
	PI(2)-IMID(1)	0.67	0.33-1.33	0.25					
	PI(2)-IMID(1)-Dara	0.48	0.17-1.30	0.147					
	PI(2)-IMID(2)	0.69	0.28-1.68	0.416					
	PI(2)-IMID(2)-Dara	**0.15**	**0.05-0.49**	**0.00155**					
	PI(3)-IMID(2)-Dara	**0.11**	**0.02-0.59**	**0.00983**					
IMS/IMWG-2d (t(14;16) & +1q, Overall)									
IMS/IMWG-2d		1.21	0.49-2.96	0.678	1.46	0.78-2.74	0.237	IMS/IMWG-2d	
Therapy line count		**1.41**	**1.23-1.62**	**9.18×10^{-7}**	-	-	-	IMID-Glu Doublet	**Line 1 drug combo**
Drug profile	IMID(1)	-	-	-	0.91	0.63-1.31	0.615	PI-Alk-Glu Triplet	
	PI(1)	1.29	0.75-2.20	0.354	0.97	0.65-1.46	0.898	PI-Glu Doublet	
	PI(1)-IMID(1)	**0.30**	**0.18-0.50**	**3.8×10^{-6}**	**0.64**	**0.45-0.91**	**0.0139**	**PI-IMID-Glu Triplet**	
	PI(1)-IMID(1)-Dara	**0.21**	**0.09-0.46**	**0.000114**	**0.60**	**0.40-0.88**	**0.009**	**Quadruplet**	
	PI(1)-IMID(2)	**0.45**	**0.22-0.91**	**0.0266**					

	PI(1)-IMID(2)-Dara	**0.08**	**0.03-0.19**	**1.81×10^{-8}**					
	PI(2)-IMID(1)	**0.32**	**0.18-0.58**	**0.000179**					
	PI(2)-IMID(1)-Dara	**0.21**	**0.09-0.50**	**0.000462**					
	PI(2)-IMID(2)	**0.42**	**0.21-0.83**	**0.0124**					
	PI(2)-IMID(2)-Dara	**0.16**	**0.08-0.34**	**1.14×10^{-6}**					
	PI(3)-IMID(2)-Dara	**0.10**	**0.04-0.28**	**8.46×10^{-6}**					
IMS/IMWG-2d (t(14;16) & +1q, ASCT)									
IMS/IMWG-2d		1.31	0.40-4.25	0.658	1.72	0.76-3.89	0.237	IMS/IMWG-2d	
Therapy line count		**1.35**	**1.12-1.62**	**0.00192**	-	-	-	IMID-Glu Doublet	Line 1 drug combo
Drug profile	IMID(1)	-	-	-	0.59	0.25-1.38	0.615	PI-Alk-Glu Triplet	
	PI(1)	0.47	0.05-4.19	0.495	0.72	0.29-1.82	0.898	PI-Glu Doublet	
	PI(1)-IMID(1)	0.29	0.04-2.14	0.225	0.56	0.25-1.27	0.0139	PI-IMID-Glu Triplet	
	PI(1)-IMID(1)-Dara	0.25	0.03-2.29	0.221	0.61	0.26-1.41	0.009	Quadruplet	
	PI(1)-IMID(2)	0.59	0.07-5.01	0.625					
	PI(1)-IMID(2)-Dara	**0.09**	**0.01-0.85**	**0.0354**					
	PI(2)-IMID(1)	0.34	0.04-2.64	0.302					
	PI(2)-IMID(1)-Dara	0.16	0.01-1.84	0.141					
	PI(2)-IMID(2)	0.76	0.10-5.97	0.791					
	PI(2)-IMID(2)-Dara	0.36	0.04-2.94	0.341					
	PI(3)-IMID(2)-Dara	0.22	0.02-2.08	0.186					
IMS/IMWG-2d (t(14;16) & +1q, Non-ASCT)									
IMS/IMWG-2d		1.61	0.39-6.59	0.506	1.74	0.63-4.79	0.288	IMS/IMWG-2d	
Therapy line count		**1.29**	**1.06-1.58**	**0.0125**	-	-	-	IMID-Glu Doublet	Line 1 drug combo
Drug profile	IMID(1)	-	-	-	1.44	0.95-2.17	0.0847	PI-Alk-Glu Triplet	
	PI(1)	**1.86**	**1.07-3.23**	**0.0284**	1.12	0.71-1.79	0.621	PI-Glu Doublet	
	PI(1)-IMID(1)	**0.54**	**0.31-0.94**	**0.028**	0.99	0.65-1.51	0.973	PI-IMID-Glu Triplet	
	PI(1)-IMID(1)-Dara	**0.33**	**0.13-0.89**	**0.028**	0.68	0.40-1.16	0.16	Quadruplet	
	PI(1)-IMID(2)	0.62	0.27-1.44	0.267					
	PI(1)-IMID(2)-Dara	**0.20**	**0.06-0.68**	**0.00937**					
	PI(2)-IMID(1)	0.59	0.30-1.19	0.142					
	PI(2)-IMID(1)-Dara	0.43	0.16-1.16	0.0963					
	PI(2)-IMID(2)	0.57	0.23-1.41	0.224					
	PI(2)-IMID(2)-Dara	**0.14**	**0.04-0.42**	**0.000481**					

	PI(3)-IMID(2)-Dara	**0.10**	**0.01-0.90**	**0.0395**					
IMS/IMWG-3a (mono-del(1p32) & +1q, Overall)									
	IMS/IMWG-3a	**2.38**	**1.55-3.67**	**8.01×10^{-5}**	**1.97**	**1.36-2.86**	**0.00035**	**IMS/IMWG-3a**	
	Therapy line count	**1.38**	**1.20-1.59**	**7.2×10^{-6}**	-	-	-	IMID-Glu Doublet	**Line 1 drug combo**
Drug profile	IMID(1)	-	-	-	0.94	0.65-1.37	0.763	PI-Alk-Glu Triplet	
	PI(1)	1.31	0.75-2.28	0.339	1.19	0.79-1.80	0.398	PI-Glu Doublet	
	PI(1)-IMID(1)	**0.31**	**0.19-0.53**	**1.42×10^{-5}**	0.70	0.49-1.01	0.0535	PI-IMID-Glu Triplet	
	PI(1)-IMID(1)-Dara	**0.21**	**0.10-0.47**	**0.000113**	**0.66**	**0.44-0.99**	**0.0469**	**Quadruplet**	
	PI(1)-IMID(2)	0.61	0.29-1.27	0.187					
	PI(1)-IMID(2)-Dara	**0.09**	**0.03-0.22**	**2.15×10^{-7}**					
	PI(2)-IMID(1)	**0.34**	**0.19-0.63**	**0.000545**					
	PI(2)-IMID(1)-Dara	**0.19**	**0.08-0.47**	**0.00029**					
	PI(2)-IMID(2)	**0.47**	**0.23-0.94**	**0.0332**					
	PI(2)-IMID(2)-Dara	**0.17**	**0.08-0.36**	**3.87×10^{-6}**					
	PI(3)-IMID(2)-Dara	**0.11**	**0.04-0.29**	**9.21×10^{-6}**					
IMS/IMWG-3a (mono-del(1p32) & +1q, ASCT)									
	IMS/IMWG-3a	**4.55**	**2.14-9.68**	**8.38×10^{-5}**	**2.73**	**1.57-4.73**	**0.000346**	**IMS/IMWG-3a**	
	Therapy line count	**1.34**	**1.10-1.63**	**0.00398**	-	-	-	IMID-Glue Doublet	Line 1 drug combo
Drug profile	IMID(1)	-	-	-	0.57	0.24-1.33	0.191	PI-Alk-Glu Triplet	
	PI(1)	0.60	0.07-5.40	0.648	0.92	0.37-2.29	0.856	PI-Glu Doublet	
	PI(1)-IMID(1)	0.28	0.04-2.08	0.215	0.51	0.23-1.17	0.113	PI-IMID-Glu Triplet	
	PI(1)-IMID(1)-Dara	0.24	0.03-2.15	0.2	0.65	0.28-1.52	0.324	Quadruplet	
	PI(1)-IMID(2)	0.78	0.09-6.72	0.825					
	PI(1)-IMID(2)-Dara	**0.07**	**0.01-0.74**	**0.0266**					
	PI(2)-IMID(1)	0.32	0.04-2.46	0.272					
	PI(2)-IMID(1)-Dara	0.12	0.01-1.41	0.091					
	PI(2)-IMID(2)	0.61	0.08-5.01	0.649					
	PI(2)-IMID(2)-Dara	0.31	0.04-2.58	0.279					
	PI(3)-IMID(2)-Dara	0.22	0.02-2.08	0.187					
IMS/IMWG-3a (mono-del(1p32) & +1q, Non-ASCT)									
	IMS/IMWG-3a	1.35	0.79-2.31	0.277	1.29	0.77-2.17	0.33	IMS/IMWG-3a	
	Therapy line count	**1.25**	**1.02-1.53**	**0.0323**	-	-	-	IMID-Glu Doublet	

Drug profile	IMID(1)	-	-	-	1.52	0.99-2.34	0.0549	PI-Alk-Glu Triplet	Line 1 drug combo
	PI(1)	**1.89**	**1.06-3.34**	**0.0302**	1.32	0.83-2.11	0.241	PI-Glu Doublet	
	PI(1)-IMID(1)	0.59	0.33-1.03	0.0619	1.20	0.78-1.85	0.396	PI-IMID-Glu Triplet	
	PI(1)-IMID(1)-Dara	**0.36**	**0.14-0.91**	**0.0308**	0.68	0.38-1.21	0.193	Quadruplet	
	PI(1)-IMID(2)	0.90	0.37-2.19	0.823					
	PI(1)-IMID(2)-Dara	0.34	0.10-1.15	0.0835					
	PI(2)-IMID(1)	0.72	0.36-1.47	0.372					
	PI(2)-IMID(1)-Dara	0.41	0.15-1.11	0.0789					
	PI(2)-IMID(2)	0.79	0.32-1.93	0.598					
	PI(2)-IMID(2)-Dara	**0.17**	**0.05-0.55**	**0.00298**					
	PI(3)-IMID(2)-Dara	**0.07**	**0.01-0.63**	**0.0174**					
IMS/IMWG-3b (bidel(1p32), Overall)									
IMS/IMWG-3b		**3.26**	**1.69-6.29**	**0.000415**	**3.64**	**2.04-6.49**	**1.17×10^{-5}**	**IMS/IMWG-3b**	
Therapy line count		**1.35**	**1.17-1.55**	**4.53×10^{-5}**	-	-	-	IMID-Glu Doublet	**Line 1 drug combo**
Drug profile	IMID(1)	-	-	-	0.95	0.65-1.38	0.774	PI-Alk-Glu Triplet	
	PI(1)	1.43	0.82-2.47	0.205	1.15	0.76-1.73	0.508	PI-Glu Doublet	
	PI(1)-IMID(1)	**0.32**	**0.19-0.54**	**2.11×10^{-5}**	**0.69**	**0.48-1.00**	**0.047**	**PI-IMID-Glu Triplet**	
	PI(1)-IMID(1)-Dara	**0.23**	**0.10-0.50**	**0.000202**	**0.65**	**0.43-0.97**	**0.0362**	**Quadruplet**	
	PI(1)-IMID(2)	0.62	0.30-1.31	0.212					
	PI(1)-IMID(2)-Dara	**0.09**	**0.04-0.23**	**3.8×10^{-7}**					
	PI(2)-IMID(1)	**0.37**	**0.20-0.67**	**0.0012**					
	PI(2)-IMID(1)-Dara	**0.23**	**0.10-0.57**	**0.00127**					
	PI(2)-IMID(2)	0.53	0.26-1.06	0.0721					
	PI(2)-IMID(2)-Dara	**0.17**	**0.08-0.36**	**5.14×10^{-6}**					
	PI(3)-IMID(2)-Dara	**0.12**	**0.04-0.32**	**2.36×10^{-5}**					
IMS/IMWG-3b (bidel(1p32), ASCT)									
IMS/IMWG-3b		1.48	0.45-4.88	0.521	**3.41**	**1.40-8.35**	**0.00716**	**IMS/IMWG-3b**	
Therapy line count		**1.24**	**1.02-1.50**	**0.0317**	-	-	-	IMID-Glu Doublet	Line 1 drug combo
Drug profile	IMID(1)	-	-	-	0.54	0.23-1.27	0.158	PI-Alk-Glu Triplet	
	PI(1)	0.63	0.07-5.71	0.684	0.86	0.34-2.14	0.739	PI-Glu Doublet	
	PI(1)-IMID(1)	0.30	0.04-2.18	0.233	0.52	0.23-1.18	0.119	PI-IMID-Glu Triplet	
	PI(1)-IMID(1)-Dara	0.26	0.03-2.40	0.236	0.63	0.27-1.47	0.286	Quadruplet	
	PI(1)-IMID(2)	0.89	0.10-7.63	0.919					

	PI(1)-IMID(2)-Dara	**0.09**	**0.01-0.86**	**0.0372**					
	PI(2)-IMID(1)	0.37	0.05-2.89	0.345					
	PI(2)-IMID(1)-Dara	0.21	0.02-2.34	0.202					
	PI(2)-IMID(2)	0.90	0.11-7.22	0.922					
	PI(2)-IMID(2)-Dara	0.43	0.05-3.49	0.426					
	PI(3)-IMID(2)-Dara	0.31	0.03-2.87	0.301					
IMS/IMWG-3b (bidel(1p32), Non-ASCT)									
IMS/IMWG-3b		**5.64**	**2.56-12.5**	**1.79×10^{-5}**	**5.18**	**2.39-11.24**	**3.16×10^{-5}**	**IMS/IMWG-3b**	
Therapy line count		**1.25**	**1.02-1.53**	**0.0296**	-	-	-	IMID-Glu Doublet	**Line 1 drug combo**
Drug profile	IMID(1)	-	-	-	**1.56**	**1.02-2.39**	**0.0415**	**PI-Alk-Glu Triplet**	
	PI(1)	**1.92**	**1.09-3.39**	**0.0243**	1.31	0.82-2.09	0.26	PI-Glu Doublet	
	PI(1)-IMID(1)	**0.56**	**0.32-0.98**	**0.0441**	1.15	0.75-1.77	0.527	PI-IMID-Glu Triplet	
	PI(1)-IMID(1)-Dara	**0.36**	**0.14-0.91**	**0.0312**	0.65	0.37-1.15	0.14	Quadruplet	
	PI(1)-IMID(2)	0.80	0.33-1.95	0.621					
	PI(1)-IMID(2)-Dara	0.33	0.10-1.13	0.0783					
	PI(2)-IMID(1)	0.73	0.36-1.48	0.389					
	PI(2)-IMID(1)-Dara	0.42	0.15-1.13	0.0862					
	PI(2)-IMID(2)	0.79	0.32-1.94	0.607					
	PI(2)-IMID(2)-Dara	**0.17**	**0.05-0.54**	**0.00266**					
	PI(3)-IMID(2)-Dara	**0.07**	**0.01-0.61**	**0.0162**					
IMS/IMWG-4 (High β2M & normal creatinine, Overall)									
IMS/IMWG-4		**1.70**	**1.19-2.45**	**0.00399**	**1.48**	**1.11-1.99**	**0.00859**	**IMS/IMWG-4**	
Therapy line count		**1.39**	**1.23-1.58**	**1.09×10^{-7}**	-	-	-	IMID-Glu Doublet	**Line 1 drug combo**
Drug profile	IMID(1)	-	-	-	0.87	0.63-1.21	0.416	PI-Alk-Glu Triplet	
	PI(1)	1.45	0.90-2.35	0.13	1.11	0.77-1.59	0.586	PI-Glu Doublet	
	PI(1)-IMID(1)	**0.29**	**0.19-0.47**	**1.88×10^{-7}**	**0.62**	**0.46-0.85**	**0.00295**	**PI-IMID-Glu Triplet**	
	PI(1)-IMID(1)-Dara	**0.21**	**0.10-0.43**	**2.2×10^{-5}**	**0.55**	**0.38-0.78**	**0.000994**	**Quadruplet**	
	PI(1)-IMID(2)	**0.53**	**0.29-1.00**	**0.0484**					
	PI(1)-IMID(2)-Dara	**0.07**	**0.03-0.16**	**9.49×10^{-10}**					
	PI(2)-IMID(1)	**0.28**	**0.16-0.49**	**7.41×10^{-6}**					
	PI(2)-IMID(1)-Dara	**0.20**	**0.09-0.44**	**6.64×10^{-5}**					
	PI(2)-IMID(2)	**0.47**	**0.26-0.86**	**0.0142**					

	PI(2)-IMID(2)-Dara	**0.16**	**0.08-0.31**	**6.04×10^{-8}**					
	PI(3)-IMID(2)-Dara	**0.10**	**0.04-0.24**	**2.45×10^{-7}**					
IMS/IMWG-4 (High β2M & normal creatinine, ASCT)									
	IMS/IMWG-4	1.43	0.78-2.60	0.247	**1.67**	**1.10-2.55**	**0.0159**	**IMS/IMWG-4**	
	Therapy line count	**1.41**	**1.19-1.66**	**5.91×10^{-5}**	-	-	-	IMID-Glu Doublet	Line 1 drug combo
Drug profile	IMID(1)	-	-	-	0.52	0.23-1.14	0.101	PI-Alk-Glu Triplet	
	PI(1)	0.43	0.05-3.89	0.455	0.82	0.35-1.90	0.643	PI-Glu Doublet	
	PI(1)-IMID(1)	0.28	0.04-2.01	0.204	0.51	0.24-1.08	0.0796	PI-IMID-Glu Triplet	
	PI(1)-IMID(1)-Dara	0.23	0.03-2.00	0.182	0.54	0.25-1.20	0.13	Quadruplet	
	PI(1)-IMID(2)	0.53	0.06-4.54	0.566					
	PI(1)-IMID(2)-Dara	**0.07**	**0.01-0.65**	**0.0195**					
	PI(2)-IMID(1)	0.26	0.03-2.01	0.197					
	PI(2)-IMID(1)-Dara	0.20	0.02-1.84	0.156					
	PI(2)-IMID(2)	0.77	0.10-5.95	0.806					
	PI(2)-IMID(2)-Dara	0.25	0.03-1.98	0.188					
	PI(3)-IMID(2)-Dara	0.17	0.02-1.46	0.106					
IMS/IMWG-4 (High β2M & normal creatinine, Non-ASCT)									
	IMS/IMWG-4	**2.02**	**1.26-3.23**	**0.00342**	1.27	0.83-1.95	0.277	IMS/IMWG-4	
	Therapy line count	**1.22**	**1.01-1.46**	**0.0343**	-	-	-	IMID-Glu Doublet	Line 1 drug combo
Drug profile	IMID(1)	-	-	-	1.32	0.91-1.91	0.142	PI-Alk-Glu Triplet	
	PI(1)	**2.03**	**1.23-3.35**	**0.00554**	1.29	0.85-1.95	0.224	PI-Glu Doublet	
	PI(1)-IMID(1)	**0.58**	**0.35-0.95**	**0.0314**	1.01	0.69-1.46	0.969	PI-IMID-Glu Triplet	
	PI(1)-IMID(1)-Dara	**0.36**	**0.15-0.88**	**0.0252**	0.64	0.38-1.08	0.094	Quadruplet	
	PI(1)-IMID(2)	0.88	0.43-1.78	0.722					
	PI(1)-IMID(2)-Dara	**0.21**	**0.07-0.65**	**0.00721**					
	PI(2)-IMID(1)	0.63	0.33-1.21	0.165					
	PI(2)-IMID(1)-Dara	0.45	0.17-1.18	0.104					
	PI(2)-IMID(2)	0.71	0.30-1.69	0.433					
	PI(2)-IMID(2)-Dara	**0.24**	**0.09-0.60**	**0.00233**					
	PI(3)-IMID(2)-Dara	**0.13**	**0.03-0.67**	**0.0147**					
IMS/IMWG Combined Final (Overall)									
	IMS/IMWG combined	**2.09**	**1.63-2.69**	**9.09×10^{-9}**	**1.70**	**1.40-2.07**	**1.27×10^{-7}**	**IMS/IMWG combined**	

Therapy line count		**1.39**	**1.21-1.61**	**5.84×10^{-6}**	-	-	-	IMID-Glu Doublet	**Line 1 drug combo**
Drug profile	IMID(1)	-	-	-	0.89	0.61-1.30	0.55	PI-Alk-Glu Triplet	
	PI(1)	1.15	0.65-2.04	0.621	1.10	0.71-1.66	0.7	PI-Glu Doublet	
	PI(1)-IMID(1)	**0.28**	**0.16-0.47**	**2.88×10^{-6}**	**0.67**	**0.46-0.96**	**0.0285**	**PI-IMID-Glu Triplet**	
	PI(1)-IMID(1)-Dara	**0.18**	**0.08-0.42**	**7.04×10^{-5}**	**0.61**	**0.40-0.92**	**0.0186**	**Quadruplet**	
	PI(1)-IMID(2)	**0.45**	**0.21-0.98**	**0.0431**					
	PI(1)-IMID(2)-Dara	**0.07**	**0.03-0.17**	**1.42×10^{-8}**					
	PI(2)-IMID(1)	**0.25**	**0.13-0.48**	**2.46×10^{-5}**					
	PI(2)-IMID(1)-Dara	**0.14**	**0.05-0.35**	**3.5×10^{-5}**					
	PI(2)-IMID(2)	**0.37**	**0.18-0.76**	**0.00649**					
	PI(2)-IMID(2)-Dara	**0.15**	**0.07-0.31**	**7×10^{-7}**					
	PI(3)-IMID(2)-Dara	**0.08**	**0.03-0.21**	**7.01×10^{-7}**					
IMS/IMWG Combined Final (ASCT)									
IMS/IMWG combined		**2.06**	**1.37-3.12**	**0.000568**	**2.06**	**1.55-2.72**	**4.25×10^{-7}**	**IMS/IMWG combined**	
Therapy line count		**1.30**	**1.06-1.60**	**0.0121**	-	-	-	IMID-Glu Doublet	Line 1 drug combo
Drug profile	IMID(1)	-	-	-	0.60	0.26-1.41	0.238	PI-Alk-Glu Triplet	
	PI(1)	0.58	0.06-5.24	0.628	0.87	0.34-2.25	0.775	PI-Glu Doublet	
	PI(1)-IMID(1)	0.24	0.03-1.82	0.169	0.55	0.24-1.25	0.151	PI-IMID-Glu Triplet	
	PI(1)-IMID(1)-Dara	0.20	0.02-1.95	0.165	0.66	0.28-1.54	0.336	Quadruplet	
	PI(1)-IMID(2)	0.54	0.06-4.77	0.576					
	PI(1)-IMID(2)-Dara	**0.06**	**0.01-0.61**	**0.0173**					
	PI(2)-IMID(1)	0.22	0.03-1.79	0.159					
	PI(2)-IMID(1)-Dara	0.07	0.004-1.13	0.0609					
	PI(2)-IMID(2)	0.61	0.07-4.98	0.645					
	PI(2)-IMID(2)-Dara	0.30	0.04-2.51	0.267					
	PI(3)-IMID(2)-Dara	0.17	0.02-1.65	0.126					
IMS/IMWG Combined (Non-ASCT)									
IMS/IMWG combined		**2.15**	**1.55-2.98**	**3.92×10^{-6}**	**1.45**	**1.09-1.93**	**0.011**	**IMS/IMWG combined**	
Therapy line count		**1.26**	**1.04-1.54**	**0.019**	-	-	-	IMID-Glu Doublet	Line 1 drug combo
Drug profile	IMID(1)	-	-	-	1.38	0.90-2.13	0.141	PI-Alk-Glu Triplet	
	PI(1)	1.48	0.82-2.69	0.193	1.21	0.75-1.95	0.427	PI-Glu Doublet	
	PI(1)-IMID(1)	**0.50**	**0.28-0.89**	**0.0194**	1.14	0.74-1.77	0.543	PI-IMID-Glu Triplet	
	PI(1)-IMID(1)-Dara	**0.28**	**0.11-0.77**	**0.0131**	0.65	0.36-1.15	0.14	Quadruplet	

	PI(1)-IMID(2)	0.86	0.35-2.11	0.749
	PI(1)-IMID(2)-Dara	**0.26**	**0.08-0.88**	**0.0297**
	PI(2)-IMID(1)	0.55	0.26-1.17	0.119
	PI(2)-IMID(1)-Dara	**0.27**	**0.10-0.77**	**0.0132**
	PI(2)-IMID(2)	0.56	0.23-1.40	0.215
	PI(2)-IMID(2)-Dara	**0.17**	**0.06-0.51**	**0.00145**
	PI(3)-IMID(2)-Dara	**0.07**	**0.01-0.60**	**0.0154**

Supplementary Table 5. Univariate survival association results of HR MM factors other than IMS/IMWG.

Compositions of baseline risk and HR patients and summary of univariate survival analyses for HR MM factors considered in this study besides IMS/IMWG. Results over all patients as well as ASCT and non-ASCT cohorts are shown together.

Factor	Patient	Negative[1]	Positive[1]	Total	Missing[2]	N
APOBEC	**Overall**	**741 (74.6%)**	**252 (25.4%)**	**993**	**-**	**993**
	ASCT	**389 (74.5%)**	**133 (25.5%)**	**522**	**-**	**522**
	Non-ASCT	**336 (75.7%)**	**108 (24.3%)**	**444**	**-**	**444**
Chromo-thripsis	**Overall**	**835 (92.2%)**	**71 (7.8%)**	**906**	**-**	**906**
	ASCT	461 (94.1%)	29 (5.9%)	490	-	490
	Non-ASCT	**374 (89.9%)**	**42 (10.1%)**	**416**	**-**	**416**
EMC92	**Overall**	**540 (67%)**	**266 (33%)**	**806**	**-**	**806**
	ASCT	**291 (67.7%)**	**139 (32.3%)**	**430**	**-**	**430**
	Non-ASCT	**237 (65.5%)**	**125 (34.5%)**	**362**	**-**	**362**
PR	**Overall**	**414 (68.9%)**	**187 (31.1%)**	**601**	**542 (47.4%)**	**1,143**
	ASCT	**229 (70%)**	**98 (30%)**	**327**	**285 (46.6%)**	**612**
	Non-ASCT	**185 (67.5%)**	**89 (32.5%)**	**274**	**257 (48.4%)**	**531**

[1]Numbers in parentheses represent percentages over "Total" (= "Positive" + "Negative"). [2]Numbers in parentheses represent percentages over "N".

Factor	Patient	OS	PFS
APOBEC	**Overall**	**HzR=1.60, CI=[1.26-2.01], p=8.16×10^{-5}, C=0.542**	**HzR=1.65, CI=[1.38-1.98], p=7.32×10^{-8}, C=0.545**
	ASCT	**HzR=2.07, CI=[1.45-2.96], p=6.81×10^{-5}, C=0.58**	**HzR=2.00, CI=[1.54-2.58], p=1.36×10^{-7}, C=0.566**
	Non-ASCT	HzR=1.35, CI=[0.99-1.83], p=0.0582, C=0.524	**HzR=1.42, CI=[1.10-1.85], p=0.00787, C=0.534**
Chromo-thripsis	**Overall**	**HzR=2.13, CI=[1.53-2.95], p=6.96×10^{-6}, C=0.541**	**HzR=1.76, CI=[1.33-2.33], p=8.86×10^{-5}, C=0.53**
	ASCT	HzR=1.62, CI=[0.87-3.02], p=0.126, C=0.519	HzR=1.47, CI=[0.93-2.32], p=0.0975, C=0.513
	Non-ASCT	**HzR=1.98, CI=[1.34-2.93], p=0.00058, C=0.546**	**HzR=1.81, CI=[1.26-2.59], p=0.00135, C=0.542**
EMC92	**Overall**	**HzR=3.23, CI=[2.55-4.09], p=2.48×10^{-22}, C=0.642**	**HzR=2.28, CI=[1.90-2.75], p=2.46×10^{-18}, C=0.600**
	ASCT	**HzR=4.76, CI=[3.27-6.93], p=3.97×10^{-16}, C=0.693**	**HzR=2.51, CI=[1.94-3.26], p=3.02×10^{-12}, C=0.615**
	Non-ASCT	**HzR=2.48, CI=[1.82-3.38], p=8.41×10^{-9}, C=0.619**	**HzR=2.11, CI=[1.62-2.75], p=3.77×10^{-8}, C=0.593**
PR	**Overall**	**HzR=2.22, CI=[1.71-2.86], p=1.21×10^{-9}, C=0.594**	**HzR=1.77, CI=[1.44-2.17], p=6.27×10^{-8}, C=0.567**
	ASCT	**HzR=2.76, CI=[1.87-4.06], p=2.66×10^{-7}, C=0.624**	**HzR=1.78, CI=[1.33-2.36], p=8.74×10^{-5}, C=0.575**

	Non-ASCT	**HzR=1.93, CI=[1.36-2.72], p=0.000202, C=0.579**	**HzR=1.81, CI=[1.34-2.44], p=9.76×10^{-5}, C=0.561**

Supplementary Table 6. Treatment heterogeneity adjusted survival association results of non-IMS/IMWG HR MM factors.

CPH survival test results of HR MM factors other than IMS/IMWG in CoMMpass data with treatment heterogeneity adjustments using the lifetime number of therapy lines and drug exposure profile for OS and drug combination in induction line therapy for PFS, respectively. Baseline levels were exposure to single IMID agent (IMID(1)) over the course of whole treatment history for OS and IMID-Glu-Doublet for PFS. Results over all patients as well as ASCT and non-ASCT cohorts are shown together.

Survival		OS			PFS			Survival	
Factor		HzR	CI	P	HzR	CI	P	Factor	
APOBEC (Overall)									
APOBEC		**1.50**	**1.17-1.92**	**0.00142**	**1.65**	**1.37-2.00**	**1.6×10^{-7}**	**APOBEC**	
Therapy line count		**1.39**	**1.21-1.60**	**2.36×10^{-6}**	-	-	-	IMID-Glu Doublet	**Line 1 drug combo**
Drug Profile	IMID(1)	-	-	-	0.85	0.59-1.21	0.362	PI-Alk-Glu Triplet	
	PI(1)	1.24	0.72-2.12	0.445	1.04	0.70-1.55	0.838	PI-Glu Doublet	
	PI(1)-IMID(1)	**0.30**	**0.18-0.50**	**4.05×10^{-6}**	**0.61**	**0.43-0.86**	**0.00496**	**PI-IMID-Glu Triplet**	
	PI(1)-IMID(1)-Dara	**0.20**	**0.09-0.44**	**4.82×10^{-5}**	**0.58**	**0.4-0.85**	**0.00579**	**Quadruplet**	
	PI(1)-IMID(2)	**0.42**	**0.20-0.85**	**0.0162**					
	PI(1)-IMID(2)-Dara	**0.07**	**0.03-0.18**	**9.83×10^{-9}**					
	PI(2)-IMID(1)	**0.29**	**0.16-0.53**	**4.6×10^{-5}**					
	PI(2)-IMID(1)-Dara	**0.20**	**0.08-0.45**	**0.000148**					
	PI(2)-IMID(2)	**0.41**	**0.21-0.82**	**0.0109**					
	PI(2)-IMID(2)-Dara	**0.14**	**0.07-0.29**	**1.71×10^{-7}**					
	PI(3)-IMID(2)-Dara	**0.09**	**0.03-0.22**	**4.59×10^{-7}**					
APOBEC (ASCT)									
APOBEC		**1.68**	**1.13-2.49**	**0.0102**	**2.09**	**1.60-2.72**	**4.48×10^{-8}**	**APOBEC**	
Therapy line count		**1.29**	**1.07-1.56**	**0.0084**	-	-	-	IMID-Glu Doublet	Line 1 drug combo
Drug profile	IMID(1)	-	-	-	0.48	0.21-1.13	0.0914	PI-Alk-Glu Triplet	
	PI(1)	0.45	0.05-4.05	0.476	0.86	0.35-2.12	0.74	PI-Glu Doublet	
	PI(1)-IMID(1)	0.25	0.03-1.84	0.174	0.45	0.20-1.03	0.0579	PI-IMID-Glu Triplet	
	PI(1)-IMID(1)-Dara	0.20	0.02-1.85	0.157	0.53	0.23-1.23	0.14	Quadruplet	

	PI(1)-IMID(2)	0.54	0.06-4.61	0.575					
	PI(1)-IMID(2)-Dara	**0.08**	**0.01-0.71**	**0.0242**					
	PI(2)-IMID(1)	0.27	0.03-2.06	0.205					
	PI(2)-IMID(1)-Dara	0.17	0.02-1.74	0.136					
	PI(2)-IMID(2)	0.58	0.07-4.63	0.609					
	PI(2)-IMID(2)-Dara	0.28	0.03-2.31	0.237					
	PI(3)-IMID(2)-Dara	0.18	0.02-1.64	0.138					
APOBEC (Non-ASCT)									
APOBEC		1.31	0.95-1.82	0.103	**1.32**	**1.00-1.74**	**0.0462**	**APOBEC**	
Therapy line count		**1.26**	**1.04-1.54**	**0.0201**	-	-	-	IMID-Glu Doublet	Line 1 drug combo
Drug profile	IMID(1)	-	-	-	1.41	0.94-2.11	0.0984	PI-Alk-Glu Triplet	
	PI(1)	**1.79**	**1.02-3.13**	**0.0412**	1.19	0.75-1.87	0.456	PI-Glu Doublet	
	PI(1)-IMID(1)	**0.56**	**0.33-0.97**	**0.0375**	1.07	0.71-1.61	0.749	PI-IMID-Glu Triplet	
	PI(1)-IMID(1)-Dara	**0.36**	**0.14-0.91**	**0.0302**	0.70	0.41-1.19	0.184	Quadruplet	
	PI(1)-IMID(2)	0.60	0.26-1.42	0.246					
	PI(1)-IMID(2)-Dara	**0.24**	**0.07-0.80**	**0.0201**					
	PI(2)-IMID(1)	0.60	0.30-1.19	0.144					
	PI(2)-IMID(1)-Dara	0.39	0.14-1.05	0.0623					
	PI(2)-IMID(2)	0.76	0.31-1.84	0.542					
	PI(2)-IMID(2)-Dara	**0.15**	**0.05-0.45**	**0.000716**					
	PI(3)-IMID(2)-Dara	**0.10**	**0.02-0.53**	**0.00683**					
Chromothripsis (Overall)									
Chromothripsis		**2.17**	**1.54-3.06**	**9.25×10^{-6}**	**1.90**	**1.43-2.53**	**9.75×10^{-6}**	**Chromothripsis**	
Therapy line count		**1.38**	**1.20-1.59**	**9.67×10^{-6}**	-	-	-	IMID-Glu Doublet	**Line 1 drug combo**
Drug profile	IMID(1)	-	-	-	0.84	0.57-1.24	0.391	PI-Alk-Glu Triplet	
	PI(1)	1.19	0.69-2.03	0.533	1.11	0.73-1.70	0.618	PI-Glu Doublet	
	PI(1)-IMID(1)	**0.29**	**0.17-0.48**	**1.52×10^{-6}**	**0.61**	**0.42-0.89**	**0.00969**	**PI-IMID-Glu Triplet**	
	PI(1)-IMID(1)-Dara	**0.20**	**0.09-0.43**	**4.67×10^{-5}**	**0.57**	**0.37-0.86**	**0.00777**	**Quadruplet**	
	PI(1)-IMID(2)	**0.35**	**0.17-0.75**	**0.00707**					
	PI(1)-IMID(2)-Dara	**0.07**	**0.03-0.19**	**3.71×10^{-8}**					
	PI(2)-IMID(1)	**0.28**	**0.15-0.51**	**2.91×10^{-5}**					
	PI(2)-IMID(1)-Dara	**0.20**	**0.08-0.49**	**0.000342**					
	PI(2)-IMID(2)	**0.42**	**0.21-0.83**	**0.0122**					

	PI(2)-IMID(2)-Dara	**0.13**	**0.06-0.27**	**1.31×10^{-7}**					
	PI(3)-IMID(2)-Dara	**0.08**	**0.03-0.22**	**7.54×10^{-7}**					
Chromothripsis (ASCT)									
	Chromothripsis	1.65	0.87-3.13	0.124	1.59	1.00-2.53	0.0502	Chromothripsis	
	Therapy line count	**1.26**	**1.03-1.54**	**0.0254**	-	-	-	IMID-Glu Doublet	**Line 1 drug combo**
Drug profile	IMID(1)	-	-	-	**0.36**	**0.13-0.99**	**0.0482**	**PI-Alk-Glu Triplet**	
	PI(1)	0.30	0.03-2.69	0.282	0.72	0.25-2.11	0.554	PI-Glu Doublet	
	PI(1)-IMID(1)	0.15	0.02-1.11	0.063	**0.35**	**0.13-0.95**	**0.0385**	**PI-IMID-Glu Triplet**	
	PI(1)-IMID(1)-Dara	0.12	0.01-1.06	0.0568	0.41	0.15-1.13	0.0847	Quadruplet	
	PI(1)-IMID(2)	0.16	0.02-1.60	0.118					
	PI(1)-IMID(2)-Dara	**0.04**	**0.00-0.45**	**0.00808**					
	PI(2)-IMID(1)	0.17	0.02-1.35	0.0944					
	PI(2)-IMID(1)-Dara	0.10	0.01-1.16	0.0657					
	PI(2)-IMID(2)	0.40	0.05-3.19	0.387					
	PI(2)-IMID(2)-Dara	0.18	0.02-1.54	0.119					
	PI(3)-IMID(2)-Dara	0.13	0.13-1.20	0.0713					
Chromothripsis (Non-ASCT)									
	Chromothripsis	**2.57**	**1.68-3.93**	**1.47×10^{-5}**	**1.88**	**1.30-2.72**	**0.000721**	**Chromothripsis**	
	Therapy line count	**1.23**	**1.01-1.50**	**0.0442**	-	-	-	IMID-Glu Doublet	Line 1 drug combo
Drug profile	IMID(1)	-	-	-	1.40	0.91-2.17	0.126	PI-Alk-Glu Triplet	
	PI(1)	1.59	0.91-2.79	0.102	1.21	0.75-1.95	0.425	PI-Glu Doublet	
	PI(1)-IMID(1)	**0.55**	**0.32-0.95**	**0.033**	1.04	0.67-1.61	0.849	PI-IMID-Glu Triplet	
	PI(1)-IMID(1)-Dara	**0.43**	**0.17-1.09**	**0.0738**	0.62	0.35-1.10	0.099	Quadruplet	
	PI(1)-IMID(2)	0.72	0.31-1.67	0.447					
	PI(1)-IMID(2)-Dara	**0.23**	**0.06-0.81**	**0.0223**					
	PI(2)-IMID(1)	0.59	0.29-1.18	0.134					
	PI(2)-IMID(1)-Dara	0.42	0.15-1.13	0.0849					
	PI(2)-IMID(2)	0.80	0.33-1.94	0.618					
	PI(2)-IMID(2)-Dara	**0.10**	**0.03-0.34**	**0.000187**					
	PI(3)-IMID(2)-Dara	**0.06**	**0.01-0.49**	**0.00911**					
EMC92 (Overall)									
	EMC92	**2.77**	**2.14-3.58**	**8.15×10^{-15}**	**2.34**	**1.94-2.83**	**1.3×10^{-18}**	**EMC92**	

	Therapy line count	**1.26**	**1.09-1.46**	**0.00188**	-	-	-	IMID-Glu Doublet	Line 1 drug combo
Drug profile	IMID(1)	-	-	-	1.02	0.67-1.55	0.934	PI-Alk-Glu Triplet	
	PI(1)	0.97	0.54-1.72	0.912	0.89	0.56-1.41	0.615	PI-Glu Doublet	
	PI(1)-IMID(1)	**0.32**	**0.19-0.55**	**4.35×10^{-5}**	0.74	0.50-1.11	0.147	PI-IMID-Glu Triplet	
	PI(1)-IMID(1)-Dara	**0.28**	**0.12-0.65**	**0.00307**	0.72	0.46-1.13	0.153	Quadruplet	
	PI(1)-IMID(2)	**0.46**	**0.22-0.99**	**0.0458**					
	PI(1)-IMID(2)-Dara	**0.10**	**0.04-0.25**	**1.76×10^{-6}**					
	PI(2)-IMID(1)	**0.36**	**0.19-0.68**	**0.00156**					
	PI(2)-IMID(1)-Dara	**0.31**	**0.12-0.79**	**0.0136**					
	PI(2)-IMID(2)	0.52	0.26-1.07	0.0742					
	PI(2)-IMID(2)-Dara	**0.16**	**0.07-0.36**	**5.15×10^{-6}**					
	PI(3)-IMID(2)-Dara	**0.12**	**0.04-0.34**	**5.61×10^{-5}**					
EMC92 (ASCT)									
	EMC92	**4.08**	**2.65-6.27**	**1.63×10^{-10}**	**2.71**	**2.08-3.53**	**2.24×10^{-13}**	**EMC92**	
	Therapy line count	1.18	0.95-1.46	0.129	-	-	-	IMID-Glu Doublet	Line 1 drug combo
Drug profile	IMID(1)	-	-	-	0.51	0.18-1.44	0.203	PI-Alk-Glu Triplet	
	PI(1)	0.19	0.02-1.81	0.15	0.61	0.20-1.84	0.384	PI-Glu Doublet	
	PI(1)-IMID(1)	0.21	0.03-1.53	0.122	0.50	0.18-1.36	0.174	PI-IMID-Glu Triplet	
	PI(1)-IMID(1)-Dara	0.24	0.03-2.16	0.201	0.58	0.21-1.62	0.3	Quadruplet	
	PI(1)-IMID(2)	0.22	0.02-2.12	0.192					
	PI(1)-IMID(2)-Dara	**0.07**	**0.01-0.70**	**0.0231**					
	PI(2)-IMID(1)	0.23	0.02-1.80	0.16					
	PI(2)-IMID(1)-Dara	0.15	0.01-1.73	0.129					
	PI(2)-IMID(2)	0.53	0.07-4.25	0.549					
	PI(2)-IMID(2)-Dara	0.19	0.02-1.59	0.125					
	PI(3)-IMID(2)-Dara	0.14	0.01-1.35	0.0889					
EMC92 (Non-ASCT)									
	EMC92	**2.31**	**1.67-3.2**	**4.98×10^{-7}**	**2.20**	**1.67-2.90**	**1.95×10^{-8}**	**EMC92**	
	Therapy line count	1.15	0.93-1.41	0.186	-	-	-	IMID-Glu Doublet	Line 1 drug combo
Drug profile	IMID(1)	-	-	-	1.58	0.99-2.53	0.0552	PI-Alk-Glu Triplet	
	PI(1)	1.49	0.82-2.72	0.187	1.00	0.60-1.69	0.993	PI-Glu Doublet	
	PI(1)-IMID(1)	0.55	0.3-1.00	0.0503	1.28	0.80-2.07	0.308	PI-IMID-Glu Triplet	
	PI(1)-IMID(1)-Dara	0.40	0.14-1.18	0.0978	0.88	0.48-1.59	0.661	Quadruplet	

	PI(1)-IMID(2)	0.84	0.36-1.96	0.692					
	PI(1)-IMID(2)-Dara	0.28	0.07-1.12	0.0708					
	PI(2)-IMID(1)	0.71	0.34-1.49	0.362					
	PI(2)-IMID(1)-Dara	0.71	0.23-2.17	0.553					
	PI(2)-IMID(2)	0.81	0.32-2.08	0.664					
	PI(2)-IMID(2)-Dara	**0.17**	**0.05-0.56**	**0.00367**					
	PI(3)-IMID(2)-Dara	**0.18**	**0.03-1.00**	**0.0494**					
PR (Overall)									
PR		**2.27**	**1.73-2.97**	**2.89×10^{-9}**	**1.82**	**1.48-2.25**	**2.48×10^{-8}**	**PR**	
Therapy line count		**1.38**	**1.18-1.61**	**4.5×10^{-5}**	-	-	-	IMID-Glu Doublet	Line 1 drug combo
Drug profile	IMID(1)	-	-	-	0.90	0.58-1.41	0.652	PI-Alk-Glu Triplet	
	PI(1)	1.04	0.58-1.87	0.888	0.87	0.53-1.41	0.568	PI-Glu Doublet	
	PI(1)-IMID(1)	**0.26**	**0.15-0.46**	**2.15×10^{-6}**	0.67	0.44-1.03	0.0651	PI-IMID-Glu Triplet	
	PI(1)-IMID(1)-Dara	**0.17**	**0.06-0.44**	**0.000297**	0.66	0.41-1.06	0.0886	Quadruplet	
	PI(1)-IMID(2)	**0.37**	**0.16-0.84**	**0.0168**					
	PI(1)-IMID(2)-Dara	**0.06**	**0.02-0.18**	**1.25×10^{-7}**					
	PI(2)-IMID(1)	**0.33**	**0.18-0.63**	**0.000736**					
	PI(2)-IMID(1)-Dara	**0.17**	**0.06-0.49**	**0.00105**					
	PI(2)-IMID(2)	**0.33**	**0.15-0.71**	**0.00457**					
	PI(2)-IMID(2)-Dara	**0.14**	**0.06-0.31**	**1.55×10^{-6}**					
	PI(3)-IMID(2)-Dara	**0.09**	**0.03-0.25**	**6.28×10^{-6}**					
PR (ASCT)									
PR		**2.50**	**1.64-3.82**	**2.09×10^{-5}**	**1.86**	**1.38-2.49**	**4.05×10^{-5}**	**PR**	
Therapy line count		**1.31**	**1.06-1.63**	**0.0123**	-	-	-	IMID-Glu Doublet	Line 1 drug combo
Drug profile	IMID(1)	-	-	-	0.67	0.21-2.17	0.504	PI-Alk-Glu Triplet	
	PI(1)	0.43	0.05-3.90	0.453	0.72	0.21-2.52	0.609	PI-Glu Doublet	
	PI(1)-IMID(1)	0.23	0.03-1.72	0.153	0.58	0.18-1.84	0.357	PI-IMID-Glu Triplet	
	PI(1)-IMID(1)-Dara	0.19	0.02-2.12	0.176	0.66	0.20-2.13	0.481	Quadruplet	
	PI(1)-IMID(2)	0.25	0.02-2.47	0.234					
	PI(1)-IMID(2)-Dara	**0.06**	**0.01-0.65**	**0.0201**					
	PI(2)-IMID(1)	0.32	0.04-2.49	0.275					
	PI(2)-IMID(1)-Dara	0.16	0.01-1.88	0.146					
	PI(2)-IMID(2)	0.55	0.07-4.52	0.581					

	PI(2)-IMID(2)-Dara	0.25	0.03-2.17	0.211					
	PI(3)-IMID(2)-Dara	0.14	0.01-1.42	0.0957					
PR (Non-ASCT)									
PR		**2.25**	**1.56-3.23**	**1.26×10^{-5}**	**1.74**	**1.28-2.36**	**0.000394**	**PR**	
Therapy line count		**1.25**	**1.00-1.57**	**0.049**	-	-	-	IMID-Glu Doublet	Line 1 drug combo
Drug profile	IMID(1)	-	-	-	1.31	0.80-2.14	0.291	PI-Alk-Glu Triplet	
	PI(1)	1.35	0.73-2.48	0.337	0.99	0.57-1.71	0.971	PI-Glu Doublet	
	PI(1)-IMID(1)	**0.50**	**0.27-0.91**	**0.025**	1.12	0.69-1.82	0.651	PI-IMID-Glu Triplet	
	PI(1)-IMID(1)-Dara	**0.23**	**0.07-0.75**	**0.015**	0.89	0.46-1.72	0.725	Quadruplet	
	PI(1)-IMID(2)	0.79	0.32-1.99	0.624					
	PI(1)-IMID(2)-Dara	**0.19**	**0.05-0.75**	**0.0182**					
	PI(2)-IMID(1)	0.61	0.29-1.31	0.207					
	PI(2)-IMID(1)-Dara	0.34	0.09-1.29	0.113					
	PI(2)-IMID(2)	0.42	0.13-1.30	0.13					
	PI(2)-IMID(2)-Dara	**0.13**	**0.04-0.42**	**0.000803**					
	PI(3)-IMID(2)-Dara	**0.13**	**0.02-0.69**	**0.0172**					

Supplementary Table 7. Multi-hit effect of HR MM factors in the ideal cohort of CoMMpass for PFS.

(a) CPH survival test results over patient groupings by the number of implicating HR factors for PFS. (b) The same results with (a) except for the detailed stratification of count = 1 cases into individual HR factors.

(a)

Factor	Median Survival (mth)	HzR [CI]	P-value
Count=0	64.9 [50.9-88.6]	-	-
Count=1	**36.3 [30.0-44.8]**	**1.66 [1.24-2.22]**	**0.000602**
Count=2	**26.7 [23.7-34.1]**	**2.58 [1.89-3.51]**	**2.03×10^{-9}**
Count=3	**15.9 [12.3-23.2]**	**4.52 [3.16-6.45]**	**1.24×10^{-16}**
Count≥4	**16.9 [9.1-29.6]**	**3.67 [2.37-5.68]**	**6.19×10^{-9}**
Log-rank test	$p=2.30\times10^{-20}$ (C=0.645)		

(b)

Factor		Median Survival (mth)	HzR [CI]	P-value
Count=0		64.9 [50.9-88.6]	-	-
Count=1	**APOBEC**	**26.9 [20.8-**44.8]	**2.45 [1.56-3.84]**	**0.000104**
	Chromothripsis	**29.2 [2.8-∞]**	**2.85 [1.25-6.51]**	**0.0130**
	EMC92	**32.4 [23.0-48.4]**	**1.95 [1.25-3.03]**	**0.00319**
	IMS/IMWG	46.8 [34.7-∞]	1.17 [0.71-1.94]	0.543
	PR	44.4 [28.0-∞]	1.24 [0.75-2.05]	0.405
Count=2		**26.7 [23.7-34.1]**	**2.58 [1.90-3.52]**	**1.87×10^{-9}**
Count=3		**15.9 [12.3-23.2]**	**4.54 [3.17-6.48]**	**1.03×10^{-16}**
Count≥4		**16.9 [9.1-29.6]**	**3.68 [2.37-5.70]**	**5.80×10^{-9}**
Log-rank test		$p=1.11\times10^{-19}$ (C=0.651)		

Supplementary Table 8. Treatment heterogeneity adjusted multi-hit effect of HR MM factors.

Treatment heterogeneity adjusted multi-hit effect of HR MM factors for (a) OS and (b) PFS are shown. Lifetime number of therapy lines and drug exposure profile were used as drug treatment variables for OS and drug combination classification in induction line were used for PFS, respectively. For drug exposure profile, patients exposed to single IMID agent (IMID(1)) were considered as baseline for OS, and patients treated with IMID-Glu Doublet regimen in induction line were considered as baseline for PFS.

(a)

Factor		HzR [CI]	P-value
Count	**1**	**1.62 [1.04-2.51]**	**0.0315**
	2	**3.16 [2.03-4.92]**	**3.26×10^{-7}**
	3	**5.61 [3.46-9.09]**	**2.49×10^{-12}**
	≥4	**6.67 [3.79-11.77]**	**5.37×10^{-11}**
Therapy line count		1.19 [1.00-1.42]	0.0532
Drug exposure profile	IMID(1)	-	-
	PI(1)	0.72 [0.38-1.36]	0.315
	PI(1)-IMID(1)	**0.22 [0.12-0.40]**	**7.36×10^{-7}**
	PI(1)-IMID(1)-Dara	**0.17 [0.06-0.49]**	**0.00107**
	PI(1)-IMID(2)	**0.32 [0.12-0.81]**	**0.0164**
	PI(1)-IMID(2)-Dara	**0.06 [0.02-0.18]**	**5.33×10^{-7}**
	PI(2)-IMID(1)	**0.27 [0.14-0.54]**	**0.000208**
	PI(2)-IMID(1)-Dara	**0.13 [0.04-0.43]**	**0.000806**
	PI(2)-IMID(2)	**0.36 [0.15-0.86]**	**0.0216**
	PI(2)-IMID(2)-Dara	**0.14 [0.06-0.33]**	**5.77×10^{-6}**
	PI(3)-IMID(2)-Dara	**0.09 [0.03-0.29]**	**6.27×10^{-5}**
Log-rank test		$p=8.07\times10^{-27}$	

(b)

Factor		HzR [CI]	P-value
Count	**1**	**1.69 [1.26-2.27]**	**0.000515**
	2	**2.65 [1.94-3.64]**	**1.40×10^{-9}**
	3	**5.41 [3.71-7.88]**	**1.67×10^{-18}**
	≥4	**4.10 [2.61-6.43]**	**8.62×10^{-10}**
Line 1 drug combo	IMID-Glu Doublet	-	-
	PI-Alk-Glu Triplet	0.78 [0.48-1.26]	0.302
	PI-Glu Doublet	0.78 [0.46-1.34]	0.367
	PI-IMID-Glu Triplet	0.63 [0.40-1.00]	0.0521
	Quadruplet	0.67 [0.40-1.13]	0.137

Log-rank test	$p=7.19\times10^{-22}$

Supplementary Table 9. Risk factor combination performance over ideal cohort patients.

All performance results of exhaustive HR factor combination survival model survey using ideal cohort patients are shown. Models with maximum *C*-statistics for OS/PFS from single- to quadruple-factor combinations are marked.

Model	OS		PFS	
	C	P	C	P
APOBEC	0.64614	7.09E-13	0.60996	1.12E-11
CHROMOTH[1]	0.6419	2.18E-11	0.60305	6.01E-09
EMC92	**0.70964**	**1.95E-26**	**0.6484**	**7.60E-20**
IMWG[2]	0.65127	7.05E-14	0.59967	7.07E-08
PR	0.67649	2.18E-17	0.61931	6.16E-12
APOBEC|CHROMOTH	0.65287	5.18E-13	0.6196	8.92E-13
APOBEC|EMC92	0.71229	2.12E-26	**0.65846**	**7.16E-22**
APOBEC|IMWG	0.65927	5.35E-15	0.6172	6.50E-12
APOBEC|PR	0.68371	2.02E-18	0.63431	2.09E-15
CHROMOTH|EMC92	0.71307	2.37E-26	0.65557	3.50E-21
CHROMOTH|IMWG	0.6591	2.82E-14	0.61533	5.95E-10
CHROMOTH|PR	0.67909	1.89E-17	0.62871	3.79E-13
EMC92|IMWG	0.71472	7.35E-27	0.65185	1.27E-19
EMC92|PR	**0.71538**	**6.35E-28**	0.65335	4.54E-21
IMWG|PR	0.68868	5.16E-20	0.62773	6.33E-13
APOBEC|CHROMOTH|EMC92	0.71462	4.07E-26	**0.66238**	**1.92E-22**
APOBEC|CHROMOTH|IMWG	0.6644	5.69E-15	0.62607	7.47E-13
APOBEC|CHROMOTH|PR	0.68486	3.87E-18	0.63882	9.19E-16
APOBEC|EMC92|IMWG	0.71649	1.39E-26	0.65969	2.61E-21
APOBEC|EMC92|PR	0.71898	1.06E-27	0.66164	1.29E-22
APOBEC|IMWG|PR	0.69242	3.05E-20	0.63883	1.81E-15
CHROMOTH|EMC92|IMWG	0.71787	1.13E-26	0.65836	8.53E-21
CHROMOTH|EMC92|PR	0.71765	1.25E-27	0.65961	7.42E-22
CHROMOTH|IMWG|PR	0.69177	8.28E-20	0.63685	8.49E-14
EMC92|IMWG|PR	**0.72018**	**2.06E-28**	0.65591	7.64E-21
APOBEC|CHROMOTH|EMC92|IMWG	0.71835	2.87E-26	0.66348	7.36E-22
APOBEC|CHROMOTH|EMC92|PR	0.72043	2.78E-27	**0.66524**	**7.26E-23**
APOBEC|CHROMOTH|IMWG|PR	0.69367	7.26E-20	0.64354	9.77E-16
APOBEC|EMC92|IMWG|PR	0.72257	5.55E-28	0.66278	4.28E-22

CHROMOTH|EMC92|IMWG|PR	**0.72293**	**4.97E-28**	0.66152	1.69E-21
APOBEC|CHROMOTH|EMC92|IMWG|PR	**0.72436**	**1.55E-27**	**0.66554**	**2.54E-22**

[1]CHROMOTH=chromothripsis; [2]IMWG=IMS/IMWG.

Supplementary Table 10. Risk factor combination performance over all patients.

All performance results of exhaustive HR factor combination survival model survey using all patients are shown. Models with maximum *C*-statistics for OS/PFS from single- to quadruple-factor combinations are marked.

Model	OS		PFS	
	C	P	C	P
APOBEC	0.64629	3.00E-20	0.61073	2.39E-17
CHROMOTH[1]	0.65492	3.17E-21	0.61233	1.76E-14
EMC92	**0.70279**	**1.29E-31**	**0.6418**	**5.14E-24**
IMWG[2]	0.67252	2.75E-24	0.62899	6.97E-17
PR	0.67077	7.43E-18	0.61408	4.38E-13
APOBEC|CHROMOTH	0.65912	5.35E-21	0.62154	2.63E-17
APOBEC|EMC92	0.70845	3.72E-31	0.65029	2.60E-25
APOBEC|IMWG	0.67747	1.44E-25	0.63707	9.45E-20
APOBEC|PR	0.67839	1.02E-18	0.62867	9.34E-16
CHROMOTH|EMC92	0.71396	3.18E-32	0.65659	7.97E-26
CHROMOTH|IMWG	0.68213	6.58E-25	0.63927	9.35E-18
CHROMOTH|PR	0.68133	3.17E-19	0.62347	2.83E-13
EMC92|IMWG	**0.72429**	**5.51E-34**	**0.66204**	**6.36E-25**
EMC92|PR	0.70424	7.39E-28	0.64265	1.73E-21
IMWG|PR	0.68813	1.15E-19	0.62925	7.18E-14
APOBEC|CHROMOTH|EMC92	0.71729	8.00E-32	0.6599	2.58E-26
APOBEC|CHROMOTH|IMWG	0.68556	3.31E-25	0.64571	5.59E-20
APOBEC|CHROMOTH|PR	0.68407	1.74E-18	0.6339	2.26E-15
APOBEC|EMC92|IMWG	**0.72787**	**1.50E-34**	**0.66661**	**6.64E-26**
APOBEC|EMC92|PR	0.71084	1.86E-27	0.6544	9.56E-23
APOBEC|IMWG|PR	0.69316	9.75E-21	0.6386	3.85E-16
CHROMOTH|EMC92|IMWG	0.72724	2.26E-33	0.66592	4.92E-25
CHROMOTH|EMC92|PR	0.71394	8.96E-28	0.65462	1.81E-22
CHROMOTH|IMWG|PR	0.693	3.49E-20	0.63888	2.27E-14
EMC92|IMWG|PR	0.71864	4.56E-28	0.65546	1.37E-21
APOBEC|CHROMOTH|EMC92|IMWG	**0.72954**	**2.03E-33**	**0.66935**	**1.06E-25**
APOBEC|CHROMOTH|EMC92|PR	0.71582	2.67E-27	0.65975	4.04E-23
APOBEC|CHROMOTH|IMWG|PR	0.69392	6.10E-20	0.64385	7.66E-16
APOBEC|EMC92|IMWG|PR	0.72279	1.15E-28	0.6623	1.38E-22
CHROMOTH|EMC92|IMWG|PR	0.72196	1.18E-27	0.66159	1.15E-21

APOBEC|CHROMOTH|EMC92|IMWG|PR	**0.72436**	**1.55E-27**	**0.66554**	**2.54E-22**

[1]CHROMOTH=chromothripsis; [2]IMWG=IMS/IMWG.

Supplementary Table 11. Multivariate CPH test results of core HR MM factors using all patients.

Summary of multivariate CPH test results of a model including core HR MM factors age, sex, EMC92, and IMS/IMWG using all patients in CoMMpass data are shown.

Factor	OS		PFS	
	HzR [CI]	*P*	HzR [CI]	*P*
Age	**1.04 [1.03-1.05]**	**7.35×10^{-10}**	**1.03 [1.02-1.04]**	**1.62×10^{-7}**
Sex	**0.69 [0.53-0.91]**	**0.00786**	**0.78 [0.64-0.96]**	**0.0197**
EMC92	**3.06 [2.34-4.00]**	**3.41×10^{-16}**	**2.33 [1.89-2.87]**	**2.62×10^{-15}**
IMS/IMWG	**1.41 [1.08-1.85]**	**0.0125**	1.21 [0.97-1.51]	0.0847
Log-rank	*P*=5.51×10^{-34} (*C*=0.724)		*P*=6.36×10^{-25} (*C*=0.662)	

Supplementary Table 12. Treatment heterogeneity adjusted survival association results of core HR MM factors over ideal cohort.

Summary of multivariate CPH test results of a model including core HR MM factors age, sex, EMC92, IMS/IMWG and treatment heterogeneity variables ideal cohort in CoMMpass data are shown. As the treatment heterogeneity variables, the lifetime number of therapy lines and exposure profile were used for OS, and drug combination classification in induction line therapy was used for PFS. For drug exposure profile, patients exposed to single IMID agent (IMID(1)) were considered as baseline for OS, and patients treated with IMID-Glu Doublet regimen in induction line were considered as baseline for PFS.

Survival		OS			PFS			Survival	
Factor		HzR	CI	P	HzR	CI	P	Factor	
Age		**1.03**	**1.02-1.05**	**6.50×10^{-5}**	**1.02**	**1.01-1.04**	**3.65×10^{-5}**	**Age**	
Sex		**0.63**	**0.45-0.85**	**0.00331**	0.82	0.65-1.03	0.0869	Sex	
EMC92		**2.56**	**1.86-3.52**	**6.87×10^{-9}**	**2.48**	**1.96-3.12**	**1.66×10^{-14}**	**EMC92**	
IMS/IMWG		**1.53**	**1.12-2.10**	**0.00792**	**1.30**	**1.02-1.66**	**0.0372**	**IMS/IMWG**	
Therapy line count		1.19	1.00-1.41	0.0515	-	-	-	IMID-Glu Doublet	Line 1 drug combo
Drug Profile	IMID(1)	-	-	-	1.07	0.66-1.75	0.786	PI-Alk-Glu Triplet	
	PI(1)	0.91	0.48-1.71	0.768	0.91	0.53-1.56	0.733	PI-Glu Doublet	
	PI(1)-IMID(1)	**0.34**	**0.18-0.62**	**0.000519**	0.90	0.56-1.45	0.670	PI-IMID-Glu Triplet	
	PI(1)-IMID(1)-Dara	**0.23**	**0.08-0.66**	**0.00655**	0.89	0.52-1.52	0.658	Quadruplet	
	PI(1)-IMID(2)	0.54	0.21-1.40	0.205					
	PI(1)-IMID(2)-Dara	**0.11**	**0.04-0.35**	**0.000145**					
	PI(2)-IMID(1)	**0.44**	**0.22-0.90**	**0.0240**					
	PI(2)-IMID(1)-Dara	**0.29**	**0.09-0.98**	**0.0465**					
	PI(2)-IMID(2)	0.49	0.21-1.17	0.109					
	PI(2)-IMID(2)-Dara	**0.24**	**0.10-0.57**	**0.00114**					
	PI(3)-IMID(2)-Dara	**0.19**	**0.06-0.62**	**0.00558**					

Supplementary Table 13. Treatment heterogeneity adjusted survival association results of core HR MM factors using all patients.

Summary of multivariate CPH test results of a model including core HR MM factors age, sex, EMC92, IMS/IMWG and treatment heterogeneity variables using all patients in CoMMpass data are shown. As treatment heterogeneity variables, the lifetime number of therapy lines and exposure profile were used for OS, and drug combination classification in induction line therapy was used for PFS. For drug exposure profile, patients exposed to single IMID agent (IMID(1)) were considered as baseline for OS, and patients treated with IMID-Glu Doublet regimen in induction line were considered as baseline for PFS.

Survival		OS			PFS			Survival	
Factor		HzR	CI	P	HzR	CI	P	Factor	
Age		**1.04**	**1.02-1.05**	**9.88×10^{-7}**	**1.03**	**1.02-1.04**	**1.49×10^{-6}**	**Age**	
Sex		**0.63**	**0.47-0.84**	**0.00141**	**0.76**	**0.62-0.94**	**0.0119**	**Sex**	
EMC92		**2.61**	**1.95-3.50**	**1.43×10^{-10}**	**2.42**	**1.95-2.99**	**4.60×10^{-16}**	**EMC92**	
IMS/IMWG		**1.53**	**1.15-2.04**	**0.00392**	**1.29**	**1.03-1.61**	**0.0273**	**IMS/IMWG**	
Therapy line count		**1.20**	**1.03-1.40**	**0.0214**	-	-	-	IMID-Glu Doublet	Line 1 drug combo
Drug Profile	IMID(1)	-	-	-	1.21	0.76-1.92	0.412	PI-Alk-Glu Triplet	
	PI(1)	1.00	0.55-1.85	0.978	1.05	0.63-1.74	0.851	PI-Glu Doublet	
	PI(1)-IMID(1)	**0.34**	**0.19-0.62**	**0.000348**	0.95	0.60-1.49	0.821	PI-IMID-Glu Triplet	
	PI(1)-IMID(1)-Dara	**0.27**	**0.11-0.67**	**0.00444**	0.98	0.60-1.62	0.950	Quadruplet	
	PI(1)-IMID(2)	0.63	0.27-1.45	0.273					
	PI(1)-IMID(2)-Dara	**0.12**	**0.04-0.34**	**5.56×10^{-5}**					
	PI(2)-IMID(1)	**0.45**	**0.22-0.88**	**0.0208**					
	PI(2)-IMID(1)-Dara	0.36	0.12-1.02	0.0536					
	PI(2)-IMID(2)	0.60	0.28-1.28	0.184					
	PI(2)-IMID(2)-Dara	**0.24**	**0.10-0.54**	**0.000604**					
	PI(3)-IMID(2)-Dara	**0.17**	**0.06-0.50**	**0.00138**					

Supplementary Table 14. Univariate and treatment heterogeneity adjusted survival association results of FHR phenotype.

(a) CPH survival test results and (b-d) treatment heterogeneity adjusted CPH survival test results of FHR phenotype over all patients as well as ASCT/non-ASCT cohorts are shown. For treatment heterogeneity adjusted results, (b) correspond to results over all patients, (c) over ASCT and (d) over non-ASCT cohorts. As treatment heterogeneity variables, the lifetime number of therapy lines and exposure profile were used for OS, and patients exposed to single IMID agent (IMID(1)) were considered as baseline for survival analysis.

(a)

Cohort	HR	CI	P
Overall	**2.70**	**1.95-3.74**	**2.58×10^{-9}**
ASCT	**3.10**	**1.83-5.24**	**2.57×10^{-5}**
Non-ASCT	**1.83**	**1.21-2.78**	**0.00456**

(b)

Factor		HR	CI	P
FHR		**2.55**	**1.79-3.64**	**2.46×10^{-7}**
Therapy line count		**1.25**	**1.05-1.49**	**0.0125**
Drug profile	IMID(1)	-	-	-
	PI(1)	0.99	0.43-2.30	0.983
	PI(1)-IMID(1)	**0.32**	**0.14-0.71**	**0.000512**
	PI-IMID(1)-Dara	**0.34**	**0.12-0.98**	**0.0459**
	PI(1)-IMID(2)	0.68	0.23-2.02	0.489
	PI(1)-IMID(2)-Dara	**0.05**	**0.01-0.24**	**0.000219**
	PI(2)-IMID(1)	**0.29**	**0.11-0.74**	**0.00924**
	PI(2)-IMID(1)-Dara	**0.25**	**0.07-0.90**	**0.034**
	PI(2)-IMID(2)	0.65	0.24-1.77	0.396
	PI(2)-IMID(2)-Dara	**0.25**	**0.09-0.69**	**0.00813**
	PI(3)-IMID(2)-Dara	**0.23**	**0.06-0.81**	**0.0224**

(c)

Factor		HR	CI	P
FHR		**2.66**	**1.39-5.09**	**0.00309**
Therapy line count		1.09	0.84-1.41	0.507
Drug profile	IMID(1)	-	-	-
	PI(1)	0.11	0.01-1.71	0.114
	PI(1)-IMID(1)	**0.13**	**0.02-0.97**	**0.047**
	PI-IMID(1)-Dara	0.11	0.01-1.29	0.0800
	PI(1)-IMID(2)	0.16	0.01-2.68	0.203
	PI(1)-IMID(2)-Dara	**0.04**	**0.00-0.49**	**0.0115**
	PI(2)-IMID(1)	**0.11**	**0.01-0.97**	**0.0473**
	PI(2)-IMID(1)-Dara	0.10	0.01-1.73	0.114
	PI(2)-IMID(2)	0.58	0.07-5.09	0.623
	PI(2)-IMID(2)-Dara	0.28	0.03-2.44	0.248
	PI(3)-IMID(2)-Dara	0.27	0.03-2.76	0.27

(d)

Factor		HR	CI	P
	FHR	**1.70**	**1.08-2.67**	**0.0218**
	Therapy line count	1.29	0.98-1.70	0.0683
Drug profile	IMID(1)	-	-	-
	PI(1)	1.39	0.57-3.41	0.47
	PI(1)-IMID(1)	0.54	0.22-1.32	0.177
	PI-IMID(1)-Dara	0.53	0.15-1.90	0.333
	PI(1)-IMID(2)	1.23	0.38-3.99	0.735
	PI(1)-IMID(2)-Dara	10^{-7}	0.00-∞	0.995
	PI(2)-IMID(1)	0.53	0.18-1.62	0.268
	PI(2)-IMID(1)-Dara	0.41	0.09-1.82	0.242
	PI(2)-IMID(2)	0.88	0.25-3.05	0.841
	PI(2)-IMID(2)-Dara	0.20	0.04-1.02	0.053
	PI(3)-IMID(2)-Dara	0.17	0.01-1.91	0.15

Supplementary Table 15. Stratification of FHR phenotype in CoMMpass data.

Summary of patient stratification of baseline risk and FHR phenotypes. Patients were stratified by the number of inflicting HR MM factors for both baseline risk and FHR phenotypes. Patients inflicted by four-or-more HR lesions were grouped together for baseline risk phenotype, and patients inflicted by one-or-more HR lesions were grouped together for FHR phenotype. Results over ideal cohort and complete FHR cohort are shown together.

Group	n(HR)	Ideal cohort	Complete FHR cohort
Baseline risk	0	121 (31.8%)	173 (33.8%)
	1	81 (21.3%)	120 (23.4%)
	2	53 (13.9%)	64 (12.5%)
	3	33 (8.7%)	44 (8.6%)
	4+	22 (5.8%)	25 (4.9%)
FHR	0	18 (4.7%)	24 (4.7%)
	1+	53 (13.9%)	62 (12.1%)
Total		381 (100.1%)	512 (100.0%)

Supplementary Table 16. Survival association of stratified FHR phenotypes.

Summary of CPH test results over stratified FHR phenotypes over (a) ideal cohort and (b) complete FHR cohort. Stratified FHR phenotypes were represented as the merger of baseline risk/FHR and the number of HR MM lesions. Patients with baseline risk of FHR with no additional HR lesions (Baseline, N=0) were used as the reference group. Patients with four-or-more HR MM lesions were merged. For PFS, patient groups based on FHR phenotypes were ignored to avoid confounding effects.

(a)

Group	OS			PFS		
	HR	CI	P	HR	CI	P
Baseline, N=1	**2.28**	**1.25-4.19**	**0.00761**	**2.06**	**1.41-3.00**	**0.000187**
Baseline, N=2	**4.12**	**2.27-7.48**	**3.31×10^{-6}**	**3.02**	**2.01-4.53**	**9.44×10^{-8}**
Baseline, N=3	**8.03**	**4.13-15.64**	**8.71×10^{-10}**	**5.93**	**3.54-9.93**	**1.29×10^{-11}**
Baseline, N=4+	**10.23**	**5.31-19.70**	**3.62×10^{-12}**	**6.15**	**3.68-10.28**	**4.37×10^{-12}**
FHR, N=0	**4.41**	**1.91-10.17**	**0.000495**			
FHR, N=1+	**8.01**	**4.53-14.19**	**9.45×10^{-13}**			

(b)

Group	OS			PFS		
	HR	CI	P	HR	CI	P
Baseline, N=1	**2.13**	**1.22-3.74**	**0.00819**	**1.93**	**1.35-2.75**	**0.000283**
Baseline, N=2	**4.28**	**2.46-7.44**	**2.75×10^{-7}**	**2.99**	**2.03-4.39**	**2.39×10^{-8}**
Baseline, N=3	**7.28**	**3.91-13.56**	**4.12×10^{-10}**	**5.75**	**3.55-9.32**	**1.22×10^{-12}**
Baseline, N=4+	**10.49**	**5.68-19.39**	**6.29×10^{-14}**	**6.31**	**3.87-10.27**	**1.42×10^{-13}**
FHR, N=0	**4.96**	**2.44-10.09**	**9.99×10^{-6}**			
FHR, N=1+	**8.09**	**4.76-13.75**	**1.18×10^{-14}**			

Supplementary Table 17. Multivariate CPH test results of IMS/IMWG and EMC92 combination.

Summary of multivariate CPH test results of a model including IMS/IMWG and EMC92 using (a) ideal cohort and (b) all patients in CoMMpass data are shown. Baseline risk group with no HR lesions in both EMC92 and IMS/IMWG was used as the reference.

(a)

HR lesion	OS		PFS	
	HzR [CI]	*P*	HzR [CI]	*P*
EMC92	**3.35 [2.42-4.64]**	**4.07×10^{-13}**	**2.27 [1.76-2.93]**	**2.65×10^{-10}**
IMS/IMWG	1.57 [1.00-2.46]	0.0503	1.19 [0.85-1.66]	0.311
IMS/IMWG & EMC92	**4.64 [3.37-6.39]**	**4.43×10^{-21}**	**2.94 [2.26-3.81]**	**5.74×10^{-16}**
Log-rank	$P=1.00\times10^{-25}$		$P=2.85\times10^{-19}$	

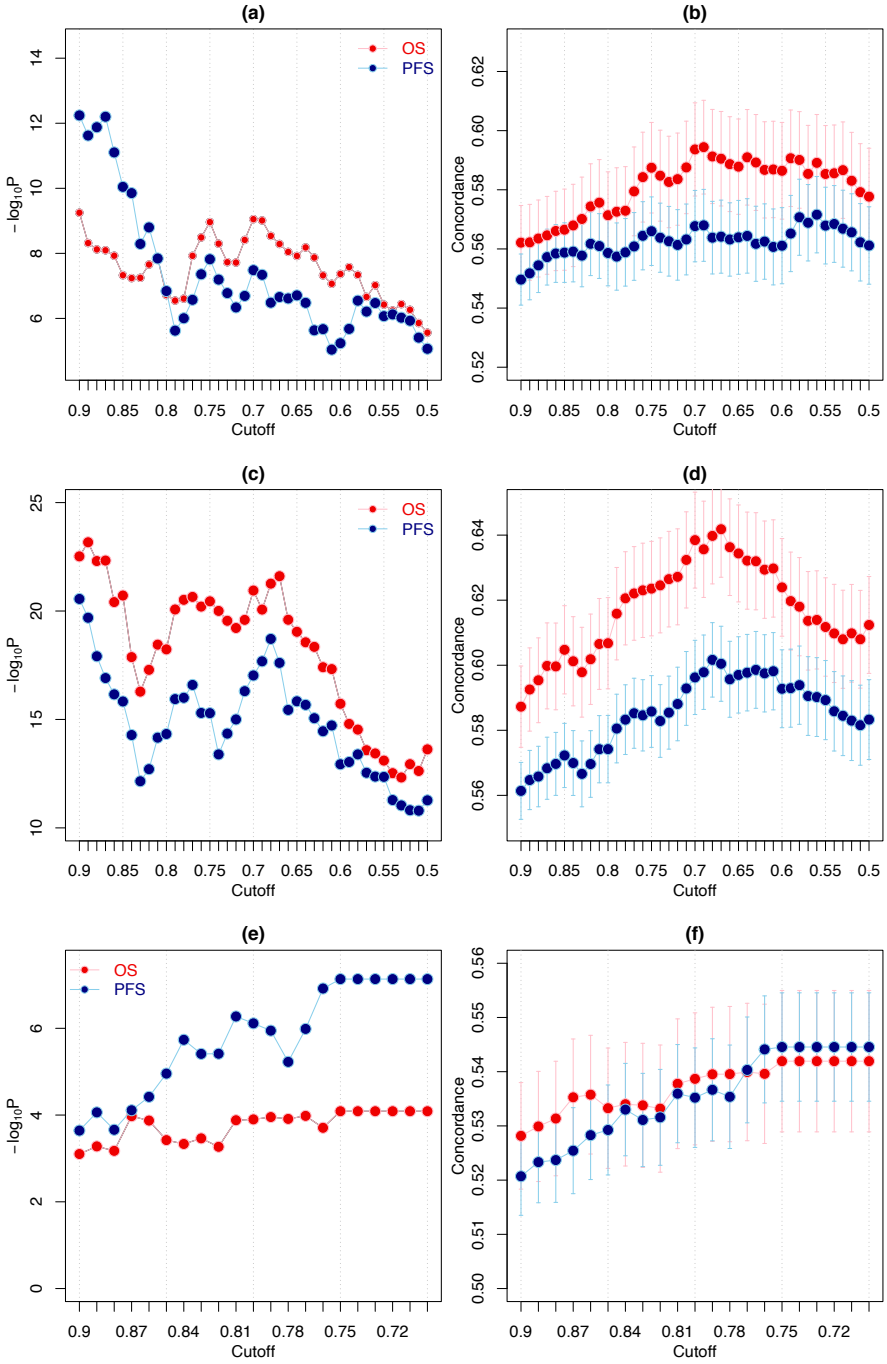
(b)

HR lesion	OS		PFS	
	HzR [CI]	*P*	HzR [CI]	*P*
EMC92	**2.64 [2.00-3.49]**	**6.45×10^{-12}**	**2.05 [1.63-2.58]**	**8.93×10^{-10}**
IMS/IMWG	1.24 [0.82-1.88]	0.305	1.08 [0.79-1.48]	0.630
IMS/IMWG & EMC92	**3.64 [2.78-4.77]**	**4.40×10^{-21}**	**2.63 [2.08-3.34]**	**9.27×10^{-16}**
Log-rank	$P=1.05\times10^{-26}$		$P=4.11\times10^{-20}$	

Supplementary Figures

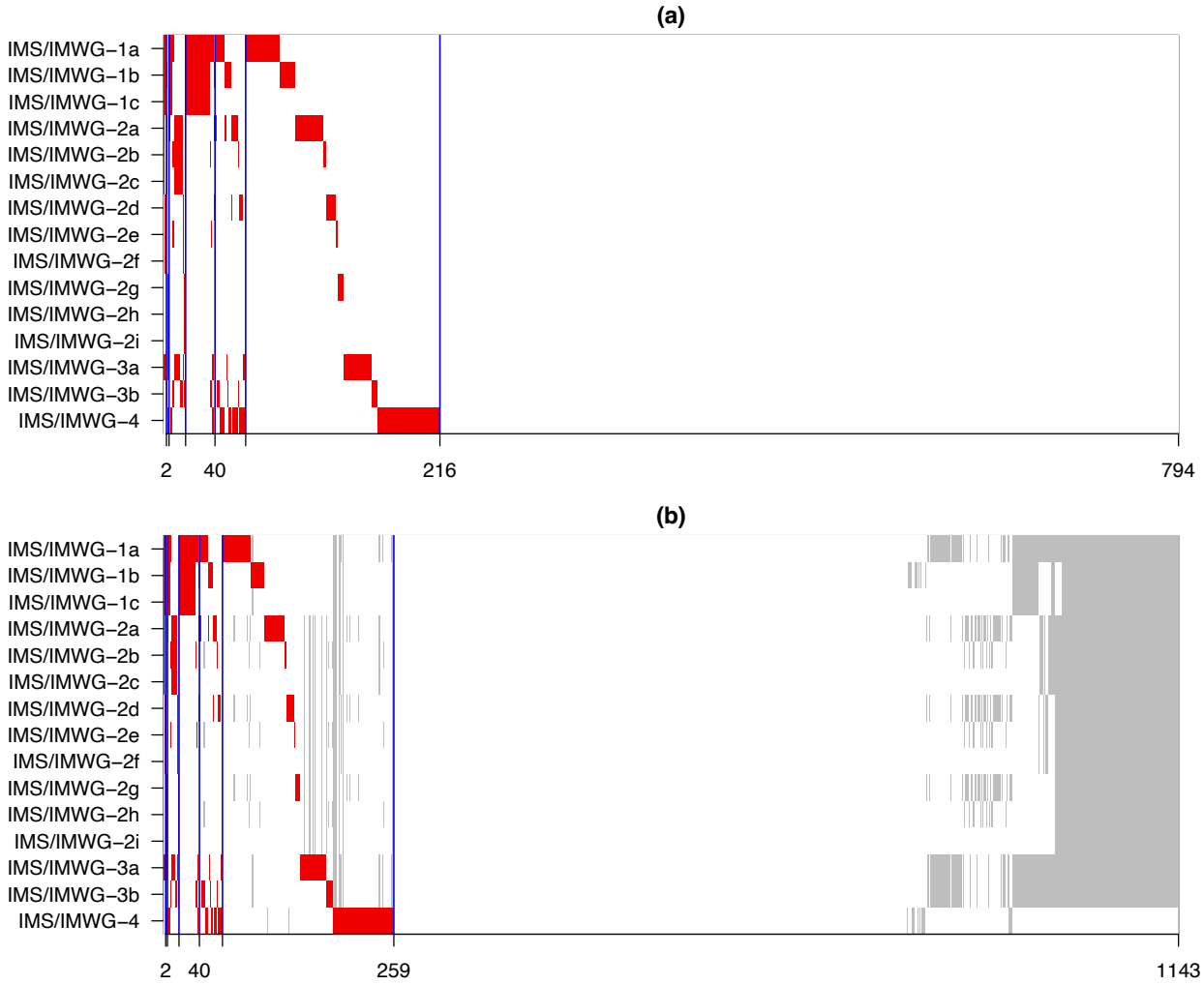
Supplementary Figure 1. HR threshold determination of continuous risk factors.

Summary of HR threshold survey for (a), (b) PR, (c), (d) EMC92, and (e), (f) APOBEC. (a), (c), (e) exhibit *p*-value profiles, and (b), (d), (f) exhibit *C*-statistics profiles, respectively.



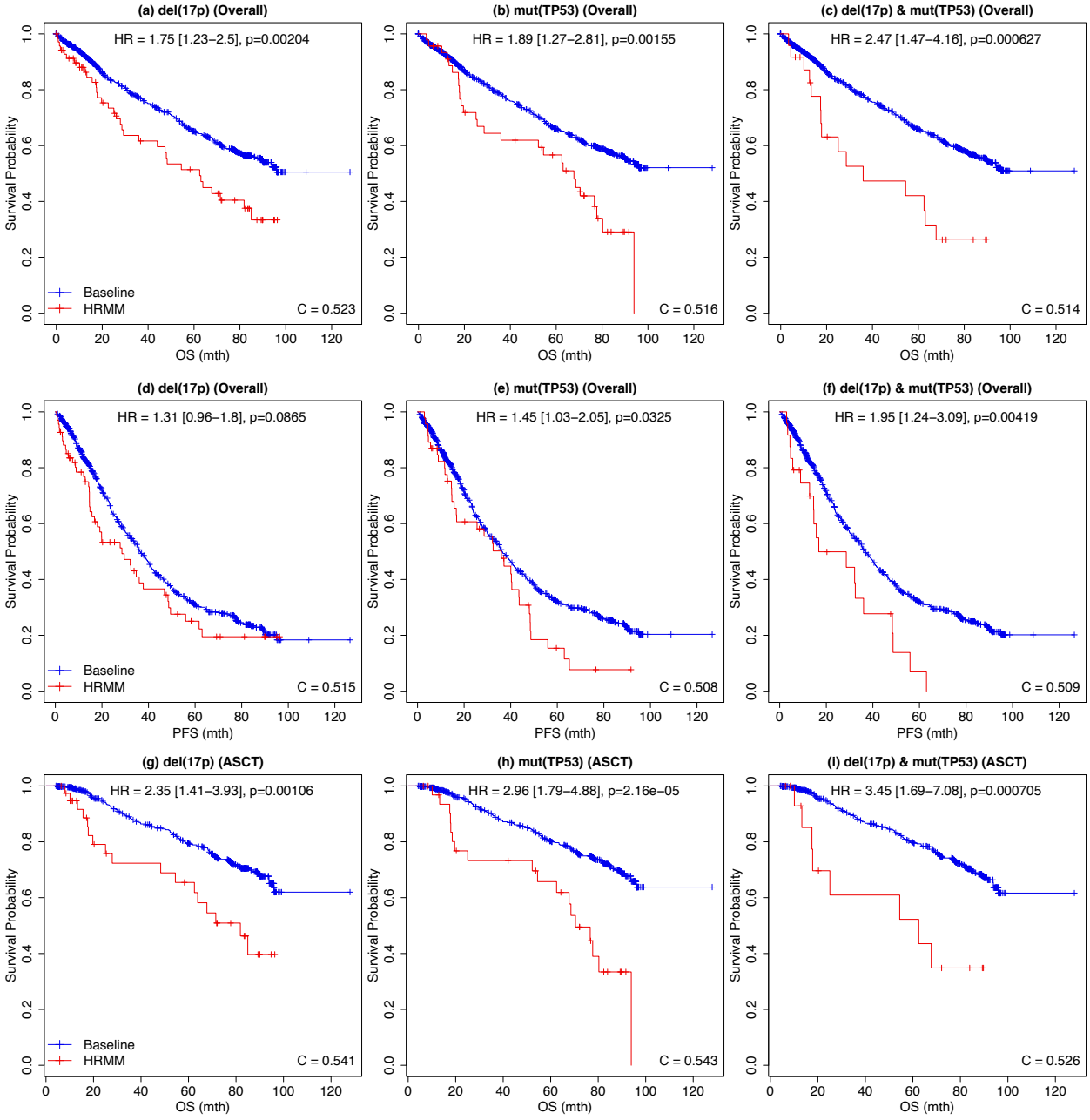
Supplementary Figure 2. Member overlap of IMS/IMWG sub-criteria.

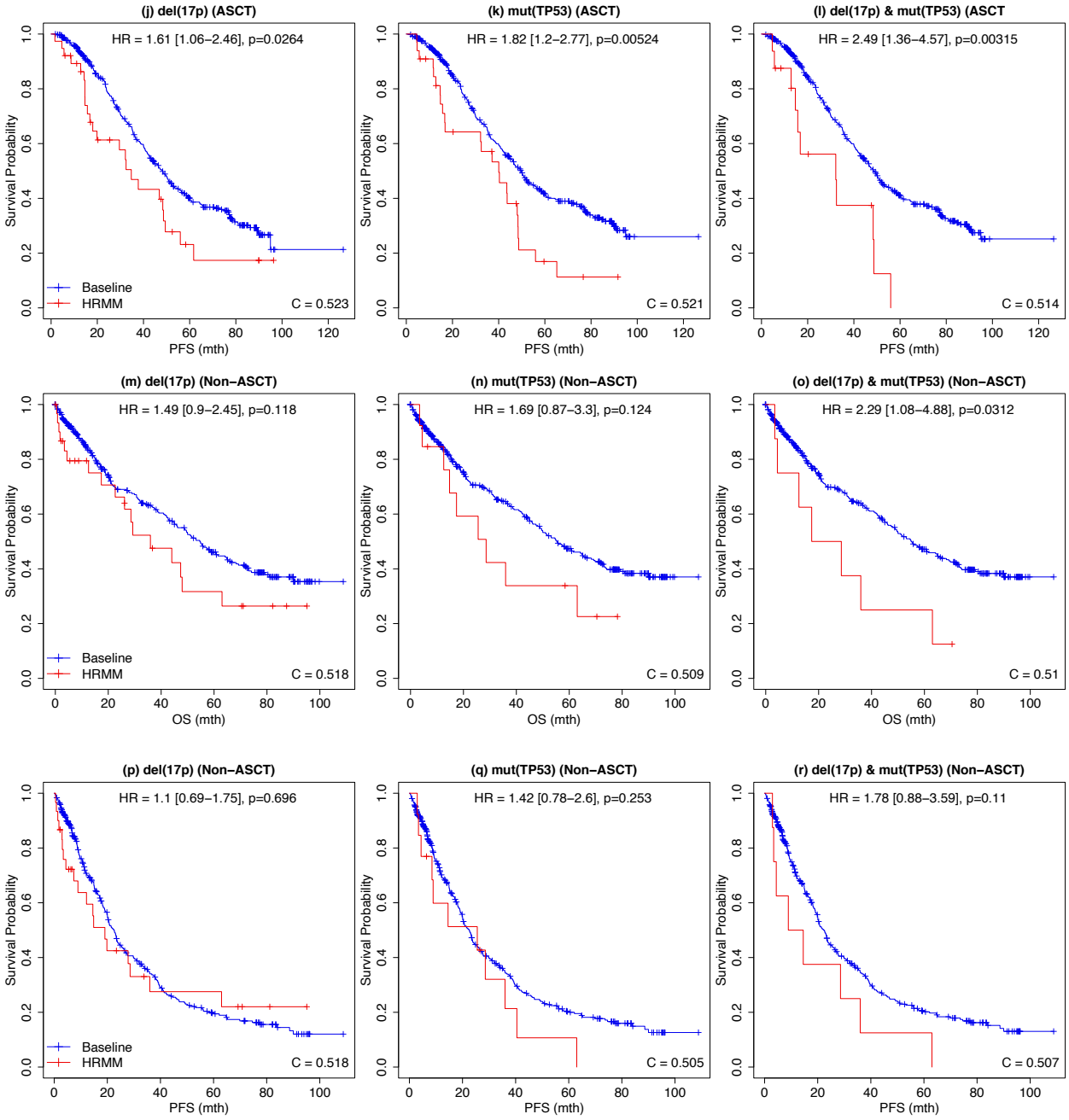
(a) Heatmap without missing values and (b) with missing values (gray) of IMS/IMWG sub-criteria. No patient was marked as HR MM by all sub-criteria in both (a) and (b). When cases with missing information were ignored, 2 (0.2%), 2 (0.2%), 13 (1.1%), 23 (2%), 24 (2.3%), 152 (16.9%), and 578 (77.3%) cases remained as HR MM by 6, 5, …, 0 criteria, respectively. When cases with missing information were included, 2 (0.2%), 2 (0.2%), 13 (1.1%), 23 (2%), 26 (2.3%), 193 (16.9%), and 884 (77.3%) cases were marked as HR MM by 7, 5, 4, …, 0 criteria, respectively.



Supplementary Figure 3. Survival curves of IMS/IMWG criterion 1.

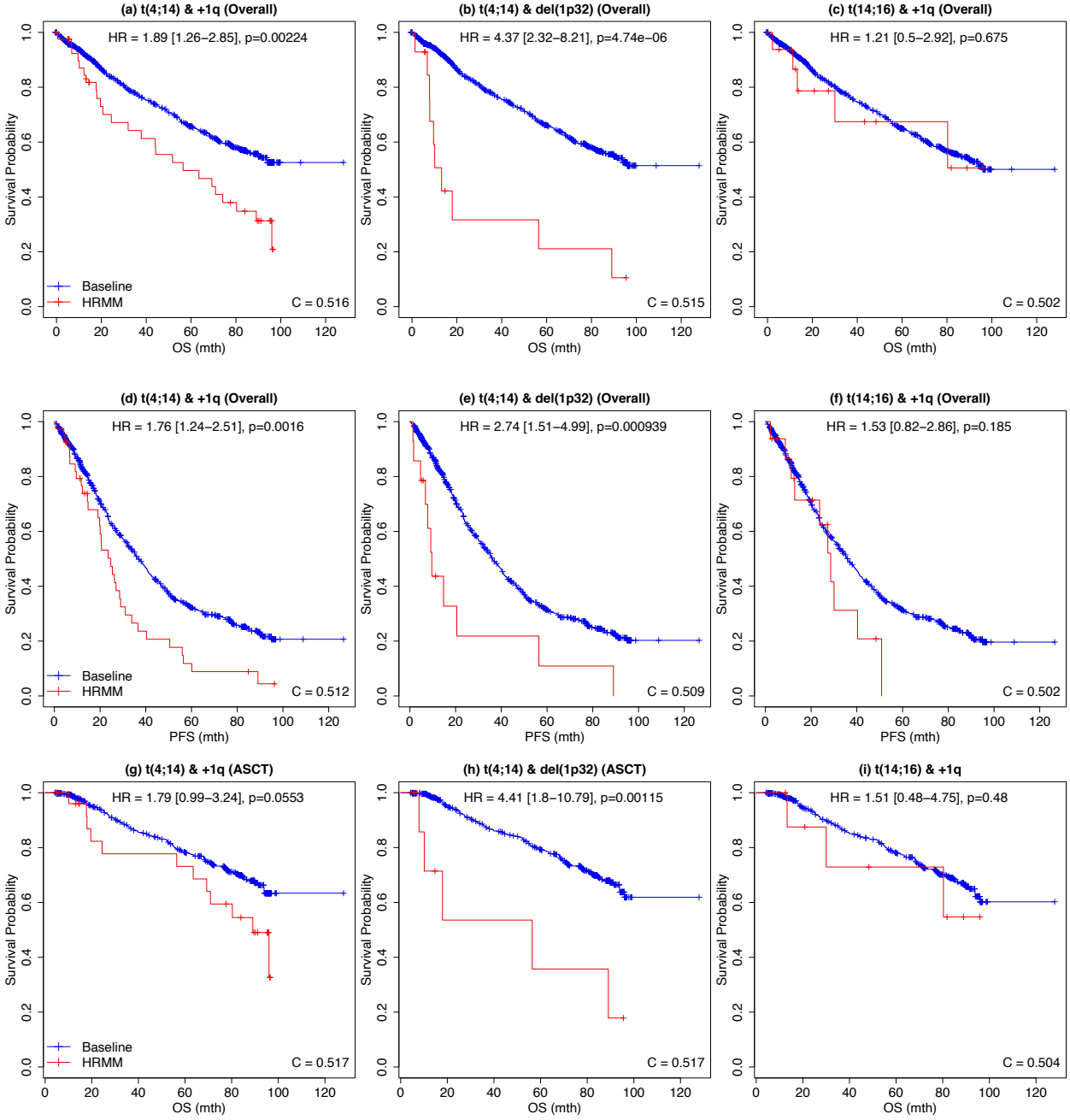
Survival curves of IMS/IMWG factor criterion 1 in CoMMpass data. Survival curves for sub-criteria 1a (del(17p)), 1b (mut(TP53)), and 1c (del(17p) & mut(TP53)) for OS/PFS over all patients ((a)-(f)), patients who underwent ASCT ((g)-(l)), and those who did not ((m)-(r)) are shown.

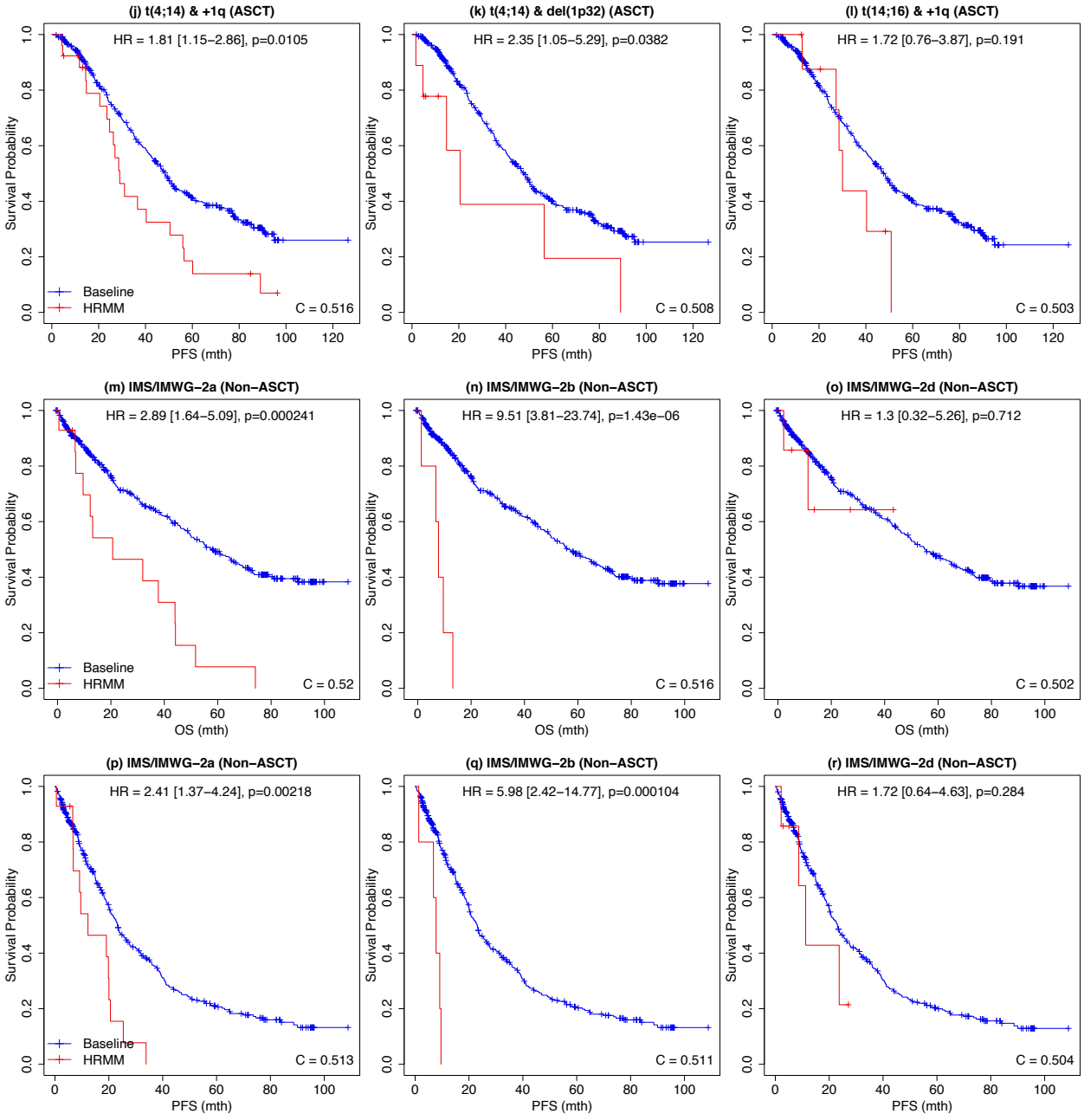



(j) del(17p) (ASCT)
HR = 1.61 [1.06–2.46], p=0.0264
Baseline
HRMM
C = 0.523
Survival Probability
PFS (mth)
(k) mut(TP53) (ASCT)
HR = 1.82 [1.2–2.77], p=0.00524
C = 0.521
PFS (mth)
(l) del(17p) & mut(TP53) (ASCT
HR = 2.49 [1.36–4.57], p=0.00315
C = 0.514
PFS (mth)
(m) del(17p) (Non–ASCT)
HR = 1.49 [0.9–2.45], p=0.118
Baseline
HRMM
C = 0.518
OS (mth)
(n) mut(TP53) (Non–ASCT)
HR = 1.69 [0.87–3.3], p=0.124
C = 0.509
OS (mth)
(o) del(17p) & mut(TP53) (Non–ASCT)
HR = 2.29 [1.08–4.88], p=0.0312
C = 0.51
OS (mth)
(p) del(17p) (Non–ASCT)
HR = 1.1 [0.69–1.75], p=0.696
Baseline
HRMM
C = 0.518
PFS (mth)
(q) mut(TP53) (Non–ASCT)
HR = 1.42 [0.78–2.6], p=0.253
C = 0.505
PFS (mth)
(r) del(17p) & mut(TP53) (Non–ASCT)
HR = 1.78 [0.88–3.59], p=0.11
C = 0.507
PFS (mth)

Supplementary Figure 4. Survival curves of IMS/IMWG criterion 2.

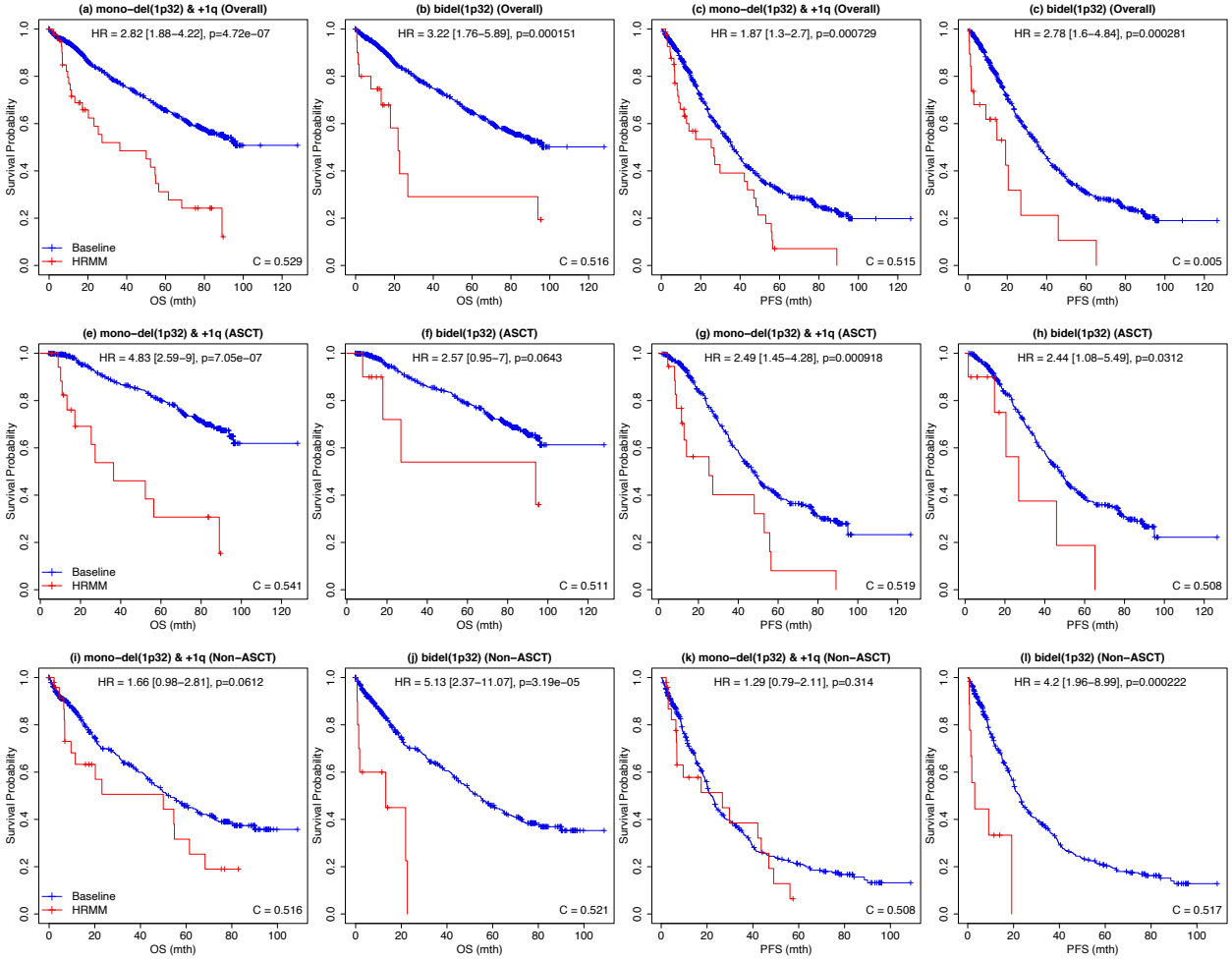
Survival curves of IMS/IMWG factor criterion 2 in CoMMpass data. Survival curves of sub-criteria 2a (t(4;14) & +1q), 2b (t(4;14) & del(1p32)), and 2d (t(14;16) & +1q) for OS/PFS over all patients ((a)-(f)), patients who underwent ASCT ((g)-(l)), and those who did not ((m)-(r)) are shown. Other sub-criteria are omitted due to insufficient number of cases for HR MM.




(j) t(4;14) & +1q (ASCT)
HR = 1.81 [1.15–2.86], p=0.0105
Baseline
HRMM
C = 0.516
Survival Probability
PFS (mth)
(k) t(4;14) & del(1p32) (ASCT)
HR = 2.35 [1.05–5.29], p=0.0382
C = 0.508
PFS (mth)
(l) t(14;16) & +1q (ASCT)
HR = 1.72 [0.76–3.87], p=0.191
C = 0.503
PFS (mth)
(m) IMS/IMWG–2a (Non–ASCT)
HR = 2.89 [1.64–5.09], p=0.000241
Baseline
HRMM
C = 0.52
OS (mth)
(n) IMS/IMWG–2b (Non–ASCT)
HR = 9.51 [3.81–23.74], p=1.43e–06
C = 0.516
OS (mth)
(o) IMS/IMWG–2d (Non–ASCT)
HR = 1.3 [0.32–5.26], p=0.712
C = 0.502
OS (mth)
(p) IMS/IMWG–2a (Non–ASCT)
HR = 2.41 [1.37–4.24], p=0.00218
Baseline
HRMM
C = 0.513
PFS (mth)
(q) IMS/IMWG–2b (Non–ASCT)
HR = 5.98 [2.42–14.77], p=0.000104
C = 0.511
PFS (mth)
(r) IMS/IMWG–2d (Non–ASCT)
HR = 1.72 [0.64–4.63], p=0.284
C = 0.504
PFS (mth)

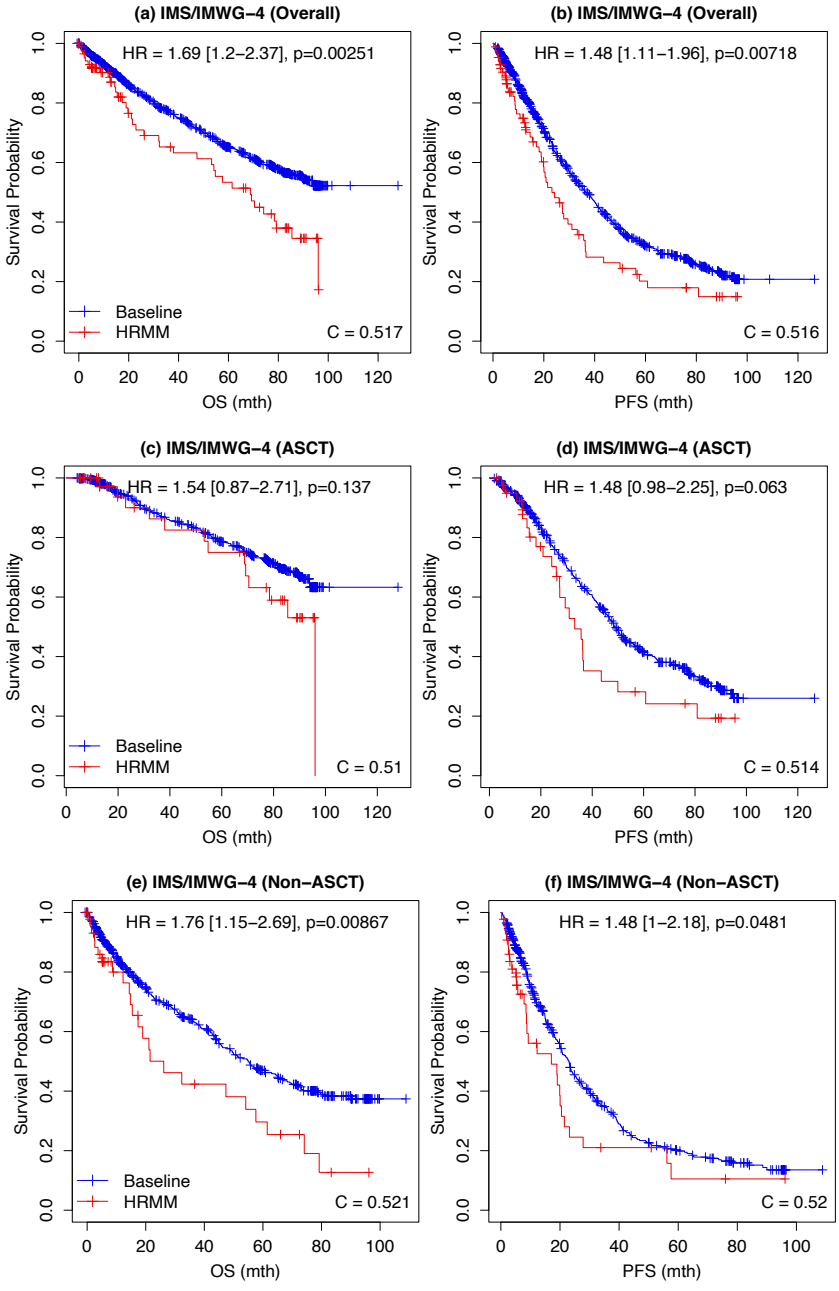
Supplementary Figure 5. Survival curves of IMS/IMWG criterion 3.

Survival curves of IMS/IMWG factor criterion 3 in CoMMpass data. Survival curves of sub-criteria 3a (monoallelic del(1p32) & +1q) and 3b (bidel(1p32)) for OS/PFS over all patients ((a)-(d)), patients who underwent ASCT ((e)-(h)), and those who did not ((i)-(l)) are shown.



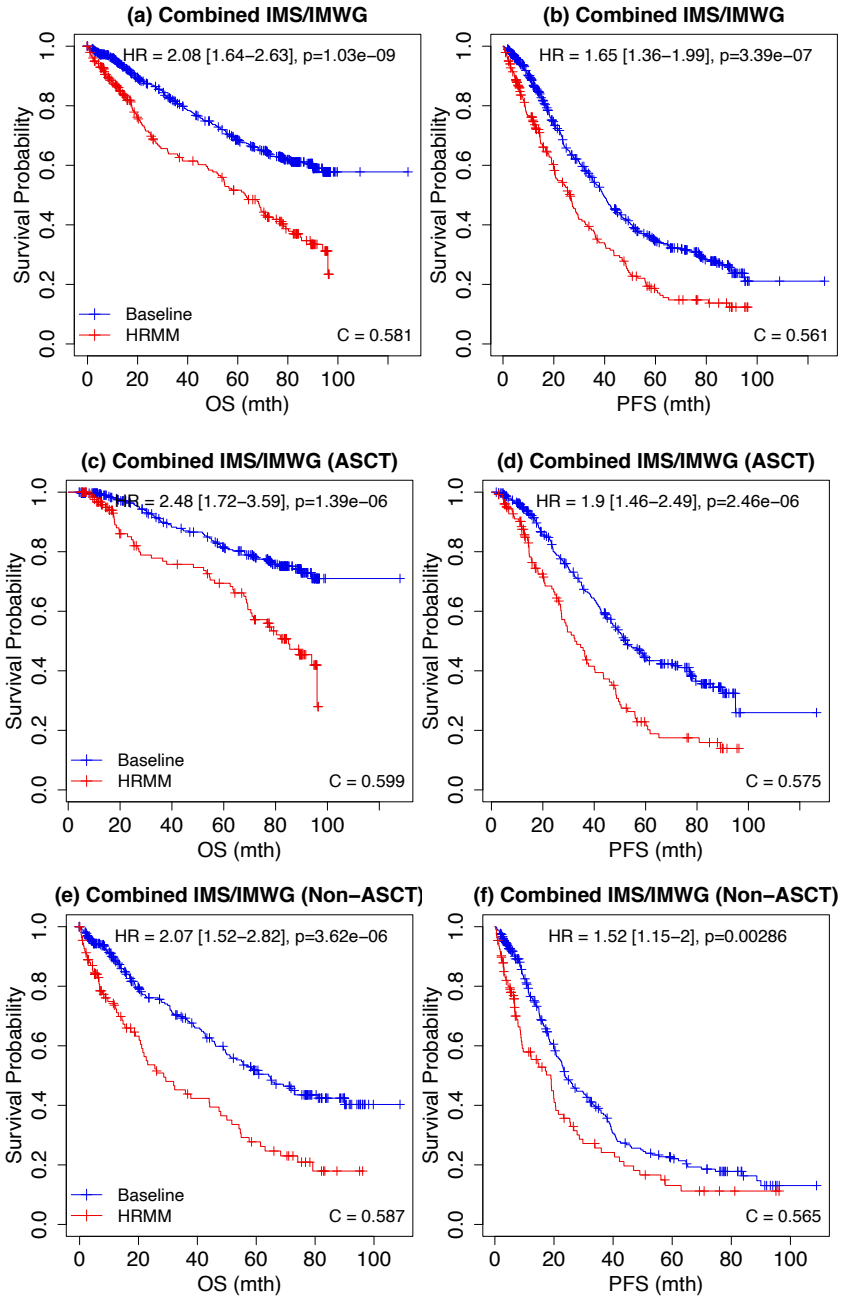
Supplementary Figure 6. Survival curves of IMS/IMWG criterion 4.

Survival curves of IMS/IMWG factor criterion 4 (high β2M & normal creatinine) in CoMMpass data. Results using all patients (a, b), and those using patients who underwent ASCT (c, d) and those not (e, f) are shown together.



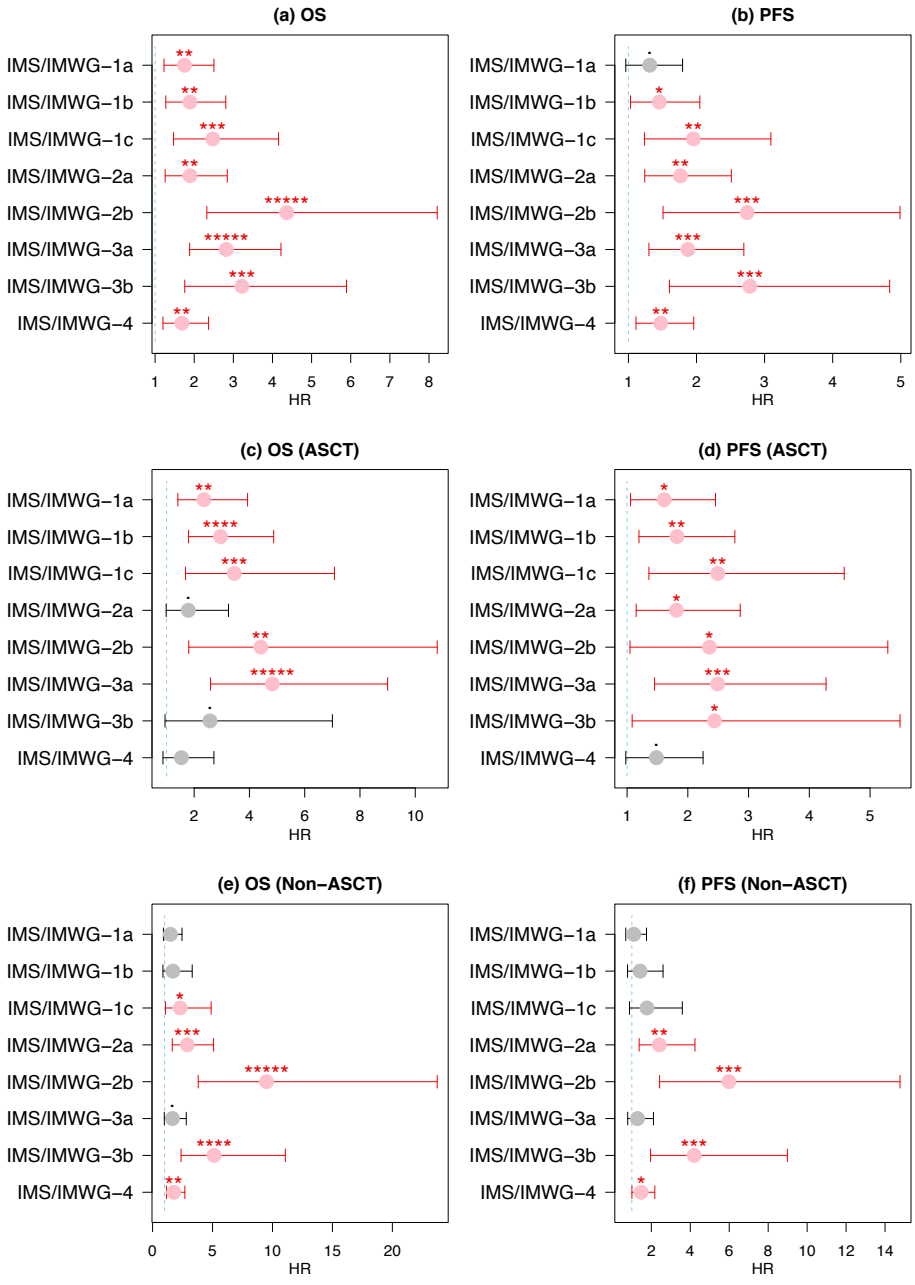
Supplementary Figure 7. Survival curves of combined IMS/IMWG signature.

Survival curves of final combined IMS/IMWG factor in CoMMpass data. Results using all patients (a, b), and those using patients who underwent ASCT (c, d) and those not (e, f) are shown together.



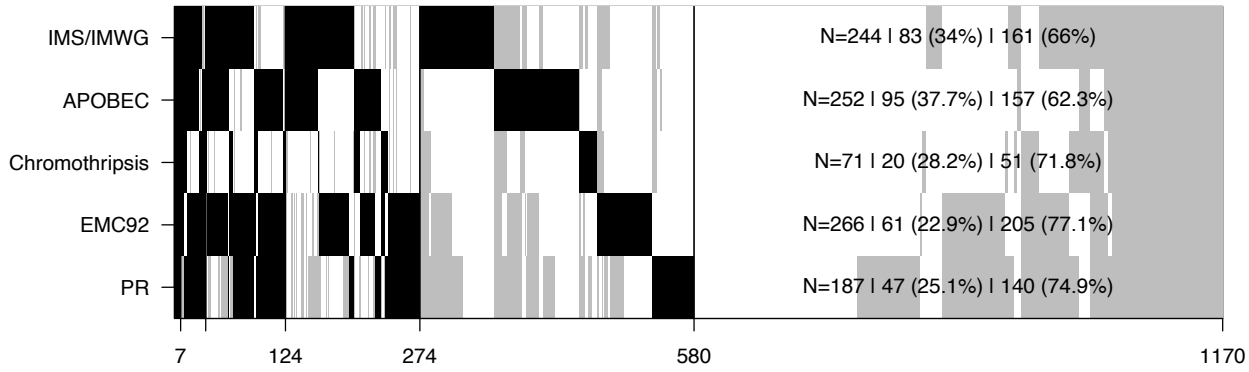
Supplementary Figure 8. Summary forest plots of survival analysis results of IMS/IMWG sub-criteria.

Forest plots of survival analysis results of nine IMS/IMWG sub-criteria with sufficiently large HR MM group over (a, b) all patients, (c, d) patients who underwent ASCT and (e, f) those who did not are shown together. Significance of survival association is represented as follows: * ($0.01 < p \leq 0.05$), ** ($0.001 < p \leq 0.01$), *** ($0.0001 < p \leq 0.001$), **** ($0.00001 < p \leq 0.0001$), ***** ($p \leq 0.00001$).



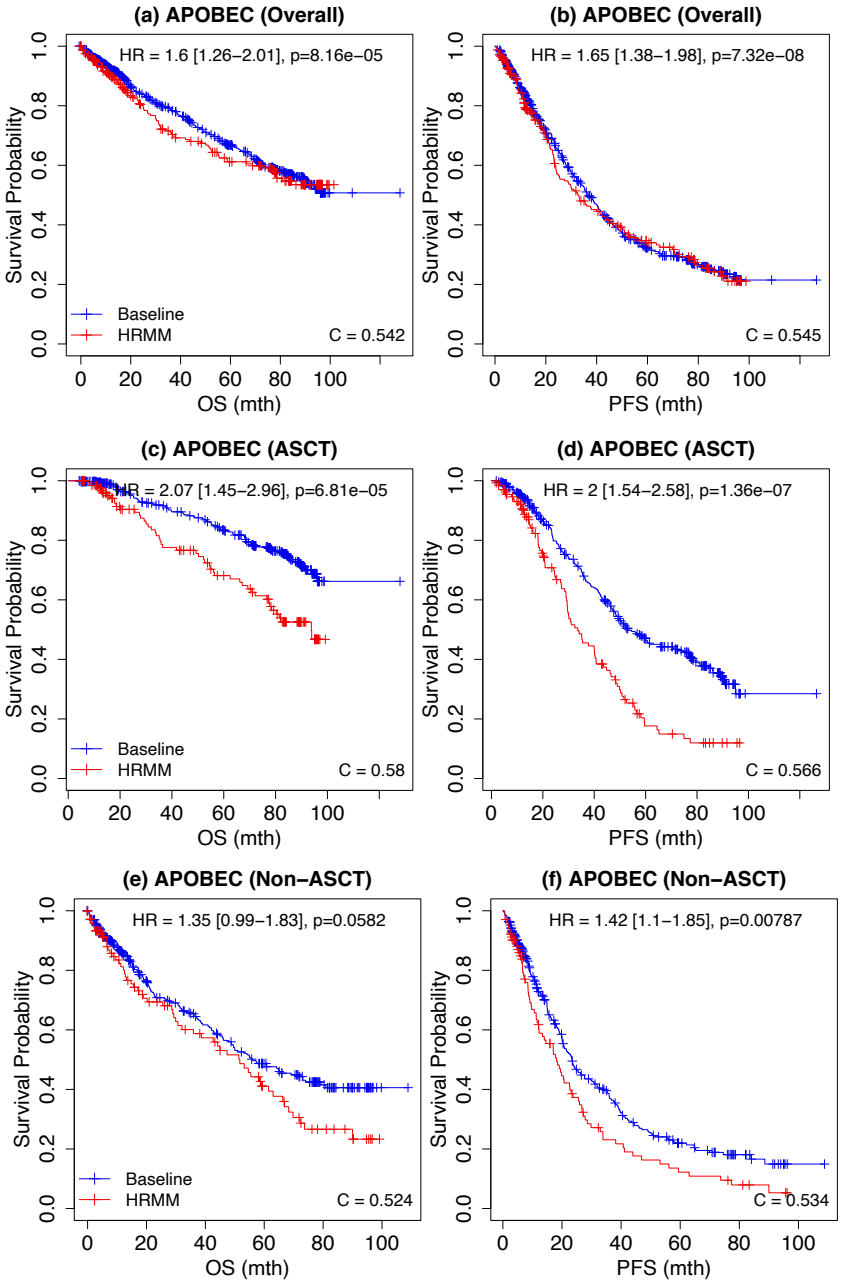
Supplementary Figure 9. Member overlap of HR MM factors.

Member overlap of HR MM factors in CoMMpass data over all patients including those with missing information (marked gray) are shown. Of 1,170 patients, 50.4% (590/1,170) of them had no implicating factor while 26.2% (306/1,170), 12.8% (150/1,170), 7.6% (89/1,170), 3.0% (35/1,170) had one, two, three, and four or more implicating factors, respectively. For each HRMM factor, total number of HR MM patients, the number (percentage) of HR MM patients inflicted solely by the factor, and the number (percentage) of HR MM patients inflicted jointly with other factors are also indicated.



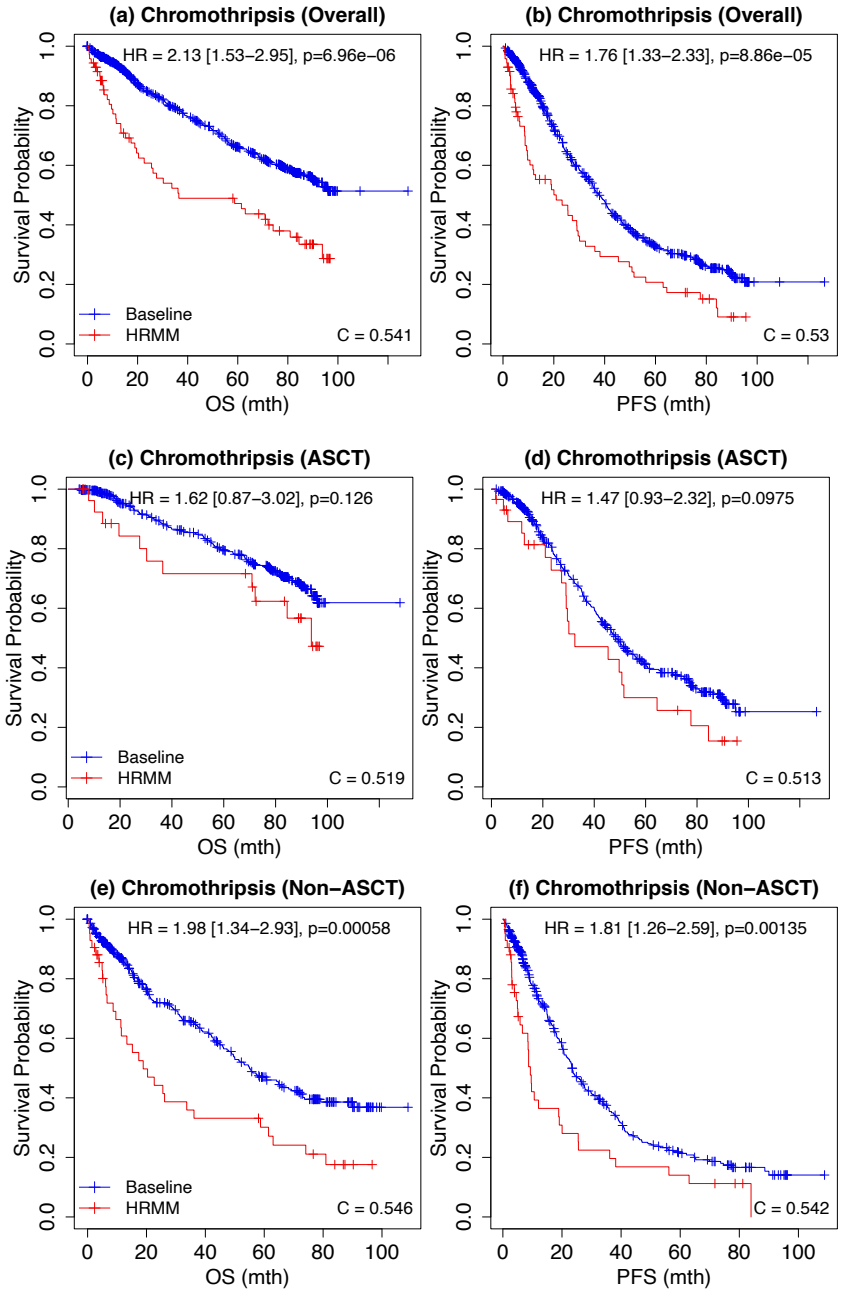
Supplementary Figure 10. Survival curves of APOBEC factor risk groups.

Survival curves of baseline risk and HR groups of APOBEC factor over (a, b) all patients, and (c, d) ASCT and (e, f) non-ASCT cohorts in CoMMpass data are shown together.



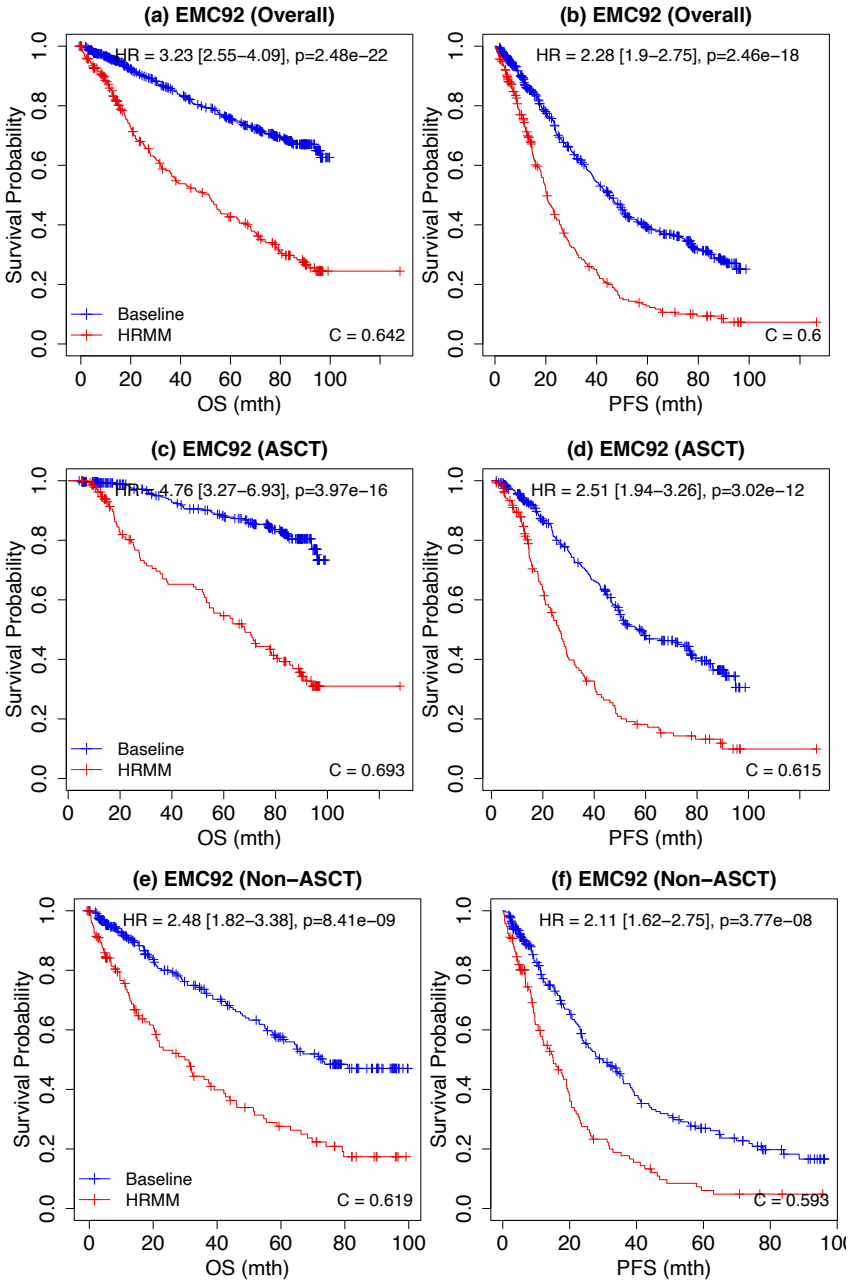
Supplementary Figure 11. Survival curves of chromothripsis factor risk groups.

Survival curves of baseline risk and HR groups of chromothripsis factor over (a, b) all patients, and (c, d) ASCT and (e, f) non-ASCT cohorts in CoMMpass data are shown together.



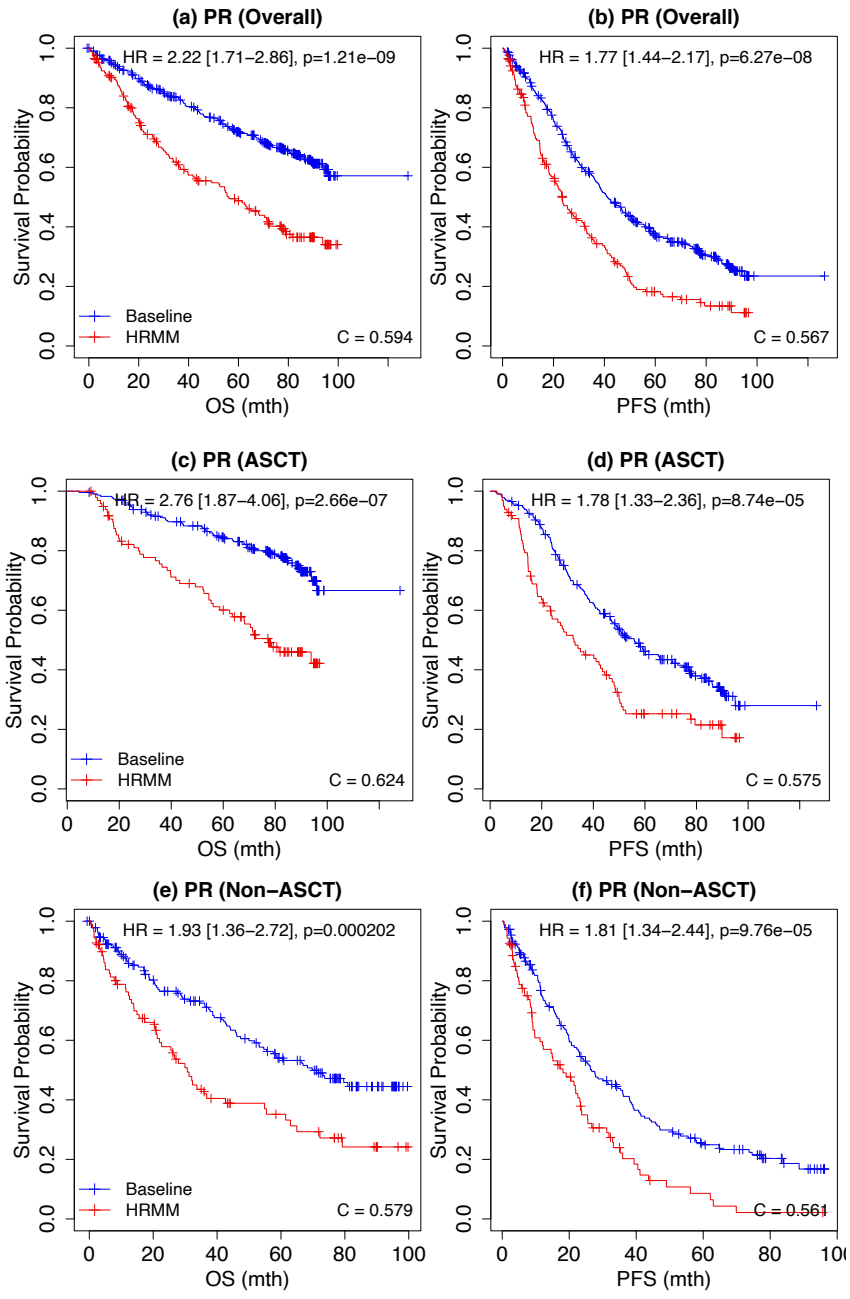
Supplementary Figure 12. Survival curves of EMC92 factor risk groups.

Survival curves of baseline risk and HR groups of EMC92 factor over (a, b) all patients, and (c, d) ASCT and (e, f) non-ASCT cohorts in CoMMpass data are shown together.



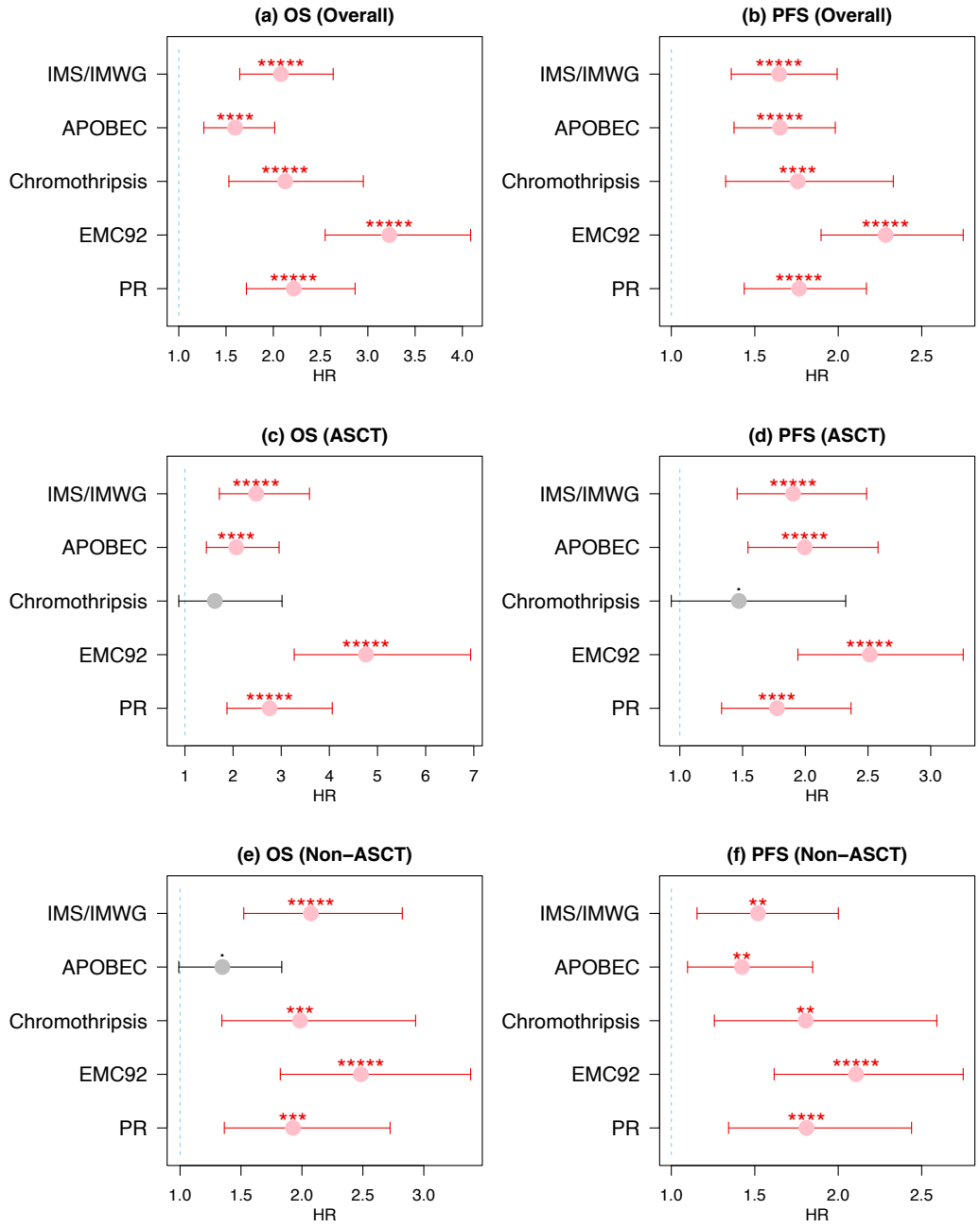
Supplementary Figure 13. Survival curves of PR factor risk groups.

Survival curves of baseline risk and HR groups of PR factor over (a, b) all patients, and (c, d) ASCT and (e, f) non-ASCT cohorts in CoMMpass data are shown together.



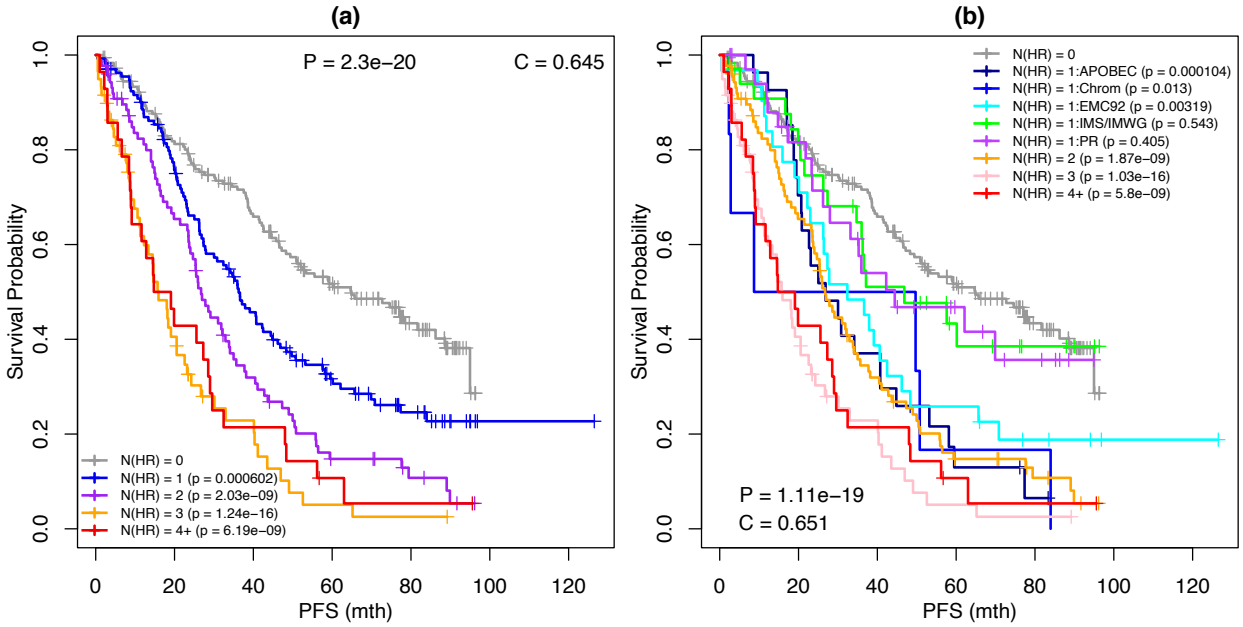
Supplementary Figure 14. Summary forest plots of survival analysis results of HR MM factors.

Forest plots of survival analysis results of six HR MM factors over (a, b) all patients, (c, d) patients who underwent ASCT and (e, f) those who did not are shown together. Significance of survival association is represented as follows: * ($0.01 < p \leq 0.05$), ** ($0.001 < p \leq 0.01$), *** ($0.0001 < p \leq 0.001$), **** ($0.00001 < p \leq 0.0001$), ***** ($p \leq 0.00001$).



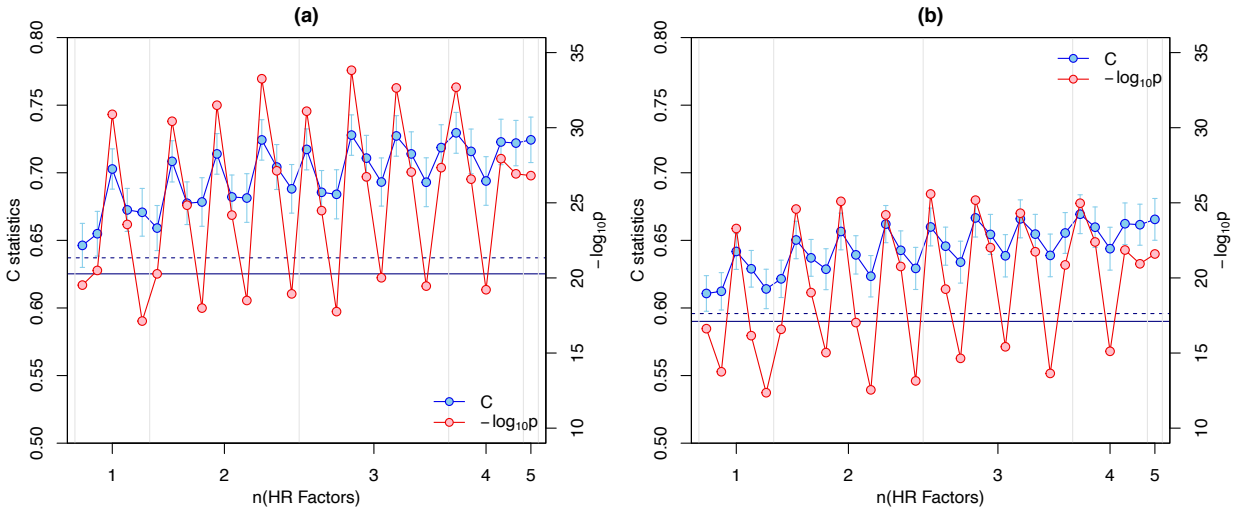
Supplementary Figure 15. Multi-hit effect of HR MM factors for PFS.

(a) Survival curves of patients separated by the number of implicating HR factors. (b) The same results with (a) except for the fine separation of patients implicated by single HR factors into groups by individual implicating HR factors. HR factors APOBEC, chromothripsis, EMC92, remained significant even after the stratification of single lesion group.



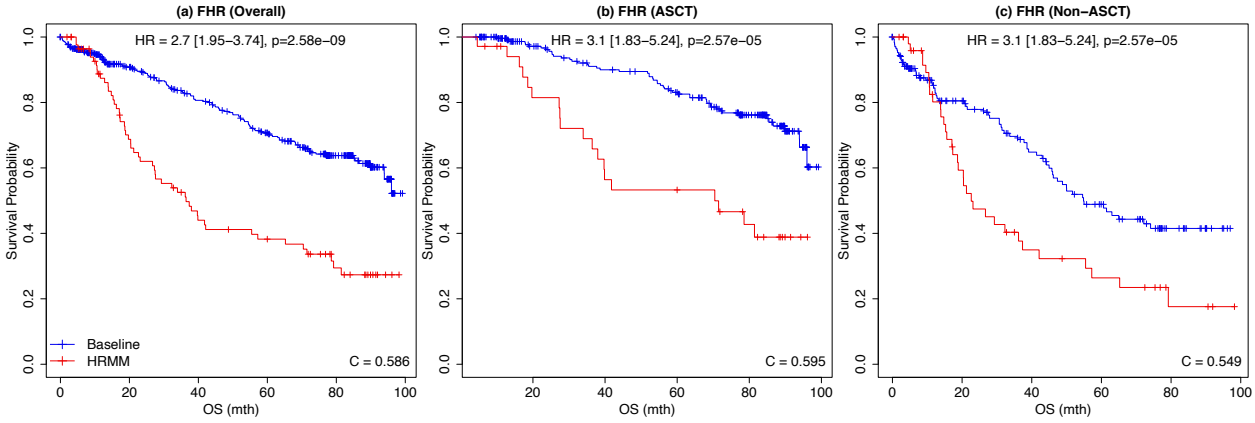
Supplementary Figure 16. Combination effect of HR factors.

C-statistics and *p*-value distribution of survival models for exhaustive combinations of HR factors for (a) OS and (b) PFS using all patients of CoMMpass data. Starting from each of HR factors, 2, 3, …, full factor combinations were separately added besides baseline model (age + sex), and *C*-statistics and *p*-values were retrieved from each survival model. Horizontal full and broken lines indicate *C*-statistics from the survival model of age alone and age + sex, respectively.



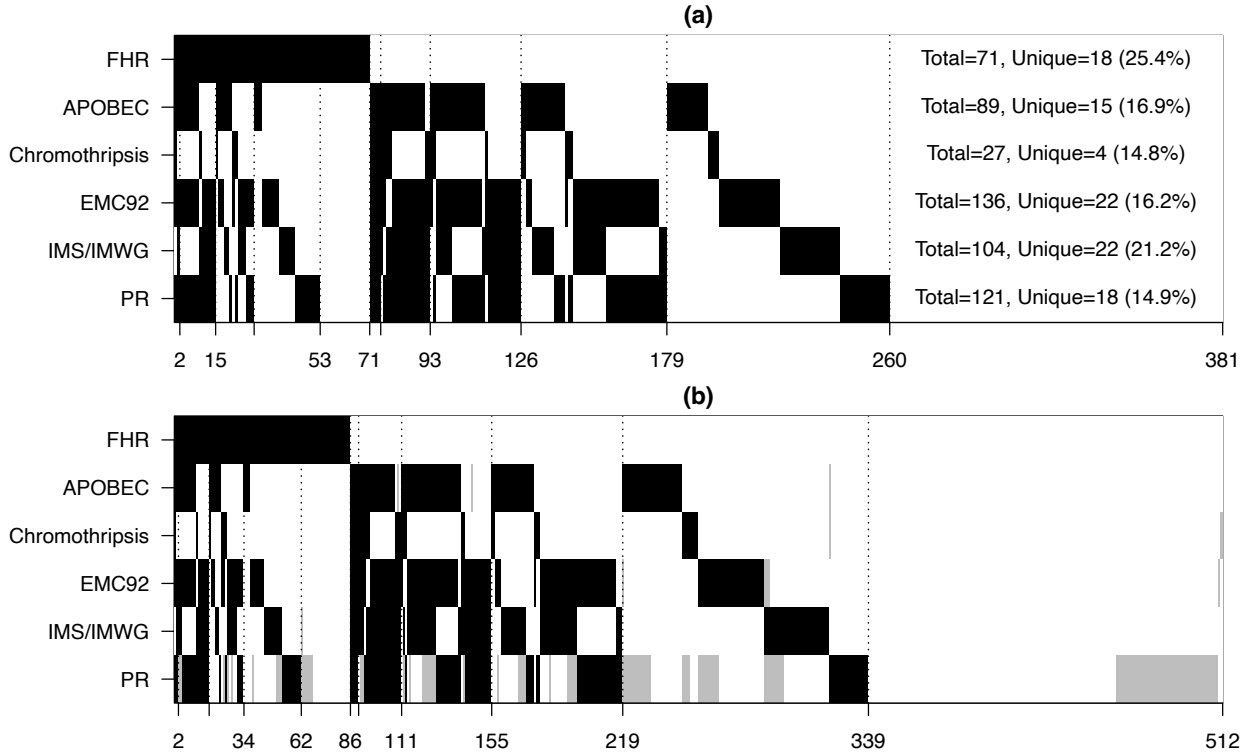
Supplementary Figure 17. Survival curves of FHR phenotype.

Survival curves of baseline risk and FHR phenotypes over (a) all patients, and (b) ASCT and (c) non-ASCT cohorts in CoMMpass data are shown. Results of PFS are omitted to avoid confounding effects.



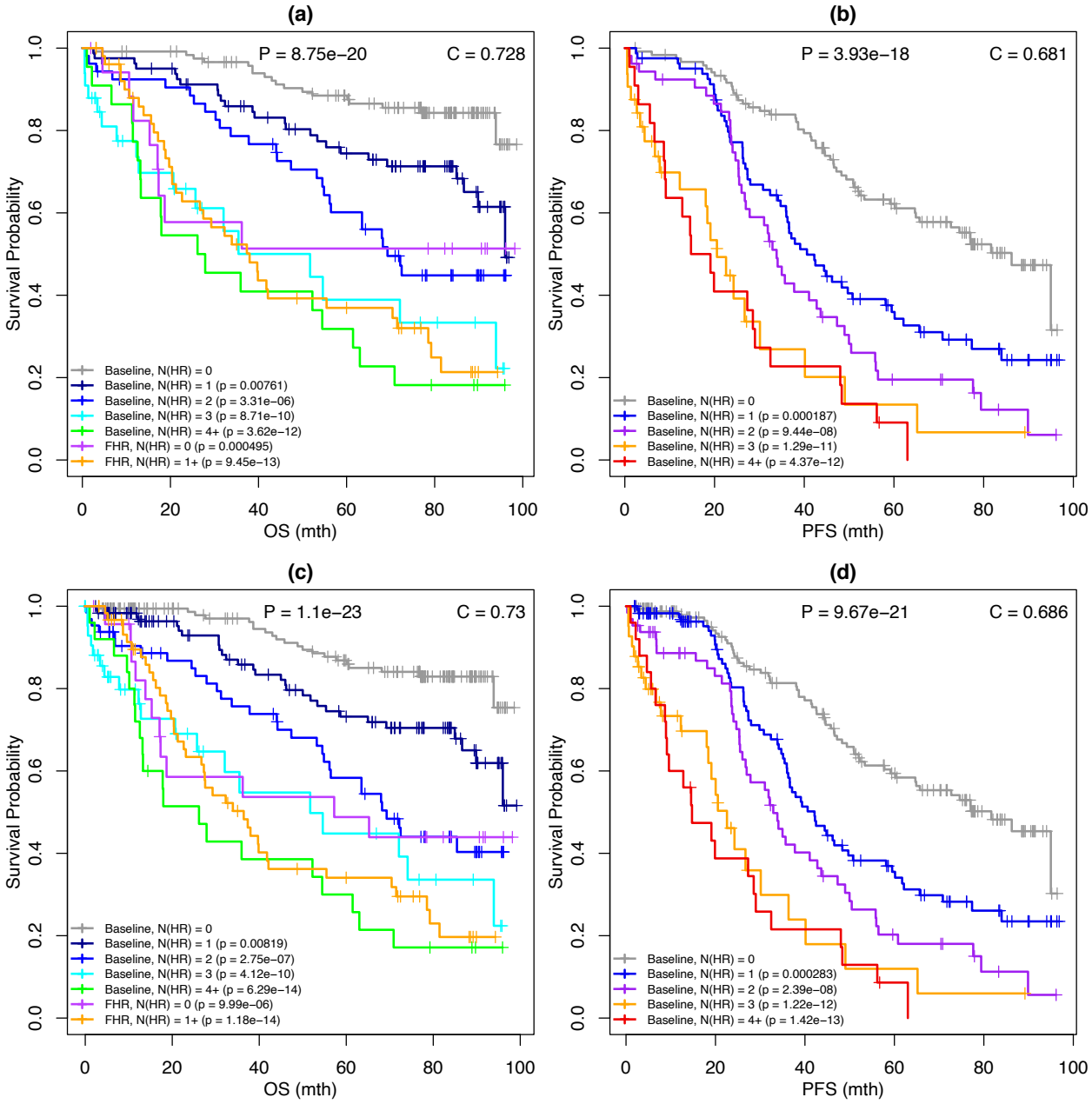
Supplementary Figure 18. Stratification of FHR phenotype.

Stratification of FHR phenotype with HR MM factors over (a) ideal cohort and (b) complete FHR cohort patients are shown. HR patients (including FHR) are marked in black and baseline risk patients are marked in white. Patients with missing data are marked in gray. In (a), total number of HR patients, the number of uniquely implicated patients by the specific factor and the fraction of uniquely implicated patients among HR patients are indicated.



Supplementary Figure 19. Survival curves of stratified FHR phenotypes.

Survival curves of stratified FHR phenotypes using (a, b) ideal cohort and (c, d) FHR ideal cohort are shown. For PFS in (b) and (d), patient groups based on FHR phenotype are omitted to avoid confounding effects. In (a) and (c), the patient group denoted as "FHR, N(HR) = 0" indicates patients uniquely inflicted by FHR lesion alone.



Supplementary Figure 20. Survival curves of IMS/IMWG and EMC92 combination.

Survival curves of IMS/IMWG and EMC92 combination using (a, b) ideal cohort and (c, d) all patients are shown.