Comparison of multiple myeloma prognostic markers: combined GEP and ISS discerns three robust risk categories

Rowan Kuiper[1], Martin van Vliet[2], Annemiek Broyl[1], Yvonne de Knegt[1], Bronno van der Holt[3], Laila el Jarari[3], George Mulligan[4], Walter Gregory[5], Gareth J Morgan[6], Hartmut Goldschmidt[7], Uta Bertsch[7], Henk Lokhorst[8], Mark van Duin[1], Erik van Beers[2] and Pieter Sonneveld[1]

[1]Department of Hematology, Erasmus MC, Rotterdam, Netherlands; [2]Skyline DX, Rotterdam, Netherlands; [3]HOVON data center, Erasmus MC, Rotterdam, Netherlands; [4]Molecular Medicine, Millennium Pharmaceuticals, Cambridge, MA; [5]Clinical Trials Research Unit, University of Leeds, Leeds, United Kingdom; [6]Centre for Myeloma Research, Division of Molecular Pathology, Institute of Cancer Research, Sutton, United Kingdom; [7]Sektion Multiples Myelom der Medizinischen Klinik V und des Nationalen Centrums für Tumorerkrankungen (NCT), University of Heidelberg, Heidelberg, Germany; [8]Department of Hematology, University Medical Center Utrecht, Utrecht, Netherlands

BACKGROUND

Multiple Myeloma (MM) is a heterogeneous disease with highly variable survival. Gene expression profiling (GEP) classifiers, such as the EMC-92 (commercially available as SKY-92), can consistently distinguish high risk patients from standard risk patients. Other prognostic markers for MM include the international staging system (ISS) and FISH. Here we compare prognostic markers in MM and introduce a novel stratification based on EMC-92 and ISS.

METHODS

Scores of the GEP classifiers EMC-92, UAMS-70, UAMS-17, UAMS-80 and MRC-IX-6 were calculated for the following five studies: HOVON-65/GMMG-HD4 (n=328; GSE19784), MRC-IX (n=247; GSE15695), UAMS-TT2 (n=345; GSE2658), UAMS-TT3 (n=238; E-TABM-1138 and GSE2658) and APEX (n=264; GSE9782). For HOVON-65/GMMG-HD4 follow-up was recently updated (median overall survival 59 months). FISH data were available for the HOVON-65/GMMG-HD4 trial and the MRC-IX trial. ISS values were available for all datasets except UAMS-TT2. Univariate associations between markers and overall survival were investigated in a Cox regression analysis, using Bonferroni multiple testing correction. All survival models have been stratified for study. The calculations were done in R using the package survival.

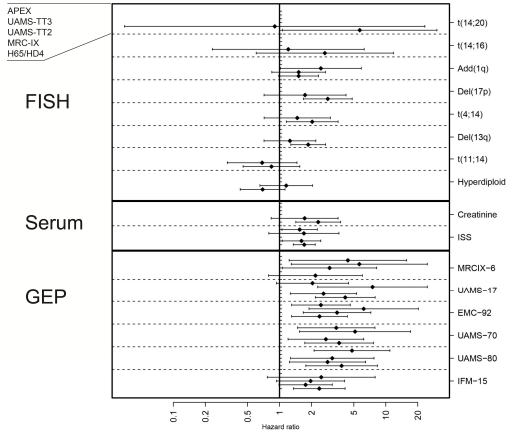

Figure 1. Univariate associations to overall survival per data set per marker. Hazard ratios and 95% confidence intervals are given; confidence intervals were Bonferroni corrected. In each panel, results from APEX, UAMS-TT3, UAMS-TT2, MRC-IX and HOVON65-HD4 is given when available. E.g. for ISS, 4 studies could be evaluated and therefore 4 HR values are shown (all except TT2).

This research was supported by the Center for Translational Molecular Medicine (BioCHIP), ZonMW, the Dutch Cancer Society (KWF/NKB), the P. Plaisier Stichting and Skyline DX B.V.

RESULTS I

GEP classifiers performed better than FISH markers (Figure 1). Of six FISH markers with known adverse risk, del(17p), t(4;14), t(14;20) and del(13q) demonstrated a significant association only in one of two data sets with available FISH (HOVON-65/GMMG-HD4). Classifiers EMC-92, UAMS-70 and UAMS-80 significantly identify a high-risk population in all evaluated data sets, whereas the UAMS-17 and the MRC-IX-6 classifiers predict high-risk patients in three of four datasets. ISS staging demonstrated stable and significant hazard ratios in three out of four datasets.

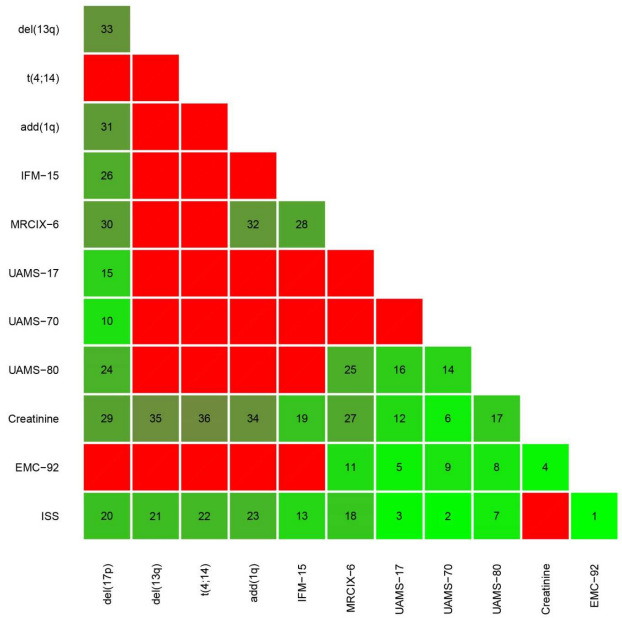

Figure 2. Pair wise analysis of all markers. The significance in the increase of partial likelihood by combining two markers was calculated (green, significant; red, not significant). The number denotes the ranking whereby 1 indicates the strongest combination and 36 the weakest. The combination ISS-EMC-92 is the strongest combination; UAMS70 combined to ISS is the next strongest combination.

Disclosures: Kuiper, Broyl , van der Holt and van Duin: no relevant conflicts of interest to disclose. Gregory: *Celgene:* Honoraria. Goldschmidt: *Johnson& Johnson:* Membership on an entity's Board of Directors or advisory committees. Lokhorst: *Genmab:* Membership on an entity's Board of Directors or advisory committees; *Celgene:* Membership on an entity's Board of Directors or advisory committees. Sonneveld: *Janssen :* Membership on an entity's Board of Directors or advisory committees; *Celgene:* Membership on an entity's Board of Directors or advisory committees; *Skyline DX:* Membership on an entity's Board of Directors or advisory committees.

RESULTS II

Markers with additive value to each other include all combinations of GEP classifiers as well as the combination of GEP classifiers together with ISS. The EMC-92 classifier combined with ISS is the best combination, as compared to other classifier-ISS combinations tested on the same independent data sets. The strongest risk stratification in 3 groups was achieved by splitting the EMC-92 standard risk patients into low risk, based on ISS stage I, and intermediate risk, based on ISS stage II and III. This stratification retains the original EMC-92 high-risk group, and is robust in all cohorts.

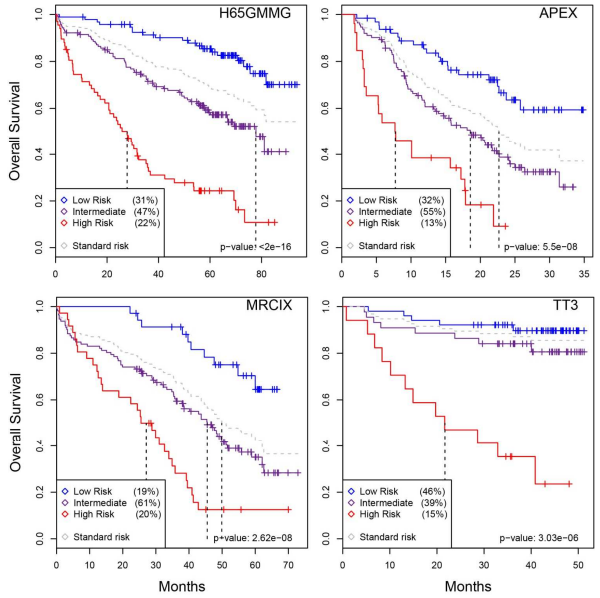

Figure 3. Combination of EMC-92 with ISS. Kaplan-Meier curves are shown for four studies; the EMC-92 standard risk (SR) is split in two groups based on ISS, with EMC-92-SR combined with ISS-I is low risk, EMC-92-SR combined with ISS-II/III is intermediate risk.

CONCLUSION

GEP signatures represent the strongest predictors for survival in multiple myeloma and are more robust than FISH. Adding ISS to EMC-92 is the strongest combination of markers evaluated. Stratification in low risk, intermediate and high risk may result in improved treatment and longer survival of MM patients.