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Prediction of High and Low-Risk Multiple Myeloma Based on the EMC92 Gene Expression Signature and the International Staging System

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Background

- Many prognostic factors are known in Multiple Myeloma.
- Currently it is unclear which marker is most optimal.
- Here, we compared conventional markers like FISH and serum proteins, and gene expression signatures. We tested the possibility of forming new pairs of prognostic factors.

Methods

- Available markers and studies are shown in Figure 1. In total 4750 patient are available
- A univariate analysis of the markers was performed to find markers suitable for forming pair wise combinations.
- Using the discovery set, pair-wise combinations of standard markers and the most optimal risk group definition of these combinations were determined, using the likelihood ratio test and Akaike's Information Criterion with finite sample correction (AIC_C). Stringent validation of the new risk definitions was performed in the validation set.
- After combining all markers with all others, their prognostic performances were ranked based on a procedure which takes into account the missing data between markers.

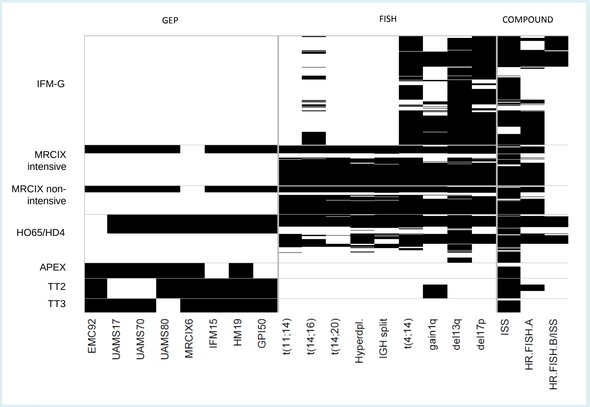


Figure 1. Overview of available markers per dataset. Visualization of available data in black and missing data in white. The data is sorted vertically per cohort. All univariate markers are shown horizontally sorted by category GEP, FISH and compound markers. It can be seen that all markers are known for large number of samples (> 1000; except the HR.FISH.B/ISS marker). Moreover, markers within the same category (FISH or GEP), tend to have larger overlap in commonly available data.

Results

- Using 17 prognostic markers, 136 unique pair-wise combinations were made and tested for meaningful novel risk group definitions**.**
- 20 novel combinations were found in the discovery set → 16 passed validation phase.
- ISS combined with GEP markers constituted 5 of 16 combinations, and ISS combined with FISH 5 of 16 combinations. ISS clearly had strong additive power to these markers. In addition, combinations of GEP (3x), FISH (3x) but no GEP with FISH were found.
- Prognostic performances of the 17 univariate markers and 16 validated combinations were ranked based on AIC_C in the validation set **(Figure 2).**
- The ISS-GEP combinations consistently ranked high with the EMC92-ISS combination demonstrating the best score **(Figure 2).**
- Other high scoring combinations were ISS-UAMS17, ISS-HM19 and ISS-UAMS70.
- The HR.FISH.B/ISS ranked 5th and ISS had demonstrated a ranking of 20th out of 33).
- Combinations of markers ranked higher than univariate markers. The best univariate marker was EMC92 in 9th position out of 33 evaluated.
- The EM92-ISS model classifies patients into four groups with proportions of 39%, 23%, 20% and 18% for the lowest to the highest-risk group with distinctive 4 years survival estimates **(Table 2A)**. The hazard ratios relative to the lowest-risk group are 2.6 (1.6 - 4.5; intermediate-low), 3.2 (1.9-5.4, intermediate-high) and 6.9 (4.1 - 11.7, high).
- Median survival times are 24 (high), 47 (intermediate-high) and 61 months (intermediate-low) for the three highest risk groups, with median survival not reached after 98 months for the lowest-risk group **(Figure 3B).**

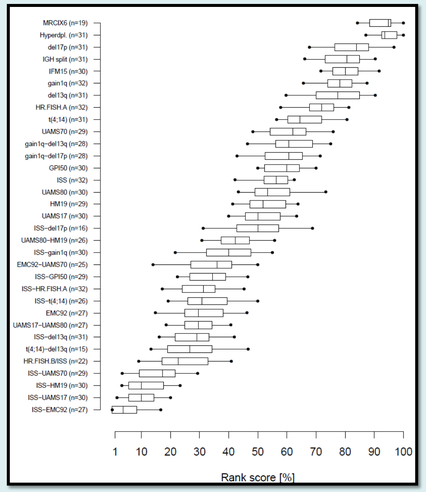
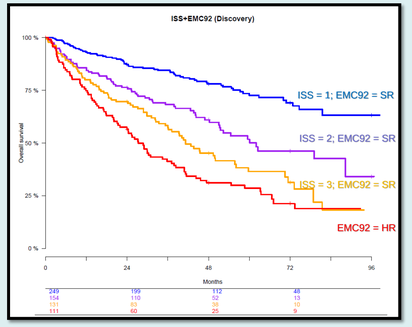


Figure 2. Ranking of all meaningful markers, including newly found combinations, in relation to overall survival (validation data). Next to the marker labels are the numbers of combinations to other markers that could be made.

Conclusions

- ISS was found to have strong additional prognostic value when added to GEP markers.
- EMC92-ISS is identified as one of the most optimal marker combinations, resulting in a risk stratification of 4 groups.



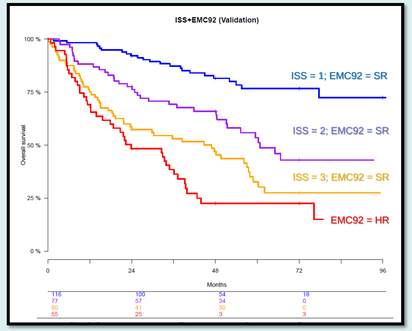


Figure 3. Survival curves of the four risk group model EMC92-ISS in the discovery set and validation set. Kaplan-Meier analysis using overall survival is shown. In order of increasing risk: Low-risk (blue); Intermediate-Low (purple); Intermediate-High (orange); High (red); SR = Standard risk; HR = High risk. Below the graph panels, the number of remaining patients at specific time points is given.

EMC92-ISS	EMC92		ISS				del17p		del13q		t(4;14)		1q gain		HR.FISH.A	
	HR	n	1	2	3	n	YES	n	YES	n	YES	n	YES	n	HR	n
Low	0%	365	100%	0%	0%	365	8%	39	44%	39	18%	40	34%	154	75%	76
Intermediate-Low	0%	231	0%	100%	0%	231	5%	60	37%	60	5%	62	34%	92	44%	70
Intermediate-High	0%	211	0%	0%	100%	211	8%	66	44%	66	10%	67	41%	101	55%	84
High	100%	166	30%	32%	39%	166	16%	38	74%	39	49%	39	76%	90	93%	76
Fisher p-value							0.32		$1.9x10^{-3}$		$4.45x10^{-7}$		$3.17x10^{-10}$		$1.60x10^{-11}$	

Table 1. Distributions of markers in each of the four EMC92-ISS defined risk groups. Analysis of the pooled cohorts for which EMC92-ISS classification could be determined**.** n = the number of patients in the EMC92-ISS defined risk group for which the specified marker was available. YES = the percentage of patients positive for the specified marker; HR = the percentage of patients indicated as high-risk according to the specified marker; Fisher p-value = the p-value obtained in a Fisher-exact test. For the markers del13q, t(4;14), 1q gain and HR.FISH.A, a clear correlation was found to the EMC92-ISS model. For instance, 49% of EMC92-ISS high risk patients have t(4;14) compared to only 5%-18% of the low, intermediate-low and intermediate-high groups.

A.

EMC92+ISS	Risk Group	Criteria	Risk proportion	OS 4yrs estimate
	Low-risk	ISS = 1 and EMC92 = SR	39 %	83 %
	Intermediate low-risk	ISS = 2 and EMC92 = SR	23 %	70 %
	Intermediate high-risk	ISS = 3 and EMC92 = SR	20 %	53 %
	High-risk	EMC92 = HR	18 %	32 %

B.

HR.FISH.B + ISS	Risk Group	Criteria	Risk proportion	OS 4yrs estimate
	Low-risk	ISS < 3 and not del(17p) and not t(4;14)	54 %	71 %
	Intermediate low-risk	ISS < 3 and [del(17p) or t(4;14)] or ISS = 3 and not del(17p) and not t(4;14)	28 %	45 %
	High-risk	ISS = 3 and [del(17p) or t(4;14)]	18 %	33 %

Table 2. Risk stratification according to GEP+ISS (A) and FISH+ISS (B). Using the EMC92+ISS a four risk group stratification results is a more detailed separation in 4yrs estimates in newly diagnosed patients than the FISH+ISS based stratification.

Disclosures: Kuiper, Broijl and van Duin: no relevant conflicts of interest to disclose. van Vliet and van Beers: Skyline Dx: Employment. Mulligan: Millennium Pharmaceuticals: Employment. Gregory: Celgene, Honoraria; Morgan: Celgene: Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees; Millenium: Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees; Novartis: Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees; Merck: Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees; Johnson and Johnson: Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees. Goldschmidt: Celgene: Consultancy, Honoraria, Research Funding; Janssen: Consultancy, Honoraria, Research Funding; Novartis: Consultancy, Honoraria, Research Funding. Lokhorst: Genmab A/S: Consultancy, Research Funding; Celgene: Honoraria; Johnson-Cilag: Honoraria; Mudipharma: Honoraria. Sonneveld: Janssen-Cilag: Honoraria; Celgene: Honoraria; Onyx: Honoraria; Janssen-Cilag: Research Funding; Millenium: Research Funding; Onyx: Research Funding; Celgene: Research Funding