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R2-ISS, a New Risk Stratification Model in Newly Diagnosed Multiple Myeloma by the European Myeloma Network Within HARMONY Big Data Platform Project

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HARMONY, European Myeloma Network - Italy, Spain, the Netherlands, Norway, Germany, United Kingdom

ABSTRACT

BACKGROUND. The Revised International Staging System (R-ISS) stratifies newly diagnosed multiple myeloma (NDMM) patients (pts) into 3 groups with different progression-free survival (PFS) and overall survival (OS) (Palumbo et al. JCO 2015). Yet, 60% of pts fall under the intermediate-risk (R-ISS2), possibly including pts with different risk of progression/death. The European Myeloma Network (EMN), within the HARMONY project, aimed to revise the R-ISS by evaluating each single baseline risk feature, including also 1q copy number alterations (CNAs), which recently proved to be a poor prognostic factor in NDMM.

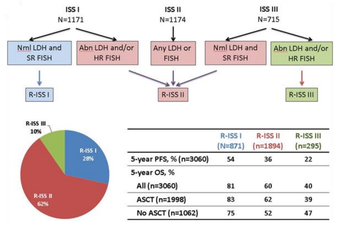
METHODS. Data from 15 European clinical trials with NDMM pts were collected through EMN in HARMONY platform. HARMONY is a European public-private partnership focusing on hematologic malignancies with unmet medical needs. OMOP Common Data Model was used to harmonize data. All pts received immunomodulatory agent (IMiD) and/or proteasome inhibitor (PI) upfront. In a multivariate Cox regression analysis adjusted for age, sex and therapy, we evaluated the impact of each risk feature on OS and PFS and used the hazard of death conferred by the most significant variables to create an additive risk score.

RESULTS. 7077 NDMM pts were registered in HARMONY platform and analyzed. Median follow-up was 75 months, median age 62 years. 65% of pts were transplant-eligible; 40% received IMiDs only, 15% PIs only, 46% both drug classes at first line. In a multivariate Cox model, ISS (2 vs 1 HR 1.55 p<0.001, 3 vs 1 HR 2.02 p<0.001), del(17p) (HR 1.74, p<0.001), LDH (HR 1.65, p<0.001), t(4;14) (HR 1.56, p<0.001) and 1q CNAs (HR 1.45, p<0.001) had the highest impact on OS. ISS (2 vs 1 HR 1.35 p<0.001, 3 vs 1 HR 1.53 p<0.001), t(4;14) (HR 1.49, p<0.001), del(17p) (HR 1.41, p<0.001), 1q CNAs (HR 1.37, p<0.001) and LDH (HR 1.33, p<0.001) had the highest impact on PFS. t(14;16) was not included in the model, as it had a significant effect on OS (HR 1.34, p=0.006) but not on PFS (HR 1.15, p=0.13). These prognostic variables were simultaneously present in 2227 pts and most of the remaining pts were excluded because 1q CNAs were missing. Based on the OS impact of these risk features in pts with complete data, we built an additive scoring system (Table 1). Pts were stratified into 4 groups: Low [n=429 (19.3%), score 0], Low-Intermediate [n=686 (30.8%), score 0.5-1], Intermediate-High [n=917 (41.2%), score 1.5-2.5] and High [n=195 (8.8%), score 3-5]. Each group had significantly different OS and PFS. Median OS was not reached vs 109.2 vs 68.5 vs 37.9 months and median PFS was 68 vs 45.5 vs 30.2 vs 19.9 months in the above 4 risk groups, respectively. Using this new model, R-ISS2 pts (n=1372) were better stratified into Low-Intermediate (n=517), Intermediate-High (n=811) and High risk (n=44) groups, confirming their highly different prognosis. Its prognostic value was maintained also in transplant-eligible and ineligible pts, and in pts receiving IMiDs, PIs or both.

CONCLUSION. This new additive scoring system may improve the current R-ISS and be the future risk stratification model for NDMM, called "R2-ISS". About 50% of the pts can be classified as Low or Low-Intermediate risk and another 50% as Intermediate-High or High risk, paving the way to risk-adapted approaches in a high number of pts. This model can easily include new prognostic variables in the future. More patient data are being added, and validation in an independent cohort is planned.

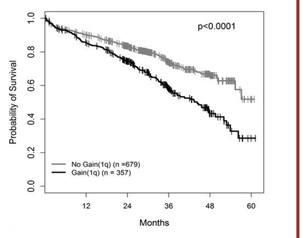
BACKGROUND

R-ISS is the standard risk stratification in NDMM[1]



	R-ISS I (N=871)	R-ISS II (n=1894)	R-ISS III (n=295)
5-year PFS, % (n=3060)	54	36	22
5-year OS, %			
All (n=3060)	81	60	40
ASCT (n=1998)	83	62	39
No ASCT (n=1062)	75	52	47

1q CNA is a poor prognostic factor in NDMM[2]



R-ISS: Revised International Staging System; NDMM: Newly Diagnosed Multiple Myeloma; CNA: Copy Number Alteration; Abn: abnormal; Nml: normal; HR-FISH: del(17p) and/or t(4;14) and/or t(14:16) by fluorescence-in-situ hybridization. Figure adapted from Dispenzieri et al ASH 2016. 1. Palumbo et al JCO 2015 Sep 10;33(26):2863-9; 2. Shah et al Leukemia 32, 102–110 (2018)

AIMS & METHODS

Aims

- Improve risk prognostication in NDMM
- Better distribute R-ISS II patients into different risk groups
- Include 1q CNA by FISH in risk calculation

Methods

- Individual patient data from 15 clinical trials enrolling NDMM patients from 2005 to 2014
- Collection through EMN, registration in HARMONY big data platform
- Harmonization through OMOP Common Data Model
- Analysis of the impact of single risk features on OS and PFS
- Definition of an additive score using the hazard of death from the most significant variables

NDMM: Newly Diagnosed Multiple Myeloma; R-ISS: Revised International Staging System; CNA: Copy Number Alteration; FISH: fluorescence-in-situ hybridization; EMN: European Myeloma Network; HARMONY: Healthcare Alliance for Resourceful Medicine Offensive against Neoplasms in Hematology; OMOP: Observational Medical Outcomes Partnership; OS: Overall Survival; PFS: Progression-Free Survival

PATIENTS' CHARACTERISTICS

Trial	Patients number	Median Follow-up
EMN01	654	69.1
GIMEMA-MM-03-05	511	71.6
IST-CAR-506	58	56.1
MMY2069	152	53.9
RV-MM-PI-114	102	57.5
RV-MM-PI-209	399	77.2
RV-MM-EMN-441	387	53.9
HOVON 65MM/GMMGHD4	827	98.1
HOVON 87/NSMG18	630	78
GEM05MENO65	389	116
GEM05MAS65	259	82.1
GEM2010MAS65	240	61.6
MM-BO2005	474	125.1
GMMG-MM5	502	63
EMN02 / HOVON 95	1493	78
Total	**7077**	**75**

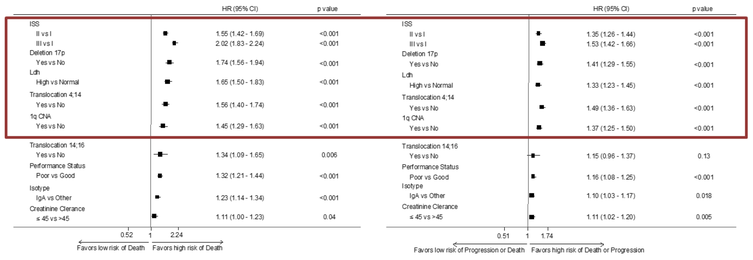
Characteristics	Patients number (%)
Age	
≤65	4398 (62)
>65	2679 (38)
Sex	
Male	3859 (55)
Female	3218 (45)
HR-CA by FISH	
No	4107 (77)
Yes	1234 (23)
Missing	1736
1q CNA by FISH	
No	1768 (64)
Yes	1003 (36)
Missing	4306
ISS stage	
I	2462 (35)
II	2726 (40)
III	1689 (25)
Missing	200
LDH level	
Normal	5562 (86)
High	877 (14)
Missing	638

Treatment	Patients number (%)
Transplant eligible	
Yes	4573 (65)
No	2504 (35)
Novel agents	
IMiDs	2825 (40)
Pis	1027 (15)
IMiDs + PIs	3225 (46)

HR-CA: High risk chromosomal abnormalities (del(17p) and/or t(4;14)); FISH: fluorescence-in-situ hybridization; CNA: Copy number alteration; ISS: International Staging System; LDH: lactate dehydrogenase; ASCT: autologous stem cell transplantation; PIs: proteasome inhibitors; IMiDs: immunomodulatory drugs

IMPACT OF SINGLE RISK FEATURES

Entire patient cohort (n= 7077)



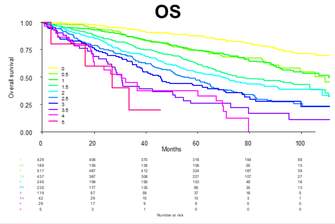
Multivariate Cox model adjusted for age, sex, transplant eligibility treatment and missing values. ISS: International Staging System; LDH: lactate dehydrogenase; CNA: Copy number alteration; OS: Overall Survival; PFS: Progression-free Survival. Poor performance status defined as ECOG>1 or Karnofsky<80.

R2-ISS SCORE DEFINITION

Patients with complete data for all risk features (n= 2227)

Risk feature	OS hazard ratio	PFS hazard ratio	Score value*
ISS II	1.75	1.44	1
ISS III	2.54	1.76	1.5
Deletion 17p	1.82	1.43	1
High LDH	1.60	1.37	1
Translocation 4;14	1.53	1.40	1
1q CNA	1.47	1.33	0.5

OS



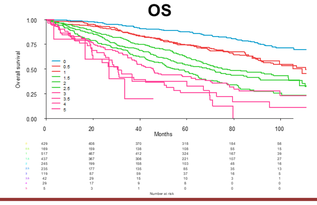
R2-ISS: Revision 2 of the International Staging System; ISS: International Staging System; LDH: lactate dehydrogenase; CNA: Copy number alteration; OS: Overall Survival; PFS: Progression-Free Survival; *calculated on the risk of death, value rounded to the nearest 0.5 with ISS II vs I comparison as reference (score = 1).

R2-ISS GROUPS DEFINITION

Patients with complete data for all risk features (n= 2227)

Risk feature	OS hazard ratio	PFS hazard ratio	Score value*
ISS II	1.75	1.44	1
ISS III	2.54	1.76	1.5
Deletion 17p	1.82	1.43	1
High LDH	1.60	1.37	1
Translocation 4;14	1.53	1.40	1
1q CNA	1.47	1.33	0.5
Group	**Number of patients (%)**		**Total additive score**
Low	429 (19.3%)		0
Low-Intermediate	686 (30.8%)		0.5-1
Intermediate-High	917 (41.2%)		1.5-2.5
High	195 (8.8%)		3-5

OS

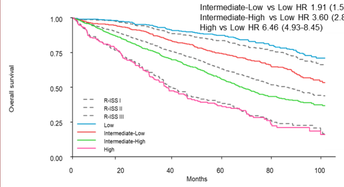


R2-ISS: Revision 2 of the International Staging System; ISS: International Staging System; LDH: lactate dehydrogenase; CNA: Copy number alteration; OS: Overall Survival; PFS: Progression-free Survival; *calculated on the risk of death, value rounded to the nearest 0.5 with ISS II vs I comparison as reference (score = 1).

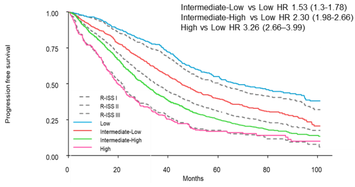
OS AND PFS ACCORDING TO R2-ISS

Group	5-y OS	Median OS (months)	5-y PFS	Median PFS (months)
Low risk	88%	Not reached	55%	68
Intermediate-low risk	75%	109.2	40%	45.5
Intermediate-high risk	56%	68.5	25%	30.2
High risk	37%	37.9	17%	19.9

OS



PFS



R2-ISS: Revision 2 of the International Staging System; R-ISS: Revised International Staging System; HR: hazard ratio; OS: Overall Survival; PFS: Progression-free Survival

CONCLUSIONS

- R2-ISS is a new scoring system identifying 4 groups of NDMM patients with different OS and PFS
- Compared to R-ISS, R2-ISS includes 1q CNA and better discriminates intermediate risk patients into different risk groups
- About 50% of patients are low/intermediate-low risk and about 50% of patients are intermediate-high/ high risk, allowing the design of risk-adapted approaches in a meaningful number of patients
- The additive scoring system is flexible, allowing the inclusion of new prognostic variables in the future (R3-ISS, R4-ISS….)
- The inclusion of new patient data and validation in an independent cohort is ongoing