First-line therapy with either bortezomib-melphalan-prednisone or lenalidomide-dexamethasone followed by lenalidomide for transplant-ineligible multiple myeloma patients: a pooled analysis of two randomized trials

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SUPPLEMENTARY APPENDIX

Additional methods

Study treatments

In the GIMEMA-MM-03-05 study, 511 patients were enrolled and randomized to receive either nine induction cycles with VMP or VMP plus thalidomide (VMPT) induction followed by bortezomib-thalidomide maintenance (VT). In the EMN01 study, 654 patients were randomized to receive nine induction cycles of either Rd, melphalan-prednisone-lenalidomide (MPR) or cyclophosphamide-prednisone-lenalidomide (CPR); after the induction phase, patients were randomized to receive lenalidomide (R) maintenance with or without prednisone until disease progression or unacceptable toxicity. Ethics committees or institutional review boards at the study sites approved both studies, which were done in accordance with the Declaration of Helsinki. All patients provided written informed consent.

Inclusion and exclusion criteria of the source trials

GIMEMA-MM-03-05

Inclusion criteria:

- Age > 65 years old and not a candidate for stem cell transplant, or younger who refuses or is not eligible for high-dose therapy
- Symptomatic multiple myeloma or asymptomatic multiple myeloma with related organ or tissue damage
- Presence of measurable disease
- Karnofsky performance status (PS) > 60% (see Appendix E)
- Able to read and complete the HRQOL instruments
- Agrees to use an acceptable barrier method for contraception for the duration of the study
- Pretreatment clinical laboratory values within 14 days of randomization:
    - platelet count ≥ $100x10^9$/L
    - hemoglobin ≥ 8 g/dL
    - absolute neutrophil count (ANC) ≥ $1.0x10^9$/L
    - AST ≤ 2.5 times the upper limit of normal
    - ALT ≤ 2.5 times the upper limit of normal
    - total bilirubin ≤ 1.5 times the upper limit of normal
    - serum creatinine ≤ 2.5mg/dL
    - corrected serum calcium <14 mg/dL (<3.5 mmol/L)
- Subjects (or their legally acceptable representatives) must have signed an informed consent document indicating that they understand the purpose of and procedures required for the study and are willing to participate in the study.
- Women of child-bearing potential must agree to use 2 methods of contraception: 1 effective (for example hormonal or tubal ligation) and 1 barrier (for example latex condom, diaphragm) for at least 4 weeks before starting the therapy, during the Treatment Period, and for 4 weeks after the last dose;
- Males must agree to use barrier contraception (latex condoms) when engaging in reproductive activity during the Treatment Period and for 4 weeks after the last dose.

Exclusion criteria:

- Diagnosis of smoldering multiple myeloma or MGUS.
- Diagnosis of Waldenstrom's disease
- Prior or current systemic therapy for multiple myeloma including steroids (with exception of emergency use of a short course [maximum 4 days] of steroids before randomization or prior or current use of bisphosphonates)
- Radiation therapy within 30 days before randomization
- Plasmapheresis within 30 days before randomization
- Major surgery within 30 days before randomization (Kyphoplasty is not considered major surgery)
- History of allergic reaction attributable to compounds containing boron or mannitol, or to Thalidomide
- Peripheral neuropathy Grade 2 or higher, as defined by National Cancer Institute Common Toxicity Criteria (NCI CTC) 3.0
- Uncontrolled or severe cardiovascular disease including myocardial infarction within 6 months of enrollment, New York Heart Association (NYHA) Class III or IV heart failure, uncontrolled angina, clinically significant pericardial disease, or cardiac amyloidosis
- Other malignancy within the past 5 years. Exceptions: basal cell or non-metastatic squamous cell carcinoma of the skin, cervical carcinoma in situ or FIGO Stage 1 carcinoma of the cervix
- Concurrent medical condition or disease (e.g., active systemic infection, uncontrolled diabetes, pulmonary disease) that is likely to interfere with study procedures or results, or that in the opinion of the investigator would constitute a hazard for participating in this study
- Use of any investigational drugs within 30 days before randomization.
- Pregnant or lactating women. A serum β-hCG pregnancy test must be performed at the Screening visit, for female patients of child-bearing potential. If the test is positive, the patient must be excluded from the study. Confirmation that the patient is not pregnant must be established by a negative serum or urinary pregnancy test with the result obtained 1 day prior to the Baseline visit (or the day of the visit if results are available before drug delivery). A pregnancy test is not required for naturally post-menopausal women (who have not had menses at any time in the preceding 24 consecutive months) or surgically sterilized women (hysterectomy, bilateral ovariectomy, bilateral salpingectomy);
- Patients or partners of patients of reproductive potential:
    - If thalidomide is taken during pregnancy (even as a single dose), it can cause severe birth defects or death of an unborn baby. Thalidomide should never be used by women who are pregnant or could become pregnant whilst taking the drug.
    - Women must not breastfeed whilst taking thalidomide, and for 8 weeks after finishing thalidomide treatment. It is also important that the female partners of male patients do not become pregnant whilst taking thalidomide.
    - Women of child-bearing potential must employ two methods of contraception (at the same time): one of which is highly effective (intra-uterine device (IUD), birth control pills, tubal ligation, or partner's vasectomy) and another additional method (condom, diaphragm, or cervical cap). These birth control methods must be used for at least 4 weeks before starting thalidomide therapy, during thalidomide therapy and for at least 4 weeks after thalidomide therapy has stopped. Women who have had a hysterectomy or have been postmenopausal for at least 24 consecutive months do not have to use the described contraceptive measures.
    - A serum β-hCG pregnancy test must be performed at the screening visit, for female patients of child-bearing potential. If the test is positive, the patient must be excluded from the study. A serum or urinary pregnancy test will be repeated 1 day prior to the baseline visit, every 4

weeks during treatment (1 day before each visit), at the End of Treatment visit, and at the Confirmation of PD visit. For female patients with irregular periods, a serum or urinary pregnancy test must be performed every 2 weeks during treatment. The pregnancy test may only be performed on the day of the visit if results are available before drug delivery.

- As thalidomide is present in semen, all male patients should use a condom during intercourse, even if they have undergone a prior vasectomy. This contraceptive measure must be employed whilst taking the drug and for 4 weeks after stopping treatment. Male patients should inform their partners of the risk of exposure and consider practicing a second method of birth control in addition to condom use.
- Patients must never donate sperm or blood whilst being treated with thalidomide and for 8 weeks after finishing treatment with thalidomide.

EMN01

Inclusion criteria:

- Patient is, in the investigator(s) opinion, willing and able to comply with the protocol requirements.
- Patient has given voluntary written informed consent before performance of any study related procedure not part of normal medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to their future medical care.
- Patient is 65 years old or older at the time of signing the informed consent or younger patients not candidate to high dose therapy.
- Female patient is either post-menopausal or surgically sterilized or, if at child-bearing
- potential, must:
    - understand that the study medication could have an expected teratogenic risk
    - Agree to use, and be able to comply with, effective contraception without interruption, 4 weeks before starting study drug, throughout study drug therapy (including dose interruptions) and for 4 weeks after the end of study drug therapy, even if she has amenorrhea. This applies unless the subject commits to absolute and continued abstinence confirmed on a monthly basis. The following are effective methods of contraception:
        - Implant
        - Levonorgestrel-releasing intrauterine system (IUS)
        - Medroxyprogesterone acetate depot
        - Tubal sterilization
        - Sexual intercourse with a vasectomized male partner only; vasectomy must be confirmed by two negative semen analyses
        - Ovulation inhibitory progesterone-only pills (i.e., desogestrel)
        - Combined oral contraceptive pills are not recommended. If a subject was using combined oral contraception, she must switch to one of the methods above. The increased risk of VTE continues for 4 to 6 weeks after stopping combined oral contraception.
        - Prophylactic antibiotics should be considered at the time of insertion particularly in patients with neutropenia due to risk of infection
    - Agree to have a medically supervised pregnancy test with a minimum sensitivity of 25 mIU/ml not more than 3 days before the start of study medication once the subject has been on effective contraception for at least 4 weeks. This requirement also applies to women of childbearing potential who practice complete and continued abstinence.

    - Agree to have a medically supervised pregnancy test every 4 weeks including 4 weeks after the end of study treatment, except in the case of confirmed tubal sterilization. These tests should be performed not more than 3 days before the start of next treatment. This requirement also applies to women of childbearing potential who practice complete and continued abstinence.
- Male subjects must:
    - Agree to use condoms throughout study drug therapy, during any dose interruption and for one week after cessation of study therapy if their partner is of childbearing potential and has no contraception.
    - Agree not to donate semen during study drug therapy and for one week after end of study drug therapy.
- All subjects must:
    - Agree to abstain from donating blood while taking study drug therapy and for one week following discontinuation of study drug therapy.
    - Agree not to share study medication with another person and to return all unused study drug to the investigator.
- Patient was previously diagnosed with symptomatic MM based on standard criteria, and has measurable disease, defined as follows:
    - Secretory myeloma: any quantifiable serum monoclonal protein value (generally, but not necessarily, greater than 1 g/dL of IgG M-Protein and greater than 0.5 g/dL of IgA M-Protein) and, where applicable, urine light-chain excretion of >200 mg/24 hours;
    - Non-secretory myeloma: > 30% plasma cells in the bone marrow and at least one plasmacytoma > 2 cm as determined by clinical examination or applicable radiographs (i.e., MRI or CT scan).
- Patient has a baseline bone marrow sample available for cytogenetics, that will be processed and eventually centralized within each country.
- Patient has a Karnofsky performance status ≥ 60%.
- Patient has a life-expectancy > 6 months
- Patients must have an adequate cardiac function
- Patients must have adequate pulmonary function
- Patient has the following laboratory values within 14 days before Baseline (day 1 of the Cycle 1):
    - Platelet count ≥75 x 109/L without transfusion support within 7 days before the test.
    - Absolute neutrophil count (ANC) ≥ 1.0 x 109/L without the use of growth factors.
    - Corrected serum calcium ≤ 14 mg/dL (3.5 mmol/L).
    - Aspartate transaminase (AST): ≤ 2.5 x the upper limit of normal (ULN).
    - Alanine transaminase (ALT): ≤ 2.5 x the ULN.
    - Total bilirubin: ≤ 1.5 x the ULN.
    - Calculated or measured creatinine clearance: ≥ 30 mL/minute.

Exclusion criteria:

- Previous treatment with anti-myeloma therapy (does not include radiotherapy, bisphosphonates, or a single short course of steroid; ≤ to the equivalent of dexamethasone 40 mg/day for 4 days).
- Any serious medical condition, including the presence of laboratory abnormalities, which places the subject at an unacceptable risk if he or she participates in this study or confounds the experimental ability to interpret data from the study.
- Pregnant or lactating females.
- Prior history of malignancies, other than multiple myeloma, unless the subject has been free of the disease for ≥ 3 years. Exceptions include the following: Basal cell carcinoma of the skin, Squamous

cell carcinoma of the skin, Carcinoma in situ of the cervix, Carcinoma in situ of the breast, Incidental histologic finding of prostate cancer (TNM stage of T1a or T1b).

Procedures

Patients in the VMP arm of the GIMEMA-MM-03-05 study received nine 6-week induction cycles of intravenous bortezomib at 1.3 mg/m2 on days 1, 4, 8, 11, 22, 25, 29, and 32 during cycles 1 to 4 and on days 1, 8, 22, and 29 during cycles 5 to 9; oral melphalan at 9mg/m2 on days 1 to 4; oral prednisone at 60 mg/m2 on days 1 to 4. The protocol was amended after the inclusion of the first 139 patients, and the schedule was changed to nine 5-week cycles and bortezomib dose was modified to 1.3 mg/m2 on days 1, 8, 15, and 22 during cycles 1 to 9. Patients in the Rd-R arm of the EMN01 study received nine 4-week induction cycles of lenalidomide at 25 mg daily on day 1 to 21; and dexamethasone at 40 mg in patients below 75 years or 20 mg in patients over 75 years, on days 1, 8, 15 and 22. Afterwards, patients were randomly assigned to receive maintenance treatment with lenalidomide alone at 10 mg on days 1 to 21 every 28 days or in combination with prednisone at 25 mg every other day continuously, until disease progression or intolerance (Rd-R).

Survival outcomes definition

Progression-free survival (PFS) was calculated from the date of diagnosis to the date of progression or death or the date the patient was last known to be in remission. Overall survival (OS) was calculated from the date of diagnosis to the date of death or the date the patient was last known to be alive.

Figure S1. Subgroup analysis of Progression-free survival for VMP versus Rd in the single high-risk cytogenetic subgroups, adjusted for age, ISS Stage, Karnofsky and extramedullary disease.

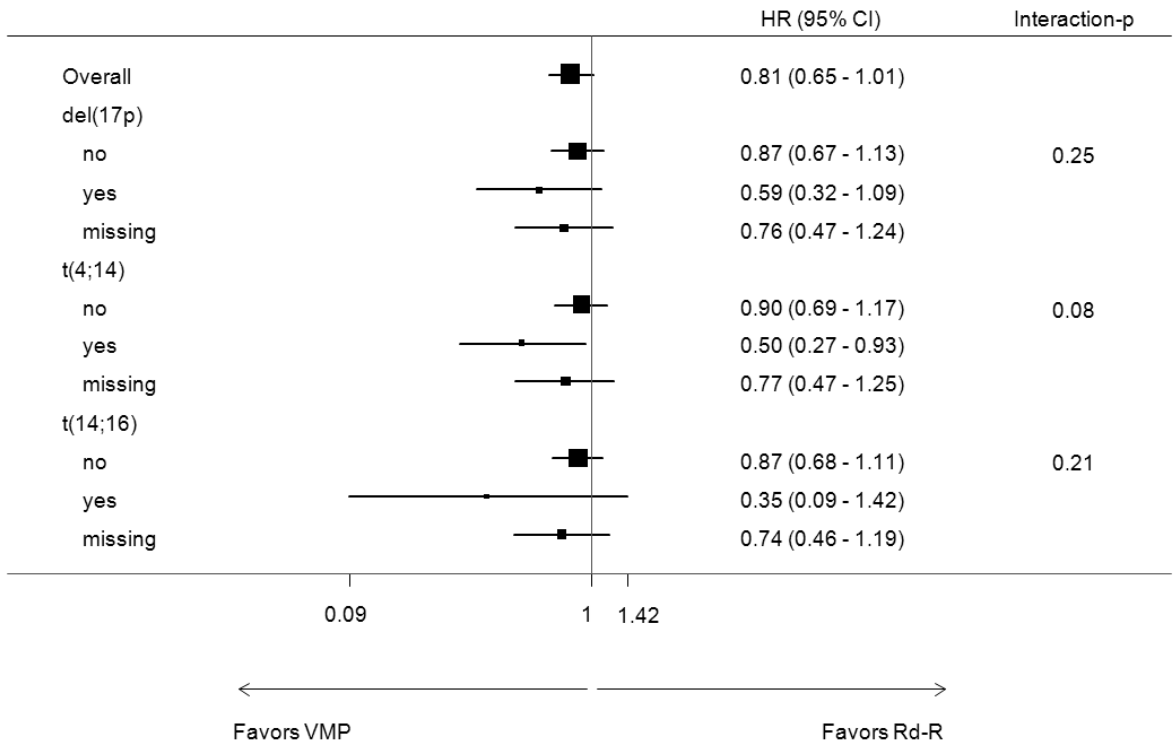

Figure S2. Subgroup analysis of Overall survival for VMP versus Rd in the single high-risk cytogenetic subgroups, adjusted for age, ISS Stage, Karnofsky and extramedullary disease.

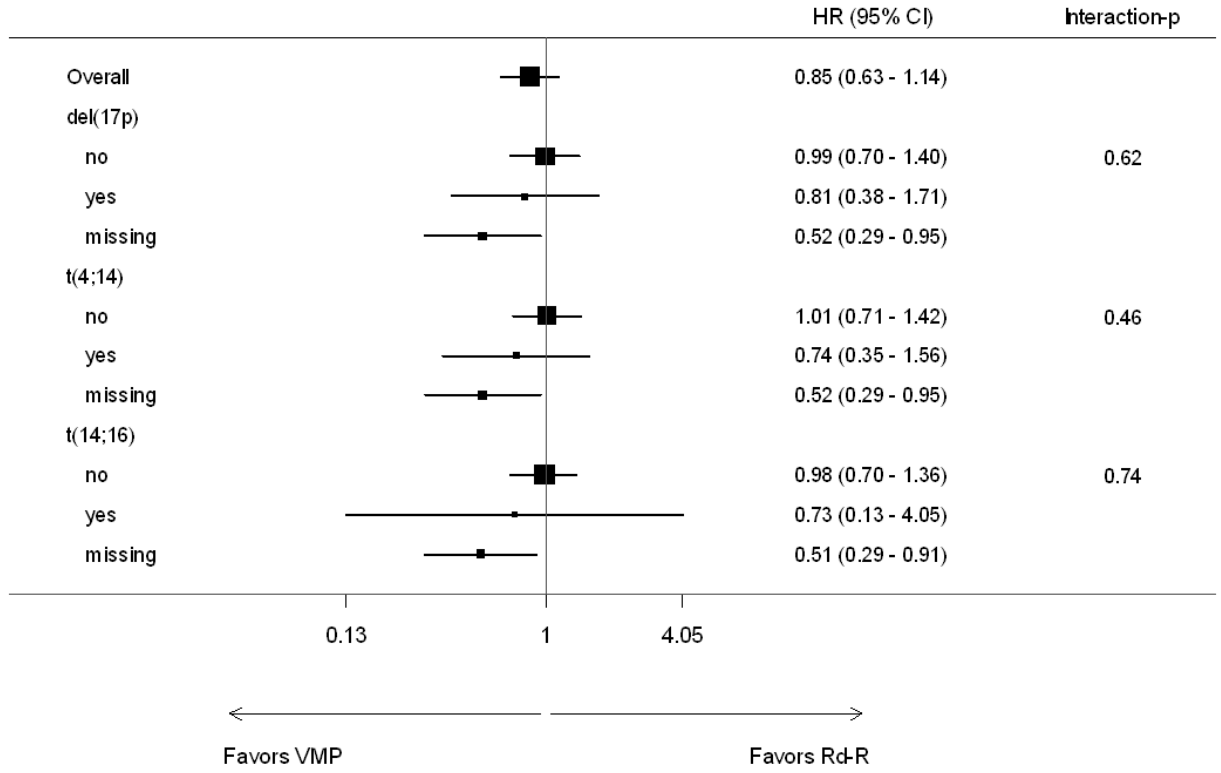

Figure S3. Subgroup analysis of Progression-free survival in the intent-to-treat population for VMP versus Rd with multiple imputation

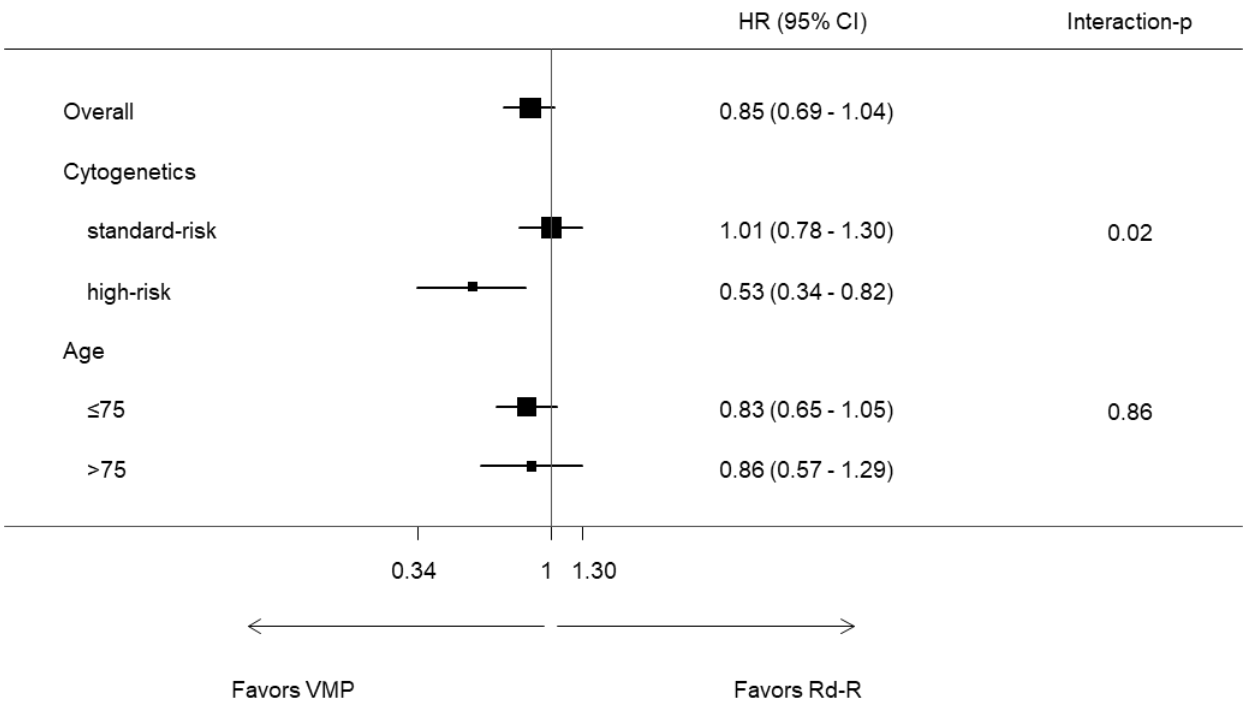

Figure S4. Subgroup analysis of Overall survival in the intent-to-treat population for VMP versus Rd with multiple imputation

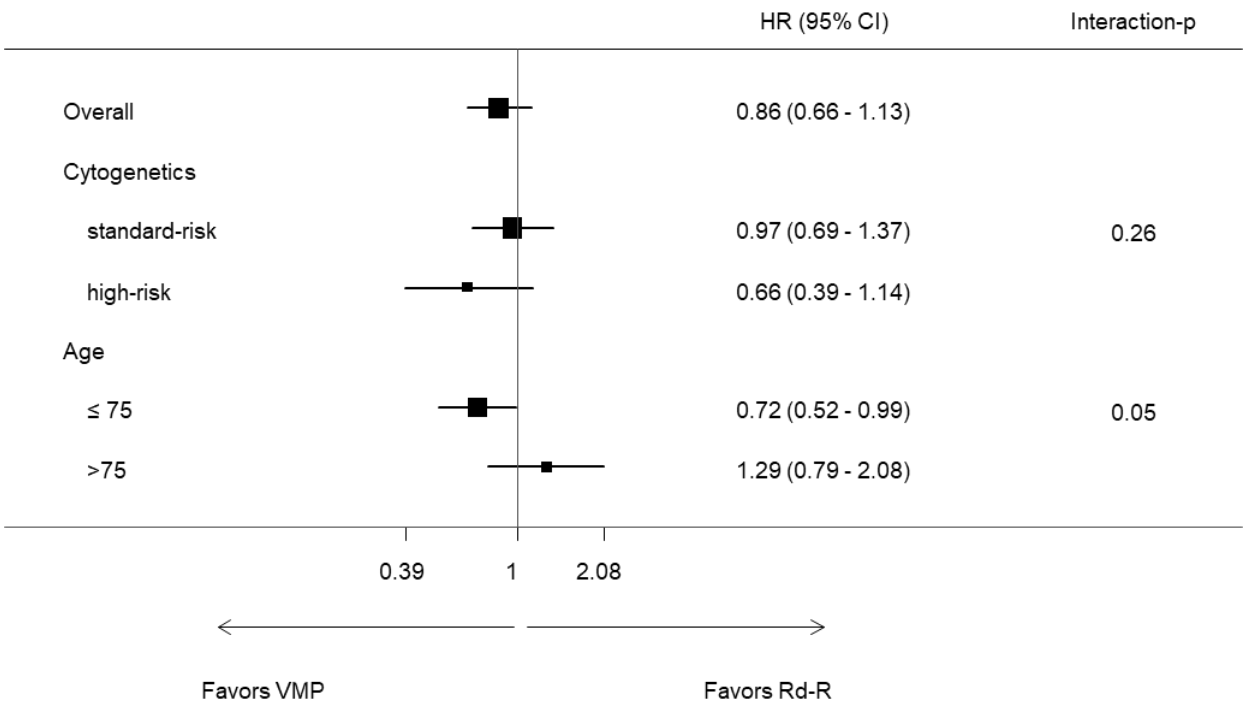

Table S1. Multivariate Cox models with multiple imputation method with 3-way interaction between treatment type, age and cytogenetics, adjusted for ISS Stage, Karnofsky, extramedullary disease and age as continuous variable.

Multiple imputation analysis	**PFS**	**OS**
	HR* (95% CI)	**HR* (95% CI)**
Standard-risk cytogenetics - Age ≤75	0.89 (0.66 - 1.19)	0.76 (0.51 - 1.13)
Standard-risk cytogenetics - Age >75	1.25 (0.78 - 2.01)	1.61 (0.89 - 2.93)
High-risk cytogenetics - Age ≤75	0.69 (0.41 - 1.16)	0.64 (0.34 - 1.21)
High-risk cytogenetics - Age >75	0.26 (0.11 - 0.62)	0.75 (0.27 - 2.05)
3-way interaction-p	0.03	0.41
2-way Cytogenetics interaction-p	0.02	0.26
2-way Age interaction-p	0.86	0.05

PFS, progression-free survival; OS, overall survival; ISS, International Staging System; CI, confidence interval.
*HR refers to the comparison between VMP vs Rd-R.