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Blood 144 (2024) 4739–4740

The 66th ASH Annual Meeting Abstracts

POSTER ABSTRACTS

654.MULTIPLE MYELOMA: PHARMACOLOGIC THERAPIES

Frailty Subgroups Determine Heterogeneous Outcomes in Elderly Patients with Newly-Diagnosed Multiple Myeloma - Long-Term Follow-up of the HOVON 143 Trial

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Introduction

Patients who are defined frail according to the International Myeloma Working Group Frailty Index (IMWG-FI) have a poor outcome, as we have shown in the prospective phase II HOVON 143 study, that was specifically designed for frail patients (Stege et al. J Clin Oncol 2021). We here present the long-term follow-up of the HOVON 143 study, including overall survival, with details regarding frailty subgroups and subsequent therapies.

Methods

Patients were treated with nine 28 days- induction cycles of ixazomib (4mg on days 1, 4, 15), daratumumab (16mg/kg iv; cycles 1-2: days 1, 8, 15, 22; cycles 3-6: days 1, 15; cycles 7-9: day 1) and low dose dexamethasone (cycle 1-2: 20mg; subsequent cycles 10mg, co-administered with daratumumab), followed by maintenance therapy of 8-week cycles with ixazomib (days 1, 8, 15, 29, 36, 43), and daratumumab (day 1) and low dose dexamethasone (day 1), until progression for a maximum of 2 years. The primary endpoint was overall response rate (ORR) after 9 induction cycles. Secondary endpoints were progression free survival (PFS), PFS2 defined as time from start of treatment until the second progression or death, and overall survival (OS).

Survival analyses were performed using the Kaplan-Meier method (R statistical program, version 4.0). This trail is registered at www.trialregister.nl as NTR6297.

Results

In total 65 frail patients (IMWG-FI score 2-5) were included. Median age was 81 years (range 70 - 92). ISS III and high-risk cytogenetics were present in 25 (45%) and 11 patients (20%) respectively. After a median follow-up of 61.5 months, median PFS was 13.8 months (95%CI 10.1-21.4), median PFS2 was 30.7 months (95%CI 22.3-41.2), and median OS was 34.0 months (95%CI 28.1-53.2).

Thirteen (20%) of patients were frail based on age >80 alone, without any impairments in (Instrumental) Activities of Daily Living ((I)ADL) or comorbidities, 32 (49%) patients were frail based on impairments and 20 (31%) patients were frail based on both age >80 and having impairments in (I)ADL and/or comorbidities, defined as 'ultra-frail'. Median PFS was 17.7 months (95%CI 12.1-NA) in patients frail based on age, 14.4 months (95%CI 8.9-36.3) in frail based on impairments and 11.0 months (95%CI 8.3-32.5) in ultra-frail patients. Median PFS2 was longer in patients frail based on age (51.0 months (95%CI 24.1-NA)), than in patients who were frail based on impairments (26.4 months (95%17.0-43.9)) and 'ultra-frail' patients (26.8 months (95%CI 15.5-NA)). For OS, these numbers were 53.2 months (95%CI 31.8-NA), 31.2 months (95% 20.5-NA), and 31.0 months (95%CI 15.5-NA) respectively. These differences were not statistically significant, probably due to small patient numbers.

Death before disease progression occurred more often both in patients who were frail based on impairments and in ultra-frail patients, as compared to patients frail based on age (22% and 35%, versus 8%). Of the frail patients who progressed after first-line therapy with ixa-dara-dex, 37/46 (80%) received second line treatment, which was mainly lenalidomide based 33/37 (89%) (20/37 len-dex (Rd), 4/37 len-cyclophosphamide-prednisone, 4/37 elotuzumab-Rd, 2/37 carfilzomib-Rd, 2 dara-Rd, 1 len-prednisone). Rates of receiving second line treatment did not markedly differ between frail subgroups (9/12 (75%) of frail based on age, 19/22 (86%) of frail based on impairments and 9/12 (75%) of ultra-frail).

Conclusion

The long-term analysis of the HOVON 143 study especially designed for frail patients showed that the outcome was poor, with a median OS of less than 3 years. However, frailty subgroup analyses revealed pronounced heterogeneity in outcome. More than a third of ultra-frail patients died even before progressive disease, driving poor long-term outcome and highlighting the unmet need for more tolerable but still effective therapies. In contrast, mortality before first progression was low in patients who were frail based on age >80 years alone, with the great majority receiving second line treatment following progressive disease. Importantly, second line treatment resulted in a longer suppression of the disease than first line treatment, suggesting frail patients based on age alone could benefit from a more intensive first line treatment. These findings warrant future trials sufficiently powered for frail subgroups.

Disclosures Groen: *BMS:* Honoraria; *Beigene:* Honoraria. **Levin:** *Janssen, AbbVie:* Other: Travel. **Stege:** *Celgene:* Consultancy, Speakers Bureau; *Takeda:* Consultancy, Speakers Bureau; *Sanofi:* Consultancy, Speakers Bureau; *Janssen:* Consultancy, Speakers Bureau. **Nijhof:** *Janssen:* Honoraria; *BMS:* Honoraria. **Timmers:** *Novartis:* Consultancy; *Janssen:* Consultancy. **Westerman:** *Janssen:* Other: Payment for lectures. **Vekemans:** *Amgen:* Membership on an entity's Board of Directors or advisory committees; *BMS:* Membership on an entity's Board of Directors or advisory committees; *Celgen:* Membership on an entity's Board of Directors or advisory committees; *Sanofi:* Membership on an entity's Board of Directors or advisory committees, Other: travel grants; *Menarini:* Membership on an entity's Board of Directors or advisory committees; *GSK:* Membership on an entity's Board of Directors or advisory committees; *Takeda:* Membership on an entity's Board of Directors or advisory committees; *Janssen:* Membership on an entity's Board of Directors or advisory committees, Other: travel expense; *Pfizer:* Membership on an entity's Board of Directors or advisory committees. **van de Donk:** *Merck:* Membership on an entity's Board of Directors or advisory committees; *Pfizer:* Membership on an entity's Board of Directors or advisory committees; *Kite Pharma:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Servier:* Membership on an entity's Board of Directors or advisory committees; *Adaptive Biotechnologies:* Membership on an entity's Board of Directors or advisory committees; *Bayer:* Membership on an entity's Board of Directors or advisory committees; *AbbVie:* Membership on an entity's Board of Directors or advisory committees; *Roche:* Membership on an entity's Board of Directors or advisory committees; *Takeda:* Membership on an entity's Board of Directors or advisory committees; *Sanofi:* Membership on an entity's Board of Directors or advisory committees; *Bristol Myers Squibb:* Membership on an entity's Board of Directors or advisory committees, Research Funding; *Cellectis:* Research Funding; *Novartis:* Membership on an entity's Board of Directors or advisory committees, Research Funding; *Celgene:* Membership on an entity's Board of Directors or advisory committees, Research Funding; *Amgen:* Membership on an entity's Board of Directors or advisory committees, Research Funding; *Janssen Pharmaceuticals:* Membership on an entity's Board of Directors or advisory committees, Research Funding. **Ypma:** *Johnson & Johnson:* Other: Partial reimbursement of conference attendance costs; remuneration as a speaker for conference without personal financial compensation; *Novartis:* Other: Remuneration as a speaker for conference without personal financial compensation. **Zweegman:** *Takeda:* Research Funding; *Sanofi:* Membership on an entity's Board of Directors or advisory committees; *Amgen:* Membership on an entity's Board of Directors or advisory committees; *BMS:* Membership on an entity's Board of Directors or advisory committees; *GSK:* Membership on an entity's Board of Directors or advisory committees; *Janssen:* Membership on an entity's Board of Directors or advisory committees, Research Funding; *Oncopeptides:* Membership on an entity's Board of Directors or advisory committees.

https://doi.org/10.1182/blood-2024-208754