

Multiple Myeloma: Herbicide Exposure, BMI, and Novel Quadraplet Regimens



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Multiple myeloma (MM) is the world’s second most common blood cancer, and its diagnosis rates are rising.¹ Most MM cases are diagnosed in individuals older than 50 years, with frailty and comorbidities more common in veteran cohorts.² MM displays substantial genetic diversity, which contributes to treatment resistance. In most patients, MM eventually relapses or stops responding to available therapies, even as newer treatments improve remission.¹

A study of Vietnam War-era veterans with high Agent Orange (AO) exposure found a heightened risk of progressing from monoclonal gammopathy of undetermined significance (MGUS) to MM compared with those without exposure, highlighting a critical link between herbicide contaminants and cancer

progression risk.³ Further, in a large VHA cohort of veterans with MGUS, higher cumulative BMI (> 25) was significantly associated with increased risk of progression to MM. Among patients with healthy BMI at diagnosis (18.5 to < 25), each 1-unit increase in excess BMI per year raised progression risk by 21%.⁴

Evidence from a meta-analysis supports quadruplet regimens with anti-cluster of differentiation 38 (CD38) antibodies for veterans with newly diagnosed MM, showing longer survival and deeper, more durable responses than triplet therapies. Given that many veterans have higher myeloma risk due to prior exposures and older age at diagnosis, these regimens could potentially improve outcomes and quality of life for veterans with MM.⁵

AO Exposure and Progression From MGUS to MM in Vietnam War-Era Veterans³

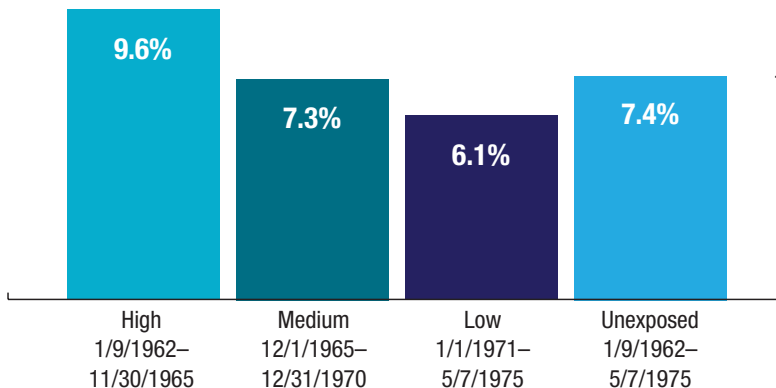


High exposure to AO was associated with a significantly higher risk of progression to MM compared with no AO exposure. Vigilant monitoring among patients with MGUS with documented AO exposure might be warranted.

Study Sample
10,847 Vietnam War-era veterans with MGUS
26.3% with documented AO exposure



MGUS to MM Progression, %: 5.2 Year Follow Up



AO Exposure Levels (by Vietnam era service dates)



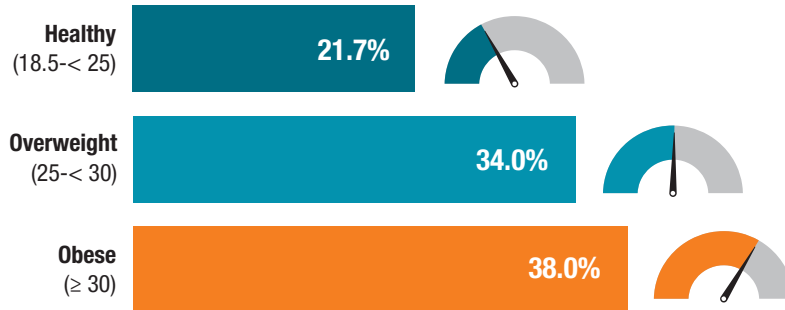
Dose-Dependence
Those with high AO exposure had a **48% increased risk** compared to unexposed veterans.

Preventing MM in Veterans Through Weight Management⁴



Quadruplet regimens incorporating anti-CD38 antibodies outperform triplet therapies in veterans with newly diagnosed MM, supporting their use as a new standard of care. In a nationwide cohort of 22,429 veterans with MGUS, higher BMI at diagnosis and greater cumulative exposure to excess BMI were associated with an increased risk of progression to multiple myeloma. These findings suggest that obesity burden over time is an important, potentially modifiable risk factor for MGUS progression.

BMI Distribution at MGUS Diagnosis



Key Findings



Overweight
aHR 1.17
(95% CI, 1.03-1.34)

Obese
aHR 1.27
(95% CI, 1.09-1.47)

...compared to healthy weight patients

aHR = adjusted hazard ratio



For healthy-weight patients:
Each +1 unit* of excess BMI/year **+21% higher MM risk** (aHR 1.21; 95% CI, 1.04-1.40)

Patients with MGUS and baseline BMI ≥ 25:
17%-27% higher risk of MM compared with patients with baseline BMI within the reference range

*A +1 unit increase in BMI corresponds to gaining enough weight to raise BMI by one point—for example, about 5–7 lb (2–3 kg) for an average-height adult (≈5'9").

Interpretations



Higher and prolonged BMI exposure **increases** MM progression risk.



Maintaining a stable, healthy weight post-MGUS diagnosis may **reduce the risk of disease progression**.

Quadruplet Therapy Provides a New Highly Effective Frontline Treatment Option in MM⁵



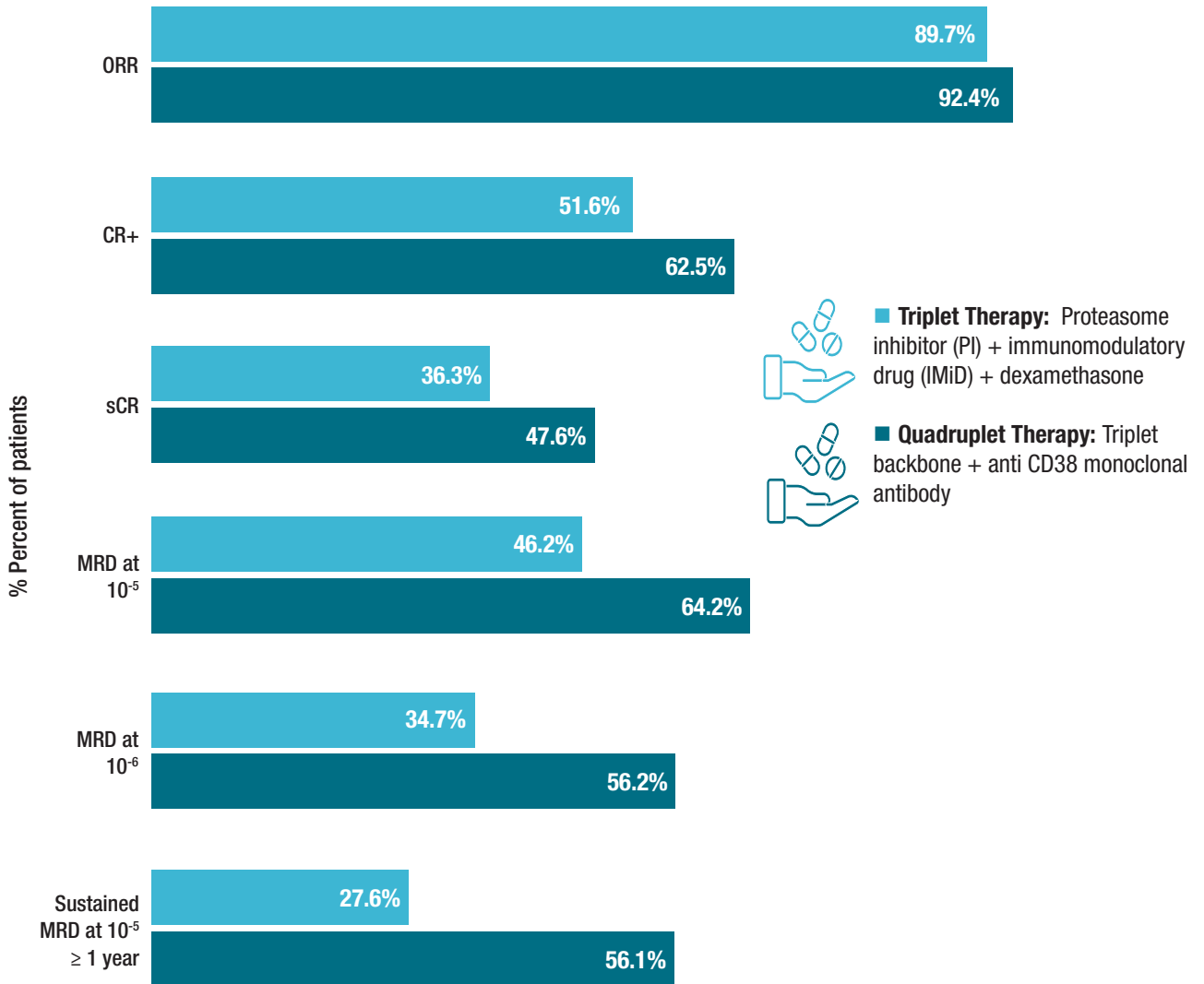
Findings from a recently published meta-analysis may lead to increased use of quadruplet induction regimens, including anti-CD38 antibodies, among veterans with newly diagnosed MM (NDMM), as these regimens offer longer survival potential and deeper, more durable responses than prior triplet therapies.

Overview



Quadruplet Therapy Provides a New Highly Effective Frontline Treatment Option in MM: Cont.⁵

Response Outcomes



CR+, complete response or better; MRD, minimal residual disease; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; sCR, stringent complete response.

MRD 10⁻⁵ and 10⁻⁶ numbers refer to how deeply MRD is measured, ie, how sensitive the test is at detecting remaining myeloma cells after treatment. Deeper MRD negativity correlates with longer progression-free survival and overall survival in MM.

Conclusions



PFS: Quadruplets reduced risk of progression or death by 45% vs triplets



OS: Quadruplets reduced risk of death by 35% vs triplets

Quadruplets = Superior efficacy (deeper and more durable responses) with manageable toxicity, particularly in transplant-eligible NDMM