Efficacy and safety of melflufen plus daratumumab and dexamethasone in relapsed/refractory multiple myeloma: results from the randomized, open-label, phase III LIGHTHOUSE study

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Received: May 12, 2023.
Accepted: August 21, 2023.
Early view: August 31, 2023.

https://doi.org/10.3324/haematol.2023.283509

Supplementary Appendix

Supplementary methods

Eligibility criteria

Patients were eligible to be included in the study only if all the following criteria apply:

1. Male or female, aged 18 years or older
2. Capable of giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the informed consent form and in this protocol
3. A prior diagnosis of multiple myeloma with documented disease progression in need of treatment at time of screening
4. Double refractory to an immunomodulatory agent and a proteasome inhibitor (PI; regardless of the number of prior lines of therapy), or have received at least 3 prior lines of therapy including an immunomodulatory agent and a PI (the definition of refractory includes intolerance to an immunomodulatory agent/PI after at least two 28-day cycles of therapy)
5. Prior treatment with daratumumab or another anti-CD38 monoclonal antibody (mAb) is allowed if the patient has:
    - Achieved at least partial response (PR) and is not refractory to previous anti-CD38 mAb treatment
    - At least 6 months since last dose of anti-CD38 mAb prior to cycle 1/day 1
    - Not discontinued anti-CD38 mAb treatment due to related grade ≥3 toxicity
6. Measurable disease defined as any of the following:
    - Serum monoclonal protein ≥0.5 g/dL by serum protein electrophoresis
    - ≥200 mg/24 hr of monoclonal protein in the 24-hour urine collection by electrophoresis

- Serum free light chain ≥10 mg/dL AND abnormal serum kappa to lambda free light chain ratio

7. Life expectancy of ≥6 months
8. Eastern Cooperative Oncology Group performance status ≤2 (patients with lower performance status based solely on bone pain secondary to multiple myeloma may be eligible following consultation and approval of the Medical Monitor)
9. Ability to understand the purpose and risks of the study, ability to participate in all the procedures required by the protocol and provide signed and dated informed consent
10. 12-lead electrocardiogram with QT interval calculated by Fridericia Formula interval of ≤470 msec
11. Adequate organ function with the following laboratory results during screening (within 21 days) and immediately before study treatment administration on cycle 1 day 1:
    - Absolute neutrophil count ≥1,000 cells/mm^3 (1.0 × 10^9/L) (Growth factors cannot be used within 10 days (14 days for pegfilgrastim) prior to initiation of study treatment)
    - Platelet count ≥75,000 cells/ mm^3 (75 x 10^9/L) (without transfusions during the 10 days prior to initiation of therapy)
    - Hemoglobin ≥8.0 g/dL (red blood cell transfusions are permitted)
    - Total bilirubin ≤1.5 x upper limit of normal, except patients diagnosed with Gilbert's syndrome that have been reviewed and approved by the Medical Monitor
    - Aspartate transaminase (also known as SGOT) and alanine aminotransferase (also known as SGPT) ≤3.0 × ULN
    - Renal function: Estimated creatinine clearance by Cockcroft-Gault formula of ≥45 mL/min

12. Must have or be willing to have an acceptable central catheter. (Port A cath, peripherally inserted central catheter line, or central venous catheter)
13. a) Male patients: Male patient who agrees to use contraception as detailed in this protocol during the treatment period and for at least 3 months after the last dose of study treatment and refrain from donating sperm during this period. b) Female patients: A female patient is eligible to participate if she is not pregnant, not breastfeeding, and at least one of the following conditions applies:
    - Not a person of childbearing potential *or*
    - A person of childbearing potential who agrees to follow the contraceptive guidance in the protocol during the treatment period and for at least 3 months after the last dose of study treatment.

Patients were excluded from the study if any of the following criteria apply:

1. Primary refractory disease (i.e., never responded with at least minimal response [MR] to any prior therapy)
2. Prior treatment with CD38 chimeric antigen receptor T-cell therapy or CD38/CD3 bispecific antibodies
3. Chronic obstructive pulmonary disease with a forced expiratory volume in 1 second less than 50% of predicted normal
4. Moderate or severe persistent asthma within the past 2 years, or currently has uncontrolled asthma of any classification
5. Evidence of mucosal and/or internal bleeding or platelet transfusion refractory (platelet count fails to increase by >10,000 cells/mm^3 after a transfusion of an appropriate dose of platelets)
6. Any medical conditions that, in the Investigator's opinion, would impose excessive risk to the patient or would adversely affect their participating in this study. Examples of such

conditions are a significant history of cardiovascular disease (e.g., heart failure class III or IV according to New York Heart Association, cardiac angioplasty or stenting, myocardial infarction, unstable angina, significant cardiac conduction system abnormalities, uncontrolled hypertension, or grade ≥3 thromboembolic event in the last 6 months)

7. Known active infection that is uncontrolled (including symptomatic or asymptomatic COVID-19) or has required intravenous systemic therapy within 14 days of randomization. Patients who have required oral anti-infective treatment within 14 days of randomization should be discussed with the Medical Monitor
8. Other malignancy diagnosed or requiring treatment within the past 3 years with the exception of adequately treated basal cell carcinoma, squamous cell skin cancer, carcinoma in-situ of the cervix or breast or very-low and low-risk prostate cancer in active surveillance
9. Serious psychiatric illness, active alcoholism, or drug addiction that may hinder or confuse compliance or follow-up evaluation
10. HIV or active hepatitis C viral infection, either known or if detected during screening
11. Hepatitis B: both active (defined as HBsAg+) or non-active hepatitis B (defined as HBsAg-, anti-HBs+, anti-HBc+):
    - Patients with prior hepatitis B vaccine are permitted (defined as HBsAg-, Anti-HBs+, Anti-HBc-)
12. Concurrent known or suspected amyloidosis or plasma cell leukemia
13. POEMS syndrome (plasma cell dyscrasia with polyneuropathy, organomegaly, endocrinopathy, monoclonal protein and skin changes)
14. Known central nervous system or meningeal involvement of myeloma
15. Any of the following treatments, within the specified timeframe:

- Previous cytotoxic therapies, including cytotoxic investigational agents, for multiple myeloma within 3 weeks (6 weeks for nitrosoureas) prior to initiation of therapy
- The use of live vaccines within 30 days before initiation of therapy
- Immunomodulatory agents, PIs and/or corticosteroids within 2 weeks prior to initiation of therapy
- Other investigational therapies and mAb within 4 weeks of initiation of therapy
- Prednisone up to but no more than 10 mg orally/day or its equivalent for symptom management of comorbid conditions is permitted but dose should be stable for at least 7 days prior to initiation of therapy

16. Residual side effects of previous therapy >grade 1 prior to initiation of therapy (alopecia any grade and/or neuropathy grade 1 without pain are permitted)
17. Prior stem cell transplant (autologous and/or allogenic) within 6 months of initiation of therapy
18. Prior allogeneic stem cell transplantation with active graft-versus-host-disease
19. Prior major surgical procedure or radiation therapy within 4 weeks of the initiation of therapy (this does not include limited course of radiation used for management of bone pain within 7 days of initiation of therapy)
20. Known intolerance to the required dose and schedule of steroid therapy, as determined by the investigator
21. Known hypersensitivity to any of the agents in this study including hyaluronidase
22. Prior treatment with melflufen

Study design

<u>Dose modifications</u>

Dose modifications of melflufen (lowest dose permitted was 10 mg) and dexamethasone (lowest dose permitted was 12 mg if a 40-mg starting dose and 4 mg if a 20-mg starting dose) for drug-related toxicity were permitted, including multiple dose reductions. If the patient was unable to tolerate the lowest dose of melflufen due to drug-related toxicity, the patient was withdrawn from treatment. There were no dose reductions for daratumumab. At the Investigator's discretion, patients who discontinued treatment with daratumumab were allowed to continue treatment with melflufen and dexamethasone, whereas patients who discontinued melflufen were allowed to continue treatment with daratumumab and dexamethasone.

Efficacy assessments

Disease status was assessed at screening and pre-dose day 1 of each cycle to assess response using M protein assessments: Free light chain and free light chain ratio, electrophoresis, serum and urine electrophoresis and immunofixation, and daratumumab immunofixation reflex assay; serum calcium; or bone marrow aspirates in patients with suspected complete response or very good partial response to confirm response for minimal residual disease (MRD) assessment by next generation sequencing. Skeletal x-rays or low-dose bone computed tomography scans were performed. Physical examinations were performed at screening, day 1 of each cycle, and the end of treatment visit while imaging for suspected extramedullary disease was performed at screening, every 2 cycles, and every 2 months during progression-free survival (PFS) follow-up until disease progression. Concomitant medications and blood products received within 21 days prior to the first dose until the end of treatment visit were recorded.

End-of-treatment visit

End-of-treatment visits were scheduled within 30 days after the last dose of study drug, followed by PFS assessments scheduled monthly until progressive disease or initiation of subsequent new therapy, and overall survival assessments were scheduled every 3 months.

Study endpoints

Primary endpoints

- PFS (time from the date of randomization to the date of first documentation of confirmed progressive disease or death due to any cause)
    - Per protocol, PFS was meant to be assessed by an independent review committee, but due to early termination of the study, PFS was based on Investigator assessment only

Key secondary endpoints

- Overall response rate (proportion of patients who achieve a best confirmed response of stringent complete response [sCR], complete response [CR], very good partial response [VGPR], or PR)
- Duration of response (time from the first evidence of confirmed assessment of sCR, CR, VGPR or PR to first confirmed disease progression, or death due to any cause. Duration of response was defined only for patients with a confirmed PR or better)
- Frequency and grade of treatment emergent adverse events
    - A treatment emergent adverse event was defined as any AE that started on or after the first day of study treatment was administered and within 30 days of the last administration of study treatment or before start of subsequent anticancer treatment (whichever occurred first) or that worsened on or after the first day of study treatment

- Because of how TEAEs are defined, some TEAEs may have been related to the disease rather than the study treatment[1]

Other secondary endpoints

- Best response (proportion of patients with sCR, CR, VGPR, PR, MR, stable disease, PD, or non-evaluable)
- Clinical benefit rate (the proportion of patients who achieve a best confirmed response of sCR, CR, VGPR, PR or MR)
- Duration of clinical benefit (time from first evidence of confirmed assessment of sCR, CR, VGPR, PR, or MR to first confirmed disease progression, or to death due to any cause). Duration of clinical benefit was defined only for patients with a confirmed MR or better
- Time to response (time from randomization to the date of the first documented confirmed response in a patient who has responded with ≥PR)
- Time to progression (time from the date of randomization to the date of the first documented confirmed PD)
- Time to next treatment (time from randomization to the date of next anti-myeloma treatment or until death)
- Overall survival (time from date of randomization to death due to any cause)

Exploratory endpoints

- Assessment of MRD status by next generation sequencing in patients who achieve a CR or VGPR
- Second objective disease progression (time from randomization to progression on next line of treatment or death from any cause, whichever occurs first)
- Value and changes in pain, in Brief Pain Inventory-Short Form and Numeric Rating Scale for measure of bone pain

- Response rate (CR and PR) according to International Myeloma Working Group consensus criteria of extramedullary myeloma (plasmacytomas)
- Number of health services; number and days of hospitalization
- Pharmacokinetic parameters of melphalan at selected time points
- Serum daratumumab concentrations
- Incidence of antibodies to daratumumab
- Incidence of antibodies to rHuPH20
    - DNA/RNA-based drug response biomarkers including but not limited to aminopeptidases and esterases
    - Serum levels of bone reabsorption-related proteins including but not limited to TRACP-5b, PINP, Total RANK, osteopontin, osteocalcin, C-terminal telopeptide of type 1 collagen, bone alkaline phosphatase
    - Serum levels of cytokines interleukin-6, interleukin-10
    - Immune profiling in peripheral blood including but not limited to regulatory T cells, myeloid-derived suppressor cells and natural killer cells
- Value and changes from baseline in European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 summary score, each scale of the EORTC QLQ-C30, EQ-5D utility index, each dimension of the EQ-5D-3L, and the visual analogue scale of the EQ-5D-3L
- Overall response rate after crossover
- Duration of response after crossover
- Best response after crossover
- Clinical benefit rate after crossover
- Duration of Clinical Benefit after crossover

- Time to response from crossover to the date of the first documented confirmed response in a patient who had responded with ≥PR
- Time to progression from crossover to the date of the first documented confirmed PD
- Time to next treatment from crossover to the date of next antimyeloma treatment or until death
- Overall survival from crossover until death of any cause
- Value and changes in pain, in BPI-SF and NRS for measure of bone pain
- Value and changes from crossover in EORTC QLQC30 summary score, each scale of the EORTC QLQC30, EQ-5D utility index, each dimension of the EQ-5D-3L, and the visual analog scale of the EQ-5D-3L
- Frequency and grade of treatment emergent adverse event

Supplementary table

Table S1. Efficacy outcomes – patients with time to progression <36 months after a prior autologous stem cell transplantation.

Efficacy category	Melflufen group (N=13)	Daratumumab group (N=12)
Progression-free survival		
Events, n (%)	2 (15)	2 (17)
Median (95% CI), months	NR (6.2-NR)	NR (4.7-NR)
Hazard ratio (95% CI)[a]	0.93 (0.13-6.59)	
P value[b]	0.9391	
Overall survival		
Events, n (%)	1 (8)	0 (0)
Median (95% CI), months	NR (NR-NR)	NR (NR-NR)
Hazard ratio (95% CI)[a]	NR (0.00-NR)	
P value[b]	0.3404	
Best confirmed response, n (%)		
Complete response	0 (0)	0 (0)
Very good partial response	2 (15)	2 (17)
Partial response	5 (39)	4 (33)
Minimal response	1 (8)	1 (8)
Stable disease	3 (23)	3 (25)
Progressive disease	0 (0)	1 (8)
Not evaluable	2 (15)	1 (8)
Overall response rate (95% CI), %	54 (25-81)	50 (21-79)
P value	0.8505	

[a]Unstratified hazard ratio. [b]Log-rank *P* value.
NR: not reached.

Reference

1. U.S. Department of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE). 2010. [June 14, 2010]. Available from: https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf.