an immunophenotype intermediate between diffuse large B-cell lymphoma and classic Hodgkin's lymphoma (positive for CD20, CD30, and CD15). Despite a complete metabolic response to DA-EPOCH-R, she had a relapse and disease progression after treatment with brentuximab; a combination of rituximab, gemcitabine, and oxaliplatin; and mediastinal radiation. She had a complete metabolic response after treatment with nivolumab and continues to be in remission on day 161 of treatment (Fig. 1E). Immunohistochemical analysis showed focal membranous PD-L1 expression (Fig. 1F).

Genetic susceptibility to immune-checkpoint inhibition that is conferred by 9p24.1 copy-number alterations is best characterized in classic Hodgkin's lymphoma. Near-uniform (97%) concordant copy-number alterations in *PD-L1*|*PD-L2* have been shown in cases of classic Hodgkin's lymphoma by means of FISH, with 2% having a translocation at this locus.[4] Nivolumab[5] and pembrolizumab have a high frequency of response in relapsed or refractory classic Hodgkin's lymphoma but not in primary mediastinal B-cell lymphoma. Recent findings indicate that mediastinal gray-zone lymphoma may be more closely related to classic Hodgkin's lymphoma than to primary mediastinal B-cell lymphoma.[2] These findings suggest that PD-1 inhibitors may be therapeutically important for mediastinal gray-zone lymphoma, which is more resistant to treatment than classic Hodgkin's lymphoma or primary mediastinal B-cell lymphoma.[2]

The high frequency of 9p24.1 copy-number alterations across mediastinal lymphomas suggests a disease-specific, genetically determined dependence on PD-1 for survival. These cases provide early evidence for using PD-1 inhibition in relapsed or refractory mediastinal gray-zone lymphoma, which warrants further testing.

Christopher Melani, M.D.
National Cancer Institute
Bethesda, MD

Ajay Major, M.D.
University of Colorado School of Medicine
Aurora, CO

Wyndham H. Wilson, M.D., Ph.D.
National Cancer Institute
Bethesda, MD
wilsonw@mail.nih.gov

Manali Kamdar, M.D., M.B., B.S.
University of Colorado School of Medicine
Aurora, CO

and Others

A complete list of authors is available with the full text of this letter at NEJM.org.

Disclosure forms provided by the authors are available with the full text of this letter at NEJM.org.

1. Traverse-Glehen A, Pittaluga S, Gaulard P, et al. Mediastinal gray zone lymphoma: the missing link between classic Hodgkin's lymphoma and mediastinal large B-cell lymphoma. Am J Surg Pathol 2005;29:1411-21.
2. Wilson WH, Pittaluga S, Nicolae A, et al. A prospective study of mediastinal gray-zone lymphoma. Blood 2014;124:1563-9.
3. Eberle FC, Salaverria I, Steidl C, et al. Gray zone lymphoma: chromosomal aberrations with immunophenotypic and clinical correlations. Mod Pathol 2011;24:1586-97.
4. Roemer MG, Advani RH, Ligon AH, et al. PD-L1 and PD-L2 genetic alterations define classical Hodgkin lymphoma and predict outcome. J Clin Oncol 2016;34:2690-7.
5. Ansell SM, Lesokhin AM, Borrello I, et al. PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma. N Engl J Med 2015;372:311-9.

DOI: 10.1056/NEJMc1704767

Drug Combinations with Transplantation for Myeloma

TO THE EDITOR: The Intergroupe Francophone du Myélome (IFM) 2009 Study by Attal and colleagues (April 6 issue)[1] showed that among patients with multiple myeloma, the combination of lenalidomide, bortezomib, and dexamethasone (RVD) plus autologous stem-cell transplantation was superior to RVD alone with respect to progression-free survival. However, overall survival did not differ significantly.

This finding should not be surprising. In the Total Therapy 2 trial, progression-free survival was longer among patients who received thalidomide plus high-dose melphalan–based chemotherapy than among those who received high-dose melphalan–based chemotherapy alone, whereas overall survival curves overlapped at a median follow-up of 42 months.[2] At 72 months, overall survival was superior, but only among

patients with an abnormal karyotype.[3] Similarly, in the IFM 1994 trial,[4] there was no difference in overall survival at 44 months (the median duration of follow-up in the IFM 2009 Study) between patients who underwent single transplantation and those who underwent double transplantation, but the difference was significant at 75 months.

It would be interesting to know whether a difference in overall survival becomes apparent with a longer follow-up (≥7 years), either among all patients or among certain subgroups. Moreover, if the first relapse already occurred at a median of 3 years, it is difficult to see how a substantial proportion of patients receiving RVD will ever reach 10 years or more of overall survival, which should be the goal of intensive chemotherapy with curative potential.[5]

Yogesh S. Jethava, M.B., B.S.

University of Iowa Hospitals and Clinics
Iowa City, IA

Bart Barlogie, M.D.

Mount Sinai School of Medicine
New York, NY

Guido J. Tricot, M.D., Ph.D.

University of Iowa Hospitals and Clinics
Iowa City, IA
guido-tricot@uiowa.edu

No potential conflict of interest relevant to this letter was reported.

1. Attal M, Lauwers-Cances V, Hulin C, et al. Lenalidomide, bortezomib, and dexamethasone with transplantation for myeloma. N Engl J Med 2017;376:1311-20.
2. Barlogie B, Tricot G, Anaissie E, et al. Thalidomide and hematopoietic-cell transplantation for multiple myeloma. N Engl J Med 2006;354:1021-30.
3. Barlogie B, Pineda-Roman M, van Rhee F, et al. Thalidomide arm of Total Therapy 2 improves complete remission duration and survival in myeloma patients with metaphase cytogenetic abnormalities. Blood 2008;112:3115-21.
4. Attal M, Harousseau J-L, Facon T, et al. Single versus double autologous stem-cell transplantation for multiple myeloma. N Engl J Med 2003;349:2495-502.
5. Barlogie B, Mitchell B, van Rhee F, Epstein J, Morgan GJ, Crowley J. Curing myeloma at last: defining criteria and providing the evidence. Blood 2014;124:3043-51.

DOI: 10.1056/NEJMc1705671

TO THE EDITOR: Attal and coworkers address the role of early transplantation in an era of RVD therapy. Clearly, early transplantation did not result in a survival benefit. With the availability of new and potent proteasome inhibitors, including carfilzomib, many practitioners might shy away from early transplantation because of the results of this trial.

Attal and colleagues stress the importance of minimal residual disease status, since survival was longer among patients in whom minimal residual disease was not detected than among those in whom it was detected. The investigators used seven-color flow cytometry to test for minimal residual disease. Can they provide some information about the availability and standardization of this method worldwide?

Also, the therapeutic pathway is guided more by a patient's cytogenetic profile than by minimal residual disease status. Myeloma with a t(4;14) translocation is now considered to be an intermediate-risk disease.[1] Attal and colleagues include this subgroup of patients among those with a high risk. However, they did not mention patients with a t(14;20) translocation. It might be worthwhile to further evaluate whether early transplantation is associated with increased survival among patients with high-risk cytogenetic characteristics — namely, 17p deletion, t(14;16), and t(14;20).

Dipesh Uprety, M.D.

Gundersen Health System
La Crosse, WI
upretydipesh@gmail.com

No potential conflict of interest relevant to this letter was reported.

1. Rajkumar SV. Multiple myeloma: 2012 update on diagnosis, risk-stratification, and management. Am J Hematol 2012;87:78-88.

DOI: 10.1056/NEJMc1705671

TO THE EDITOR: Attal and colleagues report the results of a trial incorporating stem-cell transplantation into initial therapy for multiple myeloma. They state: ". . . we observed longer overall survival among patients in whom minimal residual disease was not detected than among those in whom it was detected. . . . These findings confirm that the absence of minimal residual disease is an important treatment target in myeloma."

More than 30 years ago, Anderson et al. pointed out the error of analyzing clinical trials by comparing the survival among patients who have a response to treatment with that among those who do not have a response.[1] Anderson et

al. emphasized that patients who have a good response to therapy may simply be patients who are in an otherwise favorable subgroup. They concluded that the fact that patients who have a response live longer than those who do not "is sometimes interpreted to mean that a more aggressive treatment regimen (which produces a higher response rate) will result in longer survival. Again, this may be true but can best be demonstrated by a controlled clinical trial." In the trial reported by Attal and colleagues, the more aggressive treatment (RVD plus transplantation), which was associated with a higher response rate than RVD alone, did not increase overall survival.

David Baer, M.D.

Kaiser Permanente
Oakland, CA
david.baer@kp.org

No potential conflict of interest relevant to this letter was reported.

1. Anderson JR, Cain KC, Gelber RD. Analysis of survival by tumor response. J Clin Oncol 1983;1:710-9.

DOI: 10.1056/NEJMc1705671

THE AUTHORS REPLY: We agree with Jethava et al. regarding the usefulness of data on long-term follow-up with respect to overall survival. The results of our trial will be combined with those of the ongoing, randomized DETERMINATION study (CTN 1304; ClinicalTrials.gov number, NCT01208662) in the United States, which is being run in parallel with our trial in the United States. The DETERMINATION study has enrolled more than 700 patients and is identical to our trial except for the duration of lenalidomide maintenance therapy, which continues until disease progression, the development of adverse events, or both. The combined data set should provide important information regarding overall survival, not least because of the sample size of at least 1420 patients. However, our overall survival data are considered to be mature, and the lack of a survival benefit associated with early transplantation suggests that salvage therapy for the patients assigned to the delayed transplantation group is a critical equalizer.

We also agree with the comments of Uprety regarding the use of next-generation and potent new therapies, which may further affect successful strategies to induce remission as well as salvage therapies. Monoclonal antibodies, which have shown striking activity, hold great promise.[1] The use of minimal residual disease status to guide therapy is exciting. Although seven-color flow cytometry was used in this trial, next-generation sequencing may provide increased sensitivity and specificity. A variety of commercial tools are becoming available, but we think that minimal residual disease testing should be primarily used as a research tool for now.

Uprety further comments that it will be important to evaluate a survival benefit associated with early transplantation in patients with high-risk cytogenetic characteristics. This benefit was addressed in Figure 2 of our article. A progression-free survival benefit was seen, but no difference in overall survival was apparent.

Finally, we agree with Baer that it is intuitive that overall survival is longer among patients in whom minimal residual disease is not detected, regardless of the treatment group. Patients with a good response constitute a biologically favorable subgroup. Longer follow-up and analysis in the IFM 2009 Study and the DETERMINATION study are under way to shed further light on this question and on which subgroups might benefit most from either approach (RVD plus transplantation or RVD alone). We agree that aggressive treatment with a high response rate in our trial did not increase overall survival. However, longer follow-up and larger numbers of patients may generate important information. Baer comments that more aggressive treatment may have an adverse effect; we agree that acute as well as long-term toxic effects can affect overall survival, and subgroups of patients may benefit from less intensive therapy. In aggregate, data from our trial as well as others suggest that combination therapy along with transplantation could inform a tailored approach and further improve patient outcomes.[2]

Michel Attal, M.D.
Institut Universitaire du Cancer de Toulouse–Oncopole
Toulouse, France
attal.michel@iuct-oncopole.fr

Paul G. Richardson, M.D.
Dana–Farber Cancer Institute
Boston, MA

Philippe Moreau, M.D.
Centre Hospitalier Universitaire de Nantes–Hôtel Dieu
Nantes, France

Since publication of their article, the authors report no further potential conflict of interest.

1. Laubach JP, Tai YT, Richardson PG, Anderson KC. Daratumumab granted breakthrough drug status. Expert Opin Investig Drugs 2014;23:445-52.
2. Richardson PG, Laubach JP, Munshi NC, Anderson KC. Early or delayed transplantation for multiple myeloma in the era of novel therapy: does one size fit all? In: Hematology 2014. Washington, DC: American Society of Hematology, 2014:255-61.

DOI: 10.1056/NEJMc1705671

Body-Weight Fluctuations and Outcomes in Coronary Disease

TO THE EDITOR: Bangalore and colleagues (April 6 issue)[1] suggest that body-weight fluctuation is associated with both higher mortality and a higher rate of cardiovascular events among patients with coronary artery disease. As the authors state, already published studies are not conclusive about whether this weight variability can be treated as a risk factor, at least in the general population.[2,3]

However, we believe that the results of the present study must be viewed with some skepticism. Because a higher body-mass index (BMI) is a well-established risk factor for death from all causes,[4] we think that the amount of time that each participant had a heavier weight during follow-up is crucial. The patients who gained weight and subsequently lost it spent a specific amount of time having a heavier weight, increasing their risk of death, and should be analyzed independently from those who had a weight loss (which may decrease risk) followed by a weight gain. The definition of the direction of body-weight fluctuation would be useful not only for analytic reasons but also for further understanding of the underlying mechanism of this potential association with cardiovascular risk and the risk of death.

Constantinos Mihas, M.D., Ph.D.
Maria Kantzanou, M.D., Ph.D.

National and Kapodistrian University of Athens
Athens, Greece
gas521@yahoo.co.uk

No potential conflict of interest relevant to this letter was reported.

1. Bangalore S, Fayyad R, Laskey R, DeMicco DA, Messerli FH, Waters DD. Body-weight fluctuations and outcomes in coronary disease. N Engl J Med 2017;376:1332-40.
2. Dyer AR, Stamler J, Greenland P. Associations of weight change and weight variability with cardiovascular and all-cause mortality in the Chicago Western Electric Company Study. Am J Epidemiol 2000;152:324-33.
3. Lissner L, Odell PM, D'Agostino RB, et al. Variability of body weight and health outcomes in the Framingham population. N Engl J Med 1991;324:1839-44.
4. Berrington de Gonzalez A, Hartge P, Cerhan JR, et al. Body-mass index and mortality among 1.46 million white adults. N Engl J Med 2010;363:2211-9.

DOI: 10.1056/NEJMc1705832

TO THE EDITOR: The study by Bangalore et al. examined the effect of body-weight fluctuation on outcomes in patients with coronary heart disease. We ask that the following considerations be addressed.

First, there were significant differences in several characteristics (e.g., age, sex, current smoker, hypertension, diabetes, known cerebrovascular disease, previous percutaneous coronary intervention, and known chronic heart failure) between the patients with low body-weight variability and those with high body-weight variability (Table 1 in the article). These characteristics have major effects on the primary and secondary outcomes in this study, so subgroup analyses must be considered.

Second, in our clinical work, we found a trend that patients with obvious weight loss in a short time had worse outcomes. In the study by Bangalore et al., one of the components of the primary outcome was death from coronary heart disease, but no information about rapid body-weight fluctuation in those patients before their deaths was described. We suppose that further research regarding this issue would be needed.

Lingjie Xu, M.D.
Dongze Li, M.B., B.S.

West China Hospital
Chengdu, China
gogoxlj@163.com

No potential conflict of interest relevant to this letter was reported.

DOI: 10.1056/NEJMc1705832