Addition of cyclophosphamide on insufficient response to pomalidomide and dexamethasone: results of the phase II PERSPECTIVE Multiple Myeloma trial

Katja C. Weisel1,2, Christof Scheid3, Manola Zago4, Britta Besemer2, Elias K. Mai5, Mathias Haene6, Jan Duerig7, Markus Munder8, Hans-Walter Lindemann9, Anja Seckinger5, Christina Kunz10, Axel Benner10, Dirk Hose5, Anna Jauch11, Hans Salwender12 and Hartmut Goldschmidt5,13

Treatment of multiple myeloma (MM) has continuously improved over the recent years with a number of approved novel agents resulting in prolonged progression-free (PFS) and overall survival (OS)1. However, patients who are refractory to proteasome inhibitors and immunomodulating agents (IMiD®) have a poor prognosis with a median OS of only 15 months1,2. Furthermore, with the emerging use of lenalidomide in first-line treatment, development of novel effective treatment strategies for patients refractory to lenalidomide is of critical importance. Standard treatment of pomalidomide and dexamethasone was introduced in two large phase III trials in patients with relapsed and/or refractory multiple myeloma (RRMM) with a median of 5 prior treatment lines and exposed and/or refractory to both, bortezomib and lenalidomide and refractory the last prior treatment line3,4. In these trials an objective response rate (ORR) of 31% and 35% and a median PFS of 4.0 and 4.2 months was reached. The addition of cyclophosphamide in relapsed and refractory multiple myeloma (RRMM) with a median of 5 prior treatment lines and exposed and/or refractory to both, bortezomib and lenalidomide and refractory the last prior treatment line3,4. In these trials an objective response rate (ORR) of 31% and 35% and a median PFS of 4.0 and 4.2 months was reached. The addition of cyclophosphamide to immunomodulating agents demonstrated to improve efficacy regarding ORR and PFS5,6. Furthermore, there are clear indications that addition of cyclophosphamide may overcome IMiD® resistance2. Here, we report on the single-arm, phase II, multicenter, investigator-initiated German-speaking Myeloma Multicenter Group (GMMG) PERSPECTIVE trial (Eudra-CT No. 2013-003678-29) investigating the efficacy of adding cyclophosphamide to pomalidomide and dexamethasone in the case of suboptimal response after three cycles or primary progression during the first three cycles.

Sixty patients with relapsed and/or refractory MM after at least two prior treatment lines including bortezomib and lenalidomide and not anymore responding to the last prior treatment were included into the trial and received pomalidomide 4 mg day 1–21 of a 28-day cycle and dexamethasone 40 mg (20 mg in patients >75 years of age) on day 1, 8, 15, and 22. The criteria for addition of cyclophosphamide in the protocol were as follows: cyclophosphamide has to be added in all patients with documented disease progression (PD) during the first three cycles (documentation of one PD event was sufficient) or in patients not achieving at least partial remission (PR) after three treatment cycles. Cyclophosphamide was given in a dose of 500 mg/m² intravenously days 1 and 15 for a maximum of 12 cycles. Pomalidomide and dexamethasone were given until disease progression or unacceptable toxicity. Adverse events (AEs) were recorded and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. Response was assessed according to the IMWG criteria8. Primary endpoint was to determine the ORR. Survival time (OS, PFS, second PFS (defined at PFS from start cyclophosphamide)) and time to next treatment (TTNT) distributions were estimated by the method of Kaplan and Meier9. Primary efficacy analysis was performed after a median follow-up time of 20.1 months;
secondary objectives were analyzed after a median follow-up of 32.8 months. The intention to treat (ITT) population consisted of 59 patients. Median age was 67 years (47–81 years), median number of prior lines was 3. In total, 43.6% of analyzed patients had cytogenetic high-risk disease (del17p13, t(4;14) or >3 copies of 1q21).

ORR (≥PR) in the ITT population was 39%, which did not differ significantly from a rate of 30%, which was considered insufficient. The lower bound of the one-sided 95% confidence was 29.2%. Of the overall treated population, 14 (23.7%) patients showed a PR, 7 (11.9%) patients a very good partial remission (VGPR), and 2 (3.4%) patients a complete remission (CR). The clinical benefit rate (≥minimal remission (MR)) was 66.1% with 16 patients (27.1%) achieving a MR. In two patients, an early death occurred in or after the first cycle, both were documented as PD (Table 1).

Of 59 patients evaluable during cycle 1–3 at least for one response, 50 were assigned for the addition of cyclophosphamide according to protocol. In total, 36 (61.0%) patients actually received cyclophosphamide. Excluding the two early deaths, n = 24 patients showed PD during the first three cycles of which 16 patients received cyclophosphamide and n = 24 patients showed SD or MR of which 20 patients received cyclophosphamide. The main reason not to start cyclophosphamide was investigator’s decision in both groups (n = 6 and n = 3, respectively). This was mainly due to rapid progression together with severe deterioration of the patient, in some patients addition was missed. At start of cyclophosphamide, 16 patients (44.4%) showed PD, 15 patients (41.7%) SD, and 5 patients (13.9%) MR. After addition of cyclophosphamide, 13 patients (36.1%) achieved ≥PR (8 PR, 3 VGPR, and 2 CR). Ten patients (27.8%) showed MR. Of the 16 patients starting cyclophosphamide at primary progression under pomalidomide and dexamethasone, all patients achieved at least SD (5 MR, 3 PR, and 1 VGPR). Of 20 patients with SD or MR after 3 cycles, 9/20 (45.0%) responded with 5 patients achieving a PR, 2 VGPR, and 2 CR. Only patients under the triplet combination achieved a CR.

For those patients (n = 13) receiving pomalidomide + dexamethasone without addition of cyclophosphamide, response was documented as follows: 5 PR, 4 VGPR, and 4 MR. Median PFS of the ITT population was 6.4 months, median TTNT 11.0 months, median OS 18.3 months (Fig. 1a–c). Median second PFS from start cyclophosphamide was 4.8 months. Main toxicity was hematologic with neutropenia ≥grade 3 in 66.6%, leukopenia ≥grade 3 in 40.0%, anemia ≥grade 3 in 26.7%, and thrombocytopenia ≥grade 3 in 25.0%. The most commonly reported ≥grade 3 nonhematologic AE was pneumonia in 16.7%.

In the phase II PERSPECTIVE trial we demonstrated that addition of cyclophosphamide in patients not

| Table 1 International Myeloma Working Group (IMWG) best response (ITT population) |
|---------------------------------|---------------------------------|
| Response                        | Objective response ≥PR, n (%) |
| Overall                         | 23 (39.0%)                     |
| Best response under POM + CY + DEX according to response at start CY |
| Minimal response at start CY (n = 5) | 4 (60.0%)                     |
| Stable disease                  | 3 (60.0%)                      |
| Progressive disease             | 2 (60.0%)                      |
| Best response under POM + CY + DEX (n = 36) |
| Minimal response at start CY (n = 15) | 4 (26.7%)                     |
| Stable disease                  | 3 (18.8%)                      |
| Progressive disease             | 3 (18.8%)                      |
| Objective response ≥PR, n (%)   | 13 (36.1%)                     |
| Partial response, n (%)         | 8 (22.2%)                      |
| Very good partial response, n (%)| 2 (5.6%)                       |
| Complete response, n (%)        | 2 (5.6%)                       |
| Minimal response, n (%)         | 16 (44.4%)                     |
| Stable disease, n (%)           | 12 (33.3%)                     |
| Progressive disease, n (%)      | 4 (11.1%)                      |
| Early death, n (%)              | 2 (5.6%)                       |

PR: partial response; POM: pomalidomide; CY: cyclophosphamide; DEX: dexamethasone; Two patients were not available for response due to early death and counted as non-responder.
achieving a PR after three treatment cycles or with primary progression under pomalidomide and dexamethasone was able to rescue a substantial proportion of patients. A conversion into ≥PR was achieved in 36.1% including deep remissions with 5/36 patients achieving a VGPR or CR. Median PFS is 6.4 months and compares favorably with the median PFS reported with pomalidomide and dexamethasone. Of note, some patients initially not responding to pomalidomide + dexamethasone were able to achieve durable responses on the triplet combination with 17/36 patients staying more than 10 additional cycles and 6/36 patients staying more than 20 additional cycles on pomalidomide. While the effect of cyclophosphamide in our trial is clear in patients who experienced a primary progression under pomalidomide + dexamethasone where we could induce in all patients at least an SD, the effect of the third drug is less clear in those patients with a documented SD or MR during the first three cycles as a late response might have been occurred. Moreau et al. showed in the initial pomalidomide + dexamethasone approval trial MM-003 that 17.4% and 13.6% of patients with SD after two and four cycles, respectively, achieved a response during later cycles. With an improvement in response of 45.0% (9/20) in patients with SD or MR during the first three cycles including CR and VGPR in the here reported trial, our results indicate a potential benefit of adding cyclophosphamide even in case of early suboptimal response. Furthermore, our trial included a high rate of patients with cytogenetic high-risk disease. It was previously shown that the addition of cyclophosphamide to lenalidomide and dexamethasone might overcome lenalidomide resistance. Here, we demonstrate that the addition of cyclophosphamide is able to overcome resistance to a third-generation immunomodulatory agent. Cyclophosphamide exerts various immunomodulating effects. One potentially important mechanism is the suppression of regulatory T cells. The addition of cyclophosphamide to pomalidomide and dexamethasone was shown to be effective in other trials. Baz et al. reported a randomized phase II trial including 70 patients where pomalidomide + dexamethasone was compared to pomalidomide, cyclophosphamide, and dexamethasone showing a significant increase in ORR, median PFS, and median OS. Our trial was hampered by missed addition of cyclophosphamide in 14 assigned patients either due to protocol violation or due to early and aggressive progression with inability to keep the patient in the protocol. Overall, the triplet combination

![Fig. 1](image-url)
was feasible with the expected toxicity of the applied drugs. We saw a potential increase in cytopenias and infections when cyclophosphamide was added to pomalidomide and dexamethasone. Whether the rate of infections was exclusively due to the addition of cyclophosphamide or due to the fact that the inferior, not rapidly responding population was exposed with the triplet regimen and so was kept potentially longer under treatment, cannot be fully differentiated.

Overall, Pomalidomide-based treatment gains in importance due to the emerging use of lenalidomide in frontline treatment. In the current ESMO recommendations, primary extension of pomalidomide and dexamethasone to a triplet is recommended; however, in most countries outside US there is no approved triplet regimen. The triple combination of pomalidomide, cyclophosphamide, and dexamethasone is a cost effective and easy to administer combination treatment for patients with RMM. In light of the high tolerability and the here observed data in context with the published data and recommendations, we would propose to consider the primary use of the triplet combination rather than to use pomalidomide + dexamethasone alone.

Acknowledgements
This study was supported by research funding from Celgene Corp. to the University Hospital of Tuebingen. Celgene was not involved in the collection, analysis or interpretation of data, the writing of the manuscript or the decision for publication. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Author details
1Department of Oncology, Hematology and Bone Marrow Transplantation with Section of Pneumology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany. 2Department of Hematology, Oncology, Immunology, Rheumatology and Pulmonology, University Hospital of Tuebingen, Tuebingen, Germany. 3Department of Internal Medicine and Center of Integrated Oncology Cologne Bonn, University of Cologne, Cologne, Germany. 4Center for Clinical Trials, University Hospital of Tuebingen, Tuebingen, Germany. 5Department of Internal Medicine V, University Clinic Heidelberg, Heidelberg, Germany. 6Clinic of Internal Medicine III, Hematology and Oncology, Clinic of Chemnitz, Chemnitz, Germany. 7Department of Hematology, University Hospital Essen, Essen, Germany. 8Department of Hematology, Oncology, and Pneumology, University Medical Center Mainz, Mainz, Germany. 9Clinic for Haematology/Oncology, Catholic Hospital Hagen, Hagen, Germany. 10Division of Biostatistics, German Cancer Research Center (DKFZ) Heidelberg, Heidelberg, Germany. 11Institute of Human Genetics, University of Heidelberg, Heidelberg, Germany. 12Department of Hematology and Oncology, Asklepios Hospital Hamburg Altona, Hamburg, Germany. 13National Center for Tumor Diseases (NCT), University Clinic Heidelberg, Heidelberg, Germany.

Authors' contributions
K.W., M.Z., C.K., A.B., and H.G. designed the research study; K.W., C.S., M.Z., B.B., E.K.M., M.H., J.D., M.M., H.W.L., A.S., D.H., A.J., H.S., and H.G. performed the research; K.W., C.S., C.K., A.B., A.S., D.H., A.J., H.S., and H.G. analyzed the data. K.W. wrote the first version of the manuscript and all authors contributed to writing the paper by providing guidance and comments on its content.

Conflict of interest
K.W. reports research funding from Janssen, Amgen, Sanofi, and Celgene Corporation; honoraria from Amgen, Bristol-Myers Squibb, Celgene Corporation, Janssen, Novartis, Onyx, and Takeda, and advisory board membership for Adaptive Biotech, Amgen, Bristol-Myers Squibb, Celgene Corporation, Janssen, Novartis, Onyx, and Takeda. C.S. reports honoraria from Amgen, Bristol-Myers Squibb, Celgene Corporation, Janssen, Novartis, Sanofi, Takeda, and advisory board membership for Amgen, Bristol-Myers Squibb, Celgene Corporation, Janssen, Novartis, Sanofi, and Takeda. E.K.M. reports personal fees and other from Janssen Cilag, personal fees and other from Celgene, personal fees and other from Takeda, other from Bristol-Myers Squibb, and other from Mundipharma. M.H. reports honoraria from Novartis and Roche. J.D. reports research funding from Lead Discovery Center. M.M. reports personal fees from Celgene, personal fees and other from Janssen, grants and personal fees from Bristol-Myers Squibb, personal fees and other from Takeda, and personal fees and other from Amgen. H.S. reports research funding from Amgen, Novartis, Janssen, Bristol-Myers Squibb, and Celgene Corporation, honoraria from Novartis, Janssen, Bristol-Myers Squibb, Celgene Corporation, and Takeda, and travel support from Amgen, Celgene Corporation, and Janssen. H.G. reports personal fees and other from Amgen, personal fees and other from Bristol-Myers Squibb, personal fees and other from Celgene, personal fees and other from Chugai, personal fees and other from Janssen, personal fees and other from Sanofi, other from Mundipharma, personal fees and other from Takeda, personal fees and other from Novartis, other from Adaptive Biotechnologies, personal fees from Art Tempi, outside the submitted work. The remaining authors declare that they have no conflict of interest.

Publisher's note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Supplementary information
 accompanies this paper at (https://doi.org/10.1038/s41408-019-0206-8).

Received: 23 January 2019 Revised: 18 March 2019 Accepted: 21 March 2019
Published online: 08 April 2019

References
1. Kumar, S. K. et al. Continued improvement in survival in multiple myeloma: changes in early mortality and outcomes in older patients. Leukemia 28, 1122–1128 (2014).
2. Kumar, S. K. et al. Natural history of relapsed myeloma, refractory to immuno-modulatory drugs and proteasome inhibitors: a multicenter IMMIG study. Leukemia 31, 2445–2448 (2017).
3. Miguel, J. S. et al. Pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone alone for patients with relapsed and refractory multiple myeloma (MM-003): a randomised, open-label, phase 3 trial. Lancet Oncol. 14, 1055–1066 (2013).
4. Dimopoulos, M. A. et al. Safety and efficacy of pomalidomide plus low-dose dexamethasone in STRATUS (MM-010): a phase 3b study in refractory multiple myeloma. Blood 128, 497–503 (2016).
5. Reece, D. E. et al. Phase III trial of oral cyclophosphamide, prednisone and lenalidomide for the treatment of patients with relapsed and refractory multiple myeloma. Br. J. Haematol. 168, 46–54 (2015).
6. Schey, S. A. et al. The addition of cyclophosphamide to lenalidomide and dexamethasone in multiply relapsed/refractory myeloma patients: a phase II study. Br. J. Haematol. 150, 326–333 (2010).
7. Nijhof, I. S. et al. Phase I/II study of lenalidomide combined with low-dose cyclophosphamide and prednisone in lenalidomide-refractory multiple myeloma. Blood 128, 2297–2306 (2016).
8. Dure, B. G. et al. International uniform response criteria for multiple myeloma. Leukemia 20, 1467–1473 (2006).
9. Scheppler, M. & Smith, T. L. A note on quantifying follow-up in studies of failure time. Control. Clin. Trials 17, 343–346 (1996).
10. Walter, S. et al. Multipeptide immune response to cancer vaccine IMV901 after single-dose cyclophosphamide associates with longer patient survival. Nat. Med. 18, 1254–1261 (2012).
11. Moreau, P. et al. Multiple myeloma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann. Oncol. 28, iv52–iv61 (2017).