Treatment emergent peripheral neuropathy in the CASSIOPEIA trial

Peripheral neuropathy (PNP) is one of the most common adverse events of multiple myeloma (MM) treatment. Thalidomide and bortezomib are particularly prone to induce treatment-emergent peripheral neuropathy (TEPN).[1-4] Both agents are part of standard treatment regimens for newly diagnosed transplant-eligible MM patients. Recently, daratumumab was added to the combination of thalidomide and bortezomib, introducing a quadruplet regimen, which has significantly improved progression-free survival (PFS) in newly diagnosed MM patients, as demonstrated in the CASSIOPEIA trial.[5] Following these positive results, this quadruplet regimen was approved by the European Medicines Agency (EMA) in 2019 for use in newly diagnosed MM. TEPN however remains a concern, and whether daratumumab impacts TEPN, was analysed in this trial.

TEPN varies from mild symptoms to severe disability and is characterized by mainly sensory symptoms, such as paresthesia and neuropathic pain.[6,7] The most frequent used grading system to grade the severity of the TEPN are the common terminology criteria for adverse events (CTCAE) criteria, as used in the CASSIOPEIA trial. TEPN has a significant impact on quality of life (QoL) from grade 2 and higher, defined as "limiting instrumental activities of daily living (IADL)". Until now, the incidence of TEPN in quadruplet regimens has not been extensively analyzed. This is the first analysis which focuses on the cumulative incidence of TEPN, the impact on PFS, effect of dose adjustments and potential risk factors for TEPN in a daratumumab-based regimen.

The phase 3 CASSIOPEIA trial investigated the efficacy of adding daratumumab to bortezomib, thalidomide and dexamethasone (VTD). The trial design can be found in the *Online Supplementary Figure S1*. We analyzed PNP grade 2 to 4, scored according to CTCAE version 4. PNP that occurred after the start of induction therapy is defined as therapy-emergent neuropathy. Patients with PNP grade ≥2 at baseline were excluded from the trial. PNP was defined as peripheral sensory neuropathy and peripheral motor neuropathy and was graded and reported by investigators. The TEPN assessment was performed from start of induction until end of maintenance. The complete clinical trial report of part 1 of the study was published in 2019.[5] The cumulative incidence of PNP ≥ grade 2 was calculated. Associations of possible risk factors with the cumulative incidence of PNP were evaluated using the method of Fine and Gray, using univariate as well as multivariate

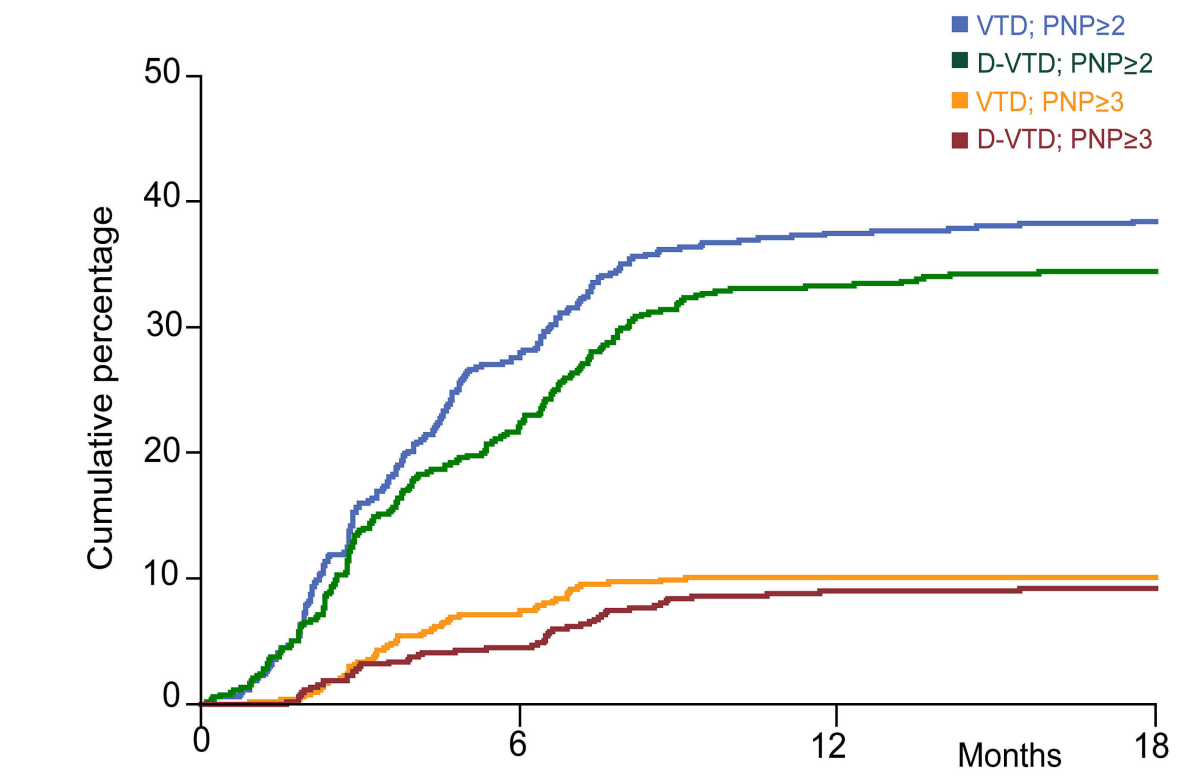

Figure 1. Cumulative incidence of treatment-emergent peripheral neuropathy grade ≥ 2 and grade ≥3 in the CASSIOPEIA trial per arm. PNP: peripheral neuropathy; VTD: bortezomib, thalidomide and dexamethasone; D-VTD: VTD plus daratumumab.

analyses. In order to evaluate the impact of PNP on subsequent PFS, two analyses were performed. First, a univariate Cox regression was performed with development of PNP ≥ grade 2 as a time-dependent covariate. This analysis included all patients and takes into account that some patients never developed PNP ≥ grade 2, and other patients at some time point developed PNP ≥ grade 2, which could imply an increased risk to progression or death (i.e., the events for PFS) from that moment on. The hazard ratio (HR) and 95% confidence interval (CI) were calculated. Second, a landmark analysis was performed in which PFS was calculated from start of consolidation, comparing patients with or without PNP ≥ grade 2 during induction treatment. While HR and 95% CI were determined again, PFS for both groups could now also be illustrated by Kaplan-Meier survival curves. In addition, the impact of dose modification of bortezomib and thalidomide on PFS from start consolidation was evaluated in patients who developed PNP ≥ grade 2 until consolidation treatment. PFS was calculated up to 3 years after randomization. A flowdiagram of patients included in the analysis is provided in the *Online Supplementary Figure S2*. A two-sided *P*-value lower than 0.05 was considered to be statistically significant.

Overall, 1,085 newly diagnosed MM patients were randomized in the CASSIOPEIA study, of which 1,074 initiated treatment in the dara-VTD arm (n=536) or VTD arm (n=538). Baseline characteristics in the two arms were similar and have been reported before.[5] At baseline 20 patients (2%) had a medical history of PNP grade 1 (D-VTD n=15; VTD n=5). During the trial, 394 patients (37%) developed grade 2-4 PNP: maximum grade 2 occurred in 289 (27%) patients, maximum grade ≥3 occurred in 105 (10%) patients. In the VTD arm 38% developed grade ≥2 PNP *versus* 35% in the dara-VTD arm. The cumulative incidence of grade ≥2 PNP was similar between both arms at 6 months 28% and 22% in the VTD and D-VTD arm respectively, grade≥3 PNP at 6 months was 7% and 4% (Figure 1).

We observed that among predefined risk factors patients with a higher body mass index (BMI) had a greater risk for the development of PNP grade ≥2. Per BMI group this risk increased: in the multivariate analysis, subdistribution HR (sHR)=1.39 (95% CI: 1.09-1.77, *P*=0.008) for BMI 25-30, sHR=1.57 (95% CI: 1.12-2.20, *P*=0.008) and sHR=2.07 (95% CI: 1.30-3.30, *P*=0.002) for BMI>35, compared to the group BMI<25 (Table 1). Another risk factor associated with a higher cumulative incidence was PNP grade 1 at baseline (sHR=2.64, 95% CI: 1.39-4.99, *P*=0.003) and an older age (sHR=1.02, 95% CI: 1.00-1.03, *P*=0.04). Multivariate analysis also indicated that the cumulative incidence of PNP grade ≥2 was significantly lower in the dara-VTD arm (33% at 12 months) when compared to the VTD arm (37%) (sHR=0.77, 95% CI: 0.63-0.95, *P*=0.01).

A significant difference in the incidence of PNP grade ≥2 between the France and the Netherlands was also observed (33% *vs*. 49%) (sHR=1.73, 95% CI: 1.30-2.30, *P*<0.001). A biological explanation for this difference has not been found.

In order to evaluate the impact of PNP during induction on subsequent PFS, two analyses were performed. First, the development of grade ≥2 PNP during any time point

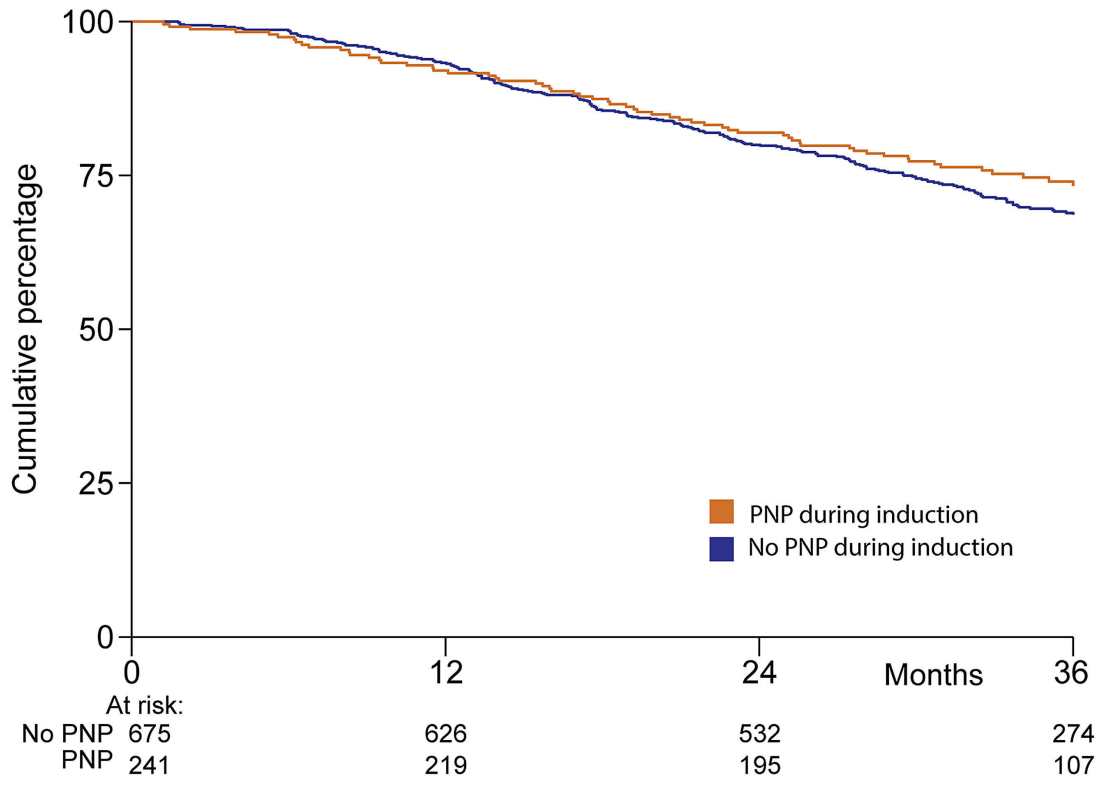

Figure 2. Kaplan-Meier curves of progression-free survival from start consolidation. Progression-free survival of patients who had experienced treatment-emergent peripheral neuropathy during induction *vs*. patients who did not experience treatment emergent peripheral neuropathy (Yes *vs*. No).

Table 1. Risk factors for treatment-emergent peripheral neuropathy grade 2-4 by uni- and multivariate analysis.

		Univariate analysis		Multivariate analysis	
	Cumulative incidence* (%)	**Risk of PNP grade 2-4 sHR (95% CI)**	***P*-value**	**Risk of PNP grade 2-4 sHR (95% CI)**	***P*-value**
Sex					
M	37				
F	33	0.89 (0.73-1.09)	0.27	0.90 (0.72-1.13)	0.37
Age group				Not included	
< 50	30				
≥ 50-65	36	1.26 (0.95-1.68)	0.11		
Age	n.a.	1.02 (1.00-1.04)	**0.01**	1.02 (1.00-1.03)	**0.04**
Arm					
No Dara	37				
Dara	33	0.86 (0.71-1.05)	0.13	0.77 (0.63-0.95)	**0.01**
Cytogenetics					
Std risk	36				
High risk	34	0.96 (0.72-1.27)	0.76	1.07 (0.79-1.44)	0.67
ISS-stage					
I	40				
II	33	0.76 (0.61-0.93)	**0.01**	0.83 (0.64-1.06)	0.14
III	30	0.69 (0.51-0.94)	**0.02**	0.78 (0.54-1.13)	0.19
Country					
France	33				
Netherlands	49	1.67 (1.28-2.17)	**<0.001**	1.73 (1.30-2.30)	**<0.001**
Belgium	38	1.19 (0.83-1.71)	0.34	1.23 (0.86-1.78)	0.26
Creat Clearance					
< 60	26				
60 – 90	36	1.48 (0.93-2.36)	0.10	1.29 (0.78-2.12)	0.32
> 90	36	1.48 (0.94-2.33)	0.09	1.10 (0.66-1.85)	0.70
DM					
No	35				
Yes	44	1.37 (0.98-1.93)	0.067	1.23 (0.88-1.73)	0.23
BMI					
< 25	29				
25-30	40	1.47 (1.18-1.83)	**0.001**	1.39 (1.09-1.77)	**0.008**
30-35	41	1.60 (1.18-2.17)	**0.002**	1.57 (1.12-2.20)	**0.008**
>35	48	2.04 (1.31-3.17)	**0.002**	2.07 (1.30-3.30)	**0.002**
ECOG PS					
0	38				
1	34	0.87 (0.71-1.07)	0.19	0.90 (0.73-1.12)	0.34
2	28	0.73 (0.50-1.06)	0.10	0.76 (0.51-1.12)	0.17
PNP gr I at baseline					
No	35				
Yes	75	3.08 (1.83-5.21)	**<0.001**	2.64 (1.39-4.99)	**0.003**
Liver function					
Normal	35				
Impaired	37	1.04 (0.75-1.44)	0.83	1.16 (0.83-1.63)	0.38
Disease type					
IgG	36				
IgA	34	0.95 (0.72-1.26)	0.71	0.96 (0.71-1.29)	0.79
Urine only	36	0.97 (0.71-1.31)	0.83	0.97 (0.63-1.48)	0.87
FLC	35	0.99 (0.68-1.43)	0.96	0.90 (0.57-1.43)	0.66
Other	31	0.91 (0.51-1.63)	0.75	0.86 (0.48-1.57)	0.63
Baseline M-prot	n.a.	0.97 (0.93-1.01)	0.12	0.99 (0.92-1.07)	0.80
Baseline % PC	n.a.	1.00 (0.99-1.00)	0.18	1.00 (0.99-1.00)	0.16

*Cumulative incidence at 1 year. ISS: International Staging System; DM: diabetes mellitus; BMI: body mass index; ECOG PS: Eastern Cooperative Oncology Group Performance Status; PNP: peripheral neuropathy; FLC: free light chain; Std: standard; DARA: daratumumab; prot: protein; gr: grade; Ig: immunoglobulin; CI: confidence interval; sHR: subdistribution hazard ratio; PC: Plasma cells, DM: is already described in the legend, n.a.: not applicable.

of the trial was included as a time-dependent covariate in a univariate Cox regression analysis (HR=0.83, 95% CI: 0.67-1.04, *P*=0.10). Second, a landmark analysis showed that PFS from start consolidation was similar, 80% *versus* 82% at 2 years (HR=0.86, 95% CI: 0.661.13, *P*=0.27) for patients developing grade ≥2 PNP during induction therapy *versus* patients who did not develop grade ≥2 PNP (Figure 2). Dose reduction and/or discontinuation of bortezomib or thalidomide due to PNP grade ≥2 did not impact PFS in comparison to patients who did not experience PNP. PFS at 2 years from start consolidation in patients who received dose modification of bortezomib and/or thalidomide was 83% *versus* 78% in patients receiving the full dosage of both (HR=1.05, 95% CI: 0.62-1.78, *P*=0.87) (*Online Supplementary Figure S3A*). There was also no significant difference in patients receiving either a reduced-dosage thalidomide or bortezomib in response to PNP grade ≥2 versus patients receiving the full dosage (*Online Supplementary Figures 3B* and *C*).

With the introduction of quadruplet regimens the impact of these regimens on QoL remains important. One of the most debilitating adverse events is peripheral neuropathy. Dara-VTD will be used widely in many countries and in this sub-analysis of the CASSIOPEIA trial we present a detailed analysis of TEPN in the two regimens used in this trial. We observed a clinically relevant cumulative incidence of 37% grade ≥2 PNP. We report an incidence of TEPN which is similar to other trials with subcutaneous bortezomib-based regimens.[8-11] When comparing triplet regimens, a high incidence of TEPN is reported in VRD and VTD treatment, whereas VCD regimens seem associated with lower incidence of TEPN.[10] Studies including daratumumab in one of the two arms reported a PNP grade ≥3 incidence which was slightly lower in the daratumumab arm[8,9] consistent with the data we present here. This suggests a possible beneficial effect of daratumumab on TEPN. However, an explanation for a possible beneficial mechanism has to our knowledge not been described. With other large phase III trials analyzing the possible beneficial effect of quadruplet therapy still ongoing, such as the Perseus (VRD *vs*. Dara-VRD) and Iskia (KRD *vs*. Isatuximab-KRD), data on the incidence of TEPN will need to be closely monitored.

The concern remains that modification of the treatment doses lead to a worse treatment response and reduced PFS.[12,13] Here, PFS at 2 years was similar in patients who did or did not receive dose modification of bortezomib and/or thalidomide. Previous studies confirm these findings, reporting no difference in PFS, response rates and OS between the patients with or without PNP.[13,14] Although PFS is not influenced by TEPN, it is known to impact other features: such as, QoL, inclusion in subsequent clinical trials - often excluding patients with a PNP grade 2 or higher - and the use of subsequent drugs. Unfortunately due to the retrospective nature of this analysis we could not generate data on these issues. This study and a recently published prespecified secondary analysis on QoL in the CASSIOPEIA trial[15] are of great importance. The incidence of TEPN in patients receiving myeloma treatment with bortezomib and thalidomide remains clinically significant. In addition, identifying the patients at risk is essential. Risk factors for the development of grade ≥2 PNP included PNP at baseline, older age and BMI >25. As Dara-VTD has been approved by EMA, this regimen will soon become the standard treatment in newly diagnosed myeloma patients in many European countries. These results highlight the need for increased awareness of TEPN.

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Contributions

AC, PM, BvdH, JJ, PvD, TC, PS and AB developed the study concept; AC, BvdH, JL, and AB set up the study methology; AC, BvdH and JL carried out the investigation; AC, BvdH and JL performed the formal analysis; PM, MvD, RW and SG provided resources; KSJ, OF, MD, AK, OL, NvdD, SZ and AB collected data; AC, BvdH and JL were in charge of data curation; AC and BvdH visualized the project; AC and AB wrote the original draft. All authors contributed to writing, reviewing and editing of the manuscript. PS acquired funding; TC, AB and PS supervised the project; AB was in charge of project administration.

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Data-sharing statment

The data sharing policy of Janssen Pharmaceutical Companies of Johnson & Johnson is available online. Requests for access to the study data can be submitted through the Yale Open Data Access Project site. For the Janssen data sharing policy see https://www.janssen. com/clinical-trials/transparency For the Yale Open Data Access Project site see http://yoda.yale.edu.

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