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Daratumumab (multiple myeloma) –

Addendum to Commission A21-101[1]

Addendum

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Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Im Mediapark 8
50670 Köln
Germany

Phone: +49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

IQWiG employees involved in the addendum

- Katrin Nink
- Lisa Junge
- Jona Lilienthal
- Sabine Ostlender

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Abbreviation	Meaning
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer – Quality of Life Questionnaire – Core 30
EORTC QLQ-MY20	European Organisation for Research and Treatment of Cancer – Quality of Life Questionnaire – Multiple Myeloma 20
EQ-5D	European Quality of Life 5 Dimensions
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
RCT	randomized controlled trial
VAS	visual analogue scale

1 Background

On 21 December 2021, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A21-101 (Daratumumab – benefit assessment according to §35a Social Code Book V) [1].

For assessing the benefit of daratumumab in adult patients with multiple myeloma who have received ≥ 2 prior lines of therapy containing lenalidomide and a proteasome inhibitor and demonstrated disease progression on or after the most recent line of therapy (research question 2 of the dossier assessment), the randomized controlled trial (RCT) APOLLO was included. This study compared daratumumab in combination with pomalidomide + dexamethasone versus pomalidomide + dexamethasone. The assessment was based on a study subpopulation which comprises patients with disease progression either on or after the most recent line of therapy and therefore also contains patients who are not therapeutically indicated for pomalidomide + dexamethasone (i.e. patients who demonstrated disease progression after the most recent line of therapy). Since the percentage of patients with disease progression on the most recent line of therapy was sufficiently large, this subpopulation was used to derive added benefit. With its comments [2], the pharmaceutical company (hereinafter "company") has submitted data on the subpopulation of patients with disease progression on the most recent line of therapy, including analyses based on new operationalizations of patient-reported outcomes.

The G-BA commissioned IQWiG with the below assessment of the analyses submitted by the company in the commenting procedure, taking into account the information provided in the dossier:

- Analysis of time to (confirmed) definitive deterioration of patient-reported outcomes.
- Where necessary, analysis of the assessment-relevant subpopulation of patients with disease progression on the most recent line of therapy. Where possible, a summary consideration of the extent to which the results presented in the written commenting procedure led to changes in the conclusion on added benefit is deemed sufficient.

The responsibility for the present assessment and the assessment result lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

2 Assessment

2.1 Patient-reported outcomes

In its dossier, the company presented responder analyses with the operationalization of time to first deterioration or improvement by a relevant response threshold [3]. The following analyses of time to deterioration were used in the benefit assessment:

- Morbidity
  - Symptoms surveyed using the European Organisation for Research and Treatment of Cancer – Quality of Life Questionnaire – Core 30 (EORTC QLQ-C30) and the EORTC QLQ Multiple Myeloma 20 (EORTC QLQ-MY20): time to deterioration by ≥ 10 points
  - Health status, surveyed using the European Quality of Life 5 Dimensions (EQ-5D) visual analogue scale (VAS): time to deterioration by ≥ 15 points
- Health-related quality of life
  - Surveyed with the EORTC QLQ-C30 and EORTC QLQ-MY20: time to deterioration by ≥ 10 points

With its comments, the company presented analyses using new operationalizations of time to deterioration/improvement by various response thresholds of the above survey instruments. The company refers to these operationalizations as time to definitive deterioration/improvement and time to confirmed definitive deterioration/improvement. As in the dossier assessment [1], only deterioration was included in the analysis. This is in line with the G-BA's commission.

Relevance of the analyses subsequently submitted

The operationalizations of patient-reported outcomes (time to first deterioration) used in the analyses of the company's dossier were already suitable. This analysis method was predefined in the statistical analysis plan. The company justifies its presentation of new analyses in its comments with the additional relevance of time to definitive deterioration in the indication of multiple myeloma, citing the procedure for isatuximab [4,5]. In the latter procedure, definitive deterioration was deemed more relevant. However, in this data situation, analyses on both first and definitive deterioration had already been presented in the dossier, rather than being submitted after the assessment of the data initially submitted in the dossier (dossier assessment).

In the present situation, it is therefore impossible to rule out reporting bias. While the subsequently submitted analyses on definitive deterioration are generally suitable analyses, the argument of potential reporting bias carries greater weight in this case. The subsequently submitted analyses on definitive deterioration were therefore excluded from the derivation of added benefit. The results are presented, as contractually agreed upon, as additional information in Appendix A.

Operationalization of definitive deterioration in the subsequently submitted analyses

Both operationalizations submitted with the company's comments, definitive and confirmed definitive deterioration, are defined as a deterioration by the respective response criterion compared to baseline, with the response criterion deemed met in all subsequent follow-up visits until the end of follow-up. Like in the dossier, death due to progression was not defined as deterioration. The two operationalizations differ, however, in the handling of patients who reported a single deterioration at the last survey time point:

- Time to definitive deterioration: patients who reported a single deterioration at the last survey time point are classified as responders.
- Time to confirmed definitive deterioration: patients who reported a single deterioration at the last survey time point are classified as non-responders.

In principle, a single deterioration at the last survey time point does not represent definitive deterioration. All things considered, only the operationalization designated by the company as confirmed definitive deterioration therefore comprises patients who deteriorated definitively, that is, in at least 2 consecutive surveys. Below, the term "definitive deterioration" is used only for this operationalization, and this operationalization is presented as supplementary information in Appendix A.

Supplementary presentation of the results of patients with disease progression on the most recent line of therapy

The company presented the analyses of definitive deterioration in patient-reported outcomes only for the subpopulation of patients with ≥ 2 prior lines of therapy and disease progression on the most recent line of therapy. To provide context for these new analyses, Appendix A additionally presents, as supplementary information, patient characteristics as well as results for the remaining outcomes, specific AEs, and subgroup analyses for this subpopulation.

2.2 Summary

The data subsequently submitted by the company in the commenting procedure do not change the conclusion on the added benefit of daratumumab drawn in dossier assessment A21-101.

The following Table 1 shows the results of the benefit assessment of daratumumab in consideration of dossier assessment A21-101 and the present addendum.

Table 1: Daratumumab in combination with pomalidomide and dexamethasone – probability and extent of added benefit

Research question	**Therapeutic indication**	**ACT[a]**	**Probability and extent of added benefit**
1	Adult patients with multiple myeloma who have received 1 prior line of therapy with a proteasome inhibitor and lenalidomide and were refractory to lenalidomide[b]	▪ Bortezomib in combination with pegylated liposomal doxorubicin or ▪ Bortezomib in combination with dexamethasone, or ▪ Carfilzomib in combination with dexamethasone, or ▪ Daratumumab in combination with bortezomib and dexamethasone	Added benefit not proven
2	Adult patients with multiple myeloma who have received ≥ 2 prior lines of therapy containing lenalidomide and a proteasome inhibitor and demonstrated disease progression on or after the most recent line of therapy[b]	▪ Bortezomib in combination with dexamethasone, or ▪ Lenalidomide in combination with dexamethasone, or ▪ **Pomalidomide in combination with dexamethasone (only for patients with disease progression <u>on</u> the most recent line of therapy)** or ▪ Elotuzumab in combination with lenalidomide and dexamethasone, or ▪ Elotuzumab in combination with pomalidomide and dexamethasone (only for patients with disease progression <u>on</u> the most recent line of therapy) or ▪ Carfilzomib in combination with lenalidomide and dexamethasone, or ▪ Carfilzomib in combination with dexamethasone, or ▪ Daratumumab in combination with lenalidomide and dexamethasone, or ▪ Daratumumab in combination with bortezomib and dexamethasone	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company is printed in bold.
b. It is assumed that high-dose chemotherapy with stem cell transplantation is not an option for the patients at the time point of their current treatment.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

The G-BA decides on the added benefit.

3 References

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5. Gemeinsamer Bundesausschuss. Tragende Gründe zum Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII – Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V Isatuximab (Multiples Myelom, mind. 2 Vortherapien, Kombination mit Pomalidomid und Dexamethason) [online]. 2021 [Accessed: 11.01.2022]. URL: https://www.g-ba.de/downloads/40-268-7999/2021-11-04_AM-RL-XII_Isatuximab_D-675_TrG.pdf.

Appendix A Results of the subpopulation (APOLLO study)

Table 2: Characteristics of the subpopulation[a] – RCT, direct comparison: daratumumab + pomalidomide + dexamethasone vs. pomalidomide + dexamethasone (multipage table)

Study Characteristic Category	Daratumumab + pomalidomide + dexamethasone N[b] = 106	Pomalidomide + dexamethasone N[b] = 105
APOLLO		
Age [years], mean (SD)	65 (10)	67 (9)
Sex [f/m], %	48/52	41/59
Ancestry, n (%)		
White	96 (91)	93 (89)
Black or African American	1 (1)	0 (0)
Asian	1 (1)	1 (1)
Unknown	8 (8)	11 (10)
ECOG-PS at randomization, n (%)		
0	68 (64)	48 (46)
≥ 1	38 (36)	57 (54)
ISS stage at baseline, n (%)		
I	46 (43)	42 (40)
II	33 (31)	39 (37)
III	27 (26)	24 (23)
R-ISS stage, n (%)		
I	17 (16)	15 (14)
II	51 (48)	65 (62)
III	16 (15)	11 (10)
Missing	22 (21)[c]	14 (13)[c]
Cytogenetic risk group, n (%)		
Standard risk	43 (41)	50 (48)
High risk[d]	32 (30)	24 (23)
Missing	31 (29)[c]	31 (30)[c]
Myeloma type based on immunofixation, n (%)		
IgG	60 (57)	60 (57)
IgA	22 (21)	17 (16)
IgM	0 (0)	0 (0)
IgD	1 (1)	2 (2)
Light chain	19 (18)	23 (22)
Kappa	7 (7)	15 (14)
Lambda	12 (11)	8 (8)
Biclonal	1 (1)	0 (0)
Negative immune fixation	3 (3)	3 (3)
Disease duration: time between first diagnosis and randomization [months], mean (SD)	4.9 (2.9)	5.4 (3.6)

Table 2: Characteristics of the subpopulation[a] – RCT, direct comparison: daratumumab + pomalidomide + dexamethasone vs. pomalidomide + dexamethasone (multipage table)

Study Characteristic Category	**Daratumumab + pomalidomide + dexamethasone N[b] = 106**	**Pomalidomide + dexamethasone N[b] = 105**
Number of prior therapies, n (%)		
2–3	90 (85)	87 (83)
≥ 4	16 (15)	18 (17)
Prior therapies, n (%)		
Alkylating drugs	97 (92)	96 (91)
Anthracyclines	29 (27)	27 (26)
PI + IMiD	106 (10)	105 (10)
PI + IMiD + alkylating agents	97 (92)	96 (91)
Bortezomib + lenalidomide	103 (97)	101 (96)
Elotuzumab	6 (6)	5 (5)
Panobinostat	1 (1)	5 (5)
Bortezomib + lenalidomide + carfilzomib	25 (24)	31 (30)
Bortezomib + lenalidomide + carfilzomib + thalidomide	13 (12)	14 (13)
Refractory to prior lines of therapy, n (%)		
of the most recent prior line of therapy	106 (100)	105 (100)
Lenalidomide in the most recent line of therapy	78 (74)[c]	72 (69)[c]
PI	66 (49)[c, e]	69 (51)[c, e]
IMiD	103 (76)[c, e]	104 (77)[c, e]
PI and IMiD	59 (44)[c, e]	59 (44)[c, e]
Treatment discontinuation, n (%)	ND[f]	ND[f]
Study discontinuation, n (%)	ND[f]	ND[f]

a. Patients with ≥ 2 prior lines of therapy and disease progression on the most recent line of therapy.
b. Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
c. IQWiG calculation.
d. Positive for del(17p), t(4;14), or t(14;16).
e. Data based on the APOLLO subpopulation (daratumumab + pomalidomide + dexamethasone: N = 135; pomalidomide + dexamethasone: N = 135) assessed in A21-101.
f. Data for the total population of the APOLLO study are found in dossier assessment A21-101 [1].

ECOG PS: Eastern Cooperative Oncology Group Performance Status; f: female; Ig: immunoglobulin; IMiD: immunomodulatory drug; IQWiG: Institute for Quality and Efficiency in Health Care; ISS: international staging system; m: male; n: number of patients in the category; N: number of randomized patients; PI: proteasome inhibitor; RCT: randomized controlled trial; R-ISS: Revised International Staging System; SD: standard deviation

Table 3: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: daratumumab + pomalidomide + dexamethasone vs. pomalidomide + dexamethasone, subpopulation[a] (multipage table)

Study Outcome category Outcome	Daratumumab + pomalidomide + dexamethasone		Pomalidomide + dexamethasone		Daratumumab + pomalidomide + dexamethasone vs. pomalidomide + dexamethasone
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value[b]
APOLLO					
Mortality (1st data cut-off, 21/07/2020)					
Overall survival	106	NR [18.79; NC] 35 (33.0)	105	20.27 [15.47; NC] 41 (39.0)	0.78 [0.49; 1.24]; 0.299
Morbidity (1st data cut-off, 21/07/2020)					
Symptoms (EORTC QLQ-C30)[c]					
Pain	106	NR [20.73; NC] 23 (21.7)	105	25.27 [13.04; NC] 25 (23.8)	0.66 [0.36; 1.19]; 0.168
Fatigue	106	25.00 [18.69; 35.45] 35 (33.0)	105	12.95 [8.35; 16.92] 43 (41.0)	0.51 [0.32; 0.83]; 0.007
Nausea and vomiting	106	NR 9 (8.5)	105	NR 10 (9.5)	0.75 [0.30; 1.87]; 0.535
Dyspnoea	106	NR [29.63; NC] 8 (7.5)	105	24.34 [18.92; NC] 11 (10.5)	0.45 [0.17; 1.18]; 0.104
Insomnia	106	NR 12 (11.3)	105	NR [19.98; NC] 13 (12.4)	0.81 [0.36; 1.80]; 0.602
Appetite loss	106	NR [27.80; NC] 12 (11.3)	105	NR 12 (11.4)	0.70 [0.31; 1.61]; 0.404
Constipation	106	NR [21.82; NC] 12 (11.3)	105	NR [17.77; NC] 16 (15.2)	0.56 [0.26; 1.22]; 0.146
Diarrhoea	106	NR [29.63; NC] 8 (7.5)	105	24.34 [18.92; NC] 11 (10.5)	0.45 [0.17; 1.18]; 0.104
Symptoms (EORTC QLQ-MY20)[c]					
Disease-related symptoms	106	NR 16 (15.1)	105	NR [18.66; NC] 18 (17.1)	0.67 [0.33; 1.33]; 0.247
Side effects of therapy	106	24.87 [18.27; NC] 21 (19.8)	105	24.34 [14.03; NC] 22 (21.0)	0.65 [0.35; 1.22]; 0.182
Health status (EQ-5D VAS)[d]	106	NR [19.32; NC] 23 (21.7)	105	NR [18.99; NC] 17 (16.2)	1.12 [0.59; 2.13]; 0.724

Table 3: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: daratumumab + pomalidomide + dexamethasone vs. pomalidomide + dexamethasone, subpopulation[a] (multipage table)

Study Outcome category Outcome	Daratumumab + pomalidomide + dexamethasone		Pomalidomide + dexamethasone		Daratumumab + pomalidomide + dexamethasone vs. pomalidomide + dexamethasone
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value[b]
Health-related quality of life (1st data cut-off, 21/07/2020)					
EORTC QLQ-C30[e]					
Global health status	106	25.00 [19.45; NC] 25 (23.6)	105	24.34 [16.53; 27.53] 21 (20.0)	0.84 [0.46; 1.55]; 0.586
Physical functioning	106	27.60 [18.69; NC] 28 (26.4)	105	20.20 [14.03; NC] 28 (26.7)	0.82 [0.49; 1.40]; 0.474
Role functioning	106	23.16 [19.19; 35.45] 31 (29.2)	105	20.04 [18.14; 24.15] 29 (27.6)	0.77 [0.45; 1.31]; 0.335
Emotional functioning	106	NR [20.73; NC] 17 (16.0)	105	20.20 [9.56; NC] 31 (29.5)	0.36 [0.19; 0.67]; 0.001
Cognitive functioning	106	25.00 [16.79; 32.69] 31 (29.2)	105	18.20 [11.27; NC] 26 (24.8)	0.74 [0.43; 1.29]; 0.292
Social functioning	106	28.71 [19.61; NC] 27 (25.5)	105	21.59 [13.31; NC] 27 (25.7)	0.71 [0.40; 1.25]; 0.231
EORTC QLQ-MY20[e]					
Future perspective	106	NR [17.41; NC] 24 (22.6)	105	17.05 [10.55; 20.20] 33 (31.4)	0.57 [0.33; 0.97]; 0.040
Body image	106	20.53 [18.43; 32.69] 28 (26.4)	105	20.89 [16.79; 24.15] 19 (18.1)	0.95 [0.52; 1.77]; 0.882
Side effects (2nd data cut-off, 15/11/2020)					
AEs (supplementary information)	104	0.26 [0.20; 0.33] 101 (97.1)	102	0.23 [0.07; 0.26] 100 (98.0)	–
SAEs	104	14.26 [7.75; 17.71] 54 (51.9)	102	14.29 [6.50; NC] 44 (43.1)	1.16 [0.78; 1.74]; 0.470
Severe AEs[f]	104	0.64 [0.49; 0.72] 89 (85.6)	102	0.72 [0.66; 0.72] 89 (87.3)	1.05 [0.78; 1.42]; 0.747
Discontinuation due to AEs (≥ 1 drug component)	104	NR 4 (3.8)	102	NR 3 (2.9)	0.95 [0.21; 4.32]; 0.944
Lymphopoenia (PT, severe AEs[f])	104	NR 14 (13.5)	102	NR 2 (2.0)	7.42 [1.68; 32.85]; 0.008
Febrile neutropenia (PT, severe AEs[f])	104	NR 9 (8.7)	102	NR 1 (1.0)	8.75 [1.11; 69.23]; 0.040

Table 3: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: daratumumab + pomalidomide + dexamethasone vs. pomalidomide + dexamethasone, subpopulation[a] (multipage table)

Study Outcome category Outcome	Daratumumab + pomalidomide + dexamethasone		Pomalidomide + dexamethasone		Daratumumab + pomalidomide + dexamethasone vs. pomalidomide + dexamethasone
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value[b]

a. Patients with ≥ 2 prior lines of therapy and disease progression on the most recent line of therapy.
b. HR (including 95% CI) and p-value calculated using a Cox proportional hazards model with treatment as the only explanatory variable, stratified by number of prior lines of therapy (2–3 vs. ≥ 4) and ISS stage (I vs. II vs. III); p-value for overall survival calculated using log rank test, stratified by number of prior lines of therapy (2–3 vs. ≥ 4) and ISS stage (I vs. II vs. III).
c. Time to definitive deterioration; a score increase by ≥ 10 points from baseline is defined as a clinically relevant deterioration (scale range 0 to 100). Corresponds to the operationalization of confirmed definitive deterioration as presented the company's comments.
d. Time to definitive deterioration; a score decrease by ≥ 15 points from baseline is defined as a clinically relevant deterioration (scale range 0 to 100). Corresponds to the operationalization of confirmed definitive deterioration as presented the company's comments.
e. Time to definitive deterioration; a score decrease by ≥ 10 points from baseline is defined as a clinically relevant deterioration (scale range 0 to 100). Corresponds to the operationalization of confirmed definitive deterioration as presented the company's comments.
f. Operationalized as CTCAE grade ≥ 3.

CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EORTC QLQ-MY20: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Myeloma Module 20; HR: hazard ratio; ISS: International Staging System; n: number of patients with (at least 1) event; N: number of analysed patients; NC: not calculable; ND: no data; NR: not reached; RCT: randomized controlled trial; VAS: visual analogue scale

Table 4: Subgroups (health-related quality of life) – RCT, direct comparison: daratumumab + pomalidomide + dexamethasone vs. pomalidomide + dexamethasone, subpopulation[a]

Study Outcome Characteristic Subgroup	Daratumumab + pomalidomide + dexamethasone		Pomalidomide + dexamethasone		Daratumumab + pomalidomide + dexamethasone vs. pomalidomide + dexamethasone	
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI][b]	p-value[b]
APOLLO						
EORTC QLQ-C30 social functioning[c] (1st data cut-off, 21/07/2020)						
Age						
< 65 years	45	NR [13.21; NC] 11 (24.4)	37	NR 4 (10.8)	2.21 [0.70; 6.97]	0.176
≥ 65 years	61	28.71 [19.61; NC] 16 (26.2)	68	15.90 [8.15; NC] 23 (33.8)	0.46 [0.23; 0.90]	0.023
Total					Interaction:	0.022
EORTC QLQ-MY20 body image[c] (1st data cut-off, 21/07/2020)						
Sex						
Male	55	20.53 [13.50; 32.69] 19 (34.5)	62	24.15 [23.85; NC] 7 (11.3)	2.09 [0.86; 5.06]	0.104
Female	51	21.82 [19.61; NC] 9 (17.6)	43	13.83 [11.66; 20.89] 12 (27.9)	0.27 [0.11; 0.69]	0.006
Total					Interaction:	0.005

a. Patients with ≥ 2 prior lines of therapy and disease progression on the most recent line of therapy.
b. Hazard ratio (including 95% CI and p-value) calculated using a Cox proportional hazards model with treatment and treatment x subgroup as explanatory variables.
c. Time to definitive deterioration; a score decrease by ≥ 10 points from baseline is defined as a clinically relevant deterioration (scale range 0 to 100). Corresponds to the operationalization of confirmed definitive deterioration as presented the company's comments.

CI: confidence interval; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EORTC QLQ-MY20: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Myeloma Module 20; HR: hazard ratio; n: number of patients with event; N: number of analysed patients; NC: not calculable; NR: not reached; RCT: randomized controlled trial

Table 5: Results (morbidity, supplementary presentation) – RCT, direct comparison: daratumumab + pomalidomide + dexamethasone vs. pomalidomide + dexamethasone; 1st data cut-off (21/07/2020), subpopulation[a]

Study Outcome category Outcome	Daratumumab + pomalidomide + dexamethasone		Pomalidomide + dexamethasone		Daratumumab + pomalidomide + dexamethasone vs. pomalidomide + dexamethasone
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value[b]
APOLLO					
Morbidity					
Health status (EQ-5D VAS)					
Definitive deterioration by ≥ 7 points[c]	106	20.73 [17.77; NC] 32 (30.2)	105	17.05 [11.30; 27.53] 34 (32.4)	0.81 [0.49; 1.33]; 0.409
Definitive deterioration by ≥ 10 points[c]	106	20.73 [19.45; NC] 31 (29.2)	105	18.99 [11.30; NC] 31 (29.5)	0.88 [0.53; 1.47]; 0.635

a. Patients with ≥ 2 prior lines of therapy and disease progression on the most recent line of therapy.
b. HR (including 95% CI) and p-value, calculated using a Cox proportional hazards model with treatment as the only explanatory variable, stratified by the number of prior lines of therapy (2–3 versus ≥ 4) and ISS stage (I versus II versus III).
c. Corresponds to the operationalization of confirmed definitive deterioration as used in the company's comments.

CI: confidence interval; HR: hazard ratio; ISS: International Staging System; n: number of patients with (at least 1) event; N: number of analysed patients; NC: not calculable; RCT: randomized controlled trial; VAS: visual analogue scale

Appendix B Figures on the analyses of the subpopulation (APOLLO study)

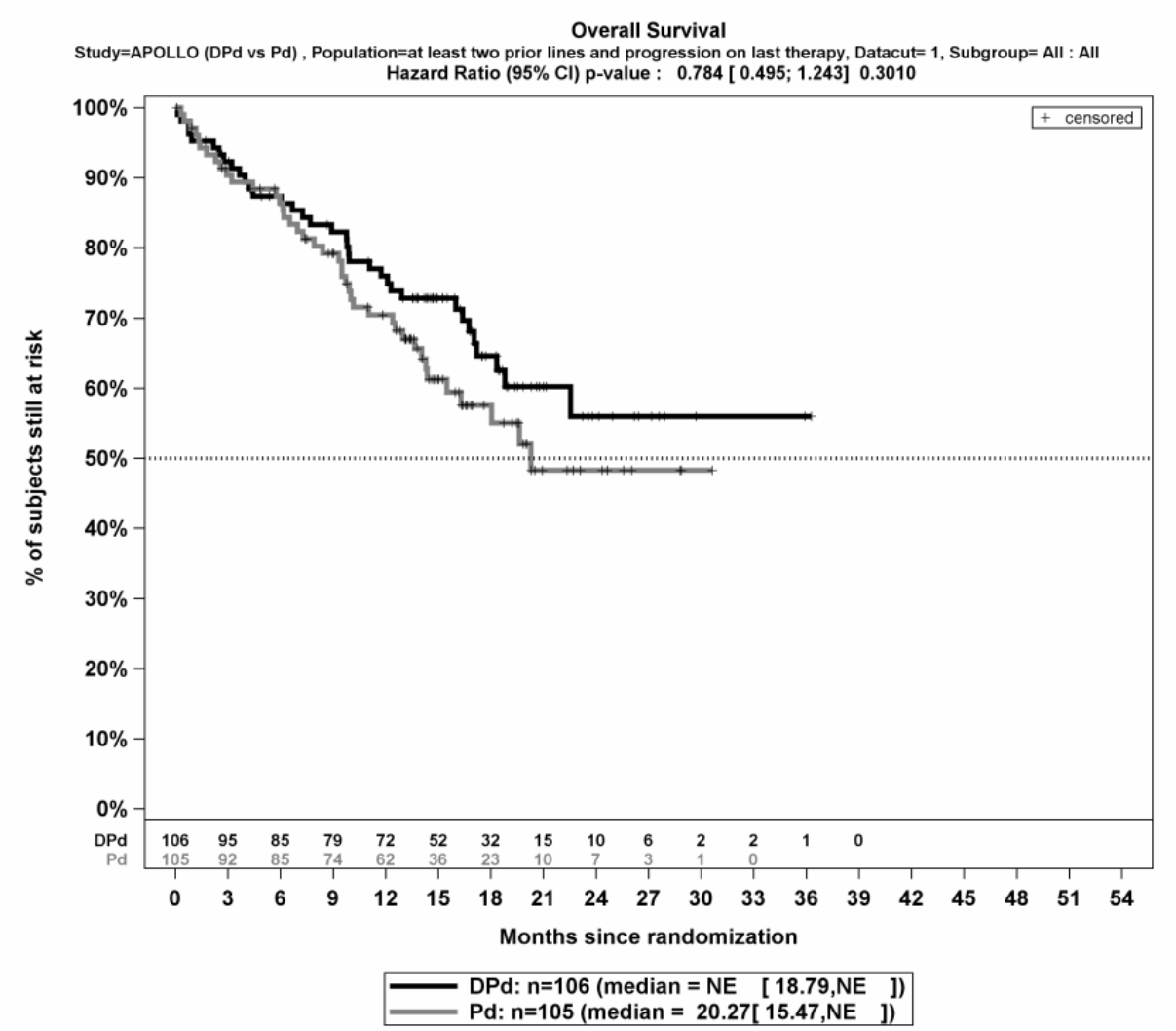

Figure 1: Kaplan-Meier curves on overall survival, APOLLO study, subpopulation of patients with ≥ 2 prior lines of therapy and disease progression on the most recent line of therapy (data cut-off: 21/07/2020)

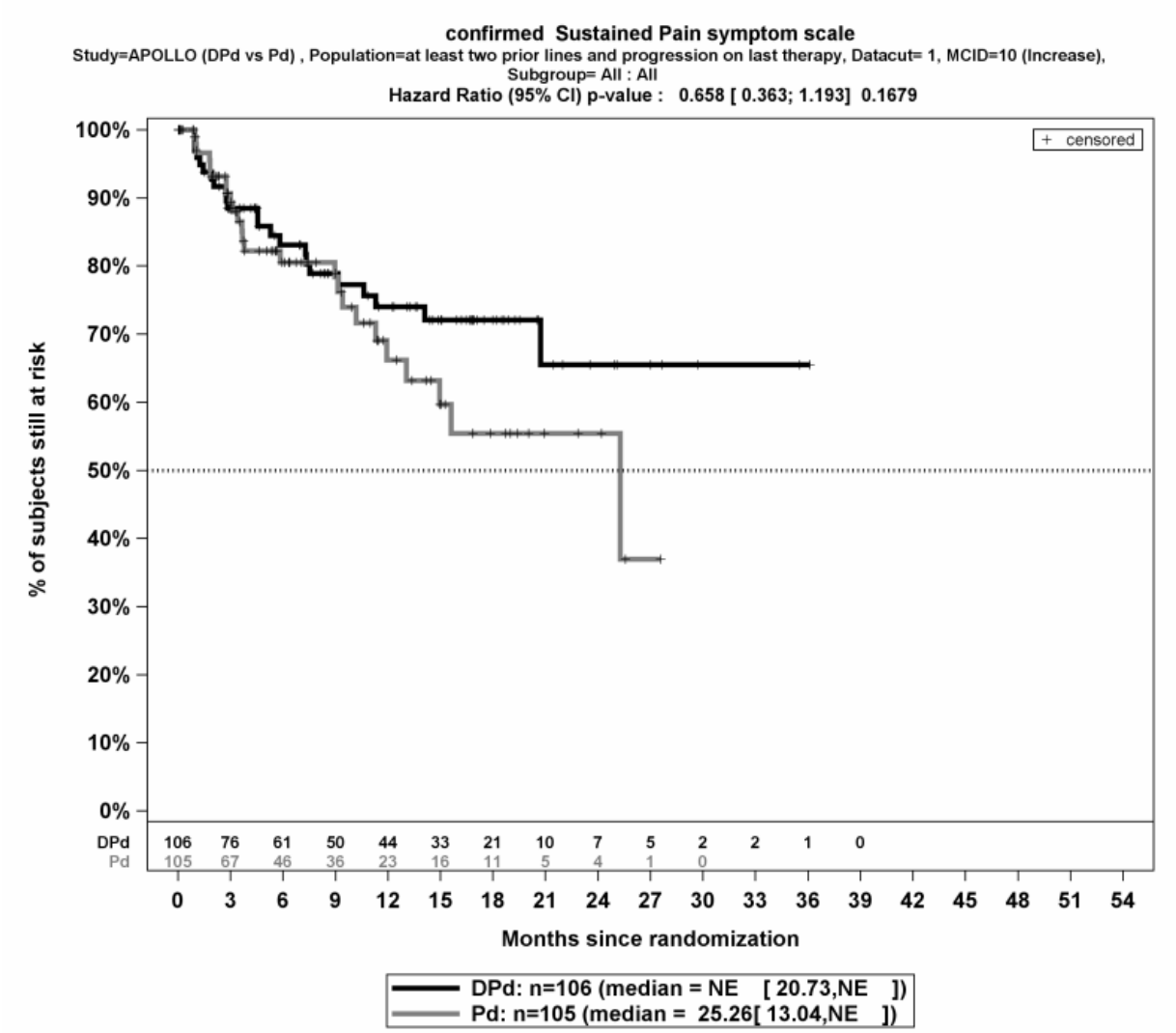

Figure 2: Kaplan-Meier curves on EORTC QLQ-C30, pain, time to definitive deterioration by ≥ 10 points, APOLLO study, subpopulation of patients with ≥ 2 prior lines of therapy and disease progression on the most recent line of therapy (data cut-off: 21/07/2020)

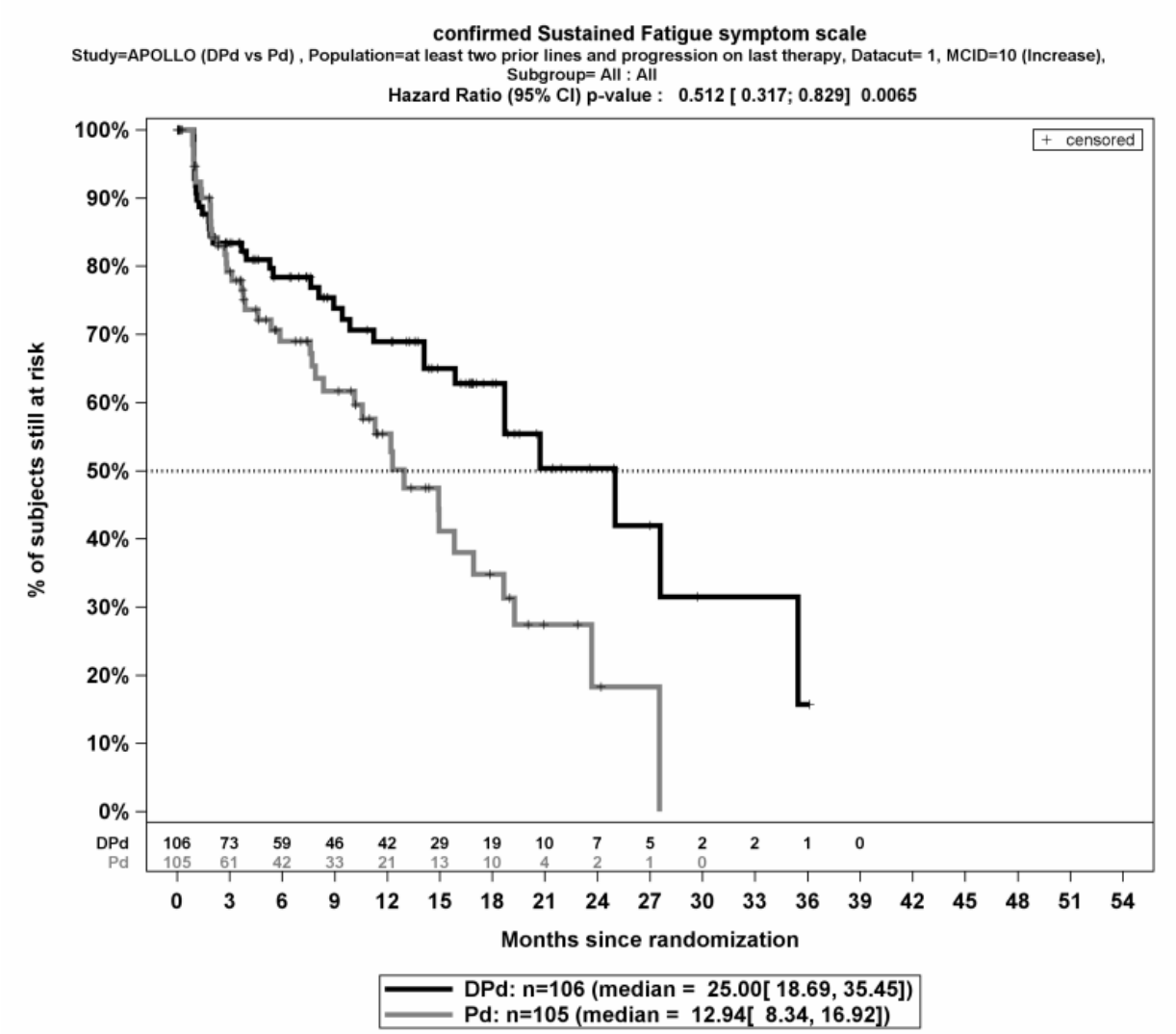

Figure 3: Kaplan-Meier curves on EORTC QLQ-C30, fatigue, time to definitive deterioration by ≥ 10 points, APOLLO study, subpopulation of patients with ≥ 2 prior lines of therapy and disease progression on the most recent line of therapy (data cut-off: 21/07/2020)

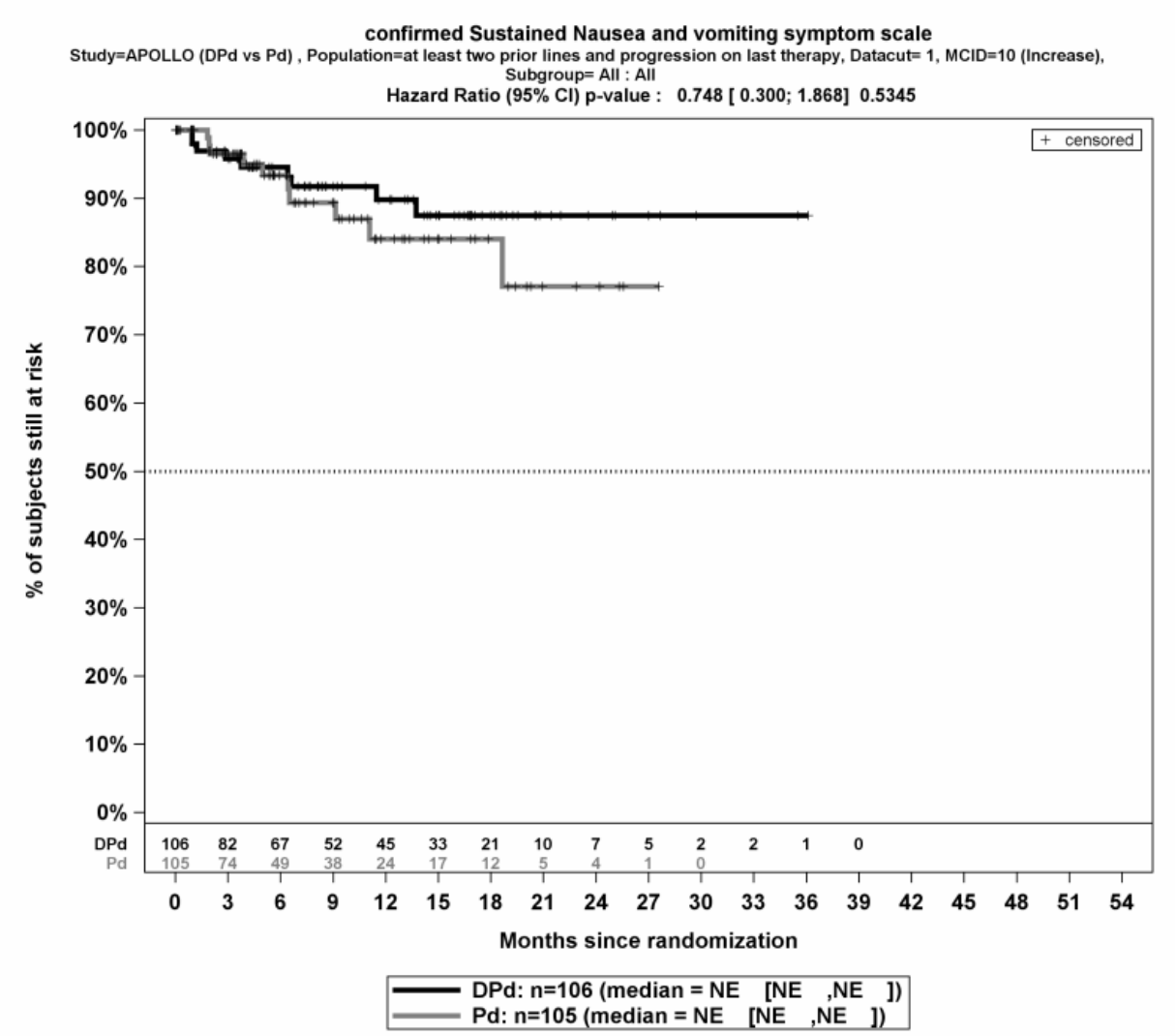

Figure 4: Kaplan-Meier curves on EORTC QLQ-C30, nausea and vomiting, time to definitive deterioration by ≥ 10 points, APOLLO study, subpopulation of patients with ≥ 2 prior lines of therapy and disease progression on the most recent line of therapy (data cut-off: 21/07/2020)

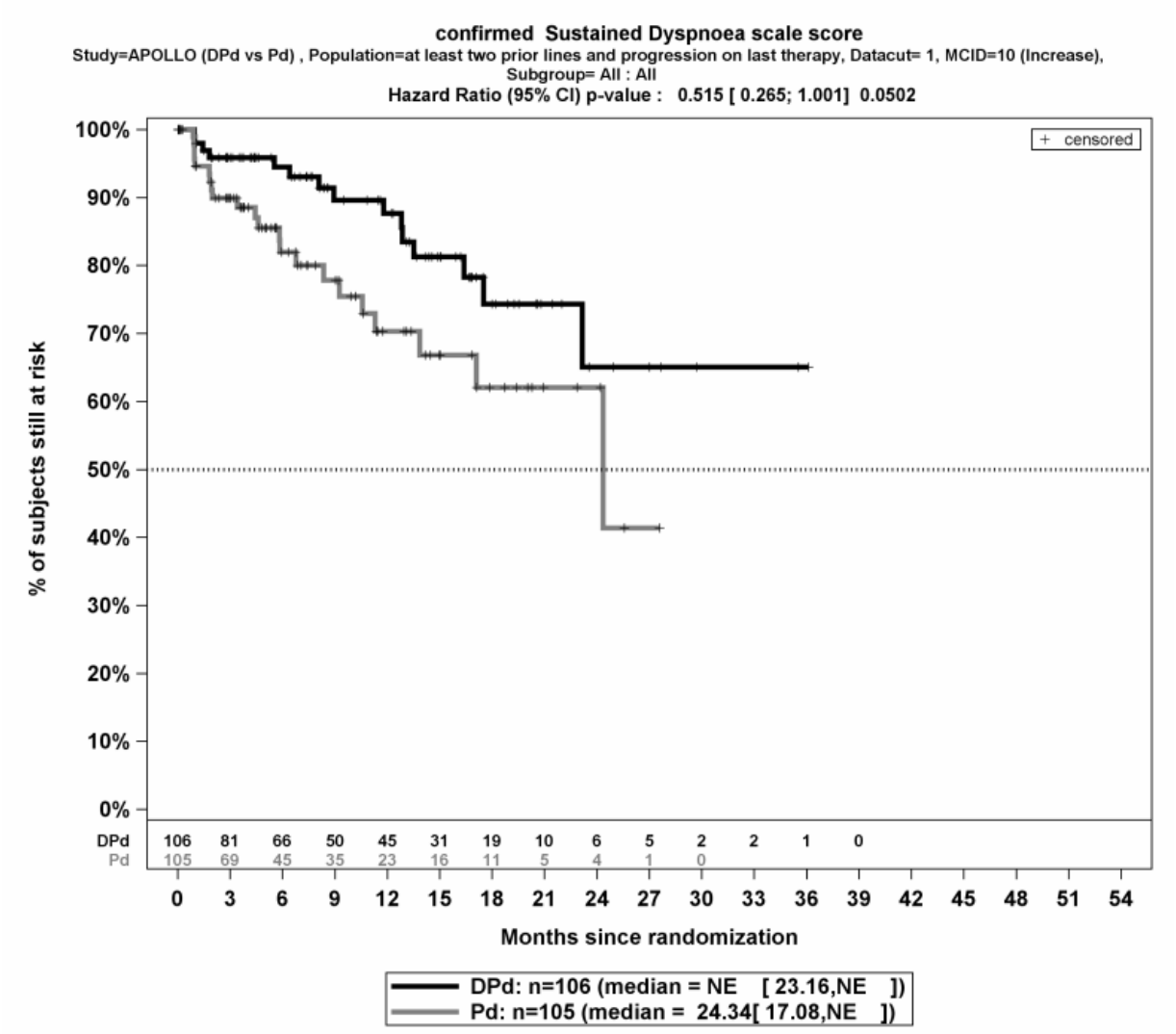

Figure 5: Kaplan-Meier curves on EORTC QLQ-C30, dyspnoea, time to definitive deterioration by ≥ 10 points, APOLLO study, subpopulation of patients with ≥ 2 prior lines of therapy and disease progression on the most recent line of therapy (data cut-off: 21 July 2020)

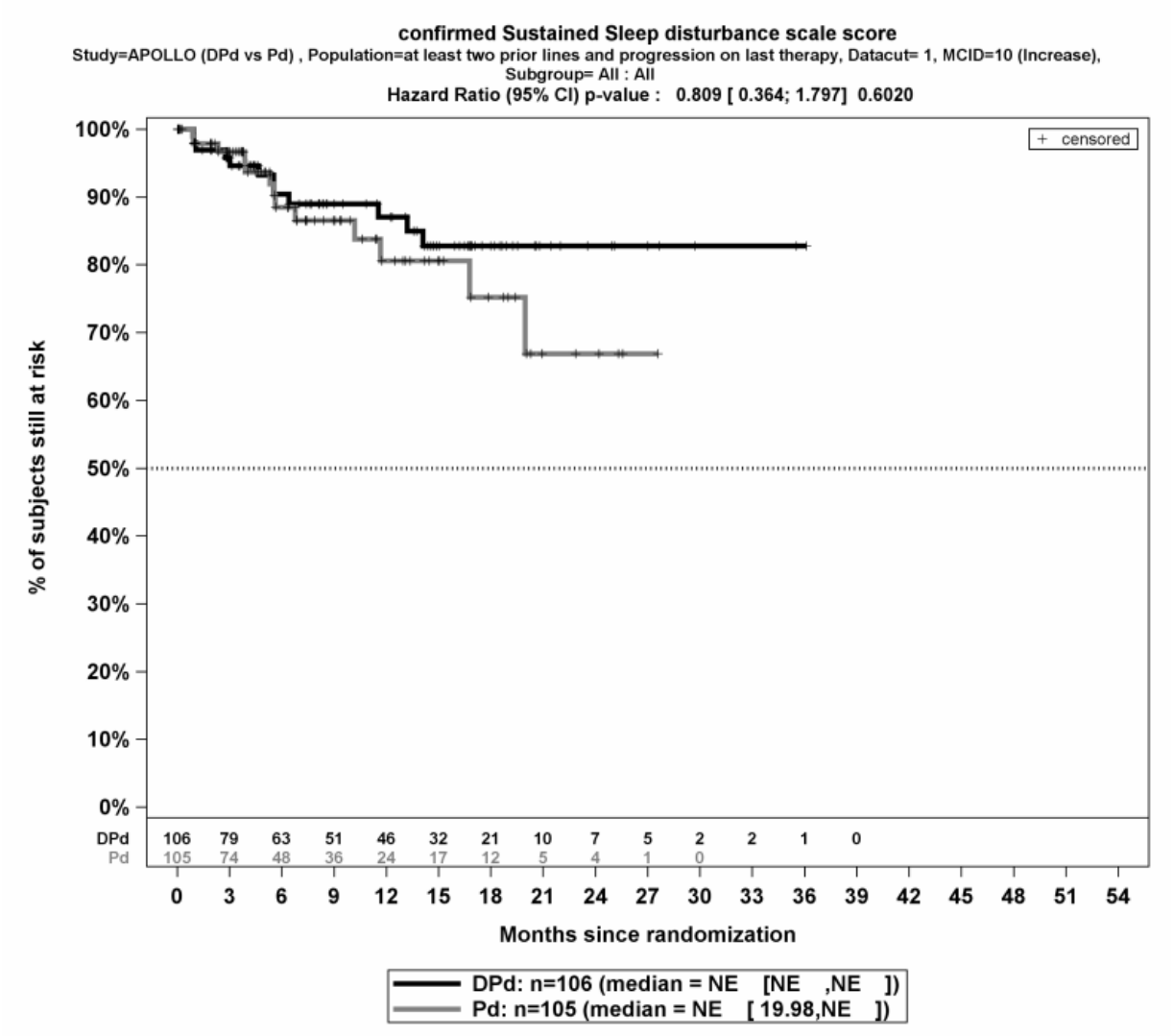

Figure 6: Kaplan-Meier curves on EORTC QLQ-C30, insomnia, time to definitive deterioration by ≥ 10 points, APOLLO study, subpopulation of patients with ≥ 2 prior lines of therapy and disease progression on the most recent line of therapy (data cut-off: 21/07/2020)

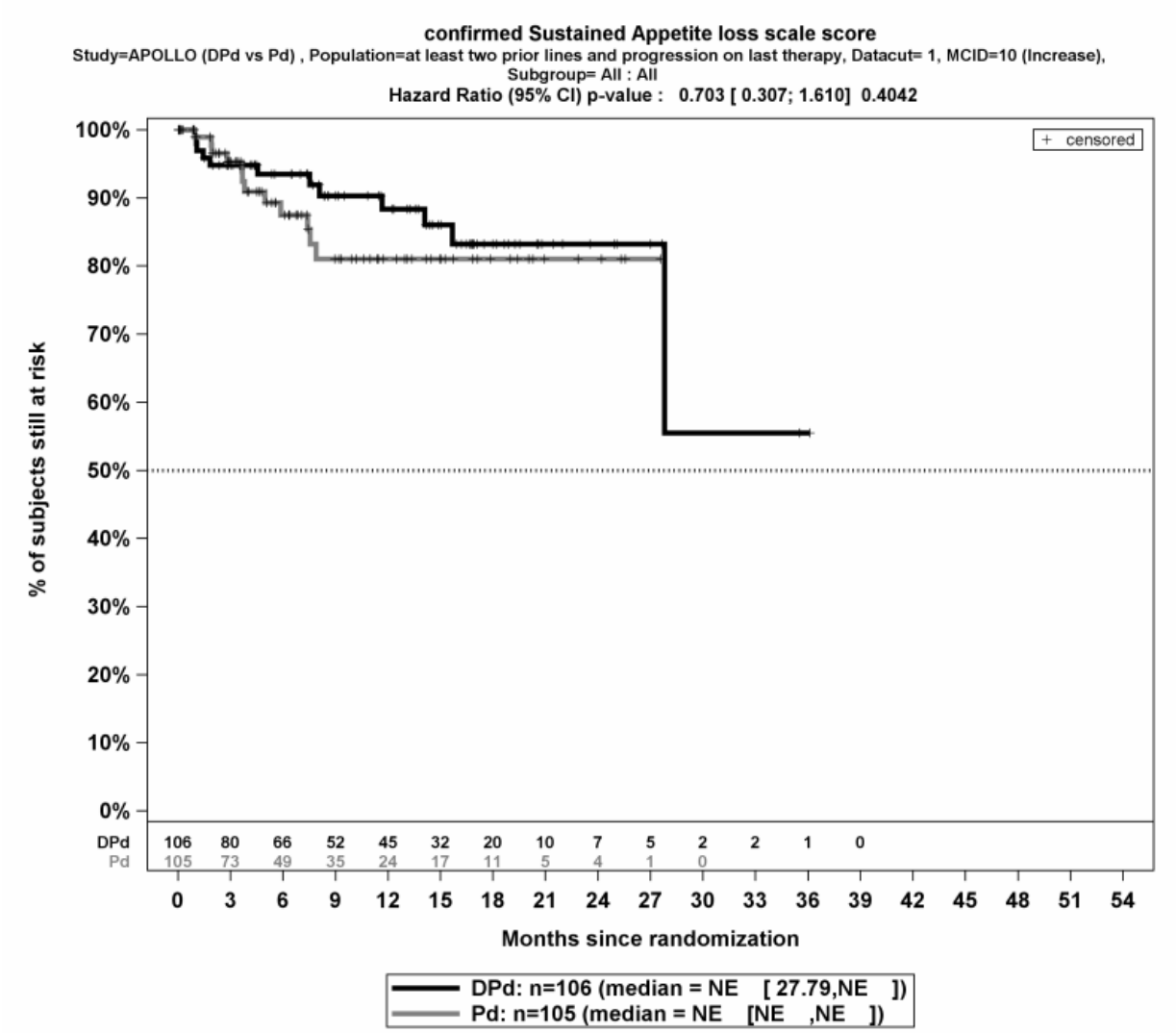

Figure 7: Kaplan-Meier curves on EORTC QLQ-C30, appetite loss, time to definitive deterioration by ≥ 10 points, APOLLO study, subpopulation of patients with ≥ 2 prior lines of therapy and disease progression on the most recent line of therapy (data cut-off: 21/07/2020)

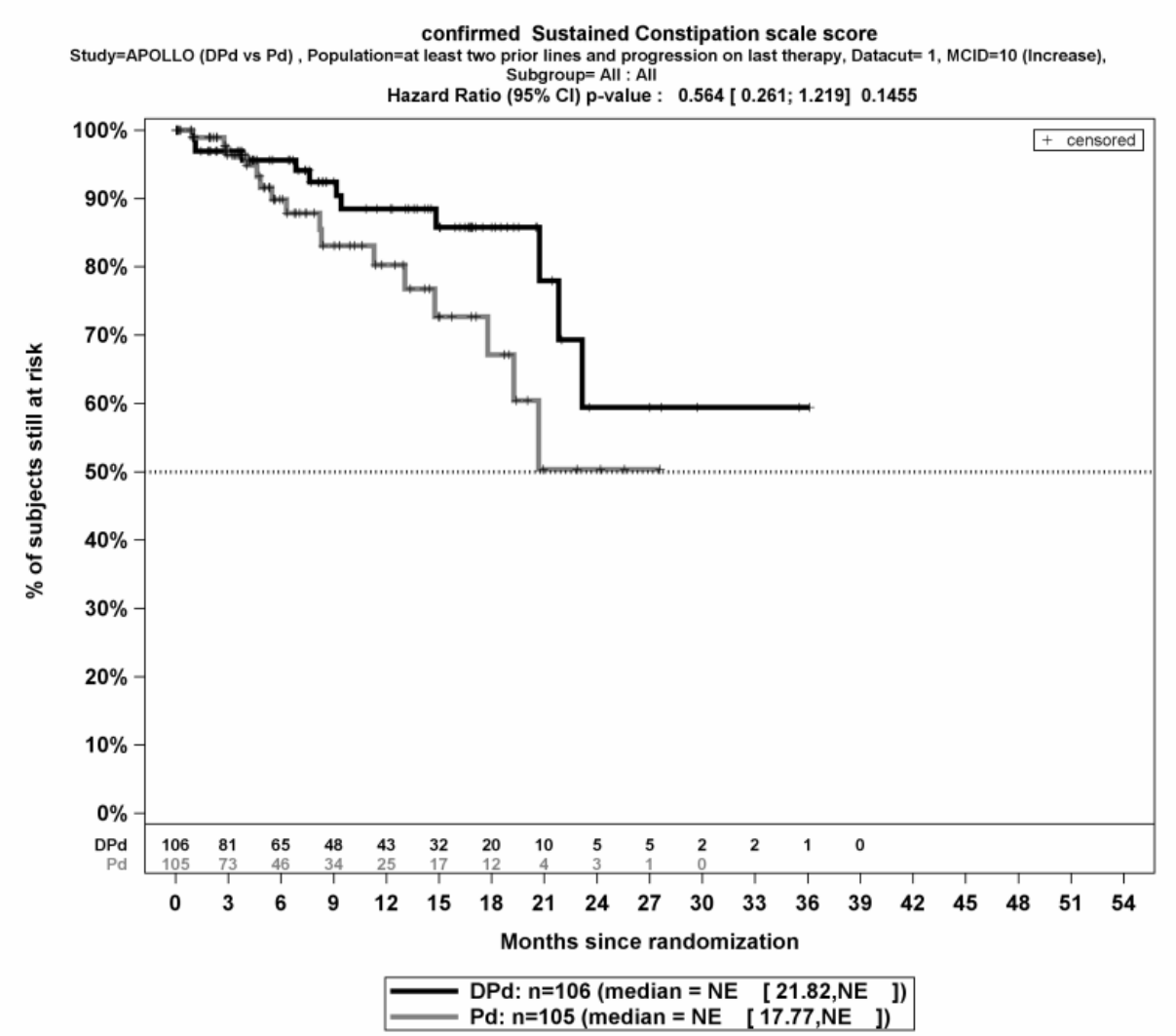

Figure 8: Kaplan-Meier curves on EORTC QLQ-C30, constipation, time to definitive deterioration by ≥ 10 points, APOLLO study, subpopulation of patients with ≥ 2 prior lines of therapy and disease progression on the most recent line of therapy (data cut-off: 21/07/2020)

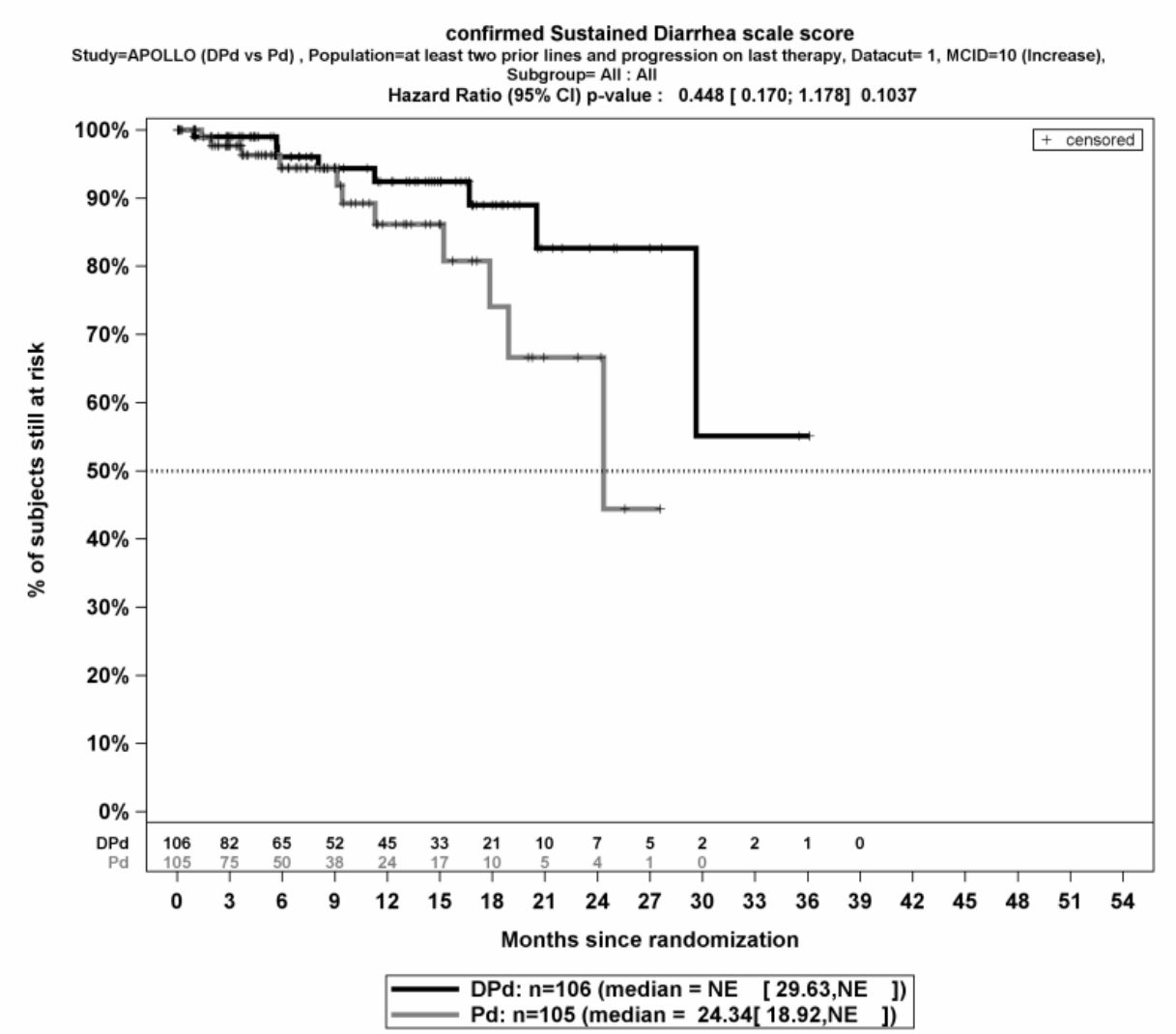

Figure 9: Kaplan-Meier curves on EORTC QLQ-C30, diarrhoea, time to definitive deterioration by ≥ 10 points, APOLLO study, subpopulation of patients with ≥ 2 prior lines of therapy and disease progression on the most recent line of therapy (data cut-off: 21/07/2020)

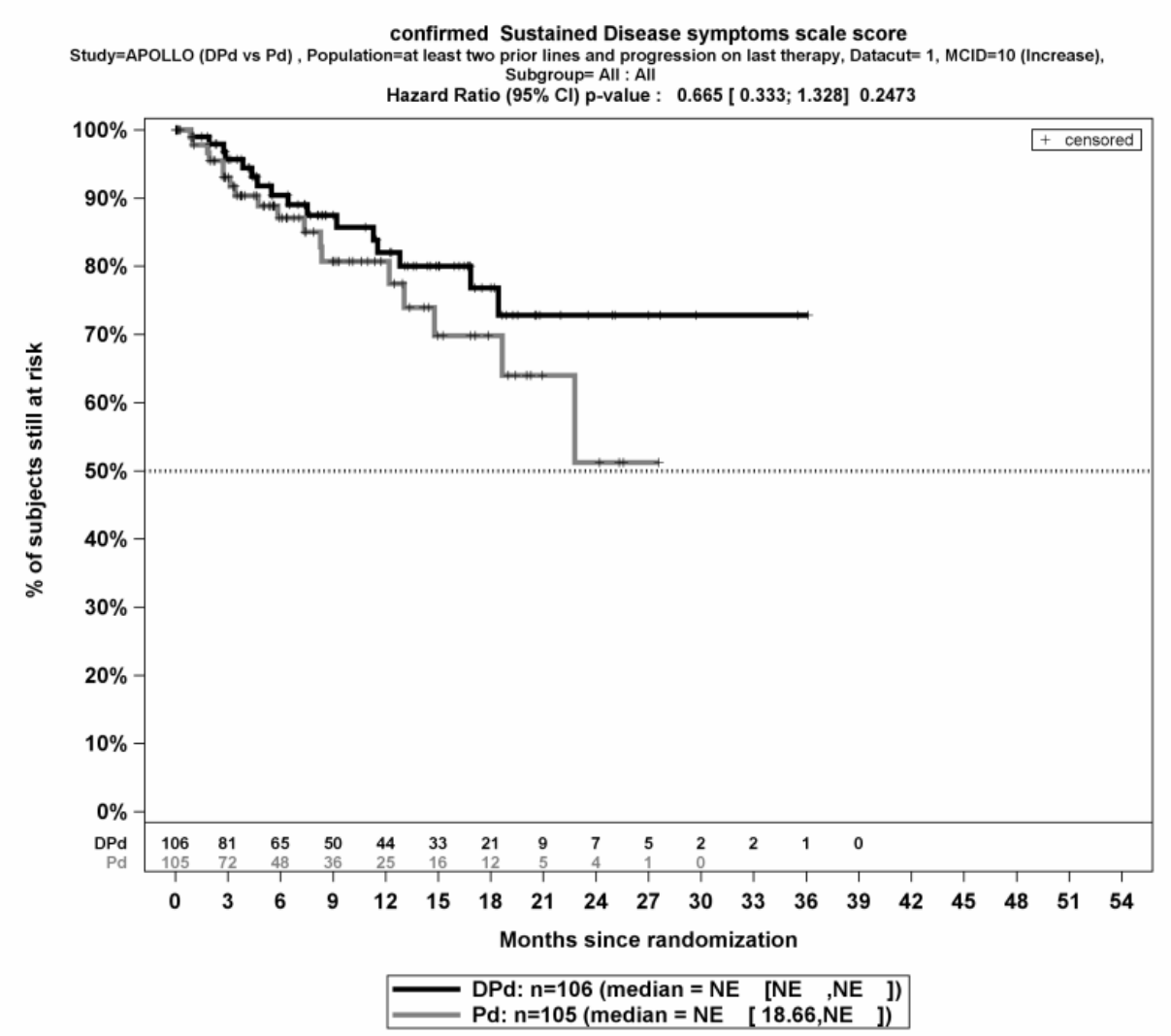

Figure 10: Kaplan-Meier curves on EORTC QLQ-MY20, disease symptoms, time to definitive deterioration by ≥ 10 points, APOLLO study, subpopulation of patients with ≥ 2 prior lines of therapy and disease progression on the most recent line of therapy (data cut-off: 21/07/2020)

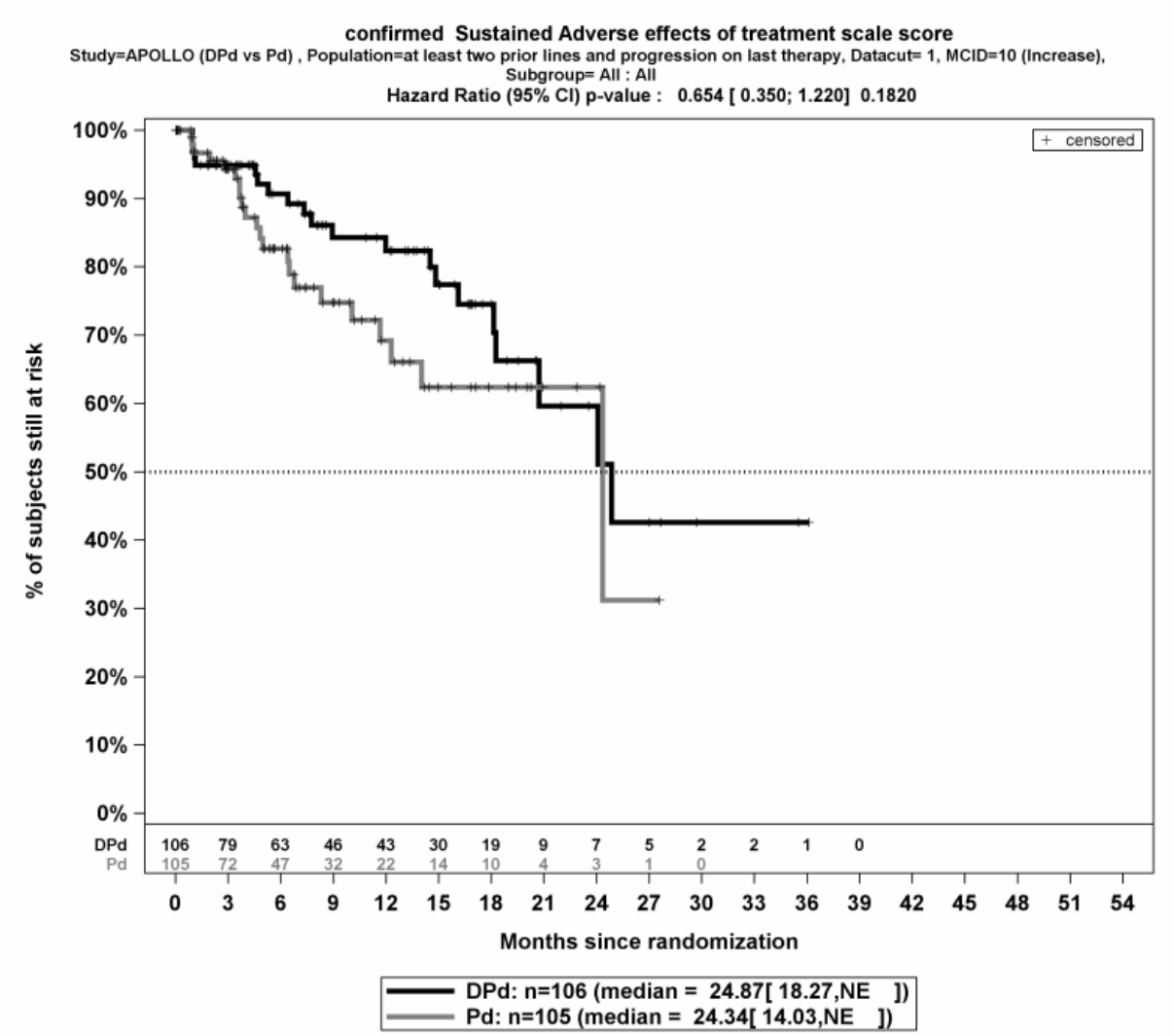

Figure 11: Kaplan-Meier curves on EORTC QLQ-MY20, side effects of therapy, time to definitive deterioration by ≥ 10 points, APOLLO study, subpopulation of patients with ≥ 2 prior lines of therapy and disease progression on the most recent line of therapy (data cut-off: 21/07/2020)

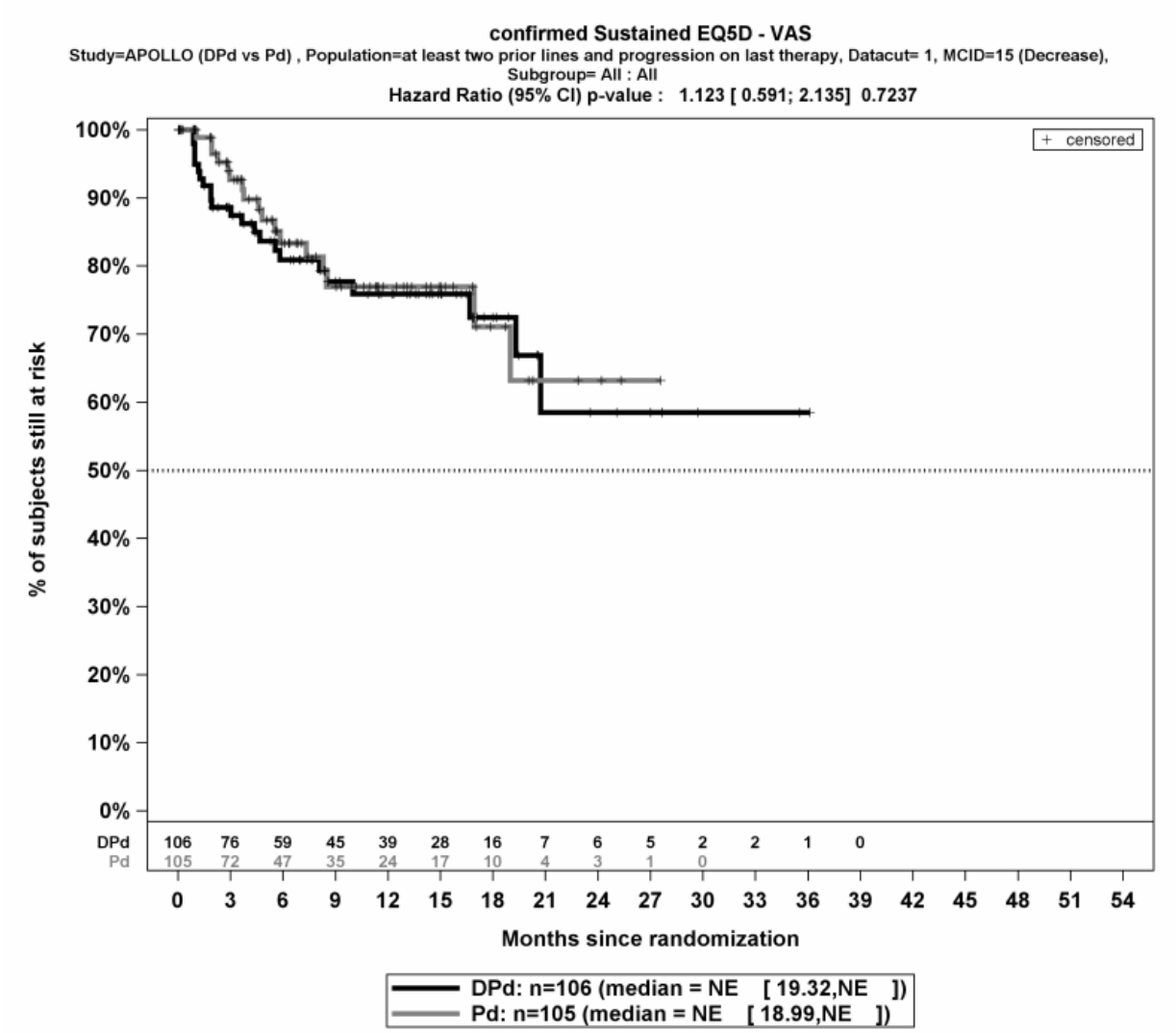

Figure 12: Kaplan-Meier curves on EQ-5D VAS, time to definitive deterioration by ≥ 15 points, APOLLO study, subpopulation of patients with ≥ 2 prior lines of therapy and disease progression on the most recent line of therapy (data cut-off: 21/07/2020)

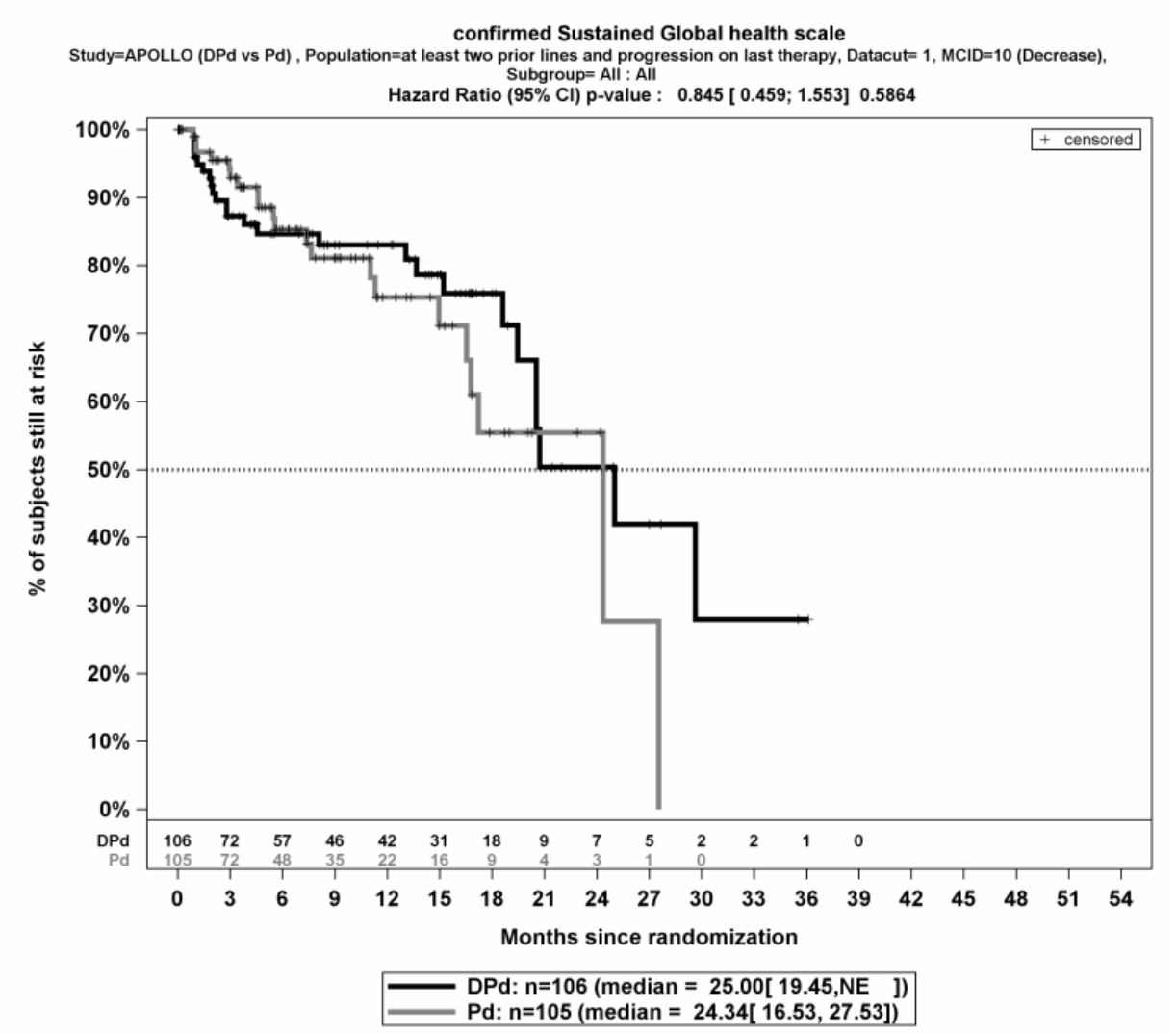

Figure 13: Kaplan-Meier curves on EORTC QLQ-C30, global health status, time to definitive deterioration by ≥ 10 points, APOLLO study, subpopulation of patients with ≥ 2 prior lines of therapy and disease progression on the most recent line of therapy (data cut-off: 21/07/2020)

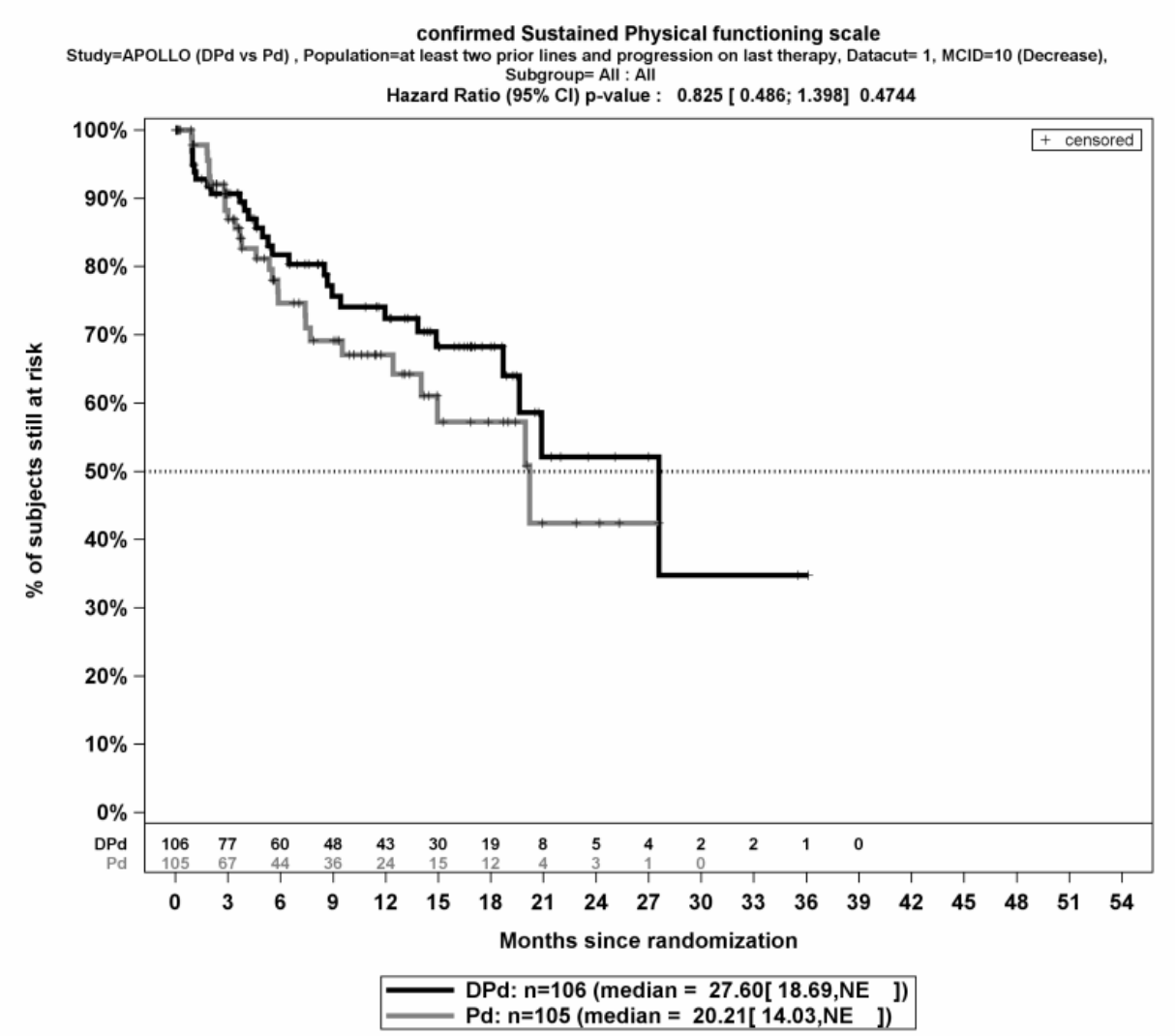

Figure 14: Kaplan-Meier curves on EORTC QLQ-C30, physical functioning, time to definitive deterioration by ≥ 10 points, APOLLO study, subpopulation of patients with ≥ 2 prior lines of therapy and disease progression on the most recent line of therapy (data cut-off: 21/07/2020)

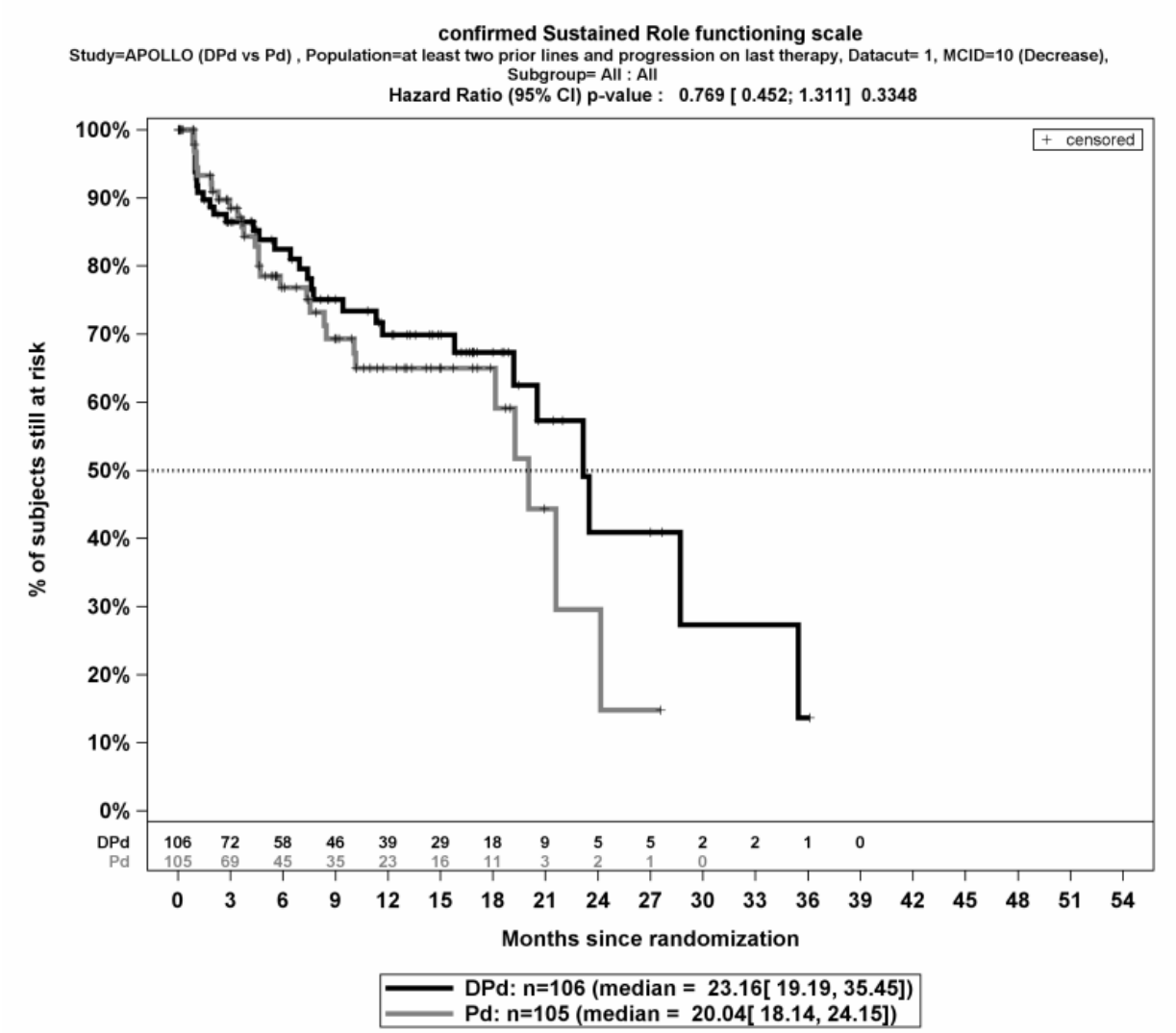

Figure 15: Kaplan-Meier curves on EORTC QLQ-C30, role functioning, time to definitive deterioration by ≥ 10 points, APOLLO study, subpopulation of patients with ≥ 2 prior lines of therapy and disease progression on the most recent line of therapy (data cut-off: 21/07/2020)

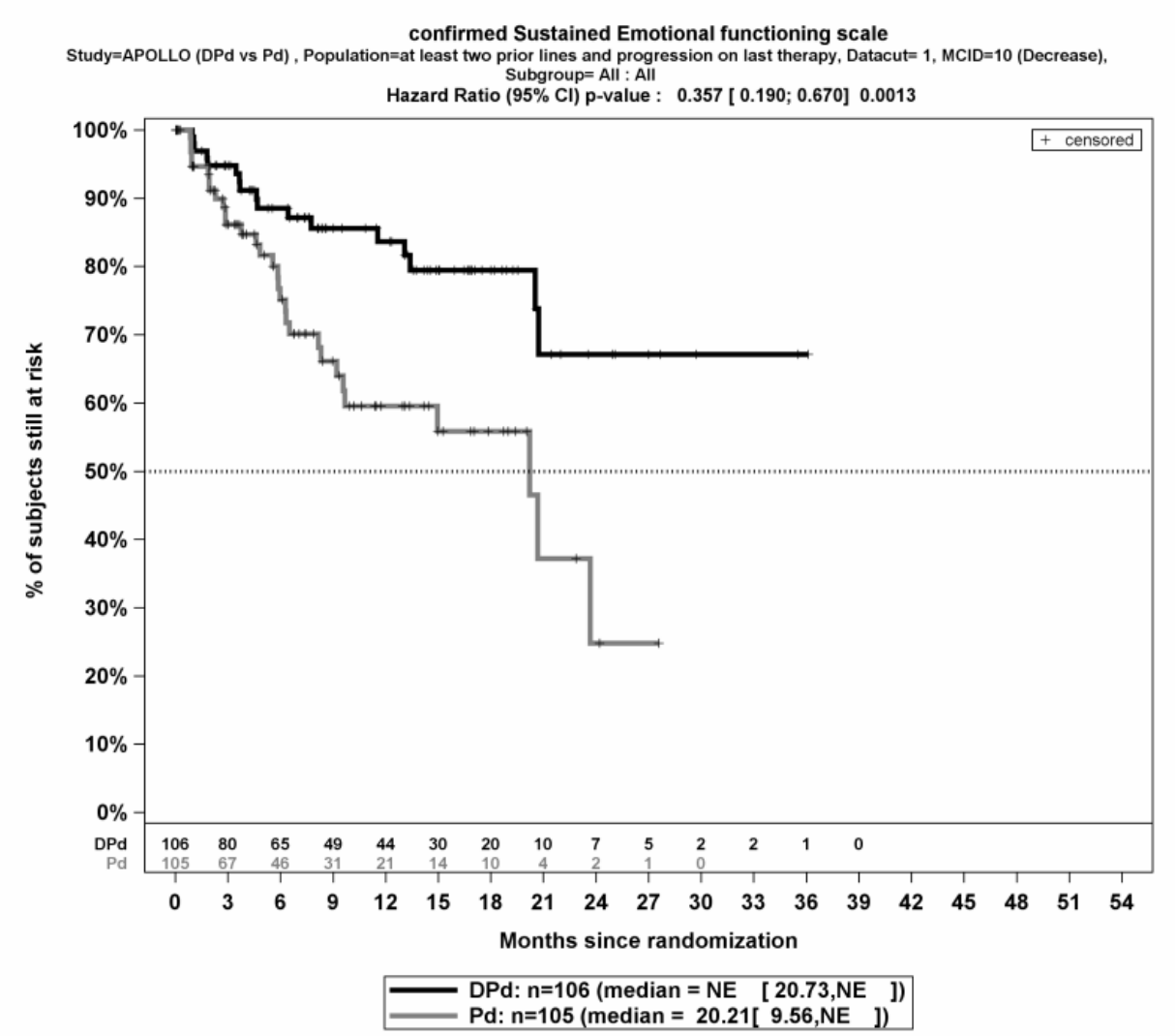

Figure 16: Kaplan-Meier curves on EORTC QLQ-C30, emotional functioning, time to definitive deterioration by ≥ 10 points, APOLLO study, subpopulation of patients with ≥ 2 prior lines of therapy and disease progression on the most recent line of therapy (data cut-off: 21/07/2020)

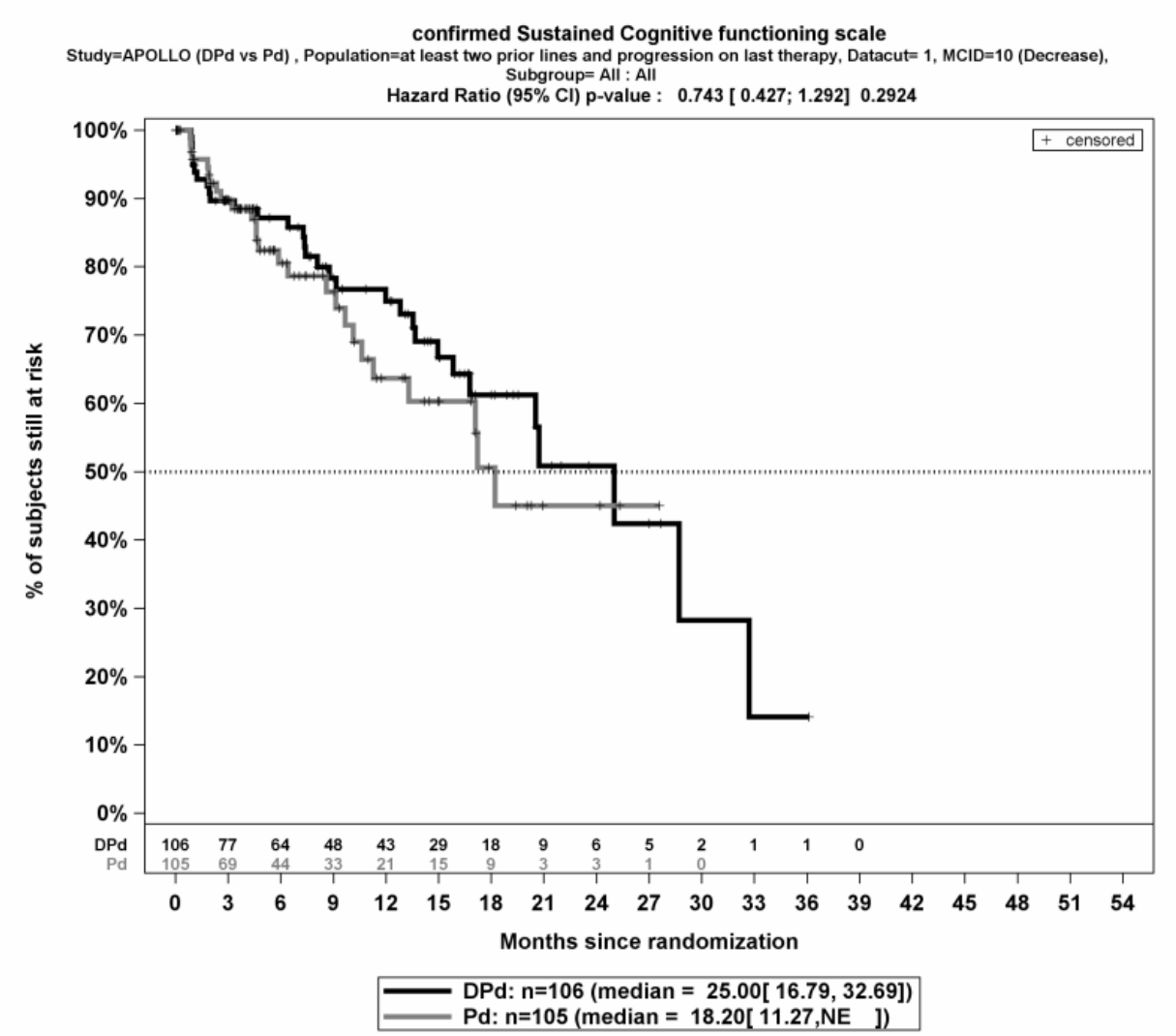

Figure 17: Kaplan-Meier curves on EORTC QLQ-C30, cognitive functioning, time to definitive deterioration by ≥ 10 points, APOLLO study, subpopulation of patients with ≥ 2 prior lines of therapy and disease progression on the most recent line of therapy (data cut-off: 21/07/2020)

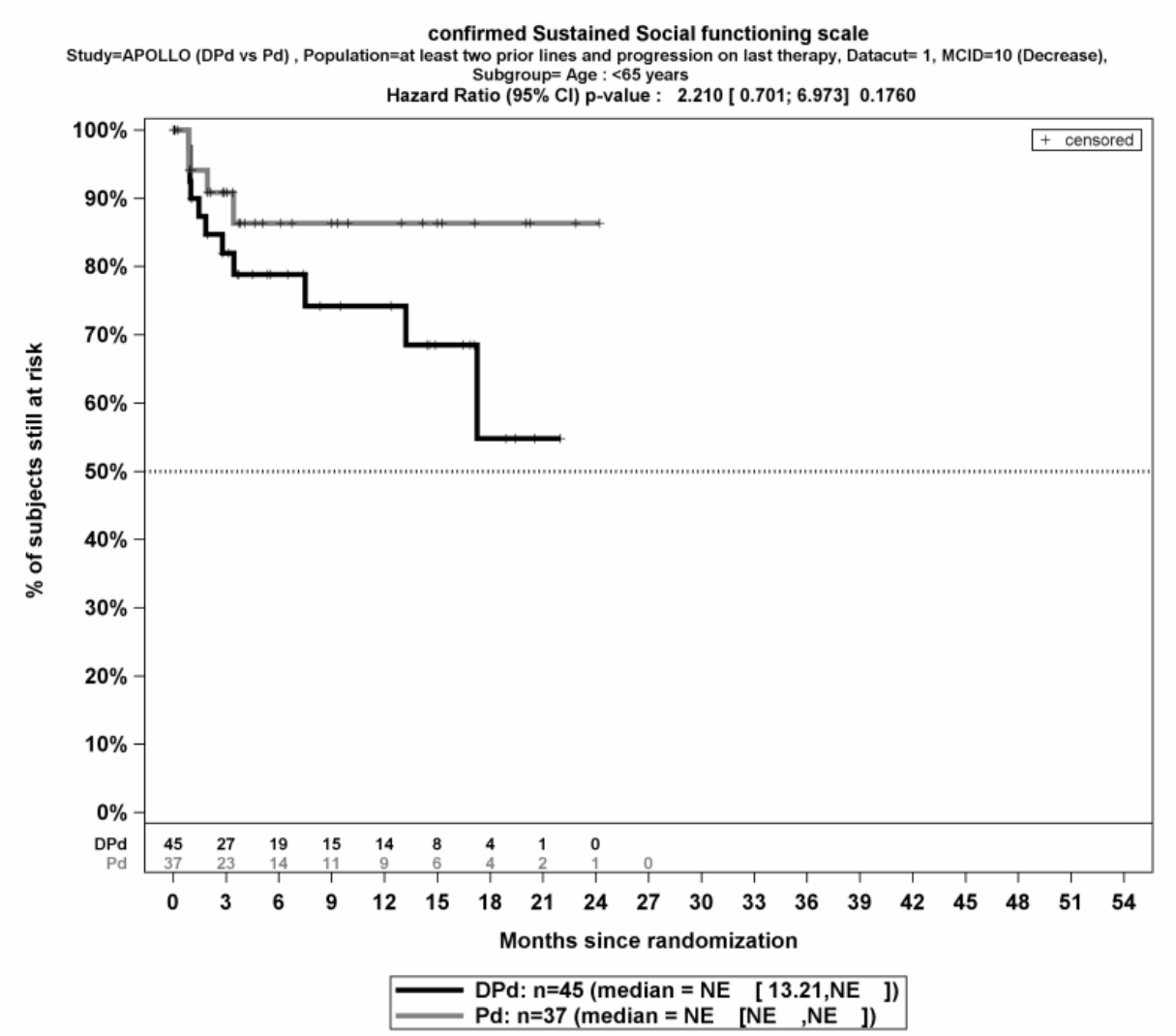

Figure 18: Kaplan-Meier curves on EORTC QLQ-C30, social functioning, time to definitive deterioration by ≥ 10 points, subgroup analysis by age (< 65 years), APOLLO study, subpopulation of patients with ≥ 2 prior lines of therapy and disease progression on the most recent line of therapy (data cut-off: 21/07/2020)

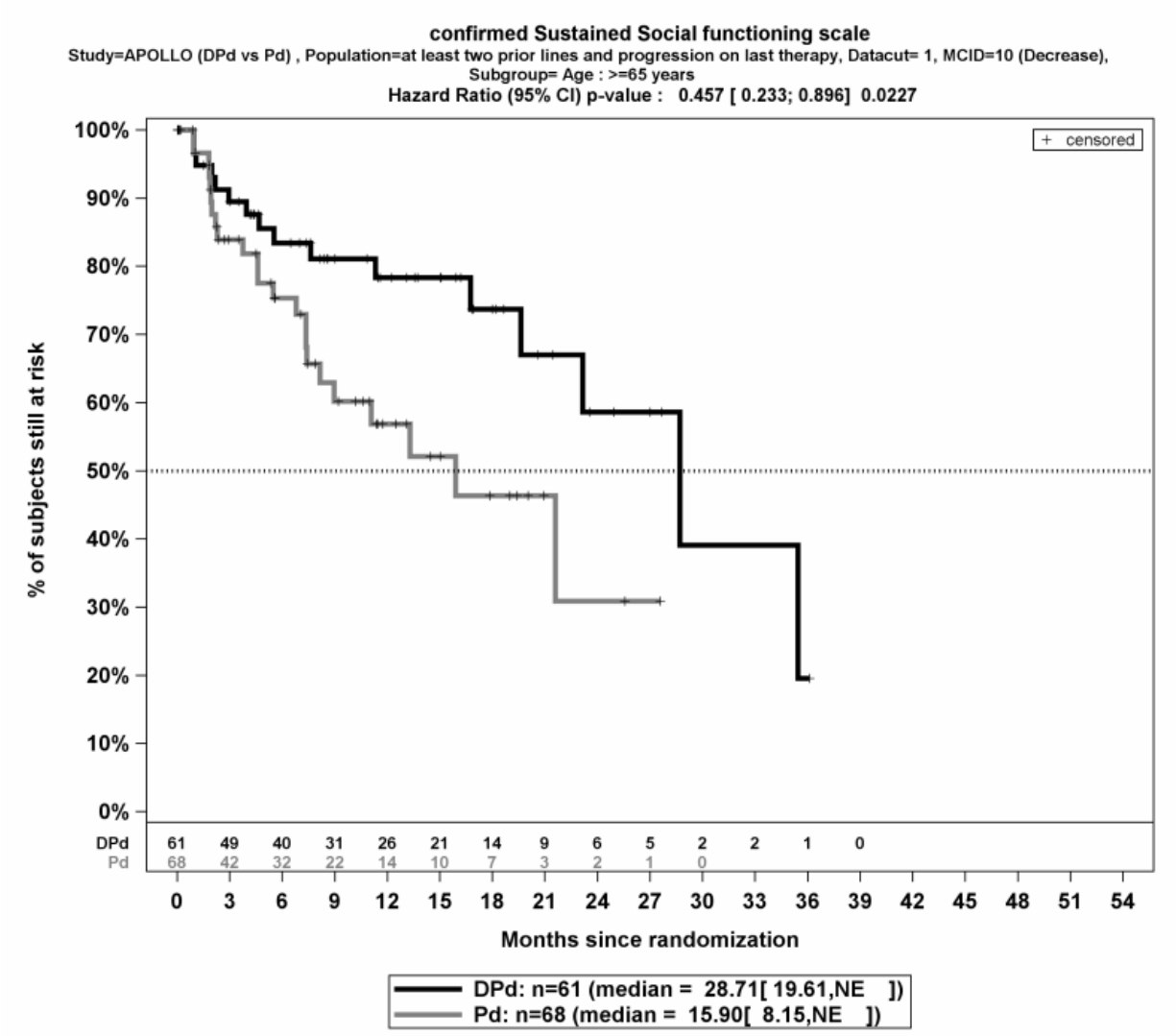

Figure 19: Kaplan-Meier curves on EORTC QLQ-C30, social functioning, time to definitive deterioration by ≥ 10 points, subgroup analysis by age (≥ 65 years), APOLLO study, subpopulation of patients with ≥ 2prior lines of therapy and disease progression on the most recent line of therapy (data cut-off: 21/07/2020)

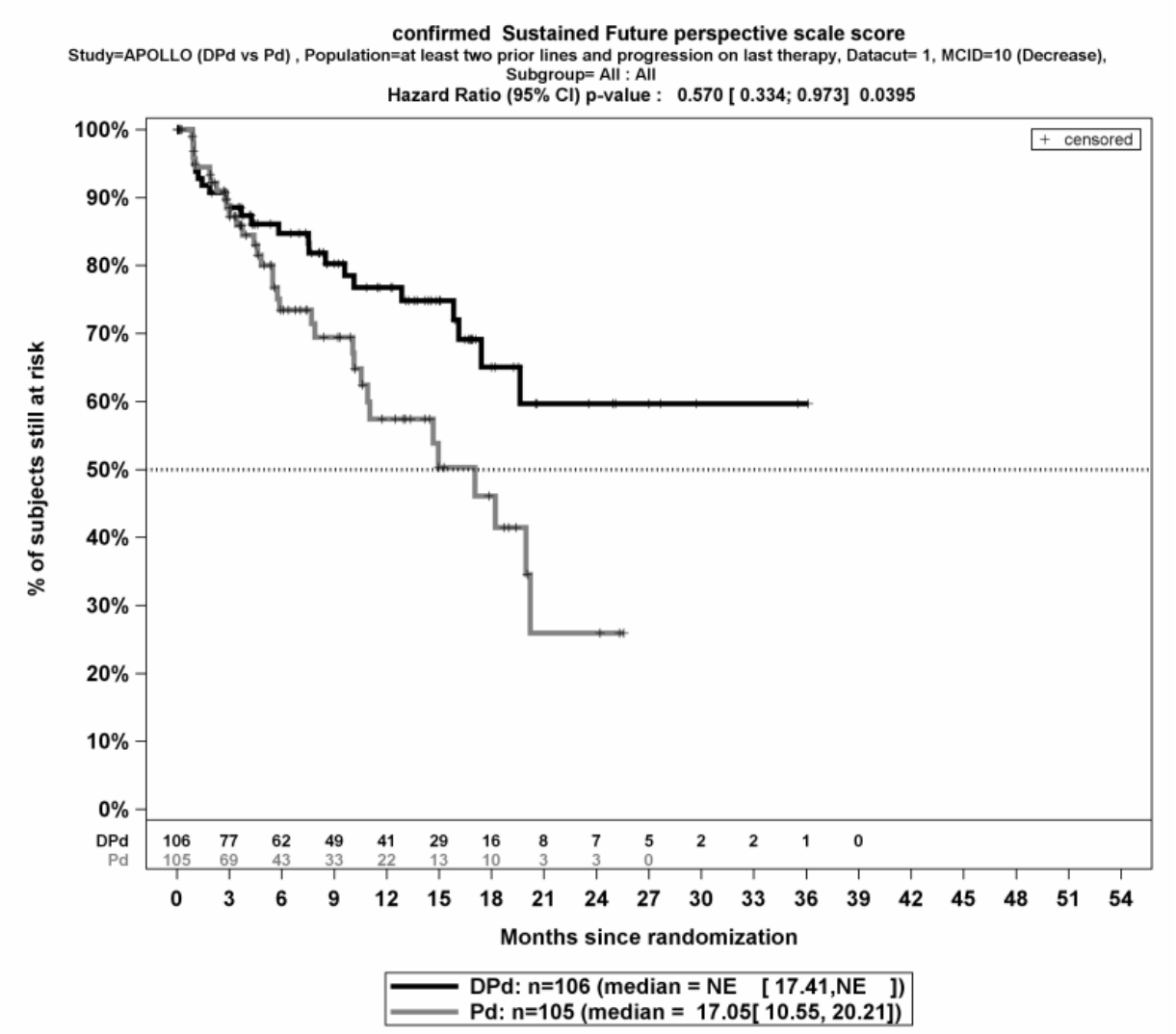

Figure 20: Kaplan-Meier curves on EORTC QLQ-MY20, future perspective, time to definitive deterioration by ≥ 10 points, APOLLO study, subpopulation of patients with ≥ 2 prior lines of therapy and disease progression on the most recent line of therapy (data cut-off: 21/07/2020)

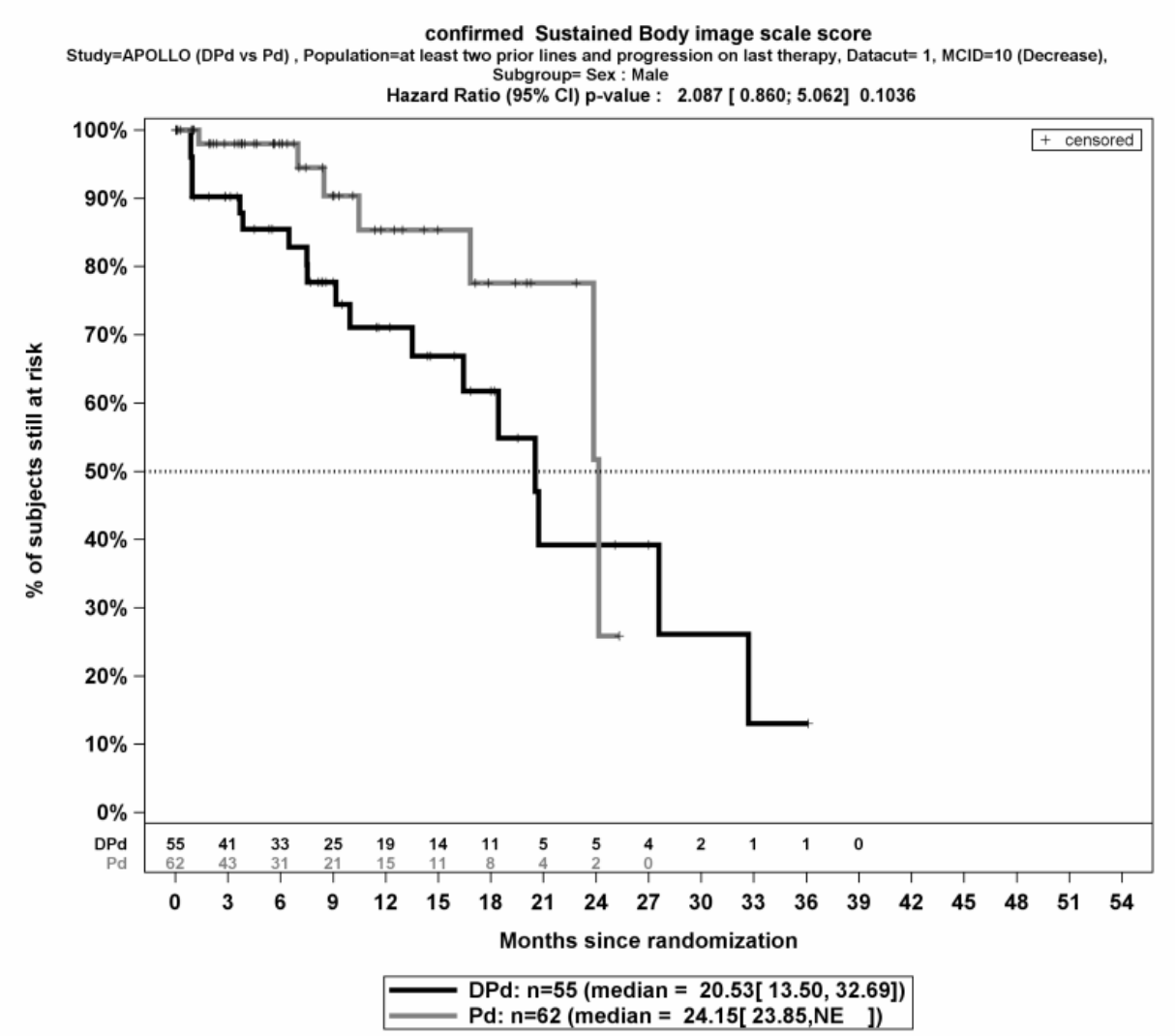

Figure 21: Kaplan-Meier curves on QLQ-MY20, body image, time to definitive deterioration by ≥ 10 points, subgroup analysis by sex (male), APOLLO study, subpopulation of patients with ≥ 2 prior lines of therapy and disease progression on the most recent line of therapy (data cut-off: 21/07/2020)

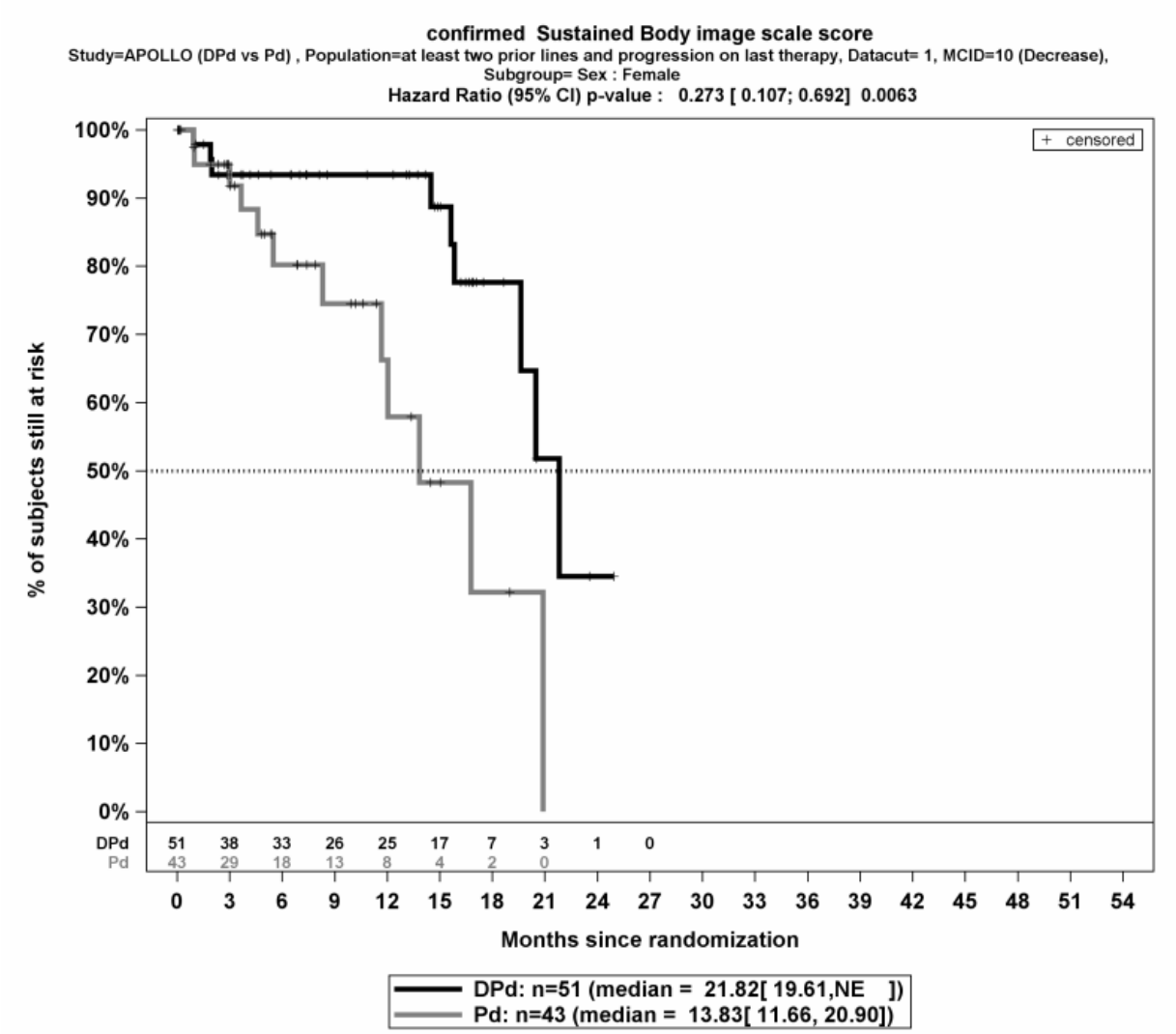

Figure 22: Kaplan-Meier curves on QLQ-MY20, body image, time to definitive deterioration by ≥ 10 points, subgroup analysis by sex (female), APOLLO study, subpopulation of patients with ≥ 2 prior lines of therapy and disease progression on the most recent line of therapy (data cut-off: 21/07/2020)

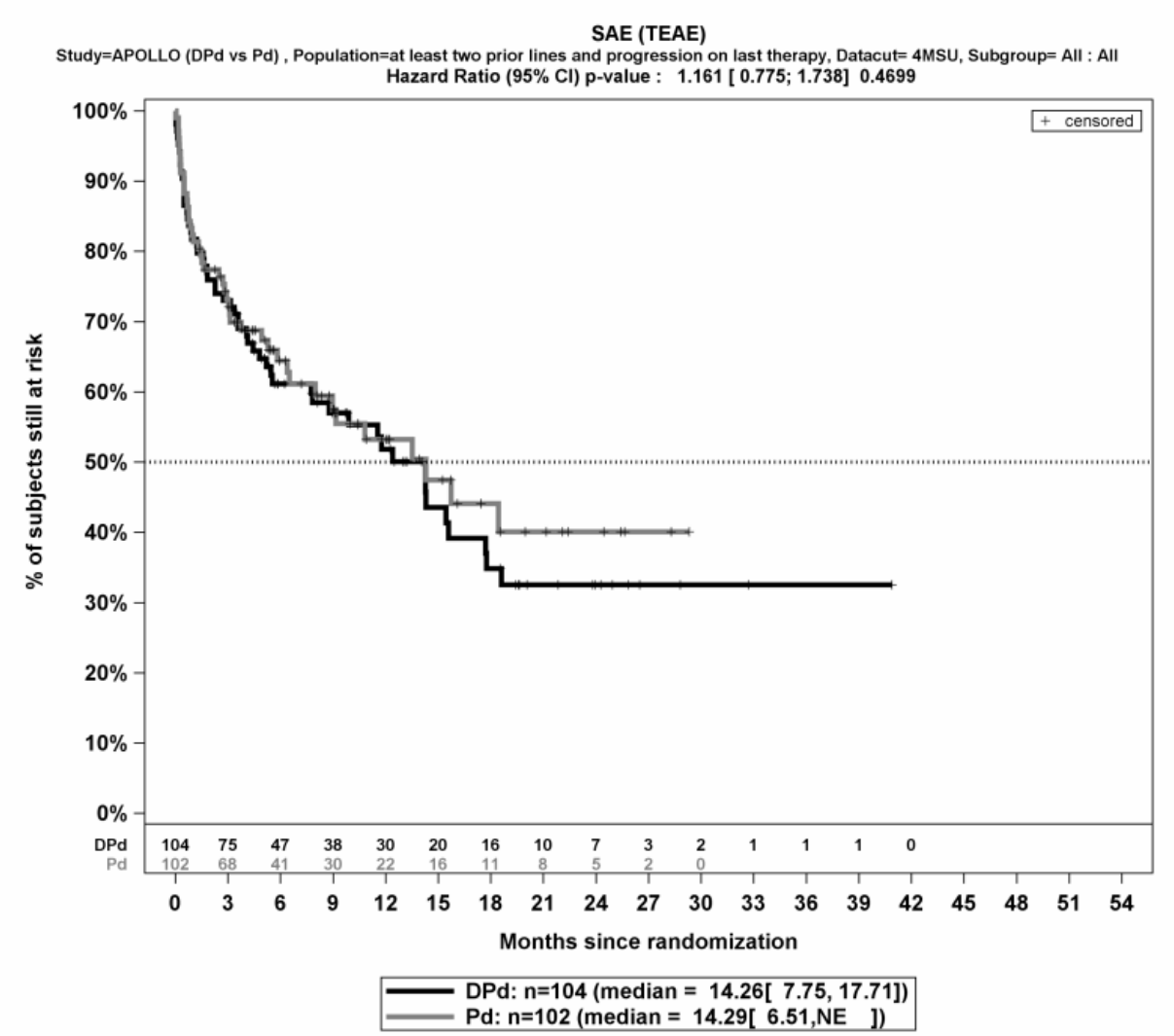

Figure 23: Kaplan-Meier curves on SAEs, APOLLO study, subpopulation of patients with ≥ 2 prior lines of therapy and disease progression on the most recent line of therapy (data cut-off: 15/11/2020)

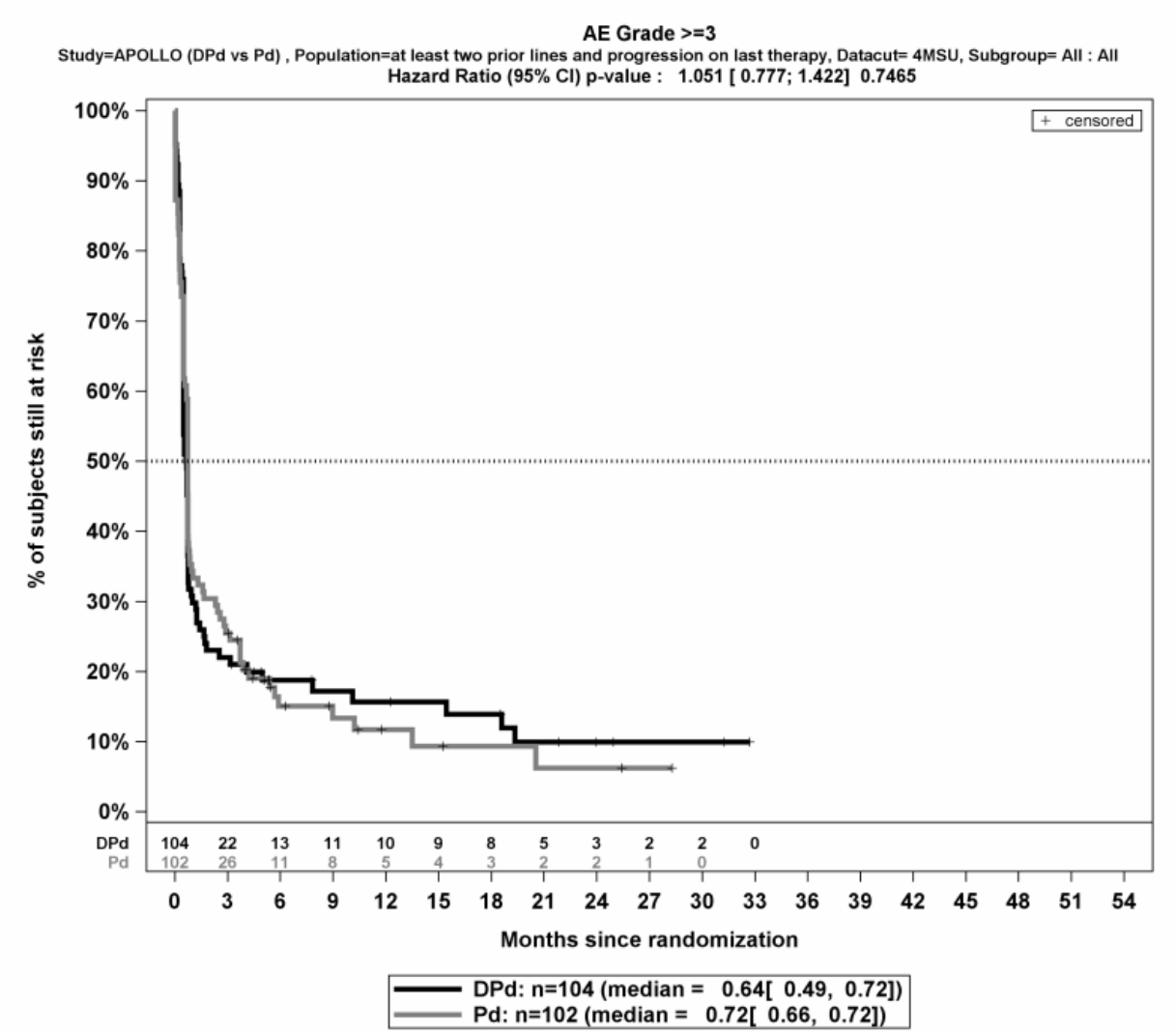

Figure 24: Kaplan-Meier curves on severe AEs (CTCAE grade ≥ 3), APOLLO study, subpopulation of patients with ≥ 2 prior lines of therapy and disease progression on the most recent line of therapy (data cut-off: 15/11/2020)

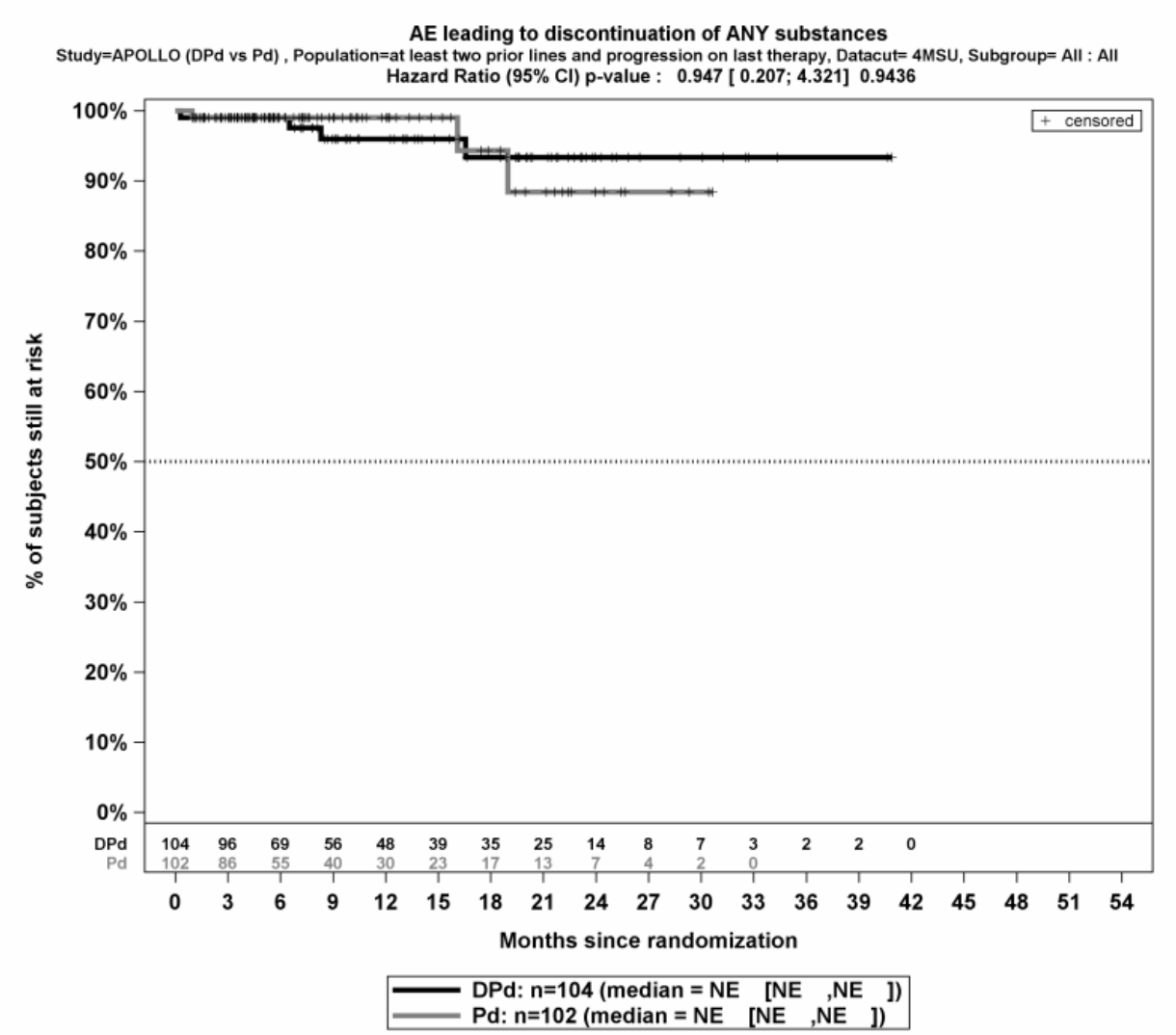

Figure 25: Kaplan-Meier curves on discontinuation due to AEs (≥ 1 drug component), APOLLO study, subpopulation of patients with ≥ 2 prior lines of therapy and disease progression on the most recent line of therapy (data cut-off: 15/11/2020)

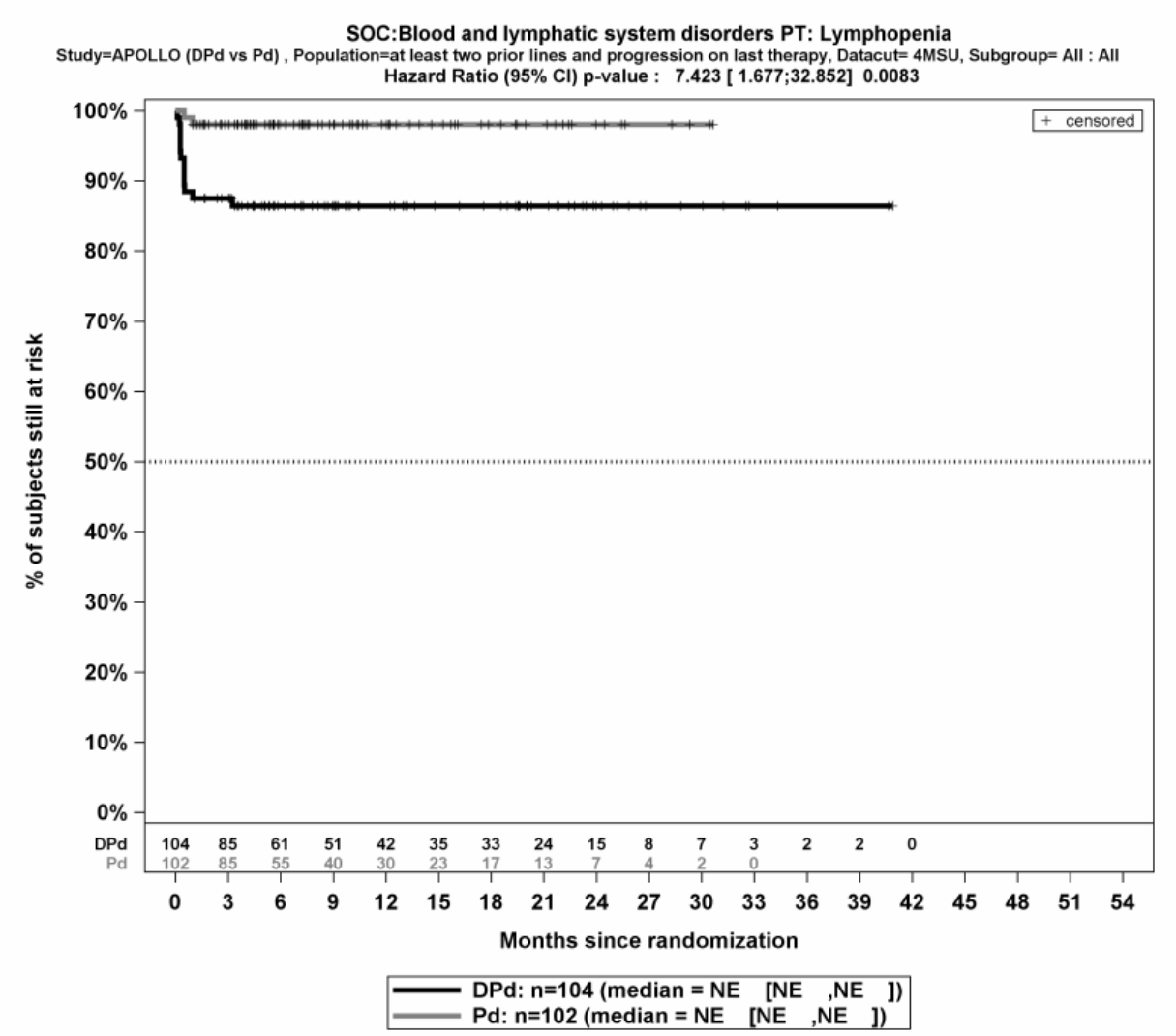

Figure 26: Kaplan-Meier curves on lymphopoenia (PT, severe AEs), APOLLO study, subpopulation of patients with ≥ 2 prior lines of therapy and disease progression on the most recent line of therapy (data cut-off: 15/11/2020)

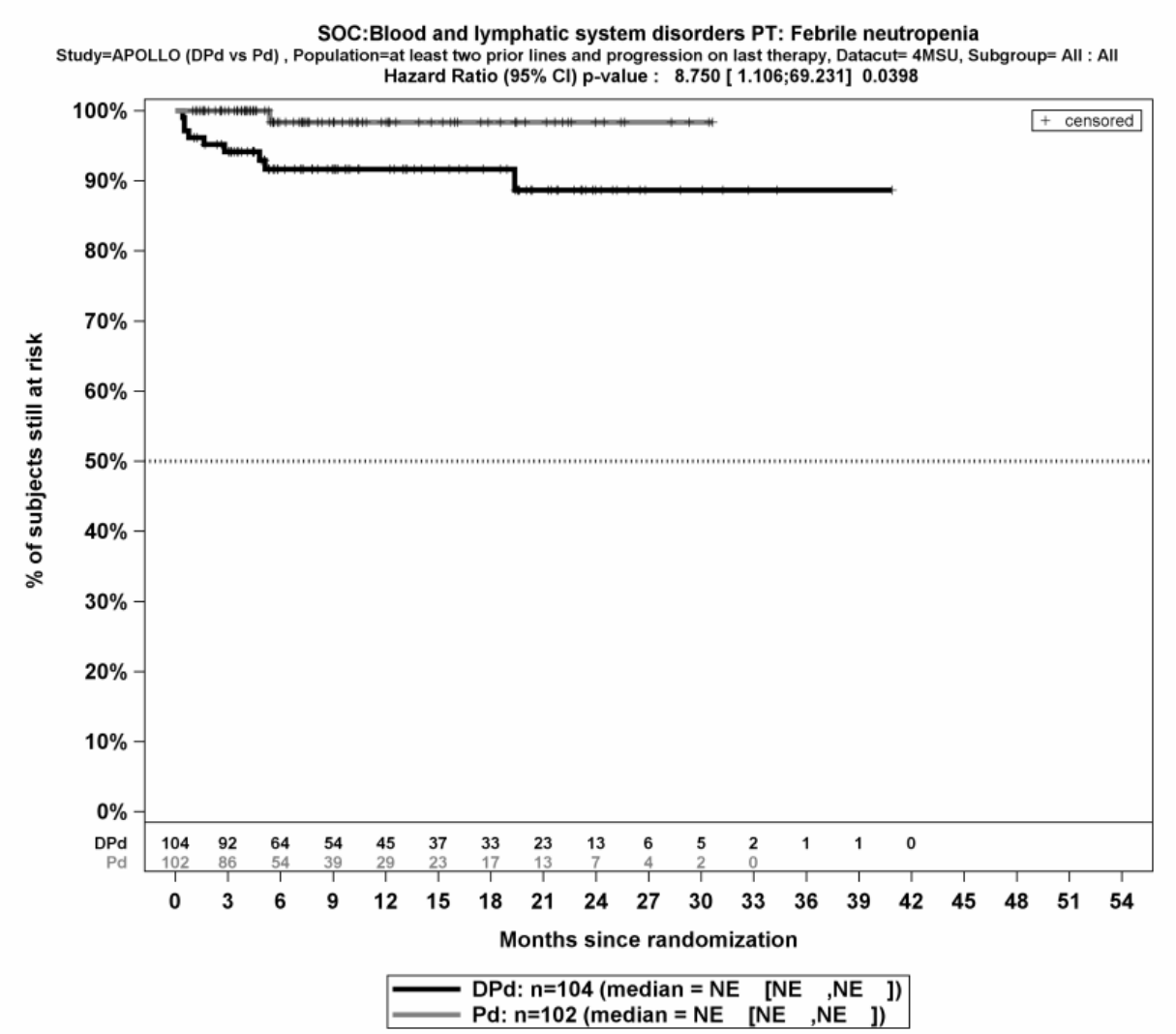

Figure 27: Kaplan-Meier curves on febrile neutropenia (PT, severe AEs), APOLLO study, subpopulation of patients with ≥ 2 prior lines of therapy and disease progression on the most recent line of therapy (data cut-off: 15/11/2020)