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Isatuximab (multiple myeloma after ≥ 2 prior therapies) –

Addendum to Commission A21-61[1]

Addendum

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List of abbreviations

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

1 Background

On 30 September 2021, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A21-61 (Isatuximab – Benefit assessment according to § 35a Social Code Book V) [1].

The ICARIA-MM study was included for assessing the benefit of isatuximab in combination with pomalidomide and dexamethasone (hereinafter referred to as "isatuximab + pomalidomide + dexamethasone") in comparison with the appropriate comparator therapy (ACT) in adult patients with relapsed and refractory multiple myeloma who have received at least 2 prior therapies including lenalidomide and a proteasome inhibitor and have demonstrated disease progression on the last therapy [1]. This open-label, randomized, controlled trial (RCT) compares isatuximab + pomalidomide + dexamethasone versus pomalidomide + dexamethasone. In the commenting procedure [2-4], the pharmaceutical company (hereinafter referred to as "company") subsequently submitted data and analyses which address points criticized in the benefit assessment.

The G-BA commissioned IQWiG with assessing the following additional data submitted by the company, taking into account the information provided in the dossier [5]:

- Analyses of "time to definitive deterioration" (European Organisation for Research and Treatment of Cancer [EORTC] Quality of Life Questionnaire Core 30 [QLQ-C30], EORTC Quality of Life Questionnaire Multiple Myeloma 20 [QLQ-MY20], European Quality of Life Questionnaire – 5 Dimensions [EQ-5D] visual analogue scale [VAS])
- Analyses of "time to discontinuation of 1 or more drug components" (2nd data cut-off)
- Subgroup analyses for the outcome of health status (EQ-5D VAS, responder analysis, 15 points)

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

2 Assessment

2.1 Subsequently submitted analyses

Time to definitive deterioration (EORTC QLQ-C30, EORTC QLQ-MY20, EQ-5D VAS)

For the patient-reported outcomes (PROs) on symptoms and health-related quality of life, surveyed by means of the EORTC QLQ-C30 and the EORTC QLQ – Multiple Myeloma 20 (MY20) as well as health status, surveyed by means of the EQ-5D VAS, the company's dossier [5] presented, among other things, results regarding time to definitive deterioration, but the dossier did not provide sufficient information on how the results were operationalized [1]. In dossier assessment A21-61, therefore, time to first deterioration was used for the EORTC scales and VAS (with a response criterion of ≥ 10 points [EORTC] or ≥ 15 points [EQ-5D VAS]; this corresponds to 15% of the scale range).

In the commenting procedure [2], the company supplied a more detailed description of the operationalization for this analysis as well as other analyses beyond the information provided in the dossier [2,3].

Accordingly, the operationalization of definitive deterioration used in the ICARIA-MM study includes patients who exhibited a change by at least the response threshold (10 points for EORTC QLQ-C30 and EORTC QLQ-MY20; 15 points for EQ-5D VAS) and were not below this threshold at subsequent measuring time points. This included patients without any documented values after the change by at least the response threshold, i.e. patients where the deterioration by at least the response threshold was observed at the last visit or the last available measuring time point [2]. In addition, the company subsequently submitted sensitivity analyses in which patients with a first deterioration by ≥ 15 points and no later data were rated as nonresponders.

The company's analyses submitted with the comments additionally show that the percentage of patients with a first deterioration and no later data varies by scale and equals up to 50% of events [2]. However, the subsequently submitted sensitivity analyses [3] which rated these patients as nonresponders show that, while the percentages of patients with first deterioration at the last visit or the last measuring time point was high in some cases, the overall results are consistent with those of definitive deterioration presented in Module 4 A.

Consequently, the dossier's analyses of time to definitive deterioration are used for the benefit assessment, replacing the previously used analyses of time to first deterioration. While both operationalizations are patient relevant, the operationalization of definitive deterioration is used because deterioration which persists for a certain period is deemed to be more relevant to patients by virtue of its persistence. Despite the more pronounced decrease of return rates in the control arm (see risk of bias section), definitive deterioration can be captured with sufficient certainty on the basis of the available evidence. Compared with the results on first deterioration (see dossier assessment A21-61), it is also unlikely for the analyses of definitive deterioration

to mask to a relevant extent any temporary deteriorations which may ameliorate or be treatable over the course of treatment.

Discontinuation due to adverse events (AEs) [2nd data cut-off]

Due to the operationalization of time to discontinuation of all components, the analyses of discontinuation due to AEs, as submitted by the company, were deemed unusable in benefit assessment A21-61 [1]. Instead, the operationalization of discontinuation of at least 1 drug component is deemed adequate because after the discontinuation of individual active substances, patients could continue treatment with the remaining active substances. In light of the present study design with 3 drug components in the intervention arm and 2 drug components in the control arm, discontinuation of all components can therefore not be meaningfully interpreted. Irrespective thereof, analyses of discontinuation of 1 or more drug components are to be preferred because any AE which leads to the discontinuation of a treatment component is relevant.

In the commenting procedure [3], the company subsequently submitted analyses of time to discontinuation of 1 or more components at data cut-off 2 (1 October 2020); this 2nd data cut-off was analysed in the dossier assessment for the side effects outcomes. Hence, these analyses were used for the benefit assessment.

2.2 Risk of bias

Risk of bias is deemed high for the results of patient-reported outcomes on symptoms (symptom scales of the EORTC QLQ-C30 and EORTC QLQ-MY20), health-related quality of life (functioning scales of the EORTC QLQ-C30 and EORTC QLQ-MY20) as well as health status (EQ-5D VAS). This is due to absence of blinding with subjective recording of outcomes as well as a decreasing questionnaire return rate, which also differed between treatment arms. This results in incomplete observations for potentially informative reasons.

Due to absence of blinding in the presence of subjective decision on treatment discontinuation, the risk of bias for the results of the outcome of discontinuation due to AEs is rated as high.

2.3 Results

Table 1 and Table 2 show the subsequently submitted analyses regarding time to definitive deterioration as well as discontinuation of at least 1 component for the outcome of discontinuation due to AEs. Definitive deterioration by ≥ 7 and ≥ 10 points, respectively, for the outcome of health status (EQ-5D VAS) is presented as supplementary information (see Appendix A). Where necessary, calculations conducted by IQWiG are provided in addition to the data from the company's dossier and comments. Kaplan-Meier curves related to the analyses are presented in Appendix B, if submitted by the company.

Table 1: Results – time to definitive[a] deterioration (morbidity, health-related quality of life, side effects) – RCT, direct comparison: isatuximab + pomalidomide + dexamethasone vs. pomalidomide + dexamethasone (multipage table)

Study Outcome category Outcome	Isatuximab + pomalidomide + dexamethasone		Pomalidomide + dexamethasone		Isatuximab + 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]
ICARIA-MM					
Morbidity					
Symptoms (EORTC QLQ-C30) – time to definitive[a] deterioration by ≥ 10 points[c]					
Fatigue	154	15.7 [11.7; NC] 59 (38.3)	153	NR [9.3; NC] 58 (37.9)	0.88 [0.61; 1.26]; 0.474
Nausea and vomiting	154	NR 19 (12.3)	153	NR 18 (11.8)	0.92 [0.48; 1.77]; 0.811
Pain	154	NR 34 (22.1)	153	NR 48 (31.4)	0.61 [0.39; 0.95]; 0.026
Dyspnoea	154	NR [15.7; NC] 44 (28.6)		NR 38 (24.8)	1.03 [0.66; 1.59]; 0.908
Sleeplessness	154	NR 30 (19.5)	154	NR 22 (14.4)	1.26 [0.73; 2.19]; 0.408
Appetite loss	154	NR 32 (20.8)	153	NR 26 (17.9)	1.11 [0.66; 1.87]; 0.682
Constipation	154	NR 25 (16.2)	153	NR 31 (20.3)	0.69 [0.40; 1.16]; 0.158
Diarrhoea	154	NR 9 (5.8)	153	NR 19 (12.4)	0.41 [0.18; 0.90]; 0.022
Symptoms (EORTC QLQ-MY20) – time to definitive[a] deterioration by ≥ 10 points[c]					
Symptoms of disease	154	NR 24 (15.6)	153	NR 33 (21.6)	0.61 [0.36; 1.03]; 0.062
Side effects	154	NR 28 (18.2)	153	NR 30 (19.6)	0.80 [0.48; 1.35]; 0.406
Health status (EQ-5D VAS) – time to definitive[a] deterioration by ≥ 15 points[d]					
EQ-5D VAS	154	NR 29 (18.8)	153	NR 32 (20.9)	0.79 [0.48; 1.30]; 0.351
Health-related quality of life (EORTC QLQ-C30) – time to definitive[a] deterioration by ≥ 10 points[d]					
Global health status	154	NR 44 (28.6)	153	NR 55 (35.9)	0.65 [0.43; 0.96]; 0.030
Physical functioning	154	NR 46 (29.9)	153	NR [14.7; NC] 48 (31.4)	0.80 [0.53; 1.20]; 0.275

Table 1: Results – time to definitive[a] deterioration (morbidity, health-related quality of life, side effects) – RCT, direct comparison: isatuximab + pomalidomide + dexamethasone vs. pomalidomide + dexamethasone (multipage table)

Study **Outcome category** **Outcome**	**Isatuximab + pomalidomide + dexamethasone**		**Pomalidomide + dexamethasone**		**Isatuximab + 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]**
Role functioning	154	NR 37 (24.0)	153	NR [9.5; NC] 60 (39.2)	0.50 [0.33; 0.76]; 0.001
Emotional functioning	154	NR 31 (20.1)	153	NR 28 (18.3)	0.95 [0.57; 1.59]; 0.859
Cognitive functioning	154	NR 37 (24.0)	153	NR 37 (24.2)	0.91 [0.58; 1.44]; 0.696
Social functioning	154	NR [14.8; NC] 46 (29.9)	153	NR 52 (34.0)	0.78 [0.52; 1.16]; 0.211
EORTC QLQ-MY20 – time to definitive[a] deterioration by ≥ 10 points[d]					
Body image	154	NR 23 (14.9)	153	NR 22 (14.4)	0.93 [0.52; 1.67]; 0.802
Future perspective	154	NR 34 (22.1)	153	NR [13.2; NC] 42 (27.5)	0.71 [0.45; 1.11]; 0.129

a. Definitive deterioration was operationalized as a change by at least the response threshold without subsequent improvement (which resulted in a change from baseline below the response threshold). The analysis includes patients whose deterioration was first identified at the last documented visit.
b. HR and CI are based on a stratified Cox proportional hazards model; p-value is based on a stratified log-rank test. Stratification factors include age (< 75 years vs. ≥ 75 years) and number of prior therapies (2 or 3 versus > 3) according to IRT.
c. Defined as a score increase by at least 10 points from baseline (scale range 0–100).
d. Defined as a score decrease by at least 10 points (EORTC) or at least 15 points (EQ-5D VAS) from baseline (scale range 0–100).

CI: confidence interval; 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; HR: hazard ratio; IRT: interactive response technology; n: number of patients with (at least 1) event; N: number of analysed patients; NC: not calculable; NR: not reached; RCT: randomized controlled trial; VAS: visual analogue scale

Table 2: Results (discontinuation due to AEs) – RCT, direct comparison: isatuximab + pomalidomide + dexamethasone vs. pomalidomide + dexamethasone

Study Outcome category Outcome	Isatuximab + pomalidomide + dexamethasone		Pomalidomide + dexamethasone		Isatuximab + 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][a]; p-value[b]
ICARIA-MM					
Side effects (data cut-off 2: 1/10/2020)					
Discontinuation due to AEs					
Discontinuation of ≥ 1 drug component(s)	152	NR 32 (21.1)	149	NR 25 (16.8)	1.20 [0.71; 2.03]; 0.491

a. Cox proportional hazards model stratified by age (< 75 years vs. ≥ 75 years) and number of prior therapies (2 or 3 versus > 3) according to IRT.
b. Log-rank test stratified by age (< 75 years vs. ≥ 75 years) and number of prior therapies (2 or 3 versus > 3) according to IRT.

AE: adverse event; CI: confidence interval; HR: hazard ratio; IRT: interactive response technology; n: number of patients with (at least 1) event; N: number of analysed patients; NC: not calculable; NR: not reached ; RCT: randomized controlled trial

Due to the high risk of bias, the available data can be used to derive at most hints, e.g. of added benefit, for morbidity and health-related quality of life outcomes as well as for the outcome of discontinuation due to AEs.

Morbidity

Symptoms (EORTC QLQ-C30 and EORTC QLQ-MY20)

Symptoms outcomes were surveyed using the disease-specific instruments EORTC QLQ-C30 and EORTC QLQ-MY20. Time to definitive deterioration by ≥ 10 points (scale range 0–100) was analysed.

Fatigue, nausea and vomiting, sleeplessness, appetite loss, constipation

For these EORTC QLQ-C30 outcomes, no statistically significant differences between treatment groups were found. Consequently, there is no hint of added benefit of isatuximab + pomalidomide + dexamethasone in comparison with pomalidomide + dexamethasone for any of them; an added benefit is therefore not proven.

Pain

For the outcome of pain of the EORTC QLQ-C30 symptom scales, a statistically significant difference between treatment groups was found in favour of isatuximab + pomalidomide + dexamethasone in comparison with pomalidomide + dexamethasone. The identified effect is no more than marginal for an outcome in the non-serious/non-severe symptoms / late complications category. This results in no hint of added benefit of isatuximab + pomalidomide + dexamethasone in comparison with pomalidomide + dexamethasone; an added benefit is therefore not proven.

Dyspnoea

For the EORTC QLQ-C30 symptom item of dyspnoea, no statistically significant difference between treatment groups was found for the total population. However, there is an effect modification by age (aggregated subgroup age < 75 versus ≥ 75 years). For patients ≥ 75 years of age, a statistically significant difference between treatment groups was found in favour of isatuximab + pomalidomide + dexamethasone in comparison with pomalidomide + dexamethasone. For this patient group, there is therefore a hint of added benefit of isatuximab + pomalidomide + dexamethasone in comparison with pomalidomide + dexamethasone. For patients < 75 years of age, in contrast, no statistically significant difference was found. Consequently, there is no hint of added benefit of isatuximab + pomalidomide + dexamethasone in comparison with pomalidomide + dexamethasone for this group of patients (see Section 2.4).

Diarrhoea

For the EORTC QLQ-C30 symptom item of diarrhoea, a statistically significant difference between treatment groups was found in favour of isatuximab + pomalidomide + dexamethasone versus pomalidomide + dexamethasone. The identified effect is no more than marginal for an outcome in the non-serious/non-severe symptoms / late complications category. This results in no hint of added benefit of isatuximab + pomalidomide + dexamethasone in comparison with pomalidomide + dexamethasone; an added benefit is therefore not proven.

Disease symptoms, side effects

No statistically significant differences between treatment groups were found for any of the symptoms outcomes of EORTC QLQ-MY20. This results in no hint of added benefit of isatuximab + pomalidomide + dexamethasone in comparison with pomalidomide + dexamethasone for any of them; an added benefit is therefore not proven.

Health status (EQ-5D VAS)

For the outcome of health status (as measured using EQ-5D VAS), the analysis of time until definitive deterioration by ≥ 15 points (scale range 0–100) was used. No statistically significant difference between treatment groups was found. This results in no hint of added benefit of isatuximab + pomalidomide + dexamethasone in comparison with pomalidomide + dexamethasone; an added benefit is therefore not proven.

Health-related quality of life

The outcomes for health-related quality of life were surveyed using the disease-specific instruments EORTC QLQ-C30 and EORTC QLQ-MY20. Time to definitive deterioration by ≥ 10 points (scale range 0–100) was analysed.

Physical functioning, emotional functioning, cognitive functioning

For the listed EORTC QLQ-C30 outcomes on health-related quality of life, no statistically significant differences between treatment groups were found. This results in no hint of added benefit of isatuximab + pomalidomide + dexamethasone in comparison with pomalidomide + dexamethasone; an added benefit is therefore not proven.

Global health status

For the outcome of global health status, a statistically significant difference between treatment groups was found in favour of isatuximab + pomalidomide + dexamethasone in comparison of pomalidomide + dexamethasone. Consequently, there is a hint of added benefit of isatuximab + pomalidomide + dexamethasone in comparison with pomalidomide + dexamethasone.

Role functioning

For the outcome of role functioning, a statistically significant difference between treatment groups was found in favour of isatuximab + pomalidomide + dexamethasone in comparison with pomalidomide + dexamethasone. Consequently, there is a hint of added benefit of isatuximab + pomalidomide + dexamethasone in comparison with pomalidomide + dexamethasone.

Social functioning

For the outcome of social functioning, no statistically significant difference between treatment arms was found in the total population. However, there is an effect modification by age (aggregated subgroup age < 75 versus ≥ 75 years). For patients ≥ 75 years of age, a statistically significant difference between treatment groups was found in favour of isatuximab + pomalidomide + dexamethasone. For this patient group, there is therefore a hint of added benefit of isatuximab + pomalidomide + dexamethasone in comparison with pomalidomide + dexamethasone. For patients < 75 years of age, in contrast, no statistically significant difference was found between treatment groups. Consequently, there is no hint of added benefit of isatuximab + pomalidomide + dexamethasone in comparison with pomalidomide + dexamethasone for this group of patients (see Section 2.4).

Body image, future perspective

No statistically significant differences between treatment groups were found for any of the listed EORTC QLQ-MY20 outcomes on health-related quality of life. This results in no hint of added benefit of isatuximab + pomalidomide + dexamethasone in comparison with pomalidomide + dexamethasone for any of them; an added benefit is therefore not proven.

Side effects

Discontinuation due to AEs

For the outcome of discontinuation due to AEs, no statistically significant difference between treatment groups was found. Consequently, there is no hint of added benefit of isatuximab + pomalidomide + dexamethasone in comparison with pomalidomide + dexamethasone; an added benefit is therefore not proven.

2.4 Subgroups and other effect modifiers

For the addendum, subgroups and other effect modifiers were analysed as in the benefit assessment [1].

Table 3 shows the results of the subgroup analyses for the comparison of isatuximab + pomalidomide + dexamethasone versus pomalidomide + dexamethasone.

Only results showing an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are presented only if there is a statistically significant and relevant effect in at least 1 subgroup. The analysis also took into account the subgroup analyses on definitive deterioration in EQ-5D VAS, which the company subsequently submitted during the commenting procedure (see Section 2.4.1); no effect modifications with statistically significant interaction were found. The company did not submit any subgroup analyses for the analyses of the outcome of discontinuation due to AEs, which were subsequently submitted with the comments.

Table 3: Results (morbidity[a], health-related quality of life[a] – time to event) – RCT, direct comparison: isatuximab + pomalidomide + dexamethasone vs. pomalidomide + dexamethasone (multipage table)

Study **Outcome** **Characteristic** **Subgroup**	**Isatuximab + pomalidomide + dexamethasone**		**Pomalidomide + dexamethasone**		**Isatuximab + 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[c]**
ICARIA-MM						
EORTC QLQ C30 dyspnoea (data cut-off 1)[d]						
Age						
< 75 years[e]	122[f]	ND 38 (31.1)[f]	124[f]	ND 27 (21.8)[f]	1.45 [0.88; 2.39][g]	0.147[g]
< 65 years	*54*	*15.7 [7.43; NC]* *20 (37.0)*	*70*	*NR [14.7; NC]* *18 (25.7)*	*1.44 [0.76; 2.74]*	*0.258*
65–75 years	*68*	*NR* *18 (26.5)*	*54*	*NR* *9 (16.7)*	*1.46 [0.66; 3.26]*	*0.349*
≥ 75 years	32	NR [11.2; NC] 6 (18.8)	29	NR [4.7; NC] 11 (37.9)	0.33 [0.12; 0.89]	0.021
Total					Interaction:	0.036[b, h]
EORTC QLQ C30 social functioning (data cut-off 1)[i]						
Age						
< 75 years[e]	122[f]	ND 41 (33.6)[f]	124[f]	ND 38 (30.6)[f]	1.06 [0.68; 1.65][g]	0.806[g]
< 65 years	*54*	*14.8 [7.4; NC]* *21 (38.9)*	*70*	*NR [12.1; NC]* *22 (31.4)*	*1.24 [0.68; 2.25]*	*0.487*
65–75 years	*68*	*NR* *20 (29.4)*	*54*	*NR* *16 (29.6)*	*0.87 [0.45; 1.69]*	*0.687*
≥ 75 years	32	NR [13.7; NC] 5 (15.6)	29	4.9 [1.3; NC] 14 (48.3)	0.23 [0.08; 0.65]	0.003
Total					Interaction:	0.014[b, h]

Table 3: Results (morbidity[a], health-related quality of life[a] – time to event) – RCT, direct comparison: isatuximab + pomalidomide + dexamethasone vs. pomalidomide + dexamethasone (multipage table)

Study Outcome Characteristic Subgroup	Isatuximab + pomalidomide + dexamethasone		Pomalidomide + dexamethasone		Isatuximab + 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[c]

a. Time to definitive deterioration, operationalized as change by at least the response threshold without subsequent improvement (which would result in a change from baseline below the response threshold). The analysis includes patients whose deterioration was first identified at the last documented visit.
b. Nonstratified Cox proportional hazards model with the factors of treatment, subgroup attribute, and interaction between treatment and subgroup attribute.
c. By means of nonstratified log rank test.
d. Defined as a score increase by at least 10 points from baseline (scale range 0–100).
e. Combination of the subgroups < 65 years and 65–75 years since no interaction was found in paired comparison.
f. IQWiG calculations.
g. IQWiG calculations: metaanalytical summary of subgroup results for age groups < 65 years and 65 to 75 years (model with fixed effect).
h. Relative to the original 3 subgroups.
i. Defined as a score decrease by at least 10 points from baseline (scale range 0–100).

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

Morbidity

EORTC QLQ-C30

Dyspnoea

The available subgroup analyses show an effect modification for the outcome of dyspnoea by the attribute of age (< 65 years versus 65 to 75 years versus ≥ 75 years). Given the available evidence, the subgroups with homogeneous effects (ages < 65 years and 65 to 75 years) were aggregated (see Figure 20 in Annex B.4).

There was no statistically significant difference between treatment arms for the aggregated subgroup of patients aged < 65 years and 65 to 75 years. For the subgroup ≥ 75 years, a statistically significant difference between treatment groups was found in favour of isatuximab + pomalidomide + dexamethasone in comparison with pomalidomide + dexamethasone. For the subgroup of patients < 75 years, this results in a hint of added benefit of isatuximab + pomalidomide + dexamethasone in comparison with pomalidomide + dexamethasone. For the subgroup of patients ≥ 75 years of age, in contrast, this results in a hint of added benefit of

isatuximab + pomalidomide + dexamethasone in comparison with pomalidomide + dexamethasone.

Health-related quality of life

EORTC QLQ-C30

Social functioning

The available subgroup analyses show an effect modification for the outcome of dyspnoea by the attribute of age (< 65 years versus 65 to 75 years versus ≥ 75 years). Given the available evidence, the subgroups with homogeneous effects (ages < 65 years and 65 to 75 years) were aggregated (see Figure 21 in Annex B.4).

There was no statistically significant difference between treatment arms for the aggregated subgroup of patients aged < 65 years and 65 to 75 years. For the subgroup ≥ 75 years, a statistically significant difference between treatment groups was found in favour of isatuximab + pomalidomide + dexamethasone in comparison with pomalidomide + dexamethasone. For the subgroup of patients < 75 years, this results in a hint of added benefit of isatuximab + pomalidomide + dexamethasone in comparison with pomalidomide + dexamethasone. For the subgroup of patients ≥ 75 years of age, in contrast, there is a hint of added benefit of isatuximab + pomalidomide + dexamethasone in comparison with pomalidomide + dexamethasone.

2.4.1 Subsequently submitted subgroups for the outcome of health status (EQ-5D VAS)

In the ICARIA-MM study, the PRO of health status was surveyed using the EQ-5D VAS instrument. For this purpose, the company's dossier [5] presented responder analyses for time to achieve a change by ≥ 7, ≥ 10 and ≥ 15 points in various operationalizations. In the dossier assessment, the response criterion of ≥ 15 points (corresponding to 15% of the scale range) was used for deriving added benefit. In addition, the dossier assessment used time to first deterioration due to uncertainties in the operationalization of definitive deterioration. The dossier provided no subgroup analyses for the response criterion ≥ 15 points. Along with its comments, the company now submitted these analyses for all operationalizations in the dossier [4].

For the outcome of health status, the subsequently submitted data reveal changes regarding the operationalization used (see Section 2.1). Hence, the subsequently submitted subgroup analyses are analysed together with the analyses of time to definitive deterioration (see Section 2.4).

2.5 Assessment of added benefit at outcome level (subsequently submitted analyses)

Table 4 shows the probability and extent of added benefit for the subsequently submitted analyses.

Determination of the outcome category for symptom outcomes

For the outcomes below, it cannot be directly inferred from the dossier or the comments whether they were serious/severe or non-serious/non-severe. The allocation of these outcomes is explained below.

Symptoms

Dyspnoea, pain, diarrhoea (EORTC QLQ-C30)

For the outcomes of pain, diarrhoea, and dyspnoea, none of the available information would lead to a severity classification as serious/severe. Therefore, the outcomes were assigned to the outcome category of non-serious/non-severe symptoms/late complications.

Table 4: Extent of added benefit at outcome level (subsequently submitted analyses): isatuximab + pomalidomide + dexamethasone vs. pomalidomide + dexamethasone (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Isatuximab + pomalidomide + dexamethasone vs. pomalidomide + dexamethasone** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability[a]**	**Derivation of extent[b]**
Symptoms		
EORTC QLQ-C30 – time to definitive deterioration by ≥ 10 points		
Fatigue	15.7 vs. NR HR: 0.88 [0.61; 1.26]; p = 0.474	Lesser/added benefit not proven
Nausea and vomiting	NR vs. NR HR: 0.92 [0.48; 1.77]; p = 0.811	Lesser/added benefit not proven
Pain	NR vs. NR HR: 0.61 [0.39; 0.95]; p = 0.026	Outcome category: non-serious/non-severe symptoms / late complications $0.90 \leq CI_u < 1.00$ Lesser/added benefit not proven[c]
Dyspnoea		
Age		
< 75 years	ND vs. ND HR: 1.45 [0.88; 2.39] p = 0.147	Lesser/added benefit not proven
≥ 75 years	NR vs. NR HR: 0.33 [0.12; 0.89]; p = 0.021 Probability: hint	Outcome category: non-serious/non-severe symptoms / late complications $0.80 \leq CI_u < 0.90$ Added benefit; extent: minor
Sleeplessness	NR vs. NR HR: 1.26 [0.73; 2.19]; p = 0.408	Lesser/added benefit not proven
Appetite loss	NR vs. NR HR: 1.11 [0.66; 1.87]; p = 0.682	Lesser/added benefit not proven
Constipation	NR vs. NR HR: 0.69 [0.40; 1.16]; p = 0.158	Lesser/added benefit not proven
Diarrhoea	NR vs. NR HR: 0.41 [0.18; 0.90] p = 0.022	Outcome category: non-serious/non-severe symptoms / late complications $0.90 \leq CI_u < 1.00$ Lesser/added benefit not proven[c]

Table 4: Extent of added benefit at outcome level (subsequently submitted analyses): isatuximab + pomalidomide + dexamethasone vs. pomalidomide + dexamethasone (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Isatuximab + pomalidomide + dexamethasone vs. pomalidomide + dexamethasone** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability[a]**	**Derivation of extent[b]**
EORTC QLQ-MY20 – time to definitive deterioration by ≥ 10 points		
Symptoms of disease	NR vs. NR HR: 0.61 [0.36; 1.03]; p = 0.062	Lesser/added benefit not proven
Side effects	NR vs. NR HR: 0.80 [0.48; 1.35]; p = 0.406	Lesser/added benefit not proven
Health status (EQ-5D VAS) – time to definitive deterioration by ≥ 15 points		
EQ-5D VAS	NR vs. NR HR: 0.79 [0.48; 1.30]; p = 0.351	Lesser/added benefit not proven
Health-related quality of life		
EORTC QLQ-C30 – time to definitive deterioration by ≥ 10 points		
Global health status	NR vs. NR HR: 0.65 [0.43; 0.96]; p = 0.030 Probability: hint	Outcome category health-related quality of life $0.90 \leq CI_u < 1.00$ Added benefit, extent: minor
Physical functioning	NR vs. NR HR: 0.80 [0.53; 1.20]; p = 0.275	Lesser/added benefit not proven
Role functioning	NR vs. NR HR: 0.50 [0.33; 0.76]; p = 0.001 Probability: hint	Outcome category health-related quality of life $0.75 \leq CI_u < 0.90$ Added benefit; extent: considerable
Emotional functioning	NR vs. NR HR: 0.95 [0.57; 1.59]; p = 0.859	Lesser/added benefit not proven
Cognitive functioning	NR vs. NR HR: 0.91 [0.58; 1.44]; p = 0.696	Lesser/added benefit not proven

Table 4: Extent of added benefit at outcome level (subsequently submitted analyses): isatuximab + pomalidomide + dexamethasone vs. pomalidomide + dexamethasone (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Isatuximab + pomalidomide + dexamethasone vs. pomalidomide + dexamethasone** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Social functioning		
Age		
< 75 years	ND vs. ND HR: 1.06 [0.68; 1.65]; p = 0.806	Lesser/added benefit not proven
≥ 75 years	NR vs. NR HR: 0.23 [0.08; 0.65]; p = 0.003 Probability: hint	Outcome category: health-related quality of life CI_u < 0.75, risk ≥ 5% Added benefit; extent: major
EORTC QLQ-MY20 – time to definitive deterioration by ≥ 10 points		
Body image	NR vs. NR HR: 0.93 [0.52; 1.67]; p = 0.802	Lesser/added benefit not proven
Future perspective	NR vs. NR HR: 0.71 [0.45; 1.11]; p = 0.129	Lesser/added benefit not proven
Side effects		
Discontinuation due to AEs	NR vs. NR HR: 1.63 [0.97; 2.72]; p = 0.062	Greater/lesser harm not proven

a. Probability is stated whenever a statistically significant and relevant effect is present.
b. Estimations of effect size are made depending on the outcome category, with different limits according to the upper limit of the confidence interval (CI_u).
c. The extent of the effect is no more than marginal for this non-serious/non-severe outcome.

AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life Questionnaire – 5 Dimensions; HR: hazard ratio; ND: no data; NR: not reached; QLQ-C30: Quality of Life Questionnaire Core 30; QLQ-MY20: Quality of Life Questionnaire Myeloma 20; R-ISS: Revised International Staging System; SAE: serious adverse event; VAS: visual analogue scale

Table 5 contrasts favourable and unfavourable effects from the assessment of isatuximab + pomalidomide + dexamethasone.

Table 5: Favourable and unfavourable effects from the assessment of isatuximab + pomalidomide + dexamethasone in comparison with pomalidomide + dexamethasone

Favourable effects	Unfavourable effects
Non-serious/non-severe symptoms / late complications ▪ **Dyspnoea** ▫ **Age ≥ 75 years** **Hint of added benefit – extent: minor**	–
Health-related quality of life ▪ **Global health status: hint of added benefit – extent: minor** ▪ **Role functioning: hint of added benefit – extent: considerable** ▪ **Social functioning** ▫ **Age ≥ 75 years** **Hint of added benefit – extent: major**	–
–	Serious/severe side effects ▪ Severe AEs: hint of greater harm – extent: considerable ▫ Specific AEs: - Disorders of the blood and lymphatic system: Hint of greater harm – extent: considerable
–	Non-serious/non-severe side effects ▪ Specific AEs: ▫ Bronchitis, hint of greater harm – extent: considerable
Results printed in **bold** are based on the analyses subsequently submitted by the company with the written comment. Results crossed out served as the basis of the benefit assessment but are now disregarded due to the changes in the evidence situation from the comment.	
No data are available on infusion-related reactions or from data cut-off 2 for the outcomes on morbidity and health-related quality of life.	
AEs: adverse events	

For the analysis of time to definitive deterioration, the present addendum reveals several favourable effects in the outcomes of morbidity and health-related quality of life, with 2 of the effects (dyspnoea, social functioning) manifesting only in the population of patients 75 years and older. However, these 2 effects do not lead to separate conclusions in terms of added benefit being drawn for different patient groups. Firstly, no sensitivity analyses which could support the analysis of definitive deterioration are available on these subgroup analyses (see Section 2.1). Secondly, the intervention's advantages regarding the EORTC scale of dyspnoea cannot be unequivocally interpreted given the absence of analyses of infusion-related reactions (common in the intervention arm, about half of them being dyspnoea; see Table 28 of dossier assessment A21-61). Interpretability is further limited by the EORTC surveys being ill-timed for documenting the effects of infusion-related reactions (such as dyspnoea) because the scales are surveyed at a later point after infusion and infusion-related symptoms consequently occur outside the time period queried by the questionnaire (see dossier assessment A21-61, p.29).

Overall, the evidence available in the addendum shows that the favourable effects regarding health-related quality of life for the total population (global health status – minor extent; role functioning – considerable extent) are offset by the unfavourable effects regarding side effects (disadvantage of considerable extent). This weighing of effects also takes into account the continued lack of data at the 2nd data cut-off regarding symptoms and health-related quality of life.

Therefore, no added benefit of isatuximab + pomalidomide + dexamethasone was found in comparison with pomalidomide + dexamethasone for adults with relapsed and refractory multiple myeloma who have received at least 2 prior therapies including lenalidomide and a proteasome inhibitor and have demonstrated disease progression on the last therapy.

2.6 Summary

The data subsequently submitted by the company in the commenting procedure do not change the conclusion drawn on the added benefit of isatuximab + pomalidomide + dexamethasone in dossier assessment A21-61.

Table 6 below shows the result of the benefit assessment of isatuximab + pomalidomide + dexamethasone taking into account both dossier assessment A21-61 and the present addendum.

Table 6: Isatuximab + pomalidomide + dexamethasone – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit[b]**
Adult patients with relapsed and refractory multiple myeloma who have received at least 2 prior therapies including lenalidomide and a proteasome inhibitor and have demonstrated disease progression on the last therapy[c]	▪ Bortezomib in combination with dexamethasone or ▪ Lenalidomide in combination with dexamethasone or ▪ **Pomalidomide in combination with dexamethasone** or ▪ Elotuzumab in combination with lenalidomide and dexamethasone or ▪ Elotuzumab in combination with pomalidomide and dexamethasone 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 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 by the company is marked in **bold**.
b. Changes in comparison with dossier assessment A21-61 are shown in **bold**.
c. High-dose chemotherapy with stem cell transplantation is assumed not to be an option for the patients at the time of the current therapy.

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

The G-BA decides on the added benefit.

3 References

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Isatuximab (multiples Myelom nach ≥ 2 Vortherapien) – Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung [online]. 2021 [Accessed: 17.08.2021]. URL: https://www.iqwig.de/download/a21-61_isatuximab_nutzenbewertung-35a-sgb-v_v1-0.pdf.

2. Sanofi-Aventis. Stellungnahme zum IQWiG-Bericht Nr. 1176: Isatuximab (multiples Myelom nach ≥ 2 Vortherapien); Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung. [Soon available under: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/687/#beschluesse in the document "Zusammenfassende Dokumentation"].

3. Sanofi-Aventis. Nachreichung zur Stellungnahme zum IQWiG-Bericht Nr. 1176: Isatuximab (multiples Myelom nach ≥ 2 Vortherapien); Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung. [Soon available under: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/687/#beschluesse in the document "Zusammenfassende Dokumentation"].

4. Sanofi-Aventis. Zusatzanalysen eingereicht mit der Stellungnahme zum IQWiG-Bericht Nr. 1176: Isatuximab (multiples Myelom nach ≥ 2 Vortherapien); Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung [unpublished].

5. Sanofi-Aventis. Isatuximab (SARCLISA); Dossier zur Nutzenbewertung gemäß § 35a SGB V [online]. 2021 [Accessed: 25.08.2021]. URL: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/687/#dossier.

Appendix A Supplementary presentation of responder analyses of EQ-5D VAS

Table 7: Results – time to definitive[a] deterioration (health status – supplementary presentation) – RCT, direct comparison: isatuximab + pomalidomide + dexamethasone vs. pomalidomide + dexamethasone

Study Outcome category Outcome	Isatuximab + pomalidomide + dexamethasone		Pomalidomide + dexamethasone		Isatuximab + 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]
ICARIA-MM					
Morbidity					
Health status (EQ-5D VAS) – time to definitive[a] deterioration[c]					
7 points	154	NR [15.5; NC] 49 (31.8)	153	NR [12.0; NC] 54 (35.3)	0.74 [0.50; 1.09]; 0.127
10 points	154	NR [15.5; NC] 44 (28.6)	153	NR 45 (29.4)	0.81 [0.53; 1.22]; 0.310

a. Definitive deterioration was operationalized as change by at least the response threshold without subsequent improvement (which resulted in a change from baseline below the response threshold). The analysis also includes patients whose deterioration occurred at the last documented visit.
b. HR and CI are based on a stratified Cox proportional hazards model; p-value is based on a stratified log-rank test. Stratification factors include age (< 75 years vs. ≥ 75 years) and number of prior therapies (2 or 3 versus > 3) according to IRT.
c. Defined as a score decrease by at least 7 or 10 points from baseline (scale range 0–100).

CI: confidence interval; HR: hazard ratio; IRT: interactive response technology; n: number of patients with event; N: number of analysed patients; RCT: randomized controlled trial; VAS: visual analogue scale

Appendix B Figures on outcome analyses

B.1Morbidity

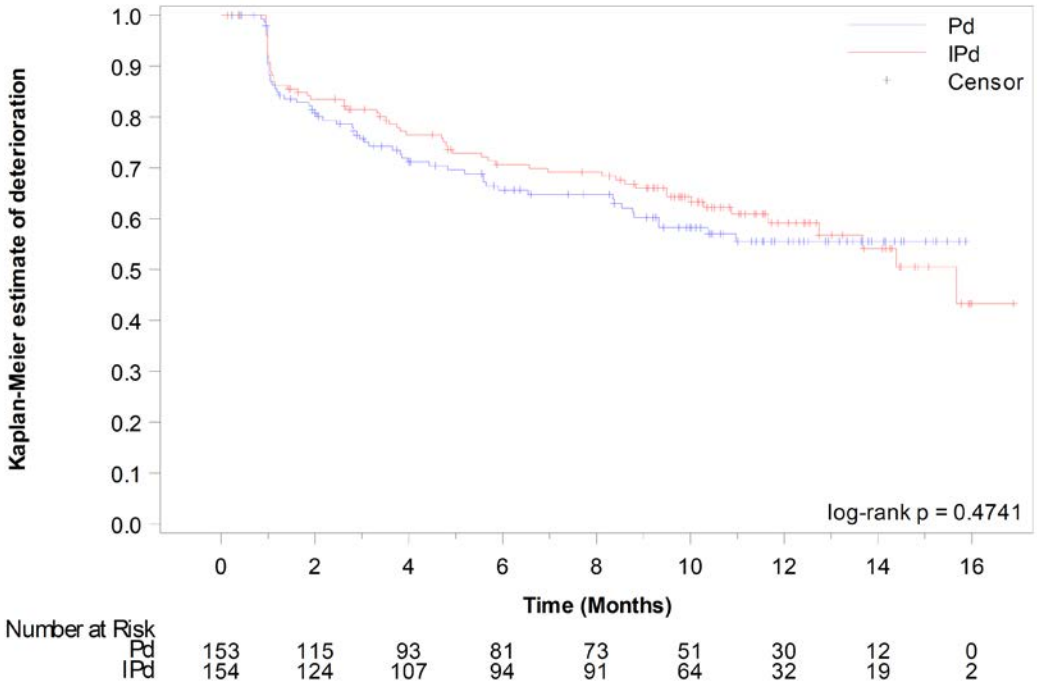

Figure 1: Kaplan-Meier curves on EORTC QLQ-C30, fatigue, time to definitive deterioration by ≥ 10 points (ICARIA-MM study, data cut-off 1)

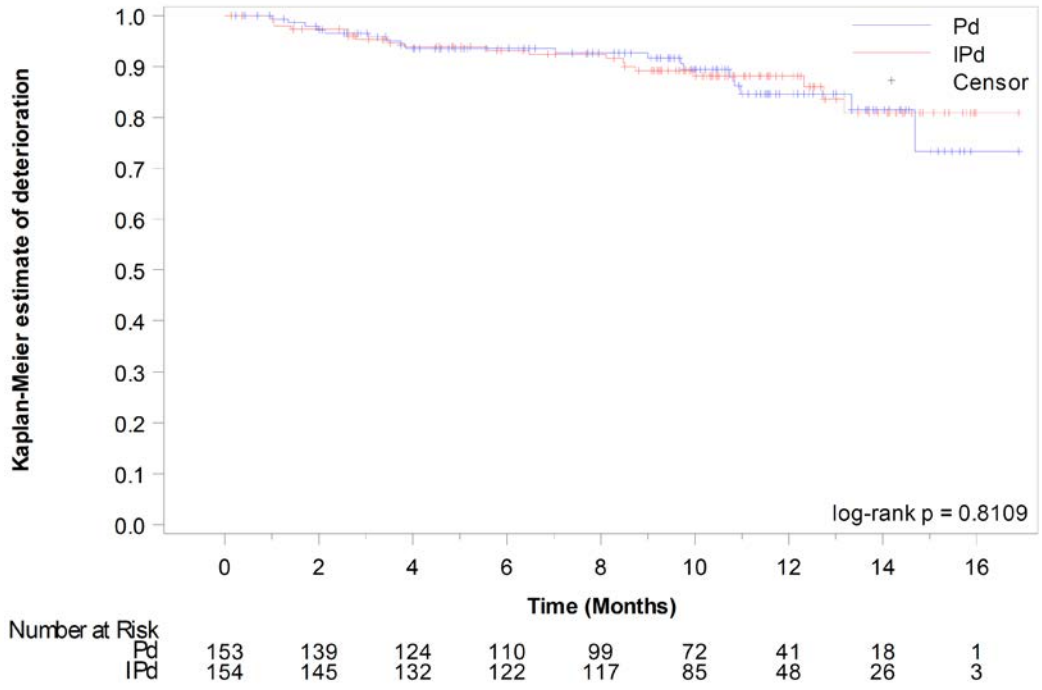

Figure 2: Kaplan-Meier curves on EORTC QLQ-C30, nausea and vomiting, time to definitive deterioration by ≥ 10 points (ICARIA-MM study, data cut-off 1)

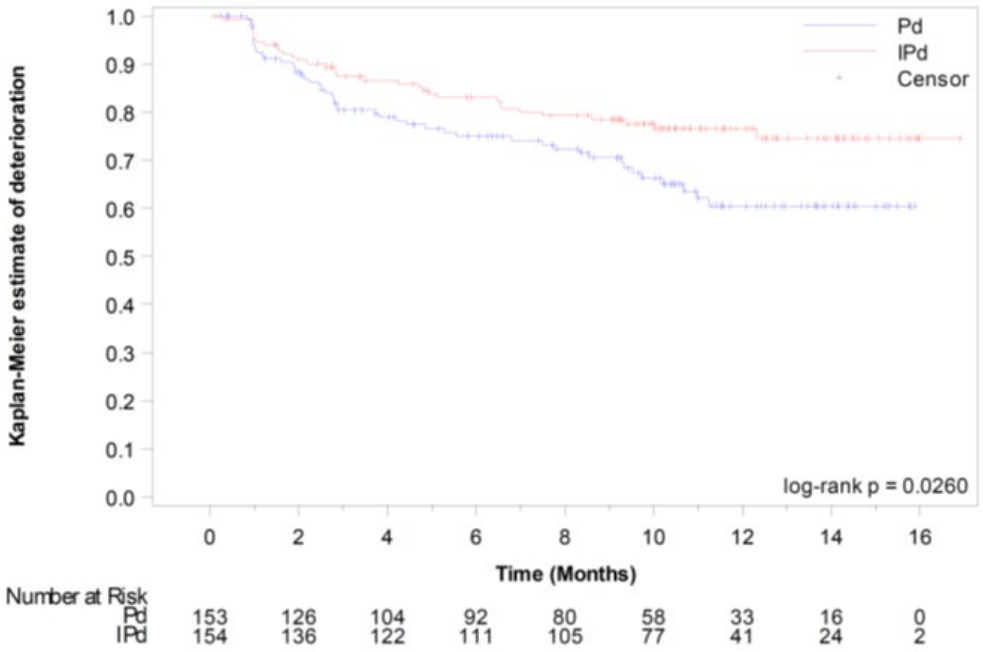

Figure 3: Kaplan-Meier curves on EORTC QLQ-C30 pain, time to definitive deterioration by ≥ 10 points (ICARIA-MM study, data cut-off 1)

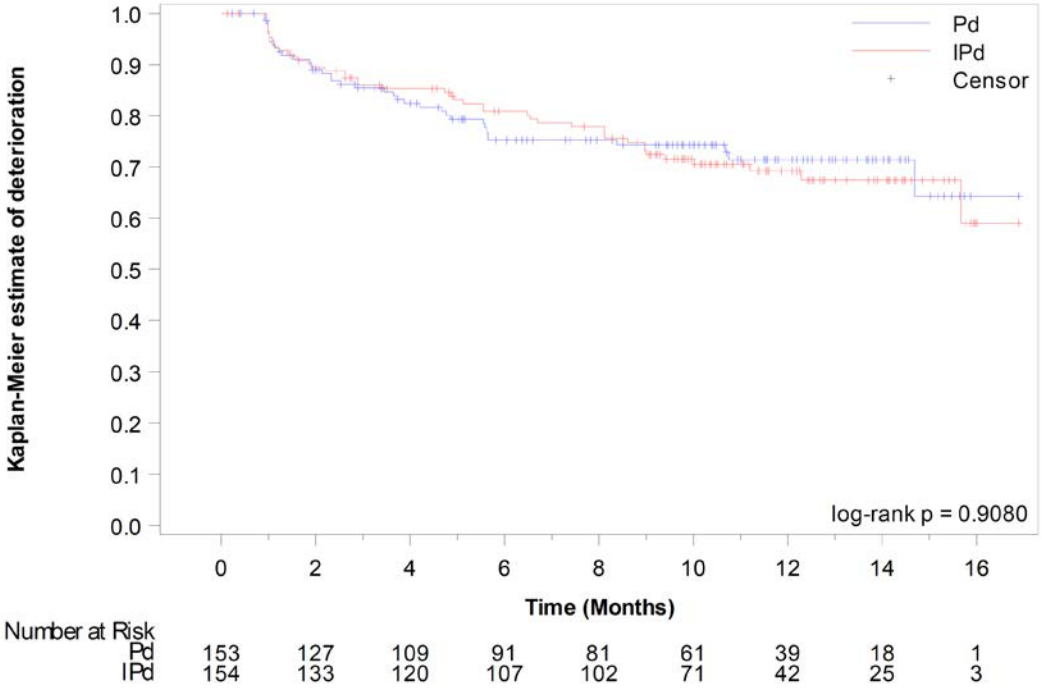

Figure 4: Kaplan-Meier curves on EORTC QLQ-C30 dyspnoea, time to definitive deterioration by ≥ 10 points (ICARIA-MM study, data cut-off 1)

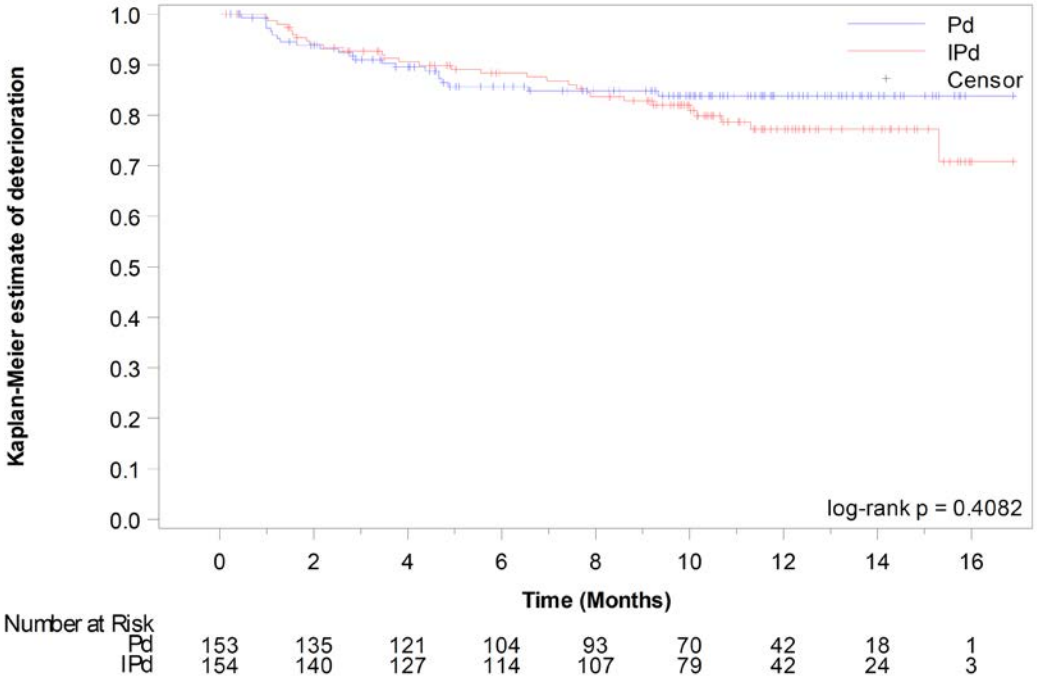

Figure 5: Kaplan-Meier curves on EORTC QLQ-C30 sleeplessness, time to definitive deterioration by ≥ 10 points (ICARIA-MM study, data cut-off 1)

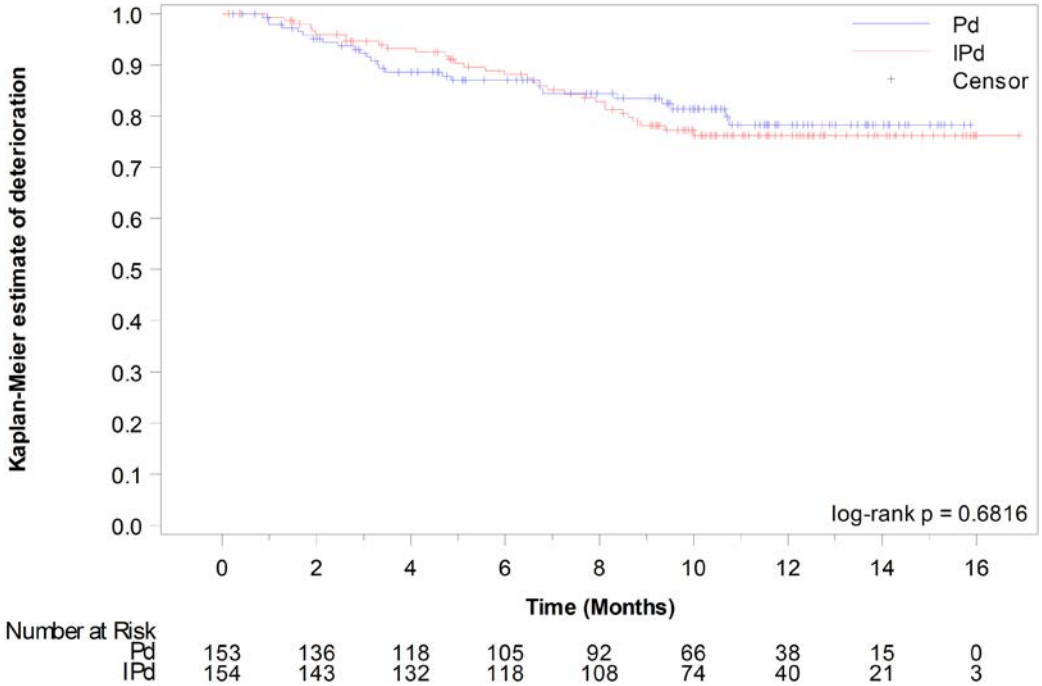

Figure 6: Kaplan-Meier curves on EORTC QLQ-C30, appetite loss, time to definitive deterioration by ≥ 10 points (ICARIA-MM study, data cut-off 1)

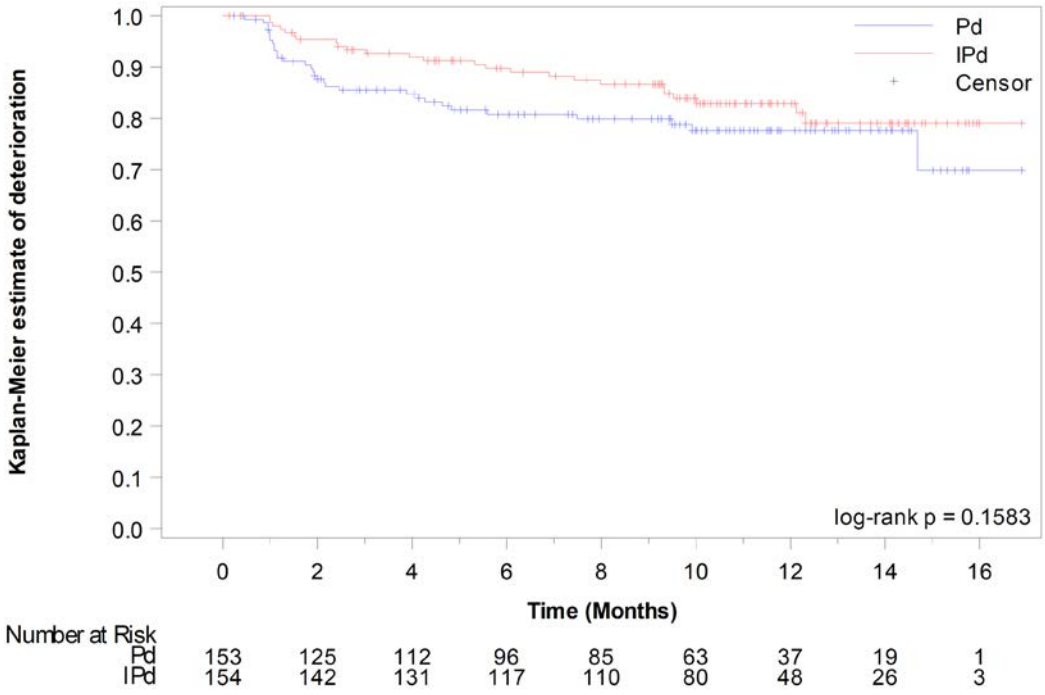

Figure 7: Kaplan-Meier curves on EORTC QLQ-C30 constipation, time to definitive deterioration by ≥ 10 points (ICARIA-MM study, data cut-off 1)

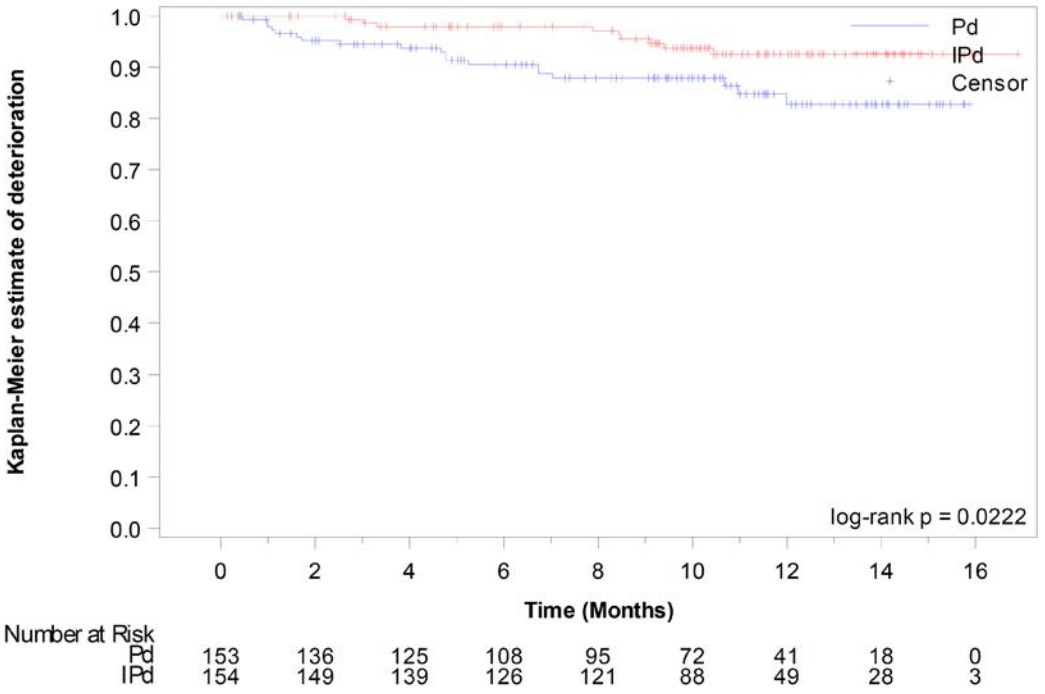

Figure 8: Kaplan-Meier curves on EORTC QLQ-C30, diarrhoea, time to definitive deterioration by ≥ 10 points (ICARIA-MM study, data cut-off 1)

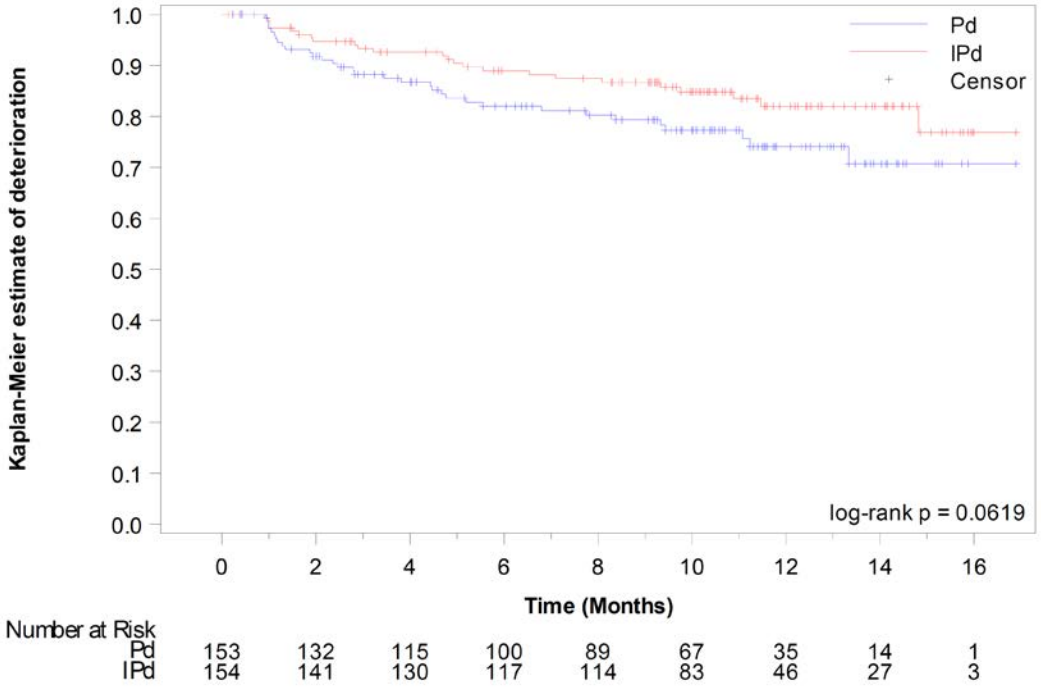

Figure 9: Kaplan-Meier curves on EORTC QLQ-MY20, disease symptoms, time to definitive deterioration by ≥ 10 points (ICARIA-MM study, data cut-off 1)

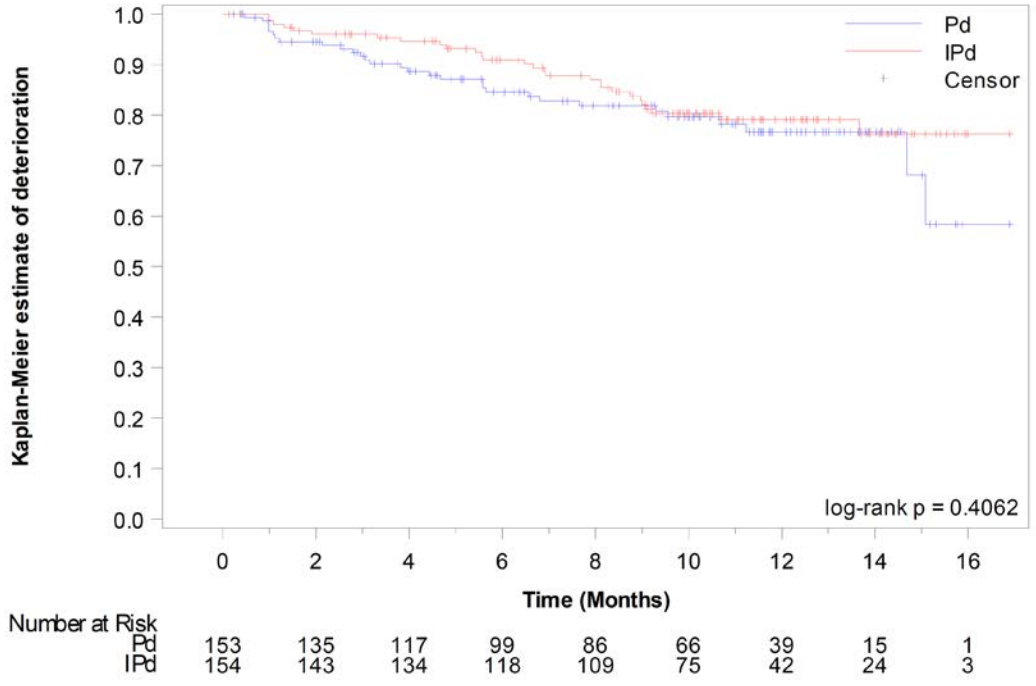

Figure 10: Kaplan-Meier curves on EORTC QLQ-MY20, side effects, time to definitive deterioration by ≥ 10 points (ICARIA-MM study, data cut-off 1)

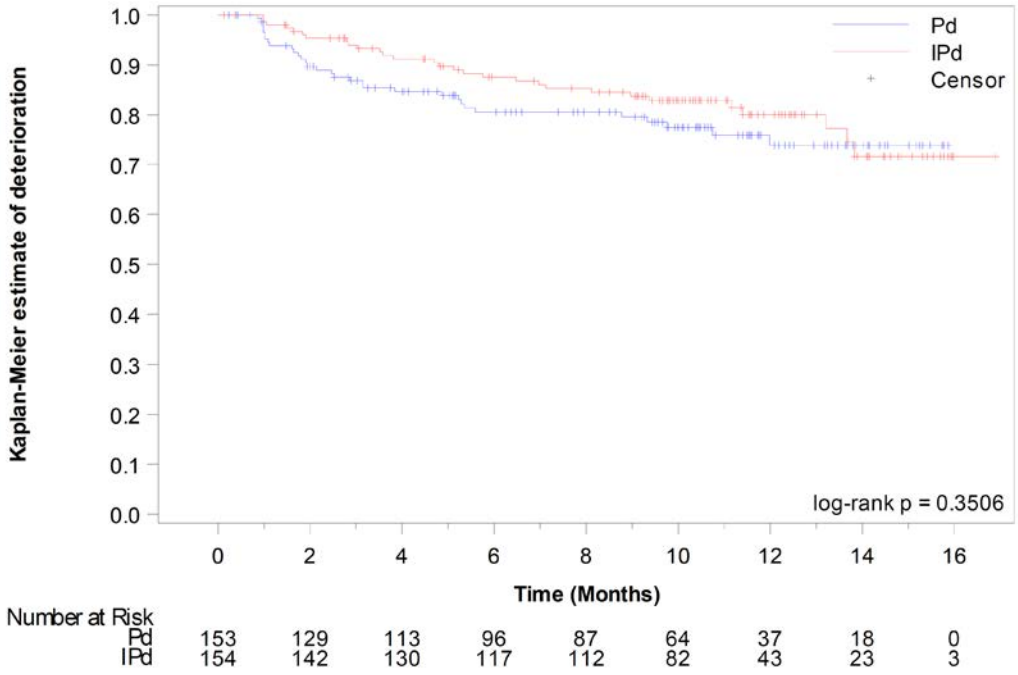

Figure 11: Kaplan-Meier curves on EQ-5D VAS, time to definitive deterioration by ≥ 15 points (ICARIA-MM study, data cut-off 1)

B.2Health-related quality of life

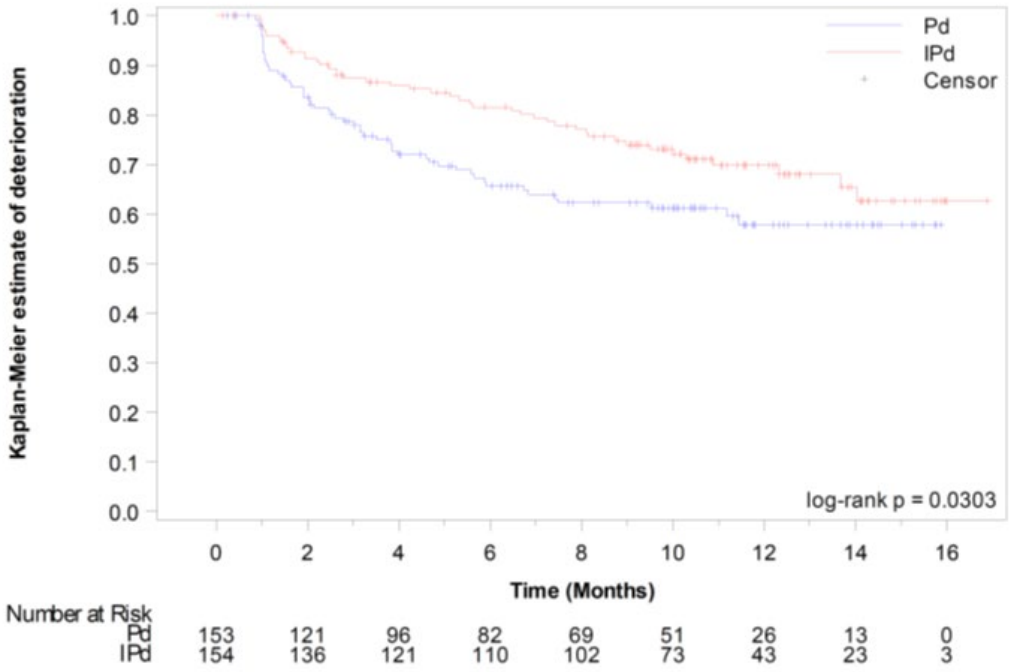

Figure 12: Kaplan-Meier curves on EORTC QLQ-C30, global health status, time to definitive deterioration by ≥ 10 points (ICARIA-MM study, data cut-off 1)

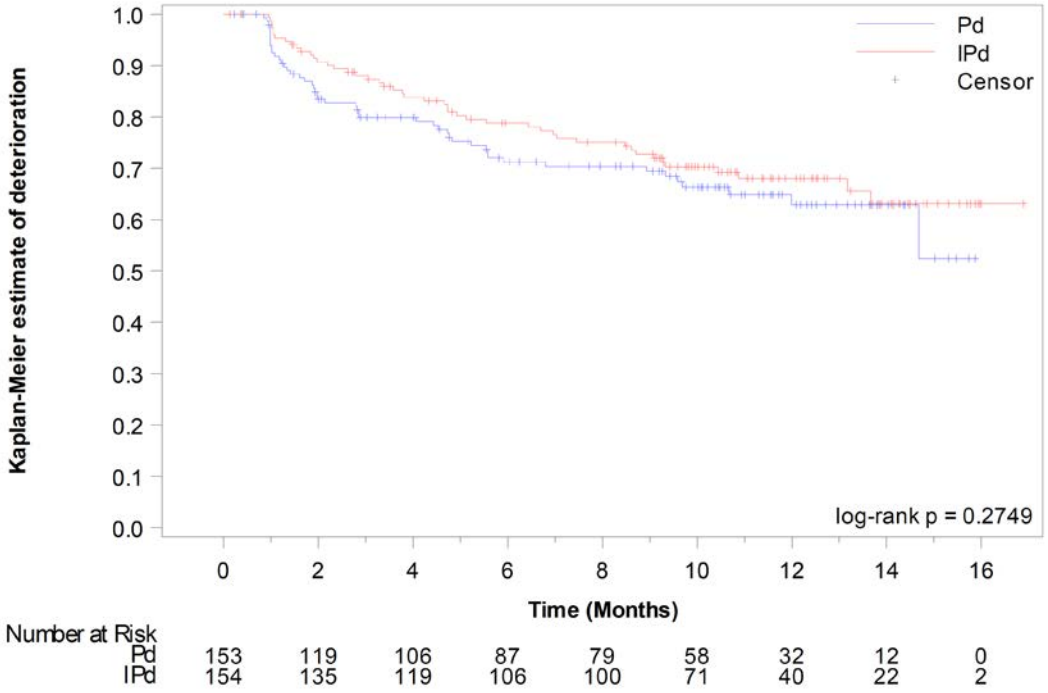

Figure 13: Kaplan-Meier curves on EORTC QLQ-C30, physical functioning, time to definitive deterioration by ≥ 10 points (ICARIA-MM study, data cut-off 1)

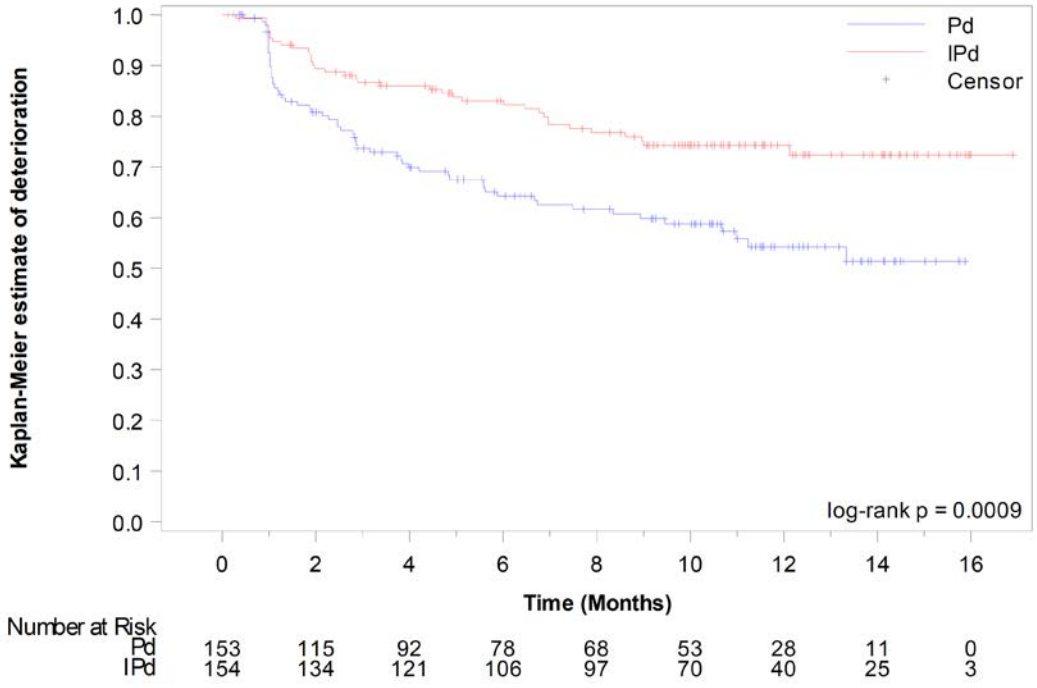

Figure 14: Kaplan-Meier curves on EORTC QLQ-C30, role functioning, time to definitive deterioration by ≥ 10 points (ICARIA-MM study, data cut-off 1)

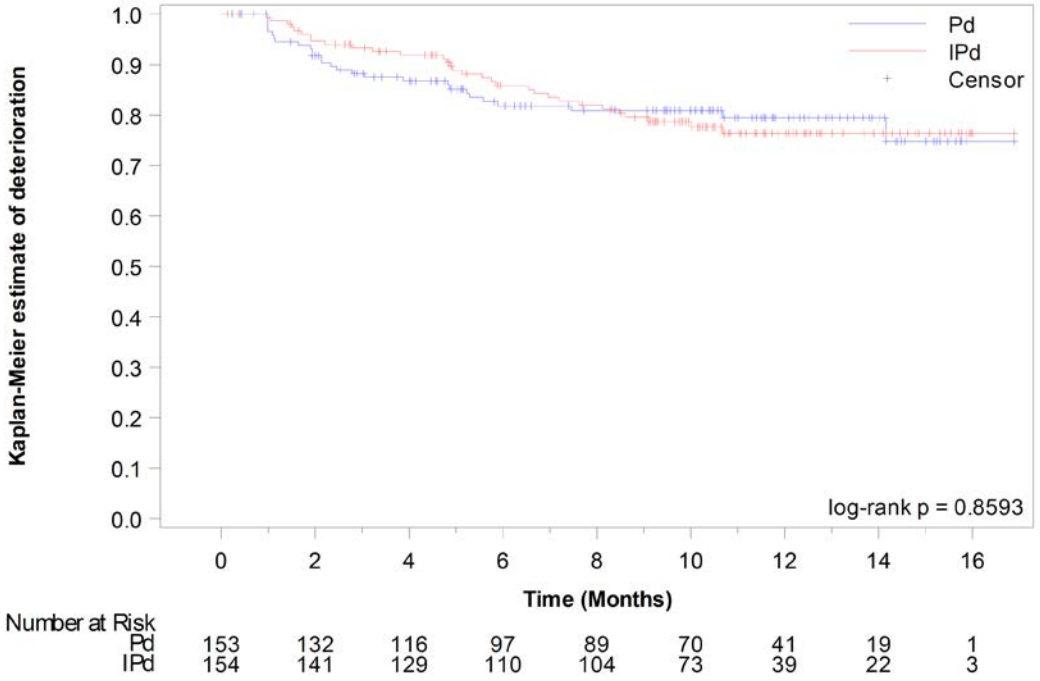

Figure 15: Kaplan-Meier curves on EORTC QLQ-C30, emotional functioning, time to definitive deterioration by ≥ 10 points (ICARIA-MM study, data cut-off 1)

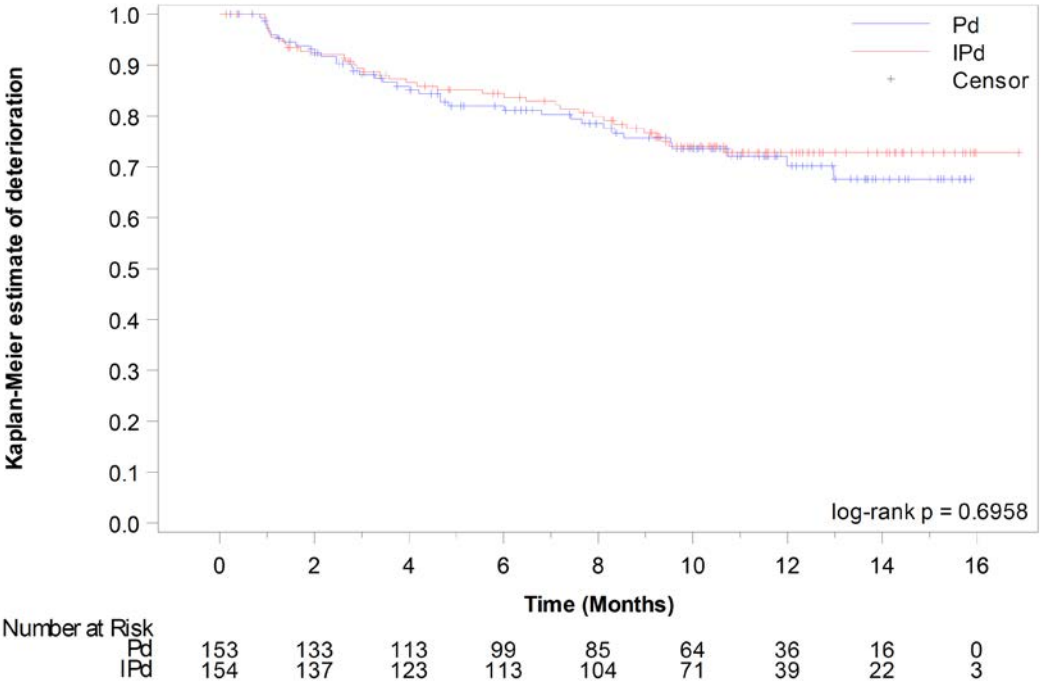

Figure 16: Kaplan-Meier curves on EORTC QLQ-C30, cognitive functioning, time to definitive deterioration by ≥ 10 points (ICARIA-MM study, data cut-off 1)

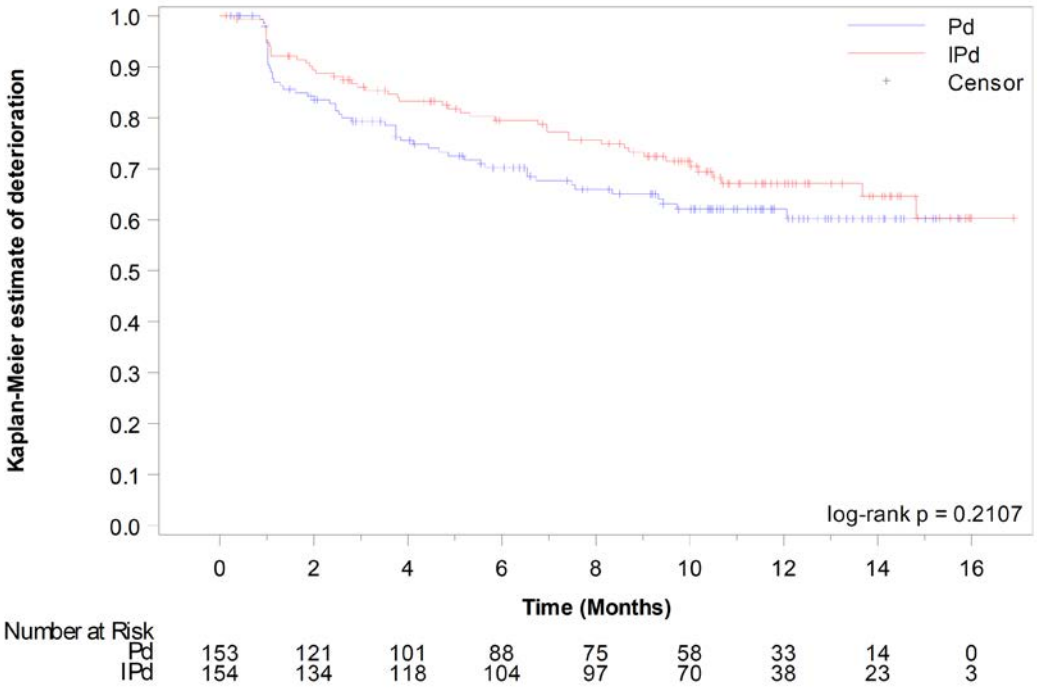

Figure 17: Kaplan-Meier curves on EORTC QLQ-C30, social functioning, time to definitive deterioration by ≥ 10 points (ICARIA-MM study, data cut-off 1)

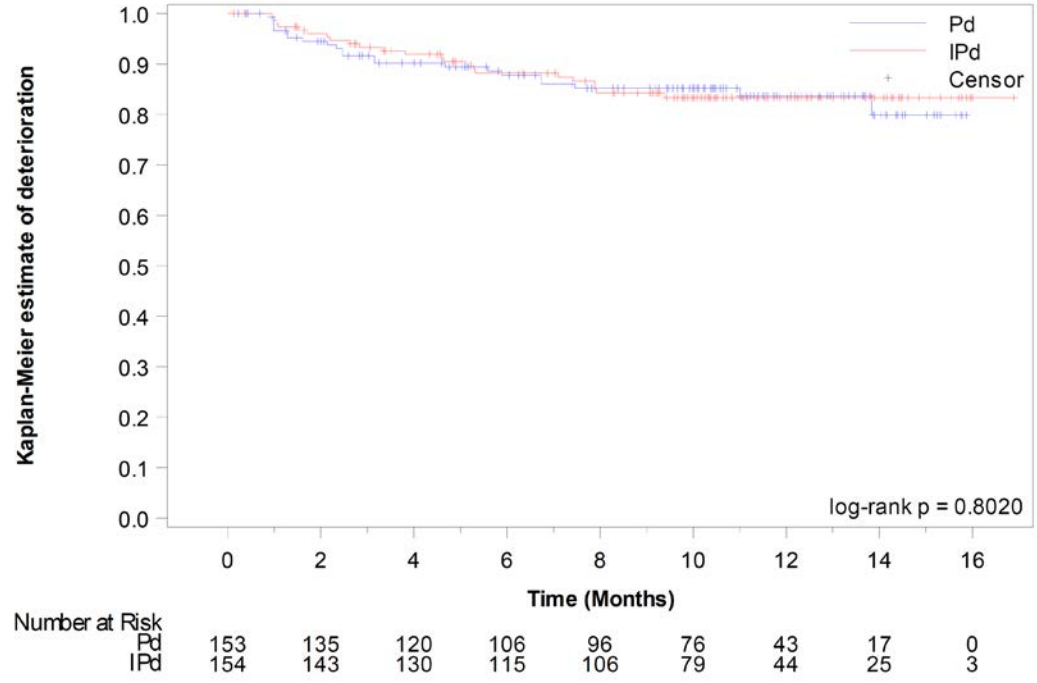

Figure 18: Kaplan-Meier curves on EORTC QLQ-MY20, body image, time to definitive deterioration by ≥ 10 points (ICARIA-MM study, data cut-off 1)

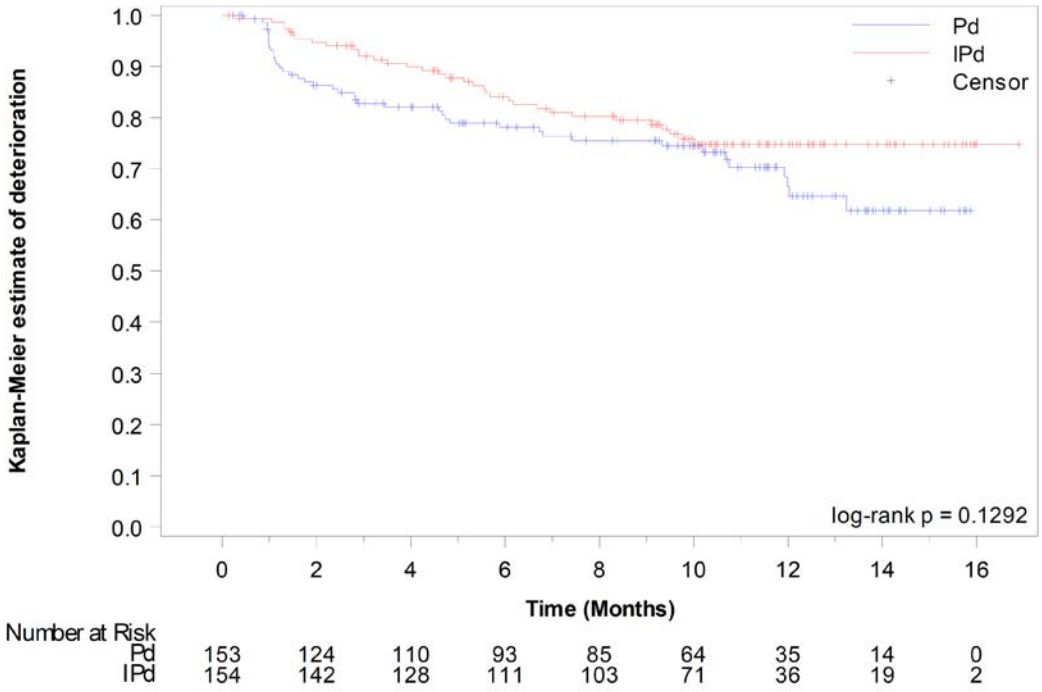

Figure 19: Kaplan-Meier curves on EORTC QLQ-MY20, future perspective, time to definitive deterioration by ≥ 10 points (ICARIA-MM study, data cut-off 1)

B.3 Side effects

The company's comment did not include any Kaplan-Meier curves on discontinuation due to AEs for the 2nd data cut-off.

B.4 Subgroup analyses

Regarding the outcomes on symptoms, health status, and health-related quality of life, Module 4 B presents Kaplan-Meier curves only for subgroups for which the company's calculations showed statistically significant interactions.

Age (< 65 years versus 65 to 75 years versus ≥ 75 years)

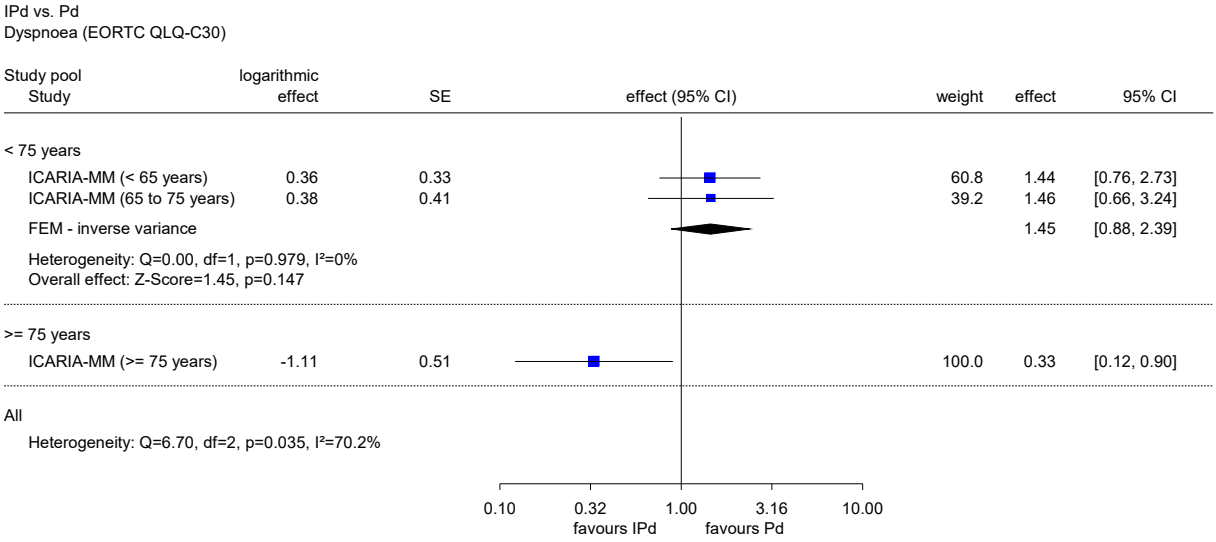

Figure 20: Forest plot for aggregated subgroups with homogeneous effects (age < 75 years vs. age ≥ 75 years) regarding EORTC QLQ C30, dyspnoea, time to definitive deterioration by ≥ 10 points (ICARIA-MM study, data cut-off 1)

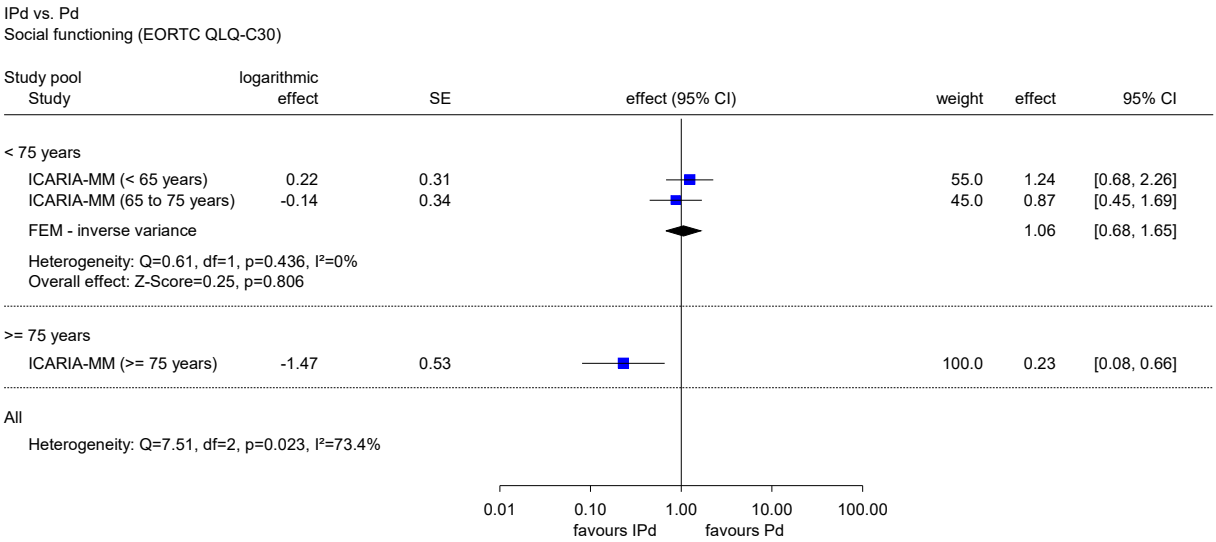

Figure 21: Forest plot for aggregated subgroups with homogeneous effects (age < 75 years vs. age ≥ 75 years) for EORTC QLQ C30, social functioning, time to definitive deterioration by ≥ 10 points (ICARIA-MM study, data cut-off 1)