IQWiG Reports – Commission No. A21-123

# Isatuximab (multiple myeloma, after ≥ 1 prior therapy) –

## Addendum to Commission A21-60[1]

## Addendum

Commission: A21-123
Version: 1.0
Status: 15 October 2021

[1] Translation of addendum A21-123 *Isatuximab (multiples Myelom, nach ≥ 1 Vortherapie) – Addendum zum Auftrag A21-60* (Version 1.0; Status: 15 October 2021). Please note: This document was translated by an external translator and is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

# Publishing details

**Publisher**
Institute for Quality and Efficiency in Health Care

**Topic**
Isatuximab (multiple myeloma, after ≥ 1 prior therapy) – Addendum to Commission A21-60

**Commissioning agency**
Federal Joint Committee

**Commission awarded on**
30 September 2021

**Internal Commission No.**
A21-123

**Address of publisher**
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**Keywords:** Isatuximab, Carfilzomib, Dexamethasone, Multiple Myeloma, Benefit Assessment, NCT03275285

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**List of abbreviations**

| Abbreviation | Meaning |
|---|---|
| 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 | Multiple Myeloma 20 |
| R-ISS | Revised International Staging System |
| 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 A21-60 (Isatuximab– Benefit assessment according to § 35a Social Code Book V) [1].

To assess the benefit of isatuximab in combination with carfilzomib and dexamethasone (hereinafter referred to as "isatuximab + carfilzomib + dexamethasone") in comparison with the appropriate comparator therapy (ACT) in adult patients with multiple myeloma who received at least 1 prior therapy, the IKEMA study was used [1]. This open-label, randomized, controlled trial (RCT) compares isatuximab + carfilzomib + dexamethasone versus carfilzomib + 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"
- 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-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]. Dossier assessment A21-60 therefore used time to first deterioration (with a response criterion of ≥ 10 points [EORTC] or ≥ 15 points [EQ-5D VAS], which 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 IKEMA study includes patients who exhibited a change exceeding the response threshold (10 points for EORTC QLQ-C30 and EORTC QLQ-MY20; 15 points for EQ-5D VAS) without falling 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 [3].

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 A21-60), 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)**

Due to the operationalization of time to discontinuation of all components, the analyses of the outcome of discontinuation due to AEs as submitted by the company were deemed unusable in benefit assessment A21-60 [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 additionally to be preferred because any AE which leads to the discontinuation of a treatment component is relevant.

In the commenting procedure [2], the company subsequently submitted analyses of time to discontinuation of 1 or more components. 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 + carfilzomib + dexamethasone vs. carfilzomib + dexamethasone (multipage table)

| **Study**<br>**Outcome category**<br>**Outcome** | **Isatuximab + carfilzomib + dexamethasone** | | **Carfilzomib + dexamethasone** | | **isatuximab + carfilzomib + dexamethasone vs. carfilzomib + dexamethasone** |
|---|---|---|---|---|---|
| | **N** | **Median time to event in months [95% CI]**<br>**Patients with event n (%)** | **N** | **Median time to event in months [95% CI]**<br>**Patients with event n (%)** | **HR [95% CI]; p-value[b]** |
| **IKEMA** | | | | | |
| **Morbidity** | | | | | |
| **Symptoms (EORTC QLQ-C30) – time to definitive[a] deterioration by ≥ 10 points[c]** | | | | | |
| Fatigue | 179 | NR [20.7; NC]<br>69 (38.5) | 123 | NR [20.6; NC]<br>47 (38.2) | 1.03 [0.71; 1.49]; 0.891 |
| Nausea and vomiting | 179 | NR<br>22 (12.3) | 123 | NR<br>19 (15.4) | 0.75 [0.41; 1.39]; 0.363 |
| Pain | 179 | 23.7 [22.6; NC]<br>56 (31.3) | 123 | NR [23.1; NC]<br>34 (27.6) | 1.17 [0.76; 1.80]; 0.465 |
| Dyspnoea | 179 | NR<br>51 (28.5) | 123 | 24.0 [21.7; NC]<br>38 (30.9) | 0.89 [0.58; 1.36]; 0.587 |
| Sleeplessness | 179 | NR<br>40 (22.3) | 123 | NR<br>29 (23.6) | 0.96 [0.59; 1.55]; 0.858 |
| Appetite loss | 179 | NR<br>36 (20.1) | 123 | NR<br>22 (17.9) | 1.10 [0.65; 1.87]; 0.727 |
| Constipation | 179 | NR<br>24 (13.4) | 123 | NR<br>15 (12.2) | 1.05 [0.55; 2.01]; 0.878 |
| Diarrhoea | 179 | NR<br>18 (10.1) | 123 | 26.4 [26.4; NC]<br>18 (14.6) | 0.68 [0.35; 1.33]; 0.259 |
| **Symptoms (EORTC QLQ-MY20) – time to definitive[a] deterioration by ≥ 10 points[c]** | | | | | |
| Symptoms of disease | 179 | NR<br>39 (21.8) | 123 | NR [23.1; NC]<br>29 (23.6) | 0.88 [0.54; 1.43]; 0.601 |
| Side effects | 179 | NR<br>47 (26.3) | 123 | NR [24.0; NC]<br>34 (27.6) | 0.92 [0.59; 1.43]; 0.700 |
| **Health status (EQ-5D VAS) – time to definitive[a] deterioration by ≥ 15 points[d]** | | | | | |
| EQ-5D VAS | 179 | NR<br>31 (17.3) | 123 | NR<br>23 (18.7) | 0.91 [0.53; 1.56]; 0.730 |

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

| Study<br>Outcome category<br>Outcome | Isatuximab + carfilzomib + dexamethasone | | Carfilzomib + dexamethasone | | isatuximab + carfilzomib + dexamethasone vs. carfilzomib + dexamethasone |
|---|---|---|---|---|---|
| | N | Median time to event in months [95% CI]<br>Patients with event n (%) | N | Median time to event in months [95% CI]<br>Patients with event n (%) | HR [95% CI]; p-value[b] |
| **Health-related quality of life (EORTC QLQ-C30) – time to definitive[a] deterioration by ≥ 10 points[d]** | | | | | |
| Global health status | 179 | NR<br>56 (31.3) | 123 | NR<br>35 (28.5) | 1.16 [0.76; 1.78]; 0.494 |
| Physical functioning | 179 | NR<br>53 (29.6) | 123 | NR<br>32 (26.0) | 1.17 [0.75; 1.82]; 0.490 |
| Role functioning | 179 | NR [22.7; NC]<br>59 (33.0) | 123 | NR [23.1; NC]<br>41 (33.3) | 1.02 [0.68; 1.52]; 0.931 |
| Emotional functioning | 179 | NR<br>34 (19.0) | 123 | NR<br>20 (16.3) | 1.14 [0.65; 1.98]; 0.647 |
| Cognitive functioning | 179 | NR [23.1; NC]<br>59 (33.0) | 123 | NR [21.5; NC]<br>38 (30.9) | 1.13 [0.75; 1.71]; 0.560 |
| Social functioning | 179 | NR<br>60 (33.5) | 123 | NR [24.0; NC]<br>39 (31.7) | 1.04 [0.70; 1.57]; 0.832 |
| **EORTC QLQ-MY20 – time to definitive[a] deterioration by ≥ 10 points[d]** | | | | | |
| Body image | 179 | 24.4 [24.4; NC]<br>42 (23.5) | 123 | NR<br>30 (24.4) | 0.90 [0.56; 1.44]; 0.653 |
| Future perspective | 179 | NR<br>50 (27.9) | 123 | NR [24.0; NC]<br>41 (33.3) | 0.83 [0.55; 1.26]; 0.375 |

a. Definitive deterioration was operationalized as change by at least the response threshold without subsequent improvement (to result 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 are the number of prior therapy lines (1 vs. > 1) as well as the R-ISS stage (I or II vs. III vs. not classified).
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; EQ-5D: European Quality of Life Questionnaire – 5 Dimensions; HR: hazard ratio; n: number of patients with (at least 1) event; N: number of analysed patients; NC: not calculable; NR: not reached; R-ISS: Revised International Staging System; RCT: randomized controlled trial; VAS: visual analogue scale

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

| Study<br>Outcome category<br>Outcome | Isatuximab + carfilzomib + dexamethasone | | Carfilzomib + dexamethasone | | isatuximab + carfilzomib + dexamethasone vs. carfilzomib + dexamethasone |
|---|---|---|---|---|---|
| | N | Median time to event in months [95% CI]<br>Patients with event n (%) | N | Median time to event in months [95% CI]<br>Patients with event n (%) | HR [95% CI]; p-value[a] |
| **IKEMA** | | | | | |
| **Side effects** | | | | | |
| Discontinuation due to AEs (≥ 1 component) | 177 | NR<br>47 (26.6) | 122 | NR<br>21 (17.2) | 1.63 [0.97; 2.72]; 0.062 |

a. HR and CI are based on a stratified Cox proportional hazards model; p-value is based on a stratified log-rank test. Stratification factors are the number of prior therapy lines (1 vs. > 1) as well as the R-ISS stage (I or II vs. III vs. not classified).

AEs: adverse events; CI: confidence interval; HR: hazard ratio; n: number of patients with (at least 1) event; N: number of analysed patients; NR: not reached; RCT: randomized controlled trial; R-ISS: Revised International Staging System

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, pain, dyspnoea, sleeplessness, appetite loss, constipation, diarrhoea*

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 + carfilzomib + dexamethasone in comparison with carfilzomib + dexamethasone for any of them; an added benefit is therefore not proven.

*Disease symptoms, side effects*

The EORTC QLQ-MY20 symptoms outcomes exhibit no statistically significant differences between treatment groups. Consequently, there is no hint of added benefit of isatuximab +

carfilzomib + dexamethasone in comparison with carfilzomib + 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. Consequently, there is no hint of added benefit of isatuximab + carfilzomib + dexamethasone in comparison with carfilzomib + dexamethasone; an added benefit is therefore not proven.

***Health-related quality of life***

The health-related quality of life 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.

*Global health status, physical functioning, role 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. Consequently, there is no hint of added benefit of isatuximab + carfilzomib + dexamethasone in comparison with carfilzomib + dexamethasone; an added benefit is therefore not proven.

*Social functioning*

For the EORTC QLQ-C30 outcome of social functioning, no statistically significant difference between treatment arms was found in the total population. However, there is an effect modification by the attribute of Revised International Staging System (R-ISS) stage (I or II versus III) at baseline. For patients in R-ISS stage III at baseline, a statistically significant difference between treatment groups was found in favour of isatuximab + carfilzomib + dexamethasone. This results in a hint of added benefit of isatuximab + carfilzomib + dexamethasone in comparison with carfilzomib + dexamethasone for this patient group. For patients in R-ISS stage I or II at baseline, no statistically significant difference between treatment groups was found. This results in no hint of added benefit of isatuximab + carfilzomib + dexamethasone in comparison with carfilzomib + dexamethasone for this patient group (see Section 2.4).

*Body image, future perspective*

For the listed EORTC QLQ-MY20 outcomes on health-related quality of life, no statistically significant differences between treatment groups were found. Consequently, there is no hint of added benefit of isatuximab + carfilzomib + dexamethasone in comparison with carfilzomib + dexamethasone; 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 + carfilzomib + dexamethasone in comparison with carfilzomib + 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 + carfilzomib + dexamethasone versus carfilzomib + 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: Subgroups (health-related quality of life, time to definitive[a] deterioration) – RCT, direct comparison: isatuximab + carfilzomib + dexamethasone vs. carfilzomib + dexamethasone

| Study<br>Outcome<br>Characteristic<br>Subgroup | Isatuximab + carfilzomib + dexamethasone | | Carfilzomib + dexamethasone | | Isatuximab + carfilzomib + dexamethasone vs. carfilzomib + dexamethasone | |
|---|---|---|---|---|---|---|
| | N | Median time to event in months [95% CI]<br>Patients with event n (%) | N | Median time to event in months [95% CI]<br>Patients with event n (%) | HR [95% CI][b] | p-value[c] |
| **IKEMA** | | | | | | |
| **Health-related quality of life (EORTC QLQ-C30) – time to definitive[a] deterioration by ≥ 10 points[d]** | | | | | | |
| Social functioning | | | | | | |
| R-ISS stage at baseline | | | | | | |
| I or II | 155 | NR<br>56 (36.1) | 103 | NR [24.0; NC]<br>30 (29.1) | 1.21 [0.77; 1.88] | 0.405 |
| III | 16 | NR [10.9; NC]<br>3 (18.8) | 8 | 5.8 [1.1; NC]<br>5 (62.5) | 0.23 [0.05; 0.95] | 0.027 |
| *Not classified*[e] | *8* | *NR [2.8; NC]*<br>*1 (12.5)* | *12* | *NR [12.9; NC]*<br>*4 (33.3)* | *0.63 [0.07; 5.63]* | 0.673 |
| Total | | | | | Interaction[f]: | 0.034 |

a. Definitive deterioration was operationalized as a score reduction by at least 10 points from baseline without subsequent improvement (to result in a change from baseline of less than 10 points). The analysis also includes patients whose deterioration occurred at the last documented visit.
b. HR and CI are based on a nonstratified Cox proportional hazards model.
c. p-value based on nonstratified log rank test.
d. Defined as a score decrease by at least 10 points from baseline (scale range 0–100).
e. Due to the unclear allocation to one of the disease stages, this subgroup was disregarded in the analysis on effect modification and presented as supplementary information here.
f. IQWiG calculations; p-value from Q test for heterogeneity, based on the 2 subgroups "I or II" and "III".

CI: confidence interval; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; HR: hazard ratio; n: number of patients with (at least 1) event; N: number of analysed patients; NC: not calculable; NR: not reached; RCT: randomized controlled trial; R-ISS: Revised International Staging System

## Health-related quality of life

### *EORTC QLQ-C30*

*Social functioning*

The available subgroup analyses show an effect modification for the outcome of social functioning by the characteristic of R-ISS stage at baseline.

For patients in R-ISS stage I or II, there is no statistically significant difference between treatment groups. For the subgroup of patients in R-ISS stage I or II, this results in no hint of

added benefit of isatuximab + carfilzomib + dexamethasone versus carfilzomib + dexamethasone.

For patients who were in R-ISS stage III at baseline, a statistically significant difference between treatment groups was found in favour of isatuximab + carfilzomib + dexamethasone in comparison with carfilzomib + dexamethasone. For the subgroup of patients in R-ISS stage III, this results in a hint of added benefit of isatuximab + carfilzomib + dexamethasone in comparison with carfilzomib + dexamethasone.

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

In the IKEMA 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 included 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.

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

| **Outcome category**<br>**Outcome**<br>**Effect modifier**<br>**Subgroup** | **Isatuximab + carfilzomib + dexamethasone vs. carfilzomib + dexamethasone**<br>**Median time to event (months)**<br>**Effect estimation [95% CI];**<br>**p-value**<br>**Probability[a]** | **Derivation of extent[b]** |
|---|---|---|
| **Morbidity** | | |
| Symptoms (EORTC QLQ-C30) | | |
| Fatigue | NR vs. NR<br>HR: 1.03 [0.71; 1.49];<br>p = 0.891 | Lesser/added benefit not proven |
| Nausea and vomiting | NR vs. NR<br>HR: 0.75 [0.41; 1.39];<br>p = 0.363 | Lesser/added benefit not proven |
| Pain | 23.7 vs. NR<br>HR: 1.17 [0.76; 1.80];<br>p = 0.465 | Lesser/added benefit not proven |
| Dyspnoea | NR vs. 24.0<br>HR: 0.89 [0.58; 1.36];<br>p = 0.587 | Lesser/added benefit not proven |
| Sleeplessness | NR vs. NR<br>HR: 0.96 [0.59; 1.55];<br>p = 0.858 | Lesser/added benefit not proven |
| Appetite loss | NR vs. NR<br>HR: 1.10 [0.65; 1.87];<br>p = 0.727 | Lesser/added benefit not proven |
| Constipation | NR vs. NR<br>HR: 1.05 [0.55; 2.01];<br>p = 0.878 | Lesser/added benefit not proven |
| Diarrhoea | NR vs. 26.4<br>HR: 0.68 [0.35; 1.33];<br>p = 0.259 | Lesser/added benefit not proven |
| Symptoms (EORTC QLQ-MY20) | | |
| Symptoms of disease | NR vs. NR<br>HR: 0.88 [0.54; 1.43];<br>p = 0.601 | Lesser/added benefit not proven |
| Side effects | NR vs. NR<br>HR: 0.92 [0.59; 1.43];<br>p = 0.700 | Lesser/added benefit not proven |
| Health status (EQ-5D VAS) | NR vs. NR<br>HR: 0.91 [0.53; 1.56];<br>p = 0.730 | Lesser/added benefit not proven |

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

| **Outcome category**<br>**Outcome**<br>**Effect modifier**<br>**Subgroup** | **Isatuximab + carfilzomib + dexamethasone vs. carfilzomib + dexamethasone**<br>**Median time to event (months)**<br>**Effect estimation [95% CI];**<br>**p-value**<br>**Probability**[a] | **Derivation of extent**[b] |
|---|---|---|
| **Health-related quality of life** | | |
| EORTC QLQ-C30 | | |
| Global health status | NR vs. NR<br>HR: 1.16 [0.76; 1.78];<br>p = 0.494 | Lesser/added benefit not proven |
| Physical functioning | NR vs. NR<br>HR: 1.17 [0.75; 1.82];<br>p = 0.490 | Lesser/added benefit not proven |
| Role functioning | NR vs. NR<br>HR: 1.02 [0.68; 1.52];<br>p = 0.931 | Lesser/added benefit not proven |
| Emotional functioning | NR vs. NR<br>HR: 1.14 [0.65; 1.98];<br>p = 0.647 | Lesser/added benefit not proven |
| Cognitive functioning | NR vs. NR<br>HR: 1.13 [0.75; 1.71];<br>p = 0.560 | Lesser/added benefit not proven |
| Social functioning<br>Disease stage at baseline (R-ISS) | | |
| I or II | NR vs. NR<br>HR: 1.21 [0.77; 1.88];<br>p = 0.405 | Lesser/added benefit not proven |
| III | NR vs. 5.8<br>HR: 0.23 [0.05; 0.95]<br>p = 0.027<br>Probability: hint | Outcome category: health-related quality of life<br>$0.90 \leq CI_u < 1.00$<br>Added benefit; extent: minor |
| EORTC QLQ-MY20 | | |
| Body image | 24.4 vs. NR<br>HR: 0.90 [0.56; 1.44];<br>p = 0.653 | Lesser/added benefit not proven |
| Future perspective | NR vs. NR<br>HR: 0.83 [0.55; 1.26];<br>p = 0.375 | Lesser/added benefit not proven |

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

| **Outcome category**<br>**Outcome**<br>**Effect modifier**<br>**Subgroup** | **Isatuximab + carfilzomib + dexamethasone vs. carfilzomib + dexamethasone**<br>**Median time to event (months)**<br>**Effect estimation [95% CI];**<br>**p-value**<br>**Probability**[a] | **Derivation of extent**[b] |
|---|---|---|
| **Side effects** | | |
| Discontinuation due to AEs | NR vs. NR<br>HR: 1.63 [0.97; 2.72];<br>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 ($CI_u$).

AE: adverse event; CI: confidence interval; $CI_u$: upper limit of 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; EQ-5D: European Quality of Life Questionnaire – 5 Dimensions; HR: hazard ratio; NR: not reached; R-ISS: Revised International Staging System; VAS: visual analogue scale

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

| **Favourable effects** | **Unfavourable effects** |
|---|---|
| **Health-related quality of life**<br>▪ **Social functioning**<br>▫ **Disease stage at baseline (R-ISS) (III) hint of added benefit – extent: minor** | |
| – | Non-serious/non-severe side effects<br>▪ Infusion-related reactions (PT "infusion-related reaction"): hint of greater harm – extent: considerable<br>▪ Skin and subcutaneous tissue disorders: hint of greater harm – extent: considerable |
| Serious/severe side effects<br>▪ Thrombocytopenia (severe AEs): hint of lesser harm – extent: considerable | – |

Results printed in **bold** are based on the analyses subsequently submitted by the company with the written comments.

AEs: adverse events; PT: preferred term; R-ISS: Revised International Staging System

The data subsequently submitted by the company change the conclusion compared to dossier assessment A21-60 [5] in that the present addendum reveals a favourable effect in the social functioning scale (extent of minor) for 1 subgroup (disease stage at baseline [R-ISS stage III]).

Unlike in dossier assessment A21-60, however, this subgroup shows no favourable effect in the physical functioning scale (in A21-60: considerable extent).

Effect modification by disease stage (R-ISS) at baseline, which was observed in only 1 outcome on health-related quality of life, still does not justify a separate conclusion on added benefit for different patient groups.

Overall, both favourable and unfavourable effects of different extents, all with the probability of hint, were still found for isatuximab + carfilzomib + dexamethasone in comparison with carfilzomib + dexamethasone. They concern both the outcome of health-related quality of life and outcomes on side effects of different severities.

Overall, the distribution of favourable and unfavourable effects is still deemed balanced, given that the unfavourable effects are from the outcome category of non-serious/non-severe side effects. In summary, there is therefore no proof of added benefit of isatuximab + carfilzomib + dexamethasone versus carfilzomib + dexamethasone in patients with multiple myeloma who received at least 1 prior therapy.

## 2.6 Summary

The data subsequently submitted by the company in the commenting procedure do not change the conclusion drawn in dossier assessment A21-60 on the added benefit of isatuximab.

Table 6 below shows the result of the benefit assessment of isatuximab + carfilzomib + dexamethasone taking into account both dossier assessment A21-60 and the present addendum.

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

| **Therapeutic indication** | **ACT[a]** | **Probability and extent of added benefit** |
|---|---|---|
| Adult patients with multiple myeloma who have received at least 1 prior therapy[b] | ▪ Bortezomib in combination with pegylated liposomal doxorubicin<br>or<br>▪ Bortezomib in combination with dexamethasone<br>or<br>▪ Lenalidomide in combination with dexamethasone<br>or<br>▪ Elotuzumab in combination with lenalidomide and dexamethasone<br>or<br>▪ Carfilzomib in combination with lenalidomide and dexamethasone<br>or<br>▪ **Carfilzomib in combination with dexamethasone**<br>or<br>▪ Daratumumab in combination with lenalidomide and dexamethasone<br>or<br>▪ 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 by the company is marked in **bold**.<br>b. As per the G-BA, it is assumed that high-dose chemotherapy with stem cell transplantation is not an option for the patients at the time of the current therapy.<br>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 ≥ 1 Vortherapie) – Nutzenbewertung gemäß § 35a SGB V (frühe Nutzenbewertung); Dossierbewertung [online]. 2021 [Accessed: 17.08.2021]. URL: https://www.iqwig.de/download/a21-60_isatuximab_nutzenbewertung-35a-sgb-v_v1-0.pdf.

2. Sanofi-Aventis. Stellungnahme zum IQWiG-Bericht Nr. 1175: Isatuximab (multiples Myelom, nach ≥ 1 Vortherapie); Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung. [Soon available under: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/685/#beschluesse in the document "Zusammenfassende Dokumentation"].

3. Sanofi-Aventis. Nachreichung zur Stellungnahme zum IQWiG-Bericht Nr. 1175: Isatuximab (multiples Myelom, nach ≥ 1 Vortherapie); Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung. [Soon available under: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/685/#beschluesse in the document "Zusammenfassende Dokumentation"].

4. Sanofi-Aventis. Zusatzanalysen eingereicht mit der Stellungnahme zum IQWiG-Bericht Nr. 1175: Isatuximab (multiples Myelom, nach ≥ 1 Vortherapie); 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/685/#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 + carfilzomib + dexamethasone vs. carfilzomib + dexamethasone

| Study<br>Outcome category<br>Outcome | Isatuximab + carfilzomib + dexamethasone | | Carfilzomib + dexamethasone | | Isatuximab + carfilzomib + dexamethasone vs. carfilzomib + dexamethasone |
|---|---|---|---|---|---|
| | N | Median time to event in months [95% CI]<br>Patients with event n (%) | N | Median time to event in months [95% CI]<br>Patients with event n (%) | HR [95% CI]; p-value[b] |
| **IKEMA** | | | | | |
| **Health status (EQ-5D VAS) – time to definitive[a] deterioration[c]** | | | | | |
| 7 points | 179 | 24.4 [23.1; 25.6]<br>58 (32.4) | 123 | NR<br>31 (25.2) | 1.24 [0.80; 1.93]; 0.328 |
| 10 points | 179 | 24.4 [23.1; NC]<br>50 (27.9) | 123 | NR<br>29 (23.6) | 1.15 [0.73; 1.82]; 0.555 |

a. Definitive deterioration was operationalized as change by at least the response threshold without subsequent improvement (to result 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 are the number of prior therapy lines (1 vs. > 1) as well as the R-ISS stage (I or II vs. III vs. not classified).
c. Defined as a score decrease by at least 7 or 10 points from baseline (scale range 0–100).

CI: confidence interval; EQ-5D: European Quality of Life Questionnaire – 5 Dimensions; HR: hazard ratio; n: number of patients with event; N: number of analysed patients; RCT: randomized controlled trial; R-ISS: Revised International Staging System; VAS: visual analogue scale

## Appendix B Figures on outcome analyses

### B.1 Morbidity

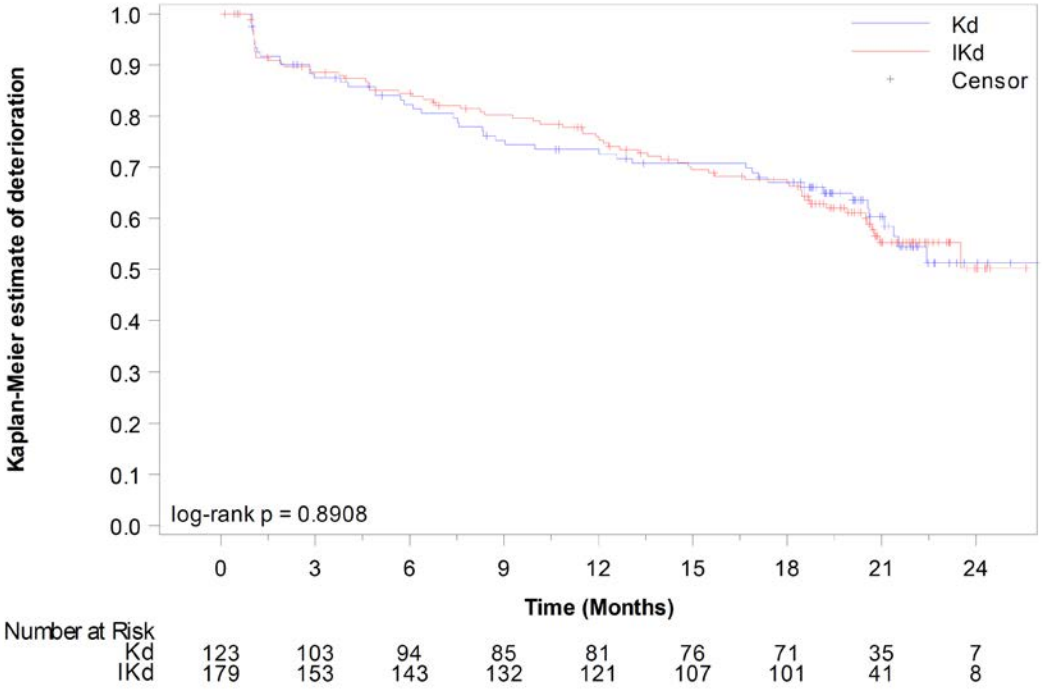


Figure 1: Kaplan-Meier curves on EORTC QLQ-C30, fatigue, time to definitive deterioration by ≥ 10 points (IKEMA study)

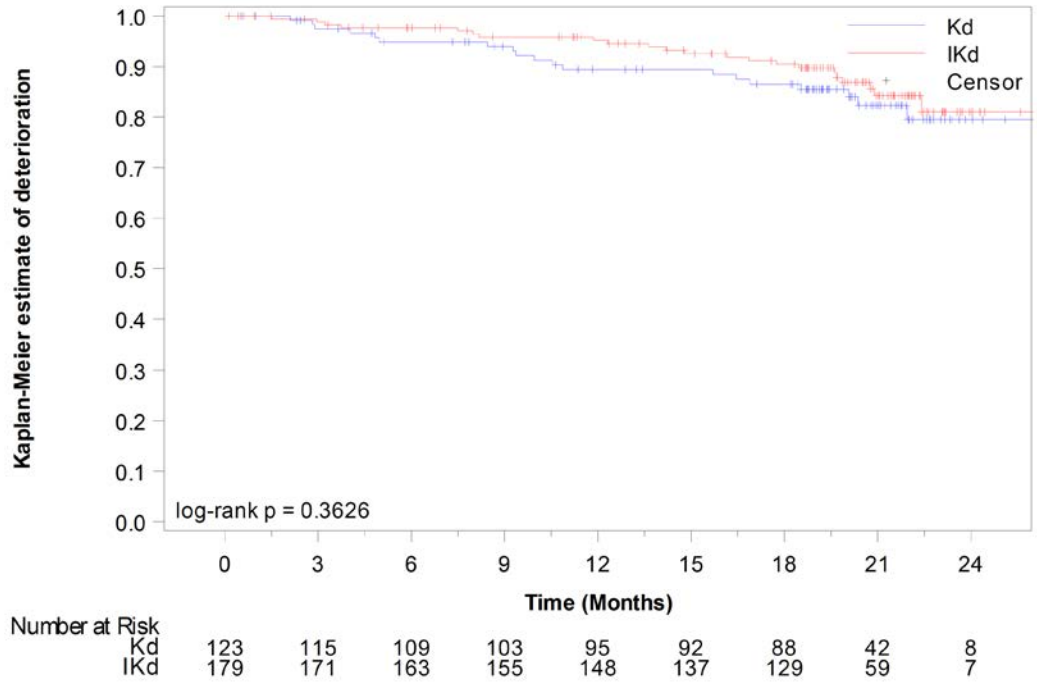


Figure 2: Kaplan-Meier curves on EORTC QLQ-C30, nausea and vomiting, time to definitive deterioration by ≥ 10 points (IKEMA study)

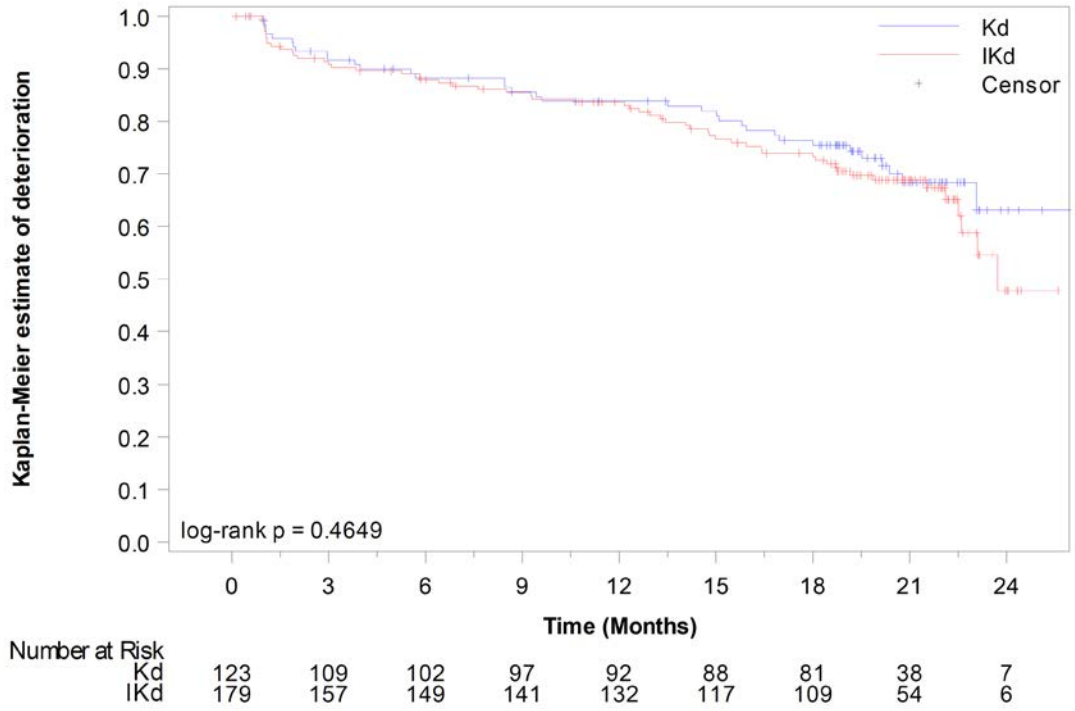


Figure 3: Kaplan-Meier curves on EORTC QLQ-C30, pain, time to definitive deterioration by ≥ 10 points (IKEMA study)

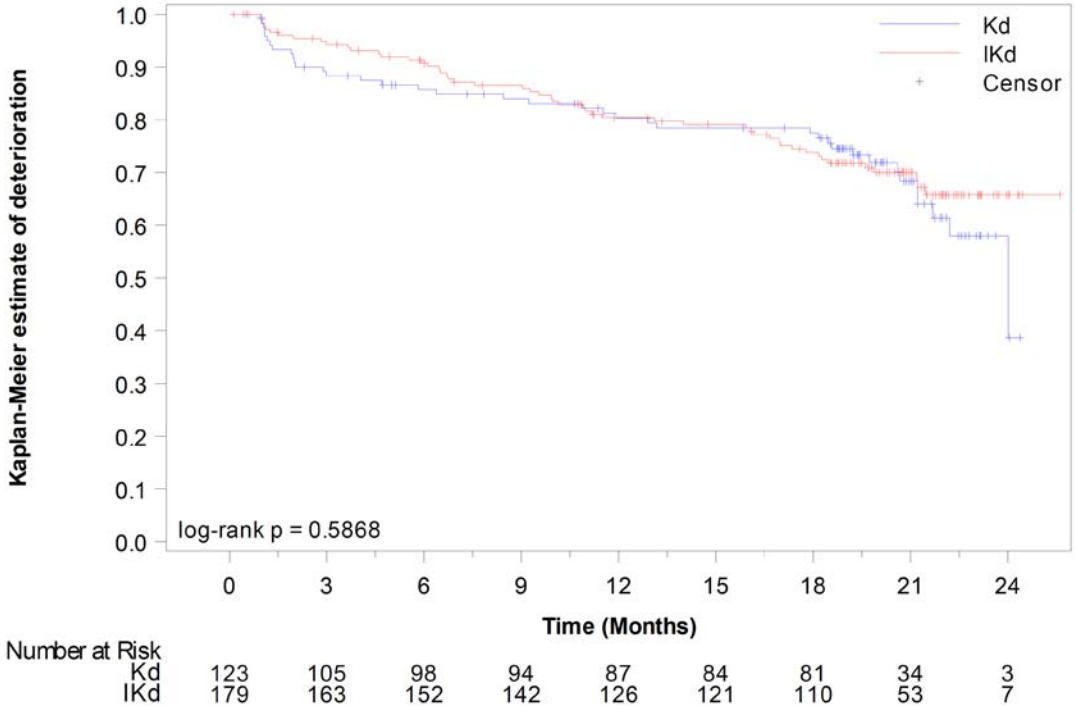


Figure 4: Kaplan-Meier curves on EORTC QLQ-C30, dyspnoea, time to definitive deterioration by ≥ 10 points (IKEMA study)

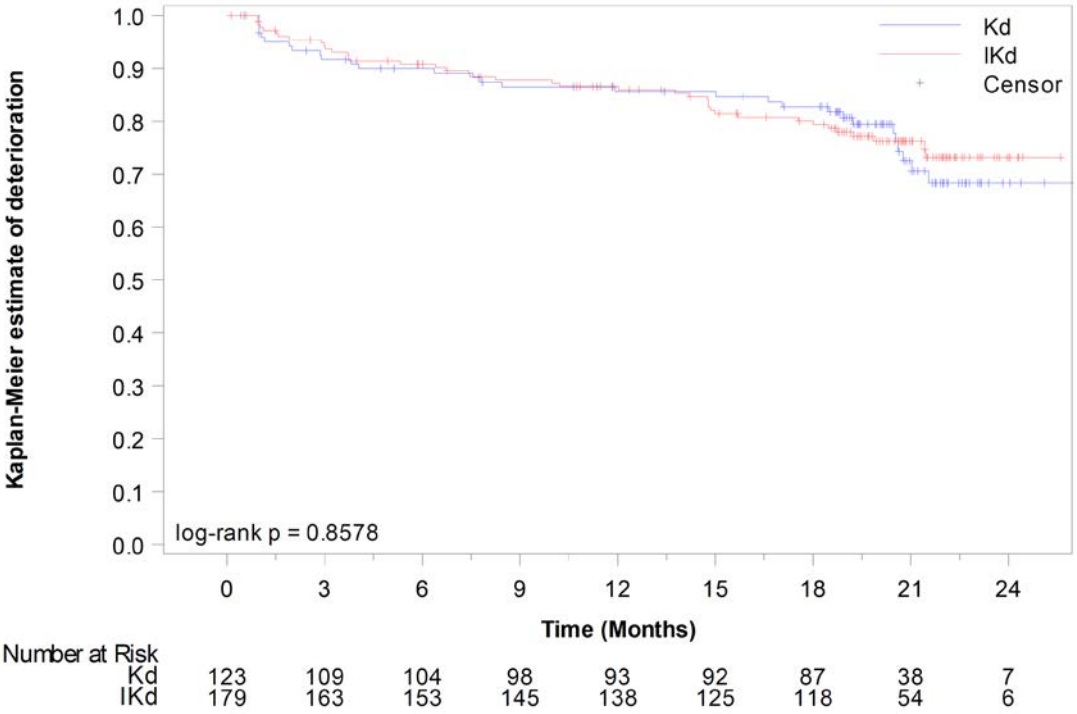


Figure 5: Kaplan-Meier curves on EORTC QLQ-C30, sleeplessness, time to definitive deterioration by ≥ 10 points (IKEMA study)

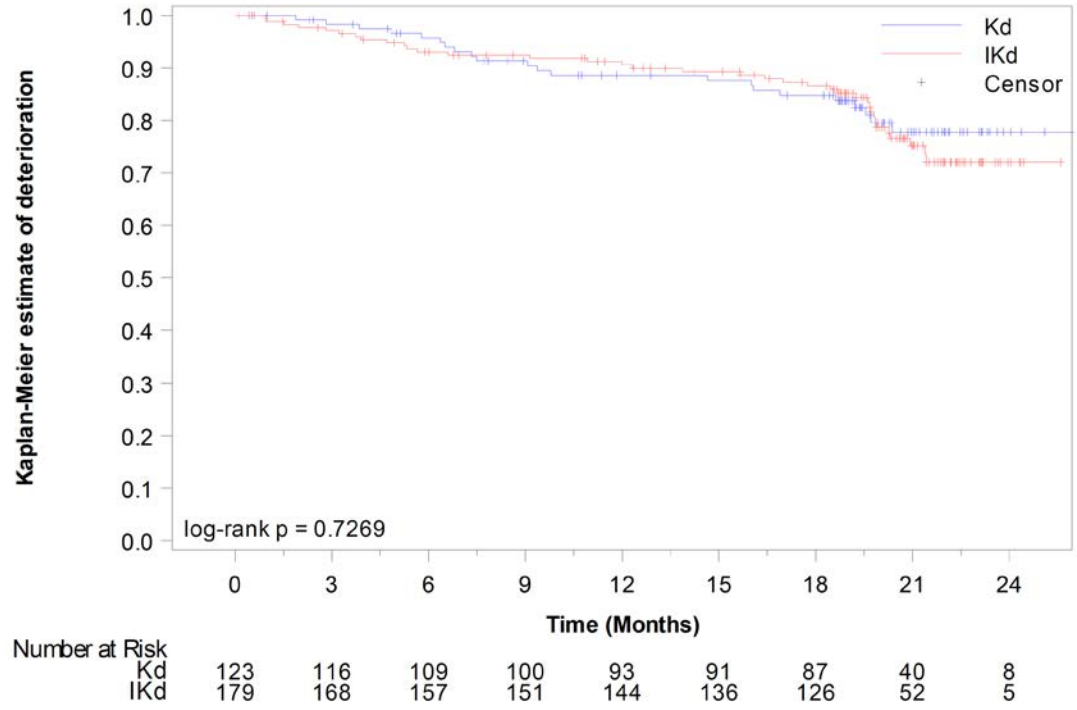


Figure 6: Kaplan-Meier curves on EORTC QLQ-C30, appetite loss, time to definitive deterioration by ≥ 10 points (IKEMA study)

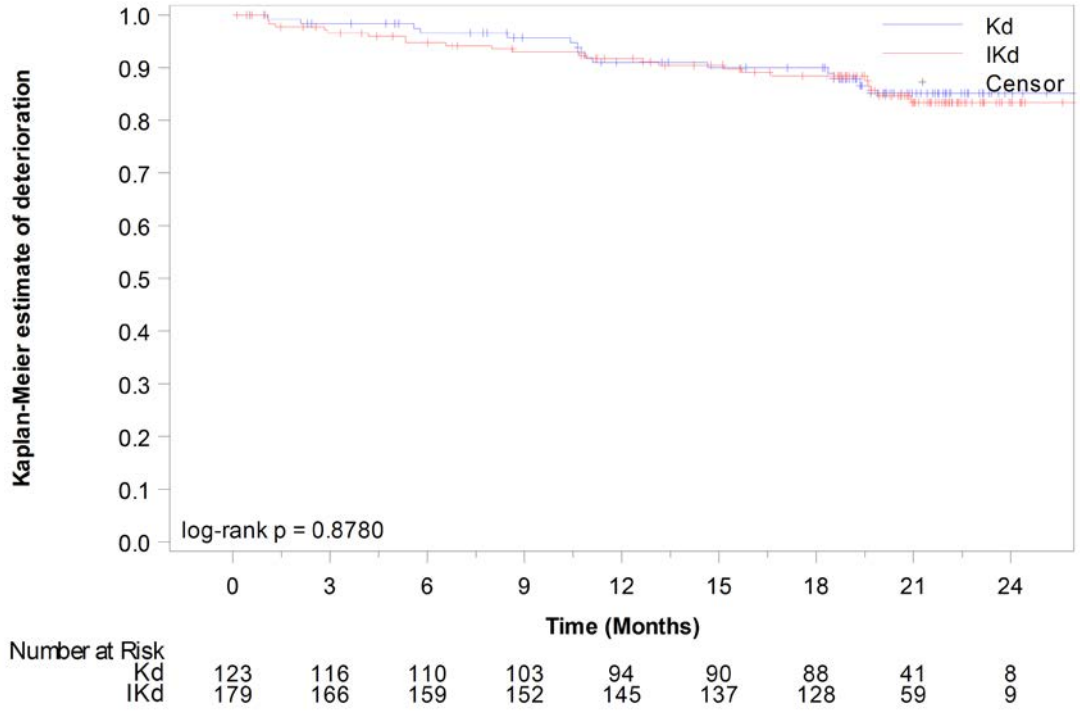


Figure 7: Kaplan-Meier curves on EORTC QLQ-C30, constipation, time to definitive deterioration by ≥ 10 points (IKEMA study)

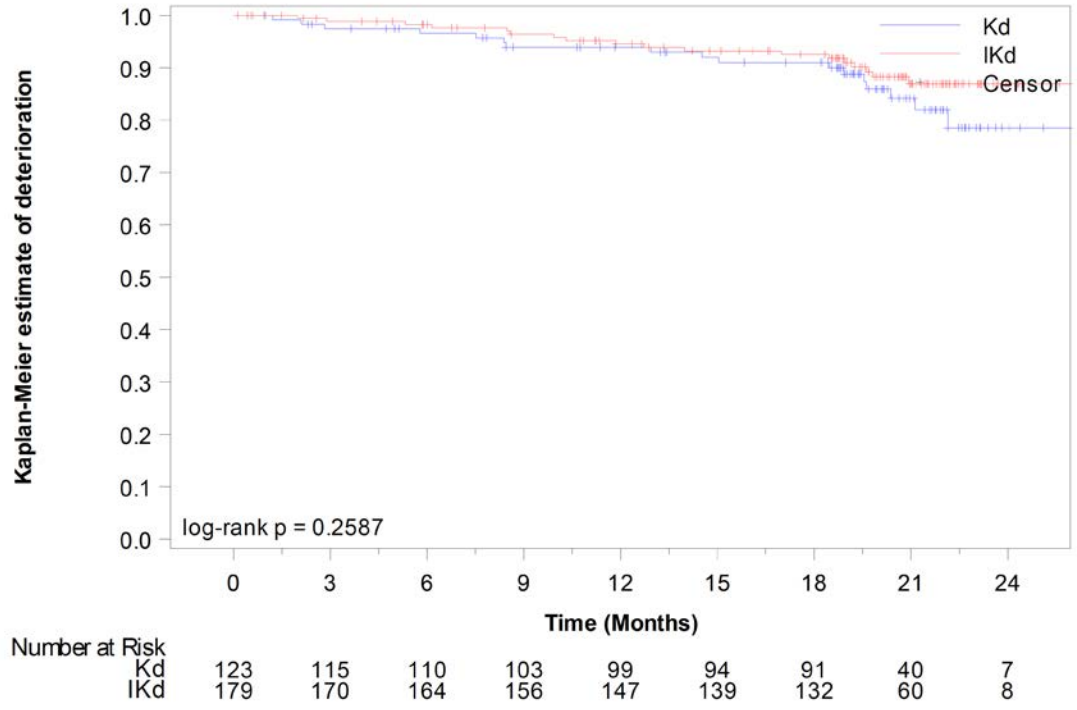


Figure 8: Kaplan-Meier curves on EORTC QLQ-C30, diarrhoea, time to definitive deterioration by ≥ 10 points (IKEMA study)

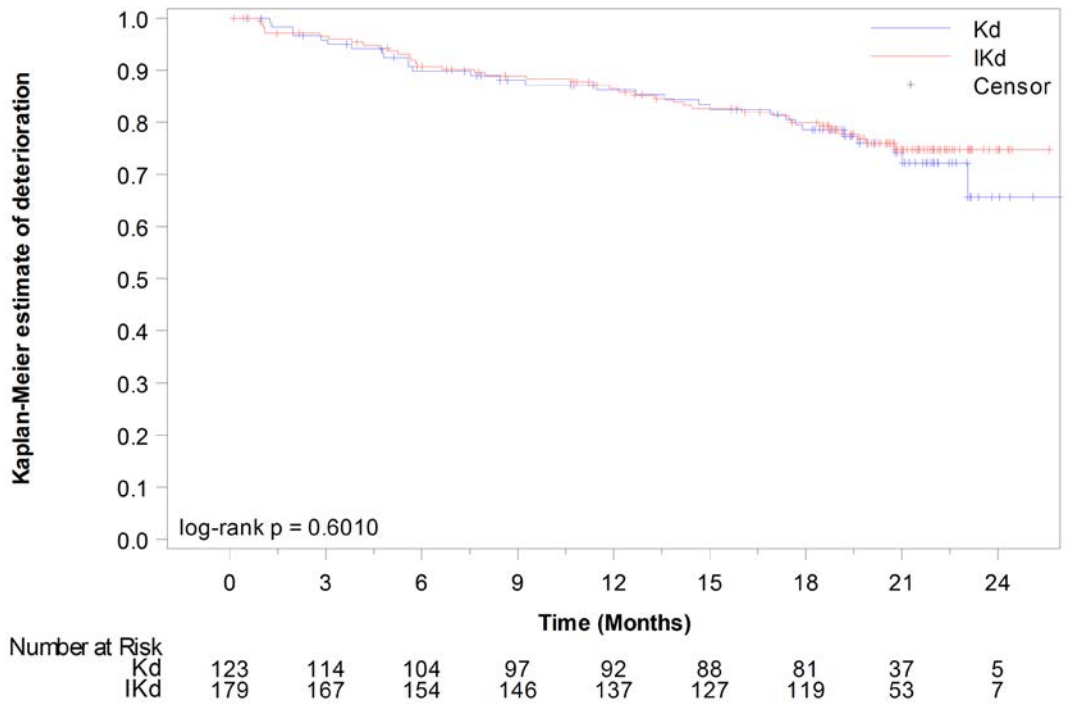


Figure 9: Kaplan-Meier curves on EORTC QLQ-MY20, disease symptoms, time to definitive deterioration by ≥ 10 points (IKEMA study)

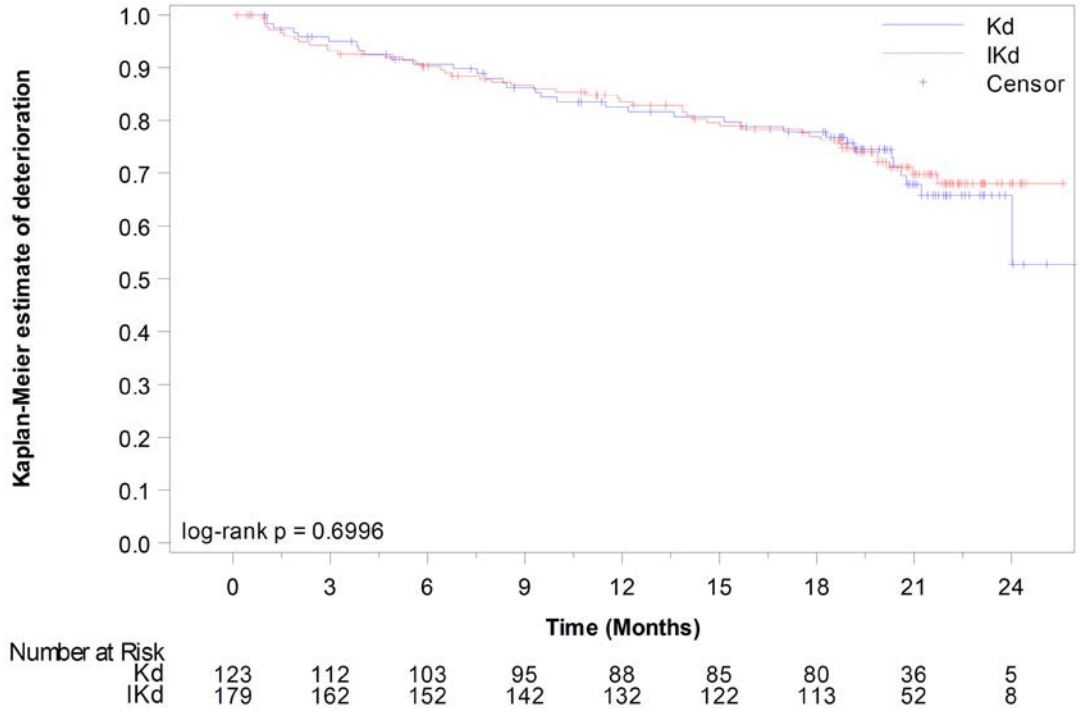


Figure 10: Kaplan-Meier curves on EORTC QLQ-MY20, side effects, time to definitive deterioration by ≥ 10 points (IKEMA study)

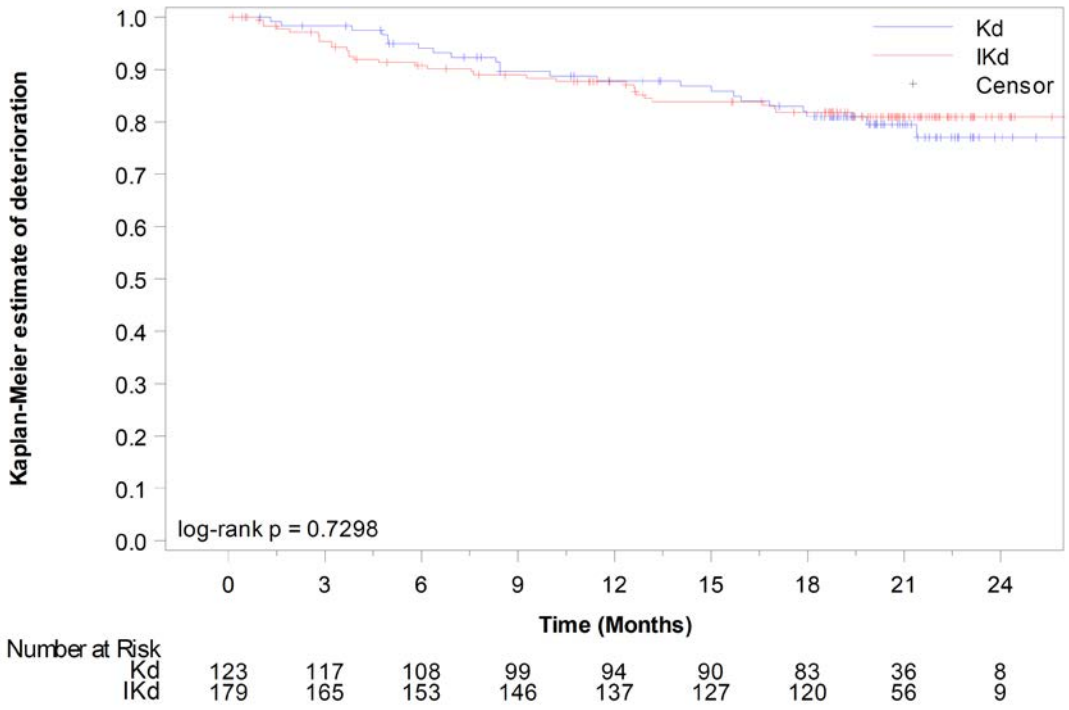


Figure 11: Kaplan-Meier curves on EQ-5D VAS, time to definitive deterioration by ≥ 15 points (IKEMA study)

## B.2 Health-related quality of life

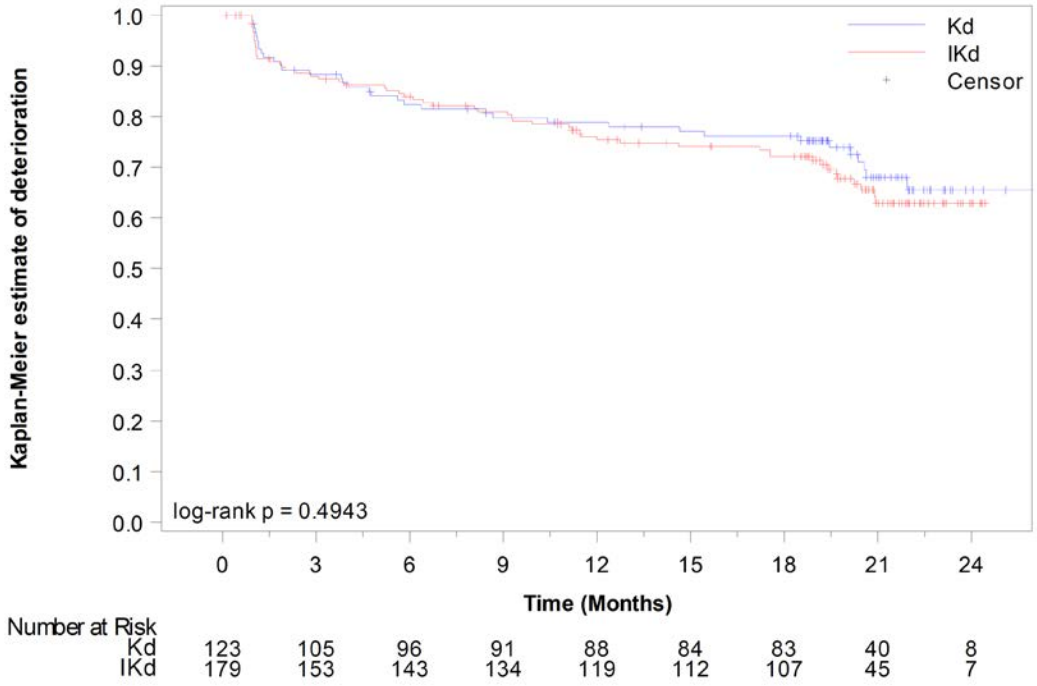


Figure 12: Kaplan-Meier curves on EORTC QLQ-C30, global health status, time to definitive deterioration by ≥ 10 points (IKEMA study)

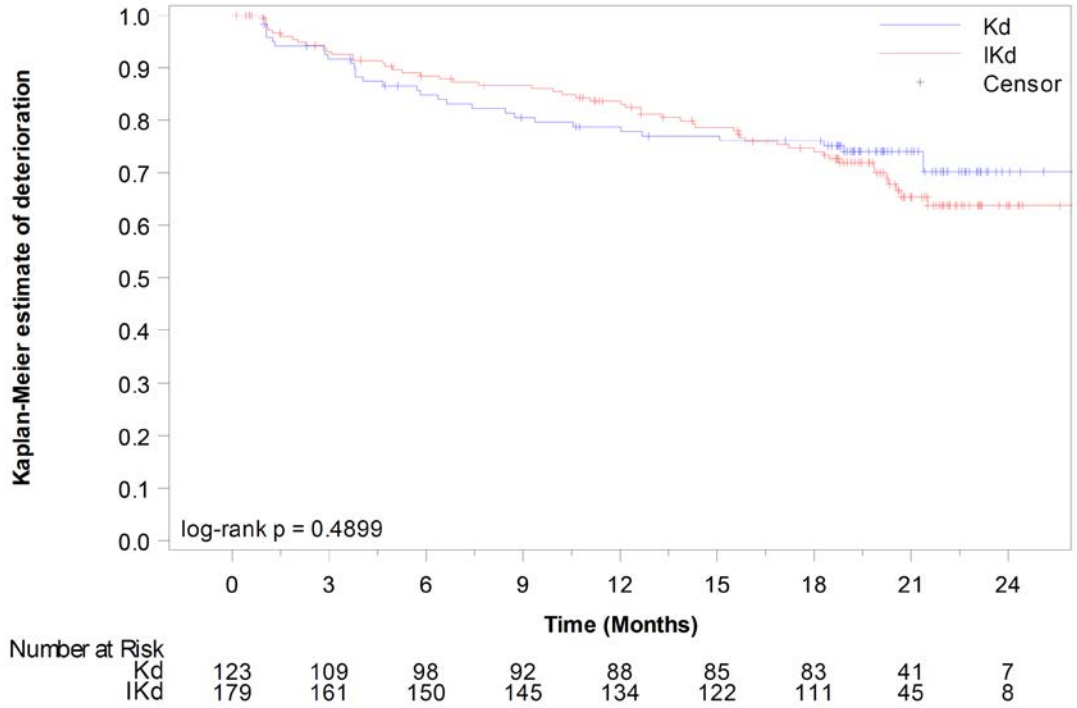


Figure 13: Kaplan-Meier curves on EORTC QLQ-C30, physical functioning, time to definitive deterioration by ≥ 10 points (IKEMA study)

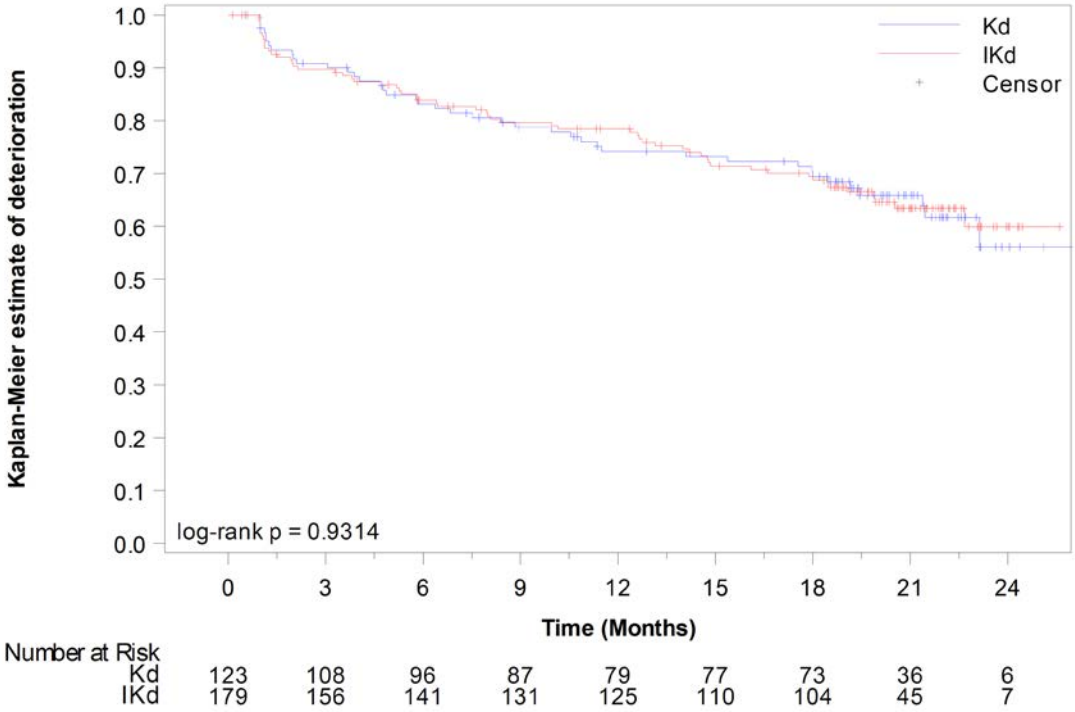


Figure 14: Kaplan-Meier curves on EORTC QLQ-C30, role functioning, time to definitive deterioration by ≥ 10 points (IKEMA study)

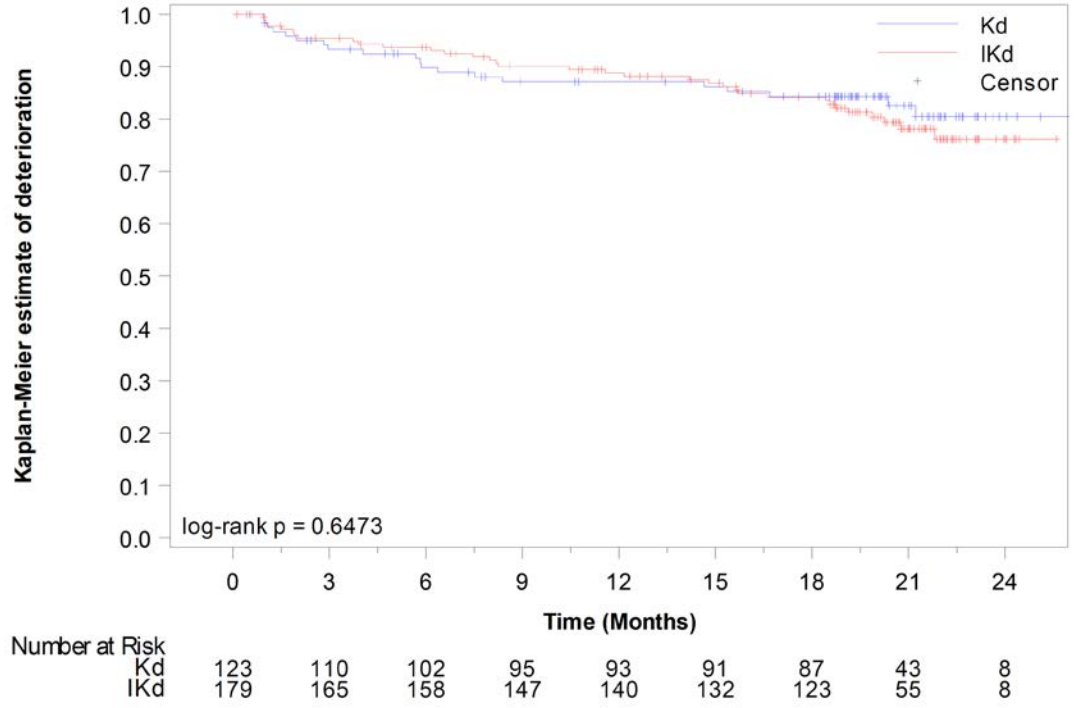


Figure 15: Kaplan-Meier curves on EORTC QLQ-C30, emotional functioning, time to definitive deterioration by ≥ 10 points (IKEMA study)

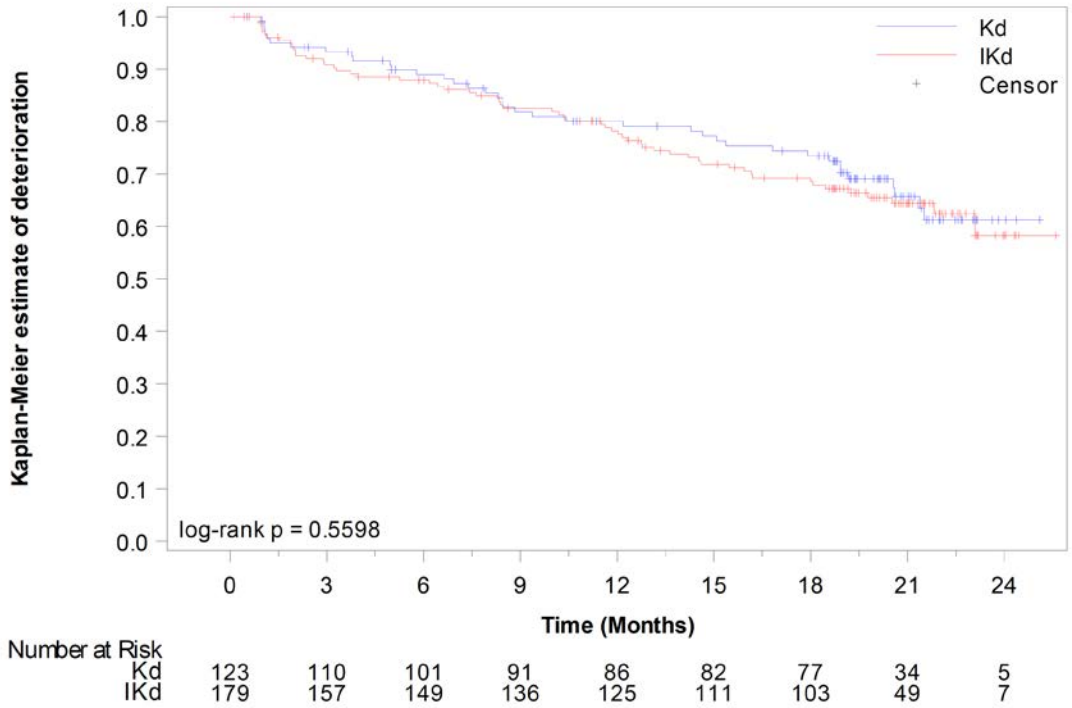


Figure 16: Kaplan-Meier curves on EORTC QLQ-C30, cognitive functioning, time to definitive deterioration by ≥ 10 points (IKEMA study)

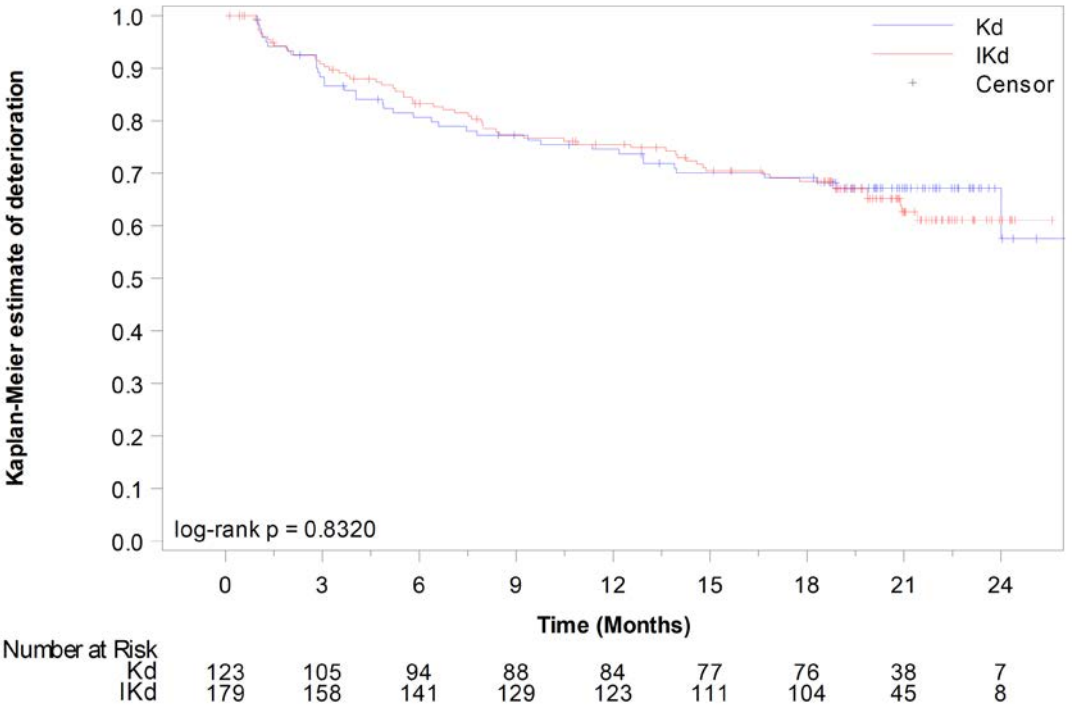


Figure 17: Kaplan-Meier curves on EORTC QLQ-C30, social functioning, time to definitive deterioration by ≥ 10 points (IKEMA study)

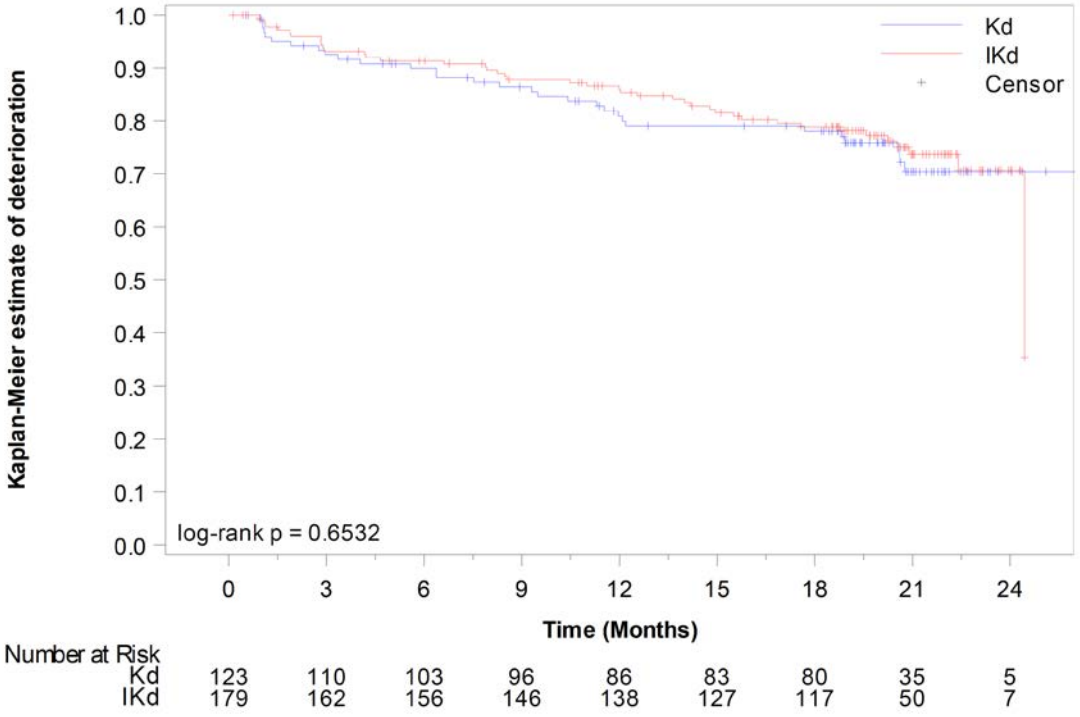


Figure 18: Kaplan-Meier curves on EORTC QLQ-MY20, body image, time to definitive deterioration by ≥ 10 points (IKEMA study)

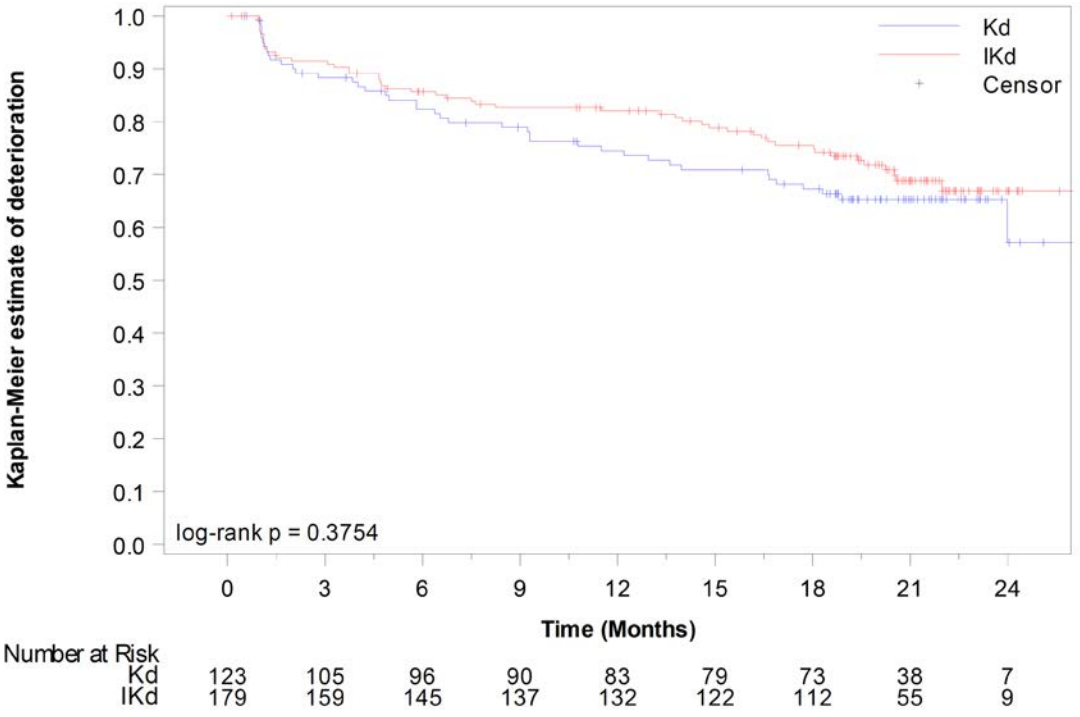


Figure 19: Kaplan-Meier curves on EORTC QLQ-MY20, future perspective, time to definitive deterioration by ≥ 10 points (IKEMA study)

### B.3 Side effects

No Kaplan-Meier curves are available for the outcome of discontinuation due to AEs (1 or more components).

### B.4 Subgroups

Regarding 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.