Durvalumab (urothelial carcinoma, neoadjuvant + adjuvant 1)

Addendum to Project A25-97 (dossier assessment)[1]

ADDENDUM (DOSSIER ASSESSMENT)

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Table of contents

List of tables

Page

List of figures

Page

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
AESI	adverse event of special interest
G-BA	Gemeinsamer Bundesausschuss
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
MIBC	muscle-invasive bladder cancer
PT	Preferred Term
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class

1 Background

On 9 December 2025, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Project A25-97 (Durvalumab – Benefit assessment according to § 35a Social Code Book V) [1].

The commission comprises the assessment of the following analyses presented by the pharmaceutical company (hereinafter referred to as “the company”) in the commenting procedure [2], taking into account the information provided in the dossier [3]:

- Data on the first subsequent antineoplastic therapy
- Recalculation of the analysis on safety based on adjusted censoring rules

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

2 Assessment

The randomized controlled trial (RCT) NIAGARA was used for the benefit assessment of durvalumab in combination with gemcitabine and cisplatin for neoadjuvant therapy followed by durvalumab as monotherapy for adjuvant therapy after radical cystectomy in comparison with the appropriate comparator therapy (ACT) in adults with resectable muscle-invasive bladder cancer (MIBC) for whom platinum-based chemotherapy is suitable. A detailed description of the study can be found in the dossier assessment [1].

In accordance with the commission, the data subsequently submitted by the company on the first subsequent antineoplastic therapy and on the outcomes of the side effects category from the NIAGARA study are assessed below, taking into account the information in the dossier.

2.1 Assessment of the data subsequently submitted on the first subsequent therapy

As described in benefit assessment A25-97 [1], the company did not provide any information on subsequent therapies in Module 4A. The CSR only provided details on all subsequent therapies used, based on the total population. Information on the first subsequent therapy was not available. As part of the comments, the company provided information on the first subsequent therapy based on the overall population.

Table 1 shows the subsequent therapy patients received after discontinuing the study medication.

Table 1: Information on subsequent antineoplastic therapies[a] – RCT, direct comparison: durvalumab + gemcitabine + cisplatin (neoadjuvant)/durvalumab (adjuvant) vs. gemcitabine + cisplatin (neoadjuvant)/watchful waiting (multipage table)

Study **drug class** **drug**	**Patients with subsequent therapy, n (%)**	
	durvalumab + gemcitabine + cisplatin/durvalumab **N = 533**	**gemcitabine + cisplatin/watchful waiting** **N = 530**
NIAGARA		
Total	53 (9.9)	93 (17.5)
Radiotherapy	18 (34.0[b])	21 (22.6[b])
Immunotherapy	8 (15.1[b])	40 (43.0[b])
Atezolizumab	0 (0[b])	8 (8.6[b])
Avelumab	0 (0[b])	1 (1.1[b])
Bintrafusp alfa	0 (0[b])	1 (1.1[b])
Blinded therapy	0 (0[b])	1 (1.1[b])
Cemiplimab	0 (0[b])	1 (1.1[b])
Durvalumab	0 (0[b])	1 (1.1[b])
Nivolumab	1 (1.9[b])	4 (4.3[b])
Pembrolizumab	7 (13.2[b])	23 (24.7[b])
SAR439459	0 (0[b])	1 (1.1[b])
Cytotoxic chemotherapy	25 (47.2[b])	33 (35.5[b])
Cabozantinib	1 (1.9[b])	1 (1.1[b])
Carboplatin	5 (9.4[b])	9 (9.7[b])
Cisplatin	7 (13.2[b])	15 (16.1[b])
Cisplatin/gemcitabine hydrochloride	0 (0[b])	1 (1.1[b])
Docetaxel	3 (5.7[b])	3 (3.2[b])
Doxorubicin	0 (0[b])	1 (1.1[b])
Fluorouracil/glucose	0 (0[b])	1 (1.1[b])
Gemcitabine	12 (22.6[b])	18 (19.4[b])
Gemcitabine hydrochloride	2 (3.8[b])	6 (6.5[b])
Methotrexate	0 (0[b])	1 (1.1[b])
Mitomycin	0 (0[b])	1 (1.1[b])
Nedaplatin	0 (0[b])	1 (1.1[b])
Paclitaxel	5 (9.4[b])	2 (2.2[b])
Vinblastine sulphate	0 (0[b])	1 (1.1[b])
Vinflunine	2 (3.8[b])	0 (0[b])
Targeted therapy	2 (3.8[b])	2 (2.2[b])
Enfortumab vedotin	1 (1.9[b])	0 (0[b])
Niraparib	1 (1.9[b])	0 (0[b])
Sacituzumab govitecan	0 (0[b])	1 (1.1[b])
Trastuzumab deruxtecan	0 (0[b])	1 (1.1[b])

Table 1: Information on subsequent antineoplastic therapies[a] – RCT, direct comparison: durvalumab + gemcitabine + cisplatin (neoadjuvant)/durvalumab (adjuvant) vs. gemcitabine + cisplatin (neoadjuvant)/watchful waiting (multipage table)

Study drug class drug	Patients with subsequent therapy, n (%)	
	durvalumab + gemcitabine + cisplatin/durvalumab N = 533	gemcitabine + cisplatin/watchful waiting N = 530
Other	3 (5.7[b])	1 (1.1[b])
Enfortumab vedotin	1 (1.9[b])	1 (1.1[b])
Enfortumab vedotin-ejfv	1 (1.9[b])	0 (0[b])
Letrozole	1 (1.9[b])	0 (0[b])

a. First subsequent therapy following discontinuation of treatment; information taken directly from study documents without adjustment.
b. Institute's calculation; percentages refer to the number of patients receiving subsequent antineoplastic therapy.
n: number of patients with subsequent therapy; N: number of analysed patients; RCT: randomized controlled trial

In its comments and in the data subsequently submitted, the company confirms that 45% of patients with recurrence in the intervention arm and 58% in the comparator arm received subsequent therapy [2].

The guideline recommendations for the advanced therapy stage of bladder cancer are decisive for the assessment of the administered subsequent therapies in the NIAGARA study. The choice of systemic therapy for advanced or metastatic bladder cancer depends on whether and which platinum-based therapy is suitable for the patient. For patients for whom platinum-based therapy is suitable, the use of enfortumab vedotin in combination with pembrolizumab is recommended as the preferred first-line standard by the German Society for Haematology and Medical Oncology [4]. Based on the patients who received a first subsequent therapy, 6% of patients in the intervention arm and 1% of patients in the comparator arm received enfortumab vedotin as their first subsequent therapy. It is not clear from the information provided whether this was a combination therapy with pembrolizumab. Uncertainties regarding the impact on overall survival entailed by the limited use of enfortumab vedotin in combination with pembrolizumab in the subsequent therapy are also addressed in the publication on the NIAGARA study [5].

In the comparator arm, only 43% of patients with subsequent therapy received immunotherapy as their first subsequent therapy. Based on patients with a recurrence, this proportion is even as low as 25%. In addition to enfortumab vedotin/pembrolizumab, the guidelines also recommend, depending on the patient's circumstances, the use of nivolumab in combination with cisplatin/gemcitabine or maintenance therapy with avelumab following

platinum-based chemotherapy [4]. As patients in the comparator arm had not previously received immunotherapy in the perioperative setting, the proportion of immunotherapies used in the comparator arm is to be rated as low against the background of the current guideline recommendations.

In summary, the data subsequently submitted in the commenting procedure do not alter the assessment from the dossier assessment. The limited use of enfortumab vedotin (in combination with pembrolizumab) as a subsequent therapy is comprehensible given that it was only approved after the data cut-off date. However, the subsequent therapies used in the NIAGARA study only provide an insufficient representation of the current health care context for advanced or metastatic bladder cancer. Furthermore, unlike in the intervention arm, the vast majority of patients in the comparator arm had not yet received an immune checkpoint inhibitor, not even as subsequent therapy. Against this background, the results regarding overall survival are still rated as uninterpretable.

2.2 Assessment of data subsequently submitted on the outcomes of the side effects category

2.2.1 Notes on outcomes

Side effects

As described in benefit assessment A25-97 [1], the effect estimates for the outcomes in the side effects category could not be interpreted and allowed only for a qualitative assessment. This was due to the fact that, in the Kaplan-Meier curves on the various outcomes, there were hardly any patients remaining at risk in the comparator arm after approximately 5 to 6 months, meaning that the adjuvant phase was barely covered. From this point onwards, events in the comparator arm carry significantly more weight than events occurring at the same time in the intervention arm, due to the much shorter observation period (intervention arm: 14.3 months; comparator arm: 5.3 months). Overall, based on the Kaplan-Meier curves available in the dossier, it cannot be assumed with sufficient certainty that the proportional hazards assumption was met in each case.

In its comments [2] and during the oral hearing [6], the company admitted that an incorrect censoring rule had been applied in the time-to-event analyses submitted in the dossier [3]. According to the company, this meant that patients without event in the comparator arm were incorrectly censored prematurely following the completion of neoadjuvant therapy. In the data subsequently submitted, patients without event were censored at the earliest of the following time points: death, initiation of subsequent therapy, data cut-off or last dose + 90 days; and, for the comparator arm, the last adjuvant study visit, provided this took place after the last study dose [2]. Accordingly, the adjuvant phase was also taken into account in the comparator arm without active treatment. Using these corrected censoring rules, the

company recalculated both the observation periods and the time-to-event analyses (including Kaplan-Meier curves) for the outcomes of the side effects category. The median corrected observation period was 14.3 months (minimum: 0.3 months; maximum: 24.6 months) in the intervention arm and 11.3 months (minimum: 0.3 months; maximum: 16.0 months) in the comparator arm. The median observation period for the outcomes in the side effects category is therefore slightly shorter in the comparator arm than in the intervention arm. The corrected censoring rules of the company are comprehensible. Therefore, the analyses subsequently submitted by the company on the outcomes in the side effects category may be used for the assessment of added benefit.

Discontinuation due to adverse events (AEs)

In the current data situation, there are no suitable data available for the outcome discontinuation due to AEs. This is justified below. Whilst active therapy was administered throughout the entire duration of the study in the intervention arm, patients in the comparator arm received active therapy only during the neoadjuvant phase; during the adjuvant phase, they were simply monitored during study visits. Consequently, treatment discontinuations in the comparator arm can only occur during the neoadjuvant phase, i.e. roughly during the first three months. During the subsequent adjuvant phase, the event discontinuation of treatment is no longer observed, even when AEs occur that would have led to discontinuation during active treatment. The Kaplan-Meier curves for the outcome discontinuation due to AEs (Figure 9) also show that, in the comparator arm, events occur only during the first 3 months, before a plateau is reached. For the reasons outlined above, the results on the outcome discontinuation due to AEs are not suitable for this benefit assessment.

Immune-mediated AEs

As described in benefit assessment A25-97 [1], AEs of special interest (AESI) for durvalumab, except for infusion-related reactions and hypersensitivity/anaphylactic reactions, can be used to illustrate immune-mediated AEs. However, the dossier did not provide any information on whether infusion-related reactions and hypersensitivity/anaphylactic reactions were subtracted from the AESI analyses. In its comments [2], the company confirms that infusion-related reactions and hypersensitivity/anaphylactic reactions were not considered in the analyses. The presented operationalization of the AESIs can therefore be used to illustrate immune-mediated AEs.

2.2.2 Risk of bias

The outcome-specific risk of bias of the results on the outcomes of the side effects category was rated as high. In each case, this was due to incomplete observations for potentially informative reasons. All outcomes in the side effects category were recorded up to 90 days after the last dose of the study medication (intervention arm) or the last adjuvant study visit

(comparator arm). Patients in whom no event occurred during the observation period were censored, as described in the section 'Notes on side effect outcomes'. Here, the median observation period differed between the arms (14.3 vs. 11.3 months). In particular, however, no information is available regarding the reasons for discontinuation during the adjuvant phase of the trial. It is therefore not possible to assess with sufficient certainty to what extent the reasons for discontinuation of the study medication, or for premature discontinuation of follow-up in the comparator arm, differ between the study arms. However, it must be assumed that the reasons for discontinuation during the adjuvant phase differ between the arms. For example, as described, treatment discontinuation due to AEs is only possible in the intervention arm.

For the specific AEs that are not serious or severe, another reason for a high risk of bias is the lack of blinding in subjective recording of outcomes. No suitable data are available for the outcome discontinuation due to AEs; therefore, the risk of bias of the results is not assessed.

2.2.3 Results

Table 2 shows the results of the analyses subsequently submitted for the outcomes of the side effects category. The Kaplan-Meier curves on time-to-event analyses are presented in Appendix A of the full dossier assessment. Results on common AEs, serious AEs (SAEs), severe AEs, as well as results on common immune-mediated AEs, immune-mediated SAEs, and immune-mediated severe AEs, are presented in dossier assessment A25-97 [1].

Table 2: Results (side effects) – RCT, direct comparison: durvalumab + gemcitabine + cisplatin (neoadjuvant)/durvalumab (adjuvant) vs. gemcitabine + cisplatin (neoadjuvant)/watchful waiting: (multipage table)

Study outcome category outcome	Durvalumab + gemcitabine + cisplatin/durvalumab		Gemcitabine + cisplatin/watchful waiting		Durvalumab + gemcitabine + cisplatin/durvalumab vs. gemcitabine + cisplatin/watchful waiting
	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[a]
NIAGARA					
Side effects					
AEs (supplementary information)	530	0.1 [0.1; 0.1] 527 (99.4)	526	0.1 [0.1; 0.2] 525 (99.8)	–
SAEs	530	5.3 [4.7; 6.1] 326 (61.5)	526	6.0 [5.1; 8.2] 287 (54.6)	1.10 [0.93; 1.29]; 0.263
Severe AEs[b]	530	3.3 [2.7; 3.8] 380 (71.7)	526	2.7 [2.3; 3.5] 365 (69.4)	0.95 [0.82; 1.10]; 0.500
Discontinuation due to AEs	No suitable data[c]				
Immune-mediated AEs (supplementary information)	530	9.9 [8.0; 13.9] 262 (49.4)	526	NA 139 (26.4)	–
Immune-mediated SAEs	530	NA 24 (4.5)	526	NA 5 (1.0)	4.48 [1.85; 13.31]; < 0.001
Immune-mediated severe AEs[b]	530	NA 23 (4.3)	526	NA 7 (1.3)	3.11 [1.40; 7.85]; 0.006
Skin and subcutaneous tissue disorders (SOC, AEs)	530	14.5 [10.6; NC] 237 (44.7)	526	NA 157 (29.8)	1.55 [1.27; 1.91]; < 0.001
Pulmonary embolism (PT, SAEs)	530	NA 18 (3.4)	526	NA 5 (1.0)	3.50 [1.40; 10.59]; 0.008
Anaemia (PT, SAEs)	530	NA 5 (0.9)	526	NA 17 (3.2)	0.28 [0.09; 0.72]; 0.008
Cardiac disorders (SOC, severe AEs[b])	530	NA 23 (4.3)	526	NA 10 (1.9)	2.16 [1.06; 4.76]; 0.038

a. HR and CI from unstratified Cox proportional hazards model; p-value from unstratified log-rank test.
b. Operationalized as CTCAE grade ≥ 3.
c. See Section 2.2.1 for a rationale.

Table 2: Results (side effects) – RCT, direct comparison: durvalumab + gemcitabine + cisplatin (neoadjuvant)/durvalumab (adjuvant) vs. gemcitabine + cisplatin (neoadjuvant)/watchful waiting: (multipage table)

Study outcome category outcome	Durvalumab + gemcitabine + cisplatin/durvalumab		Gemcitabine + cisplatin/watchful waiting		Durvalumab + gemcitabine + cisplatin/durvalumab vs. gemcitabine + cisplatin/watchful waiting
	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[a]
AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NC: not calculable; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class					

On the basis of the available information, at most hints, e.g. of an added benefit, can be determined for outcomes in the side effects category.

Side effects

SAEs and severe AEs

No statistically significant difference between treatment groups was shown for either of the outcomes of SAEs and severe AEs. There is no hint of greater or lesser harm from durvalumab + gemcitabine + cisplatin (neoadjuvant) followed by durvalumab (adjuvant) in comparison with gemcitabine + cisplatin (neoadjuvant) followed by watchful waiting; greater or lesser harm is therefore not proven.

Discontinuation due to AEs

No suitable data were available for the outcome discontinuation due to AEs. There is no hint of greater or lesser harm from durvalumab + gemcitabine + cisplatin (neoadjuvant) followed by durvalumab (adjuvant) in comparison with gemcitabine + cisplatin (neoadjuvant) followed by watchful waiting; greater or lesser harm is therefore not proven.

Immune-mediated SAEs and immune-mediated severe AEs

A statistically significant difference to the disadvantage of the intervention was found for each of the outcomes of immune-related SAEs and immune-related severe AEs. In each case, there was a hint of greater harm from durvalumab + gemcitabine + cisplatin (neoadjuvant) followed by durvalumab (adjuvant) in comparison with gemcitabine + cisplatin (neoadjuvant) followed by watchful waiting.

Other specific AEs

Skin and subcutaneous tissue disorders (System Organ Class [SOC], AEs), pulmonary embolism (Preferred Term [PT], SAEs) and cardiac disorders (SOC, severe AEs)

For each of the outcomes skin and subcutaneous tissue disorders (SOC, AEs), pulmonary embolism (PT, SAEs) and cardiac disorders (SOC, severe AEs), there is a statistically significant difference to the disadvantage of the intervention. In each case, there was a hint of greater harm from durvalumab + gemcitabine + cisplatin (neoadjuvant) followed by durvalumab (adjuvant) in comparison with gemcitabine + cisplatin (neoadjuvant) followed by watchful waiting.

Anaemia (PT, SAEs)

There was a statistically significant difference in favour of the intervention for the outcome anaemia (PT, SAEs). There was a hint of lesser harm from durvalumab + gemcitabine + cisplatin (neoadjuvant) followed by durvalumab (adjuvant) in comparison with gemcitabine + cisplatin (neoadjuvant) followed by watchful waiting.

2.2.4 Subgroups and other effect modifiers

The subgroup characteristics age (< 65 vs. ≥ 65 years), sex (male vs. female) and clinical tumour status at baseline according to the IVRS (T2N0 vs. > T2N0) are considered for this addendum (see also benefit assessment A25-97 [1]).

In the subsequently submitted analyses of the side effects category, the company presented subgroup analyses for the outcomes SAEs, severe AEs, immune-mediated SAEs and immune-mediated severe AEs. However, subgroup analyses at SOC/PT level were missing in the analyses. These analyses would be necessary for a comprehensive balancing of the added benefit, however.

Based on the available subgroup results for the outcomes SAEs, severe AEs, immune-mediated SAEs and immune-mediated severe AEs, no effect modifications were shown when the methods described in dossier assessment A25-97 were applied. It is not possible to assess whether effect modifications occur in the AE outcomes of further specific AEs. However, it is not assumed that this uncertainty regarding individual SOCs and PTs will affect the overall assessment, as there are no effect modifications in the overall rates of the present AE outcomes and immune-mediated AEs.

2.3 Probability and extent of added benefit

The probability and extent of added benefit at outcome level are derived below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [7].

The approach for deriving an overall conclusion on the added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

2.3.1 Assessment of added benefit at outcome level

The extent of the added benefit at outcome level was estimated based on the results presented in Table 2. Table 3 only presents the results of the side effect outcomes assessed in the present addendum.

Table 3: Extent of added benefit at outcome level: durvalumab + gemcitabine + cisplatin (neoadjuvant)/durvalumab (adjuvant) vs. gemcitabine + cisplatin (neoadjuvant)/watchful waiting (multipage table)

Outcome category **outcome** **effect modifier** **subgroup**	**Durvalumab + gemcitabine + cisplatin/durvalumab vs. gemcitabine + cisplatin/watchful waiting** **median time to event (months)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Outcomes with shortened observation period		
Side effects		
SAEs	5.3 vs. 6.0 HR: 1.10 [0.93; 1.29]; p = 0.263	Greater/lesser harm not proven
Severe AEs	3.3 vs. 2.7 HR: 0.95 [0.82; 1.10]; p = 0.500	Greater/lesser harm not proven
Discontinuation due to AEs	No suitable data	Greater/lesser harm not proven
Immune-mediated SAEs	NA vs. NA HR: 4.48 [1.85; 13.31] HR: 0.22 [0.08; 0.54][c]; p < 0.001 probability: hint	Outcome category: serious/severe side effects CI_u < 0.75, risk < 5 % greater harm, extent: “considerable”
Immune-related severe AEs	NA vs. NA HR: 3.11 [1.40; 7.85] HR: 0.32 [0.13; 0.71][c]; p = 0.006 probability: hint	Outcome category: serious/severe side effects CI_u < 0.75, risk < 5 % greater harm, extent: “considerable”
Skin and subcutaneous tissue disorders (AEs)	14.5 vs. NA HR: 1.55 [1.27; 1.91] HR: 0.65 [0.52; 0.79][c]; p < 0.001 probability: hint	Outcome category: non-serious/non-severe side effects CI_u < 0.80 greater harm, extent: “considerable”

Table 3: Extent of added benefit at outcome level: durvalumab + gemcitabine + cisplatin (neoadjuvant)/durvalumab (adjuvant) vs. gemcitabine + cisplatin (neoadjuvant)/watchful waiting (multipage table)

Outcome category **outcome** **effect modifier** **subgroup**	**Durvalumab + gemcitabine + cisplatin/durvalumab vs. gemcitabine + cisplatin/watchful waiting** **median time to event (months)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Pulmonary embolism (SAEs)	NA vs. NA HR: 3.50 [1.40; 10.59] HR: 0.29 [0.09; 0.71][c]; p = 0.008 probability: hint	Outcome category: serious/severe side effects CI_u < 0.75, risk < 5 % greater harm, extent: “considerable”
Anaemia (SAEs)	NA vs. NA HR: 0.28 [0.09; 0.72]; p = 0.008 probability: hint	Outcome category: serious/severe side effects CI_u < 0.75, risk < 5 % lesser harm, extent: considerable
Cardiac disorders (severe AEs)	NA vs. NA HR: 2.16 [1.06; 4.76] HR: 0.46 [0.21; 0.94][c]; p = 0.038 probability: hint	Outcome category: serious/severe side effects 0.90 ≤ CI_u < 1.00 greater harm, extent: minor

a. Probability provided if there is a statistically significant and relevant effect.
b. Depending on the outcome category, estimations of effect size are made with different limits based on the upper limit of the confidence interval (CI_u).
c. Institute's calculation; inverse direction of effect to enable use of limits to derive the extent of the added benefit.

AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; HR: hazard ratio; NA: not achieved; SAE: serious adverse event

2.3.2 Overall conclusion on added benefit

Table 4 summarizes the results taken into account for the overall conclusion on the extent of the added benefit.

Table 4: Positive and negative effects from the assessment of durvalumab + gemcitabine + cisplatin (neoadjuvant)/durvalumab (adjuvant) in comparison with the ACT

Positive effects	**Negative effects**
Outcomes with observation over the entire study duration	
Morbidity serious/severe symptoms/late complications ▪ failure of the curative treatment approach: indication of an added benefit – extent: "considerable"	–
Outcomes with shortened observation period	
–	Health-related quality of life EORTC QLQ-C30: ▪ role functioning ▫ female: hint of lesser benefit – extent: "minor" ▪ social functioning ▫ female: hint of lesser benefit – extent: "minor"
Serious/severe side effects ▪ anaemia (SAEs): hint of lesser harm – extent: "considerable"	Serious/severe side effects ▪ immune-mediated SAEs: hint of greater harm – extent: "considerable" ▪ immune-related severe AEs: hint of greater harm – extent "considerable" ▪ pulmonary embolism (SAEs): hint of greater harm – extent: "considerable" ▪ cardiac disorders (severe AEs): hint of greater harm – extent: "minor"
–	Non-serious/non-severe side effects ▪ skin and subcutaneous tissue disorders (AEs): hint of greater harm – extent: "considerable"
No suitable data are available for the outcomes overall survival, discontinuation due to AEs and PRO-CTCAE.	
AE: adverse event; EORTC: European Organisation for Research and Treatment of Cancer; PRO-CTCAE: Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events; QLQ-C30: Quality of Life Questionnaire-Core 30; SAE: serious adverse event	

Compared with benefit assessment A25-97, a quantification of the added benefit is possible due to the subsequently submitted analyses for the outcomes of the side effects category.

In the overall consideration, there were both positive and negative effects of durvalumab + gemcitabine + cisplatin (neoadjuvant) followed by durvalumab (adjuvant) in comparison with gemcitabine + cisplatin (neoadjuvant) followed by watchful waiting. For the outcomes in the categories health-related quality of life, serious/severe side effects and non-serious/non-severe side effects, these relate exclusively to the shortened period (until disease recurrence, initiation of subsequent therapy or study discontinuation, or up to 90 days after the last dose of the study medication [intervention arm] or after the last adjuvant study visit [comparator arm]).

In terms of positive effects, there is an indication of considerable added benefit for the outcome failure of the curative treatment approach. In addition, there is a hint of lesser harm in the outcome category serious/severe side effects with the extent “considerable”. In contrast, there are negative effects in two aspects of health-related quality of life, which are shown in the subgroup of women due to effect modification. In addition, negative effects with the extent ‘considerable’ or ‘minor’ are shown in the serious/severe side effects for several outcomes. A negative effect with the extent ‘considerable’ is shown in a specific AE for the non-serious/non-severe side effects,.

In summary, for patients with resectable MIBC for whom platinum-based chemotherapy is suitable, there is an indication of minor added benefit of durvalumab in combination with gemcitabine and cisplatin for neoadjuvant treatment, followed by durvalumab as monotherapy for adjuvant treatment, compared with the ACT.

2.4 Summary

The data subsequently submitted by the company in the commenting procedure have not changed the conclusion on the added benefit of durvalumab in combination with gemcitabine and cisplatin for neoadjuvant treatment, followed by durvalumab monotherapy for adjuvant treatment from dossier assessment A25-97.

Table 5 below shows the result of the benefit assessment of durvalumab + gemcitabine + cisplatin (neoadjuvant)/durvalumab (adjuvant) taking into account dossier assessment A25-97 and this present addendum.

Table 5: Durvalumab + gemcitabine + cisplatin (neoadjuvant)/durvalumab (adjuvant) – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Adults with resectable muscle-invasive bladder cancer (MIBC) for whom platinum-based chemotherapy is suitable; neoadjuvant and adjuvant therapy after radical cystectomy	A therapy regimen consisting of[b] ▪ neoadjuvant therapy with cisplatin in combination with gemcitabine followed by radical cystectomy and: ▫ watchful waiting or ▫ nivolumab (is only an option for patients with tumour cell programmed cell death ligand 1 (PD-L1) expression ≥ 1% and at high risk of recurrence following radical resection)	Indication of minor added benefit[c]

a. Presented is the ACT specified by the G-BA.
b. The ACT specified here comprises several alternative treatment options. However, individual treatment options only represent a comparator therapy for those members of the patient population who meet the patient and disease characteristics shown in brackets.
c. Only patients with an ECOG PS of 0 or 1 were included in the NIAGARA study. It remains unclear whether the observed effects are transferable to patients with an ECOG PS ≥ 2.

ACT: appropriate comparator therapy; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee; PD-L1: programmed cell death ligand 1

The G-BA decides on the added benefit.

3 References

The reference list contains citations provided by the company in which bibliographical information may be missing.

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Appendix A Kaplan-Meier curves

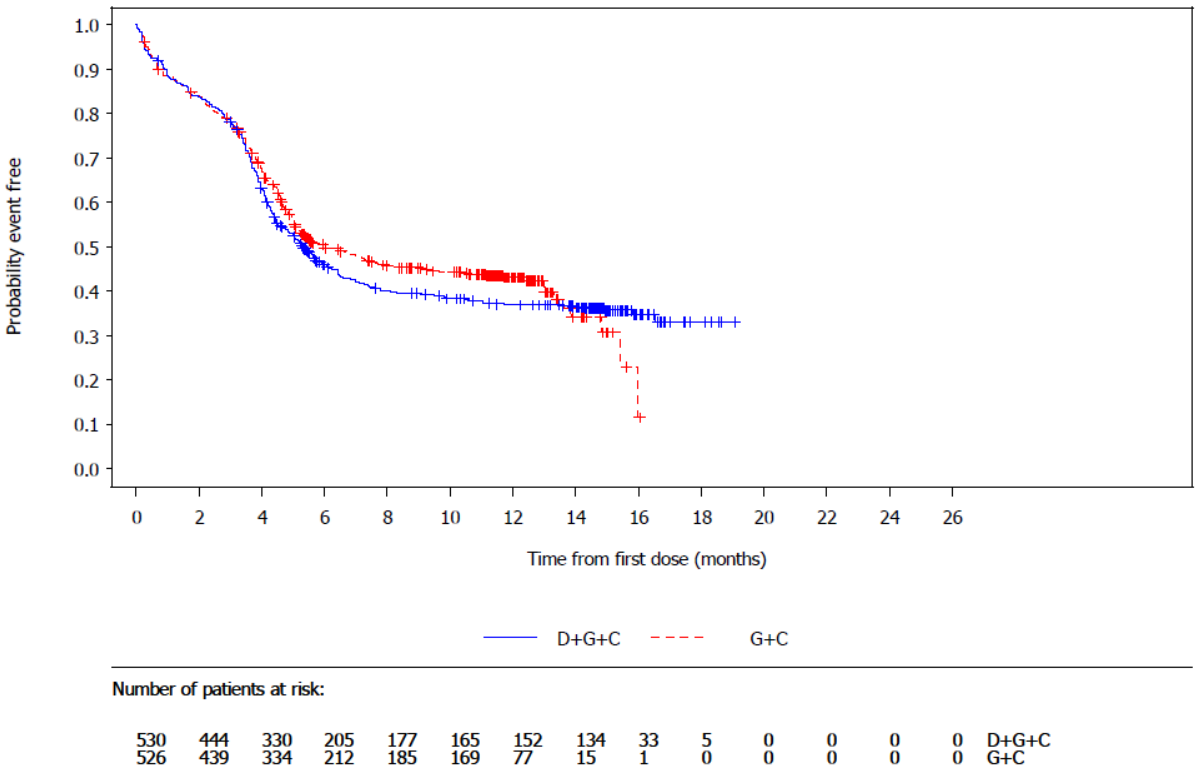

Figure 1: Kaplan-Meier curves for the outcome SAEs

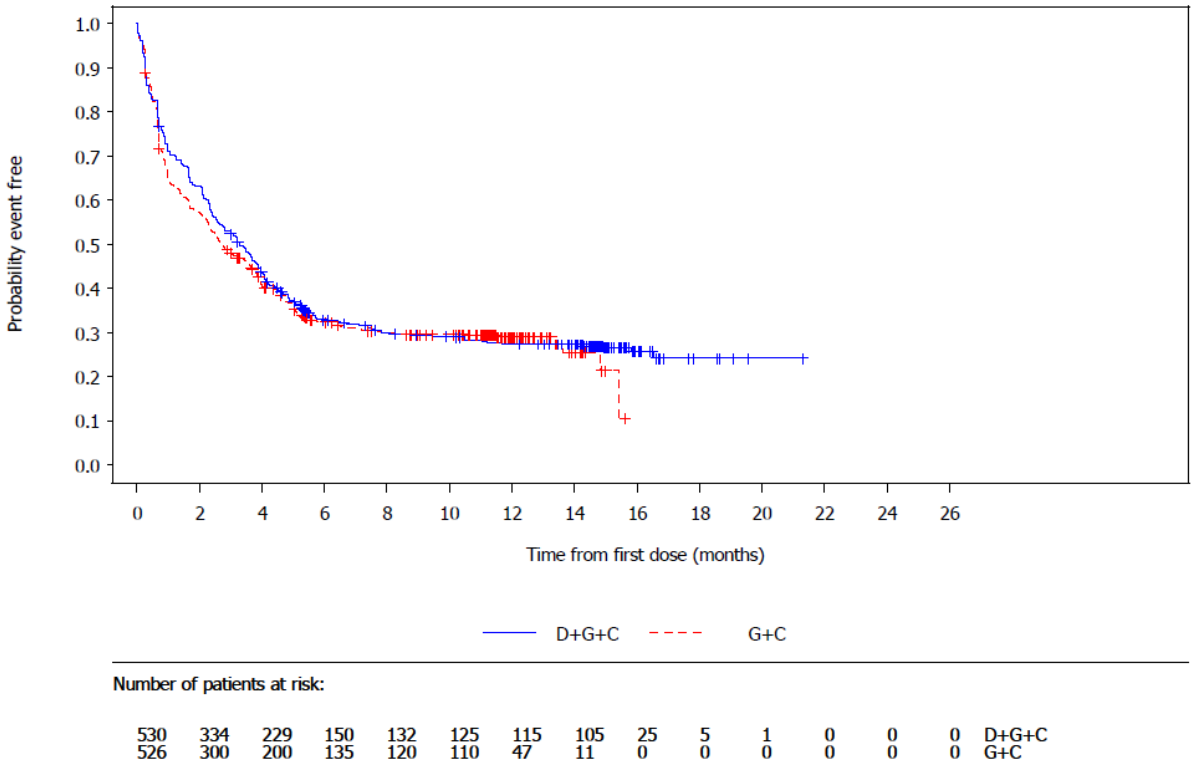

Figure 2: Kaplan-Meier curves for the outcome severe AEs (CTCAE grade ≥ 3)

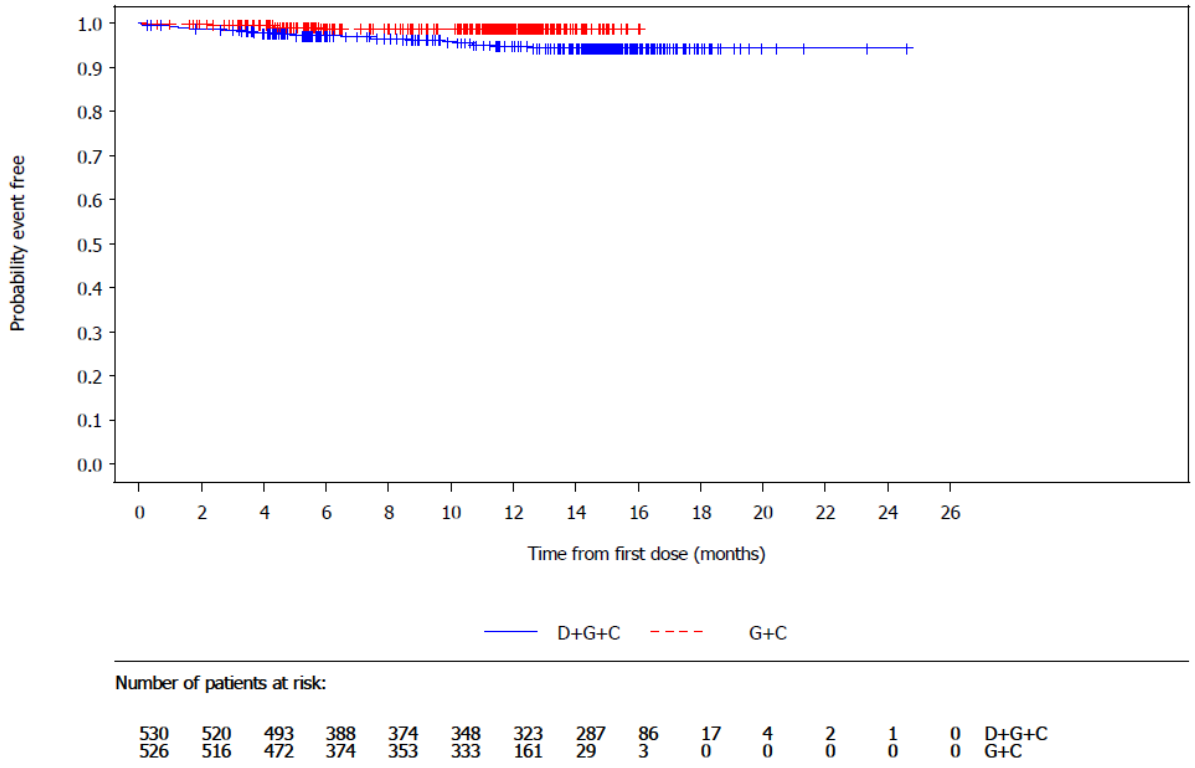

Figure 3: Kaplan-Meier curves for the outcome immune-mediated SAEs

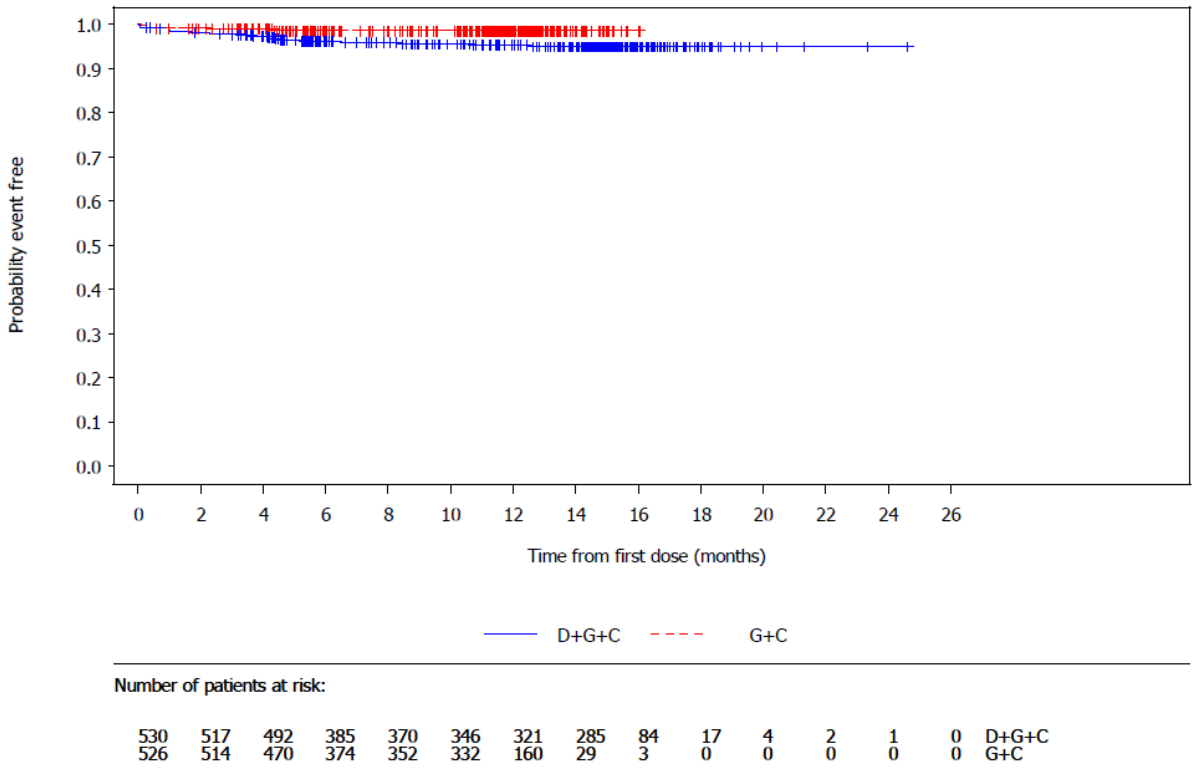

Figure 4: Kaplan-Meier curves for the outcome immune-mediated severe AEs (CTCAE grade ≥ 3)

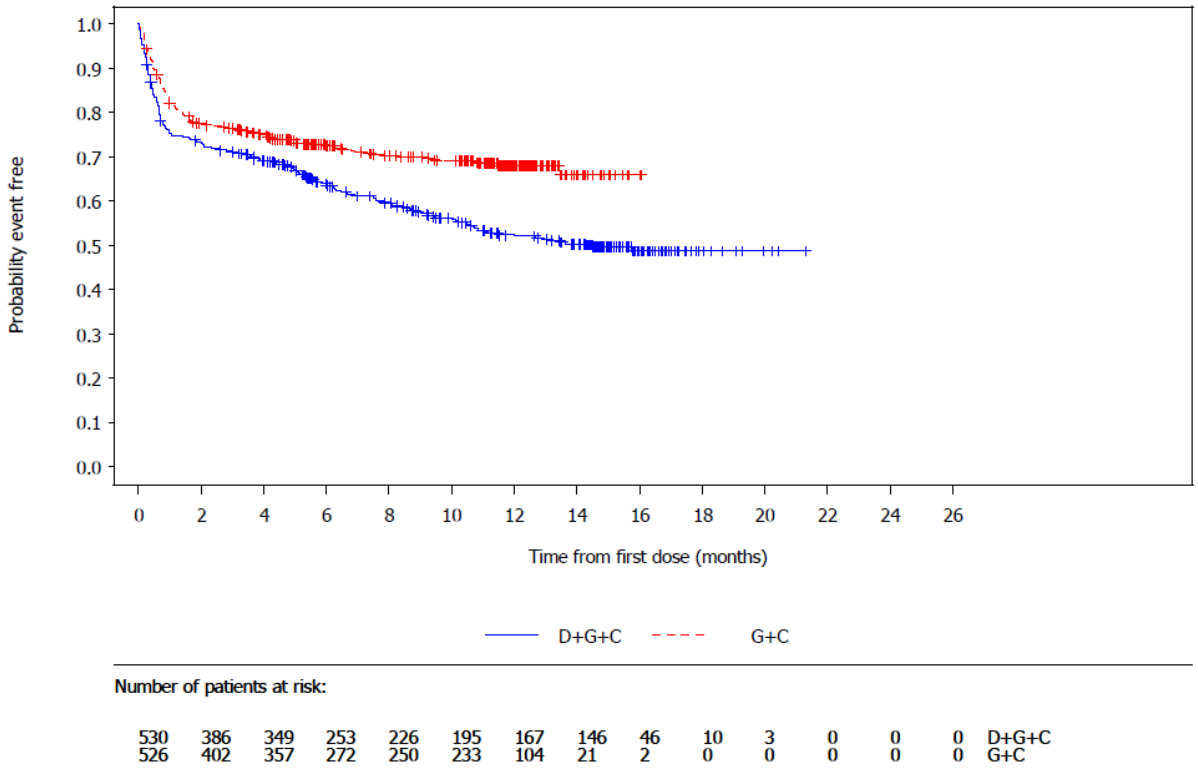

Figure 5: Kaplan-Meier curves for the outcome skin and subcutaneous tissue disorders (SOC, AEs)

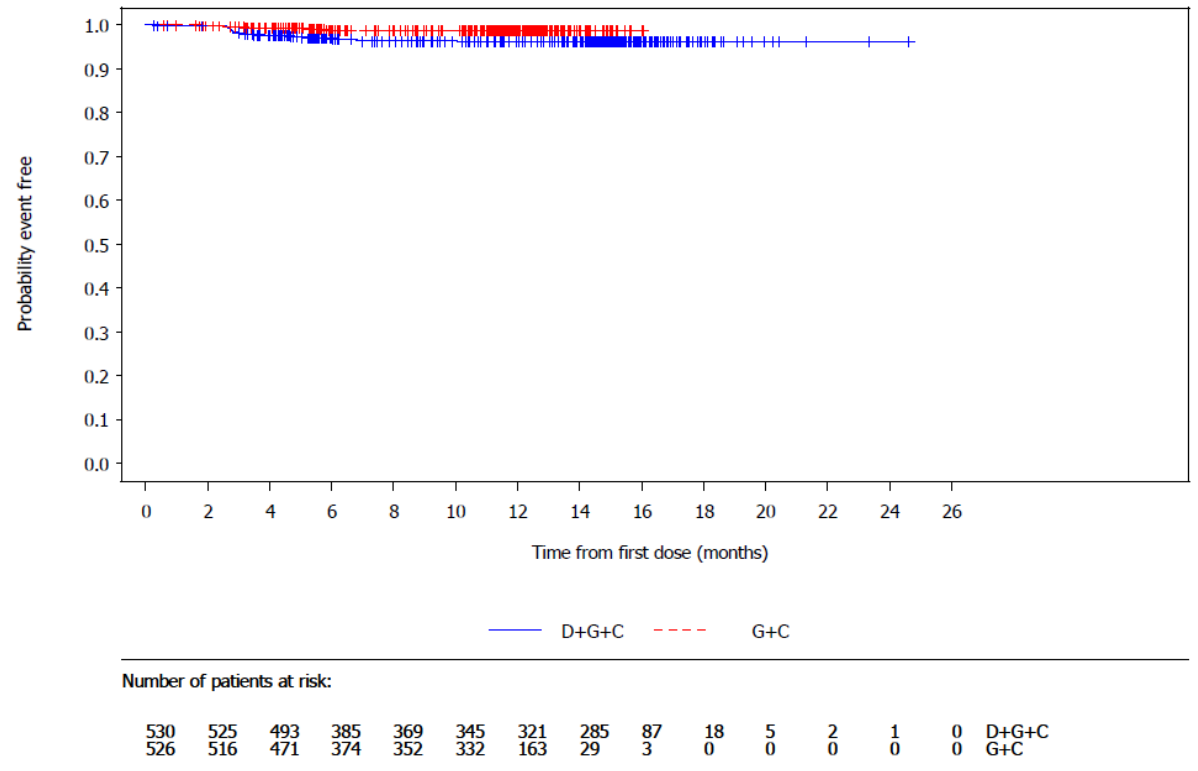

Figure 6: Kaplan-Meier curves for the outcome pulmonary embolism (PT, SAEs)

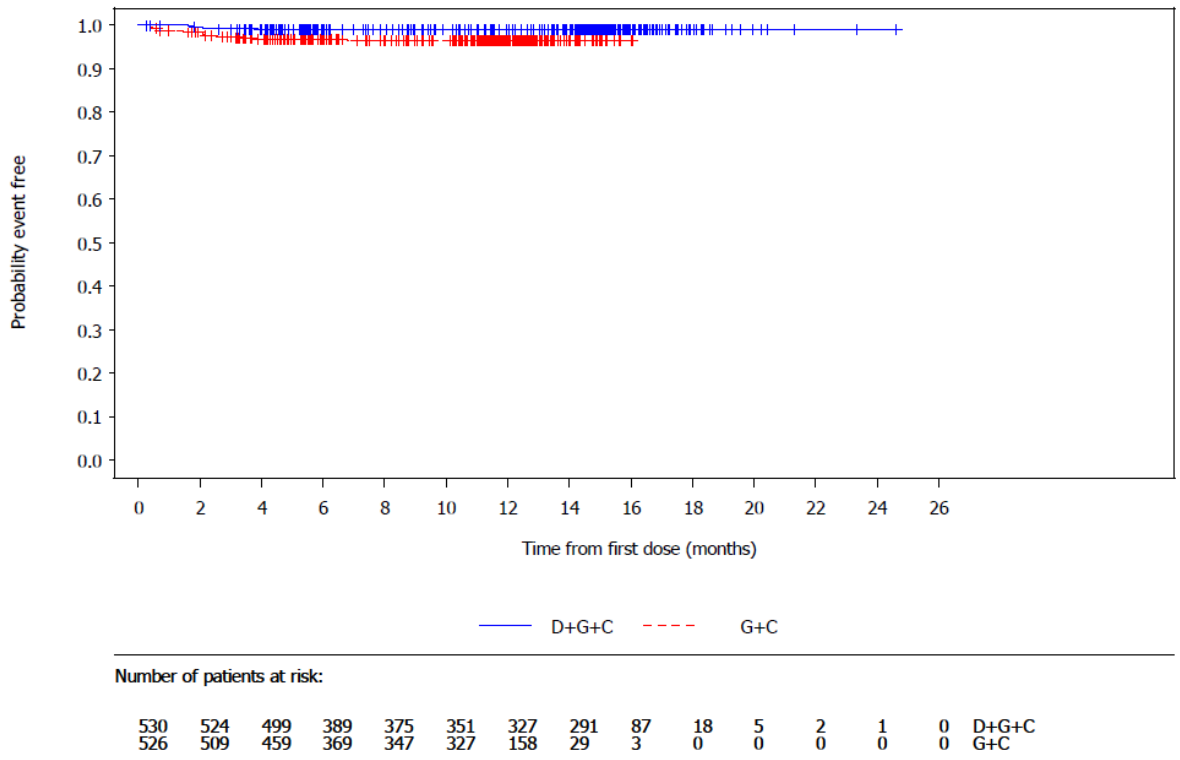

Figure 7:Kaplan-Meier curves for the outcome of anaemia (PT, SAEs)

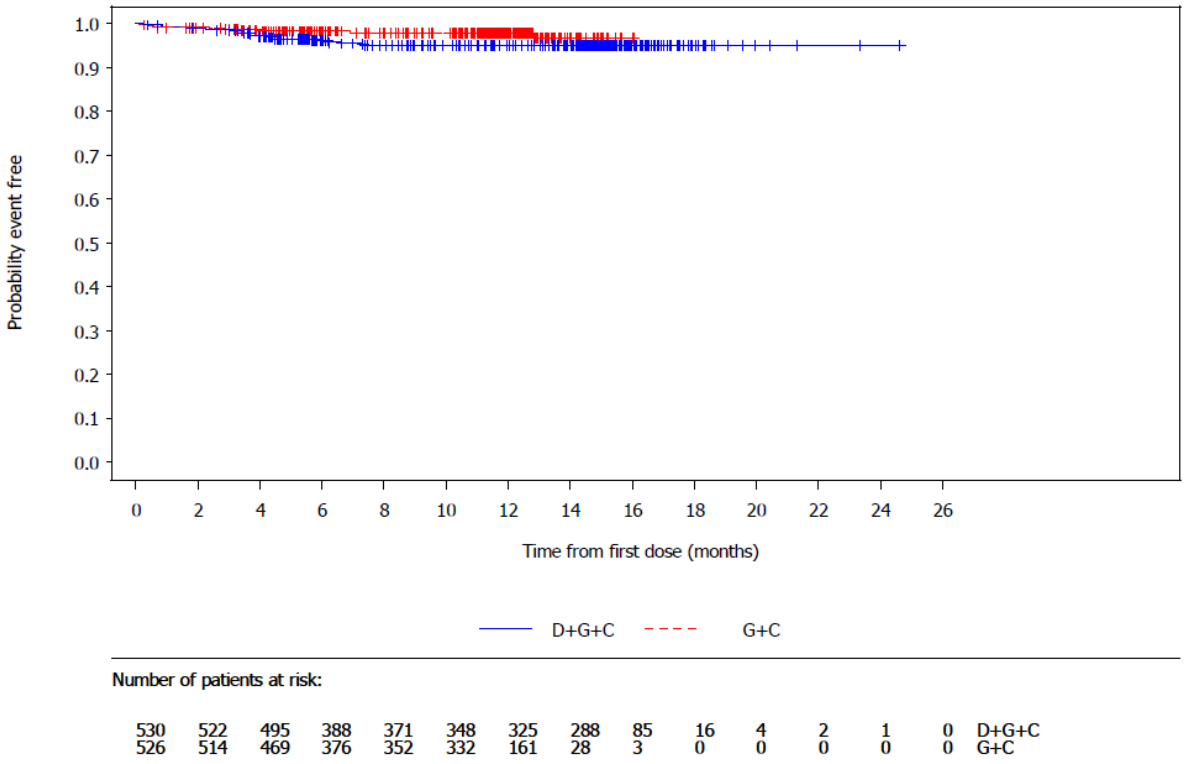

Figure 8: Kaplan-Meier curves for the outcome cardiac disorders (SOC, severe AEs [CTCAE grade ≥ 3])

Appendix B Results on the outcome discontinuation due to AEs presented as supplementary information

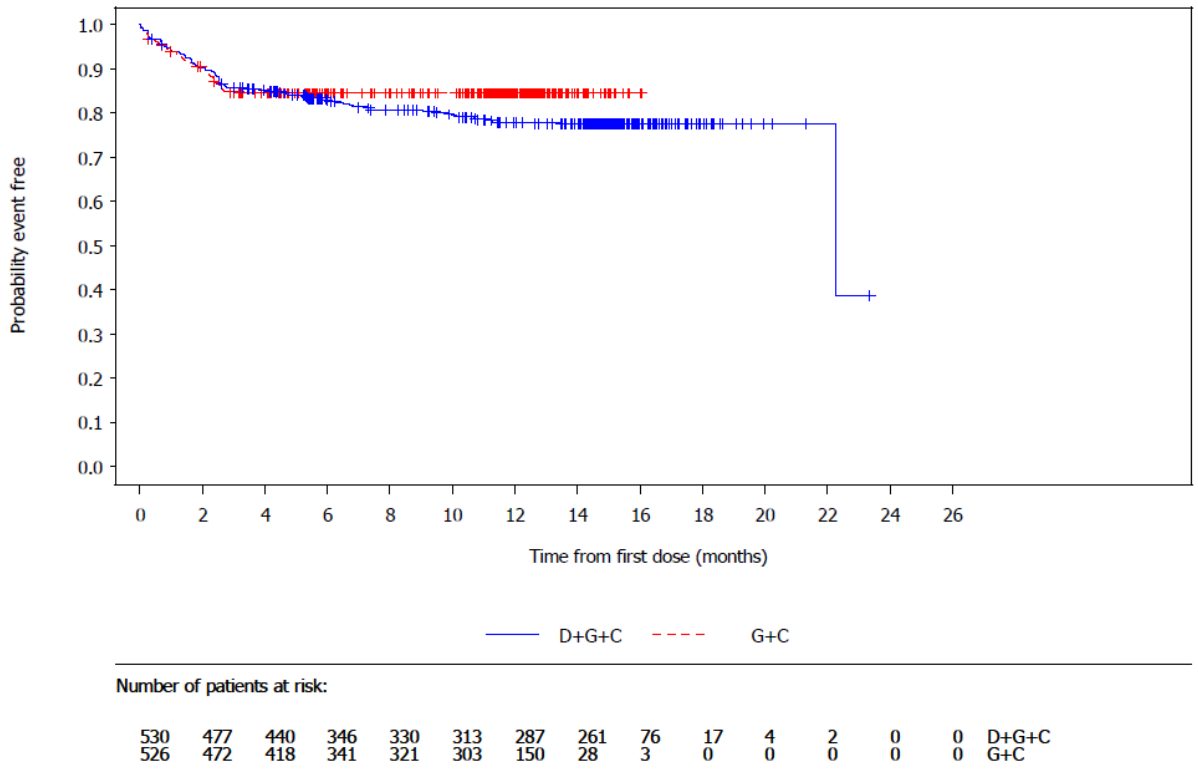

Figure 9: Kaplan-Meier curves for the outcome discontinuation due to AEs