Pembrolizumab (cervical cancer, combination with radiochemotherapy)

Addendum to Project A24-110 (dossier assessment)[1]

ADDENDUM (DOSSIER ASSESSMENT)

Project: A25-43 Version: 1.0 Status: 25 Apr 2025 DOI: 10.60584/A25-43_en

[1] Translation of the addendum *Pembrolizumab* (*Zervixkarzinom, Kombination mit Radiochemotherapie) – Addendum zum Projekt A24-110 (Dossierbewertung)*. Please note: This translation 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

Pembrolizumab (cervical cancer, combination with radiochemotherapy) – Addendum to Project A24-110

Commissioning agency

Federal Joint Committee

Commission awarded on

25 March 2025

Internal Project No.

A25-43

https://doi.org/10.60584/A25-43_en

Address of publisher

Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Siegburger Str. 237
50679 Köln
Germany

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

Recommended citation

Institute for Quality and Efficiency in Health Care. Pembrolizumab (cervical cancer, combination with radiochemotherapy); Addendum to Project A24-110 (dossier assessment) [online]. 2025 [Accessed: DD.MM.YYYY]. URL: https://doi.org/10.60584/A25-43_en.

Keywords

Pembrolizumab, Uterine Cervical Neoplasms, Benefit Assessment, NCT04221945

IQWiG employees involved in the addendum

- Sebastian Meller
- Moritz Felsch
- Ana Liberman
- Katrin Nink

Table of contents

Page

List of tables v
List of figures vi
List of abbreviations vii
1 Background 1
2 Assessment 2
2.1 Results 2
2.1.1 Subgroups and other effect modifiers 4
2.1.2 Assessment of added benefit at outcome level 4
2.1.3 Overall conclusion on added benefit 5
2.2 Summary 6
3 References 8
Appendix A Kaplan-Meier curves for the event time analyses presented in the addendum 9

List of tables

Page

Table 1: Results (side effects) – RCT, direct comparison: pembrolizumab + radiochemotherapy versus placebo + radiochemotherapy 3
Table 2: Extent of added benefit at outcome level: pembrolizumab + radiochemotherapy vs. radiochemotherapy 5
Table 3: Positive and negative effects from the assessment of pembrolizumab + radiochemotherapy in comparison with radiochemotherapy 6
Table 4: Pembrolizumab + radiochemotherapya – probability and extent of added benefit 7

List of figures

Page

Figure 1: Kaplan-Meier curves for the outcome of SAEs of the subpopulation (FIGO 2014 Stage III - IVA) of the KEYNOTE A18 study 9
Figure 2: Kaplan-Meier curve for the outcome of severe AEs of the subpopulation (FIGO 2014 Stage III - IVA) of the KEYNOTE A18 study 9
Figure 3: Kaplan-Meier curves for the outcome of discontinuation due to AEs of the subpopulation (FIGO 2014 Stage III - IVA) of the KEYNOTE A18 study 10
Figure 4: Kaplan-Meier curve for the outcome of immune-mediated severe AEs of the subpopulation (FIGO 2014 Stage III - IVA) of the KEYNOTE A18 study 10
Figure 5: Kaplan-Meier curves for the outcome of anaemia (PT, SAEs) of the subpopulation (FIGO 2014 Stage III - IVA) of the KEYNOTE A18 study 11
Figure 6: Kaplan-Meier curves for the outcome of hypokalaemia (PT, severe AEs) of the subpopulation (FIGO 2014 Stage III - IVA) of the KEYNOTE A18 study 11

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
FIGO	International Federation of Gynecology and Obstetrics
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
PT	Preferred Term
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class

1 Background

On 25 March 2025, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Project A24-110 (Pembrolizumab – Benefit assessment according to §35a Social Code Book V) [1].

In its comments, the pharmaceutical company (hereinafter referred to as “the company”) presented additional data [2] that go beyond the information in the dossier [3]. The commission comprises the assessment of the time-to-event analyses for adverse events (AEs) subsequently submitted in the commenting procedure, taking into account the information provided in the dossier.

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

2 Assessment

The randomized controlled trial (RCT) KEYNOTE A18 was used to assess the added benefit of pembrolizumab in combination with radiochemotherapy (external beam radiotherapy followed by brachytherapy) versus the appropriate comparator therapy (ACT) in patients with locally advanced cervical cancer (stage III to IVA according to the International Federation of Gynecology and Obstetrics [FIGO] 2014) who have not received prior definitive therapy. A detailed description of the study can be found in dossier assessment A24-110 [1].

For outcomes in the side effects category, the company's dossier included analyses on the proportion of patients with at least 1 event, with the effect measure “relative risk”. However, as there is a relevant difference between the median observation periods in the intervention and the comparator arm, the relative risk could only be interpreted to a limited extent. As part of the commenting procedure, the company therefore subsequently submitted time-to-event analyses with hazard ratio as an effect measure. The analyses subsequently submitted are used for the benefit assessment.

It should be noted that a presentation of the results on immune-related AEs at Preferred Term (PT) or System Organ Class (SOC) level is missing in the subsequently submitted documents for this addendum. The absence of these analyses in the dossier [3] has already been described in the dossier assessment. The company still did not present any results in its comments.

In the following, the time-to-event analyses on AEs subsequently submitted by the company are assessed as commissioned.

2.1 Results

Table 1 shows the results of the analyses subsequently submitted for the outcomes of the side effects category.

Kaplan-Meier curves on the event time analyses are presented in Appendix A.

Table 1: Results (side effects) – RCT, direct comparison: pembrolizumab + radiochemotherapy[a] versus placebo + radiochemotherapy[a]

Study outcome category outcome	Pembrolizumab + radiochemotherapy		Placebo + radiochemotherapy		Pembrolizumab + radiochemotherapy vs. placebo + radiochemotherapy
	N	median time to event in weeks [95% CI] patients with event n (%)	N	median time to event in weeks [95% CI] patients with event n (%)	HR [95% CI]; p-value[b, c]
KEYNOTE A18					
Side effects					
AEs (supplementary information)	295	0.6 [0.4; 0.7] 295 (100.0)	304	0.6 [0.4; 0.6] 302 (99.3)	–
SAEs	295	NA 100 (33.9)	304	NA 99 (32.6)	1.03 [0.78; 1.37]; 0.813
Severe AEs[d]	295	5.3 [4.6; 6.0] 232 (78.6)	304	5.6 [4.9; 6.1] 213 (70.1)	1.15 [0.95; 1.38]; 0.153
Discontinuation due to AEs	295	NA 62 (21.0)	304	NA 46 (15.1)	1.39 [0.95; 2.03]; 0.091
Immune-related severe AEs[d, e]	295	NA 12 (4.1)	304	NA 4 (1.3)	2.96 [0.95; 9.18]; 0.061
Anaemia (PT, SAEs)	295	NA 13 (4.4)	304	NA 3 (1.0)	4.40 [1.25; 15.46]; 0.021
Hypertension (PT, severe AEs[d])	295	NA 22 (7.5)	304	NA 10 (3.3)	2.28 [1.08; 4.81]; 0.031

a. External beam radiotherapy in combination with cisplatin, followed by brachytherapy.
b. Cox proportional hazards model.
c. Wald test (two-sided).
d. Operationalized as CTCAE grade ≥ 3.
e. Determined using Version 23.1 of a PT list of immune-related adverse events predefined by the company.

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; RCT: randomized controlled trial; SAE: serious adverse event

Side effects

Serious adverse events (SAEs)

For the outcome of SAEs, there is no statistically significant difference between the study arms. There is no hint of greater or lesser harm from pembrolizumab + radiochemotherapy in comparison with placebo + radiochemotherapy; greater or lesser harm is therefore not proven.

Severe AEs (CTCAE grade ≥ 3)

There is no statistically significant difference between the treatment arms for the outcome of severe AEs. There is no hint of greater or lesser harm from pembrolizumab + radiochemotherapy in comparison with placebo + radiochemotherapy; greater or lesser harm is therefore not proven.

Discontinuation due to AEs

There was no statistically significant difference between the study arms for the outcome of discontinuation due to AEs. There is no hint of greater or lesser harm from pembrolizumab + radiochemotherapy in comparison with placebo + radiochemotherapy; greater or lesser harm is therefore not proven.

Immune-related severe AEs (CTCAE grade ≥ 3)

No statistically significant difference between the study arms was shown for the outcome "immune-related severe AEs" (CTCAE grade ≥ 3). There is no hint of greater or lesser harm from pembrolizumab + radiochemotherapy in comparison with placebo + radiochemotherapy; greater or lesser harm is therefore not proven.

Anaemia (SAEs) and hypokalaemia (severe AEs)

A statistically significant difference to the disadvantage of pembrolizumab + radiochemotherapy in comparison with placebo + radiochemotherapy was shown for each of the outcomes “anaemia (SAEs)” and "hypokalaemia (severe AEs)". In each case, there is a hint of greater harm from pembrolizumab + radiochemotherapy in comparison with placebo + radiochemotherapy.

2.1.1 Subgroups and other effect modifiers

The company has not submitted any subgroup analyses on the subsequently submitted analyses.

In the overall consideration of results, it cannot be assumed that in the present case the results of the subgroup analyses on side effects have a relevant influence on the overall assessment of the added benefit.

2.1.2 Assessment of added benefit at outcome level

The extent of the added benefit at outcome level is estimated from the results presented in Table 1. Table 2 only presents the results of the side effect outcomes assessed in the present addendum.

Table 2: Extent of added benefit at outcome level: pembrolizumab + radiochemotherapy[a] vs. radiochemotherapy[a]

Outcome category **outcome**	**Pembrolizumab + radiochemotherapy vs. radiochemotherapy** **median time to event (months)** **effect estimation [95% CI];** **p-value** **probability[b]**	**Derivation of extent[c]**
Outcomes with shortened observation period		
Side effects		
SAEs	NA vs. NA HR: 1.03 [0.78; 1.37] p = 0.813	Greater/lesser harm not proven
Severe AEs	5.3 vs. 5.6 HR: 1.15 [0.95; 1.38]; p = 0.153	Greater/lesser harm not proven
Discontinuation due to AEs	NA vs. NA HR: 1.39 [0.95; 2.03] p = 0.091	Greater/lesser harm not proven
Immune-related severe AEs	NA vs. NA RR: 2.96 [0.95; 9.18]; p = 0.061	Greater/lesser harm not proven
Anaemia (SAEs)	NA vs. NA HR: 4.40 [1.25; 15.46]; HR: 0.23 [0.06; 0.80][d]; p < 0.021 probability: “hint”	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ greater harm, extent: "considerable"
Hypokalaemia (severe AEs)	NA vs. NA HR: 2.28 [1.08; 4.81]; HR: 0.44 [0.21; 0.93][d]; p < 0.031 probability: “hint”	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ greater harm, extent: minor

a. External beam radiotherapy followed by brachytherapy.
b. Probability provided if a statistically significant and relevant effect is present.
c. Depending on the outcome category, estimations of effect size use different limits based on the upper limit of the confidence interval (CI_u).
d. Institute’s calculation; reversed direction of effect to enable the use of limits to derive the extent of added benefit.

AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; HR: hazard ratio; SAE: serious adverse event

2.1.3 Overall conclusion on added benefit

Table 3 summarizes the results taken into account in the overall conclusion on the extent of added benefit.

Table 3: Positive and negative effects from the assessment of pembrolizumab + radiochemotherapy[a] in comparison with radiochemotherapy[a]

Positive effects	Negative effects
Outcomes with observation over the entire study duration	
Mortality ▪ overall survival: hint of an added benefit – extent: "non-quantifiable"	–
Outcomes with shortened observation period	
–	Serious/severe side effects ▪ anaemia (SAEs): hint of greater harm – extent: "considerable" ▪ hypokalaemia (severe AEs): hint of greater harm – extent: "minor"
a. External beam radiotherapy followed by brachytherapy. AE: adverse event; SAE: serious adverse event	

The overall analysis showed both a positive effect and several negative effects of pembrolizumab + radiochemotherapy in comparison with radiochemotherapy.

In terms of positive effects, there is a hint of a non-quantifiable added benefit for the outcome of overall survival. In contrast, there are hints of greater harm with the extents "minor" to "considerable" for outcomes in the category of serious/severe side effects.

The advantage in the outcome of overall survival dominates in the assessment of the added benefit, but is relativised by the disadvantages in the side effects, the specific SAEs and severe AEs.

In summary, for patients with locally advanced cervical carcinoma (FIGO 2014 Stage III - IVA) who have not received prior definitive therapy, there is a hint of a non-quantifiable added benefit of pembrolizumab in combination with radiochemotherapy (percutaneous radiotherapy followed by brachytherapy) compared with the ACT.

2.2 Summary

The data subsequently submitted by the company in the commenting procedure have not changed the conclusion on the added benefit of pembrolizumab from dossier assessment A24-110.

Table 4 below shows the result of the benefit assessment of pembrolizumab, taking into account dossier assessment A24-110 and the present addendum.

Table 4: Pembrolizumab + radiochemotherapya – probability and extent of added benefit

Therapeutic indication	**ACT[b]**	**Probability and extent of added benefit**
Adults with locally advanced cervical cancer (FIGO 2014 Stage III - IVA) who have not received prior definitive therapy	Radiochemotherapy consisting of external beam radiotherapy (EBRT) in combination with cisplatin (monotherapy), followed by brachytherapy	Hint of non-quantifiable added benefitc

a. External beam radiotherapy followed by brachytherapy.
b. Presentation of the ACT specified by the G-BA.
c. Only patients with an ECOG PS of 0 or 1 were included in the KEYNOTE A18 study. It remains unclear whether the observed effects can be transferred to patients with an ECOG PS of ≥ 2.

ACT: appropriate comparator therapy; EBRT: external beam radiotherapy; ECOG PS: Eastern Cooperative Oncology Group – Performance Status; FIGO: International Federation of Gynecology and Obstetrics; G-BA: Federal Joint Committee

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.

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Pembrolizumab (Zervixkarzinom, Kombination mit Radiochemotherapie); Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung [online]. 2025 [Accessed: 17.02.2025]. URL: https://doi.org/10.60584/A24-110.

2. MSD Sharp & Dohme. Stellungnahme zum IQWiG-Bericht Nr. D-1123: Pembrolizumab (Zervixkarzinom, Kombination mit Radiochemotherapie). 2025: [Demnächst verfügbar unter: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/1149/#beschluesse in the document "Zusammenfassende Dokumentation"].

3. Merck Sharp & Dohme. Study of Chemoradiotherapy With or Without Pembrolizumab for the Treatment of High-risk, Locally Advanced Cervical Cancer [online]. 2024 [Accessed: 04.12.2024]. URL: https://euclinicaltrials.eu/search-for-clinical-trials/?lang=en&EUCT=2022-501972-25-00.

Appendix A Kaplan-Meier curves for the event time analyses presented in the addendum

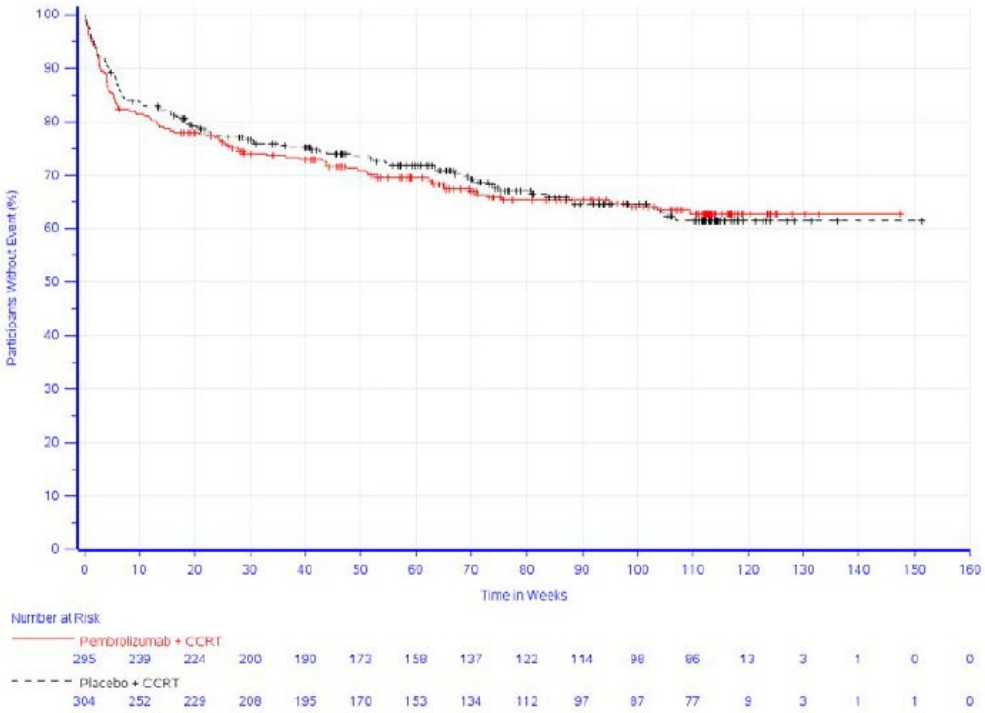

Figure 1: Kaplan-Meier curves for the outcome of SAEs of the subpopulation (FIGO 2014 Stage III - IVA) of the KEYNOTE A18 study

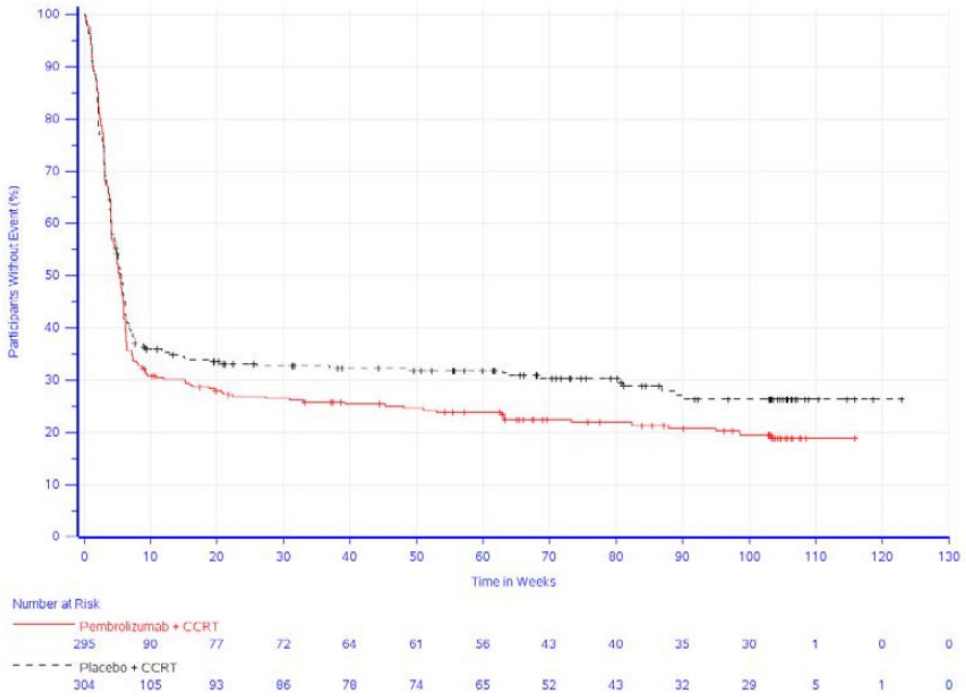

Figure 2: Kaplan-Meier curve for the outcome of severe AEs of the subpopulation (FIGO 2014 Stage III - IVA) of the KEYNOTE A18 study

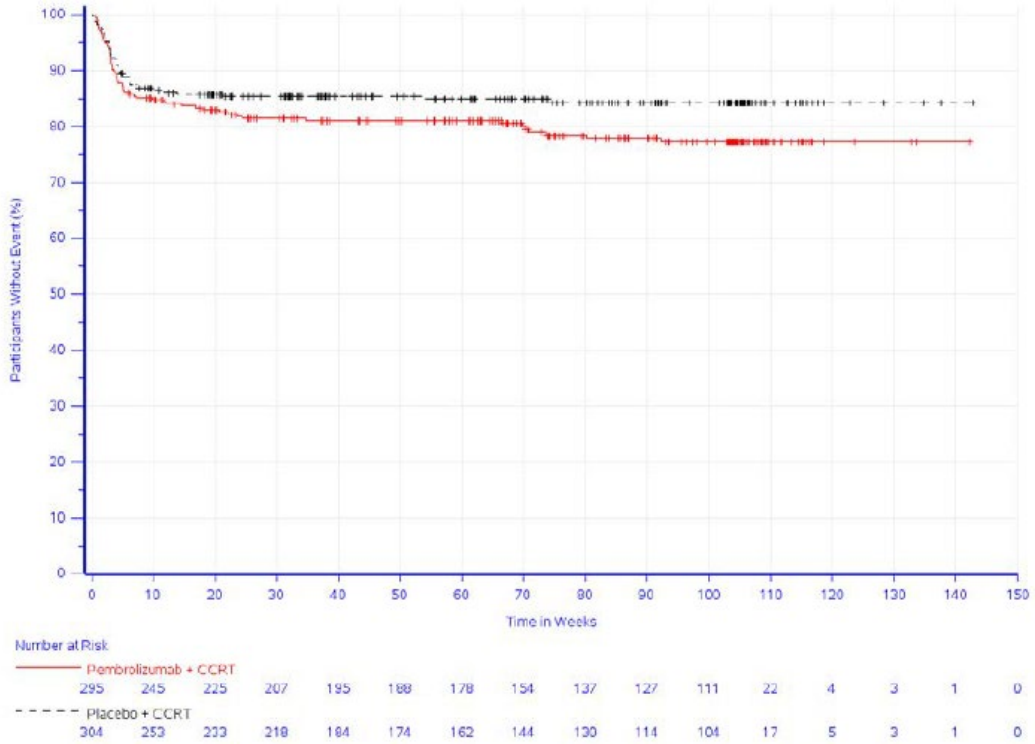

Figure 3: Kaplan-Meier curves for the outcome of discontinuation due to AEs of the subpopulation (FIGO 2014 Stage III - IVA) of the KEYNOTE A18 study

Figure 4: Kaplan-Meier curve for the outcome of immune-mediated severe AEs of the subpopulation (FIGO 2014 Stage III - IVA) of the KEYNOTE A18 study

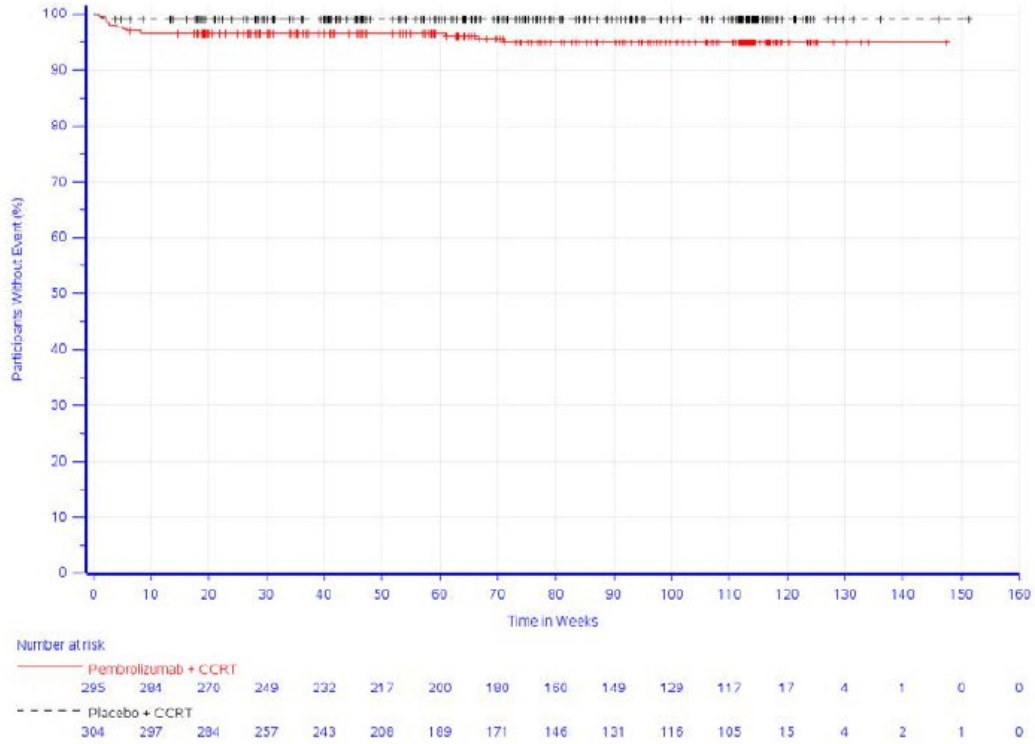

Figure 5: Kaplan-Meier curves for the outcome of anaemia (PT, SAEs) of the subpopulation (FIGO 2014 Stage III - IVA) of the KEYNOTE A18 study

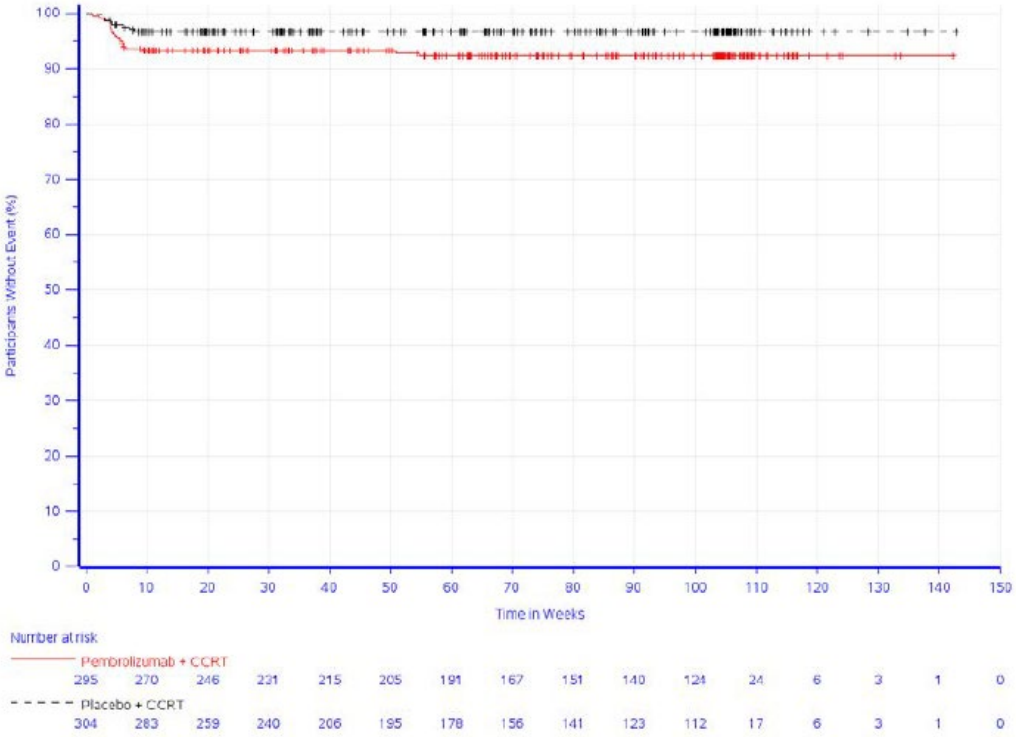

Figure 6: Kaplan-Meier curves for the outcome of hypokalaemia (PT, severe AEs) of the subpopulation (FIGO 2014 Stage III - IVA) of the KEYNOTE A18 study