

Pembrolizumab (head and neck squamous cell carcinoma, neoadjuvant and adjuvant)

Addendum to Project A25-148
(dossier assessment)¹



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List of abbreviations

Abbreviation	Meaning
BICR	blinded independent central review
CPS	Combined Positive Score
EFS	event-free survival
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
PD-L1	programmed death-ligand 1
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)

1 Background

On 08 April 2026, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Project A25-148 (Pembrolizumab [head and neck squamous cell carcinoma, neoadjuvant and adjuvant] – 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]:

- All subsequently submitted analyses on the outcome event-free survival (EFS):
 - Overview of the individual components on the outcome post-hoc adapted EFS
 - Sensitivity analyses 1 to 3 on the EFS: results and individual components for each analysis
 - Overview of the follow-up period after the end of treatment

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 KEYNOTE 689 study was used to assess the benefits of pembrolizumab in adult patients with resectable locally advanced head and neck squamous cell carcinoma whose tumours express programmed death-ligand 1 (PD-L1) [Combined Positive Score (CPS) ≥ 1]. A detailed description of the study can be found in dossier assessment A25-148 [1].

As described in dossier assessment A25-148, the failure of the curative treatment approach constitutes a patient-relevant outcome in the present therapeutic indication. However, the analyses submitted by the company on the EFS are not suitable for reflecting the outcome failure of the curative treatment approach and were therefore not used for the benefit assessment. This was primarily due to the fact that the observation period was too short at the time of the data cut. Furthermore, the qualifying events described deviated from the prespecified events for the EFS, and it was not ensured that the included subcomponent of local progression necessarily reflected the failure of the curative treatment approach. Furthermore, data are missing on how the 34 patients in the comparator arm who did not commence treatment following randomization were taken into account in the analyses.

In its comments, the company presented additional information on the follow-up period and the qualifying events, as well as three sensitivity analyses for the outcome EFS. In the following, the data subsequently submitted by the company are assessed as commissioned.

2.1 Follow-up period remains insufficient

Table 1: Information on the follow-up period after the end of treatment – Randomized controlled trial (RCT), direct comparison: neoadjuvant pembrolizumab, surgery, adjuvant pembrolizumab + radiotherapy ± cisplatin vs. surgery, adjuvant radiotherapy ± cisplatin

Study duration of the study phase	Pembrolizumab neoadjuvant + adjuvant and radiotherapy ± cisplatin N = 345	Radiotherapy ± cisplatin N = 300
KEYNOTE 689		
Theoretical maximum follow-up period after the end of treatment [months] ^{a, b}		
Median [Q1; Q3]	30.9 [16.9; 44.8]	33.7 [19.7; 49.2]
[Min; max]	[0.02; 64.7]	[2.1; 66.3]
Mean (SD)	30.7 (17.4)	34.6 (17.0)
Actual duration of follow-up after the end of treatment [months] ^{b, c}		
Median [Q1; Q3]	20.3 [7.7; 36.3]	21.0 [10.5; 37.8]
[Min; max]	[0.02; 63.3]	[0.02; 66.3]
Mean (SD)	22.9 (17.4)	24.9 (17.9)
a. Calculated as the time from the last treatment to the database lock. b. Institute's calculation. c. Calculated as the time from the last treatment to death, last contact or database lock, if the patient was still alive. max: maximum; min: minimum; N: number of analysed patients; Q1: first quartile; Q3: third quartile; RCT: randomized controlled trial; SD: standard deviation		

The company presented data on the theoretical maximum follow-up period (the time from the last treatment to the database lock) and the actual follow-up period after the end of treatment (the time from the last treatment to death, last contact or database lock, if the patient was still alive) (see Table 1). The theoretical maximum follow-up period is the decisive factor for the assessment of whether the follow-up period in the KEYNOTE 689 study is adequate to assess the outcome failure of curative treatment with sufficient certainty. It reports the follow-up period from the end of treatment to the database lock, irrespective of the occurrence of qualifying events (such as, for example, death).

According to the guidelines, the majority of relapses in this therapeutic indication occur within a high-risk period of 2 years following completion of initial treatment [4-7]. In the analyses presented by the company, the first quartile for the theoretical maximum follow-up period is 16.9 months in the intervention arm and 19.7 months in the comparator arm. This means that at least 25% of the patients in KEYNOTE 689 were followed up for significantly less than two years after the end of treatment. The high-risk period for the occurrence of relapses is therefore not covered for a relevant proportion of patients in both study arms. However, it is

not possible to estimate exactly how many patients this affects on the basis of the available information. It should also be noted that the randomized but untreated patients (3 in the intervention arm versus 34 in the comparator arm) are not taken into account in the information on the follow-up period.

The data subsequently provided by the company thus confirm the assessment from dossier assessment A25-148, stating that, due to the insufficient length of the follow-up period, the results on EFS are not suitable to reflect the outcome failure of the curative treatment approach with sufficient certainty.

2.2 EFS analyses can only be interpreted to a limited extent, regardless of the follow-up period

In its dossier [3], the company presented analyses of the outcome EFS according to Blinded Independent Central Review (BICR), referred to by the company as the primary analysis) and according to the investigator (which will not be considered further below, as there are only minor discrepancies compared with the analysis by means of BICR), with the following qualifying events:

- Death
- Distant metastases
- Local progression and distant metastases
- Local progression/recurrence

Moreover, the company presented analyses which it describes as post-hoc adapted EFS according to BICR. In addition to the qualifying events mentioned above, these also include the following two components:

- no R0 resection
- no surgery

Based on the analyses submitted by the company in its dossier, it remains unclear whether the qualifying event 'local progression' prevented the curatively intended surgery or the subsequent radiotherapy, and therefore shows that the curative treatment strategy has failed. Furthermore, the presented qualifying events deviated from the prespecified events in the outcome EFS as set out in the study protocol. Thus, it remained unclear how the qualifying events recorded in the study according to the study protocol were assigned to the qualifying events presented. Furthermore, the company provided no information on how 34 patients in the comparator arm who had not commenced treatment following randomization were taken into account in the analyses.

Subsequently submitted data on the EFS analyses according to BICR set out in the dossier

In its comments, the company clarifies that the component of the outcome EFS, introduced with Amendment 8 (7 September 2023) to the study protocol, namely ‘radiological disease progression during the neoadjuvant phase that prevents surgery’, was applied consistently and without restriction to the entire data set – that is, regardless of the time point of the patients’ enrolment in the study. According to the company, radiological disease progression during the neoadjuvant phase (provided it did not prevent curatively intended surgery) was not counted as an event. This is appropriate.

However, there is still a discrepancy between the qualifying events in the outcome EFS according to BICR recorded according to the study protocol, and those presented in the dossier. Furthermore, there is no detailed processing of the qualifying events analogously to the post-hoc adapted EFS analyses (see below for further details). There is still a lack of explicit information in the analyses regarding the management of patients who did not commence treatment following randomization. The results of this analysis are described in Section 2.3.

The post-hoc adapted EFS presented in the dossier and the subsequently submitted sensitivity analyses for the post-hoc adapted EFS 1 to 3

With regard to the analysis presented in the dossier and referred to as a post-hoc adapted EFS, the company stated in its comments that the randomized but untreated patients (3 in the intervention arm versus 34 in the control arm) were classified as qualifying event ‘no surgery’ at the time of randomization. This is not appropriate, as it cannot be assumed that none of these patients underwent surgery and that the curative treatment approach had therefore failed. This is also evident from the fact that some of these patients had undergone surgery outside the study, or that further information on the course of the disease was available and could accordingly be taken into account in the analyses (see below: outcome post-hoc adapted EFS – Sensitivity analysis 2). Furthermore, given the significant imbalance between the intervention and the comparator arm in patients who did not receive treatment, the assumption of an event at the time of randomization also leads to an unfair comparison. The outcome post-hoc adapted EFS described in the dossier is therefore unsuitable and will not be considered further below.

Through sensitivity analyses 1 to 3 on the post-hoc adapted EFS, presented as part of the comments, the company addresses the aspect of randomized but untreated patients and also sets out the qualifying events in detail. These three sensitivity analyses are described below and assessed in terms of their suitability.

- Post-hoc adapted EFS – Sensitivity analysis 1: this analysis does not consider randomized but untreated patients. As a result, the number of patients included in the analysis was reduced from 347 to 344 in the intervention arm and from 335 to 301 in the comparator

arm. As further information on the course of the disease was available for some of these patients (see Sensitivity Analysis 2), this approach is not appropriate. This analysis is therefore not presented. The results can be found in the company's comments [2].

- Post-hoc adapted EFS – Sensitivity analysis 2: In this analysis, successful surgery is assumed for all randomized but untreated patients, provided that no EFS event had occurred prior to the hypothetical surgery and no death had been recorded. These patients were only included in the analysis as an event if a protocol-defined event (e.g. recurrence, distant metastases, death) had occurred at a later point in time; otherwise, they were censored (time point unclear). The results of this analysis are described in Section 2.3.
- Post-hoc adapted EFS – Sensitivity analysis 3: This analysis takes into account the fact that 6 of the 37 randomized but untreated patients underwent surgery outside the study. As there are no pathological findings for these surgeries, the company assumed an R0 resection for this sensitivity analysis. Accordingly, subsequent EFS events (e.g. recurrence or death) were assessed at the time defined in the protocol for these 6 patients, whilst patients without an event were censored at the time point of the last disease assessment. The remaining 31 randomized but untreated patients were assigned an EFS event no later than the latest possible time for surgery as specified in the study protocol. As most of the remaining 31 patients were in the comparator arm (1 vs. 30), the assumption of an early EFS event in the company's analyses primarily affects the comparator arm. This approach results in an unfair comparison and is therefore not appropriate. This analysis is not presented. The results can be found in the company's comments [2].

There is also an superordinate uncertainty regarding the qualifying event 'no R0 resection', which is taken into account in all analyses of the post-hoc adapted EFS, including the sensitivity analyses. During the oral hearing on A25-148, the expert societies pointed out that failure to achieve an R0 resection status does not necessarily indicate that the curative treatment approach has failed [8]. This is in line with the guidelines, according to which an R1 resection constitutes an indication for adjuvant chemoradiotherapy with curative intent and does not represent a transition to a palliative treatment situation [5,7]. This issue was taken into account in the interpretation of the results (see Section 2.3).

Summary of the available analyses on the EFS

All the analyses presented for the outcome EFS have limitations – regardless of the fact that the follow-up period is, in principle, too short to reflect the outcome failure of the curative treatment approach (see Section 2.1). The post-hoc adapted EFS presented in the dossier, as well as the associated Sensitivity analyses 1 and 3, cannot be meaningfully interpreted due to the included assumptions regarding patients who did not commence treatment after randomization. These are therefore not presented. The results of the analyses on the EFS

according to BICR, as well as Sensitivity analysis 2 on the post-hoc adapted EFS are presented and discussed in Section 2.3.

2.3 Results on EFS

Table 2: Results (EFS) – RCT, direct comparison: neoadjuvant pembrolizumab, surgery, adjuvant pembrolizumab + radiotherapy ± cisplatin vs. surgery, adjuvant radiotherapy ± cisplatin (multipage table)

Study outcome category outcome	Pembrolizumab neoadjuvant + adjuvant and radiotherapy ± cisplatin		Radiotherapy ± cisplatin		Pembrolizumab neoadjuvant + adjuvant and radiotherapy ± cisplatin vs. radiotherapy ± cisplatin
	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
KEYNOTE 689					
Morbidity					
EFS according to BICR					
Event rate	347	128 (36.9)	335	156 (46.6)	RR ^b : 0.79 [0.66; 0.95]; 0.001
Death	347	63 (18.2)	335	62 (18.5)	–
Distant metastases	347	24 (6.9)	335	51 (15.2)	–
Local progression and distant metastases	347	4 (1.2)	335	6 (1.8)	–
Local progression/recurrence	347	37 (10.7)	335	37 (11.0)	–
EFS	347	59.7 [37.9; NC] 128 (36.9)	335	29.6 [19.5; 41.9] 156 (46.6)	0.70 [0.55; 0.89]; 0.003
Post-hoc adapted EFS – sensitivity analysis 2					
Event rate	347	154 (44.4)	335	177 (52.8)	RR ^b : 0.84 [0.72; 0.98]; 0.028
Death	347	43 (12.4)	335	49 (14.6)	–
Distant metastases	347	18 (5.2)	335	40 (11.9)	–
Local progression and distant metastases	347	1 (0.3)	335	0 (0)	–
Relapsed	347	22 (6.3)	335	28 (8.4)	–
Recurrence and distant metastases	347	1 (0.3)	335	4 (1.2)	–
No R0 resection	347	32 (9.2)	335	45 (13.4)	–

Table 2: Results (EFS) – RCT, direct comparison: neoadjuvant pembrolizumab, surgery, adjuvant pembrolizumab + radiotherapy ± cisplatin vs. surgery, adjuvant radiotherapy ± cisplatin (multipage table)

Study outcome category outcome	Pembrolizumab neoadjuvant + adjuvant and radiotherapy ± cisplatin		Radiotherapy ± cisplatin		Pembrolizumab neoadjuvant + adjuvant and radiotherapy ± cisplatin vs. radiotherapy ± cisplatin
	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
No surgery	347	37 (10.7)	335	11 (3.3)	–
Progression that prevents the planned surgery ^{d, e}	347	14 (4.0)	335	4 (1.2)	–
Other reasons ^f	347	23 (6.6)	335	7 (2.1)	–
EFS	347	37.5 [25.5; NC] 154 (44.4)	335	18.4 [10.3; 26.9] 177 (52.8)	0.74 [0.59; 0.92]; 0.006

a. Cox proportional-hazards model stratified by primary tumour location (oropharynx/oral cavity vs. larynx vs. hypopharynx) and tumour stage (III vs. IVA); ties were handled using Efron's method.
c. Institute's calculation of RR, 95% CI (asymptotic), and p-value (unconditional exact test, CSZ method according to [9]).
c. Without consideration of the subcomponent 'no R0 resection', the results are as follows: 122/347 (35.2%) vs. 132/335 (39.4%); RR: 0.89; 95% CI: [0.73; 1.08]; p = 0.266.
d. Two patients in the intervention arm with concurrent events were included in this category. The events 'local progression/recurrence' and 'progression that prevents the planned surgery' occurred in one patient, the events 'distant metastases' and 'progression that prevents the planned surgery' occurred in one other patient.
e. Four randomized but untreated patients in the comparator arm who experienced local progression prior to their planned surgery were included in this category.
f. Reasons for absence of surgery: physician's decision, adverse event, withdrawal of consent, an unresectable tumour, a cancer treatment not included in the study, and loss to follow-up.
BICR: blinded independent central review; CI: confidence interval; EFS: event-free survival; HR: hazard ratio; n: number of patients with (at least 1) event; N: number of analysed patients; NC: not calculable; RCT: randomized controlled trial

EFR according to BICR

For the outcome EFS according to BICR, there was a statistically significant difference between the treatment groups in favour of pembrolizumab, both in the time-to-event analysis and in the event rate. In addition to the uncertainties described in Section 2.1, the Kaplan-Meier curves (see Figure 1) yield further limitations regarding the interpretability of these results: in both study arms, there were 28 (approximately 8% each) potentially informative censorings at Month 6. The company did not give reasons for these early censorings.

Post-hoc adapted EFS – sensitivity analysis 2

In sensitivity analysis 2, patients who were randomized but not treated were taken into account on the basis of the available information on their course of disease (see Section 2.2). Overall, the following information can be derived from the data provided by the company on the post-hoc adapted EFS and the associated sensitivity analyses for the randomized but untreated patients: 18 of the 34 randomized but untreated patients in the comparator arm experienced a qualifying event (13 deaths, 1 recurrence, 4 disease progressions that prevented the planned surgery), whilst 16 were censored in the analyses (time point unclear). In the intervention arm, 2 of the 3 patients who were randomized but not treated were included in the analysis as deaths and 1 as censoring.

For the outcome post-hoc adapted EFS – Sensitivity analysis 2 – there is a statistically significant difference between the treatment groups in favour of pembrolizumab, both in the time-to-event analysis and in the event rate. In this analysis, too, there were 23 and 27 (7% and 8%, respectively) potentially informative censorings in both study arms at Month 6, for which no reasons were given. Furthermore, the qualifying event ‘no R0 resection’ has a relevant impact on the effect in the composite outcome, with a 4% difference in the proportion of events (32 [9%] vs. 45 [13%]). However, this qualifying event does not necessarily represent a failure of the curative treatment approach (see Section 2.2). Without this qualifying event, there is no statistically significant difference in the event rate between the treatment groups (RR: 0.89; 95% CI: [0.73; 1.08]; $p = 0.266$, see Table 2, Footnote c).

2.4 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 A25-148.

The G-BA decides on the added benefit.

3 References

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[https://doi.org/10.1016/0167-9473\(94\)90148-1](https://doi.org/10.1016/0167-9473(94)90148-1).

Appendix A Kaplan–Meier curves on EFS

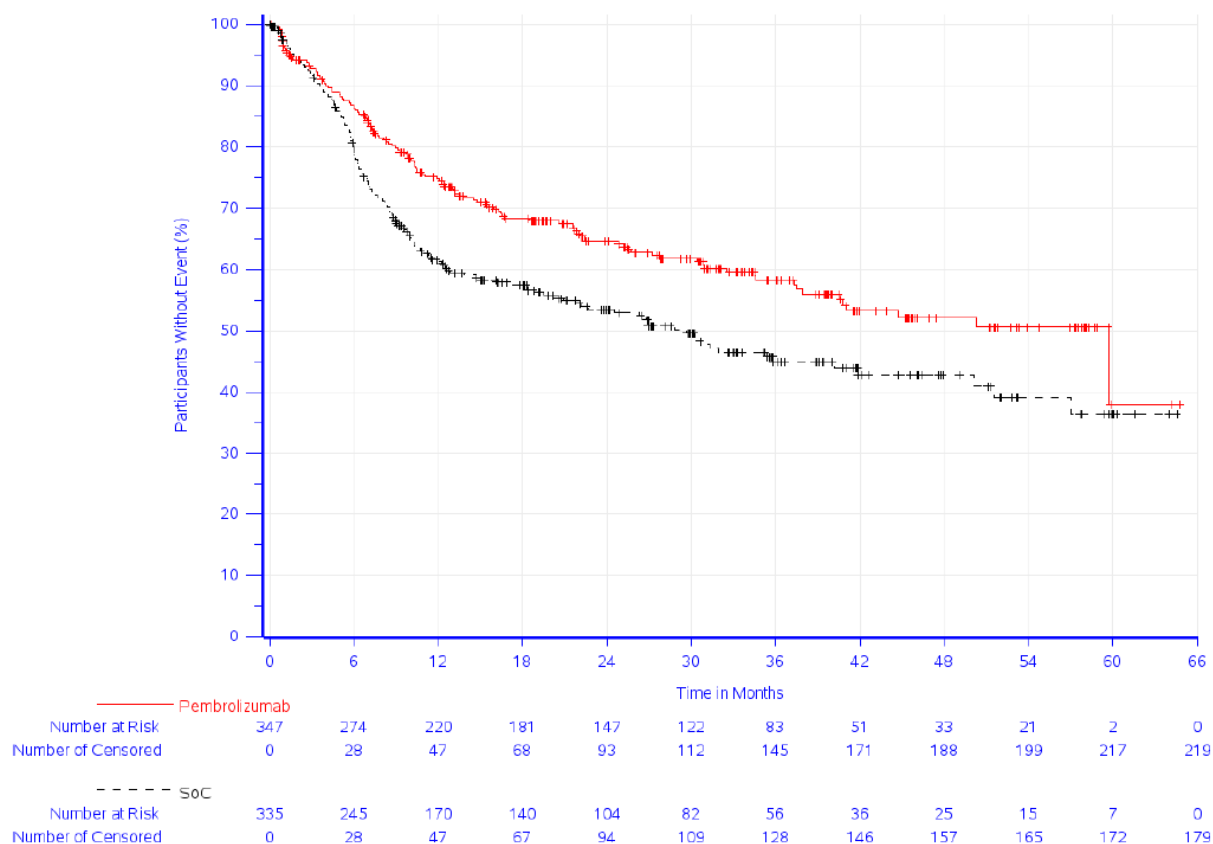


Figure 1: Kaplan-Meier curves for the outcome EFR according to BCIR in the KEYNOTE 689 study

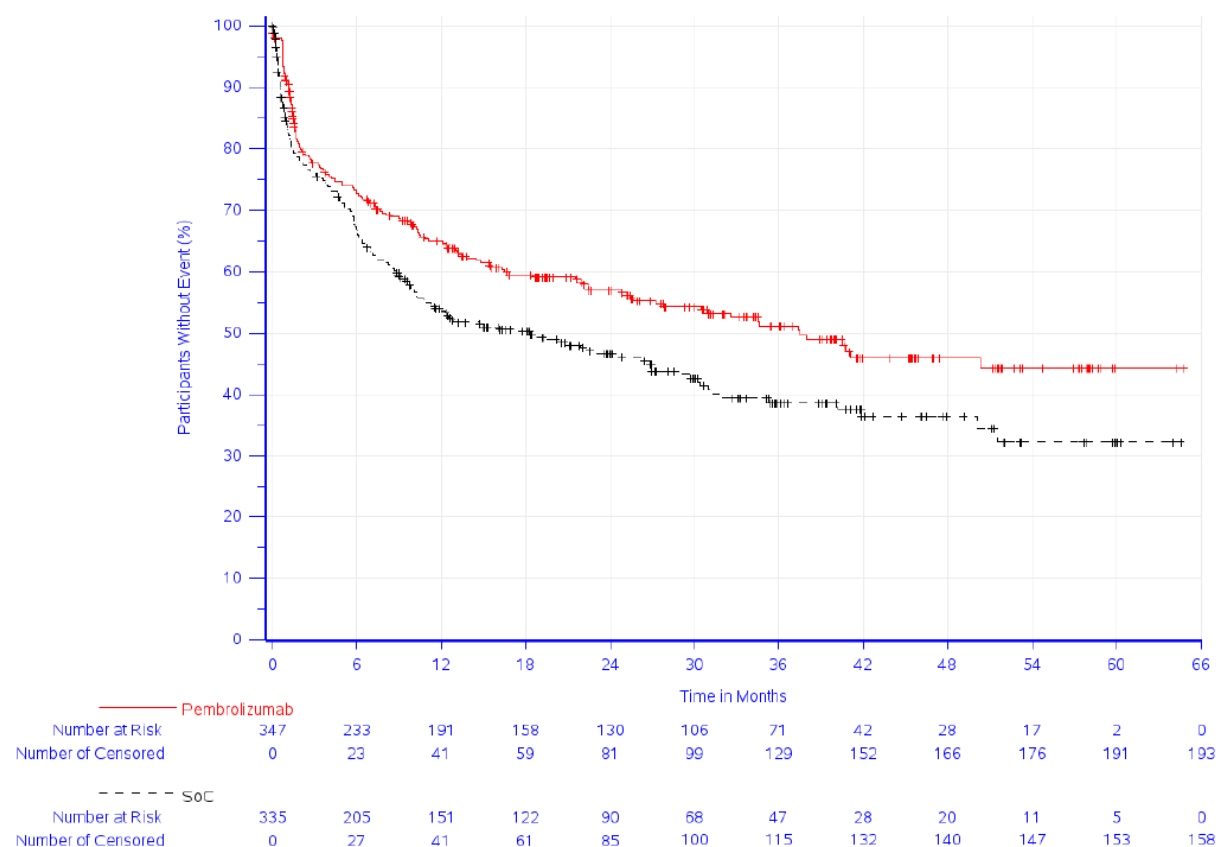


Figure 2: Kaplan-Meier curves for the outcome post-hoc adapted EFS – sensitivity analysis 2 of the KEYNOTE 689 study