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Avelumab (urothelial carcinoma) –

Addendum to Commission A21-23[1]

Addendum

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List of abbreviations

Abbreviation	Meaning
AE	adverse events
BSC	best supportive care
CTCAE	Common Terminology Criteria for Adverse Events
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
SAE	serious adverse event

1 Background

On 9 July 2021, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A21-23 (Avelumab – Benefit assessment according to § 35a Social Code Book V) [1].

For the benefit assessment of avelumab as first-line maintenance therapy in adults with locally advanced or metastatic urothelial carcinoma who are progression-free following platinum-based chemotherapy, the dossier of the pharmaceutical company (hereinafter the "company") presented the JAVELIN Bladder 100 study [2]. In the operationalization submitted in the dossier, the analyses of the immune-mediated adverse events (AEs) identified as relevant were deemed unusable [1]. In the commenting procedure [3,4], the company submitted further analyses of immune-mediated AEs beyond the information provided in the dossier.

The G-BA commissioned IQWiG with the compete evaluation of the subsequently submitted analyses of immune-mediated AEs.

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 of immune-mediated AEs

In the benefit assessment, the analyses of immune-mediated AEs submitted by the company were deemed unusable [1]. The operationalization was based on a predefined list of preferred terms (PTs). For an AE to be recorded as immune-mediated, other successive and causally linked criteria had to be met as well [2]. One of these criteria was treatment with corticosteroids, other immunosuppressants, or hormone therapy. Another criterion was the absence of an alternative clear explanation for the AE other than an immune-mediated aetiology and/or the presence of a histopathological finding or biopsy finding that was compatible with an immune-mediated mechanism. This operationalization was viewed as not being reliably measurable because it fails to ensure that all immune-mediated events are represented.

In the commenting procedure, the company submitted analyses of immune-mediated AEs based on the predefined list of PTs without further causal, stepwise exclusion, broken down by AEs, severe AEs (as per Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3), and serious AEs (SAEs).

Note on the operationalization of immune-mediated AEs deemed meaningful for the benefit assessment

In its comment, the company states that the subsequently submitted analyses represent an overestimate of the events to be actually deemed immune-mediated. It argues that without a further selection of potentially immune-mediated AEs, the event rates would likely be higher than in the prespecified analysis, particularly for patients in the control arm, who did not receive any immunotherapy. Indeed, without further causal selection based on defined criteria, more AEs were included in the analysis of immune-mediated AEs (e.g. immune-mediated AEs without selection 59.9% [avelumab] vs. 18.3% [best supportive care, BSC] and with selection 29.4% [avelumab] vs. 1.4% [BSC]). However, any evaluation of causes (in this case: immune-mediated or not) always includes a subjective component since no reliable method currently exists for confidently categorizing AEs as immune-mediated or not on an individual patient level, e.g. based on biomarkers or tissue biopsies [5,6]. This is particularly the case in open-label studies, such as the JAVELIN Bladder 100 study assessed here. In clinical practice, a causality evaluation is useful for deciding which therapeutic measure, if any, a patient needs (e.g. corticosteroid administration) [5,7,8]. However, this benefit assessment focuses not on the clinical decision on a specific algorithm for treating potentially immune-mediated AEs, but rather on the AE itself as a patient-relevant event. For patients, it is irrelevant whether the AE (e.g. skin rash, pneumonitis) is indeed immune-mediated. The company's operationalization based on defined selection criteria is therefore unsuitable for the benefit assessment, as already discussed in dossier assessment A21-23 [1]. Implementing the selection criteria (AE treatment as well as aetiological evaluation of causality) fails to adequately ensure the representation of all immune-mediated AEs that occurred in the JAVELIN Bladder 100 study.

Nonspecific T-cell activation and immunostimulation associated with the administration of checkpoint inhibitors results in numerous AEs which can manifest as inflammatory changes in almost any organ and at different times [6,9]. The purpose of a nonselected, predefined list of PTs is to uncover effects of potentially immune-mediated AEs which would be impossible to detect via analyses of individual PTs or system organ classes (SOCs). The PTs included by the company in the analysis of immune-mediated AEs (see Appendix B) comprise the AEs known from the literature and typically deemed potentially immune-mediated AEs [5-8,10].

Overall, therefore, a predefined list of PTs comprising AEs that are typically immune-mediated, but not selected based on defined criteria, is deemed a meaningful operationalization for the benefit assessment. The nonselected analysis of such lists of PTs is conducted in awareness of the fact that not all AEs included in the analysis will actually be immune-mediated (e.g. diarrhoea). The analysis adequately ensures, however, that all immune-mediated AEs which occurred are represented in a pooled operationalization for the benefit assessment.

In the commenting procedure, the company submitted such analyses for immune-mediated AEs (broken down into AEs, SAEs, and severe AEs). For the total rate of immune-mediated AEs, it is unclear which percentage of events are not patient relevant (e.g. asymptomatic AEs of CTCAE grade 1 [11]). The included PTs' CTCAE grades, which are needed for assessing patient relevance, were not submitted. The total rate of immune-mediated AEs is therefore presented as supplementary information only. The results for immune-mediated SAEs and severe AEs are presented and assessed below.

Risk of bias

As was the case for the assessment of specific AEs in dossier assessment A21-23 [1], the risk of bias for serious and severe immune-mediated AEs was rated as high for potentially informative reasons due to incomplete follow-up for potentially informative reasons.

Results

As part of the commenting procedure, the company submitted not only the results for immune-mediated AEs, SAEs, and severe AEs, but also the event rates for clusters it created from interconnected PTs (e.g. immune-related colitis or immune-related skin rash). The event rates on the cluster level are presented as supplementary information in Appendix A. Appendix B presents the PTs rated as potentially immune-mediated, which were included in the analyses of the clusters.

Table 1 shows the results for the outcomes of immune-mediated AEs (AEs, SAEs, severe AEs [CTCAE grade ≥ 3]). No Kaplan-Meier curves are available for the subsequently submitted analyses of immune-mediated AEs.

Table 1: Results (immune-mediated AEs) – RCT, direct comparison: avelumab + BSC vs. BSC

Study Outcome category Outcome	Avelumab + BSC N	Avelumab + BSC Median time to event in months [95% CI] Patients with event n (%)	BSC N	BSC Median time to event in months [95% CI] Patients with event n (%)	Avelumab + BSC vs. BSC HR [95% CI]; p-value[a]
JAVELIN Bladder 100, 1st data cut-off 21/10/2019)[b]					
Side effects					
Specific AEs					
Immune-mediated AEs[c]	*344*	*4.5 [3.6; 6.4]* *206 (59.9)*	*345*	*NR [18.9; NC]* *63 (18.3)*	–
Immune-mediated SAEs	344	NR 30 (8.7)	345	NR 13 (3.8)	1.86 [0.97; 3.60]; 0.059
Immune-mediated severe AEs[d]	344	NR 45 (13.1)	345	NR 16 (4.6)	2.45 [1.38; 4.35]; 0.002

a. Effect, CI, and p-value: no data on calculation method.
b. Outcomes of the side effects category were surveyed for up to 90 days after the last dose of the study drug in the intervention arm or after the last visit in the comparator arm (see dossier assessment A21-23 [1]).
c. Presented as supplementary information due to the unknown percentage of events which are not patient relevant (e.g. asymptomatic AEs of CTCAE grade 1 [11]).
d. Operationalized as CTCAE grade ≥ 3.

AE: adverse event; BSC: best supportive care; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; 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; SAE: serious adverse event

Due to the high risk of bias, at most hints of greater/lesser harm can be derived from the available data for immune-mediated SAEs and severe AEs.

Side effects

Immune-mediated SAEs

For the outcome of immune-mediated SAEs, no statistically significant difference between treatment groups was found. Consequently, no hint of greater or lesser harm from avelumab + BSC can be derived in comparison with BSC; greater or lesser harm is therefore not proven.

Immune-mediated severe AEs (CTCAE grade ≥ 3)

For the outcome of immune-mediated severe AEs, a statistically significant difference between treatment groups was found to the disadvantage of avelumab + BSC. Hence, there is a hint of greater harm from avelumab + BSC in comparison with BSC.

Subgroups and other effect modifiers

The company did not submit any subgroup analyses for the analyses on immune-mediated AEs which were subsequently submitted with the comment.

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

Table 2 shows the probability and extent of added benefit for the subsequently submitted analyses.

Table 2: Extent of added benefit at outcome level: avelumab + BSC vs. BSC

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Avelumab + BSC vs. BSC** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Side effects		
Immune-mediated SAEs	NR vs. NR HR: 1.86 [0.97; 3.60]; p = 0.059	Greater/lesser harm not proven
Immune-mediated severe AEs[d]	NR vs. NR HR: 2.45 [1.38; 4.35]; HR[d]: 0.41 [0.23; 0.72] p = 0.002 Probability: hint	Outcome category: serious/severe AEs $CI_u < 0.75$; risk ≥ 5% Greater harm; extent: major

a. Probability is stated whenever a statistically significant and relevant effect is present.
b. Estimations of effect size are made depending on the outcome category, with different limits according to the upper limit of the confidence interval (CI_u).
c. Operationalized as CTCAE grade ≥ 3.
d. IQWiG calculation; reversed direction of effect to enable use of limits to derive the extent of the added benefit.

AE: adverse event; BSC: best supportive care; CI: confidence interval; CI_u: upper confidence limit; CTCAE: Common Terminology Criteria for Adverse Events; HR: hazard ratio; NR: not reached; SAE: serious adverse event

2.3 Overall conclusion on added benefit

Table 3 summarizes the results of the benefit assessment for commission A21-23 and the present addendum, both of which were used to inform the overall conclusion on the extent of added benefit.

Table 3: Favourable and unfavourable effects from the assessment of avelumab in comparison with BSC

Favourable effects	**Unfavourable effects**
Mortality ▪ Overall survival Indication of added benefit – extent: considerable	–
–	Non-serious/non-severe AEs ▪ Hypothyroidism, gastrointestinal disorders, infections and infestations, respiratory, thoracic, and mediastinal disorders, diseases of the skin and subcutaneous tissue for each, hint of greater harm – extent: considerable ▪ Arthralgia ▫ Age (≥ 65 years) Hint of greater harm – extent: considerable
Serious/severe AEs ▪ Benign, malignant, and unspecified neoplasms (incl. cysts and polyps) (severe AEs) Hint of lesser harm – extent: minor	Serious/severe AEs ▪ Severe AEs Hint of greater harm – extent: major Including ▫ Elevated lipase, elevated amylase for each, hint of greater harm – extent: considerable ▫ Metabolic and nutritional disorders Hint of greater harm – extent: minor ▫ **Immune-mediated severe AEs** **Hint of greater harm – extent: major**
No usable data were available for health-related quality of life, infusion-related reactions, or for the outcome of discontinuation due to AEs.	
Results printed in **bold** are based on the analyses subsequently submitted by the company with the written comment. AE: adverse events	

For immune-mediated severe AEs, the data subsequently submitted in the commenting procedure alongside the favourable and unfavourable effects presented in dossier assessment A21-23 result in another hint of greater harm of major extent. This unfavourable effect is apparent already in the outcome of severe AEs.

Furthermore, since the unfavourable effects do not fully call into question the favourable effect regarding the outcome of overall survival, an indication of minor added benefit of avelumab + BSC versus BSC can be derived for adult patients with locally advanced or metastatic urothelial carcinoma who are progression-free following platinum-based first-line chemotherapy.

2.4 Summary

The data subsequently submitted by the company in the commenting procedure do not change the conclusion on the added benefit of avelumab drawn in dossier assessment A21-23.

Table 4 below shows the result of the benefit assessment of avelumab in consideration of both dossier assessment A21-23 and the present addendum.

Table 4: Avelumab – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Adults with locally advanced or metastatic urothelial carcinoma who are progression-free following platinum-based chemotherapy	BSC	Indication of minor added benefit[b]
a. Presented is the respective ACT specified by the G-BA. b. The JAVELIN Bladder 100 study included almost exclusively patients with an ECOG-PS of 0 or 1. Patients with active brain metastases were excluded. It remains unclear whether the observed effects are transferable to patients with an ECOG-PS ≥ 2 or active brain metastases. ACT: appropriate comparator therapy; BSC: best supportive care; G-BA: Federal Joint Committee		

The G-BA decides on the added benefit.

3 References

The list of references contains citations by the company which may lack some bibliographic information.

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Appendix A – Supplementary results on immune-mediated AEs at the cluster level

Table 5: Cluster of immune-mediated AEs – RCT, direct comparison: avelumab + BSC vs. BSC

Study	Patients with event n (%)	
Cluster[a]	Avelumab + BSC N = 344	BSC N = 345
JAVELIN BLADER 100		
Total rate of immune-mediated AEs	206 (59.9)	63 (18.3)
Immune-related colitis[b]	66 (19.2)	20 (5.8)
Immune-related endocrinopathies: adrenal insufficiency	5 (1.5)	0 (0)
Immune-related endocrinopathies: thyroid disorders[c]	56 (16.3)	3 (0.9)
Immune-related endocrinopathies: diabetes mellitus type 1	16 (4.7)	9 (2.6)
Immune-related hepatitis	26 (7.6)	7 (2.0)
Immune-related nephritis and renal dysfunction	22 (6.4)	14 (4.1)
Immune-related pancreatitis	4 (1.2)	1 (0.3)
Immune-mediated pneumonitis	12 (3.5)	1 (0.3)
Immune-related skin rash[d]	108 (31.4)	17 (4.9)
Other immune-related AEs: encephalitis	0 (0)	1 (0.3)
Other immune-related AEs: Guillain-Barré syndrome	1 (0.3)	0 (0)
Other immune-related AEs: myositis	17 (4.9)	2 (0.6)
Other immune-related AEs: uveitis	1 (0.3)	1 (0.3)
Other immune-related AEs: other	9 (2.6)	1 (0.3)

a. Cluster name adopted unchanged from the company's comment. The PTs potentially included in each cluster are listed in Appendix B.
b. Includes, in particular, the PT of diarrhoea (avelumab [17.7%] vs. BSC [5.8%]).
c. Includes, in particular, the PTs of hyperthyroidism (avelumab [6.1%] vs. BSC [0.3%]) and hypothyroidism (avelumab [11.6%] vs. BSC [0.6%]).
d. Includes, in particular, the PTs of pruritus (avelumab [17.2%] vs. BSC [2.3%]) and rash (avelumab [11.6%] vs. BSC [1.7%]).

AE: adverse event; BSC: best supportive care; n: number of patients with at least 1 event; N: number of analysed patients; PT: preferred term; RCT: randomized controlled trial

Table 6: Cluster of immune-mediated SAEs – RCT, direct comparison: avelumab + BSC vs. BSC

Study	**Patients with event n (%)**	
Cluster[a]	**Avelumab + BSC N = 344**	**BSC N = 345**
JAVELIN BLADER 100		
Total rate of immune-mediated SAEs	30 (8.7)	13 (3.8)
Immune-related colitis	5 (1.5)	1 (0.3)
Immune-related endocrinopathies: adrenal insufficiency	0 (0)	0 (0)
Immune-related endocrinopathies: thyroid disorders	2 (0.6)	0 (0)
Immune-related endocrinopathies: diabetes mellitus type 1	0 (0)	1 (0.3)
Immune-related hepatitis	3 (0.9)	2 (0.6)
Immune-related nephritis and renal dysfunction	11 (3.2)	8 (2.3)
Immune-related pancreatitis	2 (0.6)	0 (0)
Immune-mediated pneumonitis	2 (0.6)	1 (0.3)
Immune-related skin rash	1 (0.3)	0 (0)
Other immune-related AEs: encephalitis	0 (0)	1 (0.3)
Other immune-related AEs: Guillain-Barré syndrome	1 (0.3)	0 (0)
Other immune-related AEs: myositis	3 (0.9)	0 (0)
Other immune-related AEs: uveitis	0 (0)	0 (0)
Other immune-related AEs: other	1 (0.3)	0 (0)

a. Cluster name adopted unchanged from the company's comment. The PTs potentially included in each cluster are listed in Appendix B.

BSC: best supportive care; n: number of patients with at least 1 event; N: number of analysed patients; PT: preferred term; RCT: randomized controlled trial; SAE: serious adverse event

Table 7: Cluster of immune-mediated severe AEs (CTCAE ≥ 3) – RCT, direct comparison: avelumab + BSC vs. BSC

Study	**Patients with event n (%)**	
Cluster[a]	**Avelumab + BSC N = 344**	**BSC N = 345**
JAVELIN BLADER 100		
Total rate of immune-mediated severe AEs (CTCAE ≥ 3)[a]	45 (13.1)	16 (4.6)
Immune-related colitis	6 (1.7)	2 (0.6)
Immune-related endocrinopathies: adrenal insufficiency	0 (0)	0 (0)
Immune-related endocrinopathies: thyroid disorders	1 (0.3)	0 (0)
Immune-related endocrinopathies: diabetes mellitus type 1	8 (2.3)	2 (0.6)
Immune-related hepatitis	9 (2.6)	2 (0.6)
Immune-related nephritis and renal dysfunction	7 (2.0)	9 (2.6)
Immune-related pancreatitis	2 (0.6)	1 (0.3)
Immune-mediated pneumonitis	1 (0.3)	0 (0)
Immune-related skin rash	6 (1.7)	0 (0)
Other immune-related AEs: Encephalitis	0 (0)	1 (0.3)
Other immune-related AEs: Guillain-Barré syndrome	1 (0.3)	0 (0)
Other immune-related AEs: myositis	6 (1.7)	0 (0)
Other immune-related AEs: Uveitis	0 (0)	0 (0)
Other immune-related AEs: Other	2 (0.6)	0 (0)

a. Cluster name adopted unchanged from the company's comment. The PTs potentially included in each cluster are listed in Appendix B.

AE: adverse event; BSC: best supportive care; CTCAE: Common Terminology Criteria for Adverse Events; n: number of patients with at least 1 event; N: number of analysed patients; PT: preferred term; RCT: randomized controlled trial; SOC: system organ class

Appendix B Clusters (PT lists) created by the company regarding immune-mediated AEs

Table 4-76 (appendix): PTs for the definition of immune-mediated adverse events

Group	PT
Immune-mediated pneumonitis	
Immune-mediated pneumonitis	Acute interstitial pneumonitis, autoimmune lung disease, immune-mediated pneumonitis, interstitial lung disease, pneumonitis
Immune-related hepatitis	
Immune-related hepatitis	Acute liver failure, elevated alanine aminotransferase, elevated aspartate aminotransferase, autoimmune hepatitis, drug-induced liver injury, elevated liver enzyme elevated, liver failure, abnormal liver function, hepatitis, acute hepatitis, hepatocellular damage, liver toxicity, hypertransaminasaemia, immune-mediated hepatitis, liver disease, abnormal liver function test, elevated liver function test, liver injury, elevated transaminases
Immune-related colitis	
Immune-related colitis	Acute haemorrhagic ulcerative colitis, allergic colitis, autoimmune colitis, autoimmune enteropathy, colitis, colitis cystica profunda, erosive colitis, ischaemic colitis, microscopic colitis, psychogenic colitis, ulcerative colitis, Crohn's disease, diarrhoea, haemorrhagic diarrhoea, neonatal diarrhoea, enteritis, enterocolitis, haemorrhagic enterocolitis, eosinophilic colitis, immune-mediated enterocolitis, eosinophilic colitis, immune-mediated enterocolitis, inflammatory bowel disease, necrotizing colitis, neutropenic colitis, pseudopolyposis, segmental diverticular colitis
Immune-related endocrinopathies	
Adrenal insufficiency	Addison's disease, adrenal androgen deficiency, adrenal atrophy, adrenal insufficiency, adrenal suppression, acute adrenocortical insufficiency, cortisol deficiency, glucocorticoid deficiency, aldosterone deficiency, mineral corticoid deficiency, primary adrenal insufficiency, secondary adrenocortical insufficiency, steroid withdrawal syndrome
Hypophysitis	Hypophysitis, hypopituitarism, lymphocytic hypophysitis
Thyroid diseases: hyperthyroidism	Basedow disease, low serum thyreotropin, hyperthyroidism, Marine-Lenhart syndrome, primary hyperthyroidism, secondary hyperthyroidism, thyroid dermopathy, thyrotoxic crisis, thyrotoxic periodic paralysis, elevated thyroxine level, toxic goitre, toxic nodular goitre
Thyroid diseases: hypothyroidism	Autoimmune hypothyroidism, elevated serum TSH level, hypothyroidism goitre, hypothyroidism, immune-mediated hypothyroidism, myxoedema, primary hypothyroidism, secondary hypothyroidism, tertiary hypothyroidism, thyroid atrophy, transient hypothyroxinaemia of prematurity
Thyroid diseases: thyroiditis	Immune thyroiditis, immune-mediated thyroiditis, silent thyroiditis, abnormal thyroid function test, thyroiditis, acute thyroiditis, chronic thyroiditis, chronic fibrous thyroiditis, subacute thyroiditis
Type 1 diabetes mellitus	Diabetes mellitus, diabetic ketoacidosis, hyperglycaemia, latent autoimmune diabetes in adults, type 1 diabetes mellitus

Figure 1: Clusters (PT lists) created by the company, part 1

(Source: Module 4 A, p. 294 [2])

Group	PT
Hypogonadism	Hypogonadism, hypogonadism in women, hypogonadism in men, late-onset hypogonadism syndrome, primary hypogonadism, secondary hypogonadism
Immune-related myocarditis	
Immune-related myocarditis	Autoimmune myocarditis, immune-mediated myocarditis, myocarditis
Immune-related nephritis and renal dysfunction	
Immune-related nephritis and renal dysfunction	Acute renal damage, autoimmune nephritis, immune-mediated nephritis, lupus nephritis, nephritis, haemorrhagic nephritis, perinephritis, renal failure, renal dysfunction, tubulointerstitial nephritis, tubulointerstitial nephritis with uveitis syndrome
Immune-related pancreatitis	
Immune-related pancreatitis	Autoimmune pancreatitis, immune-mediated pancreatitis, pancreatitis, acute pancreatitis, necrotizing pancreatitis
Immune-related skin rash	
Immune-related skin rash	Acute generalized exanthematous pustulosis, autoimmune dermatitis, cutaneous vasculitis, acneiform dermatitis, bullous dermatitis, exfoliative dermatitis, generalised exfoliative dermatitis, drug rash, drug reaction with eosinophilia and systemic symptoms, epidermal necrosis, erythema, erythema multiforme, exfoliative skin rash, immune-mediated dermatitis, oculomucocutaneous syndrome, pemphigoid, pruritus, allergic pruritus, rash, erythematous skin rash, macular rash, maculopapular rash, papular rash, rash with itching, pustulous rash, skin necrosis, skin reaction, skin toxicity, Stevens-Johnson syndrome, target lesion, acute toxic epidermolysis, toxic skin rash
Other immune-related adverse events	
Encephalitis	Autoimmune encephalopathy, encephalitis, autoimmune encephalitis, encephalopathy, immune-mediated encephalitis
Guillain-Barré syndrome	Autoimmune demyelinating disease, demyelization, Guillain-Barré syndrome, Miller-Fisher syndrome
Myasthenic syndrome	Myasthenia gravis, myasthenic syndrome
Myositis	Autoimmune myositis, elevated creatin phosphokinase in blood, immune-mediated myositis, myositis, polymyositis, rhabdomyolysis
Uveitis	Autoimmune uveitis, immune-mediated uveitis, iridocyclitis, iritis, uveitis, Vogt-Koyanagi-Harada disease
Graft-versus-host syndrome	Acute graft-versus-host disease, acute graft-versus-host disease of the intestine, acute graft-versus-host disease of the liver, acute graft-versus-host disease of the skin, chronic graft-versus-host disease, chronic graft-versus-host disease of the intestine, chronic graft-versus-host disease of the liver, chronic graft-versus-host disease of the skin, graft-versus-host syndrome, graft-versus-host reaction of the eye, graft-versus-host disease of the gastrointestinal tract, graft-versus-host reaction of the liver, graft-versus-host reaction of the lung, cutaneous graft-versus-host reaction
Other	Aplastic anaemia, autoimmune anaemia, autoimmune aplastic anaemia, autoimmune arthritis, autoimmune disease, autoimmune disease of the eye, autoimmune haemolytic anaemia, autoimmune neuropathy, autoimmune neutropenia, autoimmune pancytopenia, autoimmune pericarditis, autoimmune retinopathy, integumental lupus erythematosus, psoriasiform dermatitis, duodenitis, facial nerve disorder, gastritis, haemolytic anaemia, haemophagocytic lymphohistiocytosis, histiocytic necrotizing lymphadenitis, hypoglossal nerve paresis, third cranial nerve paresis, immune thrombocytopenic purpura, immune-mediated arthritis, immune-mediated neuropathy, immune-mediated pancytopenia, fourth cranial nerve paresis, meningitis, myelitis, pericarditis, peripheral nerve paresis, polymyalgia rheumatica, psoriasis, rheumatoid arthritis, sarcoidosis, Sjogren syndrome, rejection of solid organ transplant, systemic inflammatory response syndrome, systemic lupus erythematosus, trigeminal nerve paresis, vasculitic ulcer, vasculitis, sixth nerve paresis, vitiligo
The PTs to be taken into account were defined in the safety review (list of tier 1 AEs) and are subject to regular review [70]. AE: adverse event; PT: preferred term	

Figure 2: Clusters (PT lists) created by the company, part 2

(Source: Module 4 A, p. 295 f. [2])