Diversity in Safety Data Analysis in German AMNOG Benefit Assessments for Multiple Myeloma

PCN309

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Background

- Following the German Pharmaceuticals Market Reorganization Act (Arzneimittelmarktneuordnungsgesetz, AMNOG) it is mandatory for pharmaceutical companies of new drugs to submit a dossier to the Federal Joint Committee (Gemeinsamer Bundesausschuss, G-BA).
- Despite the fact that safety data are essential for the AMNOG and incomplete safety data harbor the risk for a dossier to be incomplete, the current rules of procedure do not provide specifications on how to report safety data.
- This lack of specifications resulted in a highly heterogenous way how to report safety data both in their nature as well in their extent.

Objective

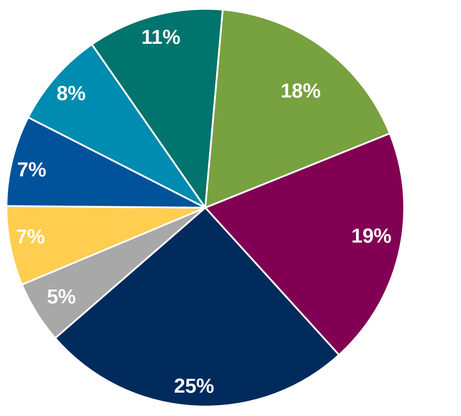
- Multiple Myeloma in adults is a highly dynamic indication. Therefore, it was chosen to give an overview on the diversity of displayed safety data and to exemplify G-BA's requirements.

Methods

- A database containing all assessed AMNOG dossiers published on the G-BA website (https://www.g-ba.de) from 2011 until end of August 2018 was screened for dossiers in Multiple Myeloma.
- For all relevant dossiers module 4 of the manufacturer, corresponding G-BA or Institute for Quality and Efficiency in Health Care (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen, IQWiG) assessments and the official documentation of G-BA's decision making (Tragende Gründe) on added benefit were used to extract information on safety data.
- Dossiers were screened for
  - Categories for overall rates
  - Categories for detailed analyses of specific AE
  - Thresholds for frequency of AE
  - Levels of the Medical Dictionary for Regulatory Activities (MedDRA) hierarchy
  - Grading of severity by Common Terminology Criteria (CTC) for AE

Results

Figure 1. Proportion of Assessments for Oncology and Multiple Myeloma in the Total Quantity of Assessed AMNOG Dossiers



- Out of 341 AMNOG dossiers published from 2011 to August 2018 and conclusively assessed by the G-BA, 128 AMNOG dossiers with 217 subpopulations were in the field of oncology (**Figure 1**).
- Ten relevant AMNOG dossiers with twelve subpopulations were identified regarding six active agents (Carfilzomib, Daratumumab, Elotuzumab, Ixazomib, Panobinostat, Pomalidomide) (**Table 1**). Two assessments were excluded, because no safety data were available: one evaluation process of Daratumumab in 2017 was terminated by G-BA and for one subpopulation of Pomalidomide in 2015 the manufacturer showed no separate safety data.
- Of these, six AMNOG dossiers were assessed as an orphan drug and one AMNOG dossier underwent full evaluation (**Table 1**).
- At the time of approval nine active agents were granted with an orphan status. In case of an orphan status, medical benefit is considered as proven in accordance with the legal
- Three orphan drug dossiers (Carfilzomib, Daratumumab, Pomalidomide) were reassessments due to exceeding the annual costs to the statutory health insurance (Gesetzliche Krankenversicherung, GKV) of 50 million Euro (**Table 1**).

Adverse Events: Overall Rates

Table 1: Overview on Adverse Event Rates in Assessed Myeloma AMNOG Dossiers

AMONG Dossier	Indication	Assessor	Any AE	Any SAE	Withdrawal due to AE	AE by severity	AE leading to death
Pomalidomide (orphan) 2013	A	Manufacturer	✓	✓	✓	✓	✓
		G-BA	✓	✓	✓	✓	✓
Pomalidomide (>50 Mio) 2015	A	Manufacturer	✓	✓	✓	✓	✓
		G-BA/IQWiG	✓	✓	✓	✓	✓
Carfilzomib (orphan) 2015	A	Manufacturer	✓	✓	✓	✓	✓
		G-BA	✓	✓	✓	✓	✓
Panobinostat (orphan) 2015	A	Manufacturer	✓	✓	✓	✓	✓
		G-BA	✓	✓	✓	✓	✓
Daratumumab (orphan) 2016	A	Manufacturer	✓	✓	✓	✓	✓
		G-BA	✓	✓	✓	✓	✓
Carfilzomib (orphan, Type II variation) 2016	B	Manufacturer	✓	✓	✓	✓	✓
		G-BA	✓	✓	✓	✓	✓
Elotuzumab 2016	A	Manufacturer	✓[a]	✓[a]	X[a]	✓[a]	X[a]
		G-BA/IQWiG	✓	✓	X	✓	X
Daratumumab (>50 Mio) 2017	A	Manufacturer	✓	✓	✓	✓	✓
		G-BA/IQWiG	✓	✓	✓	✓	X
	B	Manufacturer	✓	✓	✓	✓	✓
		G-BA/IQWiG	Excluded from assessment: Indirect comparison was inappropriate				
Carfilzomib (>50 Mio) 2017	A	Manufacturer	✓	✓	✓	✓	✓
		G-BA/IQWiG	✓	✓	✓	✓	X
	B	Manufacturer	✓	✓	✓	✓	✓
		G-BA/IQWiG	✓	✓	✓	✓	X
Ixazomib (orphan) 2017	A	Manufacturer	✓	✓	✓	✓	X
		G-BA/IQWiG	✓	✓	✓	✓	X

a: Data submitted in written statement due to new data cut off were taken into account.

- In all AMNOG dossiers overall rates of adverse events (AE), severe AE (SAE) and withdrawals due to AE were displayed in module 4, which was generally well accepted by G-BA/IQWiG.
- In case of Elotuzumab, overall rates of withdrawals due to AE were presented in module 4 (**Table 1**). However, in the written statement after the assessment by IQWiG and prior to the public hearing new data based on a second data cut-off were submitted and the category withdrawals from the therapy due to AE were not displayed anymore.
- Eight AMNOG dossiers with nine subpopulations also presented overall rates of AE leading to death (**Table 1**).
- Overall rates of AE by CTC grade (≥3 or 3+4) were presented in all AMNOG dossiers (**Table 1**). However, if the manufacturer only presented AE by CTC grade 3+4 this was recently criticized by G-BA/IQWiG due to the lack of severe AE with CTC grade 5 (**Table 2**).

Results (cont.)

Adverse Events: Detailed Analyses for Specific AE

Table 2: Detailed Presentation of Adverse Events in Multiple Myeloma AMNOG Dossiers by Manufacturer and G-BA

AMONG Dossier	Indication	Detailed Constitution of AE/SAE by SOC and PT		Assessment by G-BA/IQWiG	
		Severity	Threshold	Severity	Threshold
Pomalidomide (orphan) 2013	A	-	-	AE (all CTC grades) by SOC and PT	≥10 %
		AE CTC grade 3+4 by PT	≥5 %	AE CTC grade 3+4 by SOC and PT	≥5 %
Pomalidomide (>50 Mio) 2015	B	-	-	AE (all CTC grades) by SOC and PT	≥5 %
		AE CTC grade 3+4 by PT	≥5 %	AE CTC grade 3+4 by SOC and PT	≥5 %
		-	-	SAE by SOC and PT	≥2 %
Carfilzomib (orphan) 2015	A	-	-	AE (all CTC grades) by SOC and PT	≥10 %
		AE CTC grade ≥3 by PT	≥10 %	AE CTC grade ≥3 by PT	≥2 %
		SAE CTC grade ≥3 by PT	≥10 %	SAE CTC grade ≥3 by PT	≥1 %
Panobinostat (orphan) 2015	A	AE (all CTC grades) by PT	≥10 %[a]	AE (all CTC grades) by PT	≥10 %
		AE CTC grade 3+4 by PT	≥2 %[a]	AE CTC grade 3+4 by PT	≥2 %[a]
Daratumumab (orphan) 2016	A	-	-	AE (all CTC grades) by PT	≥10 %
		AE CTC grade ≥3 by PT	≥5 %	AE CTC grade ≥3 by PT[b]	-
Carfilzomib (orphan, type II variation) 2016	B	-	-	AE (all CTC grades) by SOC and PT	≥10 %
		AE CTC grade ≥3 by PT	≥5 %	AE CTC grade ≥3 by PT	≥2 %[a]
		-	-	SAE (all CTC grades) by SOC and PT	≥1 %
Elotuzumab 2016	A	AE (all CTC grades) by PT[c]	≥10 %[c]	AE (all CTC grades) by SOC and PT	≥10 %
		AE CTC grade 3+4 by PT[c]	-[c]	AE CTC grade 3+4 by SOC and PT	≥5 %[a]
		-	-	SAE (all CTC grades) by SOC and PT	≥3 %
Daratumumab (>50 Mio) 2017	A	AE (all CTC grades) by PT [data cut off 1 and 2]	≥10 %	AE (all CTC grades) by PT [data cut off 1]	≥10 %
		AE CTC grade ≥3 PT [data cut off 1 and 2]	≥5 %	AE CTC grade ≥3 PT [data cut off 1]	≥5 %
		SAE (all CTC grades) by PT [data cut off 1 and 2]	≥2 %	SAE (all CTC grades) by PT [data cut off 1]	≥2 %
	B	AE (all CTC grades) by PT	≥10 %	Excluded from assessment: Indirect comparison was inappropriate	
		AE CTC grade ≥3 by PT	≥5 %		
		SAE (all CTC grades) by PT	≥2 %		
Carfilzomib (<50 Mio) 2017	A	-	-	AE (all CTC grades) by SOC and PT[d]	≥10%
		AE CTC grade ≥3 by PT	≥5 %	AE CTC grade ≥3 by SOC[d] and PT	≥3 %
		SAE CTC grade ≥3 by SOC[e] and PT	≥5 %	SAE (all CTC grades) by SOC and PT	≥1 %
Carfilzomib (>50 Mio) 2017	A	-	-	AE (all CTC grades) by SOC and PT[d]	≥10%
		AE CTC grade ≥3 by PT	≥5 %	AE CTC grade ≥3 by SOC[d] and PT	≥3 %
		SAE CTC grade ≥3 by SOC[e] and PT	≥5 %	SAE (all CTC grades) by SOC and PT	≥1 %
Ixazomib (orphan) 2017	A	-	-	AE (all CTC grades) by SOC and PT	≥10 %

a: Threshold was not explicitly mentioned and was therefore derived from the presented data.
b: Just mentioned but not listed in detail by the G-BA.
c: Data submitted after oral hearing due to new data cut off were taken into account.
d: G-BA emphasized that due to lack of analysis, statements about advantages/disadvantages of specific AE were not possible.
e: Data submitted in written statement were taken into account.

Categories and Thresholds

- Commonly, G-BA/IQWiG referred to the categories AE (all CTC grades), AE by CTC grade (≥3 or 3+4) and SAE by CTC grade (≥3 or 3+4). The data submitted by the manufacturer often deviated from that. In these cases, the corresponding data were subsequently published in assessment documents by G-BA/IQWiG.
- The category AE (all CTC grades) was originally only presented in the AMNOG dossiers of Panobinostat, Elotuzumab and Daratumumab (<50 Mio) (**Table 2**).
- In general, for these three categories different thresholds were chosen. Here, the higher the severity the lower was the threshold. This was well accepted by G BA/IQWiG despite of slight differences in the approach of the individual AMNOG dossiers. The only exception was seen in the three AMNOG dossiers of Carfilzomib. While a threshold of 10 % was displayed in the first dossier of 2015, a lower threshold of 5 % was chosen in the following AMNOG dossiers. This was overruled by the G-BA, who chose a stricter threshold (**Table 2**).

Levels of MedDRA Hierarchy

- In all AMNOG dossiers detailed analyses for specific AE were presented by preferred term (PT). This was frequently overruled and hence G-BA/IQWiG listed additional safety data by system organ class (SOC) in the corresponding assessment documents. In case of Carfilzomib (>50 Mio), G-BA criticized selective submission of safety analysis, particularly missing survival analysis for AE (all CTC grades) by SOC and PT, AE CTC grade ≥3 and SAE CTC grade ≥3 by SOC (**Table 2**).

Severity

- Regarding severity being presented by CTC the description of safety data varied from CTC grade ≥3 and CTC grade 3+4. Lately, it was criticized that the latter category is not adequate as severe AE with CTC grade 5 are missing (see Elotuzumab). This should be taken into account (**Table 2**).

Proposed Changes of the Rules of Procedure by the G-BA

Table 3: Proposed Changes by G-BA

Category	G-BA Criteria
1	Overall rate of **AE**
2	Overall rate of **SAE**
3	Overall rate of **withdrawals** due to AE
4	Overall rates of **AE by severity** (e.g. according to CTCAE) including a serious and non-serious AE if this was planned in the relevant trial.
5	For categories 1-4 a. Complete evaluations based on **SOC and PT** according to MedDRA (or corresponding) b. Evaluation for **specific disease concepts** (e.g. standardized MedDRA queries [SMQs]) if this was planned in the relevant trial.
Further Notes	▪ If **disease-related events** (e.g. progression, exacerbation) are considered in categories 1-5, additional AE analyses should be conducted in which these events are unconsidered. ▪ If **additional analyses** are conducted (e.g. survival time analyses; analyses for a relevant partial population of a study), these analyses must always be conducted for all AE (especially for all **SOC and PT**, and all **specific disease concepts** defined in the relevant trial [e.g. SMQ]). ▪ All evaluations based on SOC and PT according to MedDRA (or corresponding) and, if applicable, specific disease concepts defined in the relevant trial [e.g. SMQ]) can be presented in a **separate attachment** of module 4. Here, the output of the statistics software can be used without modification if all necessary information are included.

- On March 16, 2018, the G-BA proposed several changes to the rules of procedure. These changes also affected safety analyses.
- Overall, G-BA requested adequate analyses and specified distinct analyses:
  - Overall rates of AE, SAE, withdrawals due to AE and of AE by severity needs to be displayed.
  - Regarding these four categories detailed analyses for specific AE are required, e.g. by SOC and PT and by specific disease concepts.
- However, the proposed changes to the rules of procedure are still under evaluation. It is not yet known when they will come into effect and if there will be further changes.

Conclusions

- In the current rules of procedure explicit requirements for the analysis of safety data are not specified leading to a high heterogeneity of the reported safety data in AMNOG dossiers.
- Overall, there was consistency in the reporting of overall rates in AMNOG dossiers, which was generally accepted for G-BA assessment.
- However, there was diversity in the evaluation of specific AE such as different AE categories, evaluation by SOC and PT and the chosen thresholds.
- In general, G-BA insisted on detailed analyses in the three categories: frequent AE (all severity), severe AE by CTC grade and severe SAE by CTC grade. In addition, these should be analyzed by SOC and PT.
- Regarding severe AE and SAE by CTC grade, G-BA recently requested that the analysis of severe AE and SAE should not only focus on CTC grade 3+4 but should also consider CTC grade 5.
- In March 2018, G-BA published a draft of an updated version of the rules of procedure. This update also addresses detailed criteria for safety analyses, reflecting the present diversity in AMNOG dossiers in that regard. This version of the rules of procedure is currently under development.

ISPOR Europe 2018 | November 10-14, 2018 | Barcelona, Spain | Funded by Xcenda

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