APPROPRIATE COMPARATOR IN GERMAN AMNOG BENEFIT ASSESSMENTS IN MELANOMA – A DYNAMIC SITUATION

#PCN304

Nadia Italia, MPH; Susanne Kossow, PhD; Anne-Kathrin Claes, PhD; Corinna Templin, PhD; Werner Kulp, PhD

Xcenda GmbH, Hannover, Germany

Background

- In the German Pharmaceuticals Market Reorganization Act (AMNOG) process the medical benefit of new drugs is evaluated against an appropriate comparator, which is determined by the Federal Joint Committee (Gemeinsamer Bundesausschuss, G-BA).
- To provide evidence against the appropriate comparator is critical for a compound to receive an added medical benefit from G-BA.
- G-BA applies certain criteria to define the appropriate comparator (**Table 1**). Over time, the defined appropriate comparator for an indication can change (e.g., due to updates in relevant clinical guidelines).

Table 1: Criteria for Determining the Appropriate Comparator According to the G-BA Rules of Procedure

	G-BA Criteria
1	If a **drug** is considered as an appropriate comparator, the drug must have an **approval** for the **area of application**.
2	If a **non-drug treatment** is considered as an appropriate comparator, it must be **performable within** the **framework** of the **statutory health insurance** (Gesetzliche Krankenversicherung).
3	**Preferably**, drugs or non-drug treatments whose **patient-relevant benefit** has **already been determined** by G-BA, must be taken into consideration as an appropriate comparator.
4	The appropriate comparator **must belong** to the **appropriate therapy** in the area of application, according to the general recognized **state of the art** of **medical knowledge**.

Objectives

- Melanoma in adults is a highly dynamic therapeutic space. Melanoma was, therefore, chosen to exemplify G-BA's approach of how to account advances in medical treatment when defining the appropriate comparator.

Methods

- A database containing all assessed AMNOG dossiers published on the G-BA website (https://www.g-ba.de) from January 2011 until the end of August 2018 was screened for dossiers in melanoma.
- For all relevant dossiers the official documentation of G-BA's decision-making (Tragende Gründe) was screened for further information on the appropriate comparator and granted added medical benefit.
- Information concerning the defined appropriate comparator by G-BA and the decision on added benefits were extracted for relevant dossiers.

Results

- 341 AMNOG dossiers were published from January 2011 to August 2018 and conclusively assessed by G-BA. These dossiers included 692 separately evaluated indications and relevant subpopulations (**Figure 1**).
- Out of 128 AMNOG dossiers with 217 subpopulations in the field of oncology, 13 AMNOG dossiers for melanoma in adults with 23 subpopulations were identified (**Figure 2, Table 2**).
- In the relevant dossiers in melanoma appropriate comparators were defined as one specific drug, a list of equivalent drugs (out of which the manufacturer can choose freely), patient individual therapy, and best supportive care (**Tables 3-5**).
- Although the product labels of ipilimumab, nivolumab, pembrolizumab and talimogen laherparepvec do not take BRAF mutation status into account, G-BA considered two subpopulations (BRAF+/BRAF-). As those subpopulations are considered to be different entities in clinical guidelines and are managed differently in clinical practice, specific appropriate comparators therapies were defined by G-BA based on subpopulations (BRAF+/BRAF-) (**Tables 3 and 4**) and treatment line regardless of BRAF mutation status (**Table 5**).

Figure 1. Distribution of Assessed AMNOG Dossiers Since 2011

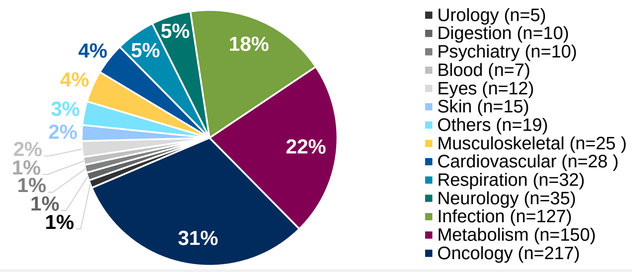

Figure 2. Proportion of Assessments for Oncology and Melanoma in the Total Quantity of Assessed AMNOG Dossiers

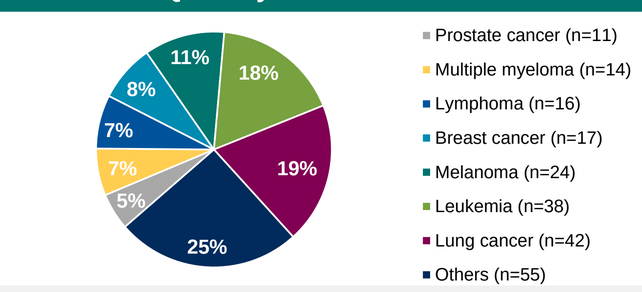

Table 2: AMNOG Dossiers in Melanoma

Compound	Year	Subpopulations		
		BRAF+	BRAF-	Pretreated
Ipilimumab	2011	-	-	Defined by label
Vemurafenib	2012	Defined by label	-	-
Vemurafenib (re-evaluation)	2013	Defined by label	-	-
Dabrafenib	2013	Defined by label	-	-
Ipilimumab	2013	Defined by G-BA	Defined by G-BA	-
Nivolumab	2015	Defined by G-BA	Defined by G-BA	Defined by G-BA
Pembrolizumab	2015	Defined by G-BA	Defined by G-BA	Defined by G-BA
Trametinib	2015	Defined by label	-	-
Dabrafenib+ Trametinib	2015	Defined by label	-	-
Cobimetinib+ Vemurafenib	2015	Defined by label	-	-
Talimogen laherparepvec	2016	Defined by G-BA	Defined by G-BA	Defined by G-BA
Nivolumab+ Ipilimumab	2016	Defined by G-BA	Defined by G-BA	Defined by G-BA

Results (cont.)

BRAF+ Melanoma Specific Benefit Assessments

- The first AMNOG dossier in melanoma for the BRAF+ population was published in 2012. For vemurafenib, G-BA defined dacarbazine as the appropriate comparator and assigned a considerable added benefit in overall survival (**Table 3**).
- Then in 2013, taking the degree of the added medical benefit into account, vemurafenib was defined as appropriate comparator for the dossier of dabrafenib.
- Until 2016 vemurafenib remained the appropriate comparator for the nine following melanoma dossiers. This static constellation might be attributable to the fact that for five dossiers (dabrafenib, 2013; ipilimumab (first-line), 2013; nivolumab, 2015; pembrolizumab, 2015; trametinib, 2015) no added medical benefit had been attested.
- In 2015, both for dabrafenib+trametinib and cobimetinib+vemurafenib a considerable added medical benefit was assigned by G-BA.
- Again, and similar to the assessment of vemurafenib in 2012, G-BA took the added medical benefit of dabrafenib+trametinib and cobimetinib+vemurafenib into account and included these regimens in the list of appropriate comparators for talimogen laherparepvec and nivolumab+ipilimumab.

Table 3: AMNOG Dossiers in the Field of Melanoma with BRAF+ Specific Appropriate Comparator

Compound	Year	Appropriate Comparator Defined by G-BA	Degree of Added Medical Benefit by G-BA
Vemurafenib	2012	Dacarbazine	Considerable
Vemurafenib (re-evaluation)[a]	2013	Dacarbazine	Considerable
Dabrafenib	2013	(Dacarbazine)[b] Vemurafenib	None
Ipilimumab (first-line)	2013	Vemurafenib	None
Nivolumab	2015	Vemurafenib	None
Pembrolizumab	2015	Vemurafenib	None
Trametinib[c]	2015	Vemurafenib	None
Dabrafenib+ Trametinib	2015	Vemurafenib	Considerable
Cobimetinib+ Vemurafenib	2015	Vemurafenib	Considerable
Talimogen laherparepvec	2016	(Vemurafenib)[b] Vemurafenib or Cobimetinib+Vemurafenib or Dabrafenib+Trametinib	None
Nivolumab+ Ipilimumab	2016	(Vemurafenib)[b] Vemurafenib or Cobimetinib+Vemurafenib or Dabrafenib+Trametinib	None

a: After expiration of time-limited first assessment
b: In the course of the process G-BA changed its initial definition of the appropriate comparator
c: The assessment of trametinib+dabrafenib was considered once only and the results shown under dabrafenib+trametinib

BRAF- Melanoma Specific Benefit Assessments

- In the assessment of ipilimumab, first-line, in 2013, G-BA considered two subpopulations BRAF+ (**Table 3**) and BRAF- (**Table 4**). For the BRAF- population dacarbazine was defined as the appropriate comparator.
- Despite the fact that for ipilimumab, both in BRAF+ and in BRAF- patients, no added medical benefit was attested by G-BA, ipilimumab was added to the list of appropriate comparators for nivolumab (2015) and was the sole appropriate comparator for pembrolizumab (2015). For talimogen laherparepvec (2016), nivolumab+ipilimumab (2016), and nivolumab+ipilimumab (2017), ipilimumab was initially chosen as the appropriate comparator.
- The considerable added medical benefit for nivolumab (2015) and pembrolizumab (2015) in overall survival triggered the G-BA to update the initial choice of the appropriate comparator (ipilimumab → nivolumab or pembrolizumab).

Table 4: AMNOG Dossiers in the Field of Melanoma with BRAF- Specific Appropriate Comparator

Compound	Year	Appropriate Comparator Defined by G-BA	Degree of Added Medical Benefit by G-BA
Ipilimumab (first-line)	2013	Dacarbazine	None
Nivolumab	2015	Dacarbazine or Ipilimumab	Considerable
Pembrolizumab	2015	Ipilimumab	Considerable
Talimogen laherparepvec	2016	(Ipilimumab)[a] Nivolumab or Pembrolizumab	None
Nivolumab+ Ipilimumab	2016	(Ipilimumab)[a] Nivolumab or Pembrolizumab	None
Nivolumab+ Ipilimumab	2017	(Ipilimumab)[a] Nivolumab or Pembrolizumab	None

a: In the course of the process G-BA changed its initial definition of the appropriate comparator

Benefit Assessments in Melanoma (pretreated)

- At the time of the assessments, no drugs where labeled according to the BRAF mutation status in second-line patients. Consequently, G-BA did not define specific drugs as appropriate comparators.
- Instead, best supportive care (ipilimumab, 2011) and patient-individual care (nivolumab, 2015; pembrolizumab, 2015; talimogen laherparepvec, 2016; nivolumab+ipilimumab, 2016) were defined as appropriate comparators (**Table 5**).
- Only for ipilimumab (2011) and pembrolizumab (2015) an added medical benefit was granted.

Table 5: AMNOG Dossiers in the Field of Melanoma for Pretreated Patients

Compound	Year	Appropriate Comparator Defined by G-BA	Degree of Added Medical Benefit by G-BA
Ipilimumab	2011	Best supportive care	Considerable
Nivolumab	2015	Patient-individual care	None
Pembrolizumab	2015	Patient-individual care	Considerable
Talimogen laherparepvec	2016	Patient-individual care	None
Nivolumab+ Ipilimumab	2016	Patient-individual care	None

Conclusions

- Labels nonspecific to BRAF mutation status were segmented by G-BA in subpopulations by BRAF mutation status and therapy lines (if in line with the label). Thus, individual appropriate comparator therapies were defined for those subpopulations for the assessments of ipilimumab, nivolumab, pembrolizumab, talimogen laherparepvec and nivolumab+ipilimumab (**Table 2**).
- G-BA does take the dynamic nature of treatment of an indication into account. For melanoma, the observed time span for updating the appropriate comparator is between one and two years. This could be attributable to the fact that a considerable added medical benefit in overall survival was attested and, in parallel, a fast uptake in medical practice occurred. Whether these findings can be transferred to other indications is out of the scope of this analysis.
- Even compounds with no added benefit (ipilimumab first-line, 2013; **Table 1, Criterion 3**) were chosen as appropriate comparators. It can be assumed that other reasons are being factored in the decision defining the appropriate comparator (e.g., clinical practice).
- The uncertainty in the treatment guidelines and medical practice (**Table 1, Criterion 4**) translates into the setting of patient-individual care as appropriate comparator for pretreated patients.

Presented at ISPOR 21st Annual European Congress | November 14, 2018 | Barcelona, Spain | Funded by Xcenda

Xcenda® AmerisourceBergen