Added Benefit Assessment of ATMPs in Germany: Does the Data Basis Meet HTA Requirements?

PBI68

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Background

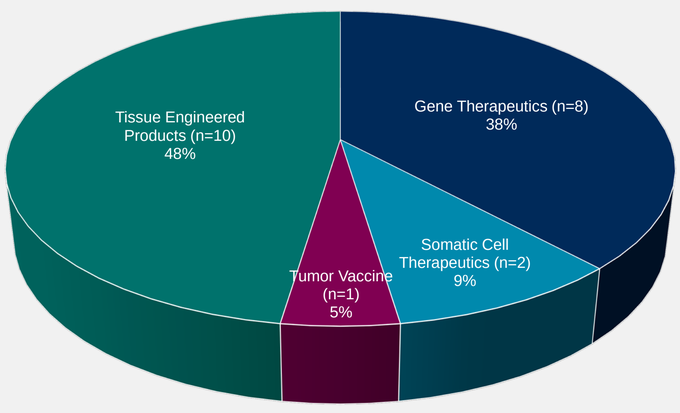
- Like all newly approved pharmaceuticals in Germany, ATMPs undergo an assessment of the additional medical benefit if they are based on a gene therapy or a somatic cell therapy.
- There are several reasons why the “standard” assessment conducted by the German HTA bodies (G-BA and IQWiG) is not fully adequate for the assessment of the added medical benefit of ATMPs:
  - The evidence base of pivotal studies for ATMP approval often is not comparative and therefore insufficient to quantify the added medical benefit.
  - Low patient numbers in the relevant indications.
  - Highly individualized therapies and often exclusive hospital-based usage also impede the assessment.
- The aim of this study is to analyze the evidence base and the outcome of ATMP assessments and to deduce challenges and strategies for future benefit assessment of ATMPS in Germany.

Objective and Methods

- Information on the assessment of ATMPs were retrieved from a databank containing information on all AMNOG procedures. Relevant documents were analyzed on indication, evidence base and outcome. Additionally, assessments of non-ATMP pharmaceuticals with low evidence base (single arm trials, registry data) were analyzed for supplemental information.

Results

Figure 1. ATMPs Approved in Germany



- In Germany 21 ATMPS have been approved so far (**Figure 1**):
  - 10 (48%) tissue engineered products
  - 8 (38%) gene therapeutics
  - 2 (9%) somatic cell therapeutics
  - 1 (5%) tumor vaccine

Gene therapeutics and somatic cell therapeutics are approved centrally by EMA, whereas most of tissue engineered products and tumor vaccines have a national authorization.

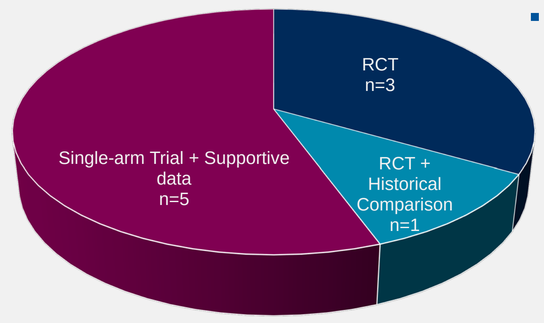
Table 1: Obligation for AMNOG Benefit Assessment for ATMPs

Drug	Label	EMA Approval Date	EMA Approval Status	AMNOG assessment
Gene Therapy Medicinal Products				
Glybera	Familial lipoprotein lipase deficiency	25/10/2012	Withdrawn	Yes
Imlygic	Melanoma	16/12/2015	Authorised	Yes
Kymriah	ALL + DLBCL	22/08/2018	Authorised	Yes
Luxturna	Retinal dystrophy	22/11/2018	Authorised	Yes
Provenge	CRPC	06/09/2013	Withdrawn	Yes
Strimvelis	ADA-SCID	26/05/2016	Authorised	No
Yescarta	DLBCL + PMBCL	23/08/2018	Authorised	Yes
Zynteglo	β-Thalassemia	29/05/2019	Authorised	Unclear
Somatic Cell Therapy Medicinal Products				
Alofisel	Rectal Fistula	23/03/2018	Authorised	Yes
Zalmoxis	HSCT/ GvHD	18/08/2016	Authorised	Yes

- Gene therapy medicinal products and somatic cell therapy medicinal products are obliged to AMNOG assessment since they are rated as “drugs” in Germany (**Table 1**).
- Tissue engineered products are rated as part of new treatment methods and therefore not subject to AMNOG benefit assessment (**Table 1**).
- Strimvelis is not available in Germany and therefore not obliged to AMNOG (**Table 1**).
- Yescarta and Kymriah are covered by changed rules of procedures in Germany: hospital only products have to undergo AMNOG assessment since March 2018 (**Table 1**).
- Zynteglo has been approved by EMA, but information on AMNOG assessment is not available (**Table 1**).

Results (cont.)

Figure 2. Evidence Base for AMNOG Assessment of ATMPs



- The assessment of the added medical benefit of eight ATMPS in Germany was based on following evidence:
  - 4 ATMPs: Single-arm study and retrospective data (e.g. registry data or patient chart reviews)
  - 3 ATMPs: RCT
  - 1 ATMP: RCT and Historical Comparison (interventional data)

Table 2: Outcome of AMNOG Benefit Assessment

Drug	OD Status	Data base	Study population (N)*	Benefit Rating
Gene Therapy Medicinal Products				
Glybera	OD	Single-arm study + retrospective data (patient chart review)	27	Non quantifiable
Imlygic	Non-OD	RCT + historical comparison (vs. interventional study)	436	No added benefit
Kymriah	OD	Single-arm study + historical comparison (vs. interventional study)	127 (ALL) 147 (DLBCL)	Non quantifiable
Luxturna	OD	RCT + single-arm long time follow-up	31	Considerable
Provenge	Non-OD	RCT	737	Non quantifiable
Yescarta	OD	Single-arm study + historical comparison (vs. interventional study)	119 (DLBCL + PMBCL)	Non quantifiable
Somatic Cell Therapy Medicinal Products				
Alofisel	OD	RCT	212	Non quantifiable
Zalmoxis	OD	Single-arm study + registry data (matched-pair analysis)	57	Non quantifiable

* Combined population from interventional studies presented in the respective dossier, N refers to the number of included patients.

- One of eight assessed ATMPs gained a quantified benefit rating (i.e. minor, considerable, major) (**Table 2**).
- Six ATMPs were designated as orphan drugs (**Table 2**). For orphan drugs the added medical benefit is set by law and no appropriate comparator is defined.
- For Imlygic an added medical benefit was not proven (**Table 2**).

Table 3: Terms and Conditions of ATMP Assessments

Drug	Conditional G-BA resolution	Requirements for re-assessment
Glybera	Yes	Registry data
Imlygic	No	-
Kymriah	Yes	Additional evidence from interventional and observational studies
Luxturna	Yes	Registry data (Safety)
Provenge	Yes	Not defined
Yescarta	Yes	Additional evidence from interventional and observational studies
Alofisel	No	-
Zalmoxis	Yes	Results from ongoing RCT

- Six of eight assessments resulted in a conditional G-BA resolution (**Table 3**).
- Conditions for re-assessment were the collection of post-hoc interventional and observational data (**Table 3**).
- Recently a law was adopted to make additional data acquisition (e.g. registry) legally binding if approval data are insufficient for the benefit assessment. This law will most likely apply to future AMNOG assessments of ATMPs.

Conclusions

- Main points of criticism in G-BA assessments are:
  - Limitations of evidence base (e.g. no comparative data, study population does not match label population, study duration is too short).
  - Methodological deficiencies regarding historical comparisons (e.g. missing information on patient characteristics, off-label use of drugs used in comparator arms).
- The data base for ATMPs at time of first EU approval does not necessarily meet the requirements for benefit assessment in Germany.
- A support of single arm interventional trials by carefully collected historical/registry data might fill the data gap. Until now this approach was not successful for ATMPs.

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