What is the impact of orphan drug re-assessments in Germany on their additional benefit and price?

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Introduction

- Under the AMNOG legislation introduced in 2011, the additional benefit (AB) of orphan drugs with annual sales below €50 mn is deemed proven by the marketing authorization. In these cases, the G-BA determines only the extent of AB, based on an abbreviated submission.
- However, when annual sales exceed this €50 mn threshold, a re-assessment is triggered, requiring a full submission. The certainty and extent of AB is determined, followed by price re-negotiations with the GKV-Spitzenverband.
- Recently launched orphan drugs, such as tisagenlecleucel and axicabtagene ciloleucel (both initially assigned a non-quantifiable AB), are associated with relatively high costs and thus may rapidly exceed the annual sales threshold, leaving only limited time for longer-term or additional data to emerge for a full submission.
- To understand the challenges for such products, we evaluated the impact of re-assessments on the AB rating and negotiated drug price.

Methods

- All G-BA assessments[1] of orphan products conducted before 2 May 2019 were reviewed.
- To quantify the change in AB between the initial and the re-assessment, a point value was assigned (amended from de Millas et al., 2016[2]). To this end, the extent and certainty of AB assigned to each subgroup was coded based on an ordinal scale from −3 to +9 (Table 1).

Table 1: Point values assigned to additional benefit ratings

		Certainty			
		Proof	Indication	Hint	Not proven
Extent	Major	9	8	7	–
	Considerable	6	5	4	–
	Minor	3	2	1	–
	None	–	–	–	0
	Smaller than comparator	−3	−2	−1	0
	Non-quantifiable	4	3	2	–

- However, a non-quantifiable AB could reflect an extent between minor and major, so unlike de Millas et al.,[2] we assigned values based on the midpoint, i.e. considerable extent, but subtracted 2 points to reflect the uncertainty of non-quantifiable outcomes.
- For G-BA assessments differentiating the AB for subgroups, the overall value was weighted based on the size of the subgroups stated in the G-BA resolution. If the size was not stated, an equal distribution was assumed.
- Launch and negotiated reimbursed prices were retrieved from Lauer-Taxe.[3]

Results

- A total of 71 orphan product assessments were identified.
- Only 8 products (approximately 11%) had been re-assessed (Table 2). Re-assessments of ivacaftor and nintedanib are ongoing.

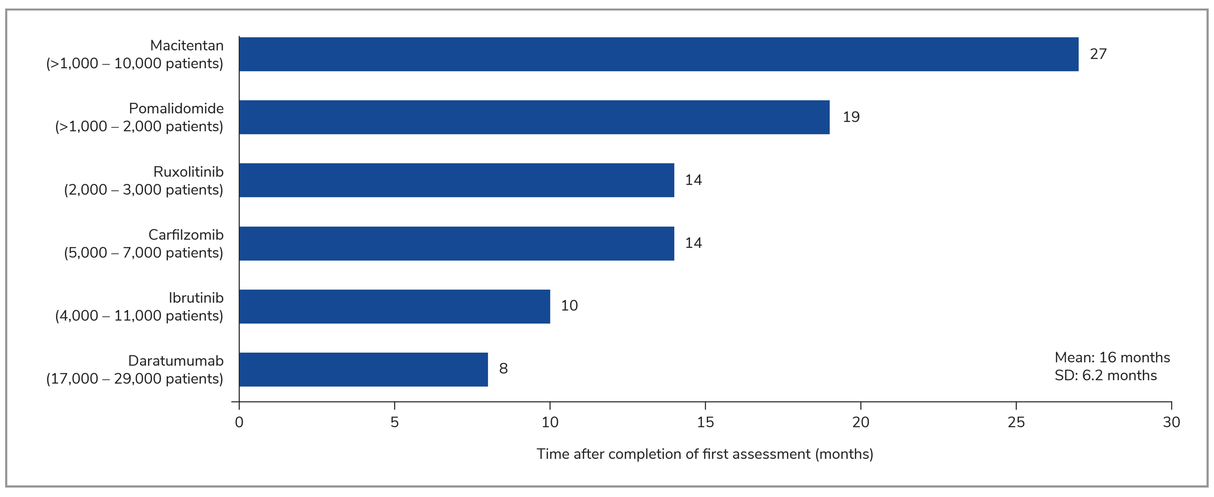
Table 2: Orphan drugs: initial and re-assessments

Product, indication	Orphan drug assessment (AB deemed proven)		Re-assessment after exceeding threshold	
Ivacaftor, CF	**7 Feb 2013** Two placebo-controlled double-blind Phase 3 RCTs (102 and 103)	Children aged 6–11 years: Extent: minor • Minor morbidity benefit	Sales threshold exceeded in Q1 2019 Re-assessment expected soon	
		Adolescents and adults: Extent: considerable • Considerable HRQL benefit		
Ruxolitinib, myelofibrosis	**7 Mar 2013** Extent: minor • Double-blind Phase 3 RCT (COMFORT-I) and open-label Phase 3 RCT (COMFORT-II) • Minor morbidity benefit		**6 Nov 2014** Hint of considerable AB • Double-blind Phase 3 RCT (COMFORT-I) and open-label Phase 3 RCT (COMFORT-II) • Statistically significant OS benefit • HRQL and morbidity benefits	
Pomalidomide, RRMM	**20 Feb 2014** Extent: considerable • Open-label Phase 3 RCT (CC-4047-MM-003) • Statistically significant OS benefit • No HRQL benefits		**17 Mar 2016** Open-label Phase 3 RCT (CC-4047-MM-003)	Eligible for high-dose dexamethasone: Hint of considerable AB • Statistically significant OS benefit • Maintenance of HRQL • No disadvantages in AEs
				Not eligible for high-dose dexamethasone: AB not proven • No data submitted
Macitentan, PAH	**17 Jul 2014** Extent: minor • Placebo-controlled double-blind Phase 3 RCT (SERAPHIN) • Minor morbidity benefit		**7 Apr 2017** AB not proven • Placebo-controlled double-blind Phase 3 RCT (SERAPHIN) • No adequate use of appropriate comparator therapy	
Ibrutinib, CLL, MCL	**16 Apr 2015** CLL: Extent: non-quantifiable • Open-label Phase 3 RCT (PCYC 1112-CA and single-arm Phase 1b/2 study (PCYC-1102-CA) • OS benefit, but immature data		**21 Jul 2016** CLL, eligible for chemotherapy: AB not proven • Double-blind RCT (CLL3001) • Study not accepted, as ibrutinib was not used according to license • Non-adjusted ITC using open-label Phase 3 RCT (PCYC-1112-CA) and comparator arm from double-blind RCT (CLL3001) was not accepted (no adequate use of appropriate comparator therapy) • Adjusted ITC using open-label Phase 3 RCT (PCYC-1112-CA) and open-label study OMB114242 was not accepted (study population not sufficiently comparable)	
			Open-label Phase 3 RCT (PCYC-1112-CA)	CLL, 1L, with 17p del/TP53 mut: Hint of non-quantifiable AB • Statistically significant OS benefit • High uncertainty in transfer of results for pre-treated to treatment-naive patients
				CLL, not eligible for chemotherapy: Hint of non-quantifiable AB • Statistically significant OS benefit • Disadvantages in morbidity, HRQL, and AEs
	MCL Extent: non-quantifiable • Single-arm study (PCYC-1104-CA) • OS and morbidity benefits, but high risk of bias • Some disadvantages in SAEs		Open-label Phase 3 RCT (MCL3001)	MCL, eligible for temsirolimus: Indication of considerable AB • Minor morbidity benefits • Statistically significant HRQL and AE benefits
				MCL, not eligible for temsirolimus: AB not proven • No data submitted
Nintedanib, IPF	**3 Sep 2015** Extent: minor • Two placebo-controlled double blind Phase 3 RCTs (INPULSIS-1 and INPULSIS-2) • Minor morbidity and HRQL benefit		Ongoing; expected 17 Oct 2019	
Daratumumab, RRMM	**1 Dec 2016** Extent: non-quantifiable • Two single-arm Phase 1/2 studies (SIRIUS and GEN501) • Non-licensed dosage used for some patients • No HRQL data • ITC was not accepted		**15 Feb 2018** As monotherapy: AB not proven • Historical comparison was not accepted	
				In combination: Indication of considerable AB • Two open-label Phase 3 RCTs (CASTOR and POLLUX) • Statistically significant OS benefit
Carfilzomib, RRMM	**2 Jun 2016, combination with lenalidomide and dexamethasone** Extent: non-quantifiable • Open-label Phase 3 RCT (ASPIRE PX171-009) • OS benefit, but immature data • HRQL benefit, but methodological limitations		**15 Feb 2018** Hint of considerable AB • Two open-label RCTs (ASPIRE and ENDEAVOR) • Statistically significant OS benefit • HRQL and morbidity benefits • No disadvantages in AEs	
	19 Jan 2017, combination with dexamethasone Extent: minor • Open-label Phase 3 RCT (ENDEAVOR) • No OS or morbidity benefits • No disadvantages in AEs			

AB, additional benefit; AE, adverse event; CF, cystic fibrosis; CLL, chronic lymphoblastic leukemia; del, deletion; HRQL, health-related quality of life; IPF, idiopathic pulmonary fibrosis; ITC, indirect treatment comparison; MCL, mantle cell lymphoma; mut, mutation; OS, overall survival; PAH, pulmonary arterial hypertension; RCT, randomized controlled trial; RRMM, relapsed/refractory multiple myeloma; SAEs, serious adverse events

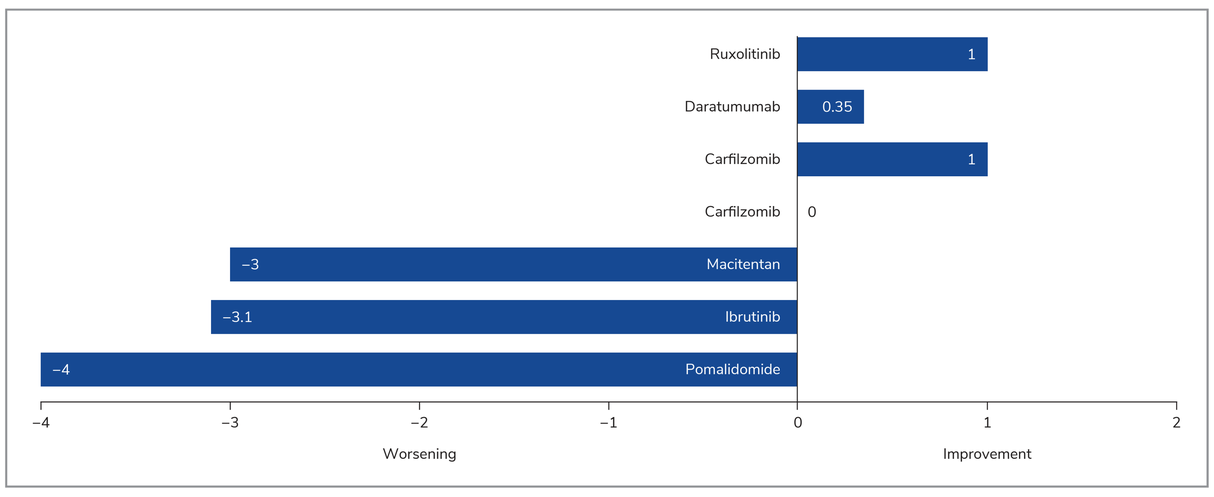
- On average, re-assessment was initiated after 16 months (range: 8–27 months) (Figure 1). Since the manufacturer is given a 3 month period to re-submit a dossier, this means on average the orphan drug threshold was exceeded after 13 months.
- As expected, this duration seems correlated with the number of patients expected to receive the product, as a higher number of patients is likely to result in greater sales, and therefore the orphan drug threshold will be exceeded more quickly.

Figure 1: Duration until initiation of re-assessment



- The most relevant analogues for tisagenlecleucel and axicabtagene ciloleucel were the re-assessments of products approved based on single-arm trials, i.e., daratumumab and ibrutinib.
- The overall AB rating improved for daratumumab (Figure 2), based on new comparative Phase 3 studies, but worsened for ibrutinib as the new indirect treatment comparison (ITC) was not accepted.
  - For the remaining products, ratings improved for carfilzomib and ruxolitinib, based on longer-term overall survival data.
  - The overall AB rating worsened for pomalidominde and macitentan, as the re-assessment was lacking data for a subgroup or did use a non-G-BA-defined comparator.

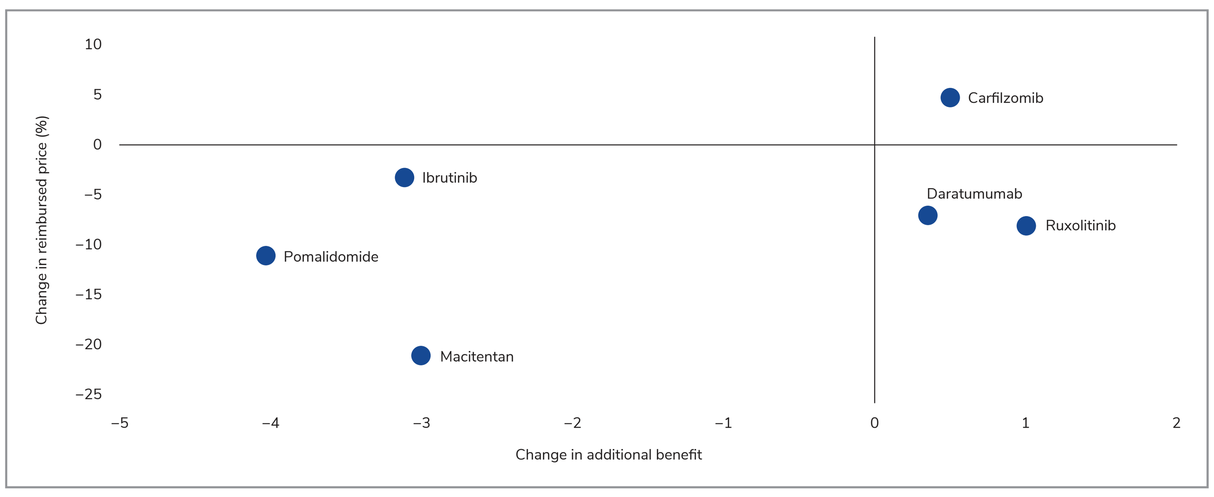
Figure 2: Change in AB



The change in AB between the initial and the re-assessment was quantified by assigning a point value accounting for the extent and certainty of AB based on an ordinal scale from −3 to +9 (amended from de Millas et al., 2016[2]).

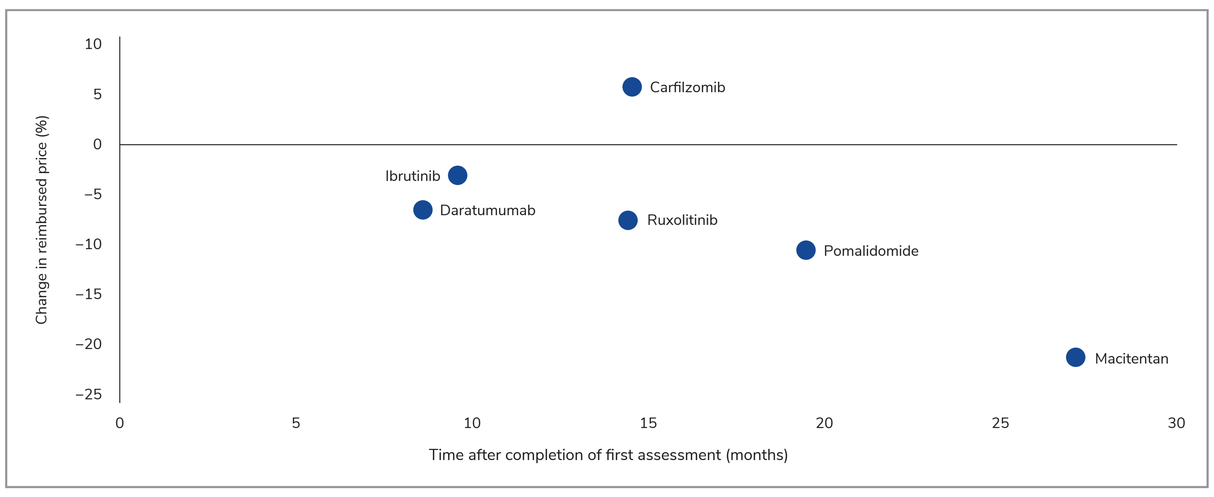
- There was not a clear correlation between the change in price (+5% to −21%) and AB (Figure 3). However, the three products with an AB improvement had smaller price decreases (−7 or −8%), or even a price increase (+5%).

Figure 3: Correlation of change in AB and reimbursed price



- The time until the re-assessment is initiated appears to be correlated with the change in the reimbursed price (Figure 4).
- The longer the duration until re-assessment, the higher was the negotiated price discount.
- However, the limited number of assessments in this study (6) means that conclusions cannot be drawn about this relationship.

Figure 4: Correlation of change in AB and reimbursed price



Conclusions

- Re-assessments of products initially assessed with single-arm studies required a comparative study or acceptable ITC to maintain an AB.
- With multiple costly one-off orphan treatments in development, re-assessments are expected to become more frequent. Future re-assessments of chimeric antigen receptor T-cell therapies may provide good case studies to understand evidence generation activities to support the re-assessment and pricing for high-cost agents.

Limitations

- This analysis is based on the small number of G-BA re-assessments conducted to date (n=6).
- The AB rating is only one factor in price negotiations. The size of the patient population, the comparator treatment costs, and the price of the treatment in reference countries are also considered.
- In addition, 2 of the 6 products (carfilzomib and ibrutinib) have been evaluated for other indications between the initial orphan drug assessment and the re-assessment after the sales threshold was exceeded. Thus, the AB rating achieved in the other indications could have also influenced the price re-negotiations.

References

1. G-BA. https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/
2. de Millas, et *al.* (2016) Marktdurchdringung von neuen Arzneimitteln. Gesundheitsökonomie & Qualitätsmanagement. 22. 10.1055/s-0042-122162.
3. Lauer-Taxe. https://webapo-info.lauer-fischer.de/LTO40.160101/taxe

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