German HTA Added-Benefit Outcomes for Oncology Drugs With or Without a Biomarker Target:
Higher Ratings but Lower Confirmation

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BACKGROUND

- Biomarker-targeted oncology drugs often treat small, molecularly defined populations.
- Under Germany's AMNOG legislation, the added benefit of orphan drugs is deemed proven while statutory health insurance revenue stays below a threshold (currently €30 million), recognizing the difficulty of generating comparative evidence and the frequent absence of therapeutic alternatives.[1]
- Biomarker-defined subsets of common tumors may not qualify for orphan status.[2]

OBJECTIVE & HYPOTHESIS

Objective
To compare added-benefit ratings and price changes of biomarker-targeted vs non-biomarker oncology drugs, overall and by orphan status.

Hypothesis
Biomarker-targeted drugs are disadvantaged: small populations face higher evidentiary hurdles, and orphan protection is granted less often.

METHODS

- **Data:** 521 oncology procedures assessed by IQWiG/G-BA, 2011 to 17 May 2026 (Cellbyte database): 237 biomarker-targeted, 284 non-biomarker
- **Biomarker:** companion-diagnostic or target biomarker in the indication (e.g., EGFR, ALK, BRAF, KRAS, HER2, BRCA, PD-L1, MSI/dMMR, NTRK)
- **Orphan:** procedures below the statutory revenue threshold; orphans above it analyzed as non-orphans
- **Sensitivity analysis (evidence vs legal grounds):** orphans rated 'non-quantifiable' with ≥1 positive endpoint category (↑/↑↑) in the physician information system (AIS) = evidence accepted;
without positive endpoint = not accepted (added benefit on legal grounds)
- **Price:** mean list-price change up to 18 months after the G-BA resolution (n=270); descriptive analysis

RESEARCH QUESTION

Are oncology drugs with a biomarker target disadvantaged in the German benefit assessment (AMNOG), and what role does legal orphan protection play?

RESULTS

1 RATINGS
Added-benefit ratings were assessed for oncology drugs with and without a biomarker target (Figure 1)

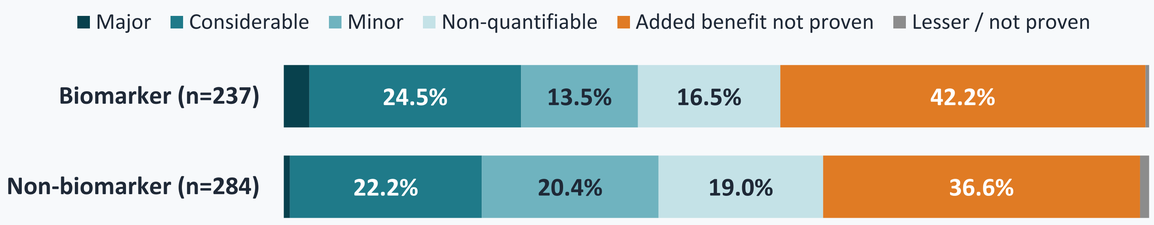


Figure 1. Added-benefit ratings of biomarker-targeted vs non-biomarker oncology procedures (% of procedures; IQWiG/G-BA assessments 2011 to 17 May 2026). n = number of procedures.

- 'Major' rating 2.9% vs 0.7%
- 'Considerable or better' rating 27.4% vs 22.9%
- 'Minor' rating 13.5% vs 20.4%

2 OVER TIME
'Added benefit not proven' ratings were assessed over time, by biomarker status (Figure 2)

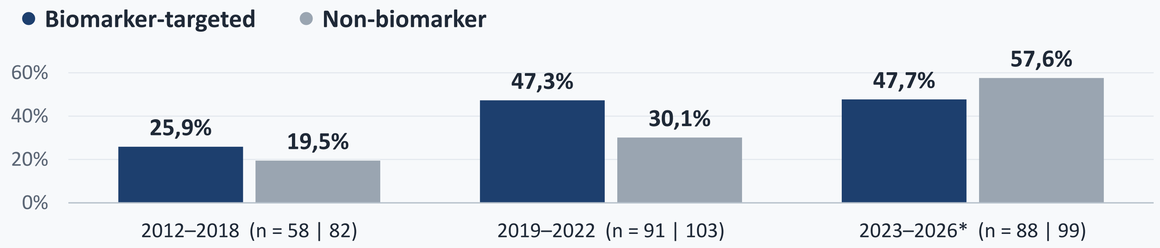


Figure 2. Share of procedures rated 'added benefit not proven' by period, biomarker-targeted vs non-biomarker (% of procedures; n = procedures per period, biomarker | non-biomarker). *2026: until 17 May.

- 2019–2022: 47% vs 30% 'added benefit not proven' ratings
- Since 2023 non-biomarker higher: 48% vs 58%

3 ORPHAN STATUS
As orphan added benefit is deemed proven by law, ratings were assessed separately by orphan status (Figure 3A)

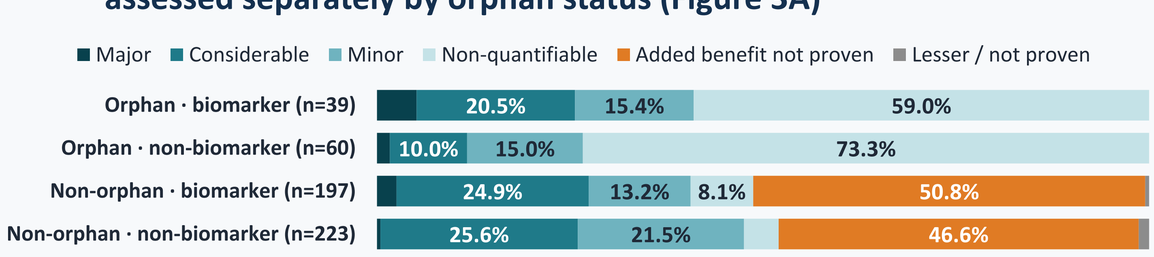


Figure 3A. Added-benefit ratings by orphan status and biomarker status (% of procedures). Orphan = only if below the statutory revenue threshold.

- Orphans: 'considerable or better' rating biomarker 25.6% vs non-biomarker 11.7%
- Non-orphans: 'added benefit not proven' rating biomarker 50.8% vs non-biomarker 46.6%
- Orphan protection less common with biomarker 16.5% (39/237) vs non-biomarker 21.1% (60/284) | EU orphan designation, incl. procedures above the revenue threshold: 18.6% vs 35.2%

Sensitivity: to test whether orphan protection masks evidence gaps, orphans rated 'non-quantifiable' were split by the presence of a positive endpoint in the AIS (Figure 3B)

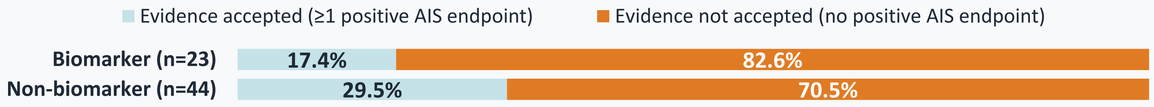


Figure 3B. Orphan procedures rated 'non-quantifiable', by AIS evidence acceptance (≥1 positive AIS endpoint vs none; % of procedures).

- Biomarker orphans with non-quantifiable rating more often lack a positive endpoint in the AIS: 82.6% vs 70.5%

4 PRICE
To see how ratings translate into prices, list-price changes were assessed by biomarker status (Figures 4A and 4B)

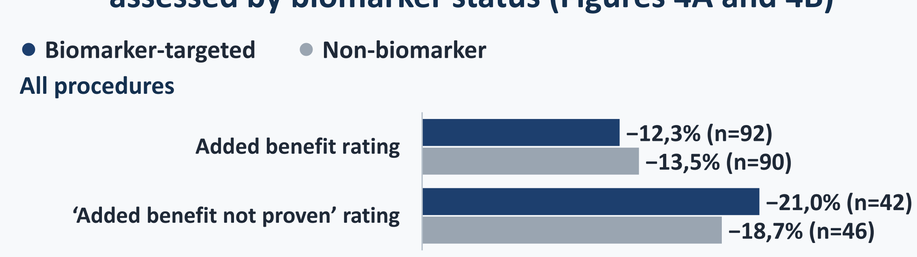


Figure 4A. Mean list-price change up to 18 months after the G-BA resolution. Added benefit = major, considerable, minor or non-quantifiable. n = all procedures with available price data, rebates related to multiple resolutions counted as one.

Orphans (below revenue threshold, evidence-adjusted)



Figure 4B. Mean list-price change up to 18 months after the G-BA resolution, orphan procedures (below revenue threshold) by AIS evidence acceptance. n = subset of figure 4A (n = 77).

- All procedures: mean change −12.3% vs −13.5% with added benefit; −21.0% vs −18.7% with 'added benefit not proven'.
- Orphans with accepted evidence: −8.8% vs −12.5%; without: −19.6% vs −20.1%.

DISCUSSION

Biomarker-targeted oncology drugs address smaller, molecularly defined populations, which creates specific challenges for evidence generation in the German AMNOG process. Our analysis shows a polarized pattern. When the G-BA accepted their evidence, biomarker-targeted drugs received higher added-benefit ratings than non-biomarker drugs, possibly reflecting larger treatment effects. At the same time, they were more often rated 'added benefit not proven', reflecting how difficult it is to generate evidence that meets G-BA requirements in small populations.

Biomarker-targeted oncology drugs were less often designated as orphan drugs by the EMA, both across all procedures (18.6% vs 35.2%) and among those below the revenue threshold (16.5% vs 21.1%). A likely reason is that the EMA generally does not accept a biomarker-defined subset as a distinct condition. As a result, many biomarker-targeted oncology drugs do not benefit from the orphan privilege in the German assessment.

Even within the orphan subgroup, evidence for biomarker-targeted drugs was less often accepted than for non-biomarker drugs, most likely because their target populations are even smaller (mean 626 vs 1,984 patients per indication). This matters for pricing, which followed the assessment outcome rather than biomarker status (Figure 4A). Among orphans, the acceptance of evidence also mattered: −8.8% vs −12.5% with accepted evidence and −19.6% vs −20.1% without (Figure 4B), similar to biomarker procedures rated 'added benefit not proven' (−21.0%). A legally granted benefit alone therefore did not protect prices, and orphan designation does not fully offset the methodological challenges specific to biomarker-defined populations.

Of note, the difference between biomarker and non-biomarker drugs disappeared over time. A likely explanation is that non-biomarker drugs increasingly target narrower populations as well, so both groups may now face similar evidentiary hurdles.[3]

Both legal protection and adapted evidence requirements are needed to prevent initial 'added benefit not proven' ratings and potential subsequent market withdrawals, thereby preserving patient access and ensuring fair assessments and pricing.

Limitations: retrospective and descriptive analysis; no causal inference; a missing positive AIS endpoint does not distinguish absent from non-assessable evidence; mean-based price comparisons are sensitive to outliers.

CONCLUSIONS

All values: **biomarker-targeted vs non-biomarker**

Biomarker-targeted drugs showed:

1 Higher ratings

4.2×

'Major added benefit' rating 2.9% vs 0.7% (Figure 1)

2 Higher 'added benefit not proven' ratings overall

42.2% vs 36.6%

Higher until 2022 (2019–2022: 47% vs 30%); no longer higher since 2023 (Figures 1, 2)

3 Less likely orphan protection

16.5% vs 21.1%* | 18.6% vs 35.2%**

*Below-threshold orphan protection | **EU orphan designation (Figure 3A, Results 3)

4 A legally granted benefit does not prevent rebates

–19.6% vs –21.0%

Biomarker orphans without accepted evidence vs biomarker procedures rated 'added benefit not proven' (Figures 4A, 4B)

- Biomarker-targeted drugs were less often protected as orphan drugs and, without protection, more often rated 'added benefit not proven'.
- Orphan protection alone was not sufficient: their evidence was less often accepted, and a benefit granted on legal grounds only was followed by price reductions similar to 'added benefit not proven' ratings.
- AMNOG modernization should therefore combine legal protection with evidence standards adapted to small, molecularly defined populations, an issue increasingly relevant across oncology.

References: 1. § 35a (1) SGB V. 2. Tomeczkowski J, et al. German HTA outcomes for rare disease drugs when orphan designation does not legally determine added benefit. ISPOR Europe 2025, HTA162. 3. Tomeczkowski J, et al. ISPOR Europe 2026, HTA251.

Abbreviations: AIS, Arzt-Informationssystem (G-BA physician information system); AMNOG, Pharmaceutical Market Restructuring Act; EMA, European Medicines Agency; G-BA, Federal Joint Committee; IQWiG, Institute for Quality and Efficiency in Health Care.