KEEPING UP WITH THE COMPARATORS: TRENDS IN TARGETED CANCER THERAPIES BECOMING RIGHT COMPARATORS FOR PAYERS

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OBJECTIVES

Innovative cancer therapies that target specific genes and proteins to slow or prevent carcinogenesis and tumor proliferation are being increasingly used in clinical practice.

These targeted therapies have been included in standard of care (SoC) in many markets for various indications in which they have shown to offer a clear benefit to patients over standard chemotherapies[1]. The evolving SoC is monitored by payer bodies and as a result, they have adopted targeted therapies as appropriate comparators in cancer health technology assessments (HTAs).

The objective of this analysis was to evaluate comparator guidelines for EU3 payers and examine the trends and exact drivers for targeted therapies to replace traditional chemotherapy as appropriate comparator therapy (ACT) for EU3 HTAs in oncology. Finally, this research sheds light on the impact of this switch on HTA outcomes for subsequent assessments.

METHODS

HTA guideline documents of Germany's G-BA (*Gemeinsamer Bundesausschuss*), France's HAS (*Haute Autorité de santé*) and the UK's NICE (*National Institute for Health and Care Excellence*) were compared to each other, in particular the sections that clarify the criteria for comparator drugs.

All HTAs published between January 1st 2011 and August 29th 2018 in melanoma, breast, colorectal, kidney, lung, ovarian, prostate, renal, and lung cancer by G-BA, HAS and NICE were screened using the IQVIA proprietary HTA Accelerator database. Of these, only published, single drug assessments were included in the analysis. Assessments for targeted cancer therapies (as per the National Cancer Institute [1]) that received European Medicines Agency (EMA) marketing authorization (MA) before 2011, as well as targeted cancer therapies that did not commercially launch in any market have been excluded from the analysis. For a subset of the analysis, assessments of drugs targeting ALK, BRAF, MEK and PD-L1 were screened as for these four molecular targets, the 1st in class and at least one additional drug (2nd in class) launched post 2011.

Publicly available documents (i.e. submission dossiers and payer assessment reports) were reviewed to identify changes and drivers in appropriate comparator from traditional chemotherapy to targeted therapies.

IQVIA proprietary MIDAS data was reviewed to identify commercial launch dates of targeted treatments in abovementioned indications.

RESULTS

Payer ACT guidelines

For each payer, there are guidelines specifying a set of guiding criteria for ACTs (**table 1**). While all three agencies consider EMA MA, the G-BA is the only agency that formally requires an ACT to have MA. Both NICE and the G-BA specify the importance of drugs being established in clinical practice, while HAS does not specifically do so. Reimbursement status is mentioned in guideline from HAS only. NICE is unique in considering cost-effectiveness (a positive HTA recommendation). All three agencies would include non-drug treatments as comparators.

Table 1. ACT criteria for payers in EU3 as per agency guidelines

Criterion	G-BA [2]	HAS [3]	NICE [4]
EMA MA for indication	✓	✓	✓
Assessed by agency	✓	*Not specified*	✓
Positive HTA recommendation	*Not specified*	*Not specified*	✓
Established as SoC	✓	*Not specified*	✓
Reimbursed	*Not specified*	✓	*Not specified*
Acceptance of non-drugs	✓	✓	✓

✓ Guiding ACT criterion as per payer guideline

General trend

In total, 208 assessments of 41 targeted cancer therapies were screened for relevant comparator changes. Targeted cancer drugs have been increasingly listed as ACT (from 15% [n=2] in 2011 to 67% [n=26] in 2018) albeit varying by tumour type and agency. A targeted drug was considered the only ACT in 48% [n=19] of assessments in 2018, whereas this was 0% in 2011.

Between 2011 and 2018, targeted treatments have been listed as ACT by payers in 70% of all renal cell carcinoma assessments [n=18] whereas this was lowest (11%, [n=1]) in ovarian cancer, where payers listed either chemotherapy as relevant comparator (33%, n=3]), or none at all (56%, n=5). In both these cancer types, targeted treatments launched prior to 2011.

On average, there was a lag of 19 months (range 2 to 47) between launch of targeted treatment and start date of a subsequent assessment where this targeted treatment was considered an ACT by the payer. This was highest in Germany where the average time from launch to becoming an ACT was 41 months (range 19 to 88). In the UK, the average lag-time was 37 months. Interestingly, the average time between becoming an ACT for payer and becoming the only ACT for payer is shortest in the UK (average = 1 month), compared to France and Germany (5 and 11 months respectively) (**figure 1**).

Time from launch of 1st in class to becoming ACT

All cancer therapies (n=11) that target ALK, BRAF, MEK and PDL1 launched after 2011. In 19 cases, a payer assessed the 1st in class and the 2nd in class treatment for the same indication. In 89% of these cases (n=17), the 1st in class targeted treatment was found to be listed as ACT in the subsequent assessment of the 2nd in class treatment. 1st in class treatments were not listed as ACT in two cases only where the 2nd in class product launched within 6 months (1 and 3,5 months, NICE and G-BA respectively) after the 1st in class. In all other cases, where the 2nd in class launched 6+ months after the 1st in class product, the 1st in class was listed as ACT. It was found that for a 1st in class targeted treatment to replace chemotherapy as ACT (i.e. becoming the only relevant comparator for payer), the drug had to be launched at least 12 months before the 2nd in class product (**figure 1**).

CONCLUSIONS

- **Our analysis shows that targeted therapies are increasingly regarded as ACTs for payers when assessing new cancer drugs. In almost all cases (89%), the 1st in class treatment targeting ALK, BRAF, MEK or PDL1 was found to be listed as ACT in the subsequent assessment of the 2nd in class treatment.**
- **The eventual impact of a change in relevant comparator can have significant impact, especially in Germany and France.**
- **The most important driver for being accepted as ACT is proof that a targeted cancer therapy is established in clinical practice. This research demonstrates that manufacturers have the opportunity to change the payer's view on this if submitting robust evidence.**
- **Our research indicates that early engagement with payers is vital to ensure that appropriate evidence can be generated to meet HTA requirements, in general, and to demonstrate that the comparator in pivotal trial is established in clinical practice.**

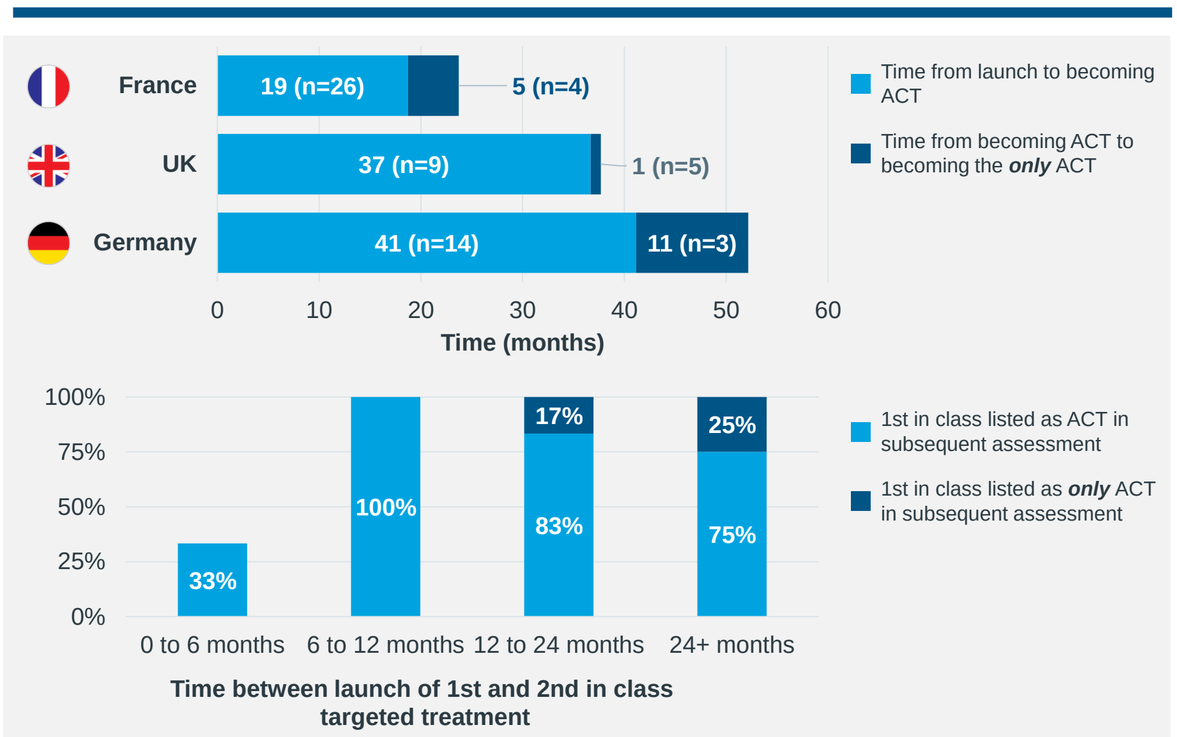

Figure 1. (Top) Average time from launch (first sales) to becoming ACT of any targeted therapy launched post 2011 in any of the indications in scope (bottom) Percentage of 1st in class therapies targeting ALK, BRAF, MEK and PDL1 that became ACT in subsequent assessment (of 2nd in class therapy)

ACT drivers as per HTA reports

Of the 45 targeted treatments evaluated, 29 became an ACT for at least one payer. In 91% of cases, targeted therapies became a relevant comparator following a positive recommendation from the agency. However, even in cases where a drug did not receive a prior positive recommendation – or a low rating - payers did consider this drug a relevant comparator in subsequent assessments. This was seen in HAS assessments of osimertinib for lung cancer where afatinib was added as ACT despite ASMR V, and trametinib for melanoma, where dabrafenib was an appropriate comparator despite having an ASMR V. In both cases the targeted therapy was considered clinically relevant while in the latter chemo was specifically stipulated to no longer be relevant. The G-BA included ipilimumab as ACT for nivolumab although it had shown no added benefit as first-line treatment, because the G-BA was convinced that chemo will lose its relevance in the context of the "dynamic development of new drugs for melanoma". For HAS a prior payer decision is not required, as seen in atezolizumab being added for the trametinib+dabrafenib assessment in lung cancer while its own assessment was still ongoing.

In Germany, an off-label drug can become an ACT as seen with docetaxel for prostate cancer that was added for abiraterone mid-way through the assessment. This however, is not in line with G-BA's guideline. Moreover, both HAS and G-BA rejected ipilimumab as comparator in the melanoma assessment in adolescents despite it being the only drug with MA at time of assessment. Both payers cited that current practice is to treat them like adults, where PDL1, BRAF, and MEK-inhibitors are preferred.

Reimbursement status and cost-effectiveness of targeted treatments were not found to be driving uptake of these as relevant comparators by any of the payers.

In 8 cases (5: G-BA; 1: HAS; 2 NICE) targeted therapies were not considered relevant comparators for payers in subsequent assessments as they were 'too new' or 'not (yet) routinely used', in 6 cases of which these therapies even received a positive payer rating. Time from launch to the assessment where the therapy was considered 'too new' ranged from 0 days (talimogene laherparepvec in melanoma) to 412 days (afatinib; lung cancer). One other reason for targeted therapies to not be considered relevant to the payer based on market withdrawal (sipuleucel-T in prostate cancer; G-BA).

Impact of change in ACT on HTA outcome

Looking at the 12 cases where targeted treatments became the only ACT for the first time, the impact of this change was most notable in Germany where in 2 of 3 cases this resulted in a low benefit rating as ITCs were rejected; while the one positive was due to H2H data being available. Remarkably, in one case (dabrafenib in melanoma), this was actually triggered by the submitting manufacturer (**figure 2**). In France, a similar trend to reject ITC data was seen in 1 of the 4 cases, but in the other 3 cases placebo or chemo was still accepted despite the switch, as HAS took into account simultaneous development of drugs. As NICE uses the least costly product and this is often chemo, the expectation is that the impact of a change in comparator would only be seen in cases like these where chemo was entirely replaced. However, in all 5 cases NICE accepted either an ITC or placebo data, thus its criteria seem more relaxed in this context too.

The impact in the change in SoC and ACT can stretch beyond the next TT to be marketed: E.g. in melanoma nivolumab/ipilimumab got a no added benefit in Germany due to no H2H data 1378 days after the vemurafenib assessment where 6 other TT drugs were assessed in the meantime.

LAUNCH OF TARGETED TREATMENTS IN BRAF V600+ MELANOMA

Vemurafenib was the first targeted treatment to launch for treatment of BRAF V600+ melanoma in Germany. At the time of its assessment, dacarbazine (chemotherapy) was considered the relevant comparator. Dabrafenib launched 17 months after vemurafenib. During G-BA consultation it was agreed that dacarbazine (chemo) was the ACT for dabrafenib and G-BA stated that "vemurafenib was not yet SoC".

ROLE OF MANUFACTURER IN DETERMINING PAYER-RELEVANT COMPARATOR

At start of the dabrafenib assessment, the manufacturer argued that vemurafenib should be added as ACT and submitted an indirect treatment comparison. In December 2013, IQWiG concluded **"no added benefit" versus chemotherapy.**

After IQWiG's decision, the manufacturer submitted evidence (international treatment guidelines including NCCN and ESMO, malignant melanoma S3-guideline and IMS Health prescription data) to convince the G-BA that vemurafenib (targeted treatment) should be considered SoC. G-BA changed its opinion and replaced dacarbazine as ACT with vemurafenib. As the manufacturer had not conducted a head-to-head trial versus vemurafenib, G-BA concluded **"no added benefit" (versus vemurafenib)**. As a result, however, the manufacturer had to offer a limited rebate (6%) during subsequent negotiation with the GKV-SV. The fact that the manufacturer achieved "no added benefit" versus the targeted therapy (and not versus chemo) likely contributed to securing a negotiated price point at which the annual treatment costs of dabrafenib was about 20 times higher than dacarbazine (chemotherapy).

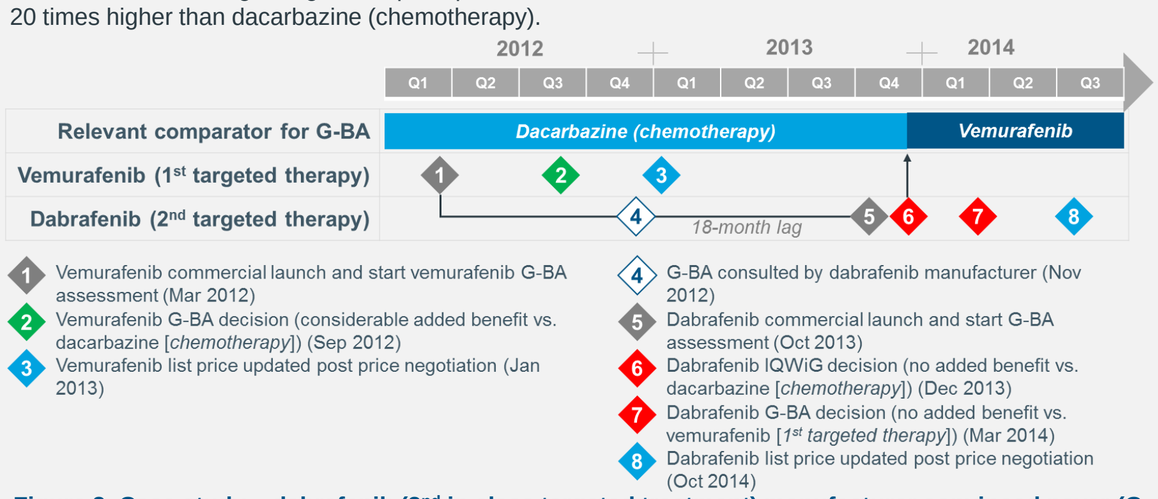

Figure 2. Case study – dabrafenib (2nd in class targeted treatment) manufacturer convinced payer (G-BA) that the initially agreed ACT in melanoma was no longer relevant as SoC had evolved

[1] National cancer institute (www.cancer.gov), accessed 01 August 2018
[2] Verfahrensordnung, G-BA, version 12 April 2018
[3] Renouvellement d'inscription ou reevaluation d'un medicament, HAS, version 27 August 2018
[4] Guide to the methods of technology appraisal 2013, NICE, 04 April 2013