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 Europe, vemurafenib has been a cornerstone of the standard of care in melanoma. The mechanism of evocing SoC is monitored by payers bodies and as a result, these have adopted targeted therapies as appropriate comparator in HTA submissions, which contributed to the complexity of the evaluation process.

The objective of this analysis was to evaluate comparator guidelines for EU payers and examine the trends and criteria for targeted therapies as appropriate comparator in HTA (ACT) for EU HTA 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 (Gesetzliche Bundesversicherung), France’s HAS (HAS: Haute Autorité en Santé) and UK’s NHS, were reviewed using the IQVIA proprietary HTA Accelerator database. Of these, only published, single drug assessments were included in the analysis. All documents for targeted cancer therapies (as per Figure 1) that were available in the database where HTAs published before June 1, 2011 (i.e., the date that received European Medicines Agency (EMA) marketing authorization (MA) before 2011, as well as targeted cancer therapies as per Figure 1) 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 PDL-1 were screened as these criteria are not considered relevant throughout the entire analysis.

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 database was reviewed to identify commercial launch dates of targeted treatments in absence of HTA documents.

RESULTS

Payer ACT guidelines

For each payer, these guidelines specifying a set of guiding criteria for ACT (Table 1). While all these guidelines considerEMA, the G-BA is the only agency that formally requires an ACT to have MA. Both NE C and HAS require relevant comparator, while HAS does not specifically state. Reimbursement status is mentioned in guidance from HAS only. NICE is unique in considering cost-effectiveness (a positive HTA recommendation). All these guidelines would include non-drugs treatments as comparators.

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

<table>
<thead>
<tr>
<th>ACT criteria</th>
<th>has</th>
<th>NICE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EMA MA for indication</strong></td>
<td>Not specified</td>
<td>Not specified</td>
</tr>
<tr>
<td><strong>Assessed by agency</strong></td>
<td>Not specified</td>
<td>Not specified</td>
</tr>
<tr>
<td><strong>Positive HTA recommendation</strong></td>
<td>Not specified</td>
<td>Not specified</td>
</tr>
<tr>
<td><strong>Established as SoC</strong></td>
<td>Not specified</td>
<td>Not specified</td>
</tr>
<tr>
<td><strong>Reimbursed</strong></td>
<td>Not specified</td>
<td>Not specified</td>
</tr>
<tr>
<td><strong>Acceptance of non-drugs</strong></td>
<td>Not specified</td>
<td>Not specified</td>
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</tbody>
</table>

Guiding ACT as per payer guideline

General trend

In total, 288 assessments of 41 targeted cancer treatments were screened for relevant comparator changes. Targeted treatments were listed as ACTs (HTA) in 2011 to 67% in 2021, albeit varying by tumour type and age. 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 had been listed as ACT by payers in 70% of all renal cell carcinoma assessments (n=18); whereas this was lowest (11%, n=3) in ovarian cancer, where payers listed another therapy as the 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 submission assessment where a targeted therapy was considered 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 77 months). In the UK, a lag of 10 months was recorded. 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 to launch of 1st in class becoming ACT

All cancer therapies (n=11) that target ALK, BRAF, MEK and PDL-1 launched after 2011. In 19 cases, a payer assessed the 1st in class and the 2nd in class for the same indication. In 89% of these cases (n=17) the 1st in class targeted therapy was listed as ACT in the subsequent assessment of the 2nd in class treatment. In 11% of cases targeted treatments were listed as ACT in both the assessment of the 2nd in class treatment. In 2 cases where the 2nd in class treatment was launched first, the payer assessed the 2nd in class treatment as ACT.

In 19% of cases, a payer assessed the 1st in class targeted therapy for reimbursement as ACT, and the 2nd in class targeted therapy for reimbursement as non-AC T. It is 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 (98%), the 1st in class treatments were listed as ACT (HAS, NICE and Germany). The 2nd in class treatments were listed to be as ACT in the subsequent assessment of the 2nd in class treatment.
- The important impact of a change in relevant comparator can have significant impact, and impact on Germany’s cancer treatment landscape. 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 is submitted and is considered in relevant guidelines.

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 added to the indication, the one positive was due to HUS 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 ITCs data was seen in 1 of the 4 cases, but in the other 3 cases placebo or chemo was assessed. In the 3 cases, where a sub-group was assessed, the sub-group was assessed as either being no improvement or account simultaneous development of new drugs. As NICE uses the lowest cost product this is often chemo, the expectation is that impact of a change in comparator can make payers only be assessed against the comparator and not account simultaneous development of new drugs.

The impact in the change in SoC and ACT can stretch beyond the next 10 years to be reported as: e.g. in melanoma putumblastoma gliomas got a no added benefit in Germany for 2012 data 1376 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 cancer in melanoma, and was used in 6 cases of these therapies even received a positive payer rating. Time from launch to the assessment where the therapy was assessed to being considered a positive price at which point the manufacturer, was required to conduct a head-to-head trial versus chemotherapy.

After IOQVs decision, the manufacturer submitted evidence (intentional treatment guidelines including NCNN and ESMO, malignant melanoma S3-guideline and IM Health prescription data) to convince the G-BA that vemurafenib (targeted treatment) should be considered SoC. G-BA changed its opinion and replaced dabrafenib 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, the manufacturer considered an alternative regimen which the manufacturer achieved “no added benefit” versus the targeted therapy (and not versus chemo) likely caused by evaluating a negative price point at which the annual treatment costs of dabrafenib was about 20 times higher than dabrafenib 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 2016
3 Ministry of Health [www.moh.gov.hk], accessed 01 August 2016
4 Ministerie van Volksgezondheid, Welzijn en Sport [www.cf.nl], accessed 01 August 2016
5 Remuneration d’inscription ou rémunération d’un médicament, HAS, version 27 August 2018
6 Gérontologie et la Santé dépendance et soins infirmiers, HAS, version 27 August 2018
7 Copyright © 2018 IQVIA. All rights reserved. International Society for Pharmacoeconomics and Outcomes Research, 21st Annual European Congress, poster presentation PCN217.