The role of companion diagnostics in HTAs of drugs in France, Germany, and the UK

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Introduction

Personalized medicine (also referred to as precision or stratified medicine) offers benefits for a variety of stakeholders (drug developers, payers, clinicians, patients): improved patient selection, resulting in more efficient use of drugs and improved efficacy. However, payers are presented with specific challenges when assessing drugs indicated only for a subpopulation of patients with a particular tumor type, who must be identified by the results of an in vitro diagnostic test (companion diagnostic, CDx). As payers try to maximize the value from drugs, we were interested to determine whether they were using CDx test results to limit access to innovative oncology medicines. We reviewed the results of health technology assessments (HTAs) of a number of drugs with a CDx or targeting a specific biomarker in France, Germany, and the UK to understand the extent to which the diagnostic was considered, and the potential impact on patient access to the drug.

Methods

- Products were selected from the US Food and Drug Administration (FDA)'s list of oncology products with a CDx, supplemented with hand searches for relevant products not on the list.
- Indications for these products authorized by the European Medicines Agency (EMA) were identified.
- HTAs of each product were identified from the databases of the UK National Institute for Health and Care Excellence (NICE), the French Transparency Commission (TC), and the German Federal Joint Committee (Gemeinsamer Bundesausschuss, G-BA).
- Comments on the use of diagnostics, including biomarker-defined subpopulations, were extracted.
- The final HTA results (i.e., the reimbursed or recommended indication), particularly any population or access limitations, were compared with the authorized indications.

Results

We identified 24 medicines from the FDA list, used in 12 tumor types (figure 1). After hand searching we added nivolumab to the products to be analyzed, as other products in the same class (PD-1 inhibitors) have a CDx. The number of products with a CDx has increased in recent years, although the number of biomarkers used is still limited. Between 2000 and 2008, the EMA authorized 5 products with a CDx, whereas in the last 3 years alone, the agency has approved a further 10 products for 11 tumor types (figure 2).

In cases where a biomarker has been adopted to define subtypes of disease (e.g., BRAF in melanoma), all three agencies have used biomarkers to define subpopulations in which they assessed efficacy separately from the overall licensed population

Table 1: G-BA

Drug	Indication of interest	G-BA comments
Pembrolizumab	Treatment of advanced (unresectable or metastatic) melanoma.	Hint of considerable additional benefit for untreated BRAF V600 wild-type tumor; no additional benefit for BRAF V600-mutated tumors.
Osimertinib	Treatment of adults with locally advanced or metastatic EGFR T790M mutation-positive NSCLC.	Subgroups considered: • Patients with T790M mutation after pre-treatment with an EGFR TKI • Patients eligible for cytotoxic chemotherapy • Patients not eligible for cytotoxic chemotherapy • Treatment-naive patients with a de novo T790M mutation • Patients with EGFR-activating mutations, or • Patients with ECOG performance status 0, 1, or 2 • Patients after treatment with platinum-based chemotherapy and with a de novo T790M mutation • Patients for whom treatment with docetaxel, pemetrexed, gefitinib, or erlotinib is indicated • Patients for whom treatment with docetaxel, pemetrexed, gefitinib, or erlotinib is not indicated No additional benefit for any subgroup.
Afatinib	Treatment of EGFR TKI-naive adults with locally advanced or metastatic NSCLC with activating EGFR mutation(s).	• Indication for major additional benefit only for EGFR mutation: del(19) subgroup. • No additional benefit for patients with L858R and other EGFR mutations.
Nivolumab	Treatment of advanced (unresectable or metastatic) melanoma as monotherapy, or in combination with ipilimumab.	• Indication of considerable additional benefit for untreated BRAF V600 wild-type tumors. • No additional benefit for BRAF V600-mutated tumors, or previously treated patients.

ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; G-BA, Gemeinsamer Bundesausschuss (Federal Joint Committee), NSCLC, non-small cell lung cancer; TKI, tyrosine kinase inhibitor

The G-BA often defines subgroups based on prior or subsequent treatments and patient status. In the assessments of nivolumab and pembrolizumab for advanced melanoma, varying levels of additional benefit were awarded according to BRAF V600 status. In another assessment – afatinib for locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating EGFR mutations not previously treated with EGFR tyrosine kinase inhibitors (TKIs) – subpopulations were defined based on the biomarker directly associated with the drug. The regulatory indication was split into three subpopulations – del(19) mutation, L858R mutation, and other EGFR mutations – only one of which, del(19) mutation, was awarded an "indication of major additional benefit".

NICE has used biomarkers to restrict its recommendation to a narrower population than that covered by the marketing authorization in two cases: trastuzumab for gastric cancer (HER-2 expression) and in the final appraisal document for nivolumab for NSCLC (PD-L1 expression).

For trastuzumab the modeled overall survival gain was higher in patients with HER-2 IHC3-positive tumors than in the overall population, and the in situ hybridization test is not required for this subpopulation. It was only in this restricted population that trastuzumab was considered cost-effective at the threshold for end-of-life treatments of £50,000 per quality-adjusted life-year gained.

In initial appraisal consultations for nivolumab, NICE did not recommend the drug for patients whose tumors expressed PD-L1 at less than 10% and was "minded not to recommend" it in cases of where expression was over 10%; the agency therefore invited submissions for consideration by the Cancer Drugs Fund (CDF). In the subsequent assessment, three levels of PD-L1 expression were considered for non-squamous NSCLC (>1%, >5%, and >10%), along with non-quantifiable expression. After the submission of cost-effectiveness data for each level of expression, NICE recommended nivolumab for funding through the CDF for non-squamous NSCLC with any level of PD-L1 expression. For squamous NSCLC, NICE concluded that "the results did not suggest a clinically significant difference according to PD-L1 expression"; the agency therefore did not restrict its recommendation based on PD-L1 expression in the final appraisal determination for nivolumab in squamous NSCLC.

Table 2: NICE

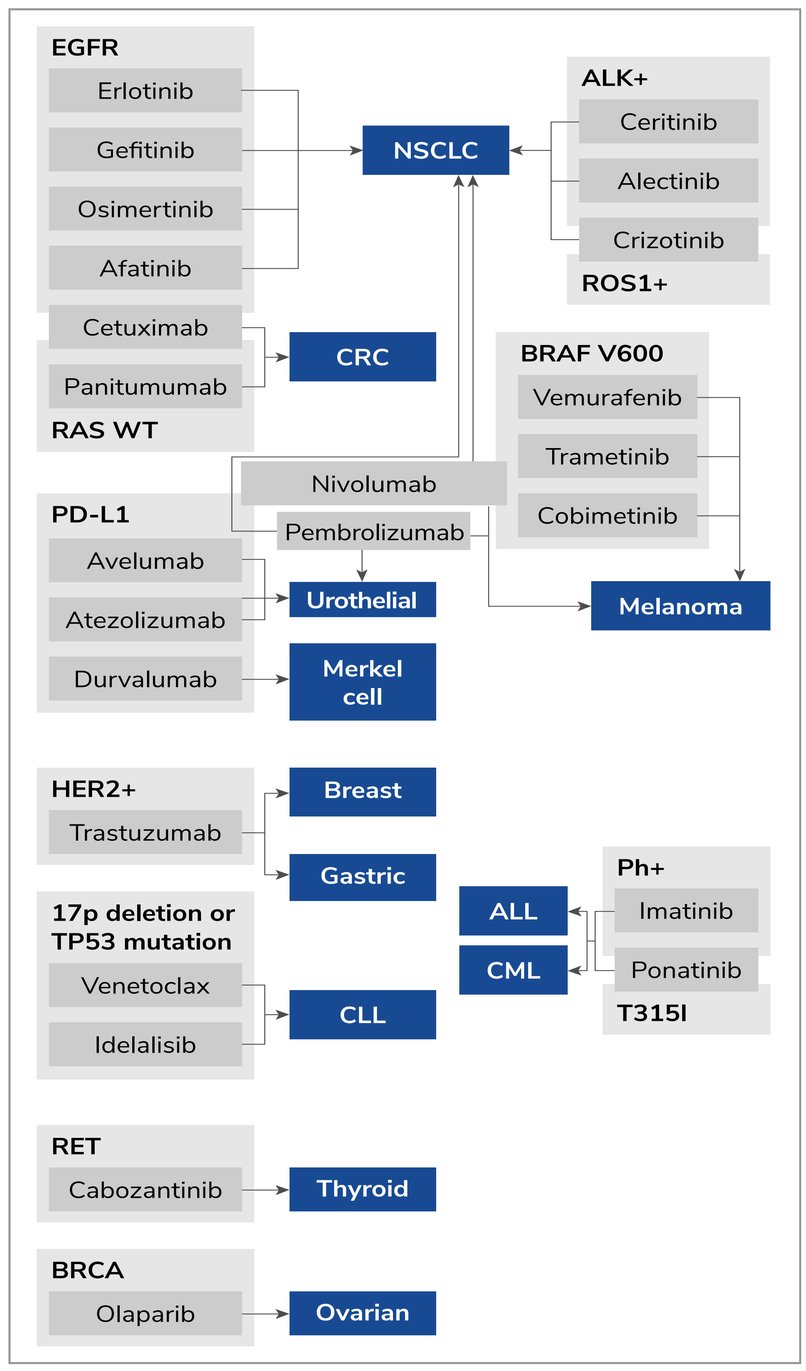
Drug	Indication of interest	NICE comments
Trastuzumab	• In combination with capecitabine or 5-FU and cisplatin for the treatment of patients with HER2+ metastatic adenocarcinoma of the stomach or gastroesophageal junction who have not received prior anticancer treatment for their metastatic disease. • Trastuzumab should only be used in patients with metastatic gastric cancer whose tumors have HER2 overexpression as defined by IHC2+ and a confirmatory SISH or FISH result, or by an IHC3+ result. Accurate and validated assay methods should be used.	Recommended for the treatment of people with HER2+ metastatic adenocarcinoma of the stomach or gastro-oesophageal junction who: • have not received prior treatment for their metastatic disease • have tumors expressing high levels of HER2 as defined by a positive immunohistochemistry score of 3 (IHC3 positive).
	For the treatment of adults with HER2+ early and metastatic breast cancer.	The cost of HER2 testing for the total population of women with early-stage breast cancer was included in the economic analyses (TA for adjuvant treatment of early stage HER+ breast cancer).
Nivolumab	For the treatment of locally advanced or metastatic non-small cell lung cancer after prior chemotherapy in adults.	Non-squamous: Recommended for use through the CDF for patients with PD-L1-expressing tumors. Data were submitted for >1%, >5%, and >10% PD-L1 expression, with the greatest benefit seen with >10% PD-L1 expression. However, due to the overall improved efficacy vs docetaxel for any level of PD-L1 expression it was decided to recommend for any quantifiable level of PD-L1 expression. Squamous: Similar analysis led to a recommendation for use in the CDF with no mention of PD-L1 levels.

CDF, Cancer Drugs Fund; FISH, fluorescence in situ hybridization; 5-FU, 5-fluorouracil; IHC, immunohistochemistry; SISH, silver in situ hybridization; TA, technology appraisal

Other NICE technology appraisals discussed the possibility that clinical benefit may vary between subpopulations defined by biomarker expression, and whether the cost of testing was included in the economic analyses, among other commentary on testing.

There was little mention of biomarkers in TC appraisals and no explicit examples of the TC using biomarkers to restrict access to medicines. However, in the appraisal of olaparib for ovarian cancer, the TC specified that the BRCA test should be carried out at a limited number of centers, potentially limiting access to the test and therefore to olaparib, while also noting that some efficacy had been shown in the BRCA-negative population. In the appraisal of nivolumab for melanoma, the TC specified that PD-L1 expression could not be used as a biomarker to determine a difference in efficacy. The TC did, however, consider efficacy in the BRAF mutation-negative and -positive populations, but this did not appear to affect the final decision to award an ASMR (amélioration du service médical rendu, improvement in medical benefit) rating of 3.

Figure 1: Medicines from the FDA list with tumor type and biomarker considered at HTA



Conclusions

HTA agencies vary in their approaches to considering CDx in drug assessments. To date, CDx test results have been used to limit access to innovative oncology drugs only in a few cases; however, there have been more cases where differing efficacy between subpopulations defined by biomarker expression could have influenced price negotiations.

The G-BA cannot restrict the authorized indication; however, it has examined biomarker-defined subgroups and assigned different levels of additional benefit for each subpopulation. Awarding a lower level of additional benefit for some subpopulations may have affected subsequent price negotiations, particularly if the proportion of the population with lower benefit is large.

We found only two instances where NICE restricted its recommendation based on the result of a diagnostic test; however, it is expected that this approach will be applied more widely in the future.

With the introductions of the new In Vitro Diagnostic Regulation and increasing scrutiny of CDx data by the EMA, we suggest that the importance of CDx-related data in HTA submissions will increase, and we may see more CDx-related restrictions to access.

References

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Tagrisso (osimertinib): https://www.g-ba.de/downloads/40-268-3972/2016-09-15_AM-RL-XII_Osimertinib_D-219_TrG.pdf

Afatinib: https://www.g-ba.de/informationen/nutzenbewertung/87/#tab/zweckmaessige-vergleichstherapie

Nivolumab: https://www.g-ba.de/informationen/nutzenbewertung/179/#tab/zweckmaessige-vergleichstherapie

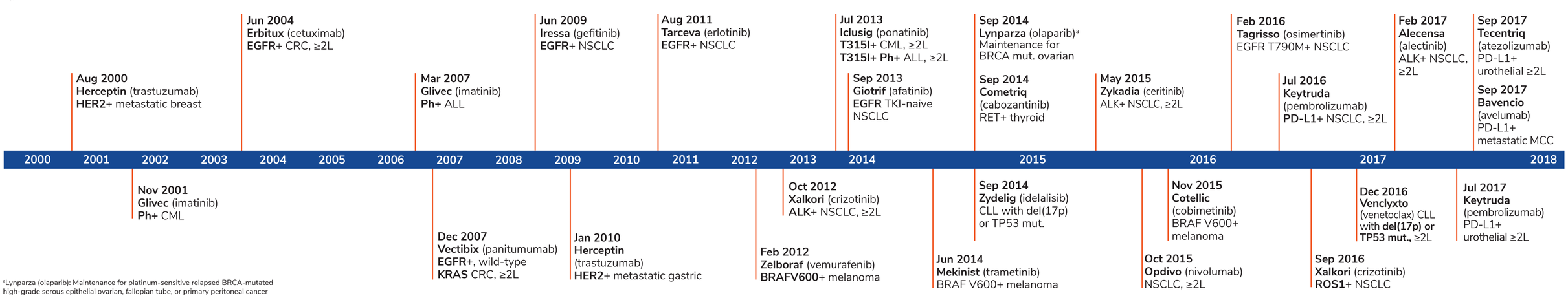
NICE: Trastuzumab TA 208: https://www.nice.org.uk/guidance/ta208/resources/trastuzumab-for-the-treatment-of-her2positive-metastatic-gastric-cancer-pdf-82600195913413

TA 107 (early-stage BC): https://www.nice.org.uk/guidance/ta107/resources/trastuzumab-for-the-adjuvant-treatment-of-earlystage-her2positive-breast-cancer-pdf-82598017451461

Nivolumab FAD: https://www.nice.org.uk/guidance/gid-tag524/documents/final-appraisal-determination-document

TC: https://www.has-sante.fr/portail/upload/docs/evamed/CT-14098_LYNPARZA_PIC_INS_Avis2_CT14098.pdf

Figure 2: European approval timeline



[a]Lynparza (olaparib): Maintenance for platinum-sensitive relapsed BRCA-mutated high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer