Actual developments in European regulatory and health technology assessment of new cancer drugs: what does this mean for oncology in Europe?

Introduction

The incidence of cancer has been estimated at 11 million cases per year with a global prevalence of 25 million cases, and the World Health Organisation (WHO) has predicted that within the next decade these figures could increase up to 50%, reaching 15 million new cases per year by 2020 [1, 2]. In Europe, there were an estimated 3.2 million new cases of cancer and 1.7 million deaths from cancer in 2008 [2, 3]. As such, there is a current and growing requirement for more emphasis on cancer prevention, research, therapy in general and better targeted anticancer drugs. Rapid licencing and market availability of innovative, more effective oncology drugs are also a necessity.

Inevitably, health care policy makers have to balance between the infinite level of healthcare demands and their finite healthcare resources. This means that oncology drugs have to be assessed not only on their clinical merit, but also on their cost-effectiveness in comparison with currently available alternative therapies. Currently, this system involves input from two different bodies which increases not only the workload associated with drug development, but also the costs. Most EU member states have delegated these so called relative efficacy, relative effectiveness and cost-effectiveness assessments to dedicated health technology assessment (HTA) agencies. Despite commonalities in scope of the assessments conducted by regulatory agencies and HTA bodies, the applied evidentiary and analytical standards, extrapolations from the underlying clinical evidence base as well as scientific value judgements for the same drug differ substantially between the regulatory and HTA agencies [4, 5].

The current system—status and limitations

different assessments by regulators and HTA bodies

Under the current system, new oncology drugs in the EU are assessed under a centralised procedure by the European Medicines Agency (EMA) in the network of over 40 regulatory agencies from all Member States [6]. Based on the opinion of EMA’s Committee for Medicinal Products for Human Use, the European Commission decides on granting a European marketing authorisation (European MA), which applies to all EU member states. But, because of the various healthcare systems in the EU member states and the strong subsidiarity principle in the field of health care, each member state negotiates on drug price, reimbursement status and allocated funding independently in light of different healthcare system priorities and affordability. These decisions are made on a national or even regional level and usually are based on a formal assessment of the product by HTA bodies. Examples of HTA bodies are the National Institute for Health and Clinical Excellence in the UK, the Haute Autorité de Santé in France and the Institute for Quality and Efficiency in Health Care in Germany. The principles underlying HTA have been described elsewhere [4, 5, 7].

It is important to note that even if a European MA has been granted, this does not imply that the product will be available to patients everywhere in the EU. If public reimbursement is declined based on the negative result of the assessment by the HTA bodies and corresponding payer decisions, the vast majority of patients will not be able to afford the product.

evidence requirements of regulators

(See supplementary file S1, available at Annals of Oncology online.)

use of biomarkers in clinical trials for registration

(See supplementary file S1, available at Annals of Oncology online.)

evidence requirements of HTA bodies

(See supplementary file S1, available at Annals of Oncology online.)

different approaches across Europe

The approaches to HTA vary across different EU countries with regards to evaluative perspective (payer versus societal), the scope of assessments, and more specifically the use of informal or formal cost-effectiveness assessments and methodology as cost per quality of life gained (QALY) versus other methods, modelling techniques and discounting, and budget impact analysis.

In Germany, for example, drugs are usually available for reimbursed use as soon as European MA is granted. In 2011, the act for restructuring pharmaceutical market statutory health insurance (AMNOG) was introduced in Germany, giving the
licence holder the freedom to set the price of the drug for the
first 12 months after launch, only.

(See supplementary file S2, available at Annals of Oncology
online.)

In most other countries, pricing and reimbursement negotia-
tions precede the broad reimbursed use of drugs which take fre-
quently up to a year or even longer. A major challenge is the
interdependence between the prices negotiated in the various
countries. As a consequence, prices are much more uniform
between member states with different ability to afford innovative
cancer care than desirable. As a result of these misaligned HTA,
pricing and reimbursement systems, the access to oncology
drugs is anything but equal for patients within Europe [http:
://www.cancerresearchuk.org/cancer-help/about-cancer/cancer-
questions/cancer-drugs-fund]]\[8, 9\].

Adopting different evidentiary and methodological standards
may lead to a varying stringency of HTA evaluation. Although
direct comparisons between fundamentally different approaches
are inherently difficult, general trends can be perceived. On one
side, patients in Denmark and Germany appear to have the best
patients’ access to new drugs due to a more lenient HTA in
Denmark and in Germany, the HTA conducted under the remit
of AMNÖG is not aiming at restricting access beyond the regu-
latory label but to guide price (‘rebate’) negotiations. On the
other side, the UK is viewed as more stringent but with better
cost control [8].

(See supplementary file S2, available at Annals of Oncology
online.)

Variations in the HTA procedure not only result in divergent
prices but also affects the time it takes for new oncology agents
to reach the market. Across Europe the average time taken from
a drug receiving European MA to market access and thus
factual availability for the patients ranges from 0 days as best to
more than 450 days in average as worst situation in different
European countries [7].

Against this background, formal arrangements between
payers and manufacturers with the aim of sharing the financial
risk due to uncertainties surrounding the introduction of new
medicines have been developed and increasingly utilised for in-
novative oncology medicines in order to enable earlier access
\[10–12\]. These agreements carry different labels and can take
different forms, including price–volume agreements, outcome
guarantee, coverage with evidence development and disease
management programmes.

Based on the rather mixed experience with risk-share arrange-
ments to date, a multi-stakeholder group facilitated by Tapestry
Networks issued a set of recommendations and a framework that
supports the constructive engagement of pharmaceutical manufac-
turers with regulatory and reimbursement decision-makers when
addressing remaining uncertainty that can be resolved post-launch
http://www.tapestrynetworks.com/initiatives/healthcare/upload/

changing the current system
potential improvements

A European HTA procedure should provide a scientifically
sound and transparent high quality assessment of a drug’s
relative clinical efficacy profile. The application for marketing
authorisation precedes any HTA assessment. The regulatory as-
essment by EMA of the benefit–risk is based on the evaluation
of the pharmaceutical quality, safety and efficacy and should be
a plausible first building block for the subsequent work of HTA
bodies. Therefore, at the time of launch, the effectiveness of a
drug can only be inferred from efficacy and safety data gathered
during drug development which has been the basis of the pre-
ceding regulatory approval process. While the comparators used
in the HTA may differ between countries and from those that
have been used in the pivotal studies and have been considered
relevant by regulators, it is more difficult to understand why
clinical end points and other clinical trial design elements as
well as analytical methods considered valid and reliable by regu-
lators are questioned and sometimes not accepted by HTA agen-
cies and payers. Therefore, a consensual and aligned or at least
not contradictory scientific interpretation of the available data
by regulators and HTA bodies would be a more consistent basis
for local price negotiations and would be an essential ingredient
of more consistent patient access to innovative oncology drugs
in Europe

EUnetHTA

In 2008, a report by the High-Level Pharmaceutical Forum
(HLPF) suggested that the EMA should consider how to further
contribute to relative effectiveness assessments of novel drugs.
The findings from the HLPF also encouraged the European
Commission (DG SANCO) to reconsider its activities and in-
vestment into the collaboration of HTA agencies across the EU.
Building on the existing elements of EUnetHTA, EC and
member states initiated a Joint Action on HTA which among
other prioritised subjects was charged with the development of
standards in the field of relative (clinical) effectiveness of phar-
maceuticals and a related pilot assessment of a drug in 2010.
Relative (clinical) effectiveness was considered the most univer-
sal HTA domain, hence most eligible for collaborative effort
among member state HTA agencies, which explains this particu-
lar focus of EUnetHTA [13].

EUnetHTA currently consists of 34 government-appointed
organisations from 23 EU member states, Norway and Croatia.
An important activity is collaboration with EMA with the ob-
jective of identifying opportunities for improving European
Public Assessment Reports and making them more useful as a
basis for subsequent HTA. Areas of improvement include har-
monising structure and the level of details required, the use of
standard efficacy tables, data that reflect standard EU treat-
ments, justification regarding the choice of comparator and an
explanation of the benefit–risk assessment.

the tapestry network

A second process was initiated in 2010 by Tapestry Networks
with the aim of developing and accessing a novel collabora-
This initiative was based on the recommendations of disease-
specific working groups, convened to develop a shared under-
standing of value across stakeholders in type 2 diabetes and
breast cancer. The working groups agreed that both public- and private-sector stakeholders in the drug development system lack sufficient information to support and assess the development of innovative medicines that address unmet needs at reasonable cost. They recommended the creation of multi-country, multi-stakeholder consultations as a way to create greater clarity in value assessment to inform development decisions.

European healthcare leaders recently piloted such a multi-country, multi-stakeholder early advice forum, which brought medicine developers together with regulators, HTAs, payers, clinical experts and patient/policy representatives. The advice is used to inform a medicine-specific development plan and inform the best approach to demonstrating a medicine’s value (Figure 1, supplementary Figure S1, available at Annals of Oncology online). Through six early advice consultations, each involving an innovative medicine in a pharmaceutical company’s pipeline, the pilots demonstrated the benefits of early, focused engagement on strategic questions among drug developers and their key European constituencies. After successful pilot projects run by Tapestry, the procedure for parallel scientific advice by EMA and HTA bodies is now available for all applicants and the request need not be made via Tapestry but can be made directly to the EMA and HTA agencies.

**Conclusions**

Based on these approaches, it appears that a system of co-ordination is evolving, in which regulators and HTAs work together using their preferred methodology to assess different aspects of a drug. The continued dialogue and collaboration will help both regulators and HTA bodies to develop scientific positions that may have a different focus without being contradictory or mutually exclusive (Figure 1). These collaborative efforts will also help manufacturers to better anticipate evidentiary expectations and to plan the production of relevant evidence for future oncology drugs at earlier stages in development.

A long-term vision could be a system, in which the EMA and HTA agencies work together to assess the drug based on a pre-agreed effectiveness standard. The EMA should focus on quality, safety, efficacy and risk–benefit; while the HTA agencies/payers focus on the ‘value for money’ aspect, and the more context-specific HTA domains. Both the groups then come together to discuss relative efficacy and effectiveness based on the data they have obtained [14].

The steps described in this paper to improve the interface between regulators and HTA bodies are promising, but will not be sufficient to overcome heterogeneous HTA assessments between HTA agencies. The current Joint Action on HTA (‘EUNetHTA’) is an important step towards harmonisation of relative effectiveness assessments and for creating a single
network for improving communication among HTAs and regulators in Europe. Another major issue is—and will remain for the foreseeable future—the heterogeneity of patient access decisions of pharmaceutical payers across Europe which is due to (i) considerably different scientific approaches and methodology to the more or less formal evaluation of cost-effectiveness; (ii) differing health priorities across the countries that reflect historically developed cultural differences and values or different unmet medical needs and (iii) different economic strengths among nations, regions and locales that necessarily drive health care budgetary decisions.

Overall, the first point can be addressed through scientific discussion and exchange to better align drug regulation and reimbursement assessments. The latter two points are even more difficult to overcome and will require fundamental changes in European health care politics. But beyond finding a science-based common position on methodology, greater commitments by politicians and healthcare decision makers will be needed to ensure equal access for patients across the EU to antitumor medicines.


1Medical Clinic II, University Hospital, Frankfurt
2Federal Institute for Drugs and Medical Devices (BfArM), Bonn, Germany
3Hoffmann-la-Roche, Basel, Switzerland
4SENDO, Southern European New Drugs Organization, Milano, Italy
5Tapestry Networks, Inc., London
6University of Edinburgh, Edinburgh, UK
7Edinburgh Cancer Research Centre, Internal Medicine V, Innsbruck Medical University, Innsbruck, Austria (*E-mail: L.Bergmann@em.uni-frankfurt.de).

acknowledgements

The authors thank Francesco Pignatti, EMA London, for his helpful input in the discussion and review of the manuscript.

disclosure

It is stated that the authors do not declare a conflict of interest with the content of this manuscript except A. H., who is an employee of Hofmann-La Roche. All the remaining authors have declared no conflicts of interest.

references