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Review

Assessment of benefits and risks in development of targeted therapies for cancer – The view of regulatory authorities



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ARTICLE INFO

Article history:

Received 8 July 2014

Received in revised form

8 October 2014

Accepted 9 October 2014

Available online 16 October 2014

Keywords:

Targeted therapies

Drug regulation

Benefit-risk balance

ABSTRACT

Drug licensing and approval decisions involve the balancing of benefits against the risks (harms) in the presence of uncertainty. Typically, the benefits are estimated from primary efficacy endpoints from confirmatory (phase III) clinical trials although exceptions where promising early data from single-arm studies have led to accelerated approvals are not uncommon, particularly for cancer drugs.

The challenge for regulators is to balance early evidence of efficacy that might support approval versus the need to establish clinical benefit based on conclusive evidence. Targeted agents offer the promise that knowledge about the mechanism of the disease will help identify patients with tumors likely to respond, resulting in higher efficacy and less toxicity, and earlier regulatory decisions based on convincing evidence of clinical benefit. In this paper, we describe methods and examples of benefit-risk assessment of targeted drugs, recent initiatives from EMA and FDA on improving communication about benefits and risks, and discuss future steps.

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1. Regulatory requirements for approval; benefit-risk balance definitions

The balance of benefits and risks occupies a central place in licensing and approval decisions. In the European pharmaceutical legislation, it is defined as an evaluation of the positive therapeutic effects in relation to any risks as regards patients' health or public health, or any risks to the environment (Directive 2001/83/EC, 2001). An approval shall not be granted if the benefit-risk balance is not considered to be favorable.

Similar requirements exist in US Food, Drug and Cosmetic Act and the Code of Federal Regulations, where balanced consideration of benefits and risks is used for decision-making. The safety of the product is weighed against its efficacy to determine whether there is substantial evidence that the drug will have the effect it purports in the labeling (Federal Food Drug, and Cosmetic Act, 1938). In reviewing marketing applications for drugs to treat life-threatening and severely-debilitating illnesses, FDA recognizes the need for a medical risk-benefit judgment in making the final

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<http://dx.doi.org/10.1016/j.molonc.2014.10.003>

1574-7891/Published by Elsevier B.V. on behalf of Federation of European Biochemical Societies.

decision on approvability. As part of this evaluation, FDA considers whether the benefits of the drug outweigh the known and potential risks of the drug and the need to answer remaining questions about risks and benefits, taking into consideration the severity of the disease and the absence of satisfactory alternative therapy (CFR, 1988).

Thus, the broad aim of clinical development of a new drug is to find out whether there is a dose range and schedule at which the drug can be shown to be safe and effective, to the extent that the risk-benefit balance is considered favorable. For targeted agents, there is an opportunity (and a necessity) to characterize both patient and disease characteristics to allow more individualized therapy, e.g., individual dosing depending on the pharmacogenomic profile of each individual and identifying tumor targets to enrich the trial population.

When assessing the evidence, regulators need to strike a balance between early access for patients affected by conditions with high unmet medical need versus having as complete information as possible on the benefits and risks (Eichler et al., 2008). A number of regulatory mechanisms exist to manage early access and the related uncertainties (conditional marketing authorization in the EU and accelerated approval in the US) (Pignatti et al., 2011; Johnson et al., 2011). Due to the large unmet need associated with most cancer indications, more emphasis has often been on efficacy rather than safety, reflecting high acceptance of risks by patients when there are no effective standard treatments or their efficacy is known to be very limited.

Regulatory approval is based on objective evidence of efficacy, safety and pharmaceutical quality, to the exclusion of economic considerations, the latter being the responsibility of health technology assessment organizations and payers based on relative-effectiveness and cost-effectiveness. Different evidentiary standards between regulators and payers may lead to divergent appraisals of benefit-risk versus cost-effectiveness (Littlejohns, 2009). This issue calls for good understanding and interaction between the two communities, possibly in the format of iterative discussions and agreement during drug development (Eichler et al., 2012).

2. Benefits; efficacy endpoints and (likely) surrogates; clinical relevance

Firm evidence in support of claims requires that the results of confirmatory trials demonstrate that the investigational product under test has clinical benefits. In this respect, targeted agents are no different than any other type of agent. There should be sufficient evidence that the primary variable of confirmatory (phase III) trials can provide a valid and reliable measure of some clinically relevant and important treatment benefit in the patient population described by the inclusion and exclusion criteria. When direct measurement of the clinical benefit is not practical, indirect criteria (surrogate variables) may be considered. There are two main concerns with the introduction of any proposed surrogate variable. First, it may not be a true predictor of the clinical outcome of interest. For example it may measure treatment activity associated with one specific pharmacological mechanism, but may not provide full information on the range of actions and ultimate

effects of the treatment, whether positive or negative. Secondly, proposed surrogate variables may not yield a quantitative measure of clinical benefit that can be weighed directly against the risks. Validating surrogate variables requires extensive data which are often not available at the time of new drug approval. In practice, the strength of the evidence for surrogacy depends upon (i) the biological plausibility of the relationship, (ii) the demonstration in epidemiological studies of the prognostic value of the surrogate for the clinical outcome and (iii) evidence from clinical trials that treatment effects on the surrogate correspond to effects on the clinical outcome (International Conference, 1998).

A number of different endpoints have been used for approval of targeted agents. For advanced solid tumors, this includes overall survival, progression-free survival and objective response rate. While the clinical relevance of overall survival is undisputed, that of progression-free survival is more debated, whereas response rate is usually reserved for situations where dramatic activity can be shown in single-arm studies leading to early approval with a requirement to provide confirmatory data post-approval. In the EU, and also now in the US, there has been a tendency to recognize progression-free survival as a clinical benefit endpoint in itself, leading to standard approvals. Progression-free survival has been reported as a valid surrogate endpoint for overall survival in some situations (e.g., advanced colorectal cancer). However, the validity of the surrogate may be questioned as it is always context-dependent. In the absence of formal validation, acceptance of this endpoint relies on assumptions about the expected clinical benefits of delaying progression (e.g., delaying onset of symptoms), which, may be controversial unless the magnitude of the effect is substantial (European Medicines Agency, 2013; Food and Drug Administration, 2007). Other surrogate endpoints that have recently been proposed for approval in specific situations are pathological complete response in neoadjuvant treatment of breast cancer and minimal residual disease in hematological malignancies (Johnson et al., 2011; Sridhara et al., 2010; Johnson et al., 2003; Wilson et al., 2013; Powell and Pazdur, 2012).

The choice of clinical efficacy endpoints remains a controversial topic. However, it is important to stress that assessment of the benefit-risk balance is more complex than simply observing statistically significant effects in terms of the primary efficacy endpoint. The benefit-risk balance is a complex problem of balancing multiple efficacy and safety outcomes, their probability and uncertainty, using value judgments. Today this complex task is done mostly implicitly (holistically) based on expert judgment. In clear-cut situations (large effect on clinically relevant endpoint; mild toxicity profile), decisions are straightforward, and the complex “balancing” task can be avoided. For instance, if clinical benefit has been shown compared (head-to-head) to a standard, and toxicity is “manageable” and “acceptable” for the disease setting, the balance is by definition positive. There is ample discretion on what constitutes “acceptable” toxicity. This reflects the likely bias towards over-valuing efficacy endpoints by patients, practitioners, and regulators in view of the high unmet medical need of many cancer patients. In situations where there is no standard to compare to (e.g., add-on or no standard treatment), and where the benefits and risks

are relatively close, decisions are more complex and may require more precise balancing of benefits and risks.

3. Risks; treatment emergent signs and symptoms; risk management

The toxicity profile of targeted agents is often as significant as that of traditional chemotherapy drugs including drug reactions such as diarrhea, hepatitis, rash, impaired wound healing, high blood pressure, and gastrointestinal perforation.

The safety and tolerability properties of a drug are commonly summarized across trials continuously during an investigational product's development and, in particular, at the time of a marketing application. The presentation of safety data concerning oncology products is often challenging because the symptoms of the disease are often prominent and in many cases indistinguishable from the corresponding drug reaction (e.g. fatigue, weight loss). This is particularly difficult in the case of single-arm trials where the true adverse drug reactions frequencies cannot be estimated due to the absence of a parallel control. For example, ponatinib (Iclusig) is an ABL and pan-tyrosine kinase inhibitor indicated for different disease stages and entities of chronic myeloid leukemia (CML), and Ph+ acute lymphoblastic leukemia (ALL). The safety and efficacy of ponatinib were evaluated in a single-arm trial. Many of the observed adverse events could be expected as signs or symptoms of the underlying hematological malignancy, such as myelosuppression, infection, and bleeding. In the absence of a randomized controlled trial it is impossible to estimate the proportion of adverse events that are caused by the drug and the disease, respectively. To obviate this, more importance is often given to treatment-emergent (i.e., emerging during treatment having been absent pre-treatment, or worsening relative to the pre-treatment) signs and symptoms, together with adverse events, by severity category.

The analysis safety data from clinical trials is generally presented in a cumulated fashion (worst grade toxicity experienced on study or during follow-up). However, depending on the toxicity profile, it is sometimes necessary to analyze toxicity over time (e.g., using time to event, time-adjusted analyses). Other important aspects are the extent to which toxicity leads to treatment discontinuation and the effectiveness of dose-reductions in managing toxicity. When assessing the benefit-risk balance, the most important unfavorable effects of the product and the level of uncertainty about those effects are weighted against the benefits. Often, explicit trade-offs between benefits and risks are not necessary as it is possible to judge the acceptability of the safety profile by comparing important adverse drug reactions, their severity, duration and reversibility to standard of care or drugs of the same pharmacological class.

It is recognized that at the time of authorization, information on the safety of a medicinal product is relatively limited. This is due to many factors including the relatively small numbers of subjects in clinical trials compared with the intended treatment population, restricted population in terms of age, gender and ethnicity, restricted co-morbidity, restricted co-medication, restricted conditions of use, relatively short

duration of exposure and follow up, and the statistical problems associated with looking at multiple outcomes. Thus, many of the risks associated with the use of a medicinal product will only be discovered and characterized post-authorization. Identified risks and the remaining uncertainties are managed following an agreed risk-management plan.

4. Biomarkers in the development of targeted therapies to optimize benefit-risk balance

Alongside conventional aims such as defining the proper dose(s) and schedule(s), it is important to identify a target population with optimized benefit risk in exploratory studies. Irrespective of pharmacological class, it is assumed that entry into clinical development of a new molecule today is guided by translational research.

A suitable biomarker may be identified and measured by a variety of different diagnostic approaches (e.g., expression profiling of transcripts, differential antigen expression, and genetic diagnostics, including next generation sequencing). Currently, most of the regulatory experience with biomarkers is based on genomic biomarkers and protein expression. The development of biomarker diagnostic methods (if specific to the identified biomarkers) should be considered early in clinical development, maximizing the clinical application of the technology.

While it is acknowledged that drug development for compounds with a single main target for activity, such as mutated BRAF, is more straightforward, it is still expected that the pharmacological rationale behind poly-targeting compounds is reflected in the exploratory studies program, e.g., in terms of biomarkers selected in order to identify the proper target population for treatment.

The decision of when there is sufficient evidence for pursuing development only in a biomarker-defined subgroup (e.g., biomarker-positive) is a complex one. While pharmacology data may suggest that one subgroup is the most likely to respond, the complementary subgroup may still benefit from the drug, depending on the association of the biomarker and dose-response which may or may not be anticipated based on pharmacological grounds. This may lead to delayed access in subgroups that have been excluded based on the wrong assumptions. For example, cetuximab was initially developed in EGFR-positive colorectal cancer based on the supposed mechanism of action. It was later found out that the response in "EGFR-negative" tumors was no different and that the relevant biomarker was actually KRAS, or perhaps RAS. There is also generally a need to study the effect of a drug in the biomarker negative population as a way to validate the utility of the test (Parkinson et al., 2014).

Equally though, inclusion of a subgroup with little or no expectation of a clinically relevant effect may not be in the patients' best interest and may unnecessarily inflate the size and prolong the duration of the trial. For patient stratification, if convincing evidence of biomarker selectivity is established early in the non-clinical and clinical development phase, confirmatory evidence in the biomarker-negative population may not be required. Where there is insufficient information about the benefit-risk balance in the biomarker-negative

population, such studies may be requested post-approval. For example, crizotinib is indicated for the treatment of adults with previously treated anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC). At the time of approval, it was not known whether crizotinib was only effective in patients with ALK-positive tumor status. Thus, the enrollment of patients with “ALK-negative” (but positive for ROS1 or MET) NSCLC as new cohorts in the ongoing pivotal phase I/II study was requested as post-marketing requirement (European Medicines Agency, 2012a).

It is acknowledged that biomarkers tested in early clinical trials are often exploratory in nature, but it is essential that technical and quantitative reliability is assured. While serum biomarkers or other less invasive sources of biological samples are being explored for solid tumors, tumor samples are expected to constitute an integral part of biomarker discovery. Normal tissues samples may also be used for pharmacodynamic information in early clinical studies, provided that non-clinical studies indicate that there is a correlation between the changes observed in normal tissues and the tumor.

Regulators have recommended using predictive biomarkers throughout phases of clinical drug development of oncology drugs. Prospective randomized clinical trials provide the gold standard for the validation of biomarkers. The possibility of retrospective validation with replication of findings is contemplated in EU guidelines. Such retrospective validation is only appropriate if the data of these trials were not used for the biomarker identification and multiplicity is appropriately handled to take into account the number of candidate biomarkers investigated in the replication studies (European Medicines Agency, 2010a).

Strong signals from exploratory analyses may be considered, in particular if these can be supported with additional knowledge, such as improved knowledge of the role of the biomarker in the pathogenesis of the disease along with some confirmatory evidence from other trials. For example, in the EU the interaction between EGFR FISH or EGFR mutation status, with gefitinib was evaluated in several studies (ISEL, INTEREST, and IPASS) in patients with non-small cell lung cancer in a retrospective analysis (only the INTEREST study included a prospective analysis based on EGFR FISH-positivity as co-primary objective), leading to approval. The differential response rates noted in these studies might have been influenced by differences in patient, disease and treatment characteristics. The differences in the number of subjects with known marker status may also have played a role. Notwithstanding the differences, the pooled analysis suggested benefit from gefitinib therapy in the case of EGFR mutation positive tumors because of the directional concordance between various comparisons and the replicated interaction between EGFR mutation status and response to gefitinib. Thus a restricted indication was accepted in the EU. This example highlights two important aspects of retrospective evaluation of biomarkers: the need for replication in different studies and populations, and secondly, the need for minimizing missing data (European Medicines Agency, 2010a).

The study identifying the association between wild type KRAS in metastatic colorectal cancer and improved progression-free survival after the EGFR-directed antibody panitumumab provides another such example of retrospective

validation. In this instance, a differential effect of panitumumab between carriers of wild type and mutated KRAS suggested by a post hoc analysis, along with a biological plausibility for the association derived from trials of another EGFR-directed antibody (cetuximab), formed the basis of conditional authorization in the EU. The authorization stipulated that further data to provide a better understanding about the interaction between panitumumab and KRAS mutation status would have to be generated prospectively (European Medicines Agency, 2010a; European Medicines Agency, 2007).

Regardless of the approach, there is a need to plan for a learning phase and a confirmatory phase, aiming to minimize bias and control for multiplicity. If subgroups are selected without appropriate adjustment, the treatment effect estimates will be biased and the false positive rate will be inflated because of the arising multiplicity problem. Other critical aspects include handling of continuous marker variables, handling of missing data, planning and interpreting subgroup analyses, establishing clinical utility, and handling of uncertainty in the regulatory decision (Pignatti et al., 2014).

5. Evaluating the benefit-risk balance of targeted drugs: successes and failures; next steps

Regulators have recommended using predictive biomarkers throughout phases of clinical drug development of oncology drugs. A number of approved products currently contain relevant pharmacogenomics information for patient selection. Nevertheless, biomarker identification and validation remain challenging.

The current experience with targeted agents has delivered mixed results. Rituximab for non-Hodgkin lymphoma is probably the first targeted agent that has shown a very clearly positive benefit-risk balance. Many tyrosine kinase inhibitors for CML have also been clear breakthroughs in radically changing the natural history of the disease. In these situations, development can be rapid, since confirmatory evidence of efficacy may not be needed at the time of approval when there is dramatic evidence of activity in phase I–II (refractory setting or lack of good alternatives) (Sharma and Schilsky, 2012; Pazdur, 2013).

The benefit-risk balance was less clear-cut for other targeted agents. This has led to narrow benefit-risk balances and sometimes discordant regulatory decisions (Table 1). The EMA has advocated rigorous biomarker validation methods whenever possible while also considering results from exploratory analyses, in particular if these can be supported with corroborative evidence, such as improved knowledge of the role of the biomarker in the natural history of the disease and evidence from other trials (European Medicines Agency, 2010a). FDA has recommended that analytically and clinically validated companion diagnostics tests be available at the time of drug approval to ensure the safe and effective use of a targeted therapy (Food and Drug Administration, 2011).

Still, the modest success of some targeted cancer drugs highlights the incomplete knowledge about the mechanism of action and patient and disease characteristics that should guide the development. Extensive exploratory biomarker and pharmacology studies before defining the design of the

Table 1 – Examples of issues for discussion during the analysis of benefit-risk balance of targeted cancer drugs.

Drug name target	Indication (short)	Benefits (Primary and secondary endpoints)	Risks	Issues	Ref.
Bevacizumab (Avastin) VEGF	Metastatic breast cancer in combination with paclitaxel	PFS: 5.5 months difference in medians v. paclitaxel alone; HR _(PFS) = 0.48, (95%CI: 0.38, 0.61, $p < 0.001$); OS: 1.7 months difference in medians; HR _(OS) = 0.87, (95% CI: 0.72, 1.05, $p = 0.14$).	Sensory neuropathy (25% v. 18%), hypertension (16% v. 1%), infection (9% v. 5%), neutropenia (8% v. 4%), arterial thromboembolic event (4% v. 0%). Risks include severe hypertension; bleeding, hemorrhage; heart failure; perforations (nose, stomach, and intestines).	No effect on OS shown; Magnitude of PFS effect not confirmed in subsequent studies; Negative results in combination with other taxanes; Benefit-risk balance?	(Miller et al., 2007; European Medicines Agency, 2011; United States Food and Drug Administration, 2011)
	Glioblastoma in combination with CT/RT	PFS: 4.4 months difference in medians v. CT/RT; HR _(PFS) = 0.64 (95% CI: 0.55, 74; $p < 0.001$).	Grade ≥ 3 AEs (66.8% v. 51.3% for CT/RT). SAEs (38.8% vs. 25.6%), including more frequent bleeding, complications of wound healing, gastrointestinal perforation, and congestive heart failure compared to CT/RT.	No effect on OS shown. Clinical relevance of PFS endpoint in glioblastoma for drugs targeting VEGF?	(Chinot et al., 2014; European Medicines Agency, 2010b; Cohen et al., 2009; European Medicines Agency, 2014)
Panitumumab (Vectibix) EGFR	Metastatic colorectal cancer	PFS (Overall): 0.7 weeks difference in medians v. BSC; HR _(PFS-Overall) = 0.54 (95% CI: 0.44, 0.66; $p < 0.001$). PFS (KRAS wild-type): 5 weeks difference in medians; HR _(PFS-KRAS wild-type) = 0.45 (95% CI: 0.34–0.59; $p < 0.001$).	The most serious AEs were pulmonary fibrosis (<1%); grade 3–4 dermatologic toxicity (16%), abdominal pain (7%), hypomagnesemia (4%), nausea (1%), vomiting (2%), diarrhea (2%), and constipation (3%).	Borderline effect in unselected population. Retrospective identification of KRAS wild-type subgroup.	(Giusti et al., 2007; European Medicines Agency, 2007a; Van Cutsem et al., 2009; Amado et al., 2008)
Cetuximab (Erbix) EGFR	Metastatic colorectal cancer, in combination with irinotecan (EGFR-positive)	ORR: 12.1% difference in overall response rate v. cetuximab alone (22.9 [17.5–29.1] v. 10.8 [5.7–18.1]; $p = 0.007$); HR _(TTP) : 0.54 (95% CI: 0.42, 0.71; $p < 0.001$).	Severe anaphylactic reactions (1.2%) overall. No treatment-related deaths. Acne-like rash (9.4% v. 5.2%), diarrhea (21.2% v. 1.7%) and neutropenia (9.4% v. 0%) for cetuximab + irinotecan compared to cetuximab alone.	Both treatment groups of the pivotal study contained cetuximab; Surrogacy of ORR not formally established; Efficacy in EGFR-negative subgroup?	(Cunningham et al., 2004; European Medicines Agency, 2006)
Erlotinib (Tarceva) EGFR	Pancreatic cancer in combination with gemcitabine	OS: 2 weeks difference in medians v. gemcitabine + placebo; HR _(OS) : 0.79 (95% CI: 0.66, 0.95; $p = 0.011$); PFS: 0.9 weeks difference in medians; HR _(PFS) : 0.77 (95% CI: 0.64, 0.92; $p = 0.004$).	Rash (69% v. 30%), diarrhea (48% v. 36%), infection (31% v. 24%), stomatitis (22% v. 12%); SAEs regardless of causality (51% vs. 39%).	Modest survival difference may not be considered clinically meaningful; Toxicity is more pronounced for the combination; Benefit-risk balance?	(Moore et al., 2007; European Medicines Agency, 2007b)
Gefitinib (Iressa) EGFR	NSCLC, EGFR mutation	ORR: 23.9% increase (95% CI: 12.0%, 34.9%) v. carboplatin/paclitaxel; PFS: 3.2 months difference in medians; HR _(PFS) : 0.48 (95% CI: 0.36, 0.64; $p < 0.0001$).	Grade 3–5 AEs (31.6% v. 62.5%) v. carboplatin/paclitaxel; rash/acne (49% v. 10%), diarrhea (35% v. 25%), ILD (2.6% v. 1.4%) v. docetaxel.	Retrospective selection of biomarker subgroup; Data on biomarker status frequently missing; Possible small detriment in OS v. docetaxel (non-inferiority not established in per protocol analysis).	(European Medicines Agency, 2009; Mok et al., 2009; Kim et al., 2008)
Vanetanib (Caprelsa) RET	Medullary thyroid cancer	PFS: 11.2 months increase in median compared to placebo; HR _(PFS) : 0.46 (95% CI: 0.31, 0.69; $p = 0.0001$).	Rash (89% v. 23%), diarrhea (57% v. 27%), nausea (36% v. 20%), QTc related events (16% v. 4%), headache (25% v. 9%).	Management of the risk of QTc prolongation; Activity in patients with RET mutation negative tumors?	(European Medicines Agency, 2012b; Thornton et al., 2012; Wells et al., 2012)

Abbreviations: VEGF, vascular endothelial growth factor; PFS, progression-free survival; OS, overall survival; CT/RT, chemotherapy plus radiotherapy; (S)AE, (serious) adverse event; EGFR, epidermal growth factor receptor; RAS, rat sarcoma; TTP, time-to-progression; RET, rearranged during transfection; BSC, best supportive care; NSCLC, non-small-cell lung carcinoma; ORR, objective response rate.

late stages of clinical development are still paramount. One can only hope that our understanding of the biology of cancer advances as rapidly as “-omics” and computational technologies so that the development of targeted agents in oncology can be shifted from large trials to detect small differences to small trials to detect bigger differences.

The importance of the patient’s point of view on their health status is fully acknowledged and such information may in principle be used in drawing regulatory conclusions regarding treatment effects. However, although there are a number of validated tools for collecting patient reported outcome measures, interpretation of these data has often been difficult due to methodological issues, mainly related to missing data and potential bias due to open-label nature of the studies. Still, although patient reported outcomes have rarely been convincing enough to help establish the efficacy of new drugs, these data may be valuable, for example, to explore the impact of side effects.

An expected natural evolution of regulatory systems is towards more patient involvement in the decision-making process, e.g., by helping to establish the context in which the particular decision is made or by providing value judgments to help interpret benefits and risks. Cancer patient perceptions about benefits and risks have been shown to differ from those of physicians and the general public, with cancer patients being less risk-averse and willing to trade important toxicity for small benefits (Matsuyama et al., 2006; Slevin et al., 1990; Bremnes et al., 1995; Hirose et al., 2005). Eliciting patient preferences and benefit-risk trade-offs is a formidable task but one worth pursuing if patients’ value judgments are to inform benefit-risk decisions (Johnson et al., 2010). Simple approaches based on “patient juries” including patients or patient advocates to elicit utilities once regulators have performed the scientific assessment and are able to define benefits, risks and uncertainties, are also being explored (Genetic Alliance UK, 2012). Eichler et al. have pointed out that regulators need to refine their methods of assessing benefit–risk balances and switch from “implicit” to “explicit” decision making — that is, to an approach involving explicit descriptions not only of all decision criteria and interpretations of data but also valuations, such as weighing factors for potential treatment outcomes (Eichler et al., 2009). Better communication will also facilitate the cost-effectiveness exercise. Frameworks for better structuring and communicating the assessment are being assessed by EMA, FDA and the pharmaceutical industry (Phillips et al., 2011; Food and Drug Administration, 2013; Mt-Isa et al., 2014; Levitan et al., 2011).

Implementation of personalized medicine will challenge the current oncology practice, regulatory standards for drug access and approval, and reimbursement policies (Tsimberidou et al., 2013). While the randomized controlled trial is the golden standard for producing evidence on benefits and risks, equipoise may be lost when patients need to consider randomization between promising new agents against standards that are considered practically ineffective (Harmon, 2010). Clinical trial designs need to adapt to patients’ needs, depending on the context, their risk attitude, and the expected treatment effect. Novel innovative master protocol designs such as “umbrella” studies (e.g., LUNG-MAP) (LUNG-MAP, 2014), “basket” studies (e.g., BRAF, PDGFR) (Tabernero

et al.; ClinicalTrials.gov, 2014), or other studies using adaptive designs (e.g., I-SPY, BATTLE) (Kim et al., 2011; Barker et al., 2009) may facilitate more efficient exploration and confirmation of drug-biomarker approvals. It is acknowledged that in small trials the true effectiveness in terms of true endpoints can often only be assumed but this is the opportunity cost one has to pay in such situations. Post-marketing data and trials in related indications may help to mitigate the gap to aid the cost-effectiveness assessment. Lastly, for some of the very rare tumors or subgroups identified by relevant mutations, it is expected that regulators will have to deal with the fact that complete clinical data on benefits and risks can only be collected progressively in the product’s life span using observational, real-world data (Eichler et al., 2012).

There is also a need to ensure efficient access to promising drugs outside clinical trials according to the available mechanisms of compassionate or off-label use, as well as an opportunity to maximize learning from these treatment modalities (Schilsky, 2014). The reality today, is that clinical trials are often conducted in few centers of excellence in a few countries, and that access to unapproved drugs under investigation poses insurmountable administrative and financial challenges. In the US, single patient compassionate use requests are instigated by the physician, but the pharmaceutical manufacturer must agree to provide the drug. In the vast majority of cases, FDA grants these requests. As more targeted cancer drugs are developed with the promise of dramatic activity and minimal toxicity, early access for patients must remain the priority.

Publication disclaimer

The views expressed are the result of independent work and do not necessarily represent the views and findings of the European Medicines Agency, Läkemedelsverket or the US Food and Drug Administration.

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