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Personalised reimbursement: a risk-sharing model for biomarker-driven treatment of rare subgroups of cancer patients

Precision medicine in oncology is based on the premise that every tumour is unique and therefore requires a thorough molecular analysis to identify the best possible targeted treatment. In general, access to precision medicine, especially outside an approved indication is challenging. There are several barriers and concerns. Although the paradigm of precision medicine in cancer is to target a specific genetic aberration, there is uncertainty regarding effectiveness for every biomarker–tumour–drug combination. Various other factors, such as post-transcriptional modifications, protein expression, tissue context, heterogeneity of the tumour and its microenvironment, variations in patient characteristics, and prior treatments also contribute to uncertainty of treatment outcome.

Collecting data and generating evidence on off-label use are complex outside a clinical trial. Randomised clinical trials are difficult to conduct as small numbers of patients carry a particular genetic aberration in a specific tumour type. Clinical evidence is therefore mostly based on case-studies or small single-armed trials. Historical data are often not available to compare treatment outcome to conventional treatment, as earlier studies have not always taken the genetic make-up of the tumour into account.

However, regulatory agencies have developed tools (e.g. conditional market authorisation or accelerated approvals) to address this problem and facilitate timely access to the patient.

An illustrative example of the latter is the accelerated approval of the checkpoint inhibitor pembrolizumab for adult and paediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) advanced solid tumours that have progressed following prior treatment and who have no satisfactory alternative treatment option. The U.S. Food and Drug Administration (FDA) approval was tissue/site-agnostic and based on retrospective analysis of data from 149 patients, including 90 patients with metastatic colorectal cancer (mCRC), across 5 single-arm clinical trials [1]. MSI-H tumours are rare and their prevalence varies widely among tumour types. Bonneville et al. [2] detected MSI-H with a prevalence >1% in 12 out of the 39 different types of cancers, which severely hampers the execution of adequately powered randomised trials.

In June 2017, the application of another checkpoint inhibitor, nivolumab, for MSI-H or dMMR mCRC patients with the European Medicines Agency (EMA) was withdrawn as the evidence presented to the EU Committee for Medicinal Products for Human Use (CHMP) at the EMA was considered insufficient. Major concerns were the non-comparative design of the pivotal study, the limited number of patients ($n = 74$), the absence of overall survival data, and high discordance between local and central MSI testing. In addition, CHMP had concerns regarding the placing of nivolumab in second line (after prior fluoropyrimidine-based therapy), in the absence of convincing evidence and with several established treatment options are available [3].

In the Netherlands, a non-randomised, multi-centre basket trial, The Drug Rediscovery Protocol (DRUP) [4], is active to specifically identify signals of clinical benefit of approved drugs used outside their label in rare, molecularly defined subsets of patients who have exhausted standard-of-care treatment options. The trial also contains an MSI cohort in which patients with MSI-H tumours are treated with nivolumab, irrespective of their tumour type (with the exception of approved indications). The results of this cohort of 30 patients are in line with the retrospective data used for the FDA accelerated approval of pembrolizumab, further underlining the efficacy of checkpoint inhibitors in patients with these tumours.

Currently, as the MSI-H cohort of the DRUP trial has reached target recruitment and is therefore closed, newly diagnosed patients in the Netherlands have no access to treatment. There is also no coverage by health insurers for this biomarker-driven indication with promising data. This poses a serious dilemma and it is likely that other anticancer agents with high antitumour activity in non-randomised studies will encounter similar barriers.

As a consequence, there is a growing need for a learning health care model which enables early access to potentially effective therapies, where no other established treatment options are available, without overestimating the findings that are based on small cohorts of patients. Continuous monitoring to enrich a real-world database is essential for this learning model.

In the Netherlands, the government determines the content of the standard health insurance package that covers necessary healthcare costs. Subsequently, this package is offered by all insurers. The government is advised by the National Health Care Institute (Zorginstituut Nederland), an independent health technology assessment (HTA) authority that evaluates interventions, to ensure that the standard health insurance package is cost-effective, evidence-based, and in accordance with state of the art and state of the practice. In some cases, the health insurers can decide to reimburse drugs which are not included in the package, for instance, when a disease is extremely rare (prevalence <1/150 000) and no other treatment option is available [5].

The Dutch government regularly negotiates price/volume agreements for drugs with a high budget impact. The immune

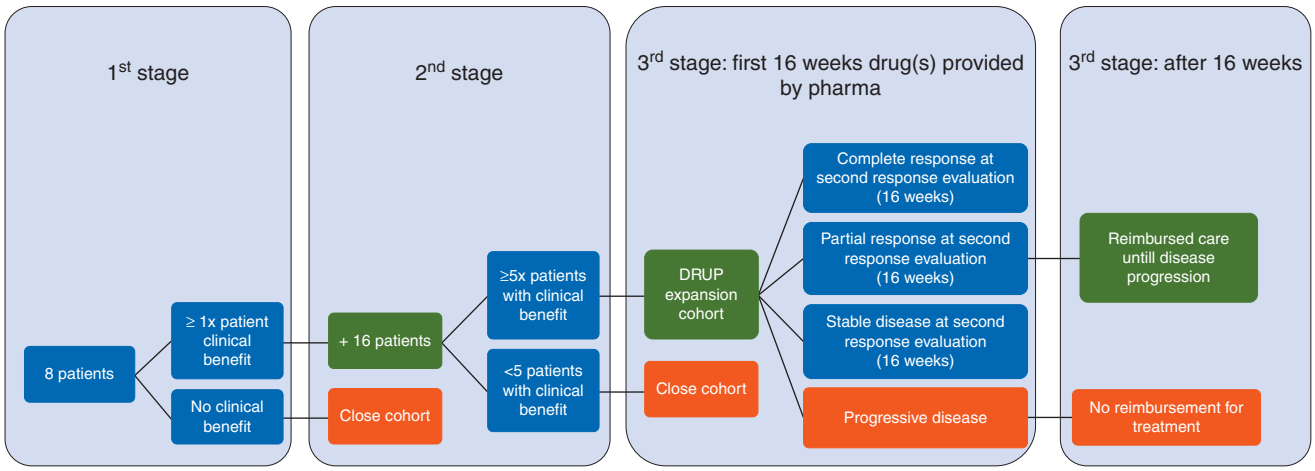

Figure 1. A performance-based, personalised reimbursement scheme after 16 weeks of clinical benefit at stage III, when the effectiveness is proven for an individual patient, commercial medication will be reimbursed by payers.

checkpoint inhibitors have also been subjected to confidential national price agreements. However, off-label use of expensive drugs is usually not covered by payers. As the health care budget is limited and there is a continuous rise in expenditure, the payers are obliged to allocate their budgets reasonably and responsibly. This presents a dilemma, especially when clear clinical benefit is seen in a small patient population such as MSI-H patients. In the case of MSI-H, the Health Insurers in the Netherlands and the National Health Care Institute acknowledge the medical need in patients who have exhausted other treatment options. This prompted us to collaborate in developing a personalised decision-making model to enable early access to potentially effective therapies whilst being aware of the increased pressure on the health care budget.

Here, we present a performance-based, personalised reimbursement scheme that enables access to precision medicine in rare biomarker-defined subgroups. In the Netherlands, this scheme will be an integral part of the ongoing DRUP trial. In this trial, eligible patients for a particular tumour–drug combination are recruited based on Simon's two-stage design approach. Eight patients are enrolled in stage I and 16 more in stage II, if more than 1 response is observed in the first stage. If less than five patients show an objective tumour response or stable disease at 16 weeks, the cohort is closed (Figure 1). However, when the second stage is successful with five or more patients benefitting from the therapy, the cohort will be expanded to a third stage, with defined inclusion criteria, duration of treatment and number of patients needed to confirm the initial results. The first two stages of the DRUP trial are exploratory, with medication considered to be investigational medicinal products provided for free by the marketing authorisation holder (MAH). The third stage is designed to confirm the findings in the first and second stages and can be partly reimbursed based on a pay for performance model. In this model, patients start on treatment with the investigational medicinal product as provided by the MAH and continue on the regular drug product which is reimbursed in case of adequate individual treatment response. Adequate response is defined as complete remission or partial remission based on RECIST 1.1 (or iRECIST for in case of ICI) at 16 weeks or prolonged stable disease (at least 16 weeks but duration can vary depending on tumour–drug combinations).

Although this model provides access to potentially effective drugs for patients without other treatment options and allows risk-sharing between the manufacturer and payers, there are some considerations and limitations:

1. The manufacturers are needed to partner in this approach by providing investigational medicinal product for free until a meaningful clinical response is achieved at 16 weeks.
2. Payers and HTA authorities need to approve the model, preferably by embracing general rules of the proposed scheme. In fact, the presented scheme is a result of close collaboration among medical oncologists, National Health Care Institute, and health insurers in the Netherlands, all of whom support this model.
3. A molecular tumour board, which consists of a multidisciplinary team of experts, should evaluate molecular and clinical data and provide recommendations on inclusion in the DRUP study.
4. The patient should be notified of the experimental nature of the treatment and provide consent, and also to allow further (translational) research.
5. As the magnitude of benefit on overall survival and quality of life is unclear, it is important to periodically analyse the results. The structure of a clinical trial with predefined number of patients, pre-planned interim analysis, and futility assessments can save resources.
6. It is important to gather biomarker data that can be used to further refine patient selection in the future and hence improve quality of care.
7. Nationwide, patients need to have equal access to the treatment and treatment evaluations need to be harmonised.
8. The necessity of the continuation of the performance-based reimbursement scheme should regularly be evaluated based on predefined outcome criteria and availability of better treatment options.

9. Organisation of such personalised reimbursement schemes is complex in terms of infrastructure and administrative burden.

The performance-based reimbursement scheme that we propose here will run as a pilot, using the infrastructure of the DRUP trial. By integrating into the current infrastructure of the DRUP trial, through expanding the trial to a third stage, we will guarantee careful data-management and uniform genomic and MSI testing and evaluation. This stepwise approach can be used in the future for other rare molecular subgroups.

To our knowledge, this is the first time that a risk-sharing model has been set up between pharmaceutical industry and payers for biomarker-driven, tissue-independent, cancer treatment. The learning health care scheme proposed here allows patients with various tumour types to have early access to potentially effective off-label drugs based on their specific molecular profile, while at the same time real-world evidence for precision medicine is generated. In the pilot, to be run in the Netherlands, the performance-based reimbursement step will run alongside the national financial agreements with manufacturers to ensure responsible use of health care resources. This model can be a step forward in delivering precision medicine in a sustainable and affordable manner.

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Enthuse for PERUSE: when clinical judgment overcomes regulatory boundaries

Contemporary treatment of human epidermal growth factor 2 (HER2)-positive breast cancers is a successful example of the rationale development of molecularly targeted therapies. The observation that HER2 overexpression or gene amplification was associated with more aggressive phenotype and poorer prognosis has laid the groundwork for developing agents to antagonize this pathway [1].

The humanized monoclonal anti-HER2 antibody trastuzumab combined with cytotoxic agents was rapidly established as the standard therapy of early and advanced HER2-positive breast cancer in light of its unquestionable efficacy [2–5]. But this was just the beginning. Indeed, metastatic breast cancer is still incurable. The importance of maintaining the inhibition of the pathway has been demonstrated across further lines of anti-HER2-based therapies speeding up the development of new HER2-targeted agents including lapatinib, pertuzumab and T-DM1 [6–8]. The appealing synergy of dual anti-HER2 targeting fully revealed its clinical value in the Clinical Evaluation of Pertuzumab and Trastuzumab study (CLEOPATRA). In this trial, the addition of pertuzumab to trastuzumab and docetaxel as first-line therapy resulted, among other things, in a 15.7-month overall survival improvement [9–11]. The results of the CLEOPATRA trial led to regulatory approval of pertuzumab–trastuzumab and docetaxel as first-line therapy for HER2-positive advanced breast cancer patients.

Despite EMA and FDA labels including docetaxel as the chemotherapy backbone, in routine oncology practice, paclitaxel is often preferred in the metastatic setting because of its more favorable safety profile.