Novel risk-sharing scheme puts the spotlight on biomarkers

A more widespread adoption of an approach taken by a new scheme in which payment for an anticancer drug is linked to treatment response might create stronger incentives and opportunities for the discovery and application of clinically relevant biomarkers.

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On 24 October, the UK's National Institute for Health and Clinical Excellence (NICE) issued final guidance on the use of bortezomib (Velcade; Janssen-Cilag) for the treatment of multiple myeloma. The guidance confirms a 'risk-sharing' scheme proposed by the manufacturer that ensures that the National Health Service (NHS) only pays for the drug when patients show a full or partial response to treatment (*Nature Rev. Drug Discov.* 6, 508–509; 2007).

"NICE itself does not 'adopt' risk-sharing schemes; the one for Velcade was endorsed by the government and then we used it as a basis for assessing the cost-effectiveness of the drug," says Sir Michael Rawlins, Chairman of NICE. Rawlins anticipates that risk-sharing agreements will be used in future NICE health-technology appraisals, provided that the government has agreed them with the relevant manufacturers.

To implement this risk-sharing agreement, clinicians are required to measure the levels of serum M protein — a specific biomarker for tumour load — after a maximum of four cycles of treatment. If the patient has a reduction in serum M protein of 50% or more, known as a complete or partial response, treatment will continue and the NHS will pay. If not, the manufacturer must rebate the full cost.

"Allowing this scheme for Velcade was possible because, among other reasons, the biomarker clearly shows whether or not the drug is working," says Richard Ley, spokesperson for the Association of the British Pharmaceutical Industry, "this requirement limits whether or not this type of scheme can be more broadly extended."

Jeffrey Moe, Senior Director of Business Development at GlaxoSmithKline and Adjunct Associate Professor at Duke University Fuqua School of Business, North Carolina, USA, agrees: "This scheme is going to be confined to therapeutic areas where we have confidence in the marker's relationship to disease progression and where the drug can be isolated as having direct influence on variation in the marker irrespective of other factors in the treatment regime." For example, there is no biomarker for selective serotonin reuptake inhibitors used to treat depression. Physicians have to empirically try one medication after another until they find one that works and rely on the patient to self-report efficacy.

Using biomarkers to help decide whether drugs should be reimbursed is not a new idea. Currently, in the United States, the Centers for Medicaid and Medicare Services (CMS) reimburse the use of erythropoiesis-stimulating agents (ESAs) until a patient achieves a haemoglobin level of 10 g per dl, despite changes to FDA labelling stating that ESA use should stop only when it reaches 12 g per dl. "The ESA manufacturers are saying that the CMS have overstepped their bounds by linking reimbursement to a specific haemoglobin level. Clinicians agree with the objection arguing that the marker is not stable enough to determine when to initiate or cease therapy," says Moe.

Extending such schemes from the single-payer market, as in the UK, into the private sector would require absolute confidence in the biomarker to be able to link it directly to reimbursement. "It's simply too new and perhaps too early in the adoption of pharmacogenomics and biomarkers to link reimbursement to them," says Moe. "Rather than deny care, private insurers are more likely to ask for cost-sharing arrangements to limit their risk of expensive therapies or diagnostics," he adds.

If payers do adopt risk-sharing schemes more frequently it may create bigger incentives for companies to focus on identifying clinically relevant biomarkers for existing and pipeline products, says Patricia Danzon, Professor of Health Care Systems and Insurance at the University of Pennsylvania, USA. However, Danzon cautions that "it may also mean that companies are less willing to invest in drugs where they don't have those biomarkers... which would ultimately affect R&D incentives."

Mark Trusheim, Executive in Residence and Visiting Scientist at the Massachusetts Institute of Technology (MIT) Sloan School of Management, USA, argues that such risk-sharing schemes may actually have a positive impact on R&D: "What biomarkers promise, and now this payment structure is enabling, is the ability to profitably target smaller markets with drugs that would not historically gain approval, and so increase physicians' armamentarium."

Ensuring that the right patients receive treatment may also benefit the biopharmaceutical industry financially, says Danzon. This potential benefit is dependent on being able to identify patients who will respond to a drug in advance of treatment. The Velcade biomarker is not ideal because you have to treat the patient before you know whether the therapy works. A biomarker such as HER2, used to identify patients who are likely to respond to trastuzumab (Herceptin; Roche), is more appropriate. "If it is possible to identify the patients who will respond in advance then it becomes a much better value proposition for the payer. It might be reasonable to expect them to pay higher prices," says Danzon.

Trusheim concludes: "This is a tremendous opportunity for manufacturers with confidence in their drugs to receive value-based compensation if they possess the courage to take on some of the risk that patients in real-world conditions will truly benefit."