

ability to access these trials usually depends on their clinician's involvement. Obtaining information about trials is often very challenging for patients. The main issue is time, which cancer patients lack.

HTAs sometimes present barriers to patient access. Different countries take different approaches to HTAs and sometimes arrive at different conclusions about a given treatment. The process delays patient access. If a product is approved, is its use guaranteed or merely a recommendation? If it is not approved, the regulatory agency needs to be transparent about the reason. Benefits include more than just survival endpoints; quality of life and symptom control are also very important. Extending life, if only by a few months, can be critical to some patients. Having a life-threatening disease also affects the degree to which patients are willing to take risks. Therefore, measuring cost effectiveness is complex, and priorities might be very different near the end of a patient's life.

CONFLICT OF INTEREST STATEMENT: The Roy Castle Lung Cancer Foundation is a registered UK Charity which has received multiple project grants from a number of pharmaceutical companies, strictly within our Policy for working with Commercial Organisations. Dr Fox has been invited to present at a number of meetings, at the invitation of pharmaceutical organizers, but Dr Fox has no personal financial interests with the pharmaceutical industry.

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Case stories

PHARMACOECONOMIC (REIMBURSEMENT) CHALLENGES WITH ANTICANCER VACCINES

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In principle, reimbursement for oncology therapeutics is extremely good, especially in the United States. Medicare is required to pay for indicated and compendia-listed off-label uses regardless of price. There is currently no system in place to measure cost-benefit and impact of a new therapy. The trend in pricing of new therapies has been steadily upward with cost in the range of US \$55,000 to \$100,000 currently being obtained. Oncology drug

pricing has recently come under scrutiny, and if prices go too high, the legislature would probably consider instituting some limits. Co-payments are becoming a concern, however; Medicare patients have to pay 20% out of their own pockets – a significant sum considering the annual cost of some treatments. Nevertheless, secondary coverage is available, and many drug companies have programs to help patients.

In the United States, payers and oncologists consider cost to be of lower priority than clinical measures (Fig. 1). Sixteen payer plans do not consider the cost of cancer treatment in their coverage decisions at all, largely because they follow Medicare coverage which is required to pay for approved oncology therapeutics. However, oncologists' treatment choices can be affected by their perception of patients' ability to pay.¹

Favril is the manufacturer of a personalised active immunotherapy product for B-cell non-Hodgkin's lymphoma known as mitumprotimut-T (Favil[®], Id-KLH, Idiotypic vaccine) which is given together with granulocyte-macrophage colony-stimulating factor (Leukine[®], sargramostim, GM-CSF). It is custom-prepared from individual patients' tumour cells. Currently in phase III trials, this immunotherapy appears to meet the criteria of what the Centres for Medicare and Medicaid Services (CMS) would consider an oncology therapeutic.

There are four main issues of concern for the reimbursement of active immunotherapies in the United States: (1) Coverage under Medicare Part B (physician administered) for a non-intravenously administered (i.e. sub-cutaneous or intra-muscular) product will require justification for the treatment to not be considered self-administered (2) Co-administration of GM-CSF (Leukine[®], sargramostim) will require coverage for use with the active immunotherapy (3) 3rd party payer misconceptions that this treatment should be covered in the same manner as prophylactic vaccines, which are generally sub-optimal in the US, and needs to be pro-actively addressed. (4) Coverage of a processing fee could be problematic as this is usually associated with diagnostic procedures not therapeutics.

In the European Union, drug costs continue to be an issue despite strict protocols for the use of expensive oncology products. Centralised procedures exist for the assessment of new products and their cost-effectiveness, the most well known being NICE in the United Kingdom. Furthermore, the majority of cancer care in Europe is delivered through specialised, tertiary care centres or hospitals. These centres for the most part have fixed annual budgets and treatment decisions are guided by set protocols. An expensive new oncology therapeutic, such as an active immunotherapy, must have sufficient supportive clinical and pharmacoeconomic evidence to change these protocols and compete for the limited financial resources of the institution. Gleevec[®] is an example of an expensive, novel, oncology therapeutic that has achieved success in Europe despite these hurdles – sales in Europe as a percentage of global sales exceed those of the US.

In summary, reimbursement is not a significant concern if the following criteria are met:

- Significant improvements in meaningful clinical endpoints are demonstrated (e.g. time to disease progression, overall survival in randomised studies).
- Payment and reimbursement should be on a final per-product-vial basis; avoid processing charges, which can complicate the reimbursement process.

Cost: Lower priority than clinical measures for payers and oncologists

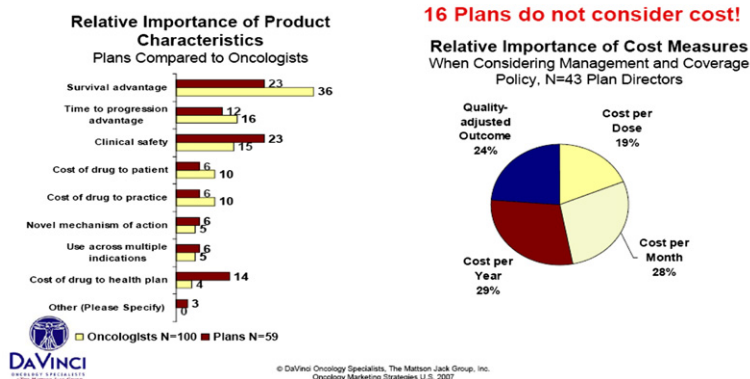


Fig. 1 – Cost is of lower priority compared with clinical measures for oncologists and payers (chart on left) when it comes to choosing therapies. The right-hand figure shows relative importance of various factors considered by payers making decisions about treatment coverage.²

- The price of the product should reflect the improvement in patient outcomes. About \$55,000 per annum for a novel therapy is the current US benchmark, and Euro 55,000 per quality-adjusted life year (or progression-free year) is probably a reasonable assumption about the practical price limit in Europe. In the United States, patient assistance programs and co-pay assistance can help patients obtain reimbursement and minimise the possibility that co-payments would limit use. For Europe, a pharmacoeconomic study is needed.

Increasing cost containment is already taking place in both Europe and the United States.

When considering clinical trial design, appropriately sized patient subgroups with a higher likelihood of a treatment benefit should be prospectively defined to increase the likelihood of a positive outcome of the study. Furthermore, clinical end-points, the efficacy improvement required in the treatment arm and the control arm selected should all be considered with pharmacoeconomic and reimbursement relevance in mind. Ideally, future pivotal trials should include a built-in pharmacoeconomic assessment.

CONFLICT OF INTEREST STATEMENT: David Guy the author of this report is a full time employee of Favril, Inc., he can confirm that there is no conflict of interest involved with any matters presented in this paper.

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ERLOTINIB IN PANCREATIC CANCER

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Pancreatic cancer is the fourth leading cause of cancer death and has a median overall survival of 6 months. The median progression-free survival time (PFS) is 3 months. One-year overall survival is about 19%, and the 5-year overall survival is about 2%. Gemcitabine used to be the only approved agent for treating the disease in the European Union.

Both epidermal growth factor receptor (EGFR) and Her-2/neu are overexpressed, activated, or both in most pancreatic cancers¹. *In vitro* data and animal models support EGFR as a potentially promising agent in pancreatic cancer,² providing a rationale for use of erlotinib (Tarceva®), an orally available, reversible tyrosine kinase inhibitor of EGFR.

A phase III trial of erlotinib plus gemcitabine compared with gemcitabine monotherapy in patients with advanced pancreatic cancer³ revealed no significant difference in the sum of complete responses plus partial responses, but a difference was detected when stable disease was also considered. A comparison of overall survival in the two study arms revealed little difference, but PFS was slightly but significantly improved among patients receiving the combination therapy. The advantage in PFS became apparent at 3–4 months of treatment, after which the curves for both study arms were parallel (Fig. 1).

In sum, the combination of erlotinib plus gemcitabine improved overall survival by about 12 days by delaying progression of disease. Side effects such as rash and diarrhoea were more common in the combination-therapy group, but grade 3 or 4 toxicities were rare in both groups. Interestingly, patients who received combination therapy and experienced skin toxicity exceeding grade 1 in severity had better overall and 1-year survival.³ Exploratory subpopulation analyses suggest that patients in generally good condition or with distant metastases may derive enhanced survival benefit.