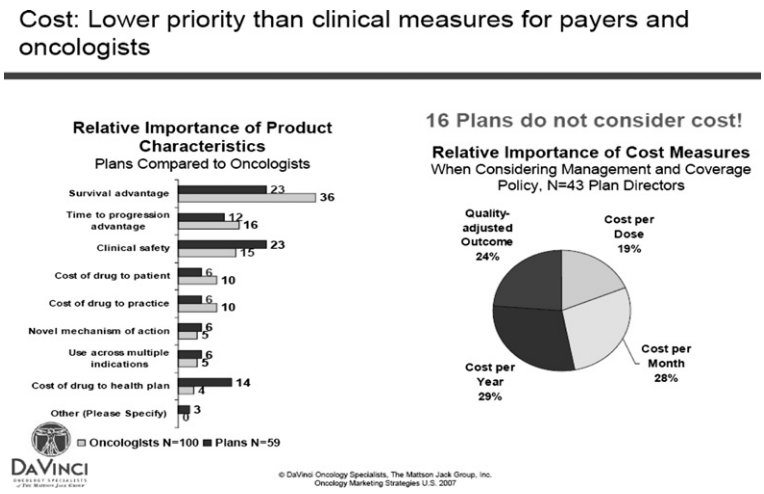

Fig. 1 – Cost is of lower priority compared with clinical measures for oncologists and payers (chart on left) when it comes to choosing therapies. The right-hand figure shows relative importance of various factors considered by payers making decisions about treatment coverage.[2]

- 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 Favrille, 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 cancers[1] *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 cancer[3] 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 grade1 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.

Both the study design and results can be criticised, noting that the benefit conferred by the erlotinib and gemcitabine combination therapy was very limited (i.e., 12 days). No tumour biopsies were taken to discern which patient subgroups might benefit more from the addition of erlotinib to their treatment regimens. Certain subgroups appear to have increased overall survival with the combination therapy (those who experience ⩾grade 1 rash or have distant metastases), but this aspect of the study was not sufficiently powered to explore possible correlations via subgroup analyses. Also, exploratory subpopulation analyses have not been the basis for further confirmatory studies.

Ultimately, both the FDA and EMEA approved the erlotinib–gemcitabine combination therapy. Committee members struggled with whether such a small survival improvement – which could be accompanied by an increase in diarrhea and skin rash – was enough to justify an approval recommendation. In the end, most committee members agreed that the approval would be an important 'first step' toward new options for what is an almost uniformly fatal form of cancer'.[4]

Several questions were posed for the BDA delegates' consideration:

- Is a median survival advantage of 12 days a clinically relevant benefit in pancreatic cancer?
- Is there a positive balance between benefit and risk?
- Which is the most relevant endpoint in the demonstrated study design (overall survival, PFS, relative risk)? Is the primary endpoint of overall survival the most meaningful in this setting?
- Can therapy decisions be based on initial side effects as a surrogate marker for survival?
- Which translational research data would have been of relevance for a better study design to avoid ineffective treatments in nonresponding patients?

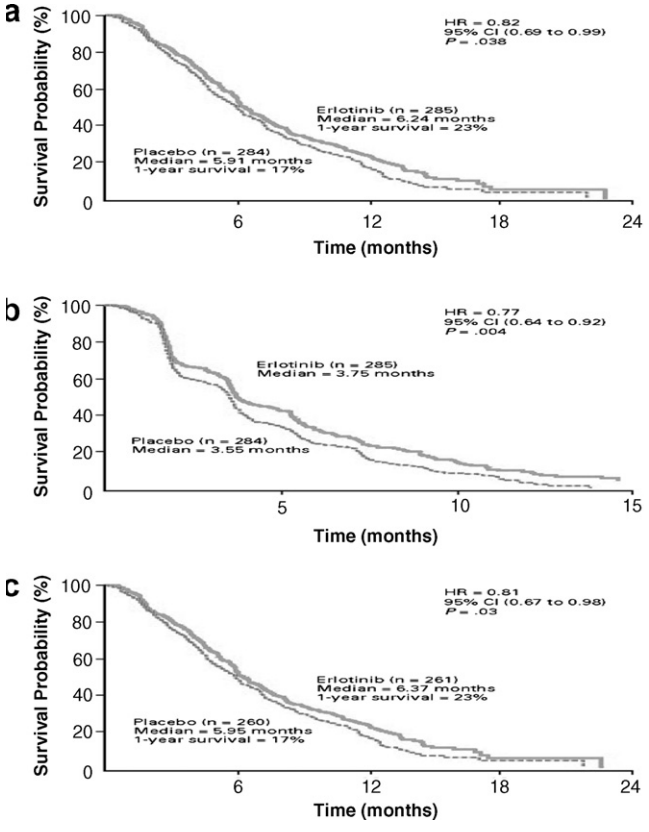

Fig. 1 – One-year overall survival of patients on gemcitabine plus erlotinib compared with gemcitabine monotherapy.[3] OS = overall survival; HR = hazard ratio, KI = confidence interval. Reproduced from J Clin Oncol 2007;25(15):1960–6.

It was acknowledged that the shape of the survival curves says a great deal about the effect of the drug combination; given the hazard ratio, the benefit appears to translate to 5 or 6 weeks, a clinically relevant benefit. But the advantage seems to be limited to a particular subset of patients. The lack of translational research connected to the clinical trial seems to represent a lost opportunity. It would have been interesting to examine more closely which patients derived benefit from the erlotinib–gemcitabine combination. Also of note, a patient must be alive to experience drug side effects, such as rash. Thus one would certainly expect a correlation between side effects and survival.

L. Bergmann underscored the necessity of undertaking a risk–benefit analysis when considering whether to approve a drug. To a patient with pancreatic cancer, is living another 12 days in such a situation really worth the risks of treatment? Fox, speaking as a patient advocate, said that another 12 days, even with diarrhoea and rash, might be very compelling to some patients. It is of critical importance to provide clear, forthright information to patients so that they can make such decisions.

CONFLICT OF INTEREST STATEMENT: Prof. Dr. med. L. Bergmann discloses that there is no financial or personal relationship that could inappropriately influence the work carried out or in publication of this report.

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