THE LANCET

Volume 371 · Number 9625 · Pages 1637–1722 · May 17–23, 2008 www.thelancet.com

"The search for a safer cigarette is akin to alchemists seeking to turn lead into gold."

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better than bortezomib, and so on. However, instead of continuing this trajectory, researchers are increasingly introducing new treatment combinations in small phase II trials, thus avoiding direct head-to-head comparisons of the key treatment options available. Is melphalan–prednisone–thalidomide or lenalidomide–dexamethasone better than bortezomib in combination with melphalan–prednisone? Do new drug combinations obviate transplantation? Is lenalidomide–dexamethasone better than bortezomib–doxorubicin in a salvage setting?

Current commercial and public interests are not aligned to answer these questions. The answers are important for patients but not for drug manufacturers, which are reluctant to sponsor trials because of the fear that their drug might turn out to be inferior to a competitors'. When commercial and public interests diverge, all too often clinical research produces meaningless results that serve no one. Here is where public funding must step in: we should not wait another 30 years for the convergence of public and industry interests to get the answers patients need now.

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We declare that we have no conflict of interest.

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Alchemy, the safer cigarette, and Philip Morris

20 years ago Philip Morris, the manufacturer of Marlboro cigarettes, noted in its annual report to shareholders that the company accounted for just 7% of worldwide cigarette sales, but added determinedly that "since our share of most international cigarette markets is still far below our US level, we have considerable room for future growth".[1] The prophetic rise in Philip Morris' market share of current global cigarette sales to 15·6% has culminated in the March spinoff of Philip Morris International (PMI).[2] This means that PMI, newly headquartered in Lausanne, Switzerland, is now an entirely separate corporation that is traded on the New York Stock Exchange, as is Altria, which is the parent entity of Philip Morris USA (as well as a new cigar acquisition, John Middleton).

PMI is the world's most profitable publicly traded tobacco company, with operations in 160 countries. Yet just 5% of PMI's profits are from Asia and Eastern

Europe, which account for 60% of international cigarette consumption.[3] Now with a headquarters in Switzerland and thus with far less exposure than in the USA to tobacco-product litigation, federal and state regulations, antismoking activism, and strict prohibitions on public smoking, PMI is introducing a host of new cigarette products targeted at these emerging markets.[4-6]

The spinoff of PMI and its global marketing push would seem to contradict Philip Morris' carefully cultivated image of social responsibility in the USA in recent years, as epitomised by its breaking ranks with the rest of the industry to support putative regulation of tobacco products by the Food and Drug Administration (FDA), by its advertising campaigns touting the company's charitable giving, and by the name-change of its parent corporation to the altruistically sounding Altria.[7-9] Could Philip Morris' makeover have diverted attention from the move of most of the company's assets to a safe haven?

The vestigial entity, Philip Morris USA, remains America's dominant cigarette-maker by far, with a 50% share of a declining but still highly profitable market. In Richmond, VA, USA, where it has consolidated all operations, the company has opened a US$350-million research centre that will employ 500 scientists, engineers, and technical staff. Chief executive officer Louis Camilleri (whose masterminding of the company's expansion into developing nations propelled him into its top job) has promised that the facility will be "dedicated to enhancing scientific research, developing new technologies and new products that might help address the harm caused by smoking".[10]

With this tactic, the company may be counting on the public's short memory. Indeed, the gleaming Philip Morris Center for Research and Technology is the tobacco giant's fourth such incarnation since the 1950s ostensibly aimed at eliminating the risks of smoking. And Philip Morris' newly professed commitment to public health is reminiscent of the ignominious "Frank statement to cigarette smokers", a 1954 advertisement in major newspapers written by the newly formed Tobacco Industry Research Committee (which included Philip Morris) after cigarette sales flattened on the heels of growing evidence that smoking caused lung cancer. "We accept an interest in people's health as a basic responsibility, paramount to every other consideration in our business", asserted the Committee, which pledged "aid and assistance to the research effort into all phases of tobacco use and health".[11]

Yet in the ensuing half-century, virtually all reports of diseases caused by smoking were disputed by the tobacco industry, which claimed that more research was needed.[12] Only in 1999, confronting massive litigation, did Philip Morris acknowledge "the overwhelming medical and scientific consensus that cigarette smoking causes lung cancer, heart disease, emphysema, and other serious diseases in smokers".[13] Meanwhile, as millions died from cigarette smoking, research funded by the tobacco industry resulted in a plethora of filters, "low tar" products, "reduced emission" cigarettes, and "mild", "light", or "ultra-light" brands, none of which has made smoking safer.[14,15]

The hoopla over Philip Morris' new centre (the company has even advertised for researchers in *Science*) is synergistic with its backing of the bill to permit FDA regulation of tobacco products. The imprimatur of the FDA would provide much-needed credibility for research initiated by Philip Morris now that the company has been found by Federal Judge Gladys Kessler (Aug 17, 2006) to have violated civil racketeering laws over a 50-year period by deceiving the public about the dangers of smoking, by manipulating the design of cigarettes, and by suppressing research.[16]

A Frank Statement To Cigarette Smokers

RECENT REPORTS on experiments with mice have given wide publicity to a theory that cigarette smoking is in some way linked with lung cancer in human beings.

Although conducted by doctors of professional standing, these experiments are not regarded as conclusive in the field of cancer research. However, we do not believe results are inconclusive, should be disregarded or lightly dismissed. At the same time, we feel it is in the public interest to call attention to the fact that eminent doctors and research scientists have publicly questioned the claimed significance of these experiments.

Distinguished authorities point out:

That medical research of recent years indicates many possible causes of lung cancer.

That there is no agreement among the authorities regarding what the cause is.

That there is no proof that cigarette smoking is one of the causes.

That statistics purporting to link cigarette smoking with the disease could apply with equal force to any one of many other aspects of modern life. Indeed the validity of the statistics themselves is questioned by numerous scientists.

We accept an interest in people's health as a basic responsibility, paramount to every other consideration in our business

We believe the products we make are not injurious to health.

The 1954 advertisement in US newspapers
Start of the advertisement signed by 14 tobacco companies and trade associations.[11]

Since existing brands will remain essentially untouched by the FDA bill, Marlboro, with a 41% US market share (or more than five times that of its nearest competitor), is unlikely to experience a significant sales decline. Philip Morris will thus continue to have deep pockets to promote the chimera that research will make smoking safer. To this end, the company is increasing ties to academic medical centres, such as the University of Virginia, to which it has given $25 million.[17]

The search for a safer cigarette is akin to alchemists seeking to turn lead into gold. Perpetuating the myth to the medical community and the public at large may also be worth its weight in gold to Philip Morris.

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Trastuzumab: possible publication bias

Publication bias is of increasing concern, entrenching the use of inferior treatments.[1] This concern now extends to adjuvant trastuzumab (Herceptin) in women with early breast cancer that is ERBB2 (HER2) positive, because a key clinical trial[2] has been only selectively published.[3] As such, patients are being given an important treatment sequence that may be much less effective than currently thought.[4,5]

Adjuvant trastuzumab can be given in two main sequences: concurrently with or sequentially after other chemotherapy.[6] Sequential treatment is licensed,[4,5] is standard practice, and is the publicly funded regimen in many countries, such as most of Europe (UK included). One randomised trial (out of six relevant trials[6–8]), by the North Central Cancer Treatment Group (NCCTG), trial NCCTG-N9831,[7] has studied sequential and concurrent treatments head-to-head, together with a control or usual-care group. However, although this three-group study has important implications for how best to use trastuzumab, it has only been partly published. Data from the 985 women given 12-month sequential trastuzumab in this study are in effect missing,[4,5] despite publication of data from the 12-month concurrent and control groups of the same trial nearly 3 years ago.[9]

Interim results for all three groups of the NCCTG trial were presented orally in 2005 at the American Society of Clinical Oncology's annual meeting.[7] After 1·5 years of median follow-up, sequential trastuzumab gave a comparatively[4] small 13% relative reduction in disease events compared with usual care—with a reasonable chance of being no better than the control group (hazard ratio 0·87, 95% CI 0·67–1·13). Conversely, concurrent trastuzumab was significantly more effective than sequential therapy, reducing disease events by a third (0·64, 0·46–0·91).[7]

Soon after, Romond and colleagues published the concurrent and control group results from the NCCTG