Preface

Defining the Lung Cancer Problem

Lung cancer is the leading cause of cancer death in the world.\textsuperscript{1} It kills almost as many Americans as cancers of the breast, prostate, colon, rectum, pancreas, and kidney combined, and accounts for 28.6\% of all US cancer deaths.\textsuperscript{2} With an increase in the 5-year relative survival rate from 13\% to only 16\% in the more than 30 years from 1974 to the present,\textsuperscript{2} it will take us another 840 years to eradicate lung cancer deaths if we do not improve the current rate of progress.

As discussed in this text, lung cancer prevention has received substantial attention. The decrease in smoking in recent decades has helped, but smoking is not the only problem. Lung cancer in people who have never smoked is currently the 5th leading cause of cancer death in the United States.\textsuperscript{3}

Several factors contribute to the lethality of lung cancer, including the rapidity of tumor growth, advanced stage at diagnosis (due to nonspecificity of early symptoms and the uncertain efficacy of screening), early development of metastases, and resistance to therapy. Several chapters in this book discuss new molecular targets that may be potentially exploitable in the future, as well as discussing our track record to date in exploiting them.

Over the last few decades, we have made several errors that have slowed our pace in the war against lung cancer. For example, until recently, most nonsmall cell lung cancers were treated more or less as if they were the same disease. It has been postulated that common cancers are both common and resistant to therapy since many different mutations may give rise to them, and that each underlying mutation may require a different treatment approach.\textsuperscript{4} Hence, there may never be one silver bullet for lung cancer. We may need instead 20 or 30 different agents, each targeting a molecularly distinct subpopulation of patients. Large randomized trials ignore this possibility and try to overpower biological realities by using the statistical power of large patient numbers to achieve a significant p value. Hence, we have ended up with a variety of therapies that achieve statistical significance, but with survival gains of mere weeks.\textsuperscript{5}

There are two major problems with this. The first is that if the p value is not significant, a drug may be abandoned despite being of marked benefit in a small
subject to a subpopulation of patients, as happened with gefitinib. The other side of the problem is that when \( p < 0.05 \), the drug may be accepted as being “effective”, and the drug may be applied widely at high cost and potential toxicity, despite being of value in only a small subpopulation of patients. We feel that progress against lung cancer and other malignancies has been slowed by our placing the efficacy bar too low, using large randomized trials to eke out small gains.\(^5\) We would argue that we need small trials looking for large gains, not large trials looking for small gains. We need to molecularly characterize the tumors of all patients from the earliest phase I trials onward and use the results of this molecular profiling to identify those most and least likely to benefit from the therapy.\(^5\)

If we do randomized trials without fully characterizing patients, we may well be misled. For example, simulations suggest to us that if a new therapy quintuples survival in a 10% subpopulation of patients whose tumors express a particular target, this will be missed unless around 2,000 patients are included in the trial. If the new agent only doubles survival in this 10% subpopulation, then more than 5,000 patients may be needed to detect the benefit. As discussed earlier, at the end of the study, we will either conclude that the therapeutic approach is “effective” and inappropriately apply it widely, or we will conclude that it is “ineffective” and inappropriately discard it. If, however, one correctly identifies the required target, then one may get the correct answer (that the agent is effective in the subpopulation with the target) with fewer than 20 patients if survival is quintupled and with fewer than 100 patients if survival is only doubled. At $26,000 per patient (the amount that it currently costs per patient on a phase III trial\(^6\)), the money saved by reducing phase III trial sizes would pay for very extensive molecular profiling of every patient to ever participate in phase I and II trials of the agent, and correlating these profiles with % tumor shrinkage or with some other measure of tumor cell kill would go a long way toward defining the population that should subsequently be targeted in phase III trials.

There are also other problems with randomized trials in unselected patients. The study may indicate that the agent was not helpful when in fact benefit in one subpopulation was balanced by harm in another, as may be the case with EGFR inhibitors in patients with EGFR vs. Kras mutations.\(^7\) Furthermore, if an agent hitting a target present in 5% of the population is compared to another hitting a target present in 40% of the population, the agent hitting the more common target will win and will be the new “standard of care”. It will be incorrectly concluded that this agent is the “better” agent when in fact it is not: it just hits a more common target. If there is no exploitable target that is present in >40% of patients, progress will plateau and we would make no further gains. In addition, an agent which increases the survival of all patients by 30% (equivalent to increasing median survival from 6 months to 7.8 months) may consistently beat an agent which increases survival 5-fold in a 10% subpopulation, but we would argue that the latter agent is the more important one. Contrary to this, some newer statistical approaches such as randomized discontinuation strategies\(^8\) are specifically designed to try to identify small advances, and in our opinion contribute to the problem. Overall, as stated above, we feel that it is of paramount importance to molecularly characterize all
patients on study, and then to aim for large gains in appropriate subpopulations rather than using unselected patients to aim for small gains in large studies.\(^5\)

In addition to the efficacy bar being set too low, we feel that the safety bar has been set too high for fatal, incurable diseases like cancer.\(^5\) We recently calculated that increasingly stringent research regulations might have decreased toxic death rates by 0.3% for patients on study. However, with the cost of complying with these regulations running at an estimated $8,000 per patient studied and an estimated life expectancy for patients on study of 1 year, this translates into $2.7 million per year of life gained - an amount far higher than either other preventive measures or the figure of $50,000–$100,000 per year of life gained that is regarded as being acceptable for therapies.\(^9\) In addition, if 5,000–10,000 patients need to be treated on studies to make a small advance (e.g., a new therapy that increases cure rate of lung cancer by 1% through improved adjuvant therapy and that increases survival of incurable patients by a median of 3 months), the regulations would have led to a savings of 15–30 life-years (5,000–10,000×0.3%×1 year), but if the regulations slow the advance by a conservatively estimated 5 years, the regulation-induced delays will have cost 285,000 life-years in the United States and almost 2 million life-years worldwide, seriously challenging equipoise. We feel that the regulations governing cancer research need to change.\(^5\)

Overall, lung cancer remains a formidable foe. While we have made some progress, much remains to be done. In this book, we give a brief description of where we stand today, as well as offering a glimpse of the path forward.

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References

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