

# PRECISION & ACCURACY:

## A WAY FORWARD IN CANCER MEDICINE

by W. Gillies McKenna, MD, PhD

**W**e have reached a point where in the last 30 years your chance of surviving cancer has increased from 1 in 4 to roughly 50%. This is the good news, but the bad news is that your chance of getting cancer has also doubled over the same period, and the trend of increasing incidences shows no sign of abating. The problem is that cancer like dementia and cardiovascular disease is largely a disease of old age, and we as a society grow ever older, and live to ages our grandparents generation never dreamed of. Our progress against these diseases has been very mixed. Against cardiovascular disease we have made great strides, only to find ourselves as older people between the Scylla and Charybdis of cancer and dementia. How could we get ahead of the game and start curing people at a faster rate than the incidence is rising?

For 25 years we have been telling people that the answer is “personalized” therapy, and what we usually meant by that is some how using information derived from the genetics of cancer to treat cancer: using biologically targeted agents in therapies driven by biomarkers or genomic sequencing. The first evidence that cancer was a genetic disease came from the recognition of the Philadelphia chromosome by Nowell and Hungerford in 1960. They noticed a consistent rearrangement between chromosomes 9 and 22 in patients with CML. Further knowledge about this chromosomal re-arrangement showed that the two regions involved were the *abl* gene on chromosome 9 and a region and a region on chromosome 22 called the breakpoint cluster region (or *bcr*) on 22. This re-arrangement producing a new constitutively active oncogene, *bcr-abl*. Almost by serendipity one of the earliest biologically

### CURRENT PARADIGM

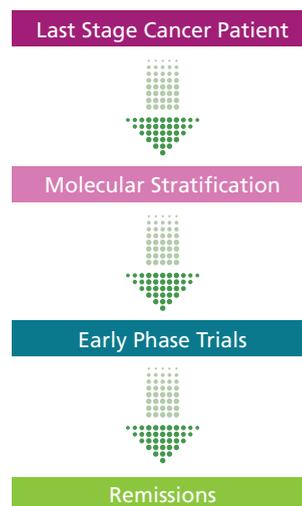


FIGURE 1: The standard paradigm for assessing molecularly targeted agents in early phase trials. Patients who have failed previous therapies are placed on trials on the basis of molecular stratification.

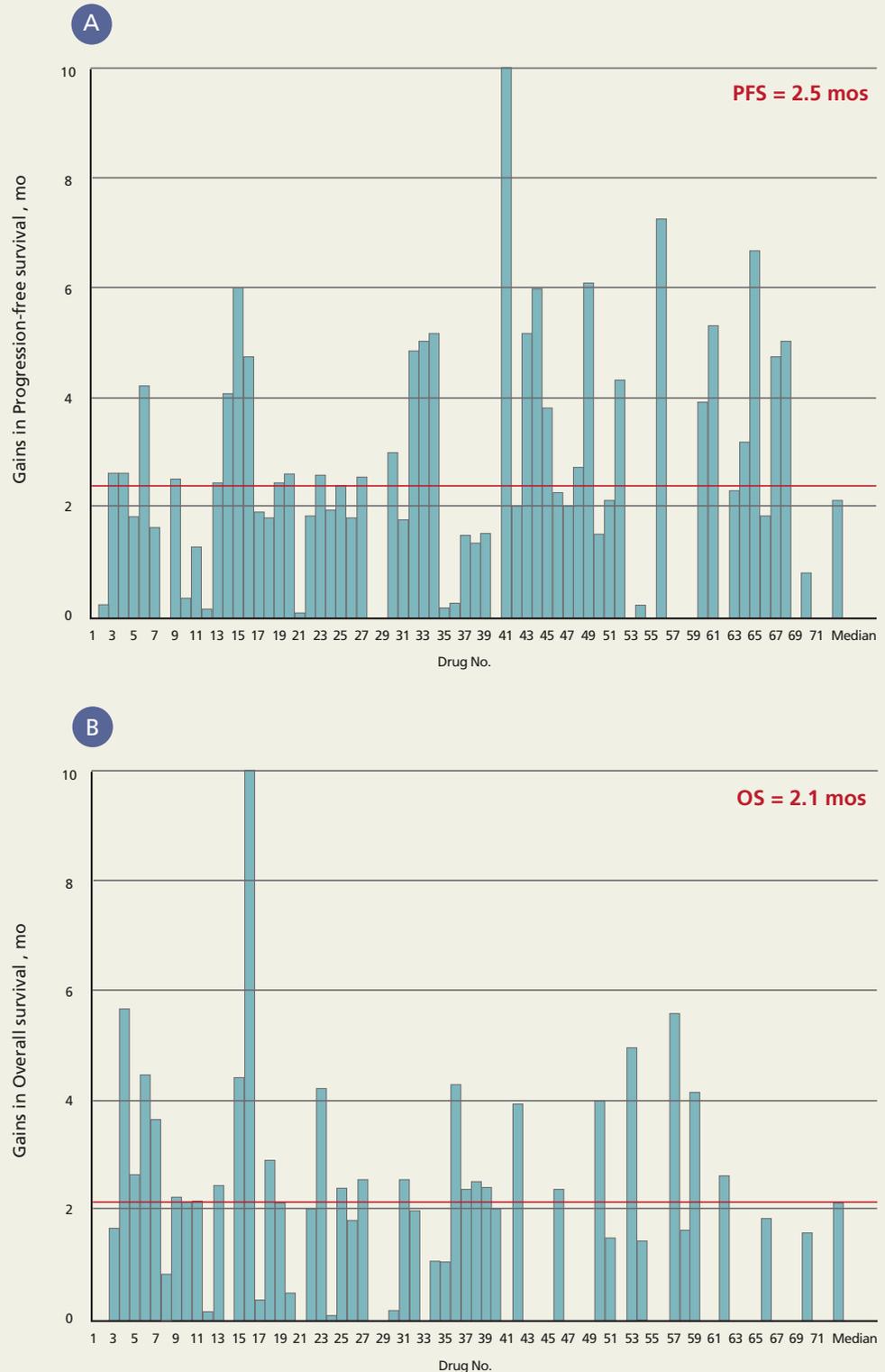
active drugs was also produced against this gene. When Glivec was given to patients with CML a large percentage went into what appeared to be sustained complete remission. Brian Druker, the clinician who led many of these early studies, was quoted as saying, “This is one of the best examples I’ve ever seen of science triumphing over disease.” Indeed, many oncologists thought the long awaited revolution in cancer care had arrived.

The fact that as time went on we confronted the reality that cancer had a bewilderingly large number of mutations was somewhat discouraging, but Hanahan and Weinberg, in two now classic publications, calmed our nerves somewhat by introducing the idea that although there were many, many mutations, they could be clustered into certain “hallmarks” or shared functions that all cancer cells must have

into order to become cancer. Thus all cancers had to evade growth suppression or induce angiogenesis. Their idea was that we needed to understand the unique hallmarks that were driving each cancer. This hallmark would be a clonally dominant trait; and for each hallmark there would be a drug. Knowledge of the hallmarks would produce new therapies that would work for each cancer the way Glivec worked for CML. Certainly the pharmaceutical industry seemed to buy into this view. As each new hallmark was identified there was a rush to bring targeted agents into the clinic. Thus, for example, sustained angiogenesis often seemed to be driven by altered expression of VEGF or VEGFR, and there are now close to 150 drugs targeting this pathway either already in the clinic or in preclinical testing.

We have now reached a point where we can begin to examine how this hypothesis is holding up. Within the last ten years we have recognized that 40-60% of patients with melanoma are carrying activating mutations of the BRAF oncogene. A number of drug companies tried to produce inhibitors of BRAF and Plexxicon was the first to get their drug, PLX4032 or Vemurafenib, into clinical trial. When this drug was first given to patients the results were often astonishing. Patients with widespread metastases saw them melt away. The results were so astonishing that they were widely reported in the lay press, and there was even some controversy about proceeding with the clinical trial. The New York Times managed to find two cousins both with metastatic melanoma, only one of whom was randomized to receive the drug, and they asked whether it was ethical to withhold such an obviously effective drug. In 2011, however, when Wagle et al. published the results of the trial a more disturbing picture emerged. It was true that many patients had dramatic responses but equally within a relatively short time all relapsed. The median overall improvement in survival was nine weeks. Indeed, in a recent review by Fojo et al. of the 71 drugs approved for treatment of disseminated cancer from 2002-2014, they showed that the median improvement in Overall Survival for all 71 drugs

## 71 drugs approved for Cancer by the FDA 2002-2014

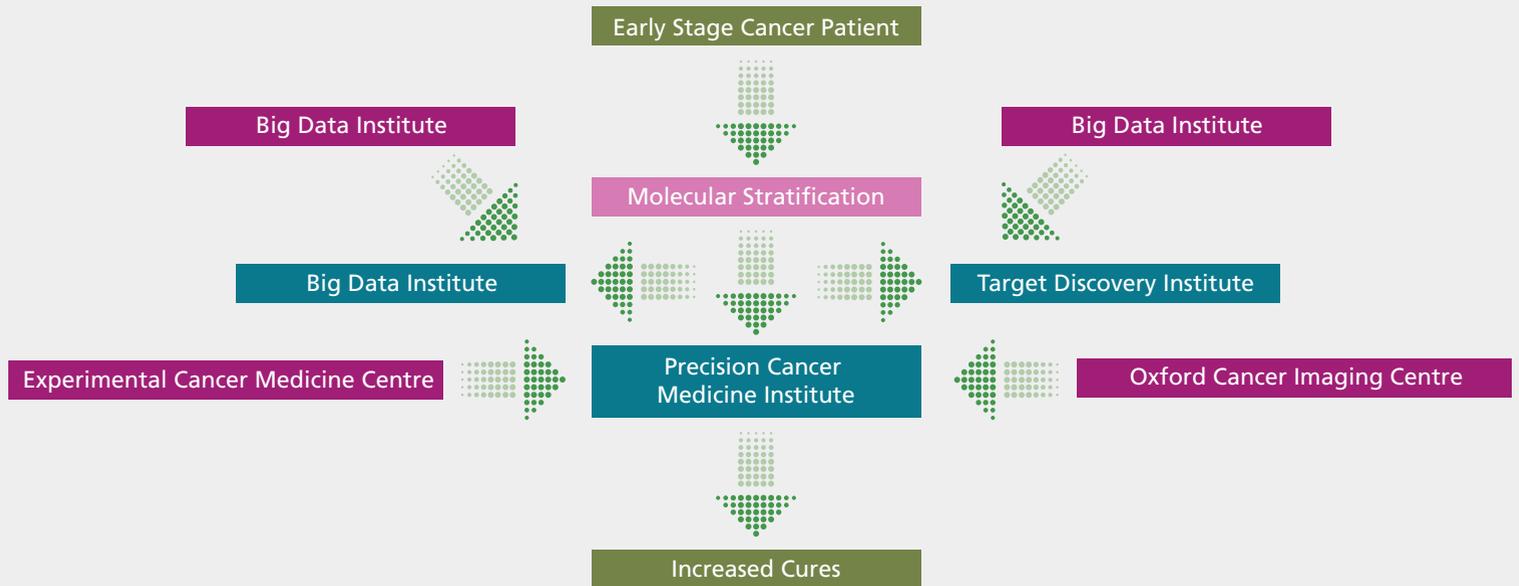


was 2.1 months. Vemurafenib turns out to be much closer to the norm than Glivec.

Some insight into what may be going on comes from the work of Swanton. He studied renal cell carcinoma and instead of sequencing a single sample he took samples from different parts of the same tumor and from several sites of metastatic disease. As predicted he found many mutations. He then classified the

FIGURE 2: Gains in progression-free survival (PFS) and overall survival (OS) for the 71 drugs approved by the FDA from 2002 to 2014 for advanced cancer. Adapted from Fojo et al. JAMA Otolaryngol Head Neck Surg. 2014;140:1225-1236.

## THE NEW PARADIGM



New institutes represent \$400 million investment in Oxford

mutations into whether they were ubiquitous, shared or private. By ubiquitous he meant they were found in all the samples regardless of where the biopsy was taken. Shared meant that some but not all of the biopsy sites showed the mutation, and by private he meant they were unique to the site of the biopsy. What he found was that the ubiquitous mutations were uncommon, indeed rare, and that by far the largest number of mutations were private, i.e. not shared with any other site even within the same tumor from a single patient. When he expanded the study to look at a larger number of tumors from multiple patients an even more discouraging result emerged. Different biopsy sites from the same tumor within a single patient were often no more related to one another than were tumors derived from different patients. This was a very disturbing result for the concept of personalized therapy. We had always anticipated that each patient might need a unique solution, but if different parts from even a single tumor were not more related than tumors from different people how could personalized therapies be developed. Swanton's own conclusion was that clonal dominance was an illusion, and this was a key concept for the

application of therapy targeting hallmark lesions. Furthermore, he suggested, "The presence of subclonal driver events in solid tumours may provide an explanation for the inevitable acquisition of resistance to targeted therapeutics." This study was limited to renal cell carcinoma, but Vogelstein's group had come to a very similar conclusion looking at the evolution of "acquired" resistance to targeted EGFR blockade in colorectal cancer. The resistance was not "acquired" in response to treatment but was present as resistant subclones before treatment was initiated, and what appeared to the clinician as a "response" was simply the time required for the resistant subclones to re-populate the lesion. "Resistance is therefore a fait accompli," they concluded.

These disturbing results may explain some other equally disturbing data. Oncology has the lowest success rate for introducing new therapies into the clinic of any field of medicine. 95% of the drugs in the pipeline never make it into the clinic. Drugs for cancer fail at all stages of development, from phase 1 trials to registration. 70% of oncology drugs

FIGURE 3: A new paradigm for early phase trials in therapy naive patients with early stage disease. This paradigm for windows trials takes advantage of the windows of opportunity that exist within standard regimens of curative therapy to use molecular and functional imaging to determine the ability of molecularly targeted agents to hit their targets and modify the behavior of the tumor cells. Agents will be chosen based on molecular stratification of the patients, but also using big data analysis to determine which pathways are most likely to yield targetable lesions.

that enter phase 2 fail to enter phase 3, 59% of oncology drugs that enter phase 3 also fail. And some evidence suggests that the failure rate may be increasing for the novel targeted agents. The simple fact is that although we have been talking about personalisation of cancer therapy for 25 years, nobody knows how to do it. And a consequence is that what we brand success seems to be purchasing ever smaller increments in survival at ever increasing cost. This is hardly surprising since Pharma seeks to recover the high cost of failure from the trickle of novel agents that reach the clinic. Drugs costing hundreds of thousands of dollars for a course of treatment become ever more common and the million dollar drug may be in sight.

I started this opinion piece however by pointing out that the chance of surviving cancer had never been higher. How can this be true? If we examine what leads to cure it is apparent that 90% of all the patients who are cured of cancer are cured still by surgery or radiation therapy, and two factors have enabled them to maintain their predominant role in curative cancer therapy: early diagnosis and the development in minimally invasive treatments. Although less publicized, at least in the popular press, neither surgery nor radiotherapy have stood still in the 25 years. From the first developments in laparoscopic (keyhole) surgery in the 1960s to modern robotic surgery surgeons have continuously moved to more effective but less invasive and debilitating treatments. New tools continue to be developed for them in imaging, and in adjuncts to resection such as HIFU, cryotherapy and PDT. Radiotherapy has in some ways followed a very similar trajectory. Beginning with the wide-spread availability of the linear accelerator by the 1970s, radiation oncologists too have continuously refined their technology and techniques towards more precise and less toxic treatment. Intensity Modulated Radiation Therapy (IMRT) and Image Guided Radiation Therapy (IGRT) are routinely available in clinics around the world. These developments in surgery and radiotherapy were largely driven by the revolution in imaging that has occurred in the last 25 years. The earliest CT scanners in the 1970s gave fuzzy views of the brain, but the full gamut of modern imaging with CT, MRI, PET, dynamic imaging, image fusion and so on, mean that not only is diagnosis and staging immensely more accurate, but also means that the surgeons and radiation oncologists are working in a much more precise space with much more knowledge of how to plan and execute their therapies.

Given this, how do we derive from this a new strategy to improve the outcomes of cancer treatment? It can surely not be the case that we conclude that there is no future in molecularly targeted therapies. Cancer is fundamentally a genetic disease, where we are failing in using this knowledge to develop strategies for

improving the outcomes of cancer treatment. It is possible that the genetic diversity of cancer is so great even in very early disease that molecularly targeted agents will never provide more than very temporary extensions of survival. Another possibility is that we are looking for effect in the wrong population. That by always assessing novel agents in the setting of very advanced disease that has already failed treatment we are maximizing the probability that we will fail to detect a response. It may be that we are even discarding agents that might have been useful if used in another setting. The successes in cancer treatment in the last few decades have come from combined modality treatment in patients with early stage disease. Could we use the concept of Precision Medicine to change the paradigm for looking for novel therapies to that setting? Could we transform the paradigm into one where we focus on early stage, therapy naïve patients and use them to look for combinations of molecular and interventional therapies that would optimize the chance for cure?

To do this would require an integration of a number of elements into the treatment path. Target discovery would have to be linked with capabilities from big data analysis and molecular and functional imaging into pathways that would still offer the patients access to state of the art interventional therapies that would maximize their opportunity for cure. This definition starts by optimizing the physically targeted interventions that would yield the maximum opportunity for cure with minimal toxicity. This means having capabilities to continually upgrade the interventional facilities to provide capabilities such as robotic surgery, or particle therapy of HIFU, as the case demands. It requires state of the art functional and molecular imaging, not only to guide therapy but also to monitor therapy, since imaging may frequently be used as a surrogate endpoint for detection of response. Finally, it is in this setting that one would seek to introduce molecularly targeted therapies, biologically targeted agents, or trials driven by genomic sequence information or biomarkers. A Precision Cancer Medicine Clinic to carry out such research

would require five components: Molecular Diagnostics, Molecular Imaging, A Window of Opportunity Trials Unit, Advanced Radiotherapy and a Minimally Invasive Interventions Center.

Molecular Diagnostics is a critical component because each treatment plan and trial will need to be driven by a full characterization of a patient's tumor before entry into any trial. This must go beyond DNA sequence analysis to RNA sequencing and proteomics and the ability to analyse microRNAs and epigenomics. Analysis of histopathology must extend to digital pathology and cloud pathology, use of novel antibodies and superresolution microscopy. These must all be linked by enhanced clinical informatics with a data warehouse and the ability to create extended integrated genotype-phenotype reporting. Molecular Diagnostics must be forward looking to novel areas of phenotyping. The exact role that cancer immunology will play in the future is still unknown, but its role in research is already apparent. Therefore the Molecular Diagnostics unit must be capable of immunoproteomic characterization, and identification and quantitation of immune cells including not only T and B cells but also components of the innate immune system such as macrophages and neutrophils. The center must be capable also of quantitating other biomarkers, such as exosomes, circulating DNA and tumor cells and metabolomics. The aim will be to derive as much information as possible from small numbers of patients, intensively studied, than from large numbers superficially analysed. Links to big data will be essential. It is already that the genetic diversity of cancer cells suggests an almost exponentially large number of evolutionary paths, and in such a setting models outgrow computation. Therefore we will need big data analysis so that we do not naively simulate all possible mutational histories but rather try to target the histories that matter most.

To then use this information to study novel agents we need two additional components: Molecular Imaging and a Windows Trials Unit.

Windows Trials, or window of opportunity trials, take advantage of the natural breaks that occur in conventional therapy to introduce the study of novel interventions. Thus, for example, if an early stage cancer patient were to be referred for potentially curative radiotherapy, an interval could extend for several weeks between diagnosis and the initiation of a course of radiation treatment. This interval is not due necessarily to inefficiency, but is simply due to the fact that developing a treatment plan for some of the more advanced forms for radiotherapy involves often several weeks of additional imaging studies and complex treatment planning before the therapy can be delivered. Thus, this interval could be used for evaluation of novel molecularly targeted agents, in a window of opportunity trial, with the use of molecular imaging as a surrogate endpoint of response. We have carried out such studies looking for a response to avastin in breast cancer patients prior to lumpectomy, to focus on agents that improve tumor hypoxia prior to radiation treatment in lung cancer and in other similar studies. Window of opportunity trials will not tell you about efficacy but will enable you determine whether a drug is hitting its proposed target and whether it's having a desired biological response. Data from the FDA DataMonitor in 2011 suggested that even among the top 15 approved molecularly targeted agents more than half the spend of multiple billions of dollars was in giving the drugs to non-responders. Establishing response early in a drug's development could not only improve the path to the clinic but could do so with substantial societal benefit.

To enter a window of opportunity trial for a patient with a potentially curative tumor there must be no trade-off for the patient. Therefore, a precision medicine clinic must offer access to state-of-the-art interventional therapies. Surgery and radiotherapy have maintained their pre-eminent role in curative cancer management by continuously moving towards less invasive, more accurate and less

toxic treatment. These qualities have not only enabled curative treatment to be extended to more patients, but they are also the qualities that allow surgery or radiotherapy to be more easily combined with systemic treatment, avoiding unnecessary normal tissue toxicity and enabling synergistic interaction. Particle therapy centers offer many possibilities for such trials. Since there is no normal tissue that benefits from any dose of radiation, and since radiation side effects typically occur in irradiated tissue, the targeted nature of Particle Therapy in confining the high dose region offer many unique opportunities to explore radiation - drug interactions. Furthermore they offer unique opportunities for hypofractionation of treatment which may be a key mechanism for maximizing the response to immune modulators as one of many examples. This is not the only technology that should be considered. The MR-Linac offers not only the ability to perform some forms of functional imaging actually during radiotherapy delivery, but again by tracking intrafraction motion during treatment offers the possibility for correcting treatment failures that may result from tumor motion. There are similar opportunities for adding additional imaging capabilities during robotic surgery that would extend the surgeon's field of vision outside the visible spectrum, creating the possibility of intraoperative molecular imaging. A precision cancer medicine clinic should be intent in going beyond simply the delivery of molecularly targeted systemic agents or improved molecular diagnosis but should also aim to continuously refine the interventional techniques that continue to play such a key role in curative cancer management.

While cancer outcomes have improved over the last decades, the advances have not been uniform. Many cancer types have shown little improvement in that time. These would include brain tumors, esophagus, pancreas and lung. These are all tumors in which surgery and radiotherapy are the only therapies that offer

any curative potential, but where the outcomes even with the most aggressive treatments remain poor. These are ideal tumors to be addressed in a Precision Cancer Medicine Center. Applications of molecular diagnosis, molecular imaging and molecularly targeted agents could be readily assessed and the outcomes of such interventions could be readily detected. Surgery and radiotherapy could still remain central to the management but there would substantial opportunities to improve the translational pipeline toward more effective treatment.

**Professor Gillies McKenna** is a world expert in radiotherapy research. In 2006, he was recruited to the UK from the US to lead the Cancer Research UK - MRC Gray Institute for Radiation Oncology and Biology in Oxford. His research has focused on effects of radiation on cancer cells and on mechanisms of resistance to radiation with the goal of sensitizing cells to radiation by blocking mechanisms that control cell survival. Specifically he is interested in oncogenically activated signal transduction pathways that exert a radioprotective effect on tumor cells. His group has shown that the EGFR-Ras-PI3K-PTEN-Akt pathway appears to be the major radioprotective pathway active in most solid tumors and this pathway then presents targets that could be manipulated in a clinical setting to modify the radiation response. His clinical interests are the treatment of lung cancer, soft tissue sarcomas, skin cancer, head and neck cancer, and melanomas.