Message to Returning Walkers – June 1, 2014

Welcome home! I am glad the weather was so much kinder to you this year! Congratulations on completing another wildly successful Just 'Cause walk. I am so sorry that I am unable to be with you this year. As I am writing this I am on my way to Chicago to attend the annual meeting of the American Society of Clinical Oncology. I am hungry to hear what is new in clinical cancer research, and eager to bring back new therapies to the clinic.

I promised I would give you an update on the state of breast cancer research at MGH. It has been a very exciting year. Technology is advancing rapidly, and we are now able to analyze and understand cancers in much more detail than we have ever been able to do before. You will hear a number of seasoned clinical researchers profess that we are finally near to finding cures for cancer (note that I say "cures", not "cure" because cancer is not a single disease but many diseases and the cure will be different for each).

Just a couple of years ago, on the heels of the first successful sequencing of the human genome, leading cancer researchers were able to sequence the entire genomes of some cancers through great effort and enormous cost. Through a quantum leap in technology called massively parallel sequencing they are now able to sequence a cancer genome in a much shorter time and at a reasonable cost. But with this accomplishment comes the danger of information overload – there are too many alterations in a cancer cell compared

to a normal one for us to see easily and clearly what the critical changes are.

Fortunately, out of chaos is now coming order. Although each individual cancer might have hundreds of mutations in its DNA, when the mutations in the different cancers are lined up for comparison, the exciting discovery has been that there seem to be only a few hundred "driver" mutations responsible for promoting growth of all cancers. Driver mutations are the important ones – the ones that make a cancer cell cancerous. The global mission of cancer researchers is to understand, and be able to target, each one of these driver mutations.

A major focus of today's breast cancer research is to identify, in each individual's cancer, which mutations are the drivers. I told you last year that we have been using a tool called the SnapShot to identify the driver mutations in recurrent breast cancers in order to match them up with appropriate targeted therapies. This work is going well, and we have just introduced the 2nd generation SnapShot test. We are now able to demonstrate over 160 of the critical changes that can occur in breast cancer cells in over 2 dozen of the genes for which we have candidates for targeted therapy.

We can identify mutations that might be targetable in more than half of the breast cancers we are testing. Some of these mutations can be matched up with drugs already on the market, but most of the time the presence of the mutation points the way

to participation in a clinical trial designed to exploit the dependence of the cancer cell on the pathway activated by the mutation.

For example, it has recently been discovered that the receptor for estrogen, present in 75% of breast cancers, becomes mutated in at least 30% of these cancers with the passage of time after they have spread within the body. Our current anti-estrogens may not recognize this mutated molecule and are therefore ineffective. We are therefore trying to match up these cancers with a new anti-estrogen that has the ability to bind the mutated receptor and inactivate the estrogen pathway; preliminary results are very encouraging.

Similarly, in HER2 positive cancers, which represent 20% of breast cancers, mutations in genes downstream from the receptor itself can overcome the benefit from inhibiting the receptor with the HER2 targeting antibody Herceptin, and we are having encouraging results from targeting the pathway activated by HER2 at these downstream positions.

The hardest cancers to treat are the so-called triple negative. These do not have receptors for estrogen, progesterone or HER2, the natural targets for most of the successful therapy in the majority of breast cancers. It has been found that some of these have developed mutations in the same pathways as those that occur in women with inherited mutations in the BRCA genes. We are having more success treating these women with platinum drugs which are not otherwise widely used in breast cancer, and with new

drugs called PARP inhibitors which show promise in the BRCA population.

But the most exciting development in treating the triple negative breast cancers is coming from a totally new discovery, namely that we can use the patient's own immune system to fight the cancer. The background for this discovery came from research on treating malignant melanoma. We have known for years that this type of cancer can sometimes be put into a durable remission, most likely a cure, if the immune system can be activated to reject it. The therapies were, however, quite complex and toxic and only worked in a small percentage of patients. A major breakthrough occurred when it was discovered that many of these melanomas carry a molecule on the surface of the malignant cells that is actively inhibiting the immune system from attacking them. When this molecule is itself inactivated by means of a targeting antibody the immune system is able to attack and eliminate the cancer.

So here is the really exciting news: the cancer cells of about one third of the patients with triple negative breast cancers also express this inhibitory molecule. We have recently opened up one of the clinical trials using the antibody that attacks this inhibitory molecule to treat these women, and the preliminary results suggest that half of the women treated are deriving a benefit. What is most exciting about this is that, based on the melanoma experience, we expect that some of these responses will result in a long-term remission even after therapy has been completed, and

we are hopeful that this may translate, for the first time, into a realistic chance of a cure.

I have been telling my patients with metastatic breast cancer that, if I cannot cure them, I aim to keep them alive until the cure is found. This breakthrough for the triple negative cancers may in fact be that cure for a number of these women, so you can see why I am so excited.

But before I leave you with the idea that we have solved the breast cancer problem, let me remind you that we are still on the first day of our own 3-day walk. The path we are to walk to bring all of this to fruition is now clear, but we have a lot of work to do to conduct all the trials necessary to identify the right cocktails of drugs that will do the job more effectively and without excess toxicity. It will take years, but we are encouraged that we are now sure we are on the right path, and we are convinced that if we just keep putting one foot in front of the other we will get to the end of the road.

I am hoping that in this coming year we will be able to plan new antibody trials to include more breast cancer patients and improve the responses by coupling the antibody therapy with other targeted drugs. The trials themselves are so expensive that only the drug companies can afford to sponsor them. But the money you bring in to the Breast Center can make a huge difference to us as it will help us afford technical help which is a key factor in preparing and running a successful trial. So please know that the successes we

are talking about today are YOUR successes too. We could not do this without efforts like yours. You make a HUGE difference in helping to get projects from dreams to reality. We all thank you from the bottom of our hearts for your amazing accomplishments over the years and for your continuing inspiration to us to keep pushing on towards the cure. Bless you all!

Sincerely,

Irene Kuter.