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Metastatic Patients in need of Parallel Tracks

The problem:

It is a well discussed fact that many clinical trials are under enrolled:

> A staggering number of clinical trials fail to meet recruitment goals, which leads to delays, early trial termination, or inability to draw conclusions at trial completion due to loss of statistical power. A recent analysis found that 19% of registered trials that closed or terminated in 2011 either failed to meet accrual goals (85% of expected enrollment) or were terminated early due to insufficient accrual.[1]

In our earlier paper, "Metastatic Patients and Clinical Trials", we discussed the many barriers that prevent our participation in clinical trials.[2] For this paper, we will focus on two of the main eligibility barriers:

1. Metastatic breast cancer patients quickly become "heavily pretreated" (usually more than 2 standard lines of chemotherapy)
2. We are often diagnosed with brain metastases (Central Nervous System involvement).

When we exhaust the typical, standard of care chemotherapy treatments and/or have brain metastases but are asymptomatic, we are ineligible for most clinical trials and have no other treatment options left and die.

This current state of affairs is unacceptable to us for two reasons:

1. Stringent, antiquated eligibility requirements result in metastatic patients being denied the opportunity to access cutting edge treatment within the format of the clinical trial structure
2. Denial of metastatic patients' participation in clinical trials leaves a void in the body of scientific data generated by heterogenous enrollees, especially those for whom the treatment is intended

We will discuss these problems and propose a remedy: Parallel Tracks.

A brief historical perspective of Treatment Investigational New Drugs and Parallel Tracks:

Treatment Investigational New Drugs (INDs) provide a way for patients and their doctors to access a promising experimental drug that is in the process of being investigated in clinical trials. However, if the drug can be obtained, it is NOT administered within the structure of the clinical trial, so the patient's experience does not become part of the trial data. Historically, AIDS patients and providers expressed dissatisfaction with Treatment INDs:

> With one exception, they say, treatment INDs have simply bridged the gap between the end of clinical trials and full FDA approval. They have not increased access to drugs at earlier stages of development or helped patients who were ineligible for conventional clinical trials. Another criticism of the treatment IND regulations has been that they increased, rather than decreased, confusion about the parameters of expanded access. People inside and outside the government had hoped that the regulations would furnish a framework for all of the different approaches to providing experimental drugs to desperately ill patients. Instead, the regulations defined one particularly narrow approach and left other options open. Early dissatisfaction with the treatment IND led to calls for a more flexible solution to the access problem. [3]

The concept of "Parallel Tracks" in clinical trials was introduced by Dr. Anthony Fauci in 1989 in an effort to specifically address the AIDS/HIV epidemic:

> For almost a year after the release of the new IND regulations, patient advocates, community physicians, and government scientists exchanged ideas about other possible ways to expand access to experimental drugs. Finally, at a meeting in San Francisco in June 1989, Anthony Fauci, director of the National Institute of Allergy and Infectious Diseases, presented the concept of the "parallel track" protocol. The parallel track would make selected drugs available to HIV-infected patients who could not participate in conventional clinical trials and who had no therapeutic alternatives, without disrupting the progress of controlled clinical trials. Parallel track protocols could be approved for promising investigational drugs when the evidence for effectiveness was less than that required for a treatment IND.[4]

METUP's viewpoint on Parallel Tracks

We believe that clinical trials for metastatic/Stage IV patients should include Parallel Tracks. This would allow clinical trials to accommodate typically ineligible patients while working within the existing clinical trial structure. Parallel Tracks also have the potential to give patients extra time to live as well as provide the trial designers with information on the trial drug's effectiveness in the patient population for whom the drug, once approved is intended.

> Although eligibility criteria are a necessary aspect of clinical protocols, their purpose is to define the characteristics of the intended patient population to receive the study drug. However, as trial designs adapt to incorporate molecular medicine, so must eligibility criteria. From a design perspective, restrictions on eligibility are effective only if the restrictions lead to increased statistical power of the study. In clinical practice, eligibility criteria employed on clinical trials are rarely adhered to.[5]

Parallel Tracks will encourage the evolution of Eligibility criteria

As noted above, clinical trials need to enroll patients but it is perhaps less well known that many metastatic patients desperately want to participate in clinical trials. A terminal diagnosis and rapidly dwindling treatment options make the risks of participating in clinical trials acceptable for many patients. Yet, restrictive eligibility requirements severely limit trial enrollment.

> Many barriers contribute to non-enrollment in clinical trials, including patient, physician, institution, protocol, and regulatory barriers. At the protocol level, eligibility criteria have become a large roadblock to clinical trial accrual. Over time, eligibility criteria have become more and more restrictive. To accrue an adequate number of patients to molecularly driven trials, we should consider eligibility criteria

> carefully and attempt to reduce restrictive criteria. Reducing restrictive eligibility criteria will allow more patients to be eligible for clinical trial participation, will likely increase the speed of drug approvals, and will result in clinical trial results that more accurately reflect treatment of the population in the clinical setting.[6]

-There is a growing body of literature and opinion that supports broadening eligibility requirements, particularly beyond Phase 1.

> Unnecessarily restrictive inclusion and exclusion criteria limit accrual and access to trials and result in studies that fail to capture the heterogeneity of the patient population that will use the drug after approval. Food and Drug Administration (FDA) regulations state that a "protocol is required to contain the criteria for patient selection and for exclusion of patients" but do not contain detailed language regarding clinical trial eligibility criteria. Regulatory approval, however, must be predicated on data pertinent to the enrolled patients and relevant to the U.S. population and U.S. medical practice.[7]

-Restrictive eligibility requirements are a source of frustration and desperation for doctors as well as patients. The emphasis on recruiting only healthy, "olympian athletes" to maximize trial results has exacerbated this problem.

> The fault lies not with our patients, but with those who design these studies. To maximize the likelihood of detecting clinically meaningful effects from the drugs being studied, trials seek fit, homogenous patient populations. At first blush, this makes sense: investigators, and the Food and Drug Administration (FDA,) want to clearly define a drug's safety and efficacy, and avoid erroneously attributing consequences of other medical conditions to the drug. It wouldn't be fair, for example, in a patient with severe cardiac disease who experiences a heart attack while on a clinical trial, to say that this unfortunate event was unequivocally caused by a study drug.
>
> As a consequence, many adults with cancer flunk the eligibility criteria that would allow them to join these trials, and the patients who are enrolled in these studies don't truly reflect the U.S. population who will ultimately be treated by the approved drug.[8]
>
> We must be concerned that the study population is not accurately reflecting associated toxicities seen with these novel agents if only the youngest and healthiest patients qualify for study enrollment.[9]

While some research oncologists try to find flexibility in eligibility criteria to accommodate more patients, it is ultimately up to the sponsor to determine who can enter their trial.

> "My friend and I went to the San Antonio Breast Cancer Symposium in December 2016 and we went to some of the poster sessions together, specifically looking for clinical trials for triple negative metastatic breast cancer that she might be eligible to enter. Time and again the presenters told us that she was ineligible because of her prior treatments. She died in July."
>
> Patient Anecdote

Parallel Tracks have the potential to broaden eligibility criteria, resulting in greater subject enrollment and providing more options for doctors, patients and the drug development process.

Research and opinion are growing to support the inclusion of a greater range of patients in clinical trials. Inclusion and enrollment of typically ineligible patients in clinical trials has been tried and results have been examined:

> In a subsequent study we presented at the American Society of Hematology annual meeting this month, we analyzed 13 leukemia trials conducted through the National Cancer Institute's Southwest Oncology Group between 2005-2015. Each included patients who didn't actually meet the stringent entry criteria, but whose ineligibility wasn't discovered until the studies had been completed.
>
> What we found was that these "ineligible" patients were just as likely to go into remission of their leukemia, and to live just as long, as eligible patients. As in our previous study, the eligibility criteria appeared to be needlessly restrictive. Further evidence that the bar is set too high for patients seeking enrollment in clinical trials.[10]

A study done at MD Anderson, designed specifically for patients who would otherwise be ineligible for clinical trials due to poor performance, organ dysfunction or comorbidities concluded:

> In our initial exploratory study, a majority of patients were able to complete at least one cycle of therapy without major toxicity, and obtain clinical benefit with acceptable responses and survival despite their high comorbidity burden. The fact that we could compute the toxicity profile, response rates, assess treatment exposure for at least 4 weeks and perform pharmacodynamics assays, strongly support the concept that this group of patients can be included in clinical trials.[11]

There is also growing support for a more nuanced approach to including typically ineligible patients, such as those with brain metastases:

> Carden et al advocate that we should rethink exclusion of patients with asymptomatic brain metastases from clinical trials. Because of the development of more-sensitive brain-imaging techniques, metastatic brain lesions are often detected earlier and may be asymptomatic at the time of detection. In many trials, brain imaging is a part of the screening workup for trial eligibility. Traditionally, patients with brain metastases have been excluded from trial participation because of the shortened life expectancy associated with symptomatic brain metastases and a concern that the patient would not receive a sufficient duration of the study drug; therefore, clinical benefit would not be expected and may confound study results. Although safety is a priority, universally precluding patients with brain metastases from clinical trials limits their access to potentially effective therapy, making it difficult to extrapolate the use of these drugs to the general population.[12]

We would also like to see more flexibility in allowing "heavily treated" patients to enroll in trials. As some metastatic patients are living longer (beyond the median 3-year survival rate), we have the benefit of accessing multiple chemotherapies and treatments. However, most clinical trial eligibility requirements limit previous treatments to 2, sometimes 3 chemotherapies. This excludes many older metastatic patients or patients who have the "good fortune" to live beyond the expected time frame. Thus, while we may be feeling relatively well and have no other excluding factors, we are ineligible for many clinical trials.

> "I've had 7 chemos over the last 8 years. Most studies cap at 3 previous chemos. I guess I've lived too long?" Tweetchat on Clinical Trials Social Media (#CTSM) April 2017

Additionally, patients who are experiencing better than average disease control while on traditional chemotherapy should get individual consideration for entering trials, even if they exceed the typical number of prior treatments.

> In molecularly driven trials, eligibility criteria related to patient characteristics, including restrictions on age, performance status, laboratory findings addressing organ function, and history of previous cancer diagnosis, previous antineoplastic therapy, or evidence of metastatic disease to the brain, have become cumbersome.[13]

> "I was on a CDK 4/6 combination trial for one year and it was a really good experience. Since then, I've been on the same, traditional chemotherapy for over 2 years. But, because it's my 3rd line of treatment (in the 9 years since my metastatic diagnosis), my oncologist told me I'm ineligible for some trials that otherwise sounded appropriate for me. **Who decided that 3 chemos is the magic cutoff number?** Doesn't it count that I'm having a somewhat remarkable run on my current chemo? No wonder trials are under enrolled! " Patient anecdote

Including historically ineligible metastatic patients in Parallel Tracks has the potential to benefit 3 sets of stakeholders:
-Patients: Allowing us to contribute our data to research and possibly extend our lives
-Doctors: Presenting more treatment options for terminally ill patients
-Sponsors: Providing studies with invaluable data on target populations.

> Inclusion of representative patient cohorts could offer regulatory incentives for the pharmaceutical industry. One such incentive could be an expanded marketing claim when a broader patient cohort had been adequately studied; for example, if efficacy and safety were demonstrated in patients with brain metastases, a marketing claim could include an indication for this population in addition to the general indication.

> We recognize that enrolling a less homogeneous group of patients in trials may result in different efficacy and safety outcomes. In addition, patient safety can be compromised if enrollment criteria are not rigorously considered. However, a logical approach to defining eligibility could allow for detection of safety signals in early clinical trials that use broad eligibility criteria and permit modification of subsequent criteria throughout the drug-development process as knowledge emerges.[14]

<u>Parallel tracks can be incorporated into the existing clinical trial design and structure.</u>

We are not asking to recreate the clinical trial model or to be given the "right to try" drugs outside of the clinical trial structure. We are asking to modify existing structures to include Parallel Tracks for metastatic patients. Researchers need to find the right place in clinical trials to include parallel tracks. For example, Phase I may not be the best entry point, since that is a time when optimal results in efficacy and safety are sought so the trial can continue. However, Phase 2 might be an appropriate time to implement a parallel track so researchers can observe the effects of the drug(s) on the target population.

We are adamant that we, the patients with the least amount of time to live, should be able to contribute to the science that will help others like us live longer and hopefully better while in treatment.

Conclusion

> The way that clinical trials are designed and run may need to be revolutionized, but "there's not going to be a single solution because it's a multifactorial process," says Richard Schilsky, an oncologist at the University of Chicago, Illinois. "Everybody who is a stakeholder in the clinical-trial process has to contribute to the solutions."[15]

The metastatic breast cancer community in the U.S. has been dying at a rate of approximately 40,000/year since 2000 with 40,890 men and women estimated to have to died in 2016.[16]

> It's worth noting that, in 1992, at the height of the AIDS crisis in this country 75,457 people died in the US, with a rapid decline in deaths from that point.[17]

While we know that AIDS and metastatic breast cancer are radically different diseases, we feel the same sense of desperation and urgency that the AIDS activist community demonstrated to bring about change.

We can no longer tolerate being denied access to trial drugs because of our diagnosis and "eligibility status."

We can no longer endure the desperate encounters with our oncologists when we are told that we have no more treatment options and that we are not eligible for clinical trials.

We are in favor of the Parallel Track option because we want to contribute to the science that is working to help us live longer and, perhaps, find a cure. By participating in the clinical trial structure, we hope to ensure that our deaths as well as our lives will be meaningful.

We want to work within the clinical trial structure so our responses to trial drugs are monitored and become part of the broader body of accrued scientific knowledge of investigational drugs. It is time for the FDA and trial sponsors to recognize this intolerable situation and act with the same sense of urgency that we, our families and healthcare providers live with everyday until we die.

With gratitude to the lives and memories of Angela Shartrand and Beth Calabotta, who inspired and contributed to this paper before their deaths and the over 40,000 metastatic breast cancer patients who die every year in this country.

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August 2017

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