



Metastatic Exchange to Unleash Power

www.metup.org

Metastatic Patients and Clinical Trials

Clinical trials have the potential to extend and possibly save lives. But they are not readily accessible to patients with metastatic cancer. They place undue burdens on patients, employ restrictive eligibility requirements and do not reflect the perspective of the metastatic population, making it difficult to impossible for patients to participate in appropriate, convenient trials in a timely manner. Clinical trials are often the last resort for metastatic patients, who have exhausted all “standard of care” options. Yet, for that very reason, metastatic patients are typically excluded from most clinical trials.

METUP presents the following issues based on patient input:

1. Clinical trials place disproportionate burdens on patients

It is too difficult for patients to find appropriate clinical trials. Patients have to do most of the work to find the trials for which they are eligible. This is an arduous task at the best of times, it is a horrendous burden for terminally ill patients.

Patients are on their own when it comes to finding clinical trials. First, they need to identify trials that they are eligible for, whittle those down to a short list, and then go to each trial site in person to meet with the trial team. After that, they have to compare the slots they've been offered (because even though one might appear to qualify for a trial, they may not offer that slot, often for unknown reasons). Once patients have their offered slots, they need to make a decision based on data that may not yet be available or easily comparable. Then patients have to factor in timing, logistics and overall risk/benefit.

“No one at my home hospital knows a damn thing about metastatic triple negative breast cancer trials. I am the fucking expert! I have to learn everything I can because I'm the one who's going to die if it doesn't work.”

“Cancer Commons put me at the center of their matching service and helped me advocate for what I wanted. Even if it wasn't the ‘best’ trial, they supported my decision.”

Clinical trials are inaccessible to the majority of patients due to geography and related expenses. Costs can be too high for patients.

Access to the best and greatest number of clinical trials is often limited to major cancer centers and typically requires frequent, often distant travel. Additionally, many metastatic patients can no longer work, due to their treatment schedules and disease symptoms. Thus, they have Medicaid insurance, which typically does not fund treatment across state lines.

“There were some clinical trials I would have liked to have been tested for to see if I could have qualified but the out-of-state hospitals said they could not treat me with my current insurance. This was very upsetting to me--.”

Even if direct travel costs are covered, there are usually indirect costs that are not reimbursable, such as childcare, foregone wages and activities of daily life that the patient might not be able to do such as housecleaning and cooking. Furthermore, patients have to weigh whether the time away from family and additional unproductive time due to side effects will be offset by the uncertain gain in lifespan by participating in the trial.

Clinical trials require repetitious, often invasive and expensive pre-screening and monitoring procedures that typically must be done at the research center, not the patient’s local hospital.

“I tried to find out if my biopsy procedure can provide tissue for multiple trials (one at Hospital A and one at Hospital B) but both institutions seemed skeptical that that could happen. Which means I potentially have to undergo two liver biopsies this week.”

Research institutions require all baseline tests to be done at their sites which often means the patient gets redundant tests, which is a massive waste of time, money and patient effort. Trial designers need to be willing to help the patient get their scans and pre-screening tests in the most efficient way possible. If that means Premier Hospital A has to settle for Premier Hospital B’s MRI machine and biopsy tissue, so be it (After all, they are both part of the Premier Healthcare system, so there should be standardization).

2. Clinical trials employ rigid, exclusive eligibility criteria

Clinical trials exclude metastatic patients for reasons that are inherently part of a metastatic breast cancer (MBC) diagnosis.

The majority of metastatic breast cancer trials exclude “heavily pretreated” patients (usually more than 2 lines of prior chemotherapy in the metastatic setting) and patients who have brain metastases (CNS involvement). Thus, metastatic patients who have exhausted Standard of Care options are shut out of their only other possible treatment avenue.

In a small trial conducted at MD Anderson Cancer Center in Houston, Texas, typically ineligible patients were enrolled and their cancer improved at the same rates and they experienced similar side effects when compared with eligible patients in similar trials (<https://www.ncbi.nlm.nih.gov/pubmed/27795561>)

This study determined “this subset of patients can be safely treated within clinical trials and derive clinical benefit,” and concluded, “Relaxation of standard exclusion criteria may increase the pool of patients likely to benefit from therapy.” [Please note that the full text was not available due to a

firewall. This is another way patients are disadvantaged when trying to access information that may extend their lives.]

“In AIDS, what happened was patients couldn't get access to drugs because it was taking too damn long for them to go through trials and many patients were too sick to be eligible for trials, so they offered parallel trials, where patients were getting access to experimental drugs, and they tracked the data about how it worked. Because, when patients couldn't get newer drugs, they turned to manufacturing the drugs themselves. -- they just looked up the formula in the patent documents and took it to the pharmacies anyway. Long story, but my point is, I don't think FDA and NCI want cancer patients doing that, but when people are desperate to live, they do desperate things. Giving them access to experimental treatments is often the only way they have a shot at staying alive.”

Most trials also require a 28-day “washout” period between the end of the patient’s last treatment and the start of the trial. However, for metastatic patients, that 28-day period with no treatment often results in disease progression which can disqualify a patient from entering that very trial, leaving him/her worse off than before. In the real world, patients receiving standard of care transition from treatment to treatment without a break. Additionally, in the past 40 years, treatment has expanded beyond IV chemotherapy to include oral chemotherapies, hormonal therapy and targeted therapies. The clinical trial protocols have not evolved to reflect the real world practices of zero wait to change therapies (for oral chemo, oral hormonal treatment or oral targeted therapies) and a 1-2 week wait for most IV chemotherapies.

“I know doctors are all about do-no-harm, but when your option is try a drug, or just die, I mean, you're not actually doing harm, right?”

3. People of color are not adequately represented in the clinical trial population.

This is a well acknowledged issue that has been difficult to address, for many of the reasons noted above, in addition to lack of awareness of trials, language barriers and cultural and historical issues (See the Tuskegee Airmen Study, <https://www.cdc.gov/tuskegee/timeline.htm>)

In December 2016, the New York Times published an article describing the racial disparities in clinical trials and efforts to correct the problem:

<http://www.nytimes.com/2016/12/23/health/cancer-trials-immunotherapy.html>

Another example of efforts to reach out to and recruit minority communities into clinical trials is the Smilow Cancer Hospital’s OWN IT! Program in New Haven, CT:

<http://www.nhregister.com/general-news/20170107/new-haven-cancer-doctors-working-to-draw-people-of-color-into-clinical-trials>

One important component of this program includes caring for patients at satellite centers closer to their homes, families and friends, an issue that is significant to all patients in clinical trials.

4. The patient perspective is absent from most trial design

“Researchers think that the barrier to clinical trial participation is that patients don't understand the benefits of participating in clinical trials. So they write article after article promoting the benefits of clinical trial participation, distributing in venues the patient never sees. They don't ask patients what they need to change so that participation could be broadened.”

Clinical trials are a partnership. The stakeholders are the patients, clinical researchers and funders (often pharmaceutical companies). Yet, patient experience shows that many researchers and funders are so focused on their area of study and outcome that the needs of trial participants are often minimized or unrecognized.

“I left (the major research center) feeling I'd met a researcher who was excited to learn as quickly as possible how to make immunotherapy work and work better in breast cancer. I did not leave feeling as if I had a doctor who was interested in helping ME.”

“I've always known that the primary interest is in getting me into the trial that is best for the trial, not best for me as the patient. Hopefully, they sometimes overlap but I wish I had the sense that they knew which trial was the best one for me, taking into consideration: I'm a parent, I can't travel more than a few hours, and I want the longest durability for the least side effects. Sometimes that won't be at my current cancer institution and they should be able to tell me that.”

Failure to acknowledge the initial gap between caring for all of the patient's best interests while working to understand the science as quickly as possible is a critical factor that limits patient participation in trials.

Clinical trials need to have patient participation up front in the design. The patients who participate in reviewing the design should be the target audience for the clinical trial and should also include at least one patient who has previously participated in a clinical trial.

These are some of the concerns patients have voiced about clinical trial design:

Schedule and format

The clinical trial format is too complicated, rigid and lengthy for terminal patients. At present, trials are designed to accommodate the researchers and funders with less consideration of the needs of metastatic patients. Consent paperwork is often lengthy (15-30 pages), the wording can be complex and the schedule (Study Plan) of screening procedures and monitoring appointments can be staggering. Research doctors, nurses and assistants can help in decoding and facilitating these processes. Still, the decision to consent and the complex burden of participating in clinical trials is particularly difficult for metastatic patients.

“You have to be more flexible---These are drugs that are going to be used in real life but some of these drugs need to be tested in real life.” Dr. Andrea Silber, Oncologist and Director of the OWN IT! Program, Smilow Cancer Hospital, New Haven, CT (see article link below)

Data

Patients need access to clinical trial data so they can make informed treatment decisions about appropriate trials for which they are eligible. But there is no consistent means of comparing data amongst trials. Additionally, negative results must be published in a timely fashion to save lives. However, such results frequently are not reported. Patients risk their lives to participate in clinical trials and endure the certainty of side effects with a pretty small chance of a gain. Access to trial data would allow them to make better, more informed choices.

“I know not all of this data is available but a lot of it is for Phase II trials and it would make my decision a lot easier if they could just have this data in the same format across all trials.”

Patients often are not allowed to see their own data generated from their tissue and blood samples as part of clinical trials (tumor sequencing, circulating tumor cell). For example, genomic profiling is frequently done as part of the trial protocol because the companies are looking for biomarkers to identify subsets of patients that have benefited from the treatment. Patients who want their own copy of that information for future treatment decisions often do not have access to it and must replicate the analysis at considerable expense.

“If the problem getting our information back to us is with lab certification, why isn’t CLIA certification required for all trial protocols?” (Clinical Laboratory Improvement Amendments, <https://wwwn.cdc.gov/clia/>)

Patients who participate in a clinical trial should have a say in how and if their data is shared. The Cancer moonshot has recognized that data silos need to be broken down. The participants in clinical trials should have the right to choose if their data is shared broadly to further benefit science.

The Demands of participation

The paperwork and bureaucratic hurdles for participation can be onerous, especially for patients coping with the demands and distractions of terminal illness, often resulting in lost time, a luxury that is not afforded metastatic patients.

The burden of enduring washout periods can result in harmful disease progression while waiting to start a new trial, leaving the patient ineligible for the desired trial and having to initiate a new trial search, with reduced options due to the progression.

Patients often undergo painful, invasive procedures, some with recognized risk, and repeated testing to generate baseline and monitoring data. Yet, these data are often “siloeed” and not typically shared between study sponsors and different research institutions for the greater good.

There is no consistent means of reimbursing patients for trial related expenses (travel, parking, meals, lodging), some procedure related expenses (e.g., liver biopsies may require an overnight stay for those living a distance from the hospital) and unanticipated expenses incurred due to procedural cancellations and managing the varying degrees of side effects.

Summary

Clinical trials hold the promise of new, life-prolonging treatments and possible cures, but enrolling and participation is often onerous for metastatic patients. It is extremely difficult for patients to find appropriate trials for which they meet eligibility criteria and to which they can readily travel. Entry into clinical trials is demanding of patients' time, endurance and finances, factors which are particularly limited in the metastatic population. These issues often result in terminal patients forgoing novel treatments that may potentially give them more time to live.

The eligibility criteria for clinical trials are exclusive, precluding many metastatic patients from enrollment. By definition, metastatic patients have complex diagnoses and treatment histories. In an effort to maximize outcomes, trial designers limit entry to the healthiest patients, thus excluding metastatic patients who might benefit from possible life-extending treatments.

People of color are not adequately represented in clinical trials. This clearly affects researchers understanding of why different populations might have different disease and treatment outcomes.

The design of clinical trials omits the metastatic patient perspective. Participation in a clinical trial can mean the difference between longer life and imminent death for a metastatic patient. However, metastatic patient input appears to be lacking from trial design and implementation.

→ METUP proposes the following to reduce the burden on metastatic patients who want to participate in clinical trials

- ◆ There should be a “one-stop” site for patients to easily find the most appropriate clinical trials for which they are eligible. Ideally, this site should have an online “chat” capability.
- ◆ Patients need doctors and/or patient advocates to assist them in finding and referring them to the most appropriate trial as quickly as possible.
- ◆ Hospitals and research centers need to collaborate to reduce stress on patient participants. This would require trials to accept scans and pre-screening tests in the most efficient and humane way possible.
- ◆ Clinical trials need to take place at community hospitals as well as major research centers.

- ◆ Trials need to make data available in a consistent format that would allow doctors and patients to make comparisons between trials in the best interest of the patient. This data should include:
 - ◆ 1) Median Progression Free Survival
 - ◆ 2) Median Overall Survival
 - ◆ 3) Response rate
 - ◆ 4) Number of biopsies required
 - ◆ 5) Number of hours required per month
 - ◆ 6) Number of scans per year
 - ◆ 7) Percent of people experiencing various side effects
 - ◆ 8.) Median duration of response

- ◆ Patients need to be fully informed of the risks and benefits of participation in a clinical trial. To do this, all of the detailed protocols for phase 2 and phase 3 clinical trials should include summarized information on previous trial results as well as any relevant published material. This information should be shared with patients, not just the researchers. In addition, data on the percentage of patients seeing benefit for participating in phase 1,2 and 3 trials should be summarized and published each year.
- ◆ Negative results should be reported and written up in as timely a manner as positive results.
- ◆ Clia lab certification should be a requirement for clinical trial design to give patients access to all their data and results generated from their samples, particularly genomic profiling, that could be used for future treatment decisions.
- ◆ Facilitate compassionate use of experimental drugs and capture data about compassionate users.
- ◆ To accommodate metastatic patients who might otherwise be excluded from trials, we propose a parallel, “Fast Track” level. This would have limited eligibility requirements, no washout periods and run for a shorter duration. This model would allow greater enrollment opportunities, faster generation of data and quicker reporting back of results. Including these patients would expand the patient groupings in studies and ultimately give oncologists more information on how the drug will be tolerated in “real world” patients once it’s been approved.
- ◆ Include the metastatic patient perspective in all trial designs starting with the initial discussion. Concerns about time demands, physical and bureaucratic stress, financial burden and population diversity need representation.

We would like to thank the following for their input and guidance in the writing of this paper:

Beth Calabotta Angela Shartrand Beth Caldwell Jamie Holloway Stephen Perkins

Phyllis Groskin and the members of METUP
February 2017

