NEXT GENERATION ONCOLOGY CLINICAL TRIAL ENROLLMENT

Understanding Clinical Trials and Their Role in Treating Myelofibrosis

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OBJECTIVES

- Recognize and describe the current challenges concerning Oncology Clinical Trials
- Summarize how clinical trials drive innovation, align with clinical pathways, and promote quality patient care
- Increase clinical trial aptitude to advance patient understanding of clinical trials
- Discuss the right infrastructure to encourage clinical trial participation
- Identify the technology available to assist care providers in identifying patients for participation in clinical trials
- Inform about the importance of clinical trials to treat myelofibrosis

According to NCI, clinical trials are research studies that involve people. Through clinical trials, doctors find new ways to improve treatments and the quality of life for people with disease. Trials are available for all stages of cancer. It is a myth that they are only for people who have advanced cancer that is not responding to treatment.

Reference: https://www.cancer.gov/about-cancer/treatment/clinical-trials/what-are-trials

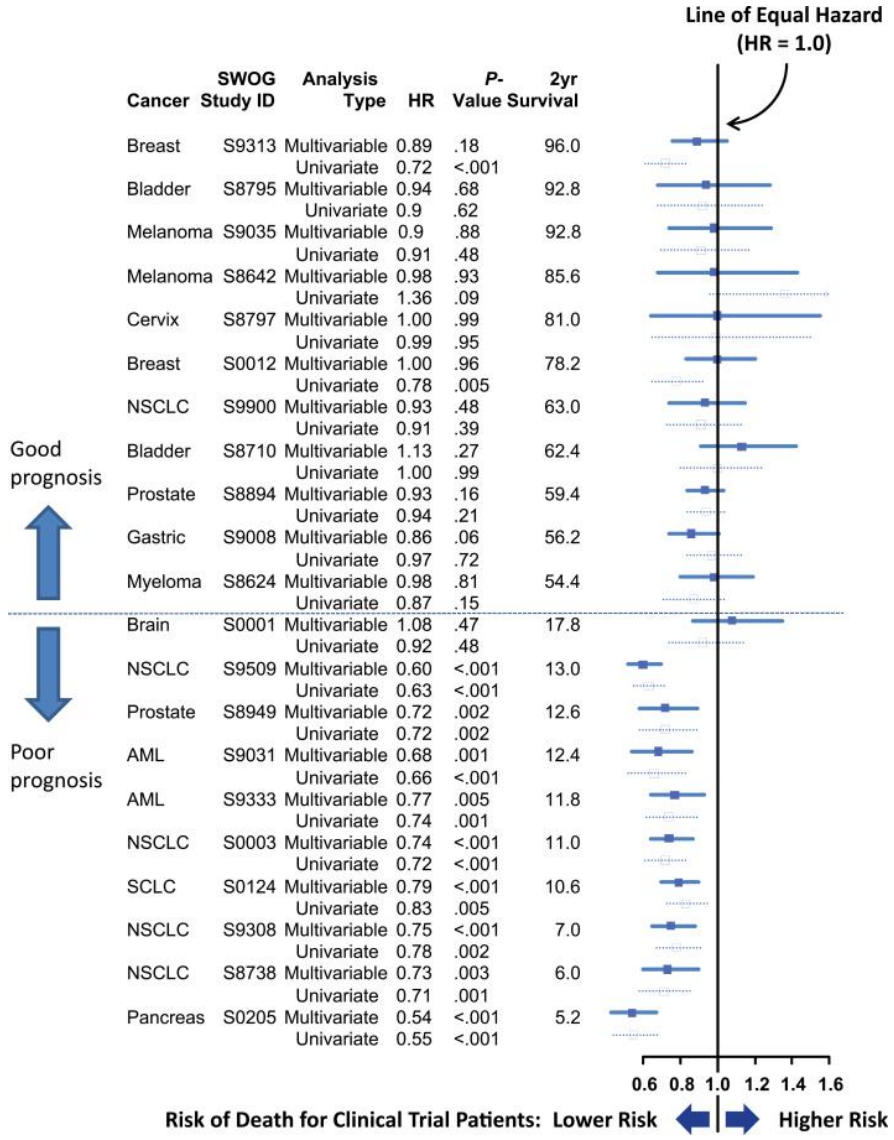
PHASES OF CLINICAL TRIALS

Phase 1	Phase 2	Phase 3	FDA Approval	Phase 4
Tests drug on healthy individuals	Tests on larger group of effected individuals	Tests on new and wider demographic	Treatment determined effective and safe for public use	Continues to test for effectiveness and safety
Tests for safety, dosage and side effects	Tests for efficacy and side effects	Tests for long term effectiveness and comparisons with other medications		Can be taken off the market if necessary

Reference: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3272827/

CLINICAL TRIAL IMPACT

Forest plot of univariate and multivariable hazard ratios (HRs) for overall survival, by study, ordered in descending order of average 2-year overall survival. In univariate analyses, two of 11 (18%) good-prognosis studies and nine of 10 (90%) poor-prognosis studies showed evidence of a survival benefit for trial patients (*P* = .002 by Fisher exact test).
In multivariable analyses, zero of 11 good-prognosis studies and nine of 10 poor-prognosis studies showed evidence of a survival benefit for trial patients (*P* < .001). AML = acute myeloid leukemia; NSCLC = non–small cell lung cancer; SCLC = small cell lung cancer.



Reference: Unger JM, Barlow WE, Martin DP, Ramsey SD, Leblanc M, Etzioni R, Hershman DL. Comparison of survival outcomes among cancer patients treated in and out of clinical trials. J Natl Cancer Inst. 2014 Mar;106(3):dju002. doi: 10.1093/jnci/dju002. Epub 2014 Mar 13. PMID: 24627276; PMCID: PMC3982777.

CLINICAL TRIAL PARTICIPATION AND COMMUNITY PRACTICE IMPLICATIONS

Studies at academic and community treatment sites have quantified barriers preventing patient enrollment in clinical trials and show that most patients will not have the opportunity to enroll in a clinical trial

CLINICAL TRIAL ENROLLMENT PATTERNS FOR MULTIPLE STUDIES IN THE LITERATURE[1]

	TRIAL UNAVAILABLE	INELIGIBLE	NOT ENROLLED	ENROLLED
Academic Centers				
Average rate[2]	41.4%	24.3%	19.5%	14.8%
Community Centers				
Average rate[2]	59.9%	15.7%	17.9%	6.3%
Combined				
Adjusted rate[3] All studies	56.2%	17.4%	18.2%	8.0%

1 Adapted from Unger et al., 2018, in press.
2 Calculated using a weighted average based on study size
3 Based on multiple sources, we estimated that approximately 80% of patients receive their care in community-based cancer centers. Thus the overall average rate was weighted at a ratio of 4:1 based on average estimates from community:academic centers.

Reference: “Barriers to Patient Enrollment in Therapeutic Clinical Trials for Cancer” A Landscape Report by American Cancer Society, https://www.fightcancer.org/policy-resources/clinical-trial-barriers
and also, the references of the report on page 56

BENEFITS OF CLINICAL TRIALS TO PATIENTS

Active	Play an active role in their own health care
Access	Gain access to new treatments before they are widely available
Options	Increase the options for treatment when standard therapy has failed
Expert	Obtain expert medical care at leading health care facilities during the trial
Help	Help others by contributing to the advancement of medical knowledge

Reference: https://www.nia.nih.gov/health/clinical-trials-benefits-risks-and-safety

PATIENT JOURNEY PRIOR TO CONSENT

- Publicly available data and research
  - Google search
  - Patient advocacy group
  - Publicly available clinical trials lists and databases, e.g., ClinicalTrials.Gov
  - Clinical trial matching companies
- Discussion with treating provider and/or clinical staff
- Scheduling a visit to the clinical research site
- Insurance coordination
- Frustrated and lost patient!

PATIENT JOURNEY AFTER CONSENT

- Discovery
- Informed consent
- Screening
- Treatment or control group assignment (if applicable)
- Regularly scheduled visits with data collection
- Continued visits with their physician for routine health care throughout the study

PATIENT PERCEIVED BARRIERS

- Am I going to be a guinea pig?
- Can I afford going to a clinical trial?
- Do I need to travel to go to a clinical trial?
- Can I enroll to a clinical trial even my physician doesn't know about clinical trials?

BENEFITS OF CLINICAL TRIALS TO PROVIDERS

- You can be top-advocates for patient participation
- Clinical trials may offer ideal alternative solutions for patients
- Patients expect their providers to be experts on the subject
- Providers rely on the knowledge gained from clinical research
- Providers can improve their relationships with their patients by offering additional treatment options

PROVIDER PERCEIVED BARRIERS

- How do I find the best clinical trial to my patient during my busy clinic?
- Do I always have to refer the patient to another facility?
- Is it too difficult to run a clinical trial at my own hospital? I don’t have enough time and resources.
- Does pharmaceutical companies pay for clinical trials and how much?
- Am I going to lose the patient if I refer out?

IMPORTANCE OF CLINICAL TRIAL AWARENESS

Several studies indicate that awareness changes attitudes toward clinical trials, enrollment, and the benefits of participation.

- 85% of patients were either unaware or unsure that participation in a clinical trial was an option at the time of diagnosis.
- 75% of these patients said they would have been willing to enroll had they known it was possible.
- Focus groups find that many patients lack familiarity with clinical trials and are unaware of opportunities for participation by healthy volunteers. They generally expressed negative attitudes about participation. These attitudes significantly changed after learning more about clinical trials.

Reference: Harris Interactive. 2001. Misconceptions and lack of awareness greatly reduce recruitment for cancer clinical trials. Health Care News 1(3).

AN IMPORTANT REMINDER

- A clinical trial system that enrolls patients at higher rates produces treatment advances faster and corresponding improvements in cancer population outcomes.

- Thus, fewer barriers to trial participation would allow trials to complete more quickly and improve trial results' generalizability. However, crucially as well, increased accrual to trials is vital to patients since trials provide patients the opportunity to receive the newest treatments.

- In an era of increasing emphasis on a treatment decision-making process that incorporates the patient perspective, patients' opportunity to choose trial participation for their care is vital.

FACTS ABOUT MYELOFIBROSIS (MF)

- Myelofibrosis is a rare bone marrow cancer that is related to a group of blood cancers known as myeloproliferative neoplasms (MPNs) in which bone marrow cells that produce the blood cells develop and function abnormally.
- Primary myelofibrosis is a type of chronic leukemia that can either occur on its own or as a result of another bone marrow disorder.
- Other MPNs that can progress to myelofibrosis include polycythemia vera and essential thrombocythemia.
- Myelofibrosis is usually very slow growing, and many people can live symptom-free for years before requiring treatment. However, frequent monitoring is recommended.
- When an unknown gene mutation occurs in blood stem cells, myelofibrosis develops.
- Between 50 and 60% of people with myelofibrosis have a JAK2 gene mutation.
- Signs and symptoms of myelofibrosis can include:
  - Anemia, or low red blood cell count, which in turn causes fatigue, weakness, and shortness of breath
  - Splenomegaly (enlarged spleen) which in turn causes pain or bloating on the left side of the abdomen below the ribs
  - Neutropenia, or low white blood cell count, which causes frequent infections, and thrombocytopenia, or low platelet count, which causes easy bleeding or bruising
  - Enlarged liver
  - Weight loss
  - Fevers
  - Night sweats and pale skin
  - Bone or joint pain

TREATMENT FOR MYELOFIBROSIS

- The goal of treatment for most patients with myelofibrosis is symptom relief and reduction of complication risk.
- Treatment for myelofibrosis can include:
  - Blood transfusions
  - Chemotherapy
  - Radiation Therapy
  - Splenectomy (removal of the spleen)
  - Drugs to treat anemia
  - Allogeneic stem cell transplantation (ASCT)
  - Clinical Trials
- Ruxolitinib (Jakafi) is a type of chemotherapy and the first drug approved by the FDA for treatment of myelofibrosis.
  - This drug has been shown to reduce MF-related symptoms and control spleen enlargement.
- Allogeneic stem cell transplantation is the only potential cure for MF.
  - Many things are taken into consideration prior to ASCT such as age, the course of each patient's disease, and other health problems because of the considerable risk for life-threatening side effects.

CLINICAL TRIALS FOR MYELOFIBROSIS

- Clinical trial enrollment is especially important for those with myelofibrosis due to the lack of approved treatment options for this disease type.
- The JAK2 mutation is one of several gene mutations believed to be involved in the development of MF.
  - Since the discovery of the JAK2 gene mutation in 2005, which is found in approximately 50-60% of people with myelofibrosis, several clinical trials utilizing JAK2 or JAK1/JAK2 inhibitors for the treatment of MF have been studied.
    - Ruxolitinib is an approved drug that targets JAK2 and other associated mutations. It was studied vigorously in clinical trials before being approved for the treatment of MF
    - Fedratinib is another oral JAK2 inhibitor that was studied in clinical trials and recently approved for treatment of MPN-associated MF.
- There are currently combinations of drugs, including several JAK inhibitors and other pathway inhibitors, being evaluated in clinical trials. Some of the classes of drugs and other novel therapies currently being studied in clinical trials include:
  - Other JAK inhibitors – The six drugs currently being studied, which do not yet have names, are showing effectiveness in reducing spleen size and improving anemia and problematic symptoms such as night sweats and fatigue.
  - Histone deacetylase (HDAC) inhibitors – This currently includes three drugs, Panobinostat (LBH589) and givinostat (ITF2357), as well vorinostat (Zolinza), which is FDA approved for treatment of cutaneous T-cell lymphoma.
  - Immunomodulatory drugs (IMiDs) – This class of drugs work against cancer cells by affecting the functions of the immune system. There are currently two drugs being studied for the treatment of MF that are already FDA approved to treat myeloma patients, including thalidomide (Thalomid) and lenalidomide (Revlimid), as well as one drug that is also being studied for treatment of myeloma, pomalidomide (Actimid).
- **By enrolling in a clinical trial for myelofibrosis, patients can have an increased chance of survival as well as early access to a new and improved drug to treat their myelofibrosis.**

CONTACT MASSIVE BIO TO LEARN MORE ABOUT MYELOFIBROSIS CLINICAL TRIALS

Massive Bio can help you enroll to any clinical trial that is actively recruiting on ClinicalTrials.Gov

Below are some of the actively recruiting clinical trials:

- NCT04576156: A Randomized Open-Label, Phase 3 Study to Evaluate Imetelstat (GRN163L) Versus Best Available Therapy (BAT) in Patients With Intermediate-2 or High-risk Myelofibrosis (MF) Refractory to Janus Kinase (JAK)-Inhibitor (https://clinicaltrials.gov/ct2/show/NCT04576156)
- NCT04603495: A Phase 3, Randomized, Double-blind, Active-Control Study of CPI-0610 and Ruxolitinib vs. Placebo and Ruxolitinib in JAKi Treatment Naive MF Patients (https://clinicaltrials.gov/ct2/show/NCT04603495)
- NCT04472598: A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study Of Navitoclax In Combination With Ruxolitinib Versus Ruxolitinib In Subjects With Myelofibrosis (TRANSFORM-1) (https://clinicaltrials.gov/ct2/show/NCT04472598)
- NCT04468984: A Randomized, Open-Label, Phase 3 Study Evaluating Efficacy and Safety of Navitoclax in Combination with Ruxolitinib Versus Best Available Therapy in Subjects With Relapsed/Refractory Myelofibrosis (TRANSFORM-2) (https://clinicaltrials.gov/ct2/show/NCT04468984)
- NCT04173494: A Randomized, Double-Blind, Phase 3 Study of Momelotinib vs Danazol in Symptomatic, Anemia Subjects With Previously JAKi Treated Myelofibrosis, Post-Polycythemia Vera Myelofibrosis, or Post Essential Thrombocythemia Myelofibrosis (https://clinicaltrials.gov/ct2/show/NCT04173494)
- NCT03165734: A Randomized, Controlled Phase 3 Study of Pacritinib Versus Physician's Choice in Patients With Primary Myelofibrosis, Post Polycythemia Vera Myelofibrosis, or Post-Essential Thrombocythemia Myelofibrosis With Severe Thrombocytopenia (PACIFICA) (https://clinicaltrials.gov/ct2/show/NCT03165734)
- NCT04551066: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of the Combination of PI3Kδ Inhibitor Parsaclisib and Ruxolitinib in Participants With Myelofibrosis (https://clinicaltrials.gov/ct2/show/NCT04551066)
- NCT04551053: A Randomized, Double-Blind, Placebo-Controlled Study of the PI3Kδ Inhibitor Parsaclisib Plus Ruxolitinib in Participants With Myelofibrosis Who Have Suboptimal Response to Ruxolitinib (https://clinicaltrials.gov/ct2/show/NCT04551053)

QUESTIONS?

Please submit any questions directly to kjohnston@massivebio.com.

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JOIN OUR JOURNEY

Massive Bio is rebuilding oncology clinical trials from the inside out with AI driven technology and high value-added services to enable improved clinical and financial outcomes for cancer patients, community oncologists and pharmaceutical companies.

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