ATLANTA AREA MULTIPLE MYELOMA SUPPORT GROUP, INC.

Northside Meeting

January 11, 2020

The Northside meeting was replaced by the ASH review at Emory/Winship, which was attended by 65 people from both the Northside and Southside groups. The doctors reviewed the clinical trials presented at ASH and thanked all the patients who make a difference by joining a clinical trial. Dr. Nooka also thanked those patients who donate a little extra bone marrow for the research lab. That helps the researchers see how drugs interact with myeloma cells.

The first presenter was Dr. Nisha Joseph, who gave an overview of MM and how it is diagnosed and tracked. She reviewed the criteria for MGUS, Smoldering myeloma (**SMM**), and active MM. MGUS is an M-protein less than 3g/dL in blood or greater than 500 mg/24 hours in urine, bone marrow plasma cells (**BMPC**) greater than 10%, and no **SLiM-CRAB** criteria. CRAB criteria defines active myeloma: C = Calcium elevated, R = renal insufficiency with creatinine greater than 2 mg/dL. A = Anemia with hemoglobin less than 10 g/dL, and B = bone disease with 1 or more lytic lesion or plasmacytoma. SLiM criteria, added to CRAB by the IMWG, includes: S = bone marrow plasma cells (BMPC) $\geq$ 60%, Li = serum Free Light Chain (**FLC**) ration $\geq$ 100, and M = one MRI focal lesion $\geq$ 5 mm. The Mayo Clinic followed 250 SMM patients for over 26 years and found a set of patients that progressed to MM within the first few years and a set of patients who had still not progressed after more than 20 years, and those in the middle. The challenge was to define who will progress sooner. At ASCO last June, Mayo presented the 20-2-20 criteria: FLC ratio > 20, M-protein > 2, and BMPC > 20%. A patient with 2 or 3 of these factors is considered high risk of progressing to active MM within two years, high risk smoldering MM (**HRSMM**). Clinical trials showed the benefit of treatment with Revlimid. After three years, 91% of the treatment group had not progressed to MM while 66% of the non-treatment group had not progressed.

In newly diagnosed MM patients, high risk is defined as abnormal chromosomes t(4;14), t(14;16), del (17p). Emory has an algorithm for newly diagnosed patients with groups divided if transplant eligible or not and by risk. High-risk MM (**HRMM**) transplant eligible patients get Kyprolis, Revlimid, and dex (KRd). Standard risk (both transplant and not) get RVd with Darzalex. High-risk non transplant get RVd for up-front and maintenance. Other trials are showing a significant improvement in **PFS** (progression free survival) with the addition of Darzalex in up-front treatment. MRD negative increased more than twice with the addition Darzalex to Rd in older or transplant ineligible patients. MRD negative has been shown to increase the time before relapse and overall survival. Another study showed that Darzalex has no impact on transplant engraftment of stem cells.

The next presenter was Dr. Madhav Dhodapkar, Director of Center for Cancer Immunology. Why focus on the immunology for MM? Immunology is more specific than chemo. Immunology

could create a more durable response, which has the potential for a cure, and reduce the need for ongoing therapy. The immune system is as complex as cancer and we need a complex answer to a complex problem. He gave an overview of the monoclonal antibodies that target CD38 and BCMA. CAR T-cell therapy builds MM fighters that can get into the tumor and destroy it. The antibody on the T-cell is delivered to the tumor cells. BiTEs use the BCMA target and create a bridge to link the T-cells to the tumor to destroy it. CAR-T therapy is built from the patients T-cells, much like a transplant of stem cells. It is customized for each patient. BiTEs are "off the shelf" treatment of a drug that connects to the T-cells and the MM cells. T-cells have a memory of childhood diseases and vaccines. This memory is believed to be the key to a long-term treatment against MM. Another challenge is that tumors have a cloak from T-cells. Checkpoint inhibitors can open the tumor to T-cells. A trial is expected to open at Winship within the next few months.

Dr. Dhodapkar talked about the high response rate from CAR-T therapy, but many patients still relapse. There are several trials at Emory for relapsed and refractory MM (**RRMM**), HRMM, and patients with a high risk for relapse since they have had several lines of therapy. The next challenge is how to improve the response by looking for the "one and done" approach. Emory is building a facility in the new Hospital Tower that will open in the Spring of 2020 and will make CAR T-cells. The goals are to establish an on-site manufacturing system and scale production to lower cost. Then move this science to other labs locally (GA Tech) and to regional and national networks – other NCI-funded centers, LLS Special Centers for Research. The primary goal is to get patients off all medications. One of the keys to the immunology research is the generous donation of 1022 bone marrow samples from 741 patients at Emory. These are used in multiple labs for the advancement of treatment to benefit patients.
Questions/Answers: **Q** - Does a patient need to be local to participate in a clinical trial? **A** - Patients on clinical trials need to be closely monitored and will require additional visits to the Winship center. This could be difficult for patients farther away. **Q** – Are CAR-T clinical trials in-patient or out-patient? **A** – They start as in-patient since the side effects are quite scary and need to be monitored around the clock. After initial stages, the patient is released to go home and return regularly for follow-up. **Q** – What is the quality of the CAR-T therapy? **A** – This is in the early stages of testing and there is a lot of room for improvement. One approach for improvement is to evaluate the timing of collection of the T-cells and the return to the patient. **Q** – Does CAR-T therapy have FDA approval? **A** – The FDA is monitoring the clinical trials and approval is expected in 2020, but hard to be certain. At Emory, there are 3-4 CAR-T clinical trials underway.

The next speaker was Dr. Vikas Gupta who has been at Emory for ten years and did his residency at Emory. He is working with Dr. Nooka on the EMPACT study where 741 patients have allowed an extra small amount of bone marrow to be taken during a biopsy and donated to the research team. There are 1022 samples so multiple samples are from individual patients. This allows the researchers to see how MM cells change over multiple therapies and may provide insight into relapse. Dr. Gupta and Dr. Boise are researching BCL-2 family of inhibitors, which include Venetoclax and AXD5991. CD28 and CD86 are survival factors for MM and to inhibit them may cause cell death. There is also research on MM genetics and how they differ from person to person, as well as how they differ from normal cells. There are studies on how drugs are metabolized to kill MM cells and not affect the rest of the body. The team is studying racial/ethnic differences in the natural history and response to therapy. Emory sees

1700 MM patients a year with 150 new diagnoses. 30% if the patients are African American (**AA**) vs. 15% in other studies. Much of what is called high risk cytogenetics comes from studies where African Americans (AA) were underrepresented. Current FISH testing has three translocations and six copy number alterations, but no mutations. Genetic experiments are looking at more translocation regions for all 26 chromosomes. How do mutated genes impact MM and outcomes?
Question/Answers: **Q** - What is high risk myeloma? **A** – It is now based on 3-4 events: t(4;14), t(14;16), del (17p), but there may be more with differing impact. **Q** – Are any meds more effective in AA and any studies at ASH for AA? **A** – In Emory study of RVd, AA do just as well as Caucasians. Not seeing much difference with RVd, but more studies are needed on other treatments. **Q** – How do current patients volunteer to donate samples? **A** – When you have your next bone marrow biopsy, ask to donate samples to the research team. We thank you for doing so.

Kathryn Maples, PharmD, BCOP is the clinical Pharmacy Specialist in MM. The role of the pharmacist is:

- Provide education/counseling when starting a new treatment regimen; review all of your medications and screen for drug-drug interactions;
- Recommend dose modifications due to organ function or tolerability concerns;
- Recommend interventions for supportive care concerns such as peripheral neuropathy (**PN**), nausea/vomiting (**N/V**), diarrhea/constipation (**D/C**), etc.;
- Submit appeals to insurance for denied medications.

She then reviewed side effects by drug classes.

- Immunomodulatory drugs –
    - Thalidomide – PN, constipation, drowsiness
    - Revlimid – neutropenia, thrombocytopenia, rash, fatigue, diarrhea
    - Pomalyst – myelosuppression, fatigue, D/C
    - Revlimid diarrhea is due to bile acid malabsorption which is treated with sequestrant daily– Colestipol, Questran, or Welchol. Imodium or Lomotil are not ideal choices for Revlimid diarrhea.
    - Thrombosis (blood clots) need prevention for duration of therapy: aspirin, Enozaparin, or oral anticoagulant rivarozaban/apixavan
- Proteasome inhibitors -
    - Velcade – PN, D/C, N/V, fatigue, thrombocytopenia
    - Kyprolis – Myelosuppression, N/V, diarrhea, infusion reactions, heart failure, edema, cough.
    - Ninlaro – D/C, Thrombocytopenia, PN, N/V.
    - Peripheral neuropathy is cumulative and dose related. Velcade administered sub-Q had a significant reduction of PN with same effectiveness against MM.

    - Treat PN with gabapentin, pregabalin, duloxetine, compounded topical gel, or tricyclic antidepressant.
- Selinexor – thrombocytopenia, fatigue, N/V, diarrhea, decreased appetite, weight loss, hyponatremia, hypokalemia, dyspnea. It is approved for use with dex in patients who have failed on a PI, Imid, and monoclonal antibody (triple refractory).
    - Selinexor nausea/vomiting – Selinexor can be taken with or without food, Zofran and Compazine can be alternated. Zyprexa can be started about two night prior to taking selinexor and take continuously.
- Venetoclax – Tumor lysis syndrome, neutropenia, diarrhea, and nausea. Used in patients with t(11:14).

Dietary Supplements – Herbs and supplements are not benign medications. They are not tested by the FDA for quality or effectiveness. Adverse reactions, increased pill burden, and herb-drug interactions with chemotherapy:

- Ginseng induces CYP3A4 which affects the metabolism of drugs that are substrates of this enzyme
- St. John's Wort has many drug interactions
- Saw Palmetto interacts with anticoagulants, antiplatelet therapy, NSAIDS
- Echinacea interacts with CYP substrates, tamoxifen, docetaxel, etoposide

DELCaP study: Diet, Exercise, Lifestyle, and Cancer Prognosis

- Primary goal – to determine whether the use of supplements during chemotherapy, particularly antioxidants, has any effects on survival outcomes
- Correlative study to a phase III trial led by SWOG in breast cancer patients
- 1134 patients were queried on their use of supplements both prior to and during treatment
- Recurrence and survival were indexed at 6 months after enrollment

DELCaP results –

- The use of any antioxidant supplement (vitamins A, C, and E; carotenoids; coenzyme Q10) both before and during treatment was associated with a 41% increase in hazard of recurrence.
- No associations were found between the use of antioxidants and chemo induced PN.
- Multivitamin use was not associated with survival outcomes.

In MM, Vitamin C and antioxidants inhibit Velcade. Please inquire with the team before starting new meds or supplements.

Questions/Answers: **Q** – Imodium (loperamide) is not for Revlimid diarrhea? **A** – The mechanism of bile acid malabsorption is not appropriate for Imodium. **Q** – Do you see pancreatitis in MM? **A** – Not commonly. **Q** – Do you recommend not taking Co Q10? **A** – Typically, yes. **Q** – What about alpha lipoic acid? **A** – In context and with review. **Q** – Are Medicare plans receptive to the new treatments? **A** – No clear information on this. **Q** – Is private insurance better than Medicare? **A** – Insurance varies too much to answer. **Q** – What about vitamin B for PN? **A** – No evidence on PI neuropathy and not helpful on chemo PN. **Q** –

Calcium? **A** – Yes. **Q** Turmeric? **A** – No, drug interactions.

Dr.Nooka gave an update on MRD and new drugs. He first expressed thanks to patients for helping Emory to achieve clinical advancement through patient data. All patients, through the last ten years, represent a diverse population. We learn more about MM through patient help. Outcomes by race helps with better treatment. Less than 5% decline to give sample to research, which is an amazing level!

M-spike, started in 1937, is an old test and has limitations on monitoring the disease. MRD at 10^{-6} is looking for one MM cell in a million bone marrow cells. Sequencing in MRD is looking for specific DNA sequence associated with malignant B-cells or T-cells. No MRD test is performed if patient is not in complete remission (**CR**). Even in stringent CR, only one third are MRD negative. MRD negative has shown that patients will stay in remission longer and better overall survival. A study was reported on 81 patients after Dara+KRd induction, transplant, and consolidation. If MRD positive, they were not tracked. 31 patients were MRD negative and went on observation only with no maintenance. Watch for results on this study in next six months to a year. MRD negative is not a cure, but an indicator of better outcomes.

Antibody Drug Conjugates (**ADC**) are a new type of treatment where chemo is attached to immune therapy that targets proteins on the MM cells and delivers the chemo to those cells. In Phase I, a very good partial response (VGPT) was attained in 60% of the patients. This level is not common for Phase I. This treatment has eye toxicity, but no one lost vision and was resolved in 30 days. Patients are evaluated prior to each dose. ADC is now in Phase II and going to the FDA for approval. Selinexor is approved by FDA for multi-refractory patients in combo with a PI. This drug is getting a 26% response rate in patients refractory to five lines of therapy. Major side effect is anorexia and supportive care is focused on this.
Question/Answers – **Q** – Will we move away from bone marrow biopsies? **A** – Bone marrow tests are being compared to blood tests, but a marrow sample is still needed periodically to verify the blood test. **Q** – Why do patients go off maintenance? **A** – Mostly due to lack of tolerance or relapse. **Q** – I saw a Winship clinic in Buford. Can I get treatment there? **A** – Once a treatment plan is created, the infusion can be delivered locally, at a Winship clinic or through other hematologists. Check with your Emory team.

Dr. Craig Hofmeister talked about immunotherapy. Darzalex binds to MM cell and hopes that the immune system sees it. BiTEs bind with the MM cell and bring the immune system over to kill the MM cells. REGN5458 trial at Emory is in Phase I. There were four responses in seven patients and they are still not at the highest dose. BMS-CC93269 has 14 patients with an overall response rate at 35%. At the highest dose there was an 88% response rate for patients penta-refractory (5 lines of therapy). One patient died from **CRS** (cytokine release syndrome) as seen in CAR-T therapy. CRS is when the treatment excites the immune system and it looks like sepsis. Dr. Hofmeister's slides are at – https://tinyurl.com/w9zgf4o
Questions/Answers – **Q** – Should a patient join a clinical trial early or later in treatment? **A** – This is based on lines of therapy and the requirements of the trial. 1-3 relapses are considered early, more than three is considered later. **Q** – What is an oncolytic virus? **A** – On Good Morning America several years ago a patient was treated with measles virus and got a good response, but later relapsed. Oncolytic virus is injected into the tumor to get an immune response. It is combined with PI and allows the virus to infect the MM cells and die. As the cell

dies, PD-1 is expressed on the surface of the cell. Adding this drug to a PD-1 target opens the MM door for new therapy. **Q** – If I am on a SMM clinical trial, can I change from one clinical trial to another? **A** – It depends on clinical trial criteria. Usually SMM suggests no prior treatment.

Submitted by Nancy Bruno

Southside Myeloma Support Group
January 25, 2020

Next speaker: **Leon Bernal, MD.** Oncologist-Hematologist at Grady and Emory Winship. Dr. Bernal will share his research on inflammation and myeloma; will speak to the (usual) differences in lab values for blacks and whites; and, will share other research updates. Additionally, **Natalie Hernandez, PhD** from Morehouse School of Medicine will share results from a study conducted about Clinical trials in African Americans.
The meeting was opened with a moment of silence by Doris.

Our guest speaker was Oncology Nurse Practitioner, Christina Chase. Christina supports several oncologists at Emory Winship Cancer Institute, including Dr. Heffner. Her topic was **The Realities of Clinical Trials in Multiple Myeloma: Myths versus Facts.**

Christina wasted no time in shining a light on the horrors of the U.S. Syphilis Study at Tuskegee and of how the very popular research HeLa cell line came to be from Henrietta Lacks. These studies and many more lesser known studies led to many protections from the federal government. Some of those protections include going from “consent” forms to “**Informed Consent.”** Some features of Informed Consent include having an **8th grade reading** level or less, encouraging potential patients to take the form home for closer review before signing (and that they have their own copy of the consent form), and emphasizing that they are able to withdraw from the study at any time without penalty. Institutional Review Boards **(IRBs**) are established at all research institutions to review and serve as an oversight Committee for all research conducted with Humans. There is usually a patient or community representative on this Board. Overall, the protections strive to make participation in Clinical Trials (CTs) as transparent as possible.

In general, participation in Clinical trials include 7% African Americans, 76%

white, 11% Asian, and 6% other racial/ethnic groups. For Myeloma studies, African Americans make up 9% of clinical trial participants, 91% other groups. This can be a problem in developing appropriate treatments, considering myeloma occurs in blacks at 2-3 times the rate of whites, at an earlier age, and mortality in higher in blacks than white.

What are the benefits of participating in CTs?

- There are usually good results
- You will have early access to new medications
- You always have access to a clinical coordinator'
- You have the satisfaction of knowing you have contributed to the advancement of the science of treatment though you may not always benefit personally from the treatment

Potential Negatives in participating in CTs

- You usually have more clinic visits
- Potential side effects different from standard of care
- You may not respond well to the new therapy or standard therapy
- The new therapy is potentially not as effective as the standard therapy
- Insurance does not always cover the cost of new medications

There are several concerns about Clinical Trials that patients have shared with Christina in her practice.

Patient Concern	**Response**
"If I don't want to participate in Clinical trials (CT), what are my options?"	The approved regimens which may no longer be effective with you.
Clinical trials are riskier than other treatments.	Drugs used in CTs are FDA approved
I want the gold standard – current treatment.	Since there is no cure, there will likely be relapse at some point.

Clinical trials are for people that do not have other options.	Some people volunteer for CTs because they know the benefit it can mean for the future. It is true that some people have no other options.
If my doctor does not mention a Clinical Trial, it must not be for me.	Research facilities like Emory keep up with the current trials, especially in the fast-moving research and progress in the myeloma area. Multiple myeloma is a complex disease, with varying treatment regimens based on the unique situation of the patient. Most general oncologists are not current on the science of the treatment or the research trials.
"Trials are more important than the patient.	You can stop participation in CT at any point. Some say you get 'Cadillac' service with CT participation.
I do not want to run the risk of getting a placebo.	Most trials do not have a placebo. You either get the current standard treatment or the new treatment on trial to see if the newer treatment is better than what is already available.
If I do not enroll in the CT, my physician team will not treat me with the best current option.	You will be treated with the current standard of care for the level of your disease.

Always ask questions before consenting to participate.
Do ask: What are the standard care alternatives? Who is the Principal Investigator? What medications am I not allowed to take with this medication? With the increased number of visits, will the study pay for travel and/or parking? What Phase of Clinical Trial is this?

Phases of Clinical Trials – clinical trials.gov., National Library of Medicine. All Phases are FDA approved before they begin.

- **Phase 1:** Studies that are usually conducted with healthy volunteers and emphasize safety. The goal is to find out what the drug's most frequent and serious side effects are and evaluate different dose levels. Usually conducted for several months with less than 20 volunteers.
- **Phase 2:** Studies that gather preliminary data on effectiveness (whether the drug works in people who have a certain disease or condition). For example, participants receiving the drug may be compared with similar participants receiving a different treatment, usually the standard of care. Safety continues to be evaluated, and short-term adverse events are studied. Usually for one year with 100 -300 participants.
- **Phase 3:** Studies that gather more information about safety and effectiveness by studying different populations and different dosages and by using the drug in combination with other drugs. No placebos are used in myeloma studies. Usually over 1-2 years with thousands of patients in different research centers.
- **Phase 4:** Studies occurring after FDA has approved a drug for marketing. These including post-market requirement and commitment studies that are required of or agreed to by the sponsor. These studies gather additional information about a drug's safety, efficacy, or optimal use

How to find Clinical Trials available to you (Vena, Pat, and others)

Unfortunately, the Emory Winship website can be difficult to navigate. We will find out if there is an easy way to identify myeloma CTs at Emory. The IMF sponsors the **Myeloma Matrix 2.0** that can guide you through studies close to your geographic area. https://www.myeloma.org/clinical-trial-search

There are three national studies that are currently recruiting participants;

MYDRUG (Myeloma **– D**eveloping **R**egimens **U**sing **G**enomics**)**

The MyDRUG clinical trial studies the impact of several different drugs that target the genetic mutations and other molecular abnormalities identified in CoMMpass. This kind of clinical trial, known as a platform study, not only has the potential to accelerate the speed by which new treatments are tested, it

also more efficiently matches patients to treatments that are most likely to work. It is the first and only clinical trial of its kind in multiple myeloma. Through CoMMpass, we learned that multiple myeloma is not just one disease. Multiple myeloma is made up of at least 12 different sub-types, each of which is defined by specific genetic mutations and other abnormalities that affect how the disease responds to specific treatments. https://themmrf.org/we-are-curing-multiple-myeloma/mydrug/

The Promise Study.
The first study to test healthy people who may be at risk for early warning signs of a blood cancer called multiple myeloma. Seeking **first degree family members of patients (mother, father, sister, brother) over the age of 45 with family members of MGUS, smoldering myeloma, multiple myeloma patients and African American patients, who are 3 times as likely to develop multiple myeloma. Joining the study is easy. You are mailed a kit which you take to a lab and the lab takes care of sending the samples to the researchers. What can we learn from the study of 50,000 people who are likely to be at risk for early myeloma conditions and their family members?** This study aims to make multiple myeloma a cancer that is preventable. **https://www.enroll.promisestudy.org/**

Total Cancer Care
The Total Cancer Care® protocol is intended to help understand how cancer differs in every patient.
By studying large numbers of patients, with and without cancer, and studying their tissue samples, we will be able to move cancer research forward and personalize cancer care, which we expect will make cancer care more effective. Simply put, the **Total Cancer Care®** protocol is designed to help us find ways to individualize your care.
https://winshipcancer.emory.edu/patient-care/clinical-trials/total-cancer-care.html

Action item:
With so many decisions patients are expected to make, the group thought there should be a Clinical Trials participation Checklist or “Cheat Sheet”. Vermell, Christina, and Gail agreed to work on this checklist and distribute it to the clinics and to patients. The checklist should include important questions patients should ask and understand before consenting to participate in trials.

All patients and caregivers provided updates to their therapy. More than one patient experienced low white blood cell counts after being on Rev for 28 -day cycles. After **Carole** asked her provider about the 7-day rest (21 days on, 7 days off), her blood levels returned to normal. Some people are on 14 days on, 14 days off schedule like **Doris**; **Ted** is on Rev, Darzalex, and Dex. He was approved for injectable Darzalex but stressed the importance of providers including patients at every stage of treatment. He was not aware approval was being sought; **Gloria** shared that she was on dialysis for four months at diagnosis in 2009 and was told she would never work again. She recently reduced her work hours because she enjoys her work and is doing very well. She stresses to us to be strong, be positive in everything you do; Alma is on the CC220 CT and so far all is well.

Respectfully submitted, Gail