

Myeloma Foundation Uses Patient Connections To Help Speed Drug Trials

Bolstered by a huge patient database, the Multiple Myeloma Research Consortium is helping to speed trials of new therapies, including some of the most talked about investigational drugs in the disease space, like carfilzomib and pomalidomide.

An arm of the Multiple Myeloma Research Foundation, the research consortium is an affiliation of about 16 centers, including the Dana Farber Cancer Research Institute and the University of California-San Francisco. In recognition that 80% of myeloma patients are seen at community centers, the MMRC has been looking to boost participation in that setting and of its 16 members, three are currently community-based.

Founded in 1998 by myeloma patient and former pharmaceutical industry executive Kathy Giusti, the MMRF is dedicated to speeding drug development and takes a business-minded approach to achieving its goals. Rather than create an organization that would mainly foster education about the disease, Giusti founded the MMRF to provide among other things, direct financial grants to biotechs and also direct support in planning and running trials. In 2004, the MMRF spun off the MMRC as a group of trial centers unified by agreed good practice standards.

The MMRF has about half the U.S. myeloma patient population in its database. About 20,000 patients are newly diagnosed each year in the U.S. and more than 60,000 have myeloma at any given time. Using the database, the MMRF is able to alert patients to trial openings in their areas. The MMRF website boasts about 200,000 members, including patients, caregivers and professionals, and the organization is looking to further develop its online community in the future, including stratification by genetic disease type.

Trials Open 60% Faster Than Industry Norms

An analysis of the 21 trials supported by the MMRC from May 2006 to June 2010 showed that myeloma trials done partly with consortium resources opened 60% faster than the industry benchmark in oncology, according to a poster presentation at the American Society of Hematology meeting in December.

One of the major studies that MMRC helped along was a successful Phase II 003 A1 trial of **Onyx's** proteasome inhibitor carfilzomib in the relapsed/refractory setting. Carfilzomib is being positioned as a potential successor to **Takeda Pharmaceutical Co. Ltd.**'s blockbuster *Velcade* (bortezomib) ("Carfilzomib Works Well As Salvage Treatment; Momentum Builds For Frontline Role," "The Pink Sheet" DAILY, Dec. 7, 2010). Results from nine other trials that included MMRC participation were also presented at the 2010 ASH meeting, including tests of the immunomodulator pomalidomide, **Celgene Corp.**'s successor to the blockbuster *Revlimid*, and **Bristol Myers-Squibb Co./Facet Biotech Corp.**'s monoclonal antibody elotuzumab.

Overall, the MMRF has a yearly research budget of about \$15 million, about \$7 to \$8 million of which is devoted to the MMRC.

Foundations have been playing an important role in developing drugs for rare diseases, led by the Cystic Fibrosis Foundation and other groups. The need for involvement of disease-centered groups and philanthropy has grown even stronger with the decline of financial markets ("Venture Philanthropy: The New Venture Capital?" Start-Up, March 2007.) Having raised more than \$120 million to date, the MMRF claims to be the world's top funder of myeloma research.

While not unique in its support of clinical trials in its disease space, the MMRF has made impressive strides in improving clinical trial conduct and pushing centers towards best practices.

Incentives For Centers To Speed Trials

To become part of the MMRC network, institutions agree to conduct early-stage myeloma trials using consistent metrics. If a company wants to work with sites in the network, it signs only one standard agreement to connect to all of the MMRC members.

With increasing understanding of the heterogeneity of many cancers and the variety of genes at play, the MMRC sites are trying to move the field forward. Specimens for genetic testing can often be difficult to access in oncology research, in part due to the lack of sharing among academic institutions. There are other challenges as well. Patients may not have enough myeloma cells for some tests and tissue samples must be prepared and stored if they are to be of any use.

Members of the MMRC agree to contribute to a shared tissue bank which now has over 3,000 specimens of bone marrow (which contains myeloma cells) and “matching” peripheral blood. Because myeloma doesn’t usually circulate in peripheral blood, the peripheral blood serves as a matched control.

All MMRC members are required to have a project manager on site. But this full-time staff person is provided free of charge for the top-third of member institutions, based on their record of meeting guidelines for trial timetables and quality metrics. The MMRF also provides partial funding for project managers to other sites in the middle third of the MMRC. This system provides an incentive for institutions to speed trials, explained Anne Quinn Young, VP of communications at the MMRF.

MMRF’s CMO Susan Kelley and other key staff members are also available to help with planning protocols and other aspects of running clinical trials.

The organizational support appears to be paying off for sponsors. In the poster presentation analyzing trial timetables, the foundation noted that enrollment in trials involving the MMRC was completed two months (14%) earlier than industry norms. And MMRC sites typically enrolled 25% more patients than the number initially agreed upon with companies.

Overall the MMRC has worked on 27 clinical trials and 15 novel compounds (*see chart for current trials*).

The MMRC’s work with carfilzomib dates back to an initial agreement in 2006 with **Proteolix**, which initially developed the candidate; Onyx acquired Proteolix in October 2009. The MMRC was involved from day one on carfilzomib clinical trial development. Its role lay in brokering relationships with the myeloma community, selecting trial sites and drafting trial protocols, explained Quinn Young. Two trials were launched, including the just-reported 003 A1, which could serve as the basis for accelerated approval.

In a Phase I/II trial of pomalidomide in 30 patients, the MMRC network accounted for 45% of the total sites but enrolled 90% of patients accrued. Recruitment in that trial wrapped up four months early and is due to complete in September 2011.

Among other things, the foundation wants to ensure that research for a relatively rare disease, such as multiple myeloma, does not falter following the release of a number of successful drugs that have improved the outlook for patients with the disease in the last decade

From Pharma To Venture Philanthropy

MMRF CEO Kathy Giusti’s approach to disease advocacy is rooted in her professional background. She began her career in 1980 with **Merck & Co. Inc.**, and her last position before founding the MMRF was executive director at **G.D. Searle & Co.**

The introduction of Celgene's *Thalomid* (thalidomide) and Revlimid and Takeda/Millennium's Velcade have dramatically improved the outlook for patients, increasing average survival for normal-risk patients to eight to 10 years ("Market Snapshot: Myeloma Drugs Promise To Live Up To Hype," "The Pink Sheet," Feb. 15, 2010).

Though survival on average is 7 to 8 years, the picture doesn't look nearly as good for the 10% to 15% of patients with genetic aberrations of the disease, who have a life expectancy of only one to two years.

"It's still highly fatal for many patients, but we have been able to extend life," Giusti said during Faster Cures' Partnering for Cures meeting in New York on Dec. 14. Unmet need is still high for relapsed/refractory myeloma patients, whose response rates typically fall below 35%.

"The field is now crowded and we have to find ways to de-risk [development]," said Giusti, who noted that she has been on all of the approved drugs and many investigational treatments since she was diagnosed in 1998 with a high-risk form of myeloma and given three years to live.

Next Step: Personalized Medicine Initiative

During the Partnering for Cures meeting, Giusti stressed the need to understand the genetics of the disease and how that relates to tendency for relapse.

Working with MIT and Harvard's Broad Institute, a genomics research organization, the MMRF has been analyzing specimens from its tissue bank to come up with a more extensive genetic analysis of myeloma. A study of 250 bone marrow samples and gene sequencing for 38 patients is expected to be published next year in *Nature*. This represents one of the largest sets of sequenced patient samples for any cancer, according to the MMRF, and will be key for identifying targets that can be used to develop diagnostics and therapeutics. Several new genes were identified for the first time, the group reports.

Based on this research, sometime in 2011, the MMRF will be unveiling a new personalized medicine initiative that will cost another \$30 million to \$40 million above current fundraising in the next five years.

"We are now putting a huge amount of money into epigenetics," Giusti said.

Among other things, the initiative will include a longitudinal study of 1,000 patients. The MMRF already encourages patients who are seen at MMRC member centers to bank their tissue when they need a bone marrow test for diagnostic reasons. In the future, patients will be able to enroll in the longitudinal study at participating centers and have their full molecular profiling done. Participating sites will be listed online.

Giusti, who has a background in consumer marketing, said the foundation also plans to greatly develop its large online community, gathering more information about patients and creating parts of the site that are tailored to patients based on their molecular profiling. For example, some genetic types respond better to proteasome inhibitors like Velcade and carfilzomib. An online community could be developed for these disease subtypes and could provide more targeted education to patients as well as help more effectively recruit patients for appropriate trials.

"We want to get to the point where patients are not receiving therapy they are not likely to benefit from," Giusti said.

By Emily Hayes

Drug Research Supported By The Multiple Myeloma Research Foundation

The Multiple Myeloma Research Foundation aims to speed drug development through direct grants to biotechs and via access to its network of 16 sites, mostly U.S. academic institutions with some community centers. The drugs below received some form of support, either grant funding or involvement in trials by the MMRC, the foundation's clinical trials network arm.

Drug & Developer	Trials
AT7519 Inhibitor of cyclin-dependent kinases (CDK) Astex Therapeutics	Phase I/II with bortezomib (Millennium/Takeda's proteasome inhibitor <i>Velcade</i>) in relapsed and refractory patients
Bendamustine (<i>Treanda</i>) Inhibitor of mammalian target of rapamycin (mTor) approved for chronic lymphocytic leukemia and non-Hodgkin lymphoma Cephalon	Phase I with lenalidomide (Celgene's immunomodulatory drug <i>Revlimid</i>) and dexamethasone in relapsed/refractory myeloma
Carfilzomib Proteasome inhibitor Onyx	Phase III with lenalidomide and dexamethasone vs. lenalidomide/dexamethasone alone in relapsed/refractory myeloma after one to three prior therapies
Dovitinib (TKI-258) Kinase inhibitor that targets fibroblast growth factor receptors (FGFR) expressed in myeloma patients with translocation of chromosomes 4 and 14	Phase I in patients with translocation of chromosomes 4 and 14, initially studied in all comers in the MMRC
Elotuzumab Humanized monoclonal antibody that binds to CS1, a cell-surface glycoprotein Facet Biotech/Bristol-Myers Squibb	Entering Phase III for 2011 in relapsed/refractory myeloma after one to three prior therapies
Everolimus (RAD001, <i>Afinitor</i>) mTor inhibitor approved for renal cell cancer Novartis	Studied in preclinical models with MMRF grants
GRN163L Telomerase inhibitor Geron	Phase I in refractory/relapsed myeloma (closed to enrollment)
INK128 mTor inhibitor (TORC1 and TORC2) Intellikine	Phase I in relapsed/refractory myeloma
MLN8237 Aurora A kinase inhibitor Millennium/Takeda	Phase I with bortezomib in relapsed/refractory myeloma
NPI-0052 Proteasome inhibitor isolated from <i>Salinispora tropica</i> , a newly discovered marine actinomycete Nereus Pharmaceuticals	Phase I in relapsed/refractory myeloma
Panobinostat (LBH589) Histone deacetylase (HDAC) inhibitor Novartis	Phase III with bortezomib vs. bortezomib alone in relapsed/refractory myeloma after one to three prior therapies

PD0332991 Specific inhibitor of CDK4 and CDK6 Pfizer	Phase I/II with bortezomib and dexamethasone in refractory myeloma after one prior therapy
Perifosine (KRX0401) Inhibits Akt activation in the phosphoinositide 3-kinase (PI3K) pathway, among other signal transduction pathways Keryx Biopharmaceuticals	Phase III with bortezomib vs. bortezomib alone in patients with one to three prior therapies
Plitidepsin (<i>Aplidin</i>) Novel cytotoxic originally isolated from the marine tunicate <i>Aplidium albicans</i> and now made synthetically PharmaMar	Phase III with dexamethasone vs. dexamethasone alone in relapsed/refractory myeloma after three to six prior therapies
Pomalidomide Immunomodulator, successor to lenalidomide Celgene	Phase II enrollment in relapsed/refractory myeloma complete. Phase III slated to open in late 2010 or early 2011 in relapsed/refractory patients with one to three prior therapies
Sorafenib (<i>Nexavar</i>) Multikinase inhibitor approved for renal cell and liver cancer Onyx/Bayer	Studied in preclinical models with support from MMRF grants
Temsirolimus (<i>Torisel</i>) mTor inhibitor approved for renal cell carcinoma Wyeth/Pfizer	Phase I/II investigator-sponsored trial in relapsed/refractory myeloma
Vorinostat (<i>Zolinza</i>) HDAC inhibitor approved for cutaneous T-cell lymphoma Merck	Phase III with bortezomib vs. bortezomib alone in patients with one to three prior therapies
<i>Sources: MMRF, company websites</i>	

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