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FOLLOWING COMMPASS

BY ERIN MCCALLISTER, SENIOR EDITOR

Amidst a flood of promising data for hot targets, indications and technologies at this year's American Society of Hematology meeting, one collection of presentations stands out not only for the wide-reaching implications of their data, but also for how the data came to be. It is now apparent that CoMMpass — a massive clinical study in multiple myeloma that was conceived of and is led by patients — is influencing what drugs are developed and will influence how they are used after approval.

The Multiple Myeloma Research Foundation (MMRF) launched CoMMpass in 2011 to identify molecular drivers in MM with the goal of discovering new drug targets and treatment combinations that could result in better outcomes. The trial is a public-private partnership with four industry members (see "Building CoMMpass," page 4).

Results reported at ASH represented the most robust data set yet for the trial, with seven abstracts and analyses derived from more than 700 patients. Among the key findings highlighted by MMRF, MM companies and clinicians was the identification of four previously described genes and targets as driver mutations in newly diagnosed patients.

The trial has also revealed genomic differences that could lead to targeted therapies for African-Americans, who are twice as likely to get MM; and findings related to disease burden and quality of life (see "Highlighting CoMMpass," page 4).

One MM company contacted by BioCentury is already using the data to evaluate new drug candidates, while other companies are querying the results to better understand how patients in their clinical trials might respond to drug candidates.

The CoMMpass data also will inform the treatment arms in a collaborative MM master protocol trial that is expected to begin next year.

"I DON'T THINK ANYBODY COULD HAVE BROKERED SOMETHING LIKE THIS BESIDES A PATIENT ADVOCACY GROUP."

DIXIE ESSELTINE, TAKEDA

But companies and doctors are most excited about future data from CoMMpass, which both groups believe will allow them to choose, sequence and combine established and newly approved therapies in the real world, as well as identify new drug candidates that could lead to a cure.

EARLY RETURNS

CoMMpass is a sequencing study that is following 1,000 patients for eight years to determine how molecular profiles change with response and retreatment.

Patients have a bone marrow biopsy at study entry and each time their disease progresses. The biopsy is sequenced and investigators collect response data, including levels of minimal residual disease (MRD), as well as quality of life and toxicity data.

The protocol specifies first-line treatment with physician's choice of either doublet therapy — dexamethasone plus either an immunomodulatory agent or a proteasome inhibitor — or triplet therapy with all three types of agents. There is no specified treatment regimen after first relapse.

MMRF and its collaborators, including the Translational Genomics Research Institute (TGEN), analyze the data from CoMMpass every three months and conduct predetermined analyses based on work plans agreed to by an advisory board. The board includes MMRF, industry and academics.

Collaborators have exclusive access to the data for six months, after which the data are uploaded to an online portal that is available to the public.

CoMMpass hit its 1,000 patient target this September, and MMRF said enrollment in the international trial would be open through year end to allow up to 100 more patients to enroll.

This year's ASH presentations confirmed earlier findings and generated new hypotheses about what might be driving the disease.

The first interim look in 2013, consisting of one abstract including data from 178 patients, identified a handful of genes that were mutated frequently. These included BRAF; neuroblastoma Ras viral (v-Ras) oncogene (NRAS); K-Ras (KRAS); mitotic control homolog (DIS3); family with sequence similarity 46 member C (FAM46C); TNF receptor-associated factor 3 (TRAF3); and zinc finger protein 100 (ZNF100).

Updated analyses of data from 760 patients, which TGEN presented at ASH, show 20 mutated genes that are significantly associated with MM. A different analysis of the data set that looked for genes that drive MM in newly diagnosed patients identified 18 genes, not all of which are frequently mutated in CoMMpass (see "Initiating Mutations," page 5).

In fact, only four genes appeared in both analyses: DIS3, KRAS, NRAS and TRAF3.

A separate presentation by TGEN compared the genomic profiles of 93 self-identified African-Americans enrolled and 377 European Americans. The prevalence of MM in African-Americans is twice that of European Americans; however, clinical trials often enroll only about 10% African-Americans.

Four genes were mutated at a higher frequency in African-Americans, including the novel target patched domain containing 3 (PTCHD3). African-Americans had a lower frequency of the high-risk translocation 14q32.

A third presentation, by GNS Healthcare Inc., found that the RNA, 7SK small nuclear (RN7SK) gene was part of the cyclin dependent kinase 9 (CDK9)/cell division cycle 7-related protein kinase (CDC7) pathway, and that inhibitors of the pathway could be beneficial. However, the model found that it may take a year to see a treatment response.

"Now that we know it's going to take longer to see a response, maybe we design a trial for long-term assessment rather than short term," said GNS EVP Iya Khalil.

MMRF announced a collaboration in January to use GNS's artificial intelligence platform to develop *in silico* models of MM based on the CoMMpass data.

Otsuka Pharmaceutical Co. Ltd.'s Astex Therapeutics Ltd. subsidiary has AT7519, an inhibitor of CDK1, CDK2, CDK4, CDK5 and CDK9. The compound is in Phase II testing in combination with Velcade bortezomib from Takeda Pharmaceutical Co. Ltd. and Johnson & Johnson to treat previously treated MM.

Martin Buckland, chief corporate officer at Astex, told BioCentury the company is reviewing the results to determine how they might affect a potential regulatory path for AT7519.

"THIS NEW DATA NOW PROVIDES THE RATIONALE FOR STUDYING THOSE DRUGS IN PATIENTS WITH THOSE MUTATIONS."

CRAIG TENDLER, JANSSEN

Tolero Pharmaceuticals Inc. has a Phase II program against CDK9, alvocidib, for acute myelogenous leukemia (AML) and chronic lymphocytic leukemia (CLL).

LEARNING INTEGRATION

Companies in the CoMMpass collaboration are already using the results to inform development decisions and assess clinical findings.

"We are starting to see an emergence of certain mutations that are lending themselves to new targets that could be drugged," said Blake Morrison, VP of medical and scientific affairs at MMRF.

Craig Tendler said the new TGEN analysis identified mutations that are targets of candidates in development for other indications at J&J's Janssen Research & Development LLC unit.

"This new data now provides the rationale for studying those drugs in patients with those mutations who might be particularly sensitive," said Tendler, who is VP of late-stage development and global medical affairs for oncology, hematology and supportive care.

Specifically, Tendler pointed to the data on KRAS, as Janssen has a KRAS inhibitor in discovery.

"That's not something that we had known before," he said. "These new findings now open up the possibility of using it not just in lung cancer, where we also see that mutation, but now we will be thinking about it in multiple myeloma."

Dixie Esseltine, Takeda VP of oncology clinical research, said Takeda is also evaluating its pipeline, though it may be too soon to make any decisions about advancing programs based on CoMMpass.

"We are alert to and evaluating our pipeline for opportunities to explore. We understand, however, that to date the follow-up is short, and the treatment is only with the IMiD/proteasome inhibitor combinations," she said.

"I believe that the evidence generated that will be the most useful will be as patients go through the first phases of the natural history of the disease, and we are able to understand what is the biology of those patients with early relapses and who responds," added Jesus Gomez-Navarro, head of clinical research at Takeda.

Esseltine also noted that the public data portal enables companies to query the data based on unexpected findings in the clinic.

"If we see an unexpectedly good response or a mutation not usually associated with multiple myeloma, I can go through the open access, interrogate the CoMMpass database and say have you seen this, and see if we have a mutation or target that is worth tracking in the sense that it shows up in the database as being linked to the disease," she told BioCentury.

The toxicity and quality of life data could be useful for similar purposes.

"If there is an association between the genomic profile and toxicity, it might help us to better direct less toxic therapies to certain patients," Esseltine said.

She is also hopeful that additional data from African-American patients enrolled in CoMMpass will help to validate the early findings.

"This is a group of patients that we don't know that much about, and this poster suggests some tantalizing clues of what may be important drivers of their disease. But we need more patients and long-term follow-up to see the more exact relationships," Esseltine said.

Amgen Inc. is in the interesting-but-early camp. "It's possible that new targets could emerge as we do this dense molecular profiling of tumors, but it's still early," said David Reese, SVP of translational research.

KEYS TO THE COMBINATION

In addition to identifying new targets for drug development, MMRF thinks CoMMpass could help doctors determine which therapies to give when, and in what combination, which becomes more difficult and complex as more drugs are approved.

Ten drugs are approved for MM in the U.S., including three approved in the past month: Darzalex daratumumab from J&J and Genmab A/S, Takeda's Ninlaro ixazomib and Bristol-Myers Squibb Co.'s Empliciti elotuzumab.

Each was approved in a slightly different setting. Darzalex was approved as a monotherapy in patients who had failed at least three prior therapies. Ninlaro was approved in combination with Celgene Corp.'s Revlimid lenalidomide and dexamethasone for patients who had failed at least one

BUILDING COMMPASS

The Multiple Myeloma Research Foundation conceived of the CoMMpass study in 2009 to capitalize on insights into the molecular profile of multiple myeloma gleaned from the foundation's ongoing MM Genomics Initiative, which resulted in the first sequencing of the MM genome that same year.

"We saw the promise of the data generated from the genomics initiative and we realized that there was a need to follow patients from their very first diagnosis and throughout their journey with the disease, sequencing patients' myeloma cells at each disease recurrence to see how they adapted in response to the treatments they were exposed to," said MMRF SVP of Research Daniel Auclair.

But before MMRF could launch CoMMpass, it had to get buy-in from patients and industry.

MMRF surveyed patients to get feedback on enrollment criteria and to gauge their willingness to participate in a study in which their data would be made public.

"We did some extensive qualitative and quantitative research with patients to figure out if they would consider enrolling in such a study, how often they would be willing to get bone marrow biopsies, would they commit to being followed longitudinally for several years and would they commit to having their data in the public domain," said Anne Quinn Young, VP of development and strategic partnerships for MMRF.

Patients' biggest concern was the frequency of biopsy. "We had suggested every three months, and they said that was too much," Young said.

MMRF designed the protocol to require biopsies prior to treatment and at relapse, which Young said is "standard practice at some centers" and was acceptable to patients.

Next, MMRF sought industry support to help fund the trial and to ensure that, if new targets were found, there would be companies involved that could or would be interested in developing candidates against them.

But the foundation found companies reluctant to participate because of concerns over sharing data and the fact that resulting discoveries would not be patentable. MMRF offered companies a first look at the data six months before they would be made public.

Takeda Pharmaceutical Co. Ltd. became the founding industry partner in September 2011, followed by Onyx Pharmaceuticals Inc. that December. Bristol-Myers Squibb Co. signed on in December 2012, followed by Johnson & Johnson's Janssen Research & Development LLC in June 2013. Amgen Inc. is now listed as partner after it acquired Onyx in 2013.

"I don't think anybody could have brokered something like this besides a patient advocacy group. It is a valuable piece of research that required multiple stakeholders and patients pointing us in the right direction," said Takeda VP of Oncology Research Dixie Esseltine.

— ERIN MCCALLISTER

HIGHLIGHTING COMMPASS

Results from the CoMMpass study presented at this month's **American Society of Hematology** meeting included seven abstracts and analyses derived from over 700 multiple myeloma patients. The **Multiple Myeloma Research Foundation** (MMRF) and its collaborators presented data from three different analyses, which identified driver mutations in newly diagnosed patients, as well as a novel mutation in African-American patients. Researchers at other institutions presented their analyses of the publicly available data, which detailed associations between quality of life and disease burden metrics. (A) MMRF collaborator; *Source: American Society of Hematology*

Presenter	Findings
GNS Healthcare Inc. (A)	Computational analyses using in silico models of MM identified RNA 7SK small nuclear (RN7SK) as a mutated gene that plays a role in the cyclin dependent kinase 9 (CDK9)/cell division cycle 7-related protein kinase (CDC7) pathway, and suggested inhibitors of the pathway could produce a treatment response.
Icahn School of Medicine at Mount Sinai	Computational analyses of data from 92 samples identified mutated genes, including fibroblast growth factor (FGF) receptor 3 (FGFR3; CD333), that affect multiple pathways in MM, including RNA processing and translation. FGFR3 had been previously identified by MMRF collaborators as being frequently mutated in MM patients.
Translational Genomics Research Institute (TGEN) (A)	Cluster analysis of genomic data from 760 newly diagnosed patients found 18 disease-initiating mutations; also identified linkage between triplet therapy and improved progression-free survival (PFS).
TGEN (A)	Analysis of 93 self-identified African-Americans and 377 European Americans with MM found that the African-Americans had a higher frequency of mutated patched domain containing 3 (PTCHD3) (6% vs. 0.04% in European Americans, p=7.07E-06). The African-American group had a lower frequency of the high-risk translocation 14q32 (10% vs. 37% for European Americans, p-value not given).
Washington University School of Medicine	An evaluation of disease burden in 92 patients ≥75 and 533 patients <75 years of age found that older patients had higher disease burden and performance status, but improved emotional functioning and reduced financial burden than younger patients.
Washington University School of Medicine	An analysis of 475 patients found that those with poorer performance status also had lower overall quality of life. When looking at the individual QOL domains, physical function was more closely associated with performance status than emotional function.
Washington University School of Medicine	An evaluation of disease and symptom burden by International Staging System classification found that burden was similar between stage I and II patient groups, suggesting ISS may not adequately distinguish between the two.

INITIATING MUTATIONS

Data from the CoMMpass study presented at this month's **American Society of Hematology** meeting identified 18 disease-initiating mutations in newly diagnosed multiple myeloma patients. *Source: Translational Genomic Research Institute*

Gene/target
Actin gamma 1 (ACTG1)
Early growth response 1 (EGR1)
Family with sequence similarity 46 member C (FAM46C)
K-Ras (KRAS)
Mitotic control homolog (DIS3)
Neuroblastoma Ras viral (v-Ras) oncogene (NRAS)
Tumor necrosis factor (TNF) receptor-associated factor 3 (TRAF3)
Ataxia telangiectasia mutated (ATM)
Cyclin D1 (CCND1; BCL1)
DNA (cytosine-5-)-methyltransferase 1 (DNMT1)
Epidermal growth factor receptor 4 (EGFR4; HER4; ErbB4)
ETS variant gene 1 (ETV1)
Eukaryotic translation initiation factor 2B subunit epsilon (EIF2B5)
Fibrous sheath interacting protein 2 (FSIP2)
Obscurin (OBSCN)
Paired box 6 (PAX6)
Piccolo presynaptic cytomatrix protein (PCLO)
Ryanodine receptor 2 (RyR2)

prior therapy. Empliciti was approved in combination with Revlimid for patients who had failed one to three prior therapies.

Doctors in the audience and on a panel during an ASH session focused on the new drugs said they are eager but uncertain about using the drugs in combinations and settings other than what was tested in clinical trials.

"What CoMMpass gives us is an indication of how to combine," said Liviu Niculescu, VP of global medical affairs at Takeda.

Suzanne Lentzsch, director of multiple myeloma and amyloidosis at New York Presbyterian/Columbia University Medical Center, thinks the ability of CoMMpass to identify and track changes to driver mutations as patients relapse will be most useful in guiding therapy.

Ravi Vij, professor of medicine in the division of medical oncology at Washington University School of Medicine, added: "The data from CoMMpass has the potential to be very powerful in answering questions around how do we incorporate and sequence these drugs."

"It will give us clues and help to bring in an era of personalized medicine to multiple myeloma. But to definitively answer the question of how to sequence and combine the new therapies, you would need another trial," Vij said.

COMMPASS MASTER

MMRF is working with regulators to finalize an MM master protocol to do just that. The group first announced plans for the study in 2014 and plans to start it next year.

The protocol will allow simultaneous, parallel Phase II testing of multiple MM drug candidates within a single study design.

The trial will enroll relapsed patients who would be assigned to a specific treatment arm based on their genomic profile.

"From CoMMpass we are generating clinical-grade reports on patients' mutation profile," which will inform the different molecular cohorts in the master protocol trial, said Daniel Auclair, SVP of research at MMRF.

While the complete set of genomic cohorts and drug candidates isn't yet finalized, Auclair said BRAF would be one of the arms.

For Tendler, CoMMpass and the master protocol trial go hand-in-hand.

"This is really how the CoMMpass data becomes applicable to treatment choices," he said. "This really will accelerate drug development and identify potential targets that may have a very useful role in the specific subtype of melanoma."

Morrison said MMRF has submitted CoMMpass data abstracts to the American Association for Cancer Research (AACR) annual meeting next April in New Orleans and expects more abstracts to be presented at the American Society of Clinical Oncology (ASCO) meeting next June as well. bc

COMPANIES AND INSTITUTIONS MENTIONED

American Association for Cancer Research (AACR), Philadelphia, Pa.
American Society of Clinical Oncology (ASCO), Alexandria, Va.
American Society of Hematology (ASH), Washington, D.C.
Amgen Inc. (NASDAQ:AMGN), Thousand Oaks, Calif.
Bristol-Myers Squibb Co. (NYSE:BMY), New York, N.Y.
Celgene Corp. (NASDAQ:CELG), Summit, N.J.
Genmab A/S (CSE:GEN; Pink:GMXAY), Copenhagen, Denmark
GNS Healthcare Inc., Cambridge, Mass.
Johnson & Johnson (NYSE:JNJ), New Brunswick, N.J.
Multiple Myeloma Research Foundation (MMRF), Norwalk, Conn.
New York Presbyterian/Columbia University Medical Center, New York, N.Y.
Otsuka Pharmaceutical Co. Ltd., Tokyo, Japan
Takeda Pharmaceutical Co. Ltd. (Tokyo:4502), Tokyo, Japan
Translational Genomics Research Institute (TGEN), Phoenix, Ariz.
Tolero Pharmaceuticals Inc., Lehi, Utah
U.S. Food and Drug Administration, Silver Spring, Md.
Washington University Medical School, St. Louis, Mo.

REFERENCES

Tkach, K. "Cause, not correlation." *BioCentury Innovations* (2015)
Usdin, S. "Mastering protocol." *BioCentury* (2013)