



# Shadow of the Future:

# Precision Medicine in Multiple Myeloma

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## Introduction

Despite significant progress in the treatment of multiple myeloma (MM), not all patients receive clinical benefit from available therapies. Novel approaches to drug development are needed to address the unmet medical need of patients with high-risk or refractory/resistant disease. Here, we describe application of a reverse translational approach in MM to define disease and patient subgroups by molecular and clinical features, to identify novel targets, and describe how these efforts may lead to new therapies. Our approach was powered by the results of a collaboration between large MM centers and foundations to collect the largest dataset with complete genomic and clinical outcomes data from newly-diagnosed MM patients for analysis by the Myeloma Genome Project (MGP). The size of the dataset enabled identification of new disease drivers and prognostic segments and comprehensive investigation of disease biology. Our long-term goal of research in MM is to develop precision medicines for treating the *right patient*, with the *right therapy*, at the *right dose*, for the *right duration*.

## Reverse Translational Drug Development and Precision Medicine

In the traditional “bench to bedside,” drug development approach, a putative target is typically identified from literature-based

understanding of the target’s role in disease biology. Once a target is chosen, there are many steps to identify a clinic-ready chemical or biological compound. The process starts by identifying multiple hit compounds and narrowing these to a few lead compounds (**Figure 1, top**). Optimized leads (typically one or two) are tested in preclinical models of efficacy and safety to receive drug candidate nomination and finally enter first-in-human clinical study to establish pharmacology and toxicology profiles.<sup>12</sup> The indication choice for the molecule is based on evidence of clinical activity in patients. This process has been successfully followed for most therapies available today; however, the failure rate of individual molecules is high (~1 in 15 oncology agents entering Phase 1 trials reaches FDA approval).<sup>34</sup>

One challenge of this approach is the uncertainty whether the efficacy/safety observed in preclinical models will translate to patients. Once the candidate drug enters clinical trials its efficacy can be tested in a particular patient population, where unfortunately, up to 85% of drugs fail due to intolerability or limited efficacy.<sup>5</sup> In a complex treatment landscape such as MM, the need to establish a patient selection strategy, the ability to match the *right patient* with the *right drug*, has become more important. With the traditional approach, patient selection, if pursued at all, may not begin until

the therapy is in mid- or late-stage clinical development. Despite recognition of the challenges most pharmaceutical and biotech companies have not fully explored alternative strategies to overcome these limitations and improve the odds of clinical, regulatory, and commercial success. In MM, the focus on developing improved or more intensive combination strategies has helped improve outcomes overall, but a new drug development strategy for high-risk and resistant disease is yet to be established.

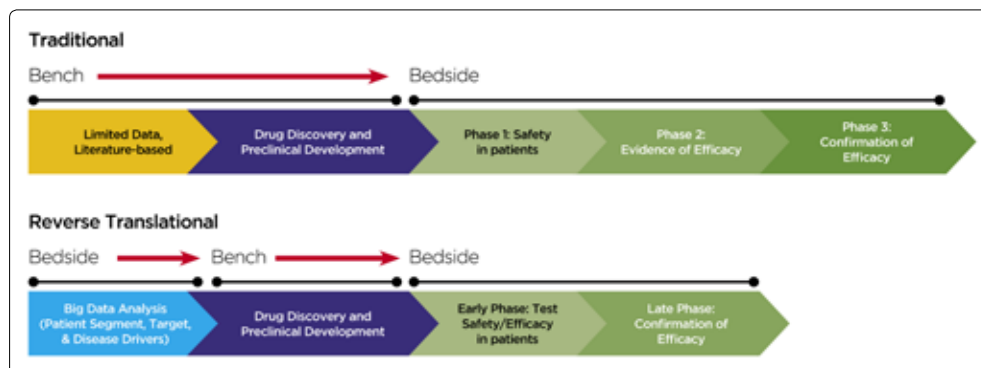
In contrast to the traditional drug development process, reverse translational drug development starts from the patient.<sup>6</sup> (**Figure 1, bottom**) Initial research and discoveries are based on patient samples, complemented by validation in pre-clinical models, and provide an opportunity to identify patient-, disease-, and therapy-related biomarkers that accelerate and increase the success rate of drug development. Review of clinical development success rates for investigational new drugs suggest that programs with a biomarker-based patient selection strategy are less likely to fail in late stage development.<sup>37</sup> While a reverse translational approach is generally applicable, we describe a specific example of this approach with our efforts to define MM patient populations with unmet needs, including those at high risk of early progression or those who relapse or are refractory to current therapies. ▶

## Progress vs Unmet Need in MM

MM is the second most common hematologic cancer in the United States, with over 32,000 new cases estimated for 2019.<sup>8</sup> MM develops from clonal expansion of malignant plasma cells in the bone marrow which disrupt normal function and lead to symptoms such as anemia, bone pain, infection, and renal impairment.<sup>9</sup> There has been tremendous improvement in overall survival (OS) of patients with MM due to multiple approvals of effective therapies (see therapies listed by mechanism of action in **Table 1**). This benefit can be seen from improvement since the chemotherapy era to today (median OS 23 mo vs 72 mo, **Figure 2**).<sup>10,11</sup> Although OS of newly-diagnosed MM (ndMM) patients has increased, those with high-risk disease have not received the same clinical benefit from available therapies.<sup>12</sup> There has been significant focus on trying to overcome the poor outcomes of high-risk patients using risk-adjusted therapy.

The original International Staging System (ISS) for MM risk stratified patients based upon high serum  $\beta$ 2-microglobulin ( $\beta$ 2M) and low serum albumin which allowed splitting patients into 3 groups with differing outcome, where ISS3 patients have poorest prognosis.<sup>13</sup> Approaches to define and identify high-risk patients have improved, however, the population of “high-risk” patients still varies in size and characteristics due to differing definitions and methodologies. Several disease- and patient-related risk factors have been described in MM, as well as multiple prognostic gene expression signatures (eg, GEP70, EMC92, IFM15, MRC6)<sup>14,23</sup> and new signatures are being developed.<sup>24</sup>

In addition to the clinical features that



**Figure 1: Traditional Vs Reverse Translational Drug Development Process**

The process for traditional “bench to bedside” drug development (top) versus reverse translational development (bottom).

### What is Reverse Translational Drug Development?

Reverse translation inverts the traditional drug development process by starting with analysis of patient samples and data, instead of pre-clinical models, to identify disease drivers and potential therapeutic targets.

comprise the ISS, chromosomal abnormalities were also linked to poor outcome in MM. These include translocations (rearrangements that connect a region of one chromosome to another) which place oncogenes under the control of the immunoglobulin heavy chain promoter,<sup>25-28</sup> and copy number changes (chromosomal gains/losses). In particular, deletion of chromosome 17p (del17p) and gain/amplification of 1q have been associated with poor outcome.<sup>28,29</sup> The ISS was recently updated (revised ISS [R-ISS]) to include presence of del17p, translocation (4;14), and translocation (14;16) detected by interphase fluorescence in situ hybridization (iFISH) as new components

for determining R-ISS.<sup>14</sup> In addition to disease-associated features, there are also patient- and treatment-related features that contribute to poor clinical outcome including comorbidities, frailty, minimal benefit from therapy, as well as new molecularly-defined high-risk patient groups (Double Hit, high-risk del17p) (**Figure 3**).

Despite continued efforts to identify high-risk MM patients, there is no agreed upon definition, uniform application, nor interpretation of high-risk markers used in the clinic. High-risk cytogenetic features (translocations, copy number changes) identified by iFISH have been a cornerstone of traditional risk criteria. However, variations in method, threshold (discussed below), and interpretation of the results, contribute to heterogeneity in risk assessment within a population of patients that were considered positive for a given abnormality.<sup>14,19,28</sup> Further, some high-risk features such as mutations of TP53 and increased copy number of chromosome 1q were not factored into the R-ISS.

The variety of high-risk definitions being used in clinical trials today have been recently summarized.<sup>28</sup> Taken together, this lack of uniform definition of high-risk has created challenges for reliably identifying high-risk patients, investigating their biology, interpreting therapeutic benefits between studies, and testing novel therapies that may provide clinical benefit for these patients. We established the Myeloma Genome Project (MGP), a global collaborative initiative focused on:

- 1) identifying uniform biomarker-defined, high-risk patient segments;
- 2) establishing a molecular classification for MM;
- 3) performing large-scale analysis of the genomic landscape of ndMM and relapsed/refractory MM (rrMM) including markers of therapeutic resistance, and

**Table 1: Available Therapies for the Treatment of Multiple Myeloma in the United States\***

Immunomodulatory Agents	Proteasome Inhibitors	Antibodies	Steroids	HDAC** Inhibitor	Chemotherapy
Revlimid® (lenalidomide)	Velcade® (bortezomib)	Empliciti® (elotuzumab)	Cadron® (dexamethasone)	Farydak® (panobinostat)	Doxil® (liposomal doxorubicin)
Pomalyst® (pomalidomide)	Kyprolis® (carfilzomib)	Darzalex® (daratumumab)	Deltasone® (prednisone)		Evomela® (melphalan)
Thalomid® (thalidomide)	Ninlaro® (ixazomib)	Xgeva® (denosumab)			Cytoxan® (cyclophosphamide)
					Adriamycin® (doxorubicin)
					Treanda® (bendamustine)
					Oncovin® (vincristine)

\* Available therapies for the treatment of MM listed by mechanism of action<sup>56,57</sup>

\*\* HDAC = histone deacetylase

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4) comprehensive immune profiling of ndMM and rrMM patients (not discussed here).

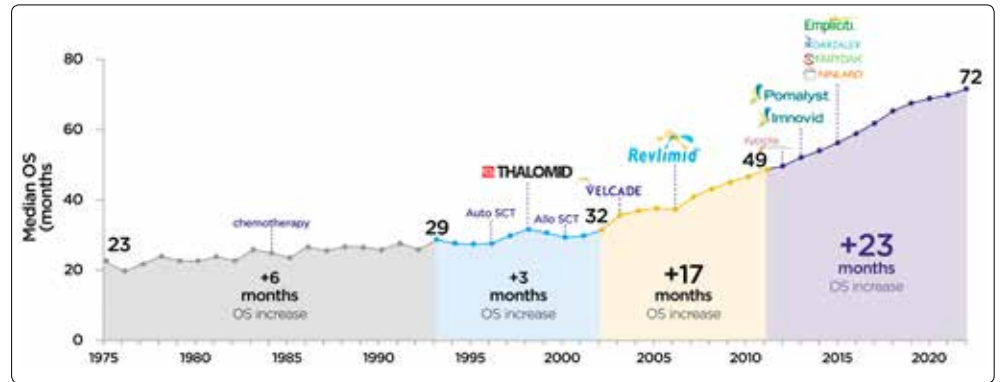
These large datasets enable better understanding of the key determinants of disease and resistance, identification of molecularly-defined patient and disease segments, and a drug development approach that contrasts the current approach.

## Identification of Molecularly-defined High-risk Patient Segments in MM

### Double Hit Myeloma

Historically, one barrier to identification of molecularly-defined patient segments in MM has been limited samples and small datasets. Unlike solid tumors or leukemias, MM cells reside in the bone marrow. Even large-scale cancer genomic initiatives like The Cancer Genome Atlas from The National Cancer Institute which profiled >20,000 samples from 33 tumor types did not include MM. The MGP collected the largest dataset of complete clinical outcomes and genomic data from ndMM patients which were then processed with a uniform computation pipeline to determine significant genomic changes (gains/losses of chromosomes, mutations, and translocations) and allow integration of the data.

To that end, a completely analyzed dataset of 1273 patients was used to describe the landscape of DNA-based genomic abnormalities, including novel oncogenic drivers, tumor suppressors, and their interdependencies.<sup>39</sup> To investigate molecular features associated with poor clinical outcome, a subset analysis was performed on patients with complete genomic and clinical outcomes



**Figure 2: Overall Survival Gains and Treatment Advances in Multiple Myeloma**

Median overall survival (OS) in months over time (years). Timing of regulatory approvals of therapies in the United States are indicated with logos. Historical median OS for multiple myeloma patients based on analysis of the National Cancer Institute Surveillance, Epidemiology, and End Results Program. Predictive analysis of OS was modelled using data from clinical trials, cancer registries, and insight from key opinion leaders. Auto SCT = autologous stem cell transplant. Allo SCT = allogeneic stem cell transplant. Figure courtesy of Amar Drawid, Celgene Corporation.<sup>10</sup>

data (n=784, from 1273). Features significantly associated with progression free survival (PFS) were identified and used to identify patient segments with differing risk.<sup>31</sup> The group with the shortest PFS, were named Double Hit MM and defined by either:

- 1) biallelic inactivation (deletion and mutation in the two alleles) of the tumor suppressor p53, or
- 2) amplification ( $\geq 4$  copies) of chromosome 1q on a background of high disease stage (ISS3).

Double Hit MM patients have a median PFS of 15.4 months and median OS of 20.7 months (see **Figure 4 A, B**). The presence, prevalence, and clinical outcomes of Double Hit MM was validated in several independent datasets indicating that these patients have poor outcome despite a variety of standard of care / intensive treatment regimens.<sup>31</sup> For example,

Ashby et al validated the Double Hit population in a Total Therapy dataset (N=199), and both Bolli and Thanendrarajan showed that biallelic inactivation of TP53 (N=418 and N=747) resulted in poorer outcome versus patients with monoallelic inactivation (mutation or deletion alone).<sup>32-35</sup> Of highest importance, the Double Hit population identifies patients who are at high-risk of early progression/death who otherwise would have been considered standard- or intermediate-risk by traditional risk criteria and may have been undertreated as a result.<sup>31</sup>

### High-risk Del17p

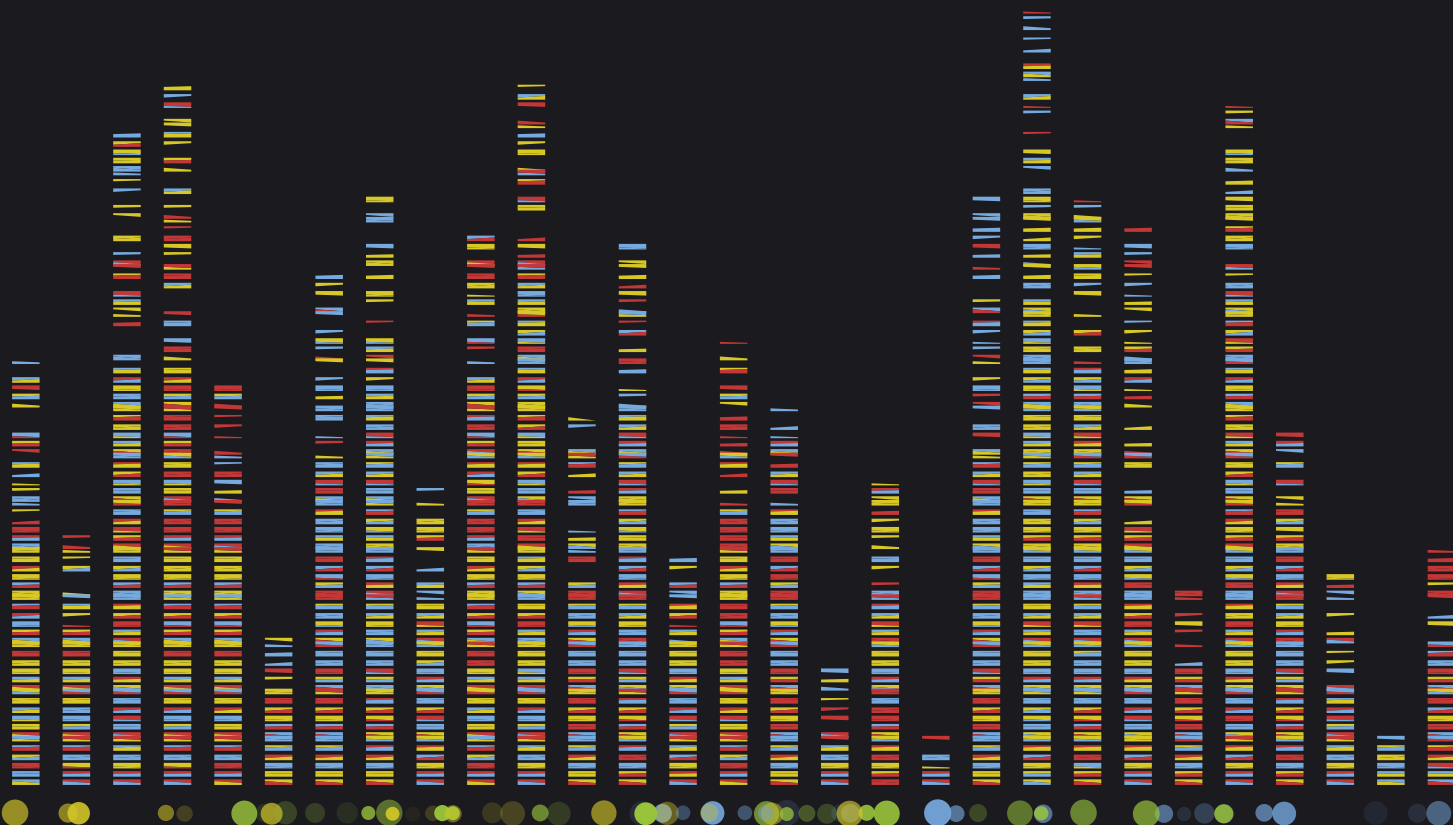
Del17p had been previously identified as a marker of poor prognosis. However, determining the optimal threshold, defined as the percentage of tumor cells positive (also known as cancer clonal fraction [CCF]), for cytogenetic abnormalities by iFISH has been one source of heterogeneity. Some groups had proposed that a patient should have ~60% cells positive for the deletion in order to be considered in the del17p subgroup; however, others used a much lower threshold (a single positive cell to 20% positive cells) to consider patients as having del17p.<sup>34-44</sup> There is at least one example of a Phase 3 clinical trial where there was no threshold given for calling del17p – if any *single cell* was positive for the abnormality, the patient was included in the del17p group.<sup>37</sup> Almost all studies were small and lacked the statistical power to provide a comprehensive analysis of del17p patients.

To address these challenges, we analyzed large iFISH and genomic datasets and systematically evaluated the association of CCF to OS in ndMM patients. Patients with greater than 55% positive cells (CCF >0.55) had shortest

Molecular Features	Clinical Features	Patient Features	Treatment Features
High risk cytogenetics	High Disease Burden (%PCs)	Older Age / Frailty	Minimal Benefit from Therapy
Gene Expression Profiles	High $\beta 2M$	Comorbidities	
Double Hit MM	High LDH		
High-risk Deletion 17p	Low Serum Albumin		

**Figure 3: High-Risk Features in Multiple Myeloma**

Graphical representation of molecular-, clinical-, patient-, and treatment-related high-risk features and groups in multiple myeloma (MM). Patients with MM may have one, or more than one, high-risk feature, which may change over the course of the disease and treatment. %PCs = percentage of plasma cells in the bone marrow.  $\beta 2M$  = beta-2-microglobulin. LDH = lactate dehydrogenase.



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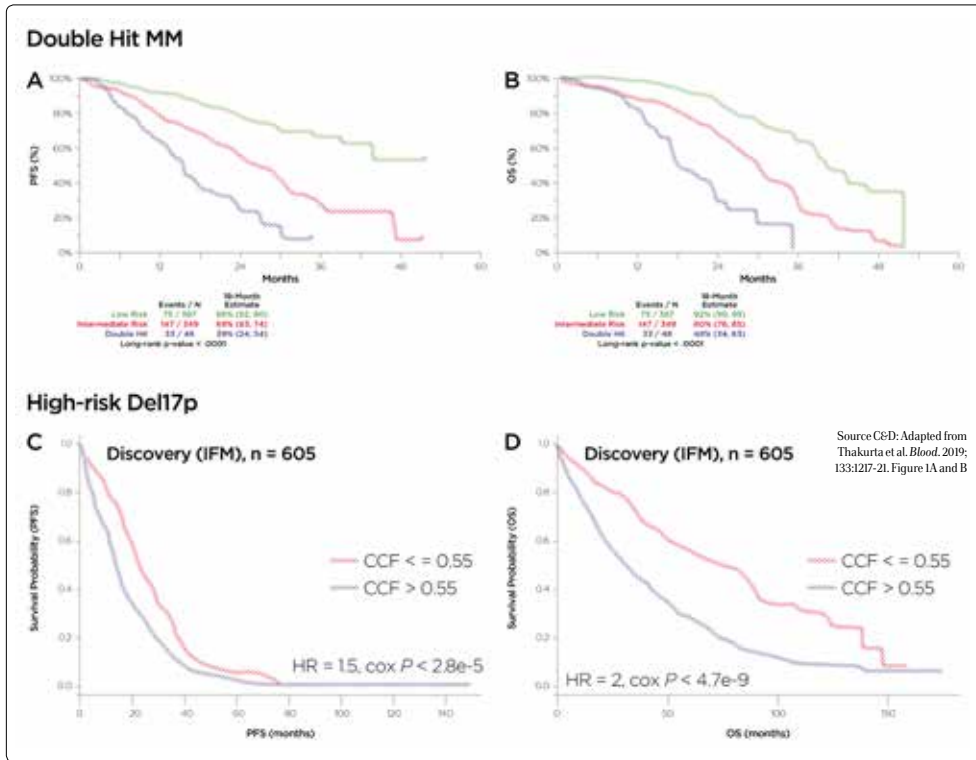
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**Figure 4: Molecularly-defined High-risk Newly Diagnosed Multiple Myeloma Patient Segments**

Clinical outcomes of two molecularly-defined high risk groups in MM: Double Hit MM (A and B) and high-risk del17p (C and D). A) Progression free survival (PFS) of Double Hit (blue) compared to intermediate-risk (red) and low-risk (green). B) As for A) except overall survival (OS). C) PFS of high-risk del17p (CCF > 0.55, blue) versus patients with del17p CCF ≤ 0.55 (red) in the discovery dataset from patients treated in IFM studies. D) As for C) except OS. IFM = Intergroupe Francophone du Myelome. Data reprinted with permission as indicated.

OS, which was validated in an independent dataset.<sup>45</sup> We found strong evidence that patients with high CCF del17p have highest risk of poor clinical outcome, with a median PFS and OS of only 14 and 32 months as compared to the low CCF group which had PFS of 23.1 months and OS of 76.2 months (Figure 4C, D).<sup>45</sup>

## Molecular Classification of Multiple Myeloma

Identification of biomarker-defined patient segments as described above will allow improved identification of high-risk patients to help guide treatment decisions with therapeutic agents available today. Without a better

### Predictive vs Prognostic Biomarkers

**Prognostic:** Biomarker used to identify the likelihood of a clinical event or outcome (eg, disease progression). These biomarkers are not associated with any specific treatment, but rather identify outcome regardless of therapy received.

**Predictive:** Biomarker used to identify patients who are more likely to have a favorable or unfavorable outcome versus patients who do not have the biomarker. These biomarkers are associated with a specific treatment.

understanding of the biological features that drive clinical outcomes, however, effective therapies to target these drivers could not be developed. To date, genomic analyses of MM patients have centered either on DNA-based variants, or separately, gene expression studies. In other cancers, an integrated analysis of DNA and RNA-based features and clinical data have been performed to define a molecular classification of disease, however this has never been described for MM.<sup>46-51</sup> In order to understand the biology of high-risk disease in a more comprehensive manner, we performed the first integrative molecular analysis of MM that included data from copy number changes, structural variants, mutations, gene expression, and clinical features from 514 patients at diagnosis.<sup>52</sup>

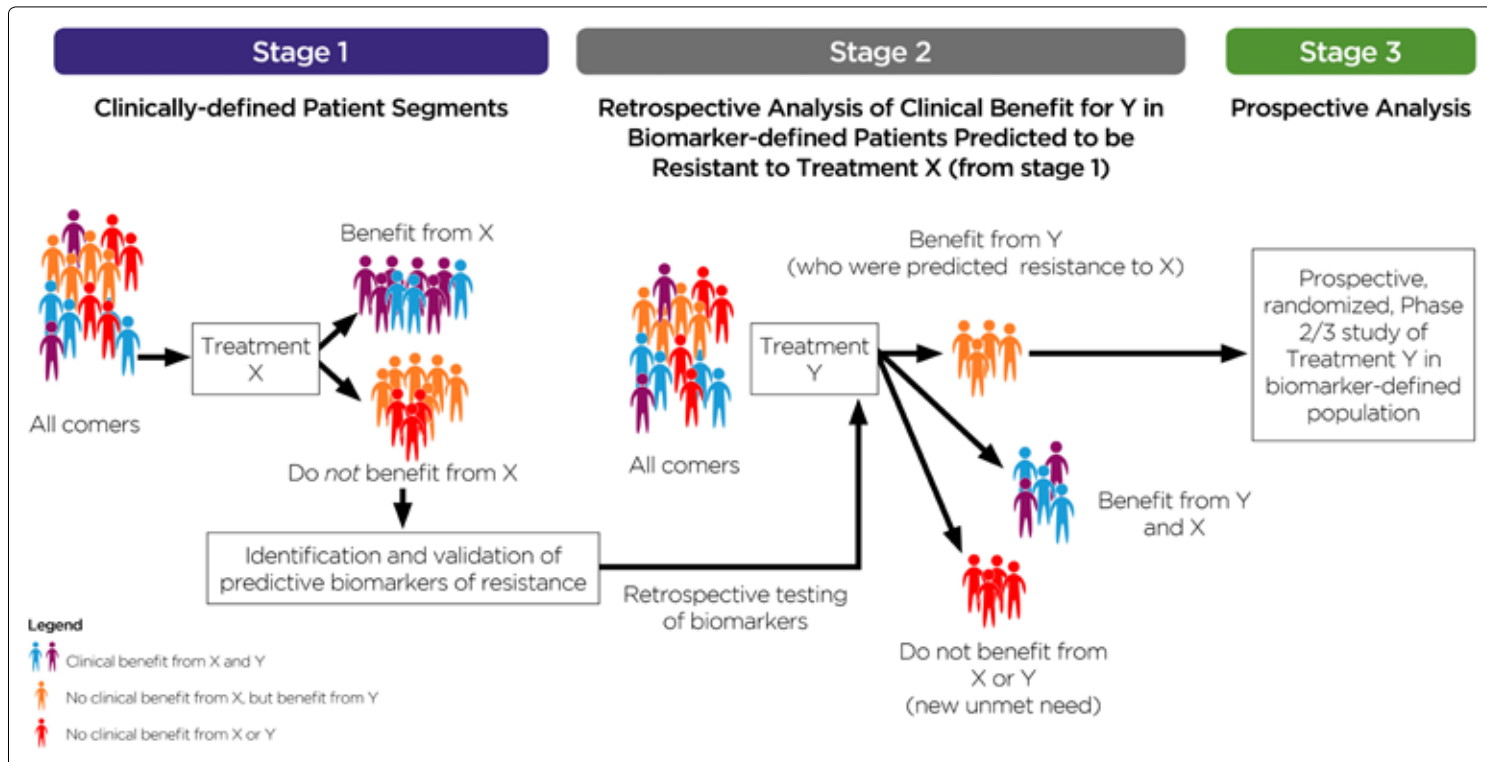
By integrating these data types and applying unsupervised clustering methodologies, we were able to identify 12 distinct biological subtypes of MM. Known features such as del17p, amp1q, biallelic inactivation of *TP53*, and others that have been associated with poor prognosis are useful markers to identify high-risk patients, but the underlying biological mechanisms that lead to the aggressive tumor

phenotype are not well described. Indeed, we discovered that these previously-described high-risk features did not necessarily cluster together, but instead were often distributed across several clusters. This finding is important because for the first time, this dataset provides an opportunity to dissect the biology between a “high-risk” patient with a given abnormality vs one that is “intermediate/standard risk” with that same abnormality – a phenomena that has been observed in the clinic. Thus, additional biomarkers beyond the genetic markers would be required to accurately identify high-risk patients.

When the clinical outcomes of these 12 disease segments were explored, differing clinical outcomes were observed with one group having very short PFS (median 15 mo). Computational analysis of this high-risk disease segment identified several novel driver genes, biological pathways, and cellular processes that appear to underlie the high-risk biology of these patients which will be described in a separate publication.<sup>52</sup> Identification and validation of the true drivers of high-risk biology in the ndMM setting provides an exciting opportunity to target those features with novel agents either alone or in combination with proven anti-MM agents. Together, these analyses may provide an opportunity to target distinct biologically-defined segments of the disease. Additionally, these identified features (those driving high-risk biology) may provide a path toward development of targeted therapeutic agents for treatment of MM patients.

## Biomarkers of Therapeutic Resistance

Despite early intervention and treatment, MM remains an incurable disease. Almost all patients will eventually relapse and become refractory to therapy.<sup>53</sup> Relapsed/refractory MM patients are commonly defined by clinical features (e.g., age, disease stage, prior treatments, comorbidities) and risk assessments (iFISH from time of diagnosis) that influence treatment selection, followed by monitoring for clinical response to therapy. In this scenario, some patients will receive clinical benefit, while other patients unfortunately will not. Unlike other malignancies, targeted therapies (e.g., inhibitors against BRAF mutations in melanoma) have not been implemented in MM, despite increasing knowledge of the mechanisms of resistance in MM and models/methods for identifying them.<sup>54</sup> A recent clinical trial is addressing this question by matching therapies to patients based on mutational profiles (Multiple Myeloma Research Foundation’s



**Figure 5: Process for Identifying and Validating a Predictive Biomarker-Defined Patient Population**

Three stages are illustrated. In stage 1, “Treatment X” is tested in a traditional, clinically-defined patient population where some patients receive clinical benefit (purple and blue) while others do not (red and orange). Biomarkers from the patients who did not benefit from Treatment X are identified and retrospectively tested in stage 2. In stage 2, some patients (orange) who were predicted to be resistant to Treatment X (from stage 1), receive benefit from Treatment Y. Other patients who would have benefited from Treatment X also benefit from Y (purple and blue) while some patients may not benefit from Y (red) and remain an unmet medical need population. In stage 3, a prospective study to test Treatment Y in the biomarker-defined population (orange) can be conducted.

MyDRUG study; see <https://clinicaltrials.gov/ct2/show/NCT03732703?term=mydrug&rank=1>. Until now, the treatment approach in MM has largely focused on combination therapy where individual therapies may be replaced based upon clinical benefit or early signs of progression. Understanding the biology of rrMM is even more challenging than at diagnosis due to the vast heterogeneity of this patient population, the complex treatment landscape, and multitude of combination regimens routinely used in the clinic.<sup>53-56</sup>

In addition to prognostic biomarkers described above, reverse translation provides an opportunity to identify predictive biomarkers of therapeutic resistance that is, identify a biomarker that can predict the clinical outcome to a specific treatment before the patient receives an ineffective treatment. By first identifying resistant biology in patients and then designing new therapies or novel combination regimens to target resistant biology, we increase the likelihood of finding new treatments directly targeting resistant MM cells. By using updated biomarkers and diagnostic assays, clinical trials can be designed to validate a clear patient selection strategy for these new agents. This approach could enable physicians

***“Of highest importance, the Double Hit population identifies patients who are at high-risk of early progression/death who otherwise would have been considered standard- or intermediate-risk by traditional risk criteria and may have been undertreated as a result”***

to tailor their treatment decisions and avoid therapies that are unlikely to be effective for that individual.

The complex process of identifying predictive biomarkers of resistance to a given therapy for clinical applications starts by analyzing samples and data from patients that did not benefit from that therapy, followed by


validation of that biomarker in independent datasets (see Treatment X in **Figure 5**, stage 1). Once validated resistance biomarker(s) for Treatment X are available, then retrospective analyses can be conducted to determine if patients predicted to be resistant to Treatment X would receive clinical benefit to Treatment Y, a new investigational agent/combination (**Figure 5**, stage 2). Only following a positive signal that Treatment Y might be effective in predicted-Treatment X resistant patients, would a prospective randomized Phase 2/3 clinical study be conducted for a stringent assessment of the clinical utility of Treatment Y in patients predicted to be resistant to Treatment X (**Figure 5**, stage 3). At this stage, a companion diagnostic test would be needed to identify the patients entering any new trial. While this multi-step process may be complex, the potential to identify biomarkers of resistance and better tailor treatment decisions provides another opportunity to improve patient outcomes (particularly for complex cases like rrMM). These biomarker-driven strategies would be valuable both to physicians to inform their treatment decisions and to drug developers for differentiation and patient selection for new drugs. ▶

## Driving Precision Medicine in MM

We reason that Double Hit and high-CCF del17p are examples of the right patients for consideration for risk-adapted therapy or clinical trials and can be identified from the time of diagnosis.<sup>31,45</sup> In the complex rMM setting, we need to identify predictive biomarkers of resistance to help choose the *right drug* for patients who are unlikely to benefit from current therapies. Third, we are focusing on identifying the *right targets* through integrative genomic analysis of patient data to discover the biological

drivers of high-risk disease. We believe that by employing this approach, the right patient, the right indication, *and* the right candidate drug would be defined earlier in development, thereby increasing the likelihood of approval and providing an opportunity to address unmet medical need.

We should note that there are significant challenges to the reverse translational approach described here. The major ones include access to large patient-derived datasets with mature clinical data, and the

need for computational infrastructure to house and analyze extremely large datasets. In the case of MGP, an industry-academic collaboration provided solutions to many challenges which had previously prevented any single group from pursuing a project of this scale. We believe that innovative strategies such as a reverse translational approach and large-scale collaborations may foster a new era of drug development to optimize options for all MM patients in the future. 

### References

- US Food and Drug Administration. The Drug Development Process. <https://www.fda.gov/forpatients/approvals/drugs/> (2018).
- Sinha, S. & Vohora, D. in *Pharmaceutical Medicine and Translational Clinical Research* (eds Divya Vohora & Gursharan Singh) 19-32 (Academic Press, 2018).
- Hay, M., Thomas, D. W., Craighead, J. L., Economides, C. & Rosenthal, J. Clinical development success rates for investigational drugs. *Nature Biotechnology* 32, 40, doi:10.1038/nbt.2786 <https://www.nature.com/articles/nbt.2786#supplementary-information> (2014).
- Arrowsmith, J. & Miller, P. Phase II and Phase III attrition rates 2011–2012. *Nature Reviews Drug Discovery* 12, 569, doi:10.1038/nrd4090 (2013).
- Mak, I. W., Evaniw, N. & Ghert, M. Lost in translation: animal models and clinical trials in cancer treatment. *American journal of translational research* 6, 114-118 (2014).
- Wagner, J. A. Patient-Centered Reverse Translation. *Clinical Pharmacology & Therapeutics* 103, 168-170, doi:10.1002/cpt.1902 (2018).
- Jardim, D. L., Groves, E. S., Breitfeld, P. P. & Kurzrock, R. Factors associated with failure of oncology drugs in late-stage clinical development: A systematic review. *Cancer Treatment Reviews* 52, 12-21, doi:10.1016/j.ctrv.2016.10.009 (2017).
- The National Cancer Institute. Cancer Stat Facts: Myeloma. <https://seer.cancer.gov/statfacts/html/mulmy.htm> (2019).
- Rajkumar, S. V. et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. *The Lancet Oncology* 15, e538-e548, doi:10.1016/S1470-2045(14)70442-5 (2014).
- Drawid, A. et al. Impact of novel therapies on multiple myeloma survival in the US: Current and future outcomes. *Journal of Clinical Oncology* 33, e19536-e19536, doi:10.1200/JCO.2015.33.15\_suppl.e19536 (2015).
- Fonseca, R. et al. Trends in overall survival and costs of multiple myeloma, 2000–2014. *Leukemia* 31, 1915, doi:10.1038/leu.2016.380 (2016).
- Kumar, S. K. et al. Continued improvement in survival in multiple myeloma: changes in early mortality and outcomes in older patients. *Leukemia* 28, 1122-1128, doi:10.1038/leu.2013.313 (2014).
- Greipp, P. R. et al. International Staging System for Multiple Myeloma. *Journal of Clinical Oncology* 23, 3412-3420, doi:10.1200/JCO.2005.04.242 (2005).
- Palumbo, A. et al. Revised International Staging System for Multiple Myeloma: A Report From International Myeloma Working Group. *J Clin Oncol* 33, 2863-2869, doi:10.1200/JCO.2015.61.2267 (2015).
- Usmani, S. Z., Rodriguez-Otero, P., Bhatani, M., Mateos, M. V. & Miguel, J. S. Defining and treating high-risk multiple myeloma. *Leukemia* 29, 2119-2125, doi:10.1038/leu.2015.209 (2015).
- Walker, B. A. et al. Mutational Spectrum, Copy Number Changes, and Outcome: Results of a Sequencing Study of Patients With Newly Diagnosed Myeloma. *J Clin Oncol* 33, 3911-3920, doi:10.1200/JCO.2014.59.1503 (2015).
- Bolli, N. et al. Heterogeneity of genomic evolution and mutational profiles in multiple myeloma. *Nat Commun* 5, 2997, doi:10.1038/ncomms3997 (2014).
- Kuiper, R. et al. Prediction of high- and low-risk multiple myeloma based on gene expression and the International Staging System. *Blood* (2015).
- Chng, W. J. et al. Gene signature combinations improve prognostic stratification of multiple myeloma patients. *Leukemia* 30, 1071-1078, doi:10.1038/leu.2015.341 (2016).
- Shaughnessy, J. D. et al. A validated gene expression model of high-risk multiple myeloma is defined by deregulated expression of genes mapping to chromosome 1. *Blood* 109, 2276-2284 (2007).
- Kuiper, R. et al. A gene expression signature for high-risk multiple myeloma. *Leukemia* 26, 2406, doi:10.1038/leu.2012.117 <https://www.nature.com/articles/leu2012117#supplementary-information> (2012).
- Magrangeas, F. et al. Gene expression profiling of multiple myeloma reveals molecular portraits in relation to the pathogenesis of the disease. *Blood* 101, 4998-5006 (2003).
- Dickens, N. J. et al. Homozygous deletion mapping in myeloma samples identifies genes and an expression signature relevant to pathogenesis and outcome. *Clinical cancer research: an official journal of the American Association for Cancer Research* 16, 1856-1864, doi:10.1158/1078-0432.CCR-09-2831 (2010).
- Dervan, A. P. et al. Crowdsourcing a High-Risk Classifier for Multiple Myeloma Patients. *Blood* 130, 265-265 (2017).
- Dewald, G., Kyle, R., Hicks, G. & Greipp, P. The clinical significance of cytogenetic studies in 100 patients with multiple myeloma, plasma cell leukemia, or amyloidosis. *Blood* 66, 380-390 (1985).
- Fonseca, R. et al. Clinical and biologic implications of recurrent genomic aberrations in myeloma. *Blood* 101, 4569-4575 (2003).
- González, D. et al. Immunoglobulin gene rearrangements and the pathogenesis of multiple myeloma. *Blood* 110, 3112-3121 (2007).
- Pawlyn, C. & Davies, F. E. Towards personalized treatment in multiple myeloma based on molecular characteristics. *Blood* (2018).
- Toth, P. J. et al. p53 haploinsufficiency and functional abnormalities in multiple myeloma. *Leukemia* 28, 2066, doi:10.1038/leu.2014.102 <https://www.nature.com/articles/leu2014102#supplementary-information> (2014).
- Walker, B. A. et al. Identification of novel mutational drivers reveals oncogene dependencies in multiple myeloma. *Blood* (2018).
- Walker, B. A. et al. A high-risk, Double-Hit, group of newly diagnosed myeloma identified by genomic analysis. *Leukemia*, doi:10.1038/s41375-018-0196-8 (2018).
- Bolli, N. et al. Analysis of the genomic landscape of multiple myeloma highlights novel prognostic markers and disease subgroups. *Leukemia* 32, 2604-2616, doi:10.1038/s41375-018-0037-9 (2018).
- Ashby, C. et al. Long-Term Follow-up Identifies Double Hit and Key Mutations As Impacting Progression Free and Overall Survival in Multiple Myeloma. *Blood* 132, 110-110 (2018).
- Thanendrarajan, S. et al. The level of deletion 17p and bi-allelic inactivation of TP53 has a significant impact on clinical outcome in multiple myeloma. *Haematologica* (2017).
- Shah, V. et al. Prediction of outcome in newly diagnosed myeloma: a meta-analysis of the molecular profiles of 1905 trial patients. *Leukemia* 32, 102-110, doi:10.1038/leu.2017.179 (2018).
- Neben, K. et al. Combining chromosomal aberrations (4;14) and del(17p13) with ISS allows a stratification of myeloma patients undergoing autologous stem cell transplantation. *Haematologica* (2010).
- Lonial, S. et al. Elotuzumab Therapy for Relapsed or Refractory Multiple Myeloma. *N Engl J Med* 373, 621-631, doi:10.1056/NEJMoa1505654 (2015).
- Boyd, K. D. et al. The clinical impact and molecular biology of del(17p) in multiple myeloma treated with conventional or thalidomide-based therapy. *Genes Chromosomes Cancer* 50, 765-774 (2011).
- Chng, W. J., Glebov, O., Bergsagel, P. L. & Kuehl, W. M. Genetic events in the pathogenesis of multiple myeloma. *Best Pract Res Clin Haematol* 20, 571-596, doi:10.1016/j.beha.2007.08.004 (2007).
- Lode, L. et al. Mutations in TP53 are exclusively associated with del(17p) in multiple myeloma. *Haematologica* 95, 1973-1976, doi:10.3324/haematol.2010.023697 (2010).
- Xu-Monette, Z. Y. et al. Dysfunction of the TP53 tumor suppressor gene in lymphoid malignancies. *Blood* 119, 3668-3683 (2012).
- An, G. et al. The Impact of Clone Size on the Prognostic Value of Chromosome Aberrations by Fluorescence In Situ Hybridization in Multiple Myeloma. *Clinical Cancer Research* 21, 2148-2156 (2015).
- Avet-Loiseau, H. et al. Genetic abnormalities and survival in multiple myeloma: the experience of the Intergroupe Francophone du Myélome. *Blood* 109, 3489-3495 (2007).
- Shah, V. et al. Sub-clonal TP53 copy number is associated with prognosis in multiple myeloma. *Blood* (2018).
- Thakurta, A. et al. High subclonal fraction of 17p deletion is associated with poor prognosis in multiple myeloma. *Blood* 133, 1217-1221 (2019).
- Papaemmanuil, E. et al. Genomic Classification and Prognosis in Acute Myeloid Leukemia. *New England Journal of Medicine* 374, 2209-2221, doi:10.1056/NEJMoa1516192 (2016).
- Ally, A. et al. Comprehensive and Integrative Genomic Characterization of Hepatocellular Carcinoma. *Cell* 169, 1327-1341.e1323, doi:10.1016/j.cell.2017.05.046 (2017).
- Berger, A. C. et al. A Comprehensive Pan-Cancer Molecular Study of Gynecologic and Breast Cancers. *Cancer cell* 33, 690-705.e699, doi:10.1016/j.ccr.2018.03.014 (2018).
- Robertson, A. G. et al. Comprehensive Molecular Characterization of Muscle-Invasive Bladder Cancer. *Cell* 171, 540-556.e525, doi:10.1016/j.cell.2017.09.007 (2017).
- Cancer Genome Atlas, N. Comprehensive genomic characterization of head and neck squamous cell carcinomas. *Nature* 517, 576-582, doi:10.1038/nature14129 (2015).
- Cancer Genome Atlas Research, N. et al. Comprehensive Molecular Characterization of Papillary Renal-Cell Carcinoma. *The New England journal of medicine* 374, 135-145, doi:10.1056/NEJMoa1505917 (2016).
- Ortiz, M. et al. A High-Risk Multiple Myeloma Group Identified by Integrative Multi-Omics Segmentation of Newly Diagnosed Patients. *Blood* 132, 3165-3165 (2018).
- Durie, B. Multiple Myeloma - Concise Review of the Disease and Treatment Options. (2018).
- Harding, T., Baughn, L., Kumar, S. & Van Ness, B. The future of myeloma precision medicine: integrating the compendium of known drug resistance mechanisms with emerging tumor profiling technologies. *Leukemia* 33, 863-883, doi:10.1038/s41375-018-0362-z (2019).
- Sonneveld, P. et al. Treatment of multiple myeloma with high-risk cytogenetics: a consensus of the International Myeloma Working Group. *Blood* 127, 2955-2962 (2016).
- National Comprehensive Cancer Network. Multiple Myeloma (Version 2.2019). [https://www.nccn.org/professionals/physician\\_gls/pdf/myeloma.pdf](https://www.nccn.org/professionals/physician_gls/pdf/myeloma.pdf)
- Drug Therapies for Multiple Myeloma. <https://themmf.org/multiple-myeloma/treatment-options/standard-treatments/>



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