Updates from the 2019 American Society of Clinical Oncology and European Hematology Association annual meetings: a Canadian perspective on high-risk cytogenetics in multiple myeloma

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ABSTRACT

The 2019 annual meetings of the American Society of Clinical Oncology and the European Hematology Association took place, respectively, in Chicago, Illinois, 31 May–4 June, and in Amsterdam, Netherlands, 13–16 June. At the meetings, results from key studies on the treatment of patients with relapsed or refractory multiple myeloma with high-risk cytogenetics were presented. Our meeting report describes those studies and includes interviews with investigators and commentaries by Canadian hematologists about the potential impact on Canadian practice.

Key Words Relapsed disease, refractory disease, multiple myeloma, high-risk cytogenetics


BACKGROUND

Multiple myeloma (MM) is a plasma cell neoplasm characterized by clonal proliferation of cytogenetically abnormal plasma cells. Canadian mortality data yielded a 2017 estimated 5-year net survival rate of 42%, an improvement from a rate of 32% in 2002–2004. That trend of improved survival has also been observed in the United States and other high-income regions across the globe and might be largely attributable to an increase in the use of autologous stem-cell transplantation for eligible patients and the availability of novel anti-myeloma therapies.

Although prognosis has steadily improved in the overall patient population, MM is a biologically heterogeneous disease, with survival outcomes varying from less than 1 year to more than 10 years. Poor prognosis in MM can be linked to several factors, including age, frailty, disease stage, and cytogenetics. Stratification of patients into high-risk and standard-risk subgroups based on evaluation of cytogenetic abnormalities (CA) is an important tool for predicting survival outcomes. The main CA that are associated with poor prognosis include del(17p), translocations involving the immunoglobulin heavy-chain on chromosome 14 [t(4;14), t(14;16), and t(14;20)], and potentially gain(1q21). Those high-risk CA can be identified in approximately 15%–20% of patients with newly diagnosed MM (ND-MM) and have been associated with a median survival of 2–3 years.

Clinical practice guidelines from Alberta Health Services (AHS), the Leukemia/Bone Marrow Transplant Program of British Columbia, and Cancer Care Ontario [created jointly with the American Society of Clinical Oncology (ASCO)] recommend risk assessment at diagnosis using the revised International Staging System, which includes fluorescence in situ hybridization (FISH) testing for t(4;14), t(14;16), and del(17p). Those recommendations are in line with other international MM guidelines. The AHS and Cancer Care Ontario guidelines also recommend repeating bone marrow FISH testing for del(17p) and gain(1q21) at the time of relapse, because acquisition of those secondary CA has been linked to aggressive disease and shorter survival. However, repeating the cytogenetic profile assessment is not currently the standard of care in Canada.
In Canada, identification of high-risk cases has implications for therapy choice in transplant-eligible ND-MM. The AHS and Cancer Care Ontario guidelines both recommend a triple combination of a proteasome inhibitor, immunomodulatory agent (if accessible), and steroid for initial treatment, followed by 1 or 2 autologous stem-cell transplantation procedures, followed by proteasome inhibitor–based maintenance therapy (with or without lenalidomide) until progression. Although those therapeutic strategies improve outcomes for patients with high-risk disease, treatment becomes more challenging because the choices for effective evidence-based therapies are limited, and other factors such as prior therapy and comorbidities must be considered. The AHS guidelines recommend that such patients be considered for clinical trials wherever possible.

Results from several recent phase III clinical trials using next-generation proteasome inhibitors have shown some improvement for high-risk patients in the relapsed setting. The ENDEAVOR trial showed that progression-free survival (PFS) was significantly extended with carfilzomib–dexamethasone compared with bortezomib–dexamethasone (Vd) in patients with R/R MM and high-risk cytogenetics (median PFS: 8.8 months vs. 6.0 months; hazard ratio [HR]: 0.65; P = 0.0075). The ASPIRE trial also showed a benefit for the addition of carfilzomib to lenalidomide–dexamethasone (KRd) in patients with high-risk cytogenetics experiencing relapse (median PFS: 23.1 months vs. 13.9 months; HR: 0.70; 95% confidence interval [CI]: 0.43 to 1.16). Finally, the TOURMALINE-MMII trial found that median PFS was significantly longer for patients with high-risk R/R MM treated with ixazomib plus lenalidomide–dexamethasone (IRd) than with Rd alone (21.4 vs. 9.7 months; HR: 0.54; 95% CI: 0.32 to 0.92) and that the experimental regimen could overcome the poor PFS associated with high-risk cytogenetics. However, the cut-off used to define del(17p) was 5%, which is lower than that used in some other studies, making cross-trial comparisons challenging.

For high-risk patients with R/R MM, a logical strategy to overcome drug resistance and to provide a durable response is to combine regimens with novel and distinct mechanisms of action. Immunotherapy agents, including daratumumab and elotuzumab, have demonstrated high efficacy in combination with other anti-myeloma agents at multiple stages of MM and are ideal candidates for investigation in patients with high-risk cytogenetics. Evaluation of high-risk patients with R/R MM in the ELOQ-2 study showed that, in those patients, median PFS was doubled for elotuzumab–Rd compared with Rd alone (15 months vs. 7 months; HR: 0.64; 95% CI: 0.43 to 0.97). The phase III CASTOR and POLLUX studies showed that daratumumab–Vd and daratumumab–Rd, respectively, are efficacious in patients with R/R MM, leading to Health Canada approval of those therapies in relapsed MM. A subgroup analysis of those studies based on cytogenetic risk is discussed later in this article.

Given that there remains a need to better characterize the effect of novel therapies on the outcomes of patients with high-risk cytogenetics, several prospective and retrospective studies at the 2019 ASCO annual meeting and the 24th Congress of the European Hematology Association (EHA) presented updated response and survival data for groups of such patients. The summary presented here highlights key findings from the studies and discusses how those findings might be relevant for Canadian oncologists and hematologists treating patients with high-risk MM, with a focus on the relapsed setting.

METHODS

Founded in 1964 by a group of 7 cancer physicians, ASCO is now the world’s leading professional organization for physicians and oncology professionals caring for people with cancer. Having grown into a diverse network of close to 45,000 oncology professionals, encompassing all oncology subspecialties, including those for hematologic malignancies. Annual meetings are generally held in Chicago, Illinois, with the 2019 meeting having taken place from 31 May to 4 June. The EHA is the principal hematologic organization in Europe, promoting excellence in patient care, research, and education. It organizes an annual congress that is held in a major European city every June, with the 2019 meeting having taken place 13–16 June in Amsterdam, Netherlands.

To determine the most impactful abstracts, we selected presentations from ASCO or EHA using the search terms “myeloma” and “cytogenetic risk.” Those search criteria identified thirteen abstracts. Of those thirty-one abstracts, we excluded the ones that focused on the treatment of ND-MM exclusively (five studies), the ones that contained no data relating to patients with high-risk cytogenetics (twelve studies), the ones that were related to measurement methods (two studies), and the ones lacking data about treatment outcomes (two studies). We included studies focused on the prognosis of patients with ND-MM and high-risk cytogenetics, because the overall survival (OS) data would also include data relating to the relapsed setting. Six studies met those a priori inclusion criteria.

Three studies examined the prognosis of high-risk patients with R/R MM and ND-MM. One study by Sandakumar et al. examined survival outcomes in patients with ND-MM, including those with high-risk disease. A second study by Ashraf et al. consisted of a systematic review examining the efficacy of treatment for high-risk patients with ND-MM and R/R MM. A study by Rosenhol et al. examined quality of life (QOL) in patients with R/R MM, including those with high-risk disease.

The remaining three studies examined specific treatment strategies for high-risk patients with R/R MM. A study by Weisel et al. examined the efficacy and safety of daratumumab–bortezomib–dexamethasone (DvD) in patients with R/R MM, including those with high-risk disease. A study by Dimopoulos et al. examined the efficacy and safety of daratumumab–lenalidomide–dexamethasone (Drd) in patients with R/R MM, including those with high-risk disease. And the final study examined a biomodulatory
therapy approach with lenalidomide, pioglitazone, dexamethasone, and metronomic low-dose chemotherapy in patients with r/r MM, with a sub-analysis of patients with high-risk disease.

The foregoing studies are summarized in the next section, accompanied by interviews with the investigators. The subsequent section presents commentaries about the potential impact of the findings on Canadian practice.

**DISCUSSION**

**Prognosis of Patients with MM and High-Risk Cytogenetics**

Continued Improvement in Survival in MM Including High-Risk Patients (ASCO abstract 8039)  
**Objectives** To examine how improvements in treatment have translated into survival outcomes in patients with ND-MM.

**Methods** Patients (n = 3449) with a diagnosis of MM made between 2004 and 2017 and seen at Mayo Clinic within 6 months of the diagnosis were included in the analysis. The study population was divided into 3 groups based on the year of diagnosis: group 1 included patients diagnosed during 2004–2007 (n = 831); group 2, during 2008–2012 (n = 1161); and group 3, during 2013–2017 (n = 1457).

**Results** Overall, 60% of the patients were men with a median age of 64 years (range: 22–96 years). The percentage of patients with high-risk MM, defined as the presence of t(4;14), t(14;16), t(14;20), or del(17p) in the absence of any trisomy, was 22% in group 1, 21% in group 2, and 25% in group 3. The median os for all patients was 5.7 years (95% CI: 5.4 years to 6.3 years); for groups 1, 2, and 3, it was 3.9 years, 6.3 years, and not reached respectively (p < 0.001). The 5-year os estimates for patients less than 65 years of age and 65 years of age and older were 63% and 46% respectively. The median os for patients with high-risk cytogenetics in groups 1, 2, and 3 was 3 years, 3.5 years, and not reached respectively (p = 0.0006, Figure 1). In comparison, the median os for patients with standard-risk cytogenetics in groups 1, 2, and 3 was 5.8 years, 9.2 years, and not reached respectively (p < 0.0001). Variables shown to be significantly associated with a reduction in os included high-risk ris1 (p = 0.0028), age (p < 0.0001), serum creatinine (p = 0.002), International Staging System score (p < 0.0001), serum calcium (p = 0.0056), and lactate dehydrogenase (p = 0.0001).

**Author Conclusions** Results confirm continued improvement in the survival of patients with ND-MM, including elderly patients and those with high-risk disease.

Investigator Commentary by Dr. Bharat Nandakumar  
Over the past decade, we have seen an improvement in os for patients with MM. This retrospective study of patients with ND-MM seen at the Mayo Clinic between 2004 and 2017 aimed to validate whether the improvement in survival for those patients was a sustained phenomenon. The data from this analysis, which was split into 3 cohorts based on time of diagnosis, showed that, indeed, os has continued to improve over time. What is particularly encouraging is that we see improvement in survival for patients with high-risk cytogenetics, particularly in the most recent time period assessed. Although that improvement in os for patients with MM and high-risk cases did not reach the same level of benefit seen for standard-risk patients, it is a step forward for the patients with a poor prognosis. The improvement in os is likely the result of several factors, including the advent of novel therapies such as proteasome inhibitors and immunomodulatory imide drugs, coupled with a risk-adapted approach, better risk stratification, and early use of autologous stem-cell transplantation.

Contemporary Therapy Efficacy for High-Risk MM: A Systemic Review (ASCO abstract e19536)  
**Objectives** To examine the efficacy of anti-myeloma therapy for high-risk ND-MM and r/r MM.

**Methods** A search of the PubMed, EBSCO, and EMBASE databases resulted in the selection of eighteen trials with outcomes data in high-risk ND-MM (n = 598) and r/r MM (n = 726). Treatment efficacy and survival data were extracted. The analysis did not include updated data from the 2018 American Society of Hematology conference or the 2019 ASCO conference.

**Results** In the overall population, overall response rates (ORRs) ranged from 31% to 100% for patients with high-risk MM (compared with 56% to 94.7% for patients with standard-risk disease), and complete response (CR) rates ranged from 10% to 58.3% (compared with 7% to 38.1%). In high-risk ND-MM, the ORRs were 71.2%–86.2% and the CR rates were 35%–58.3%, with the median PFS falling into the range of 18.0–31.3 months. The ORRs and CR rates in high-risk r/r MM were 31%–85.2% and 10%–29.2%, with the median PFS falling into the range of 3.3–23.1 months.

In patients with high-risk ND-MM treated with triplets or quadruplets, median PFS was longest with bortezomib–thalidomide–dexamethasone (23.5 months), followed by cyclophosphamide–thalidomide–dexamethasone...
(20 months) and daratumumab–bortezomib–melphalan–prednisone (18 months). Notably, quadruplet therapy with cyclophosphamide–bortezomib–dexamethasone (CyBoD) and pegylated liposomal doxorubicin resulted in the highest CR rate (58.3%) and median PFS (31.3 months). In high-risk R/R MM, DRd resulted in the highest minimal residual disease (MRD)–negative rate (21.4%). The data included in the review showed that median PFS was longest with KRd (23.1 months), followed by DRd (22.6 months), and IRd (21.4 months). As will be described later, the PFS for DRd has, with longer follow-up, been updated to 26.8 months.

**Author Conclusions** Patients with cytogenetically high-risk MM achieved high response rates, similar to those achieved in those with standard-risk disease. However, PFS is significantly shorter in high-risk disease, representing a poor prognosis.

**Impact of Patient Characteristics on Health-Related QoL in R/R MM: Results from CharisMMa (EHA abstract PF6152)**

**Objectives** To assess health-related QoL in patients with R/R MM.

**Methods** CharisMMa is an ongoing observational, cross-sectional, multicentre study involving 30 public hospitals in Spain. Patients were asked to rate their health-related QoL using the European Organisation for Research and Treatment of Cancer’s 30-question core Quality of Life Questionnaire (QLQ-C30) and its myeloma-specific module (QLQ-MM20). On the QLQ-C30, high scores on the global health status and functional scales indicate better QoL, and high scores on the scales for symptoms and financial difficulties indicate poorer QoL. On the QLQ-MM20, high scores for body image and future perspectives indicate better QoL, and high scores for disease symptoms and side effects indicate poorer QoL. Cytogenetic risk was categorized by the presence of cas: any or all of del(17p), t(14;16), or t(14;20) was defined as high risk; t(4;14) or gain(1q) or both was defined as intermediate risk; and any or all trisomies, t(11;14), or t(6;14) was defined as standard risk (see NCT03188536 at http://www.ClinicalTrials.gov/). Results of an interim analysis including 169 patients were presented.

**Results** On average, data were collected 2.15 ± 1.76 months (standard deviation) after the last relapse. The mean global score reported for the QLQ-C30 was 50.9 ± 23.0, with the functional role subscale being scored lowest (59.6 ± 34.9) and the cognitive functioning subscale being scored highest (75.3 ± 26.7). With respect to symptomatic items, fatigue (47.1 ± 27.6) and pain (40.8 ± 31.5) seemed to represent a meaningful burden for patients, while nausea and vomiting (8.8 ± 19.5), diarrhea (16.2 ± 26.4), and economic problems (15.4 ± 25.8) appeared less important. With respect to the QLQ-MM20, side effects (25.4 ± 15.9) and disease symptoms (32.1 ± 22.3) had a greater negative impact, while the scores for body image (74.0 ± 35.3) and future perspectives (57.8 ± 26.5) were better.

The QLQ-C30 global score was significantly lower for patients with high cytogenetic risk (22.5 ± 22.2) than for those with intermediate risk (55.1 ± 16.9) and with standard risk (52.1 ± 17.2), p = 0.0013. Additionally, the number of prior treatment lines was negatively associated with QoL score (1 prior line: 55.6 ± 20.1; 2 prior lines: 48.1 ± 25.5; 3 or more prior lines: 45.4 ± 23.8; p = 0.057).

**Author Conclusions** At relapse, patients with MM have an important symptomatic burden, especially pain and fatigue, that could impair their QoL. Several treatment lines and high cytogenetic risk seem to be factors related to poorer health-related QoL. Assessment of such patients could play an important role for selecting an individualized therapeutic approach.

**Investigator Commentary by Dr. Laura Rosiñol** In clinical practice, QoL is assessed during discussions with our patients, who describe their most concerning symptoms and side effects, because we generally do not have the time to conduct in depth QoL assessments. The rationale of the CharisMMa study was to understand how patients in Spain are being treated outside of clinical trials and to determine the usefulness of a new QoL assessment. Our study found that patients with high-risk cytogenetics had a significantly lower QLQ-C30 score, indicating a poorer QoL. Those findings are likely not related to the presence of high-risk cytogenetics itself, but rather to the fact that these patients have a worse prognosis, tend to relapse sooner, and receive a higher number of therapy lines. These patients are thus more frequently experiencing symptomatic MM, which will worsen their QoL. Maintaining patient QoL is particularly important in an incurable disease such as MM, and the hope is that, in the future, we can identify strategies and individualize therapy to improve QoL. Such improvements could emerge through the identification of more effective therapies for patients with high-risk cytogenetics that improve the depth and duration of response and through the development of effective therapies that improve convenience for patients (for example, oral, fixed duration).

**Treatment of Patients with R/R MM and High-Risk Cytogenetics**

**Efficacy and Safety of DRd in R/R MM: Updated Subgroup Analysis of POLLUX Based on Cytogenetic Risk (ASCO abstract 8038, EHA abstract PF591)**

**Objectives** To examine the efficacy of DRd in a subgroup analysis of patients with R/R MM at standard and high cytogenetic risk.

**Methods** The study randomized 559 patients with a median age of 66 years (range: 36–89 years) and a median of 1 prior therapy line (range: 1–11 lines) to DRd (n = 286) or Rd (n = 283), given until disease progression (Figure 2). High-risk and standard-risk cases were reported in 35 (12%) and 193 (68%) patients in the DRd group and in 35 (12%) and 176 (62%) patients in the Rd group respectively. The cases were collected by local RRV or karyotyping of bone marrow aspirates collected at screening visits. Patients who had 1 or more assessments from RRV or karyotyping were included in the analysis. Patients with high cytogenetic risk had 1 or
more of the following cases: t(4;14), t(14;16), or del(17p) (using a >50% detection cut-off)\(^3\). The primary endpoint was PFS.

**Results**  After a median follow-up of 44.3 months, PFS was significantly prolonged in patients with standard cytogenetic risk receiving DRd compared with Rd (median: not estimable vs. 18.6 months; HR: 0.43; 95% CI: 0.32 to 0.57; \(p < 0.0001\)) and also in patients with high cytogenetic risk (median: 26.8 months vs. 8.3 months; HR: 0.34; 95% CI: 0.16 to 0.72; \(p = 0.0035\); Figure 3). Additionally, for patients with standard cytogenetic risk and high cytogenetic risk, PFS was significantly prolonged in those who had received 1 prior line of therapy and who received DRd compared with Rd (standard-risk median: not estimable vs. 20.2 months; HR: 0.41; 95% CI: 0.27 to 0.63; \(p < 0.0001\); high-risk median: 29.6 months vs. 6.6 months; HR: 0.26; 95% CI: 0.09 to 0.75; \(p = 0.0083\)). And regardless of cytogenetic risk, the rates of overall response, very good partial response (VGPR) or greater, and CR or greater were higher with DRd versus Rd, regardless of cytogenetic risk status. In patients with standard cytogenetic risk, PFS was prolonged with DRd compared with Rd both in those who were MRD-positive (median: 36.4 months vs. 17.1 months; HR: 0.51; \(p < 0.0001\)) and in those who were MRD-negative (median: not estimable vs. 42.0 months; HR: 0.56; \(p = 0.2367\)). Additionally, among patients with high cytogenetic risk, PFS was prolonged with DRd compared with Rd in those who were MRD-positive (median: 20.3 months vs. 8.3 months; HR: 0.49; \(p = 0.0567\)). Median PFS with DRd was not evaluable in MRD-negative patients (Figure 4). In the standard cytogenetic risk and high cytogenetic risk subgroups, PFS was significantly prolonged with DRd compared with Rd (standard-risk median: not estimable vs. 33.3 months; HR: 0.54; \(p < 0.0001\); high-risk median: 37.7 months vs. 20.8 months; HR: 0.38; \(p = 0.0121\); Figure 5). At the time of the analysis, OS data were immature.

**Author Conclusions**  After a median of more than 3 years of follow-up, significant efficacy continued to be evident for DRd compared with Rd alone in patients with r/r MM, regardless of cytogenetic risk status.

**Investigator Commentary by Dr. Darrell White**  Currently, patients with MM who have high-risk cases are a challenge to treat because their disease tends to be resistant to standard therapies, and they experience shorter durations of response and poorer survival outcomes. It is clear that work

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**FIGURE 2**  POLLUX study design. RRMM = relapsed or refractory multiple myeloma; DRd = daratumumab–lenalidomide–dexamethasone; IV = intravenously; PD = progressive disease; PO = orally; Rd = lenalidomide–dexamethasone; PFS = progression-free survival; TTP = time to progression; ORR = overall response rate; VGPR = very good partial response; CR = complete response; MRD = minimal residual disease; OS = overall survival.

**FIGURE 3**  Progression-free survival based on cytogenetic risk status in the intention-to-treat population. HR = hazard ratio; CI = confidence interval; DRd = daratumumab–lenalidomide–dexamethasone; Rd = lenalidomide–dexamethasone.
must be done to improve the therapies available for those patients. For that reason, this sub-analysis of the POLLUX trial examined efficacy outcomes by cytogenetic risk. Previous analyses of the POLLUX study showed that compared with Rd alone, DRd is a very effective combination that significantly reduces the risk of disease progression or death in patients with relapsed RRMM (HR: 0.44). Those results are particularly impressive, given that Rd is a strong comparator, achieving a median PFS of 17.5 months (compared with 44.5 months for DRd), which is an improvement from the results of the MM-009 and MM-010 studies published more than a decade ago in which the median PFS for Rd was 11.1–11.3 months. The trial results likely reflect our increased comfort with this combination and the ability to better maintain patients with dose adjustments.

The POLLUX study had a good representation of Canadian patients from centres in Alberta, British Columbia, Nova Scotia, Ontario, and Quebec. At our centre in Halifax, we were pleased to have access to DRd through this clinical trial, enrolling 8 patients, 4 of whom continue to be followed 5 years into treatment (in both the DRd and Rd arms).

In the current analysis of the subgroup of patients with cytogenetic risk data, standard-risk and high-risk patients alike—especially those with only 1 prior line of therapy—saw a significant benefit from DRd compared with Rd. What is particularly striking is that a subpopulation of patients with high-risk cytogenetics was able to achieve MRD negativity in the DRd arm (26%), which was not observed in the Rd arm. That observation suggests that some patients with high-risk cytogenetics can achieve a deep remission with the addition of daratumumab to the standard Rd regimen. The patients who achieved MRD negativity were also able to achieve a longer remission that, hopefully, will translate into increased survival; however, that statistic has yet to be seen.

Overall, the results from POLLUX are extremely positive for patients with relapsed RRMM, and this sub-analysis shows that the addition of daratumumab to Rd is a step in the right direction for improving therapy efficacy in patients with high-risk cytogenetics. Based on what is currently available, I think that the triplet combination of DRd is the optimal choice for patients with relapsed disease and high-risk cytogenetics who are not refractory to lenalidomide. However, because this combination did not completely overcome the negative prognosis for patients with high-risk cytogenetics, there is still room for improvement. The next step would be to investigate the addition of daratumumab to existing therapies such as KRd or CyBorD to see if those quadruplet combinations can further improve outcomes for high-risk patients in the relapsed setting.

**Efficacy and Safety of DVd in R/R MM Based on Cytogenetic Risk: Updated Subgroup Analysis of CASTOR (ASCO abstract 804027, EHA abstract PF596)**

**Objective** To examine the efficacy and safety of DVd in a sub-analysis of patients with R/R MM and standard or high cytogenetic risk.

**Methods** The study randomized 498 patients with a median age of 63 years (range: 33–88 years) and a median of 2 prior therapies (range: 1–10 therapies) to DVd (n = 251) or to Vd (n = 247). Daratumumab was given until disease progression (Figure 6). High- and standard-risk cases were reported in 40 (16%) and 141 (56%) of the patients in the DVd group and in 35 (14%) and 140 (57%) of the patients in the Vd group. The cases were detected by local fish or karyotyping. Patients with 1 or more assessments from fish or karyotyping were included in the analysis. Patients with high cytogenetic risk had 1 or more of t(4;14), t(14;16), or del(17p) (using a >50% detection cut-off). The primary endpoint was PFS.
Results  After a median follow-up of 40.0 months, pfs was found to be significantly prolonged in the DVd group compared with the Vd group for patients with standard cytogenetic risk (median: 16.6 months vs. 6.6 months; hr: 0.26; p < 0.0001) and for those with high cytogenetic risk (median: 12.6 months vs. 6.2 months; hr: 0.41; p = 0.0106; Figure 7). Additionally, in patients who had received 1 prior line of therapy, pfs was significantly prolonged in the DVd group compared with the Vd group for those with standard cytogenetic risk (median: 29.8 months vs. 7.5 months; hr: 0.25; p < 0.0001) and with high cytogenetic risk (median: 20.1 months vs. 8.4 months; hr: 0.20; p = 0.0026). Rates of overall response, vgpr, and cr or greater were higher with DVd than with Vd regardless of cytogenetic risk status (standard-risk ≥ cr rate: 28% DVd vs. 10% Vd; high-risk ≥ cr rate: 28% DVd vs. 6% Vd).

Rates of mrdr negativity at the 10^-5 sensitivity threshold were higher with DVd than with Vd regardless of cytogenetic risk (standard-risk mrdr-negative rate: 11% DVd vs. 3% Vd; p = 0.0091; high-risk mrdr-negative rate: 15% DVd vs. 0% Vd; p = 0.0271). The mrdr negativity was sustained (≥6 months or ≥12 months) in a greater number of patients treated with DVd than with Vd, regardless of cytogenetic risk status. In patients with standard cytogenetic risk, pfs was prolonged in the DVd group compared with the Vd group for those who were mrdr-positive (median: 13.5 months vs. 6.5 months; hr: 0.28; p < 0.00001) and those who were mrdr-negative (median: not estimable vs. 37.6 months; hr: not estimable; p = 0.4142). Additionally, in patients with high cytogenetic risk, pfs was prolonged in the DVd group compared with the Vd group for those who were mrdr-positive (median: 10.5 months vs. 6.2 months; hr: 0.49; p = 0.0383). Median pfs with DVd in mrdr-negative patients was not evaluable (Figure 8). In the standard and high cytogenetic risk groups, pfs2 was prolonged in the DVd group compared with the Vd group (standard-risk median: 34.2 months vs. 18.5 months; hr: 0.41; p < 0.0001; high-risk median: 28.1 months vs. 19.7 months; hr: 0.58; p = 0.0915). The os data were immature at the time of the analysis.

Author Conclusions  Compared with Vd, DVd continued to demonstrate significant efficacy in patients with r/r mm regardless of cytogenetic risk status after a median of more than 3 years’ follow-up.

Investigator Commentary by Dr. Katja Weisel  This subgroup analysis of the castor study aimed to evaluate efficacy outcomes by cytogenetic risk status in patients treated with Vd or Vd, a standard regimen for patients in the relapsed setting. The primary analysis of the castor study demonstrated that, compared with patients receiving Vd, patients receiving Vd experienced a 69% reduction in the risk of disease progression or death after a median follow-up of 40.0 months. The current analysis of castor confirmed that, compared with Vd, DVd could significantly prolong pfs in patients with either standard-risk or high-risk...
cytogenetics and that the benefit was increased in patients with only 1 prior line of therapy.

A key finding in this sub-analysis was that patients with high cytogenetic risk in the DVd arm were able to achieve sustained MRD negativity at a rate similar to that in patients with standard cytogenetic risk. In contrast, MRD negativity was not achieved for high-risk patients in the Vd arm. Importantly, the deep and durable responses achieved with DVd translated into prolonged PFS for that patient group. From the efficacy results in the trial, we can conclude that the addition of an anti-CD38 antibody such as daratumumab is a good therapeutic strategy for patients with MM in the relapsed setting, regardless of cytogenetic risk status. Although treatment with DVd could not completely overcome the poorer prognosis seen in patients with high-risk cytogenetics, the substantial improvement in median PFS for the patients treated with DVd is encouraging.

Biomodulatory Therapy with Lenalidomide, Pioglitazone, Dexamethasone, and Metronomic Low-Dose Treosulfan in R/R MM (ASCO abstract 803731)

**Objectives** To examine the efficacy and safety of biomodulatory therapy in patients with lenalidomide-resistant R/R MM.

**Methods** A prospective one-arm multicentre phase II trial enrolled 39 patients with a median age of 62.5 years (range: 47–77 years) and a median of 5.5 prior therapies (range: 2–10 therapies). Of that group, 48.7% had undergone autologous stem-cell transplantation, and 89.5% were refractory to their last therapy. Patients received daily continuous oral dexamethasone (1 mg), pioglitazone (45 mg), low-dose treosulfan as metronomic chemotherapy (250 mg twice daily), and lenalidomide (15 mg).

**Results** A VGPR was achieved in 17.9% of patients, and the disease control rate was 71.8%. No patients in this study achieved CR. The median PFS and OS were 5.6 months (95% CI: 3.8 months to 8.5 months) and 17.6 months (95% CI: 14.9 months to 39.2 months) respectively. Time to progression was not significantly different between the high-risk and standard-risk patients (Figure 9). There was also no difference in progression between patients who did and did not receive lenalidomide in their last prior therapy before study start (n = 11 and n = 27 respectively). Analysis of individual patient response patterns by swimmer plot indicated that many patients were able to achieve at least stable disease, and a few patients experienced continued disease stabilization after treatment discontinuation (Figure 10). The most common grade 3 and greater adverse events were hematologic toxicity (n = 31, 67.4%) and infection (n = 7, 15.2%). Dose reductions were implemented in 61% of patients.

**Author Conclusions** The favourable efficacy and safety profile of the biomodulatory approach suggest that this strategy should be further evaluated in patients with heavily pretreated, immunomodulatory agent–resistant MM.

**Investigator Commentary by Dr. Albrecht Reichle** In many cancers, the homeostatic pathways between tumour and stroma cells are dysregulated, making communicative reprogramming of those pathways (that is, anakoinosis) a novel therapy approach in MM. In this phase II study of heavily pretreated patients with lenalidomide-resistant R/R MM, we investigated a unique cocktail of drugs targeting homeostatic pathways between MM clones and stromal cells. In the cocktail, we included dexamethasone and pioglitazone, which are both anti-inflammatory and angiostatic transcription modulators. Specifically, pioglitazone targets PPARγ (the peroxisome proliferator-activated receptor γ, a nuclear receptor family transcription factor) and has been reported to suppress STAT3 activation. The regimen also included low-dose treosulfan as metronomic chemotherapy and lenalidomide as a pleiotropic biomodulator. Because lenalidomide can upregulate PPARγ, we suspect that lenalidomide might play a synergistic role in enhancing the activity of pioglitazone. Indeed, we saw that, although none of the drugs showed significant
activity as monotherapy, they exerted concerted activity when combined.

A key finding in this study was the lack of any difference in time to progression between patients with high-risk and standard-risk cytogenetics, which is not generally seen with current MM therapies. In addition to cytogenetic risk, number of lines of therapy and refractory disease are also associated with poorer outcomes in MM. We showed in this study that this population of heavily pretreated patients could achieve OS and PFS results similar to those achieved with daratumumab monotherapy in the sirius study.35 Importantly, we also showed that anakoinosis therapy, which included lenalidomide, was able to rescue patients who were lenalidomide-refractory. Although this therapy is unusual, we believe that reprogramming of myeloma-stroma homeostatic pathways through anakoinosis therapy is an effective approach to overcome the genetic heterogeneity present in MM, particularly in patients with high-risk cytogenetics. In the future, our aim is to investigate how this therapy approach can be combined with other targeted approaches in MM at various stages of therapy.

**CLINICAL IMPACT IN CANADA**

**Question-and-Answer Session with Drs. Richard LeBlanc, Kevin Song, and Darrell White**

**Q** What treatment strategies do you use for patients with MM and high-risk cytogenetics in the first-line and relapsed settings?

**Dr. LeBlanc** Regardless of cytogenetic risk status, my principal strategy is to use each effective anti-myeloma agent available to my patients, at the optimal dose, for the longest period of time over the course of their disease and to avoid a situation in which they are no longer eligible to receive a given therapy. For high-risk patients, we try to use a proteasome inhibitor–based triplet therapy at the optimal tolerated dose in the first-line setting, because this class of agents seems to partially overcome the poor outcomes associated with high-risk disease. Based on the EMMO2 trial, we propose tandem autologous transplantation after proteasome inhibitor–based induction therapy for those who are eligible.36 For patients with del(17p), transplantation is generally followed by maintenance therapy with bortezomib for at least 2 years based on results from the novon-65 trial.36 For all other cases, continuous lenalidomide maintenance is a standard practice based on many phase III trials, including the Cancer and Leukemia Group B 100104 (Alliance) trial and meta-analysis.37,38 For patients with high-risk cytogenetics who are transplant-ineligible, we ideally would treat with CyBorD or bortezomib–melphalan–prednisone in the first line, because bortezomib-based therapy has proved to be superior to immunomodulatory agent–based therapy in this setting.40 However, many patients will receive Rd (based on the first trial)41, because the cytogenetic results typically arrive after a treatment has been initiated.

At the time of relapse, choice of treatment will depend on factors related to the patient (age, frailty, performance status, comorbidities), factors related to the disease, and treatment-related factors such as responses and tolerance to prior therapies. In my own practice, re-evaluation of cytogenetic risk is not usually performed at this time because the results will rarely change my treatment decisions, especially because the first results are typically available only after treatment has been initiated.

**Dr. Song** In the first-line setting, the major difference in therapy for transplant-eligible high-risk compared with standard-risk patients is the agent used for maintenance therapy. Patients with high-risk cytogenetics are typically given bortezomib maintenance for 2 years after transplantation; standard-risk patients typically receive maintenance lenalidomide. The option to give lenalidomide maintenance in high-risk patients is also a possibility if that is the preference of the patient and physician, usually because of personal factors such as distance needed to travel for bortezomib administration.

In the first-line transplant-ineligible setting, the presence of high-risk cytogenetics is not a significant driver of therapy choice. The relapsed setting is similar, in that most therapies used in relapsed patients have been found through randomized controlled trials to be beneficial for standard- and high-risk patients, albeit with poorer outcomes for the subgroup of high-risk patients. For that reason, we would re-test patients at relapse only for the presence of del(17p) on a case-by-case basis (for example, in patients who have progressed less than 6 months after frontline therapy), because acquisition of that CA has been associated with rapidly progressive disease.

Currently in British Columbia, funded treatment regimens after first relapse include Rd alone, D/Vd, D/Rd, K/Rd, and carfilzomib–dexamethasone regardless of cytogenetic risk status. Other therapies that can be accessed in that setting include IRd, although ixazomib can be accessed only through a compassionate program. Once patients have progressed on one of those regimens, subsequent treatment is less clear and depends on what has been used previously. Pomalidomide–dexamethasone (Pd) is an available option, but patients must have had prior exposure to lenalidomide as well as to a proteasome inhibitor.
In our province, one of the challenges we face for treatment in the relapsed setting, regardless of cytogenetic risk status, is accessing daratumumab for patients who are refractory to bortezomib and lenalidomide—a result of the negative recommendation for reimbursement of daratumumab monotherapy by the pan-Canadian Oncology Drug Review, based on the uncertainty of a net clinical benefit of daratumumab in the single-arm phase II Sirus study. Although the negative recommendation is unfortunate, one of the most obvious strategies to address the lack of effective therapies in this group of patients will be to gain access to daratumumab in combination with Pd.

**Dr. White** Treatment of patients with MM and high-risk cytogenetics is very similar to treatment for standard-risk patients. In my practice, the only differentiation of therapy between cytogenetic risk groups is in the first-line transplant-eligible setting, where high-risk patients would be offered tandem autologous transplantation. After transplantation, those patients would receive continuous lenalidomide maintenance therapy, because proteasome inhibitor–based maintenance is not funded in Nova Scotia and there is uncertainty concerning its benefits for patients with high-risk disease. At this time, the optimal therapy for patients with high-risk cytogenetics is not known, and therefore the best option for those patients would be treatment through a clinical trial.

**Q** What is your impression of the results of the Pollux and Castor studies?

**Dr. LeBlanc** The global impression is that Pollux and Castor are two practice-changing trials showing that the addition of daratumumab to standard bortezomib or lenalidomide regimens in the relapsed setting improves response rates and quality of response, including mrd negativity, duration of response, and pfs in standard-risk and high-risk patients alike. Although it is difficult to compare results between trials, the results from Pollux showing a median pfs of 44.5 months in the intention-to-treat population and 26.8 months in the high-risk population are so impressive that it is easy to state that DRd is among the best treatments studied in phase III trials in the relapsed setting. The Aspire trial, which compared KRd with Rd in patients with relapsed mm, is likely the closest to DRd in terms of good results. That study demonstrated a median pfs of 26.3 months in the intention-to-treat population. The difference in results between the two trials can be explained partly by differences in the study populations. For example, the median prior lines of therapy was 1 for Pollux and 2 for Aspire.

Although Pollux and Castor are two important trials, they present some limitations. In the Castor study, use of Vd as a comparator is not ideal because, currently, that therapy is considered a suboptimal treatment in r/r mm, particularly at a fixed duration of 24 weeks. Using CyBorD as the comparator would have provided more clinically relevant information. The Pollux study is an excellent trial; however, it did not include patients progressing on lenalidomide maintenance, which represents a significant number of patients with r/r mm. Because progression on the maintenance dose of lenalidomide likely does not render patients lenalidomide-refractory, we would like to have DRd available for such patients; however, we do not know the real impact of DRd in that group.

**Dr. Song** Given that patients with high-risk cytogenetics tend to have poorer outcomes, this sub-analysis provides important information: The addition of daratumumab to a standard regimen of Rd can improve pfs in high-risk patients, although the treatment is unable to provide the same level of pfs benefit seen in standard-risk patients. I would expect additional analyses from the Pollux study exploring efficacy outcomes based on age, International Staging System score, and renal dysfunction, which will also provide important insight into the types of patients this combination will be effective for. Particularly helpful would be an analysis of efficacy outcomes for patients by prior backbone therapy—for example, proteasome inhibitor versus immunomodulatory agent.

**Dr. White** I think that Pollux and Castor are both positive trials showing that the addition of daratumumab to Rd or Vd improves outcomes for patients with high-risk cytogenetics; however, they do not completely nullify the risk in that patient population. The evidence in the Pollux trial is more impactful, given that Rd is a strong comparator and a relevant therapeutic option in the relapsed setting in Canada. Unfortunately, the choice of Vd as a comparator in Castor was made based on labelling and U.S. Food and Drug Administration approval, but it is not a combination commonly used in Canada outside of clinical trials.

**Q** How would the results from the Pollux and Castor sub-analyses influence treatment decisions in Canada for patients with r/r mm and high-risk cytogenetics?

**Dr. LeBlanc** Because results from Castor and Pollux show that standard-risk and high-risk patients alike benefit from the addition of daratumumab in the relapsed setting, we don’t differentiate treatment between those cytogenetic risk groups. Because daratumumab is accessible only in combination with bortezomib or lenalidomide, I would consider using those drugs early in the relapsed setting—before the patient becomes refractory to those two agents. Along the same line, I would consider adding daratumumab for a patient who is receiving bortezomib or lenalidomide-based therapy, especially if the patient is already refractory to one of those two agents. Because, as of now, it would be the last chance for the patient to receive daratumumab, given that it isn’t funded as monotherapy. Because Pollux and Castor have demonstrated longer durations of response and pfs with the addition of daratumumab, I would propose adding daratumumab for a patient already on Rd even if the patient is doing well and has a good stable response.

**Dr. Song** The results from those studies as well as others in relapsed mm are helpful in that they reinforce that daratumumab in combination with a number of anti-myeloma agents including lenalidomide, bortezomib, pomalidomide, and carfilzomib can provide benefit for most eligible patients, even those with high-risk cytogenetics. Based
on the results from those trials, it would be reasonable to give DRd or DVD to any patient in the relapsed setting who is eligible. Because those two combinations have not been directly compared, it is unclear which combination would be preferred in the relapsed setting. Based on the PFS curves presented in the two abstracts, it is likely that most physicians would prefer DRd, leaving DVD for patients who are lenalidomide-refractory. Since the recent listing of DRd for patients with relapsed MM, I would consider adding daratumumab to therapy if the patient had started Rd within 6 months. The decision to add daratumumab would be partly driven by a determination of whether the patient can still access daratumumab in combination with Vd once they progress on lenalidomide therapy.

**Dr. White** Based on the results from the sub-analysis of pollux, I would use DRd in situations in which I would previously have chosen Rd. I would try to use the combination earlier in the course of the disease, before a patient has been exposed to lenalidomide—for example, in a patient who underwent transplantation without lenalidomide maintenance; however, the number of those patients is diminishing. In Canada, it is now possible to add daratumumab for a patient already on Rd therapy. I would consider adding daratumumab only for a patient who has recently started Rd therapy (within 6 months) and whose response is still improving.

Another important question in the Canadian context is how to treat a patient who has progressed on lenalidomide maintenance. Because the pollux trial did not include such patients, evidence to support the use of DRd in this situation is weak. A proteasome inhibitor–based regimen such as Dvd is likely to have relevance in Canada for these patients receiving Rd until progression; however, I would expect that most Canadian physicians will adjust the castor protocol to give bortezomib once weekly. In Nova Scotia, our preference is to give daratumumab plus CyBorD; however, in both situations, we are left extrapolating from the trial data. I think the lifespan for Dvd will be limited, and my impression is that daratumumab in combination with Pd with or without cyclophosphamide will be a better combination and will likely be challenged by pomalidomide–bortezomib–dexamethasone in the second line when it is approved and funded.

Although daratumumab is effective in combination with other myeloma agents in the relapsed setting, many Canadian physicians are impressed by the early results of the mala trial and are eager to get DRd for transplant-ineligible patients in the first-line setting.

**Q** What can the retrospective studies from the Mayo Clinic tell us about survival outcomes for patients with MM and high-risk cytogenetics?

**Dr. LeBlanc** In the overall study population, as well as in patient subgroups such as those with high-risk CAS, the Mayo Clinic study demonstrated a significant improvement in OS for patients with MM diagnosed between 2013 and 2017 compared with those diagnosed before 2013. It is encouraging that the improvement in OS was not limited to young patients with standard-risk disease and that the availability of new effective therapies to treat MM has translated into improved outcomes for all patients.

**Dr. Song** The Mayo Clinic study shows that, at their centre, progressive improvements in OS can be observed for patients with MM—even patients with high-risk disease—when they are grouped into 5-year eras. That finding is consistent with the results from sequential randomized controlled trials evaluating novel therapy combinations, which continue to show improved outcomes for patients with MM across many subgroups.

**Dr. White** Because the Mayo Clinic is a referral-based centre, this is a biased cohort of patients who would have had to be well enough and to have had the means to seek treatment at the clinic. In that regard, real-world survival data in MM from the Surveillance, Epidemiology, and End Results program database in the United States as well the Swedish Cancer Registry might be more relevant. The Mayo Clinic data are consistent with those other datasets in showing that patients diagnosed with MM in recent years, including high-risk patients and older patients, experience improved outcomes. That observation provides reassurance to physicians, regulatory agencies, and funders that the new drugs are having an impact on patient outcomes in MM.

**Q** What is your impression, based on the results of the phase III trial by Heudobler et al., of the biomodulatory regimen of lenalidomide, pioglitazone, dexamethasone, and low-dose treosulfan as metronomic chemotherapy in patients with RR MM and high-risk cytogenetics?

**Dr. LeBlanc** In that phase III trial of heavily pretreated patients with MM who were lenalidomide-refractory, 18% of the patients achieved a VGPR or better, the median PFS was 5.6 months, and the median OS was 17.6 months. Although it is difficult to compare results across studies, those results are good with respect to other trials in a similarly pretreated population. In the MM03 trial, treatment with Pd achieved a VGPR or better in 6% of patients, and median PFS was 4 months. In the sirius trial, daratumumab monotherapy achieved a VGPR or better in 12% of patients, and the median PFS was 3.7 months. For patients with high-risk cytogenetics, time to progression was not significantly different than it was in standard-risk patients. If this regimen could overcome the poor outcome associated with high-risk disease, it would therefore be a useful treatment strategy to investigate. A phase III trial comparing triplet lenalidomide-based therapy with that biomodulatory regimen in the relapsed setting with a subgroup analysis of patients with high-risk cytogenetics would provide more information about the usefulness of the regimen.

**Dr. Song** Conceptually, this biomodulatory regimen is an interesting therapeutic approach for patients with high-risk disease; however, it is not likely to affect the therapeutic landscape in Canada in the near future, for several reasons. In terms of access, treosulfan is not easily obtainable in the Canadian system, and given that treosulfan is an alkylator, I would be concerned about its chemogenic effects. Additionally, I do not believe that physicians would be comfortable
with the daily dosing of dexamethasone described in this protocol. The results achieved in this heavily pretreated population are encouraging; however, the population size is small and the follow-up is short, and therefore the applicability of this regimen in practice would require further study.

**Dr. White**  This study was difficult to interpret given that it was a small study population, and I do not have experience with two of the investigational drugs used: pioglitazone and treosulfan. What I can take away from the study is that the biomodulatory combination was tolerable and might warrant further investigation. However, it will not affect practice in Canada with the treatment schedule used.

**Dr. Leblanc**  The authors of the CharisMMa study conclude that high-risk cytogenetics appear to be a factor associated with poor qol. That observation is not unexpected, because disease progression and an increase in symptoms will happen earlier in the course of disease for patients with high-risk compared with standard-risk cytogenetics. Quality of life is an important outcome to measure; however, outside of clinical trials, we do not have the resources to routinely capture prospective patient-reported outcomes. We do retrospectively capture some patient-reported outcomes from consenting patients through the Myeloma Canada Research Network’s national myeloma database, although not extensively. With this kind of database, we could better understand how qol is affected by new therapies and specific sequencing.

**Dr. Song**  This observational study found that patients with MM in the relapsed setting who have high-risk cytogenetics have poorer qol based on the European Organisation for Research and Treatment of Cancer’s qol-C30 global score. Those results are not surprising, given that patients with high-risk cytogenetics tend to have more aggressive disease and shorter progression-free intervals. Thus, there is a lesser amount of time for a patient’s body to recover from the previous progression, resulting in an earlier deterioration in a patient’s qol.

**Dr. White**  The biggest takeaway from this study is the idea that, if the large treatment centres in Canada could cooperatively collect qol data to a national database, the data accumulated could be powerful. One of the challenges to routinely measuring patient-reported outcomes is that the standard questionnaires are quite involved. If we had a simpler method of collecting these patient-reported outcomes, gathering national qol data could be more easily achieved.

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**CONFLICT OF INTEREST DISCLOSURES**

We have read and understood *Current Oncology’s* policy on disclosing conflicts of interest, and we declare the following interests:

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