Multiple Myeloma Research Review™

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Issue 24 – 2017

In this issue:

Abbreviations used in this issue
CR = complete response
MGUS = monoclonal gammopathy of undetermined significance
MM = multiple myeloma
MRD = minimal residual disease
MRI = magnetic resonance imaging
ORR = overall response rate
OS = overall survival
PFS = progression-free survival
(VG)PR = (very good) partial response

NZMA New Zealand Medical Association

myeloma new zealand

Myeloma NZ is a new foundation in NZ to provide a deeper level of support for those who affected by multiple myeloma. If patients or their loved one have been diagnosed with multiple myeloma, Myeloma NZ can help them learn about treatment options and point them to information and services to help them cope with the disease. www.multiplemyeloma.org.nz/

Welcome to issue 24 of Multiple Myeloma Research Review.

This issue begins with research identifying specific dynamic contrast-enhanced MRI parameters that correlate with R-ISS (revised International Staging System) and adverse prognostic features of angiogenesis in MM. A pooled analysis of data from the GEM (Grupo Español de Mieloma) trials found that MRD-negative status had greater prognostic value than CR for survival outcomes across the disease spectrum, irrespective of treatment type or patient risk group. A retrospective analysis reporting low cardiac toxicity of bortezomib in patients with MM is also included. The last issue of Multiple Myeloma Research Review for 2017 concludes with a study showing cytogenetic evolution towards high-risk MM after autologous stem-cell transplantation, highlighting the importance of repeated genetic testing.

We hope you have been finding the selected papers and commentaries informative and helpful. We look forward to bringing you more interesting updates in myeloma research in 2018.

Kind regards,

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Dynamic contrast-enhanced magnetic resonance imaging parameters correlate with advanced revised-ISS and angiopoietin-1/angiopoietin-2 ratio in patients with multiple myeloma

Authors: Terpos E et al.

Summary: The value of dynamic contrast-enhanced MRI was evaluated in 60 patients with previously untreated MM, 14 with smouldering MM and five with MGUS treated with novel agents. MRI of the thoracolumbar spine and pelvis was performed prior to any therapy, and dynamic contrast-enhanced MRI was performed. The MRI perfusion parameters evaluated were wash-in, washout, time-to-peak, time-to-maximum slope and wash-in/time-to-maximum slope ratio. Compared with patients with smouldering MM or MGUS, those with symptomatic MM had significantly increased wash-in. Compared with patients with MGUS, both patients with symptomatic and smouldering MM had decreased time-to-peak and an increased wash-in/time-to-maximum slope ratio. Patients with symptomatic MM had decreased time-to-maximum slope compared with MGUS patients. For angiogenic cytokines measured on the day of MRI, compared with smouldering MM and MGUS patients, patients with symptomatic MM had a significantly reduced angiopoietin-1/angiopoietin-2 ratio. Time-to-peak was found to be correlated with angiopoietin-1/angiopoietin-2 ratio. Compared with patients with R-ISS scores of 1 and 2, those with a score of 3 had a significantly shorter median time-to-peak (23 vs. 54 and 48 sec, respectively). Patients in the lowest time-to-peak quartile had shorter time to progression than all other patients.

Comment (DS): Functional MRI scanning provides biological as well as anatomical detail, and is appealing as there is no radiation exposure to patients. In addition, functional MRI scans are cheaper and more readily available than PET scans in NZ. This paper looked at dynamic contrast-enhanced MRI in myeloma patients and found that certain characteristics were associated with increased stage and risk of progression. Potentially, this could help in selecting presymptomatic myeloma patients who require early intervention. Expect to see more functional MRIs in NZ medical practice.

Reference: Ann Hematol 2017;96(10):1707–14
Abstract

Independent commentary by Dr Ken Romeril, FRACP, FRCPA Haematologist specialising in malignant haematology, Wellington Hospital. He has a particular interest in translational myeloma research and genetics. **For full bio CLICK HERE**

Independent commentary by Dr David Simpson, MBChB, FRACP, FRCPA, Consultant Haematologist North Shore Hospital. His interests are in malignant haematology. **For full bio CLICK HERE**

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Disclaimer: This publication is not intended as a replacement for regular medical education but to assist in the process. The reviews are a summarised interpretation of the published study and reflect the opinion of the writer rather than those of the research group or scientific journal. It is suggested readers review the full trial data before forming a final conclusion on its merits.

Research Review publications are intended for New Zealand health professionals.

Daratumumab plus pomalidomide and dexamethasone in relapsed and/or refractory multiple myeloma

Authors: Chari A et al.

Summary: This report provides phase 1b safety and efficacy results of daratumumab plus pomalidomide/dexamethasone in patients with relapsed or refractory MM who had received ≥2 lines of prior therapy; it constitutes one arm of the open-label, nonrandomised, multicentre EQUULEUS; MMY1001 study. Initially six patients were enrolled and received 28-day cycles of daratumumab 16 mg/kg and pomalidomide 4mg daily for 21 days with dexamethasone 40mg each week. Once the primary endpoint of safety was assessed for these participants (including adverse event monitoring, physical examinations and electrocardiogram monitoring), an extension cohort of 97 patients was added at the same dosing schedule. The ORR was 60%, the clinical benefit rate was 62% and the PFS duration was 8.8 months. The authors concluded that the combination of daratumumab with pomalidomide/dexamethasone in patients with MM elicited no new safety concerns and resulted in deep, durable responses.

Comment (DS): Although phase 3 studies of daratumumab have been reported and showed improved efficacy, this single-arm study is informative. Despite being heavily treated and refractory, 60% of patients achieved at least a PR, 17% achieved a CR and, more remarkably, of these, 29% were MRD-negative to less than 10^{-5}. The infusion reactions were manageable and mostly mild and associated with the first infusion. There was more neutropenia seen than in pomalidomide and dexamethasone alone in another study, which is probably due to the daratumumab, but may reflect selection bias. The neutropenia improved as the myeloma was controlled. Anti-CD38 antibodies are now of established benefit to myeloma treatment in multiple settings; we just need access to them.

Reference: Blood 2017;130(8):974–81
Abstract

A multicenter, open-label, phase 1b study of carfilzomib, cyclophosphamide, and dexamethasone in newly diagnosed multiple myeloma patients (CHAMPION-2)

Authors: Boccia RV et al.

Summary: Patients with newly diagnosed secretory MM received 3+3 dose-escalated carfilzomib 36, 45 and 56 mg/m^2 twice weekly with fixed-dose oral cyclophosphamide and dexamethasone (KCd) for ≤8 cycles in the phase 1b CHAMPION-2 study. There were no dose-limiting toxicities, and carfilzomib 56 mg/m^2 twice weekly was brought forward into dose expansion in which 16 patients were treated. The ORR in the dose-expansion cohort was 87.5% and 14 participants responded in a median of 1 month. Common grade ≥3 adverse events were anaemia (25.0%), neutropenia (18.8%), acute kidney injury (12.5%) and decreased white blood cell count (12.5%). Ten participants completed all eight cycles, five discontinued before cycle 8 due to adverse events and one discontinued due to disease progression.

Comment (DS): This study looked at the safety of KCd using escalating doses of carfilzomib from 36 to 56 mg/m^2, combined with weekly cyclophosphamide 300 mg/m^2 and dexamethasone 40mg. The maximum tolerated dose was not reached and 16 patients were treated at the highest dose. The ORR was 87.5% with 50% achieving at least a VGPR. The study included older patients with a median age of 65 years. Aspirin prophylaxis was not routine and one patient died of a myocardial infarction. The results are comparable with the best CyBorD outcomes and not as good as KRd or other KCd studies, perhaps highlighting the importance of including an immunomodulatory drug at some time in induction treatment.

Reference: Clin Lymphoma Myeloma Leuk 2017;17(7):433–7
Abstract

Depth of response in multiple myeloma: a pooled analysis of three PETHEMA/GEM clinical trials

Authors: Lahuerta J-J et al.

Summary: These authors analysed median 71-month follow-up data from 609 study participants with transplant-eligible MM and elderly participants with MM who had MRD assessments 9 months after study enrolment. CR without MRD negativity was not associated with prolonged PFS or OS compared with near-CR or PR. Strong associations were seen between MRD-negative status and prolonged PFS and OS in the overall population ($p<0.001$ for both) and in subgroups defined by prior transplantation, disease stage and cytogenetics, with prognostic superiority of MRD negativity versus CR particularly evident in the high-risk cytogenetic subgroup. Accordingly, higher discrimination was seen for both PFS and OS in Cox models that included MRD (versus CR) for response assessment. Prolonged PFS was predicted by superior MRD-negative rates after different induction regimens. The probability of 'operational cure' was high for 34 MRD-negative participants with a phenotypic bone marrow involvement pattern similar to MGUS at diagnosis; median PFS was 12 years, and 10-year OS was 94%.

Comment (DS): This important paper shows MRD testing has come of age. While traditional response criteria were correlated with outcome, those who achieved a CR but were MRD-positive had similar outcomes to PR patients; conversely, those who were in less than CR but MRD-negative did as well as MRD-negative CR patients, showing MRD status supersedes IMWG response criteria. MRD was tested using flow cytometry and was sensitive to 10^{-4} to 10^{-5}. Other studies have shown the method of MRD detection does not matter, and flow cytometry is relatively cheap, quick and locally available. The next step is for the US FDA to recognise this as a surrogate endpoint for new drug approval, but even without this, it will accelerate the development of combination regimens. We also need to futureproof the nomenclature and talk about MRD4 or MRD5, rather than MRD-negative, as the deeper the response the better the outcome.

Reference: J Clin Oncol 2017;35(25):2900–10
Abstract

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Date Prepared: April 2017

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Circulating tumour DNA analysis demonstrates spatial mutational heterogeneity that coincides with disease relapse in myeloma

Authors: Mithraprabhu S et al.

Summary: These researchers evaluated plasma-derived ctDNA (circulating free tumour DNA), as an adjunct to bone-marrow biopsy, for mutational characterisation and tracking disease progression. They analysed bone-marrow MM-cell DNA and ctDNA from 33 patients with relapsed/refractory MM and 15 with newly diagnosed MM for *KRAS*, *NRAS*, *BRAF* and *TP53* mutations. There were 31 mutations detected in plasma only, 59 in bone-marrow only and 38 in both, indicating a frequency of plasma mutations of 54%. Compared with patients with newly diagnosed MM, those with relapsed/refractory MM had a higher frequency of plasma-only mutations (27.2% vs. 6.6%), confirming the existence of spatial and genetic heterogeneity in advanced disease. The prevalence of ≥1 activating *RAS* mutation was 69%, which is higher than previously described. For seven patients who underwent analyses of sequential ctDNA quantitation with droplet digital PCR through longitudinal plasma tracking of specific clones, changes were seen in fractional abundance of certain clones reflective of disease status.

Comment (DS): The clonal heterogeneity of myeloma has recently been better appreciated, especially in relapsed or refractory patients. We know that in some patients, one bone lesion may respond to treatment while another grows, and this is due to different subclones present at different sites. Sampling for mutations in a bone-marrow sample is likely to miss important changes in clones elsewhere in the body. Andrew Spencer's group has shown cell-free DNA sampling identifies more mutations than seen in the marrow alone, and becomes a feasible way to look at the mutational landscape of a patient's disease. This study also highlights the importance of *KRAS* and *NRAS* mutations in disease progression, finding even higher rates of this as a second hit than when marrow alone was analysed. The scene is being set for rational personalised medicine for myeloma patients.

Reference: Leukemia 2017;31(8):1695–705
Abstract

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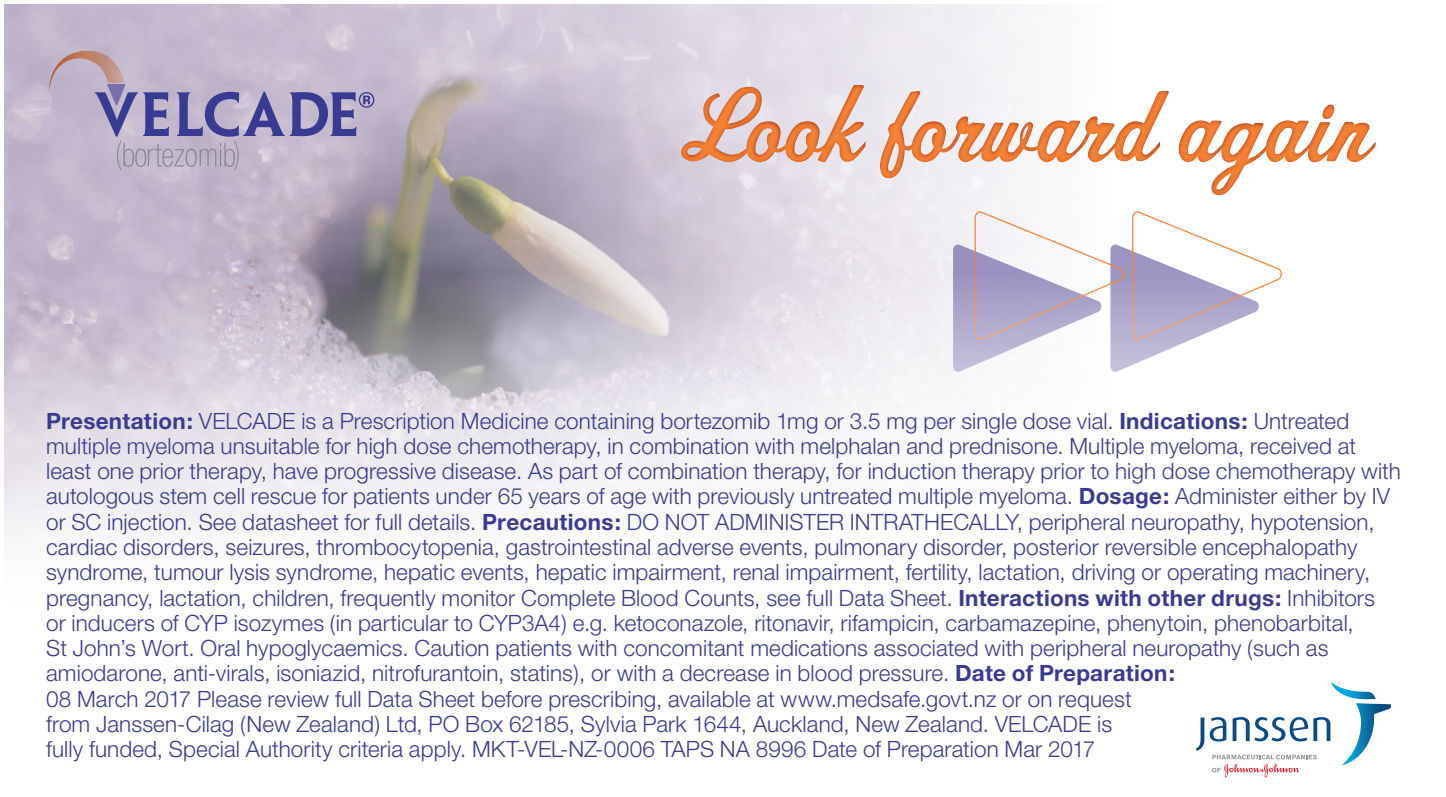
Efficacy of daratumumab-based therapies in patients with relapsed, refractory multiple myeloma treated outside of clinical trials

Authors: Lakshman A et al.

Summary: Outcomes were reported for 126 patients who received ≥1 cycle of any daratumumab-based combination therapy; one-third of the patients had high-risk cytogenetics, the study cohort had received a median of four prior therapies, the time from diagnosis to first daratumumab-based combination therapy was 4.3 years, and 13% were refractory to single-agent daratumumab. The daratumumab-based regimens included pomalidomide (n=52), lenalidomide (n=34) or bortezomib (n=23); the remaining 17 patients received other daratumumab-based combination regimens. The ORR was 47%, and over median follow-up of 5.5 months, median PFS duration was 5.5 months and median OS duration was not reached for any regimen. Median PFS duration was shorter in : i) penta-refractory MM (n=8) versus quadruple refractory MM (n=18) and others (n=100; 2.2 vs. 3.1 and 5.9 months, respectively [p<0.001]); ii) patients refractory to ≥1 agent in the daratumumab regimen versus others (4.9 vs. 8.2 [p=0.02]); and iii) patients who received >2 prior therapies versus others (5.0 months vs. not reached [p=0.002]). Infections (38%), fatigue (32%) and infusion reactions (18%) were among the nonhaematological toxicities reported, and the grade ≥3 haematological toxicity rate was 41%.

Comment (KR): In clinical trials of daratumumab in relapsed patients, PFS has been around 9–10 months. In this real-world study, PFS was lower and particularly poor in the penta-refractory group, which is not surprising. Daratumumab is a drug that is clearly much more effective if positioned earlier in the disease course and where we hope to be able to achieve access.

Reference: Am J Hematol 2017;92(11):1146–55
Abstract



Presentation: VELCADE is a Prescription Medicine containing bortezomib 1mg or 3.5 mg per single dose vial. **Indications:** Untreated multiple myeloma unsuitable for high dose chemotherapy, in combination with melphalan and prednisone. Multiple myeloma, received at least one prior therapy, have progressive disease. As part of combination therapy, for induction therapy prior to high dose chemotherapy with autologous stem cell rescue for patients under 65 years of age with previously untreated multiple myeloma. **Dosage:** Administer either by IV or SC injection. See datasheet for full details. **Precautions:** DO NOT ADMINISTER INTRATHECALLY, peripheral neuropathy, hypotension, cardiac disorders, seizures, thrombocytopenia, gastrointestinal adverse events, pulmonary disorder, posterior reversible encephalopathy syndrome, tumour lysis syndrome, hepatic events, hepatic impairment, renal impairment, fertility, lactation, driving or operating machinery, pregnancy, lactation, children, frequently monitor Complete Blood Counts, see full Data Sheet. **Interactions with other drugs:** Inhibitors or inducers of CYP isozymes (in particular to CYP3A4) e.g. ketoconazole, ritonavir, rifampicin, carbamazepine, phenytoin, phenobarbital, St John's Wort. Oral hypoglycaemics. Caution patients with concomitant medications associated with peripheral neuropathy (such as amiodarone, anti-virals, isoniazid, nitrofurantoin, statins), or with a decrease in blood pressure. **Date of Preparation:** 08 March 2017 Please review full Data Sheet before prescribing, available at www.medsafe.govt.nz or on request from Janssen-Cilag (New Zealand) Ltd, PO Box 62185, Sylvia Park 1644, Auckland, New Zealand. VELCADE is fully funded, Special Authority criteria apply. MKT-VEL-NZ-0006 TAPS NA 8996 Date of Preparation Mar 2017

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A retrospective analysis of 3954 patients in phase 2/3 trials of bortezomib for the treatment of multiple myeloma: towards providing a benchmark for the cardiac safety profile of proteasome inhibition in multiple myeloma

Authors: Laubach JP et al.

Summary: The cardiac safety profile of bortezomib was assessed in a retrospective analysis of participant-level data from one phase 2 and seven phase 3 studies in patients with previously untreated or relapsed/refractory MM; data from 2509 bortezomib recipients and 1445 nonrecipients were analysed. Grade ≥3 congestive heart failure occurred at incidences of 1.3–4.0% across studies in relapsed/refractory MM and at 1.2–4.7% across studies in previously untreated MM. The respective incidences of grade ≥2 and grade ≥3 arrhythmias were 1.3–5.9% and 0.6–4.1% across all studies, the respective incidences of any-grade and grade ≥3 ischaemic heart disease were 1.2–2.9% and 0.4–2.7%, and the incidences of cardiac-related death ranged from 0% to 1.4%. No significant difference was seen for any of these outcomes between bortezomib recipients and nonrecipients, but bortezomib recipients had higher rates of (mostly grade 1–2) oedema in one study and in a pooled transplant study analysis. Bortezomib did not impact on cardiac risk in logistic regression analyses of comparative studies.

Comment (KR): This was a very large but retrospective analysis with the shortcomings of this approach. The incidence of significant cardiac events was relatively low as compared with an agent such as carfilzomib. These results tend to make clinicians more confident of using bortezomib in older, more frail patients.

Reference: Br J Haematol 2017;178(4):547–60
Abstract

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www.nzord.org.nz/health-professionals-resources

Outcome of autologous hematopoietic stem cell transplantation in refractory multiple myeloma

Authors: Veltri LW et al.

Summary: This was a retrospective analysis of 233 patients with primary refractory or relapsed/refractory MM who had undergone autologous haematopoietic stem-cell transplantation, including 105 with double-refractory MM (refractory to ≥1 proteasome inhibitor and ≥1 immunomodulatory drug) and 128 without double-refractory MM. At median follow-up of 42 months for survivors, the respective groups of patients with and without double-refractory MM had PR or better rates of 79% and 82%, near CR or better rates of 24% and 21%, median PFS durations of 14.4 and 18.2 months, 2-year PFS rates of 35% and 40%, median OS durations of 38.9 and 56.6 months and 2-year OS rates of 71% and 76%; differences were not statistically significant.

Comment (KR): This study from Europe looked at mainly a double-refractory patient population and achieved a respectable near CR rate of 22%. We are well into the era of novel agents, but have limited options in NZ at first relapse, as we cannot use bortezomib or lenalidomide unless neuropathy is significant. The utility of a second transplant should not be overlooked if there is no relapse trial suitable, and certainly the cost is much less than some of the novel agents.

Reference: Cancer 2017;123(18):3568–75
Abstract

Impact of prior therapy on the efficacy and safety of oral ixazomib-lenalidomide-dexamethasone vs. placebo-lenalidomide-dexamethasone in patients with relapsed/refractory multiple myeloma in TOURMALINE-MM1

Authors: Mateos M-V et al.

Summary: Patients with relapsed/refractory MM who had received 1–3 prior lines of therapy were randomised to receive 28-day cycles of lenalidomide 25mg on days 1–21 and dexamethasone 40mg on days 1, 8, 15 and 22 combined with either oral ixazomib 4mg (n=360) or placebo (n=362) on days 1, 8 and 15 until disease progression in the phase 3 TOURMALINE-MMI study. This paper reported subgroup analyses according to type and number of prior regimens. Regardless of prior therapy, at median 15 months follow-up, prolonged PFS was observed in the ixazomib arm compared with the placebo arm (20.6 vs. 14.7 months). All subgroups evaluated of previous exposure (proteasome inhibitor, bortezomib, immunomodulatory drug, thalidomide, lenalidomide) also showed increases in PFS in the ixazomib group. Both subgroups of number of previous therapies (1 vs. 2–3) showed increases in PFS and time to progression and improved response rates with ixazomib versus placebo; however, the benefit was greatest in participants with 2–3 prior therapies.

Comment (KR): Several NZ centres participated in this trial and one of our colleagues is listed as an author. The trial was large and the results indicate a definite clinical benefit, albeit with only a 15-month follow-up. The treatment was well tolerated and has all the advantages of an all-oral regimen. It will be of interest to find out how the survival benefit stacks up against other competing regimens.

Reference: Haematologica 2017;102(10):1767–75
Abstract

Longitudinal fluorescence *in situ* hybridization reveals cytogenetic evolution in myeloma relapsing after autologous transplantation

Authors: Merz M et al.

Summary: This analysis of retrospective fluorescence *in situ* hybridisation data from 128 patients with paired bone-marrow samples from the time of primary diagnosis and at relapse sought to investigate cytogenetic evolution following upfront autologous stem-cell transplantation for newly diagnosed MM. Compared with primary diagnosis data, postrelapse data revealed a significantly greater likelihood of high-risk cytogenetic abnormalities (deletion 17p and/or gain 1q21) and *IGH* translocations with unknown partners, but not for defined t(4;14); t(11;14); t(14;16) *IGH* translocations or hyperdiploid karyotypes. New deletion 17p and gain 1q21 mutations were associated with cytogenetic heterogeneity, as different copy numbers were present only in subclones in some *de novo* lesions. There were no distinctive characteristics identified at baseline that were associated with new high-risk cytogenetic abnormalities following progression. The likelihood of developing high-risk aberrations was increased in patients who had relapsed following an induction regimen that included novel agents versus conventional chemotherapy (odds ratio 10.82 [95% CI 1.65, 127.66]). Survival outcomes were poor whether or not high-risk aberrations were present at baseline or after relapse (hazard ratios 3.53 and 3.06, respectively).

Comment (KR): This was a nice paper that looked in depth at this issue, which once again shows that high-risk abnormalities tend to trump everything else. It was of interest that high-risk aberrations were more evident in patients treated with novel agents. The suggestion that repeated genetic testing is important in relapsed disease will not be embraced by everyone.

Reference: Haematologica 2017;102(8):1432–8
Abstract

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