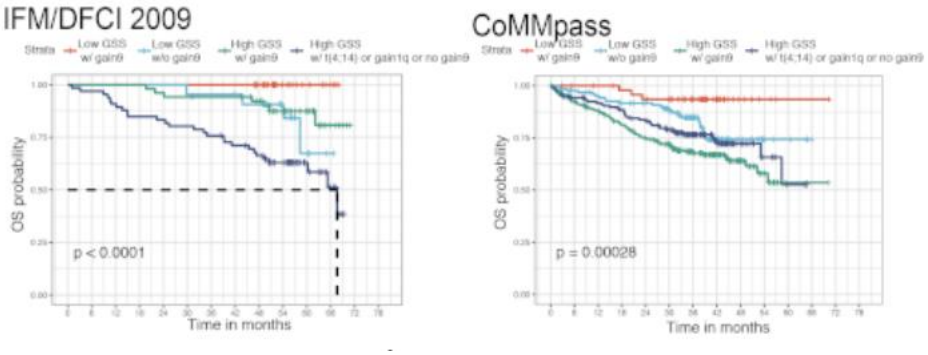
SUMMARY OF EHA 2020 MYELOMA: DISEASE BIOLOGY by Ceri Bygrave

Large scale whole genome profiling of newly diagnosed multiple myeloma patients identifies genomically defined ultra-low risk group (oral abstract #419) Mehmut Samur, Dana Faber Institute

Myeloma is a genomic and clinically heterogeneous disease and mutational load and processes are different among myeloma subgroups. Genomic studies often focus on definition of high-risk disease (CNAs, 17p abnormalities etc), with less interest in identifying patients with low risk disease. This group is equally attractive as a therapeutic target to minimise the effect of over treatment and toxicity in those with good risk disease.

Mutational load varies significantly among different myeloma sub-groups (e.g. those with t(11;14), t(4;14) abnormalities) and there are also links between high risk mutations and early events e.g. APOBEC-related mutational processes and t(14;16). Different mutational processes are active for clonal and sub-clonal mutations and for example DNA repair mutational signature is known to become more activated in later stages of the disease.

To identify a MM subgroup with superior outcome deep (60-80X) whole genome sequencing (WGS) and RNA-sequencing of CD138+ MM cells from 183 newly diagnosed patients enrolled in the Phase III IFM/DFCI clinical trial was performed. Genomic Scar Score, mutational signature and clinical outcomes were assessed and those with low GSS and gain9 were found to have a superior outcome (data also replicated in the COMPASS dataset). Low GSS and gain9 subgroup was found to be enriched with hyperdiploid patients and MYC translocations. Hyperdiploid patients can then be divided into low, intermediate and high-risk groups by stratifying by GSS. Low GSS was more common in those with t(11;14) compared to the rest (29.8% vs 14.2% respectively, p=0.02) while frequency of low GSS was significantly lower in del17p (1% vs 15%, p=0.008). Long term follow-up of the low risk cohort can provide the key to determine risk status and predict long term disease outcome. Identifying a low risk group may make this disease chronic or curable in some patients.



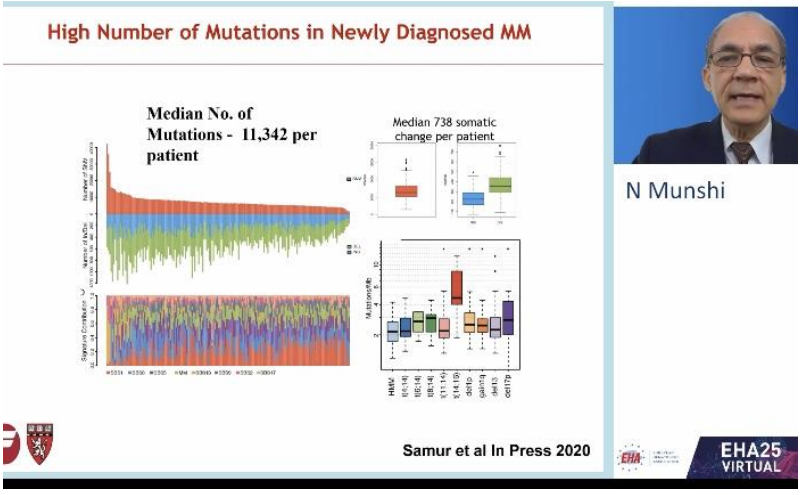
Biology of High-Risk Myeloma, N Munshi, oral presentation #p109-1

In this talk Professor Munshi reviewed the definition of high risk myeloma and condensed this to patients with the shortest survival, meaning death within 2-3 years of diagnosis. Their fate is often due to the development of rapid resistance to treatment and they constitute around 20% of all patients. Clinical definitions including those from IMWG often involve factors such as CNS, Extra Medullary disease (EMD), high LDH, plasma cell leukemia and in particular event free survival was shown to be short in those with EMD. Patients with EMD often also show high risk features by GEP70 and baseline cytogenetic abnormalities.

A second feature of high-risk disease that was discussed is response to treatment, e.g. primary resistance to PIs or IMiDs, early progression post ASCT, kinetic failure (rapid progression during treatment breaks) which can occur in the absence of high-risk baseline risk factors such as cytogenetics. Cytogenetic result by FISH remains the best described indicator of high risk disease although certain poor risk markers can sometimes be overcome by treatment in the case of t(4:14) disease and PI therapy. The penetrance of other markers can sometimes be affected by synergy e.g. ISS3 disease and +amp(1q) and bi-allelic deletion of TP53.

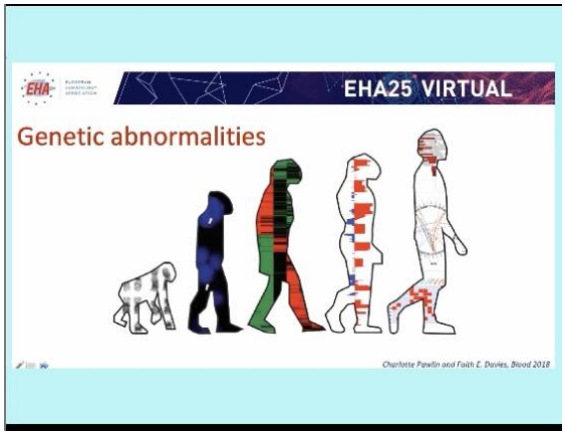
BIRC abnormalities were discussed as an example of a genetic variant which can influence survival. Mutational burden by GEP (e.g. exome sequencing) demonstrates that in many patients no single mutational abnormality drives outcome however, the frequency of mutations is important. In addition the complex relationship between abnormalities such as del(17p) and p53 mutation which can influence the cell cycle whenever there is DNA damage at multiple checkpoints due to variable effect on the expression of individual genes was discussed. Over and under function of genes can be equally important. In other words not all p53 abnormalities are the same and exert similar effects, the challenge is to identify the mechanism and end result of each on an individual basis.

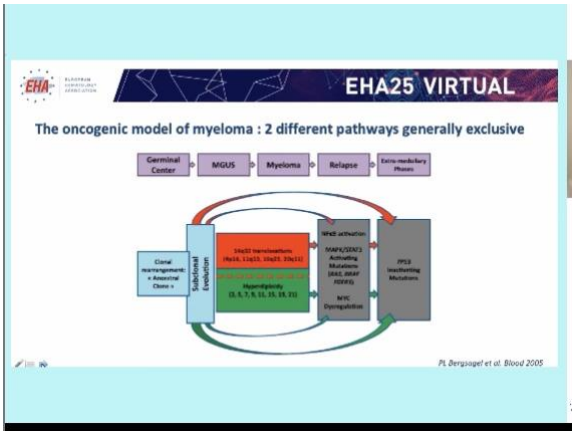
Mutational profile can be explored by deep whole genome sequencing up to 80X which can provide a lot of information about high risk disease. RNA sequencing and whole exome sequencing can also be used to show there is often a high mutational burden in patients with high risk disease.



Genetic and Risk Assessments in Multiple Myeloma, J Corre, oral presentation #p 109-2

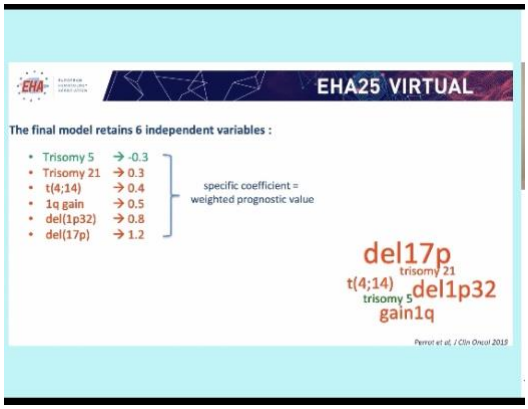
Dr Corre began by describing the variable survival duration in myeloma which can be anything between a few weeks and 20 years, this heterogeneity in outcomes means that we cannot define high risk myeloma with only 2 or 3 abnormalities. Again, she discussed that some high-risk factors are related to the patient, the tumour load, intrinsic cellular factors of the plasma cells and mixed factors. She proposed that the most important factors are genetic and response to treatment. Within the genetic factors the primary events of translocations or trisomies of odd numbered chromosomes were described followed by secondary events which can make the disease more aggressive.

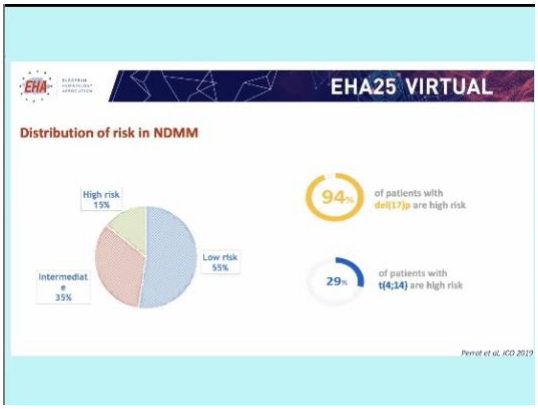




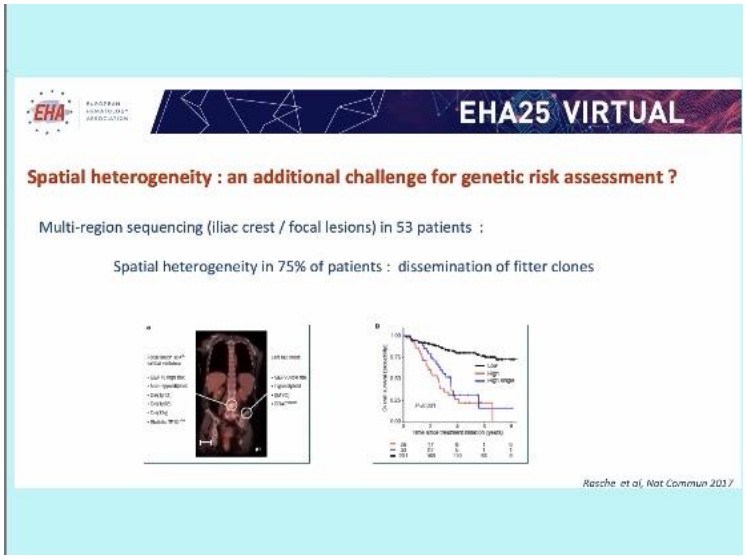
No single unifying mutation has been observed in myeloma in contrast to other tumours however certain high-risk genetic factors exists such as deletion 17p. Within patients who harbour this abnormality, the role of the size of the clonal fraction was discussed as being highly relevant with a cut off of >55% of cells. In addition, there is a group of patients with 'double hit' myeloma where there is amp1q, ISS3 and bi-allelic inactivation of TP53 who have an extremely poor prognosis. Also variability in prognosis between patients with t(4;14) may be due to the presence of additional abnormalities such as trisomies 3 and 5 (which may abrogate the negative effect) and del(1p32) or trisomy 21 which may represent poor risk t(4;14) disease when both are present.

In order to provide greater clarity on this topic the IFM group has devised a model of genetic abnormalities which have been shown to consistently affect outcome in their patient cohort. Five of the variables are adverse and 1 favourable and all can be easily assessed in routine clinical practise. Calculation of the risk score for a given patient can help identify subgroups of patients with truly 'high risk' abnormalities within accepted biomarkers such as t(4,14) and del17p.





Later Dr Corre discussed spatial heterogeneity as an additional challenge for genetic risk assessment as if sampling is done in the wrong site the patient will be misclassified. In the future NGS of circulating tumour DNA may be able to recapitulate abnormalities from all clonal fractions however this is not currently available in routine clinical practice.

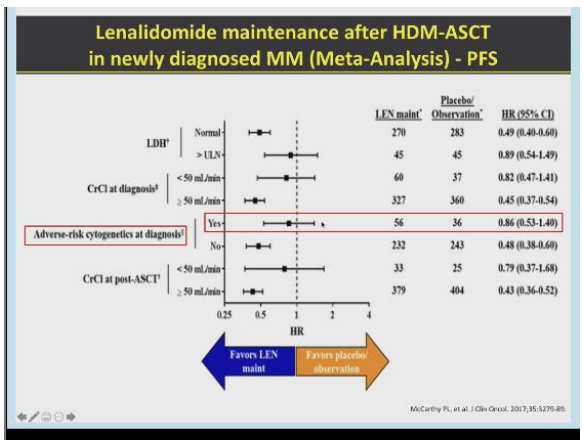


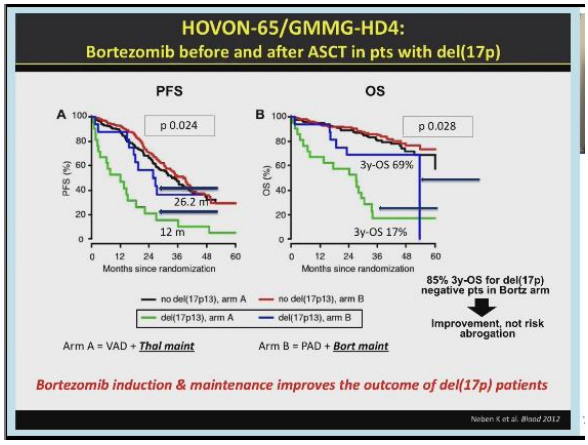
Management of High-Risk multiple myeloma patients, Jesus San Miguel, oral presentation # p109-3

Professor San Miguel began with a case study looking at a 57 year old man presenting with EMD and HR CA (p53 and t(14;16) who experienced early progression following VRD induction, tandem ASCT and consolidation. This is a problem that is all too common in UK practice (perhaps substituting VTD for VRD) and clinicians often lack a robust body of data to guide treatment decisions. Most of the benefits of novel drugs from recent trials apply to standard risk patients. Professor San Miguel proposed that the main treatment goals for the management of HR myeloma are precise methods to measure disease inside and outside the bone marrow and having treatments which can provide Early Rescue Intervention (ERI) as soon as the patient loses their response. In HR disease he suggests that eradication of all cells is necessary meaning precise methods for measuring MRD are required. Data from the Spanish group Paiva et al (JCO, 2019) shows that patients with R-ISS 3 disease who remain MRD positive do very badly due to MRD High Risk clones. Interestingly in patients with SR

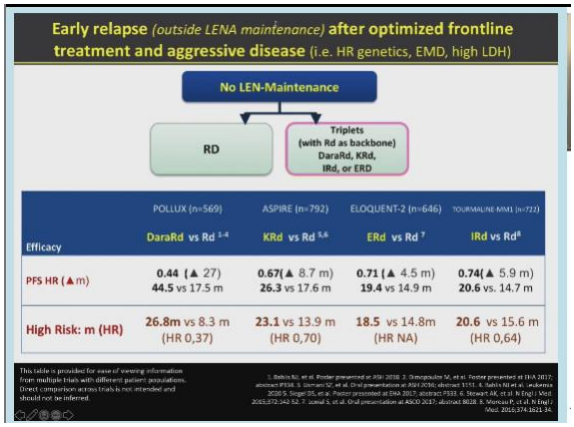
disease the MRD clones are more often associated with genetic abnormalities which may predispose cells to resist treatment where in HR disease this occurs with the primary genetic events.

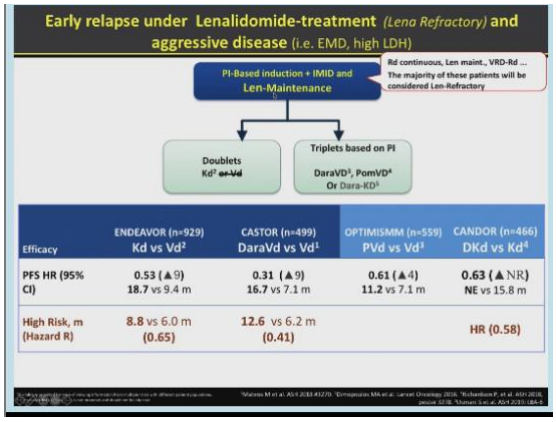
In terms of new treatment approaches the addition of a monoclonal antibody to standard induction regimens has been shown to improve ORR and depth of response for example daratumumab with VRD as shown in the Griffin trial. However, in this study the addition of daratumumab to VRD did not benefit patients with HR disease where the RVd combination performed better than D-VRD for achievement of stringent CR and MRD negativity. Data from the Forte trial showed that undergoing autologous transplantation reduced the risk of early relapse in patients with HR disease over and above chemotherapy consolidation. In addition, the Phase III EMN02/HO95 study has shown benefit of tandem over single ASCT in terms of PFS and OS in those with high risk disease with and OS at 3 years of 84.9% vs 72.8% for tandem versus single ASCT (HR 0.52, p=0.042). The benefit of lenalidomide maintenance to patients with genetic HR disease remains unclear, as described in a recent meta-analysis (McCarthy et al, JCO 2019) discussed in this talk. The UK MXI trial data has shown benefit whereas other studies have shown less effect and the overall HR 0.86 (0.53-1.40) is in line with the attenuation of the benefit of lenalidomide maintenance to overcome other adverse prognostic markers such as severe renal impairment and high LDH. Proteosome inhibitor maintenance has been shown to be beneficial in the HOVON-65-GMMG-HD4 trial where patients received PAD based induction and bortezomib maintenance and Professor San Miguel suggest that dual agent PI-IMiD maintenance may be the optimal approach for patients with genetic high-risk disease.



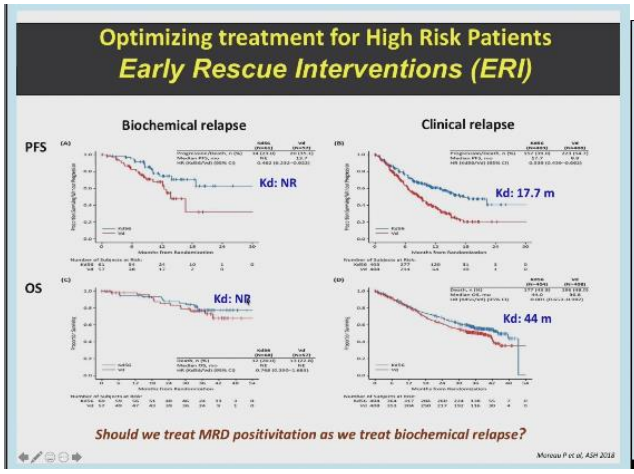


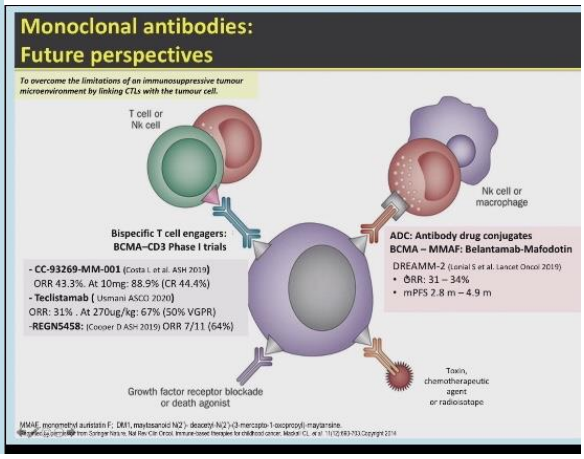
In the management of patients with relapsed HR disease a distinction was drawn based on lenalidomide resistance or not. In lenalidomide sensitive patients clearly several highly active combinations have been trialled in the first relapse space and beyond and all show activity in patients with HR disease (most notably in the Pollux study for Dara-Rd) however activity is inferior to SR patients. Lenalidomide refractory patients present an additional challenge, in this case proteasome inhibitor-based treatment, where the OPTISMM (PVD vs VD) and CANDOR (DKD vs KD) studies appear most promising, have offered some benefit for HR patients but less so than SR.

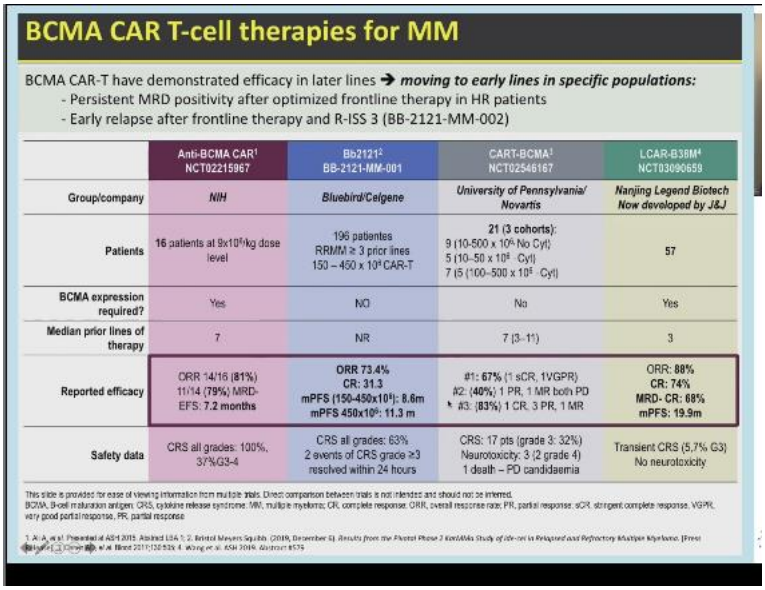




Summarising this talk there are many unsolved questions in the treatment of HR disease such as what to do with early relapses, primary refractory and extramedullary disease where there remains an absence of robust data to guide treatment. New strategies offered include the early detection of resistance through ERI and treatment at biochemical rather than clinical relapse and possibly treating patients at the time of MRD relapse with BCMA directed therapies including Belantamab where up to 1/3 or patients who are multiply resistant including anti-CD38 monoclonal antibodies can respond with an initial PFS of around 4 months offering some hope for future progress. In addition, future clinical trials for HR patients with risk adapted maintenance based on MRD result such as the UK MXV RADAR study were described as a potential means of overcoming the unpredictable nature of HR disease and the requirement to move quickly when the disease begins to escape.







BCMA CAR T-cell therapies for MM

BCMA CAR-T have demonstrated efficacy in later lines ➔ ***moving to early lines in specific populations:***

- Persistent MRD positivity after optimized frontline therapy in HR patients
- Early relapse after frontline therapy and R-ISS 3 (BB-2121-MM-002)

	Anti-BCMA CAR[1] NCT02215967	Bb2121[2] BB-2121-MM-001	CART-BCMA[3] NCT02546167	LCAR-B38M[4] NCT03090659
Group/company	***NIH***	***Bluebird/Celgene***	***University of Pennsylvania/ Novartis***	***Nanjing Legend Biotech Now developed by J&J***
Patients	16 patients at $9x10^6$/kg dose level	196 patientes RRMM ≥ 3 prior lines $150 – 450 x 10^6$ CAR-T	**21 (3 cohorts):** 9 ($10-500 x 10^6$ No Cyt) 5 ($10–50 x 10^6$ Cyt) 7 (5 ($100–500 x 10^6$ Cyt)	**57**
BCMA expression required?	Yes	NO	No	Yes
Median prior lines of therapy	7	NR	7 (3–11)	3
Reported efficacy	ORR 14/16 (**81%**) 11/14 (**79%**) MRD-EFS: **7.2 months**	**ORR 73.4% CR: 31.3 mPFS (150-450x10⁶): 8.6m mPFS 450x10⁶: 11.3 m**	#1: **67%** (1 sCR, 1VGPR) #2: (**40%**) 1 PR, 1 MR both PD #3: (**83%**) 1 CR, 3 PR, 1 MR	ORR: **88%** **CR: 74%** **MRD- CR: 68%** **mPFS: 19.9m**
Safety data	CRS all grades: 100%, 37%G3-4	CRS all grades: 63% 2 events of CRS grade ≥3 resolved within 24 hours	CRS: 17 pts (grade 3: 32%) Neurotoxicity: 3 (2 grade 4) 1 death – PD candidaemia	Transient CRS (5.7% G3) No neurotoxicity

This slide is provided for ease of viewing information from multiple trials. Direct comparison between trials is not intended and should not be inferred.
BCMA, B-cell maturation antigen; CRS, cytokine release syndrome; MM, multiple myeloma; CR, complete response; ORR, overall response rate; PR, partial response; sCR, stringent complete response; VGPR, very good partial response; PR, partial response

1. Ali A, *et al.* Presented at ASH 2015. Abstract LBA 1; 2. Bristol Meyers Squibb. (2019, December 6). *Results from the Pivotal Phase 2 KarMMa Study of idecabtagene vicleucel in Relapsed and Refractory Multiple Myeloma.* [Press release]; 3. Garfall AL, *et al.* Blood 2017;130:520; 4. Wang *et al.* ASH 2019. Abstract #579

Dr Ceri Bygrave, 7/7/20