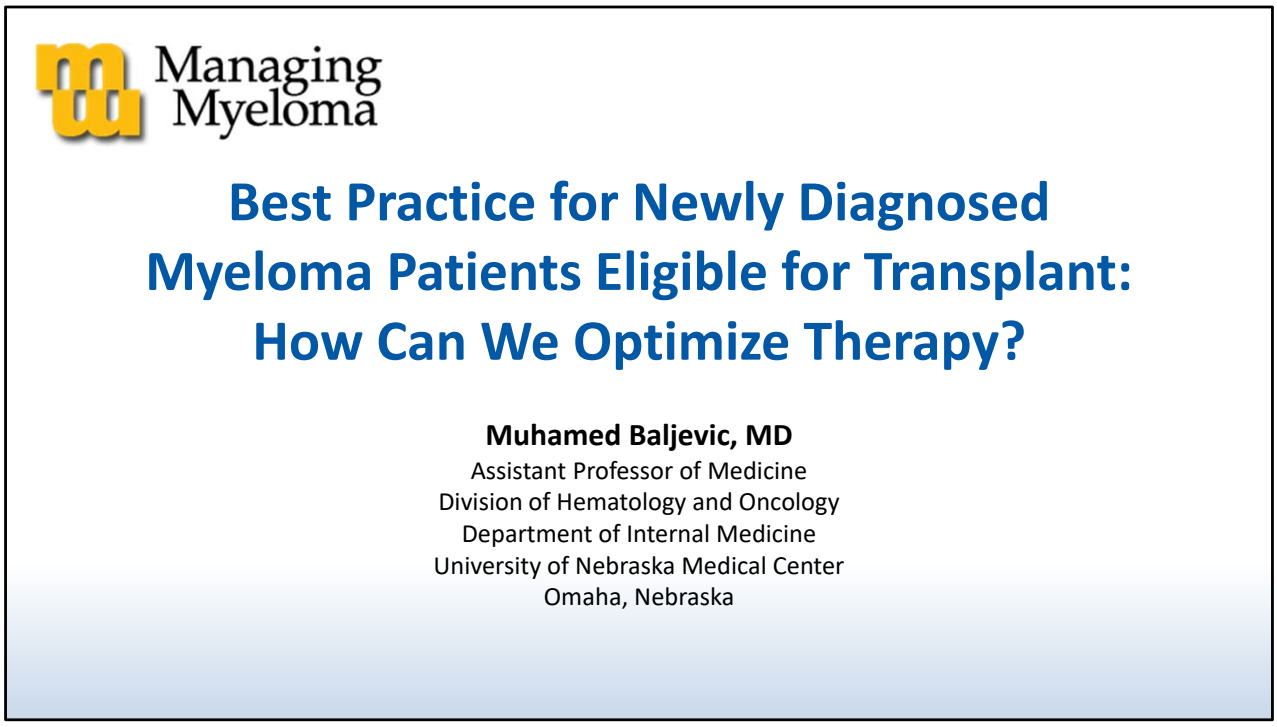


Good afternoon, everybody. My name is Muhamed Baljevic and I am a myeloma physician at the University of Nebraska Medical Center. Today it will be my pleasure to talk briefly on the topic of management of newly diagnosed transplant eligible multiple myeloma patients.

Disclosures

- Dr. Muhamed Baljevic has received honoraria related to formal advisory activities and as a consultant from Bristol-Myers Squibb Company and Celgene Corporation – A Bristol-Myers Squibb Company. He has received grant support related to research activities from Karyopharm Therapeutics.

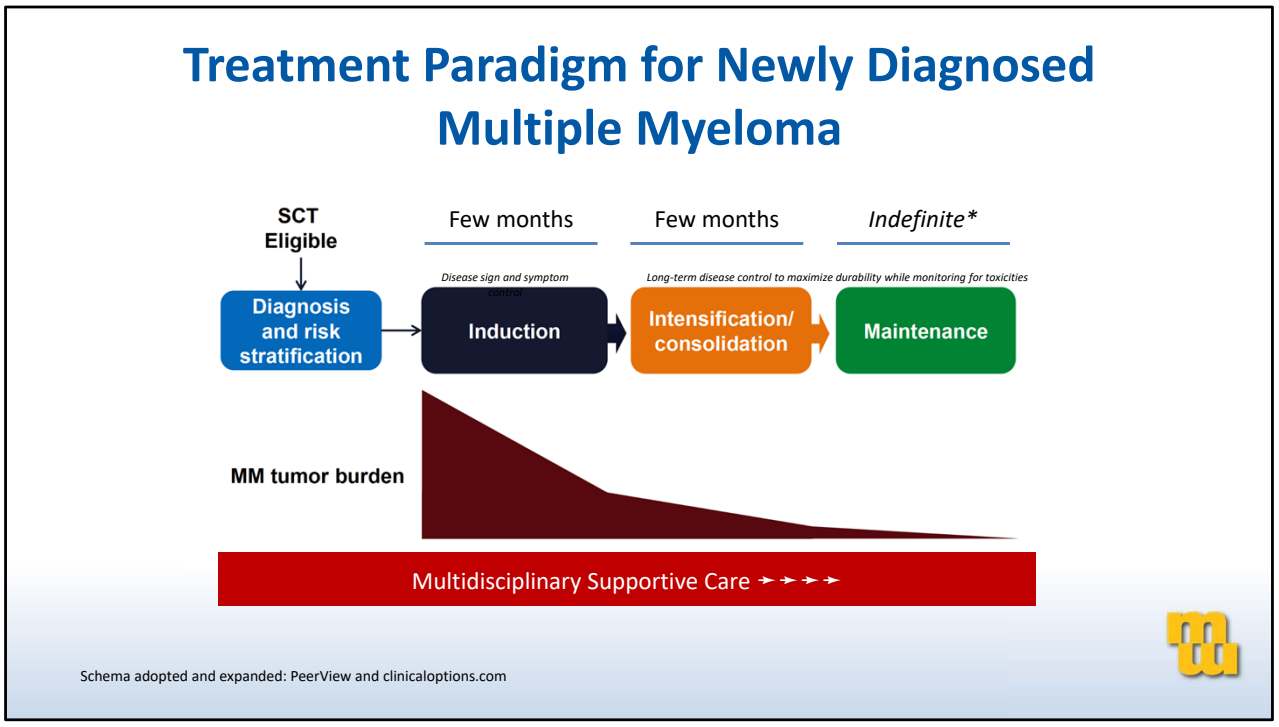
These are my disclosures for today's talk.

Learning Objectives

- Choose optimal therapeutic regimens based on specific patient- and disease-related characteristics
- Employ current guidelines and evolving data from trials evaluating novel multi-drug combinations in the front-line setting
- Identify and manage treatment-emergent adverse events associated with treatment approaches in the front-line setting

Today's learning objectives will span optimal therapeutic regiments based on scientific patient and disease-related characteristics, and review of current guidelines and evolving data from the trials evaluating novel multi-drug combinations in the frontline setting, as well as briefly touching, identifying on the management of treatment-emergent adverse events that are associated with the variety of different treatment approaches in the frontline setting for transplant eligible myeloma patients.

Best Practice for Newly Diagnosed Myeloma Patients Eligible for Transplant: How Can We Optimize Therapy?



This is schematic to briefly go over the treatment paradigm for newly diagnosed myeloma patients who may be eligible for transplant. In general, induction period is limited as well as the intensification/consolidation period, which usually involves autologous stem cell transplantation which is then followed by maintenance period, which on the North American side is more prolonged and tends to be indefinite. Assuming that no toxicities and unacceptable side effects occur during the maintenance phase. Tumor burden certainly is expected to decrease as we make a progression from these different phases all the way towards the maintenance phase. Very often, we do consider things like what type of risk patient has at diagnosis? What type of baseline, organ functions they may have? What type of biologic characteristics patients may have? Do they have any baseline neuropathy? Do they have a baseline cardiac, pulmonary or kidney disorders, or ailments that may impact how we decide what type of therapy to choose from? Throughout this entire period, of course, multidisciplinary supportive care has always provided to patients, with respect to all these different areas that can optimize the experience and success of the induction therapy in general.

Best Practice for Newly Diagnosed Myeloma Patients Eligible for Transplant: How Can We Optimize Therapy?

NCCN Regimens for Transplant Eligible NDMM

MYELOMA THERAPY[a-d]

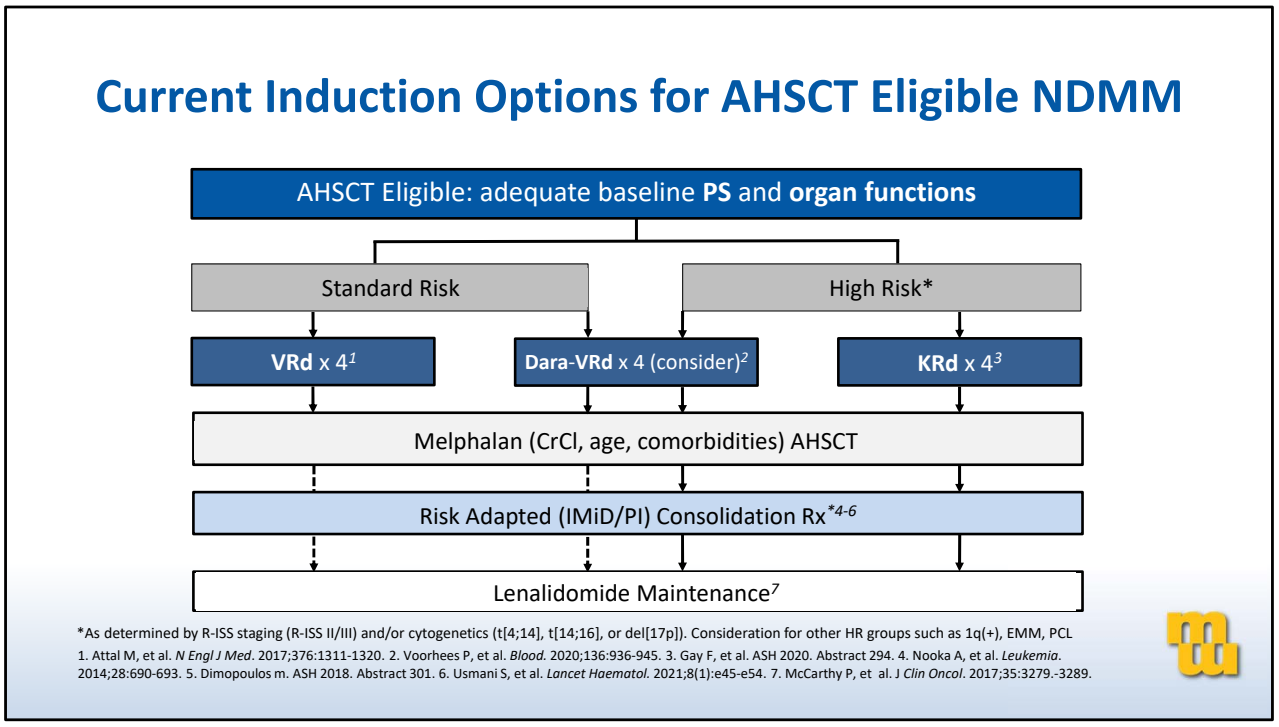
PRIMARY THERAPY FOR TRANSPLANT CANDIDATES
Preferred Regimens • Bortezomib/lenalidomide/dexamethasone (category 1) • Bortezomib/cyclophosphamide/dexamethasone[e]
Other Recommended Regimens • Carfilzomib/lenalidomide/dexamethasone • Daratumumab[f]/lenalidomide/bortezomib/dexamethasone • Ixazomib/lenalidomide/dexamethasone (category 2B)
Useful In Certain Circumstances • Bortezomib/doxorubicin/dexamethasone • Carfilzomib/cyclophosphamide/dexamethasone[g] • Ixazomib/cyclophosphamide/dexamethasone[g] • Bortezomib/thalidomide/dexamethasone (category 1) • Cyclophosphamide/lenalidomide/dexamethasone • Daratumumab[f]/cyclophosphamide/bortezomib/dexamethasone • Daratumumab[f]/bortezomib/thalidomide/dexamethasone • Dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide/bortezomib[h] (VTD-PACE)
MAINTENANCE THERAPY
Preferred Regimens • Lenalidomide[i] (category 1)
Other Recommended Regimens • Ixazomib (category 1) • Bortezomib
Useful In Certain Circumstances • Bortezomib/lenalidomide

[a] Selected, but not inclusive of all regimens.
[b] See Supportive Care Treatment for Multiple Myeloma (MYEL-H).
[c] See Principles of Myeloma Therapy (MYEL-F).
[d] See Management of Renal Disease in Multiple Myeloma (MYEL-I).
[e] Preferred primarily as initial treatment in patients with acute renal insufficiency or those who have no access to bortezomib/lenalidomide/dexamethasone. Consider switching to bortezomib/lenalidomide/dexamethasone after renal function improves.
[f] Includes both daratumumab for intravenous infusion and daratumumab and hyaluronidase-fihj for subcutaneous injection. Daratumumab and hyaluronidase-fihj for subcutaneous injection has different dosing and administration instructions compared to daratumumab for intravenous infusion.
[g] Treatment option for patients with renal insufficiency and/or peripheral neuropathy.
[h] Generally reserved for the treatment of aggressive multiple myeloma.
[i] There appears to be an increased risk for secondary cancers, especially with lenalidomide maintenance following transplant. The benefits and risks of maintenance therapy vs. secondary cancers should be discussed with patients.

NCCN Guidelines Version 4.2021

This is a list of NCCN regimens for transplant-eligible, newly diagnosed, multiple myeloma patients. Of note, we have to mention a VRd or bortezomib and lenalidomide and dexamethasone, which carries category 1 recommendation. And we will in the coming slides covered the data that has established its category 1 recommendation. Bortezomib, cyclophosphamide, and dexamethasone, or otherwise known as CyBorD, is also an important regimen that is considered for patients who present with significant renal failure or based on renal insufficiency that would otherwise preclude meaningful doses of immunomodulatory drugs during induction. A regimen of note as well in the other recommended regimens includes KRd as well as the quadruplet daratumumab, VRd. The data for all of these we will cover in the coming slides. And lastly of note is also a category 1 recommendation in regimens that are useful in certain circumstances, such as a VTd or bortezomib, thalidomide, and dexamethasone. However, this regimen is really more developed and optimized and has been studied in the European practice patterns and is not something that we commonly use on the North American side where we prefer use of lenalidomide as an immunomodulatory drug of choice in triplet or quadruplet combination regimens for newly diagnosed transplant-eligible patients.

Best Practice for Newly Diagnosed Myeloma Patients Eligible for Transplant: How Can We Optimize Therapy?

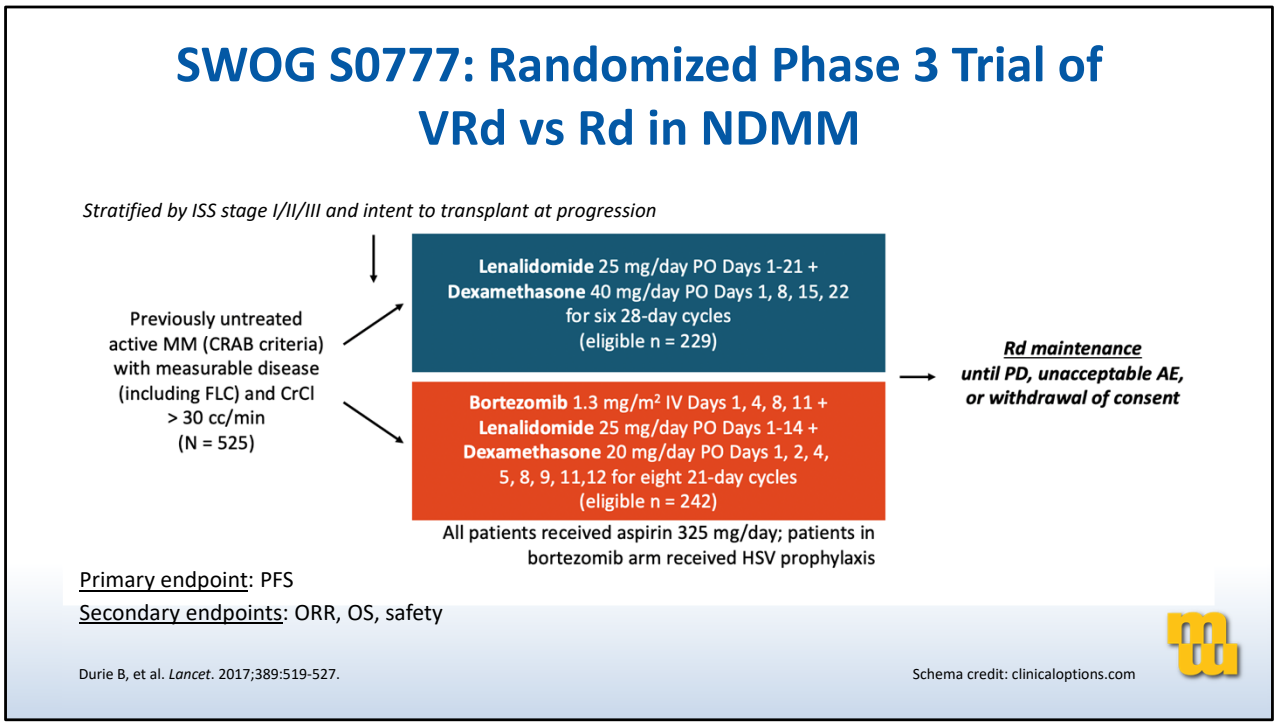


In terms of current induction options for transplant-eligible, newly diagnosed myeloma patients, this is sort of the general paradigm that can be considered when one is evaluating newly diagnosed patients and how to approach them and what type of therapy choices to consider. Newly diagnosed patients with respect to transplant are usually the ones with adequate baseline performance status, as well as organ functions, including adequate cardiac, as well as pulmonary reserves, which are particularly important in order to minimize transplant-related adverse events. Having an impaired kidney function is a common feature in myeloma patients and being on dialysis is not a preclusion factor though, of course, is something that does contribute towards a potential complication rate. Whether we're looking at the standard-risk or high-risk patients, and this is usually determined based on either Revised ISS Staging System that has been updated from the ISS Staging System some years ago, and it routinely actually considers a cytogenetic and FISH, primarily actually FISH features.

What I would add there is that consideration should also be made for other forms of higher subgroups, such as those with 1q amplification, patients with extramedullary multiple myeloma, patients with very aggressive forms of plasma cell dyscrasia, such as plasma cell leukemia, et cetera. These are all additional characteristics that help us identify those that harbor diseases with particularly aggressive features. On this slide, you can notice that bortezomib, lenalidomide, and dexamethasone for four cycles, as we mentioned, is a standard of care option, but as well as carfilzomib, lenalidomide, and dexamethasone. We will later on touch a little bit about what could help us differentiate between what to use certainly. Many academic centers at this point in time do prefer to provide care to all comers, not just for the high-risk patients, as we are all finding here.

Potential quads or quadruplet regimens that may include the addition of daratumumab to VRd backbone is certainly a consideration. At this point in time, we will cover a little bit of data in this area. Melphalan conditioning is standard. It is something that is given and adjusted based on creatinine clearance and occasionally age as well as comorbidities. Following the transplant, there is a period of risk-adapted to consolidation. Treatments for high-risk patients, in particular, is an area where we consider adding immunomodulatory drugs to produce some inhibitors and glucocorticoids for prolonged periods, followed by single-agent maintenance therapy.
Usually with IMiDs, which is then continued long-term, assuming that there is no disease progression, that there's no unacceptable toxicities, and that there are no, importantly also to note, financial toxicities for the patients throughout the treatment times.

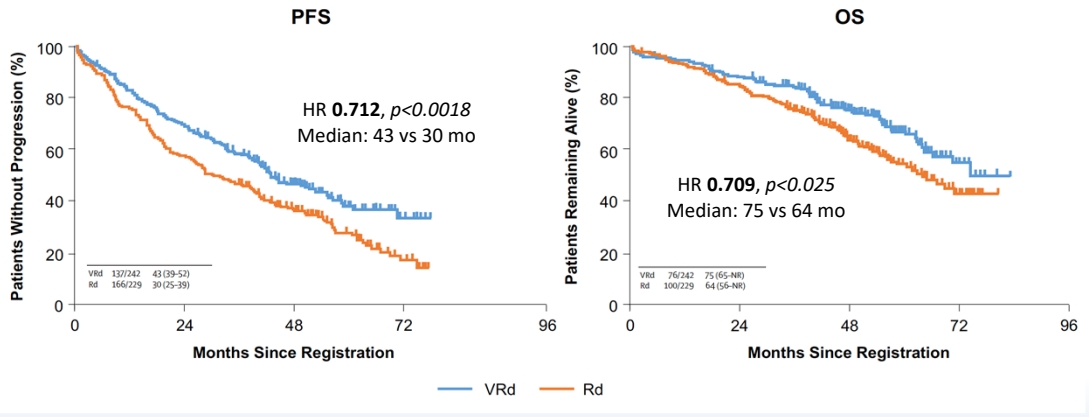
Best Practice for Newly Diagnosed Myeloma Patients Eligible for Transplant: How Can We Optimize Therapy?



SWOG S0777 study was a randomized phase 3 trial of VRd versus lenalidomide, dexamethasone. This was a trial that accrued all comers, newly diagnosed patients that were not necessarily eligible for transplantation, but as well as those who were eligible for upfront early transplantation but were willing to have a consideration for delayed transplant. It randomized between lenalidomide, dexamethasone versus a triplet bortezomib, lenalidomide, dexamethasone, which was then followed by RD maintenance until progression or unacceptable adverse events or withdrawal of consent of patients who were prophylaxed with a full-dose aspirin for VTE. The primary endpoint was PFS in this trial.

Best Practice for Newly Diagnosed Myeloma Patients Eligible for Transplant: How Can We Optimize Therapy?

SWOG S0777: Response



Durie B, et al. *Lancet*. 2017;389:519-527.

What this trial showed is significant PFS as well as OS benefits of triplet versus doublet combination. You can see clearly here a significant hazard ratios in terms of reduction for PFS as well as OS. In addition to these benefits, triplet VRd, in fact, led to doubling of the CR rates and 50% improvements in the VGPR rates in terms of response that this is clearly something of importance to us as we consider the long-term outcomes and the long-term predictors of good response and durable response in newly diagnosed multiple myeloma patients.

Best Practice for Newly Diagnosed Myeloma Patients Eligible for Transplant: How Can We Optimize Therapy?

Phase 2 KRd-based Trials in NDMM

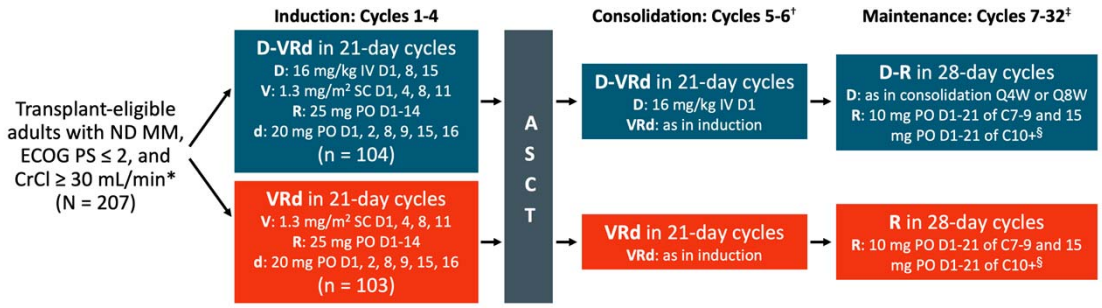
Trial	N	Response Depth	Grade 3/4 AEs
Jakubowiak, et al[1]	53	nCR: 78% sCR: 61% 24-month PFS: 92%	Hypophosphatemia: 25% Hyperglycemia: 23% Anemia: 21% Thrombocytopenia: 17% Neutropenia: 17%
Korde, et al[2]	45	CR/sCR: 56% ≥nCR: 62% ≥VGPR: 89% ≥PR: 98%	Lymphopenia: 76% Anemia: 27% Neutropenia: 33% Thrombocytopenia: 24%
Zimmerman, et al[3]	76	VGPR: 96% CR: 73% sCR: 69%	Lymphopenia: 28% Neutropenia: 18% Infections: 8%
Gay, et al[4] **FORTE trial**	474	KRd ➛ AHSCT ➛ KRd vs KRd x 12 ≥VGPR: 89% vs 87% ≥CR: 60% vs 61% sCR: 44% vs 43%	-
Costa, et al[5] **Response adapted MRD based*** **Dara-KRd x 4 ➛ AHSCT ➛ ***	81	Post Induction: sCR 39%; MRD < 10^{-5} 40% Post AHSCT: sCR 81%; MRD < 10^{-5} 73% MRD-direc. Cons.: sCR 95%; MRD < 10^{-5} 82%	Lymphopenia: 23% Neutropenia: 25% Thrombocytopenia: 5% Anemia: 11% Infections 12%

1. Jakubowiak AJ, et al. *Blood*. 2012;120:1801-1809. 2. Korde N, et al. *JAMA Oncol*. 2015;1:746-754. 3. Zimmerman T, et al. ASH 2016. Abstract 675.
4. Gay F, et al. ASH 2020. Abstract 294. 5. Costa L, et al. ASH 2019. Abstract 860.

This table here briefly summarizes some of the phase 2 KRd based trials in newly diagnosed myeloma. As you can see, these were with a slightly lower number of patients, but the main feature that we can notice here is really high-quality responses and high-quality progression-free survivals at the timepoints of evaluation. You can see that the depths of response in terms of VGPR and the CR or stringent or near stringent or near CRs were fairly high. This is where the interest initially came from considering KRd, in fact, for all comers. The last study on the bottom is not actually KRd triplet, but is in fact a response adapted MRD-based study that looked at adding daratumumab to KRd. This is a quadruplet similar to the VRd, what we saw before. However, in this design, as we said this was response-adapted MRD based after the transplantation portion. After the induction, as well as the post-transplant and after the MRD-directed approach, really high rates of stringent CR and MRD negativity were noted. What is important is, as we progress from induction to transplant, to subsequent therapy post-transplant, MRD negativity rates, as you can see in this case to the 10^{-5}, increased significantly, to very high degrees. What needs to be mentioned is that the Grade 3 and 4 adverse events were very common in terms of hematologic signals. Thrombocytopenias, lymphopenias, neutropenias, were commonly noted, lymphopenias, et cetera, as well as some electrolyte changes. One really needs to keep in mind these types of events as they continue treating their patients and monitoring them closely for any complications from hematology adverse events.

Best Practice for Newly Diagnosed Myeloma Patients Eligible for Transplant: How Can We Optimize Therapy?

GRIFFIN: Phase II Study of Daratumumab + RVd in Patients with Transplant-Eligible NDMM



*Lenalidomide dose was adjusted in patients with CrCl ≤ 50 mL/min. †Consolidation began 60-100 days after transplantation. ‡Patients completing maintenance phase were permitted to continue single-agent lenalidomide. §15 mg administered only if tolerable.

- **Primary endpoint:** Asses dose-limiting toxicities
- **Secondary endpoints:** Safety, minimal residual disease (MRD) negativity by end of consolidation and end of maintenance, stringent complete response (sCR) rate by end of consolidation and end of maintenance, progression-free survival (PFS)

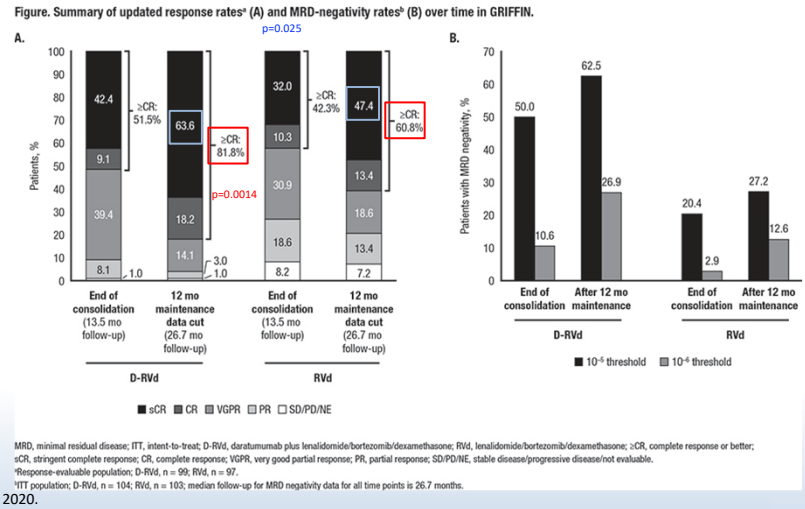
Voorhees P, et al. ASH 2020.

Schema credit: clinicaloptions.com

GRIFFIN was a phase 2 study that looked at adding daratumumab to lenalidomide, bortezomib, and dexamethasone in patients that were transplant-eligible, newly diagnosed with good performance status. The design is as outlined here, induction for four cycles, followed by transplant, followed by consolidation for further cycles. Then maintenance therapy, which was either lenalidomide single-agent in the triplet or daratumumab added to lenalidomide in the quad arm. The primary endpoint involving dose limiting toxicities as well as the MRD negativity and the depth of response as a secondary endpoint.

Best Practice for Newly Diagnosed Myeloma Patients Eligible for Transplant: How Can We Optimize Therapy?

GRIFFIN: Updated Analysis of Griffin After 12 Months of Maintenance

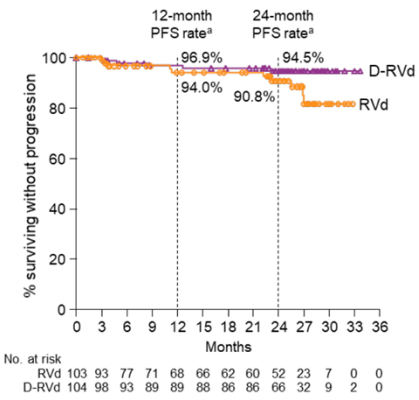


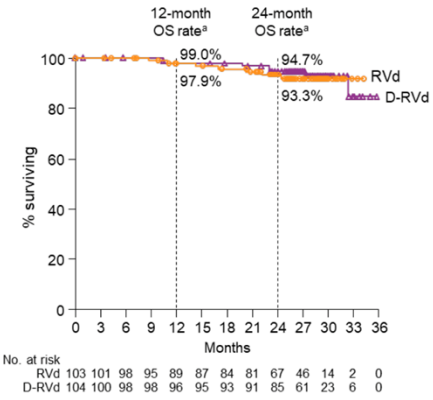
Silbermann S, et al. ASH 2020.

What was clear from the updated analysis of GRIFFIN after 12 months of maintenance is that at almost every point of analysis, the CR or better responses were much better and deeper for the quadruplet arm versus the triplet arm. You can see the CR rates of nearly 82% versus 60%. As we mentioned, as the treatment progressed from the end of consolidation to the end of maintenance, you can see that the depth of MRD response increased as well.

Best Practice for Newly Diagnosed Myeloma Patients Eligible for Transplant: How Can We Optimize Therapy?

GRIFFIN: Updated PFS and OS Analysis at 27.4 Months

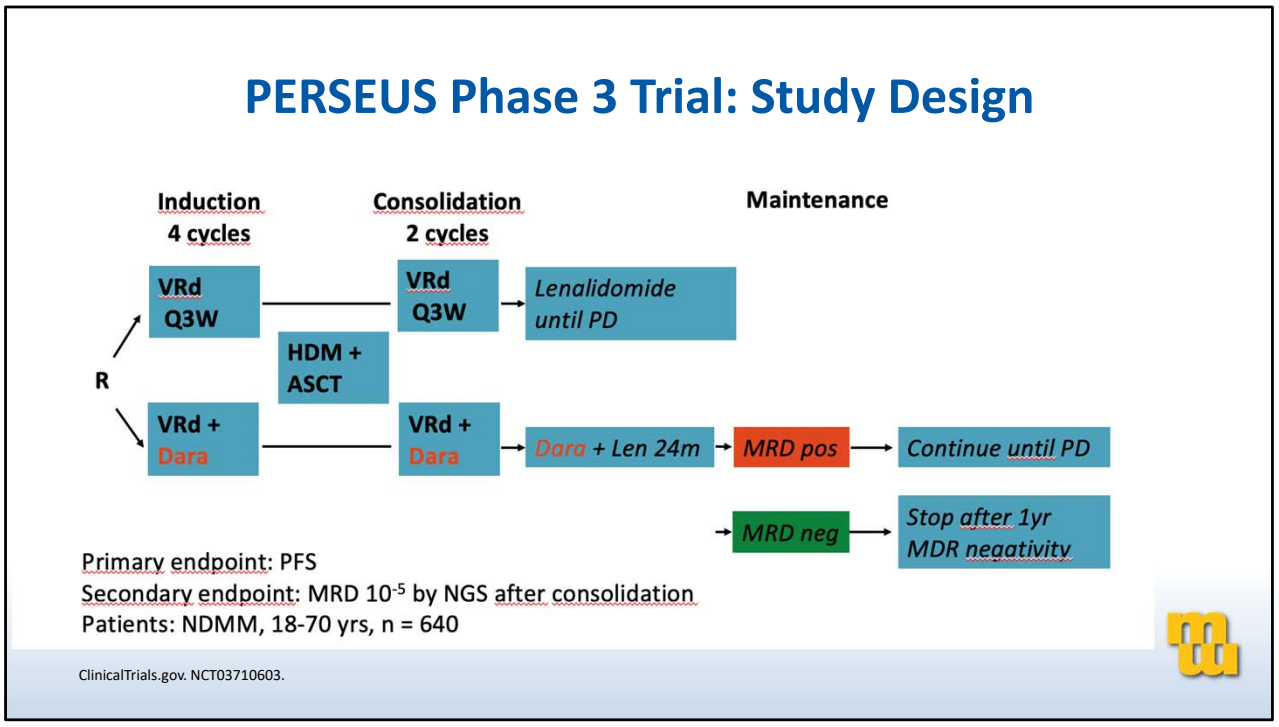




1. Kaufman J, et al. ASH 2020. Abstract 549. 2. Voorhees P, et al. *Blood.* 2020;136:936-945

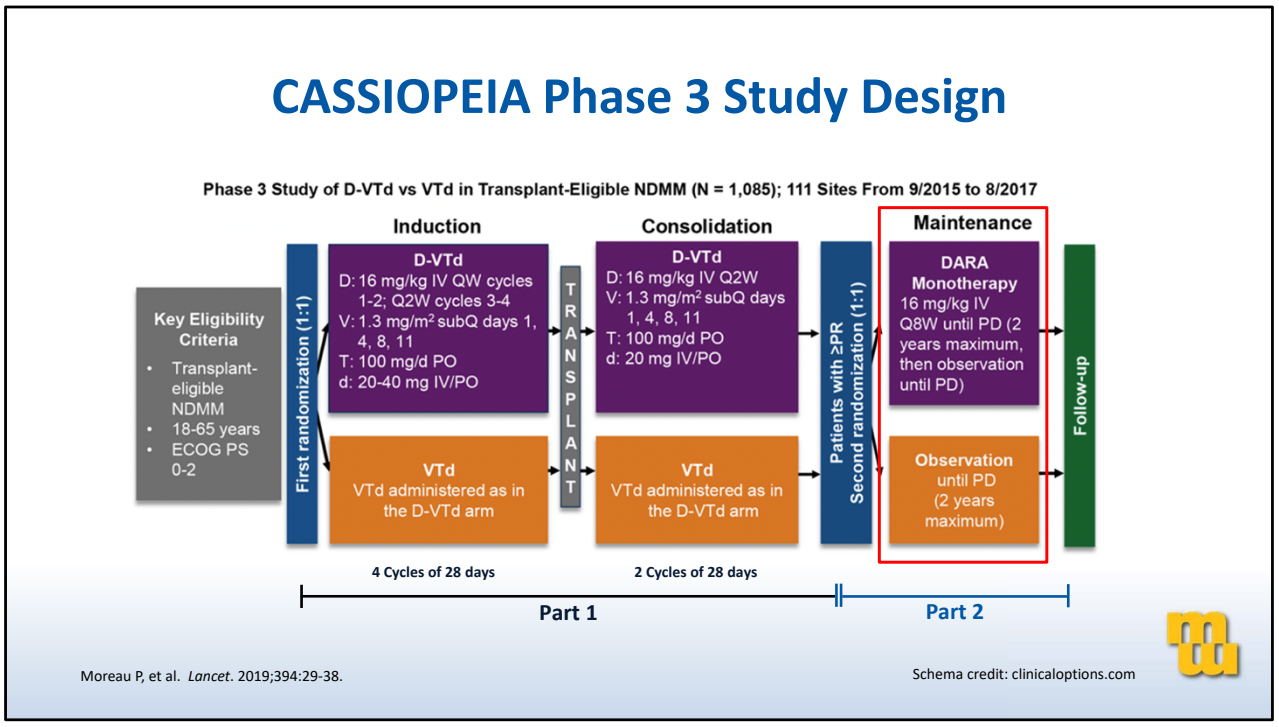
On the other hand, what we could not appreciate was significant changes in the 12- and 24-month PFS and OS rates as these curves were fairly superimposable, which is why the PERSEUS phase 3 trial is currently undergoing.

Best Practice for Newly Diagnosed Myeloma Patients Eligible for Transplant: How Can We Optimize Therapy?



This is going to be a phase trial that's going to have a PFS as a primary endpoint and as a secondary endpoint, MRD negativity to the -5 by NGS after consolidation. We hope that with phase 3 trial here as outlined, we will have an answer of whether quadruplet that involves the addition of anti-CD38 therapy can in fact lead to prolongation of progression-free survival in newly diagnosed transplant eligible patients.

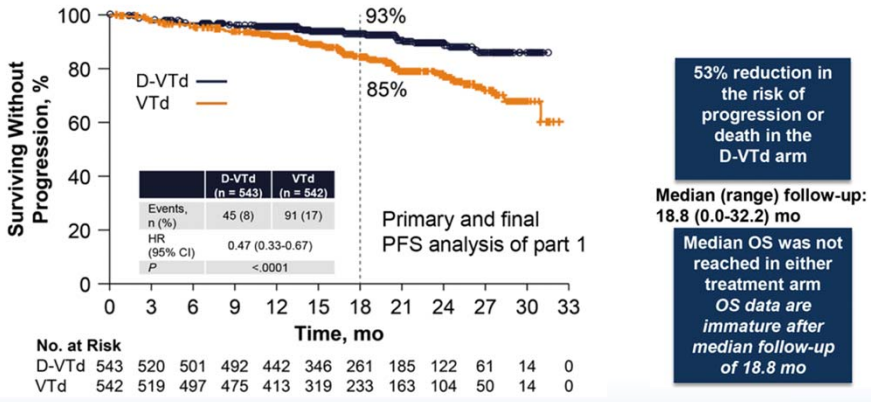
Best Practice for Newly Diagnosed Myeloma Patients Eligible for Transplant: How Can We Optimize Therapy?



CASSIOPEIA was also a phase 3 study design which involved the utilization of thalidomide as a choice of immunomodulatory drug. Instead of having daratumumab VRd, we had daratumumab, bortezomib, thalidomide, and dexamethasone versus bortezomib, thalidomide, and dexamethasone. Of note here, what needs to be pointed out is that the maintenance design of this trial was such that the quadruplet arm had the daratumumab monotherapy until disease progression while the triplet arm had observation until disease progression, two years maximum for both sides. A significant difference in terms of how the therapy was actually designed for patients following the induction, following the transplantation, and following the consolidation periods.

Best Practice for Newly Diagnosed Myeloma Patients Eligible for Transplant: How Can We Optimize Therapy?

CASSIOPEIA PFS from First Randomization



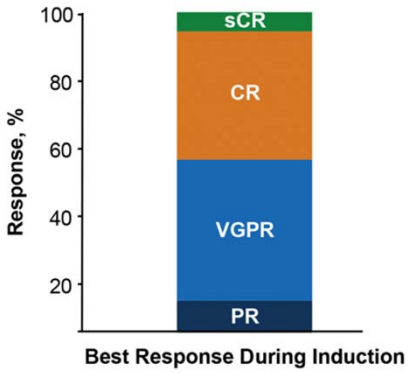
53% reduction in the risk of progression or death in the D-VTd arm

Moreau P, et al. *Lancet*. 2019;394:29-38.

What CASSIOPEIA showed was significant increase and betterment in terms of progression-free survival, 53% reduction in the risk of progression or death in the DARA-VTd arm with a median follow-up of nearly 19 months. Survival was not reached in either arm at the time of this analysis and was immature for reporting at this meeting follow-up. But certainly, this was a significant improvement in terms of progression-free survival for this particular quadruplet versus bortezomib, thalidomide, and dexamethasone.

Novel Quads in HR NDMM: Isatuximab-KRd

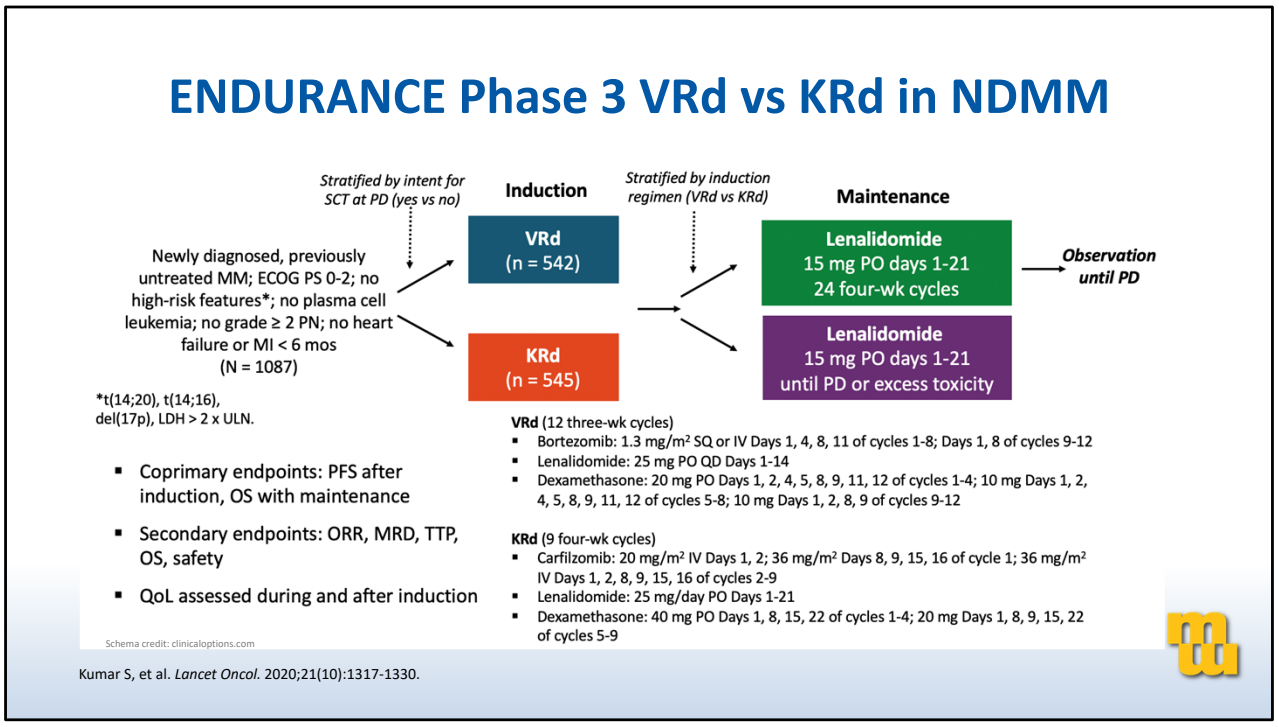
- All evaluable patients: n = 50
- ORR, ≥PR: 100%
- ≥VGPR: 90%; CR/sCR: 46%
  - Arm A: 41/46 ≥VGPR
  - Arm B: all (n = 4) VGPR
- Arm A: MRD assessment in 33 patients during induction
  - 20 patients MRD negative
  - 11 patients MRD positive
  - 2 not assessable



Weisel K, et al. ASCO 2020. Abstract 8508.

There's also an example of some other novel quads, so-called quads, quadruplets in the high-risk newly diagnosed myeloma patients. This is namely an example with isatuximab, carfilzomib, lenalidomide, and dexamethasone. This was a study that was just presented in an abstract form at ASCO just this past year with 50 patients. As you can see here, fairly deep responses, overall response rate of 100%, where the overall response was defined as at least being a PR. VGPR rates were very high, 90%, CRs/CR rates, 46%. So, really deep responses in this setting. Beyond the data that we have seen for VRd combined with DARA or KRd combined with DARA, we are also seeing some of these more innovative designs for the quadruplets in the newly diagnosed patients.

Best Practice for Newly Diagnosed Myeloma Patients Eligible for Transplant: How Can We Optimize Therapy?

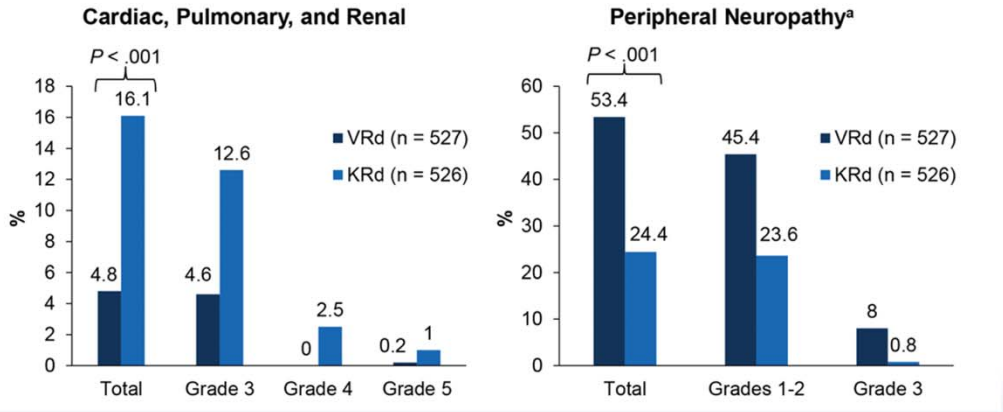


Kumar S, et al. *Lancet Oncol.* 2020;21(10):1317-1330.

ENDURANCE was a phase 3 VRd versus KRd trial in newly diagnosed, multiple myeloma. This trial accrued patients with a good baseline performance status of ECOG 0 and 2. It did not allow accrual of high-risk features. Of note, however patients with translocation 4;14 were allowed to accrue. Plasma cell leukemia patients were excluded, as well as anybody who had baseline peripheral neuropathy of Grade 2 or higher, as well as patients who had congestive heart failure or who may have had ACS or MI in the proceeding six months. Induction was given either as VRd in 12, 3-weekly cycles or KRd in 9, 4-weekly cycles. Subsequent to that, there was a certification by induction regimen followed by maintenance that was lenalidomide based in both groups, and patients were observed until disease progression. Primary endpoint for this trial was PFS after induction as well as OS with maintenance with secondary endpoints, including overall response rates, MRD, TTP, OS, as well as safety, as well as a quality of life assessed metrics during and after induction.

Best Practice for Newly Diagnosed Myeloma Patients Eligible for Transplant: How Can We Optimize Therapy?

ENDURANCE Phase 3 Notable Toxicities



Kumar S, et al. *Lancet Oncol.* 2020;21(10):1317-1330.

It must be noted that when considering either VRd or KRd as initial choice of regimen for newly diagnosed transplant-eligible patients, at least one can and should keep in mind baseline comorbidities, and probably try to avoid bortezomib-based treatments in patients who harbor significant baseline neuropathy or KRd you know, avoidance in patients with significant cardiopulmonary/renal comorbidities.

AHSCT Eligible NDMM Take-to-the-Clinics

Phase of disease	Comments
Induction	• VRd remains current standard - KRd can be considered if baseline PN and no CP issues • VCd standard for patients with AKI/CKD with plan to swap Cy for Len when feasible • Dara-VRd/KRd very attractive quads - being actively studied • Dara-VTd standard in Europe, not commonly used in NA practice
Consolidation	• AHSCT standard at present, but will CAR T cell replace as consolidation choice? • After AHSCT, IMiD/PI based current standard in HR populations
Maintenance	• Len is category 1 standard (OS benefit), Ixa a good category 1 substitute if toxicities • Novel dual approaches (eg, MRD adapted Dara-Len) • Maintenance free designs with CAR T-cells or BiTEs or DuoAbs etc?
Future	• Other quads in development such as Isa-KRd for HR NDMM • Dara-based quads for all-comers vs preferably adapted by response or risk stratification? • Molecularly driven '*penta*' upfront regimens for less long-term exposure?

Some of comments for the end here that we can keep in mind. When it comes to induction, VRd certainly remains current standard of care while KRd can be considered if baseline peripheral neuropathy is present while having no presence of cardiopulmonary and renal issues that would be prohibitory. Cyclophosphamide, bortezomib, and dexamethasone, or so-called CyBorD, can be considered certainly as a standard in patients who present with acute kidney injury or with significant baseline chronic kidney disease that would otherwise predict for really low doses of lenalidomide, with a plan to try to swap cyclophosphamide for lenalidomide when feasible with the improvement of creatinine clearance. Quadruplets such as daratumumab VRd or daratumumab KRd, and as we noted, isatuximab KRd, certainly seem very attractive. They are some of them in the late phases of studies and we may potentially very well come to the point where they may be considered standard. DARA VTd, as we showed from CASSIOPEIA study is indeed standard in Europe but not common in North American practice. Consolidation with autologous stem cell transplantation is certainly standard at present but the question remains whether employment of CAR-T cell therapies may impact utilization of autologous transplant in newly diagnosed myeloma. And for those patients that are of high-risk disease, certainly, we consider the standard of care to do combined consolidation/ maintenance with IMiDs and PIs to try to offset the expected earlier relapses that can be seen with high-risk patients. When it comes to maintenance, lenalidomide is category 1 due to survival benefit, while ixazomib is an excellent category 1 substitute if patients are unable to tolerate the lenalidomide.

There are a number of studies with innovative approaches that are looking at MRD-adapted treatments with dual maintenance with daratumumab and lenalidomide, and

certainly up and coming designs which will explore the role of CAR-T cells as well as bispecific T-cell engagement therapies with dual targeting antibodies or latest generation CELMoDs in terms of their benefits on maintenance and the depth of response that can be seen in those cases. And a final note for future is that other quadruplets are certainly being developed as we noted. And a question really is, and remains, whether the quadruplet therapies that involve CD38 targeting therapies should be considered for all-comers versus maybe preferably for high-risk patients in response adapted risk stratification, it remains to be seen in the trials that we will have data on in the near future.

Lastly, given the improvements in the way we have been able to deliver in terms of safety, some of the quadruplet therapies, questions can be raised whether even penta, or therapies with five different agents, that could also be targeting molecularly present lesions in myeloma cells could be considered for more upfront therapy and exposure to drugs that could hopefully lead to a subsequent less amount of therapy in terms of long-term follow-ups and exposures for patients.

With that, this will bring the closing remarks to the end. Thank you very much for your participation today.