

Year ⁱⁿ Review

Proceedings from a Multitumor CME Symposium Focused on the Application of Emerging Research Information to the Care of Patients with Common Cancers

Induction, Consolidation and Maintenance; Doublet versus Triplet Combinations in Relapsed/Refractory Disease — S Vincent Rajkumar, MD

Select Publications

Dimopoulos MA et al. **Carfilzomib and dexamethasone (Kd) vs bortezomib and dexamethasone (Vd) in patients (pts) with relapsed multiple myeloma (RMM): Results from the phase III study ENDEAVOR.** *Proc ASCO 2015;Abstract 8509.*

Rosenthal AC et al. **The cardiovascular impact of carfilzomib in multiple myeloma.** *Proc ASH 2014;Abstract 4748.*

Stewart AK et al. **Carfilzomib, lenalidomide, and dexamethasone for relapsed multiple myeloma.** *N Engl J Med 2015;372(2):142-52.*

Straka C et al. **Results from two phase III studies of bortezomib (BTZ) consolidation vs observation (OBS) post-transplant in patients (pts) with newly diagnosed multiple myeloma (NDMM).** *Proc ASCO 2015;Abstract 8511.*

Zimmerman TM et al. **Phase II MMRC trial of extended treatment with carfilzomib (CFZ), lenalidomide (LEN), and dexamethasone (DEX) plus autologous stem cell transplantation (ASCT) in newly diagnosed multiple myeloma (NDMM).** *Proc ASCO 2015;Abstract 8510.*

Induction, Consolidation and Maintenance; Doublet Versus Triplet Combinations in Relapsed/ Refractory Disease



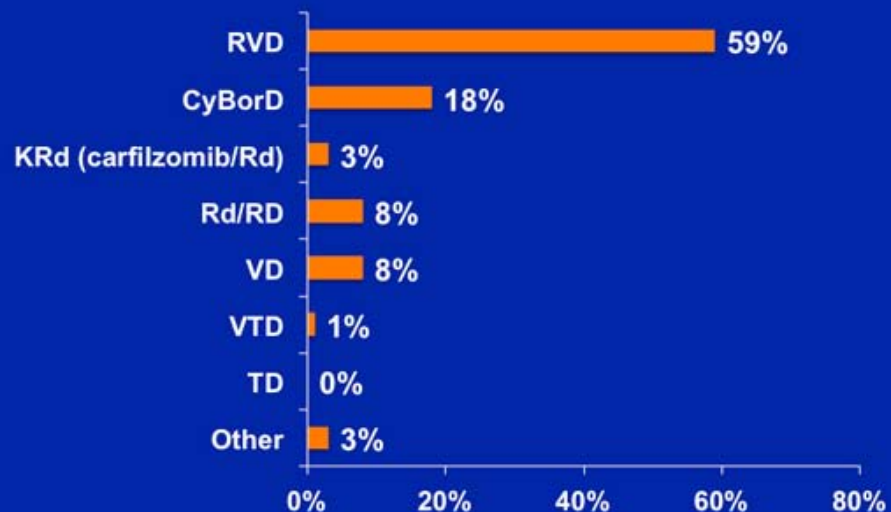
S Vincent Rajkumar, MD
Professor of Medicine
Division of Hematology
Chair, Myeloma Amyloidosis Dysproteinemia Group
Mayo Clinic
Rochester, Minnesota

Disclosures

No financial interests or affiliations to disclose.

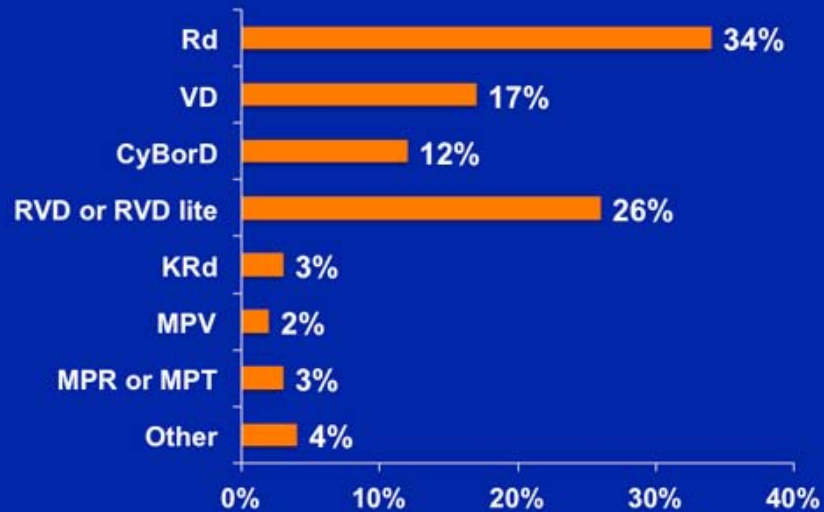
AUDIENCE POLL

An otherwise healthy 60-year-old patient presents with ISS Stage II multiple myeloma (MM). Cytogenetics and FISH reveal no high-risk features. In general, which induction treatment would you most likely recommend?



AUDIENCE POLL

What is your usual induction regimen for a 75-year-old otherwise healthy, transplant-ineligible patient with ISS Stage II MM and no high-risk features?

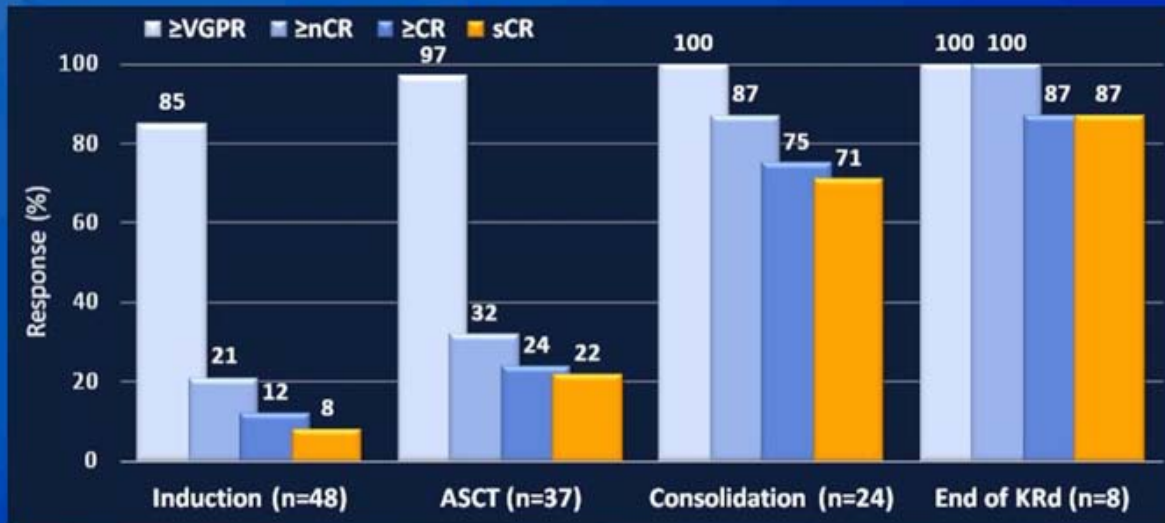


Phase II MMRC Trial of Extended Treatment with Carfilzomib (CFZ), Lenalidomide (LEN), and Dexamethasone (DEX) plus Autologous Stem Cell Transplantation (ASCT) in Newly Diagnosed Multiple Myeloma (NDMM)

Zimmerman TM et al.

Proc ASCO 2015;Abstract 8510.

Response Rates Over the Course of Treatment



Zimmerman TM et al. *Proc ASCO* 2015;Abstract 8510.

Conclusions

Critical finding(s): The triplet regimen KRd as induction therapy is highly active with an 85% ≥VGPR rate. A strategy of KRd, ASCT, KRd consolidation and lenalidomide maintenance gets >85% of patients into CR by the end of treatment.

Clinical implication(s): This is a small Phase II study. It joins two other small Phase IIs showing promise with KRd for newly diagnosed MM. KRd needs to be compared in a Phase III study to VRd. This trial (E1A11) is ongoing.

Research relevance: New clinical trial concepts that should be pursued based on these data include:

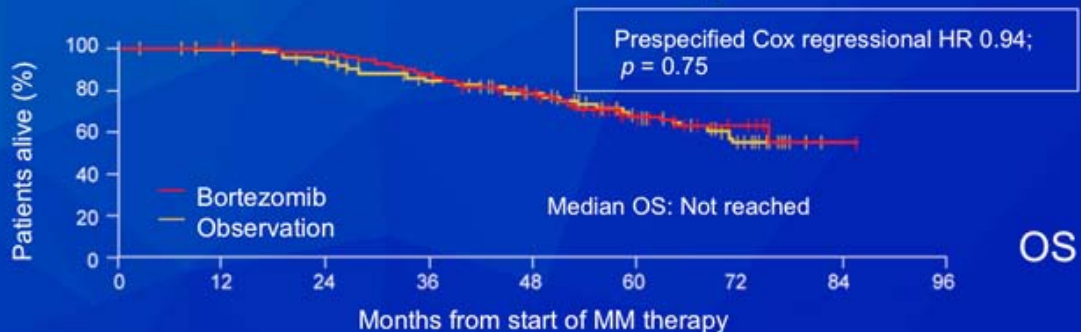
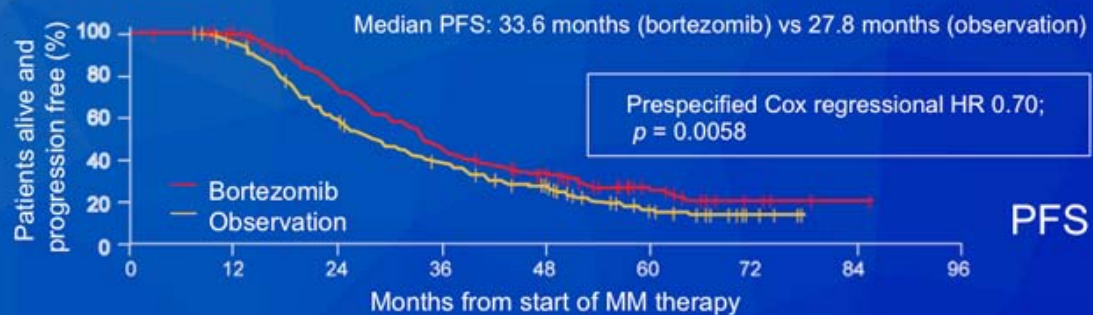
1. KRd versus KRd plus ASCT
2. KRd with a weekly schedule

Results from Two Phase III Studies of Bortezomib (BTZ) Consolidation vs Observation (OBS) Post-Transplant in Patients (pts) with Newly Diagnosed Multiple Myeloma (NDMM)

Straka C et al.

Proc ASCO 2015;Abstract 8511.

Survival – Bortezomib Consolidation vs Observation



Straka C et al. *Proc ASCO 2015;Abstract 8511.*

Conclusions

Critical finding(s): Bortezomib consolidation post-ASCT had longer PFS but also increased toxicity, and no improvement in OS is apparent so far.

Clinical implication(s):

- Consider for high-risk patients, not just for 4 cycles but rather for approximately 2 years based on HOVON-65 results.
- Not clear in other subsets since these data are from patients without len maintenance.

Conclusions

Research relevance: Need to determine the optimal consolidation and maintenance for various risk groups in MM (bortezomib alone, lenalidomide alone, VRd, et cetera). Also need to determine duration (short course of consolidation versus 2 years versus until progression).

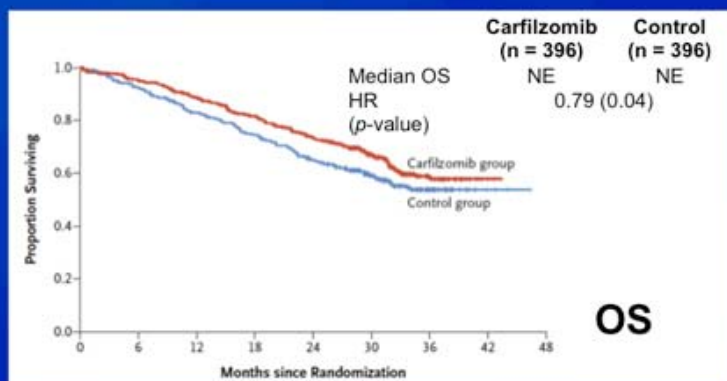
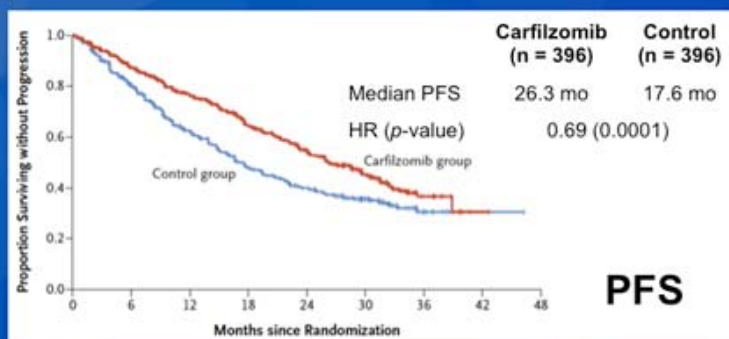
ORIGINAL ARTICLE

Carfilzomib, Lenalidomide, and Dexamethasone for Relapsed Multiple Myeloma

A. Keith Stewart, M.B., Ch.B., S. Vincent Rajkumar, M.D., Meletios A. Dimopoulos, M.D., Tamás Masszi, M.D., Ph.D., Ivan Špička, M.D., Ph.D., Albert Oriol, M.D., Roman Hájek, M.D., Ph.D., Laura Rosiñol, M.D., Ph.D., David S. Siegel, M.D., Ph.D., Georgi G. Mihaylov, M.D., Ph.D., Vesselina Goranova-Marinova, M.D., Ph.D., Péter Rajnics, M.D., Ph.D., Aleksandr Suvorov, M.D., Ruben Niesvizky, M.D., Andrzej J. Jakubowiak, M.D., Ph.D., Jesus F. San-Miguel, M.D., Ph.D., Heinz Ludwig, M.D., Michael Wang, M.D., Vladimír Maisnar, M.D., Ph.D., Jiri Minarik, M.D., Ph.D., William I. Bensinger, M.D., Maria-Victoria Mateos, M.D., Ph.D., Dina Ben-Yehuda, M.D., Vishal Kukreti, M.D., Naseem Zojwalla, M.D., Margaret E. Tonda, Pharm.D., Xinqun Yang, Ph.D., Biao Xing, Ph.D., Philippe Moreau, M.D., and Antonio Palumbo, M.D., for the ASPIRE Investigators*

Stewart AK et al. *N Engl J Med* 2015;372(2):142-52.

PFS and OS



Stewart AK et al. *N Engl J Med* 2015;372(2):142-52.

Conclusions

Critical finding(s): Improved response rate, CR, PFS, OS and QOL with KRd versus Rd for relapsed MM.

Clinical implication(s): KRd is an excellent option for relapsed MM and should be considered early in the disease course. The lack of planned crossover is a limitation. This regimen joins some other active triplets as an option for relapsed MM.

Research relevance:

1. How does this compare to other active triplets: VCD, VRd, PVD, PCP, Car-PD, Rd-Elo? Need clinical trials.
2. How will this combine with monoclonals?

The Cardiovascular Impact of Carfilzomib in Multiple Myeloma

Rosenthal AC et al.

Proc ASH 2014;Abstract 4748.

- Patients with MM frequently have baseline elevated cardiac peptide (59%) and abnormal cardiac strain (15% at new diagnosis and 36% at relapse)
- A frequent and sometimes dramatic rise in NT-proBNP occurs immediately after carfilzomib (Cfz)-based chemotherapy
- Acute structural cardiac events were uncommon (3%) in the absence of confounding illness
 - 5 of 62 (8%) patients had serious cardiac events that were probably attributable to Cfz in 3 cases (5%)

Conclusions

Critical finding(s):

1. Marked increase in NT-proBNP in 2 days
2. No significant decrease in EF on ECHO at 4 months
3. ~5% risk of serious cardiac event potentially attributable to carfilzomib

Clinical implication(s):

- Be aware of the cardiac effects. Monitor patients in the first week carefully, more carefully in patients with known cardiac dysfunction. No need for routine ECHO post-therapy.
- Wait for Phase IIIs before drawing conclusions based on Phase II data.

Conclusions

Research relevance:

- More systematic study in comparison to other proteasome inhibitors needed.
- Identify the 5% who are likely to have serious cardiac events.

Carfilzomib and Dexamethasone (Kd) vs Bortezomib and Dexamethasone (Vd) in Patients (pts) with Relapsed Multiple Myeloma (RMM): Results from the Phase III Study ENDEAVOR

Dimopoulos MA et al.

Proc ASCO 2015;Abstract 8509.

ENDEAVOR: Efficacy Results

Outcome	Kd (n = 464)	Vd (n = 465)	Hazard ratio	p-value
Median PFS	18.7 mo	9.4 mo	0.53	<0.0001
Median OS	Not estimable	24.3 mo	0.79	0.066
Outcome	n = 357	n = 291	Hazard ratio	p-value
ORR	77%	63%	Not reported	<0.0001
Median duration of response	21.3 mo	10.4 mo	Not reported	Not reported

Dimopoulos MA et al. *Proc ASCO 2015;Abstract 8509.*

Conclusions

Critical finding(s):

- Nine-month improvement in PFS by using Kd versus Vd in relapsed MM
- Trend to improved OS

Clinical implication(s):

- Dosing used is twice the normal schedule and has implications for cost and toxicity.
- Unclear how this will compare to weekly bortezomib regimens, especially VCD.

Conclusions

- Would not conclude from this trial that we should use Kd ahead of a bortezomib-based regimen since appropriate comparator was not used and we do not know what impact planned crossover will have.