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

Novel Agents: Ixazomib, Oprozomib, Panobinostat, Elotuzumab and Daratumumab — Sagar Lonial, MD

Select Publications

Berdeja JG et al. **A phase I/II study of the combination of panobinostat (PAN) and carfilzomib (CFZ) in patients (pts) with relapsed or relapsed/refractory multiple myeloma (MM).** *Proc ASCO* 2015;**Abstract 8513**.

Kumar S et al. **Long-term ixazomib maintenance is tolerable and improves depth of response following ixazomib-lenalidomide-dexamethasone induction in patients (Pts) with previously untreated multiple myeloma (MM): Phase 2 study results.** *Proc ASH* 2014;**Abstract 82**.

Kumar SK et al. **Safety and tolerability of ixazomib, an oral proteasome inhibitor, in combination with lenalidomide and dexamethasone in patients with previously untreated multiple myeloma: An open-label phase 1/2 study.** *Lancet Oncol* 2014;15(13):1503-12.

Lonial S et al. **Elotuzumab therapy for relapsed or refractory multiple myeloma.** *N Engl J Med* 2015;373(7):621-31.

Lonial S et al. **Phase II study of daratumumab (DARA) monotherapy in patients with ≥ 3 lines of prior therapy or double refractory multiple myeloma (MM): 54767414MMY2002 (Sirius).** *Proc ASCO* 2015;**Abstract LBA8512**.

Vij R et al. **Clinical profile of single-agent oprozomib in patients (Pts) with multiple myeloma (MM): Updated results from a multicenter, open-label, dose escalation Phase 1b/2 study.** *Proc ASH* 2014;**Abstract 34**.

Novel Agents: Ixazomib, Oprozomib, Panobinostat, Elotuzumab and Daratumumab

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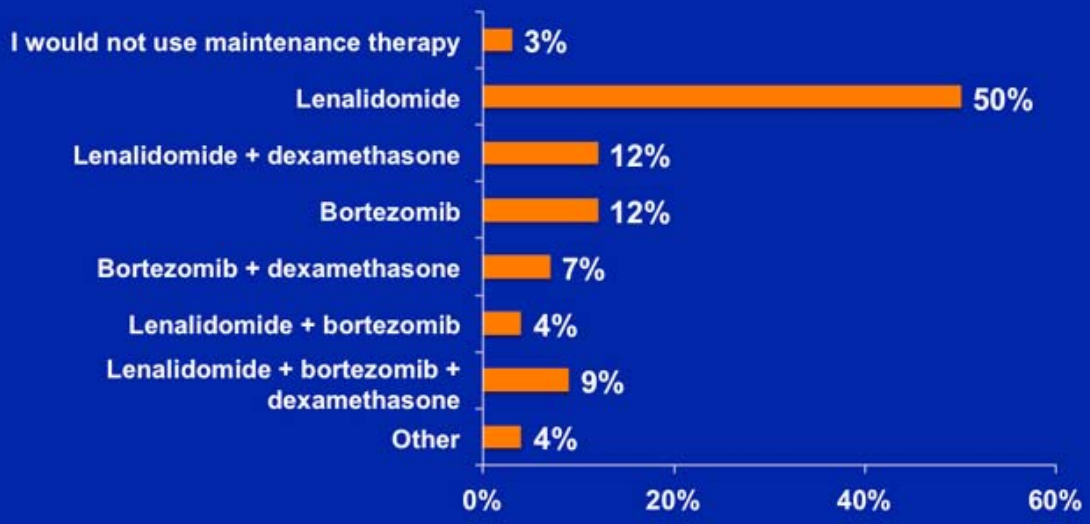
Disclosures

Advisory Committee and Consulting Agreements	Bristol-Myers Squibb Company, Celgene Corporation, Novartis Pharmaceuticals Corporation, Onyx Pharmaceuticals, an Amgen subsidiary, Sanofi, Takeda Oncology

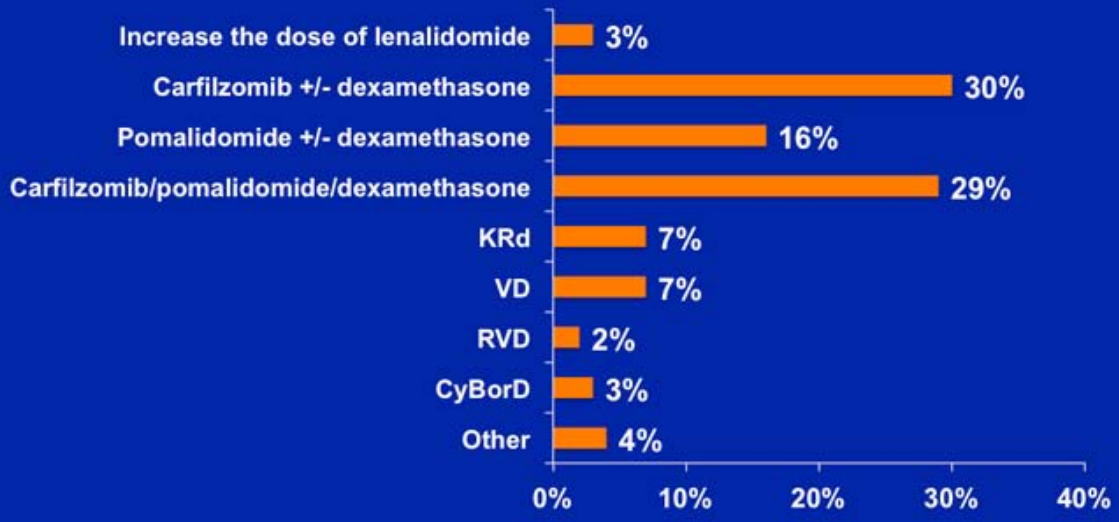
AUDIENCE POLL

A 60-year-old patient with ISS Stage II, high-risk (del17p) MM receives induction RVD, undergoes ASCT and achieves a very good partial response. Whether or not you administer consolidation therapy, what would be your choice of post-transplant maintenance therapy?



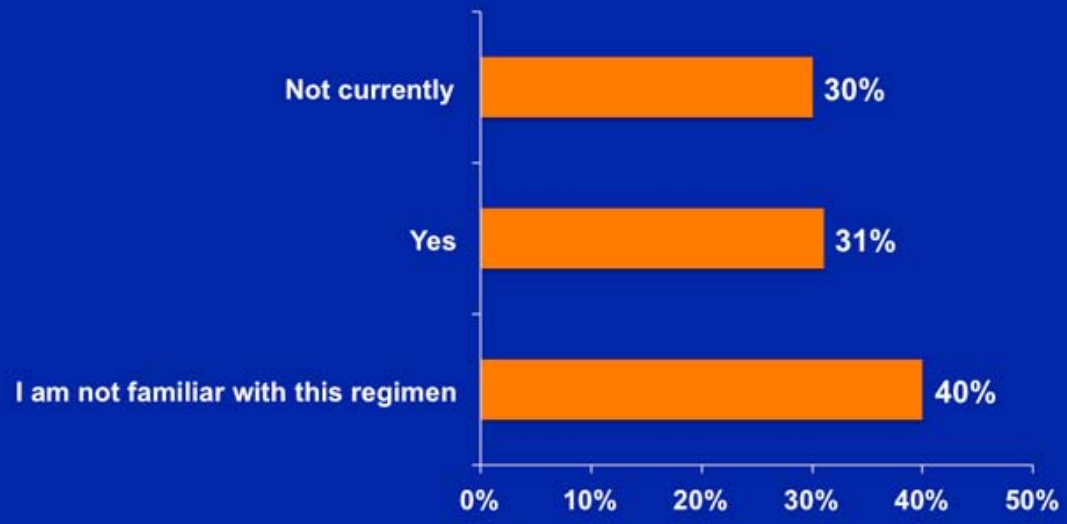
AUDIENCE POLL

What is your usual treatment recommendation for a younger patient with MM who receives RVD followed by transplant and experiences symptomatic disease relapse while completing the second year of maintenance lenalidomide?



AUDIENCE POLL

Do you see a role for the combination of panobinostat and carfilzomib in your practice?

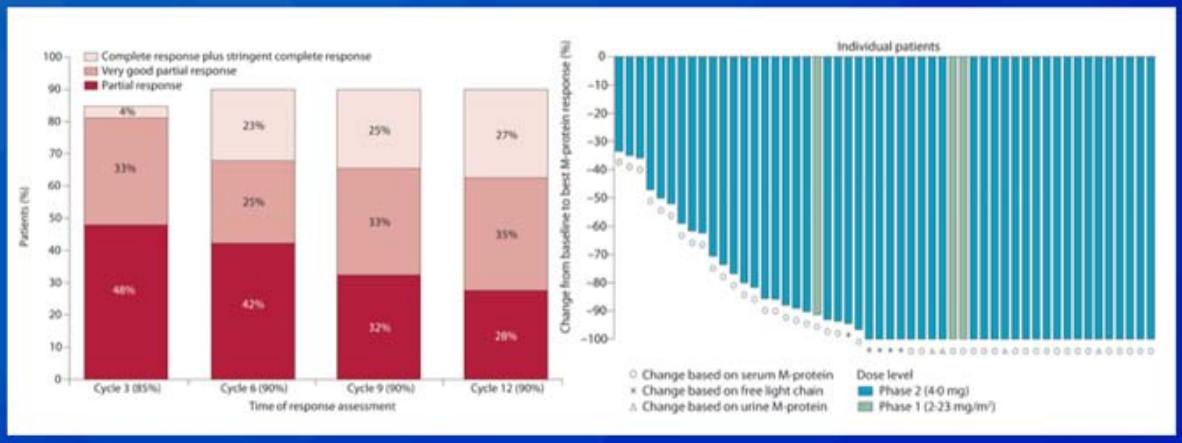


Safety and tolerability of ixazomib, an oral proteasome inhibitor, in combination with lenalidomide and dexamethasone in patients with previously untreated multiple myeloma: an open-label phase 1/2 study

Shaji K Kumar, Jesus G Berdeja, Ruben Niesvizky, Sagar Lonial, Jacob P Laubach, Mehdi Hamadani, A Keith Stewart, Parameswaran Hari, Vivek Roy, Robert Vescio, Jonathan L Kaufman, Deborah Berg, Eileen Liao, Alessandra Di Bacco, Jose Estevam, Neeraj Gupta, Ai-Min Hui, Vincent Rajkumar, Paul G Richardson

Lancet Oncol 2014;15(13):1503-12.

Response with Increasing Duration of Therapy and Best M-Protein Response among 52 Patients Treated at Recommended Phase II Dose



Kumar SK et al. *Lancet Oncol* 2014;15(13):1503-12.

Conclusions

Critical finding(s): The combination of the first oral proteasome inhibitor with len/dex is highly active and well tolerated.

Clinical implication(s): Once ixazomib is approved, the use of an all-oral induction will be an important option.

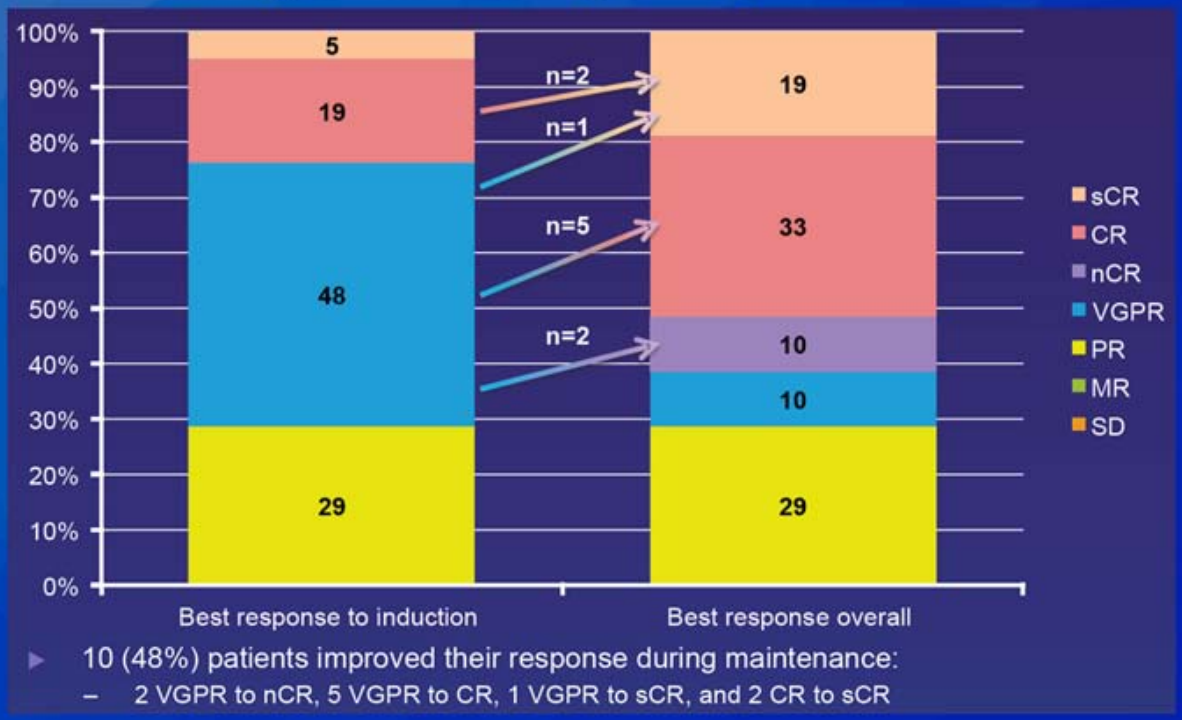
Research relevance: Consider the use of ixazomib as maintenance therapy following Tx or induction.

Long-Term Ixazomib Maintenance Is Tolerable and Improves Depth of Response Following Ixazomib-Lenalidomide-Dexamethasone Induction in Patients (Pts) with Previously Untreated Multiple Myeloma (MM): Phase 2 Study Results

Kumar S et al.

Proc ASH 2014;Abstract 82.

Best Response to Treatment in Phase II Patients Receiving Maintenance (N = 21)



- 10 (48%) patients improved their response during maintenance:
  - 2 VGPR to nCR, 5 VGPR to CR, 1 VGPR to sCR, and 2 CR to sCR

Kumar S et al. *Proc ASH* 2014;Abstract 82.

Conclusions

Critical finding(s): Long-term administration of ixazomib is safe, well tolerated and effective.

Clinical implication(s): Consider ixazomib as a long-term method for delivery of proteasome inhibition.

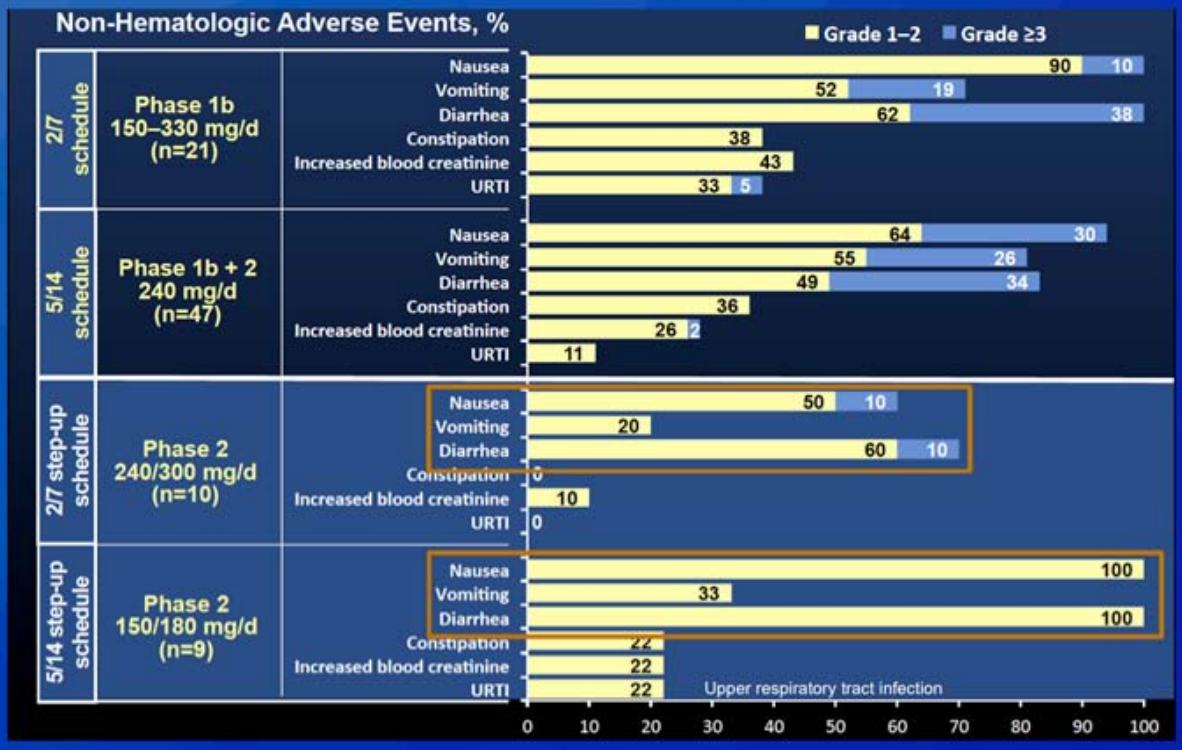
Research relevance: There are 2 maintenance trials in progress, and this work supports enrollment and excitement over its use as maintenance Tx.

Clinical Profile of Single-Agent Oprozomib in Patients (Pts) with Multiple Myeloma (MM): Updated Results from a Multicenter, Open-Label, Dose Escalation Phase 1b/2 Study

Vij R et al.

Proc ASH 2014;Abstract 34.

Safety: Nonhematologic Adverse Events



Vij R et al. *Proc ASH* 2014;Abstract 34.

Conclusions

Critical finding(s): Oral version of carfilzomib can be effective in refractory MM.

Clinical implication(s): May be a method by which proteasome inhibitor resistance can be overcome with an oral agent.

Research relevance: If a safe and effective dose/schedule can be identified, would be a great opportunity to deliver highly effective oral proteasome inhibition.

A Phase I/II Study of the Combination of Panobinostat (PAN) and Carfilzomib (CFZ) in Patients (pts) with Relapsed or Relapsed/Refractory Multiple Myeloma (MM)

Berdeja JG et al.

Proc ASCO 2015;Abstract 8513.

Conclusions

Critical finding(s): High overall response rate with low incidence of GI toxicity when panobinostat is combined with carfilzomib.

Clinical implication(s): This study shows what may be the optimal dose and schedule of panobinostat with a proteasome inhibitor. The every-other-week dosing reduces markedly the nausea and diarrhea seen with panobinostat.

Research relevance: Panobinostat/carfilzomib is an active combination that can be used now for patient care with good activity and tolerance.

The NEW ENGLAND JOURNAL of MEDICINE

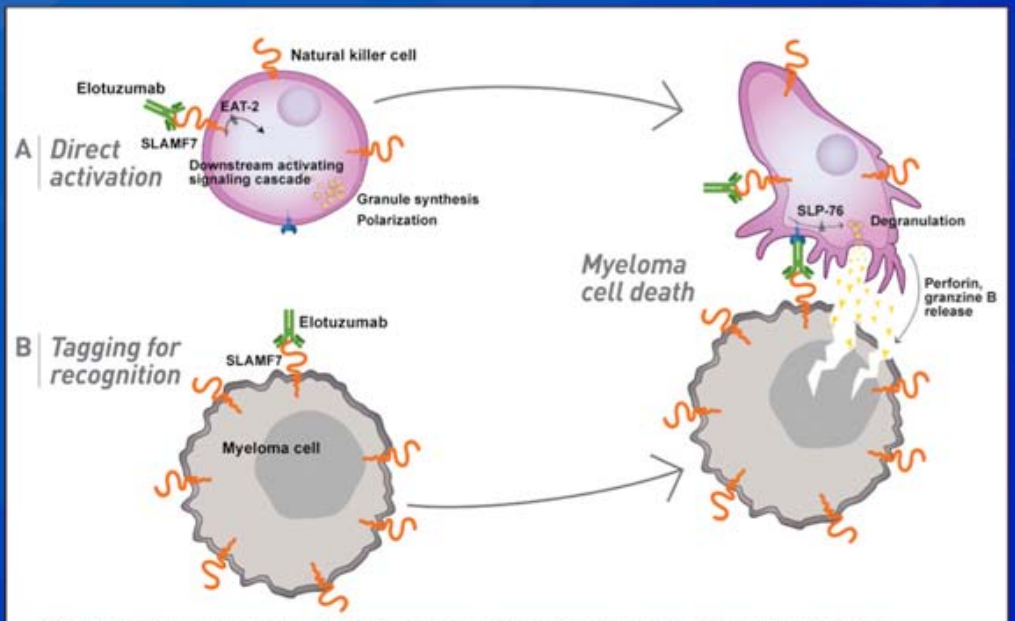
ORIGINAL ARTICLE

Elotuzumab Therapy for Relapsed or Refractory Multiple Myeloma

Sagar Lonial, M.D., Meletios Dimopoulos, M.D., Antonio Palumbo, M.D., Darrell White, M.D., Sebastian Grosicki, M.D., Ph.D., Ivan Spicka, M.D., Adam Walter-Croneck, M.D., Philippe Moreau, M.D., Maria-Victoria Mateos, M.D., Ph.D., Hila Magen, M.D., Andrew Belch, M.D., Donna Reece, M.D., Meral Beksac, M.D., Andrew Spencer, M.D., Heather Oakervee, M.D., Robert Z. Orlowski, M.D., Masafumi Taniwaki, M.D., Christoph Röllig, M.D., Hermann Einsele, M.D., Ka Lung Wu, M.D., Anil Singhal, Ph.D., Jesus San-Miguel, M.D., Morio Matsumoto, M.D., Jessica Katz, M.D., Ph.D., Eric Bleickardt, M.D., Valerie Poulart, M.Sc., Kenneth C. Anderson, M.D., and Paul Richardson, M.D., for the ELOQUENT-2 Investigators

N Engl J Med 2015;373(7):621-31.

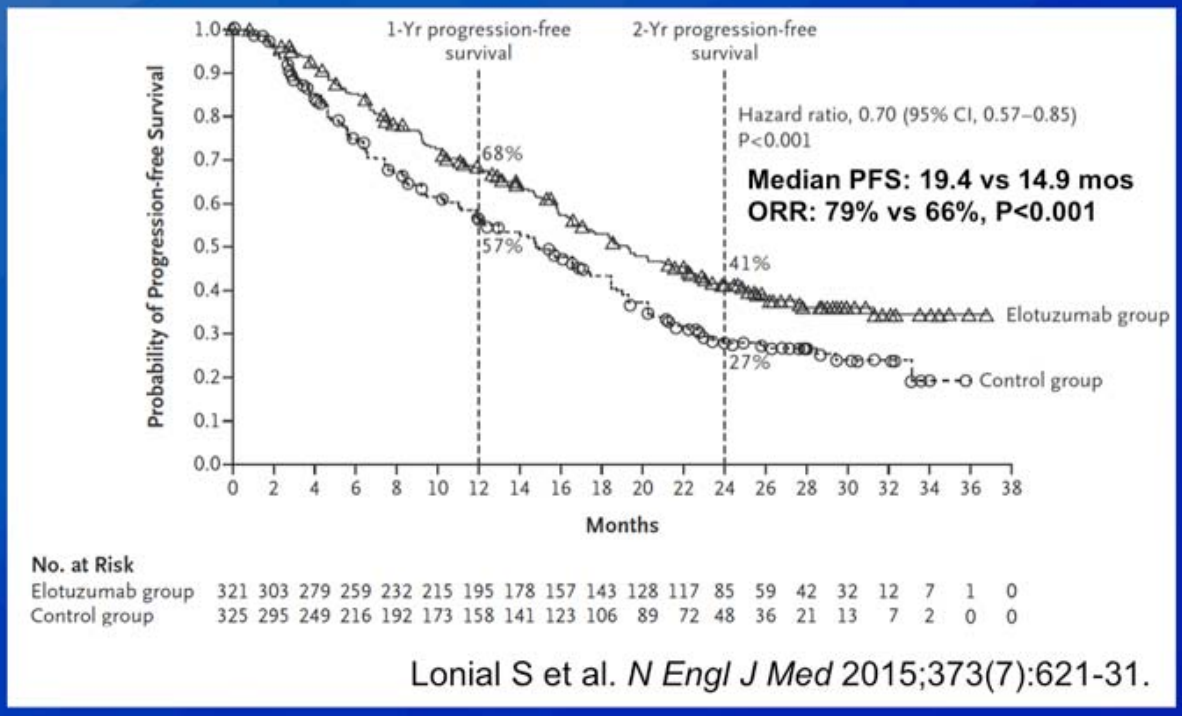
Elotuzumab Mechanism of Action



Elotuzumab works via a dual mechanism of action by both directly activating natural killer cells and through antibody-dependent cell-mediated cytotoxicity to cause targeted myeloma cell death

Courtesy of Sagar Lonial, MD

ELOQUENT-2: Progression-Free Survival



No. at Risk

Elotuzumab group	321	303	279	259	232	215	195	178	157	143	128	117	85	59	42	32	12	7	1	0
Control group	325	295	249	216	192	173	158	141	123	106	89	72	48	36	21	13	7	2	0	0

Lonial S et al. *N Engl J Med* 2015;373(7):621-31.

Conclusions

Critical finding(s): Addition of elotuzumab to len/dex improves ORR, progression-free survival and duration of response, even among high-risk and other MM patients.

Clinical implication(s): Addition of elotuzumab to len/dex is a significant benefit without new side effects.

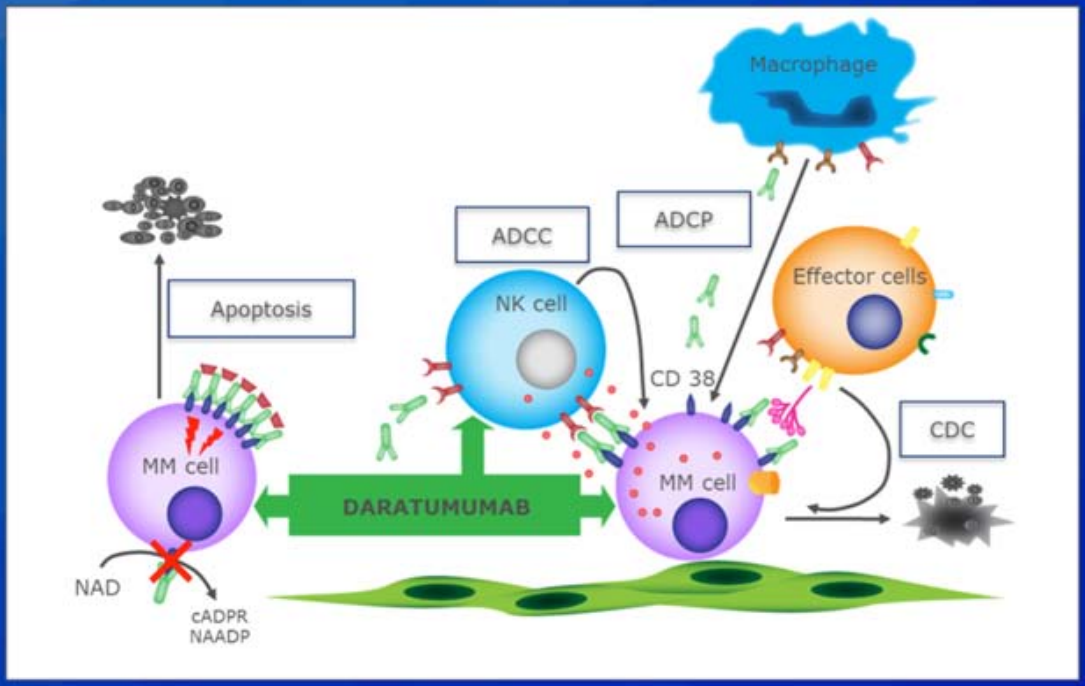
Research relevance: Once approved, knowing how to use this optimally with standard treatment and maintenance will be of great interest.

Phase II Study of Daratumumab (DARA) Monotherapy in Patients with ≥ 3 Lines of Prior Therapy or Double Refractory Multiple Myeloma (MM): 54767414MMY2002 (Sirius)

Lonial S et al.

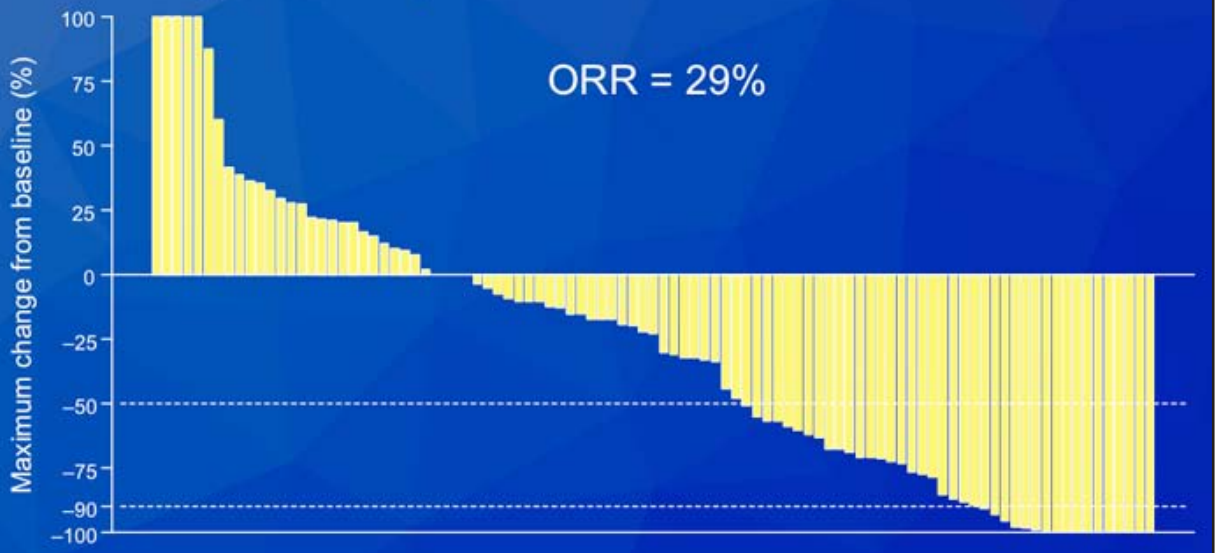
Proc ASCO 2015;Abstract LBA8512.

Daratumumab Mechanism of Action



Lonial S et al. *Proc ASCO* 2015;Abstract LBA8512.

Change in Paraprotein from Baseline



The majority of patients had reductions in paraprotein from baseline

- 40 patients (38%) had reductions >50%
- 17 patients (16%) had reductions >90%

Lonial S et al. *Proc ASCO* 2015;Abstract LBA8512.

Conclusions

Critical finding(s): Significant single-agent monoclonal antibody in MM with minimal activity

Clinical implication(s): New drug for refractory MM — Nontoxic and high activity

Research relevance: Many combination trials in progress showing critical efficacy when combined with lenalidomide and pomalidomide