5 Minute JournalClub

Key ASCO Presentations

Issue 4, 2010

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CME Information

LEARNING OBJECTIVES

- Apply the results of new clinical research with lenalidomide/bortezomib/dexamethasone (RVD) and reduced-dose bortezomib/thalidomide/dexamethasone (vTD) to the care of patients with MM.
- Counsel appropriately selected patients with MM about the efficacy and safety of lenalidomide maintenance therapy following autologous transplant.
- Demonstrate knowledge of both the survival benefit and reduction in skeletal-related events exhibited with zoledronic acid in the treatment of newly diagnosed MM.

CREDIT DESIGNATION STATEMENT

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CME Information (Continued)

FACULTY DISCLOSURES
The following faculty (and their spouses/partners) reported real or apparent conflicts of interest, which have been resolved through a conflict of interest resolution process:

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CME Information (Continued)

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Lenalidomide, Bortezomib and Dexamethasone in Patients with Newly Diagnosed Multiple Myeloma (MM): Updated Results of a Multicenter Phase I/II Study After Longer Follow-Up

Anderson KG, Richardson PG et al.

Proc ASCO 2010;Abstract 8016.

Introduction

- Combinations of bortezomib (V) or lenalidomide (R) with dexamethasone (D) are highly active as front-line therapy for multiple myeloma (MM)
  - RD (*Lancet Oncol* 2010;11:29, ASCO 2008;Abstract 8521)
  - VD (*Haematologica* 2006;91:1498, ASCO 2008;Abstract 8505)
- Preclinical data suggest synergy between V and R
  - Different but overlapping mechanisms of anti-MM activity
  - Activity of D enhanced by R and V
- RVD had demonstrated excellent activity in relapsed/refractory MM
  - 69% response rate (≥PR), including 26% CR/nCR
- Preliminary results of front-line RVD indicate that it is the first regimen of its kind to result in 100% response rate (*Blood* 2010; [Epub ahead of print])

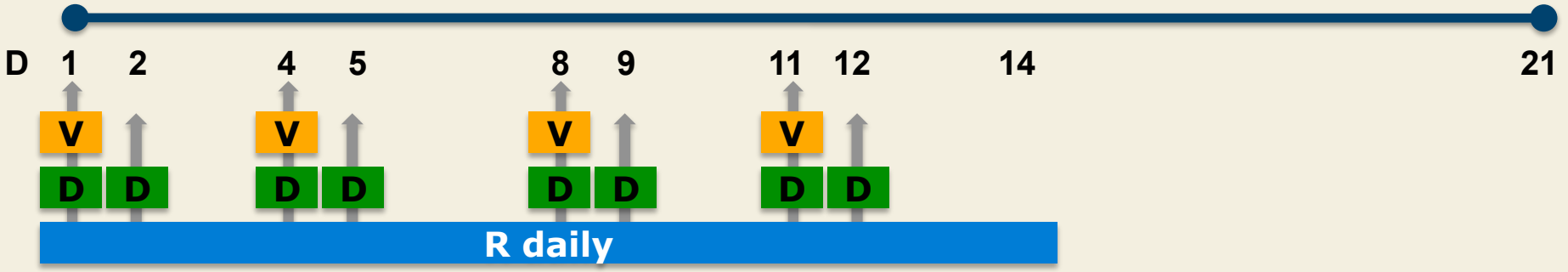
- **Current study objective:**
  - Provide updated data of front-line RVD in patients with newly diagnosed MM after a median follow-up > 27 months

Anderson KG, Richardson PG et al. *Proc ASCO* 2010;Abstract 8016.

Study Design

Eligibility (N = 66)

Newly diagnosed, untreated (bisphosphonates permitted), symptomatic MM



- Up to 8 3-wk cycles at five dose levels (1-4, 4M)
- Pts with ≥PR could proceed to ASCT after ≥4 cycles
- After 8 cycles, responding pts could receive maintenance
  - 3-week cycles of R (d 1-14), and weekly V (d 1, 8), at doses tolerated at end of cycle 8, plus D 10 mg (d 1, 2, 8, 9)
- Concomitant therapy:
  - Antithrombotic therapy with daily aspirin (81 mg or 325 mg)
  - Antiviral therapy as prophylaxis against herpes zoster
  - Vitamin supplements/amino acids/emollient creams for peripheral neuropathy
  - Bisphosphonates

Anderson KG, Richardson PG et al. *Proc ASCO* 2010;Abstract 8016.

Patient Accrual

Dose level	V dose, mg/m^2	R dose, mg	D dose, mg (cycle 1-4/5-8)	N enrolled/ treated
Phase I dose-escalation				22/21
Dose level 1	1.0	15	40/20	3/3
Dose level 2	1.3	15	40/20	3/3
Dose level 3	1.3	20	40/20	4/3
Dose level 4	1.3	25	40/20	6/6
Dose level 4M-MPD*	1.3	25	20/10	6/6
Phase I expanded cohort				11/10
Dose level 4M	1.3	25	20/10	11/10
Phase II				35/35
Dose level 4M	1.3	25	20/10	35/35

* An additional dose level 4M with reduced D dosing was included to address dose-limiting toxicity associated with higher doses of D.

Anderson KG, Richardson PG et al. *Proc ASCO* 2010;Abstract 8016.

Best Response to RVD

Response	All patients (N = 66)	Phase II (N = 35)
Complete response (CR)	29%	37%
Near CR	11%	20%
Very good partial response (VGPR)	27%	17%
Partial response (PR)	33%	26%
CR + nCR	39%	57%
CR + nCR + VGPR	67%	74%
At least PR	**100%**	**100%**

- Response improvement seen in 42/56 patients (75%) from C4-8 and 20/38 patients (53%) beyond C8
- Median time to best overall response: 2.1 months (range: 0.6-20)

Anderson KG, Richardson PG et al. *Proc ASCO* 2010;Abstract 8016.

Updated Outcomes

- Median follow-up: 27.3 months (range: 5.6-41.2)
- 44 patients alive and without disease progression
  - 1 patient with significant coronary artery disease died of cardiac ischemia
  - 21 patients experienced disease progression, of whom 3 died
- Patients were not censored at the time of ASCT in time-to-event analyses
  - Duration of reponse (DOR), progression-free survival (PFS) and overall survival (OS) are for RVD ± ASCT
- Median DOR not reached
  - 67% of patient are in response for > 24 months
- Median PFS and OS not reached
  - Estimated 24-month PFS: 68% (95% CI: 55, 78)
  - Estimated 24-month OS: 95% (95% CI: 86, 98)

Anderson KG, Richardson PG et al. *Proc ASCO* 2010;Abstract 8016.

Conclusions

- RVD is highly effective for previously untreated MM
  - First regimen to result in a 100% response rate (≥PR) without ASCT
  - Remarkably high rates of CR/nCR and ≥VGPR
- Outcomes data with RVD ± ASCT are promising
  - Estimated 24-month PFS: 68%
  - Estimated 24-month OS: 95%
- Very good tolerability over a lengthy treatment period (data not shown)
  - Manageable toxicities
  - Grade 3 sensory peripheral neuropathy: 2%
  - Deep vein thrombosis: 6%
  - No treatment-related mortality

Anderson KG, Richardson PG et al. *Proc ASCO* 2010;Abstract 8016.

Investigator comment on RVD therapy for patients with newly diagnosed myeloma

With this regimen, the rate of very good partial response or better was 74 percent, and 57 percent of patients had complete or near-complete responses. These are better rates than were seen, for example, in the study of VTD induction followed by stem cell transplant. So with RVD, you now are achieving similar response rates without the need for stem cell transplant.

Some issues arose with RVD and stem cell harvesting and, more importantly, with engraftment. Typically these issues would not be clinically relevant, but they should be considered in cases in which there is concern that there may be some difficulty collecting stem cells.

Progression-free survival in this study has been quite good, and data on the impact of cytogenetic abnormalities suggest that even in patients with high-risk features, the RVD combination is effective. For patients who are transplant eligible, we've been predominantly using this regimen. Many people feel that RVD is now the standard regimen, and many places, including the MD Anderson Cancer Center, are building on RVD by adding drugs.

Interview with Robert Z Orlowski, MD, PhD, June 18, 2010

Investigator comment on RVD therapy for patients with newly diagnosed myeloma

The RVD regimen is now becoming one standard against which other regimens are being compared. Trials are in progress, also adding a fourth agent to the combination to learn whether we can ultimately achieve a CHOP or an R-CHOP for myeloma that would potentially lead to some cures. RVD is moving into the transplant arena in trials, both as induction therapy and as consolidation.

So the fact is that while you cannot be faulted right now, in the absence of survival data, for using a two-drug combination, more and more people are adopting three-drug regimens because the majority of the data in the front-line setting, especially with transplant-eligible patients, suggest that patients who have complete responses have better overall survival. So we can either wait several years for the data to emerge, or we can make the change now and hope that we are doing good for our patients.

Interview with Ravi Vij, MD, July 1, 2010

Reduced-Dose Bortezomib plus Thalidomide plus Dexamethasone (vTD) is Superior to Bortezomib plus Dexamethasone (VD) as Induction Treatment Prior to Autologous Stem Cell Transplantation (ASCT) in Newly Diagnosed Multiple Myeloma (MM): Results of IFM2007-02 Prospective Randomized Study

Moreau P et al.

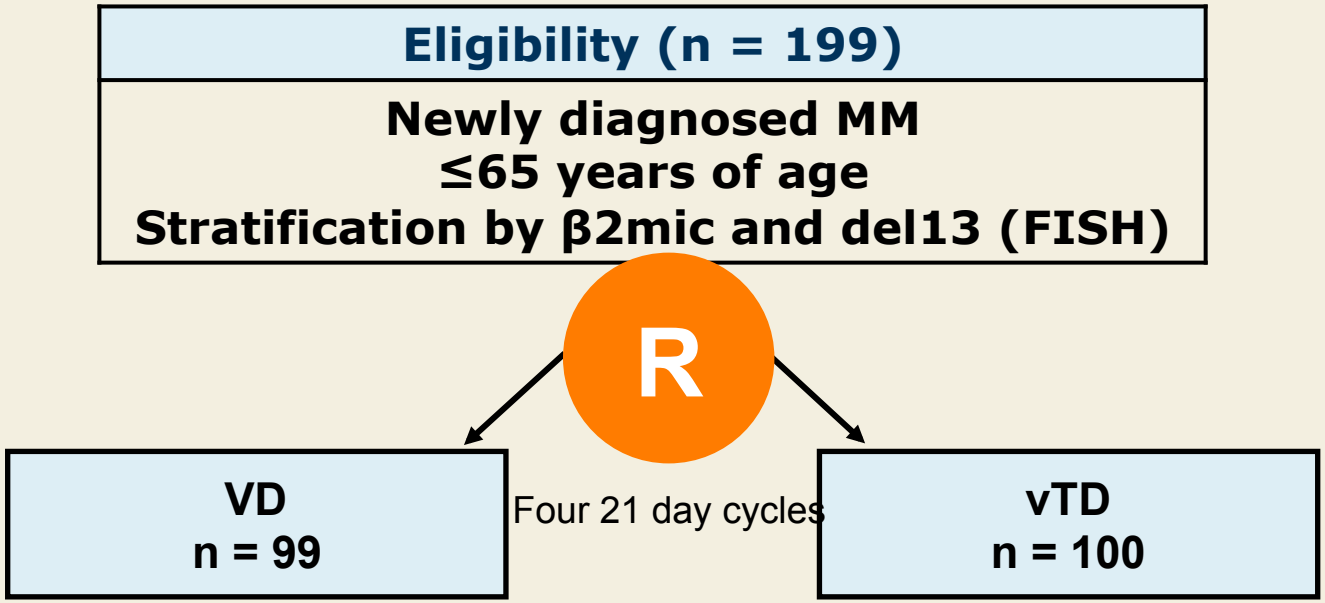
Proc ASCO 2010;Abstract 8014.

Introduction

- VD is superior to vincristine/doxorubicin/dexamethasone (VAD) for patients with newly diagnosed MM.
  - Improved progression-free survival and response rates[1] ([1] *Proc ASH* 2009;Abstract 353)
- VTD (bortezomib/thalidomide/dexamethasone) is superior to TD in patients with newly diagnosed MM.
  - Superior progression-free survival and response rates[2] ([2] *Proc ASH* 2009;Abstract 351)
- VD and VTD are associated with significant toxicity:
  - Grade 3/4 neuropathy rates
    - 7% in VD arm[1]; 9% in VTD arm[2]
- **Current study objective:**
  - Compare response and safety with vTD versus VD prior to and following ASCT in patients with newly diagnosed MM.

Moreau P et al. *Proc ASCO* 2010;Abstract 8014.

IFM 2007-02 Study Design



V, 1.3 mg/m^2 d1, 4, 8, 11
D, 40 mg d1-4, 9-12 for cycles 1 and 2
d1-4 for cycles 3 and 4

v, 1.0 mg/m^2 d1, 4, 8, 11*
T, 100 mg/d*
D, 40 mg d1-4, 9-12 for cycles 1 and 2
d1-4 for cycles 3 and 4

* Doses increased to 1.3 mg/m^2 (v) and 200 mg/d (T) if response < PR after 2 cycles

Moreau P et al. *Proc ASCO* 2010;Abstract 8014.

Response Status at Cycles 2 and 4: Intent-to-Treat

Response after 2 cycles	vTD n = 100	VD n = 99	*p*-value
≥Partial response (PR)	**90%**	**78%**	**0.008**
≥Very good PR (VGPR)	22%	20%	0.77
Complete response (CR) + near CR	15%	16%	0.95
CR	4%	6%	0.71
Response after 4 cycles	**vTD**	**VD**	***p*-value**
≥PR	90%	81%	0.079
≥VGPR	**51%**	**35%**	**0.037**
CR + nCR	32%	22%	0.104
CR	13%	12%	0.74

Moreau P et al. *Proc ASCO* 2010;Abstract 8014.

Response Status After ASCT: Intent-to-Treat

	vTD n = 100	VD n = 99	*p*-value
≥Partial response (PR)	90%	84%	0.23
≥Very good PR (VGPR)	**73%**	**59%**	**0.037**
Complete response (CR) + near CR	61%	54%	0.35
CR	30%	33%	0.65

Moreau P et al. *Proc ASCO* 2010;Abstract 8014.

Peripheral Neuropathy

	vTD	VD	*p*-value
All grades	55%	63%	0.24
Grade ≥2	15%	28%	0.03
Grade ≥3	3%	6%	0.34
Serious adverse event leading to treatment discontinuation	0%	4%	0.12

Moreau P et al. *Proc ASCO* 2010;Abstract 8014.

Conclusions

- Response rates significantly improved with vTD in comparison to VD
  - Primary objective: CR rate after induction is similar
  - CR/VGPR rate superior both after induction and after ASCT
- Decreasing the doses of bortezomib and thalidomide does not impair efficacy.
- The addition of cyclophosphamide to GCSF is required for stem cell harvest on the vTD combination (data not shown).
- Incidence of Grade III/IV adverse events was low (data not shown).
- Incidence of Grade II/III peripheral neuropathy was significantly reduced with the vTD combination.
- vTD combination is superior to VD with a good efficacy/toxicity ratio.

Moreau P et al. *Proc ASCO* 2010;Abstract 8014.

Investigator comment on the results of the IFM2007-02 study

After four cycles, a trend was apparent toward a better complete plus near complete response rate with vTD. There was also an improvement in the rate of very good partial response or better after vTD compared to VD, with a *p*-value that reached statistical significance.

People who received vTD induction did on average need more sessions of apheresis to collect stem cells. They also on average had a higher risk of needing the addition of cyclophosphamide to GCSF to mobilize enough stem cells, and fewer CD34-positive stem cells were collected in this group. So that may be a concern, especially for patients who may have some baseline difficulty with stem cell collection.

Importantly, even though vTD combines two drugs that can induce neuropathy — bortezomib and thalidomide — its use resulted in a trend toward less neuropathy because of the lower doses of bortezomib and thalidomide, supporting the concept that using bortezomib at a reduced dose twice weekly can result in less neuropathy.

Interview with Robert Z Orlowski, MD, PhD, June 18, 2010

Investigator comment on ameliorating bortezomib-associated neurotoxicity

The amelioration of bortezomib neurotoxicity is something people are pursuing with various strategies. In this IFM study by Moreau, the bortezomib neurotoxicity was ameliorated by dose reduction. In a recent Italian trial, once-weekly bortezomib led to similar outcomes as a twice-weekly schedule with less neurotoxicity. Both the Italian and the current important French trial have reduced the toxicity of bortezomib, either by less frequent administration or by dose reduction, respectively, without compromising efficacy outcomes.

Interview with Ravi Vij, MD, July 1, 2010

Lenalidomide Maintenance After Autologous Transplantation for Myeloma: First Interim Analysis of a Prospective Randomized Study of the Intergroupe Francophone du Myélome (IFM 2005-02 Trial)

Attal M et al.

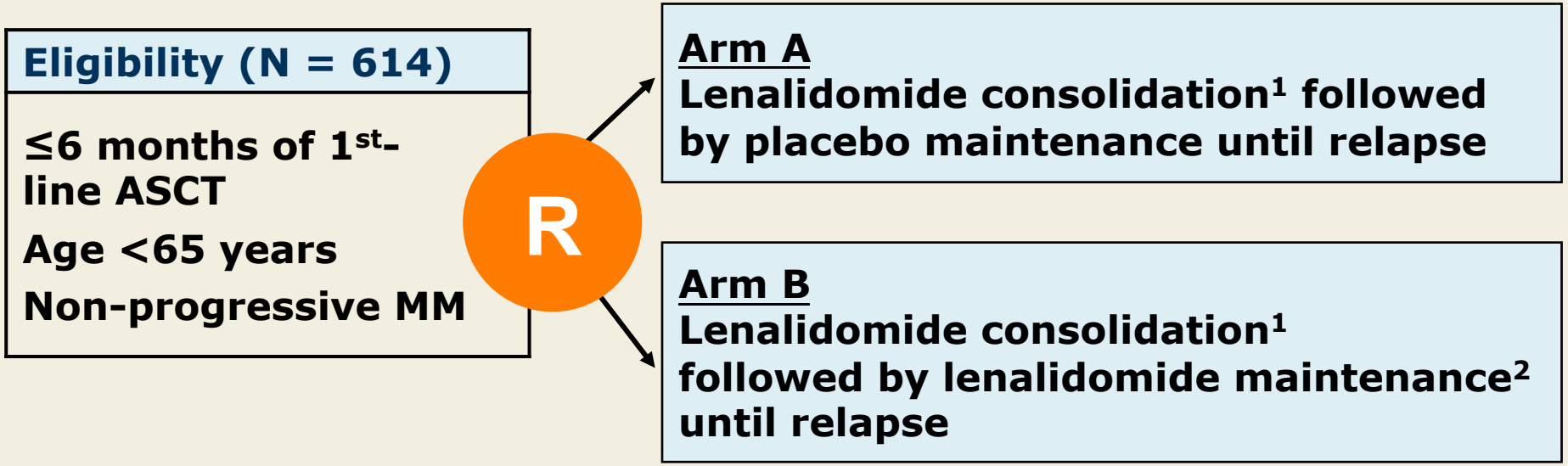
Proc ASCO 2010;Abstract 8018.

Background and Rationale

- High-dose therapy with autologous stem cell transplantation (ASCT) is standard treatment for eligible patients with multiple myeloma (MM).
- Residual disease responsible for relapse is always present.
- Maintenance thalidomide has shown improved survival (*Blood* 2006;108:3289, *J Clin Oncol* 2009;27:1788).
- Clinical use of maintenance thalidomide is limited because of peripheral neuropathy with prolonged administration.
- Lenalidomide is
  - A thalidomide analogue.
  - Devoid of neurological complications.
  - Likely to be both effective and safe with prolonged administration.

Attal M et al. *Proc ASCO* 2010;Abstract 8018.

IFM 2005-02 Study Design

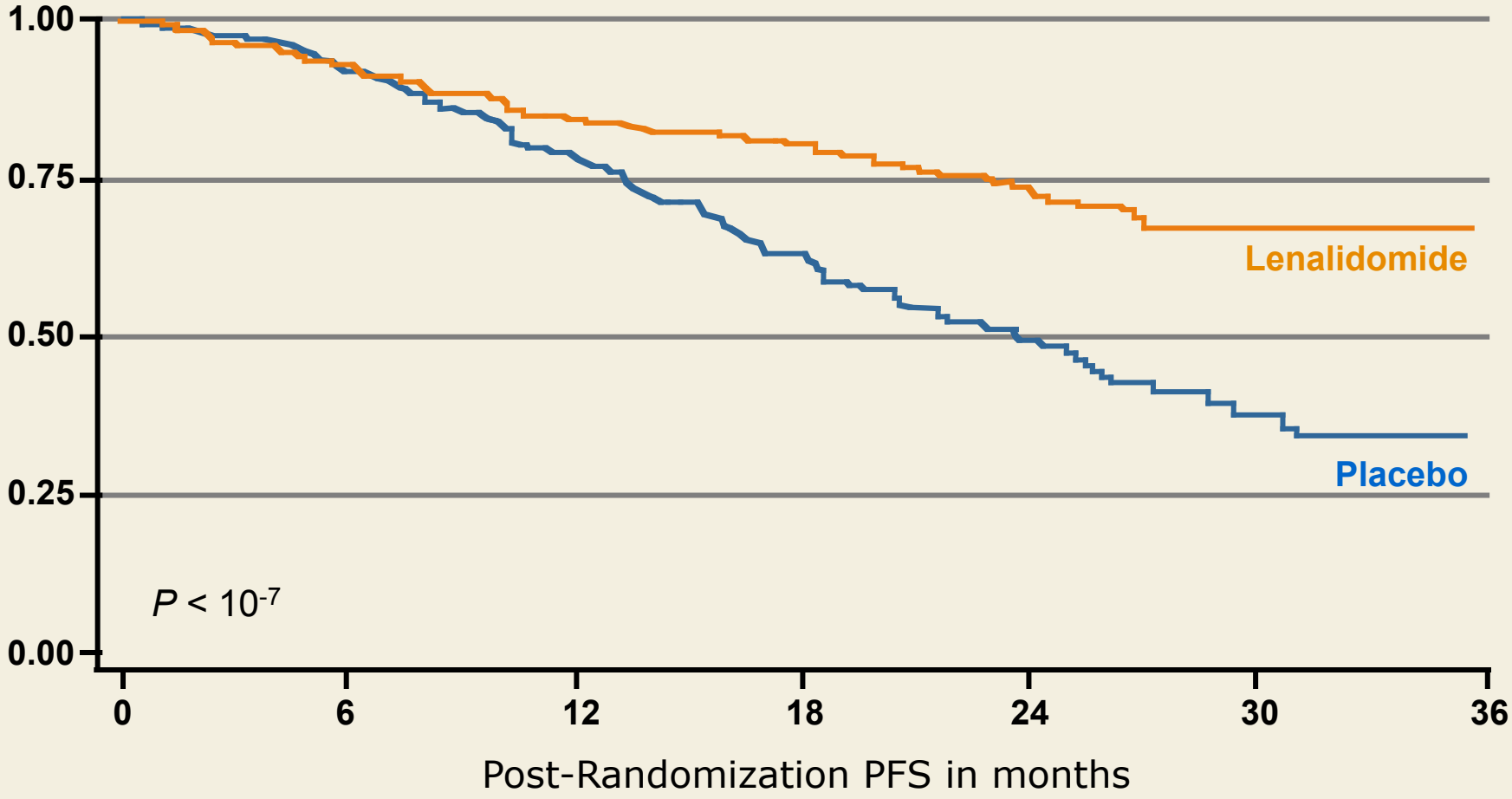


Randomization stratified according to β2 microglobulin, del 13 and VGPR

[1] Lenalidomide 25 mg/day, days 1-21 every 28 days x 2 months
[2] Lenalidomide 10-15 mg/day until relapse
VGPR = very good partial response

Attal M et al. *Proc ASCO* 2010;Abstract 8018.

IFM 2005-02: Progression-Free Survival (PFS)



With permission from Attal M et al. *Proc ASCO* 2010;Abstract 8018.

IFM 2005-02: Efficacy Evaluation

	Placebo Maintenance (n = 307)	Lenalidomide Maintenance (n = 307)	*p*-value	Hazard Ratio
Complete Response (Immunofixation Negative)	22%	25%	0.4	—
≥VGPR	70%	77%	0.08	—
Progression or Death	143 (47%)	77 (25%)	—	—
Median PFS	24 months	Not Reached	$<10^{-7}$	—
3-Year Post-Randomization PFS	34%	68%	$<10^{-7}$	0.46
3-Year Post-Randomization OS	80%	88%	Not Reported	0.88

Attal M et al. *Proc ASCO* 2010;Abstract 8018.

Conclusions

- Significant improvement in PFS with maintenance lenalidomide in:
  - Overall study population.
  - Pre-specified strata by β2-microglobulin, VGPR as well as del 13 (data not shown).
- Longer follow-up will be needed to find impact of lenalidomide maintenance on overall survival.
- No unexpected adverse events, and no increased incidence of DVT or peripheral neuropathy with lenalidomide maintenance (data not shown).

Attal M et al. *Proc ASCO* 2010;Abstract 8018.

Investigator comment on the use of lenalidomide maintenance therapy in myeloma

As I see it, the paradigm for treating myeloma has expanded from a view of an induction therapy and eventually of a consolidation therapy to the concept of a maintenance therapy. At ASCO, two highly important studies were reported from two independent groups, one a Phase III study in the US and the other a Phase III study in Europe, and both these trials clearly demonstrated the role of lenalidomide as maintenance therapy for younger patients with myeloma after autologous stem cell transplantation.

At this time we have no data concerning overall survival, but we do have data concerning decreased risk of relapse and prolonged progression-free survival. Although this approach is available at this time in the setting of younger, transplant-eligible patients with myeloma, the concept of a maintenance therapy and the value of maintenance therapy have also been reported and demonstrated for elderly, nontransplant-eligible patients.

Interview with Michele Cavo, MD, July 1, 2010

Phase III Intergroup Study of Lenalidomide versus Placebo Maintenance Therapy Following Single Autologous Stem Cell Transplant (ASCT) for Multiple Myeloma (MM): CALGB 100104

McCarthy PL et al.

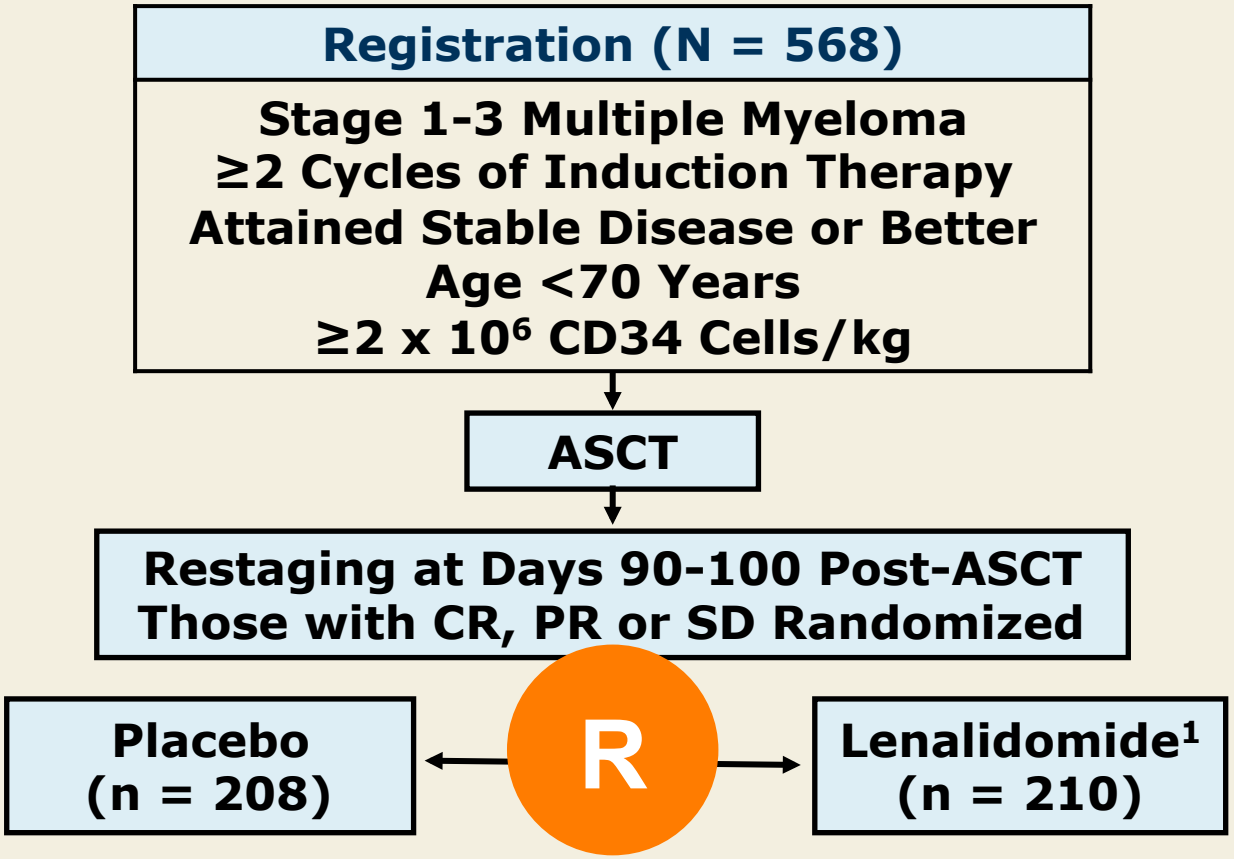
Proc ASCO 2010;Abstract 8017.

Background and Rationale

- High-dose therapy with autologous stem cell transplantation (ASCT) is standard treatment for eligible patients with myeloma.
- Disease relapse/progression is a primary cause of treatment failure after ASCT.
- Maintenance therapy may prevent or delay disease progression and improve response and survival.

McCarthy PL et al. *Proc ASCO* 2010;Abstract 8017.

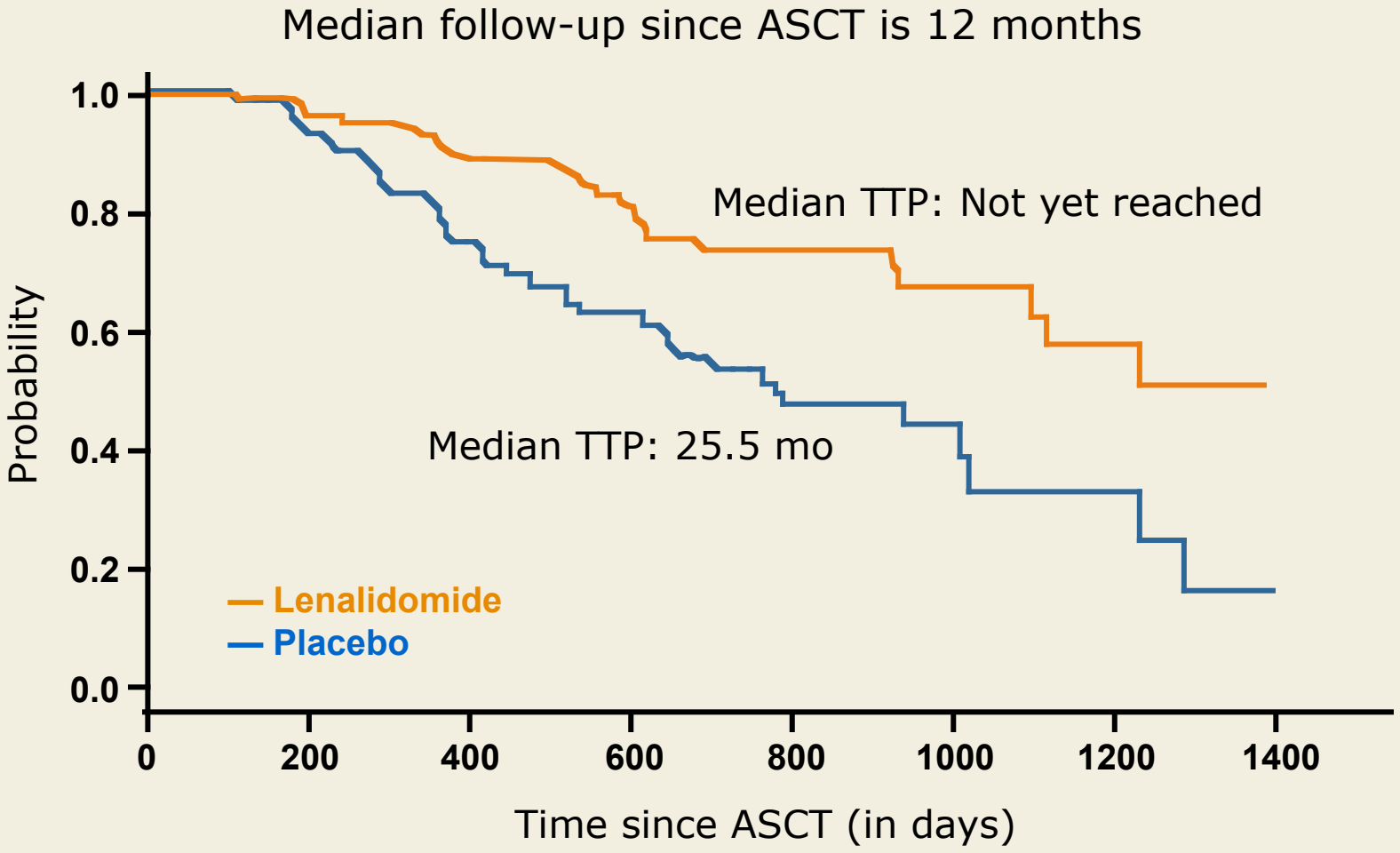
CALGB-100104 Study Design



[1] Lenalidomide 10 mg/day with increase or decrease to 5-15 mg
CR = complete response; PR = partial response; SD = stable disease

McCarthy PL et al. *Proc ASCO* 2010;Abstract 8017.

CALGB-100104: Time to Progression (TTP)



With permission from McCarthy PL et al. *Proc ASCO* 2010;Abstract 8017.

CALGB-100104: Efficacy Evaluation

	Placebo Maintenance (n = 208)	Lenalidomide Maintenance (n = 210)	*p*-value	Hazard Ratio
Progression or Death	58 (27.9%)	29 (13.8%)	<0.0001	0.42
Median Time to Progression	25.5 months	Not Reached	<0.0001	—
Death Events	17 (8.2%)	11 (5.2%)	<0.2	—

Median follow-up since ASCT is 12 months

McCarthy PL et al. *Proc ASCO* 2010;Abstract 8017.

Grade 3-5 Adverse Events During Maintenance (n = 368)

Grade 3-5 Adverse Event	Placebo (n = 174)	Lenalidomide (n = 194)	*p*-value
Anemia	1%	6%	0.0028
Thrombocytopenia	3%	12%	0.01
Neutropenia	7%	42%	<0.0001
Febrile Neutropenia	2%	6%	0.48
Infections	2%	7%	0.03

McCarthy PL et al. *Proc ASCO* 2010;Abstract 8017.

Conclusions

- Lenalidomide maintenance results in improvement in TTP in:
  - Overall study population.
  - Pre-specified strata of β2 microglobulin as well as prior exposure to lenalidomide or thalidomide (data not shown).
- Lack of survival benefit:
  - Median follow-up was one year.
  - Longer follow-up will be needed.
- Lenalidomide maintenance resulted in some hematologic toxicity, though this was not severe.

McCarthy PL et al. *Proc ASCO* 2010;Abstract 8017.

Investigator comment on the results of the CALGB-100104 study of lenalidomide maintenance therapy for myeloma

I've been recommending lenalidomide maintenance to all of my patients in the post-transplant setting. The risks are cytopenia and the potential that when their disease does relapse it may be lenalidomide resistant and that, therefore, they may have lost one treatment option in that setting. We still don't have the overall survival data from the two lenalidomide studies, which I believe will be important. If we improve progression-free survival (PFS) but don't improve overall survival, then the importance of those studies will be somewhat decreased.

Subset analyses were also done that showed that lenalidomide worked well whether patients had elevated or normal levels of beta-2 microglobulin, whether or not they were exposed to thalidomide and even whether or not they had received lenalidomide as part of their induction regimen.

The one issue that is not addressed by this study is whether, when patients do experience disease progression on lenalidomide, they no longer have disease that responds to full-dose lenalidomide. If that's the case, the benefit in terms of PFS may be lost with one less option to use in the relapsed setting.

Interview with Robert Z Orlowski, MD, PhD, June 18, 2010

Investigator comment on the use of lenalidomide maintenance therapy in myeloma

In the CALGB study patients are being allowed to cross over from observation to the arm with lenalidomide maintenance, so a survival advantage may not be demonstrated. However, in the French study, patients are being followed on their assigned arms. So perhaps in a few years we will have survival data.

People are taking different approaches to this. Some will administer maintenance therapy to everybody after transplant, and some administer it to patients who've had less than a very good PR. Others will administer it to anybody who has not experienced a complete remission. And still others are talking about administering it to patients in complete remission only if they have high-risk features.

Certainly, few people will be using maintenance thalidomide anymore, and many will be adopting lenalidomide maintenance.

Interview with Ravi Vij, MD, July 1, 2010

Investigator comment on the use of lenalidomide maintenance therapy in myeloma

In our own group we're having extensive discussions about how we're going to come up with a standardized recommendation for patients in the post-transplant setting. In the US we are quick to act on abstract data. I think what makes me feel more confident about this is that it was corroborated with two independent studies, so the data are robust.

The real question, "does there have to be a survival benefit for this to have meaningful impact?" is a tough one to answer. We may be able to show a survival benefit, but we may not. And if we don't, does that mean we should throw out maintenance lenalidomide? I don't believe so. The PFS data are fairly convincing.

Interview with Sagar Lonial, MD, June 21, 2010

Evaluating the Effects of Zoledronic Acid on Overall Survival in Newly Diagnosed Patients with Multiple Myeloma: Results of the Medical Research Council (MRC) Myeloma IX Study

Morgan GJ et al.

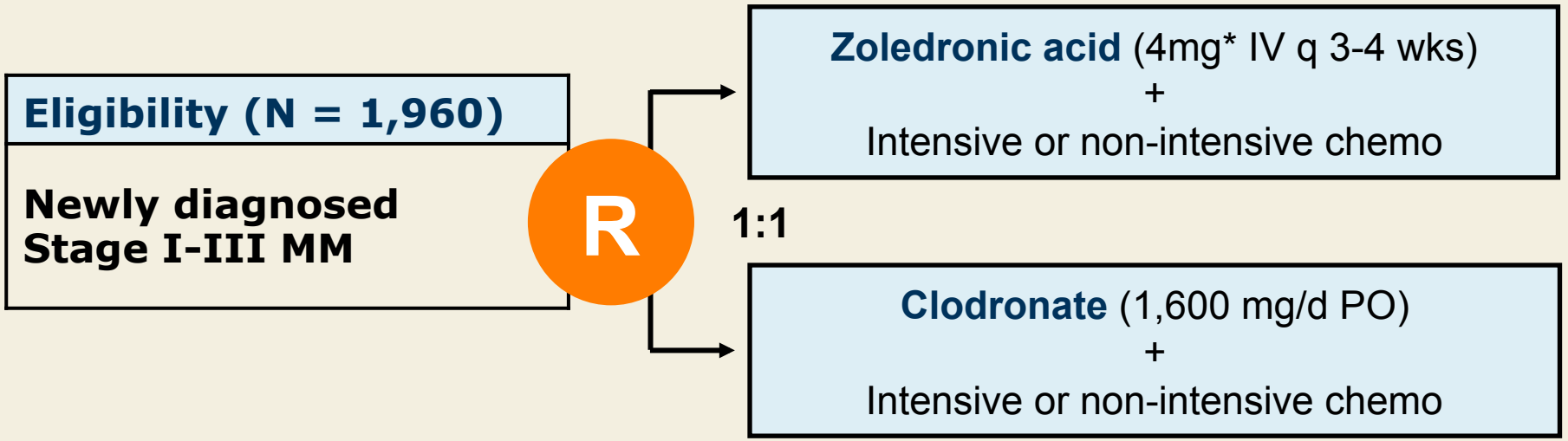
Proc ASCO 2010;Abstract 8021.

Introduction

- Indirect and direct preclinical evidence supports the potential anticancer effects of bisphosphonates in multiple myeloma (MM).
- Clinical evidence supports the anticancer effects of zoledronic acid (ZOL) and clodronate (CLO) in MM:
  - ZOL significantly increased 5-year event-free survival (EFS) and overall survival (OS) rates vs control (*Med Oncol* 2007;24:227).
  - In patients with high bone-specific alkaline phosphatase, ZOL significantly decreased the risk of death by 55% vs pamidronate (*Proc ASH* 2006;Abstract 3589).
  - CLO significantly improved survival in patients with no fractures at baseline vs placebo (*Br J Haematol* 2001;113:1035).
- **Current study objective:**
  - In patients with newly diagnosed MM, determine whether bone-targeted therapy with ZOL versus CLO can improve survival.

Morgan GJ et al. *Proc ASCO* 2010;Abstract 8021.

MRC IX Study Design



Primary Endpoint: PFS, TTP, and OS

Secondary Endpoints: Time to first SRE, SRE incidence, safety

Treatment continued at least until disease progression

* Dose-adjusted for patients with impaired renal function per prescribing information
PFS = progression-free survival; OS = overall survival;
ORR = overall response rate; SRE = skeletal-related event

Morgan GJ et al. *Proc ASCO* 2010;Abstract 8021.

Summary of Efficacy (Median Follow-Up: 3.7 Years)

Endpoint	Risk reduction (in favor of ZOL)	*p*-value
Overall survival (OS)*	16%	0.0118
Progression-free survival (PFS)*	12%	0.0179
Skeletal-related events (SREs)†	24%	0.0004
Improvement in median OS (ZOL vs CLO) = 5.5 mo, *p* = 0.04		
Is the observed OS improvement with ZOL due to SRE prevention, or does it represent an anti-myeloma effect?		
OS adjusted for SREs	15%	0.0178

* Adjusted for chemotherapy and minimization factors

† SREs defined as vertebral fractures, other fractures, spinal cord and the requirement for radiation or surgery to bone lesions or th of new osteolytic bone lesions

Morgan GJ et al. Proc ASCO 2010; Abstract 8021.

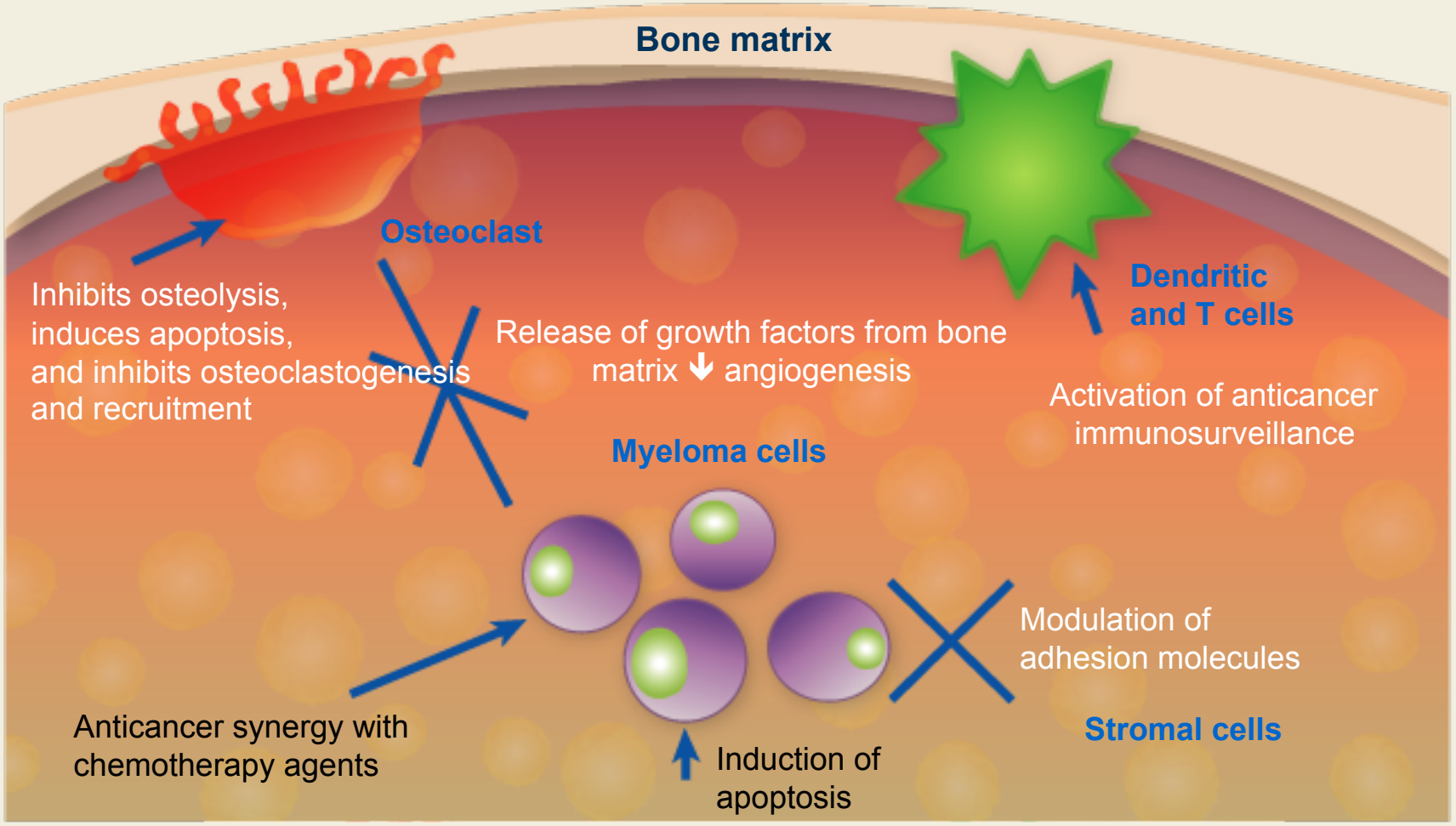
Adverse Events (AEs): Safety Population

Adverse Event	Intensive treatment			Non-intensive treatment		
	ZOL (n = 555)	CLO (n = 556)	*p*-value	ZOL (n = 428)	CLO (n = 423)	*p*-value
Acute renal failure	5.2%	5.9%	0.70	6.5%	6.4%	1.0
ONJ*	3.8%	0.4%	<0.0001	3.3%	0.2%	0.0009
Thrombo-embolic events	18.7%	14.7%	0.08	12.4%	8.3%	0.06
Infection, serious AE	9.4%	11.2%	0.37	3.7%	6.6%	0.06

* Confirmed by an independent adjudication committee
ONJ = osteonecrosis of the jaw

Morgan GJ et al. *Proc ASCO* 2010;Abstract 8021.

ZOL Exerts Both Direct and Indirect Antimyeloma Effects



Modified from Morgan GJ et al. *Proc ASCO* 2010;Abstract 8021.

Conclusions

- After a median follow-up of 3.7 years, ZOL significantly prolonged OS and PFS and reduced SREs compared to CLO.
  - Survival benefit was independent of SRE reduction.
- ZOL and CLO were generally well tolerated, with expected safety profiles.
  - ONJ incidence was low overall, but higher for ZOL vs CLO (3.6% vs 0.3%).
- These data further support the anticancer activity of ZOL and provide evidence that ZOL should be considered for early integration into treatment regimens for patients with newly diagnosed MM.

Morgan GJ et al. *Proc ASCO* 2010;Abstract 8021.

Investigator comment on the results of the MRC Myeloma IX study

One concern about the study is that the regimens used for induction were not what we would consider the current standard. The possibility exists that had modern induction regimens been used, the difference in overall survival would not have been quite as dramatic.

Regarding adverse events, this is one of the largest studies in which data were collected about ONJ (osteonecrosis of the jaw), and in the zoledronate arm from 3.3 to 3.8 percent of patients developed signs of ONJ. Overall, the data support the use of zoledronate for patients with myeloma-related bone disease. And the data suggest that it may have some benefit beyond bone health — some direct effects against multiple myeloma itself.

This study included patients with and without osteolytic bone disease, and the study population as a whole benefited from zoledronic acid. It would be interesting to see whether the subgroup without bone disease benefited by subset analysis because current ASCO guidelines do not recommend bisphosphonates for those patients.

Interview with Robert Z Orlowski, MD, PhD, June 18, 2010

Investigator comment on the results of the MRC Myeloma IX study

It is not easy to evaluate this study because it was designed for younger, transplant-eligible patients and for older, non-transplant-eligible patients, and the results reflect a mix of both younger and elderly patients with myeloma. We will need to perform post hoc subanalyses because the value of zoledronic acid in terms of antitumor activity might be quite different for the younger patient in comparison to the elderly patient.

However, I believe that another important result of this study is the significantly decreased rate of skeletal-related events in a patient population that included a group of patients who had no skeletal disease at the time of diagnosis. Based on this study, I believe that bisphosphonates should be started at the time that treatment is started for all patients with myeloma, independent of the presence or absence of osteolytic lesions.

Interview with Michele Cavo, MD, July 1, 2010

Investigator comment on the results of the MRC Myeloma IX study

This intriguing abstract adds to data in solid tumors, where zoledronate (ZDA) has been shown to have possible antineoplastic activity. We know that ZDA is active as a therapeutic agent for myeloma in the laboratory, both in vitro and in vivo murine models, where the antineoplastic effects may be somewhat distinct from its effects on bone. This clinical trial tried to control for skeletal-related events and was able to show that the survival advantage with ZDA appeared to exist irrespective of the effects on skeletal-related events, suggesting that it's due to a direct antitumor effect rather than an indirect effect from the reduction of skeletal-related events.

I don't believe that this study has many practical implications at the moment because we already use ZDA as the agent of choice in most settings. I would continue to follow the ASCO guidelines, which at the moment recommend that bisphosphonates be used for two years, after which time, if the disease is inactive, they be stopped and resumed when the disease becomes active again.

Interview with Ravi Vij, MD, July 1, 2010

Investigator comment on the results of the MRC Myeloma IX study

This zoledronate study raised a red flag. I believe that hematologists, myself included, have become a little less careful about the management of bisphosphonates, only to have a study like this show that in a recent time frame, it does matter. Although many caveats apply to this study — the newest regimens were not used and there's potential for improvement in how zoledronate was applied — it still provided patient benefit. So it's something that we need to consider in our practice. I wouldn't say it's practice changing as much as practice reaffirming and a call to more quality, principle-based practice.

Interview with Rafael Fonseca, MD, July 7, 2010