5 Minute JournalClub

POST-ASH Issue 1, 2014

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CME Information

LEARNING OBJECTIVES

- Appraise recent clinical research findings on the efficacy and safety of lenalidomide in combination with low-dose dexamethasone (Rd) as an up-front therapeutic option for elderly patients with newly diagnosed MM, and consider this information for the treatment of patients.
- Compare and contrast the benefits and risks of bortezomib/melphalan/prednisone (VMP) and Rd for elderly patients with newly diagnosed MM when administered in a sequential versus an alternating manner.
- Assess the efficacy and safety of therapeutic regimens containing an alkylating agent versus those that do not for elderly, transplant-ineligible patients with newly diagnosed MM.
- Analyze the extended and updated results from the Phase III HOVON-65/GMMG-HD4 trial of bortezomib during induction and maintenance therapy for newly diagnosed MM, including outcomes of patients with renal failure.

CME Information (Continued)

LEARNING OBJECTIVES

- Evaluate the updated patient survival outcomes from the IFM 2005-02 study and the role of lenalidomide maintenance therapy after first-line autologous stem cell transplantation in 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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Advisory Committee and Consulting Agreements: Bristol-Myers Squibb Company, Celgene Corporation, Lilly, Millennium: The Takeda Oncology Company, Novartis Pharmaceuticals Corporation, Onyx Pharmaceuticals Inc, Sanofi.

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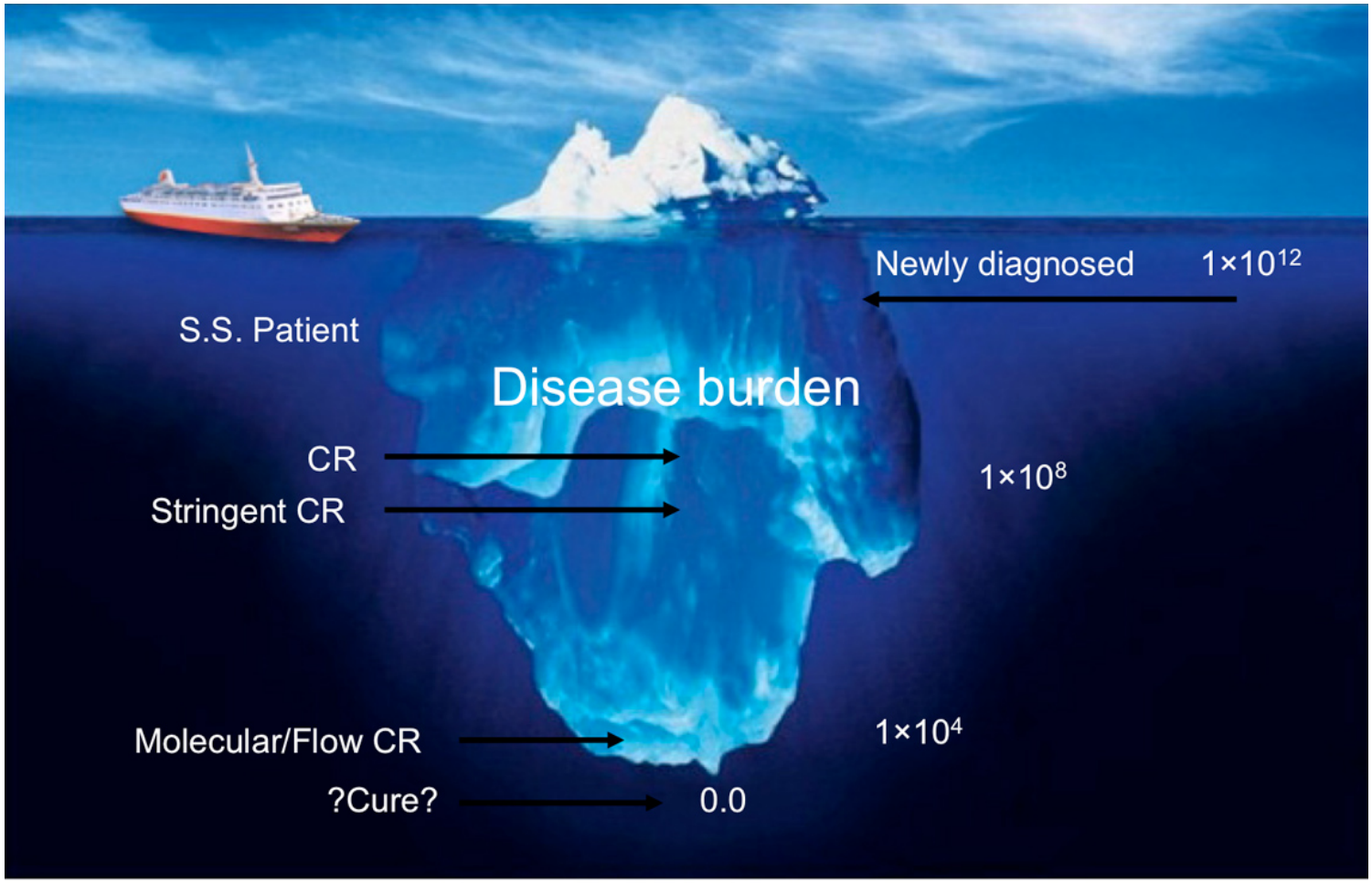
The revolution in myeloma therapy engendered by the development of proteasome inhibitors and immune modulatory drugs has not only changed the natural history of the disease but also has led some investigators to adopt a "more is better" treatment goal whereby efforts are made at diagnosis to maximally drive down the tumor burden and keep it suppressed for as long as possible. Dr Sagar Lonial is among the champions of this concept, and last week I chatted with him to further clarify his vision of this paradigm and better understand how it applies to evolving clinical research, especially new data emerging at ASH.

Sagar Lonial, MD

The fundamental idea behind this strategy is perhaps not that much different than what has been hypothesized for many cancers in the past. As depicted by the innovative "iceberg" graphic (see below) that Sagar has been using in many of his recent presentations, the goal is either a diffuse large B-cell lymphoma-like cure or a much longer duration of freedom from disease progression.



Getting to Minimal Residual Disease (MRD). Lonial, S. Reprinted with permission.

Assays to assess MRD are critical to this type of clinical research, and interestingly, Dr Lonial believes that the approach may be far less relevant in the relapsed/refractory setting, where many more mutant tumor clones have developed. The concept of prolonged disease suppression with some type of maintenance is also part of this strategy, and like a number of investigators Sagar often uses a variation of RVD maintenance, particularly in patients with higher-risk tumors.

Many oncologists — myself included — carry a hard-learned skepticism of the "more is better" paradigm from prior research in other tumors, including metastatic breast cancer, where a classic ECOG trial run by Dr George Sledge demonstrated the same survival with combination chemotherapy versus sequential single agents, and an important and vocal segment of myeloma investigators — particularly Dr S Vincent Rajkumar and his Mayo Clinic colleagues — have supported less intensive and better tolerated treatment choices in patients at standard risk. Both groups are committed to cure as a goal, but there is disagreement about what this all means to current practice, and even Sagar believes that with the available therapies a very small fraction of patients might be cured, even functionally, and he is particularly focused on patients with MRD negativity by new flow cytometry techniques along with PET scan normalization.

At the last ASCO meeting, Dr Lonial co-chaired the oral myeloma session and discussed several major up-front trials within the context of the iceberg model.

We found his take on the issue to be quite provocative and as such attempted to recreate the format for the first issue of our annual post-ASH roundup. Here is his bottom line on the most noteworthy related oral papers from New Orleans mixed with Dr Lonial's perspectives:

1. FIRST trial (Phase III): MPT versus 18 months of lenalidomide/low-dose dexamethasone versus continuous Rd until disease progression in transplant-ineligible patients

Perhaps the most visible myeloma story out of ASH was this **largely European trial** that was afforded plenary status because in many parts of the world (unlike the US) where MPT is now utilized, this study will likely establish a new standard treatment as these data demonstrate superior PFS and OS in favor of continuous Rd versus MPT. However, perhaps even more relevant was the 38% statistically significant improvement in time to progression (32.5 versus 21.9 months) for continuous Rd as opposed to 18 months, though it may be too early to evaluate OS. This long-term treatment strategy is in keeping with (and may ultimately provide support for) Dr Lonial's notion to proactively attempt to delay disease progression.

2. Other trials of up-front management

Not surprisingly, **Dr Antonio Palumbo** was again on stage at ASH presenting yet another Phase III trial of up-front treatment, this time evaluating Rd versus MPR versus cyclophosphamide/ prednisone/lenalidomide (CyPR) in elderly

patients not eligible for transplant. Building off the FIRST trial, all 3 arms of this effort yielded comparable disease-related outcomes in terms of PFS and overall response rates. Of note, patients receiving melphalan experienced more treatment-related toxicity than those receiving cyclophosphamide, and Dr Lonial sees this as one more reason that in myeloma the end may be near for melphalan.

Another important up-front trial — **HOVON-65/GMMG-HD4** — reported more follow-up at ASH. This study, which had previously demonstrated an advantage to bortezomib with doxorubicin/dex induction therapy followed by bortezomib maintenance versus vincristine with doxorubicin/dex followed by thalidomide maintenance, continues to yield a PFS and OS benefit for the bortezomib-based regimen, and the update provides further support for the use of this proteasome inhibitor in patients with renal failure and adverse risk factors. The study used a bortezomib maintenance schedule of 1 dose every other week for 2 years, but Dr Lonial notes that subcutaneous maintenance bortezomib may be even more patient friendly, and oral proteasome inhibitors such as ixazomib and oprozomib might further facilitate this strategy.

Finally, a paper by **Mateos et al** investigated the novel induction strategy of alternating Rd with VMP in elderly patients. Although Dr Mateos and her colleagues conclude that the alternating scheme is superior in efficacy versus the sequential approach, it is difficult to compare this regimen to the 3- and 4-drug combinations currently used in practice. In keeping with his intent to achieve rapid and deep responses even in older patients (with tolerable regimens), Dr Lonial favors the combination approach.

3. More data on lenalidomide maintenance

Of the 3 major Phase III trials of len maintenance, two — CALGB-100104 and the Italian MM-015 study — have demonstrated a survival benefit, and this led to a major shift in US practice. However, the **third study** from the French IFM group (IFM 2005-02), which was updated at ASH, continues to show a substantial PFS benefit without improvement in OS. In discussing this data set, Dr Lonial noted that part of this discrepancy may be related to the IFM 2005-02 trial's design, in which all patients received 2 months of post-transplant lenalidomide consolidation, including those randomly assigned to "no maintenance." Another critical difference is that the IFM stopped len maintenance treatment at 2 years as opposed to indefinite therapy until disease progression/toxicity in the other 2 studies.

Also at ASH we saw findings from a **meta-analysis** of lenalidomide maintenance, demonstrating a PFS and OS benefit. However, Dr Lonial found it difficult to dissect out the relevance of this data set because it included patients who did and did not receive a transplant. The study did, however, provide some additional insight about the incidence of second primary cancers, which to this point appears to be mainly a modest risk of hematologic neoplasms, including AML and MDS.

Although the "more is better" investigators have focused on current regimens with approved agents, it is likely that completely different classes of drugs will

be required to melt away substantially more of the iceberg, and in another myeloma issue in this series we will attempt to pick out the agents farthest along in this desperate race, including monoclonal antibodies and filanesib — a fascinating kinesin spindle protein inhibitor reported at ASH by Dr Lonial's group to cause responses (as a single agent and with low-dose dex) in patients refractory to conventional agents. Next on this series, an ASH CML update including the current status of ponatinib.

Neil Love, MD
Research To Practice
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Initial Phase 3 Results of the First (Frontline Investigation of Lenalidomide + Dexamethasone versus Standard Thalidomide) Trial (MM-020/IFM 07 01) in Newly Diagnosed Multiple Myeloma (NDMM) Patients (Pts) Ineligible for Stem Cell Transplantation (SCT)

Facon T et al.

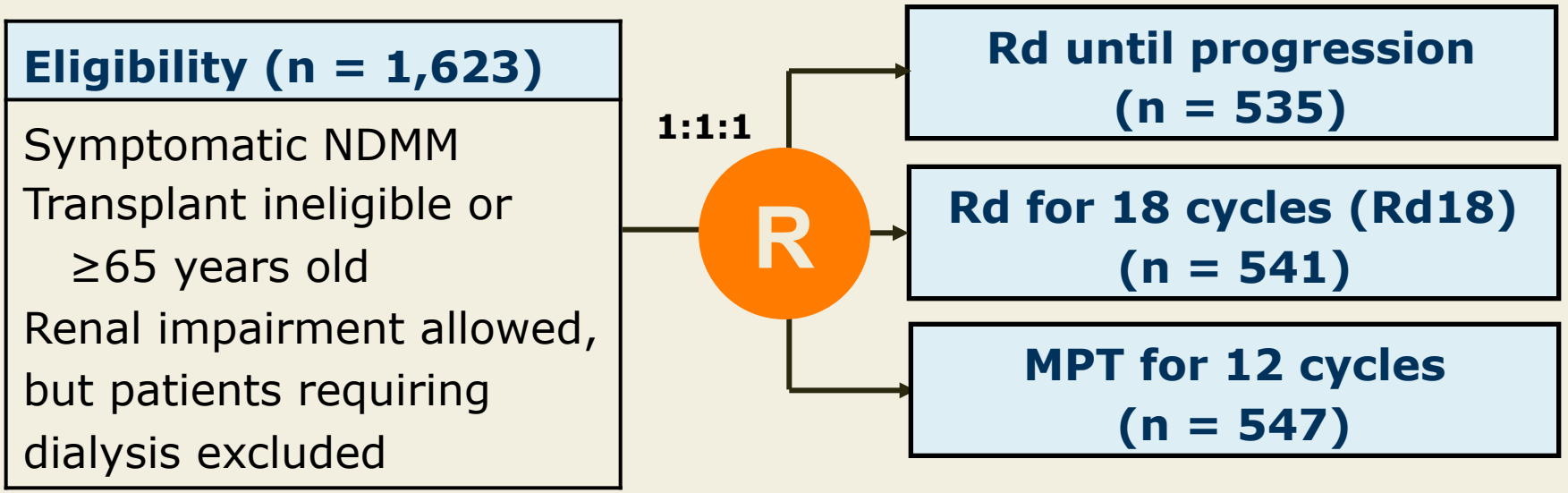
Proc ASH 2013;Abstract 2.

Background

- Melphalan/prednisone/thalidomide (MPT) is a standard therapy for patients with newly diagnosed multiple myeloma (NDMM).
  - MPT demonstrated a statistically significant advantage in overall survival (OS) and progression-free survival (PFS) compared to MP (*Blood* 2011;118(5):1239).
- The combination of lenalidomide (R) with low-dose dexamethasone increased OS with reduced toxic effects compared to R in combination with high-dose dexamethasone in NDMM (*Lancet Oncol* 2010;11(1):29).
- **Study objective:** To determine the efficacy and safety of R in combination with low-dose dexamethasone (Rd) compared to MPT in transplant-ineligible patients with NDMM.

Facon T et al. *Proc ASH* 2013;Abstract 2.

Phase III FIRST Trial Design



R: 25 mg d1-21, every 4 weeks

d: 40 mg d1, 8, 15, 22, every 4 weeks

M: 0.25 mg/kg d1-4, every 6 weeks

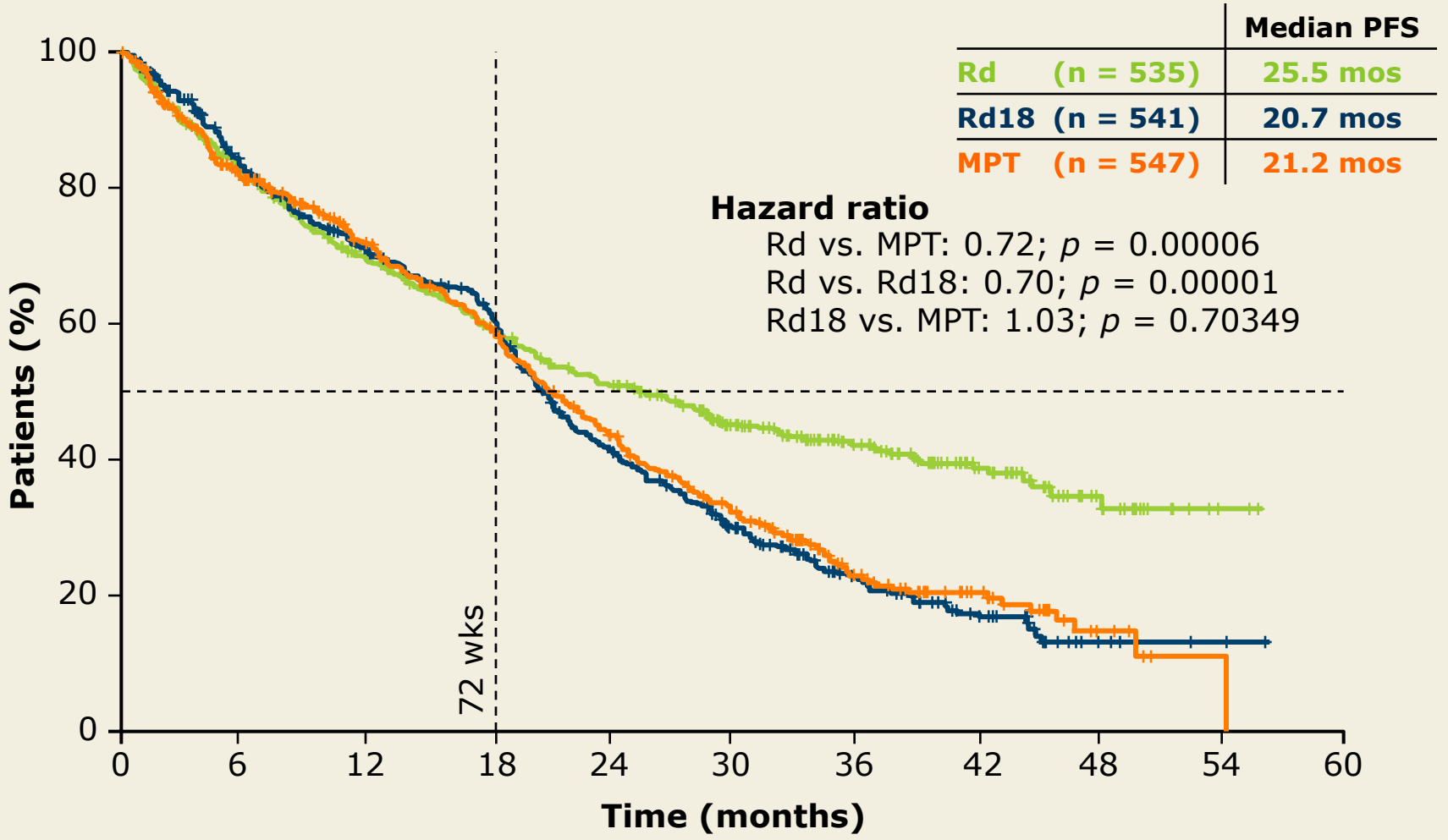
P: 2 mg/kg d1-4, every 6 weeks

T: 200 mg d1-42, every 6 weeks

- **Primary endpoint:** PFS
- Patients were stratified by age, country and ISS stage.

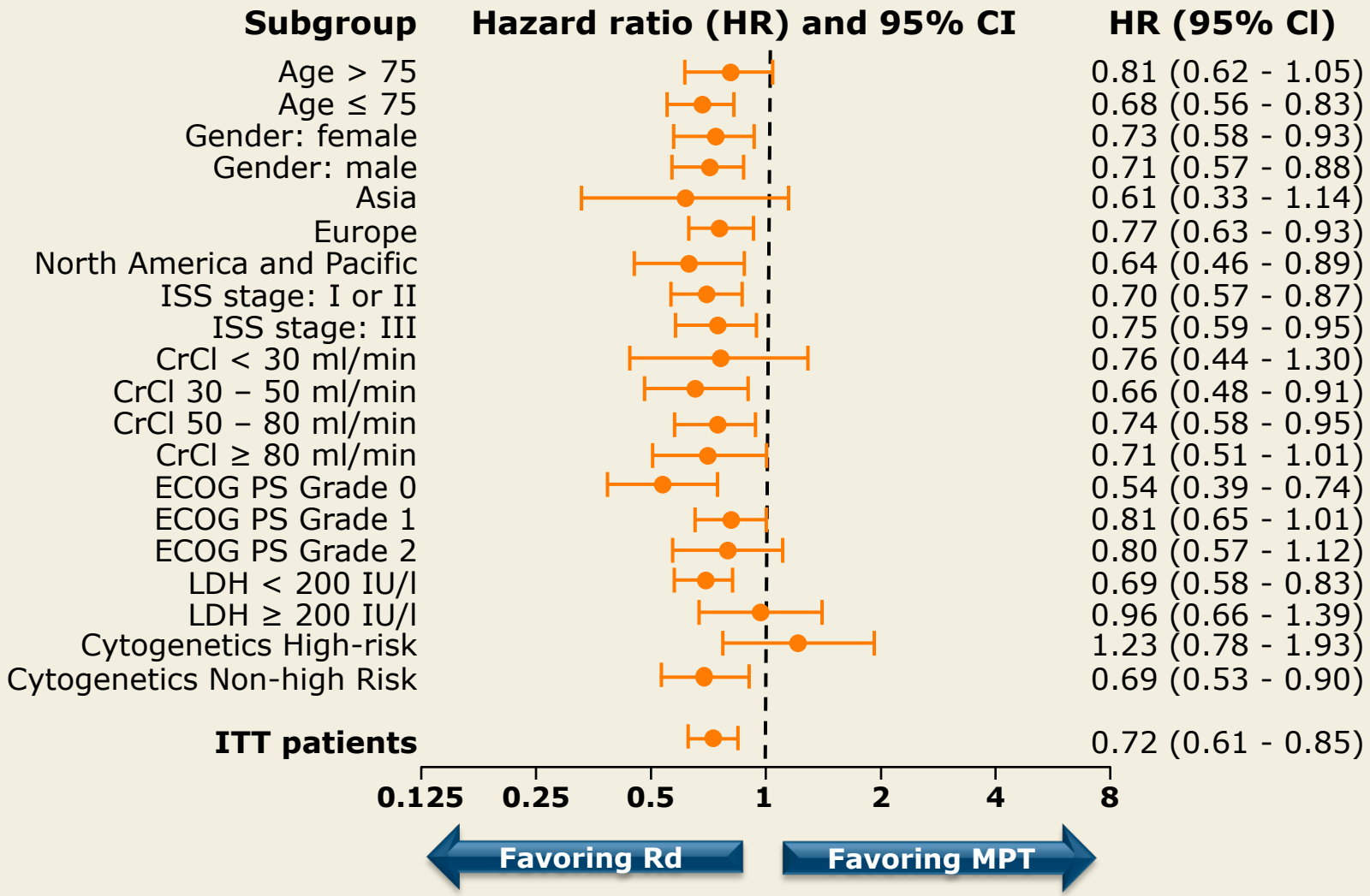
Facon T et al. *Proc ASH* 2013;Abstract 2.

PFS: Intention-to-Treat (ITT) Population



With permission from Facon T et al. *Proc ASH* 2013;Abstract 2.

PFS According to Subgroup



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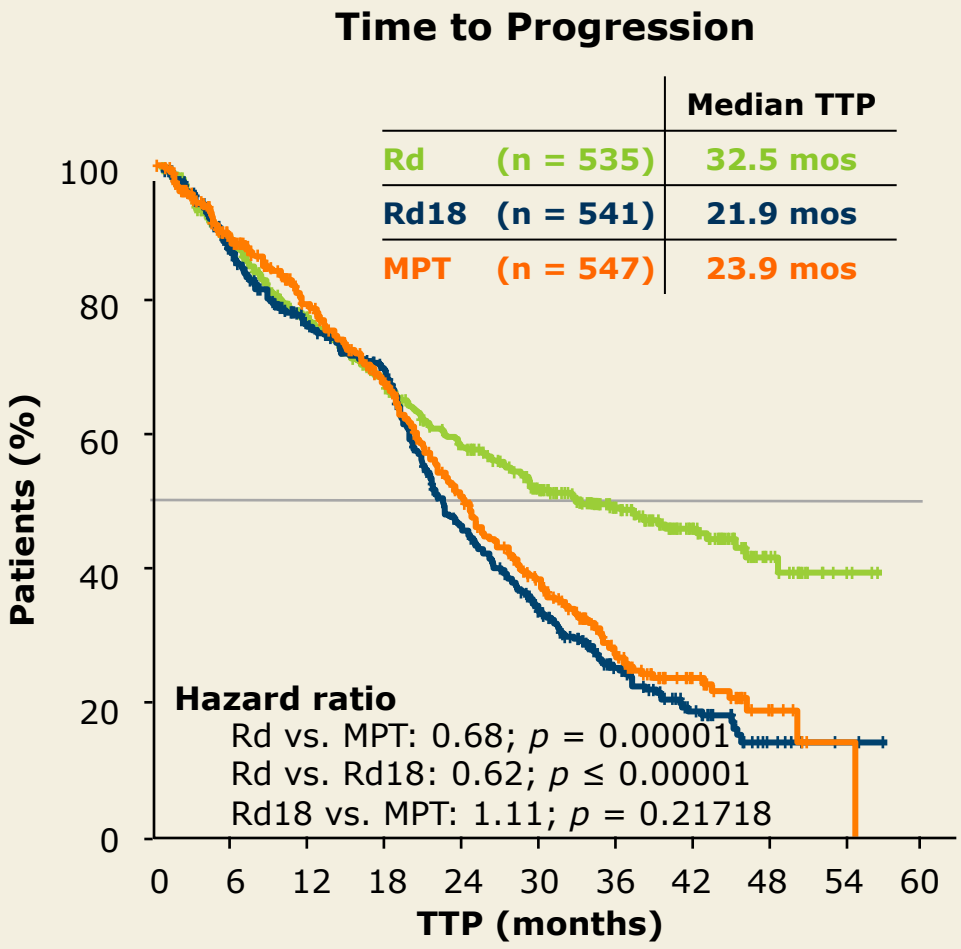
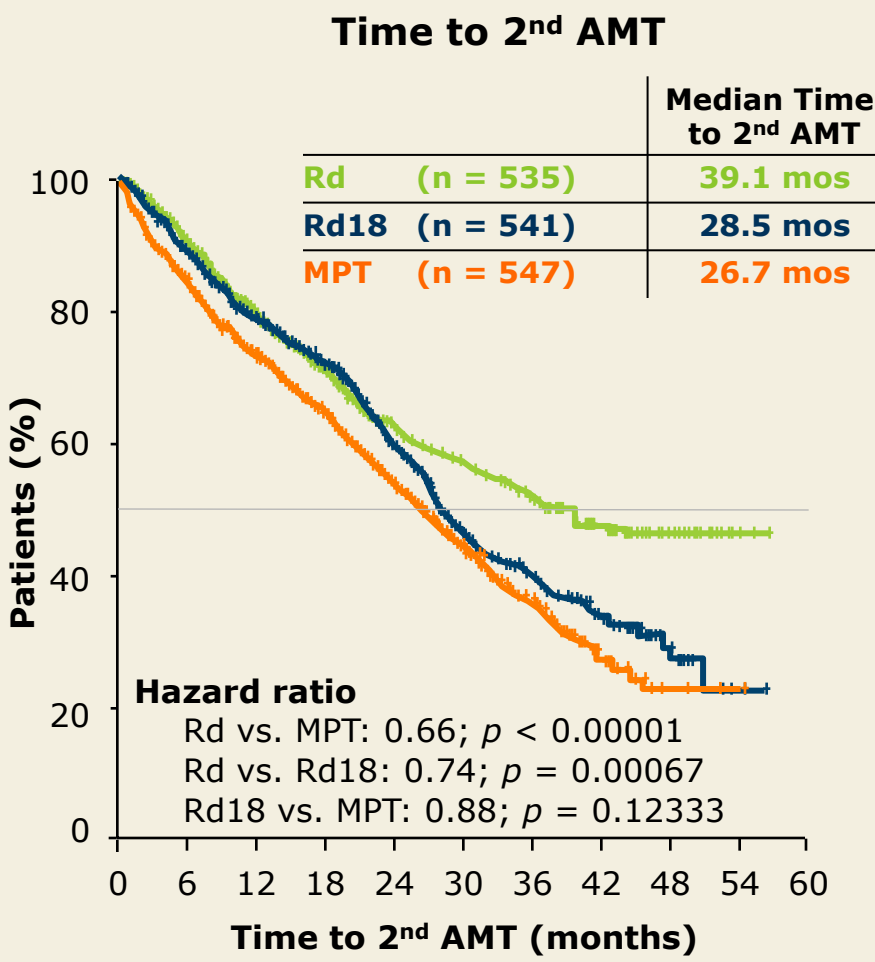
Time to Progression and Time to Second Antimyeloma Therapy (AMT)





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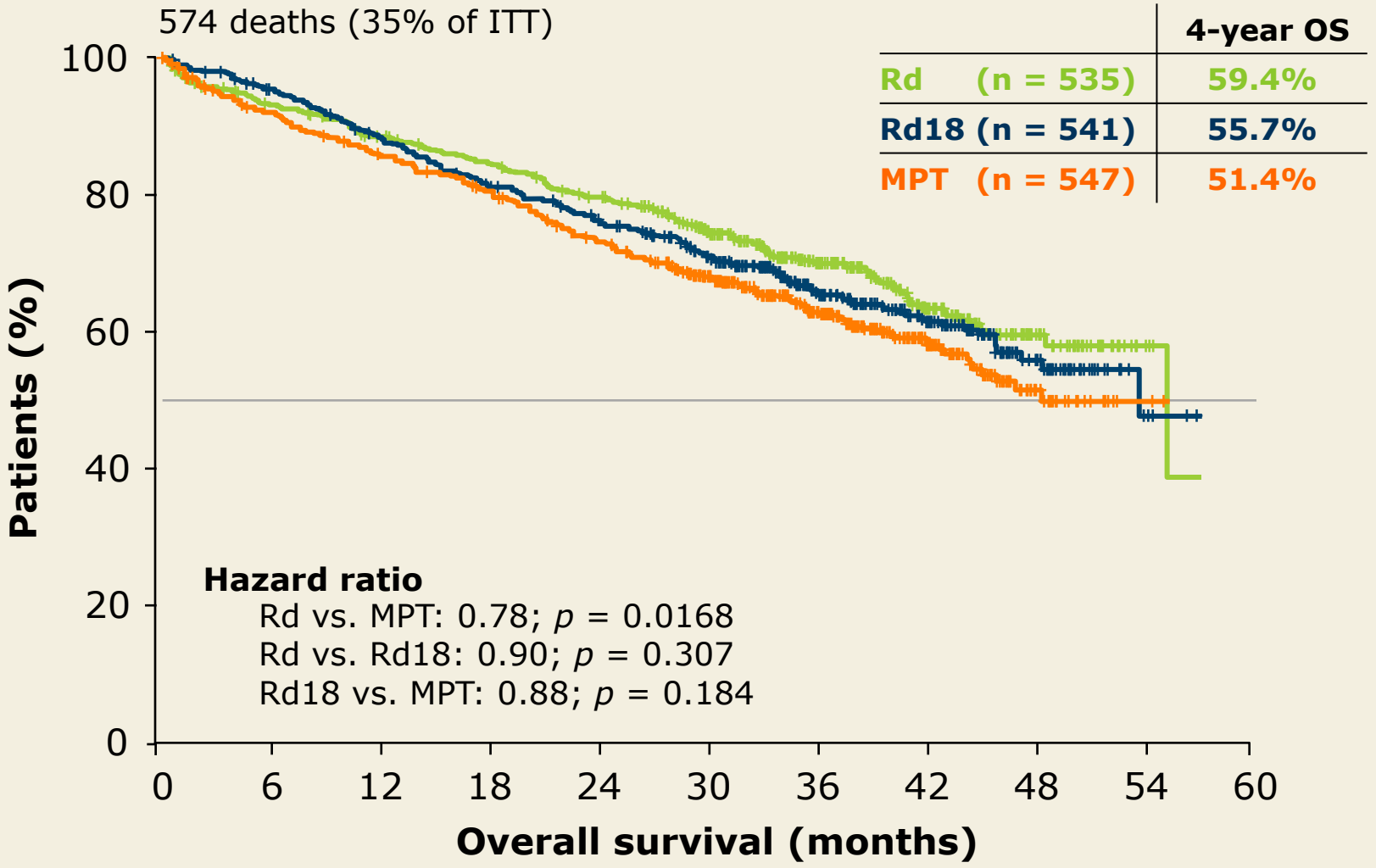
Interim Analysis of OS



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Response Rates

Response	Continuous Rd (n = 535)	Rd18 (n = 541)	MPT (n = 547)
Overall response rate	75.1%	73.4%	62.3%
Complete response	15.1%	14.2%	9.3%
Very good partial response	28.4%	28.5%	18.8%
Partial response	31.6%	30.7%	34.2%
Stable disease	18.9%	20.5%	26.5%

- Time to response: 1.8 mo (continuous Rd); 1.8 mo (Rd18); 2.8 mo (MPT)
- Duration of response: 35.0 mo (continuous Rd); 22.1 mo (Rd18); 22.3 mo (MPT)

Facon T et al. *Proc ASH* 2013;Abstract 2.

Select Adverse Events

Grade 3/4	Continuous Rd (n = 532)	Rd18 (n = 540)	MPT (n = 541)
Anemia	18.2%	15.7%	18.9%
Neutropenia	27.8%	26.5%	44.9%
Thrombocytopenia	8.3%	8.0%	11.1%
Febrile neutropenia	1.1%	3.0%	2.6%
Infections	28.9%	21.9%	17.2%
Pneumonia	8.1%	8.3%	5.7%
DVT and/or PE	7.9%	5.6%	5.4%
Cataract	5.8%	2.6%	0.6%

DVT = deep vein thrombosis; PE = pulmonary embolism

Facon T et al. *Proc ASH* 2013;Abstract 2.

Incidence of Second Primary Malignancy (SPM)

Malignancy, n (%)	Continuous Rd (n = 532)	Rd18 (n = 540)	MPT (n = 541)
AML	1 (0.2%)	1 (0.2%)	4 (0.7%)
MDS	1 (0.2%)	1 (0.2%)	6 (1.1%)
MDS to AML	0 (0%)	0 (0%)	2 (0.4%)
B-cell	0 (0%)	0 (0%)	0 (0%)
Solid tumors	15 (2.8%)	29 (5.4%)	15 (2.8%)
Invasive SPM	17 (3.2%)	30 (5.6%)	27 (5.0%)
Pts with ≥1 noninvasive, nonmyeloma skin cancer	22 (4.1%)	17 (3.1%)	21 (3.9%)

AML = acute myeloid leukemia; MDS = myelodysplastic syndromes

Facon T et al. *Proc ASH* 2013;Abstract 2.

Author Conclusions

- Continuous administration of Rd significantly extended PFS, with an OS benefit in comparison to MPT.
  - PFS results:
    - Hazard ratio = 0.72; p = 0.00006
    - Consistent benefit across most patient subgroups
    - Continuous Rd was better than Rd18
      - Hazard ratio = 0.70; p = 0.00001
  - Planned interim OS results:
    - Hazard ratio = 0.78; p = 0.0168
    - Rd was superior to MPT across all efficacy secondary endpoints.
- The safety profile with continuous Rd was manageable.
- In transplant-ineligible patients with NDMM, the FIRST trial establishes continuous Rd as a new standard.

Facon T et al. *Proc ASH* 2013;Abstract 2.

FIRST: A Phase III Trial of Continuous Rd versus Rd18 versus MPT for Patients with NDMM

Two questions were being asked: Is Rd better than MPT, and does continuous therapy improve the benefit of Rd over MPT? In terms of PFS, OS and time to second antimyeloma therapy, continuous Rd is clearly the winner. The time to progression (TTP) curve is similar for MPT and Rd when they are administered for equal durations. The SPM rate was lower with continuous Rd than in the other 2 groups. These data support the importance of continuous therapy in multiple myeloma whether patients are older, as in this trial, or younger, as in the post-transplant period. In terms of OS, it is important that continuous Rd was statistically different from MPT but not from Rd18. The difference in TTP between continuous Rd and Rd18 is big. I believe that the only way for a big OS difference to occur in an induction trial is if 1 of the arms is inferior, because patients are living so long.

We probably don’t have enough follow-up yet to see a difference in survival between continuous Rd and Rd18. Clearly Rd is better than MPT, and one wouldn’t administer MPT for longer than the duration used in this trial. The biggest issue regarding this study is that few US physicians administer MPT. It’s hard to understand what the extrapolation of this data is for similar patients in the United States.

Interview with Sagar Lonial, MD, January 22, 2014

A Randomized Phase 3 Trial of Melphalan-Lenalidomide-Prednisone (MPR) or Cyclophosphamide-Prednisone-Lenalidomide (CPR) vs Lenalidomide plus Dexamethasone (Rd) in Elderly Newly Diagnosed Multiple Myeloma Patients

Palumbo A et al.

Proc ASH 2013;Abstract 536.

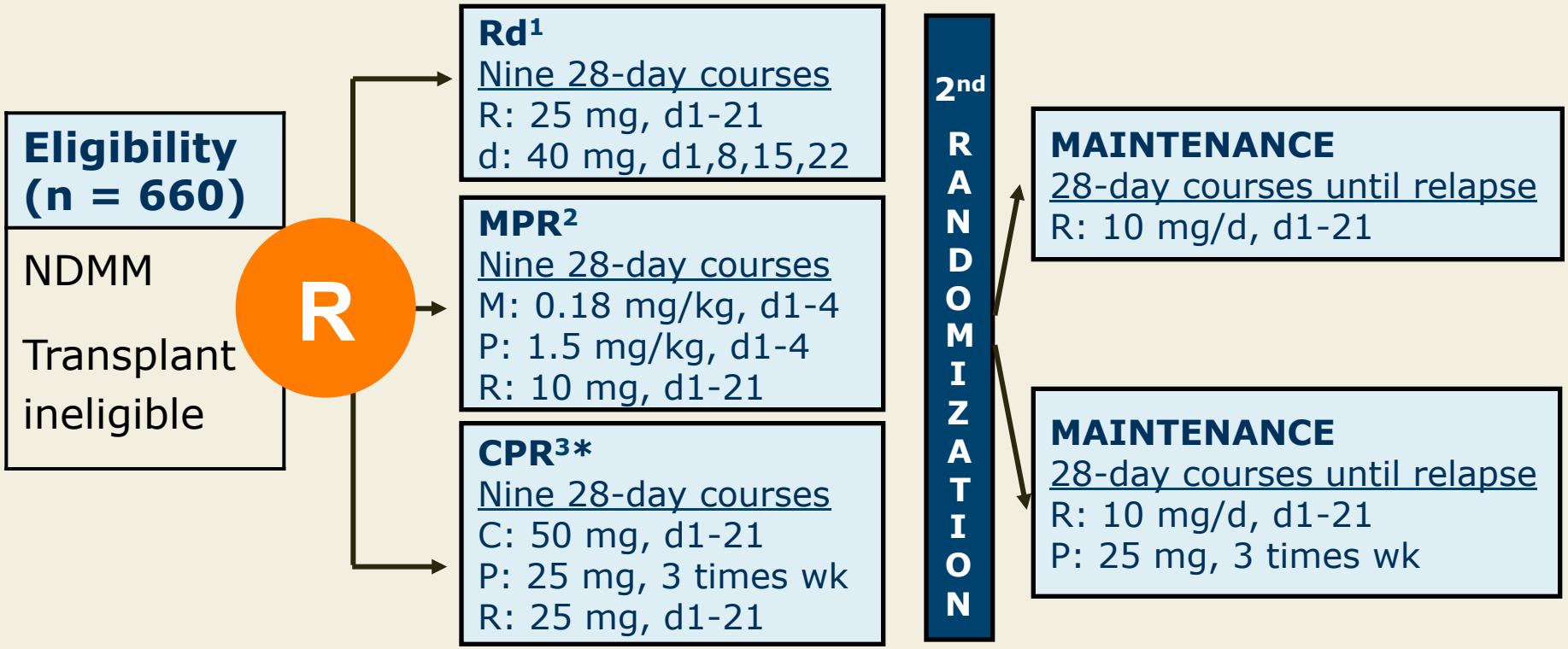
Background

- Rd and MPR are effective treatments for patients with newly diagnosed multiple myeloma (NDMM).
- Lenalidomide-based therapies involving 3-drug combinations have reported greater efficacy — complete response (CR) rates and median progression-free survival (PFS) — compared to 2-drug combinations for patients with NDMM (*Lancet Oncol* 2010;11(1):29; *N Engl J Med* 2012;366(19): 1759; *Am J Hematol* 2011;86(8):640).
- Rates of hematologic toxicities are greater with such regimens including melphalan.

- **Study objective:** To compare the efficacy and safety of a nonalkylating agent-containing regimen (Rd) to that of alkylating agent-containing regimens (MPR/CPR) in elderly transplant-ineligible patients with NDMM.

Palumbo A et al. *Proc ASH* 2013;Abstract 536.

Phase III Study Design



>75 years: [1] Dexamethasone 20 mg/wk; [2] Melphalan 0.13 mg/kg; [3] Cyclophosphamide: 50 mg qod, d1-21

* 59 patients on the CPR arm received a lower dose of lenalidomide (10 mg) and cyclophosphamide (50 mg eod)

Palumbo A et al. *Proc ASH* 2013;Abstract 536.

Patient Characteristics

	CPR (n = 222)	MPR (n = 217)	Rd (n = 220)
Median age, years (range)	73 (64-87)	74 (63-81)	73 (50-89)
>75 years	36%	40%	38%
ISS stage			
I	27%	28%	28%
II	46%	45%	45%
III	27%	27%	27%
Chromosome abnormalities			
t(4;14) or t(14;16) or del 17	22%	24%	25%
Frailty*			
Fit	44%	41%	44%
Unfit	32%	36%	26%
Frail	24%	23%	30%

* Frailty defined according to age (<75/75-80/>80 years), Charlson score (≤1/≥2), ADL (>4/≤4) and IADL indices (>5/≤5)

Palumbo A et al. *Proc ASH* 2013;Abstract 536.

Best Response Rate

	CPR (n = 220)	MPR (n = 210)	Rd (n = 211)
Complete response	5%	12%	8%
≥Very good partial response	25%	29%	32%
≥Partial response	72%	73%	74%

Palumbo A et al. *Proc ASH* 2013;Abstract 536.

Survival

Overall survival	CPR	MPR	Rd
2-year overall survival	84%	81%	80%

Rd vs MPR: HR = 0.954; p = 0.82
Rd vs CPR: HR = 1.033; p = 0.88

PFS	CPR	MPR	Rd
2-year PFS	50%	54%	48%
Median PFS*	24 mo	27 mo	22 mo

* Rd vs MPR: HR = 1.189; p = 0.20
Rd vs CPR: HR = 1.032; p = 0.81

Median follow-up = 26 months

Palumbo A et al. *Proc ASH* 2013;Abstract 536.

Survival: Age ≤75 Years

Overall survival	Hazard ratio	*p*-value
Rd versus MPR	1.285	0.42
Rd versus CPR	1.125	0.69

PFS	Hazard ratio	*p*-value
Rd versus MPR	1.38	0.07
Rd versus CPR	1.08	0.64

Palumbo A et al. *Proc ASH* 2013;Abstract 536.

Survival: Age >75 Years

Overall survival	Hazard ratio	*p*-value
Rd versus MPR	0.954	0.82
Rd versus CPR	1.033	0.88

PFS	Hazard ratio	*p*-value
Rd versus MPR	1.189	0.20
Rd versus CPR	1.032	0.81

Palumbo A et al. *Proc ASH* 2013;Abstract 536.

Select Grade 3-4 Adverse Events (AEs)

	CPR	MPR	Rd
Neutropenia	28%	65%	25%
Thrombocytopenia	9%	18%	7%
Infection	7%	12%	9%
Second primary malignancy (SPM)	1%	3%	1%

- Incidence of Grades 3 and 4 anemia and peripheral neuropathy was highest in the MPR arm
- Discontinuation due to AEs: CPR (16%); MPR (23%); Rd (15%)
- Dose reduction of lenalidomide or alkylating agent was most frequent in the MPR arm

Palumbo A et al. *Proc ASH* 2013;Abstract 536.

Author Conclusions

- In this community-based population of elderly patients with NDMM there were no major differences among response rates and long-term outcomes among the 3 treatment arms.
- Toxicities were more prominent with the combination containing melphalan, including:
  - Higher rates of SPM
  - Higher rates of discontinuation due to AE
- Among the CPR and Rd combinations there were no significant differences with regard to hematologic toxicities or infection.
- Rd is probably the well-defined treatment for all elderly patients with NDMM.
- Combination therapy with cyclophosphamide can be considered for fit elderly transplant-ineligible patients with NDMM.

Palumbo A et al. *Proc ASH* 2013;Abstract 536.

Investigator Commentary: A Randomized Phase III Trial of MPR or CPR versus Rd for Elderly Patients with NDMM

If you evaluate the 3 arms on this trial, the overall response rates and median PFS were essentially equivalent. So if you had to pick a "winner," it would be the Rd regimen because it is easier on the patients than either of the 3-drug regimens evaluated on this trial. However, if the patient needs an alkylating agent, cyclophosphamide is preferable to melphalan because we saw fewer AEs overall and fewer hematologic toxicities with cyclophosphamide.

I believe this report to be yet another piece of evidence that it's the beginning of the end for melphalan, which is currently used much less commonly in the United States than in Europe, where it is used almost exclusively for older patients. At any rate, the take-home message from this trial is that if you need to use an alkylator, use cyclophosphamide rather than melphalan.

Interview with Sagar Lonial, MD, January 22, 2014

Bortezomib Induction and Maintenance Treatment Improves Survival in Patients with Newly Diagnosed Multiple Myeloma: Extended Follow-Up of the HOVON-65/GMMG-HD4 Trial

Sonneveld P et al.

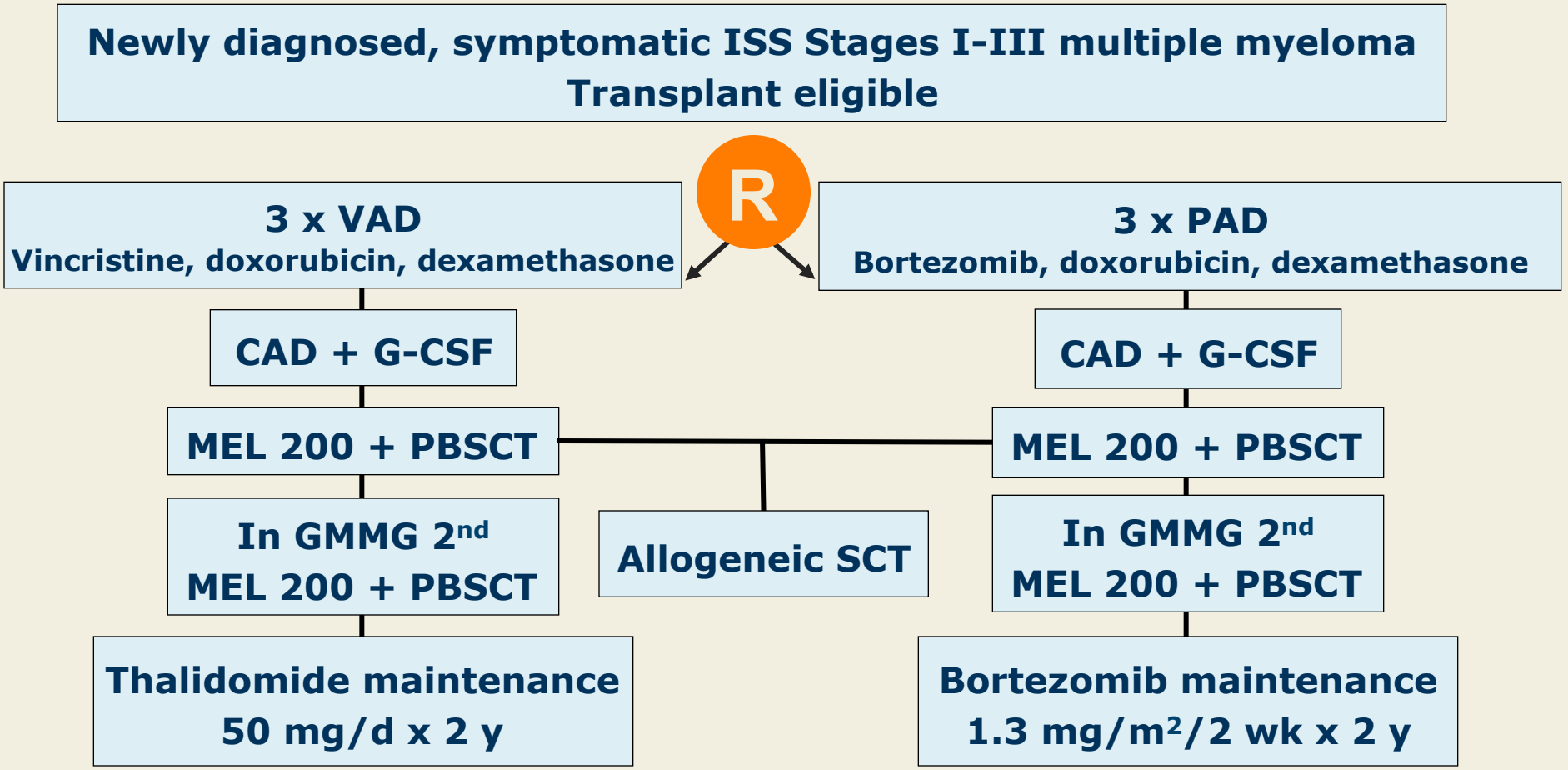
Proc ASH 2013;Abstract 404.

Background

- HOVON and GMMG performed a randomized, Phase III study from 2005 to 2008 to assess the efficacy of bortezomib as induction treatment prior to high-dose therapy and to compare bortezomib maintenance to thalidomide maintenance.
  - Higher CR and significantly improved PFS and OS with bortezomib-based treatment (*JCO* 2012;30(24):2946)
  - Superior PFS and OS with bortezomib in high-risk subgroups with renal failure and/or del17p (*Haematologica* 2014;99(1):148)
- Meta-analysis of 4 Phase III trials comparing bortezomib- to nonbortezomib-based induction treatment confirmed superior outcomes (*JCO* 2013;31(26):3279).
- **Objectives:** To present extended, updated results of the study.

Sonneveld P et al. *Proc ASH* 2013;Abstract 404.

Phase III HOVON-65/GMMG-HD4 Trial Design



PBSCT = peripheral blood stem cell transplantation; CAD = cyclophosphamide, doxorubicin, dexamethasone

Sonneveld P et al. *Proc ASH* 2013;Abstract 404.

Response

Response	VAD	PAD	*p*-value
After induction			
CR/nCR	5%	11%	0.002
≥VGPR	15%	42%	<0.001
≥PR	55%	78%	<0.001
After high-dose melphalan 1 (HDM 1)			
CR/nCR	15%	30%	<0.001
≥VGPR	36%	61%	<0.001
≥PR	77%	88%	<0.001
Best response			
CR/nCR	35%	49%	<0.001
≥VGPR	56%	75%	0.001
≥PR	83%	90%	0.003

Sonneveld P et al. *Proc ASH* 2013;Abstract 404.

Reasons for Discontinuing Maintenance Therapy

	Thalidomide	Bortezomib
Started maintenance therapy	n = 271	n = 227
Toxicity	30%	11%
Progression/relapse	33%	35%
Normal completion	28%	48%

Sonneveld P et al. *Proc ASH* 2013;Abstract 404.

Survival Analyses (N = 827)

	PAD vs VAD Hazard ratio	*p*-value
PFS (multivariate analysis)*	0.76	0.001
By renal failure (serum creatinine ≥2 mg/dL)*	0.44	0.003
From start of maintenance	Not reported	NS
OS (multivariate analysis)*	0.78	0.027
By renal failure (serum creatinine ≥2 mg/dL)*	0.38	<0.001
From start of maintenance*	0.71	0.035

NS = not significant

* PAD was superior to VAD

- Multivariate analysis of the study group effect of single HDM (HOVON) vs double HDM (GMMG) with ASCT indicated that double HDM was not superior across treatment arms for PFS but remained superior for OS (HR = 0.72; $p = 0.004$).
  - OS for single vs double ASCT is improved only for ISS 1 disease ($p = 0.02$).

Sonneveld P et al. *Proc ASH* 2013;Abstract 404.

Second Primary Malignancy

Event (n)	VAD/thalidomide (n = 414)	PAD/bortezomib (n = 413)
AML/MDS	4	1
Lymphoma	5	2
Solid cancer	8	10
Skin cancer	3	3
PCL	3	1
Total	23	17
	HR = 0.68, *p* = NS	

AML = acute myeloid leukemia; MDS = myelodysplastic syndromes;
PCL = plasma cell leukemia

Sonneveld P et al. *Proc ASH* 2013;Abstract 404.

Author Conclusions

- Bortezomib-based treatment consistently improves PFS (median 27 mo vs 36 mo) and OS (median 84 mo vs not reached, $p = 0.05$) in patients with transplant-eligible newly diagnosed multiple myeloma (data not shown).
- Bortezomib significantly improves the long-term outcome of patients presenting with renal failure ($p < 0.001$).
- Double high-dose therapy and ASCT improves PFS and OS in patients with ISS I newly diagnosed multiple myeloma in the era of novel agents.
- Bortezomib improves outcomes in patients with intermediate/poor risk based on FISH/ISS (data not shown).
- No increased risk of second primary malignancies was observed.

Sonneveld P et al. *Proc ASH* 2013;Abstract 404.

Investigator Commentary: Extended Follow-Up of the HOVON-65/ GMMG-HD4 Trial — Bortezomib Induction and Maintenance Treatment Improves Survival in Patients with Newly Diagnosed Multiple Myeloma

The randomization for this study was VAD followed by transplant followed by thalidomide maintenance versus PAD followed by transplant followed by bortezomib maintenance. This study provided longer follow-up results of the previously published Phase III trial. That is important for a couple of reasons. With longer follow-up, the study continues to demonstrate a survival benefit for patients who received bortezomib maintenance on a schedule of 1 dose every other week for 2 years.

A clear PFS benefit was also seen in patients with high-risk disease. Now that bortezomib can be administered subcutaneously, this becomes a practical approach to administering maintenance bortezomib in the post-transplant setting.

This study is important for patients with disease considered to be proteasome inhibitor sensitive, and these data provide us with a way to administer bortezomib maintenance and indicate that we're offering patients a benefit with this approach.

Interview with Sagar Lonial, MD, January 22, 2014

Comparison of Sequential vs Alternating Administration of Bortezomib, Melphalan and Prednisone (VMP) and Lenalidomide plus Dexamethasone (Rd) in Elderly Patients with Newly Diagnosed Multiple Myeloma (MM): GEM2010MAS65 Trial

Mateos MV et al.

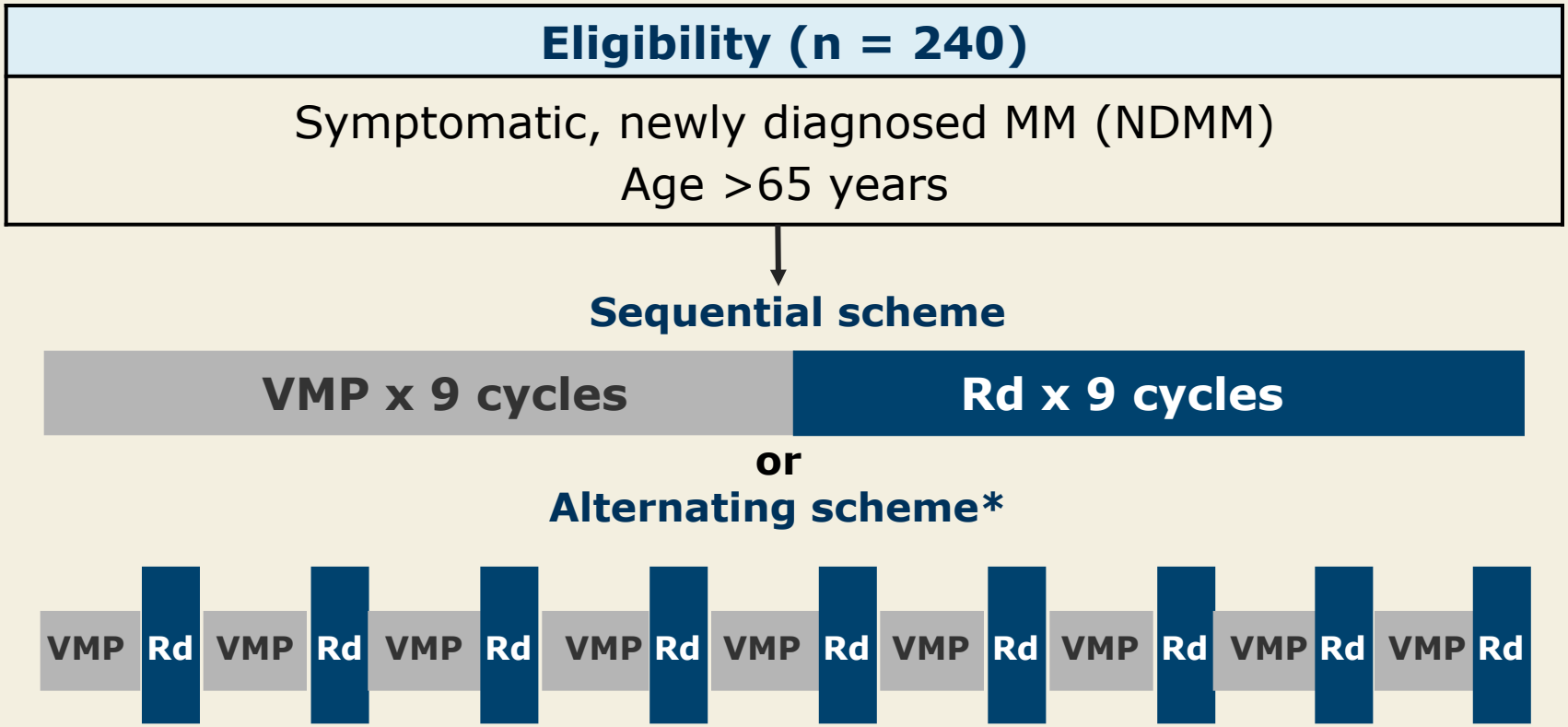
Proc ASH 2013;Abstract 403.

Background

- Two of the most efficient regimens for the treatment of newly diagnosed MM in elderly patients are bortezomib/melphalan/prednisone (VMP) and lenalidomide/low-dose dexamethasone (Rd) (*JCO* 2013;31(4):448; *Proc ASH* 2013;Abstract 2).
  - To further improve outcomes in this patient population, a possibility would be the simultaneous administration of all drugs in these regimens, but this may result in high toxicities.
  - The administration of VMP and Rd in a sequential or alternating manner could improve outcomes with acceptable toxicity.
- **Study objective:** To compare the efficacy and safety of VMP and Rd when administered in a sequential versus alternating manner in elderly patients with newly diagnosed MM.

Mateos MV et al. *Proc ASH* 2013;Abstract 403.

GEM2010MAS65 Phase II Trial Design



* Half of the patients start with VMP and half with Rd.

- Treatment duration: 74 weeks

Mateos MV et al. *Proc ASH* 2013;Abstract 403.

Response Rates After 9 Cycles

	Sequential (n = 86)	Alternating VMP and Rd (n = 86)
Overall response rate (ORR)	89%	93%
Stringent CR (sCR)	5%	11%
Complete response (CR)	21%	30%
Very good PR (VGPR)	30%	37%
Partial response (PR)	33%	15%
Stable disease (SD)	6%	5%
Progressive disease	5%	0%

- Significant differences between the sequential and alternating arms in the rate of sCR/CR/VGPR (p = 0.004) and the rate of sCR/CR (p = 0.02)
- No significant difference between VMP → Rd and Rd → VMP

Mateos MV et al. *Proc ASH* 2013;Abstract 403.

Response Rates in the Intention-to-Treat Population*

	Sequential (n = 117)	Alternating (n = 114)
ORR	89%	94%
sCR	12%	22%
CR	27%	24%
VGPR	21%	23%
PR	29%	25%
SD	7%	4%
Not evaluable	4%	2%

* After a median of 13 cycles (range: 1-18)

- Sequential vs alternating arms, sCR/CR/VGPR (p = 0.1); sCR/CR (p = 0.2)
- 33% of patients in CR in each arm achieved immunophenotypic CR
- No significant difference between VMP → Rd and Rd → VMP

Mateos MV et al. *Proc ASH* 2013;Abstract 403.

Efficacy According to Cytogenetic Abnormalities

	Standard risk		High risk	
	Sequential (n = 77)	Alternating (n = 83)	Sequential (n = 19)	Alternating (n = 14)
sCR/CR	40%	44%	47%	42%
VGPR	18%	13%	37%	28%
PR	31%	28%	11%	21%

High-risk cytogenetics: t(4;14), t(14;16), del17p

- No significant difference between the 2 alternating treatment arms

Mateos MV et al. *Proc ASH* 2013;Abstract 403.

Survival Rates at 20 Months

Survival outcome	Sequential	Alternating	
		VMP → Rd	Rd → VMP
PFS*	80%	92%	75%
OS*	88%	96%	88%
PFS by response	**Sequential†**	**Alternating†**	
sCR/CR	92%	96%	
≤VGPR	62%	78%	
OS by response	**Sequential†**	**Alternating**	
sCR/CR	100%	93%	
≤VGPR	80%	90%	

* No significant difference between arms; † Statistically significant difference between response types

- No PD in patients who achieved immunophenotypic CR

Mateos MV et al. *Proc ASH* 2013;Abstract 403.

Efficacy in Patients with Poor Prognostic Characteristics

Characteristic	sCR/CR	PFS at 20 months	OS at 20 months
Age <75 years	47%	88%	94%
Age ≥75 years	37%*	77%	84%†
ISS Stage I/II	42%	85%	93%
ISS Stage III	42%	84%	83%
No adverse cytogenetics	42%	84%	92%
t(4;14), t(14;16), 17p, 1q+	48%	87%	90%
t(4;14), t(14;16), 17p	45%	82%	82%

* CR rate in the sequential arm in patients <75 vs ≥75 years was 49% vs 29% (p = 0.01)

† A significant difference was observed in both sequential and alternating arms

Mateos MV et al. *Proc ASH* 2013;Abstract 403.

Select Grade 3/4 Adverse Events

Hematologic*	Sequential (n = 117)	Alternating (n = 114)
Anemia	2%	5%
Neutropenia	14%	24%
Thrombocytopenia	16%	20%
Nonhematologic*		
Infections	6%	7%
Skin rash	5%	4%
GI toxicity	6%	6%
Peripheral neuropathy	6%	3%
Deep vein thrombosis	2%	2%

* No significant different between arms

Mateos MV et al. *Proc ASH* 2013;Abstract 403.

Author Conclusions

- Therapeutic regimens including an alkylating agent, a proteasome inhibitor and an immunomodulatory agent, whether administered in a sequential or alternating approach, are effective and well tolerated by elderly patients.
- After 9 induction cycles, the alternating scheme is superior in efficacy, especially in terms of sCR/CR versus the sequential scheme, without additional toxic effects.
- Patients who achieve CR have a better outcome.
- The benefit of these combinations seems to be consistent in different risk groups, especially in patients with high-risk cytogenetic abnormalities.
- A longer follow-up period is required to evaluate the final benefit of the alternating versus sequential VMP and Rd schemes based on a total therapy approach for elderly patients with MM.

Mateos MV et al. *Proc ASH* 2013;Abstract 403.

Investigator Commentary: Efficacy and Safety of Sequential versus Alternating VMP and Rd for Elderly Patients with NDMM

This study was based on the hypothesis that administering VMP and Rd in an alternating scheme would result in higher efficacy because of earlier access to all the agents in both regimens.

In the sequential scheme, with disease that is more sensitive to an immunomodulatory drug (IMiD) than to a proteasome inhibitor, the effect of the IMiD would not be achieved until after 9 cycles of therapy. By alternating the regimens, exposure and response to the IMiD would occur earlier.

Alternating the regimens was undertaken in an effort to reduce toxicity. I usually take a more aggressive approach and would administer a combination of 3 or even 4 agents. The exception to using that approach is with patients who are frail and would not tolerate aggressive therapy.

Interview with Sagar Lonial, MD, January 22, 2014

Lenalidomide Maintenance After Stem-Cell Transplantation for Multiple Myeloma: Follow-Up Analysis of the IFM 2005-02 Trial

Attal M et al.

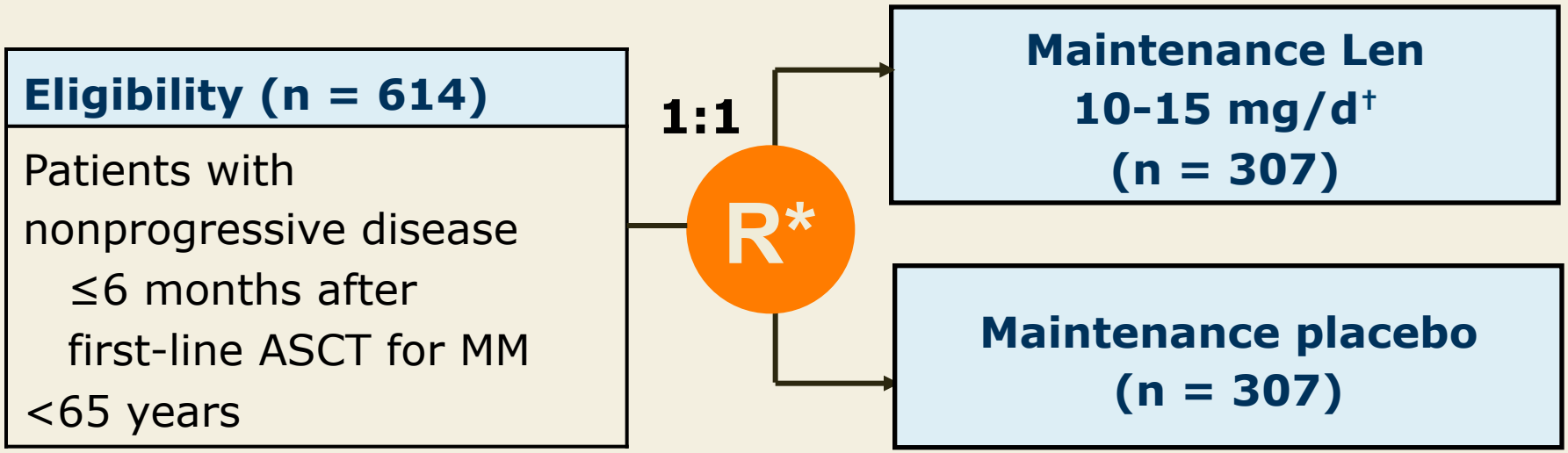
Proc ASH 2013;Abstract 406.

Background

- The IFM protocol for this study was designed to develop the role of lenalidomide (Len) as maintenance therapy after transplantation for patients with multiple myeloma (MM).
- Previously, results from the IFM 2005-02 trial, after a follow-up period of 45 months, demonstrated that Len maintenance (*NEJM* 2012;366(19):1782):
  - Significantly improved progression-free survival (PFS) without significant impact on overall survival (OS)
  - Increased rates of Grade 3/4 neutropenia, infections, deep vein thrombosis and second primary malignancies (SPMs)
- **Study objective:** To determine the efficacy and safety of Len maintenance therapy after first-line autologous stem cell transplantation (ASCT) for patients with MM after a longer follow-up period.

Attal M et al. *Proc ASH* 2013;Abstract 406.

Phase III IFM 2005-02 Trial Design



* All patients initially received consolidation therapy with Len (25 mg/d) on days 1-21 every 28 days for 2 months.

† 10 mg per day for the first 3 months, increased to 15 mg if tolerated

- Recruitment took place from July 2006 through August 2008.
- In January 2011 the Data and Safety Monitoring Board (DSMB) recommended the discontinuation of Len due to increased incidence of SPMs.
- **Primary endpoint:** PFS
- No patient on the placebo arm received Len before progression.

Attal M et al. *Proc ASH* 2013;Abstract 406; *N Engl J Med* 2012;366(19):1782-91.

Survival Results from Randomization

PFS	Len (n = 307)	Placebo (n = 307)	*p*-value
Median PFS	46 mo	24 mo	<0.001
5-year PFS	42%	18%	<0.0001
OS	**Len**	**Placebo**	***p*-value**
Median OS	82 mo	81 mo	0.80

- The median duration of Len maintenance therapy was 2 years.
- As of November 2013, the median follow-up was 77 months from diagnosis and 67 months from randomization.
- Discrepancy between PFS and OS remained:
  - Poor outcome after disease progression for patients on the Len maintenance group was a likely hypothesis.
  - In order to confirm this hypothesis, additional analyses were performed.

Attal M et al. *Proc ASH* 2013;Abstract 406.

Second PFS

	Placebo (n = 241)	Len (n = 165)	*p*-value
Median second PFS	24 mo	13 mo	<0.001

Attal M et al. *Proc ASH* 2013;Abstract 406.

Second PFS According to Treatment at First Progression

	Total (n = 614)	Placebo (n = 307)	Len (n = 307)
Patients experiencing first progression (n)	406	241	165
Patients requiring treatment for first progression (n)	369	215	154

IMiD-based regimen	**Total (n = 181)**	**Placebo (n = 134)**	**Len (n = 49)**	***p*-value**
Median second PFS	—	19 mo	8 mo	0.003
Bortezomib-based regimen	**(n = 94)**	**(n = 31)**	**(n = 63)**	
Median second PFS	—	8 mo	9 mo	0.28
No new agents	**(n = 92)**	**(n = 50)**	**(n = 42)**	
Median second PFS	—	30 mo	18 mo	0.06

Attal M et al. *Proc ASH* 2013;Abstract 406.

OS After First Progression

	Len (n = 165)	Placebo (n = 241)	*p*-value
Median OS	29 mo	48 mo	<0.001

Attal M et al. *Proc ASH* 2013;Abstract 406.

Incidence of SPMs

	Len	Placebo	Total
Hematologic	**18**	**7**	**25**
AML/MDS	7	4	11
ALL	1	1	2
Lymphoma	6	1	7
Hodgkin lymphoma	4	1	5
Solid tumor	**13**	**11**	**24**
Esophageal/hypopharynx	2	0	2
Colon and rectal	4	1	5
Prostate	3	3	6
Lung cancer	0	1	1
Bladder/renal	1	2	3
Breast	2	1	3
Melanoma	1	3	4
Noninvasive skin cancer	**9**	**5**	**14**
Total (patients can have >1 SPM)	**37 (13%)**	**21 (7%)**	**58**

Attal M et al. *Proc ASH* 2013;Abstract 406.

Author Conclusions

- This new analysis confirms that Len is an effective treatment to prolong PFS (median 46 mo vs 24 mo, $p < 0.001$) after ASCT for patients with MM:
  - Reduced second PFS (median 24 mo vs 13 mo, $p < 0.001$), possibly due to clonal selection or secondary resistance (suggested by the IMiD and No new agent groups)
- PFS benefit is not currently associated with an improved OS because of a shorter survival after the first disease progression (median 29 mo vs 48 mo, $p < 0.001$).
- The risk of SPMs increased (13% vs 7%) for patients receiving Len maintenance.
- The risk of severe neutropenia also increased (51% vs 18%) for patients receiving Len (data not shown).

Attal M et al. *Proc ASH* 2013;Abstract 406.

Investigator Commentary: Follow-Up Analysis of the IFM 2005-02 Trial of Len Maintenance After ASCT for Patients with MM

Of note, the initial analysis of the results from this IFM trial failed to show an OS benefit even though the PFS benefit was the same as in the US CALGB trial (*NEJM* 2012;366(19):1770). Some big differences between these 2 studies are that the IFM trial included 2 cycles of Len as consolidation and early trial termination resulted in patients receiving Len maintenance for a median of 2 years. The CALGB trial did not have a consolidation step and Len maintenance was administered longer, until disease progression.

After a median follow-up of 77 months, this trial continues to show an improvement in PFS but no OS benefit. We continue to see a warning about the development of SPMs for patients receiving Len maintenance. If you compare these results to the data from 2 trials that showed OS benefit — the US trial and the Phase III trial of early transplant versus no transplant with a second randomization to Len or no maintenance (*Proc ASCO* 2013;Abstract 8509) — 2 issues are evident with the use of Len maintenance. Side effects occur, and a higher risk of SPMs exists with Len maintenance, although that's a relatively low risk compared to the risk of MM relapse. If you limit therapy to 2 years, you're opening yourself up to all the risks and toxicities of therapy without necessarily allowing your patient to realize the survival benefit reported for patients who receive treatment until progression.

Interview with Sagar Lonial, MD, January 22, 2014

Lenalidomide Maintenance Therapy in Multiple Myeloma: A Meta-Analysis of Randomized Trials

Singh PP et al.

Proc ASH 2013;Abstract 407.

Background

- Conflicting results have emerged with respect to the impact on overall survival (OS) from trials evaluating lenalidomide maintenance (LM) therapy after induction therapy alone or after autologous stem cell transplant (ASCT) in multiple myeloma (MM).
- The CALGB-100104 trial reported that LM after ASCT significantly improved OS but was associated with more toxicity (*N Engl J Med* 2012;366(19):1770).
- The IFM 2005-02 study showed a significant improvement in progression-free survival (PFS) but no difference in OS with LM after transplantation (*N Engl J Med* 2012;366(19):1782).
- **Study objective:** To perform a systematic review and meta-analysis of existing outcome data from LM trials to evaluate the role of lenalidomide as a maintenance strategy in MM.

Singh PP et al. *Proc ASH* 2013;Abstract 407.

Methods

- A systematic literature search of PubMed, Embase, Scopus and Web of Science (through June 2013) and major conferences (2005-2013) was performed to identify randomized controlled trials that compared LM to placebo/no maintenance.
- Pooled hazard ratio (HR) or odds ratio (OR) estimates with 95% confidence intervals were calculated using the random-effects model for PFS, OS, response rate and adverse events (AEs), including second primary malignancies.
- Between-study heterogeneity was evaluated with the Cochran Q test, and its extent was quantified with the inconsistency index (I^2) statistic.

Singh PP et al. *Proc ASH* 2013;Abstract 407.

Trials Included in Meta-Analysis

- Data were extracted from 4 Phase III trials*: 3 publications, 1 abstract (n = 1,935)
  - IFM 2005-02 and CALGB-100104: Placebo controlled, addressed the role of LM after ASCT
  - MM-015: Placebo controlled, studied LM therapy in the nontransplant setting
  - RV-MM-PI209: 2 x 2 design comprising ASCT and nontransplant randomized arms followed by a second randomization to LM versus no maintenance

* MRC MM XI study was excluded from analyses because survival data were not available

Singh PP et al. *Proc ASH* 2013;Abstract 407.

LM and PFS

Study name	HR	*p*-value
IFM 2005-02	0.500	<0.001
CALGB-100104	0.480	<0.001
MM-015	0.340	<0.001
RV-MM-PI209	0.520	<0.001
Summary estimate	**0.491**	**<0.001**

- Outcome: HR for death or progression; LM vs no maintenance (<1 implies better outcome with LM)
- **Minimal heterogeneity for estimate of PFS:**
  - Cochran Q = 1.51 (p = 0.68), I^2 = 0%

Singh PP et al. *Proc ASH* 2013;Abstract 407.

LM and OS

Study name	HR	*p*-value
IFM 2005-02	1.060	0.664
CALGB-100104	0.610	0.008
MM-015	0.790	0.251
RV-MM-PI209	0.620	0.018
Summary estimate	**0.767**	**0.071**

- Outcome: HR for death or progression; LM vs no maintenance (<1 implies better outcome with LM)
- **Significant heterogeneity for estimate of OS:**
  - Cochran Q = 8.11 (p = 0.044), I^2 = 63%

Singh PP et al. *Proc ASH* 2013;Abstract 407.

LM and OS: Post-Transplant Group

Study name	HR	*p*-value
IFM 2005-02	1.060	0.664
CALGB-100104	0.610	0.008
Summary estimate	**0.820**	**0.462**

- Outcome: HR for death or progression; LM vs no maintenance (<1 implies better outcome with LM)
- **Significant heterogeneity for estimate of OS:**
  - Cochran Q = 5.82 (p = 0.016), I^2 = 82.8%

Singh PP et al. *Proc ASH* 2013;Abstract 407.

Grade 3/4 AEs During LM

	OR	*p*-value
Neutropenia	4.9	<0.001
Thrombocytopenia	2.7	<0.001
Fatigue	2.3	0.01
Venous thromboembolism	3.2	0.02
Treatment discontinuation	2.9	<0.001

Singh PP et al. *Proc ASH* 2013;Abstract 407.

Secondary Primary Malignancies

Study name	HR	*p*-value
IFM 2005-02	1.640	0.053
CALGB-100104	2.050	0.031
MM-015	1.430	0.412
RV-MM-PI209	0.850	0.798
Summary estimate	**1.62**	**0.006**

- Outcome: Odds of developing secondary primary malignancy; LM vs placebo/no maintenance (>1 implies increased risk of secondary primary malignancy with LM)
- **Minimal heterogeneity for estimate of secondary primary malignancy:**
  - Cochran Q = 1.67 (p = 0.644), I^2 = 0%

Singh PP et al. *Proc ASH* 2013;Abstract 407.

Author Conclusions

- Meta-analysis of randomized controlled trials demonstrates significant improvement in PFS and a trend toward improvement in OS with LM.
- LM is associated with increased risk of Grade 3/4 AEs and second primary malignancies.
- Substantial heterogeneity for estimate of OS among protocols is a limitation of this analysis.
- Lack of uniform access to lenalidomide upon disease progression in the placebo/no maintenance arms of the constituent studies should be taken into account when interpreting aggregate effect estimates for OS in this meta-analysis.
- The subset of patients benefitting the most from LM is not yet defined, and risks and benefits should be discussed with all patients.

Singh PP et al. *Proc ASH* 2013;Abstract 407.

Investigator Commentary: Meta-Analysis of Randomized Trials of LM Therapy in MM

The results of this meta-analysis showed a significant increase in PFS and a moderate improvement in OS with LM. The incidence of side effects was higher in the group that received maintenance.

This analysis included both younger and older patients. It included studies of LM in the nontransplant and post-transplant settings. That's mixing apples and oranges. I believe you need to answer the question of the role of LM after a transplant in that setting.

Two points of view exist regarding LM. I am in the camp that advocates maintenance until disease progression. I believe that a survival benefit is evident with maintenance in the CALGB-100104 trial. The other view is that maintenance can harm people. I don't believe that the results of this study are convincing one way or the other.

Interview with Sagar Lonial, MD, January 22, 2014