MYELOMA MAINTENANCE BEST PRACTICES:

POST THERAPY & POST TRANSPLANT

Aric Hall, MD

Assistant Professor

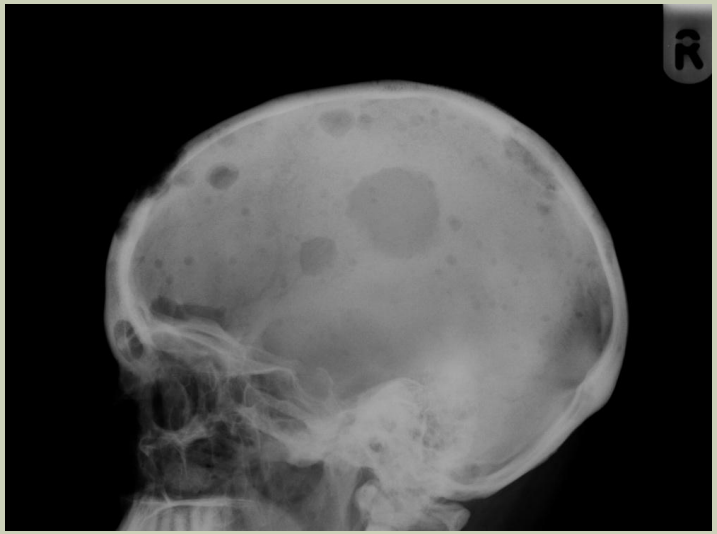
University of Wisconsin Hospital and Clinics

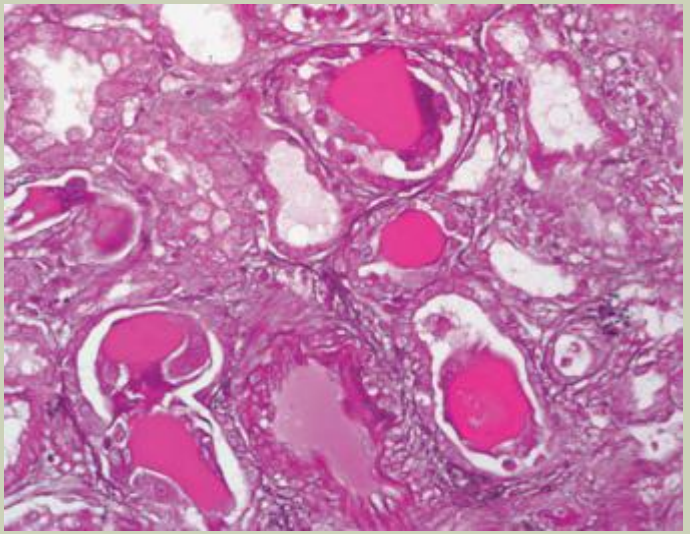
INTRODUCTION

MYELOMA

- Clonal plasma cell malignancy leading to CRAB (hyper**C**alcemia, **R**enal failure, **A**nemia, **B**one lesions) but also immune dysfunction, osteopenia, amyloidosis, etc…

- Estimated 24,050 new cases in 2014 and >83,000 individuals living with the disease



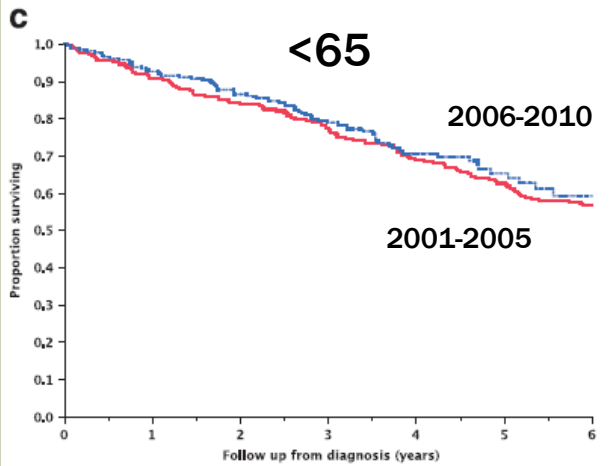


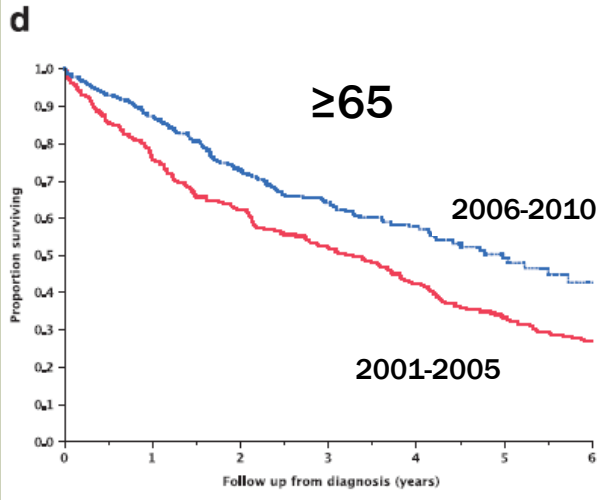
SEER data

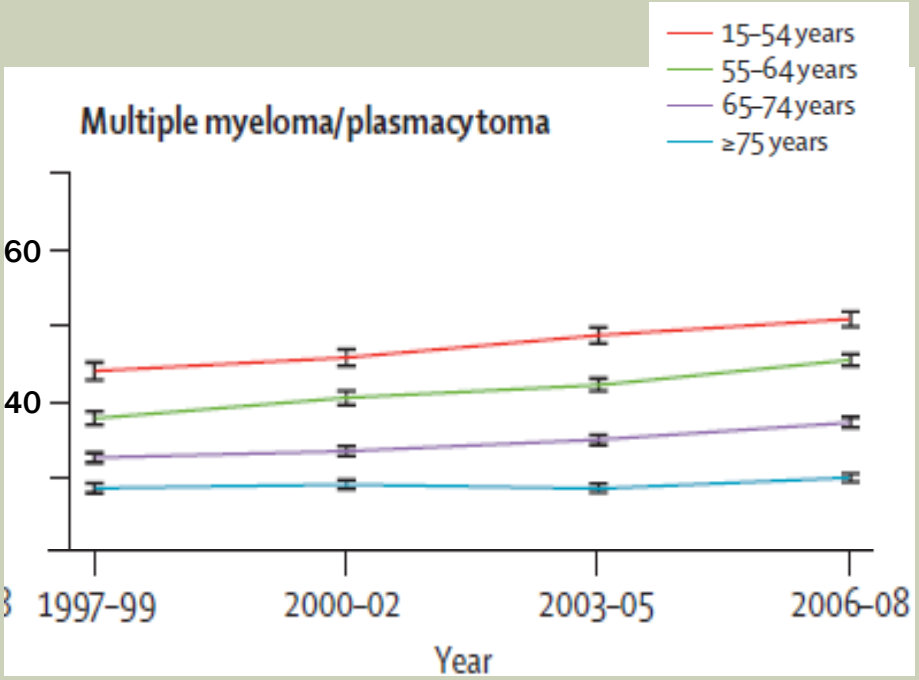
THE GOOD: PROGRESS AND NEW AGENTS

- At least seven new drugs approved in the last ten years
- Most important and revolutionary are the so-called "novel agents"
  - Proteosome Inhibitors: Bortezomib, Carfilzomib
  - IMiDS: Thalidomide, Lenalidomide, Pomalidomide
- Have led (generally) to a move away from cytotoxic chemotherapy

NEW AGENTS HAVE PRODUCED SURVIVAL GAINS







5-year survival:
29.8% → 32.7 → 35.2%→ 39.6%

Median survival
3.2 vs 5 years

Sant et al. 2014.
Kumar et al. 2014.

BENEFITS HAVE NOT EXTENDED EQUALLY TO ALL PATIENTS

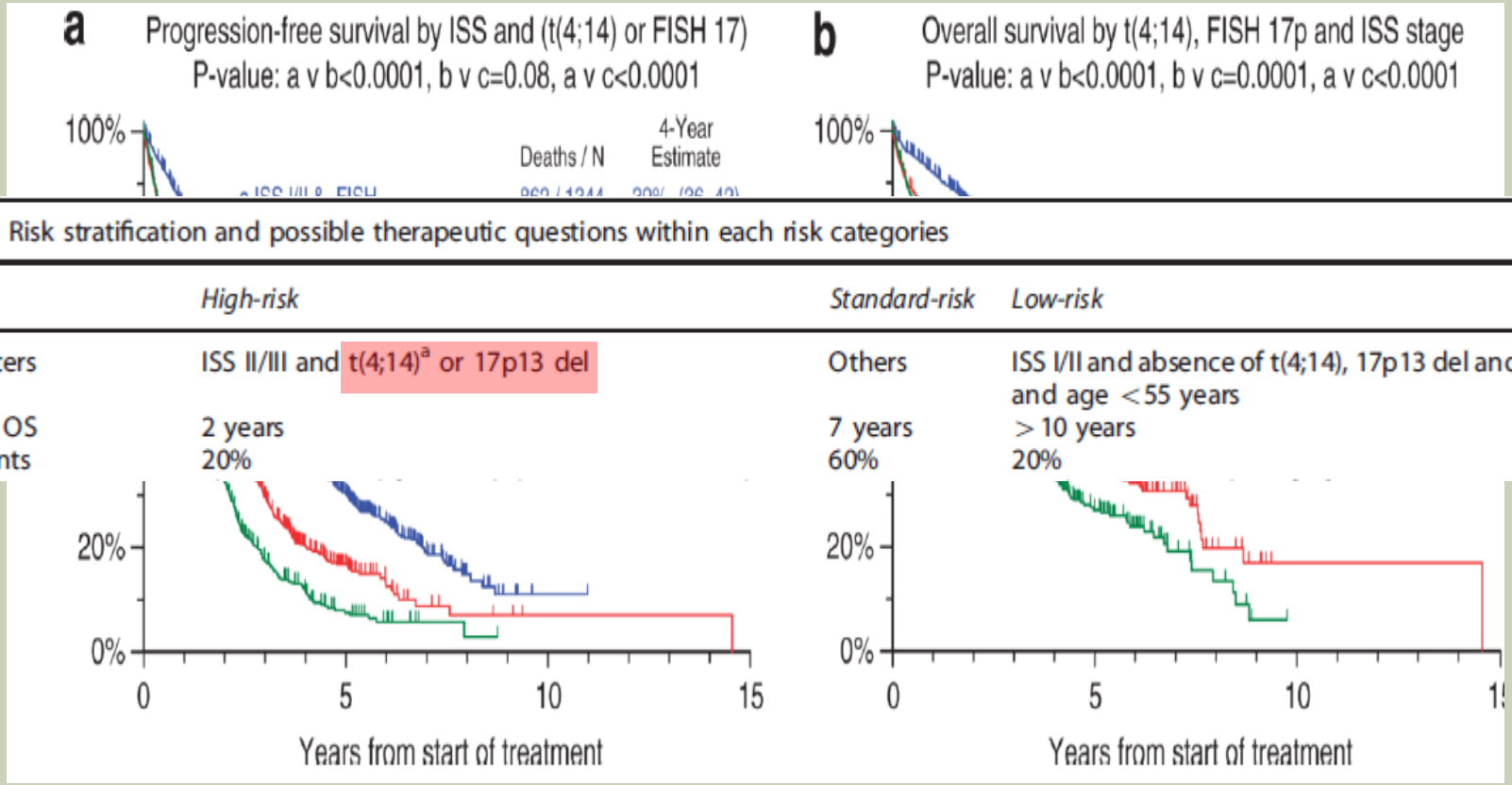
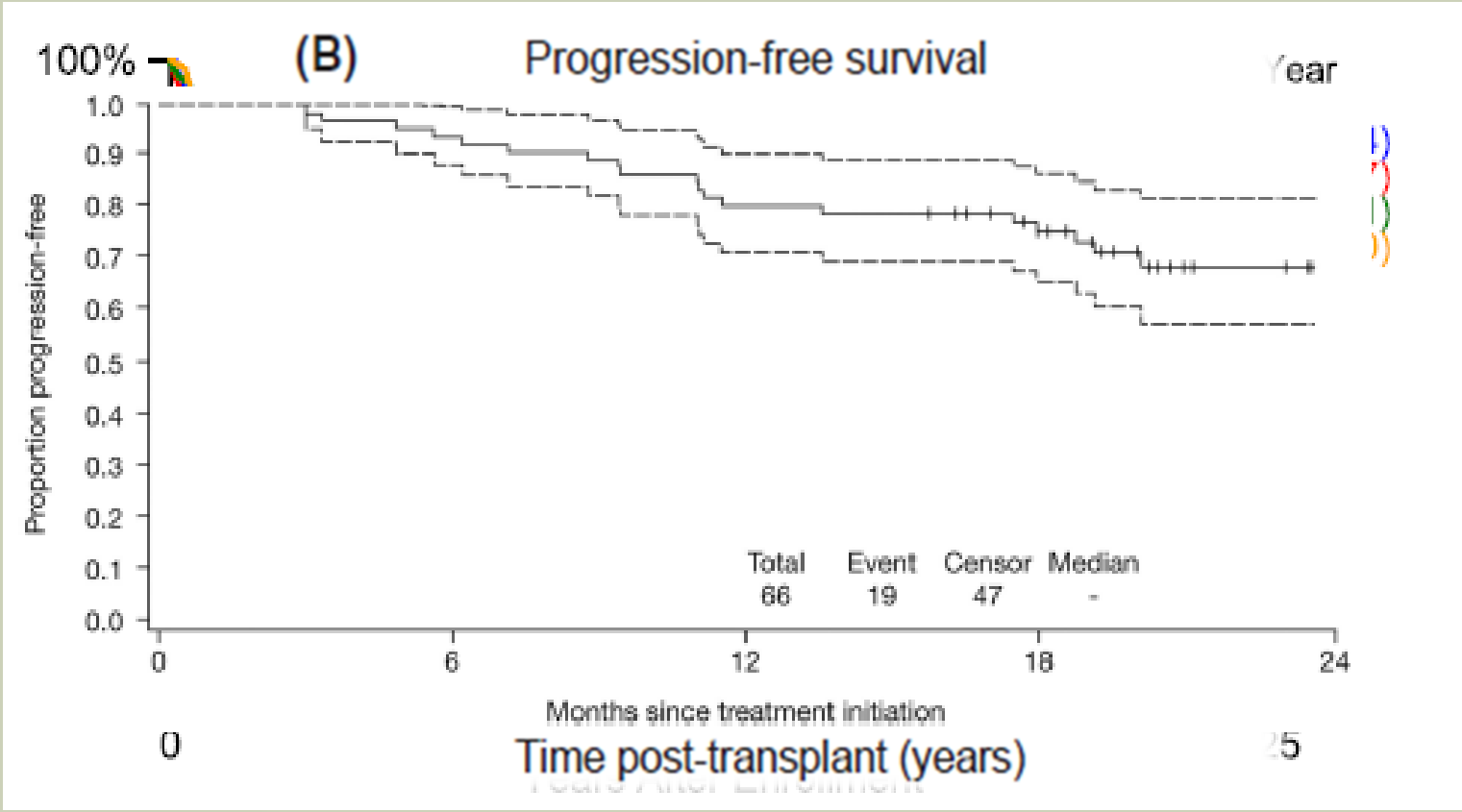


Table 3. Risk stratification and possible therapeutic questions within each risk categories

	High-risk	*Standard-risk*	*Low-risk*
Parameters	ISS II/III and t(4;14)[a] or 17p13 del	Others	ISS I/II and absence of t(4;14), 17p13 del and +1q21 and age <55 years
Median OS	2 years	7 years	>10 years
% Patients	20%	60%	20%

Avet-Louise. 2013.
Chng. 2014.

RELAPSE REMAINS A PROBLEM



Barlogie et al. *Blood*. 2014.
Richardson. *Blood.* 2010.
Sahebi et al. *BJH*. 2013.

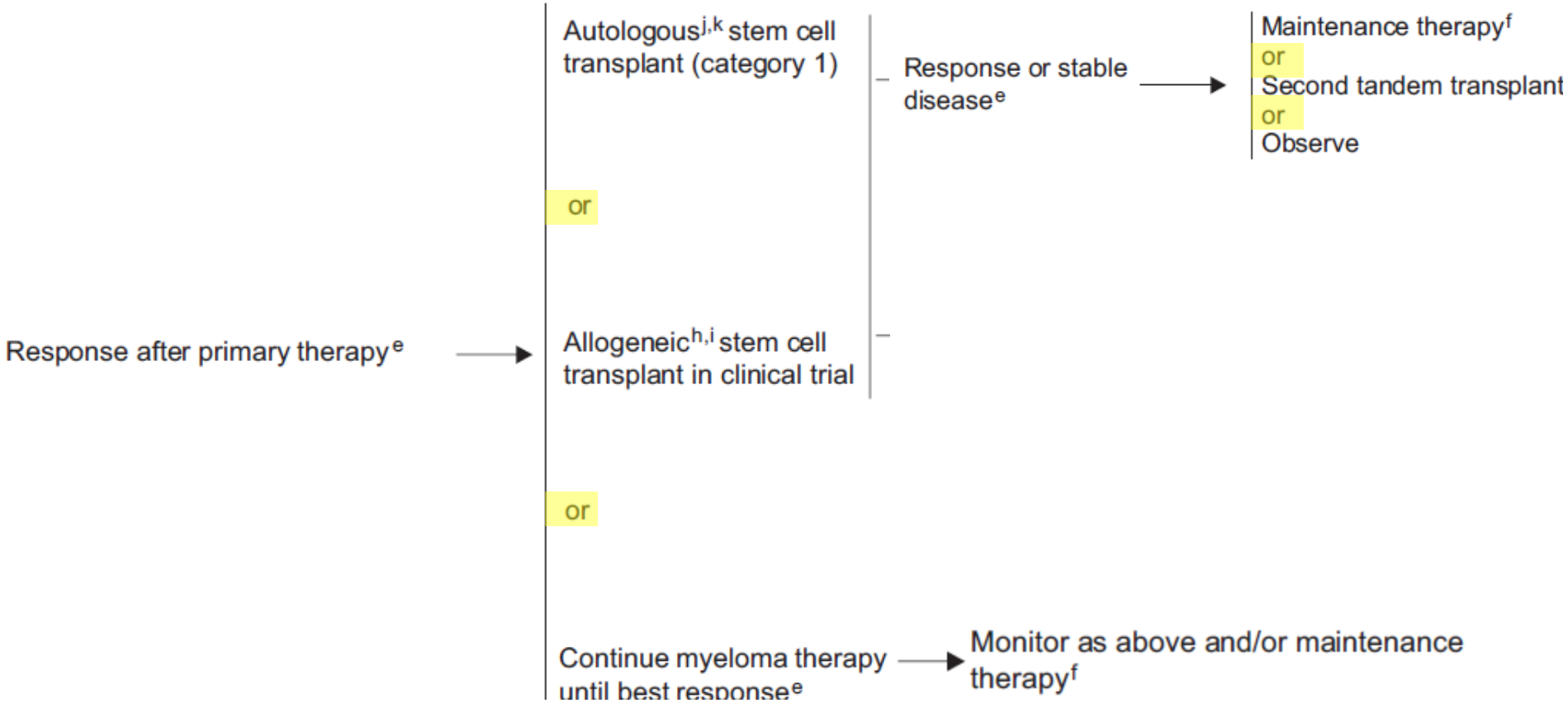
CONSOLIDATION / MAINTENANCE THERAPY

- Prolonged therapy given after initial therapy to prolong or deepen response
- Maintenance: >1 year
- Consolidation: ≤1 year

JUSTIFICATIONS TO FOCUS ON CONSOLIDATION / MAINTENANCE

- Incremental benefit with additions to upfront therapy?
- Therapy better tolerated in a minimal disease state?
- Increased chemo-sensitivity in minimal disease state?
- Increased survival? Cure?

CONFUSION: DOES ABILITY TO GIVE MORE THERAPY HELP SURVIVAL?



Anderson. *Leukemia.* 2011.

THERE IS A TENDENCY FOR DOGMATISM

- Debates about “maintenance yes” or “maintenance no” are published and discussed at meetings
- These binary arguments don’t reflect actual medical decision making, and often argue past each other invoking different benefits
- **This is confusing and somewhat frustrating to everyone…**

"ONCODOXES"

"Don't over-treat incurable disease"

"Don't miss a chance to prolong life / prevent complications"

There is not currently evidence to support a single universal approach to maintenance therapy.

"You're making more resistant disease"

We might cure people

BETTER QUESTIONS

- What maintenance and consolidation strategies have been studied?
- What are the benefits of maintenance/consolidation therapy in terms of progression free and overall survival ?
- What are the risks of maintenance and consolidation therapies?
- Which patients are most likely to benefit from maintenance or consolidation therapy?
- How can we help our patients apply their interests/values to the decision of whether to use maintenance/consolidation therapy?

OUTLINE

- History of maintenance in MM / Learning from our mistakes
- Current maintenance / consolidation strategies and their impact
- Risks / costs of consolidation and maintenance therapy
- Who is likely to benefit
- Possible paths forward
- Questions

HISTORY OF MAINTENANCE IN MM

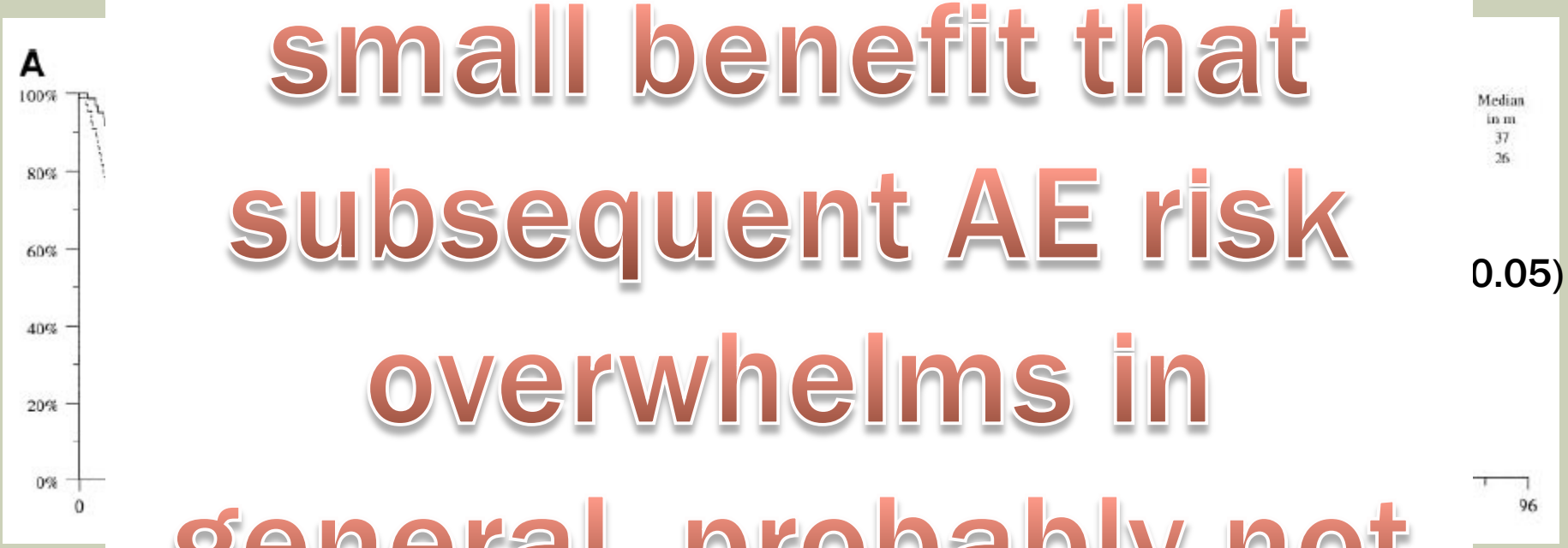
FIRST ATTEMPTS

- CHEMOTHERAPY
  - Attempted to use alklylators in a prolonged fashion (mostly melphalan)
  - Led to unreliable PFS improvement, no suggestion of OS improvement; creates high risk of 2nd cancers
- INTERFERON
  - Huge metanalysis suggests small PFS and very small OS improvement (2% ± 1.7% at 5 years)
  - Inconvenient and difficult to deliver so stopped

Myeloma Trialists Group. *Br. J. Haematology.* 2001.

STEROIDS MIGHT WORK

- 1
- S
- S



0.05)

re

. 2010.

Conclusion: May have small benefit that subsequent AE risk overwhelms in general, probably not best current option

IV BISPHOSPHONATE

Conclusion: Almost certainly a benefit in those with bone disease, probably a useful adjuvant

Morgan. *Lancet Onc*. 2010.

THALIDOMIDE MAINTENANCE

Conclusion: Likely some people benefitted but difficult to tolerate and unlikely to regain popularity in the US**

Ludwig. *Blood.* 2012

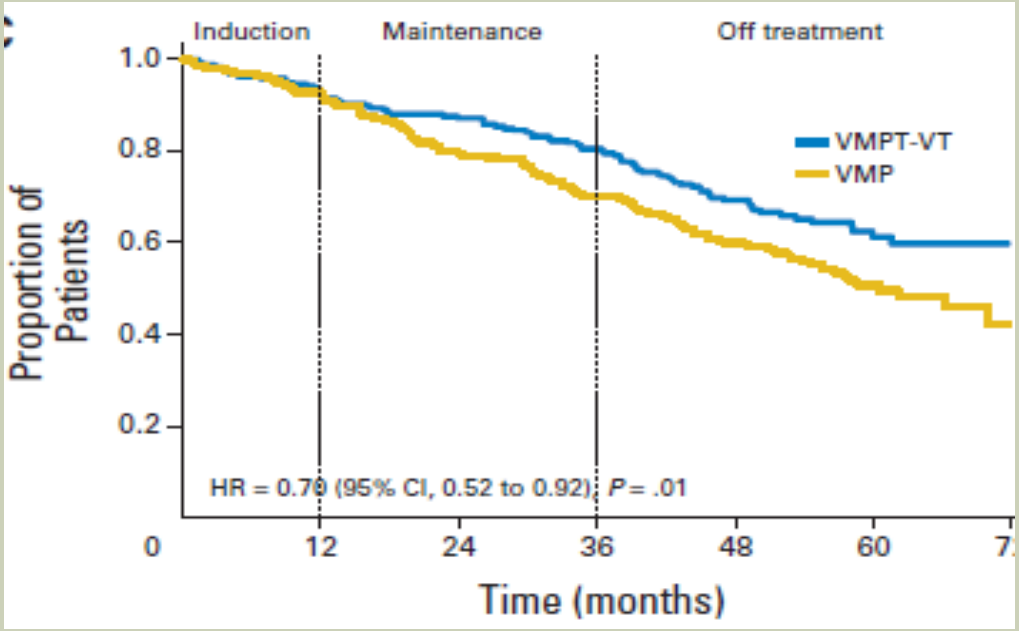
SUMMARY

- Alkylator chemotherapy is NOT effective as maintenance
- IFN maintenance inconvenient, expensive, and has marginal effect so largely discarded
- Steroid maintenance may have small benefit but dose difficult and risk/benefit precarious, not generally recommended
- IV bisphosphonate may have OS benefit, and have a good reason to use
- Thalidomide has a reproducible PFS benefit, prolonged follow up has showed an inconsistent OS benefit & agent supplanted in the US by lenalidomide

MAINTENANCE/ CONSOLIDATION STRATEGIES: TRANSPLANT INELIGIBLE

BORTEZOMIB-THALIDOMIDE (VT) MAINTENANCE

- Large Italian study of transplant ineligible patients
- VMPT (bort/melphalan/thal/pred) → VT (2 years) vs VMP → observation
- PFS and OS betterl in the quadruplet and maintenance arm
- Unclear if this is an induction or maintenance effect
- **Unlikely to become a common US induction regimen**

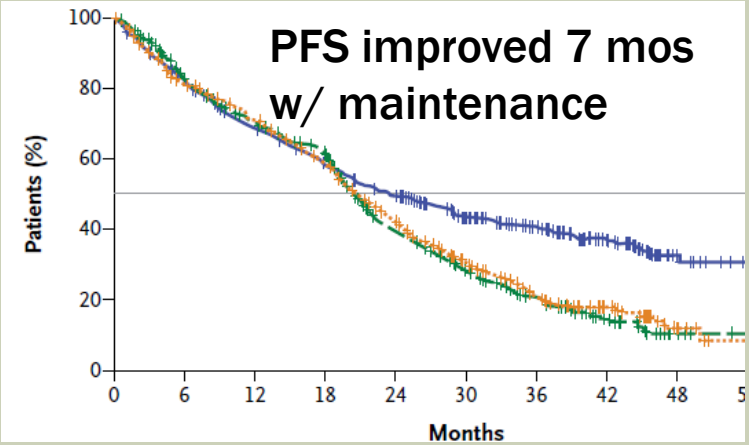


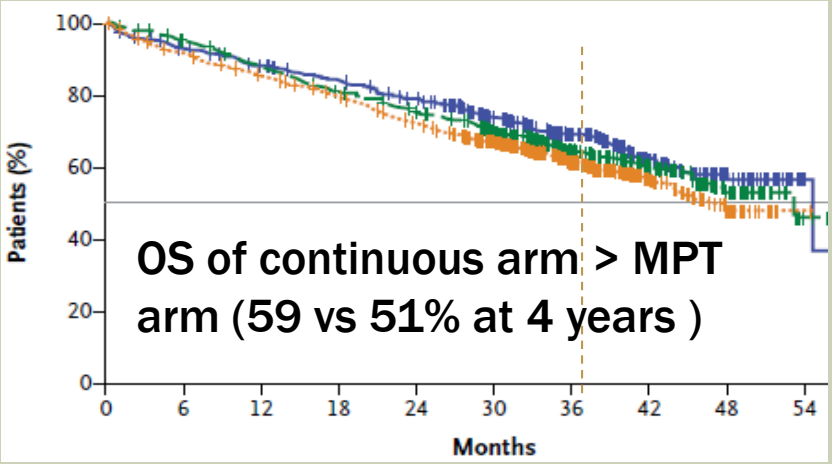
Palumbo. *JCO*. 2014.

LENALIDOMIDE MAINTENANCE TRANSPLANT INELIGIBLE

- Len maintenance after MPR induction, MPR alone, or MP
  - Maintenance prolongs PFS (by 17 mos)
  - No OS improvement with len maintenance or any induction regimen

- Lenalidomide/dexamethasone (Rd) indefinitely vs 18 mos vs MPT for 18 mos





Palumbo et al. *NEJM.* 2012; Benboubker. *NEJM.* 2014.

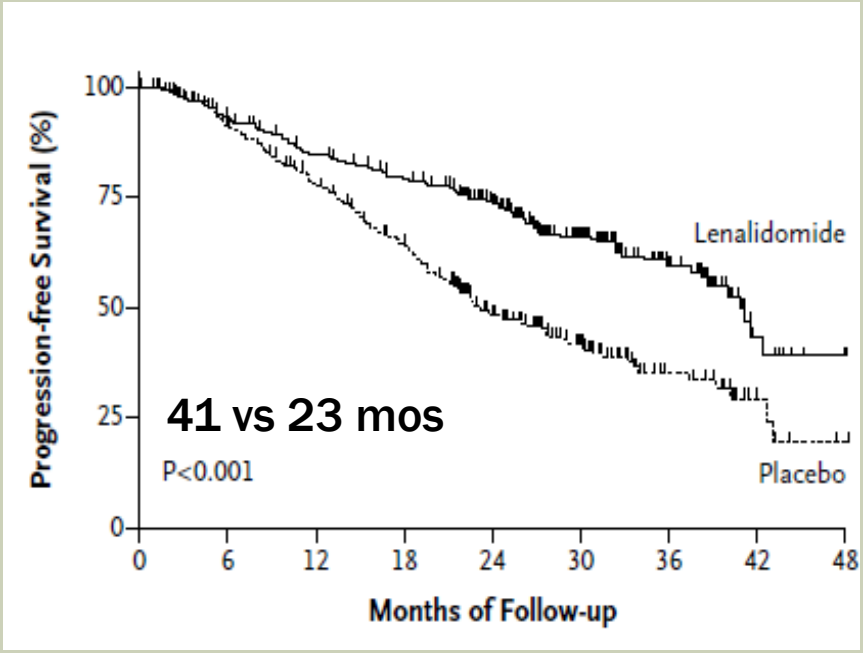
SUMMARY

- VMPT→ VT maintenance seems to improve PFS and OS over VMP without maintenance, the maintenance component of therapy was well tolerated
- Lenalidomide maintenance after MPR prolongs PFS without OS benefit
- Continuous Rd provides excellent PFS and OS in older patients with MM with less toxicity than a triplet regimen, limited course showed worse PFS but OS not significantly worse

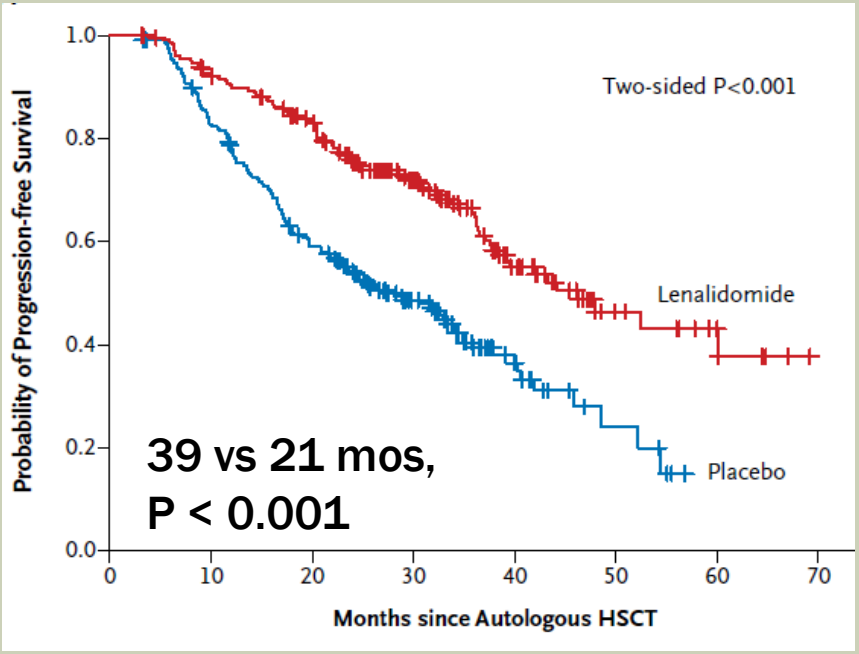
MAINTENANCE AND CONSOLIDATION: TRANSPLANT ELIGIBLE

LENALIDOMIDE AFTER AUTOSCT- PROGRESSION FREE SURVIVAL

IFM2005-2



CALGB100-104

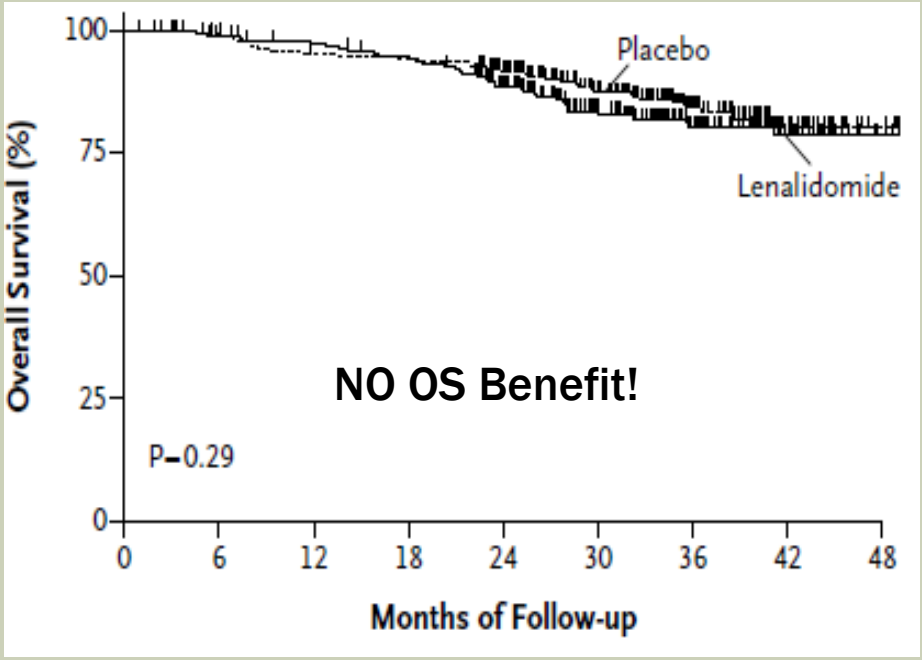


Lenalidomide after autoSCT leads to about an 18 month increase in PFS

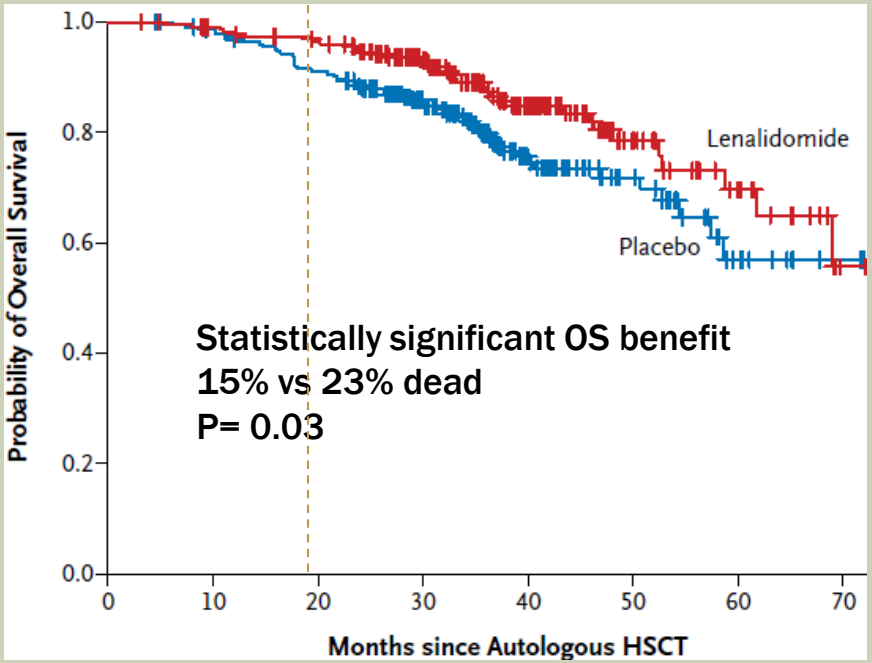
Attal. *NEJM.* 2012
McCarthy. *NEJM*. 2012.

LENALIDOMIDE AFTER AUTOSCT: OVERALL SURVIVAL

IFM2005-2



CALGB100-104



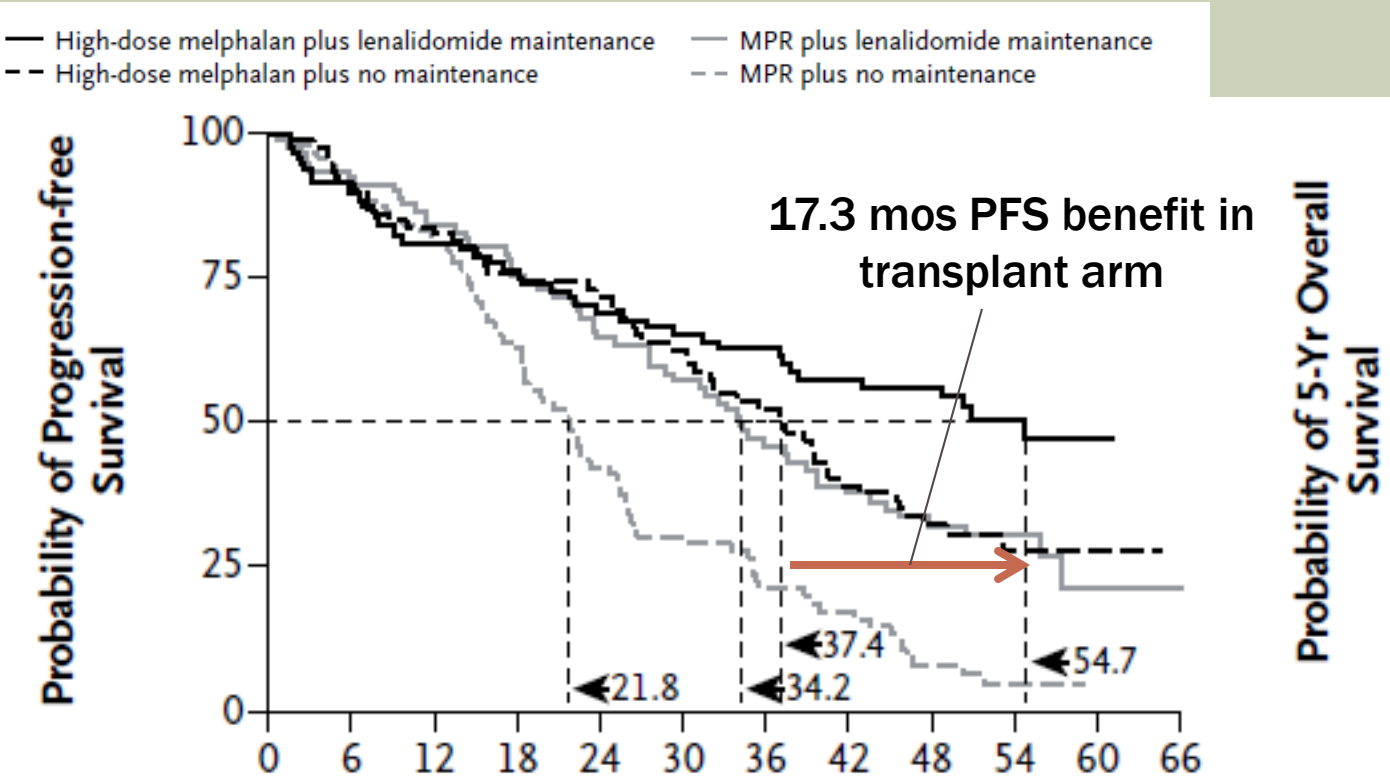
More mature data has borne out these initial findings, still PFS benefit and no OS in IFM; still OS benefit in CALGB

Attal. *NEJM*. 2012
McCarthy. *NEJM*. 2012.

LENALIDOMIDE MAINTENANCE AFTER AUTOSCT → AGAIN

RV-MM-PI-209 – Published Palumbo. *NEJM*. 2014.

- Len/Dex (Rd) → autoSCT or MPR → lenalidomide maintenance or observation



No OS benefit

HR 0.64, P=NS

This needs to mature

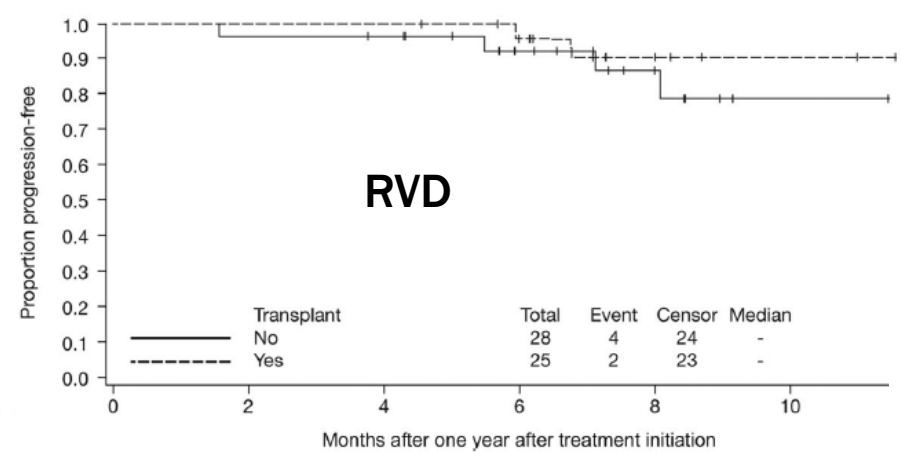
Rd still not optimal induction for this question

BORTEZOMIB MAINTENANCE AFTER TRANSPLANT

- One randomized trial from Europe (HOVON-65 / GMMG-HD4)
  - Bortezomib, Doxorubicin, Dex (PAD) → bortezomib maintenance
  - Vincristine, Doxorubicin, Dex (VAD) → thalidomide maintenance
- PFS and overall survival advantage in the bortezomib containing arm, unclear if this due to induction or maintenance
- This benefit was more marked in high risk patients

Sonneveld. JCO. 2012.

CONTINUOUS THERAPY WITH NOVEL DRUG TRIPLETS IN TRANSPLANT ELIGIBLE



Excellent PFS, good tolerability in patients selected

Overall survival data not clear yet

No good randomized data for this vs transplant based approaches (active area)

I do not tend to favor off trial, though there are patient situations where this may be reasonable

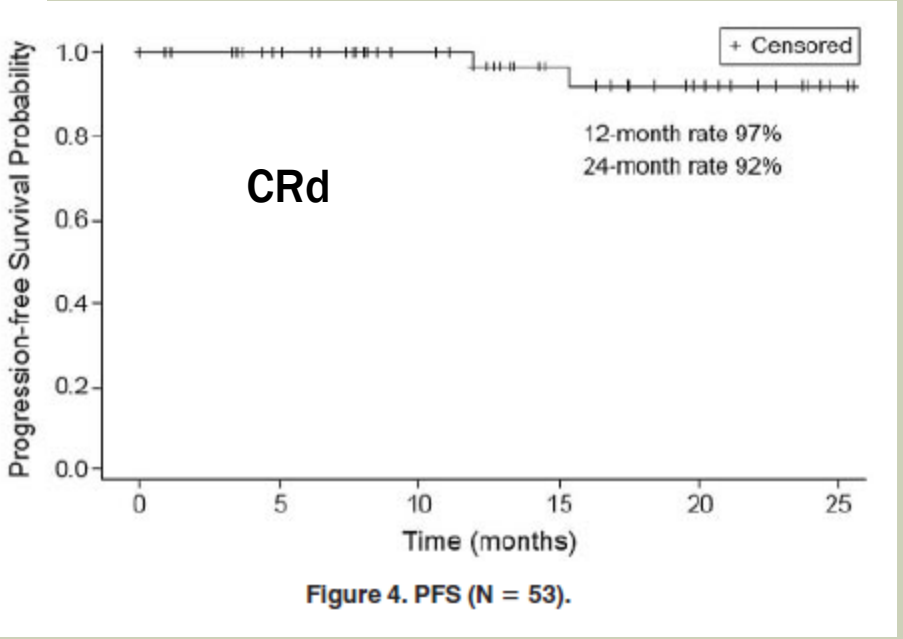


Figure 4. PFS (N = 53).

Riachardson. *Blood.* 2010.
Jakubowiak. *Blood.*2012.

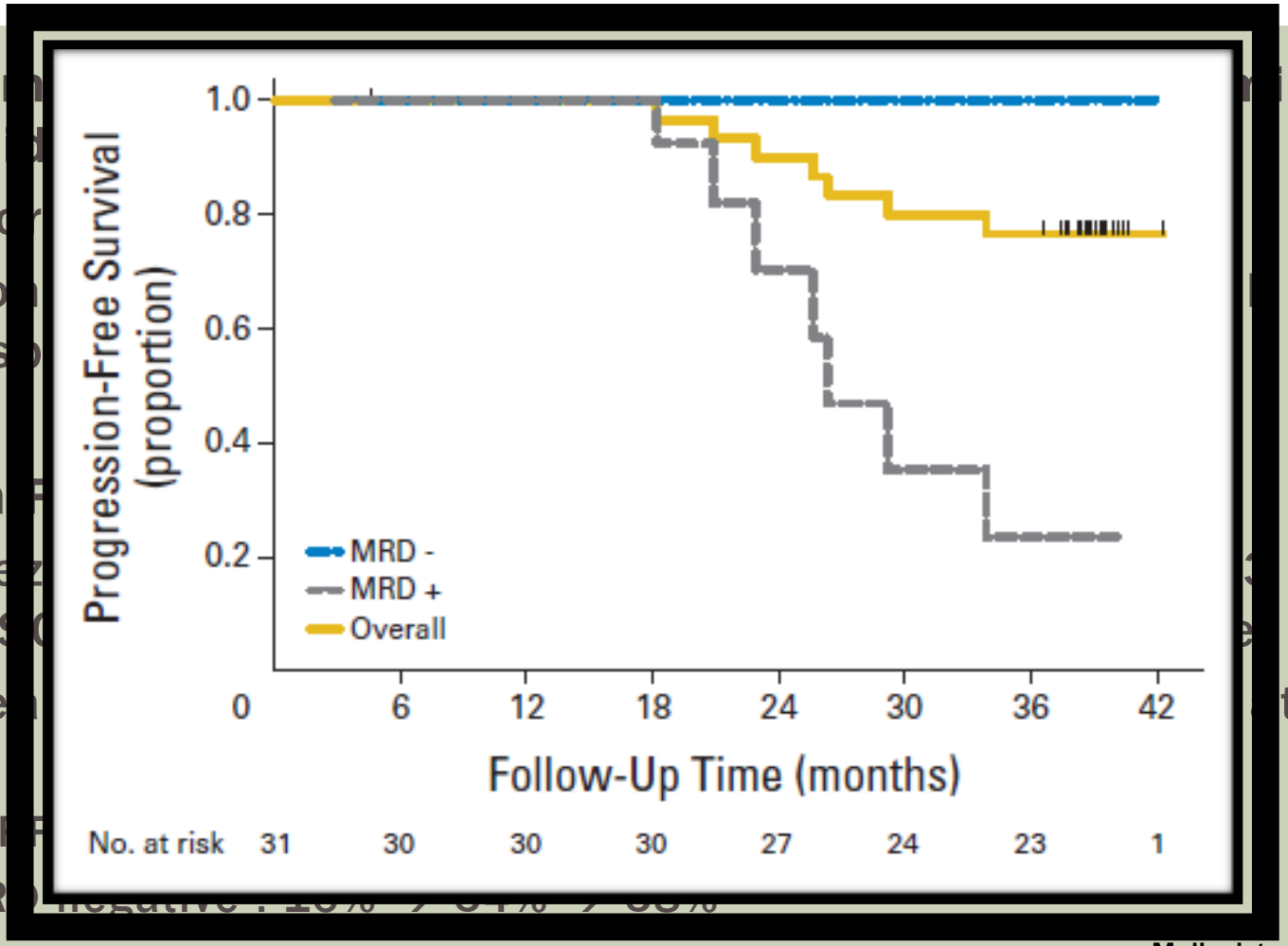
CONSOLIDATION- LIMITED COURSE CAN DEEPEN RESPONSES

Rando **ib consol**

- no bo
- 7 mo **after** trans

French

- Borte **then** auto
- Incre **t each** step
  - VG
  - MR



Mellqvist et al. *Blood.* 2013.
Roussel. *JCO.* 2014.

SUMMARY

- **Lenalidomide maintenance yields ≈ 13-18 month PFS after autologous stem cell transplant**
- 1/3 studies has shown an OS benefit from lenalidomide maintenance after autoSCT
- Bortezomib maintenance probably prolongs PFS and OS but we lack a phase III trial to address this question specifically
- Consolidation strategies may deepen initial responses and prolong PFS with more limited therapy, there is a lack of “clean” randomized data attesting to their benefit

COSTS OF CONTINUOUS THERAPY

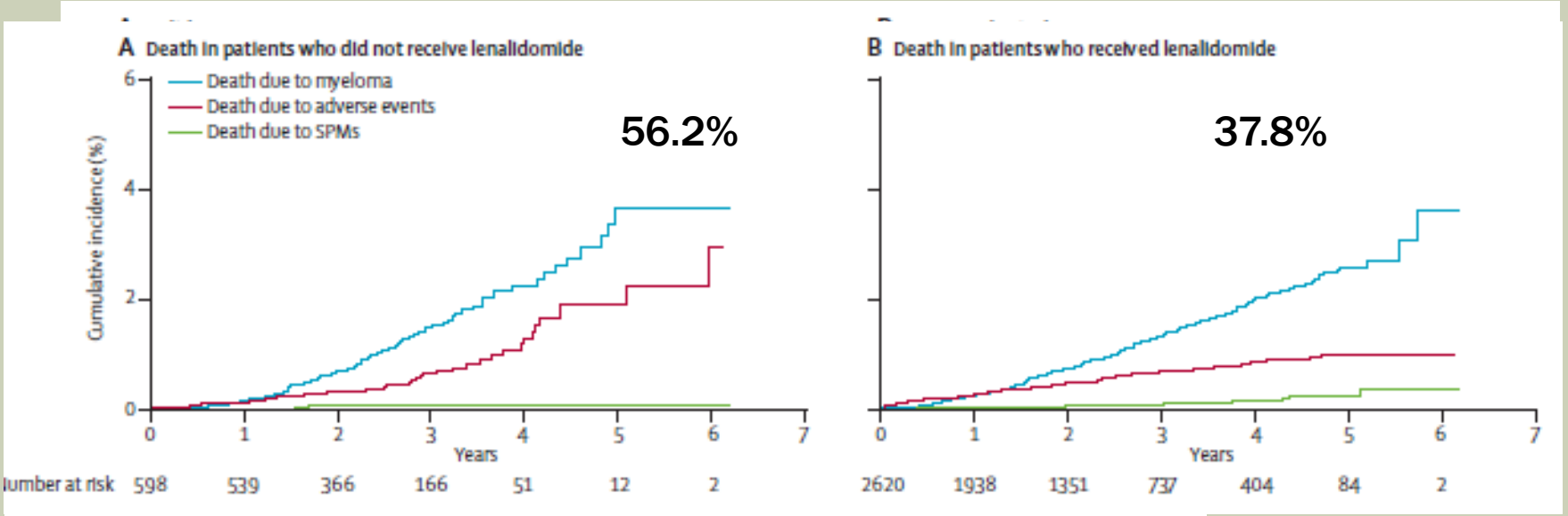
INCREASING RESISTANCE?

- Metanalysis of interferon and some thalidomide maintenance trials showed shorter survival after progression leading to same OS despite improved PFS
- May be an artifact of time of trials and lack of new agents when these trials were done
- Appears less of an issue in more recent trials
- PFS2 (time to second progression, third line therapy, or death) is being looked at as a marker for this

DRUG TOXICITIES

- A significant problem that may have limited efficacy of thalidomide and interferon maintenance
- Newer regimens have been more manageable, due to reduced doses of induction regimen
- THESE STUDIES ALL ARE PROBABLY BIASED TOWARD PATIENTS WHO TOLERATE THERAPY WELL
- It is likely you are not helping the patient if they have more than mild toxicities (If it is affecting their day to day function it is probably too much)
- PERSISTENT FUNCTIONALLY LIMITING TOXICITY MAY BURN A BRIDGE TO A NEW TRIAL OR AGENT

SECONDARY PRIMARY MALIGNANCY WITH LENALIDOMIDE



- In general risks of myeloma far overwhelm risks of a second cancer…
- Risks are highest when given with oral melphalan
- This risk is more concerning in a patient who has a very low risk of early death from myeloma

Palumbo. Lancet Onc. 2014

FINANCIAL COSTS

$563 / pill

$1428/ dose

Daily lenalidomide after autologous stem cell transplant : **$205,500/yr**

Based on 3 year OS NNT 12.5=

$5,000,000+ to prevent a death

Bortezomib per HOVONN schema after autologous stem cell transplant = $37,000/yr

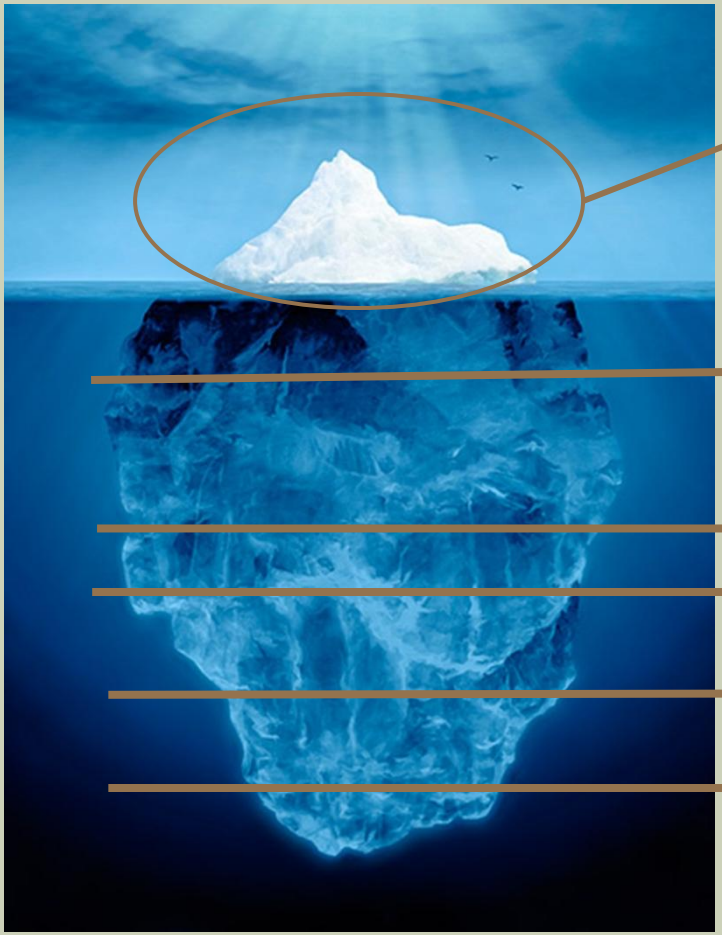
Compare to autologous stem cell transplant = $ 91,000 → 60,000 if outpatient

Based on 4 year OS NNT 6.1 =$555,100 to prevent a death

Majhail et al. 2013.
Holbro et al. 2013.

IDENTIFYING PATIENTS WHO ARE LIKELY TO BENEFIT

HOW DEEP A RESPONSE DO WE NEED?



SYMPTOMATIC MYELOMA

VGPR

CR

STRINGENT CR

MRD NEGATIVE CR

"CURE"

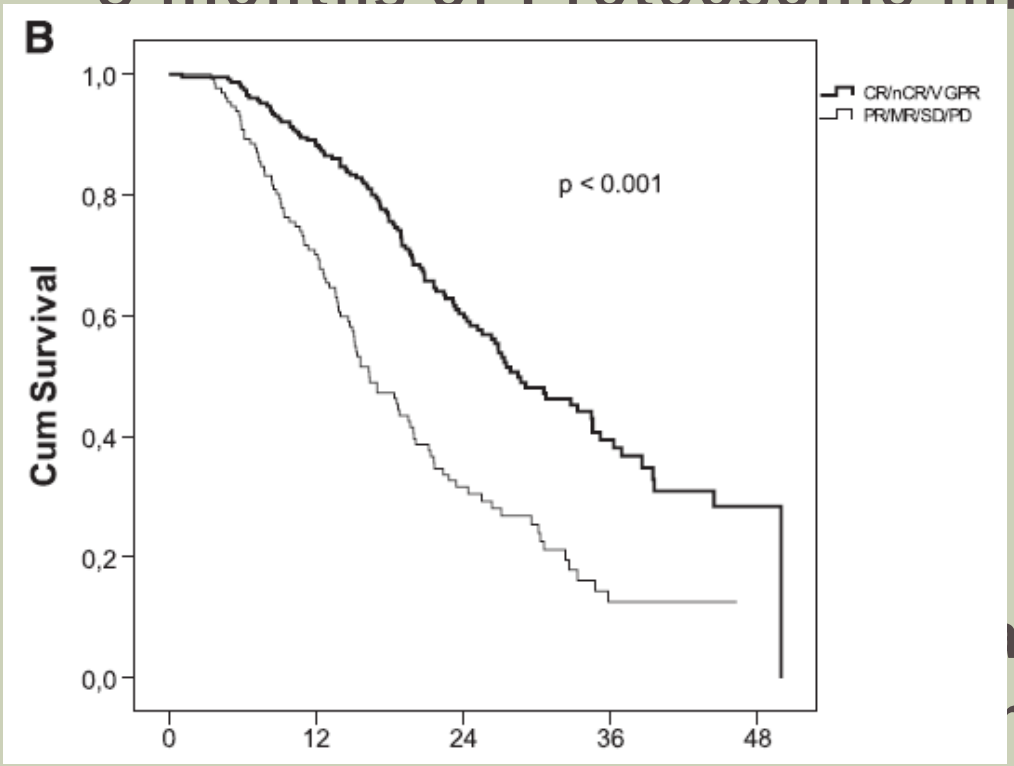
?

FOR MANY PATIENTS VGPR SEEMS A REASONABLE TARGET

- VGPR = immunofixation detectable M-spike but not detectable by standard SPEP
- French combined analysis of early transplant trials showed that EFS (42 vs 32 months) and 5 year OS (74% vs 61%) were significantly better in patients achieving at least a VGPR (Harousseau. *JCO*. 2009.)
  - This benefit was more pronounced in patients with higher risk disease
- French data suggesting second autologous transplant ("Tandem transplant") only benefitted those who did not achieve at least VGPR with first (Attal. *NEJM.* 2003.)
- **THESE ARE TRANSPLANT TRIALS, harder to set a level for non-transplant**

BACK TO BORTEZOMIB CONSOLIDATION

- 6 months of Proteosome inhi
- ≥
- fr
- s
- n



longer than those who didn't

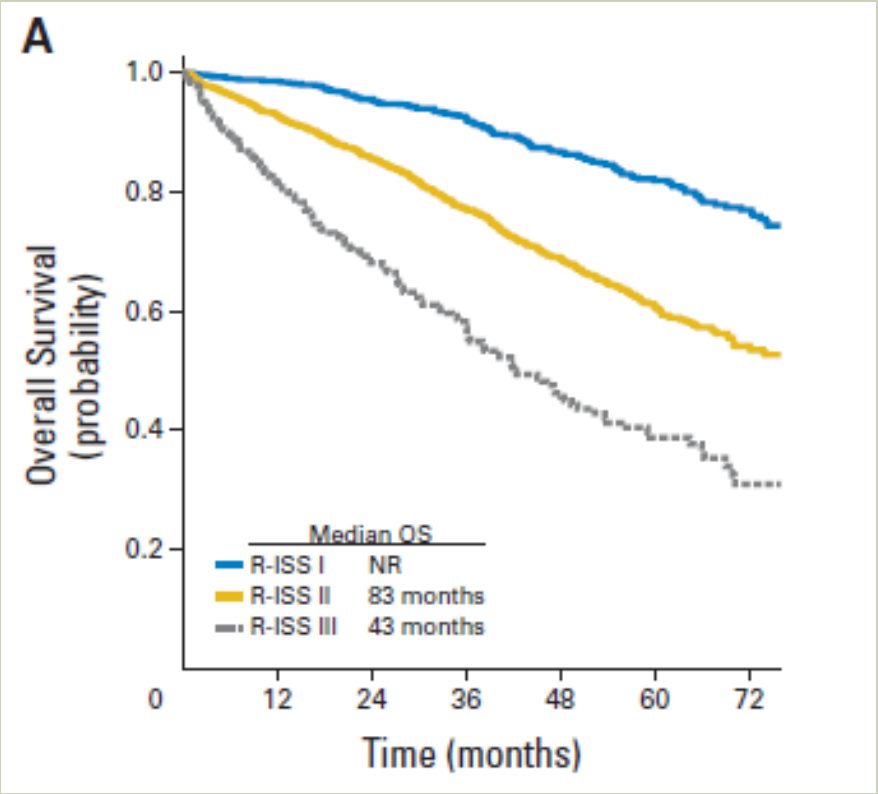
- NNT = 4.5 patients to convert one patient to ≥ VGPR
- Price for total treatment: $102, 816
- Price for one year of proteosome and lenalidomide based triplet = $200,000

Mellqvist et al. *Blood.* 2013.

CAN WE HELP PATIENTS WITH HARDER TO TREAT DISEASE?

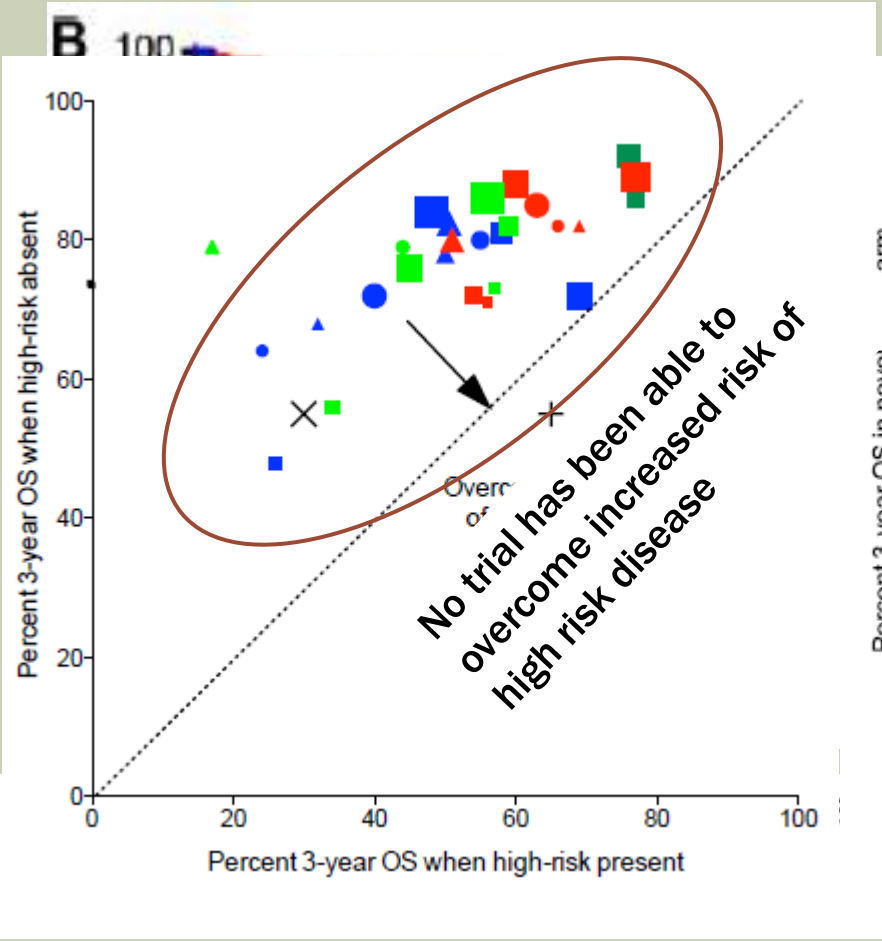
Table 1. Standard Risk Factors for MM and the R-ISS

Prognostic Factor	Criteria
ISS stage	
I	Serum β_2-microglobulin < 3.5 mg/L, serum albumin ≥ 3.5 g/dL
II	Not ISS stage I or III
III	Serum β_2-microglobulin ≥ 5.5 mg/L
CA by iFISH	
High risk	Presence of del(17p) and/or translocation t(4;14) and/or translocation t(14;16)
Standard risk	No high-risk CA
LDH	
Normal	Serum LDH < the upper limit of normal
High	Serum LDH > the upper limit of normal
A new model for risk stratification for MM	
R-ISS stage	
I	ISS stage I and standard-risk CA by iFISH and normal LDH
II	Not R-ISS stage I or III
III	ISS stage III and either high-risk CA by iFISH or high LDH

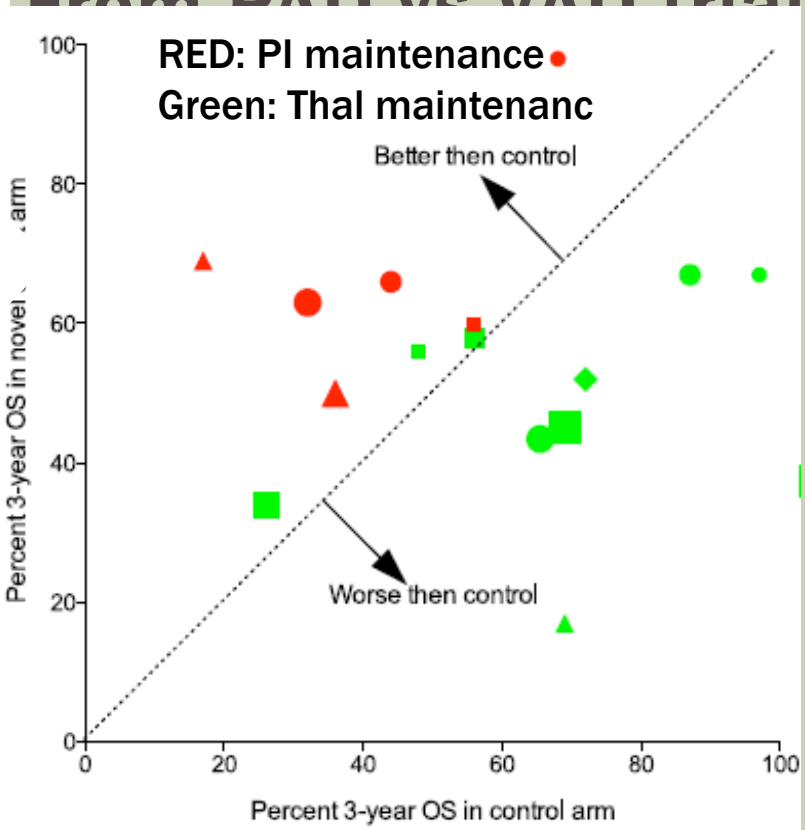


Palumbo. *JCO.* 2015.

HIGH RISK MYELOMA



From PAD vs VAD trial



Neben et al. 2012.
Bergsagel et al. 2013.

LENALIDOMIDE MAINTEANCE FOR HIGH RISK MYELOMA?

No compelling evidence that lenalidomide maintenance significantly ameliorates high risk

NEJM. 2014.

MOST AGGRESSIVE TREATMENT MAKES SENSE FOR HIGHEST RISK

Phase II trial from Emory

- 45 very high risk patients
- 42% 17p deletion, 34% PCL, others 4:14, 14:16, or 1q abnormalities
- RVD → AutoSCT → Started on RVD after transplant (weekly bortezomib, weekly dexamethasone, and 1-21 lenalidomide) up to three years then single agent lenalidomide
  - 96% > VGPR
  - PFS = 32 mos
  - Usual OS in this population would be around 2 years

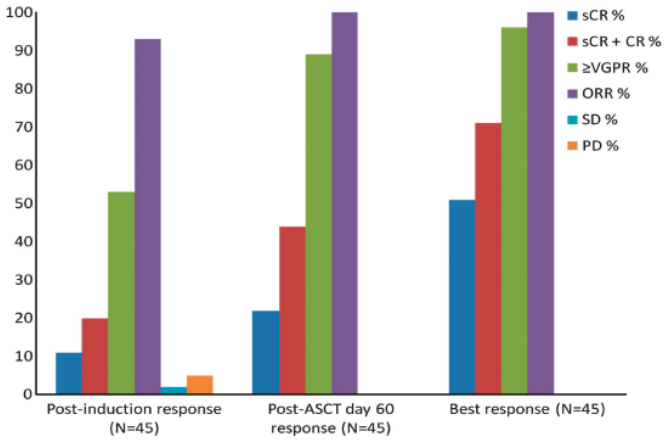


Figure 1. Response rates in patients with high-risk disease.

Nooka. *Leukemia*. 2014.

CONCLUSIONS

- Patients without at least VGPR likely to benefit from consolidation / maintenance approaches to get deeper response
- Bortezomib based maintenance appears to help diminish the increased risk associated with high risk multiple myeloma
- Lenalidomide maintenance alone DOES NOT show compelling evidence of attenuating increased hazard of high risk disease
- For fit patients with very high risk myeloma with abnormalities of p53 (17p), t(14:16), t(14:20), or PCL clinical trials remain the best option.
  - RVD induction and consolidation after transplant seem offer improved survival for patients who cannot be treated on trial

THE WAY FORWARD

ONGOING STUDIES

- BMT CTN 0702
  - RVD → autoSCT → 2nd autoSCT→ R maintenance
    →RVD consolidation→ R maintenance
    → R maintenance
- IFM/DFCI 2009 – RVD with or without transplant up-front
- E1A11: 2 years maintenance vs indefinite maintenance
- EMN trial : VRD consolidation or not after transplant

NEW AVENUES - IMMUNOTHERAPY

- Checkpoint inhibitors: being studied in relapsed/refractory disease with IMiD and alone after transplant
- Incorporation of antibody therapies into upfront therapy likely to move to maintenance approaches (see low grade lymphoma)
- Mayo Clinic Virus Therapy
- Dendritic cell /macrophage targeted vaccine and other trials
- CAR – T cell therapy (very early data <10 pts in relapsed disease)

OTHER ASPIRATIONS…

- More widely applicable minimal residual disease testing and response adapted trials (i.e. randomize patients to consolidation/maintenance strategies depending on their response to upfront therapy)
- Further study of risks / benefits of continued therapy for relapsed / refractory disease
- RESEARCH AND TRIALS REMAIN CRITICALLY IMPORTANT EVEN AS OUTCOMES IMPROVE

FINAL CONCLUSIONS

- Transplant Ineligible:
  - Continuous Rd provides a PFS benefit over the same regimen for 18 months
  - No data clearly favoring an optimal approach for high risk patients, reasonable to extrapolate transplant eligible data and aim for bortezomib based maintenance though toxicity may be more problematic
- Transplant eligible
  - Patients who do not achieve at least VGPR post transplant may benefit from further consolidation, we typically favor an additional 2-4 cycles of their initial regimen
  - Continuous treatment with frontline novel agent based triplet is promising and being studied further

FINAL CONCLUSIONS

- Transplant Eligible Maintenance By Risk Group
  - Low or standard risk myeloma without high risk cytogenetics
    - PFS benefit for lenalidomide post transplant (≈18 mos)
    - No consistent data suggesting an overall survival benefit (indefinite maintenance usually favored over 2 years, for now)
  - High risk patients
    - Bortezomib maintenance likely prolongs overall survival, 2 years is usually duration of PI based maintenance
  - Very High risk patients (17p-, t(14:16), t(14:20) or PCL)**
    - Clinical Trial best
    - Off trial RVD consolidation and indefinite maintenance may have additional benefit.

** Moving target**

BIG PICTURE

ALL OF THESE APPROACHES HAVE SIDE EFFECTS, DANGERS, AND BENEFITS. WITHOUT COMPELLING EVIDENCE OF SURVIVAL BENEFIT IT IS CRUCIALLY IMPORTANT WE INVOLVE PATIENTS IN A VALUES-BASED DISCUSSION OF MAINTENANCE DECISIONS.

QUESTIONS?

THANK YOU

REFERENCES