Maintenance Therapy

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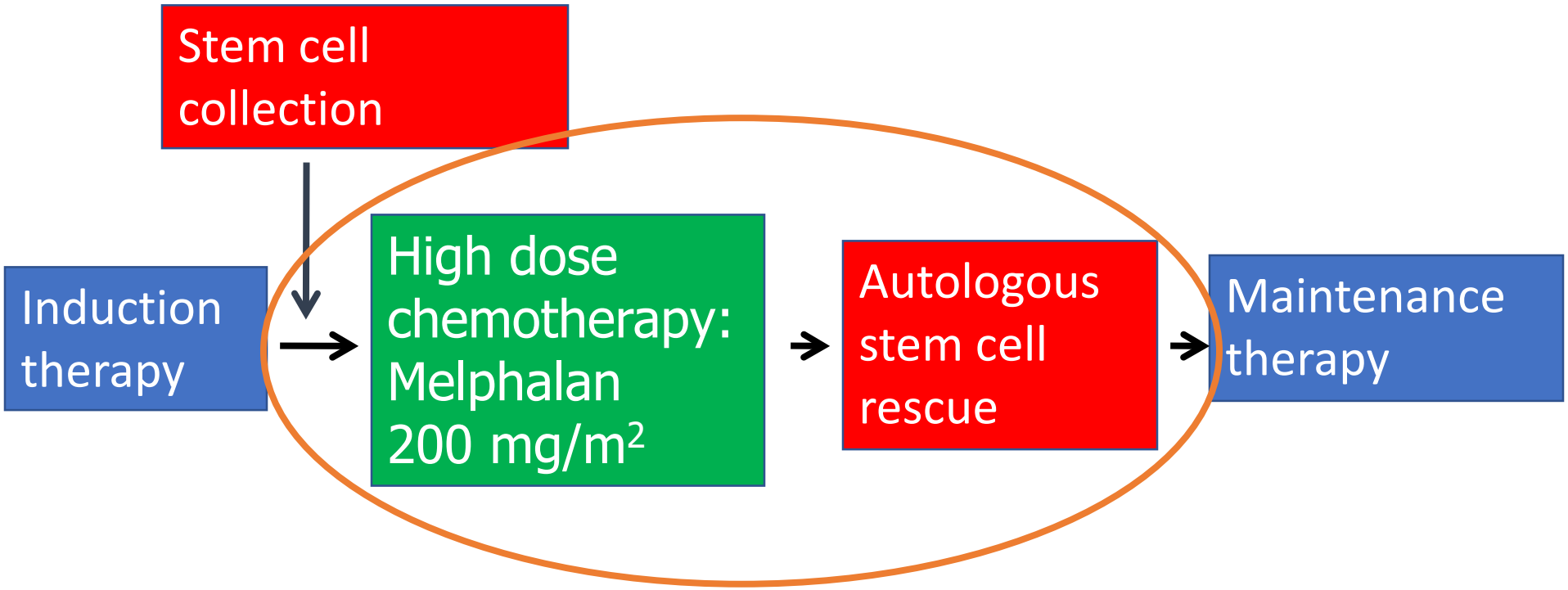
I got my transplant! Now what?

Treatment Schema for Myeloma



Why Maintenance Therapy?

Can maintenance therapy...

- Prevent or delay disease progression?
- Convert partial responses to complete responses?
- Improve overall survival?

Existing Evidence on Drugs Used as Maintenance Therapy

Revlimid

- Reduction in myeloma progression (3 large studies)
- Improved survival (1 of 3 studies)
  Small risk of second cancers when used after melphalan
- Now approved for use as maintenance treatment after ASCT

Velcade-based treatment

- Supported by several smaller studies

Ninlaro

- Oral proteasome inhibitor

Additional agent under investigation: Kyprolis

Maintenance Therapy in Myeloma

What we know

- Progression-free survival advantage
- Overall survival improvements?
- Toxicities of treatment
  - Myelosuppression
  - Second primary malignancies[1,2]
  - Quality of life
- Cost

What we don't know

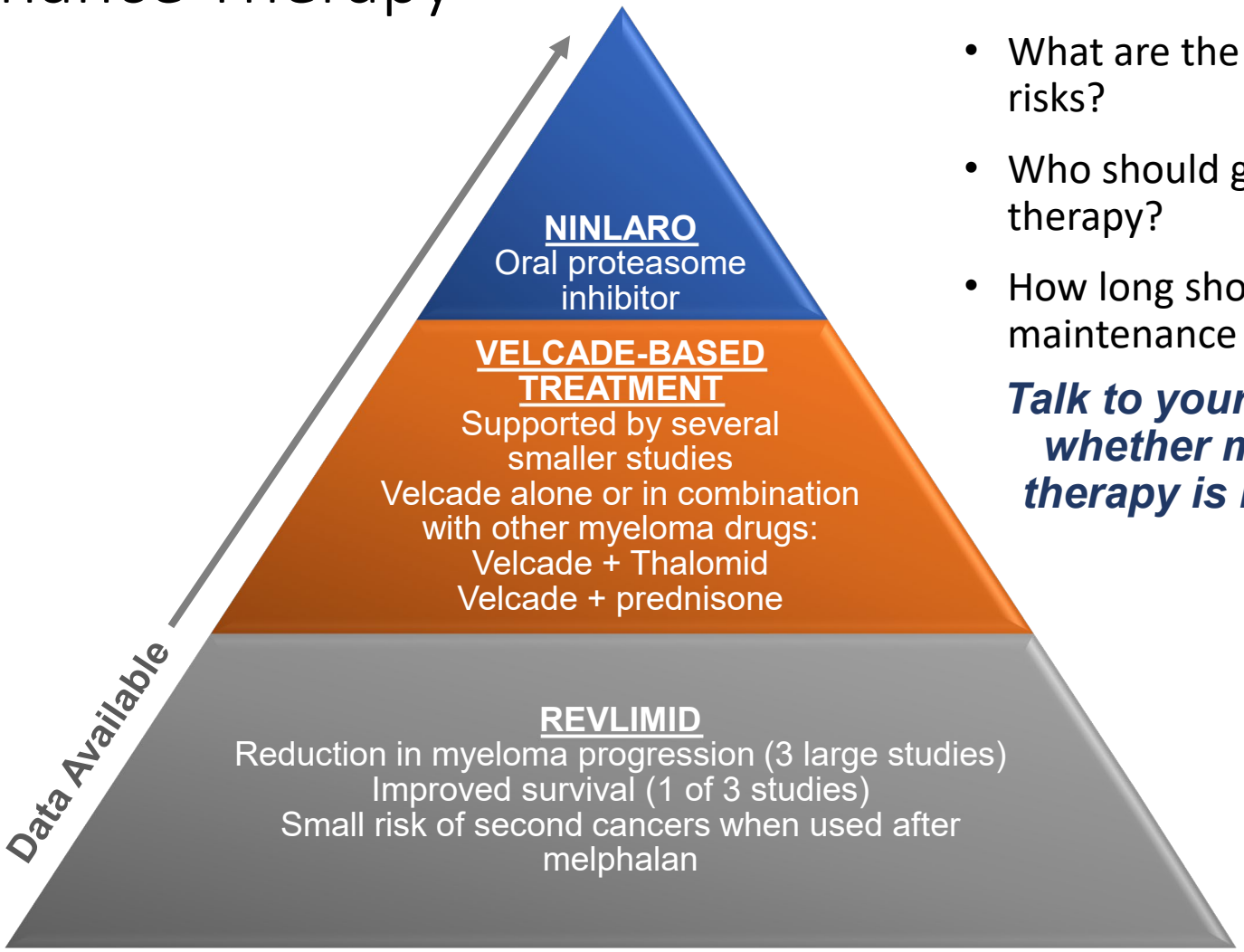
- Whether all patients benefit from maintenance
- Which agent to use and duration of therapy
- Response to higher doses of Revlimid at relapse
- Evolution of resistant clones

Maintenance Therapy Benefits and Risks

The anti-myeloma benefits of continuous therapy must be balanced with the toxicities of prolonged treatment.

A major concern with the use of maintenance therapy is the development of toxicity that limits long-term use and potentially compromises the ability to receive optimal treatment in the future.

Following Transplantation: Possible Consideration of Maintenance Therapy



- What are the benefits vs risks?
- Who should get maintenance therapy?
- How long should patients get maintenance therapy?

Talk to your doctor about whether maintenance therapy is right for you.

Maintenance Lenalidomide
Meta-Analysis

- Outcomes with maintenance lenalidomide vs placebo/observation after ASCT:

	Meta-Analysis (N = 1208)[d]
Median PFS,* mo	**52.8 vs 23.5**
Median OS,* mo	**NR vs 86.0**
SPM	↑Len vs placebo/obs

*Significantly improved with maintenance lenalidomide.

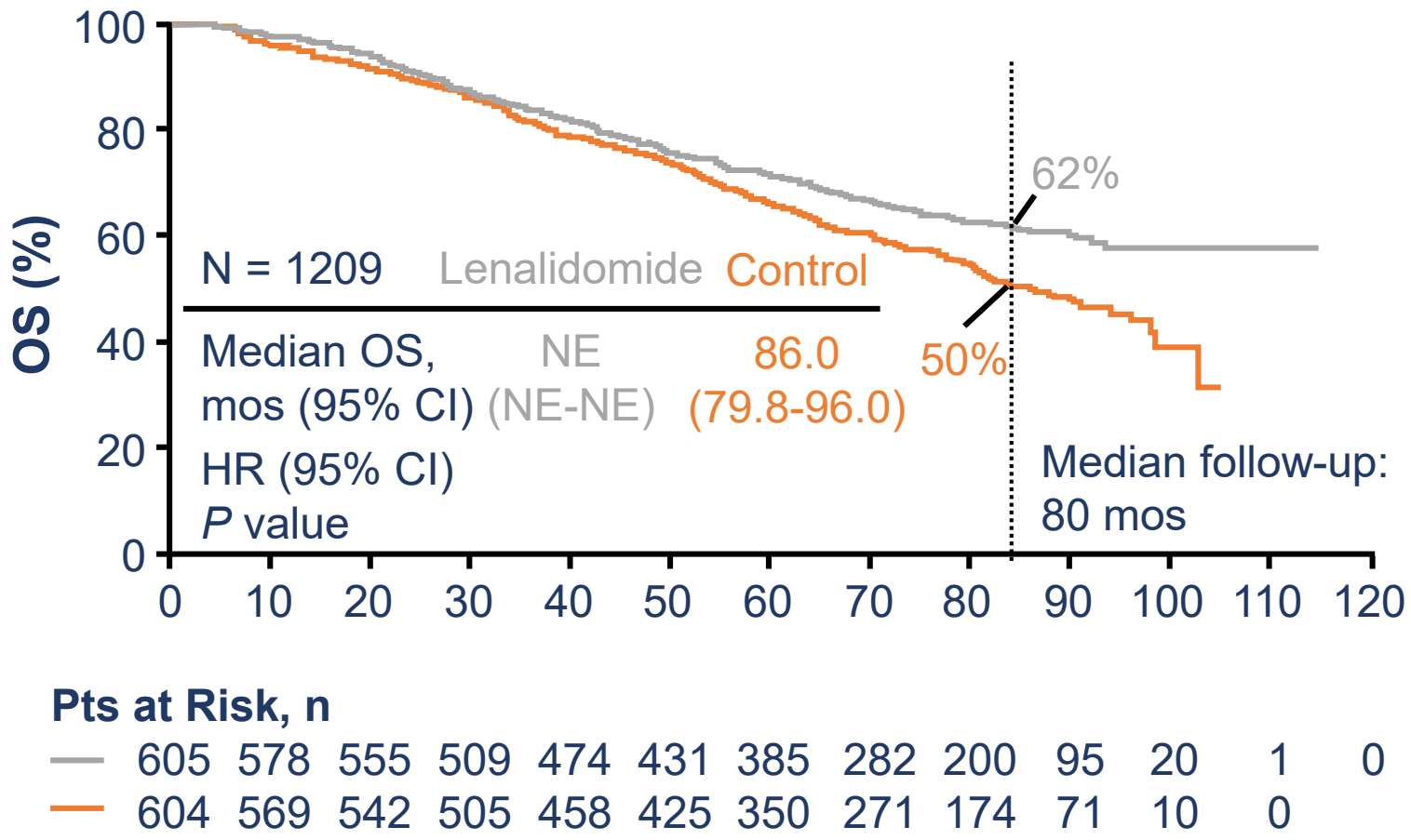
- McCarthy PL, et al. *J Clin Oncol.* 2017;35:3279-3289.

Post-transplant therapy

- American study (CALGB): improvement in PFS and OS with lenalidomide maintenance
  - Increased risk of secondary cancers 11% vs 4% (6% blood cancers vs 1%)[2]
- European study (IFM): improvement in PFS but not OS[3]
  - Increased secondary cancers (13% vs 7%)
- Meta-analysis of 3 trials:improvement in OS for maintenance groups, regardless of response to transplant[3]

1. McCarthy et al, NEJM 2012
2. Attal et al, NEJM 2012
3. Attal et al, ASCO 2016

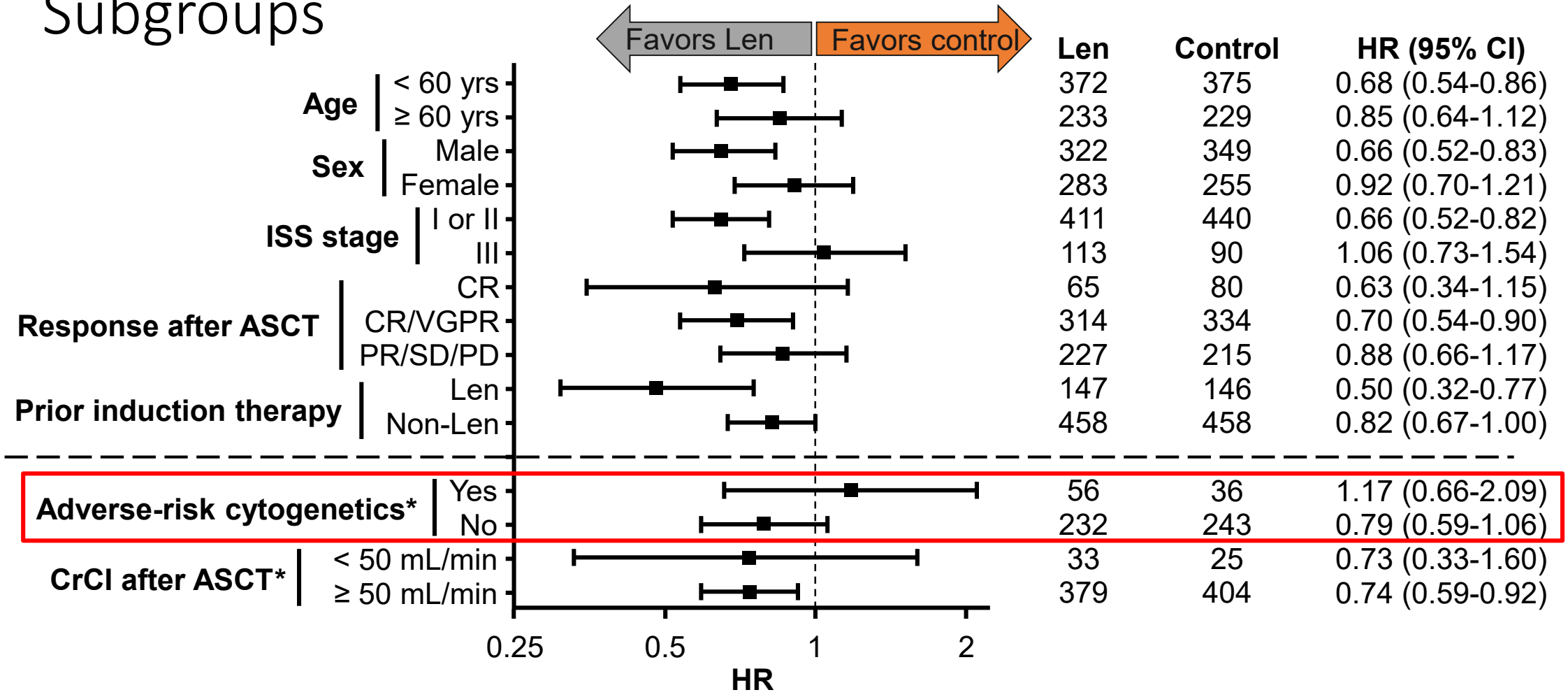
Meta-analysis of 3 Phase III Trials: OS With Len Maintenance after ASCT



26% reduction in risk of death; estimated 2.5-yr increase in median OS

McCarthy PL, et al. J Clin Oncol. 2017;[Epub ahead of print].

Meta-analysis of 3 Phase III Trials: OS Benefit in Subgroups



*Incomplete data sets: Cytogenetic data were available only for the IFM and GIMEMA studies; CrCl post-ASCT data were available only for the CALGB and IFM studies

McCarthy PL, et al. J Clin Oncol. 2017;[Epub ahead of print]

Continuous Therapy Concerns

- Effects on immune system
- Effects on blood production/bone marrow
- Potential effects on drug resistance[1,2]
- Toxicity[3]
  - *Early* → fatigue, GI toxicity, reduction in blood cell production, peripheral neuropathy, blood clots, diarrhea, others
  - *Late* → secondary primary cancer, decreased marrow reserve

Management of Common Toxicities With Revlimid Maintenance

Fatigue	Diarrhea	Rash	Thrombosis	Muscle spasms
• Dosing: every night at bedtime (?) • Dose reduction	• Antidiarrheal agents • Bile salt binders/low-fat diet (for example, colesevelam, cholestyramine)*	• Topical steroids/oral antihistamines • Hold/reduce dose	• Prophylaxis with aspirin	• Quinine sulfate 300 mg every night at bedtime • Clonazepam in severe cases

Minimizing Toxicity of Velcade

Peripheral neuropathy

- Weekly dosing[1]
- Subcutaneous administration[2]

Gastrointestinal[3]

- Ondansetron premedication
- Antidiarrheal agents
- Subcutaneous administration

Infection

- Antizoster prophylaxis with acyclovir or related antiviral agent

Summary

The body of evidence from phase 3 trials indicates that maintenance (or "continuous") therapy improves progression-free, and likely overall, survival

The optimal duration is uncertain; however, data to date suggest that it should be given until progression

- Trials are evaluating various durations of therapy (1 year, 3 years, or until progression; StAMINA, IFM/DFCI 2009 trials, respectively)

Given the heterogeneity of myeloma, some patients likely do not need maintenance, whereas others may do well with truncated courses

- However, we currently do not have the ability to determine these patients prospectively or during therapy

Minimizing toxicity and maximizing quality of life are essential to the success of maintenance therapy

- Choice of agents/regimens
- Dose adjustments
- Symptom management
- Monitoring incidence/risk factors for late toxicity important

Implementing Maintenance Therapy

Who should be offered maintenance therapy?

- Most patients, regardless of response[a]

What should they receive?

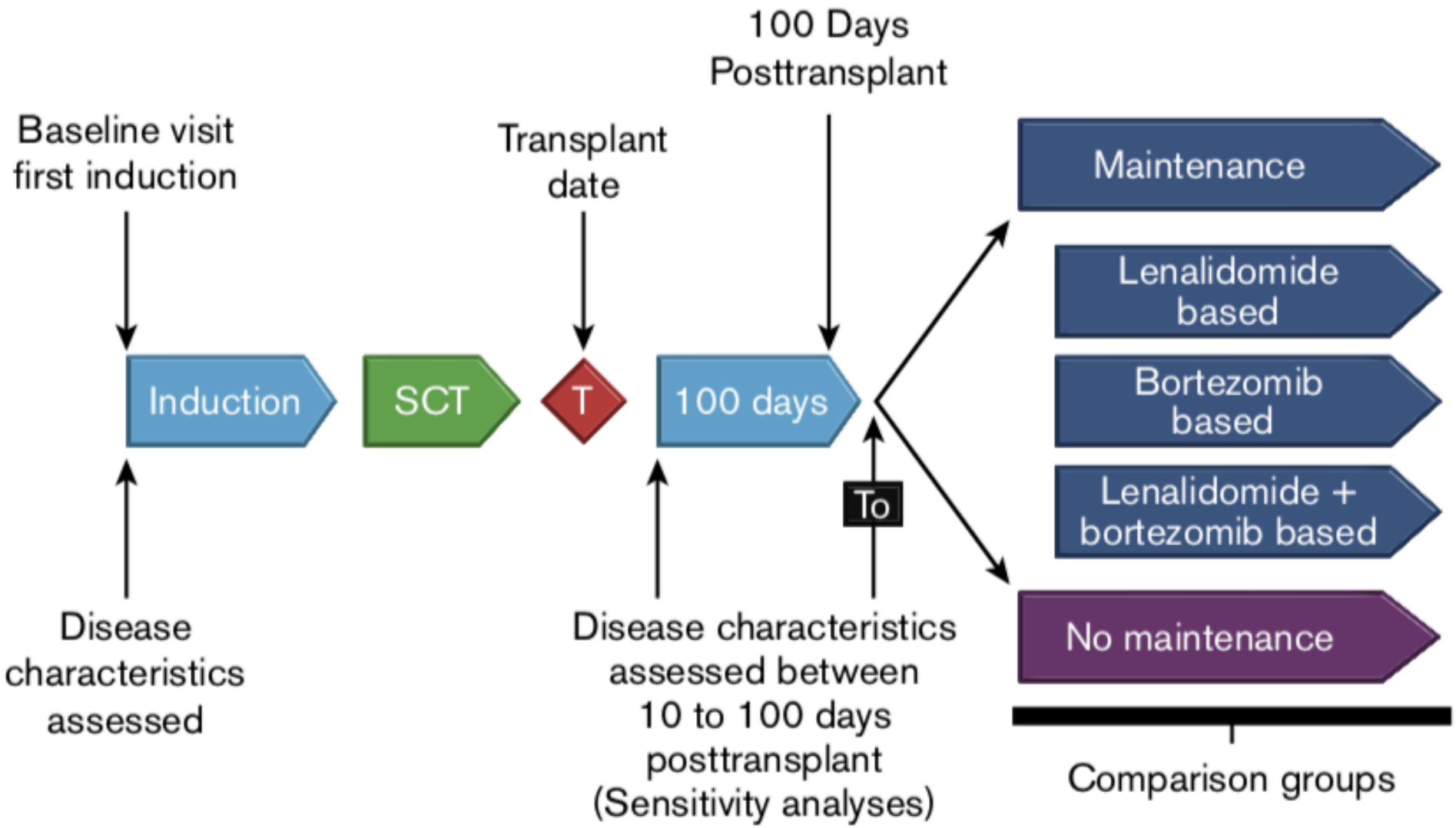
- Most patients: lenalidomide monotherapy[a]
- High-risk disease: consider proteasome inhibitor-based maintenance[b-c]

For how long should they receive it?

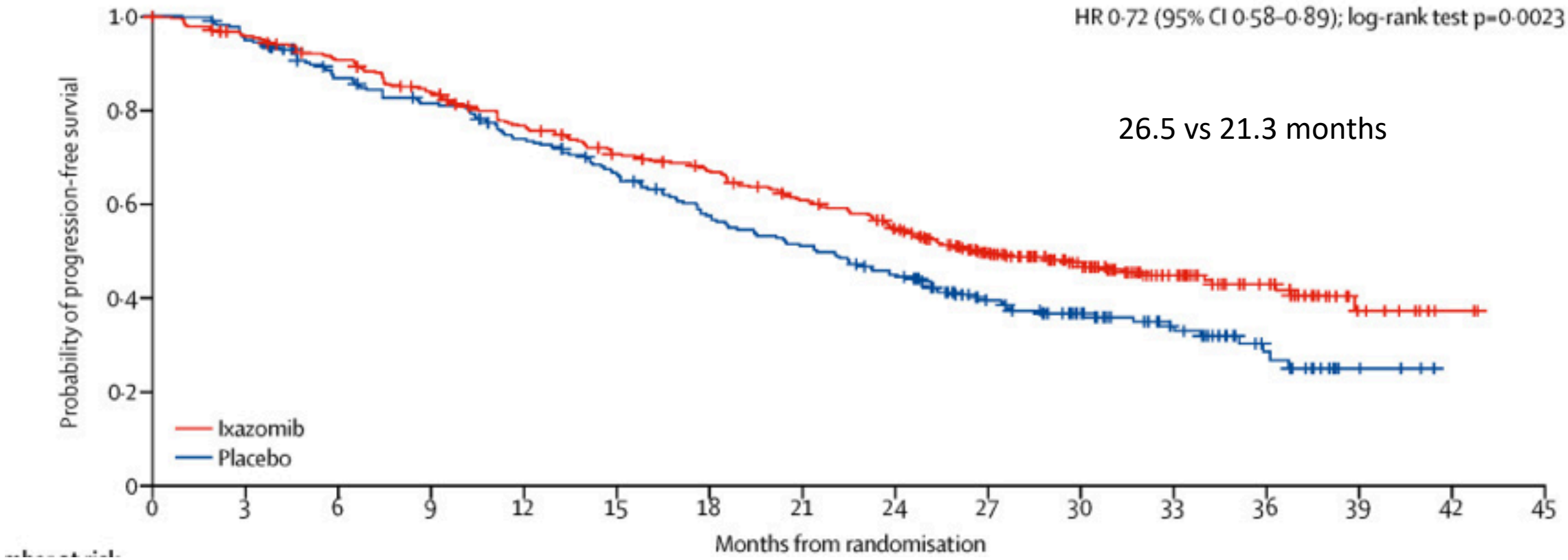
- Lenalidomide monotherapy: at least 2 years, continuing if tolerated, 10 mg to 15 mg daily, 21 d of 28 d cycle

- a. McCarthy PL, et al. *J Clin Oncol.* 2017;35:3279-3289; b. Sonneveld P, et al. *J Clin Oncol.* 2012;30:2946-2955;
- c. Nooka AK, et al. *Leukemia*. 2013;28:690-693;

Other options for maintenance regimens



Ixazomib maintenance



26.5 vs 21.3 months

Secondary Cancers

- Revlimid maintenance after transplant has been associated with a higher risk of other cancers
- In general, the risks of myeloma relapsing (100%) is far greater than the risk of getting a difference cancer from revlimid (~7%?)

Thank you…!