Maintenance Therapy

FDA:ASH Workshop

Harousseau, Munshi, Roodman, Stewart, Bross, Kaminskas

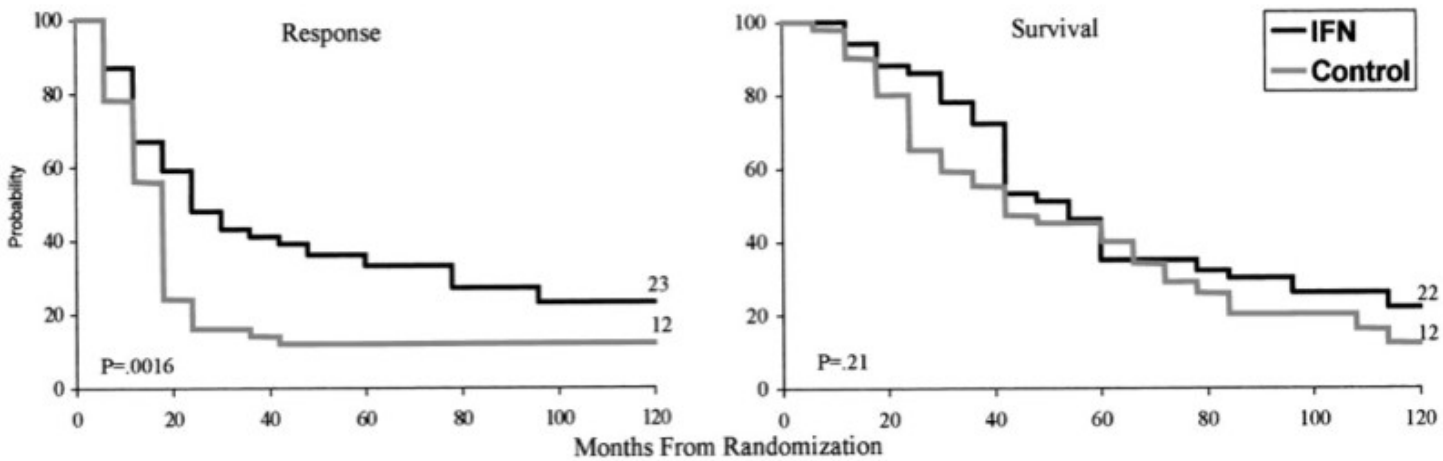
Focus

Newly Diagnosed Patients

Definition

The addition of any chronically applied therapy, following induction in responding or stable patients, with the goal of prolonging survival

EFS endpoint is Inadequate e.g. Interferon-alpha

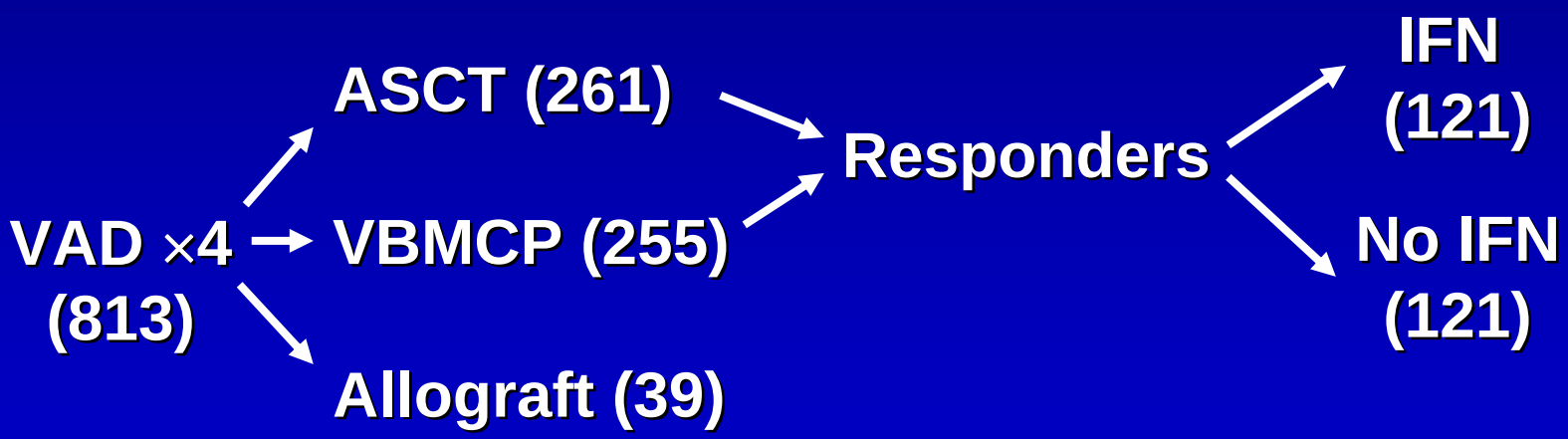


Mandelli *et al*, NEJM 1990

Months From Randomization

Maintenance with IFN after ASCT Comparable Survival in MM

In study of 899 patients, HDT (melphalan 140 mg/m^2 + TBI 12 Gy) vs standard dose VBMCP therapy showed no benefit for IFN maintenance



Barlogie, et al. *J. Clin Oncol* 2006, 24(6), 929-936]

Comparable Survival in MM With or Without IFN

	CR	PR	PFS	OS
ASCT	17%	93%	25 mo *P*=0.05	62 mo *P*=0.8
VBMCP	15%	91%	21 mo	53 mo
+ IFN			23 mo	59 mo
– IFN			18 mo	74 mo

P=NS

52% VBMCP patients had salvage ASCT→ 59% PR (OS 30 mo) vs 23 mo w/o ASCT (*P*=0.05)

Barlogie, et al. *J. Clin Oncol* 2006, 24(6), 929-936]

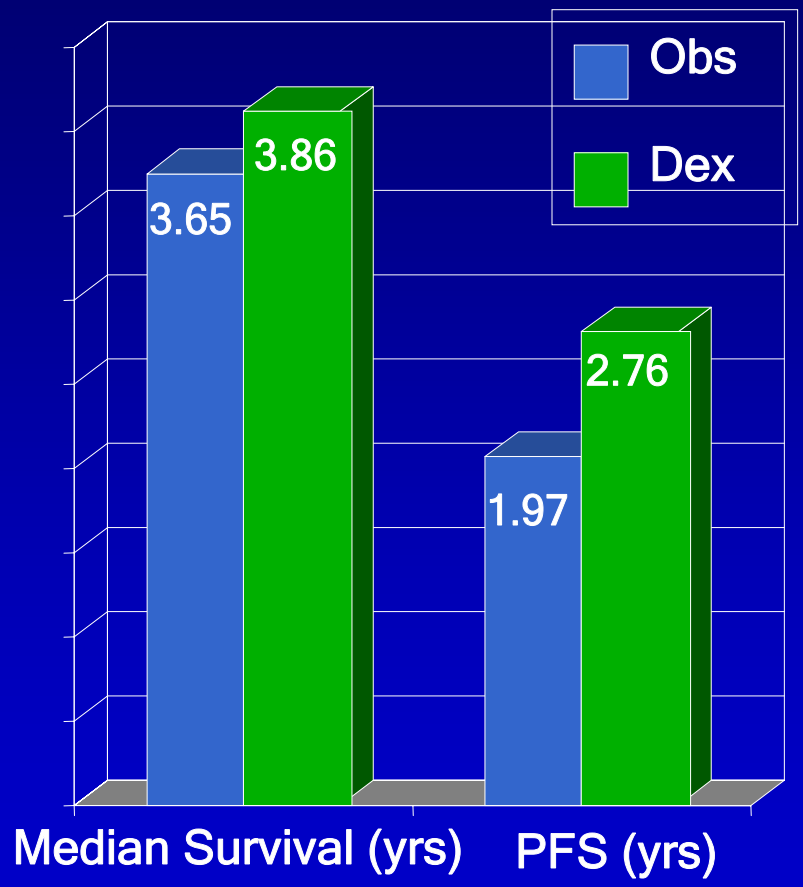
Role of Maintenance Dexamethasone

- 307 pts
- Randomized trial following MP or M-Dex therapy to: Dex versus Observation
- Progression free survival better with maintenance Dex
- But no improvement in overall survival
- Further studies of maintenance therapy using novel agents needed

C. Shustik et al. Proc ASCO 2004

Outcomes with Maintenance: Role of Quality of Life

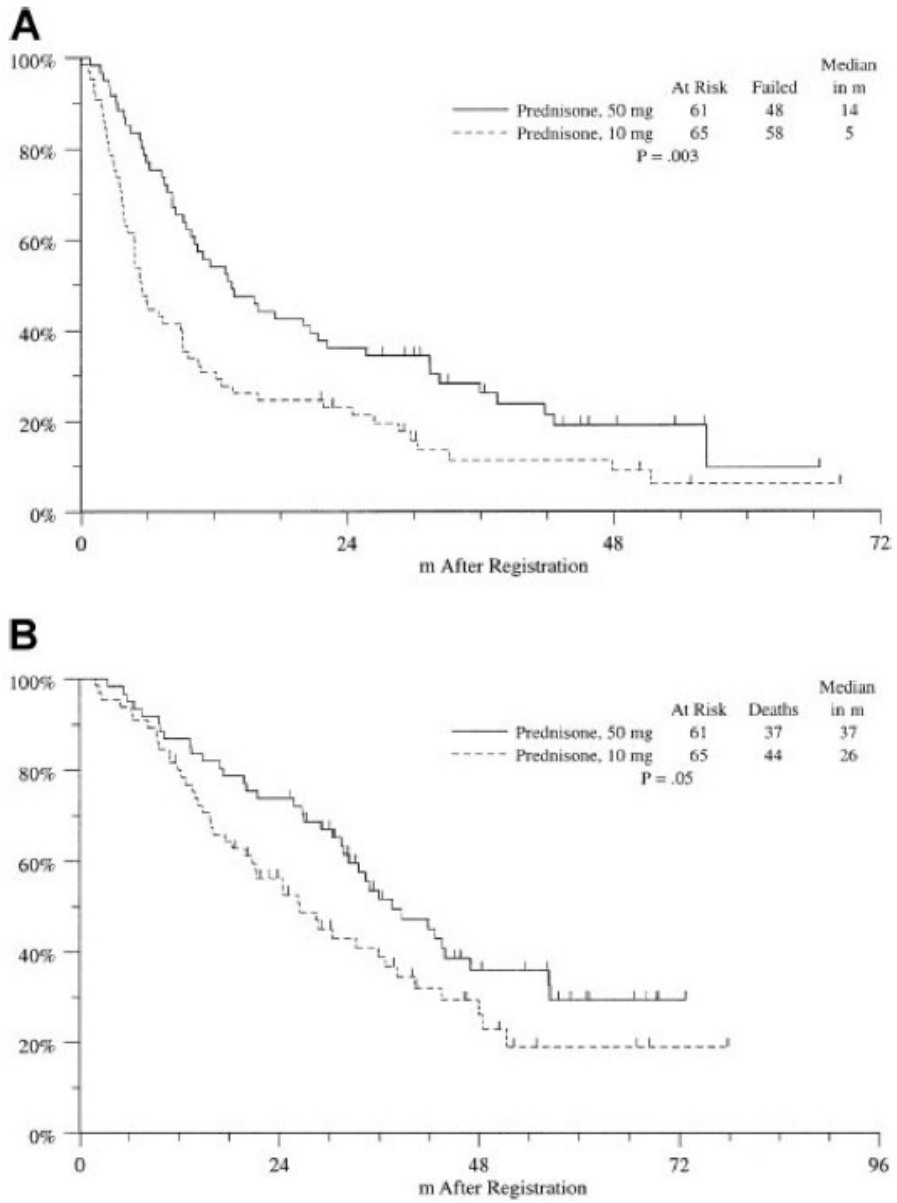
- Higher PFS
  p = 0.0001
- OS p = 0.3 (NS)
- Dex did raise the risk of infections, hyperglycemia, and neuropsychiatric complications



Shustik, C et al. ASCO Abstract 6510, 2004.

Alternate day prednisone after VAD

- OS from maintenance
- 50mg 37mo
- 10mg 26mo



Berenson *et al* BLOOD 2002

IFM 99 02: Treatment Arms

Randomization:
(3 months after the 2^{d} transplant,
no progression)

Arm A : no maintenance

Arm B : Pamidronate 90 mg/month

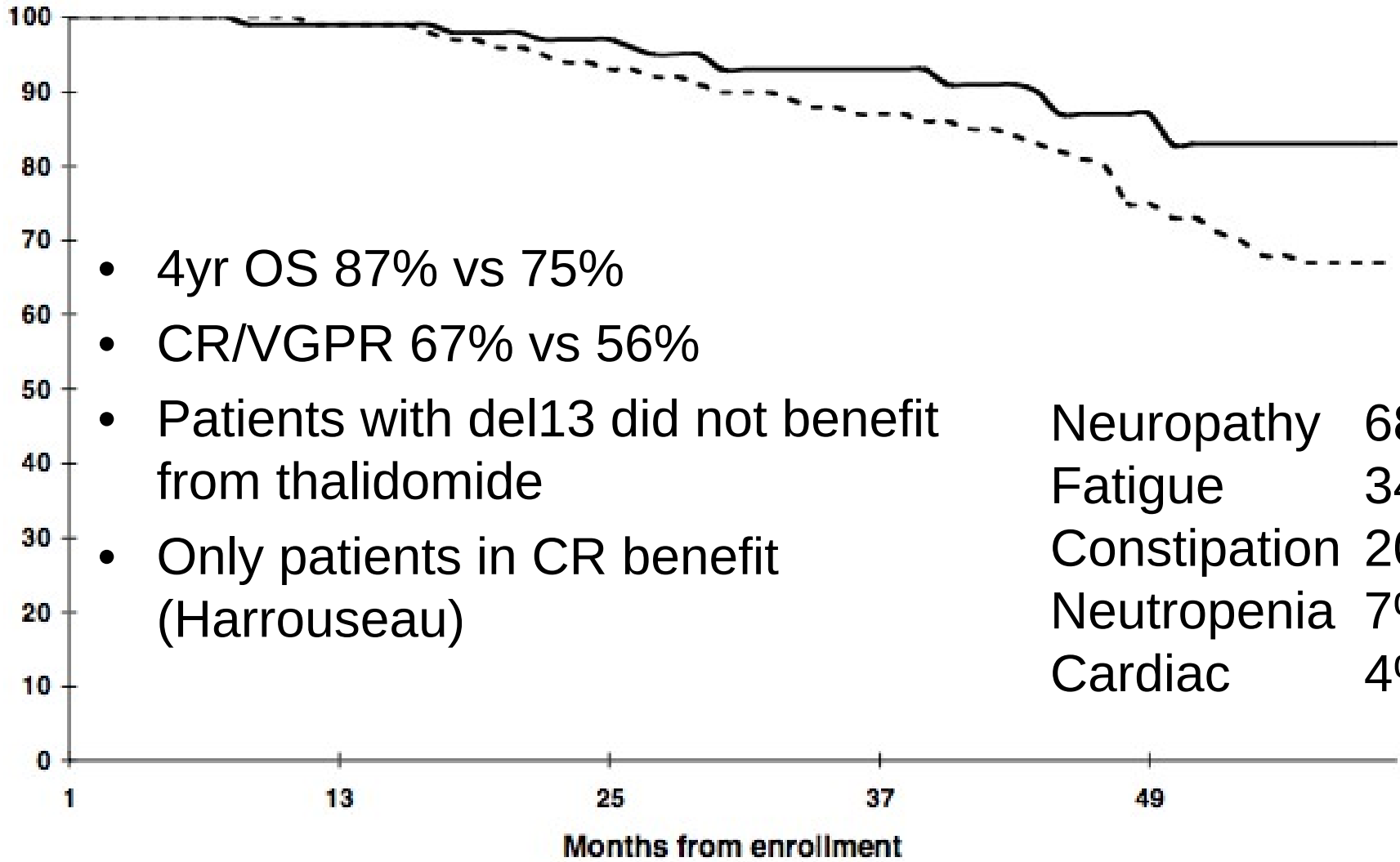
Arm C : Thalidomide 100 mg/d + Pamidronate

IFM 99 02 : PFS from Random.

	Arm A	Arm B	Arm C	p
Progression	25%	24%	15%	0.04
Median PFS	27 m	28 m	> 38 m	
3-year PFS	34%	37%	56%	0.01

ASH 2004

IFM99-02: The Role of CR



- 4yr OS 87% vs 75%
- CR/VGPR 67% vs 56%
- Patients with del13 did not benefit from thalidomide
- Only patients in CR benefit (Harrouseau)

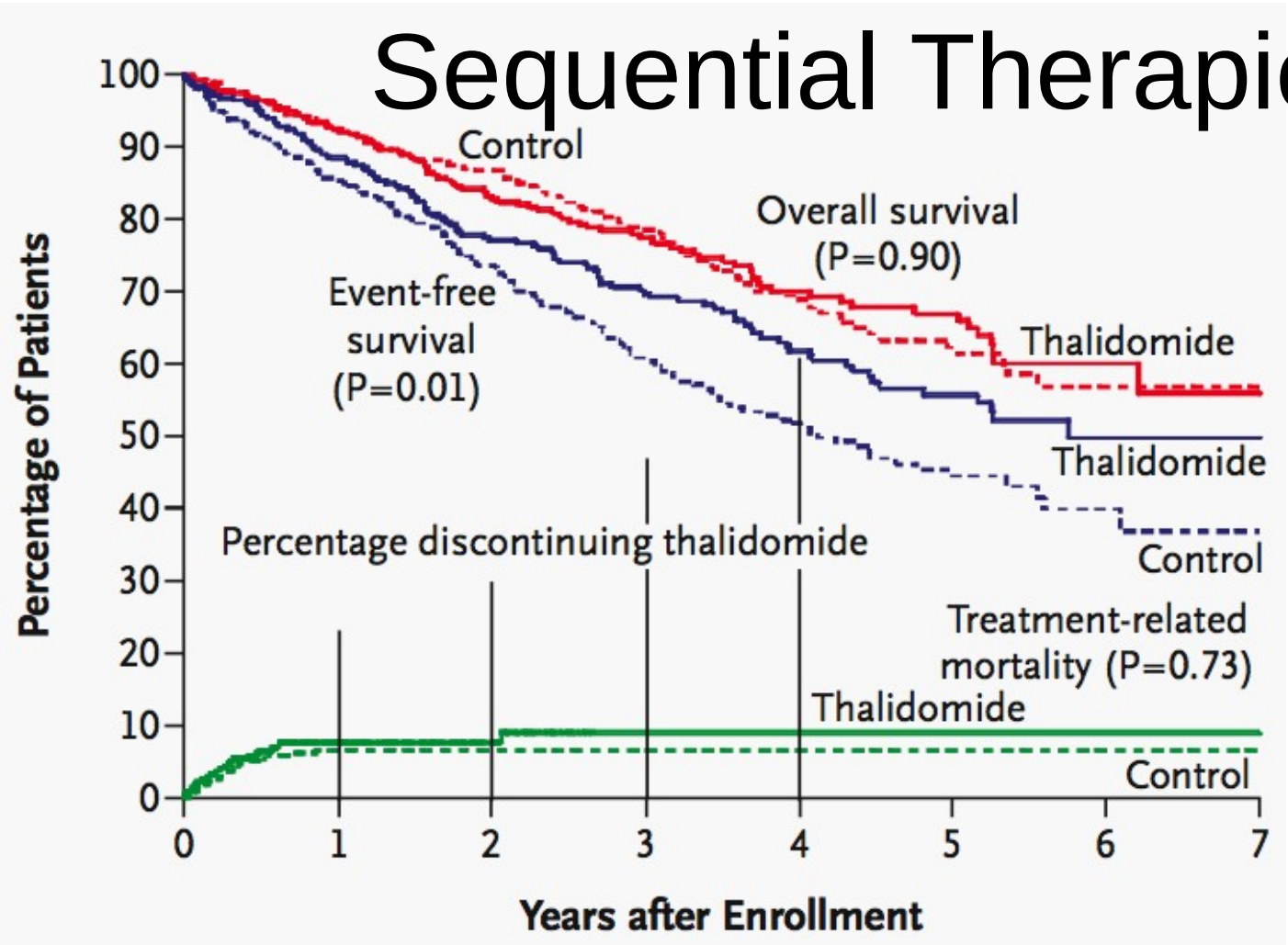
Neuropathy	68%
Fatigue	34%
Constipation	20%
Neutropenia	7%
Cardiac	4%

Attal *et al* BLOOD 2006

NCIC My9 Summary: Thal 200 versus 400

- 76% versus 41% on maintenance at 18 months
- 88% reduced thalidomide
- 72% reduced prednisone
- 15% nCR or CR at registration upgraded response in 53% of those evaluable
- 38% CR or NCR at 12 months

Maintenance versus Sequential Therapies



Neuropathy
15% vs 5%

Neutropenia
46% vs 28%

- Thalidomide 100mg qd 1st year and LMW Heparin
- Thalidomide 50mg qod after 1st year and LMW Heparin

Barlogie *et al* NEJM 2006

NCIC/ECOG: My10

Previously untreated Myeloma

↓

ASCT within 1 yr. of diagnosis

↓

Within 60 -100 days of ASCT

↓

Randomize

↓ ↓

Prednisone 50 mg Q2days + Thalidomide *200* mg / day

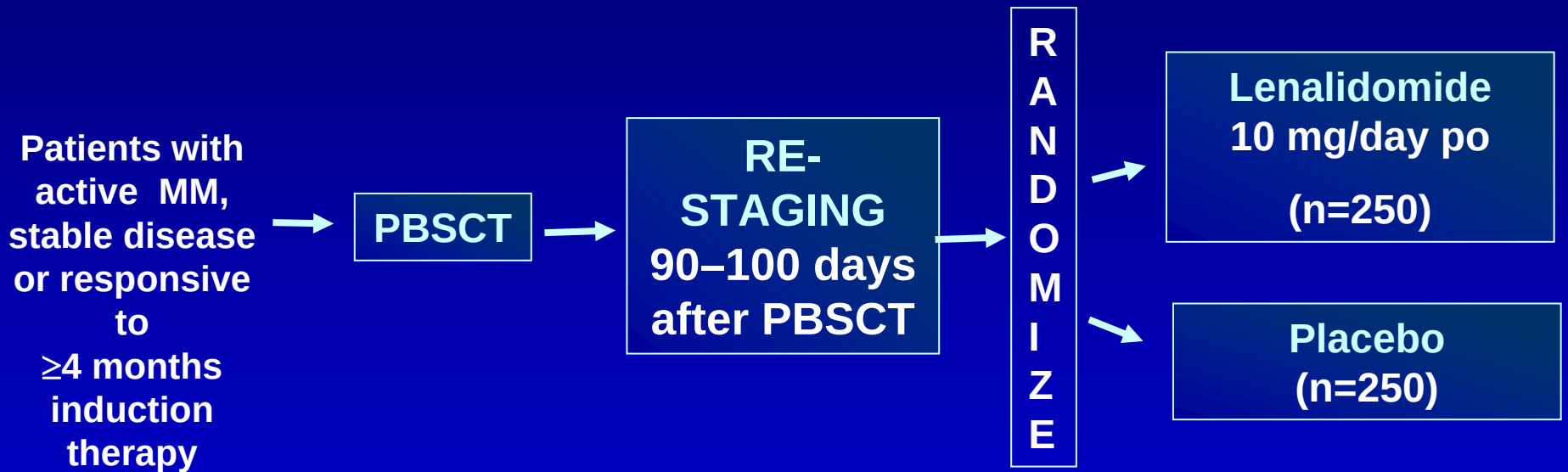
No Further Therapy

Randomized phase III design; endpoints: overall and PFS;

SS = 312

Ongoing Study of Lenalidomide As Maintenance Therapy Following Autologous PBSCT for MM

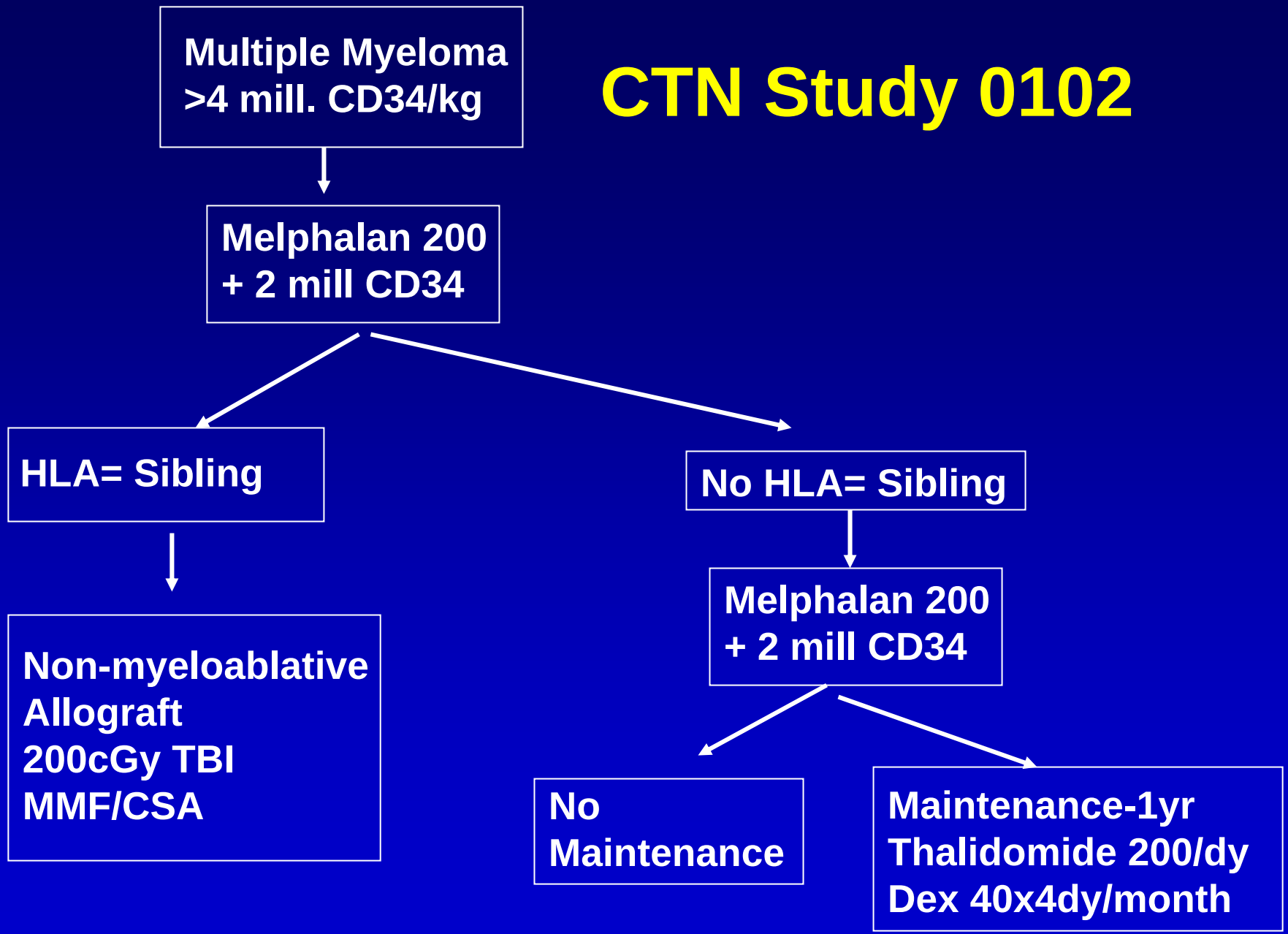
CALGB 100104: Phase III Randomized, Placebo-Controlled Trial



1° Endpoint: Time to disease progression after autologous PBSCT

2° Endpoints: CR rate, PFS, overall survival, feasibility of long-term lenalidomide

CTN Study 0102



Suggested Endpoints

- OS impractical
- EFS on its own inadequate
- CR provides guidance and is likely useful but evidence is not there to make it primary endpoint
- QOL not validated
- Consider Risk Stratification in Trials allowing OS endpoint

Suggested Endpoints

TRIAD OF:-

Improved Complete Response rate

And

Improved Event Free Survival

Supported by

Acceptable QOL change

Unanswered Questions

1. Is definition and focus on newly diagnosed patient appropriate
2. Do we agree that OS impractical (should high risk groups be the focus)
3. Is the Triad appropriate
4. If QOL is not approvable is CR plus EFS enough
5. What about health Economics
6. How do we factor in influence of sequential therapy