Continuous Therapy for Myeloma in the era of novel agents

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Definition and Aims of Consolidation, Maintenance, Continuous Therapy

Consolidation

- Increase depth of response (achieve MRD negativity ?)
  - By administration of therapy for limited (not yet strictly defined) period of time
  - Single regimen or different early and late consolidation regimens ?

Maintenance / Continuous

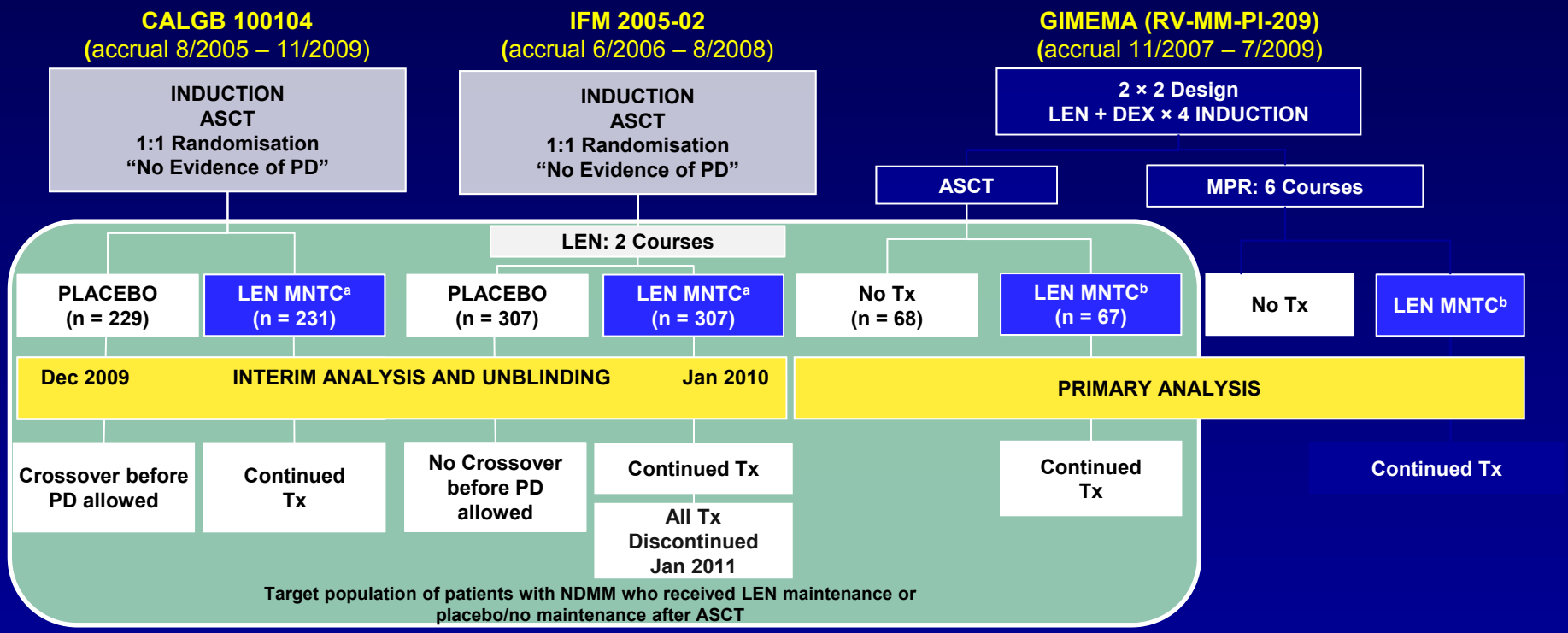
- Increase response duration, PFS, OS
  - By administration of treatment for a prolonged time period
  - In elderly patients the concept is continuous treatment

OS, overall survival; PFS, progression-free survival

Sustained responses following ASCT are needed: Impact of maintenance

LEN Maintenance After ASCT in MM: OS Analysis

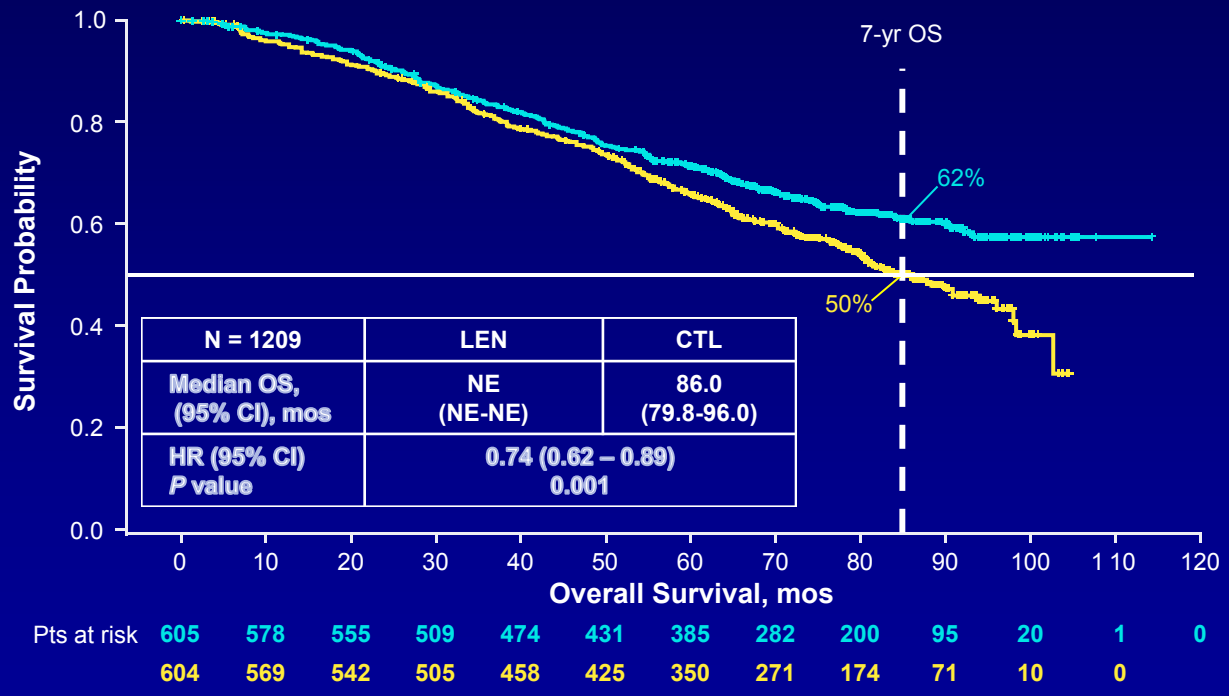
Studies Included in the Meta-Analysis



Attal M et al. *ASCO 2016*. Oral Presentation & Abstract 8001

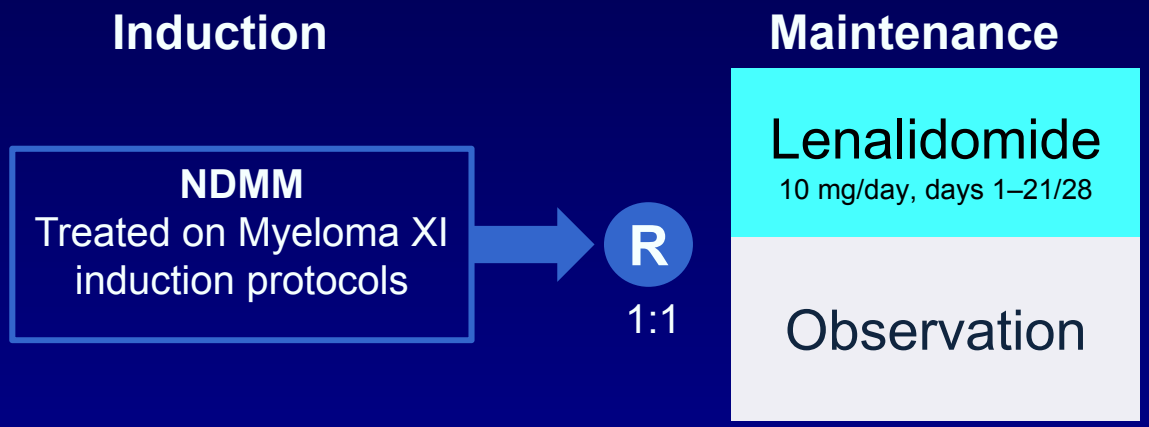
LEN Maintenance after ASCT in MM: OS Analysis

- 26% reduction in risk of death, with an estimated 2.5-year increase in median survival[a]



[a] Median for LEN treatment arm was extrapolated to be 116 months based on median of the CTL arm and HR (median, 86 months; HR = 0.74).

Myeloma XI - Lenalidomide Maintenance



N=1551 TE=828; TNE=723

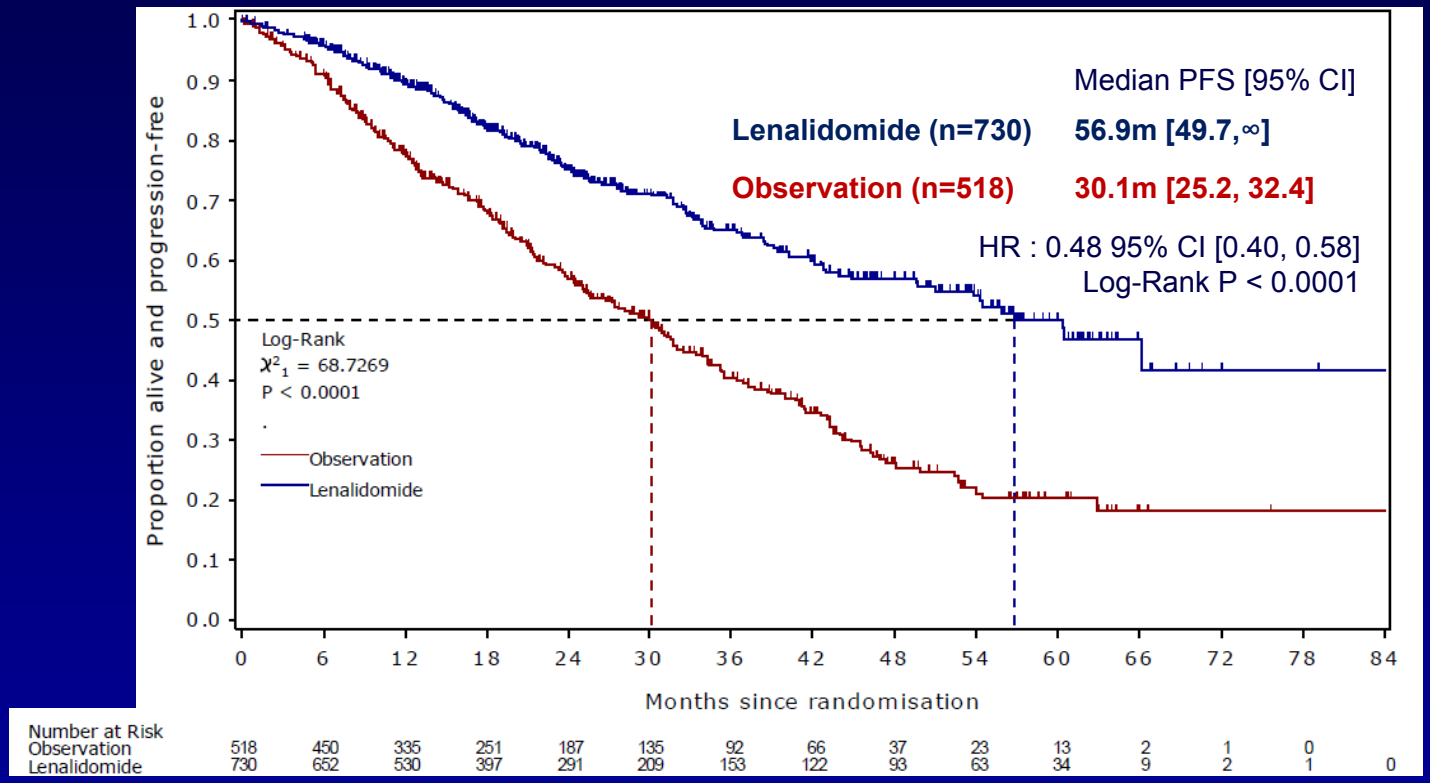
Median follow-up: 27 months (IQR 13–43)

Exclusion criteria

- Failure to respond to lenalidomide as induction IMiD, or development of PD
- Previous or concurrent active malignancies

Transplant eligible pathway

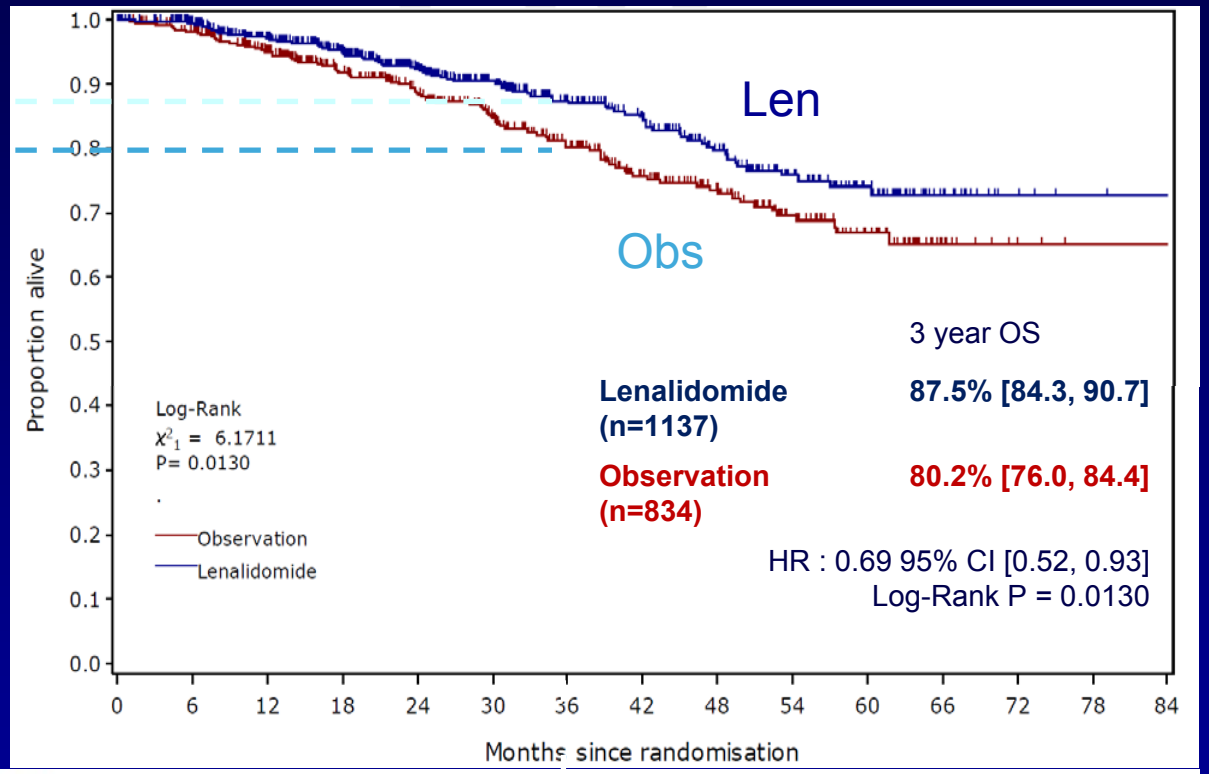
Lenalidomide improved PFS from 30 to 57 months, hazard ratio of 0.47



Transplant eligible pathway

Lenalidomide improved 3 yr OS from 80.2% to 87.5%, hazard ratio of 0.69

3 yr OS:
87.5%
80.2%

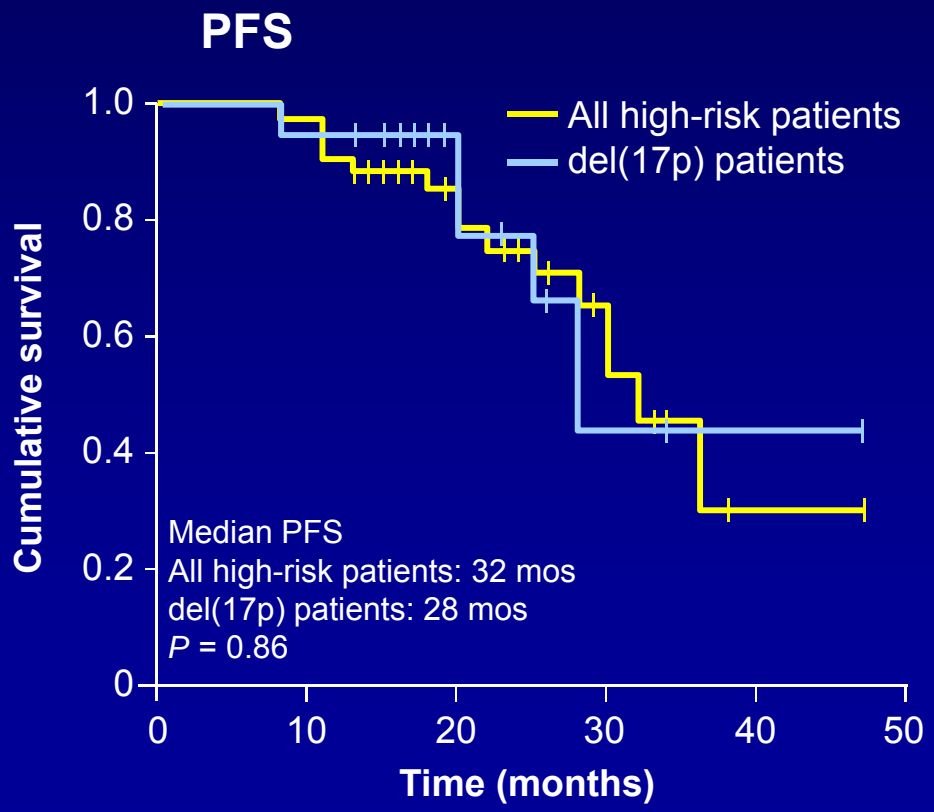


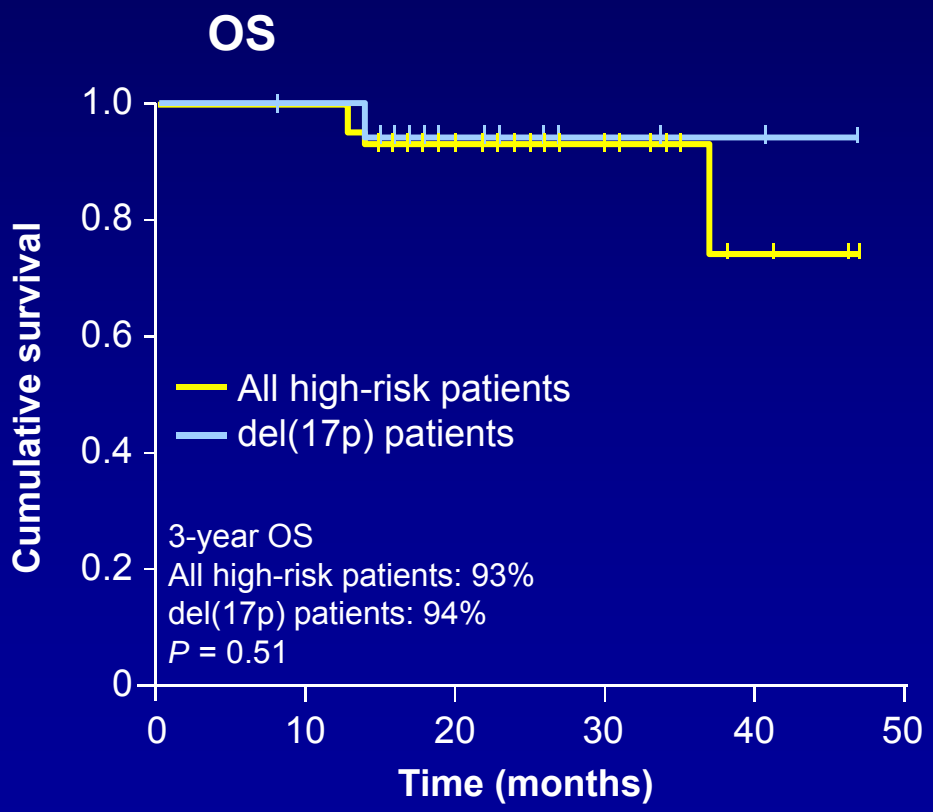
Number at Risk														
Observation	518	495	436	364	311	252	202	156	125	87	51	15	2	0
Lenalidomide	730	693	597	484	378	284	224	181	137	97	58	17	4	1	0

PFS and OS of High-Risk del(17p) Patients receiving RVD Maintenance Post-ASCT

ASCT → RVD Maintenance) (up to 3 years) → Maintenance LEN

Best response with VRD; sCR 51%, VGPR 96%

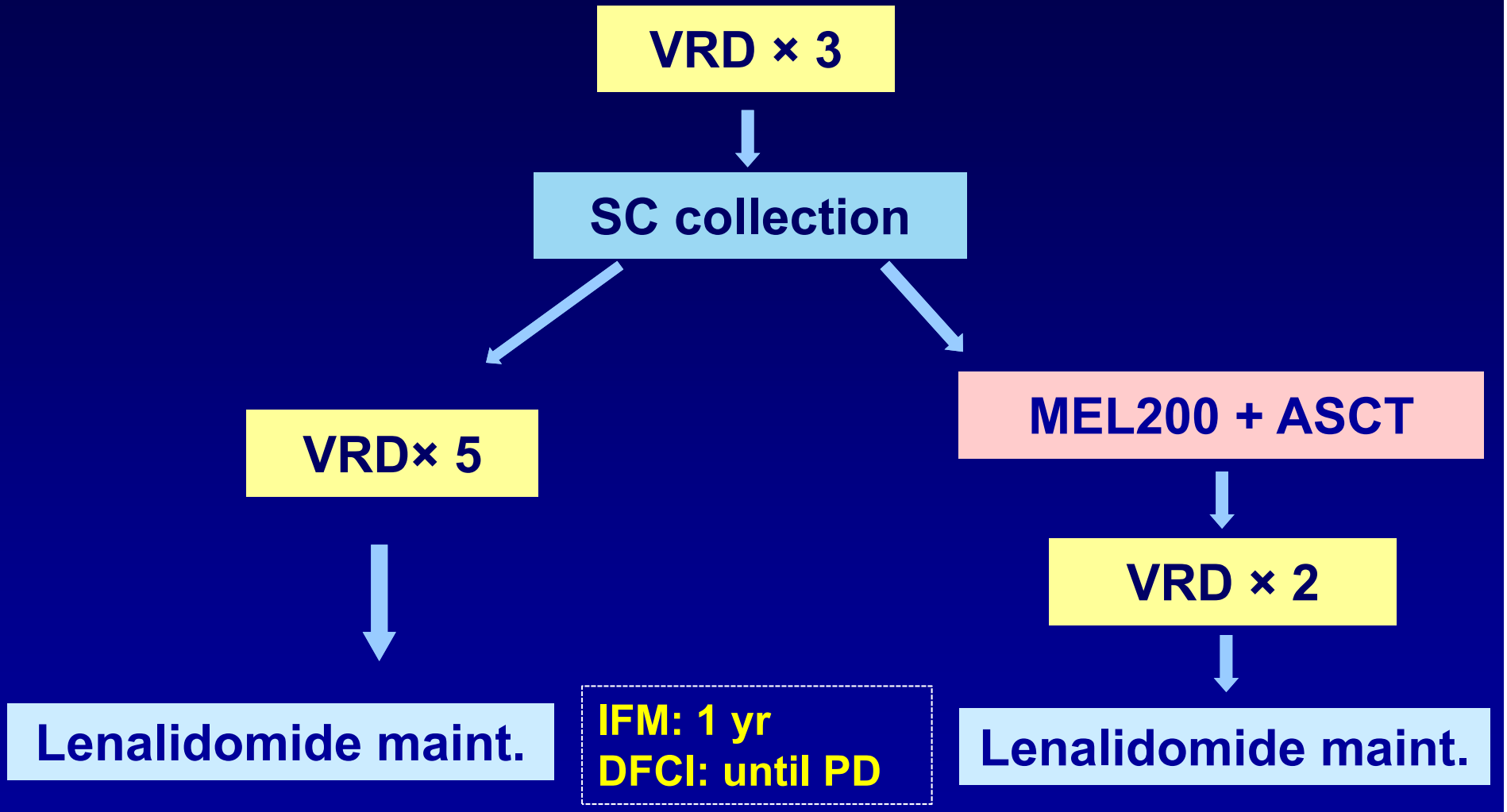




RVD, lenalidomide, bortezomib, low-dose dexamethasone
Len 10mg/d on days 1-21 of a 28-day cycle, bortezomib 1.3mg/m^2 per week SC/IV.

Nooka AK, et al. Leukemia. 2014;28:690-3.

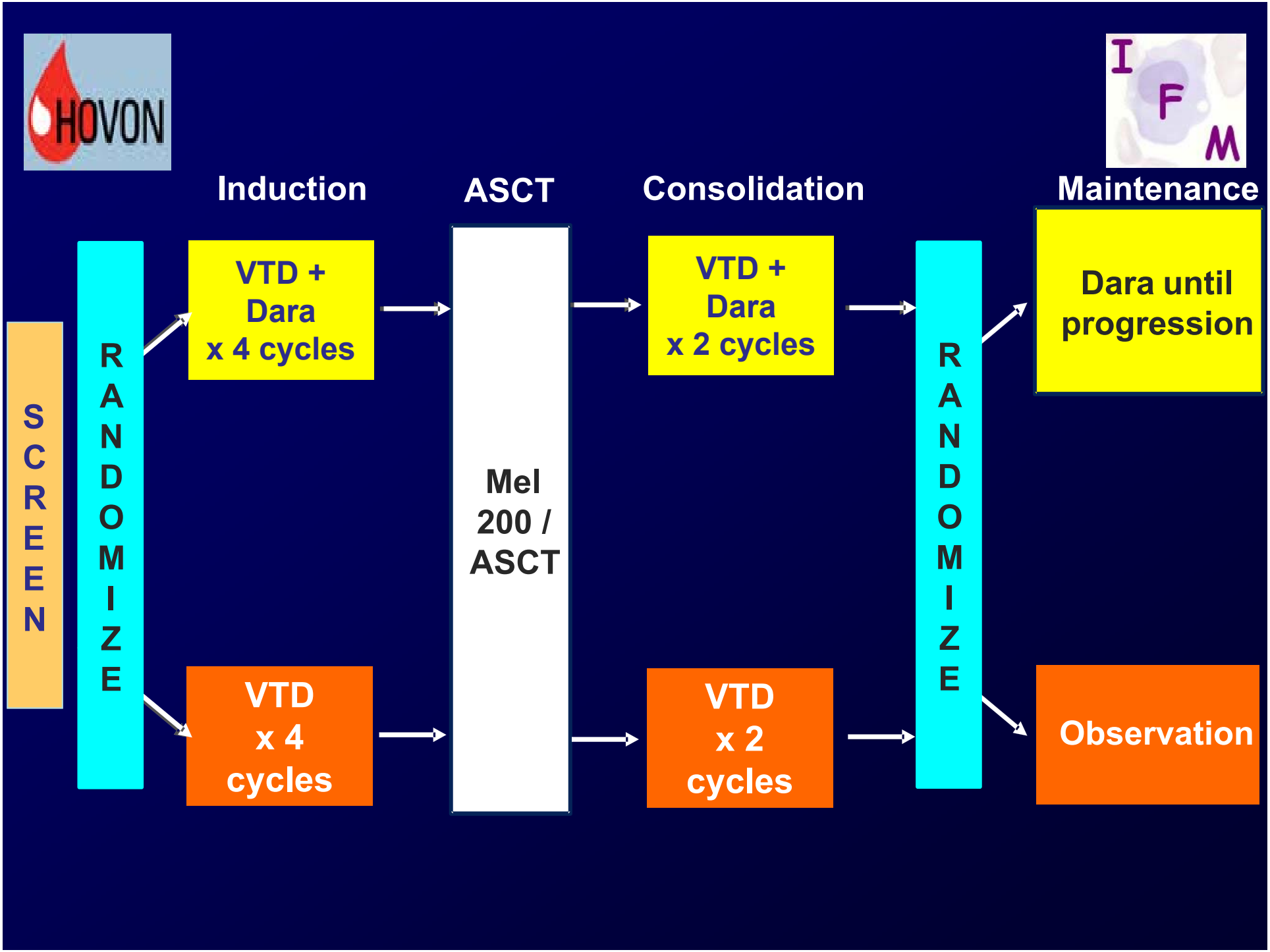
IFM 2009/DFCI Determination trial



HDM + ASCT at relapse

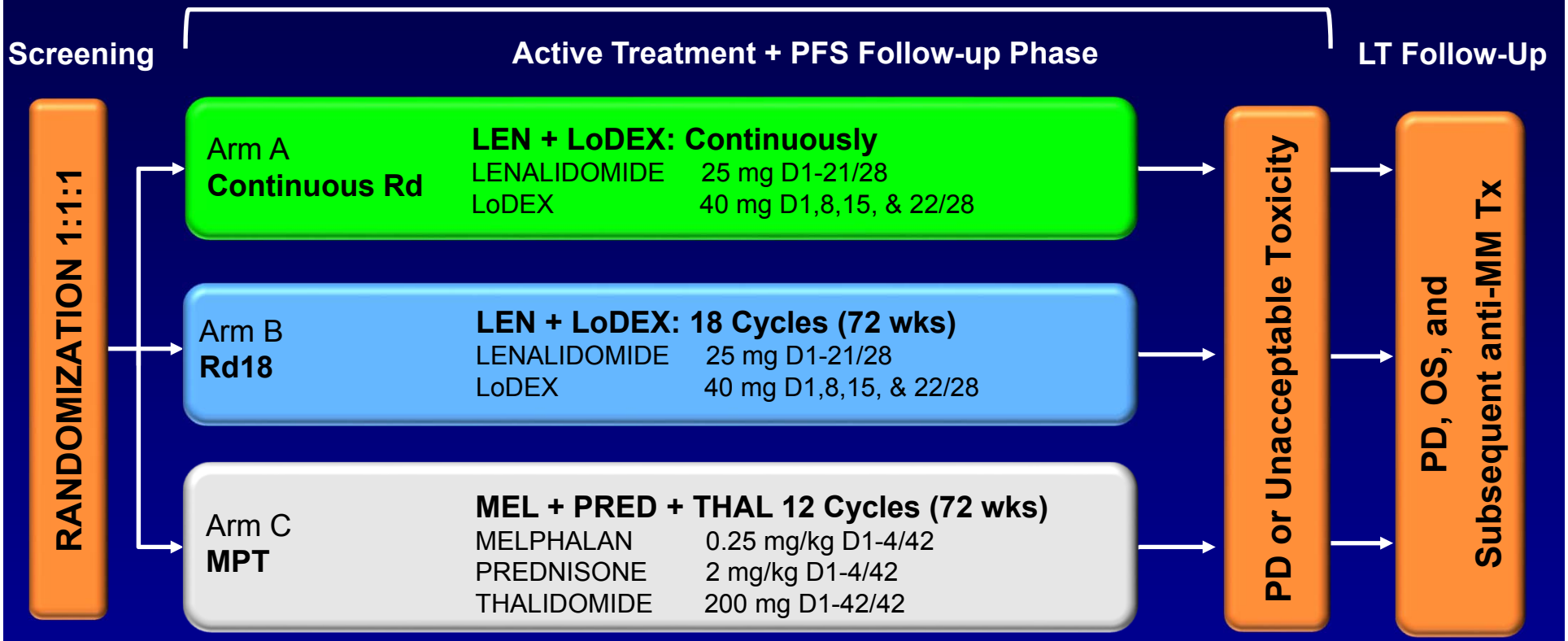
DFCI = Dana Farber Cancer Institute.

ClinicalTrials.gov: NCT01208662.


HOVON
I F M
Induction
ASCT
Consolidation
Maintenance
SCREEN
RANDOMIZE
VTD + Dara x 4 cycles
VTD x 4 cycles
Mel 200 / ASCT
VTD + Dara x 2 cycles
VTD x 2 cycles
RANDOMIZE
Dara until progression
Observation

Continuous therapy in elderly NDMM patients

FIRST Trial: Study Design



Pts > 75 yrs: Lo-DEX 20 mg D1, 8, 15 & 22/28; THAL (100 mg D1-42/42); MEL 0.2 mg/kg D1–4

- Stratification: age (≤ 75 y vs. > 75 y), country, and ISS stage (I or II vs. III)
- Thromboprophylaxis was mandatory

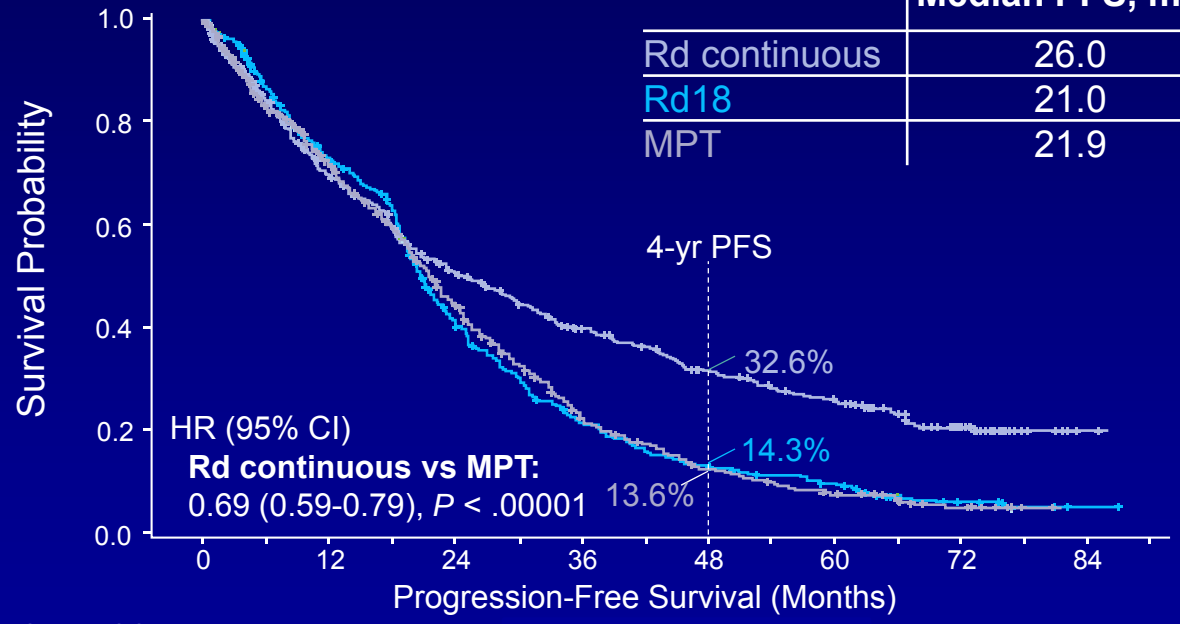
FIRST, **F**rontline **I**nvestigation of **R**evlimid and Dexamethasone versus **S**tandard **T**halidomide; ISS, International Staging System; Rd, lenalidomide plus low-dose dexamethasone; Rd18, lenalidomide plus low-dose dexamethasone for 18 cycles; LEN, lenalidomide; LoDEX, low-dose dexamethasone; LT, long-term; MEL, melphalan; MM, multiple myeloma; MPT, melphalan, prednisone, thalidomide; OS, overall survival; PD, progressive disease; PFS, progression-free survival; Pred, prednisone; pt, patient; THAL, thalidomide; Tx, treatment.

Benboubker L, et al. *NEJM*. 2014;371:906-17

Final analysis of survival outcomes in FIRST
PFS

- Results remain consistent nearly 3 yrs after the original analysis of the primary endpoint, PFS:
  - Rd continuous significantly improved PFS vs MPT ($P < .00001$)

	Median PFS, mos	4-yr PFS, %
Rd continuous	26.0	32.6
Rd18	21.0	14.3
MPT	21.9	13.6



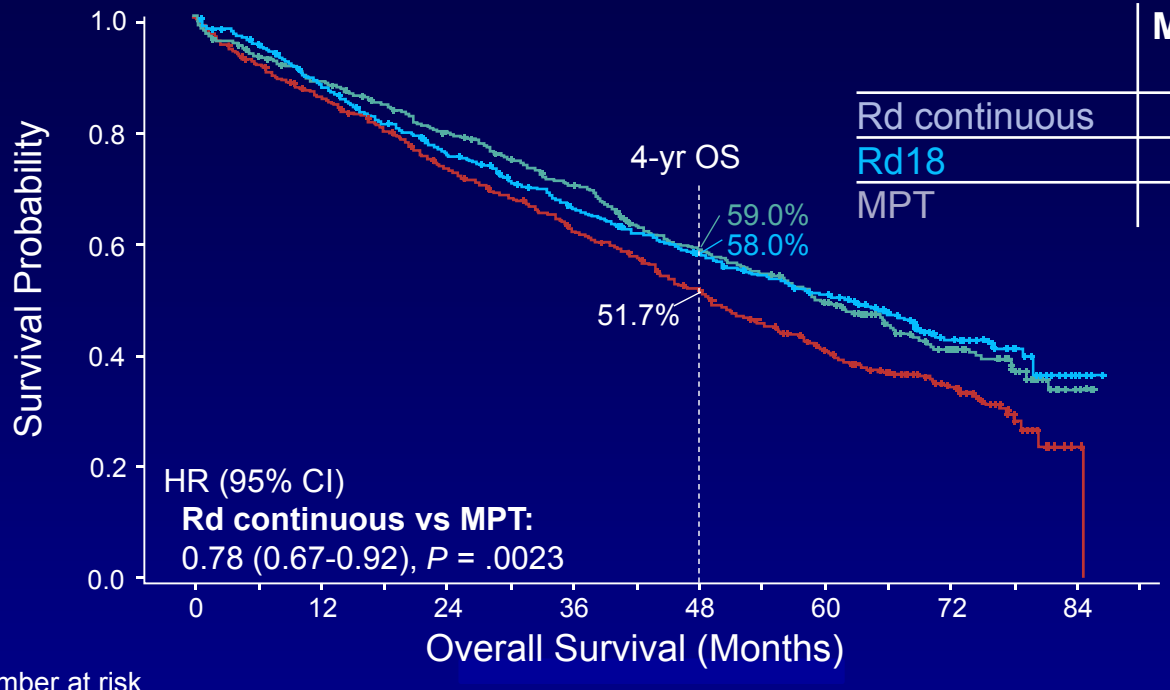
Number at risk

Rd continuous	535	330	225	160	117	91	37	2
Rd18	541	337	174	90	55	39	10	1
MPT	547	312	180	87	48	28	10	0

HR, hazard ratio; MPT, melphalan, prednisone, and thalidomide; PFS, progression-free survival; Rd, lenalidomide plus low-dose dexamethasone; Rd18, lenalidomide plus low-dose dexamethasone for 18 cycles.

Final analysis of survival outcomes in FIRST

OS



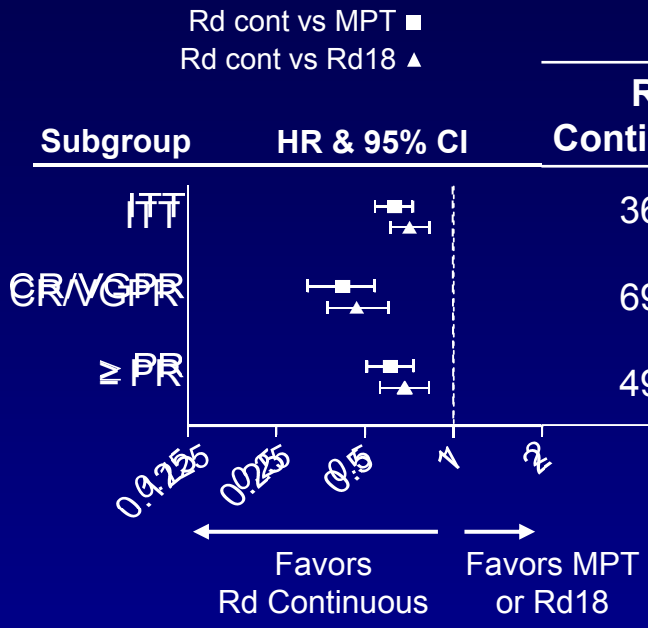
	Median OS, mos	4-yr OS, %
Rd continuous	59.1	59.0
Rd18	62.3	58.0
MPT	49.1	51.7

Number at risk								
Rd continuous	535	457	403	340	277	226	97	6
Rd18	541	465	394	333	283	239	96	7
MPT	547	448	375	313	254	192	78	2

- Rd continuous significantly extended OS vs MPT (*P* = .0023) and resulted in similar OS vs Rd18
- In patients achieving ≥ VGPR, median OS was 79.5 mos with Rd continuous, 55.7 mos with MPT, and 80.1 mos with Rd18

HR, hazard ratio; MPT, melphalan, prednisone, and thalidomide; OS, overall survival; Rd, lenalidomide plus low-dose dexamethasone; Rd18, lenalidomide plus low-dose dexamethasone for 18 cycles; VGPR, very good partial response.

Final analysis of survival outcomes in first *time to next antimyeloma Treatment*



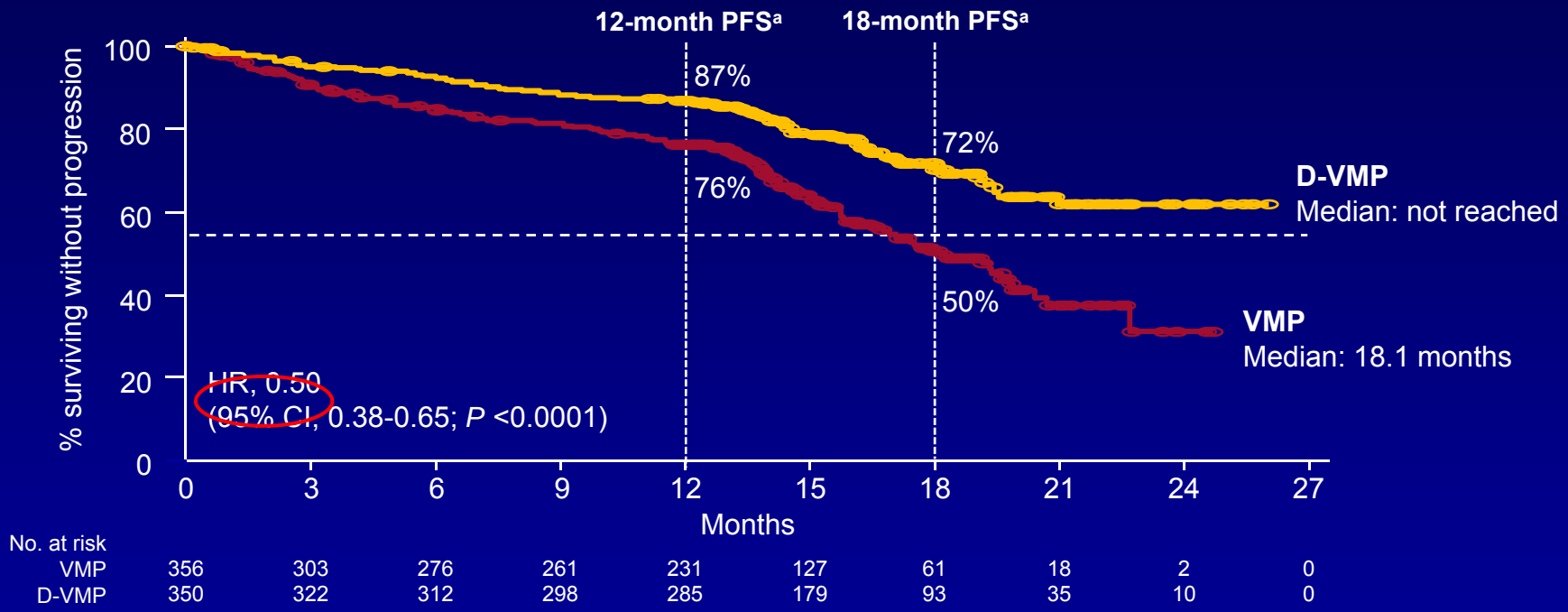
Subgroup	Median TTNT (mos)			Rd Continuous vs MPT	Rd Continuous vs Rd18
	Rd Continuous	Rd18	MPT	HR (95% CI)	HR (95% CI)
ITT	36.7	28.5	26.7	0.63 (0.54-0.73)	0.71 (0.61-0.83)
CR/VGPR	69.5	39.9	37.7	0.42 (0.32-0.54)	0.47 (0.37-0.60)
≥ PR	49.1	31.8	31.7	0.61 (0.51-0.73)	0.68 (0.57-0.80)

- Median TTNT in the ITT population was longer with Rd continuous (36.7 mos) vs MPT (26.7 mos) or Rd18 (28.5 mos)
- In patients who achieved ≥ VGPR, median TTNT was substantially longer (69.5 mos with Rd continuous vs 37.7 mos with MPT and 39.9 mos with Rd18)

CR, complete response; HR, hazard ratio; ITT, intention to treat; MPT, melphalan, prednisone, and thalidomide; PFS, progression-free survival; PR, partial response; Rd, lenalidomide plus low-dose dexamethasone; Rd18, lenalidomide plus low-dose dexamethasone for 18 cycles; TTNT, time to next treatment; VGPR, very good partial response.

Alcyone - VMP vs. D-VMP : PFS

- Median (range) follow-up: 16.5 (0.1-28.1) months



50% reduction in the risk of progression or death in patients receiving D-VMP

HR, hazard ratio; CI, confidence interval.
[a]Kaplan-Meier estimate.

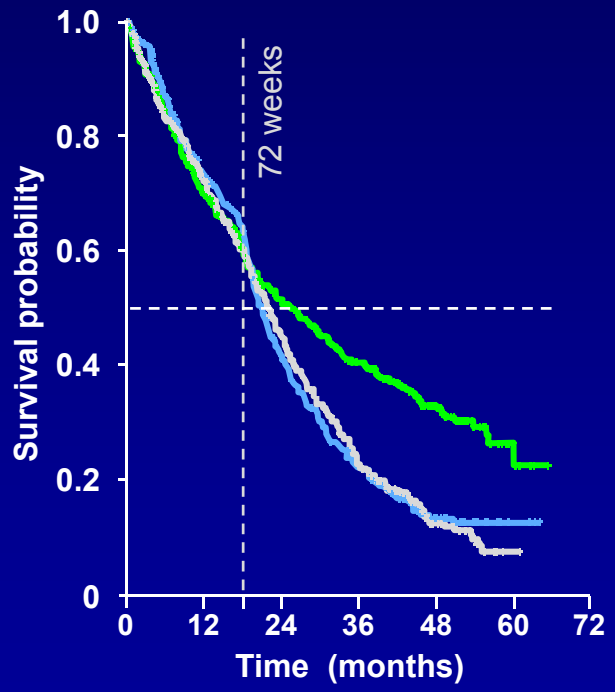
Mateos et al. NEJM 2017;378: 318-21

Benefits of continuous treatment extend across drug classes and patient populations

Continuous vs fixed duration: PFS advantage

Rd vs Rd18 vs MPT

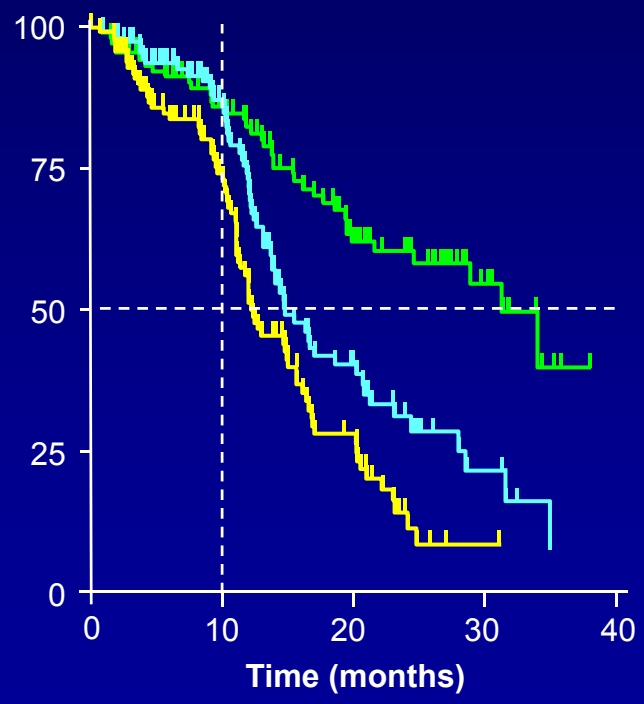
	Median
Rd	26.0 months
Rd18	21.0 months
MPT	21.9 months



Facon T, et al. J Clin Oncol. 2015;33 Suppl:abstract 8524.

MPR-R vs MPR vs MP

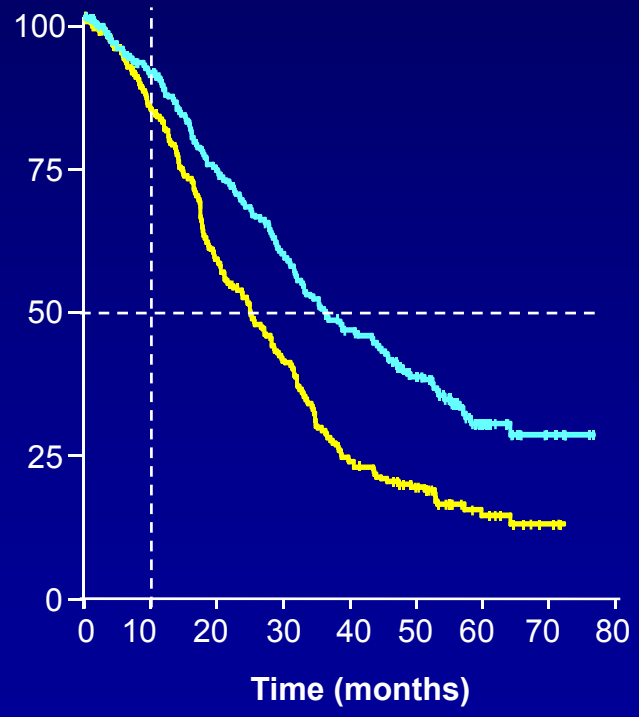
	Median
MPR-R	31 months
MPR	14 months
MP	13 months



Palumbo A, et al. N Engl J Med. 2012;366:1759-69.

VMPT-VT vs VMP

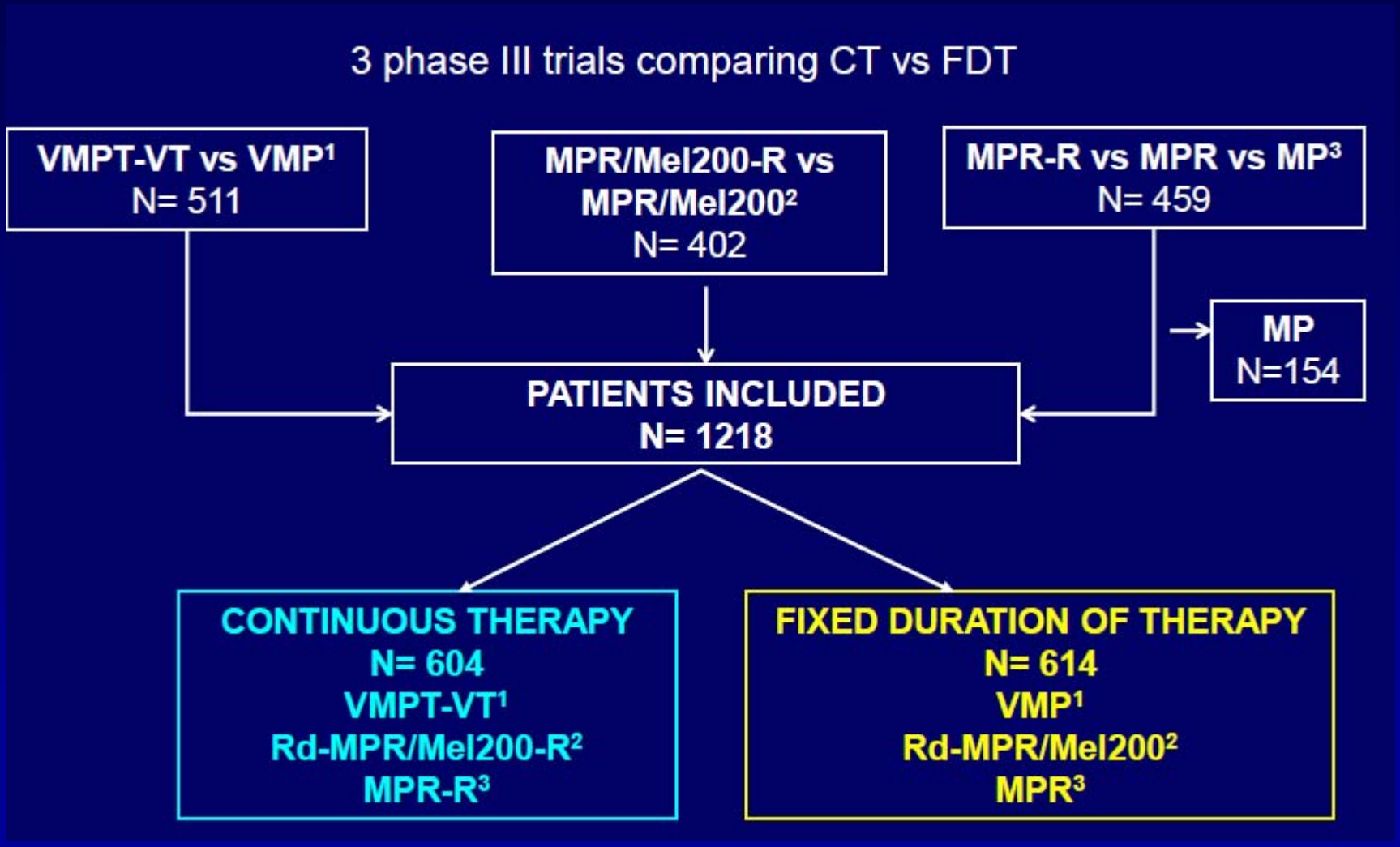
	Median
VMPT-VT	35.3 months
VMP	28.8 months



Palumbo A, et al. J Clin Oncol 2010;28:5101-9.

MP, melphalan, prednisone; MPR, MP, lenalidomide; MPR-R, MPR followed by lenalidomide maintenance; MPT, melphalan, prednisone, thalidomide; Rd, lenalidomide plus low-dose dexamethasone; Rd18, Rd for 18 cycles; VMPT, bortezomib, melphalan, prednisone, thalidomide; VMPT-VT, VMP followed by bortezomib plus thalidomide maintenance.

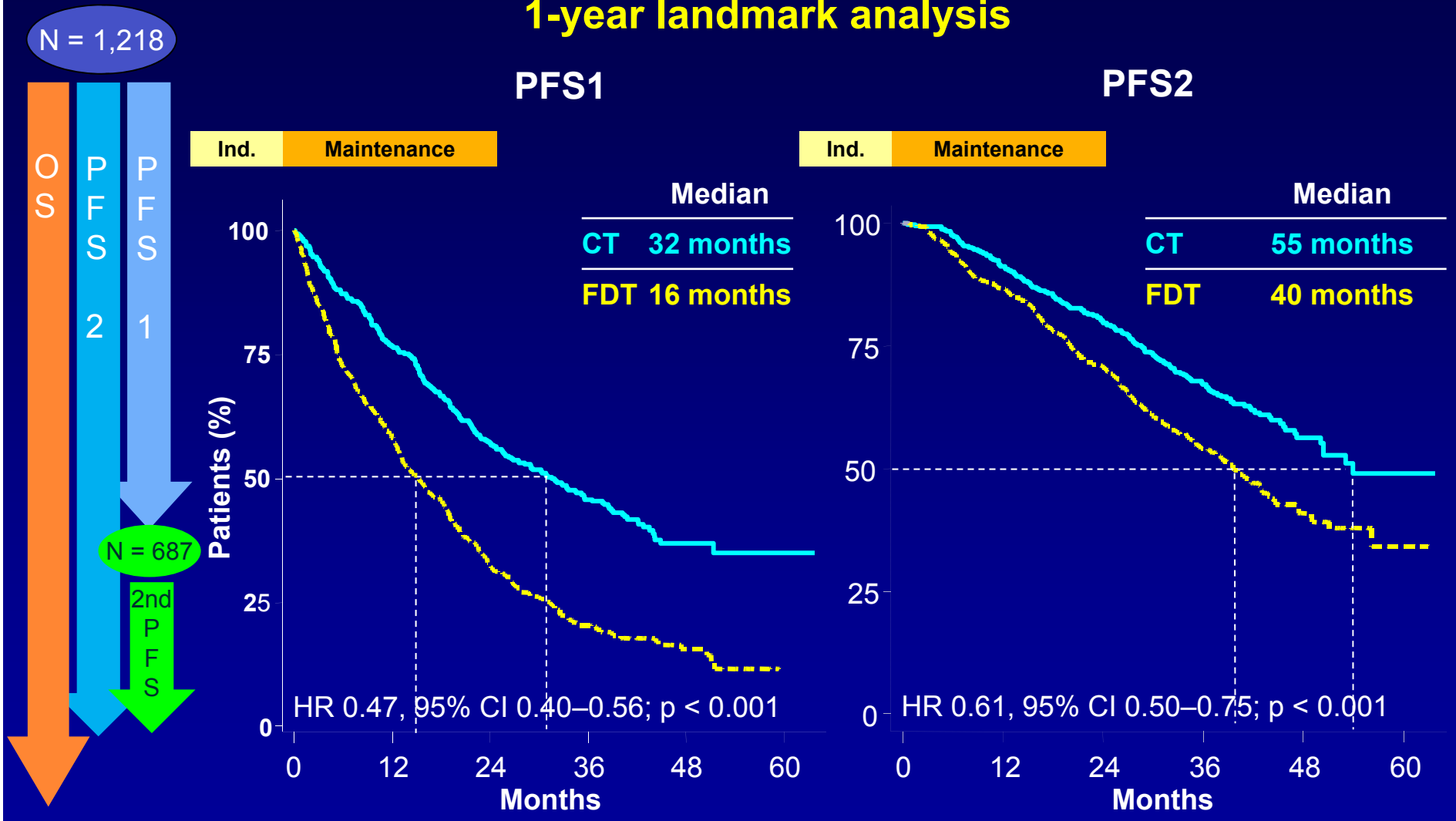
Meta-analysis of continuous vs fixed duration treatment in newly diagnosed multiple myeloma



MEL200, melphalan dose 200 mg/m^2; MPR, melphalan, prednisone, lenalidomide; MPR-R, MPR followed by lenalidomide maintenance; SCT, stem cell transplant. VMP, bortezomib, melphalan, prednisone; VMPT, bortezomib, melphalan, prednisone, thalidomide.

Palumbo A, et al. *J Clin Oncol.* 2015 Aug 17 [Epub ahead of print].

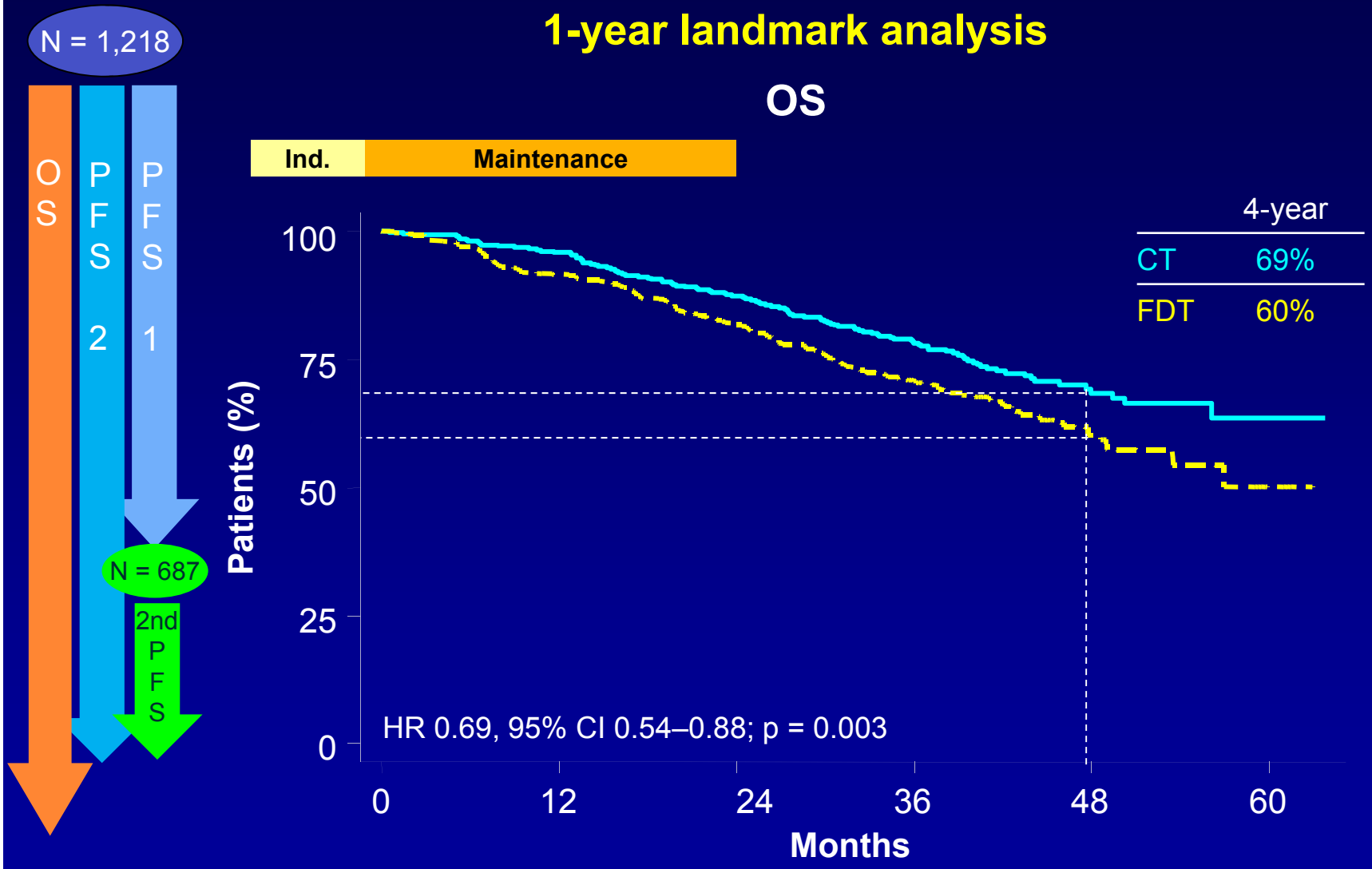
Continuous vs fixed duration: PFS1 and PFS2



CT, continuous therapy; FDT, fixed duration therapy; PFS1, time from randomization to first objective disease progression, or death from any cause, whichever comes first; PFS2, time from randomization to second objective disease progression, or death from any cause, whichever comes first.

Palumbo A, et al. *J Clin Oncol.* 2015 Aug 17 [Epub ahead of print].

Continuous vs fixed duration: OS

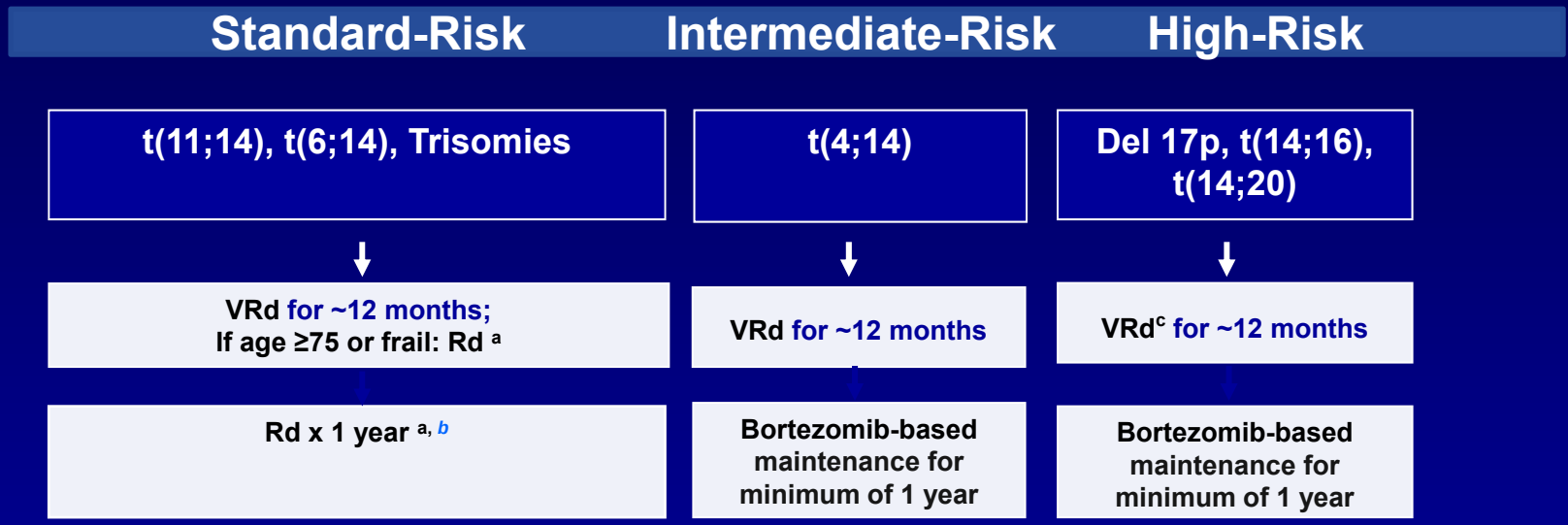


CT, continuous therapy; FDT, fixed duration therapy.

Palumbo A, et al. *J Clin Oncol.* 2015 Aug 17 [Epub ahead of print].

mSMART – Off-Study

Transplant Ineligible



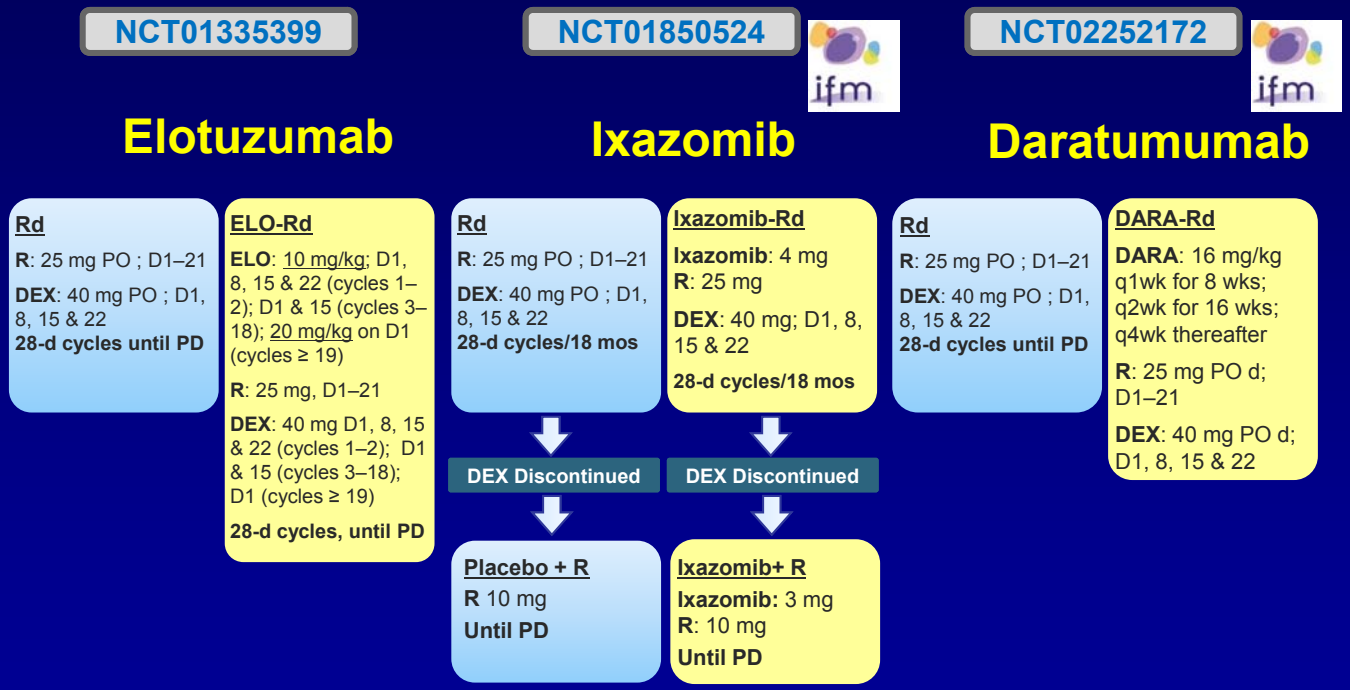
[a] In patients treated initially with Rd, continuing treatment until progression is an option for patients responding well with low toxicities;

[b] Dex is usually discontinued after first year

[c] Clinical trials strongly recommended as the first option

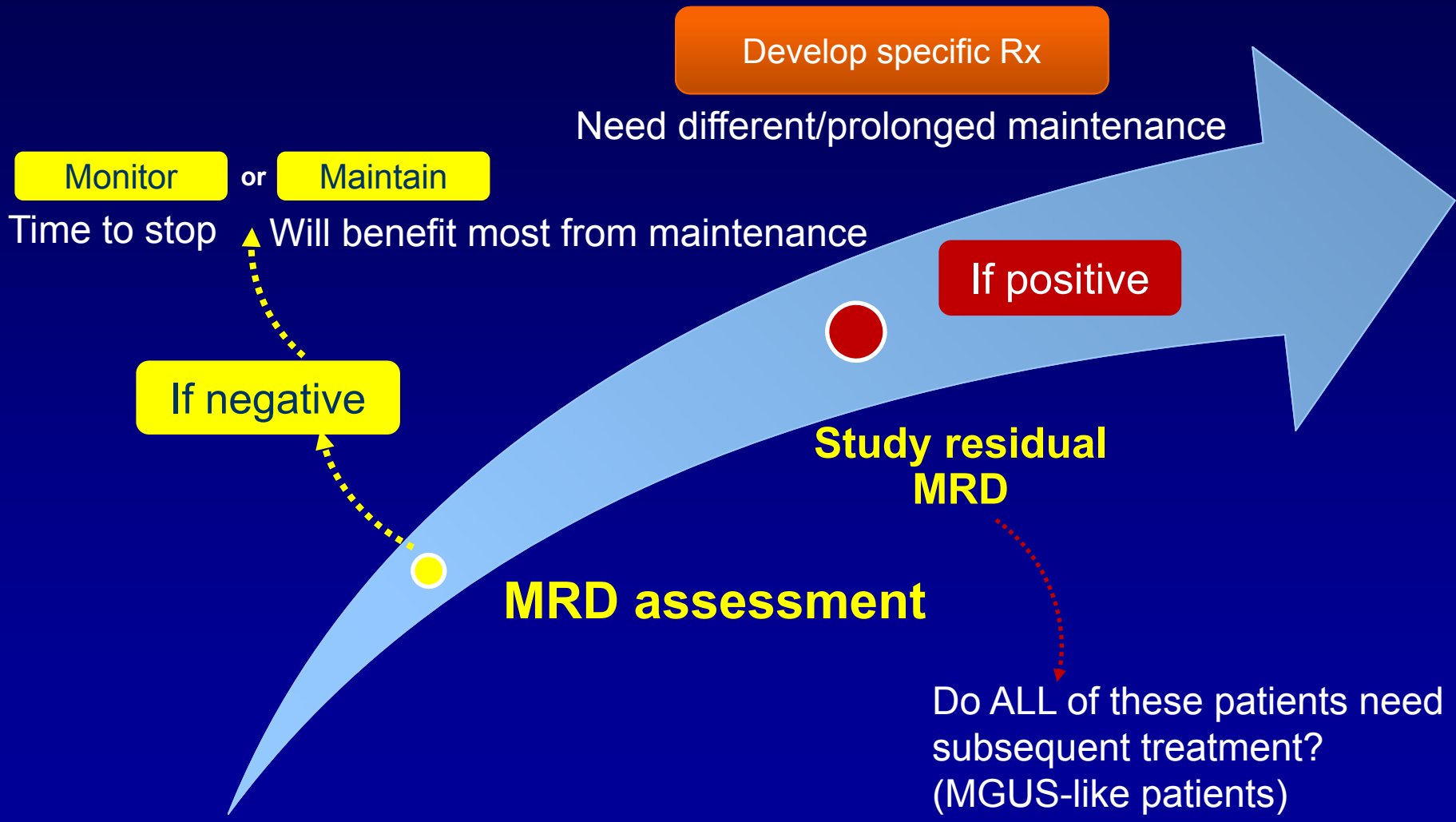
Dispenzieri et al. Mayo Clin Proc 2007;82:323-341; Kumar et al. Mayo Clin Proc 2009 84:1095-1110; Mikhael et al. Mayo Clin Proc 2013;88:360-376. v14 //last reviewed July 2016

Phase 3 Rd-based Continuous Studies for Elderly Patients



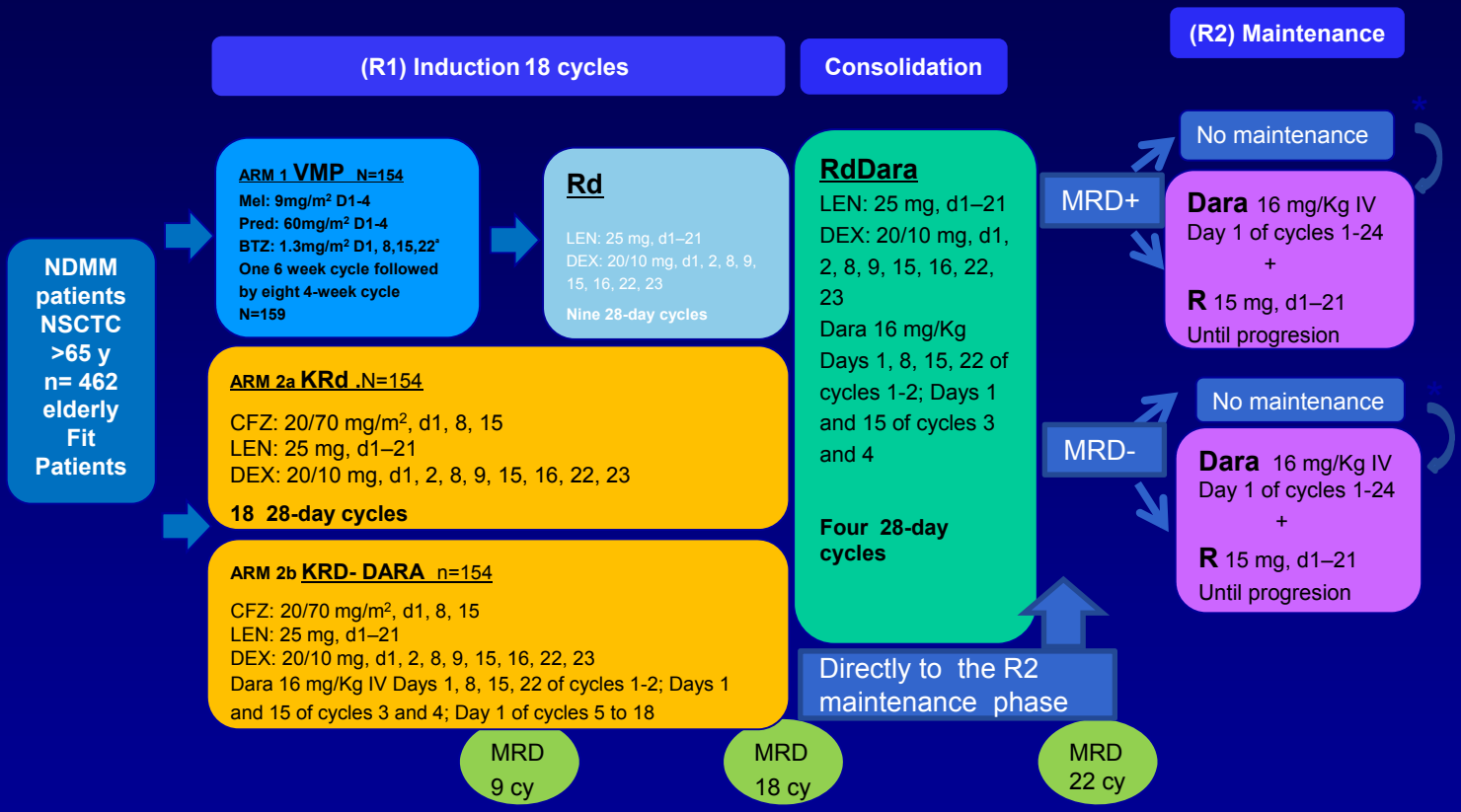
- Primary endpoint for all studies is PFS

Should Longitudinal Monitoring of MRD Status Inform Nature and Duration of Maintenance ?



MGUS, Monoclonal gammopathy of undetermined significance; Rx, retreatment.

A spanish study for fit elderly NDMM patients; GEMFIT2016



Primary endpoint immonuphenotypic complete response
Secondary exploratory outcome: PFS

Courtesy of Dr MV Mateos

CONCLUSION

As of today continuous therapy should be the rule

FDT is associated with a greater risk of providing a suboptimal outcome to patients

The role of the myeloma community is to investigate stopping rules