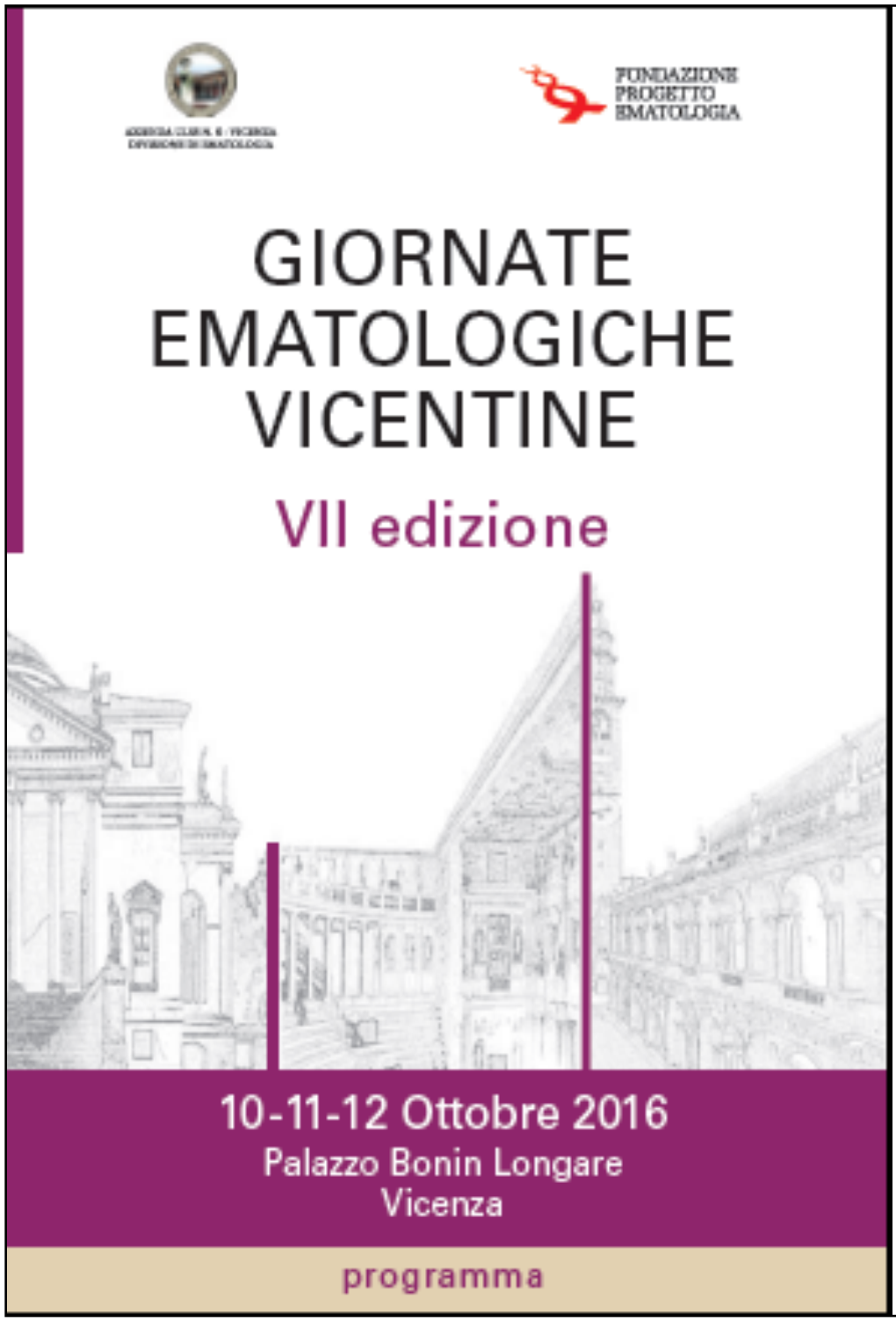


La terapia del mieloma multiplo
Ruolo della terapia di mantenimento

Elena Zamagni
Vicenza, 23 Settembre 2016

Maintenance therapy is applied for a prolonged period of time
with the goal of preventing tumor progression.

Ludwig et al. Blood 2012;119:3003-3015
Consensus Maintenance IMWG

Issues of maintenance therapy

- Impact on Progression-Free Survival

- Impact on Overall survival

- Induction of resistance

- Toxicity

- Quality-Of-Life

- Cost-effectiveness

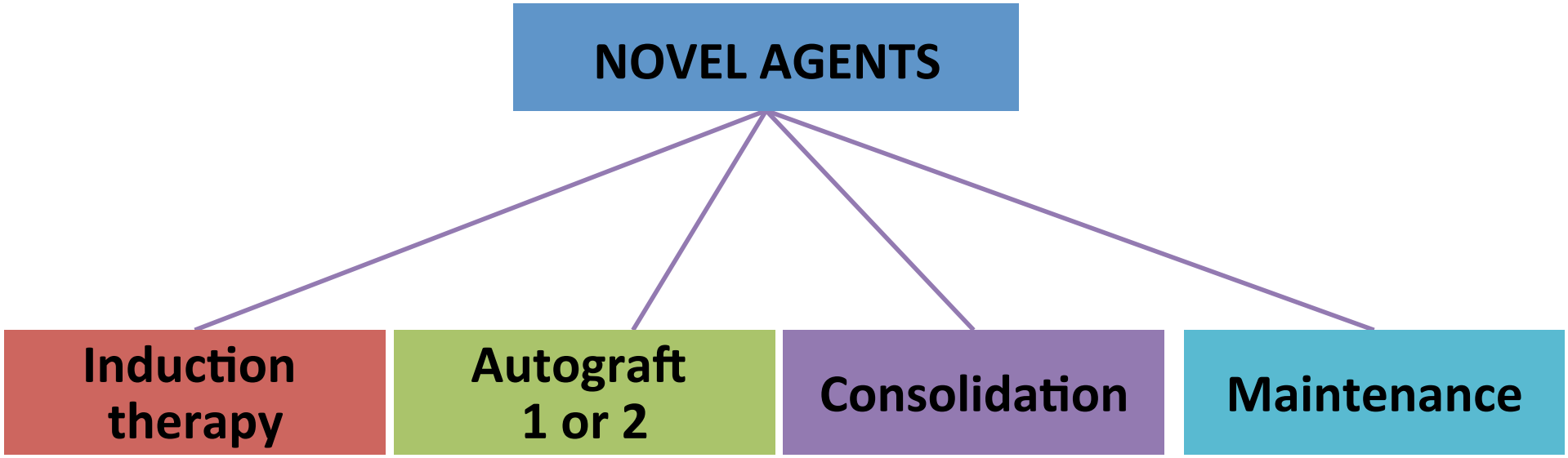
Maintenance treatment in multiple myeloma

- **Chemotherapy:**
  - no: as shown by SWOG,[1] Alexanian,[2] and Belch[3]
- **Interferon:**
  - yes: Mandelli[4]
  - no: meta-analysis showed modest increase in PFS without, or with only minimal, survival benefit[5]
- **Corticosteroids?**
  - yes: survival and duration of response[6]
  - no: no survival improvement[7,8]
- **New drugs…**

1. Southwest Oncology Group. Arch Intern Med. 1975;135:147-52 2. Alexanian R, et al. Blood. 1978;51:1005-11. 3. Belch A, et al. Br J Cancer. 1988;57:94-9. 4. Mandelli F, et al. N Engl J Med. 1990;322:1430-4. 5. Myeloma Trialists' Collaborative Group. Br J Haematol. 2001;113:1020-34. 6. Berenson, JR et al. Blood. 2002;99:3163-8 . 7. Stewart AK, et al. Clin Cancer Res. 2004;10:8170-6. 8. Alexanian R, et al. Am J Hematol :2000;65:204

Young patients eligible for ASCT

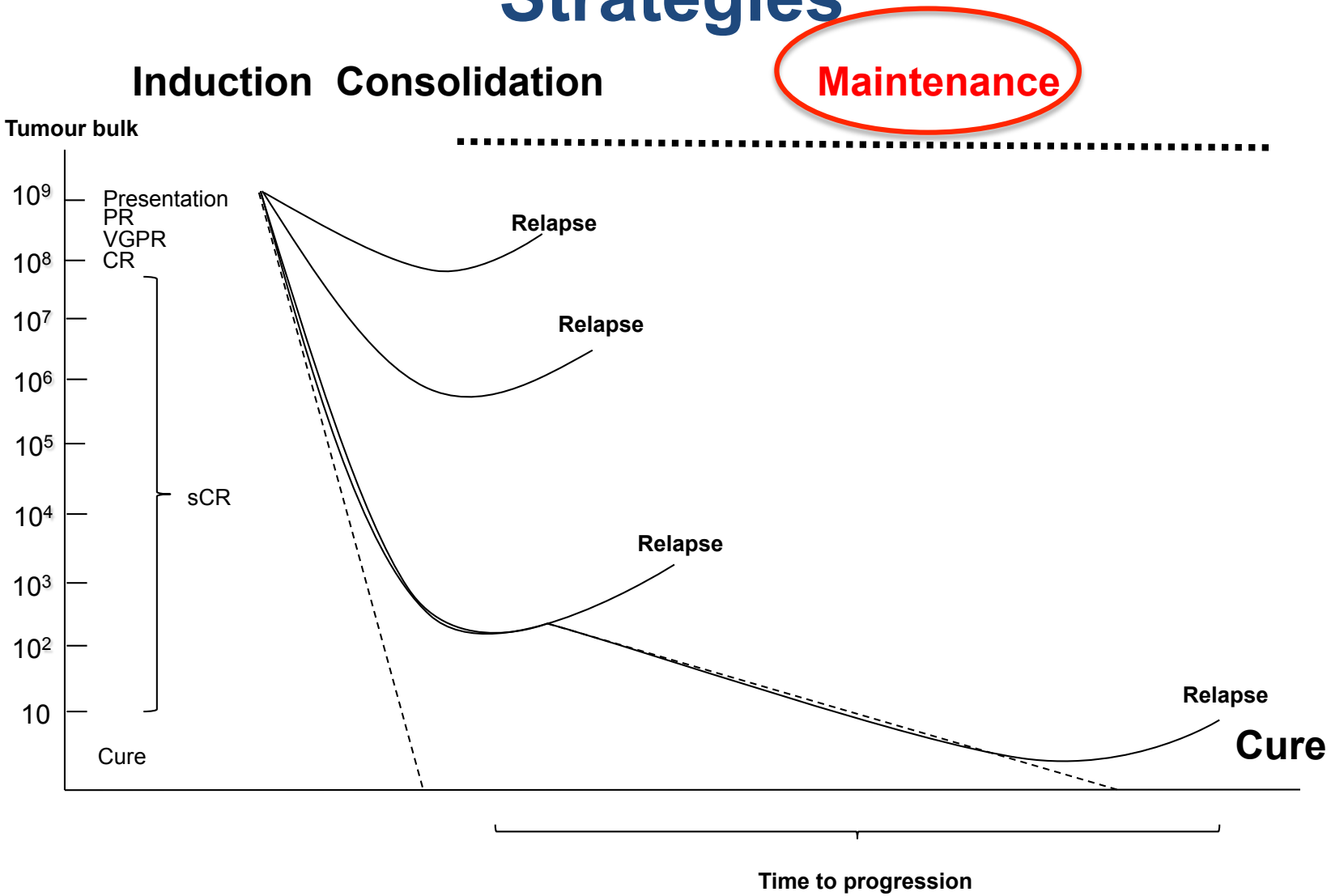
New treatment paradigm for patients who are eligible for ASCT



- Maximize the depth of response
- Minimize the burden of residual tumor cells

Cavo M et al. Blood 2011;117(23):6063-73; Cavo et al. Blood 2012;120(1):9-19.

The Key Elements of Modern Treatment Strategies



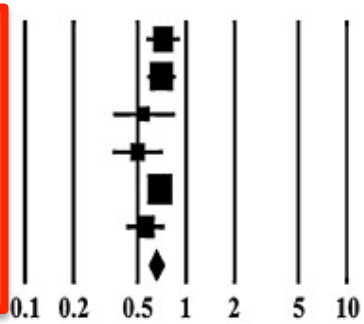
The **emergence of novel agents active on microenvironment and immune surveillance** led to a renaissance in the concept of **continuous treatment or maintenance**

Thalidomide maintenance therapy

Progression Free Survival

Study name	Hazard ratio	Lower limit	Upper limit	Z-Value	p-Value
Attal, 2006	0.72	0.57	0.91	-2.80	0.01
Barlogie, 2006	0.71	0.58	0.86	-3.48	0.00
Ludwig, 2010	0.55	0.36	0.85	-2.69	0.01
Spencer, 2009	0.50	0.35	0.71	-3.84	0.00
Morgan, 2011	0.69	0.58	0.82	-4.16	0.00
Stewart, 2010	0.56	0.43	0.73	-4.29	0.00
Total	0.65	0.59	0.73	-7.80	0.00

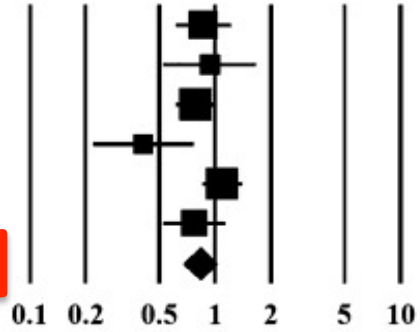
Heterogeneity: Q=5.82, p=0.32, I^2=14.01



Overall Survival

Study name	Hazard ratio	Lower limit	Upper limit	Z-Value	p-Value
Attal, 2006	0.86	0.62	1.21	-0.86	0.39
Ludwig, 2010	0.93	0.53	1.66	-0.23	0.82
Barlogie, 2006	0.78	0.62	0.99	-2.05	0.04
Spencer, 2009	0.41	0.22	0.76	-2.82	0.00
Morgan, 2011	1.09	0.85	1.39	0.69	0.49
Stewart, 2010	0.77	0.53	1.13	-1.35	0.18
Total	0.83	0.67	1.02	-1.81	0.07

Heterogeneity: Q=10.11, p=0.07, I^2=50.56

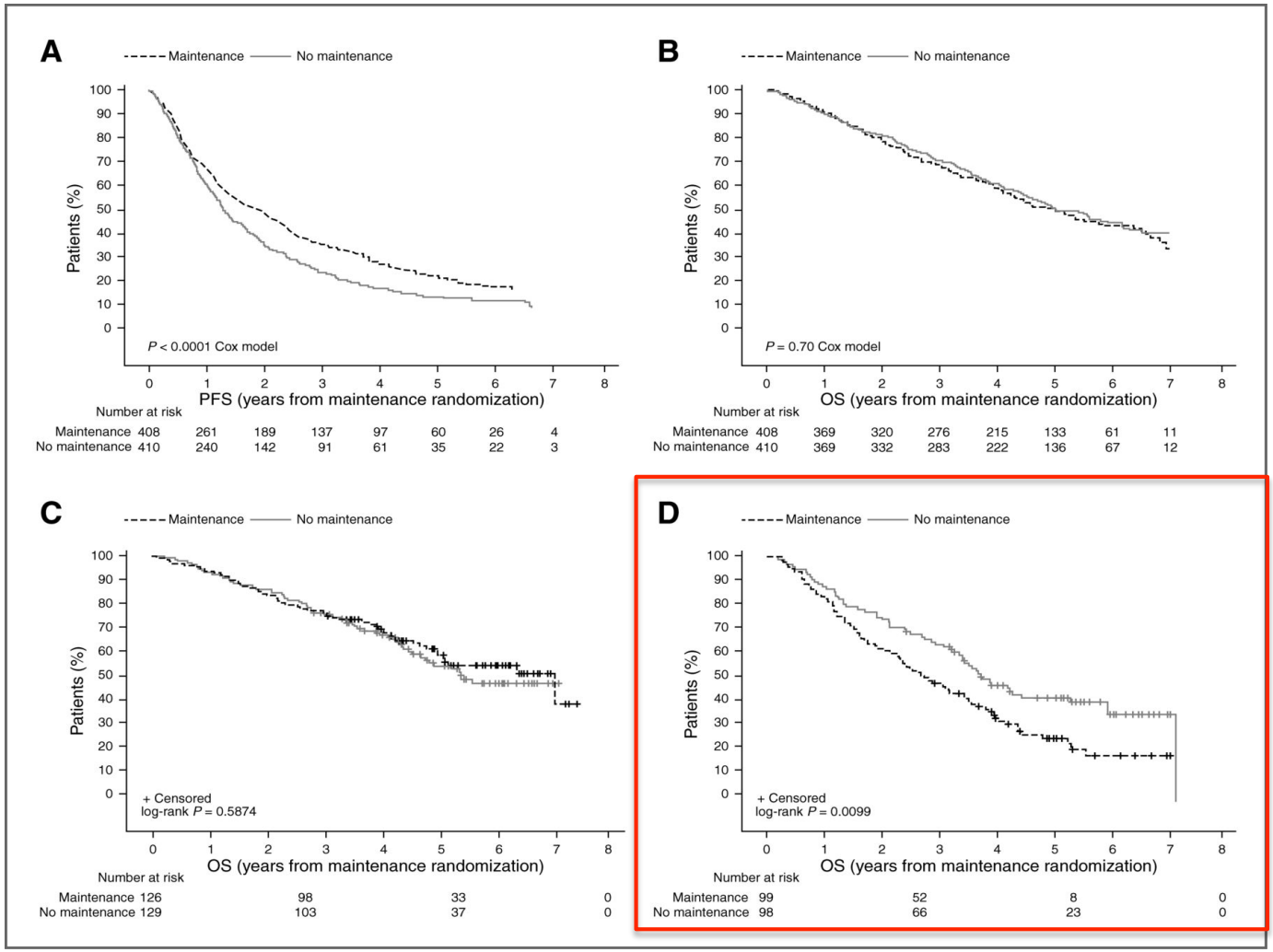


Thalidomide maintenance has limited applicability due to adverse events and side effects
In published trials **median time on thalidomide 7-24 months**

Kagoya et al. Leuk Res 2012

Survival according iFISH profiles
Thalidomide maintenance therapy

Survival according to thalidomide maintenance therapy regimen (ITT population):
(A) PFS; (B) OS; (C) OS in pts with favorable iFISH profiles; (D) OS in pts with adverse iFISH profiles



Morgan G J et al. Clin Cancer Res 2013;19:6030-6038

Thalidomide as maintenance therapy following ASCT ?

- Impact on PFS, duration of response : YES

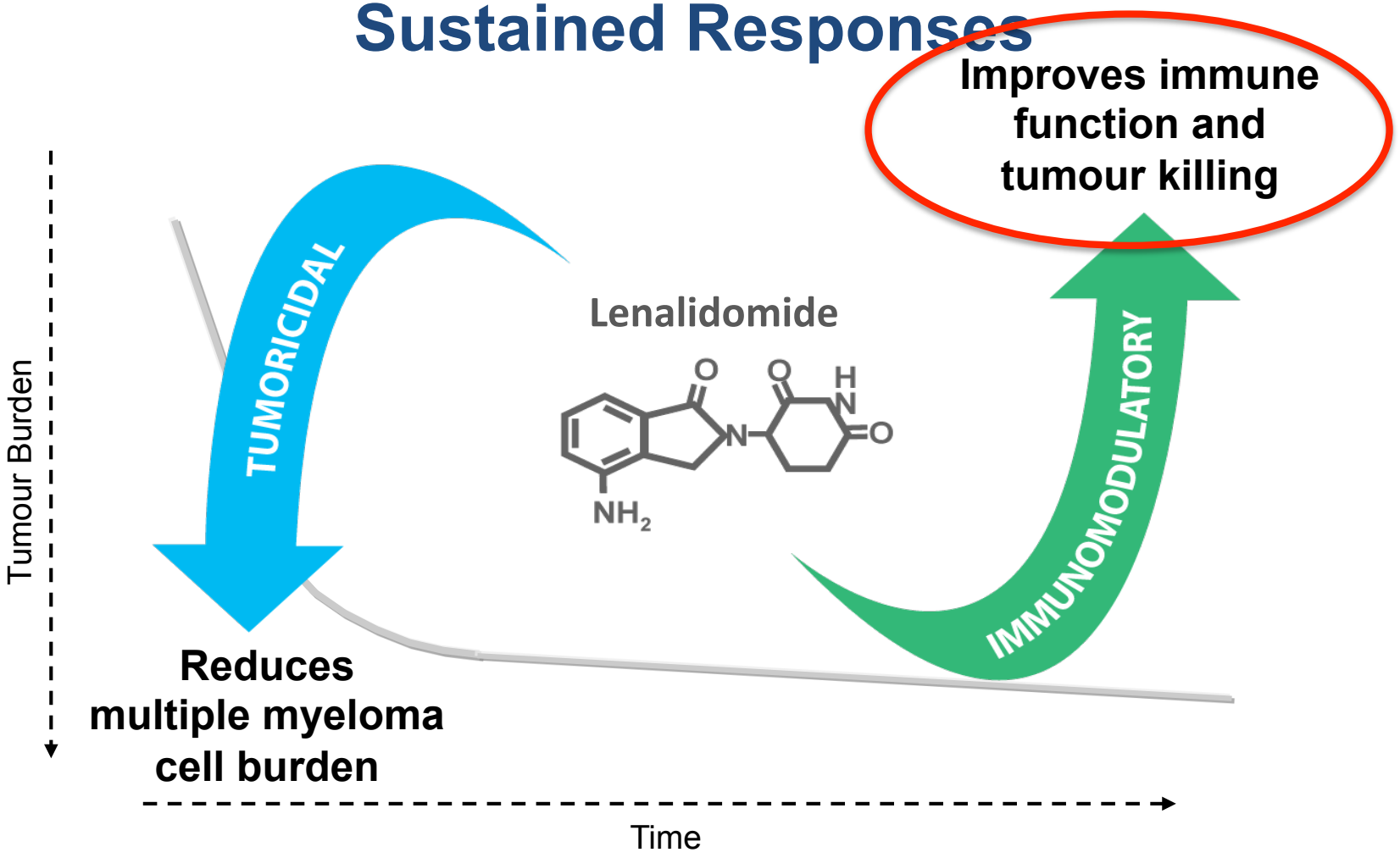
- Induction of resistance : YES ?

- Overall survival : BORDER-LINE

- Toxicity, QOL : DOSE, DURATION

- Cost-effectiveness : YES

Lenalidomide: The Tumouricidal and Immunomodulatory Effects Induce Rapid and Sustained Responses



These dual effects make lenalidomide the optimal foundation therapy for the long-term treatment that seems necessary in multiple myeloma

Lenalidomide maintenance therapy

Study details	N	Treatment	Outcome	
IFM 2005-02[1]			PFS	OS
Median follow-up from start of maintenance: 67 months	307	Lenalidomide	46 months	82 months
	307	Placebo	24 months **p<0.001**	81 months p=ns
CALGB 100104[2]			TTP	Median OS
Median follow-up from start of maintenance: 65 months	231	Lenalidomide	53 months	not reached
	229	Placebo	26 months **p<0.001**	76 months **p=0.001**
GIMEMA[3]			PFS	3-year OS
Median follow-up from enrollment (for induction): 51.2 months	126	Lenalidomide	41.9 months	88%
	125	Placebo	21.6 months **p<0.001**	79% p=0.14

Attal, et al. N Engl J Med. 2012
McCarthy, et al. N Engl J Med. 2012
Palumbo, et al. N Engl J Med. 2014

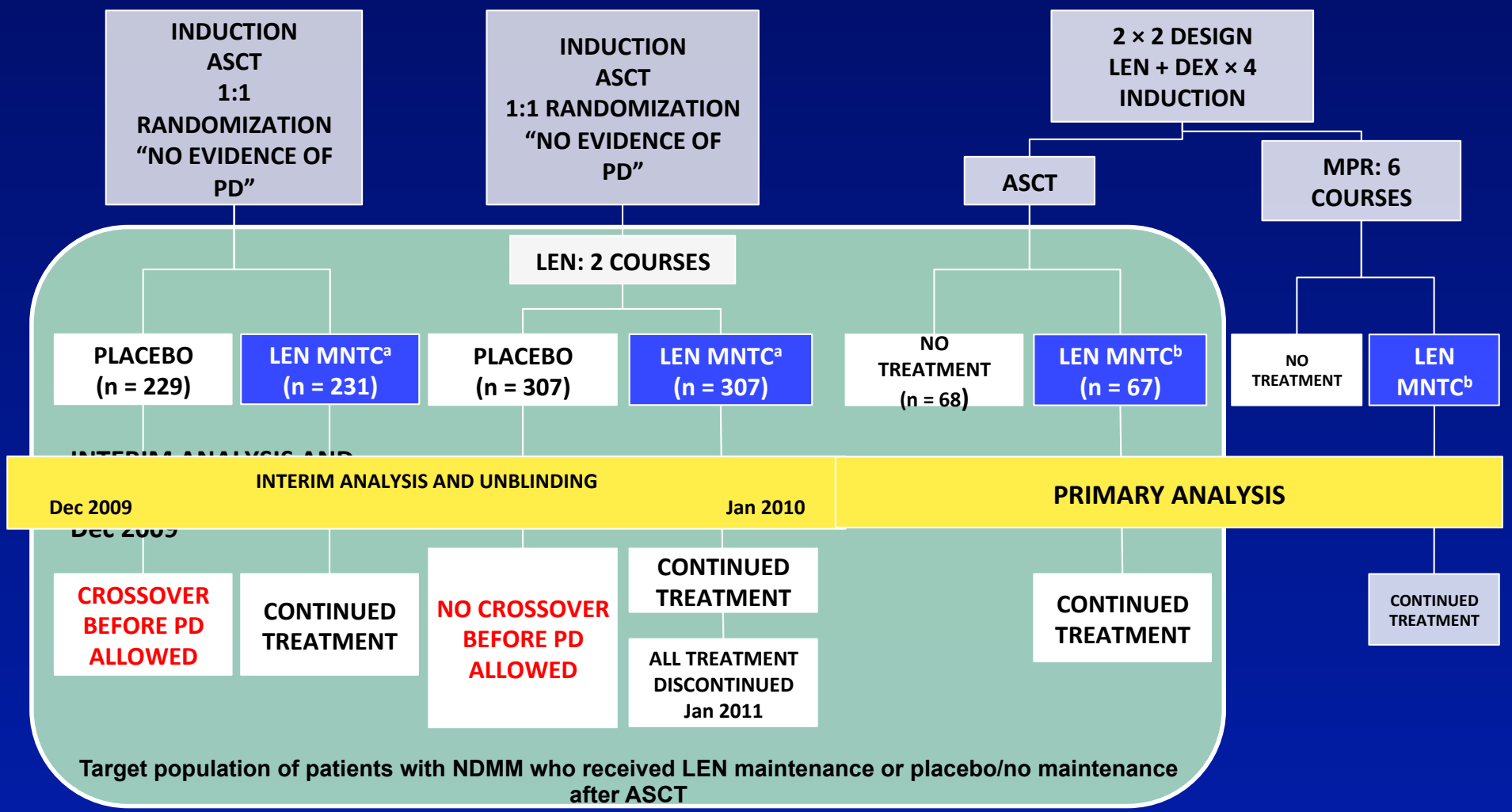
Lenalidomide Maintenance After High-Dose Melphalan and Autologous Stem Cell Transplant in Multiple Myeloma: A Meta-Analysis of Overall Survival

Michel Attal,[1] Antonio Palumbo,[2] Sarah A. Holstein,[3] Valérie Lauwers-Cances,[1] Maria Teresa Petrucci,[4] Paul Richardson,[5] Cyrille Hulin,[6] Patrizia Tosi,[7] Kenneth C. Anderson,[5] Denis Caillot,[8] Valeria Magarotto,[9] Philippe Moreau,[10] Gerald Marit,[11] Zhinuan Yu,[12] Philip L. McCarthy[13]

[1]Institut Universitaire du Cancer , Toulouse-Oncopole, France; [2]The Myeloma Unit, Department of Hematology, University of Turin, Turin, Italy; [3]Roswell Park Cancer Institute, Buffalo, NY; [4]University La Sapienza, Rome, Italy; [5]Dana-Farber Cancer Institute, Boston, MA; [6]Bordeaux Hospital University Center (CHU), Bordeaux, France; [7]Seràgnoli Institute of Hematology and Medical Oncology, Bologna University, Bologna, Italy; [8]Dijon University Hospital Center, Dijon, France; [9]University of Torino, Torino, Italy; [10]University Hospital Hôtel-Dieu, Nantes, France; [11]Centre Hospitalier Universitaire, Bordeaux, France; [12]Celgene Corporation, Summit, NJ; [13]Blood and Marrow Transplant Program, Roswell Park Cancer Institute, Buffalo, NY

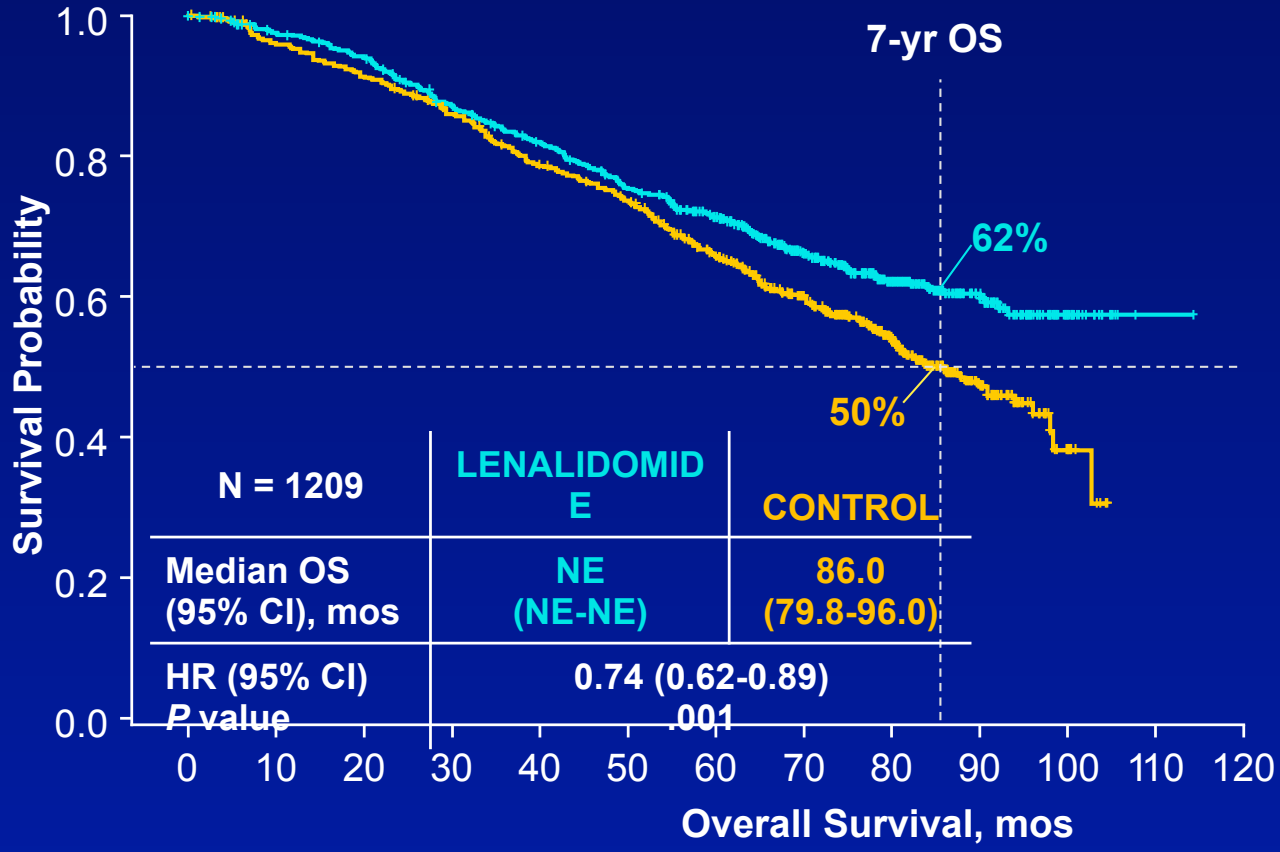
ASCO 2016

Studies Included in Meta-Analysis

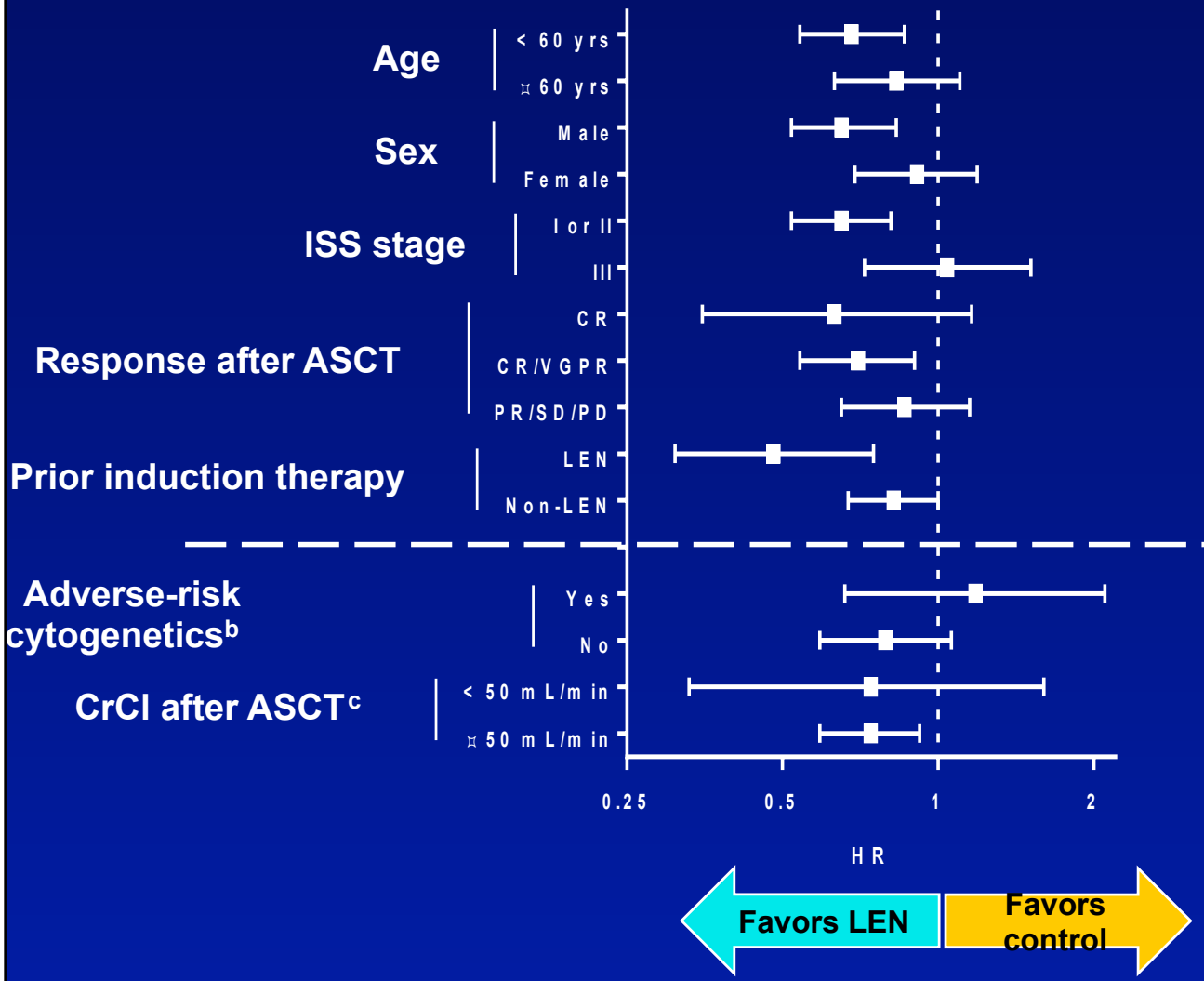


Overall Survival: Median Follow-Up of 80 Months

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



Overall Survival: Subgroup Analysis

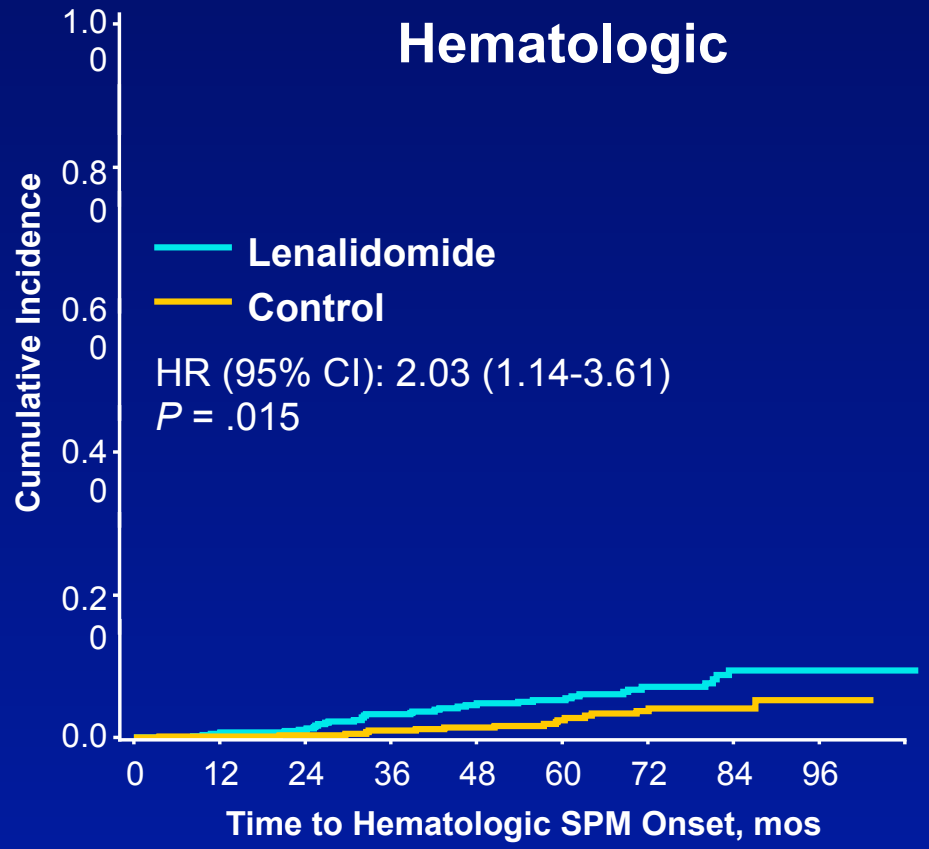


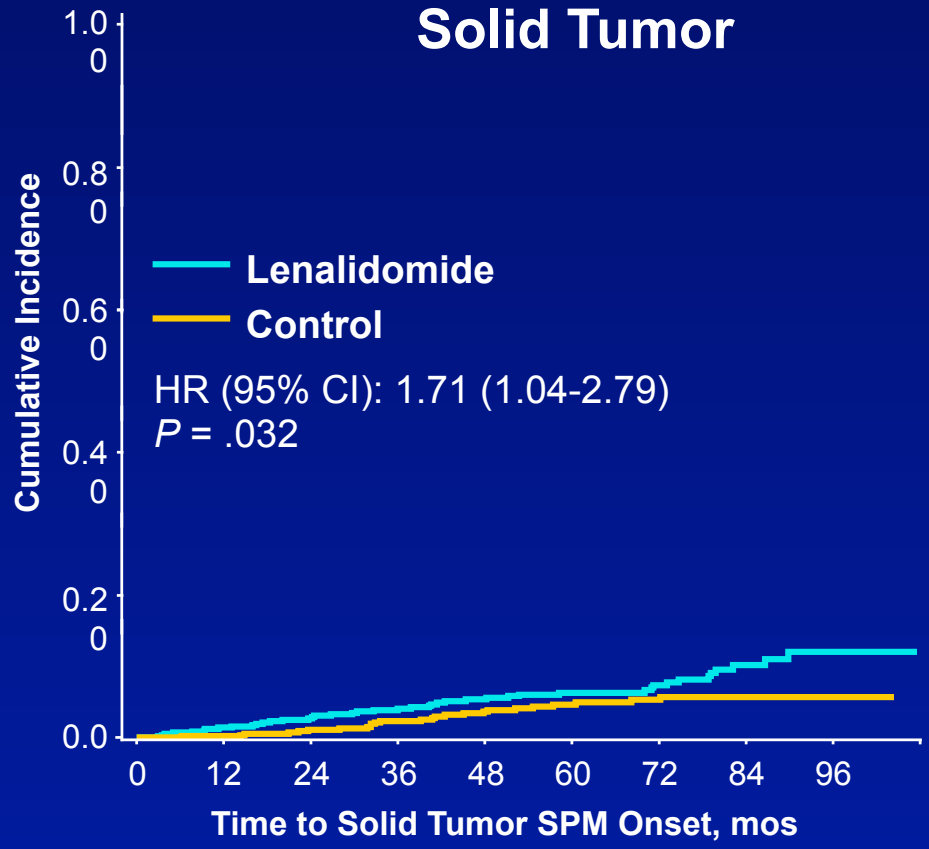
	LEN[a]	CONTROL[a]	HR (95% CI)
Age < 60 yrs	372	375	0.68 (0.54-0.86)
Age ≥ 60 yrs	233	229	0.83 (0.63-1.10)
Sex Male	322	349	0.65 (0.52-0.83)
Sex Female	283	255	0.91 (0.69-1.19)
ISS stage I or II	411	440	0.65 (0.52-0.81)
ISS stage III	113	90	1.04 (0.72-1.51)
Response after ASCT CR	66	80	0.63 (0.35-1.16)
Response after ASCT CR/VGPR	320	339	0.70 (0.54-0.90)
Response after ASCT PR/SD/PD	218	210	0.86 (0.65-1.15)
Prior induction therapy LEN	147	146	0.48 (0.31-0.75)
Prior induction therapy Non-LEN	458	458	0.82 (0.67-1.00)
Adverse-risk cytogenetics[b] Yes	56	36	1.18 (0.66-2.10)
Adverse-risk cytogenetics[b] No	231	243	0.79 (0.59-1.06)
CrCl after ASCT[c] < 50 mL/min	33	25	0.73 (0.33-1.60)
CrCl after ASCT[c] ≥ 50 mL/min	379	404	0.74 (0.59-0.92)

Treatment Duration of Maintenance

	CALGB			IFM	
		Placebo (n = 221)			
	LEN (n = 224)	Placebo Up to Crossover (n = 221)	LEN After Crossover (n = 76)	LEN (n = 306)	Placebo (n = 302)
Mean Tx duration, mos Range (min-max)	30 (0-108)	13 (0-51)	25 (0-61)	25 (0-55)	20 (0-49)
Tx duration category, %					
≥ 1 yr	67	43	61	71	70
≥ 2 yrs	52	14	43	56	40
≥ 3 yrs	37	3	32	29	11
≥ 4 yrs	24	< 1	24	4	1

Cumulative Incidence of SPMs





Lenalidomide as maintenance therapy following ASCT ?

- Impact on PFS : YES

- Induction of resistance : ? (high risk patients)

- Overall survival : YES

- Toxicity, QOL : Manageable

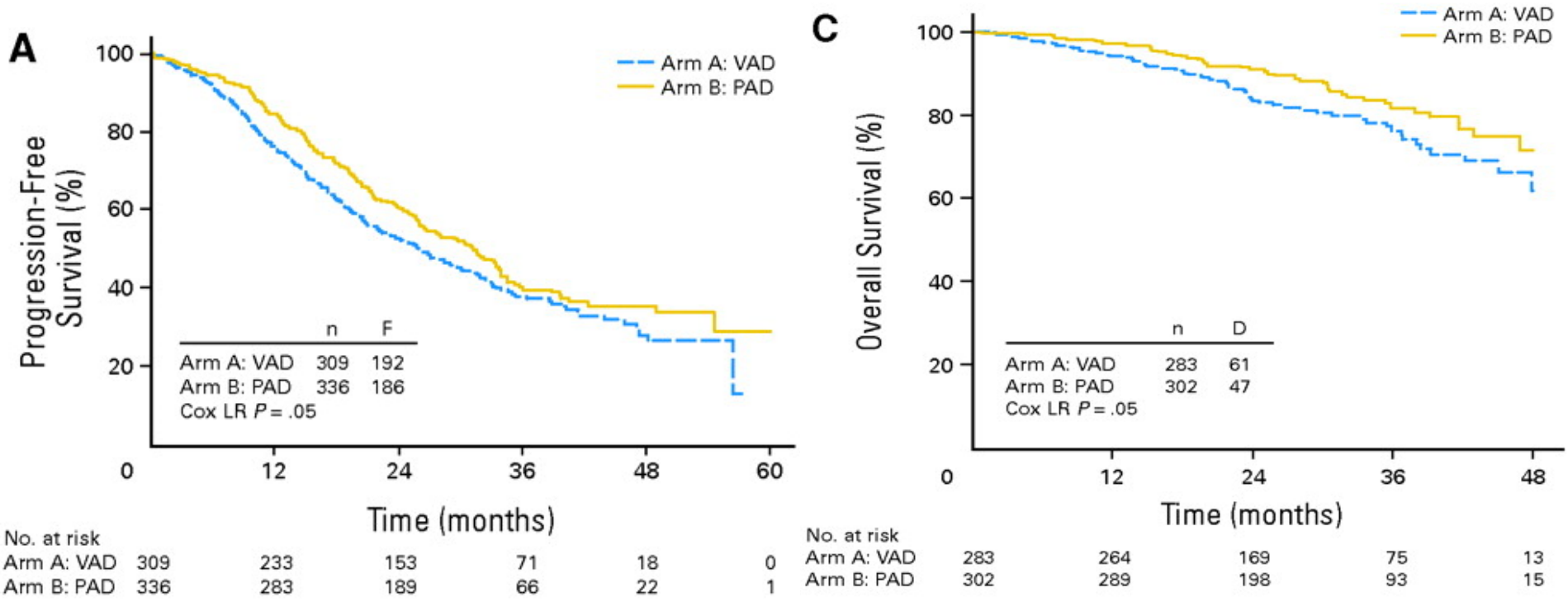
- Cost-effectiveness/optimal duration : ?

Bortezomib maintenance therapy

Study	Induction therapy	Maintenance therapy	Dose of Bort (mg/d)	Duration of maintenance	PFS/ EFS	OS
Post-ASCT						
HOVON-65/ GMMG-HD4	VAD PAD	Thal Bort	1.3 mg/m^2 every 2 weeks	For 2 years	35 mo 28 mo *P 0.002*	5 yrs 61% 55%
PETHEMA/GEM	VTD TD VBMPC/VBAD/B	VT Thal IFNα	1.3 mg/m^2 D 1,4,8,11 every 3 months	For 3 years	*P 0.0009*	p=ns

Sonneveld P et al, JCO 2012; 30: 2946-55
Rosinol L et al, ASH 2012 Abs 334

Landmark analysis starting at 12 months after random assignment: PFS and OS



Sonneveld P et al. J Clin Oncol 2012

Feasibility of maintenance treatment

	VAD arm Thalidomide %	PAD arm Bortezomib %
Started M (n)	270	229
At 6 months	78	90
At 12 months	54	76
At 18 months	40	64
At 24 months	27	47

Sonneveld P et al. J Clin Oncol 2012

Bortezomib as maintenance therapy following ASCT ?

- Impact on PFS, duration of response : YES

- Induction of resistance : ?

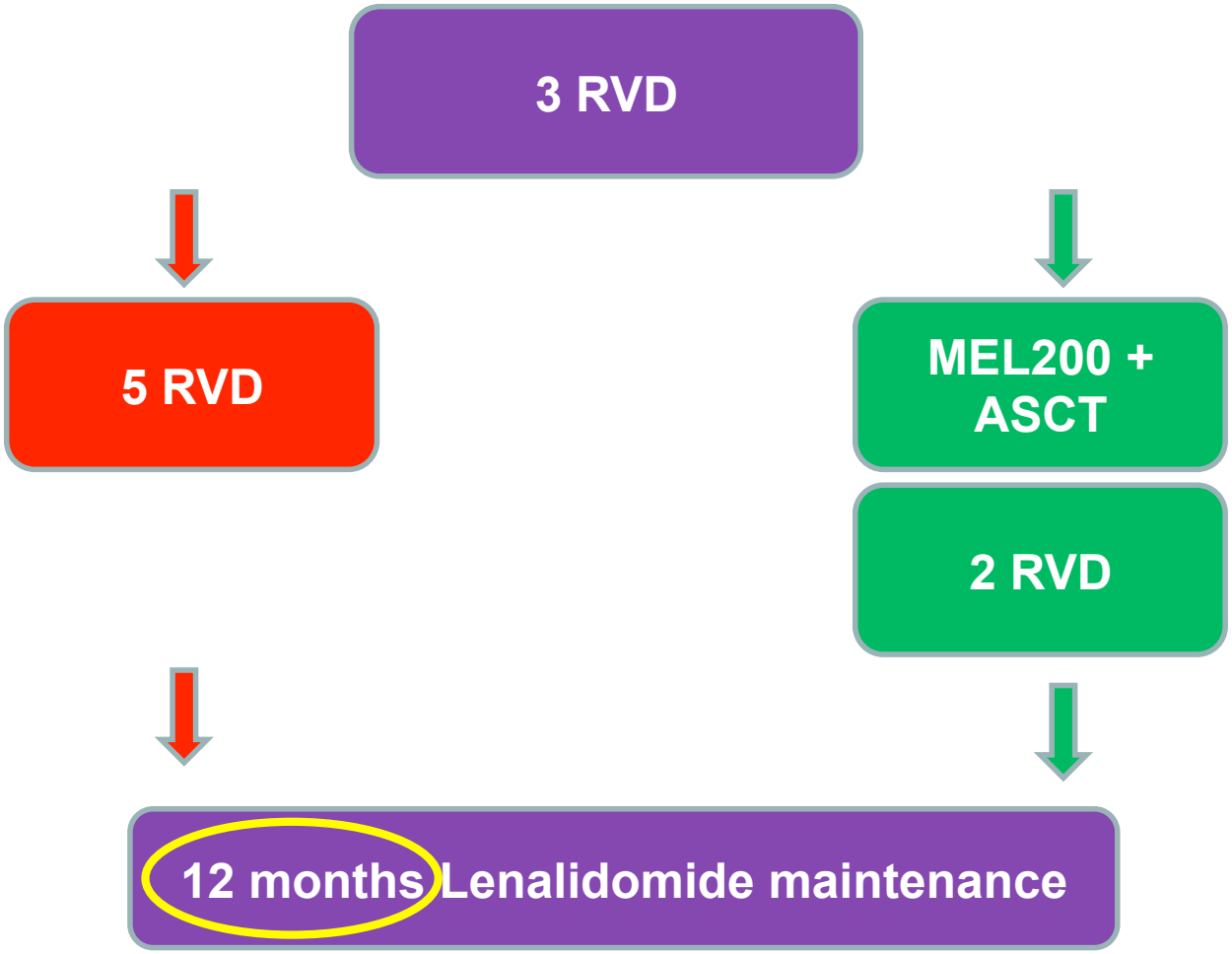
- Overall survival : YES

- Toxicity, QOL : INFECTION

- Cost-effectiveness : ?

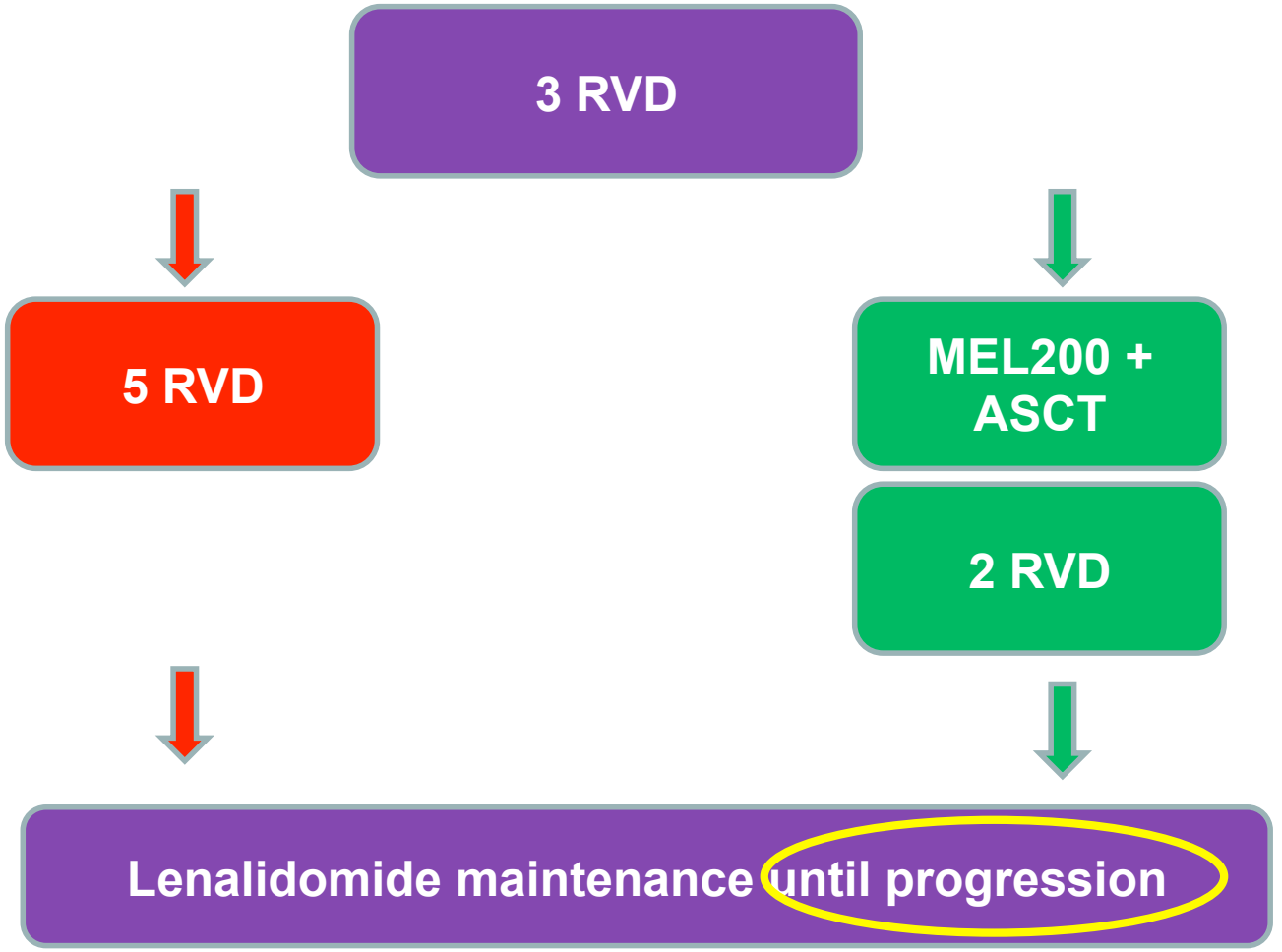
On-going trials

IFM 2009 Trial
700 patients < 66y,
Newly diagnosed symptomatic MM



Attal et al, ASH 2015

DFCI 2009 Trial
660 patients < 66y,
Newly diagnosed symptomatic MM



Alliance for Clinical Trials in Oncology

Ixazomib maintenance therapy

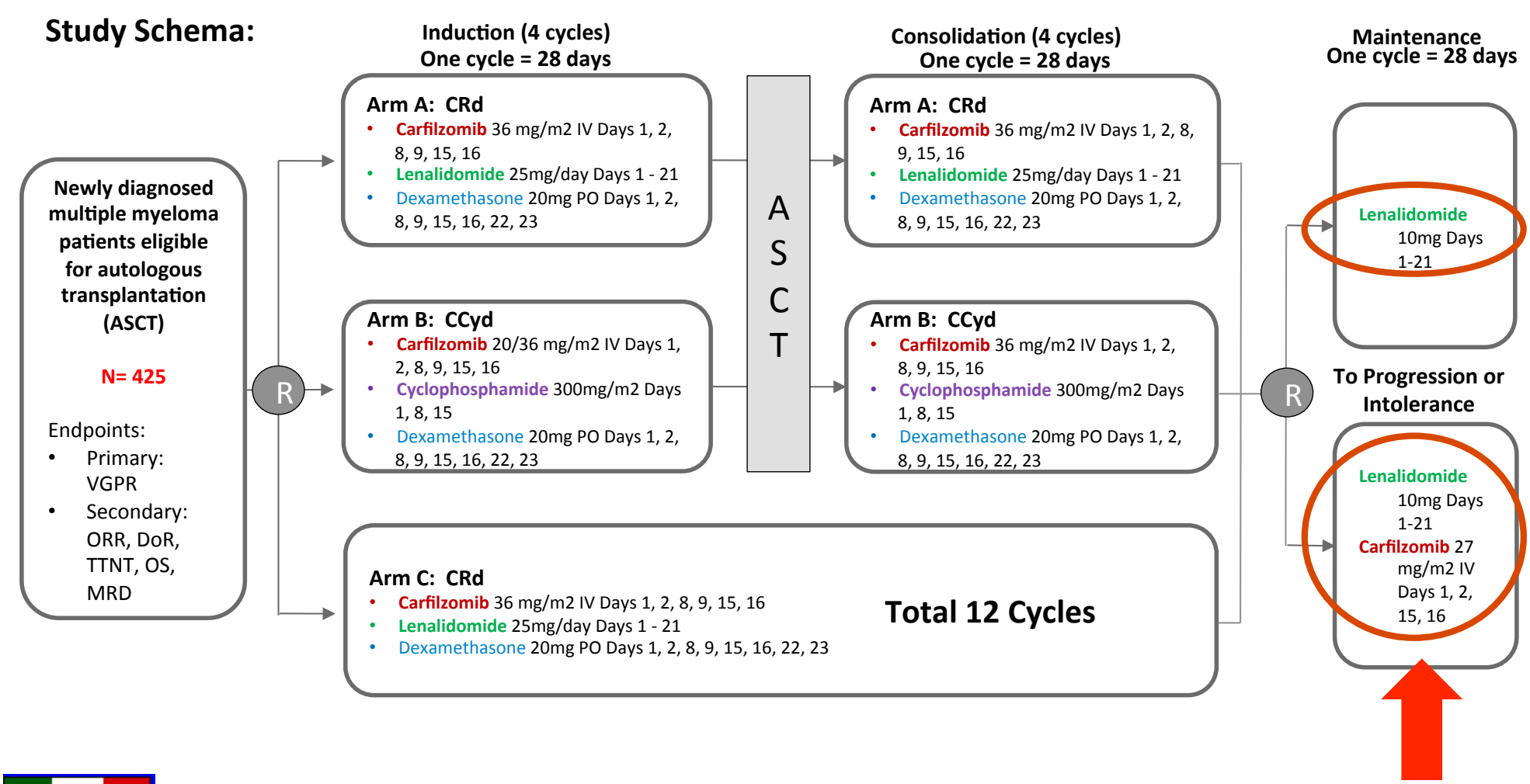
Study details	n	Treatment	PFS
MLN9708[3] Median follow-up: 31.2 months (Overall trial)	21	Ixazomib + Rd → ASCT (eligible patients) → ixazomib maintenance	Not reached

- Tourmaline MM-03: ixazomib vs Placebo as maintenance after ASCT, on-going

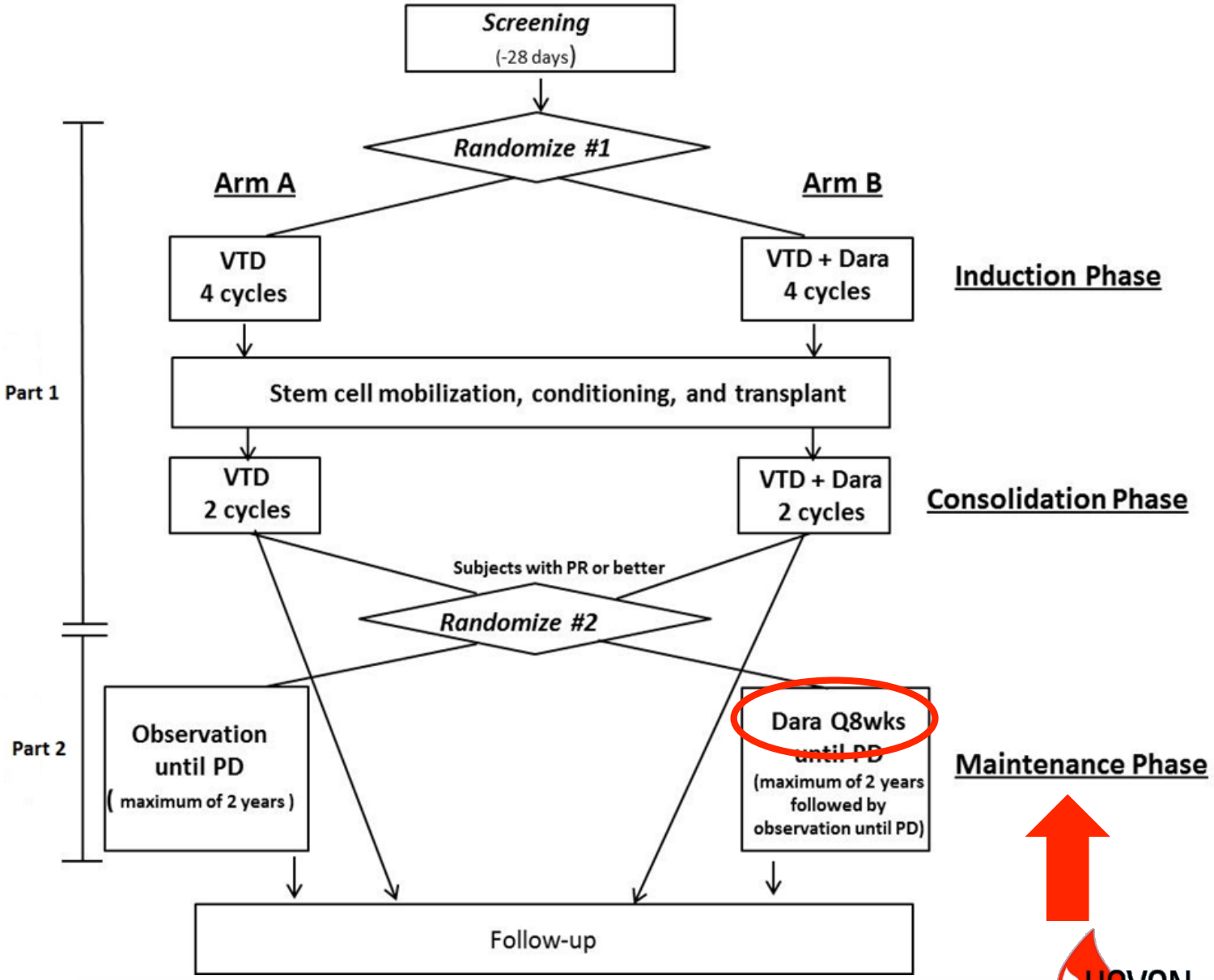
;

3. Kumar et al. ASH 2014 (Abstract 82), oral presentation.

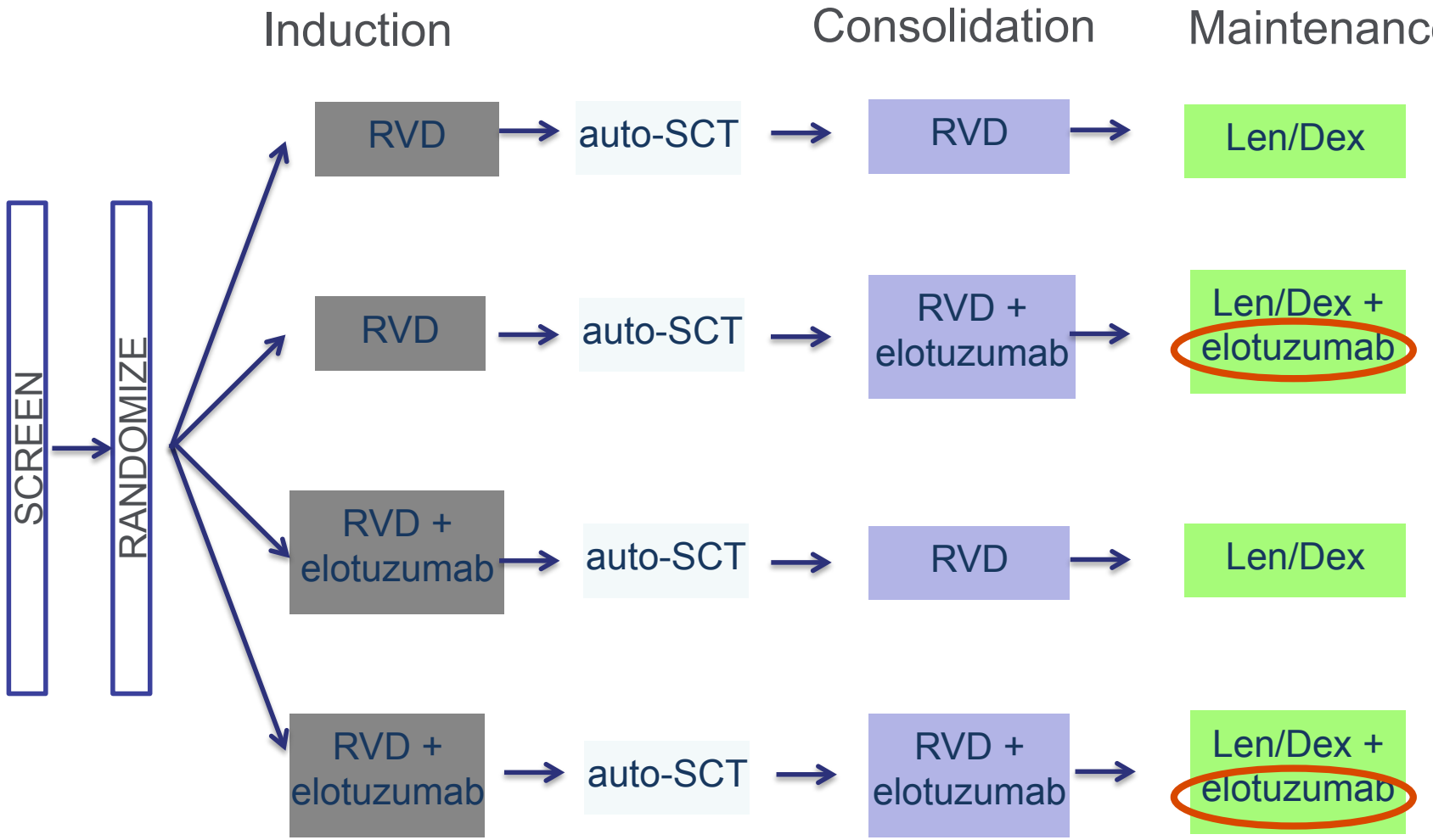
KRd study design



Study Scheme



Phase 3: Elotuzumab + VRD induction/consolidation + Lenalidomide maintenance in newly diagnosed MM (GMMG-HD6)



Conclusions
Maintenance in young patients

Maintenance post-transplant is a valuable option

- **Survival benefit with lenalidomide**
- **Other oral agents : ixazomib ?**
- **Improvement with the addition of MoAb ?**

Patients not eligible for ASCT

Maintenance treatment in the non-transplant setting: thalidomide

	Median follow-up (months)	Median PFS (months)	Median OS (months)	Reference
MPT + T	38	21.8*	45.0	*Palumbo et al. Blood 2008; 112 (8):3107-14*
vs				
MP		14.5	47.6	
MPT + T	39	13*	40*	*Wijermans et al. JCO 2010; 28(19): 3160-6*
vs				
MP		9	31	
MPT + T	42	15	29	*Waage et al. Blood 2010; 116 (9):1405-12*
vs				
MP		14	32	
CTDa/MP (CTD/CVAD) + T	46	11*	38	*Morgan et al. Blood 2012; 119 (1):7-15*
vs				
CTDa/MP (CTD/CVAD)		9	39	
Thal-IFN	35	27.7*	52.6	*Ludwig et al. Haematologica 2010; 95(9): 1548-54*
vs				
IFN†		13.2	51.4	

†Thal/Dex vs MP induction

*significant difference between arms

Phase III: VMPT + VT vs VMP in elderly patients with newly diagnosed MM – GIMEMA study

Patients (n=511): >65 years old; median age 71 years

Treatment

VMPT

9 x 5-week cycles

Bortezomib weekly

Melphalan

Prednisone

Thalidomide

Maintenance:

Bortezomib (every 15 days) +

Thalidomide for 2 years

VMP

9 x 5-week cycles

Bortezomib weekly

Melphalan

Prednisone

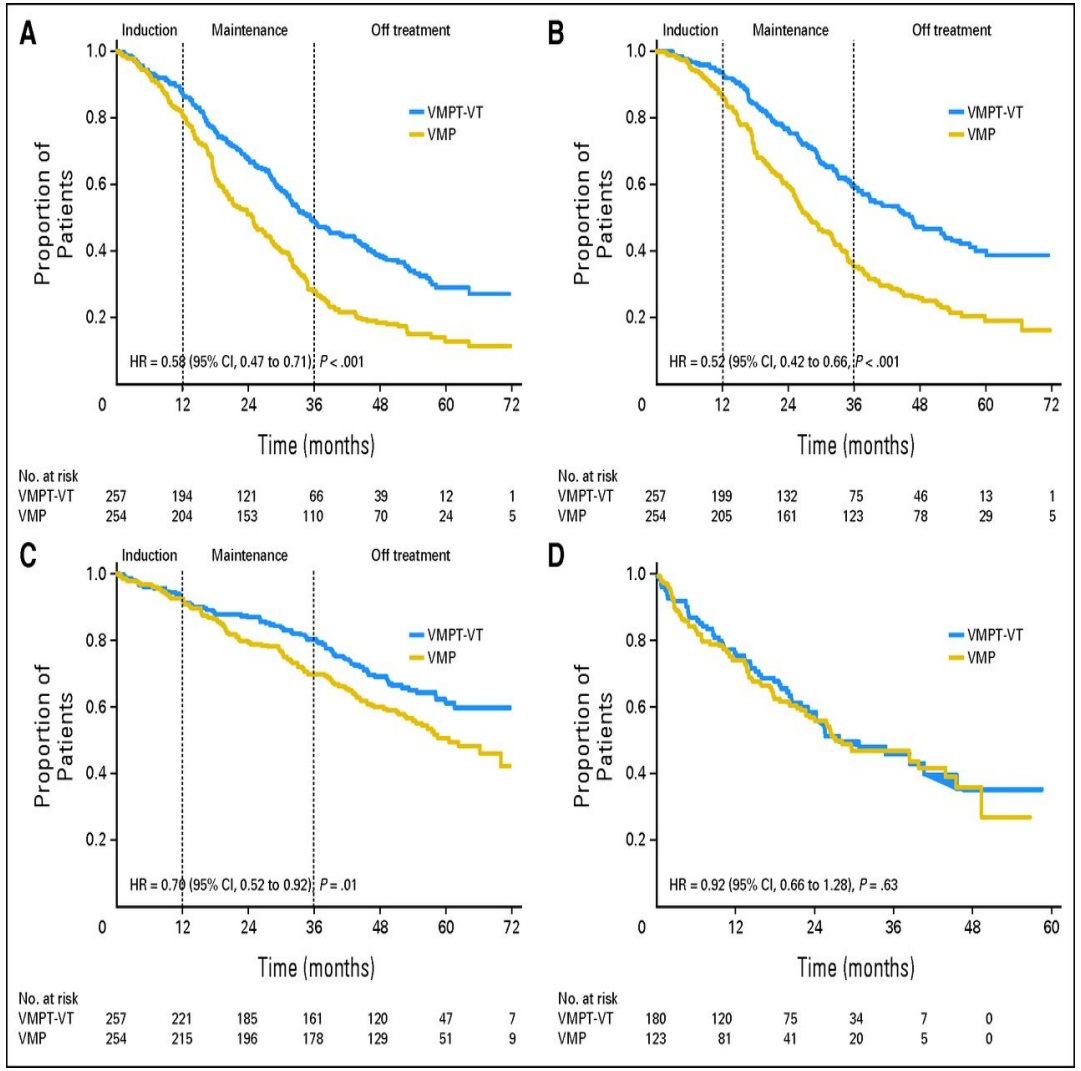
No maintenance

Palumbo *et al*. J Clin Oncol 2010

Survival outcomes in the intention-to-treat population, according to study group.

PFS

TNT



OS

OS post relapse

Palumbo A et al. JCO 2014;32:634-640

Weekly bortezomib in Elderly Patients

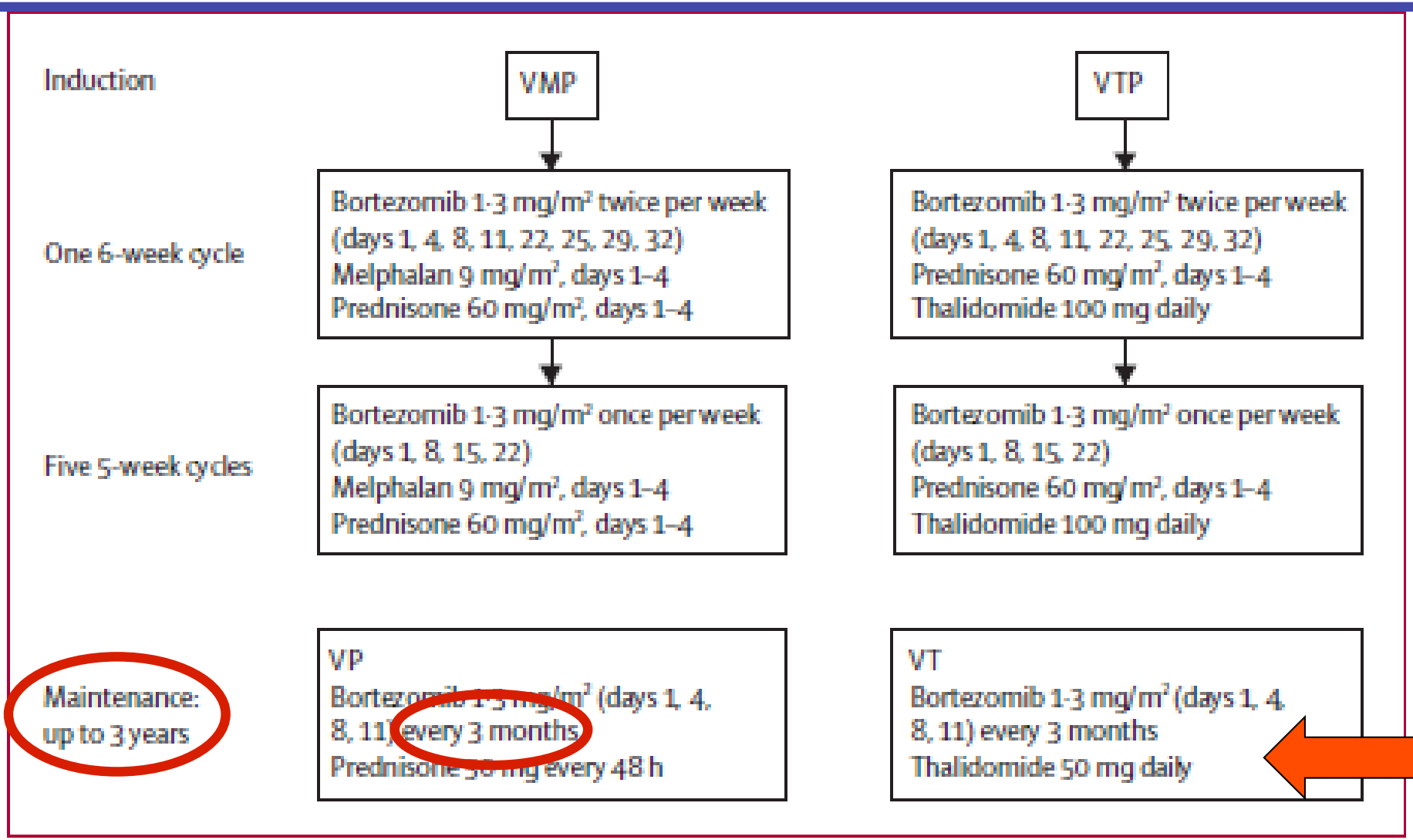


Figure 1: **Schedule of induction and maintenance treatment**
V=bortezomib. M=melphalan. P=prednisone. T=thalidomide.

Mateos MV, et al. Lancet Oncol. 2010;11:934-941.

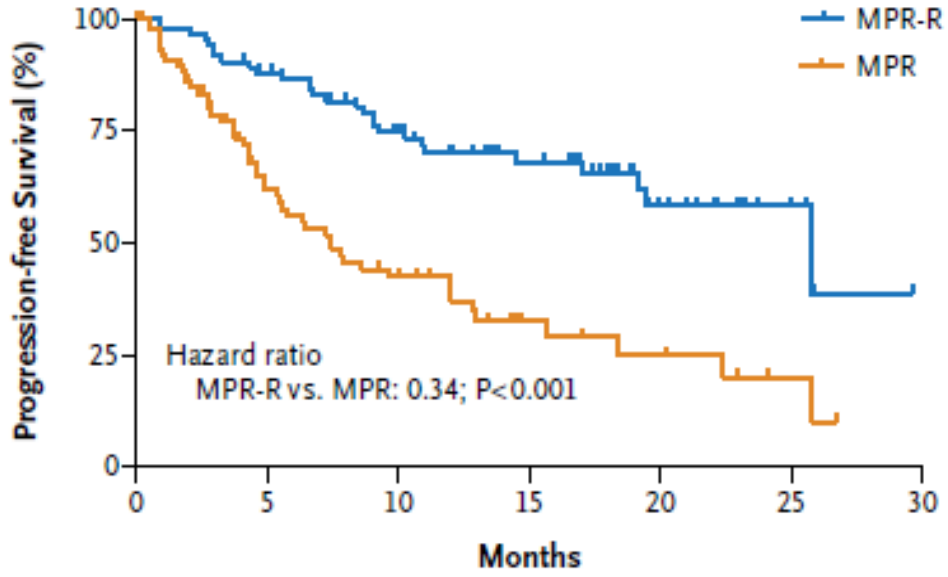
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 10, 2012 VOL. 366 NO. 19

Continuous Lenalidomide Treatment for Newly Diagnosed Multiple Myeloma

Antonio Palumbo, M.D., Roman Hajek, M.D., Ph.D., Michel Delforge, M.D., Ph.D., Martin Kropff, M.D., Maria Teresa Petrucci, M.D., John Catalano, M.B., B.S., Heinz Gisslinger, M.D., Wiesław Wiktor-Jędrzejczak, M.D., Ph.D., Mamia Zodelava, M.D., Ph.D., Katja Weisel, M.D., Nicola Cascavilla, M.D., Genadi Iosava, M.D., Michele Cavo, M.D., Janusz Kloczko, M.D., Ph.D., Joan Bladé, M.D., Meral Beksac, M.D., Ivan Spicka, M.D., Ph.D., Torben Plesner, M.D., Joergen Radke, M.D., Christian Langer, M.D., Dina Ben Yehuda, M.D., Alessandro Corso, M.D., Lindsay Herbein, B.S., Zhinuan Yu, Ph.D., Jay Mei, M.D., Ph.D., Christian Jacques, M.D., and Meletios A. Dimopoulos, M.D., for the MM-015 Investigators*

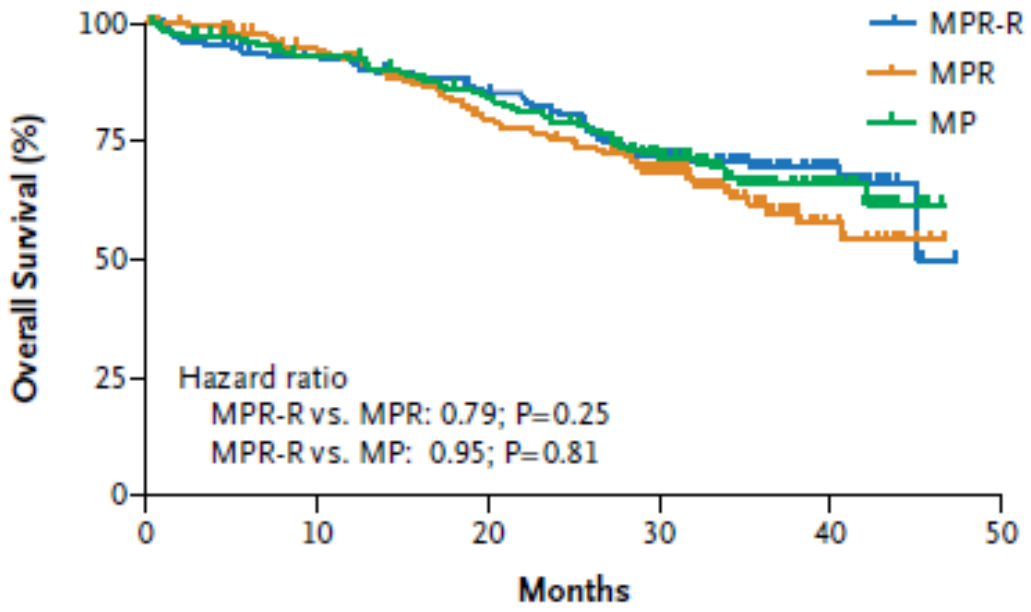
B Progression-free Survival, Landmark Analysis



No. at Risk							
MPR-R	88	71	52	33	14	5	0
MPR	94	43	27	9	6	2	0

Palumbo A, et al. N Engl J Med 2012;366(19):1759-69

C Overall Survival

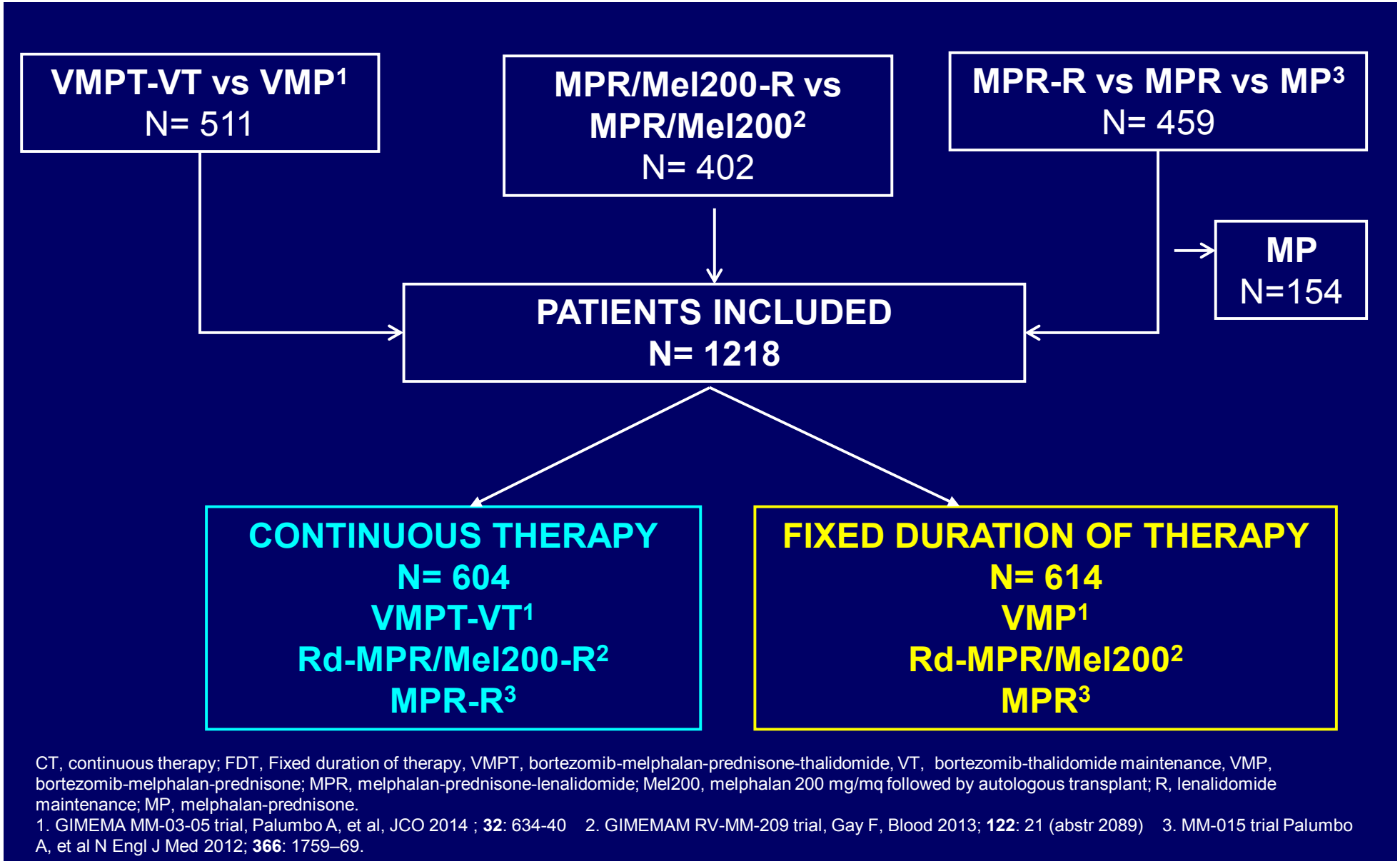


No. at Risk						
MPR-R	152	130	117	82	27	0
MPR	153	134	108	79	18	0
MP	154	134	117	84	24	0

Palumbo A, et al. N Engl J Med 2012;366(19):1759-69

Continuous vs Fixed duration

Meta-analysis of 3 studies: 1218 patients

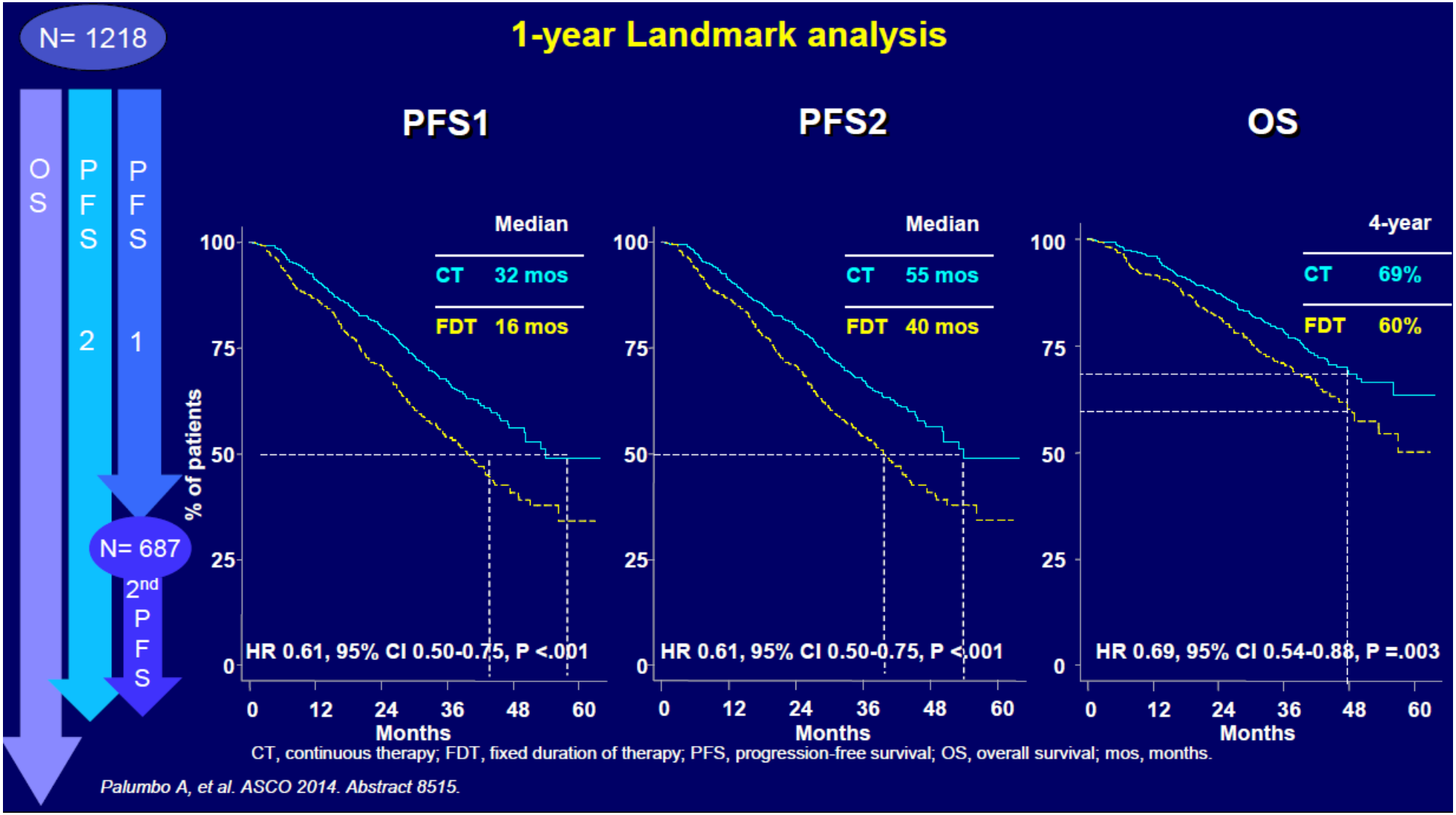


CT, continuous therapy; FDT, Fixed duration of therapy, VMPT, bortezomib-melphalan-prednisone-thalidomide, VT, bortezomib-thalidomide maintenance, VMP, bortezomib-melphalan-prednisone; MPR, melphalan-prednisone-lenalidomide; Mel200, melphalan 200 mg/mq followed by autologous transplant; R, lenalidomide maintenance; MP, melphalan-prednisone.

1. GIMEMA MM-03-05 trial, Palumbo A, et al, JCO 2014 ; **32**: 634-40 2. GIMEMAM RV-MM-209 trial, Gay F, Blood 2013; **122**: 21 (abstr 2089) 3. MM-015 trial Palumbo A, et al N Engl J Med 2012; **366**: 1759–69.

Palumbo et al., JCO 2015

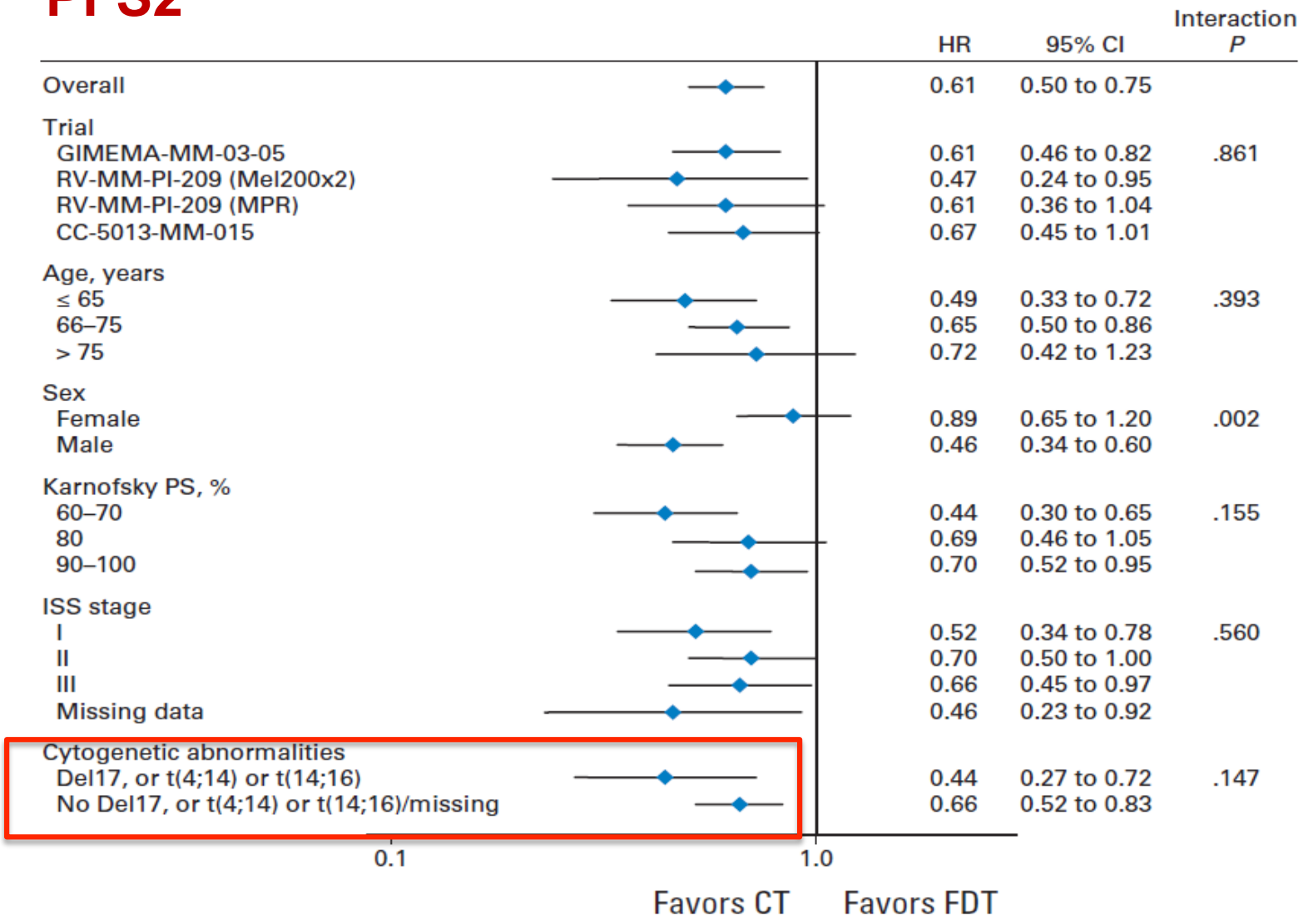
Continuous vs Fixed duration
PFS1, PFS2 and OS



Continuous treatment significantly improved PFS1, PFS2, and OS. Prolongation of PFS2 suggests that the treatment is not introducing resistance in next line therapy.

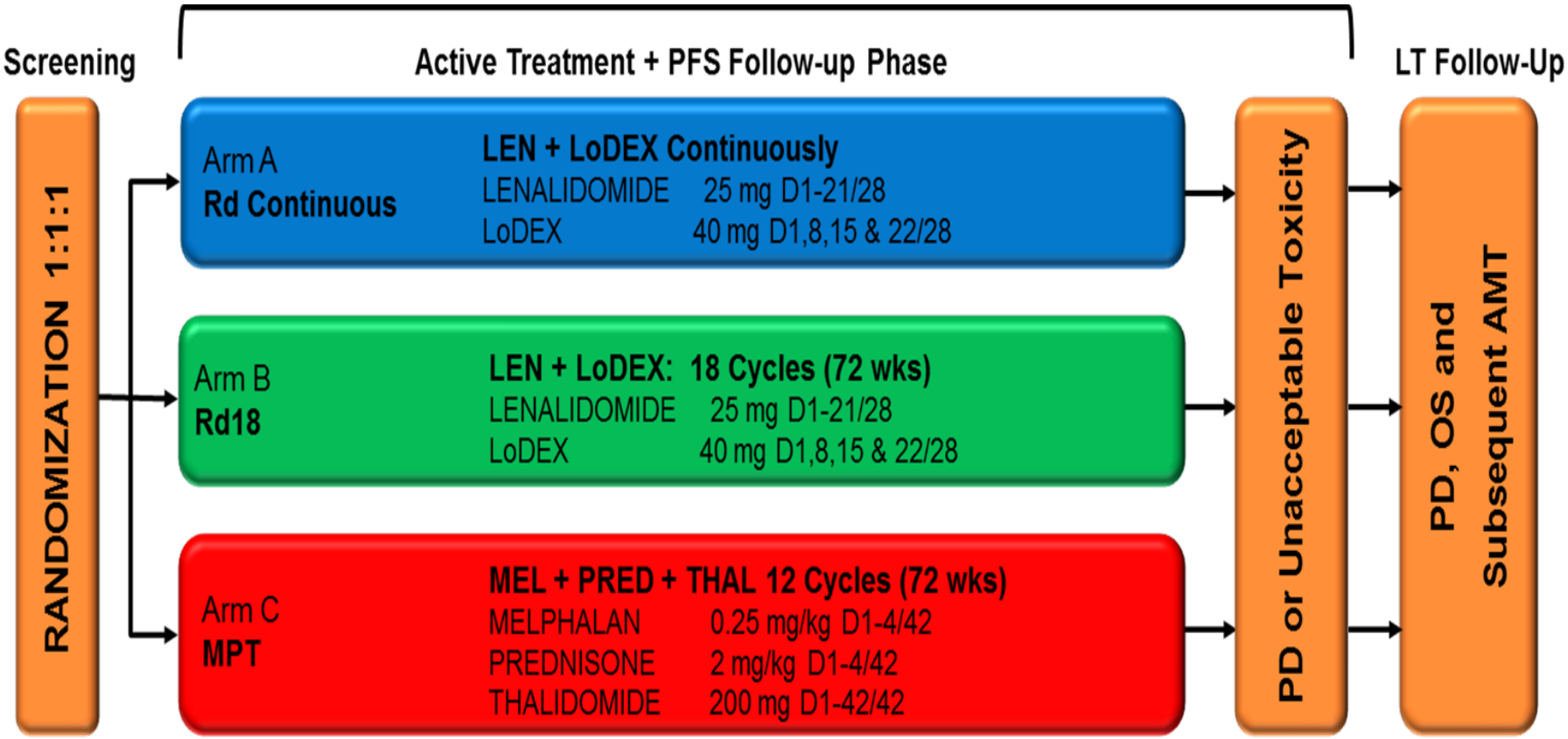
Palumbo et al., JCO 2015

PFS2



Palumbo et al., JCO 2015

FIRST/MM020/ IFM 2007-01 trial : MPT vs Len-Dex (Rd)



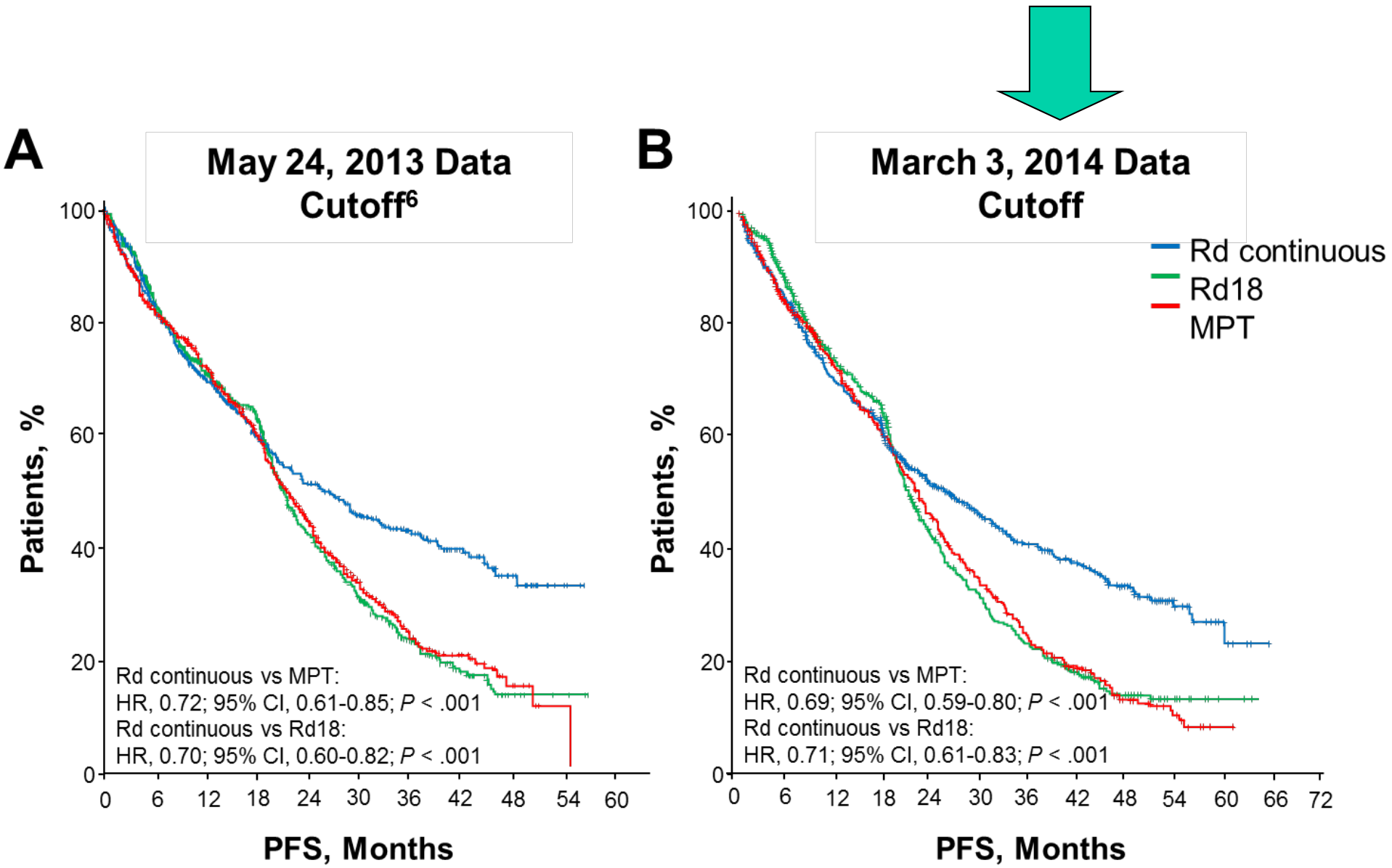
Pts > 75 yrs: LoDEX 20 mg D1, 8, 15 & 22/28; THAL 100 mg D1-42/42; MEL 0.2 mg/kg D1–4

- Stratification: age, country and ISS stage
- All patients received thromboprophylaxis
- At the time of data cutoff on March 3, 2014, median follow-up was 45.5 mo

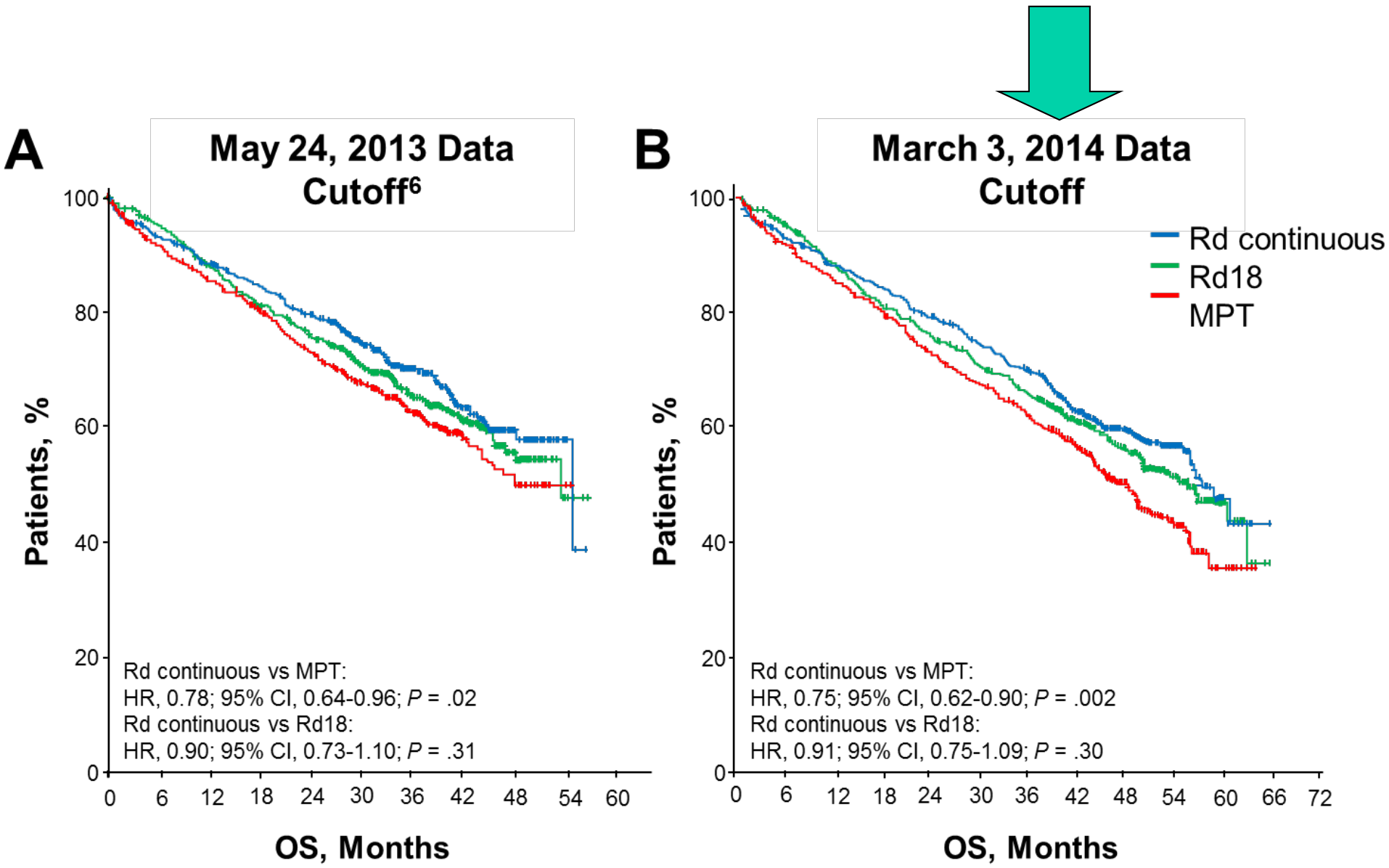
Benboubker et al. N Engl J Med. 2014 Sep 4;371(10):906-17

Lenalidomide / low-dose dex in elderly patients is proposed until progression:

Isn’t it a maintenance ?



Abstract #8524 / Facon, ASCO 2015 – Updated OS and PFS analysis of MM020 trial



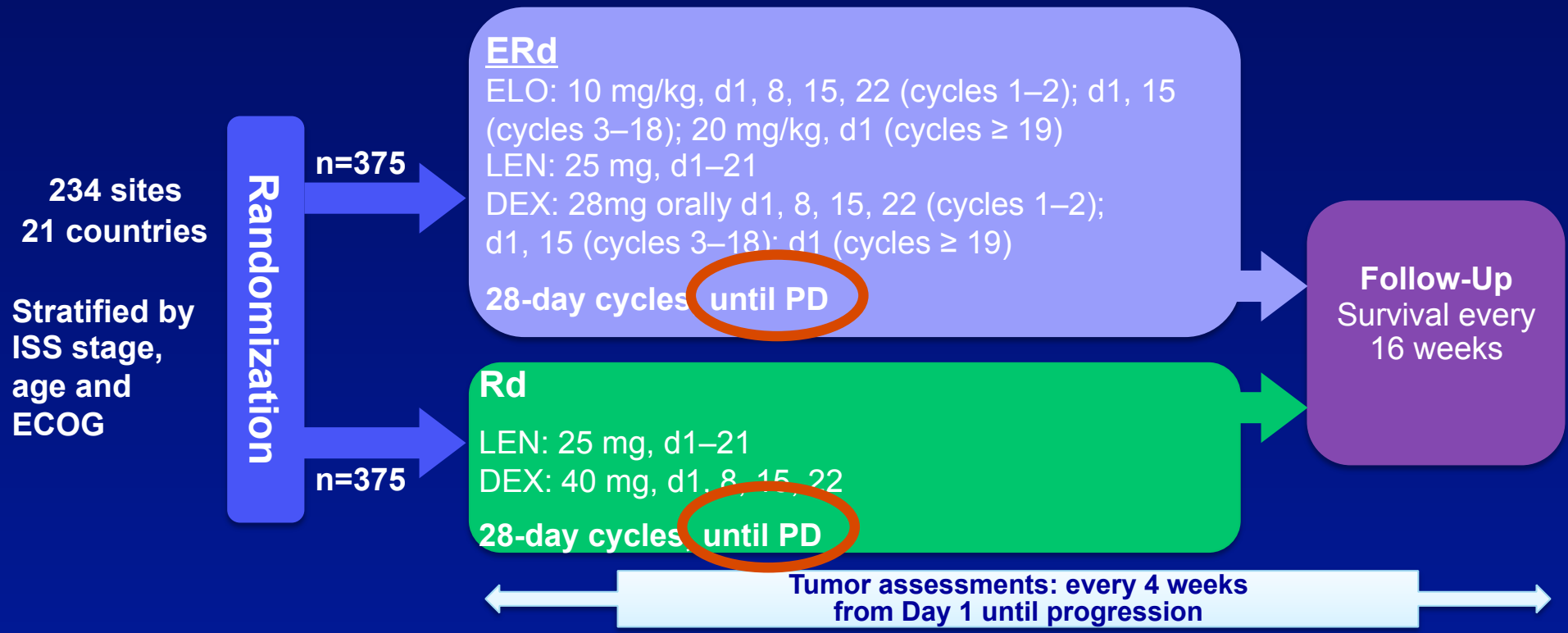
Abstract #8524 / Facon, ASCO 2015 – Updated OS and PFS analysis of MM020 trial

Len-dex until PD

How to improve ?

On-going trials

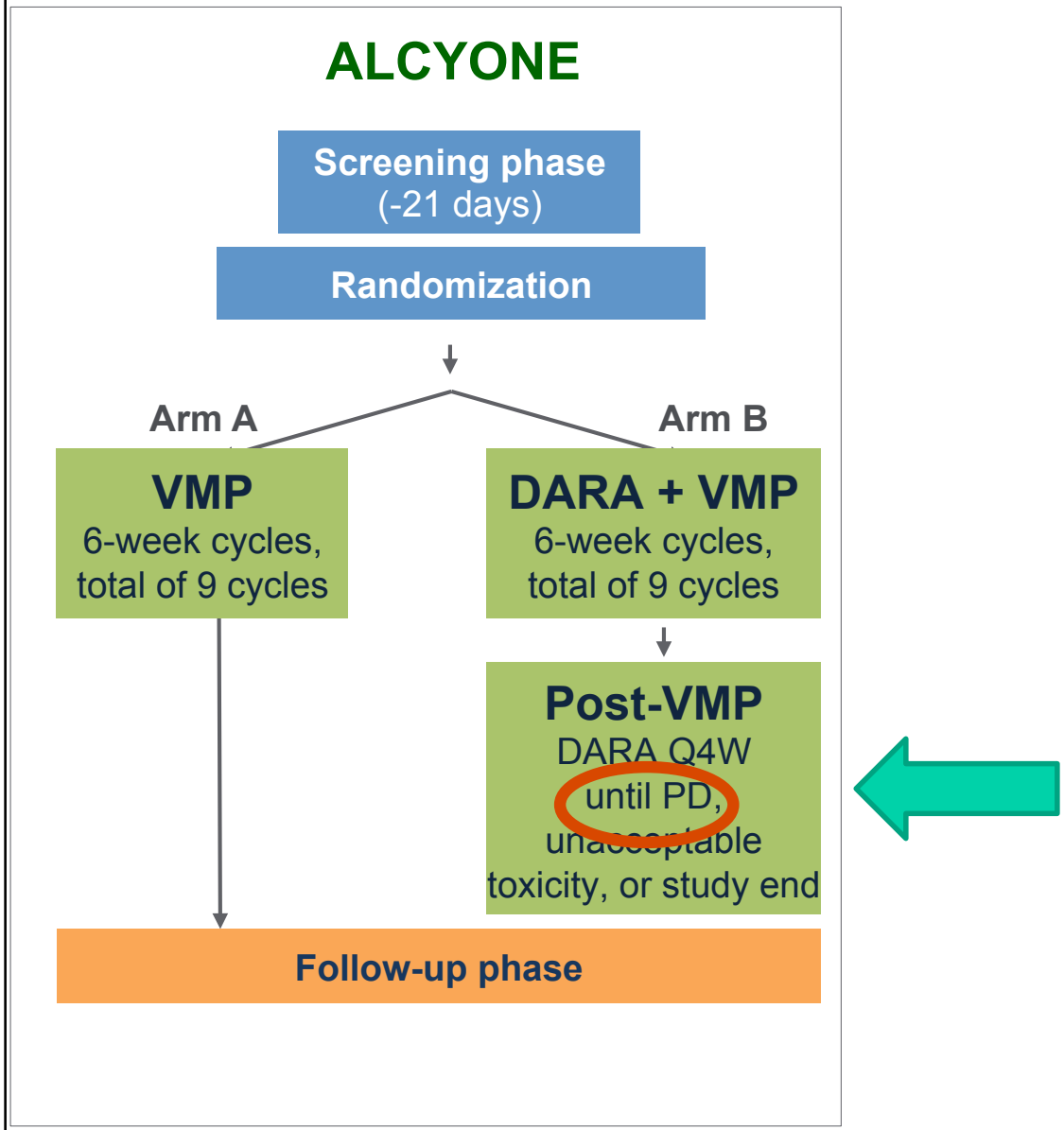
Phase 3 ELOQUENT-1 (CA204-006): ERd vs Rd in TNE NDMM



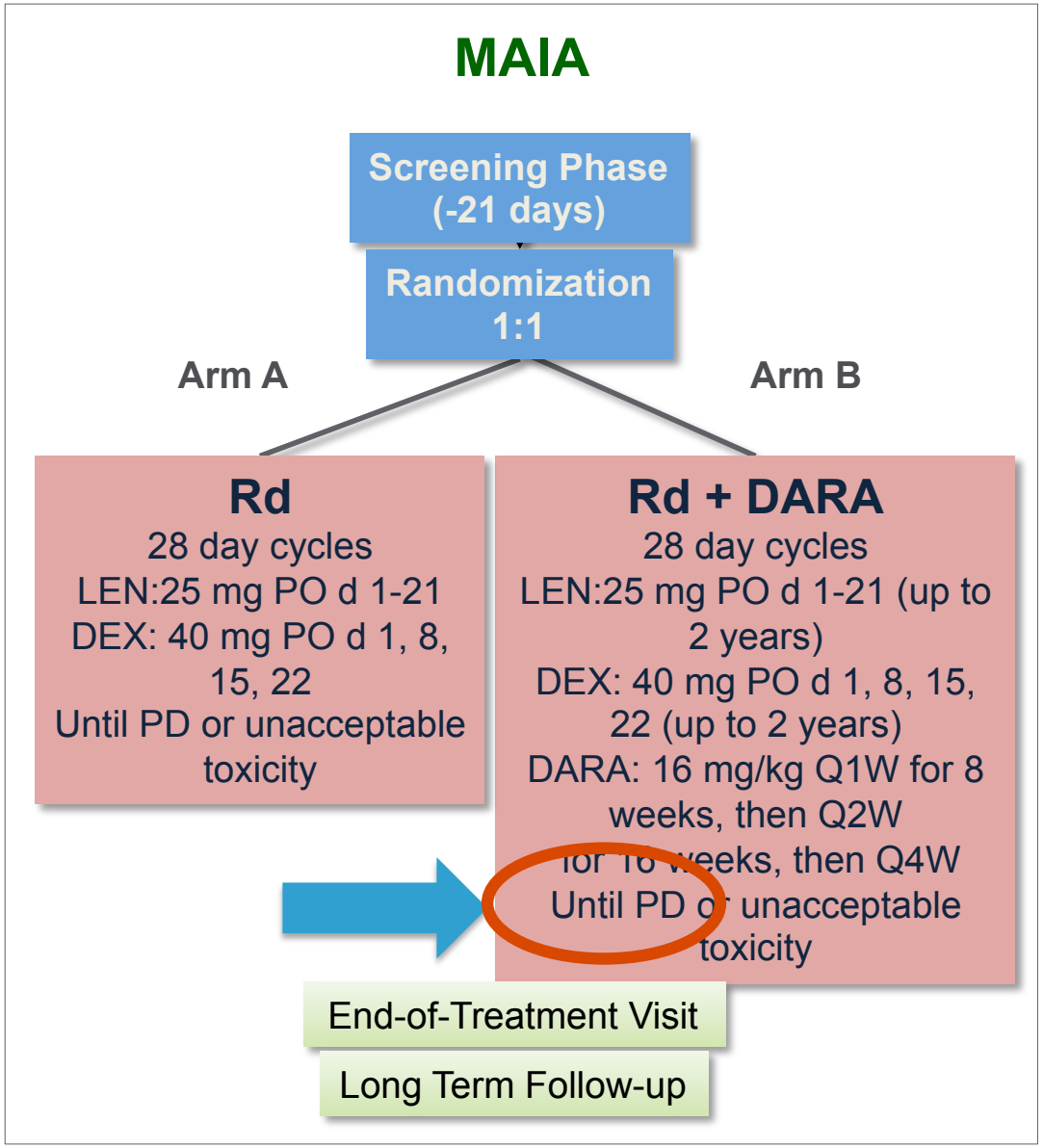
- Primary endpoint: PFS (EBMT)
  - Primary endpoint analysis expected Q4 2018
- Secondary endpoints: ORR, OS

NCT01335399. Available from: www.clinicaltrials.gov. Accessed 8 October 2013.
EudraCT 2010-022445-20

Ongoing daratumumab studies in the non-transplant setting



Ongoing daratumumab studies in the non-transplant setting



www.clinicaltrials.gov, NCT02252172

On-going trial with ixazomib

- Rd-placebo vs Rd-Ixazomib, Tourmaline MM-2
- Ixazomib vs placebo in non ASCT eligible patients after induction, Tourmaline MM-4

Conclusions
Maintenance in elderly patients

PFS improvement

FIRST trial: len-dex until progression

Ongoing trials Len-dex + …

Role of Ixazomib ?