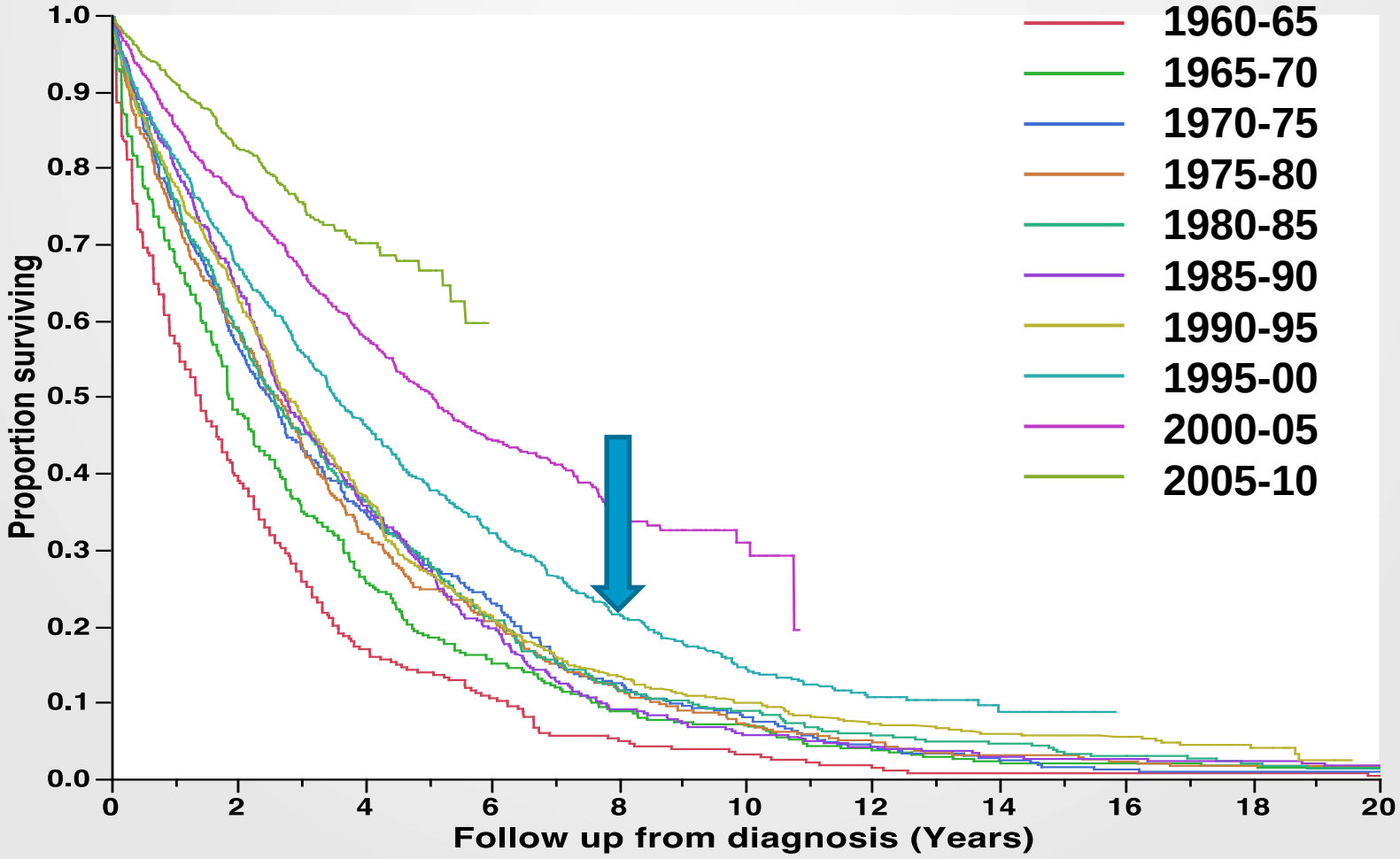
Treatment of Myeloma In 2017 Recent Advances And Current Hopes

Jean Luc Harousseau

CONFLUENT L'HÔPITAL PRIVÉ

ifm

Multiple Myeloma Survival Improving With New Drugs



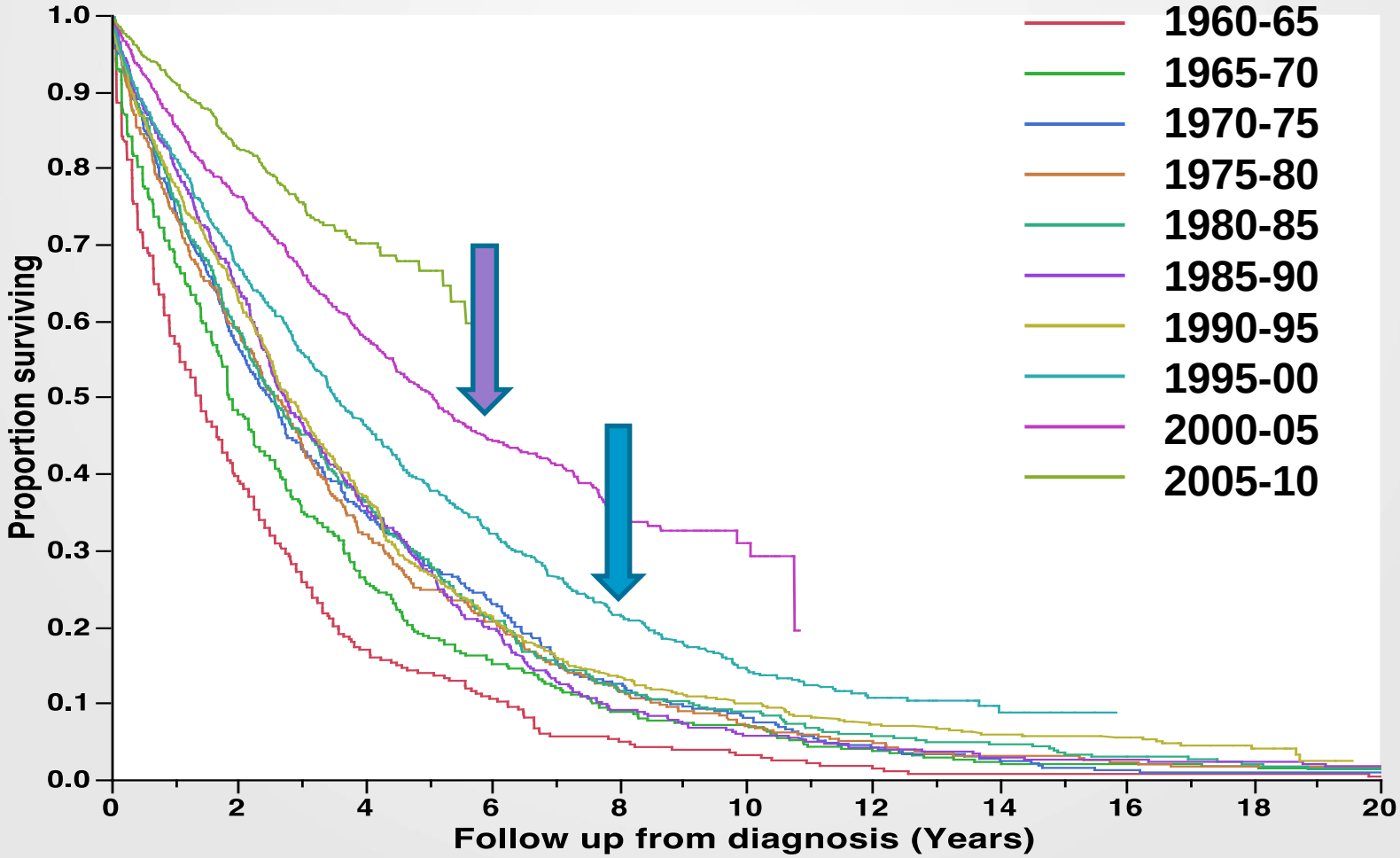
Adapted from Kumar et al *Leukemia* 2014

First improvement (in the nineties) Autologous transplantation

- Autologous stem cell transplantation is actually
  - High-dose therapy (Melphalan)
  - Supported by patients hematopoietic stem cells
  -Collected in the peripheral blood
  - Cryopreserved

- Eligible patients
  - up to 65 years of age
  - fit and without severe comorbidities

Multiple Myeloma Survival Improving With New Drugs



Adapted from Kumar et al *Leukemia* 2014

Second Improvement (2000-2005)
Thalidomide

- New possibility at the time of relapse

The NEW ENGLAND JOURNAL of MEDICINE

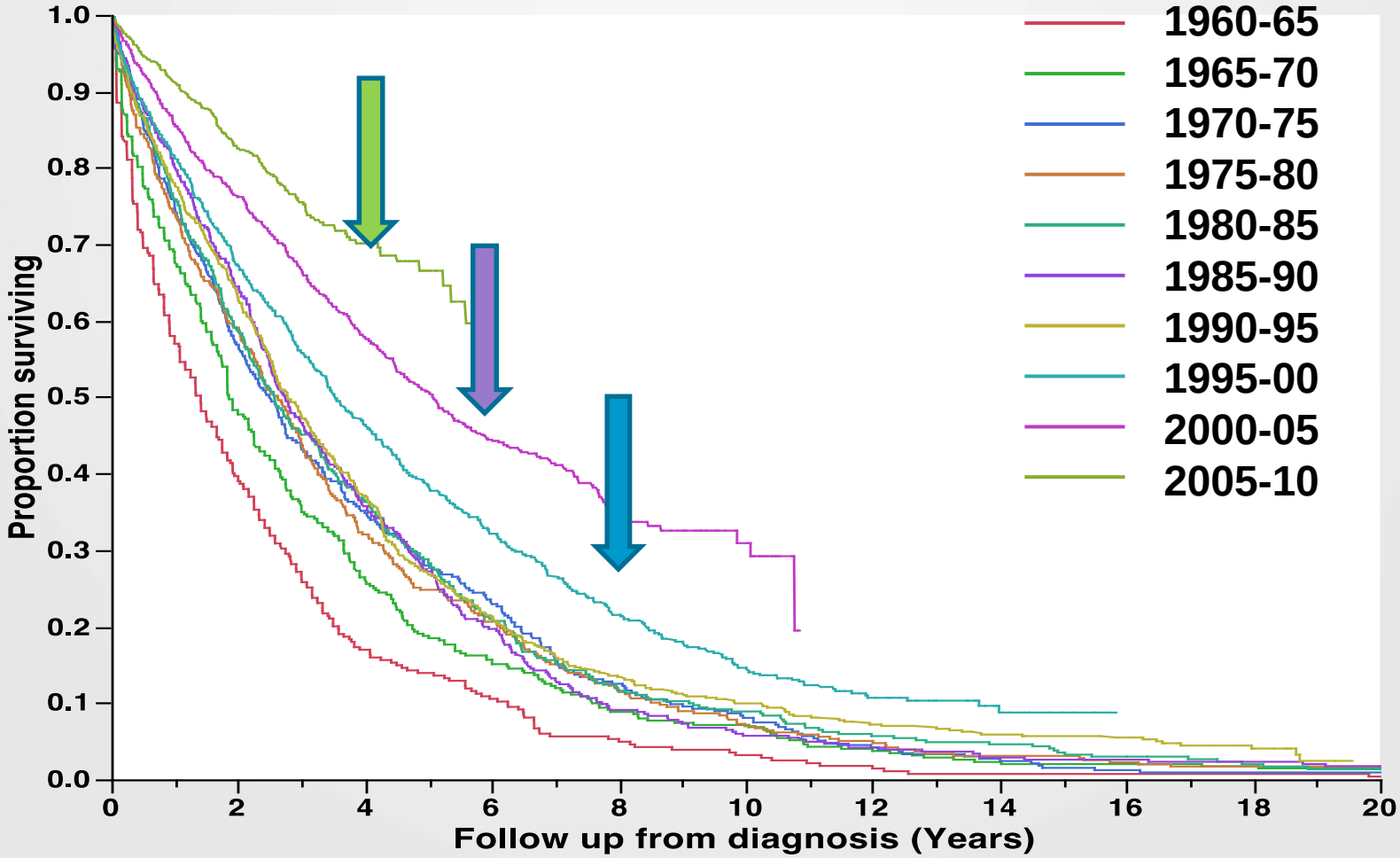
Antitumor Activity of Thalidomide in Refractory Multiple Myeloma

Seema Singhal, M.D., Jayesh Mehta, M.D., Raman Desikan, M.D., Dan Ayers, M.S., Paula Roberson, Ph.D., Paul Eddlemon, B.S., Nikhil Munshi, M.D., Elias Anaissie, M.D., Carla Wilson, M.D., Ph.D., Madhav Dhodapkar, M.D., Jerome Zeldis, M.D., David Siegel, M.D., Ph.D., John Crowley, Ph.D., and Bart Barlogie, M.D., Ph.D.

N Engl J Med 1999; 341:1565-1571 | November 18, 1999 | DOI: 10.1056/NEJM199911183412102

- New treatment for newly diagnosed patients

Multiple Myeloma Survival Improving With New Drugs



Third Improvement (2005-2010)
Thalidomide

- Introduction of 3 novel anti-myeloma agents
  - Thalidomide
  - Bortezomib (Velcade)
  - Lenalidomide (Revlimid)
- Both in relapsed MM and newly diagnosed patients
- Different modes of action than chemotherapy
- Different toxicities

Current treatment in transplant-eligible patients

In the era of « novel » agents HDT/ASCT

Is no longer just HDT supported by ASCT

But is a part of a complex multistep prodedure

Induction therapy

3-4 CYCLES « novel » agents

ASCT

Melphalan 200 mg/m^2

Consolidation

2-3 CYCLES « novel» agents

Or Second ASCT

Maintenance

Lenalidomide
Bortezomib

Induction therapy with novel agents

- Should contain Velcade
- Triple Combination > Double Combination
  - VTD > TD Cavo M Lancet 2010;376:2075
    Rosinol L Blood 2012;120:1589
  - vTD > VD Moreau P Blood 2011;118:5752
  - VTD slightly >VCD Moreau P Blood 2016;127:2569
- VTD is the standard induction regimen
  - VRD might be more effective or better tolerated
  - But is more expensive
  - No randomized comparison

Consolidation Therapy

- Currently 2-3 cycles of combination therapy (usually the same as induction therapy)

- With the objective of increasing the rate of Complete Remission

  (disappearance of all apparent disease)

- And of upgrading the level of response

  (reduces the burden of disease to levels that are detected only by sensitive methods)

Consolidation Therapy

- Currently 2-3 cycles of combination therapy (usually the same as induction therapy)

- With the objective of increasing the rate of Complete Remission

  (disappearance of all apparent disease)

- And of upgrading the level of response

(reduces the burden of disease to levels that are detected only by sensitive methods)

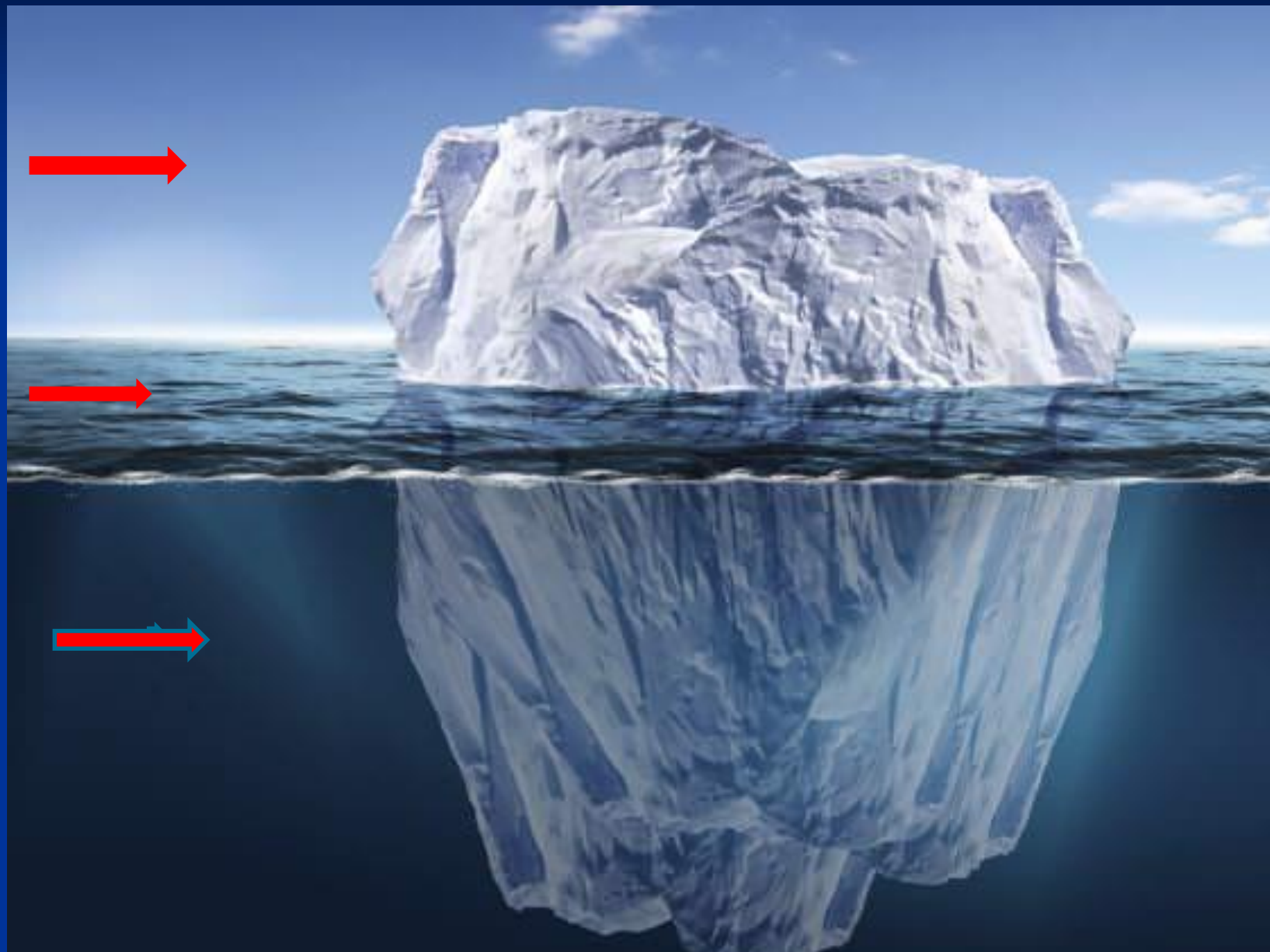
→ **Negative minimal residual disease**

What does « Minimal Residual Disease » Mean

Diagnosis

CR 1<100

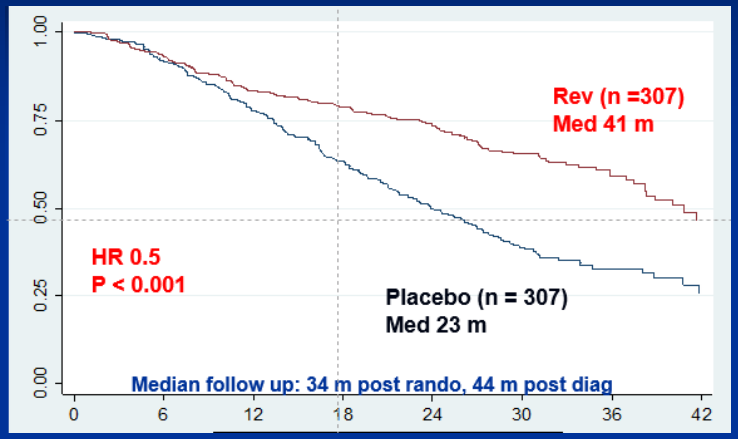
MRD<0
<1 M

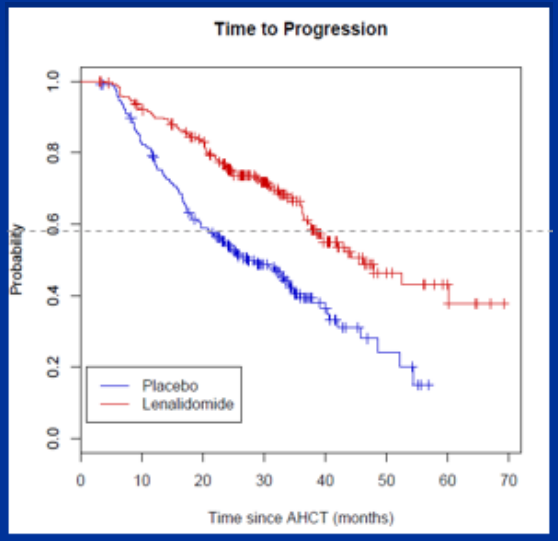


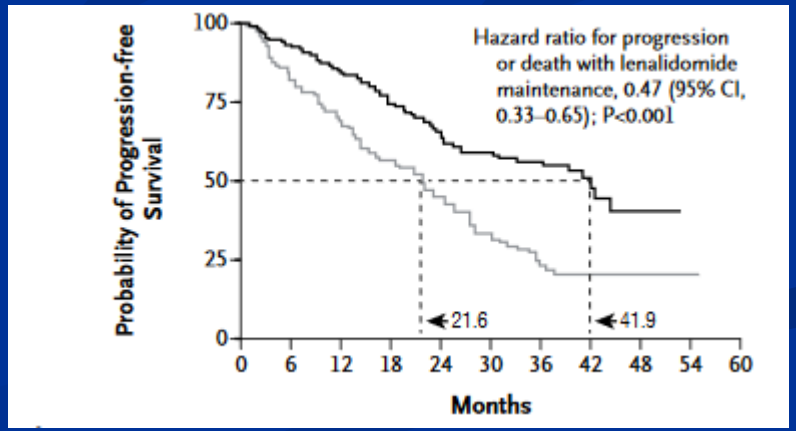
Maintenance therapy

with low-dose lenalidomide until progression dramatically improves PFS

Attal M (IFM)
NEJM 2012;366:1782





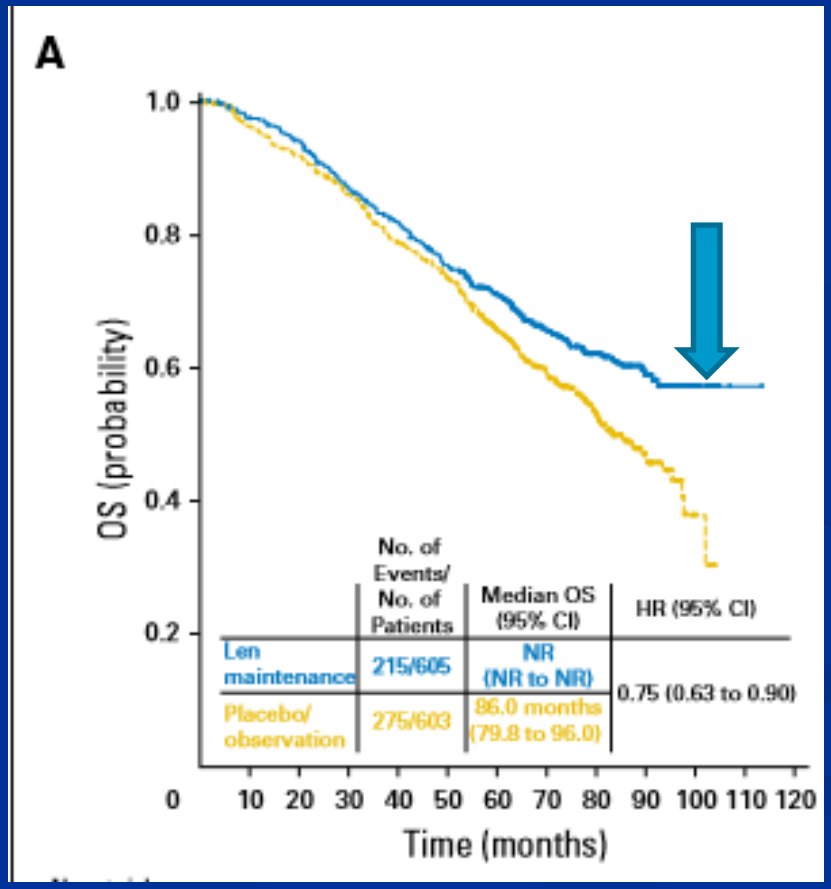


Mc Carthy P (CALGB) NEJM 2014,371:1770

Palumbo A NEJM 2014;371:895

Lenalidomide maintenance OS

- Meta-analysis of the 3 trials (1208 pts, 79.5 mo median f-up)
- The benefit of a longer duration of first response translates into a longer OS only after 5 years



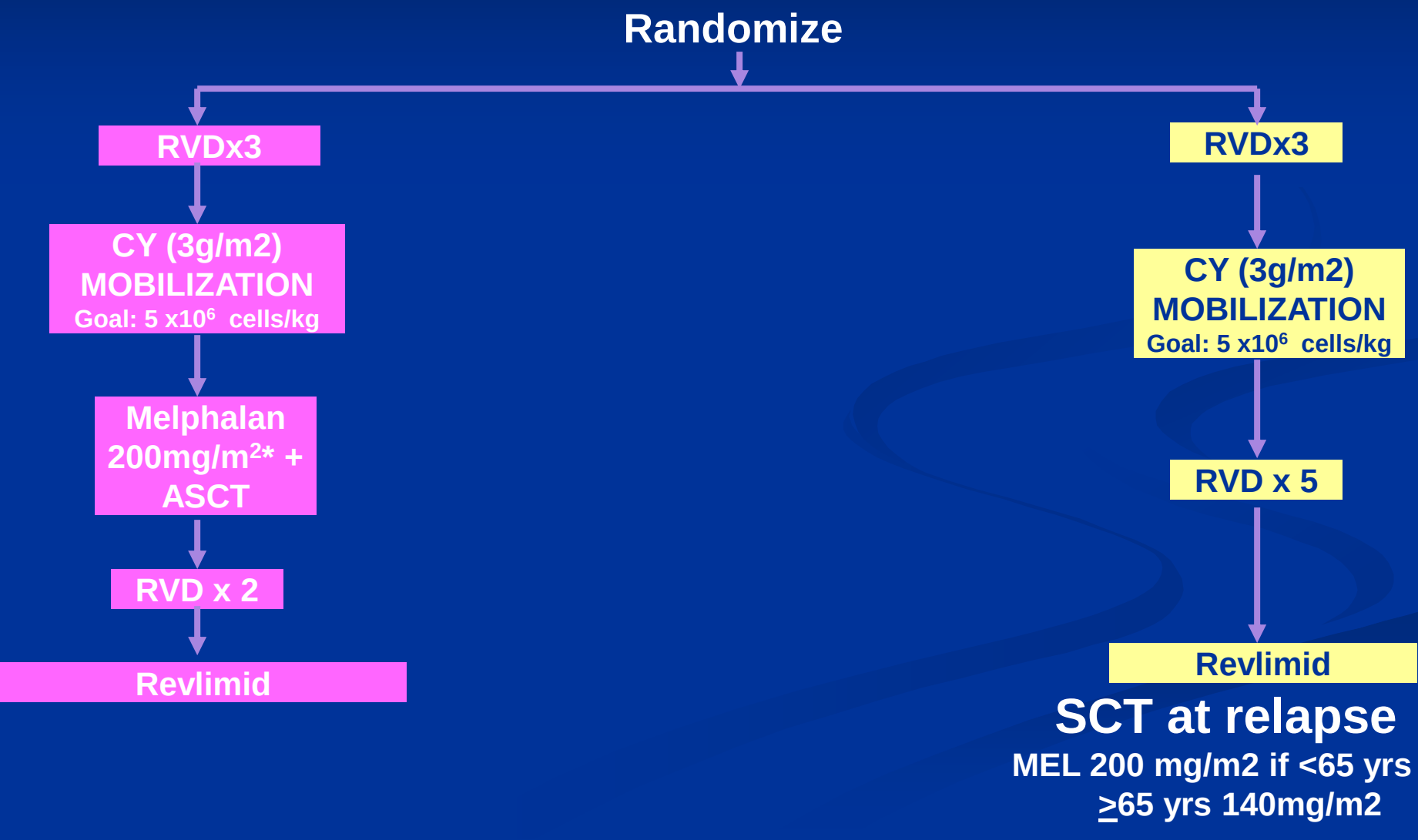
Mc Carthy P (JCO 2017 online)

LENALIDOMIDE MAINTENANCE REMAINING QUESTIONS

- Lenalidomide maintenance after ASCT is now approved by FDA and EMA
- However less convincing results in high-risk MM (ISS3, poor-risk cytogenetics) → Bortezomib ?
- Toxicity of long-term treatment
  - 29% of AE → treatment discontinuation
  - 4.3% SPM vs 1%
- Cost (unaffordable in some countries)
- Optimal duration still unknown

IS UPFRONT ASCT STILL THE STANDARD OF CARE ?

IFM/DFCI 2009 Study
Early vs Late ASCT in newly diagnosed MM pts up to 65 years



SCT at relapse

MEL 200 mg/m2 if <65 yrs , ≥65 yrs 140mg/m2

IFM 2009 (9/2015)

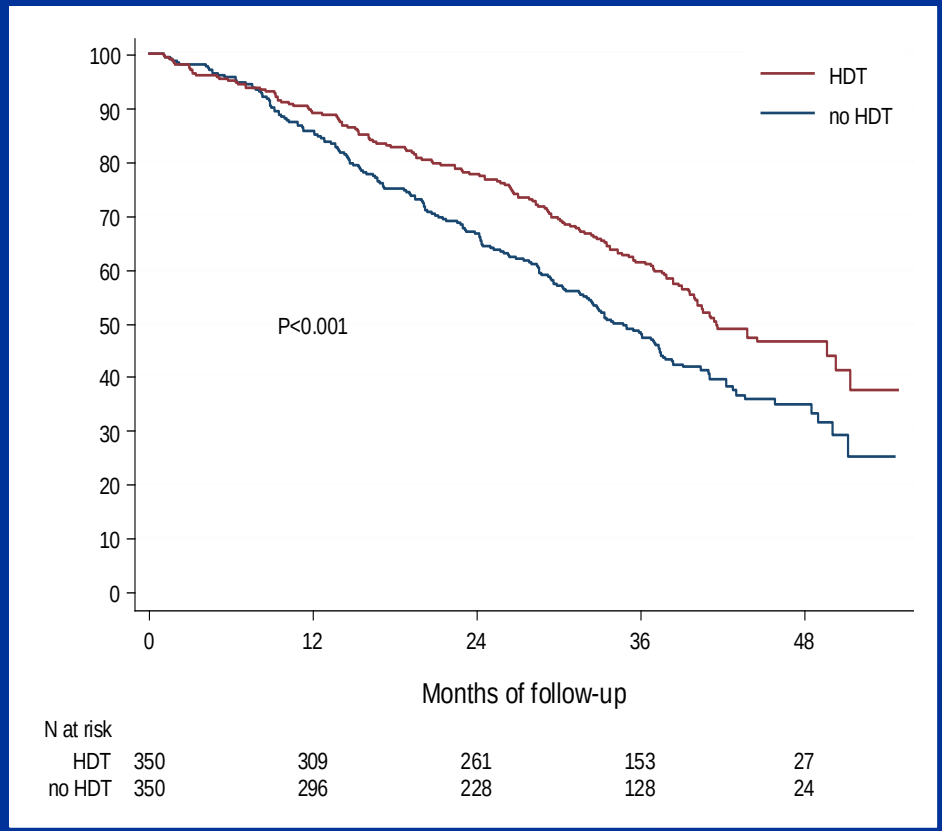
Median F-up 43 months

PFS

Median 36 m vs 50 m

4-yr PFS 35%vs 50 %

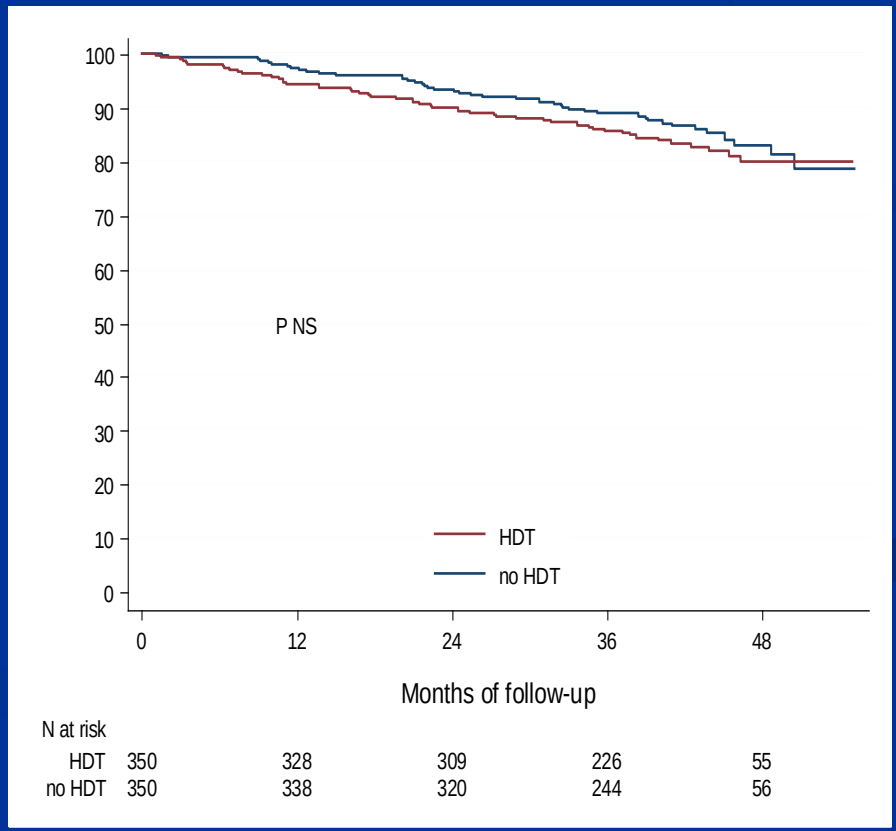
HR 0.65



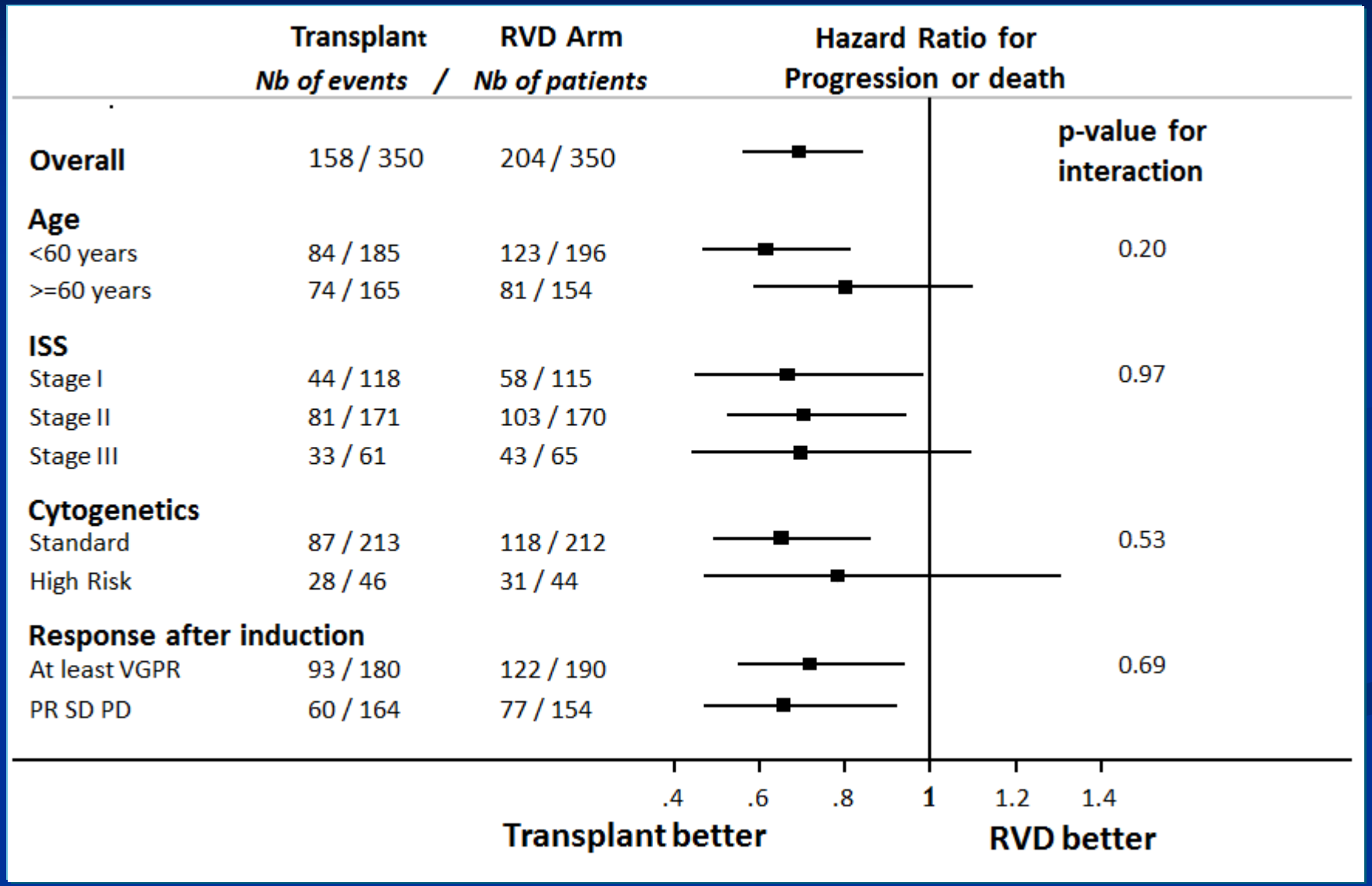
OS

4-yr SV >80 %

in both arms

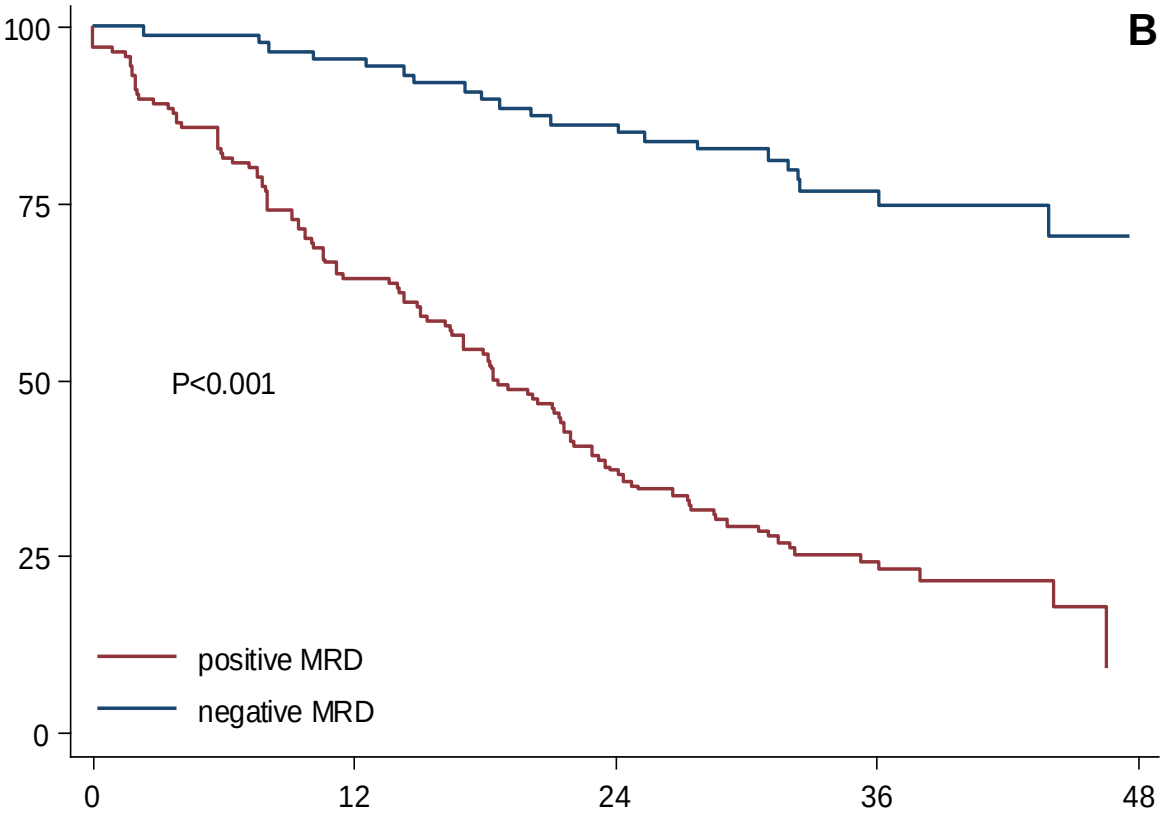


IFM 2009 : PFS

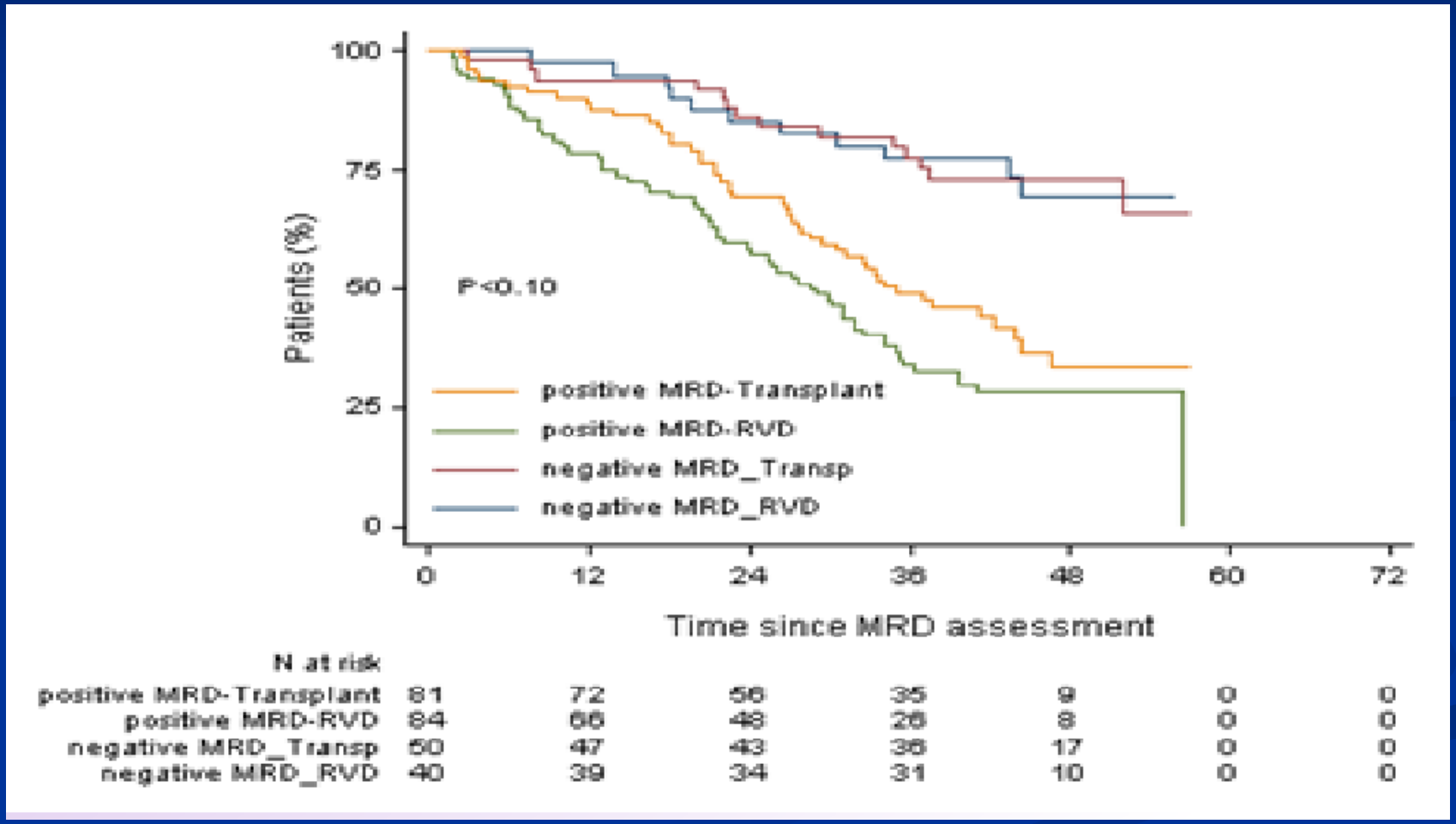

Transplant
Nb of events / Nb of patients
RVD Arm
Hazard Ratio for Progression or death
p-value for interaction
Overall
158 / 350
204 / 350
Age
<60 years
84 / 185
123 / 196
0.20
>=60 years
74 / 165
81 / 154
ISS
Stage I
44 / 118
58 / 115
0.97
Stage II
81 / 171
103 / 170
Stage III
33 / 61
43 / 65
Cytogenetics
Standard
87 / 213
118 / 212
0.53
High Risk
28 / 46
31 / 44
Response after induction
At least VGPR
93 / 180
122 / 190
0.69
PR SD PD
60 / 164
77 / 154
.4
.6
.8
1
1.2
1.4
Transplant better
RVD better

IFM 2009 trial

Post-maintenance according to 10^{-6}



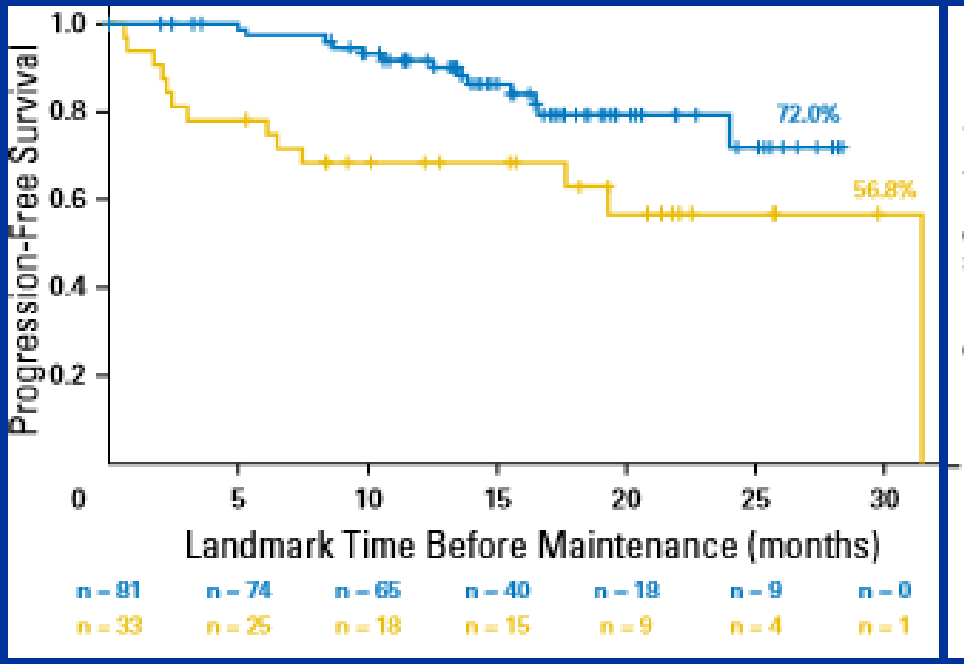
The Impact of MRD <0 is the same whatever the treatment
But more MTD<0 with intensive treatment (79%vs 65%

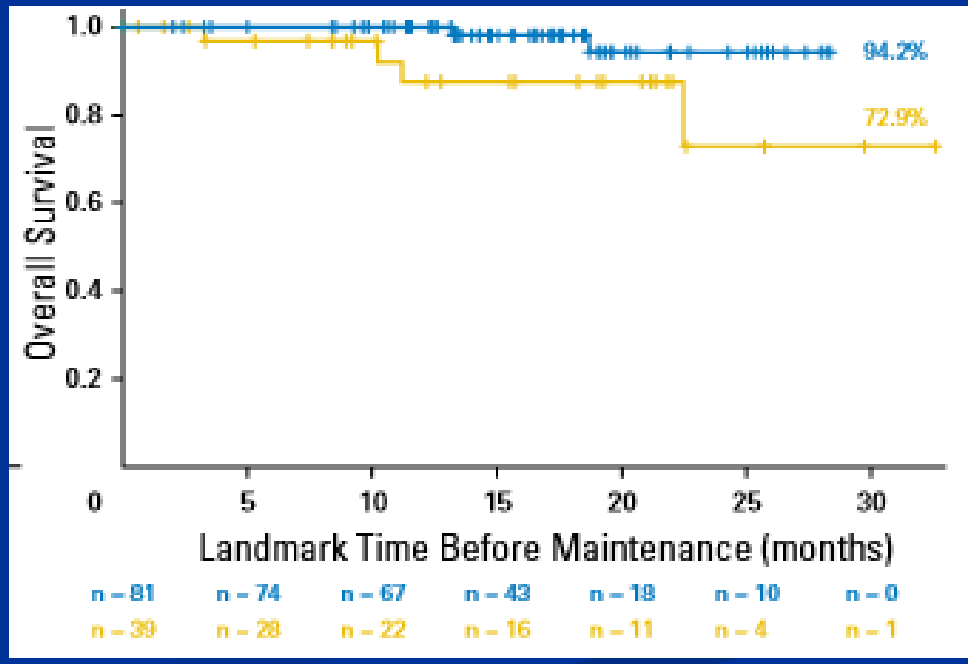


N at risk							
positive MRD-Transplant	81	72	56	35	9	0	0
positive MRD-RVD	84	66	48	26	8	0	0
negative MRD_Transp	50	47	43	36	17	0	0
negative MRD_RVD	40	39	34	31	10	0	0

Prognostic Impact of PET- CT normalization before maintenance in the IFM/DFCI trial (134 pts)

PFS p=0.011 **OS p=0.033**





Moreau P et al JCO 2017;35:2911

Summary

- Compared to the **best non-intensive treatment**

UPFRONT ASCT

- Longer PFS in all prognostic subgroups
- More patients with negative MRD

BUT

- No difference in OS….
- Due to excellent results of RVD and to more possibilities at time of relapse including ASCT in 2/3 of cases

Intensive versus non-intensive upfront treatment

- Four randomized studies

  Palumbo A et al NEJM 2014;371:895

  Gay P Lancet Oncol 2015;16:1617

  Attal M et al NEJM 2017;376:1311

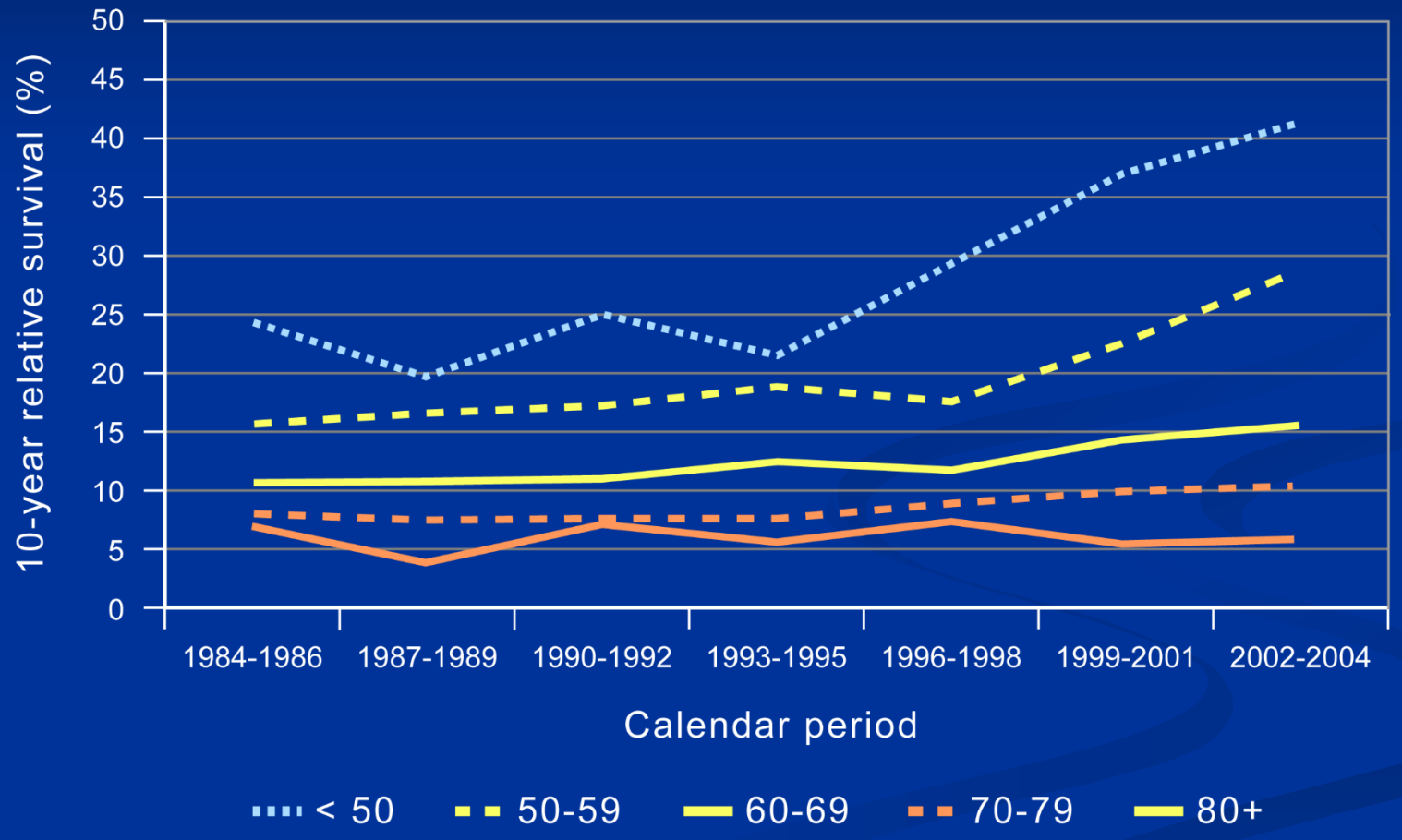
  Cavo P et al ASH 2016

- Patients could receive HDT/ASCT at relapse in the non-intensive arm
- All 4 studies show a significant benefit in terms of PFS in the intensive arm
- Autotransplantation remains he standard of care
- But non intensive treatment with RVD is a valuable alternative

Elderly patients

More than 50% patients are over the age of 70

No improvement in the 10-Yea Survival in patients over 70 years of age before introduction of new agents



Brenner et al; Blood 2008; 111:2521-26

MPT Becomes a Standard of Care

Melphalan and prednisone plus thalidomide versus melphalan and prednisone alone or reduced-intensity autologous stem cell transplantation in elderly patients with multiple myeloma (IFM 99–06): a randomised trial

Lancet 2007; 370: 1209–18

Thierry Facon, Jean Yves Mary, Cyrille Hulin, Lotfi Benboubker, Michel Attal, Brigitte Pegourie, Marc Renaud, Jean Luc Harousseau, Gaëlle Guillerm, Carine Chaleteix, Mamoun Dib, Laurent Voillat, Hervé Maisonneuve, Jacques Troncy, Véronique Dorvaux, Mathieu Monconduit, Claude Martin, Philippe Casassus, Jérôme Jaubert, Henry Jardel, Chantal Doyen, Brigitte Kolb, Bruno Anglaret, Bernard Grosbois, Ibrahim Yakoub-Agha, Claire Mathiot, Hervé Avet-Loiseau, on behalf of the Intergroupe Francophone du Myélome

blood

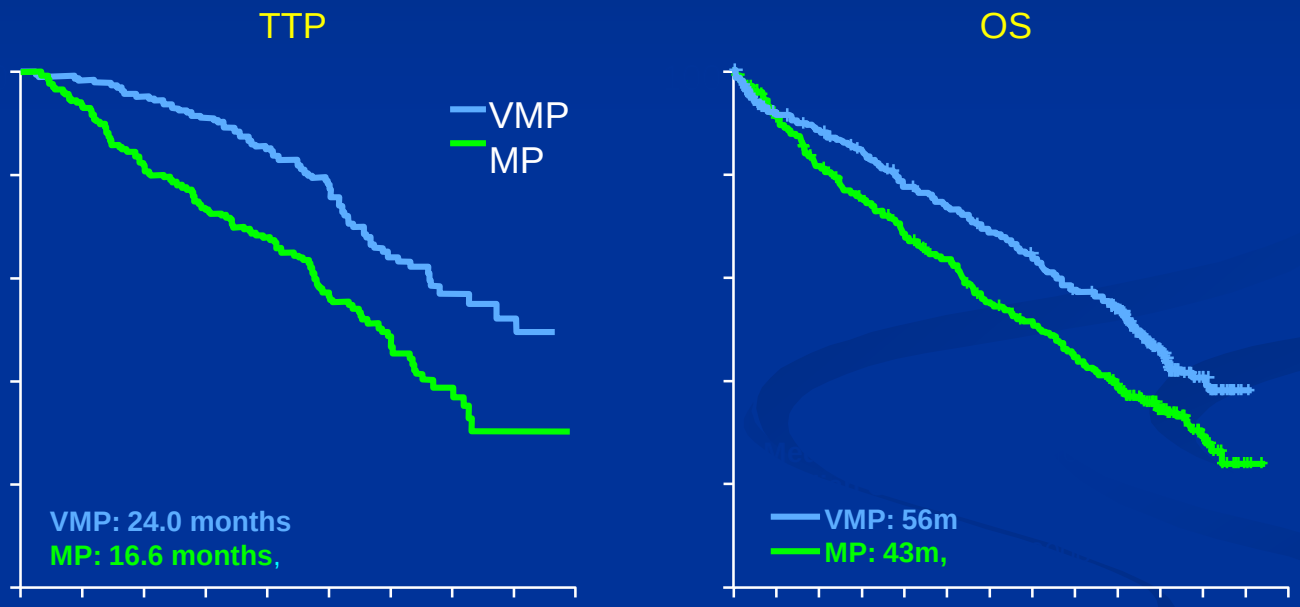
2011 118: 1239-1247
Prepublished online June 13, 2011;
doi:10.1182/blood-2011-03-341669

Thalidomide for previously untreated elderly patients with multiple myeloma: meta-analysis of 1685 individual patient data from 6 randomized clinical trials

Peter M. Fayers, Antonio Palumbo, Cyrille Hulin, Anders Waage, Pierre Wijermans, Meral Beksaç, Sara Bringhen, Jean-Yves Mary, Peter Gimsing, Fabian Termorshuizen, Rauf Haznedar, Tommaso Caravita, Philippe Moreau, Ingemar Turesson, Pellegrino Musto, Lotfi Benboubker, Martijn Schaafsma, Pieter Sonneveld, Thierry Facon and on behalf of the Nordic Myeloma Study Group, Italian Multiple Myeloma Network, Turkish Myeloma Study Group, Hemato-Oncologie voor Volwassenen Nederland, Intergroupe Francophone du Myélome, and European Myeloma Network

VMP becomes a standard of care
VISTA Trial: Final analysis

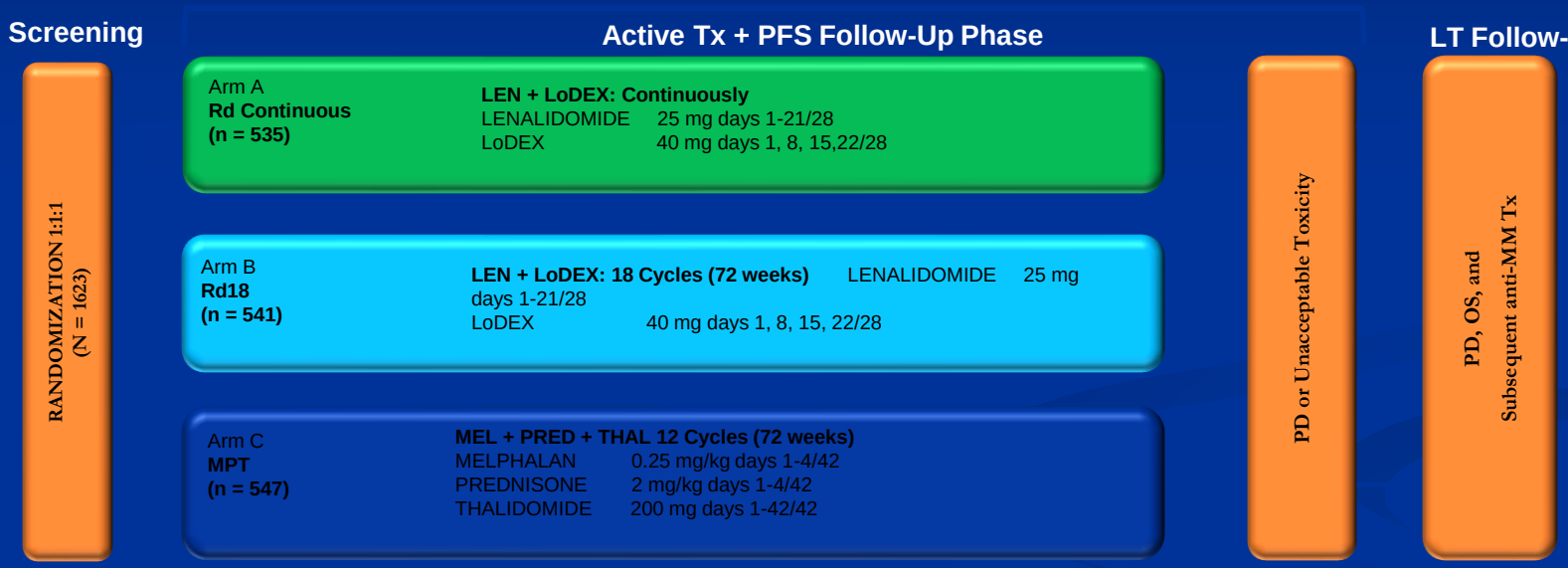
RR (CR) (%): 71(30) vs. 35(4)



San Miguel et al. JCO 2013; 31(4):448-55.

Rd becomes a standard of care

IFM 2007-01-MM-020- FIRST: Study Design

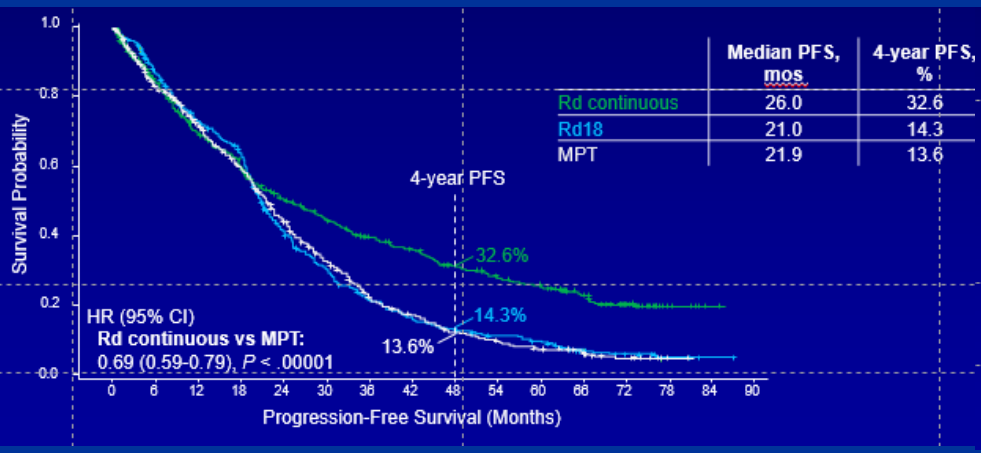


Pts aged > 75 yrs: LoDEX 20 mg days 1, 8, 15, 22/28; THAL 100 mg days 1-42/42; MEL 0.2 mg/kg days 1-4

FIRST trial (1623 pts)

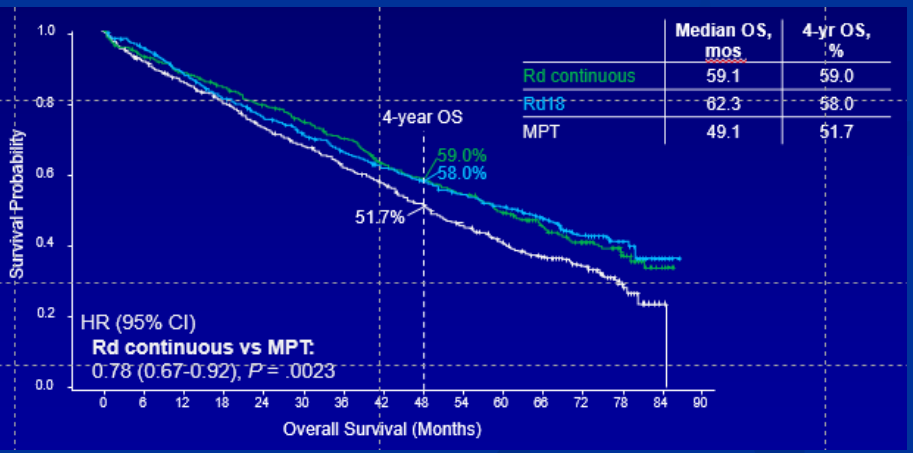
MPT 12 cycles vs Rd 12 cycles vs Rd continuous

PFS



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

OS



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

T Facon ASH 2016

Other approaches

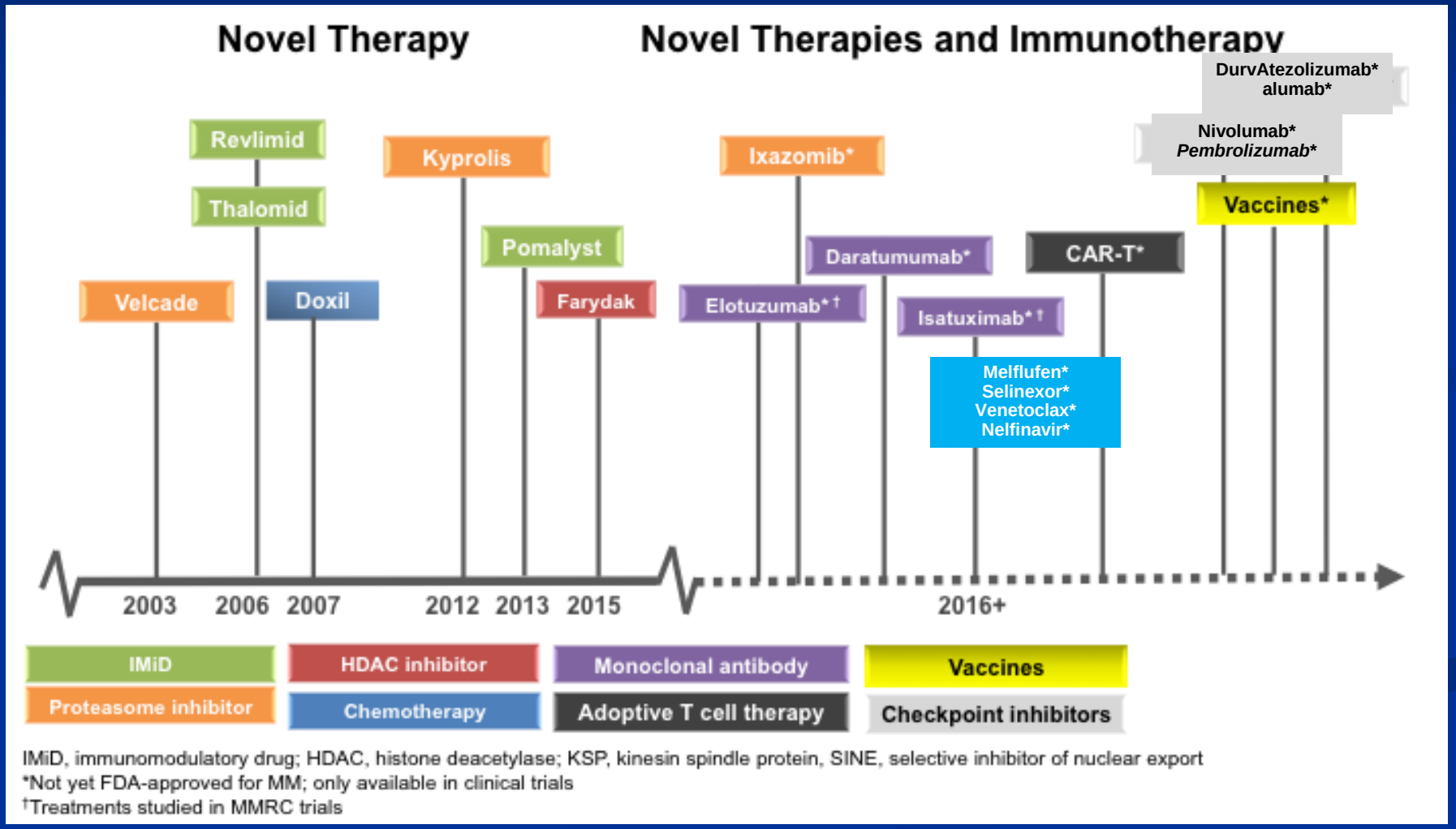
- Combine Thalidomide/revlimid with Velcade
- Use induction followed by maintenance

Conclusions in elderly patients

- Introduction of « novel » agents was actually the first improvement of MM treatment in the elderly
- Use of one or two « novel » agents increased response rate, duration of response and survival
- Prolonged treatment is important but the optimal duration is still unknown
- Assessment of fitness/frailty is necessary for optimal treatment selection

Current Hopes

Myeloma Drug Development



IMiD, immunomodulatory drug; HDAC, histone deacetylase; KSP, kinesin spindle protein, SINE, selective inhibitor of nuclear export
*Not yet FDA-approved for MM; only available in clinical trials
†Treatments studied in MMRC trials

Randomized studies comparing triplets versus doublets in RRMM

- Lenalidomide –based studies

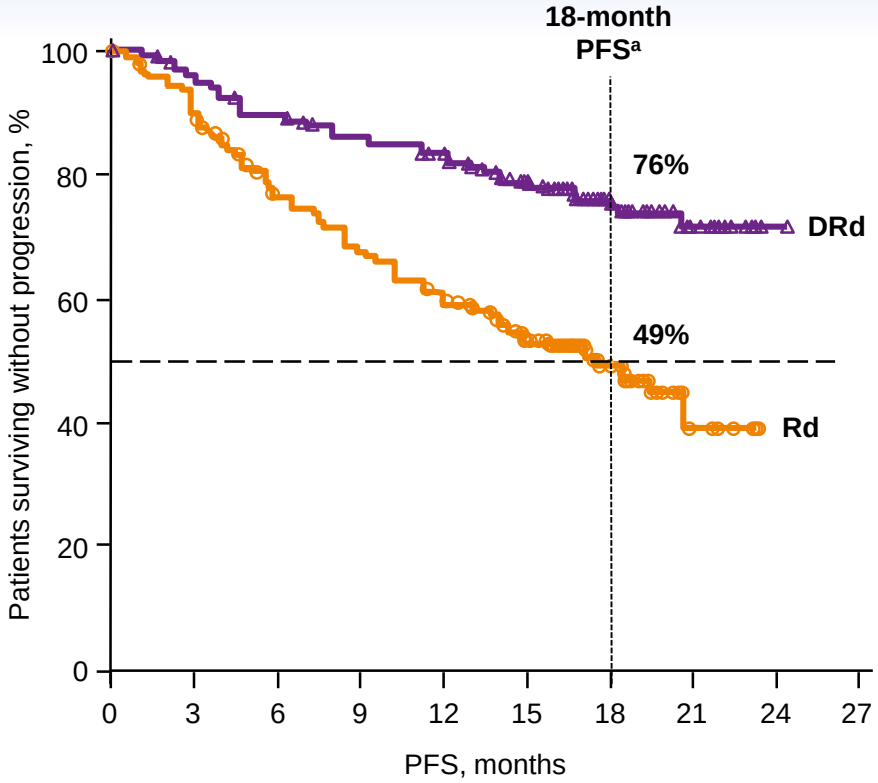
  - Carfilzomib Rd vs Rd (Aspire) Stewart AK N Engl J Med. 2015
  - Elotuzumab Rd vs Rd (Eloquent 2) Lonial S N Engl J Med 2015
  - Ixazomib Rd vs Rd (Tourmaline) Moreau P N Engl J Med 2016
  - Daratumumab Rd vs Rd (Pollux) Dimopoulos MA N Engl J Med 2016

- Bortezomib-based studies

  - Panobinostat Vd vs Vd(Panorama) San Miguel J Lancet Oncol 2014
  - Elotuzumab VD vs Vd Jakubowiak A Blood 2016
  - Daratumumab Vd vs Vd (Castor) Palumbo A N Engl J Med 2016

Updated PFS: POLLUX and CASTOR

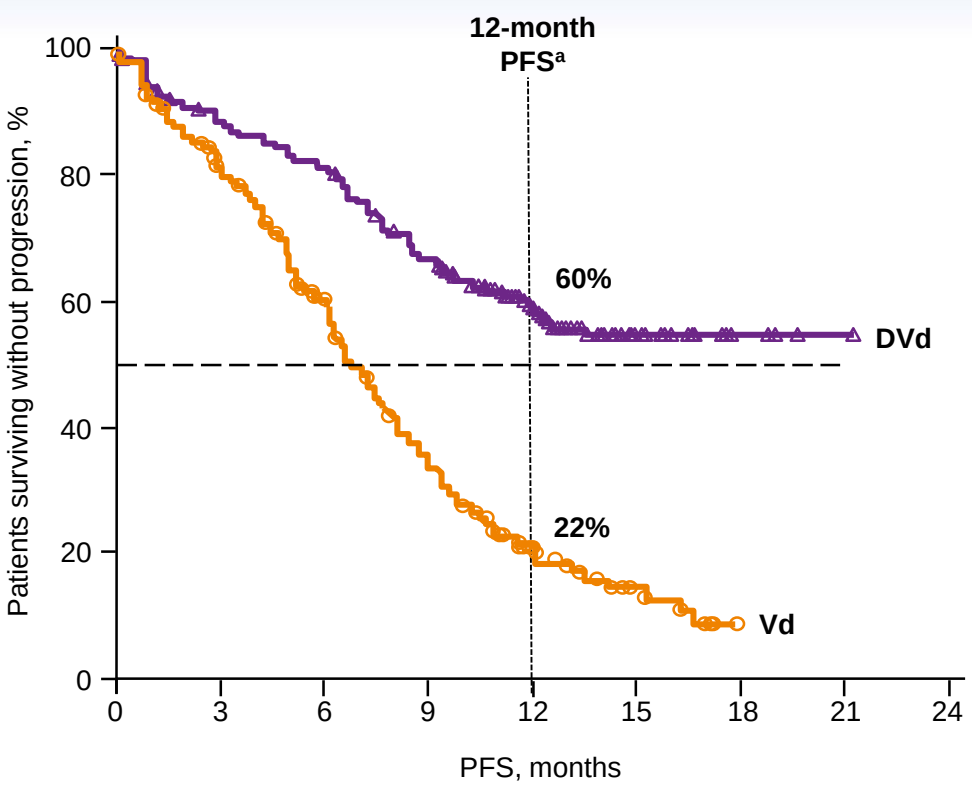
POLLUX



Median (range) follow-up:
17.3 (0-24.5) months

- **Median PFS**
  - DRd: not reached; Rd: 17.5 months
  - HR: 0.37 (95% CI, 0.28-0.50; *P* <0.0001)

CASTOR



Median (range) follow-up:
13.0 (0-21.3) months

- **Median PFS**
  - DVd: not reached; Vd: 7.1 months
  - HR: 0.33 (95% CI, 0.26-0.43; *P* <0.0001)

HR, hazard ratio; CI, confidence interval.
[a]Kaplan-Meier estimates.
Clinical cut-off: June 30, 2016.

Frontline Treatment
What are the next steps?

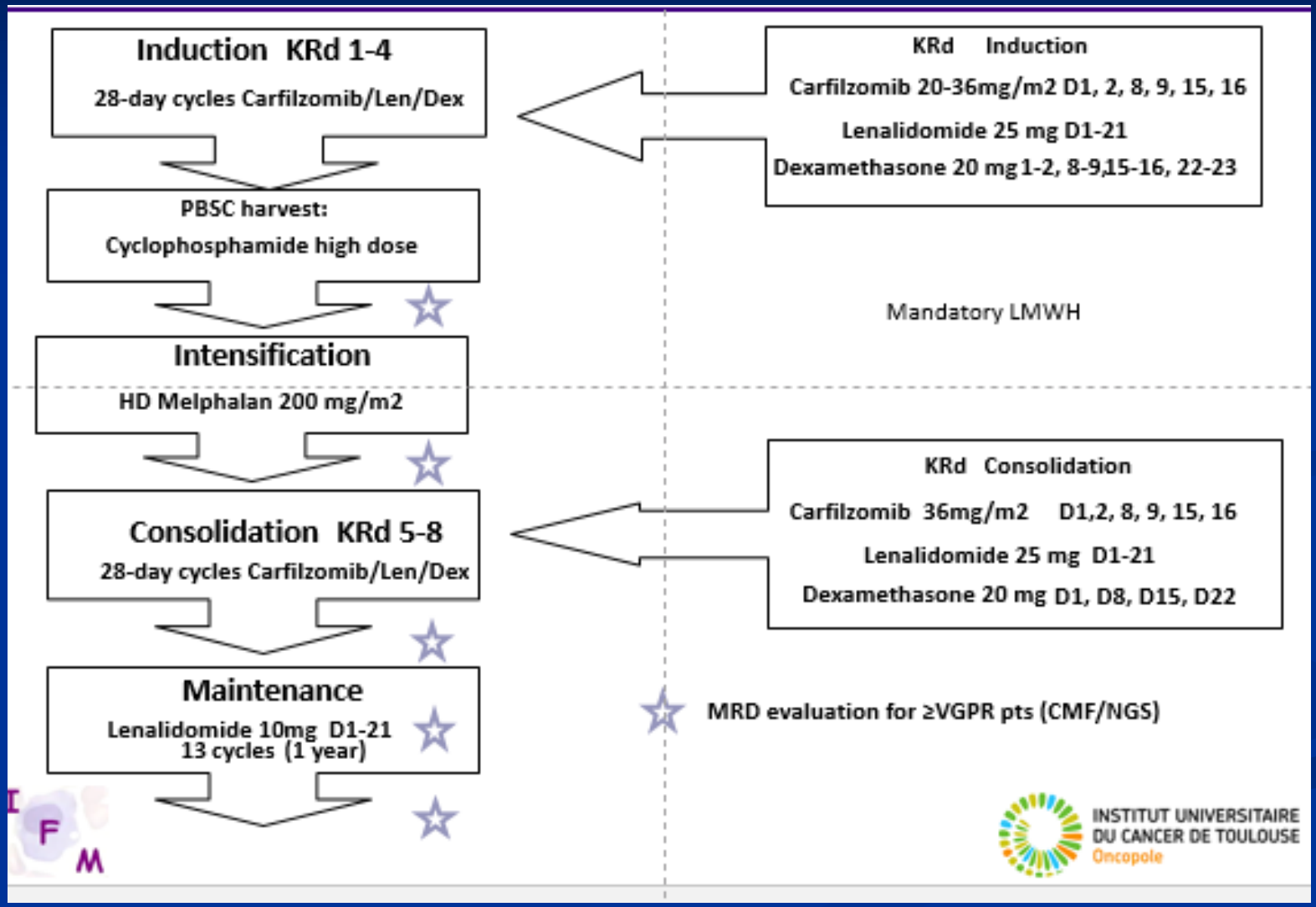
- The objective of treatment is becoming not only to achieve CR but to achieve MRD negativity

Frontline Treatment
What are the next steps?

- The objective of treatment is becoming not only to achieve CR but to achieve MRD negativity
- Introduction of second phase new agents

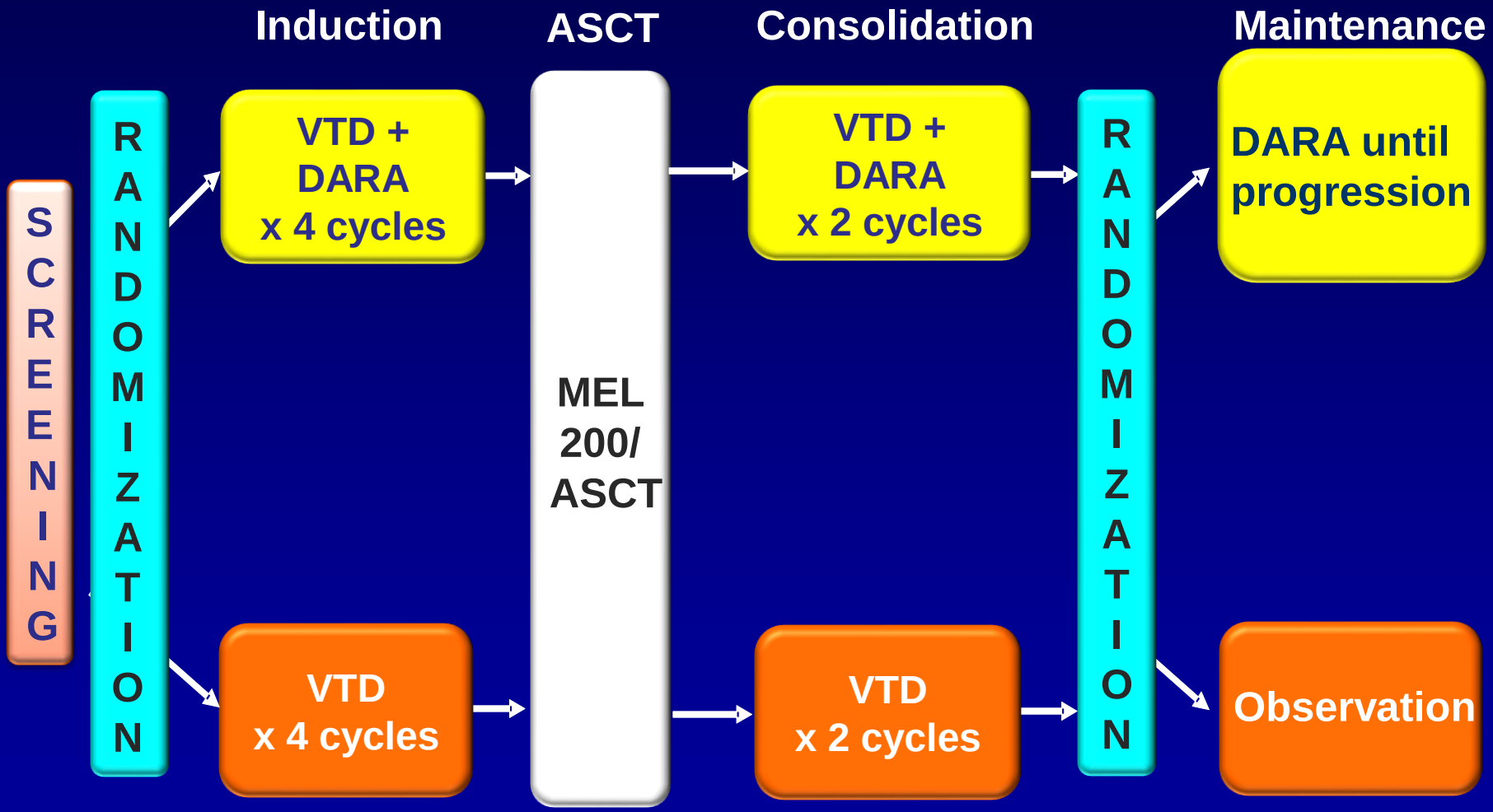
  - to increase efficacy (MRD <0)

IFM Pilot Study with KRd



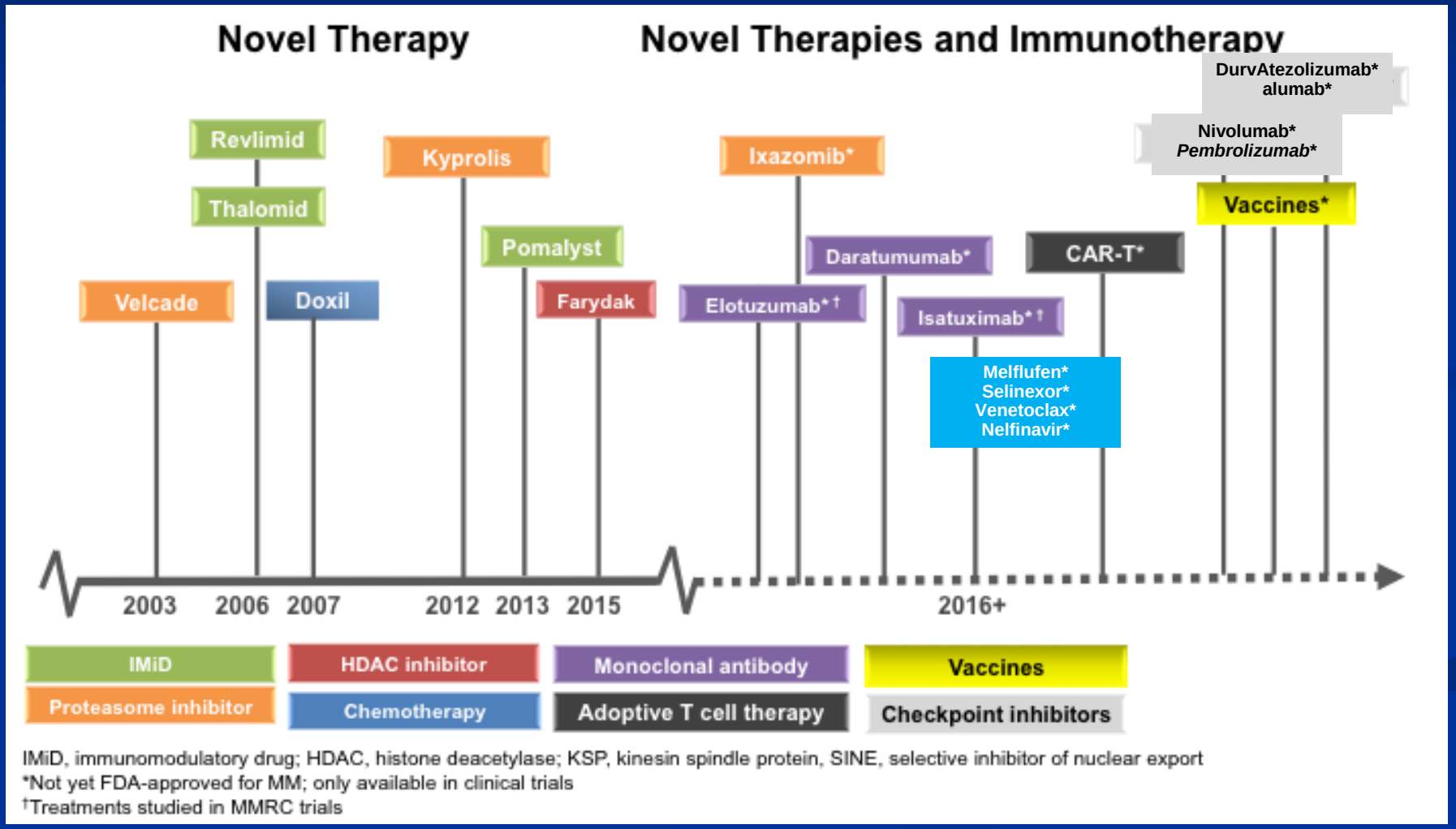
Roussel M et al ASH 2016

CASSIOPEA-MMY3006 Study design



DARA, daratumumab.

Myeloma Drug Development



IMiD, immunomodulatory drug; HDAC, histone deacetylase; KSP, kinesin spindle protein, SINE, selective inhibitor of nuclear export
*Not yet FDA-approved for MM; only available in clinical trials
†Treatments studied in MMRC trials

CONCLUSION

- The prognosis of MM patients has dramatically improved over the past 15 years with the introduction of IMIds and PI

  More CR, longer remissions, more solutions at relapse

  LONGER SURVIVALS

- MRD negativity and PETCT negativity can be obtained and are associated with longer remissions **(possibly cures ?)**

  NEW OBJECTIVE OF TREATMENT

- The addition of newer agents (anti-CD38 antibodies) Daratumumab is likely to increase the MRD <0 rate

  but are very expensive and not affordable in all countries


I F M
26 et 27 juin 2014