Traitement de première ligne

Patient éligible à l'autogreffe

Cours de DES Hématologie - Novembre 2022

Cyrille Touzeau
Nantes

CENTRE HOSPITALIER UNIVERSITAIRE DE NANTES

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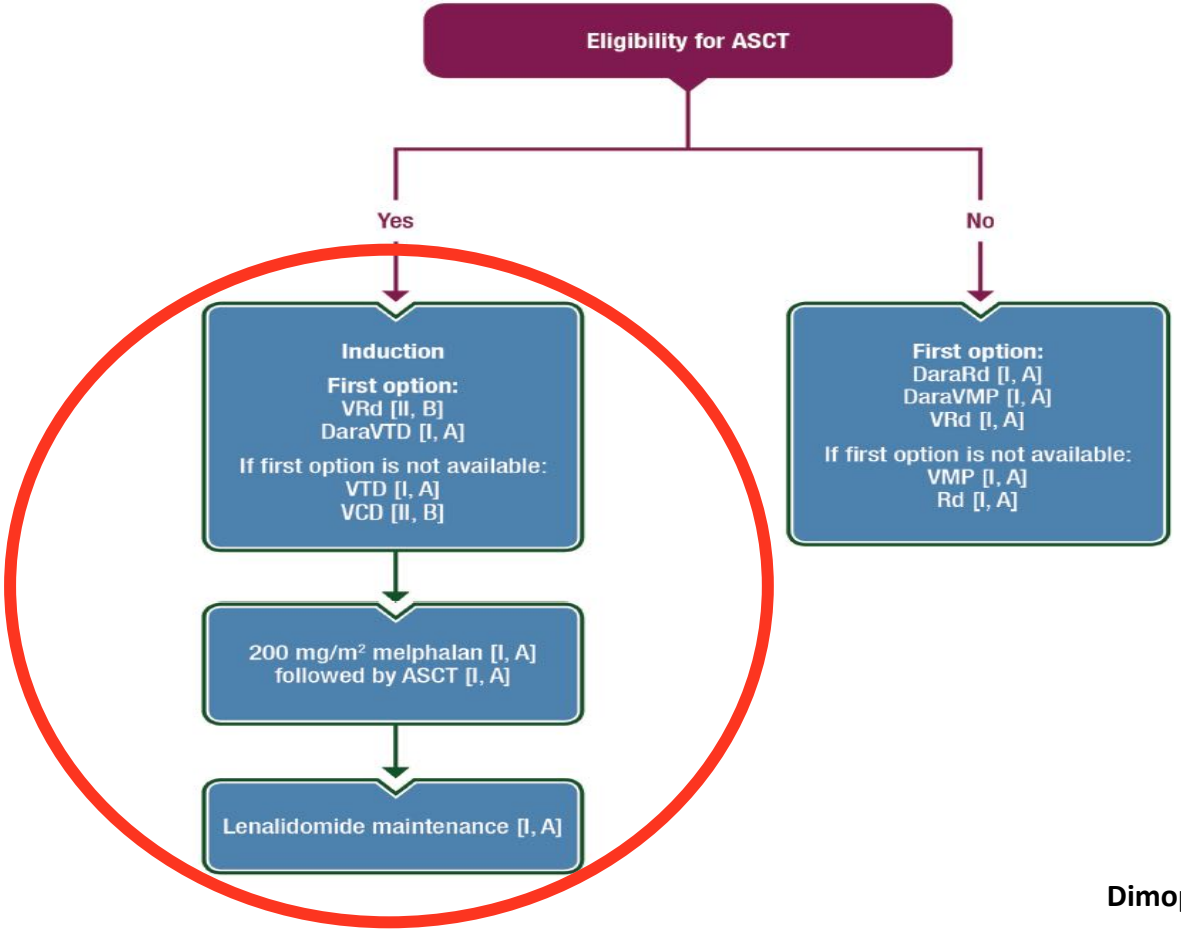
ifm

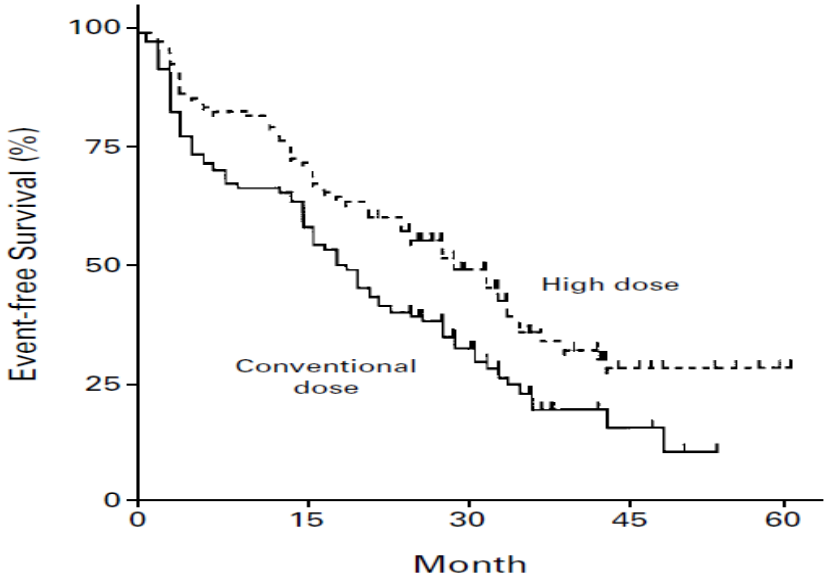
Inserm

Recommandations de l'ESMO



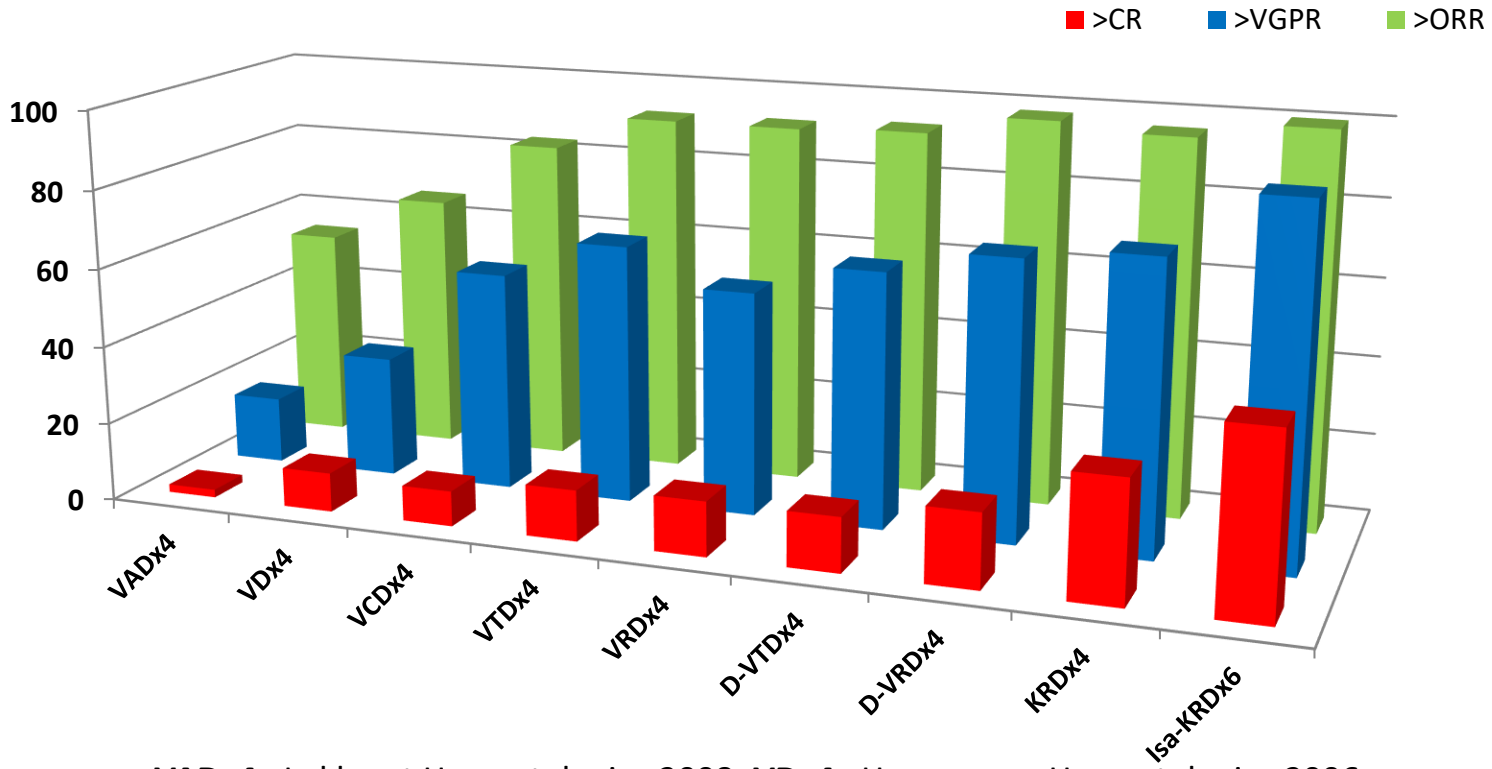
Dimopoulos et al. Hemasphere 2021

L’autogreffe, le standard depuis 25 ans



Attal et al. NEJM 1996

Evolution des schémas d'induction



VADx4 : Lokhorst Haematologica 2008; **VDx4** : Harousseau Haematologica 2006; **VCDx4** : Moreau Blood 2016; **VTDx4** : Moreau Blood 2016; **VTDx4** : Moreau Lancet 20019; **VRD :** Voorhees Blood 2020 ; ; **D-VRD :** Voorhees Blood 2020 ; **KRDx4** : Gay ASCO 2017; **IsaKRDx6** (Weisel ASH 2020)

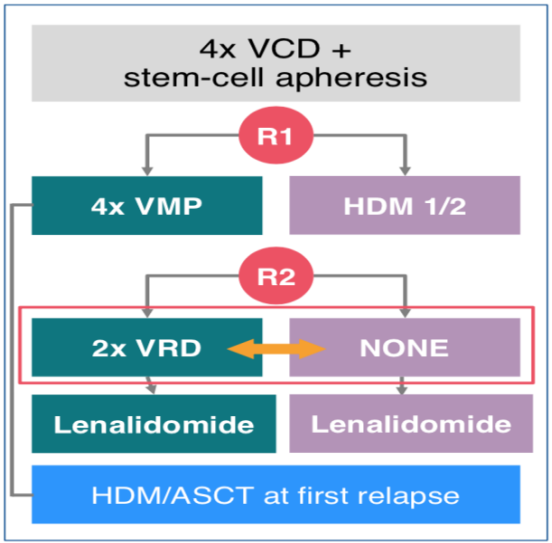
Place de l'autogreffe confortée à l'heure des "anciennes nouvelles" molécules

ESSAI IFM 2009

Arm A	Arm B
VRD x 3	VRD x 3
VRD x 5	ASCT
	VRD x 2
Len	Len

Attal et al. N Engl J Med 2017

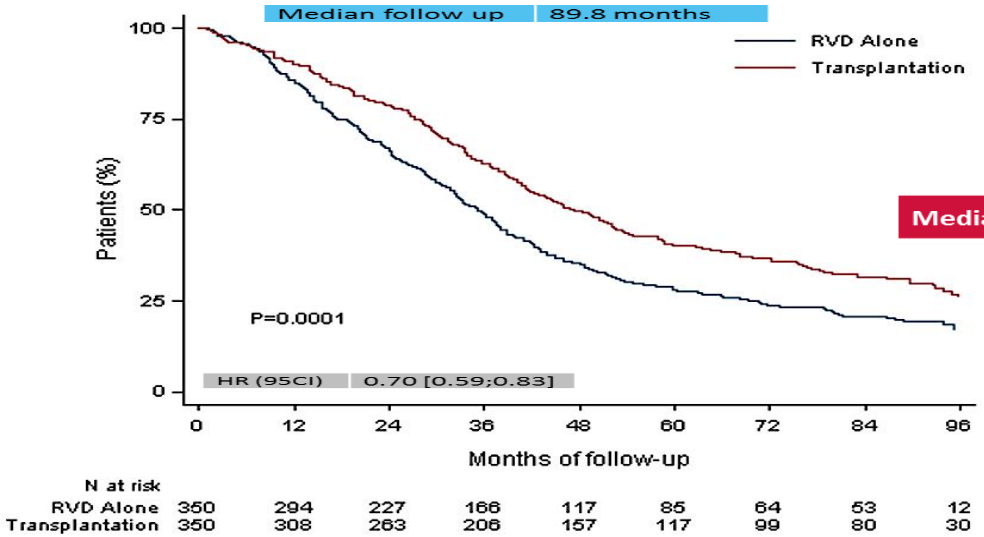
ESSAI EMN 02



Cavo et al. Lancet Hematol 2020

Place de l'autogreffe confortée à l'heure des "anciennes nouvelles" molécules

Actualisation essai IFM-2009



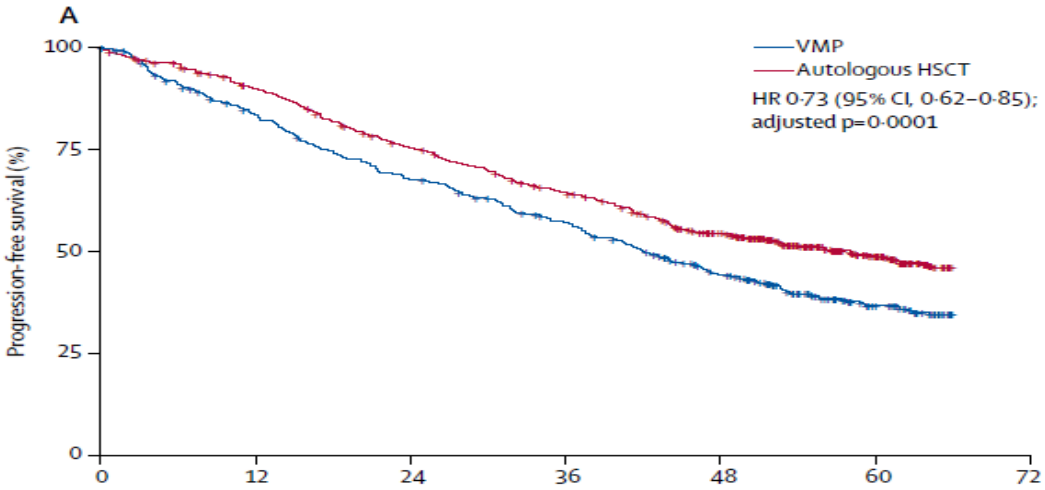
Median PFS 47.3 months (Transplantation, arm B)

Median PFS 35 months (RVD alone, arm A)

Perrot et al. ASH 2020

Place de l'autogreffe confortée à l'heure des "anciennes nouvelles" molécules

Essai EMN-02

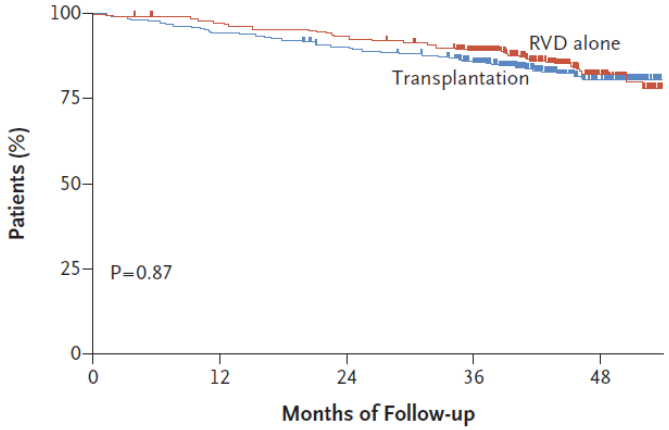


Cavo et al. Lancet Haematol 2020

Un impact de l'autogreffe sur la survie difficile à évaluer

Essai IFM 2009

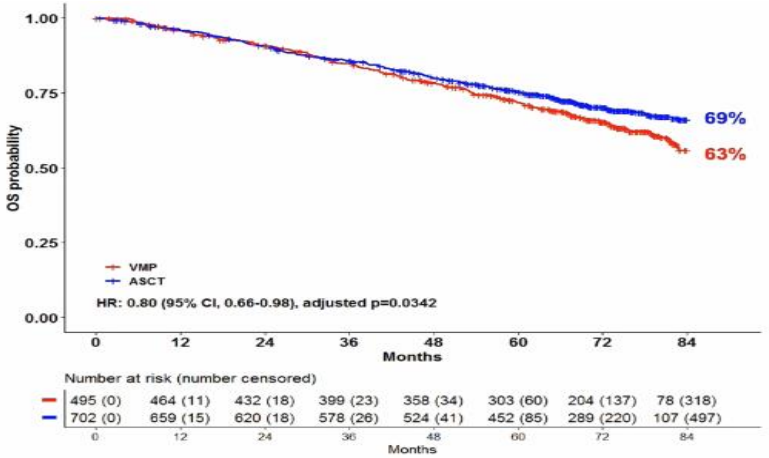
Survie globale



Attal et al, N Engl J Med 2017

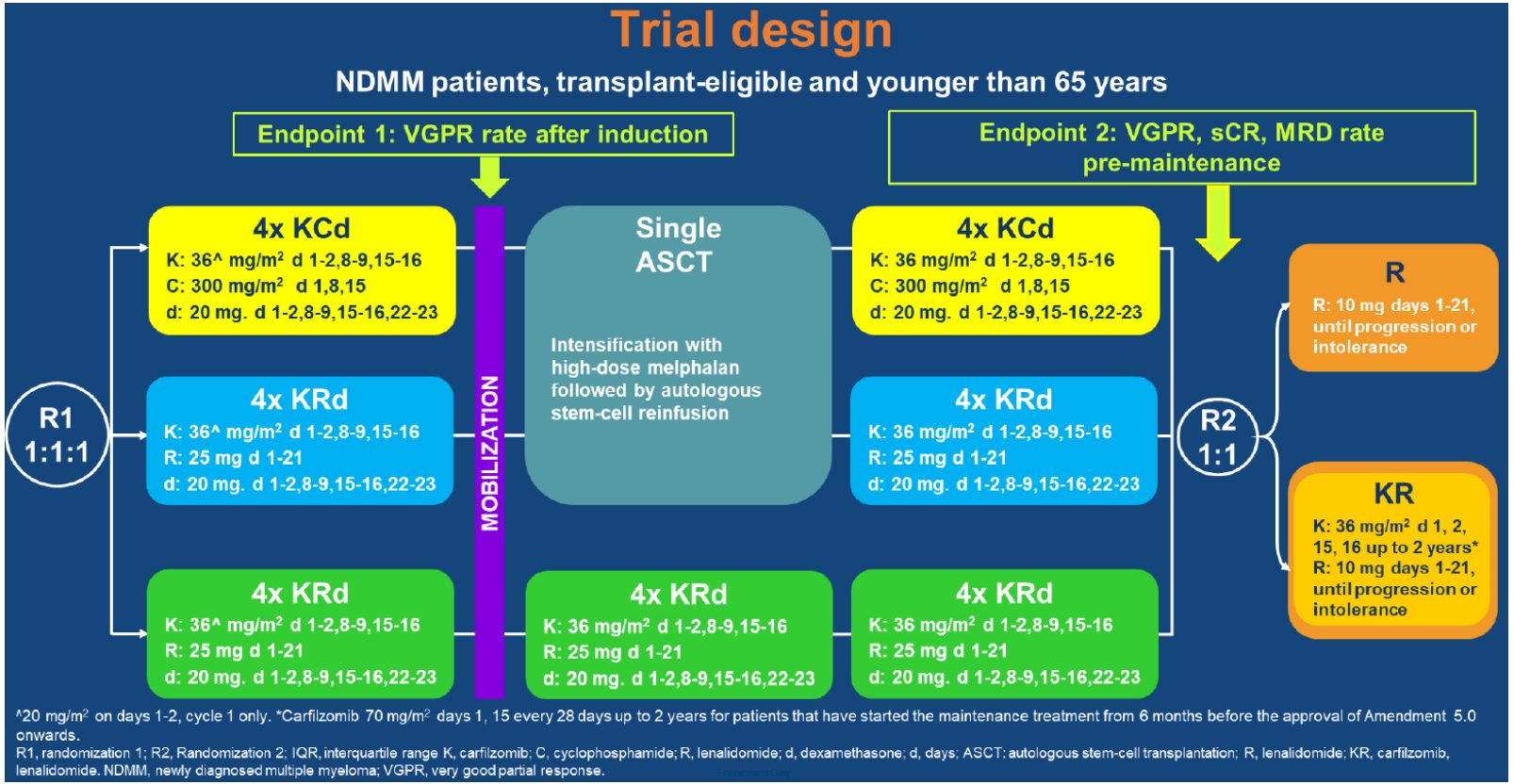
Essai EMN-02

Survie globale



Cavo et al, Lancet Haematol 2020

Place de l'autogreffe confortée à l'heure des "anciennes nouvelles" molécules



F Gay, ASCO 2019

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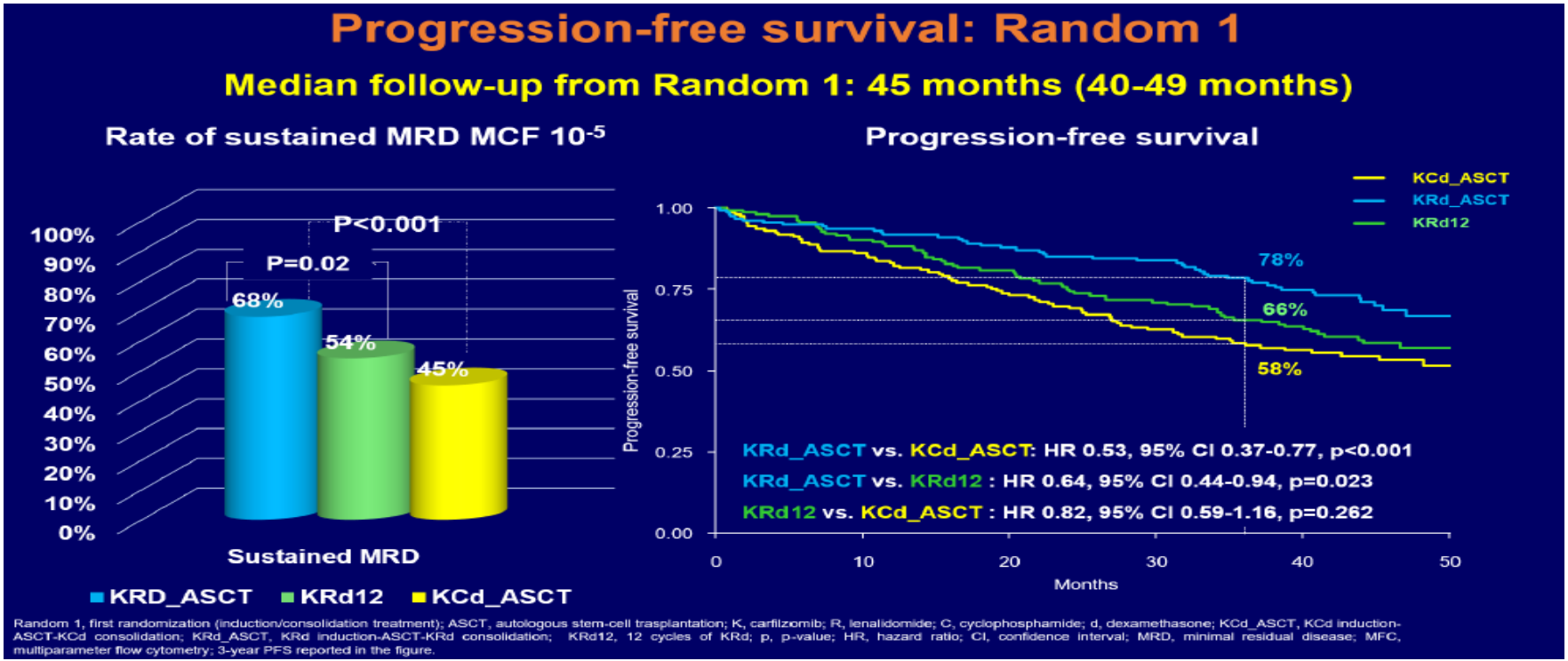


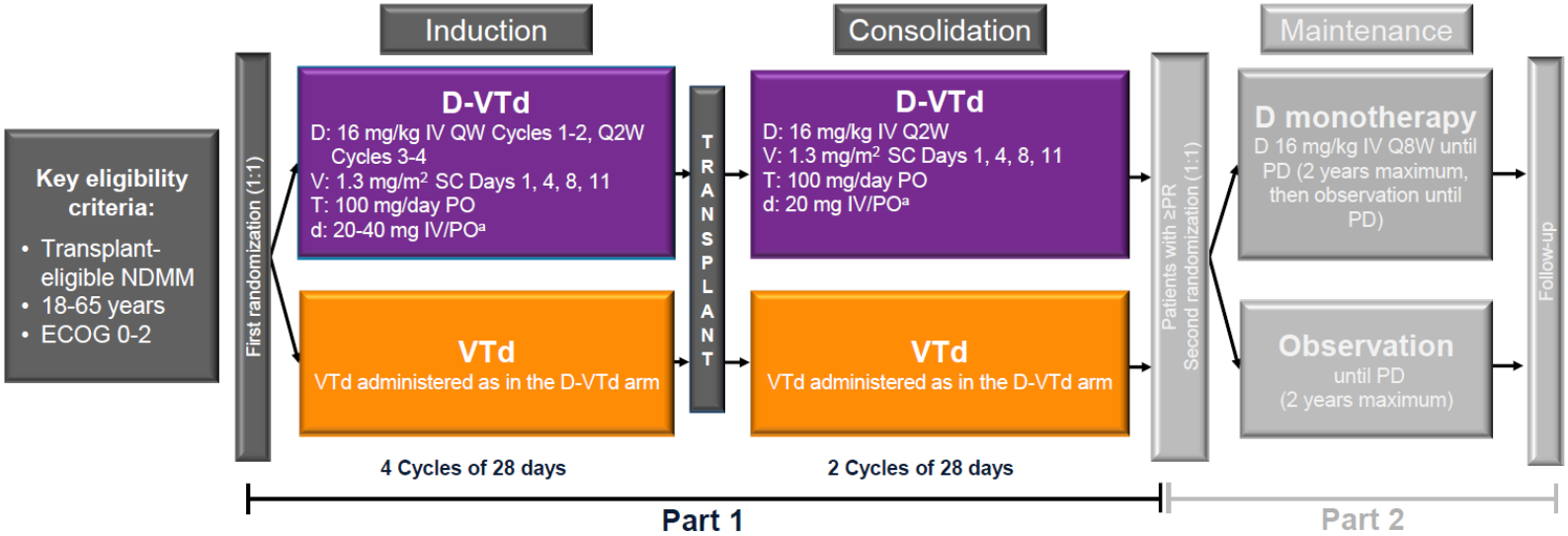
Random 1, first randomization (induction/consolidation treatment); ASCT, autologous stem-cell trasplantation; K, carfilzomib; R, lenalidomide; C, cyclophosphamide; d, dexamethasone; KCd_ASCT, KCd induction-ASCT-KCd consolidation; KRd_ASCT, KRd induction-ASCT-KRd consolidation; KRd12, 12 cycles of KRd; p, p-value; HR, hazard ratio; CI, confidence interval; MRD, minimal residual disease; MFC, multiparameter flow cytometry; 3-year PFS reported in the figure.

F Gay, ASCO 2019

Intégration des anti CD38 au traitement d'induction

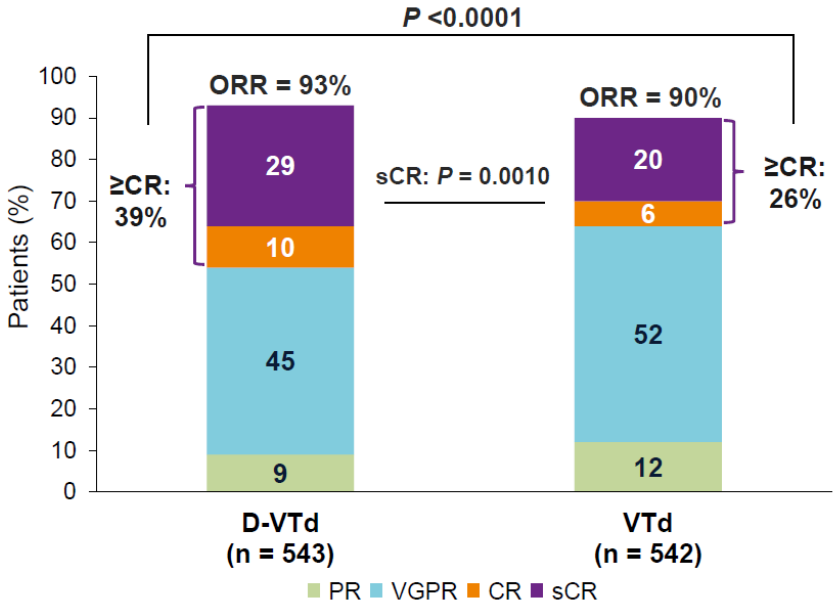
CASSIOPEIA Study Design

- Phase 3 study of D-VTd versus VTd in transplant-eligible NDMM (N = 1,085), 111 sites from 9/2015 to 8/2017



Moreau et al. Lancet 2019

Efficacy: Post-consolidation Depth of Response

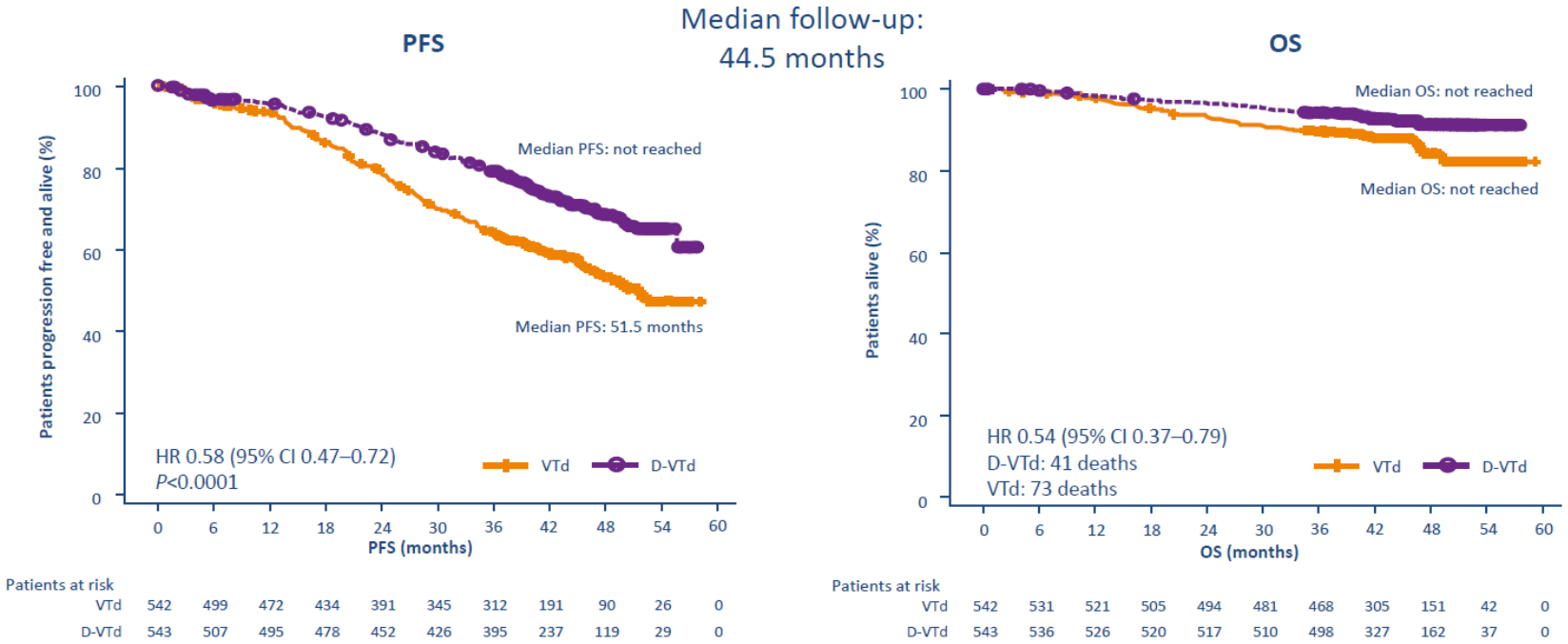


- Primary endpoint
  - Post-consolidation sCR
    - 29% D-VTd vs 20% VTd
    - Odds ratio, 1.60; 95% CI, 1.21-2.12; *P* = 0.0010
- sCR definition
  - All required:
    - SIFE negative
    - UIFE negative
    - <5% plasma cells in the BM
    - Four-color flow negativity
    - Normal FLC ratio
    - Disappearance of all plasmacytomas

The addition of daratumumab to VTd improved depth of response

Moreau P, ASCO 2019

Intégration des anti CD38 au traitement d'induction



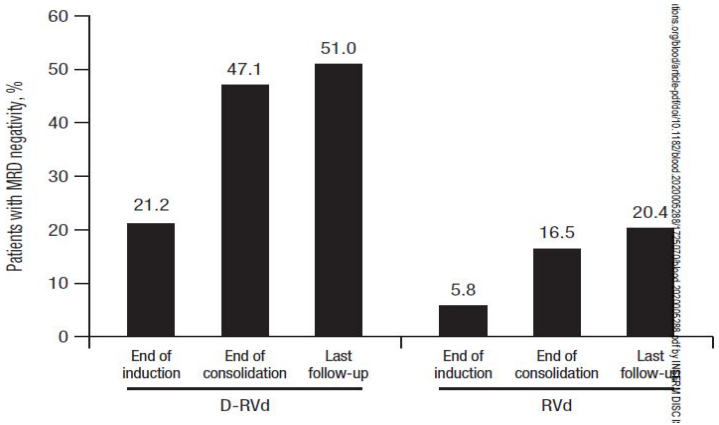
Moreau et al. EHA 2021

Intégration des anti CD38 au traitement d'induction

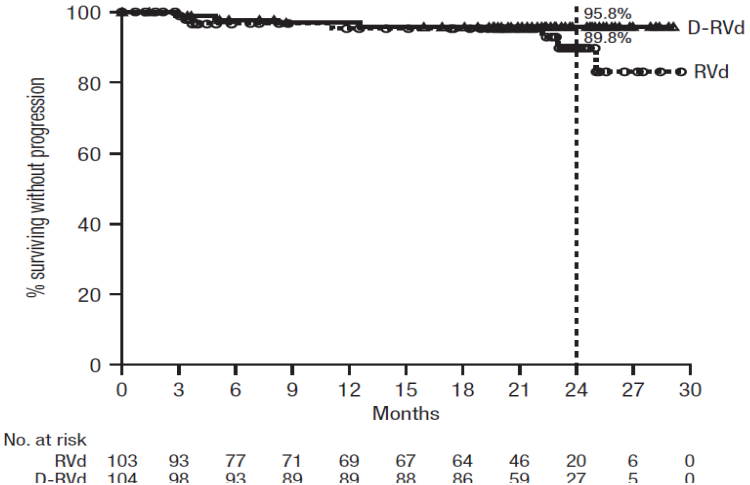
GRIFFIN

Phase 2, VRD +- dara en induction et conso de l'autogreffe

MRD (10-5 CMF)



PFS



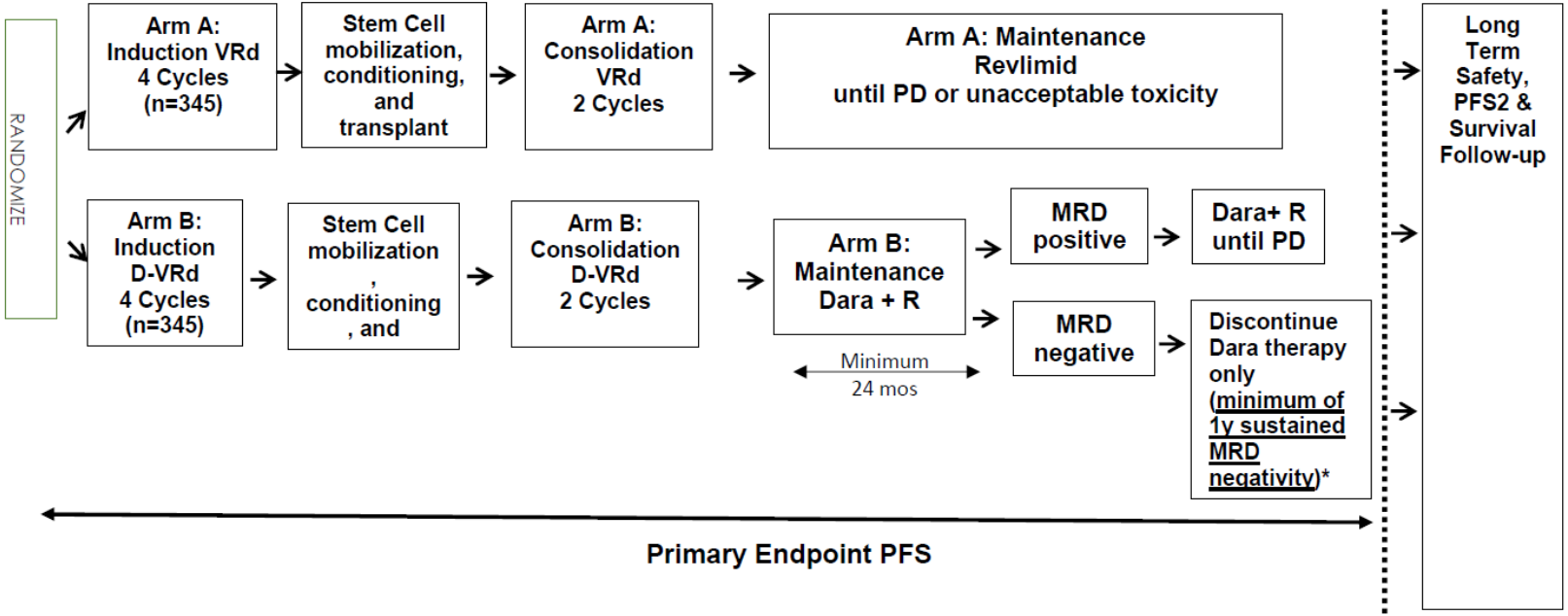
Suivi médian : 22 mois

Voorhees et al. Blood 2020

Intégration des anti CD38 au traitement d'induction

PERSEUS

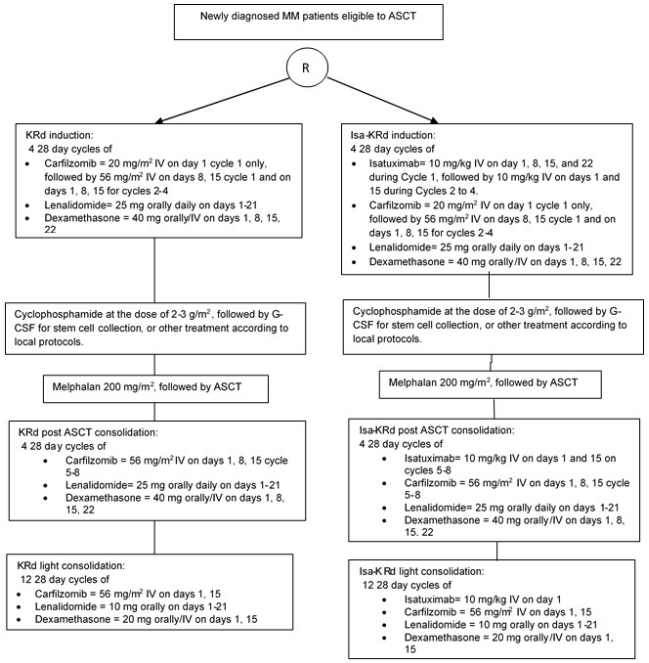
VRD +- dara



Intégration des anti CD38 au traitement d'induction

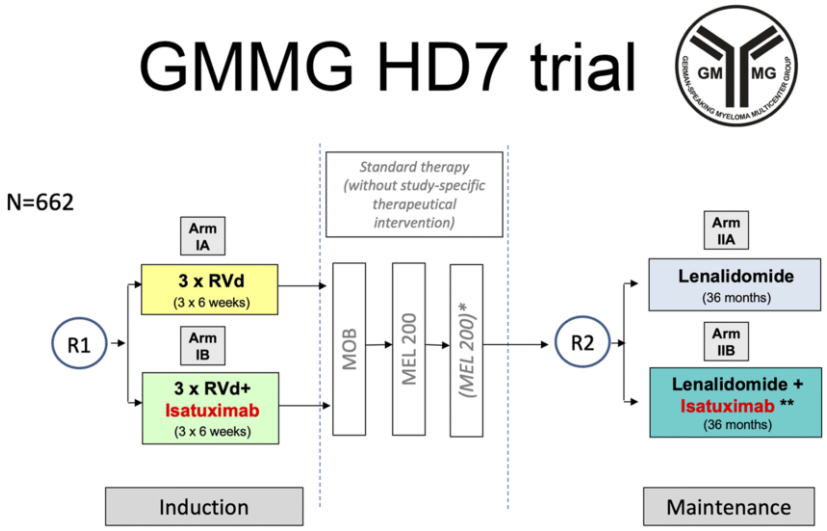
EMN24 – IsKIA

KRD +- Isa



GMMG-HD7

VRD +- Isa



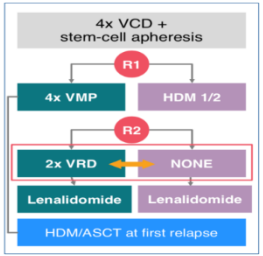
R1 = 1st randomization (at study inclusion); R2 = 2nd randomization (prior to maintenance)

* decision for 2nd high dose therapy response-adapted (in case no CR) or for high risk patients

*** Lenalidomide/Isatuximab for 36 months (thereafter, continuation of lenalidomide recommended until PD)*

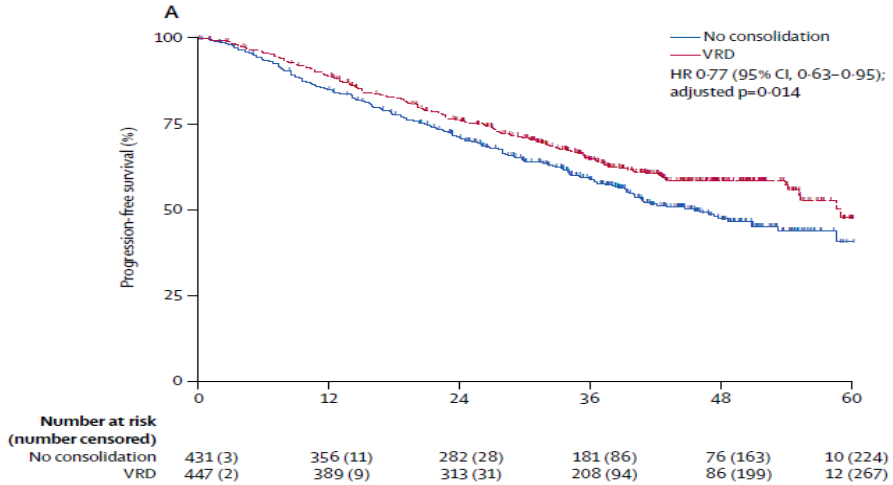
Intérêt d’une consolidation?

Intéret de la consolidation



Essai EMN02

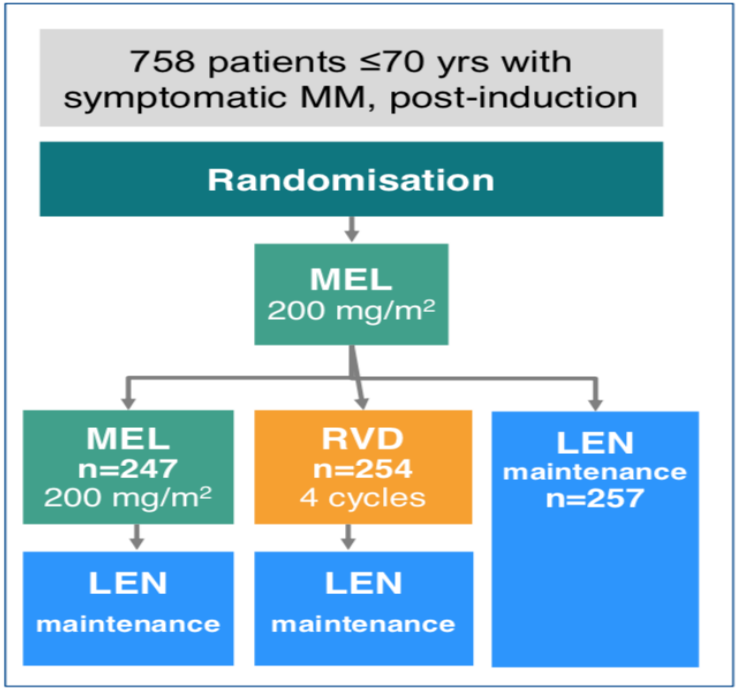
		No consolidation	VRD
Patients (n)		444	459
Response before consolidation (%)	sCR	4	4
	CR	16 } 20	22 } 26
	VGPR	47	42
	PR	27	24
Response after consolidation (%)	sCR	7	13
	CR	13 } 20	25 } 38*
	VGPR	47	39
	ORR	27	18
Overall response (%)	sCR	19	28
	CR	22 } 41	28 } 56*
	VGPR	43	30
	≤PR	16	15



Cavo et al, Lancet Haematol 2020

Intéret de la consolidation

Essai Stamina



INDUCTION

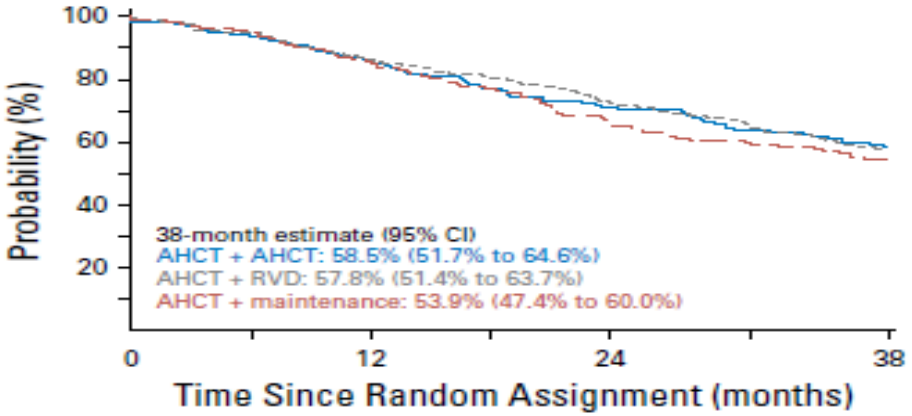
Median time since initial therapy to registration, months (range)	5 (2-14)
Initial therapy	
RVD	141 (57)
Bortezomib, cyclophosphamide, and dexamethasone	33 (13)
Len and dexamethasone	24 (10)
Bortezomib and dexamethasone	29 (12)
Other	19 (8)
Unknown	1 (< 1)

Stadtmauer et al, J Clin Oncol 2019

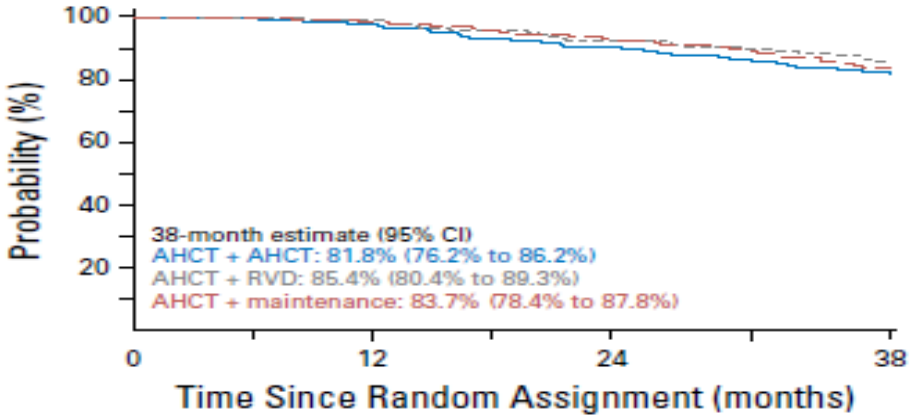
Intéret de la consolidation

Essai Stamina

PFS



OS



Stadtmauer et al, J Clin Oncol 2019

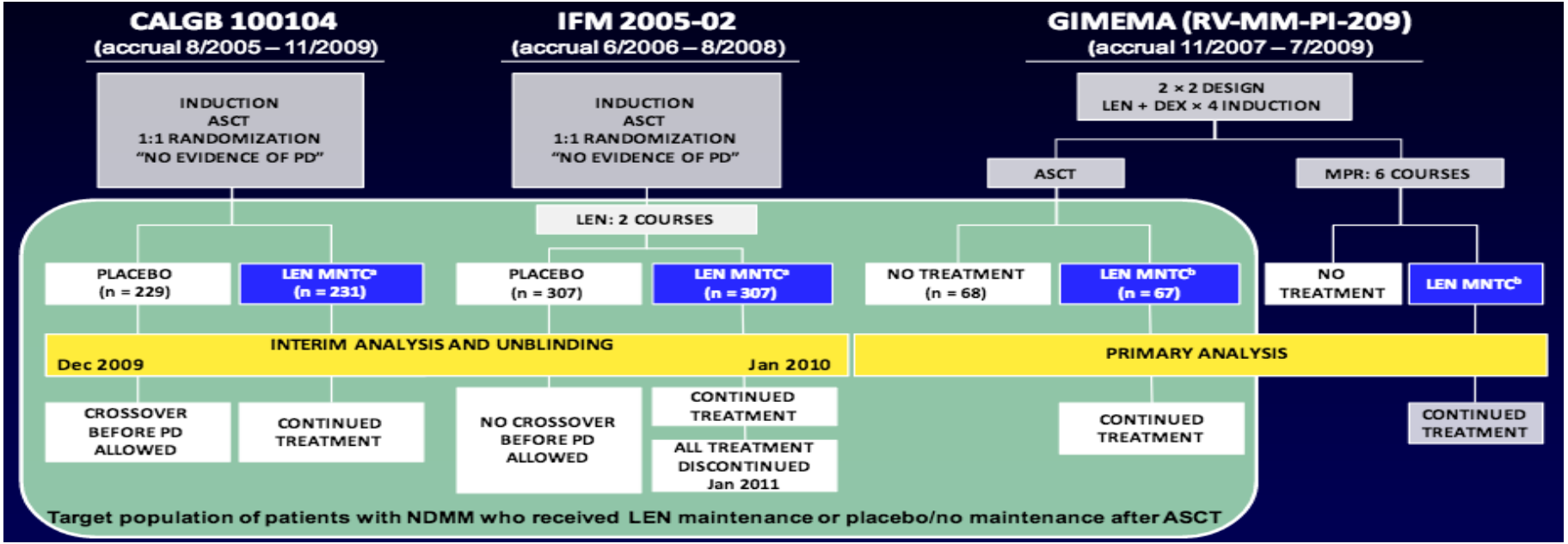
Quelle maintenance?

Intérêt du traitement continu pour maintenir améliorer la réponse

Tolérabilité du traitement

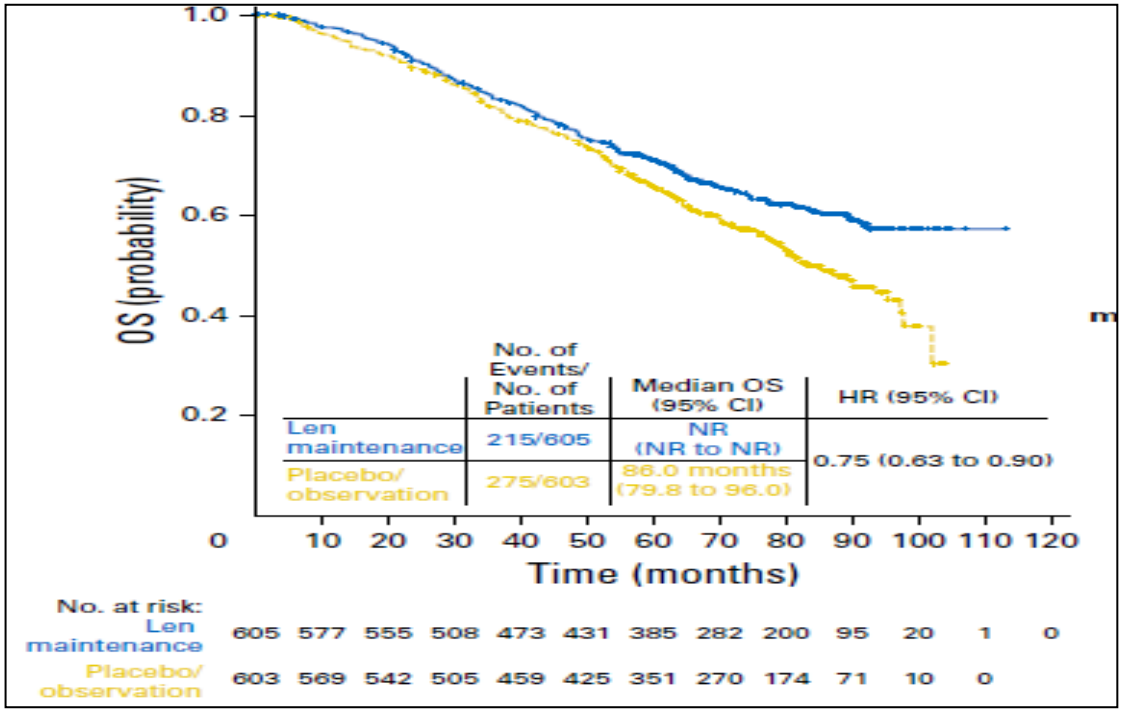
Maintenance

Méta-analyse



Mc Carthy et al. J Clin Oncol 2017

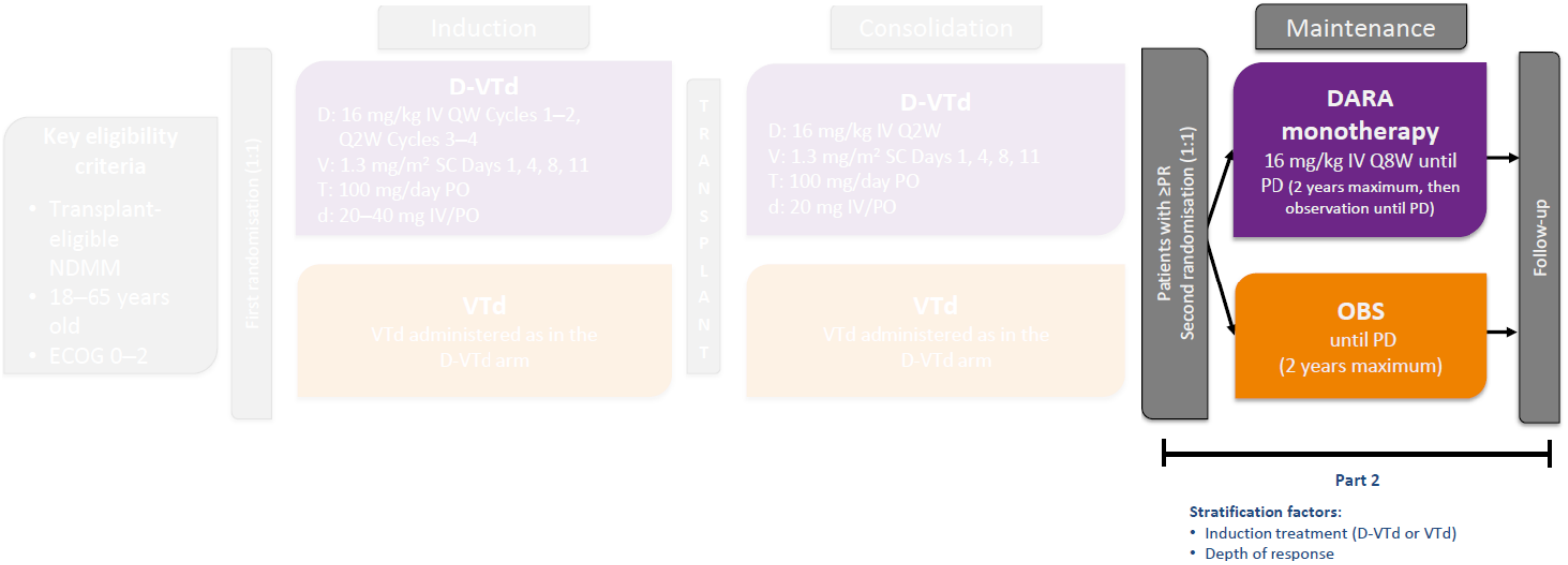
Maintenance



Mc Carthy et al. J Clin Oncol 2017

CASSIOPEIA Part 2 Study Design

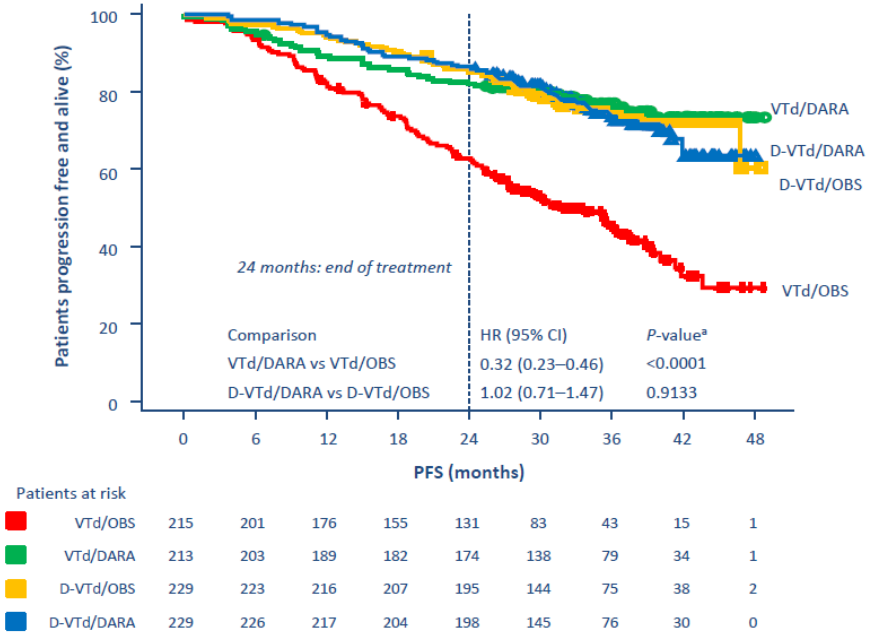
- Patients who completed consolidation and achieved ≥PR were re-randomised 1:1 to DARA 16 mg/kg IV Q8W or OBS (no maintenance) for 2 years



Moreau, Lancet Oncol 2021

DARA Significantly Improved PFS vs OBS in Patients Treated With VTd Induction/Consolidation

- A prespecified analysis showed significant interaction between maintenance and induction/consolidation therapy
- A PFS benefit was observed for VTd/DARA versus VTd/OBS
- PFS was not different for D-VTd/DARA versus D-VTd/OBS



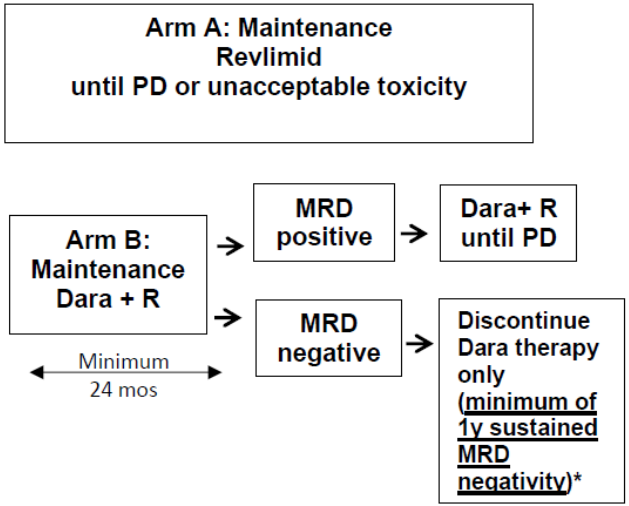
[a]Nominal *P*-value.
CI, confidence interval; DARA, daratumumab; D-VTd, daratumumab, bortezomib, thalidomide, and dexamethasone; HR, hazard ratio; OBS, observation; PFS, progression-free survival; VTd, bortezomib, thalidomide, and dexamethasone.

Moreau, Lancet Oncol 2021

Maintenance

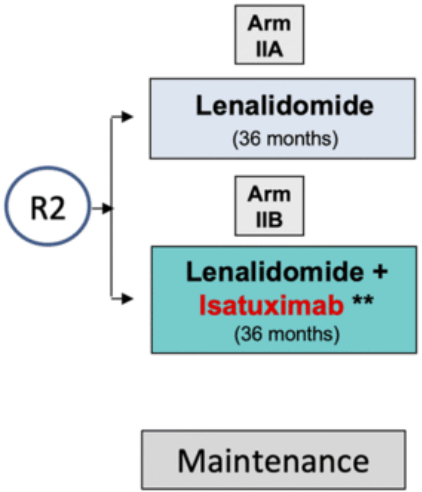
PERSEUS

Rev +- dara



GMMG-HD7

Rev +- Isa



Vers un traitement adapté au risque?

Principaux facteurs pronostiques dans le myélome multiple

AU DIAGNOSTIC

Liés à la maladie

Biochimie :

- β_2 microglobuline >5,5 mg/L
- Albumine < 35 g/L
- LDH > N

Cytogénétique

- t(4;14), t(14;16), Del 17p
- Anomalies du chromosome 1

TEP :

- Maladie para/extramédullaire
- SUV max

Liés au patient

Âge / Fragilité

Comorbidités

Insuffisance rénale

DYNAMIQUE

Réponse au traitement

Maladie résiduelle++

NGS, NGF

Réponse métabolique

TEP

Principaux facteurs pronostiques dans le myélome multiple

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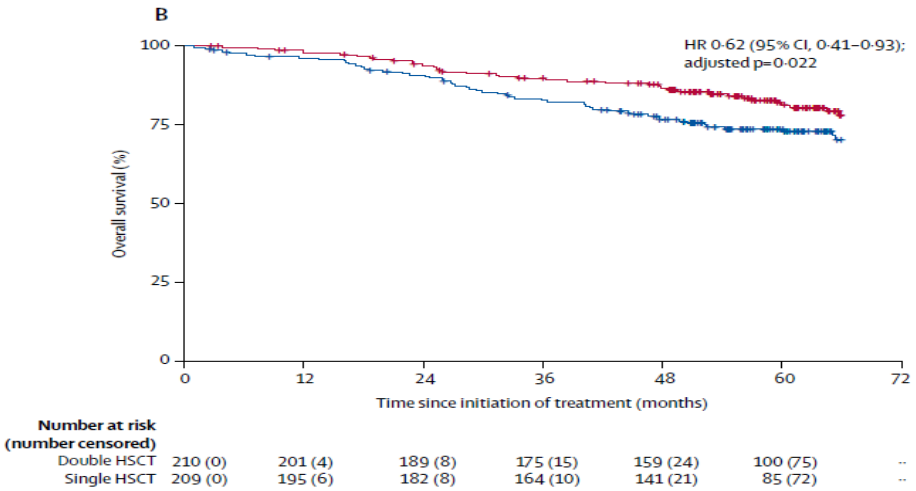
Double autogreffe pour les patients de haut risque?

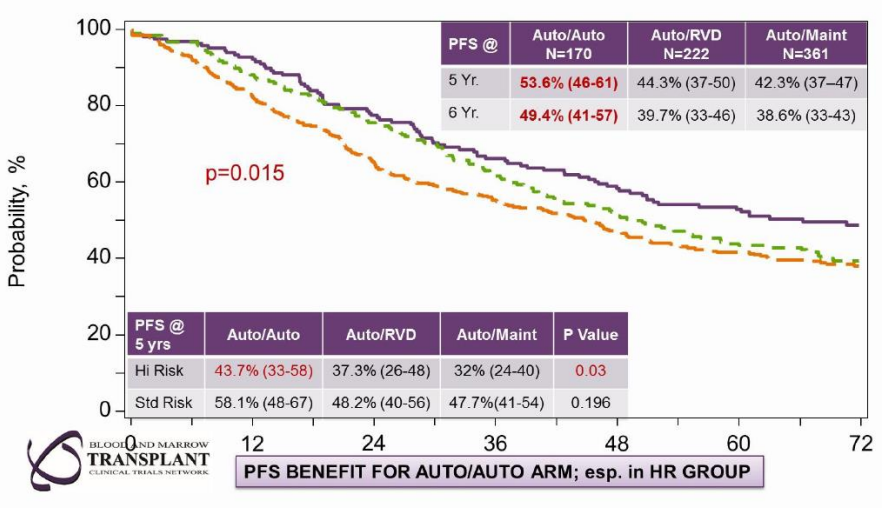
EMN02



Bénéfice en faveur de la la double autogreffe,
Essentiellement porté par les patients de haut risque

Cavo et al, Lancet Haematol 2020

STAMINA



Parameswaran H *et al. ASCO* 2020. Abstract 8506

Double autogreffe pour les patients de haut risque?

Study Design – GMMG CONCEPT (NCT03104842)

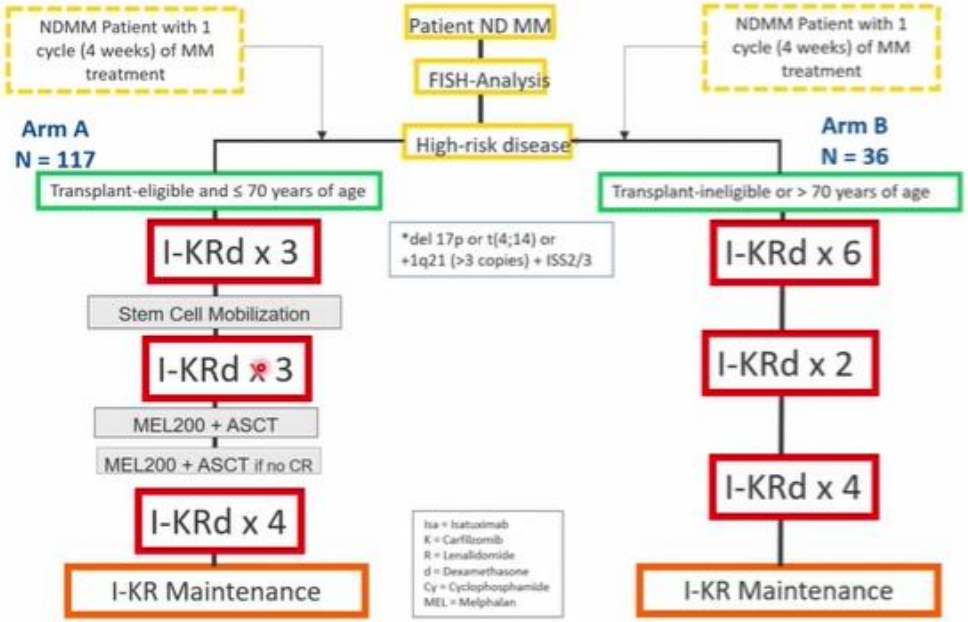


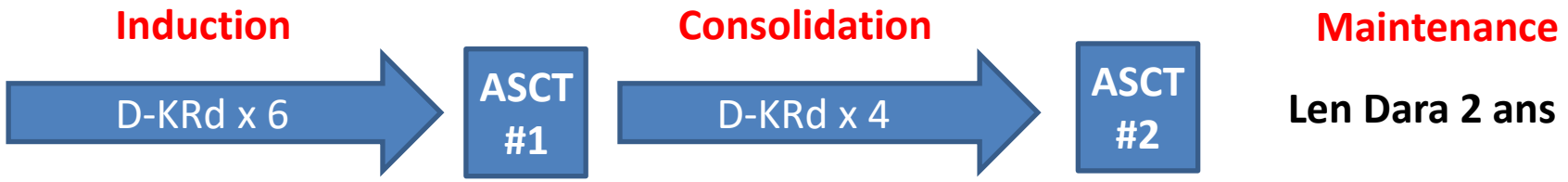
Table 1. Best response during induction.

	Arm A, *N* = 46 (%)
≥CR	23 (50)
sCR	3 (6.5)
CR	20 (43.5)
VGPR	18 (39.1)
PR	5 (10.9)
ORR	46 (100)
≥VGPR	41 (89.1)
MRD negative	20/31 (64.5)

Leypoldt et al. Leukemia 2021

Double autogreffe pour les patients de haut risque?

Phase 2 IFM 2018-04



- 50 patients
- Haut risque cytogénétique : del17, t(4;14) t(14;16)

CENTRE HOSPITALIER UNIVERSITAIRE DE NANTES

ifm

Principaux facteurs pronostiques dans le myélome multiple

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DYNAMIQUE

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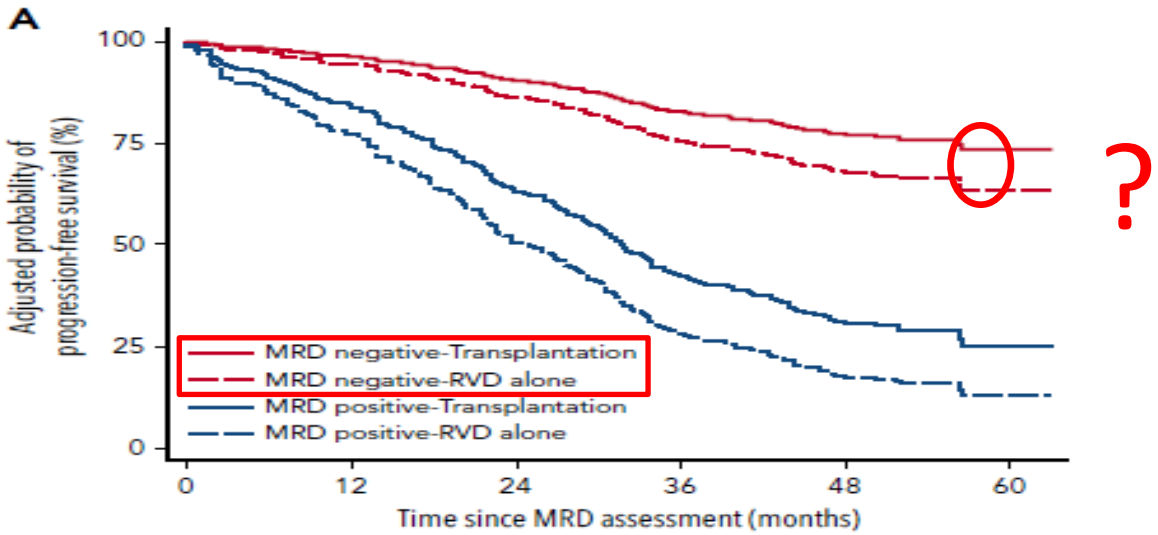
Maladie résiduelle++

NGS, NGF

Réponse métabolique

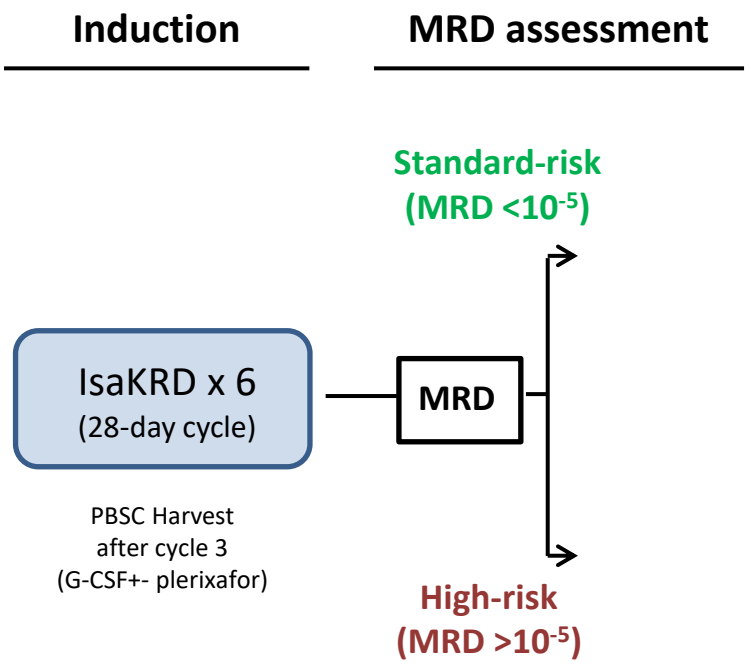
TEP

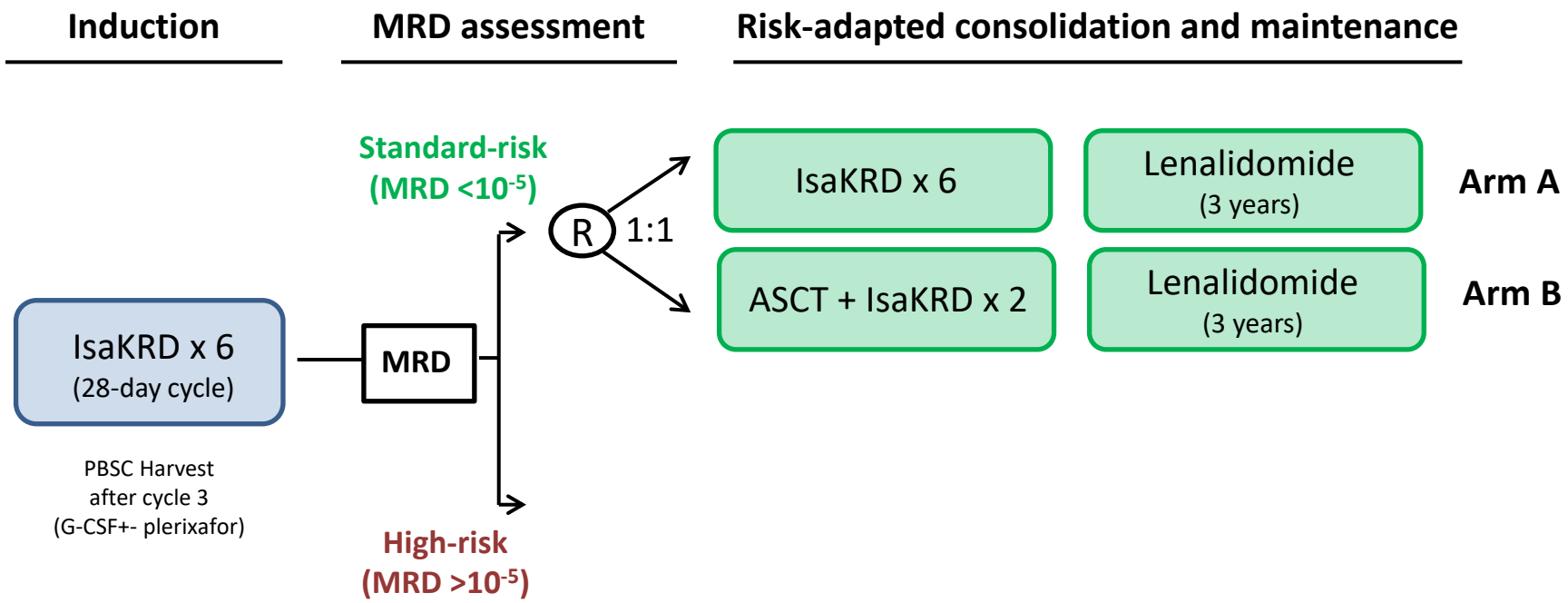
Importance pronostique de la MRD

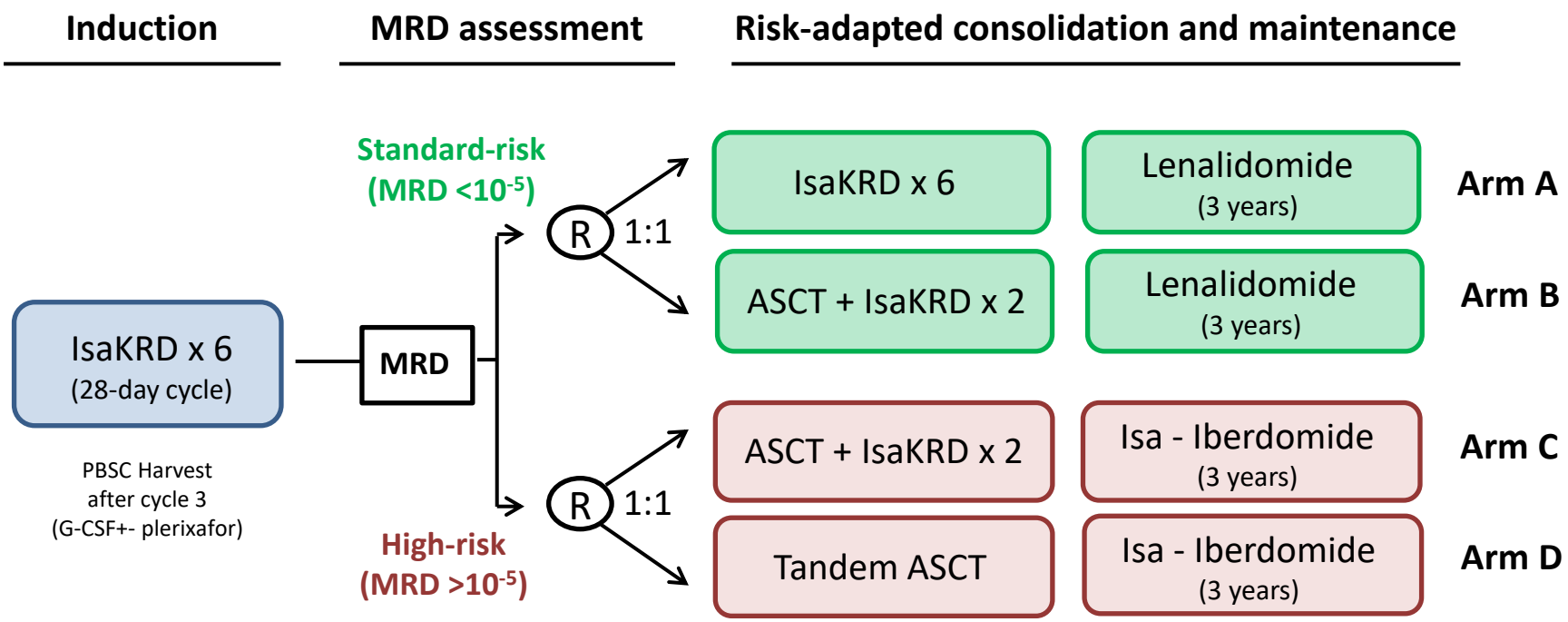


Perrot A, et al. Minimal residual disease negativity using deep sequencing is a major prognostic factor in multiple myeloma. Blood 2018;132(23):2456-64.

MIDAS
IFM


Induction
MRD assessment
Standard-risk
(MRD <10-5)
IsaKRD x 6
(28-day cycle)
MRD
PBSC Harvest
after cycle 3
(G-CSF+- plerixafor)
High-risk
(MRD >10-5)


Induction
MRD assessment
Risk-adapted consolidation and maintenance
IsaKRD x 6
(28-day cycle)
PBSC Harvest
after cycle 3
(G-CSF+- plerixafor)
MRD
Standard-risk
(MRD <10-5)
High-risk
(MRD >10-5)
R
1:1
IsaKRD x 6
ASCT + IsaKRD x 2
Lenalidomide
(3 years)
Lenalidomide
(3 years)
Arm A
Arm B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Arm A
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Lenalidomide
(3 years)
Arm B
ASCT + IsaKRD x 2
Isa - Iberdomide
(3 years)
Arm C
Tandem ASCT
Isa - Iberdomide
(3 years)
Arm D

CONCLUSION

- **L'autogreffe reste le traitement standard** chez le patient éligible

- **Schéma d'induction/ consolidation optimal** : quadruplette avec IP IMID anti CD38
  Dara VTD (AMM, remboursée), Dara VRD?

- **Maintenance :** bénéfice en survie avec lenalidomide. Bientôt len + anti CD38?

- **L'objectif du traitement : obtention d'une MRD négative (maintenue dans le temps)**

- **Les perspectives :**

  -> un traitement adapté au risque : MRD -> MIDAS
  -> intégration des CAR-T / bispécifiques au traitement de L1
  versus autogreffe ? conso pour HR? bispé en maintenance?

Merci pour votre attention !

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