Société Française d'Hématologie

10 sep 2020

Anti-CD38 : avenir incontournable du traitement de 1ère ligne ?

L Karlin

Service d'Hématologie Clinique

Hôpital Lyon Sud

Hospices Civils de Lyon

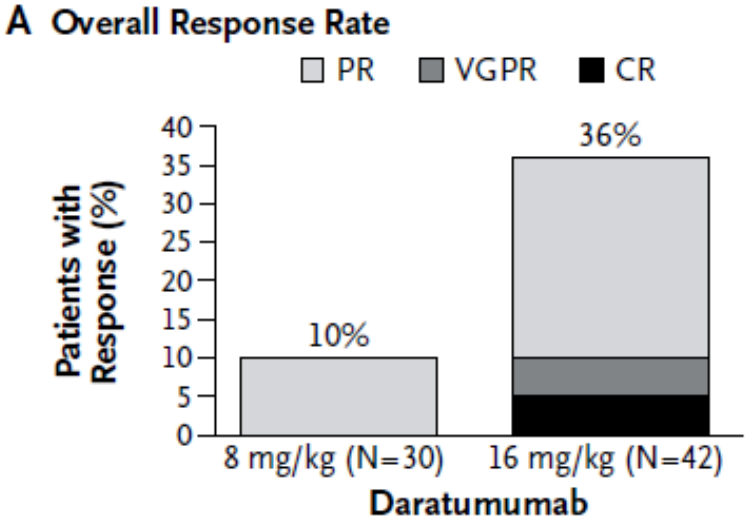
ifm

Les anticorps monoclonaux anti-CD38 : une classe thérapeutique majeure dans le Myélome ?

ORIGINAL ARTICLE

Targeting CD38 with Daratumumab Monotherapy in Multiple Myeloma

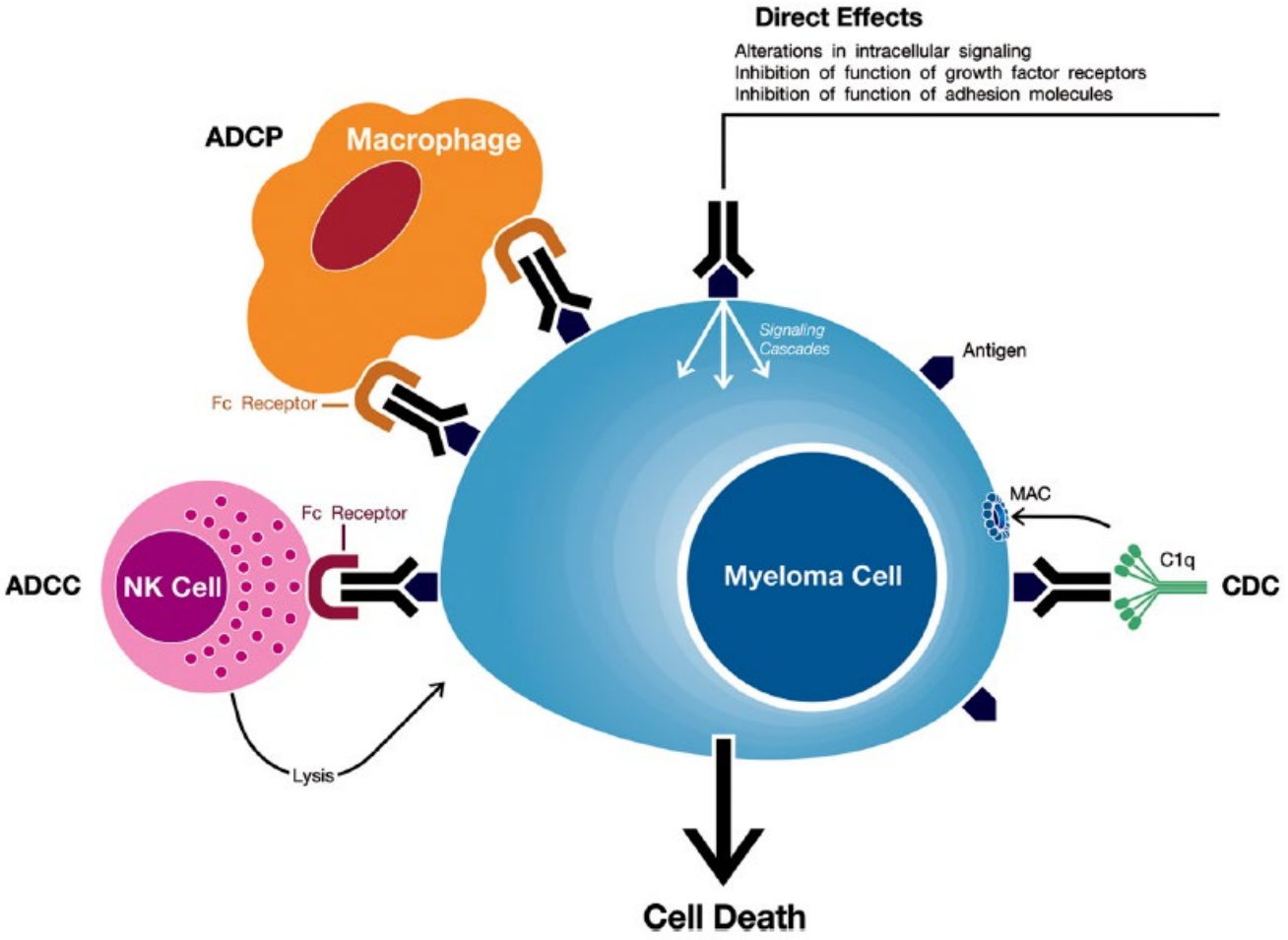
H.M. Lokhorst, T. Plesner, J.P. Laubach, H. Nahi, P. Gimsing, M. Hansson,



DOI: 10.1056/NEJMoa1506348

Anticorps anti-CD38

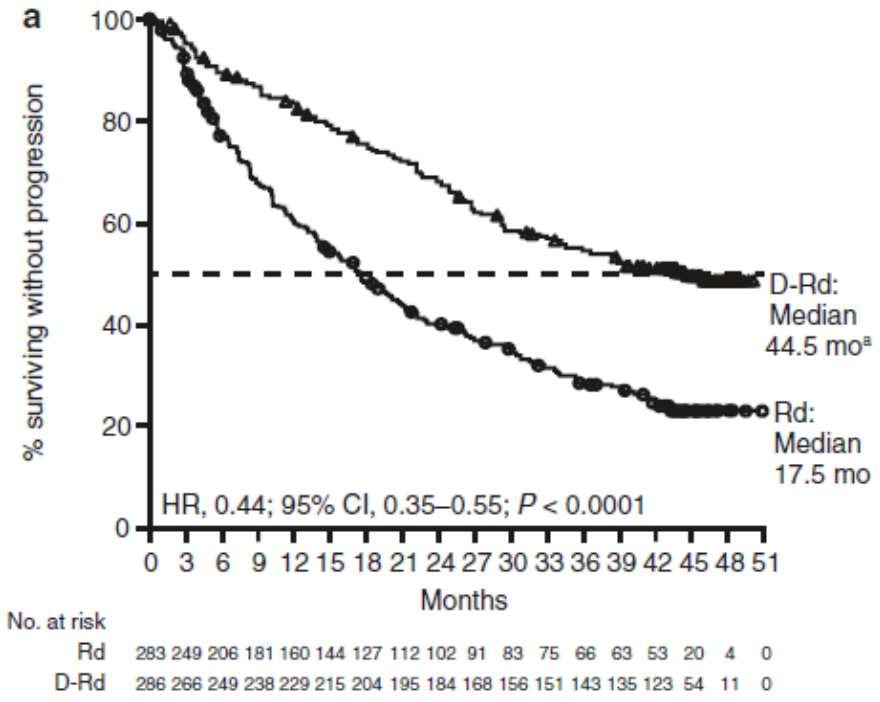
- daratumumab (IgG1-κ / humain)
- isatuximab (IgG1- κ / chimérique)
- MOR-202 (IgG1-λ / humain)

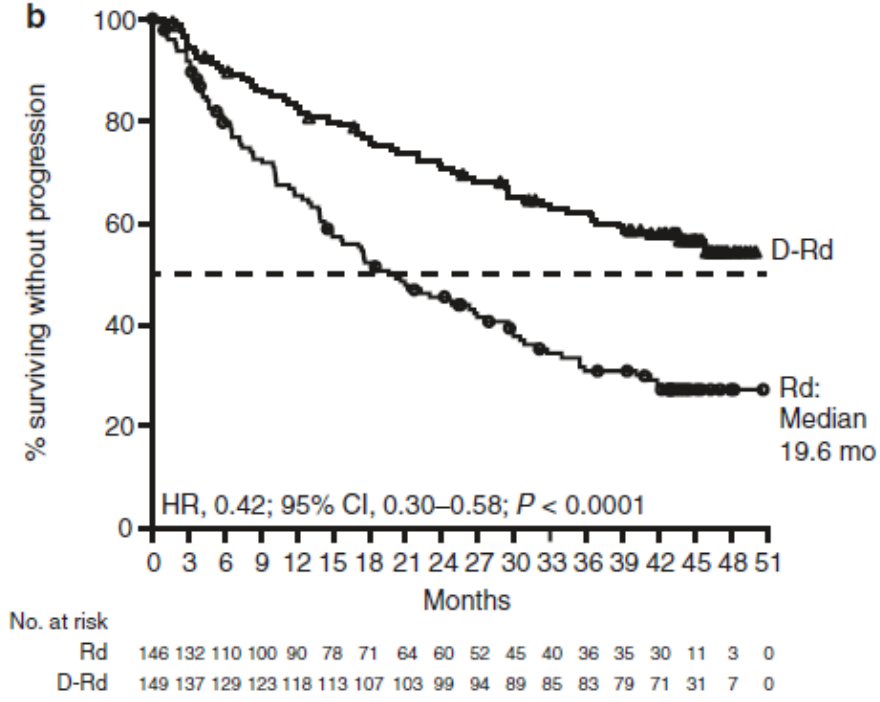


van de Donk, Blood 2016

Confirmation de l'efficacité – intérêt des combinaisons

Daratumumab plus lenalidomide and dexamethasone in relapsed/refractory multiple myeloma: extended follow-up of POLLUX, a randomized, open-label, phase 3 study





Bahlis, Leukemia 2020

Daratumumab plus lenalidomide and dexamethasone in relapsed/refractory multiple myeloma: extended follow-up of POLLUX, a randomized, open-label, phase 3 study

Table 1 Summary of best confirmed response[a] and MRD-negative[b] rates.

Variable	D-Rd ($n = 281$)	Rd ($n = 276$)	P
Overall response			
No. with response	261	211	
Rate, % (95% CI)	92.9 (89.2–95.6)	76.4 (71.0–81.3)	< 0.0001[c]
Clinical benefit, n (%)[d]	266 (94.7)	237 (85.9)	
Best overall response, n (%)			
CR or better	159 (56.6)	64 (23.2)	< 0.0001[c]
Stringent CR[e]	82 (29.2)	29 (10.5)	
CR	77 (27.4)	35 (12.7)	
VGPR or better	226 (80.4)	136 (49.3)	< 0.0001[c]
VGPR	67 (23.8)	72 (26.1)	
Partial response	35 (12.5)	75 (27.2)	
Stable disease[f]	18 (6.4)	59 (21.4)	
Progressive disease	0 (0.0)	4 (1.4)	
Response could not be evaluated	2 (0.7)	2 (0.7)	
MRD negative (10^{-5})	$n = 286$	$n = 283$	
n (%)	87 (30.4)	15 (5.3)	< 0.0001[g]

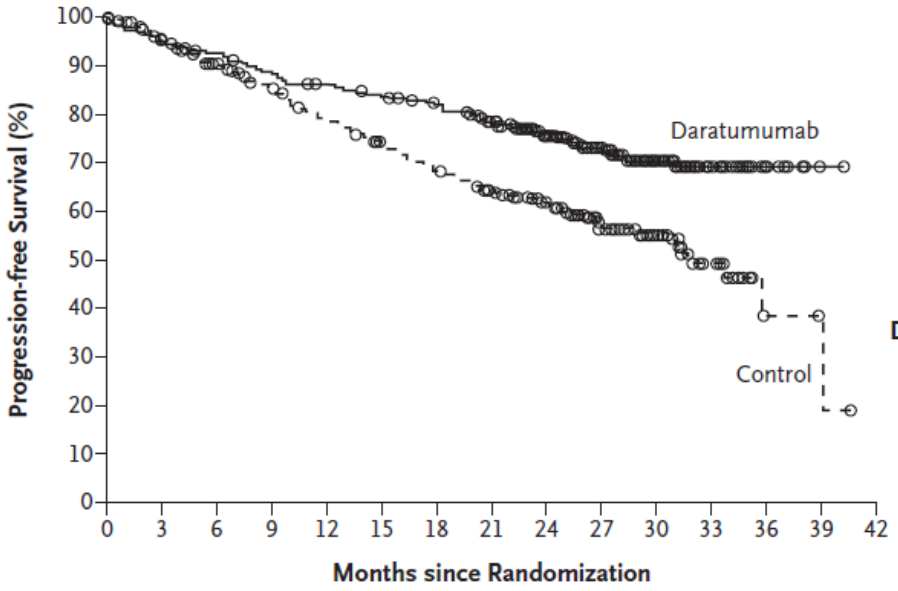
Bahlis, Leukemia 2020

Arrivée en 1ère ligne

ORIGINAL ARTICLE

Daratumumab plus Lenalidomide and Dexamethasone for Untreated Myeloma

T. Facon, S. Kumar, T. Plesner, R.Z. Orlowski, P. Moreau, N. Bahlis, S. Basu,



	No. of Patients	Median Progression-free Survival
		mo
Daratumumab	368	Not reached
Control	369	31.9

Hazard ratio for disease progression or death, 0.56 (95% CI, 0.43–0.73)
P<0.001

No. at Risk

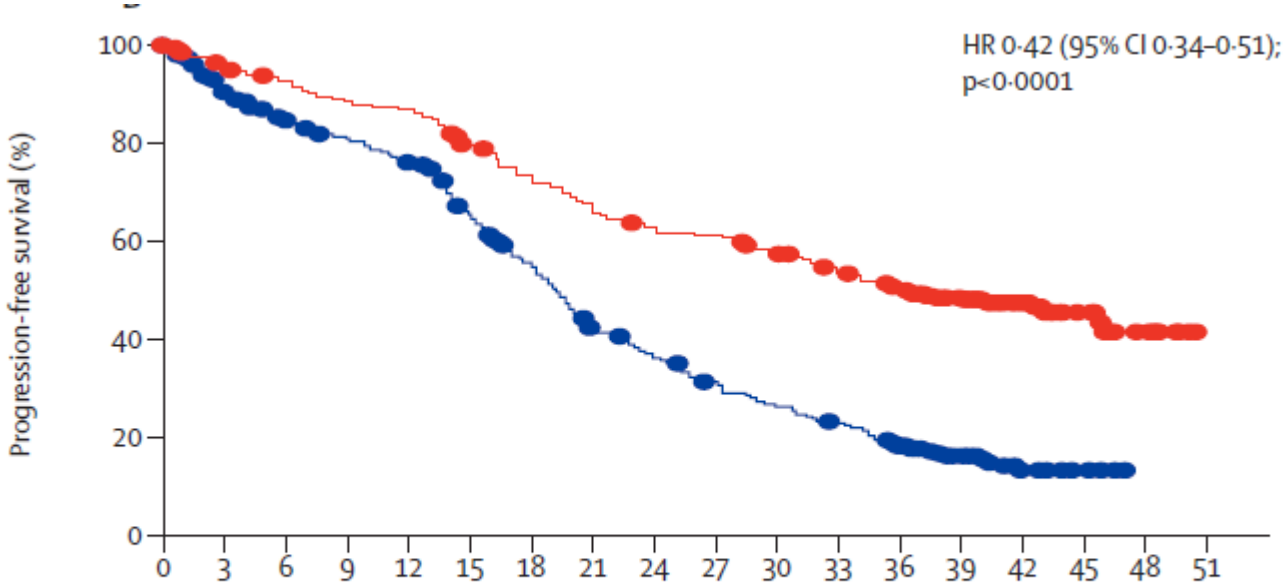
Daratumumab	368	347	335	320	309	300	290	271	203	146	86	35	11	1	0
Control	369	332	307	280	254	236	219	200	149	94	50	18	3	2	0

Table 2. Summary of Response Rates and Minimal Residual Disease Status in the Intention-to-Treat Population.*

Variable	Daratumumab Group (N=368)	Control Group (N=369)	P Value
Overall response — no. (% [95% CI])	342 (92.9 [89.8–95.3])	300 (81.3 [76.9–85.1])	<0.001†
Best overall response — no. (%)			
Complete response or better	175 (47.6)	92 (24.9)	<0.001†
Stringent complete response‡	112 (30.4)	46 (12.5)	—
Complete response	63 (17.1)	46 (12.5)	—
Very good partial response or better	292 (79.3)	196 (53.1)	<0.001†
Very good partial response	117 (31.8)	104 (28.2)	—
Partial response	50 (13.6)	104 (28.2)	—
Stable disease	11 (3.0)	56 (15.2)	—
Progressive disease	1 (0.3)	0	—
Response could not be evaluated	14 (3.8)	13 (3.5)	—
Negative status for minimal residual disease — no. (%)§	89 (24.2)	27 (7.3)	<0.001¶

Overall survival with daratumumab, bortezomib, melphalan, and prednisone in newly diagnosed multiple myeloma (ALCYONE): a randomised, open-label, phase 3 trial

Maria-Victoria Mateos, Michele Cavo, Joan Blade, Meletios A Dimopoulos, Kenshi Suzuki, Andrzej Jakubowiak, Stefan Knop, Chantal Doyen,



Number at risk

VMP	356	304	278	263	246	207	171	128	110	93	78	67	51	29	15	7	0	0
D-VMP	350	322	312	298	292	265	243	220	207	202	188	173	160	113	63	26	9	0

Lancet 2019

Overall survival with daratumumab, bortezomib, melphalan, and prednisone in newly diagnosed multiple myeloma (ALCYONE): a randomised, open-label, phase 3 trial

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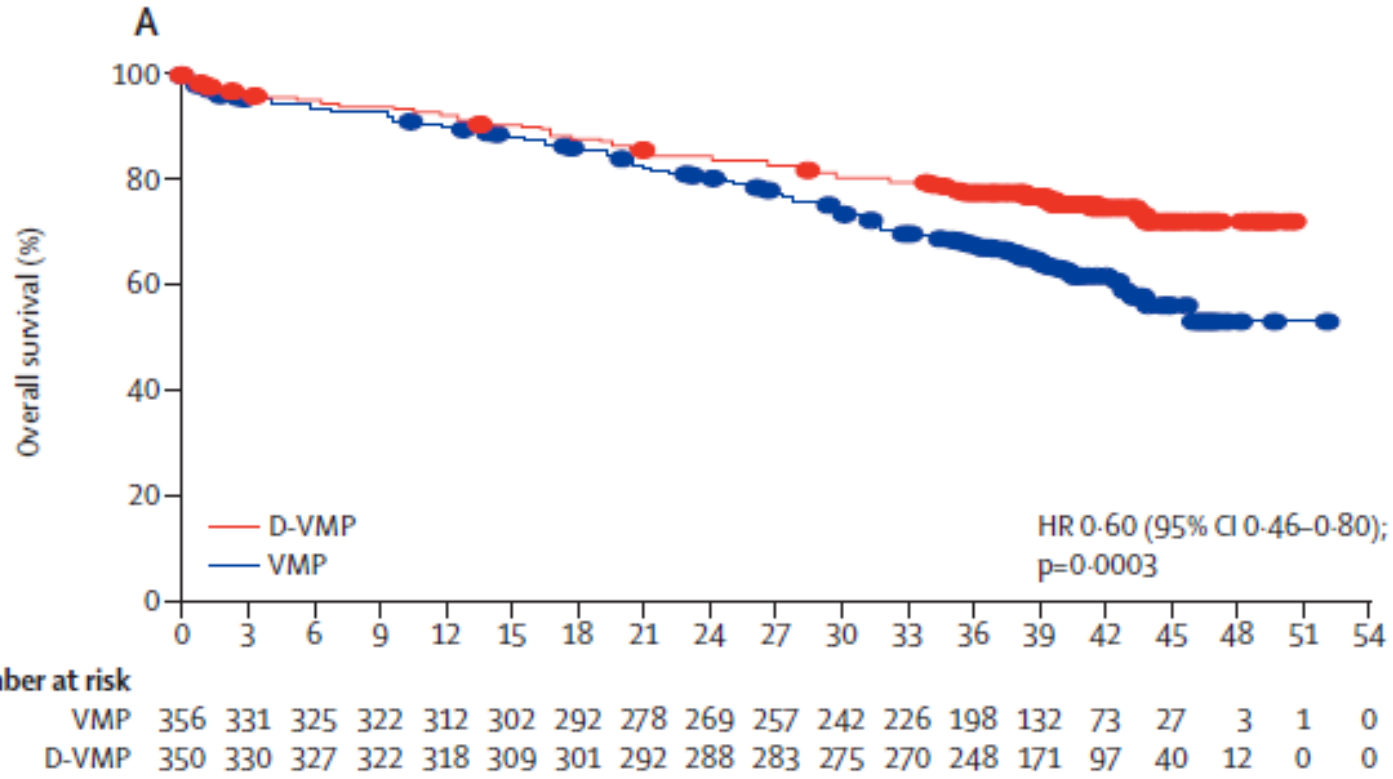


Lancet 2019

Alors, les anti-CD38 incontournables en 1ère ligne des sujets âgés ?

- **Amélioration incontestable de la survie sans progression**
- **Pas d'ajout de toxicité**
- **Partenaire privilégié : *lenalidomide***
- **Etude IMROZ : VRd +/- Isatuximab**

Schéma concurrentiel à l'autogreffe chez sujets âgés « fit » (65 – 70 ans)

Un besoin en 1ère ligne des sujets jeunes ?

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 APRIL 6, 2017 VOL. 376 NO. 14

Lenalidomide, Bortezomib, and Dexamethasone with Transplantation for Myeloma

Michel Attal, M.D., Valerie Lauwers-Cances, M.D., Cyrille Hulin, M.D., Xavier Leleu, M.D.,

Table 2. Response to Treatment.*

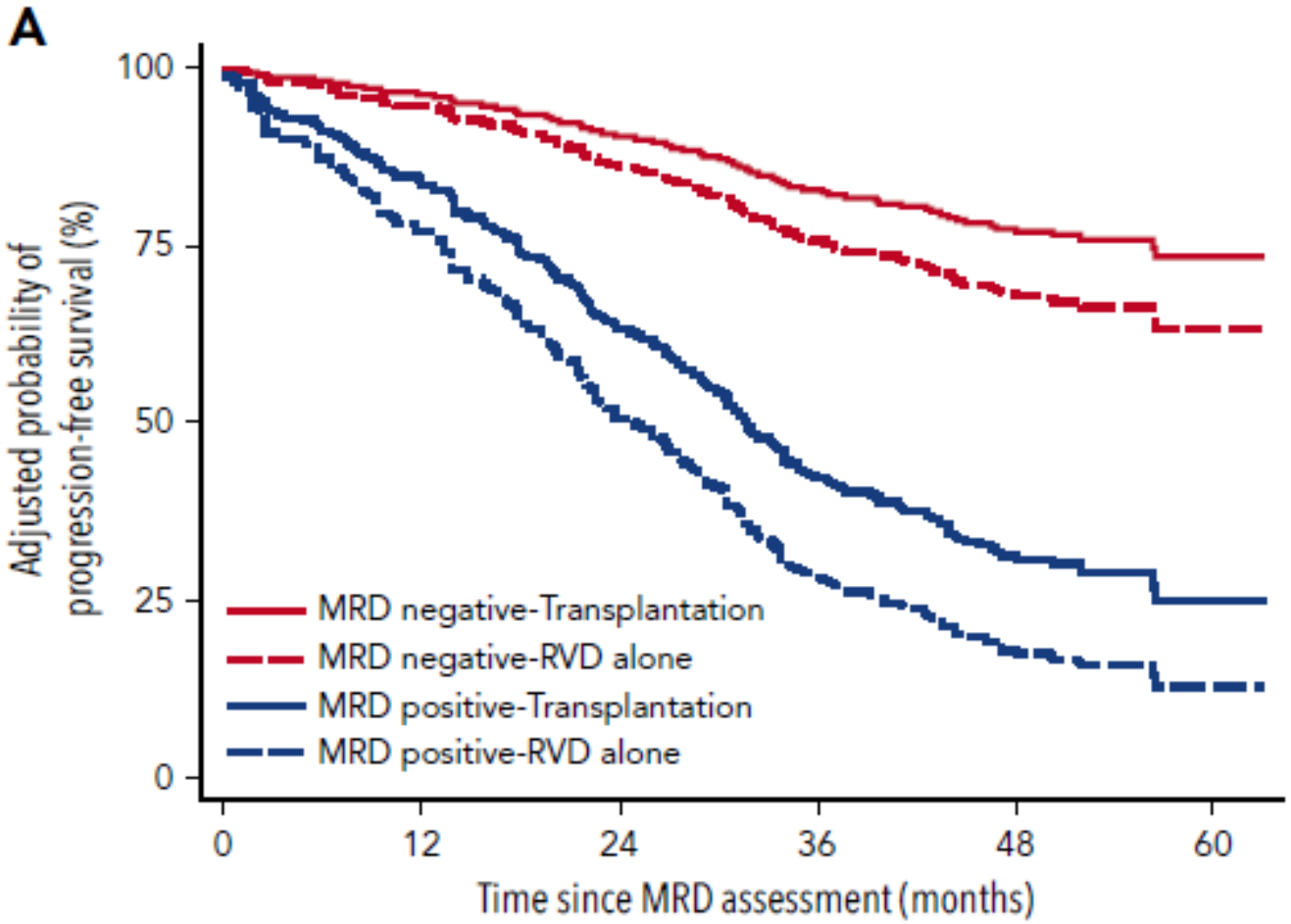
Outcome	RVD-Alone Group (N=350)	Transplantation Group (N=350)
Best response during the study — no. (%)		
Complete response	169 (48)	205 (59)
Very good partial response	101 (29)	102 (29)
Partial response	70 (20)	37 (11)
Stable disease	10 (3)	6 (2)
Complete response — no. (%)	169 (48)	205 (59)
Complete response or very good partial response — no. (%)	270 (77)	307 (88)

≥ VGPR 88%

Obtention de MRD neg (10^{-6})

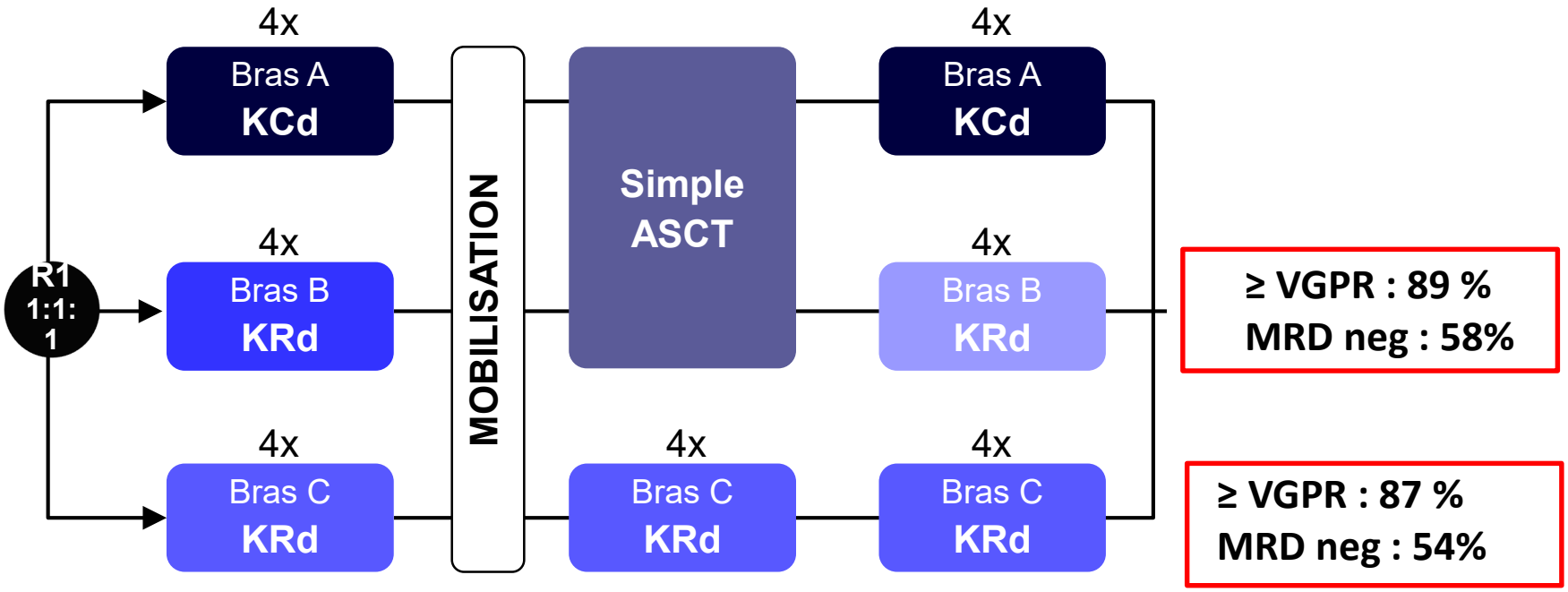
N Engl J Med 2017;376:1311-20.

Les MRD négatives…



Perrot A, Blood 2018

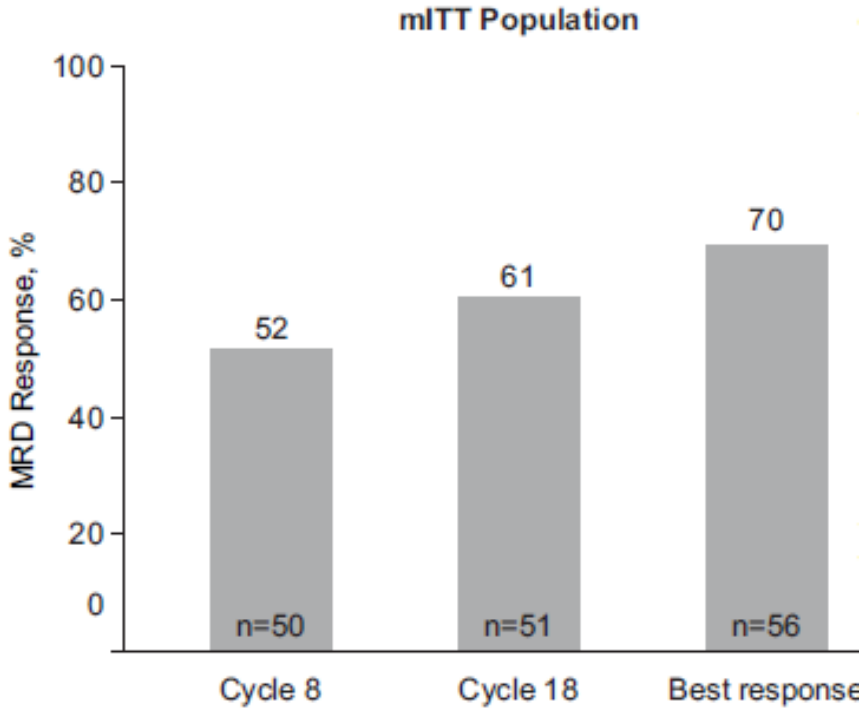
ESSAI FORTE



Gay F, ASH 2018 (#121)
Gay F, ASCO 2019 (#8002)

blood

Extended treatment with carfilzomib, lenalidomide, and dexamethasone plus transplant in newly diagnosed multiple myeloma



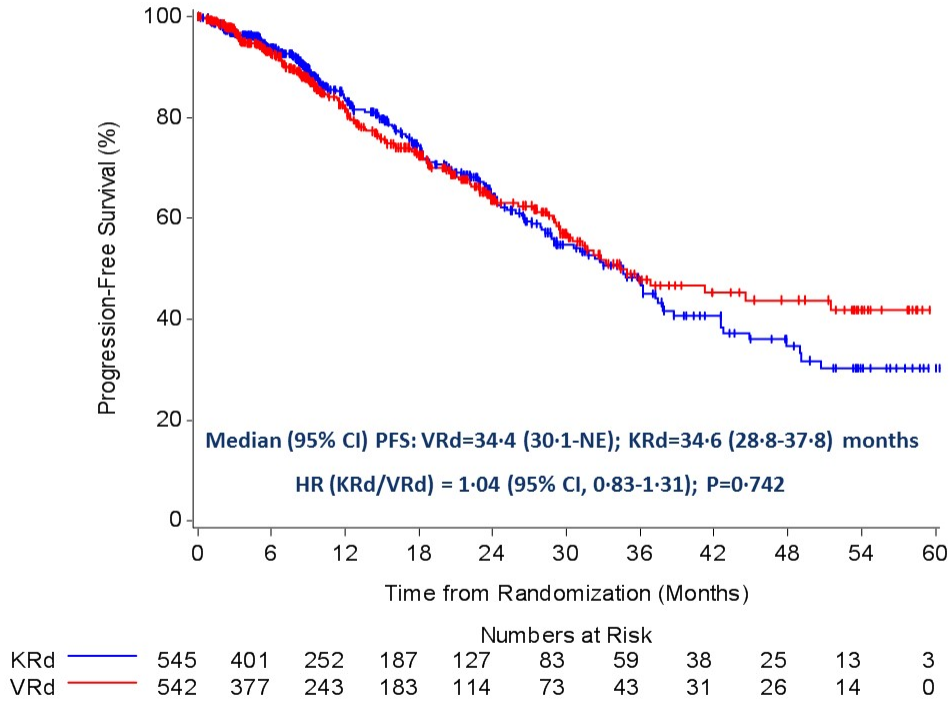
KRd x4
|
ASCT
|
KRd x4
|
KRd x10

NGS (10^{-5})

Jasielec, Blood 2020

ESSAI ENDURANCE *(ASCO 2020 – LBA 3)*

Progression Free Survival from Induction Randomization

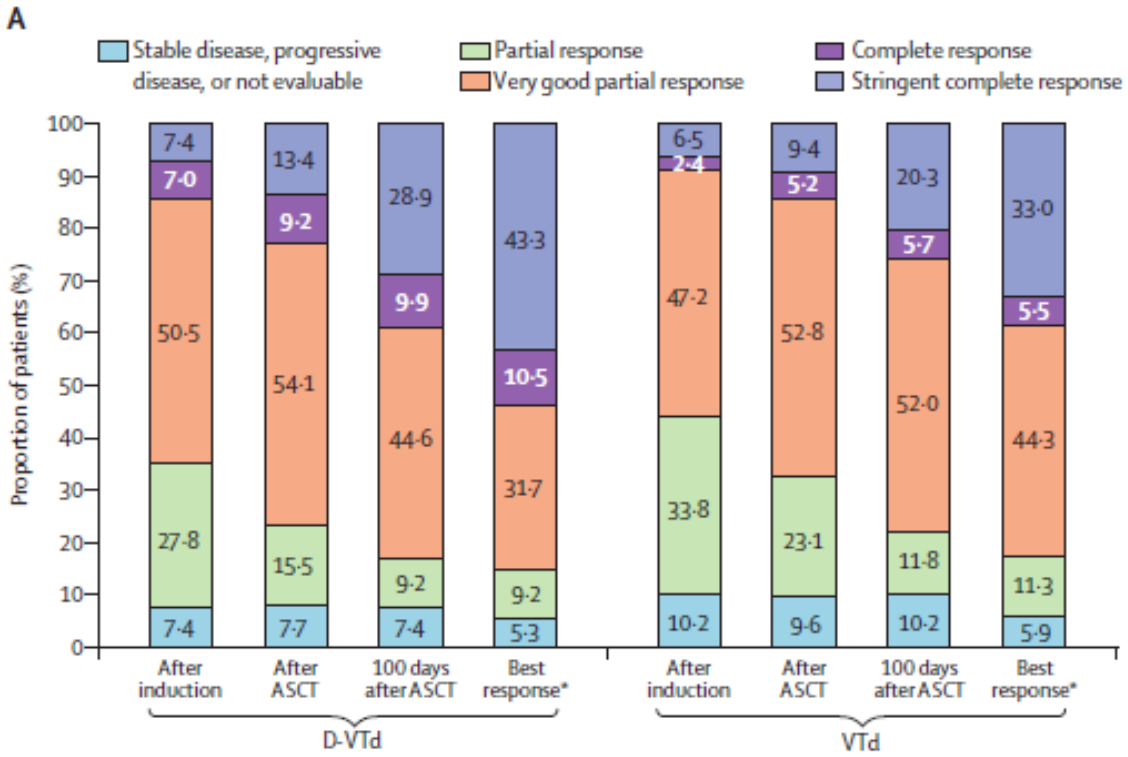


- 2nd interim analysis of PFS (Jan 2020): 298 PFS events (75% of 399 planned)
- Median (95% CI) estimated follow up of 15 (13-18) months
- For patients >/= 70 years, median PFS(95% CI) for VRd = 37 (29-NE) and KRd = 28 (24-36) months
- With censoring at SCT or alternative therapy: Median PFS (95% CI) for VRd = 31·7 (28·5-44·6) and KRd = 32·8 (27·2-37·5) months

Presented By Shaji Kumar at TBD

Bortezomib, thalidomide, and dexamethasone with or without daratumumab before and after autologous stem-cell transplantation for newly diagnosed multiple myeloma (CASSIOPEIA): a randomised, open-label, phase 3 study

Philippe Moreau, Michel Attal, Cyrille Hulin, Bertrand Arnulf, Karim Belhadj, Lotfi Benboubker, Marie C Béné, Annemiek Broijl, Hélène Caillon,



Lancet 2019

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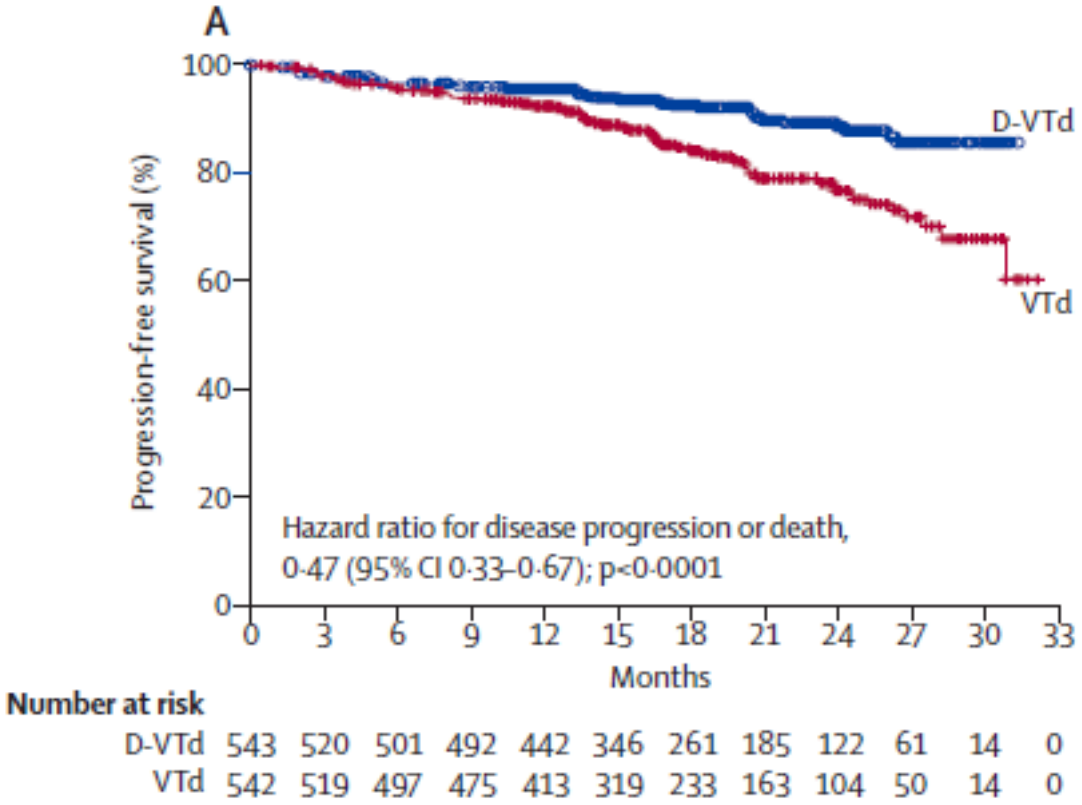
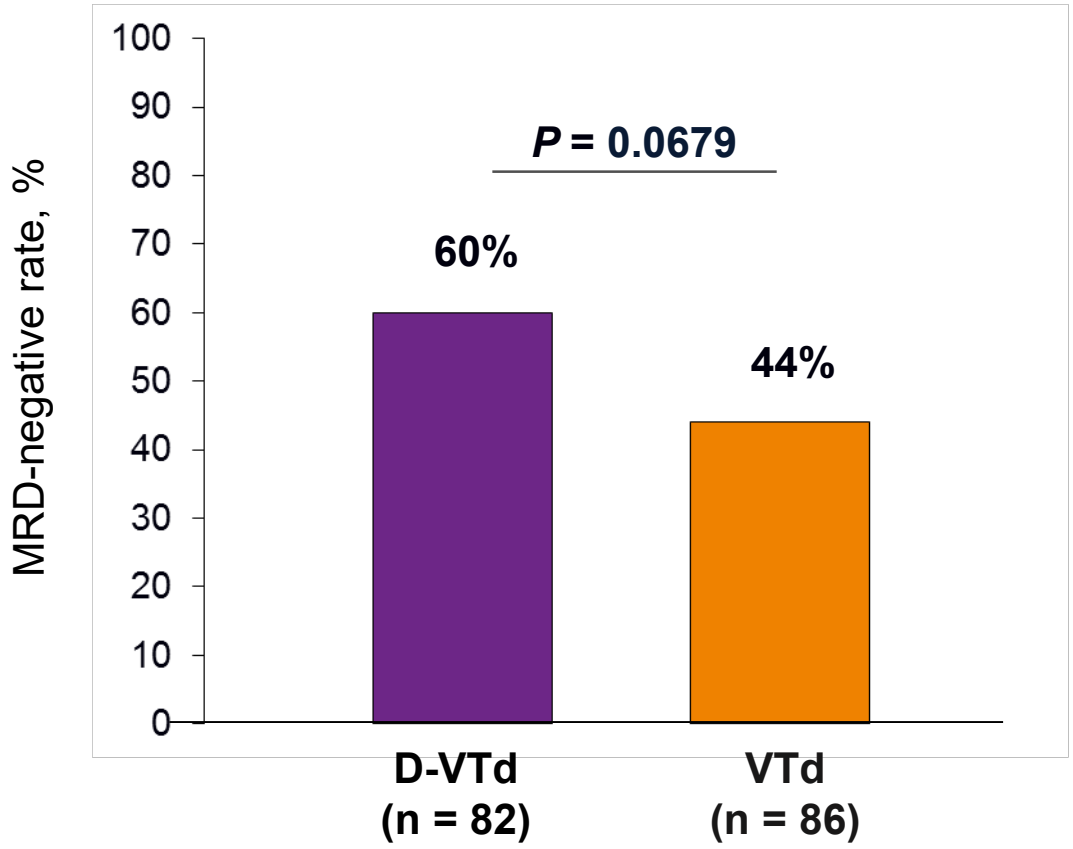


Lancet 2019

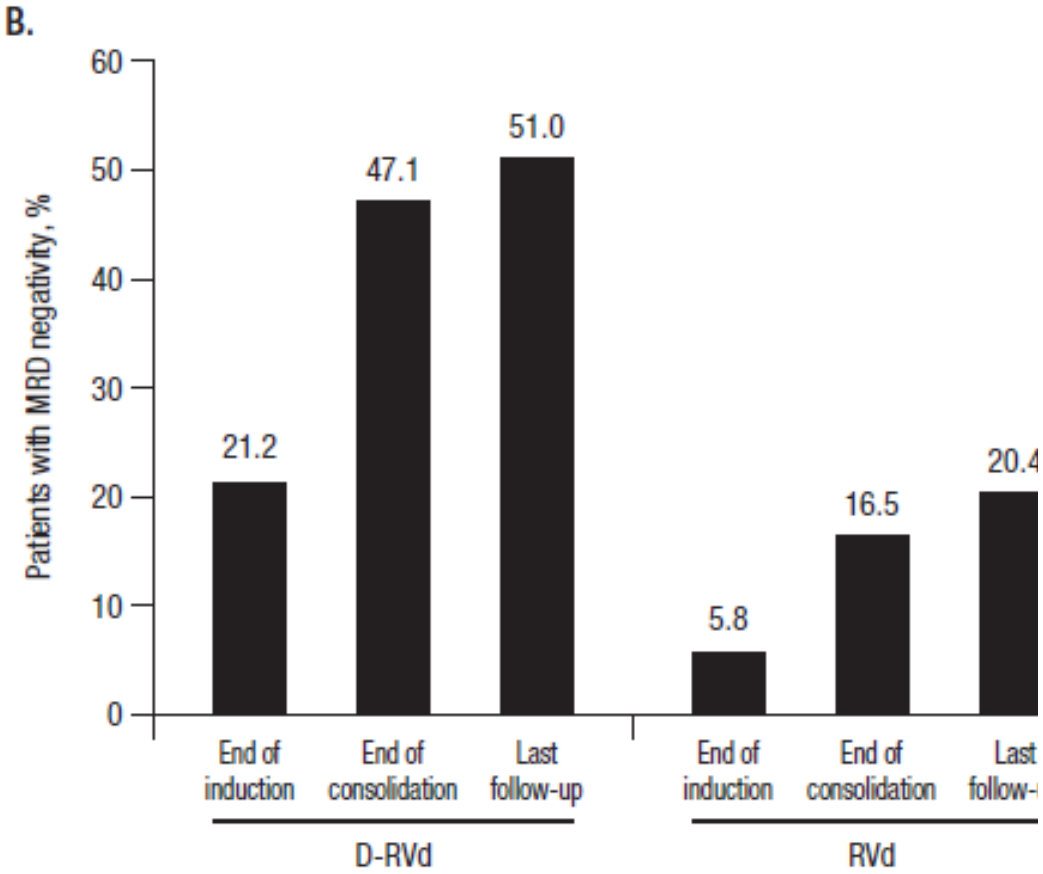
MRD en post-consolidation dans les cytogénétiques à haut risque (Flow Cytometry; 10^{-5})



IMW 2019 – présentation orale P Sonneveld
avec l'aimable autorisation de P Moreau

blood

Daratumumab, Lenalidomide, Bortezomib, & Dexamethasone for Transplant-eligible Newly Diagnosed Multiple Myeloma: GRIFFIN



VRd x4
|
ASCT
|
VRd x4
|
R

D-VRd x4
|
ASCT
|
D-VRd x4
|
D-R

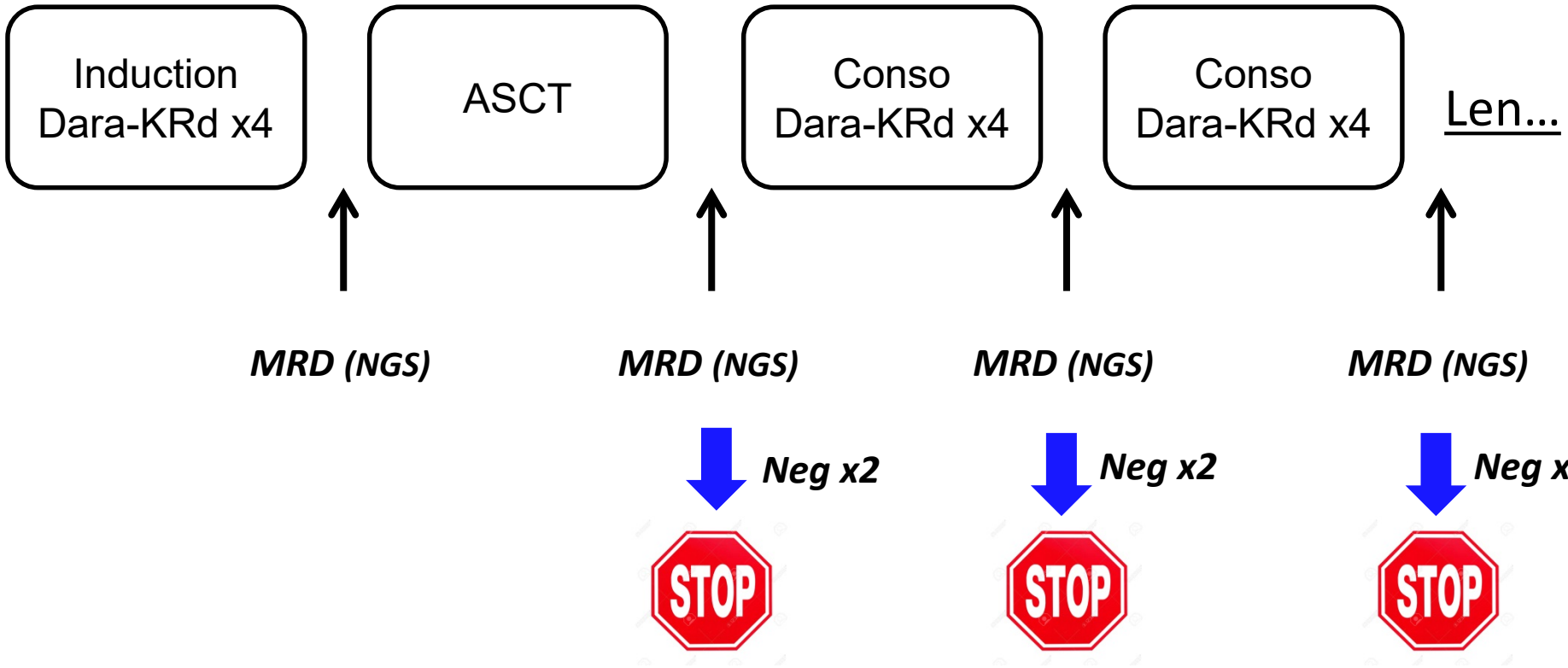
 # essai PERSEUS (EMN)

Voorhees, Blood 2020

MASTER TRIAL

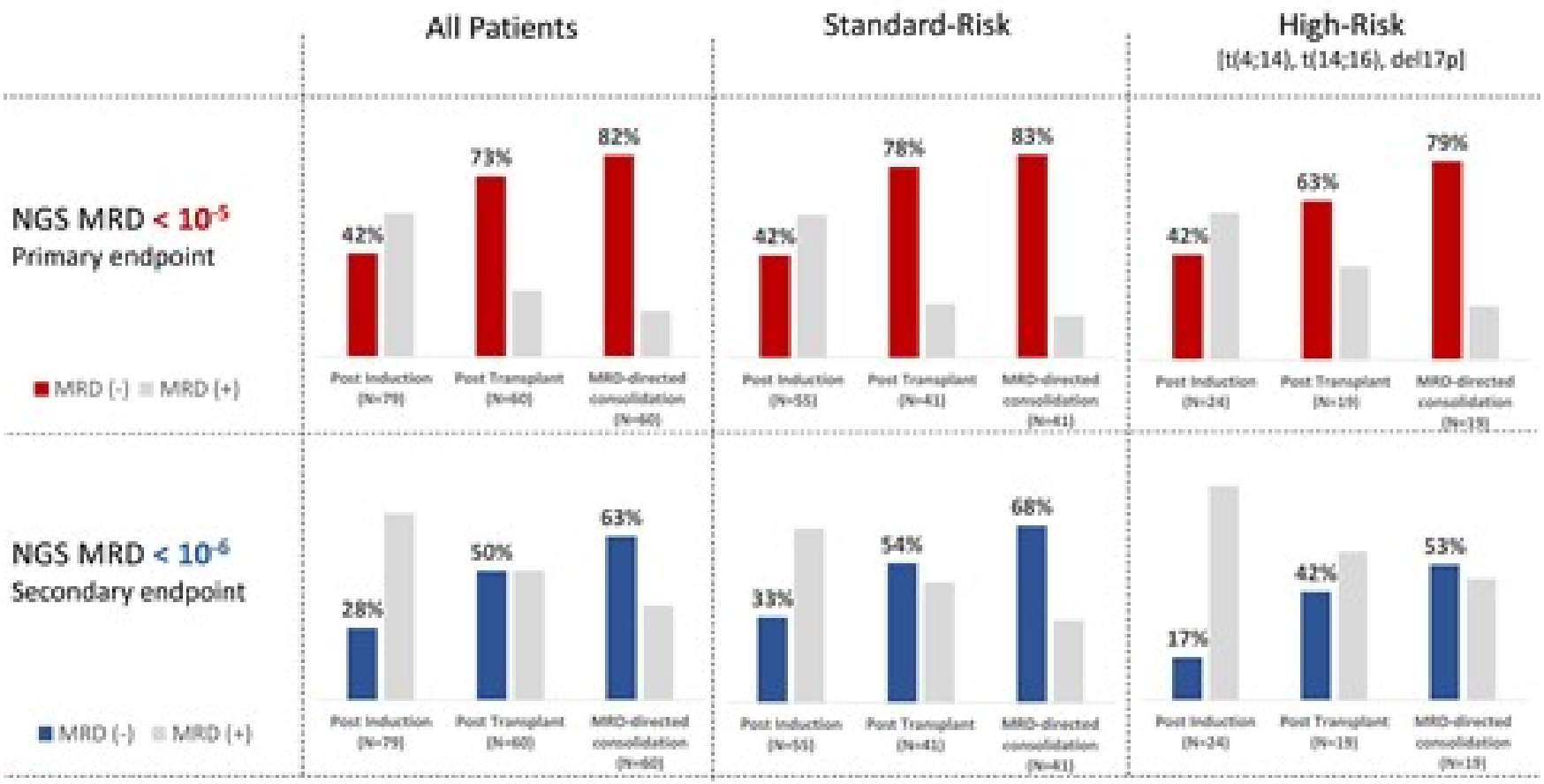
DARA-KRd

- D 16 mg/kg
- K 56 mg/m2 J1-8-15
- R 25 mg J1-21
- Dexa 40 mg J1-8-15-22



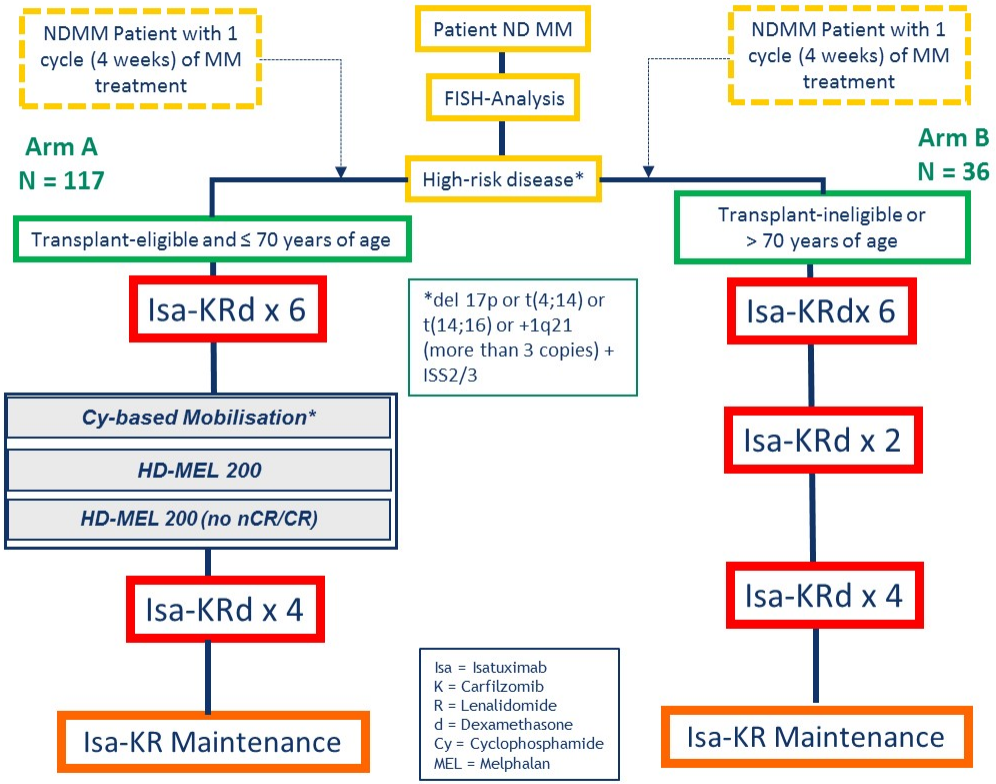
Costa, EHA 2020 Abstract: EP928

MASTER TRIAL



Costa, EHA 2020 Abstract: EP928

Study Design – GMMG CONCEPT (NCT03104842)



Isa-KRd Induction
Cycle 1

Isatuximab	10 mg/kg	day 1, 8, 15, 22
Carfilzomib	20 mg/m²	day 1, 2
Carfilzomib	36 mg/m²	day 8, 9, 15, 16
Lenalidomide*	25 mg	day 1-21
Dexamethasone**	40 mg*	day 1, 8, 15, 22
28-day-cycle		

Isa-KRd Induction
Cycle 2-6

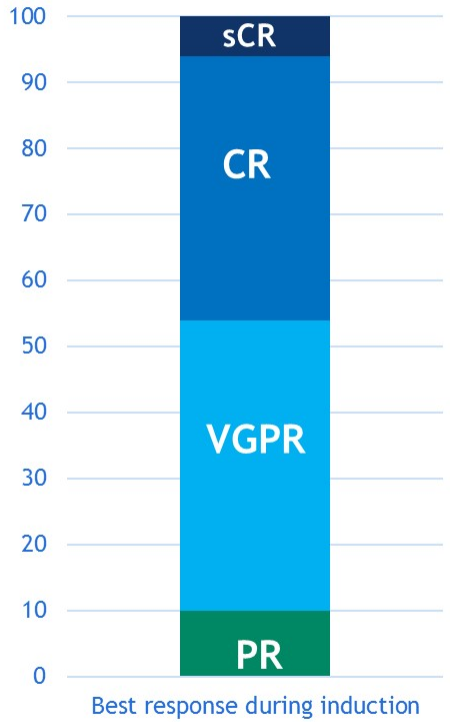
Isatuximab	10 mg/kg	day 1, 15
Carfilzomib	36 mg/m²	day 1, 2, 8, 9, 15, 16
Lenalidomide**	25 mg	day 1-21
Dexamethasone***	40 mg*	day 1, 8, 15, 22
28-day-cycle		

* Cy-based mobilisation was moved in an amendment to the time after 3 induction cycles
**Dose adaption of lenalidomide according to renal function
***20 mg in patients ≥75 years

Results: Best response to therapy, 6 induction cycles

All evaluable patients: n = 50

- Overall response rate (ORR, ≥ PR): 100%
- ≥ VGPR : 90%; CR/sCR: 46%
  - Arm A: 41/46 ≥ VGPR
  - Arm B: all (n = 4) VGPR
- Arm A: MRD-assessment in 33 patients during induction
  - 20 patients MRD negative
  - 11 patients MRD positive
  - 2 not assessable



Results of MRD assessments after induction treatment are not reported and available yet

Les anti-CD38 incontournables en 1ère ligne des sujets jeunes ?

- **Supériorité d'une « quadruplet » incluant un anti-CD38**

  → **taux de réponse, MRD négatives, SSP**

- **Pas (ou peu) d'ajout de toxicité (« pb » du recueil de CSP)**

- **Données de maintenance à venir, mais candidat qui apparaît idéal…**

Questions ?

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