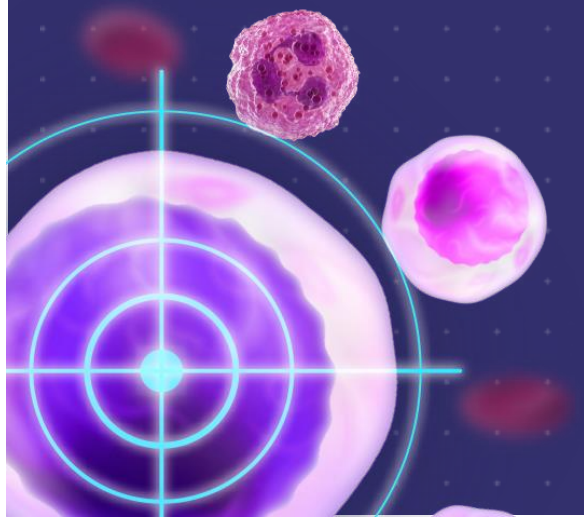
Is transplantation still relevant? If yes, in which context?

Sagar Lonial

Winship Cancer Institute of Emory University, Atlanta, US

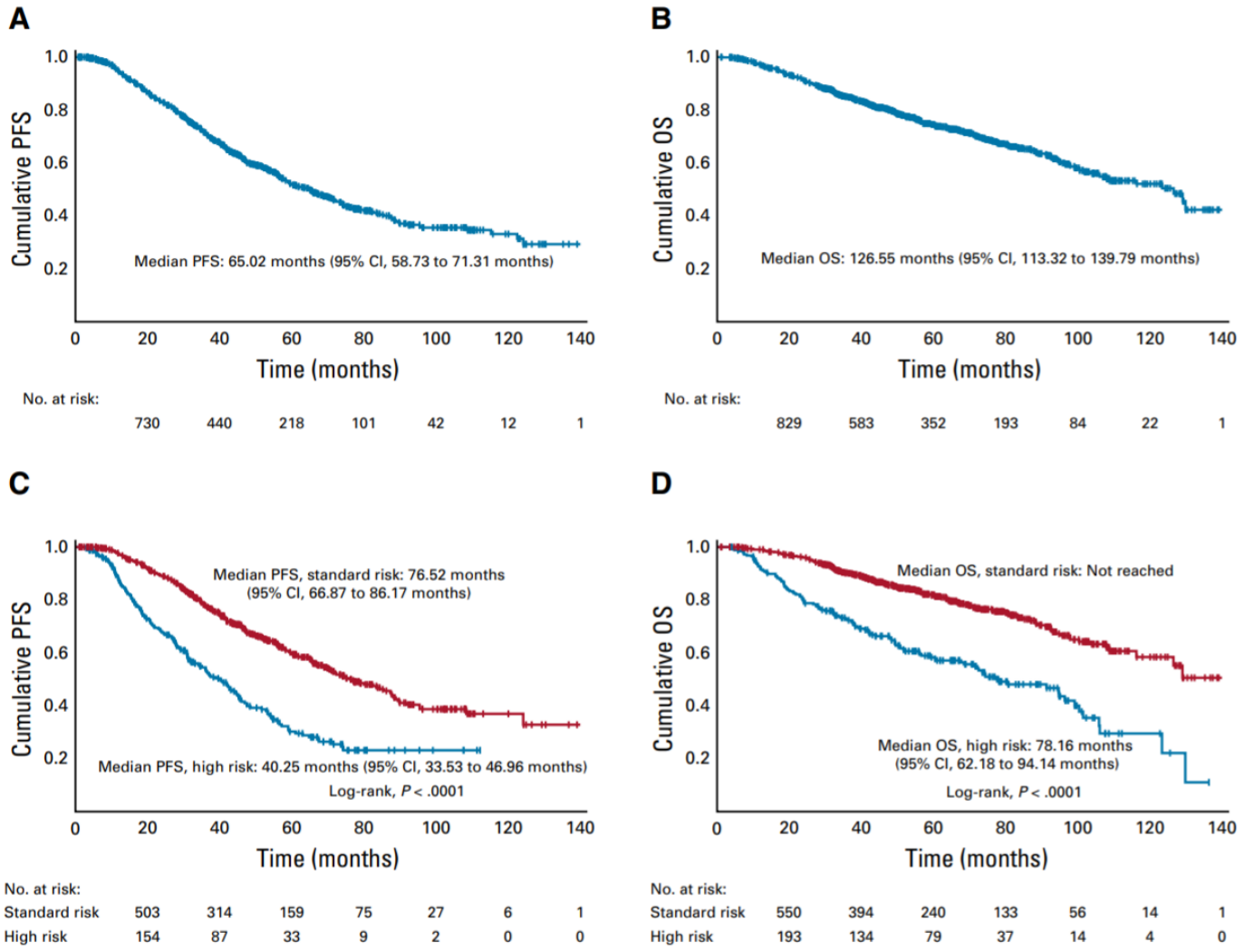


Disclosures

Research Support/P.I.	Takeda, Janssen, BMS, Celgene
Employee	NA
Consultant	NA
Major stakeholder	NA
Speakers bureau	NA
Honoraria	NA
Scientific advisory board	Takeda, Janssen, Celgene, Novartis, BMS, GSK, AbbVie, Pfizer
Board of directors	TG Therapeutics

NA, not applicable.

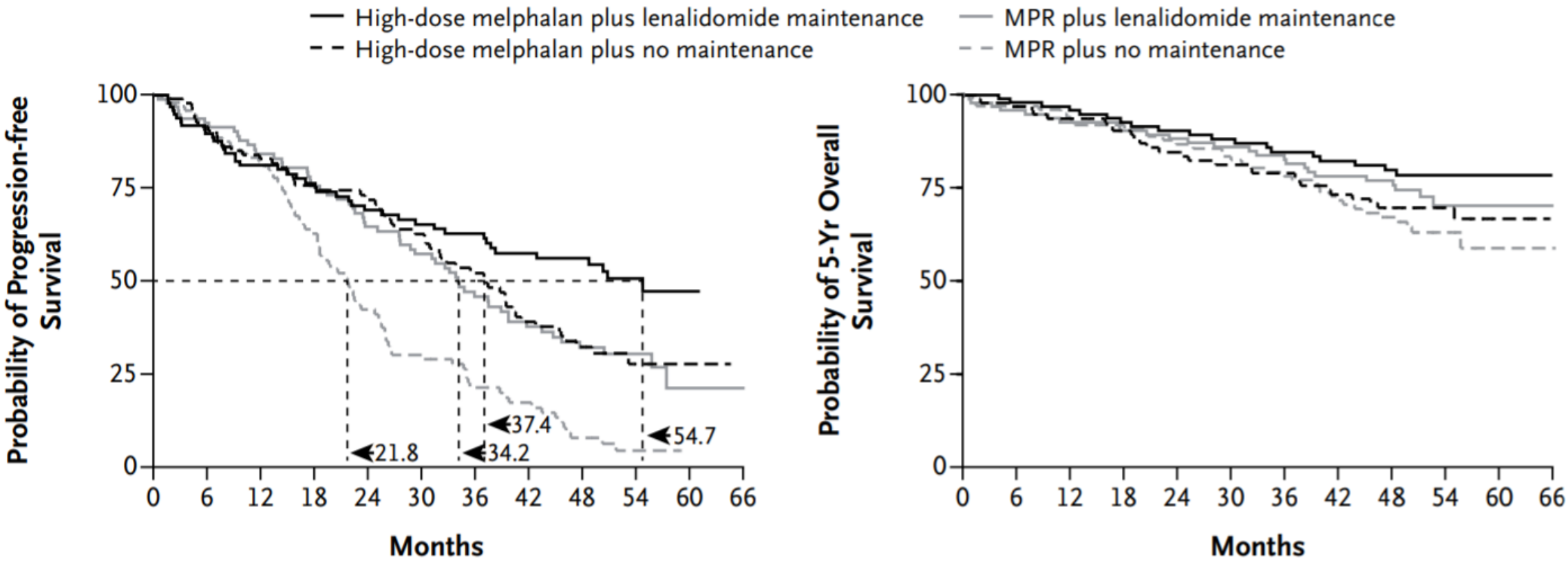
Experience from the RVD 1000 series: Transplant floats all boats



CI, confidence interval; No, number; OS, overall survival; PFS, progression-free survival; RVD, lenalidomide, bortezomib, dexamethasone.

Joseph NS, et al. *J Clin Oncol*. 2020;38(17):1928-1937.

Transplant in the era of novel agents



Median PFS from SWOG S0777 trial 40 months for RVD alone

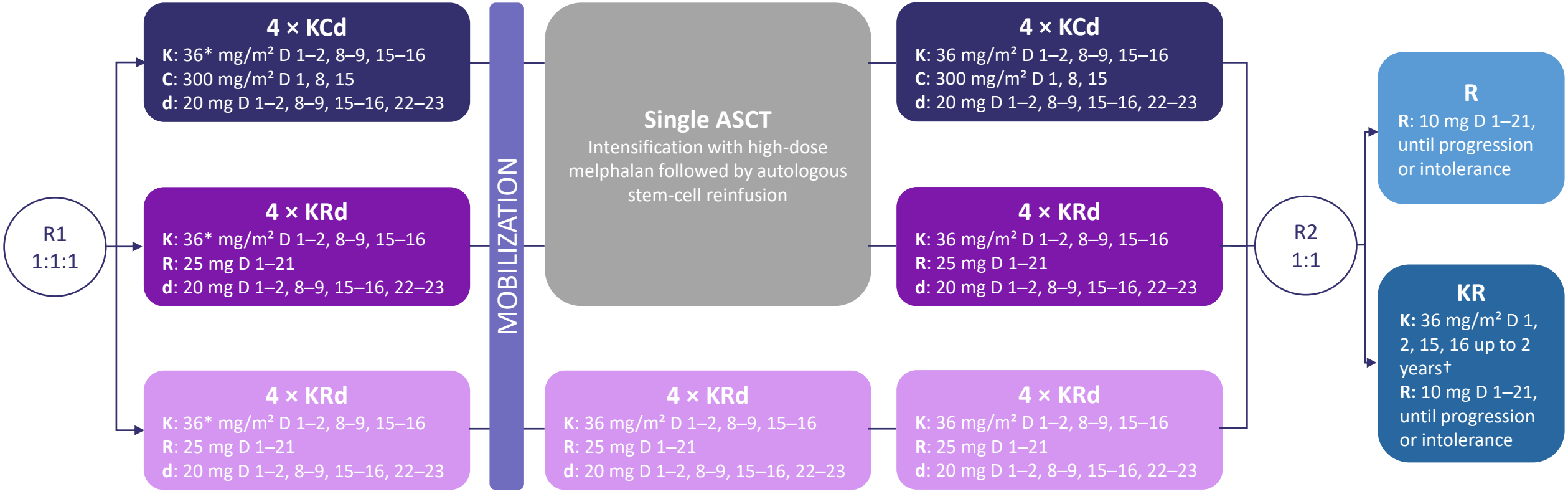
Median PFS from ENDURANCE trial (KRD vs RVD) 34 months

KRD, carfilzomib, lenalidomide, dexamethasone; MPR, melphalan, prednisone, lenalidomide; PFS, progression-free survival; RVD/VRD, lenalidomide, bortezomib, dexamethasone.

Palumbo A, et al. *N Engl J Med*. 2014;371(10):895-905. NCT00551928. NCT00644228. NCT01863550.

FORTE trial: Study design

- 474 NDMM patients, transplant-eligible and younger than 65 years



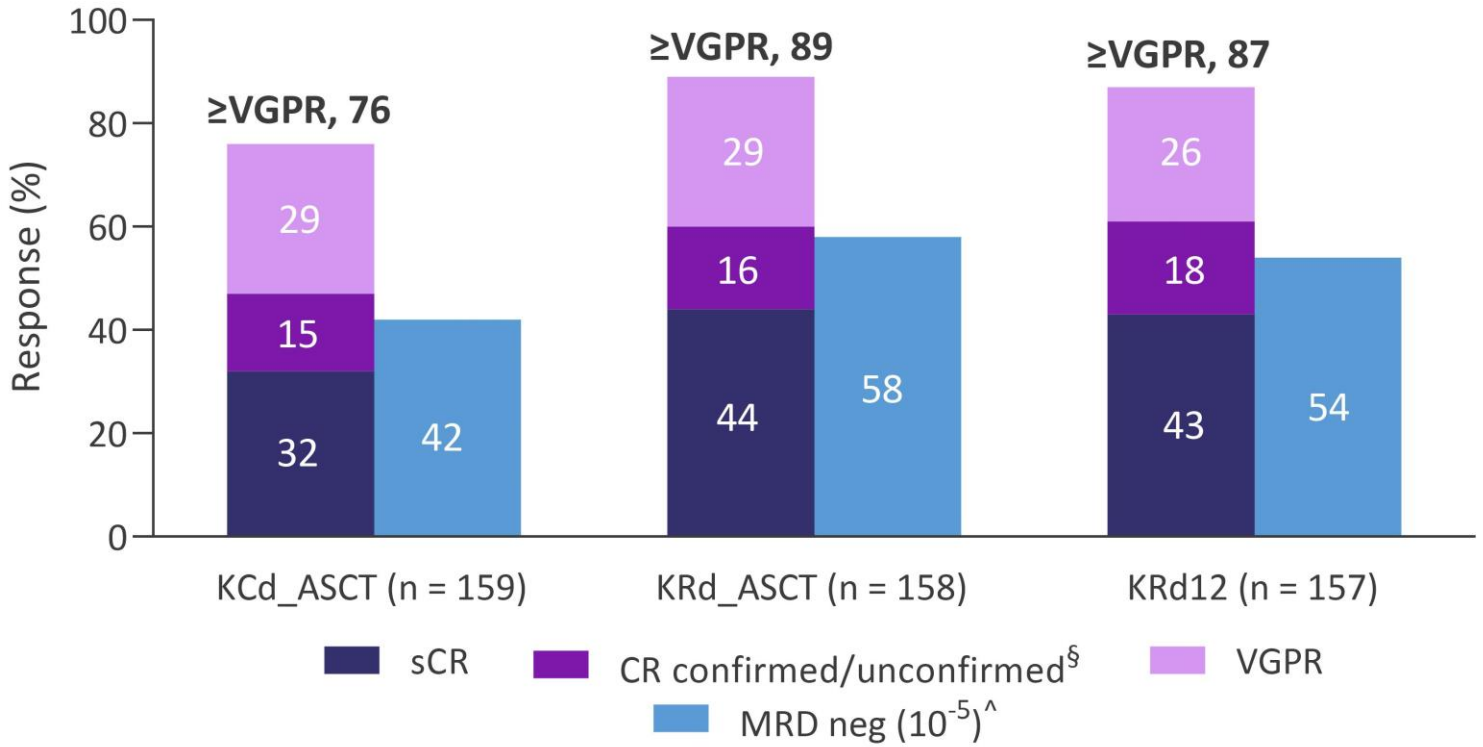
ASCT, autologous stem cell transplantation; C, cyclophosphamide; D, day; d, dexamethasone; K, carfilzomib; NDMM, newly diagnosed multiple myeloma; R, lenalidomide; R1, first randomization (induction/consolidation treatment); R2, second randomization (maintenance treatment).

*20 mg/m² on D 1–2, Cycle 1 only; †K 70 mg/m² D 1, 15, every 28 days up to 2 years for patients who have started the maintenance treatment from 6 months before the approval of Amendment 5.0 onwards.

Adapted from Gay F. Abstract #141. 62nd ASH Annual Meeting & Exposition; Dec 5, 2020; Virtual. NCT02203643.

KRd_ASCT *vs* KRd12 *vs* KCd_ASCT: Efficacy

Pre-maintenance response rate and MRD negativity ITT analysis.



	OR	*p* value*
≥VGPR		
KRd_ASCT *vs* KCd_ASCT	2.53	0.004
KRd12 *vs* KCd_ASCT	2.11	0.015
sCR		
KRd_ASCT *vs* KCd_ASCT	1.65	0.035
KRd12 *vs* KCd_ASCT	1.60	0.048
MRD neg (10^{-5})		
KRd_ASCT *vs* KCd_ASCT	2.02	0.009
KRd12 *vs* KCd_ASCT	1.73	0.042

ASCT, autologous stem cell transplantation; CR, complete response; C, cyclophosphamide; d, dexamethasone; FISH, fluorescence *in situ* hybridization; ISS, International Staging System; ITT, intent to treat; K, carfilzomib; KRd12, 12 cycles of KRd; LDH, lactate dehydrogenase; MRD neg, minimal residual disease negativity; OS, overall survival; R, lenalidomide; sCR; stringent complete response; sFLC, serum free light chain; VGPR, very good partial response; *vs*, versus.

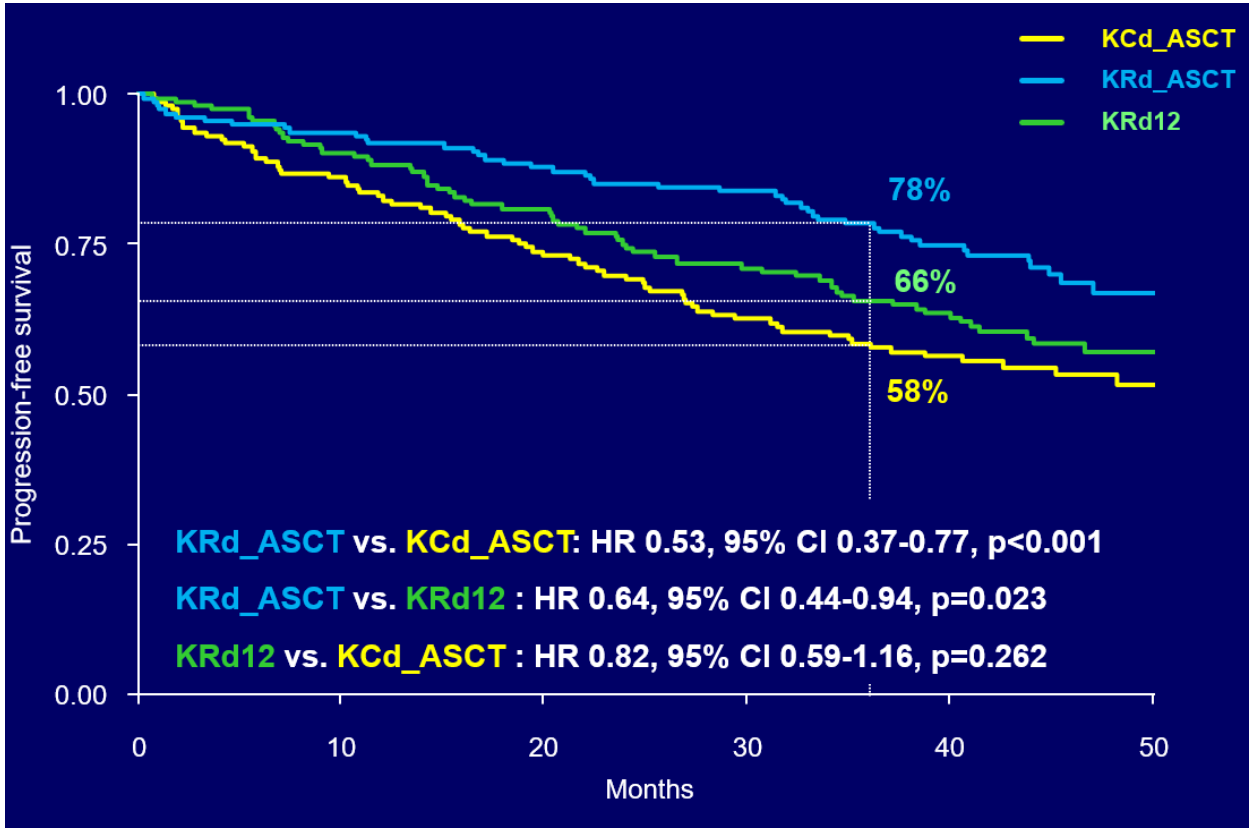
*Adjusted for ISS, age, FISH, LDH; §Unconfirmed CR/sCR: patient missing immunofixation/sFLC analysis needed to confirm CR/sCR (6% in KCd_ASCT; 8% in KRd_ASCT; 6% in KRd12); ^Patients whose samples were not available (~10%) were considered as positive.

Adapted from Gay F. Abstract #141. 62nd ASH Annual Meeting & Exposition; Dec 5, 2020; Virtual. NCT02203643.

Progression-free survival: R1

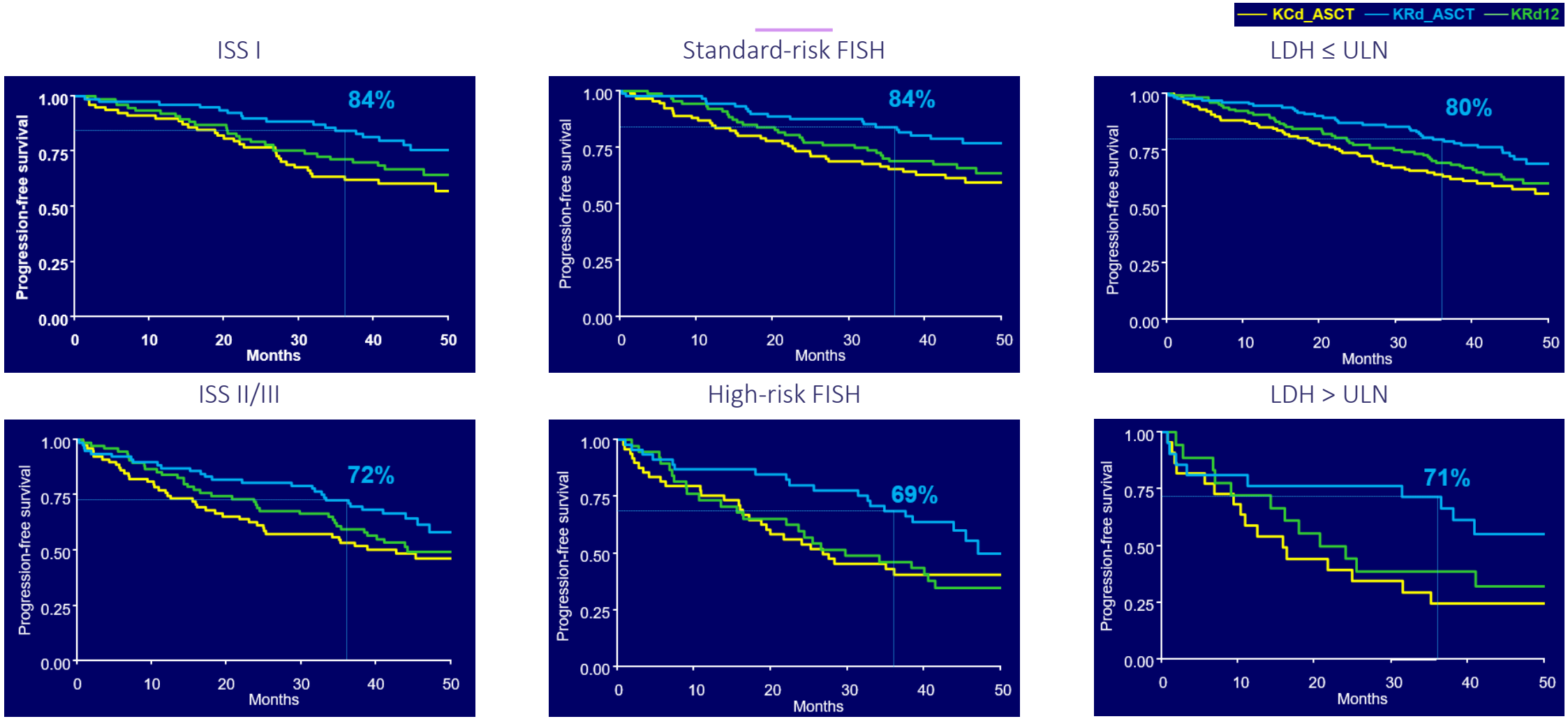
Median follow-up from R1: 45 months (40–49)

3-year PFS



ASCT, autologous stem cell transplantation; C, cyclophosphamide; CI, confidence interval; d, dexamethasone; HR, hazard ratio; K, carfilzomib; KRd12, 12 cycles of KRd; MFC, multiparameter flow cytometry; MRD, minimal residual disease; PFS, progression-free survival; R, lenalidomide; R1, first randomization; *vs*, versus.
Adapted from Gay F. Abstract #141. 62nd ASH Annual Meeting & Exposition; Dec 5, 2020; Virtual. NCT02203643.

3-year PFS: R1 subgroup analysis

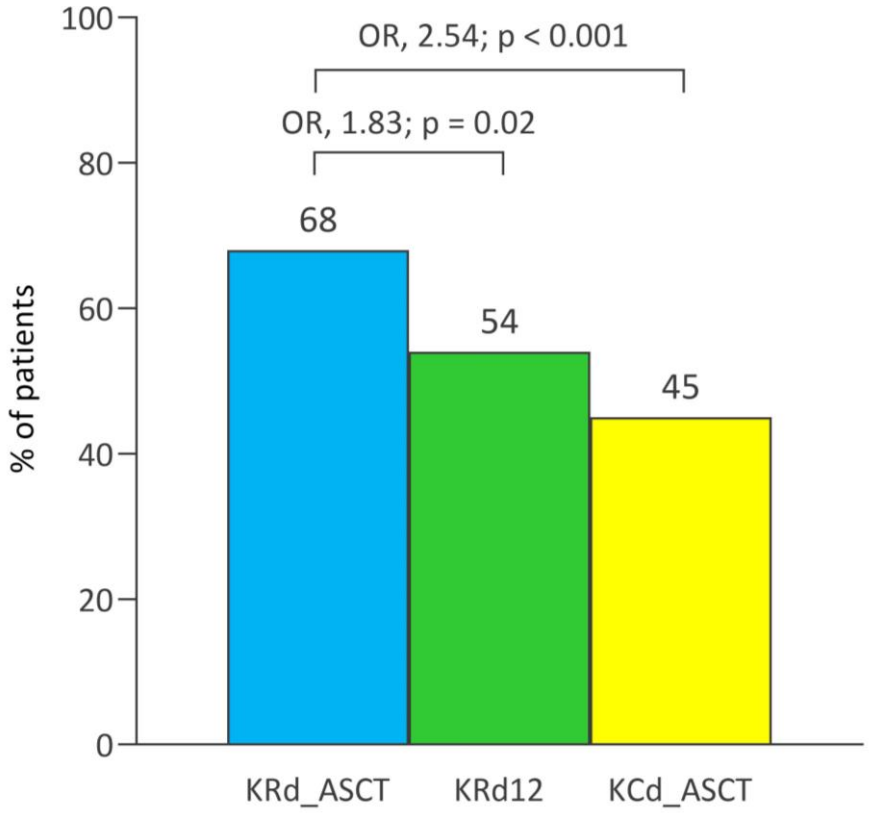


ASCT, autologous stem cell transplantation; C, cyclophosphamide; d, dexamethasone; FISH, fluorescence *in situ* hybridization; ISS, International Staging System; K, carfilzomib; KRd12, 12 cycles of KRd; LDH, lactate dehydrogenase; PFS, progression-free survival; R, lenalidomide; R1, first randomization; ULN, upper limit of normal; *vs*, versus.

Adapted from Gay F. Abstract #141. 62nd ASH Annual Meeting & Exposition; Dec 5, 2020; Virtual. NCT02203643.

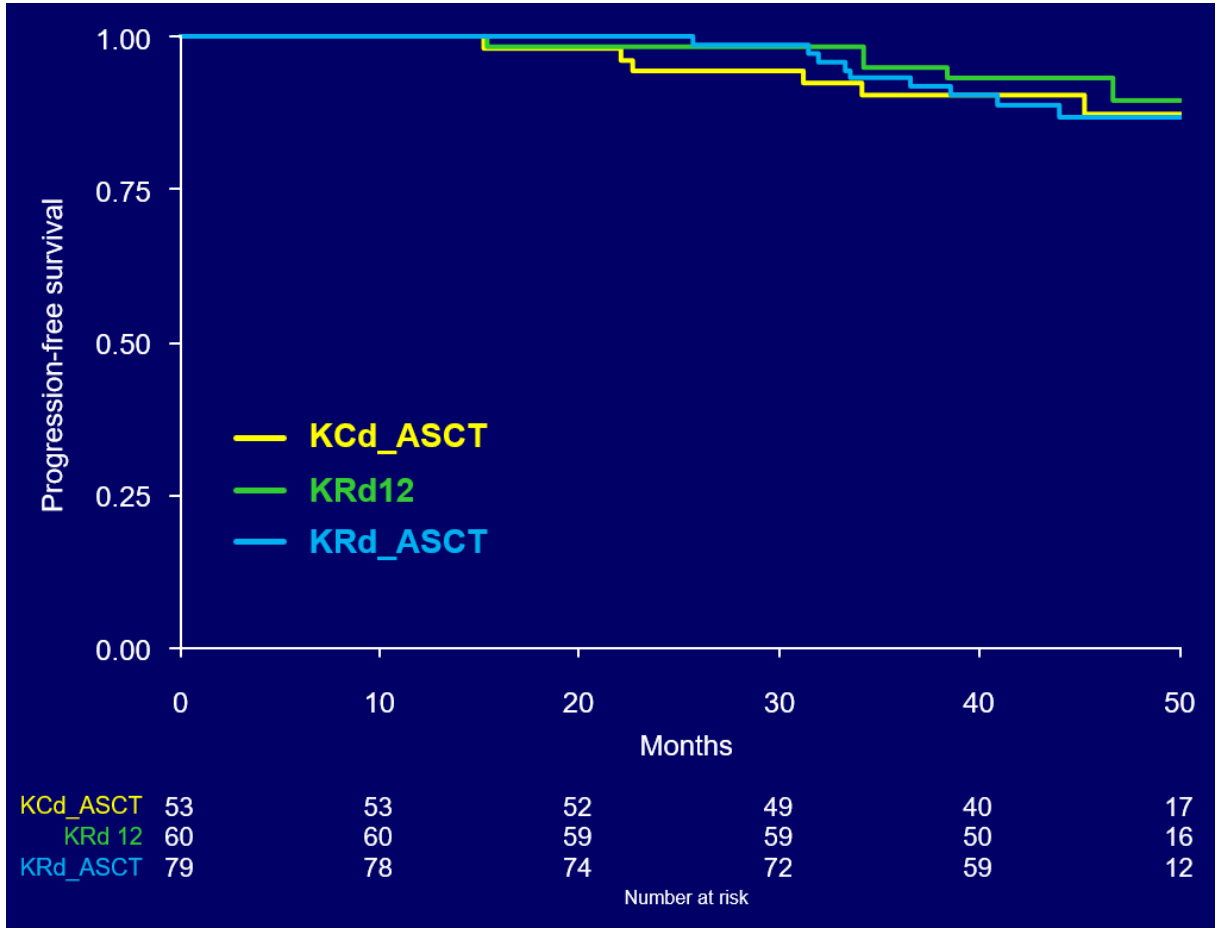
1-year sustained MRD negativity (MFC 10^{-5}) is what really matters

Rate of 1-year sustained MRD



High rate of 1-year sustained MRD neg with KRd_ASCT *vs* KRd12 and *vs* KCd_ASCT, but…

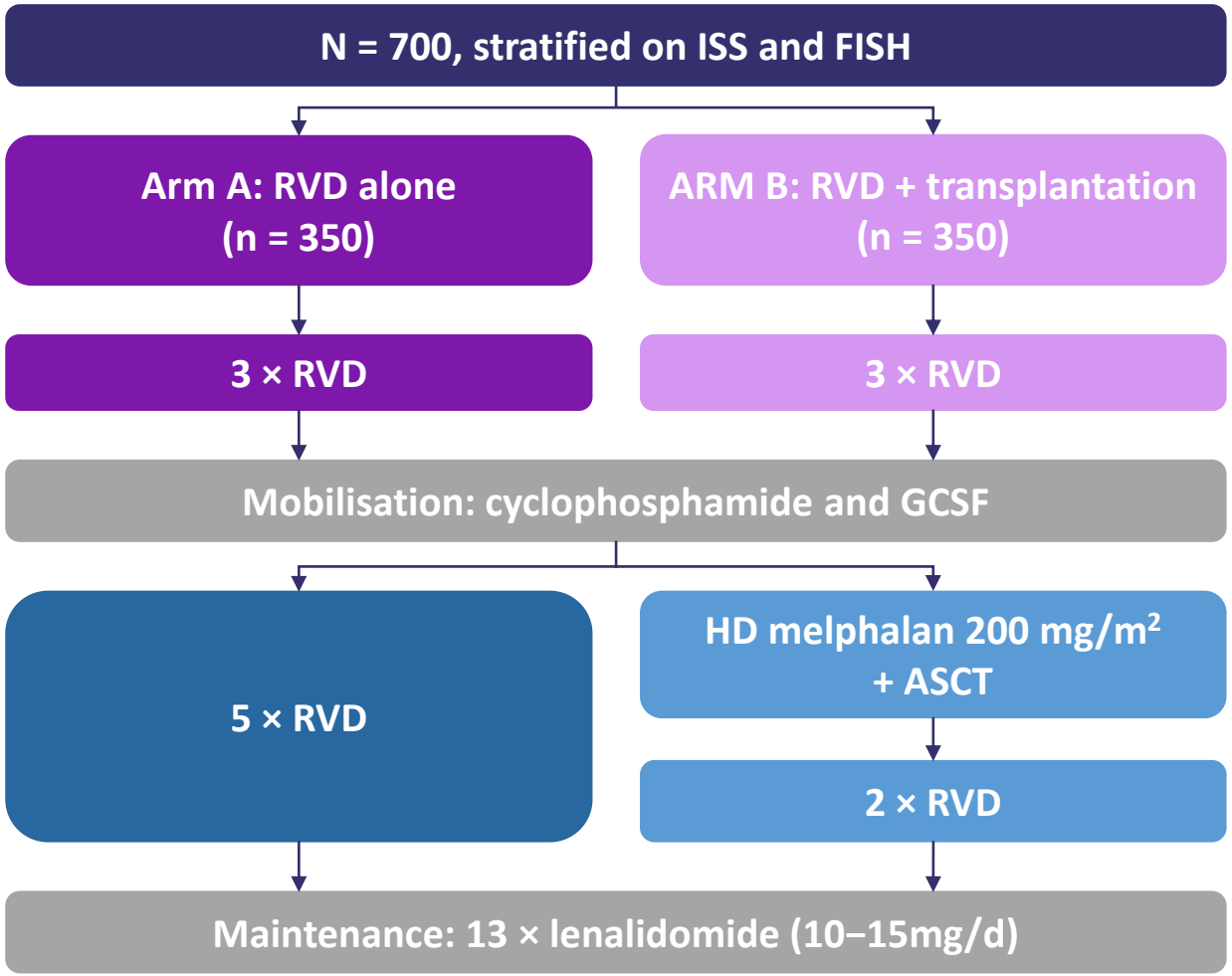
PFS of 1-year sustained MRD neg patients



ASCT, autologous stem cell transplantation; C, cyclophosphamide; d, dexamethasone; K, carfilzomib; KRd12, 12 cycles of KRd; MFD, multiparameter flow cytometry; MRD neg, minimal residual disease negative; OR, odds ratio; PFS, progression-free survival; R, lenalidomide; R1, first randomization; *vs*, versus.

Adapted from Gay F. Abstract #141. 62nd ASH Annual Meeting & Exposition; Dec 5, 2020; Virtual. NCT02203643.

IFM 2009 trial: Study design



RVD 21d cycles
R: 25 mg: d 1–14
V: 1.3 mg/m^2: d 1, 4, 8, 11
D: 20 mg: d 1, 2, 4, 5, 8, 9, 11, 12

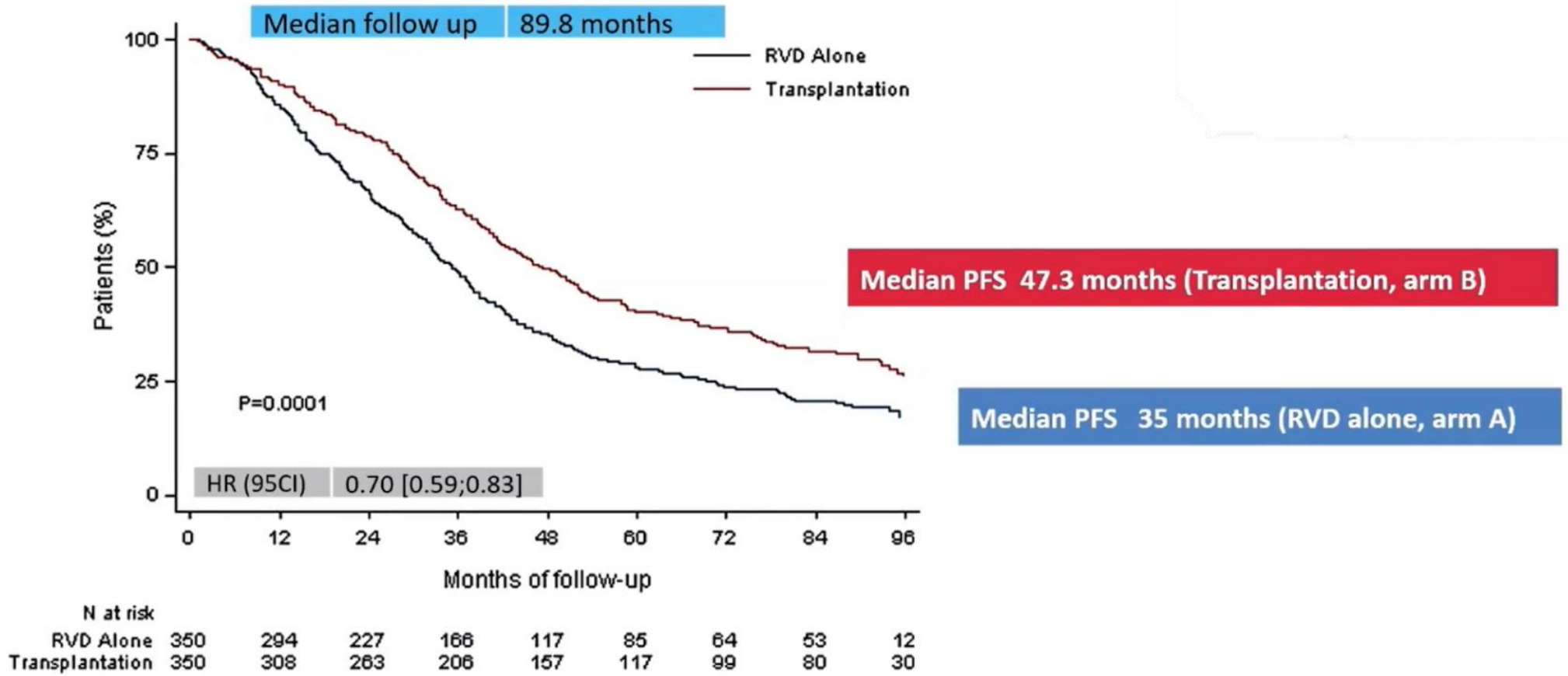
Primary endpoint:
- PFS

Secondary endpoints:
- ORR
- MRD
- TTP
- OS
- Toxicity

ASCT, autologous stem cell transplant; d, day; GCSF, granulocyte colony stimulating factor; HD, high-dose; MRD, minimal residual disease; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; RVD, lenalidomide, bortezomib, dexamethasone; TTP, time to progression.
Adapted from Attal M, et al. *N Engl J Med.* 2017;376(14):1311-1320. NCT01191060

IFM 2009: Updated PFS

30% reduction in the risk of progression or death in patients receiving transplant

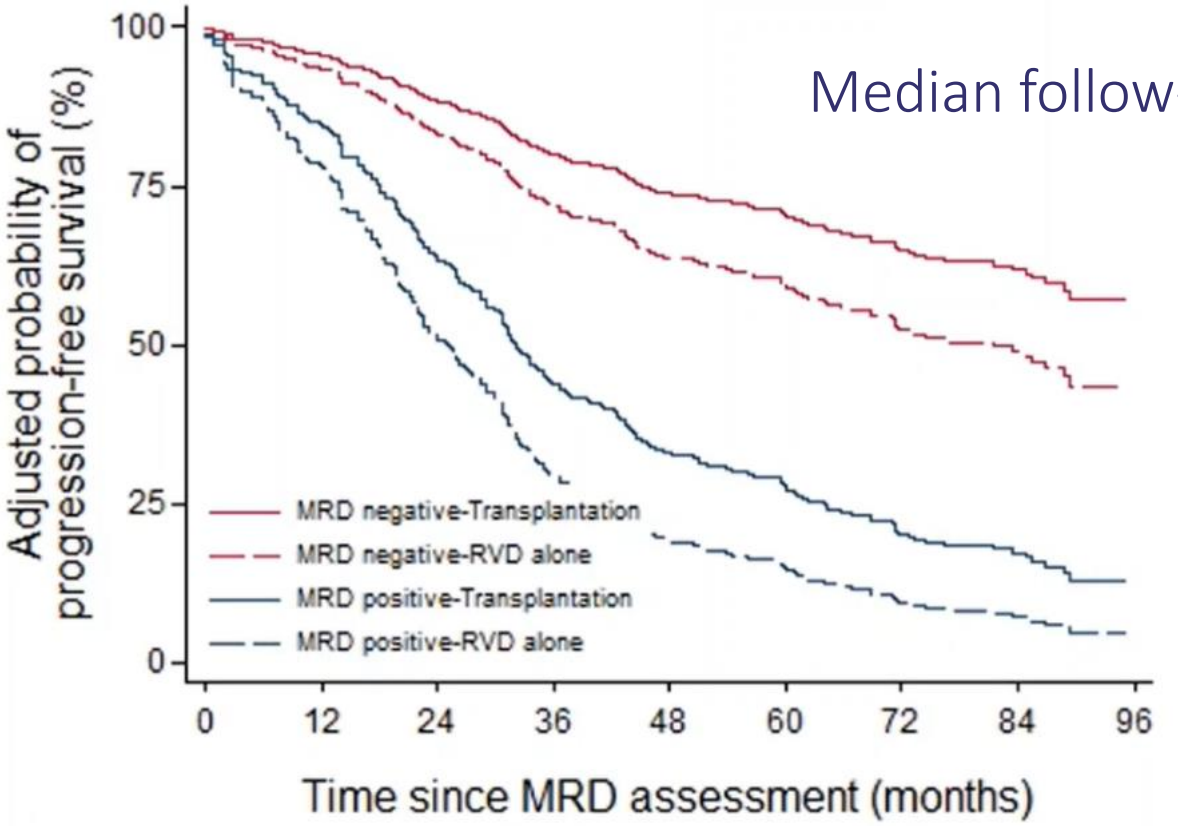


CI, confidence interval; HR, hazard ratio; N, number; PFS, progression-free survival; RVD, lenalidomide, bortezomib, dexamethasone.

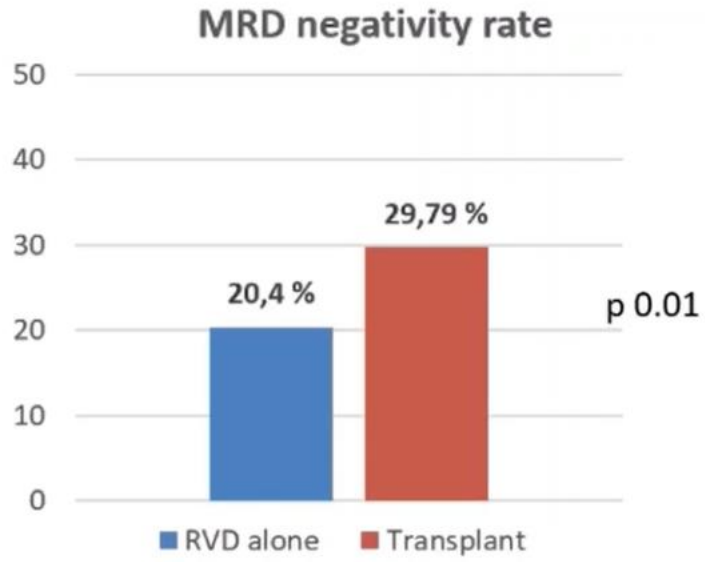
Perrot A. Abstract #143. 62nd ASH Annual Meeting & Exposition; Dec 5, 2020; Virtual. NCT03679351. NCT01191060.

Subgroup analysis: with a similar depth of response, PFS is longer with HDT

RVD + transplant is superior to RVD alone, even in patients who achieved undetectable MRD at 10^{-6}



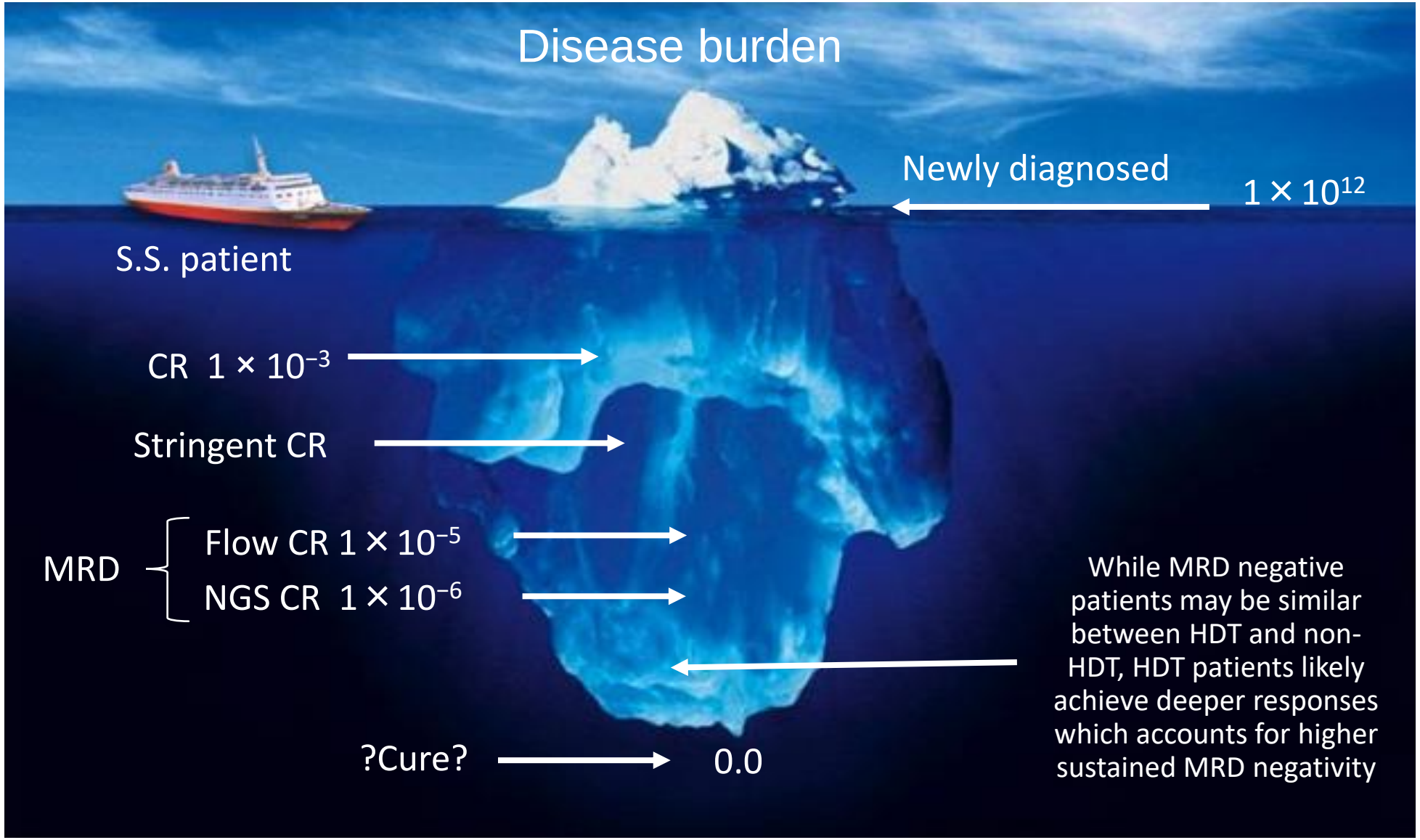
Median follow-up: 89.8 months



HDT, high dose therapy; MRD, minimal residual disease; PFS, progression-free survival; RVD, lenalidomide, bortezomib, dexamethasone.

Perrot A. Abstract #143. 62nd ASH Annual Meeting & Exposition; Dec 5, 2020; Virtual. NCT03679351. NCT01191060.

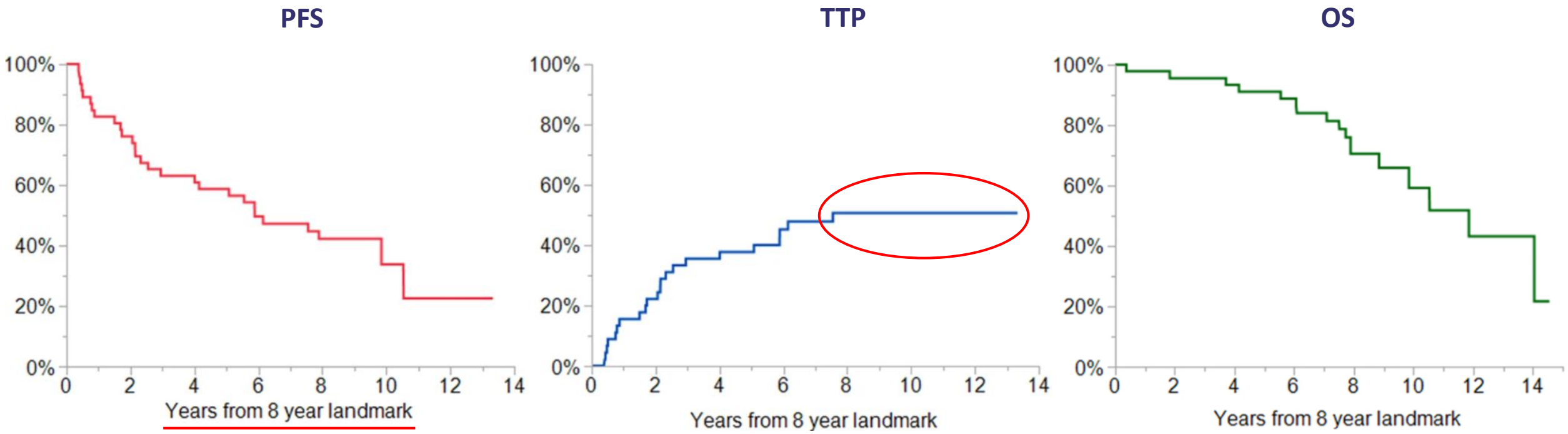
How does HDT improve PFS with similar ORR? Go to the iceberg



Landmark analysis of exceptional responders to ASCT (PFS > 8 years after diagnosis)

9% of patients treated with upfront ASCT within 12 months since diagnosis; no maintenance.

After a median follow-up 16.2 years: median PFS 13.8 years, median OS 19.9 years.



ASCT, autologous stem cell transplant; PFS, progression-free survival; OS, overall survival; TTP, time to progression.

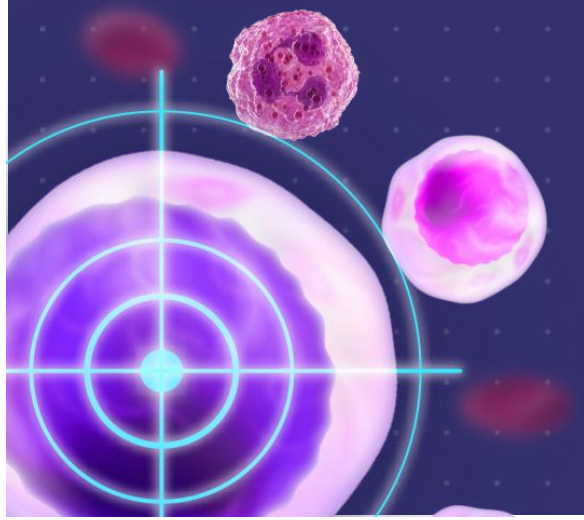
Paquin A, et al. *Blood Cancer J.* 2020;10(8):87.

On the horizon

- Improved PFS and sustained MRD continues with HDT even with new drugs
- The potential opportunity for CART to replace is dependent upon 2 factors:
  - Antigen needed for expansion
  - Evidence that PFS and persistence are longer in earlier relapse
- Simply replacing HDT is not the goal, if we are to remove it, the next treatment must be significantly better
- Understanding which patients do not benefit (small numbers currently) is an important and ongoing assessment

MultipleMyelomaHub

Thank you



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