Highlights from IMS 20th meeting 2023

Gabriele Buda

Ruolo del trapianto autologo nell'era delle terapie a quattro farmaci

30-31 gennaio 2024
BOLOGNA, Royal Hotel Carlton

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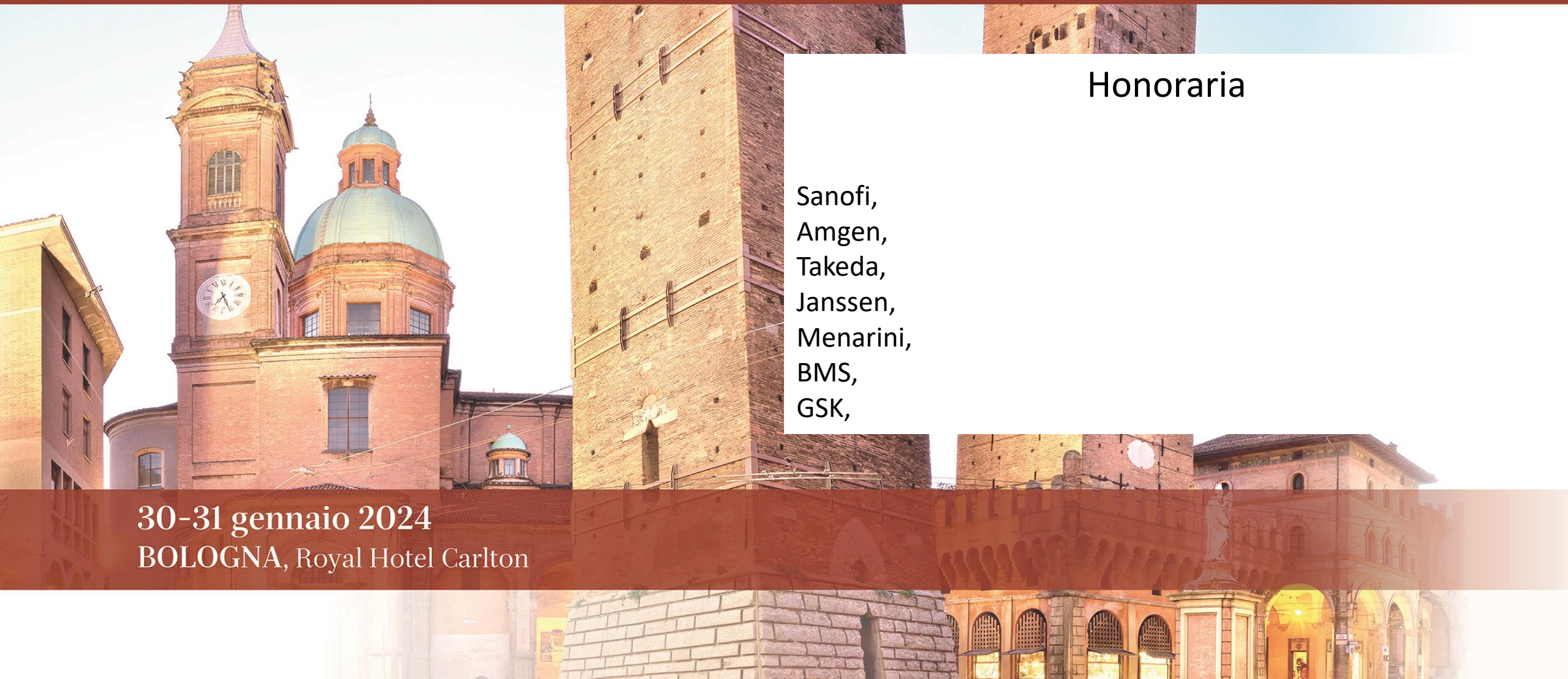


30-31 gennaio 2024
BOLOGNA, Royal Hotel Carlton

Honoraria

Sanofi,
Amgen,
Takeda,
Janssen,
Menarini,
BMS,
GSK,

Who needs an autologous stem cell transplant upfront?

Aurore PERROT
Toulouse, France

Who needs a transplant upfront?

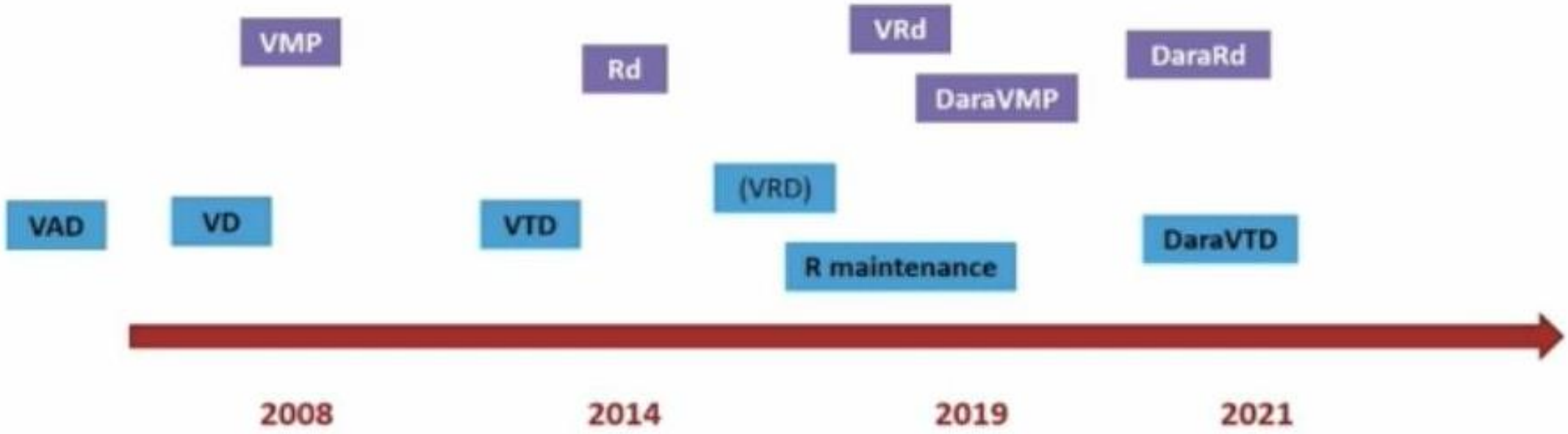
Transplant in myeloma

Who, when and why?

- For all **eligible patients, even beyong 65 years, even more if high-risk cytogenetics**
- As soon as possible **in frontline setting, after a quadruple induction and before consolidation / maintenance**
- Because **transplant is the best way to cure for now (waiting the battle with CAR T..)**

New chapters at each new drug approval

Developments in first-line treatments over the past 20 years



Despite attempts to put away…

Efficacy of triplet regimens led to the question of whether transplant is worthwhile

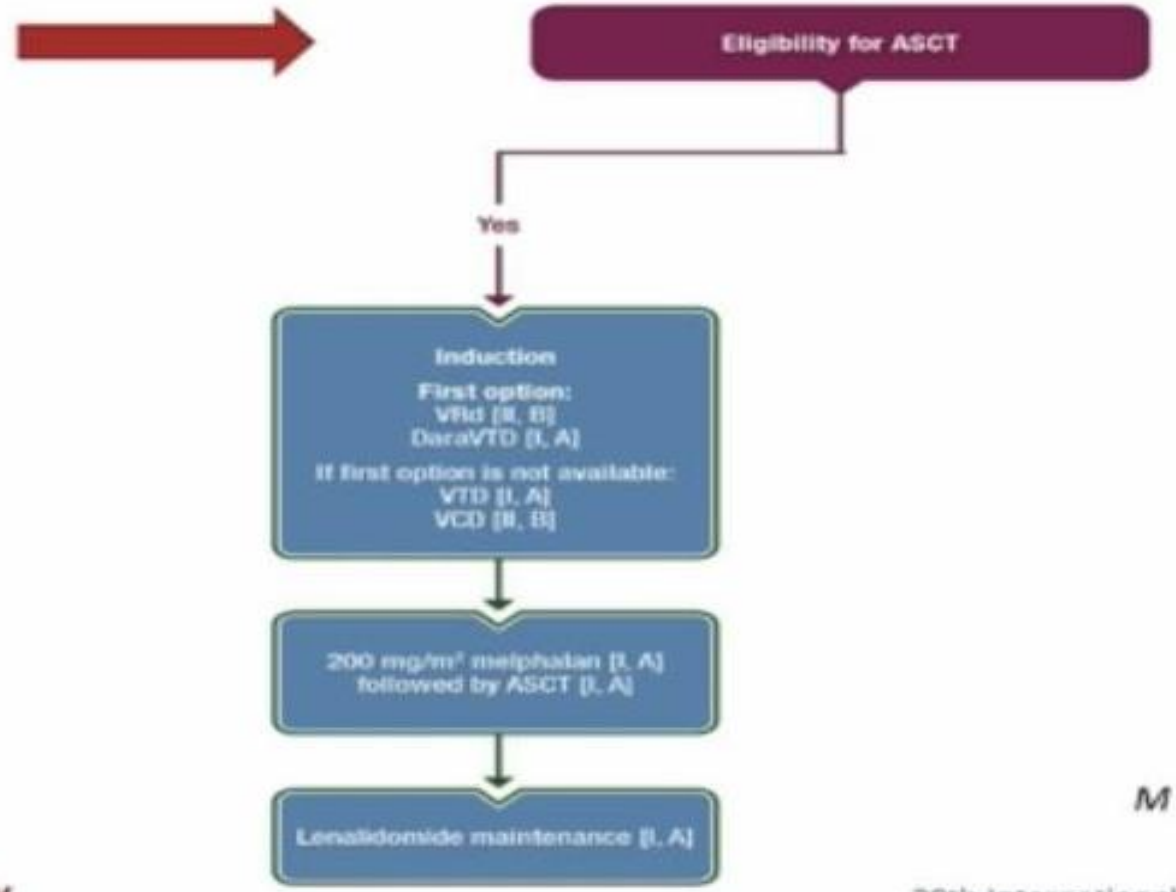
EMN02
VCD + VMP vs VCD + transplant

IFM 2009 / DFCI DETERMINATION
RVD vs RVD + transplant

FORTE
KRD vs KRD + transplant

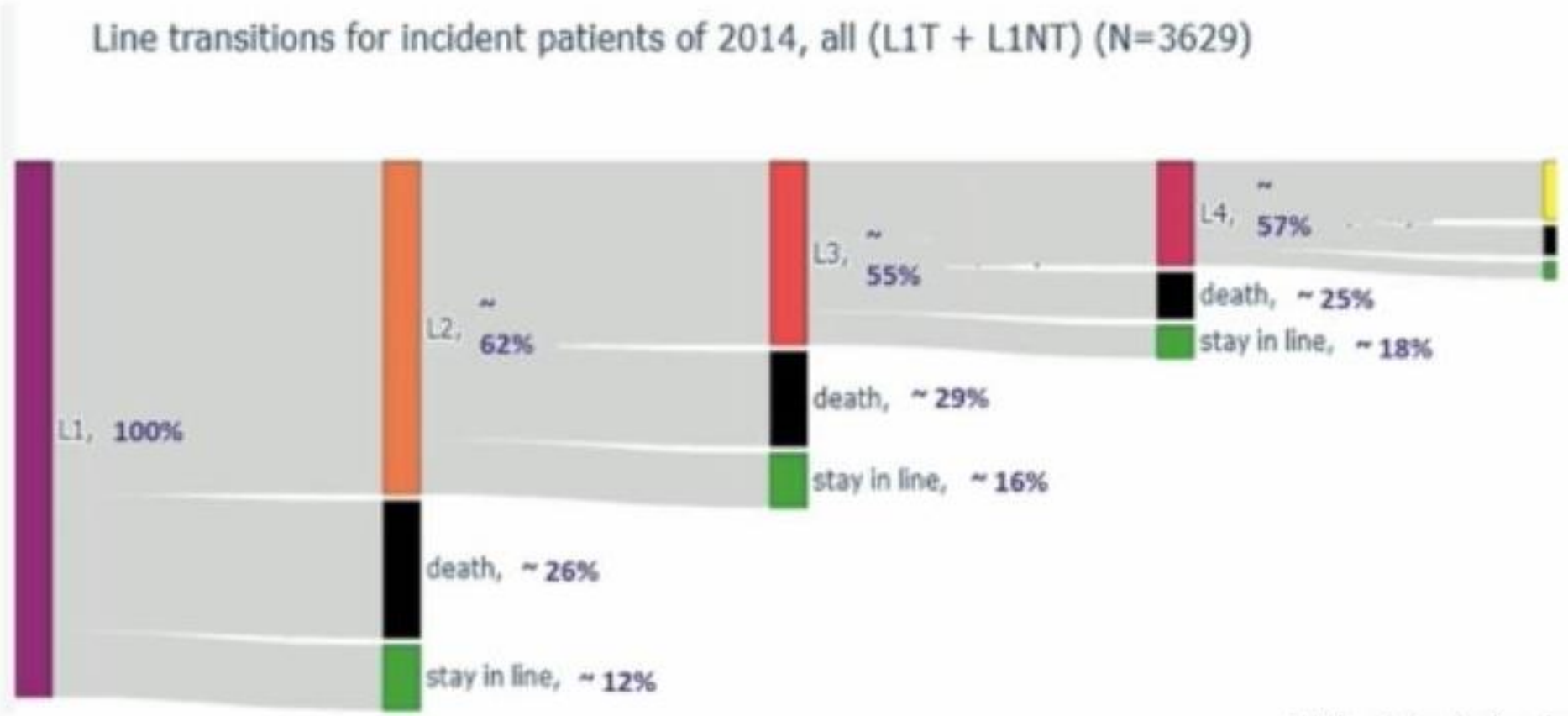
M Cavo et al, Lancet Hematol 2020,
M Attal et al, N Engl J Med 2007, P Richardson et al, N Engl J Med 2022
F Gay et al, Lancet Oncol 2021

...transplant is still standing



M Dimopoulos et al, Hemasphere 2021

The rule: use the best option at each step



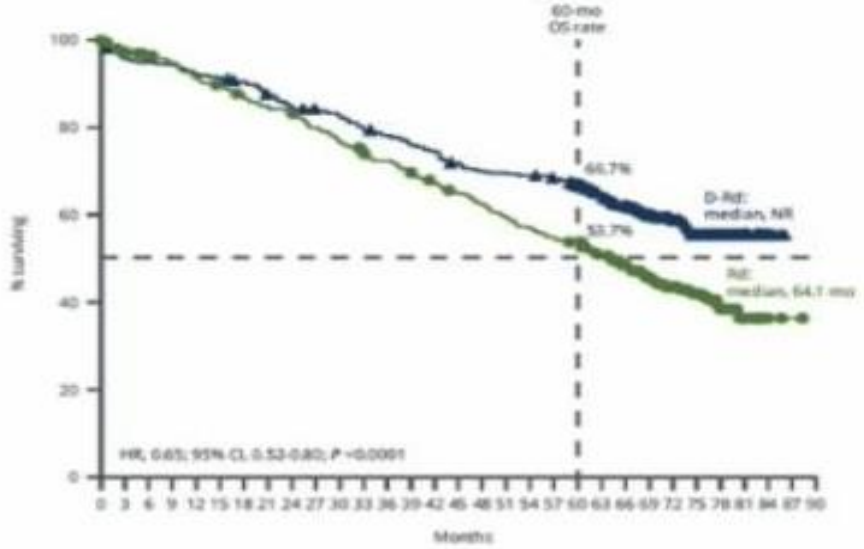
Mylord study (update unpublished)

1) Which age group needs a transplant at diagnosis?

Any NDMM patient with life expectancy > expected OS with non-transplant strategies

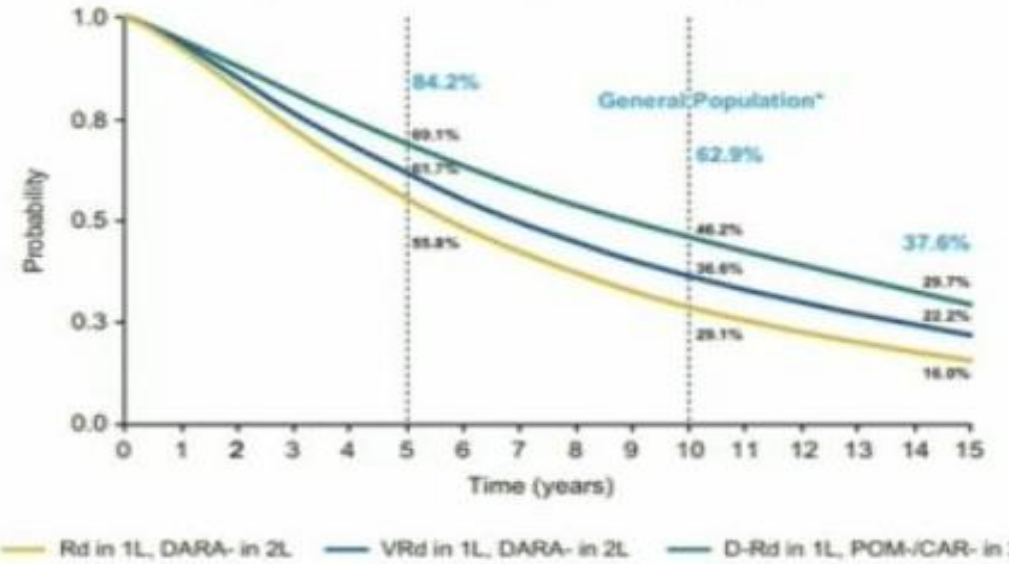
MAIA trial

FIGURE 2: OS with D-Rd and Rd in the ITT population*



S Kumar et al, ASH 2022

Simulation of OS
(based on subsequent therapies & attrition)



R Fonseca et al, Oncologist 2023

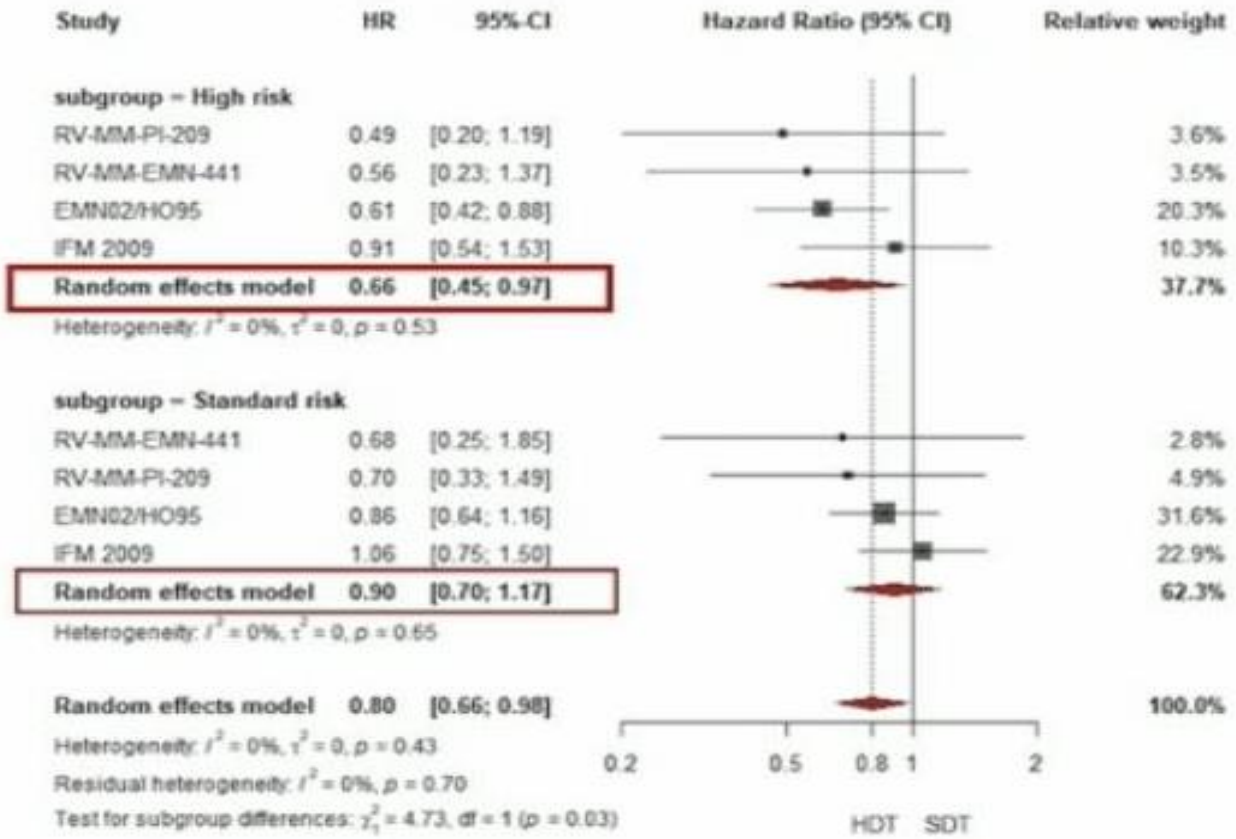
2) Which cytogenetics needs a transplant at diagnosis?

STANDARD RISK?

Meta-analysis
6 RCT, 4 with OS/cytogenetics data

2959 patients
Transplant vs standard regimens

OS benefit
- **High risk HR 0.66**
- Standard risk HR 0.90



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R Chakraborty et al, Cancer 2022

2) Which cytogenetics needs a transplant at diagnosis?

HIGH RISK +++

HR patients really need at least one transplant

Experiences from FORTE and MASTER trials suggested they need more
In order to sustain MRD negativity

G Gay et al, ASCO 2019 - LJ Costa et al, J Clin Oncol 2021

2) Which cytogenetics needs a transplant at diagnosis?

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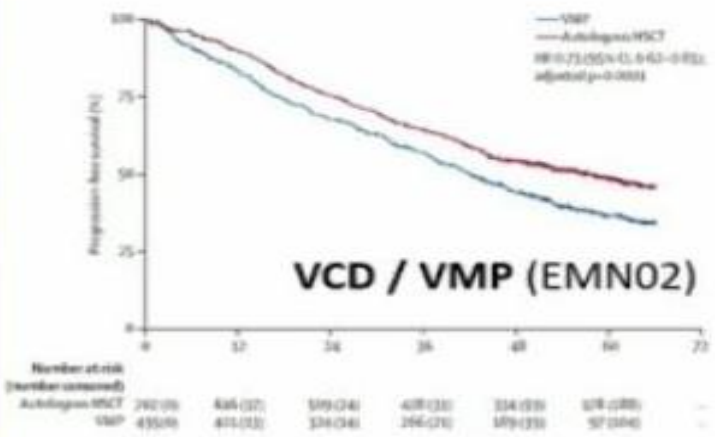
G Gay et al, ASCO 2019 - LJ Costa et al, J Clin Oncol 2021

OA-43: Analysis of sustained MRD-negativity and Progression-free Survival of Isa-KRd in High-Risk Newly Diagnosed Multiple Myeloma – Additional Data from Planned Interim Analysis of the GMMG-CONCEPT Trial	Lisa Leypoldt
OA-54: Daratumumab, Carfilzomib, Lenalidomide, and Dexamethasone with tandem transplant in high-risk newly diagnosed myeloma patients: final results of the phase 2 study IFM 2018-04	Cyrille Touzeau

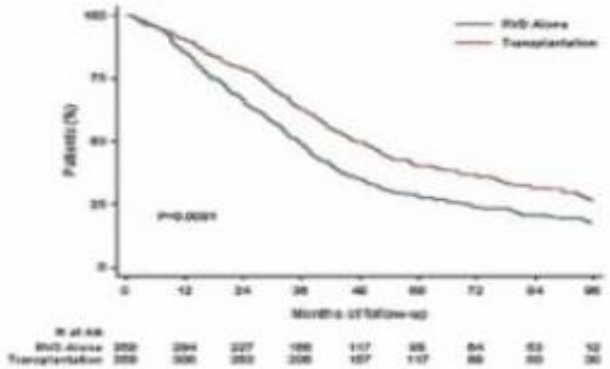
3) Which induction can avoid transplant?

No triplet

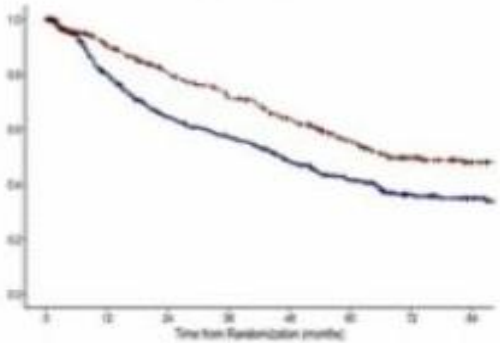


VCD / VMP (EMN02)

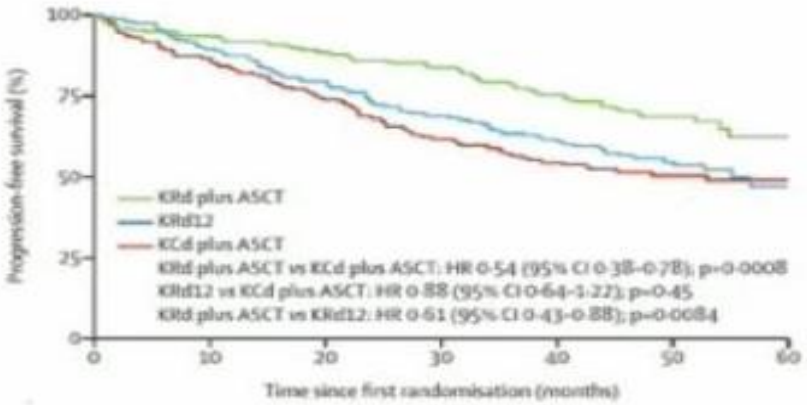
M Cavo et al, Lancet Hematol 2020



RVD (IFM2009, DETERMINATION)



M Attal et al, N Engl J Med 2007
P Richardson et al, N Engl J Med 2022

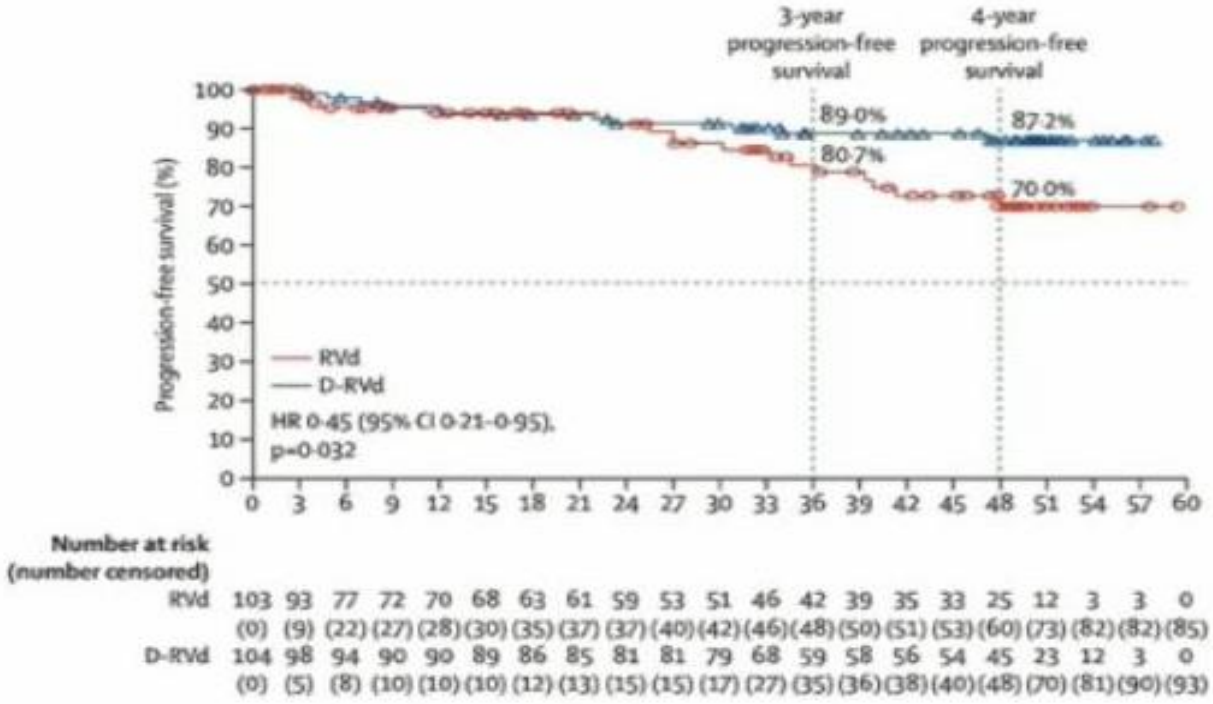


KRD (FORTE)

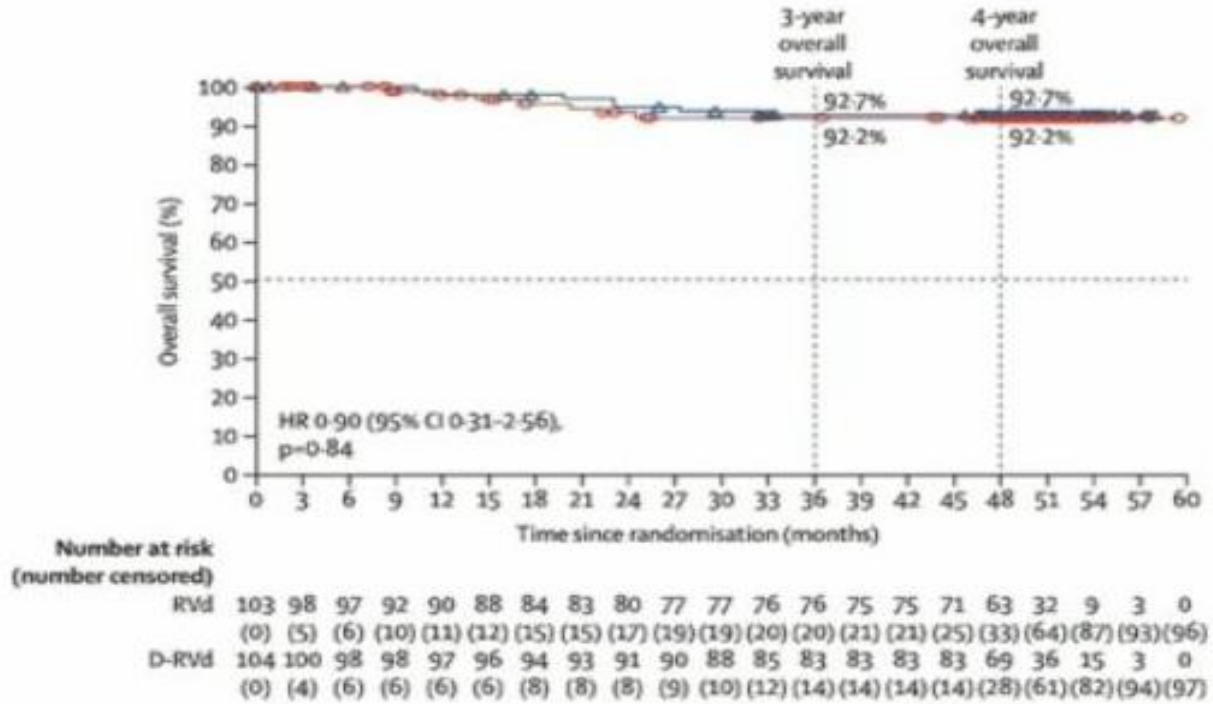
F Gay et al, Lancet Oncol 2021

3) Which induction can avoid transplant?

Quadruplets?



After CASSIOPEIA, GRIFFIN....



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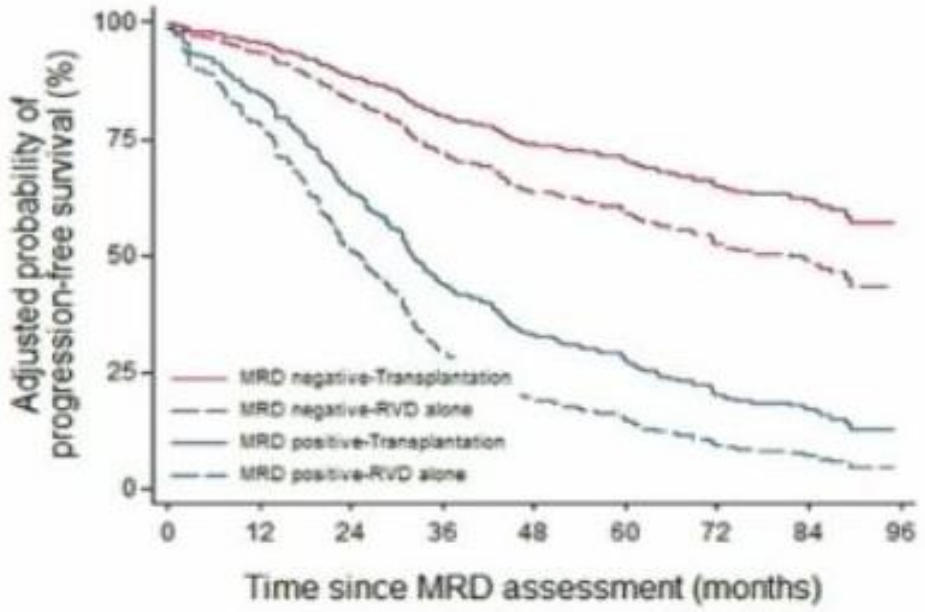
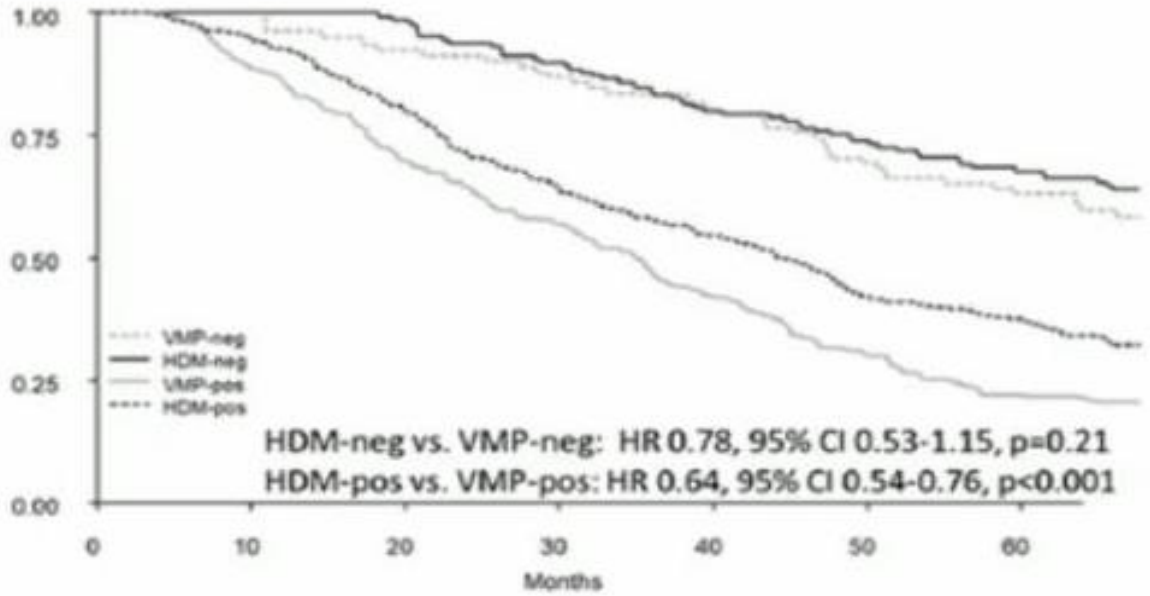
PM Voorhees et al, Lancet Haematol 2023

4) Which response depth avoid transplant?

Do patients in excellent response (MRD < 10^{-6}) need a transplant?

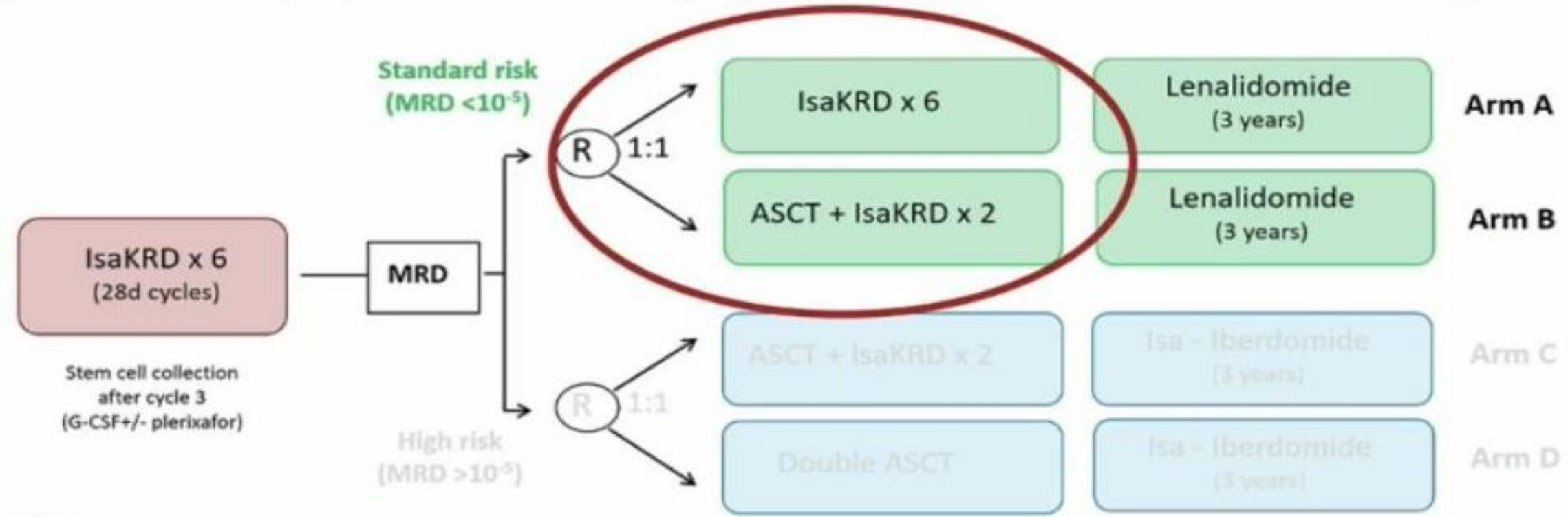


A Perrot et al, Blood 2018



S Oliva et al, B Cancer J 2021

4) Which response depth avoid transplant?



Analysis of Sustained MRD-Negativity and Progression-Free Survival of Isa-KRd in High-Risk Newly Diagnosed Multiple Myeloma – Additional Data From Planned Interim Analysis of the GMMG-CONCEPT Trial

Lisa B. Leypoldt, Diana Tichy, Britta Besemer, Mathias Hänel, Marc S. Raab, Christoph Mann, Markus Munder, Hans Christian Reinhardt, Axel Nogai, Martin Görner, Yon-Dschun Ko, Maike de Wit, Hans Salwender, Christof Scheid, Ullrich Graeven, Rudolf Peceny, Peter Staib, Annette Dieing, Hermann Einsele, Anna Jauch, Manola Zago, Axel Benner, Carsten Bokemeyer, Hartmut Goldschmidt, Katja C. Weisel

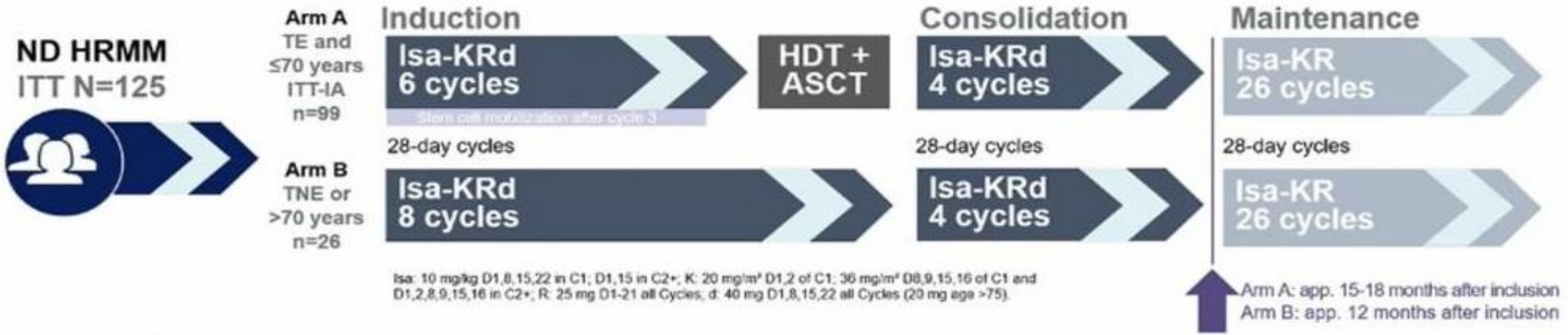
Background

- Patients with HRMM continue to show significantly poorer survival outcomes than patients without HR disease,[1-4] even in the current era of novel agents
- To date, achievement of MRD negativity is the strongest predictor of outcome[5-9]
- The phase II, investigator-initiated GMMG-CONCEPT trial (NCT03104842) is investigating the MRD negativity rate in patients with HR NDMM treated with Isa-KRd, with or without subsequent ASCT, according to age and eligibility for transplant
- We previously reported results on the primary endpoint (MRD negativity) after consolidation of the first cohort, demonstrating an MRD negativity rate of 67.7% for TE and 54.2% for TNE patients with rates of ≥VGPR of 90.9% (TE) and 88.5% (TNE) as best response[10]
- **Here, we report additional analyses of the primary endpoint with regard to survival, sustained MRD negativity, and subgroups**

ASCT, autologous stem cell transplant; HR, high-risk; HRMM, high-risk multiple myeloma; MRD, minimal residual disease; NDMM, newly diagnosed multiple myeloma; TE, transplant-eligible; TNE, transplant-noneligible; VGPR, very good partial response

1. Chaulpin T, et al. *Br J Haematol*. 2021;194:635–638; 2. Schmidt TM, et al. *Blood Cancer J*. 2021;11:83; 3. D'Agostino, et al. *J Clin Oncol*. 2022;40:3406–3418; 4. Sonneveld P, et al. *Blood*. 2016;127:2955–2962;
5. Cavo M, et al. *Blood*. 2022;139:835–844; 6. Munshi NC, et al. *Blood Adv*. 2020;4:5988–5999; 7. Golcoechea I, et al. *Blood*. 2021; 137:49–60; 8. San-Miguel J, et al. *Blood*. 2022;139:492–501; 9. Avet-Loiseau H, et al. *Clin Lymphoma Myeloma Leuk*. 2020;20:e30–e37;
10. Wetsel K, et al. Blood 2022;140:1836–1838.

Study Design

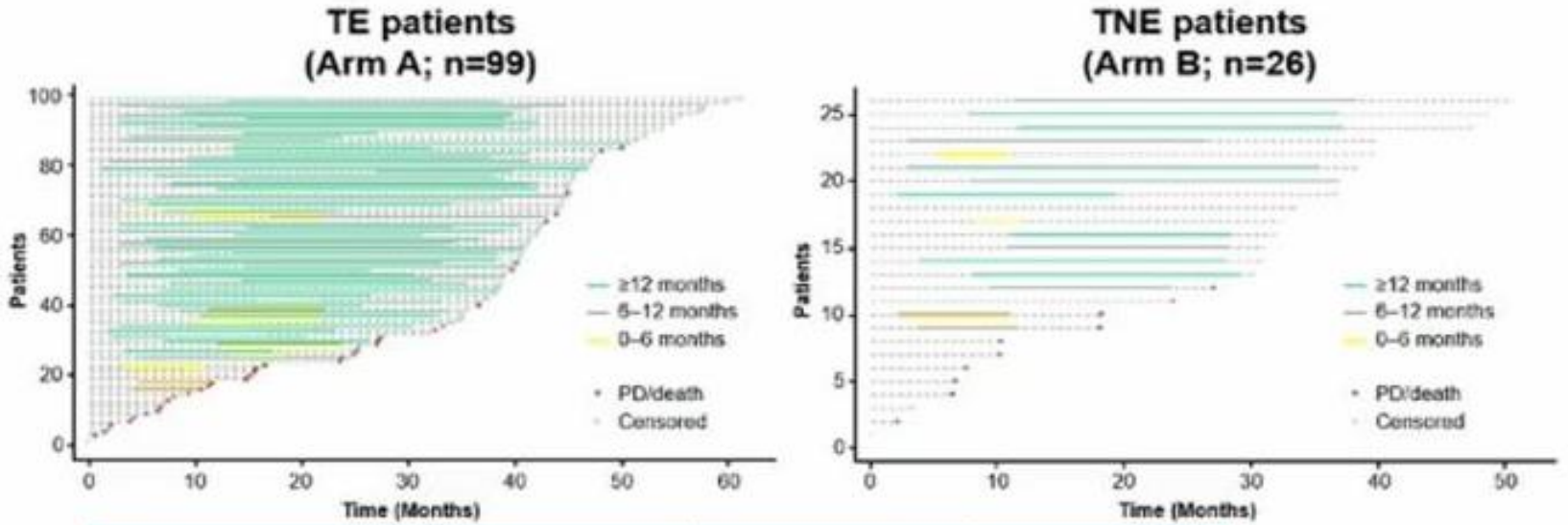


HRMM criteria: ISS stage II or III **PLUS** ≥1 of: del(17p), t(4;14), t(14;16) and/or >3 copies 1q21 (amp1q21)
Primary objective: MRD negativity after consolidation (NGF, 10^{-5})
Secondary objective: PFS; Key tertiary objectives: ORR, OS, safety

ASCT, autologous stem-cell transplant; d, dexamethasone; HDT, high-dose therapy; HRMM, high-risk multiple myeloma; Isa, isatuximab; ISS, International Staging System; K, carfilzomib; MRD, minimal residual disease; ND, newly-diagnosed; NGF, next-generation flow; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; R, lenalidomide; TE, transplant-eligible; TNE, transplant-ineligible.

High Rates of Sustained MRD Negativity

- 81.8% of TE and 69.2% of TNE patients achieved MRD negativity at any timepoint
- ≥1-year sustained MRD negativity was achieved in 62.6% of TE and 46.2% of TNE patients



n (%)	TE patients (n=99)	TNE patients (n=26)
MRD negative (any time point)	81 (81.8%)	18 (69.2%)
Sustained MRD negativity for ≥6 months	72 (72.7%)	14 (53.8%)
Sustained MRD negativity for ≥12 months	62 (62.6%)	12 (46.2%)

MRD, minimal residual disease; NE, not evaluable; PD, progressive disease; TE, transplant-eligible; TNE, transplant-noneligible

Daratumumab Carfilzomib Lenalidomide and Dexamethasone induction and consolidation with tandem transplant in high-risk newly diagnosed myeloma patients: results of the phase 2 study IFM 2018-04

Cyrille Touzeau[1], Aurore Perrot[2], Cyrille Hulin[3], Salomon Manier[4], Margaret Macro[5], Marie-Lorraine Chretien[6], Lionel Karlin[7], Martine Escoffre[8], Caroline Jacquet[9], Mourad Tiab[10], Xavier Leleu[11], Jill Corre[2], Alexandra Jobert[12], Lucie Planche[12], Hervé Avet-Loiseau[2], Philippe Moreau[1]

[1] Service d'hématologie, CHU Hotel Dieu, Nantes, France. [2] CHU de Toulouse, IUCT-O, Université de Toulouse, UPS, Service d'Hématologie, Toulouse, France. [3] Service d'hématologie, Hôpital Haut-Lévêque, CHU de Bordeaux, Pessac, France. [4] Maladies du Sang, CHRU de Lille, France. [5] Service d'hématologie, CHU Caen, France. [6] Hématologie Clinique, CHU Dijon Bourgogne, France. [7] Hôpital Lyon Sud, Pierre-benite, France. [8] Service d'hématologie, CHU de Rennes, France. [9] Service d'hématologie, CHU Nancy, Vandoeuvre-lès-Nancy, France. [10] Service d'hématologie, Centre Hospitalier Departemental, La Roche sur Yon, France. [11] Service d'hématologie, CHU de Poitiers, France. [12] Département de recherche clinique, CHU Hotel Dieu, Nantes, France.

2018-04 study design

Key inclusion criteria:

- Age < 66
- **Newly diagnosed multiple myeloma**
- **Transplant-eligible**
- **High-risk FISH :** t(4;14), 17p Del, t(14;16)
- ECOG 0-2

Objectives:

- **Primary Objective :** Feasability
  primary endpoint : >70% patients receiving 2nd transplant
- **Secondary Objectives:** Safety, ORR, PFS, OS, stem-cell collection

Induction Dara-KRd x 6	Stem cell collection	ASCT#1	Consolidation Dara KRd x 4	ASCT#2	Maintenance Dara Len 2 years
Dara : 16 mg/kg IV D1,8,15,22 (cycle 1 and 2) D1 D15 (Cycle 3 to 6) **K : (20)36 mg/m2 IV** D1-2, 8-9, 15-16 **Len : 25 mg** D1-21 **Dex : 20 mg** D1-2, 8-9, 15-16, 22-23 **28-day cycle**	Cyclo GCSF +/- Plerix	**Mel 200**	**Dara : 16 mg/kg IV** D1 D15 **K : 56 mg/m2 IV** D1, 8, 15 **Len : 15 mg** D1-21 **Dex : 40 mg** D1, 8, 15, 22 **28-day cycle**	**Mel 200**	**Dara :** 16 mg/kg IV every 8 weeks **Len :** 10 mg 21/28

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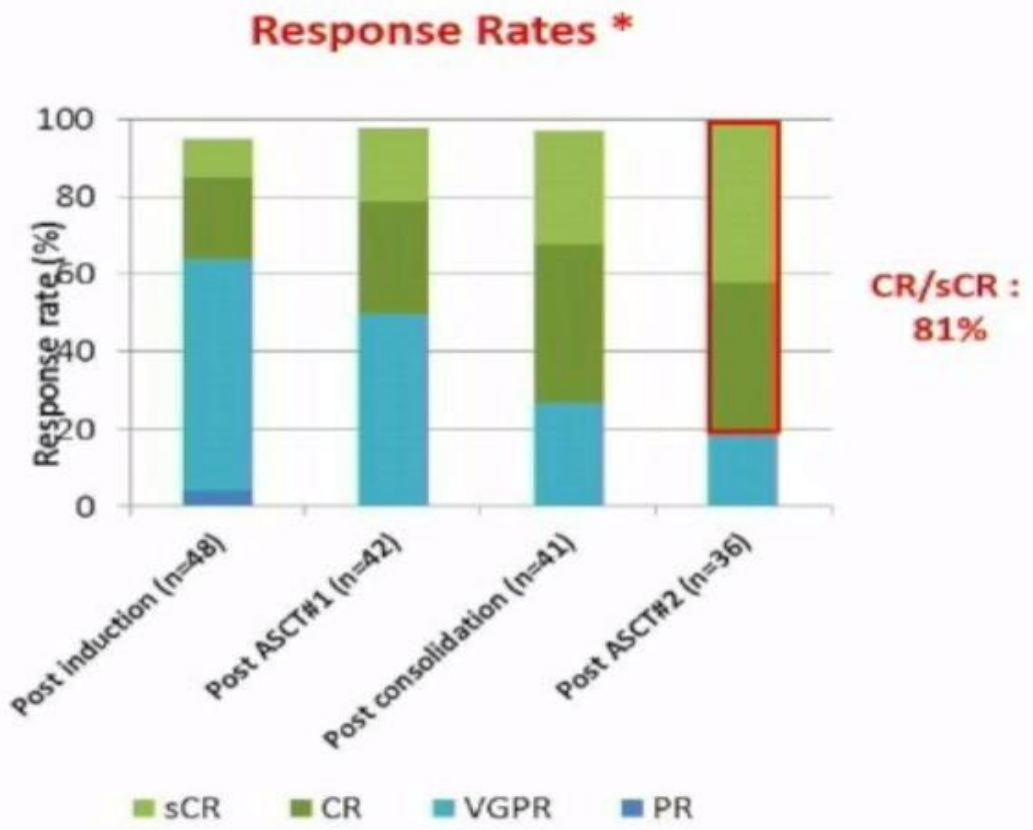
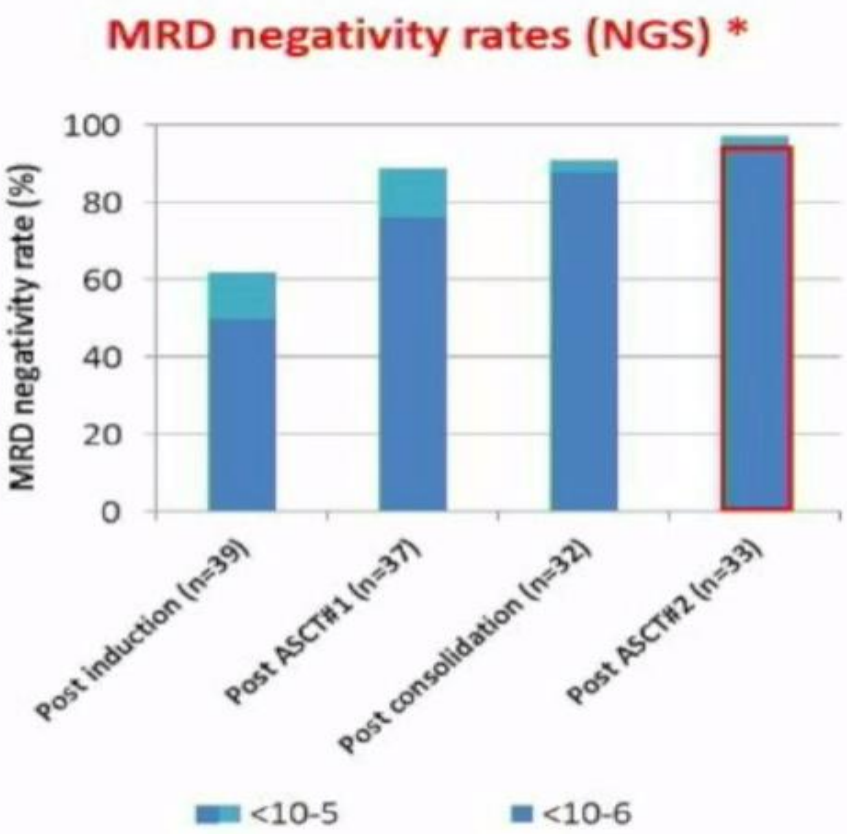
Response rates and MRD



CR/sCR : 81%



MRD (-) 10-6 = 94%

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* Per protocol analysis

Who need a transplant?

- **All eligible NDMM patients** until new data are available
- **Future challenges**
  - Compare new immunotherapies to transplant (EMN-CARTITUDE 6)
  - Define predictive factors for adapted strategies: MRD, sustained MRD?
  - Find tools to reach a sensitivity to 10^{-7}, 10^{-8}?