Efficacy and safety of Isa-KRD induction before response-adapted consolidation in transplant eligible newly diagnosed multiple myeloma: an interim analysis of the IFM2020-02 MIDAS study

A Perrot, C Touzeau, J Lambert, C Hulin, D Caillot, L Karlin, B Arnulf, P Rey, L Garderet, M Macro, M Escoffre-Barbe, J Gay, T Chalopin, K Belhadj, JM Schiano, M Tiab, M Mohty, F Kuhnowski, J Fontan, S Manier, F Orsini-Piocelle, L Vincent, X Leleu, J Corre, P Moreau

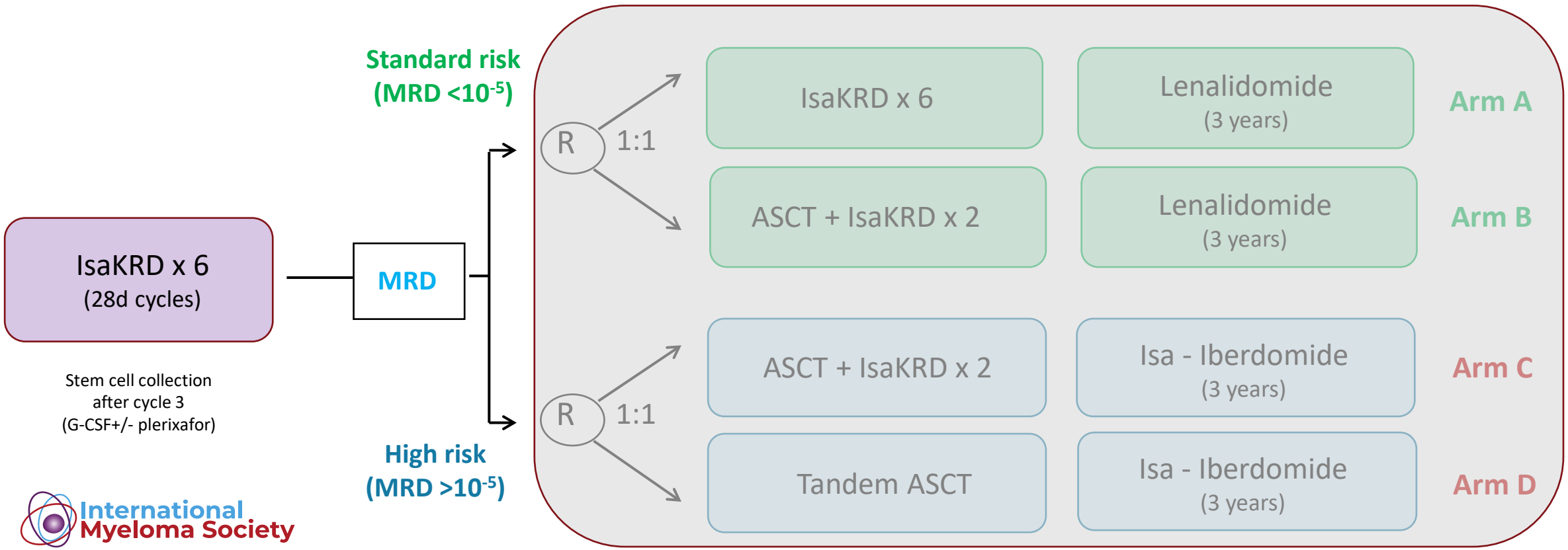
On behalf the IFM group

Background

- In patients with TE NDMM, induction therapy with a quadruple regimen before ASCT is standard.
- **Quadruplet regimens have revolutionized frontline therapy, significantly improving prognosis**.
  - CASSIOPEIA (*Moreau P et al., Lancet 2019*; *Moreau P et al., Lancet Oncol 2024*)
  - GRIFFIN & PERSEUS (*Voorhees PM et al., Lancet Haematol 2023*; *Sonneveld P et al. N Engl J Med 2024*)
  - IsKia (*Gay F et al. ASH 2023*)
- **To date, no prospective trials have compared upfront ASCT versus no ASCT following quadruplet induction. The role of upfront ASCT remains a topic of debate**, and risk-adapted strategies are needed to determine its utility after quadruplet induction.
  - Tools for stratifying risk: (R-)ISS, cytogenetics at diagnosis, depth of response/MRD
  - First trial on MRD-driven consolidation: MASTER phase 2 trial (*Costa LJ et al., Lancet Haematol 2023*)
- **The phase 3 IFM2020-02-MIDAS trial is an ongoing study assessing a MRD-adapted consolidation and maintenance strategy following IsaKRD induction.**
- **Here, we present the efficacy and safety data of this induction regimen.**

Study design

MIDAS = MInimal residual Disease Adapted Strategy



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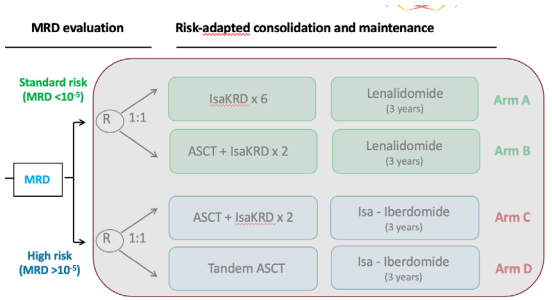


Induction

IsaKRD x 6
(28d cycles)

Stem cell collection
after cycle 3
(G-CSF+/- plerixafor)

Isatuximab 10 mg/kg C1: D1, D8, D15, D22
C2+: D1, D15

Carfilzomib C1: 20 mg/m^2 D1, then 56 mg/m^2 D8, D15
C2+: 56 mg/m^2 D1, D8, D15

Lenalidomide 25 mg/d, D1-D21

Dexamethasone 40 mg weekly

International Myeloma Society

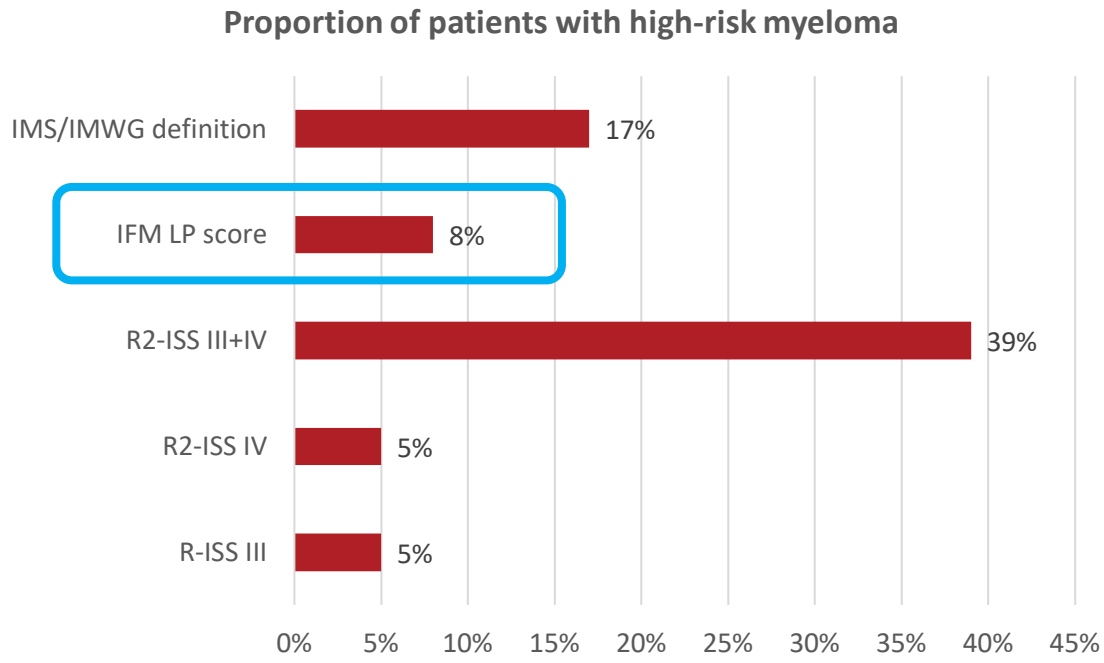
Patients' characteristics

791 patients were included in 72 centers between 8 Dec 2021 and 10 Jul 2023

Characteristic		Whole cohort (N = 791) N (%)
Age (years), median [range]		58.7 [25.4-66]
>60 years		330 (42%)
Gender	Male	454 (57%)
	Female	337 (43%)
ECOG performance status	0	338 (43%)
	1	355 (45%)
	2	98 (12%)
Criteria for symptomatic MM		
CRAB		726 (92%)
Osteolytic lesions		595 (75%)
Anemia		206 (26%)
SLiM only		61 (8%)
ISS stage	I	346 (44%)
	II	346 (44%)
	III	99 (13%)
Elevated LDH		212 (27%)
Extramedullary disease		5 (1%)
Circulating plasma cells (by morphology)	Any	53 (7%)
	>5%	9 (1%)

Cytogenetics at diagnosis

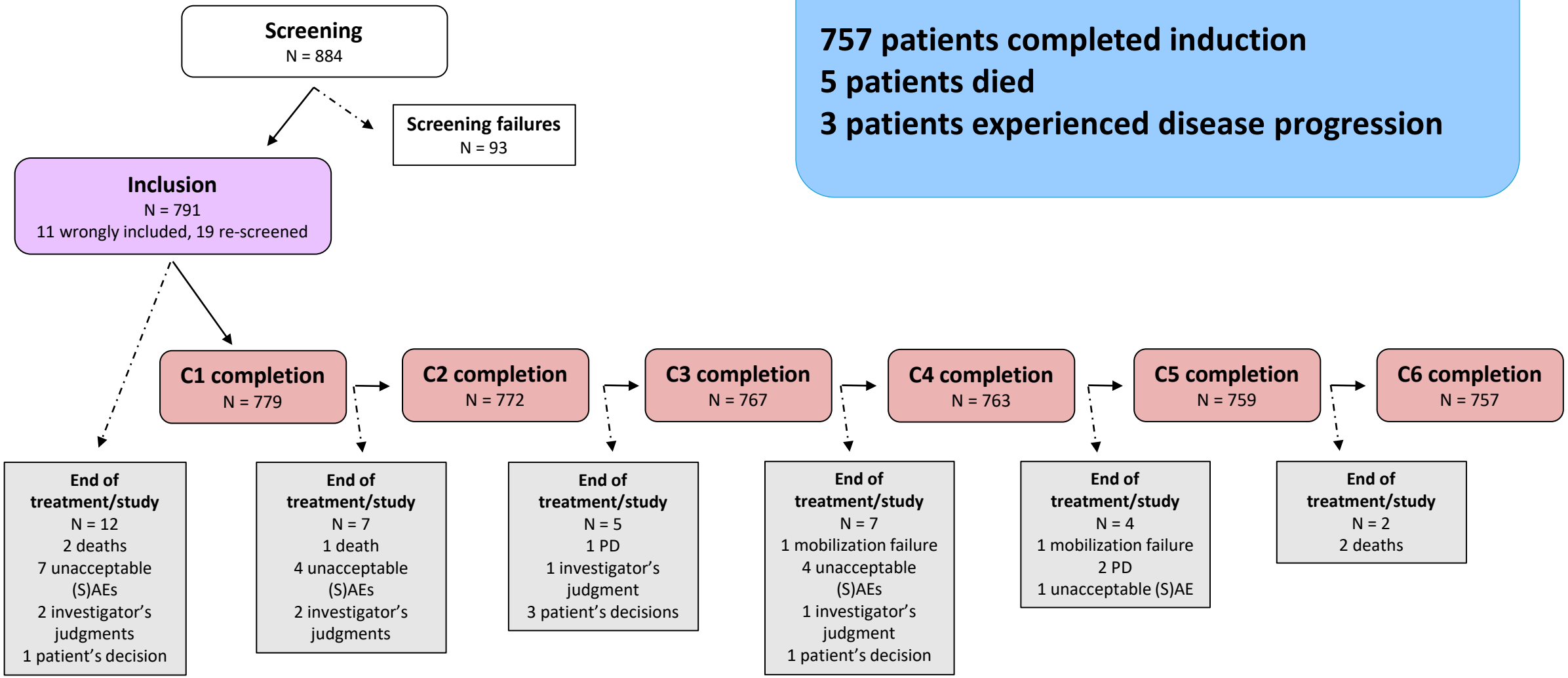
Cytogenetics abnormalities/scores	Whole cohort (N = 791) N (%)
R-ISS stage I	236 (30%)
II	511 (65%)
III	43 (5%)
R2-ISS stage I	193 (25%)
II	273 (36%)
III	265 (34%)
IV	36 (5%)
Cytogenetic score LP >1	63 (8%)
IMS/IMWG consensus HRMM	135 (17%)
Detailed cytogenetic abnormalities	
t(4;14)	63 (8%)
t(14;16)	19 (3%)
t(14;20)	11 (1%)
t(11;14)	199 (26%)
1q gain	200 (26%)
monoallelic del(1p32)	55 (7%)
biallelic del(1p32)	8 (1%)
del(17p)*	46 (6%)
TP53 mutation	31 (4%)
trisomy 5	307 (41%)
trisomy 21	202 (27%)



* cut-off 55%

Patients' flowchart

757 patients completed induction
5 patients died
3 patients experienced disease progression



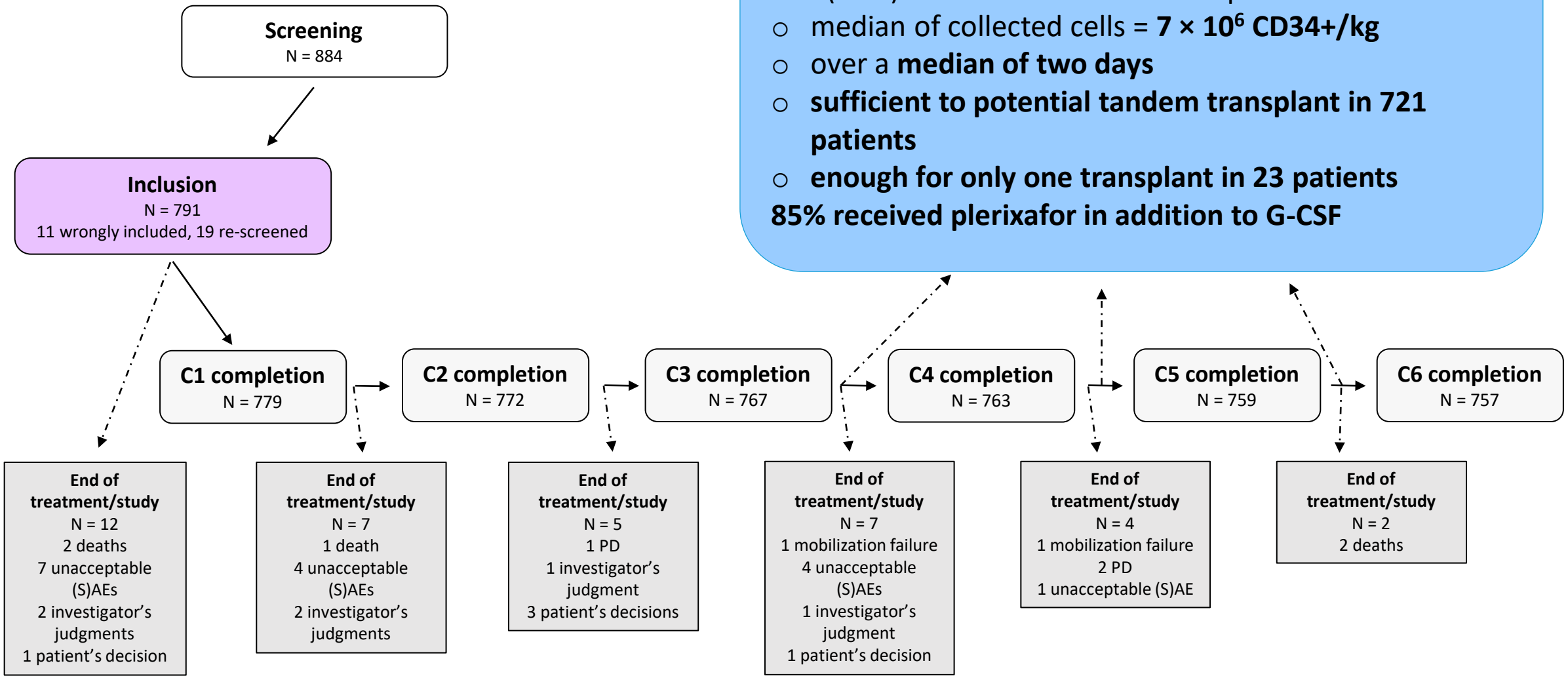
Stem cell harvest

766/767 patients initiated PSC mobilization

761 (99%) underwent at least one apheresis session:

- median of collected cells = **7 × 10^6 CD34+/kg**
- over a **median of two days**
- **sufficient to potential tandem transplant in 721 patients**
- **enough for only one transplant in 23 patients**

85% received plerixafor in addition to G-CSF



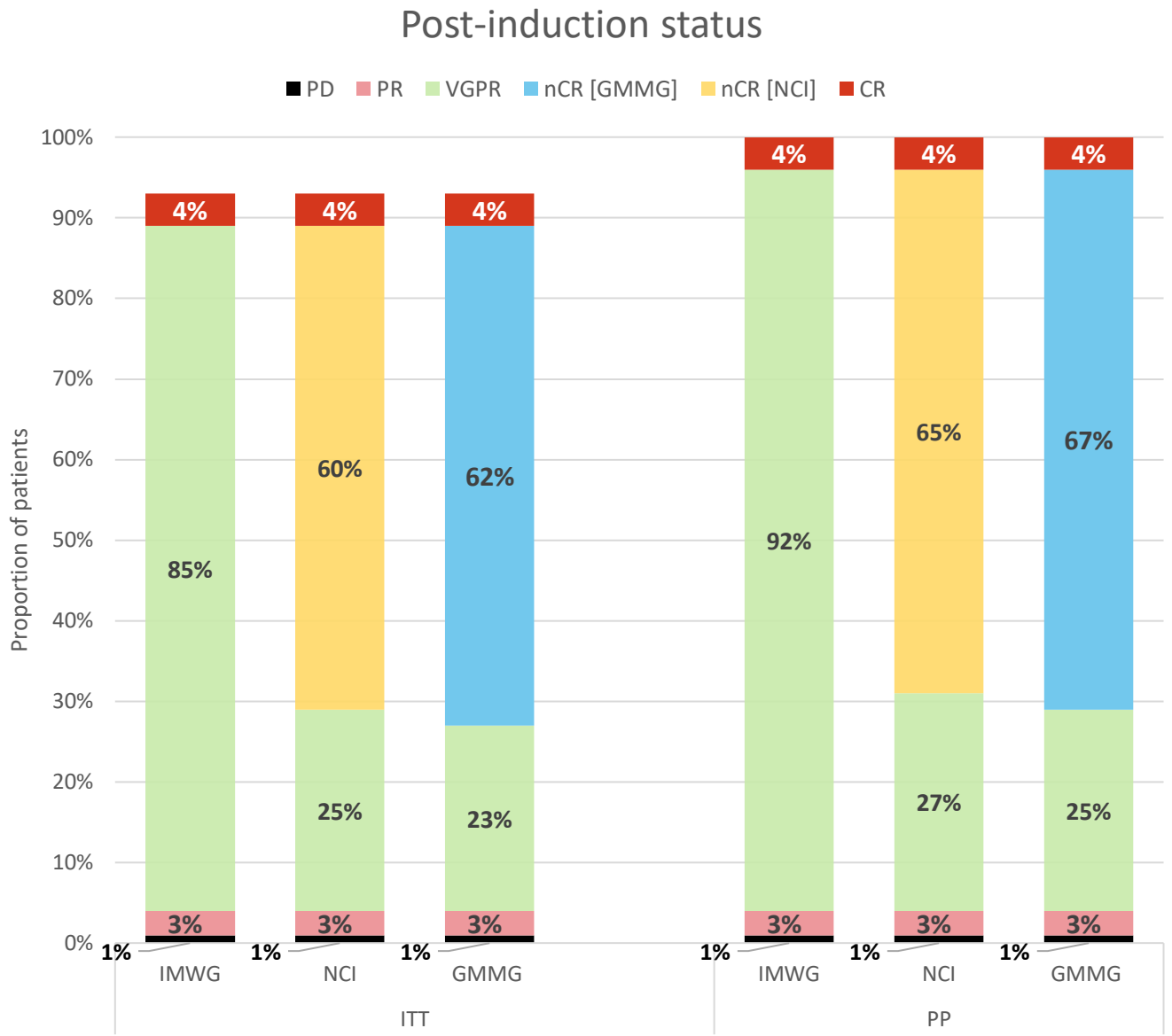
Response rates after induction

Intent-to-treat (ITT) population

- **92% of patients achieved VGPR or better**
- **64-66% of patients achieved nCR/CR**

Per protocol (PP)

- 99% of patients achieved VGPR or better
- 69-71% of patients achieved nCR/CR

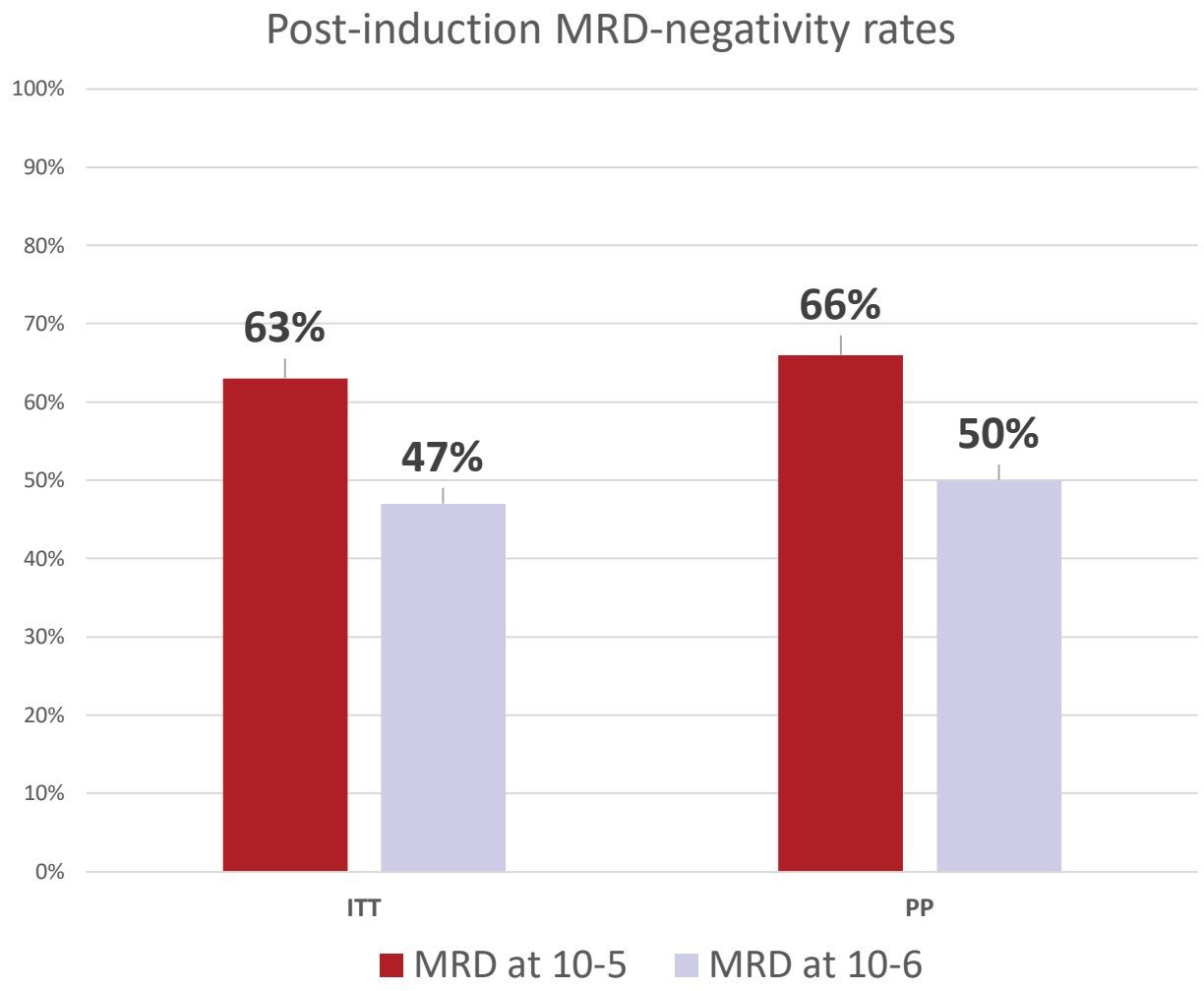


MRD-negativity rates after induction

MRD was evaluated at C6D28 in 751 patients, regardless of response

- primarily using NGS
- flow cytometry for 16 patients

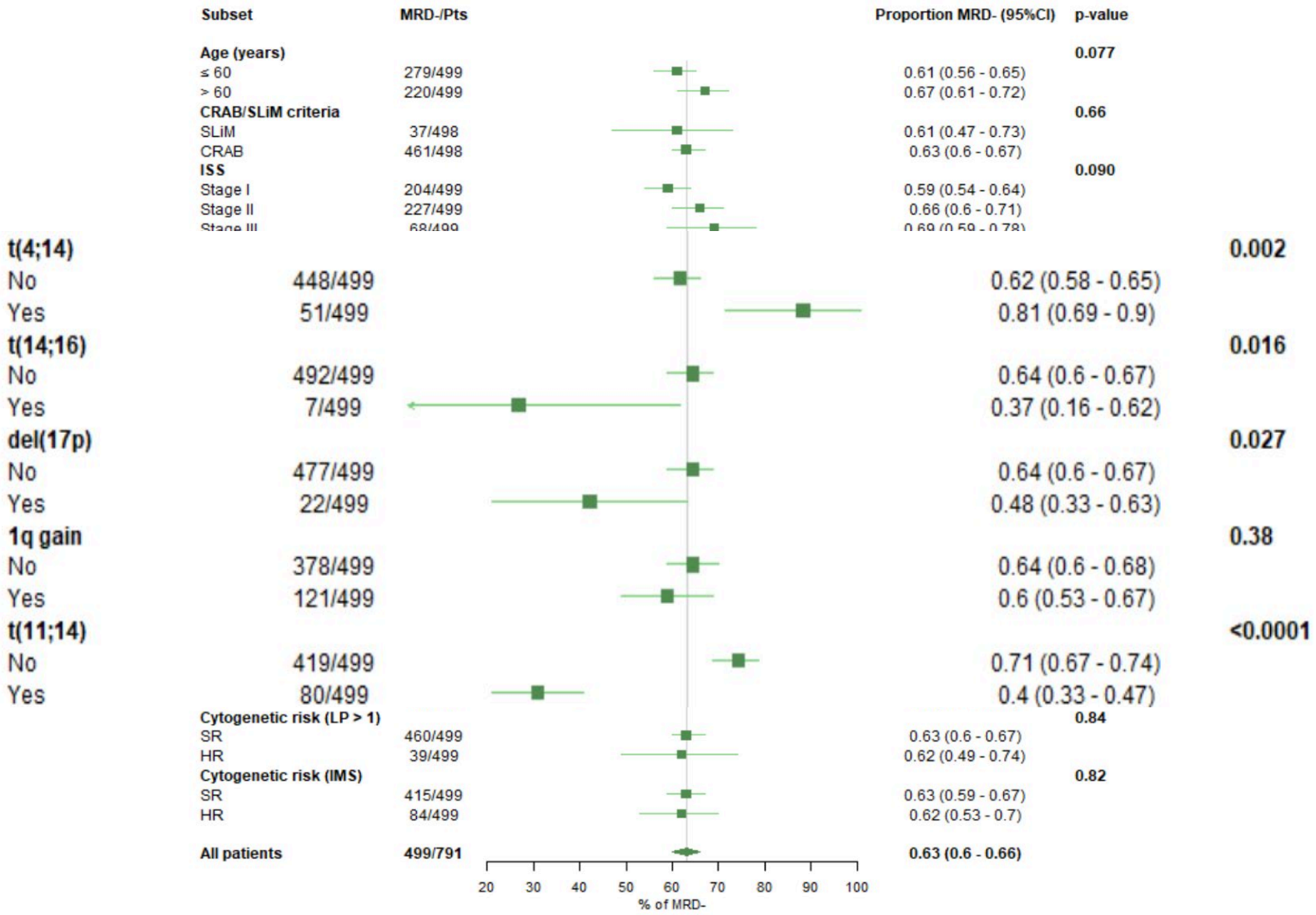
MRD-negativity rate: 63% at 10^{-5}



Subgroup analyses of MRD-negativity

No significant differences according to:

- Age
- ISS stage
- R-ISS stage
- R2-ISS stage
- IFM LP score
- IMS/IMWG consensus definition



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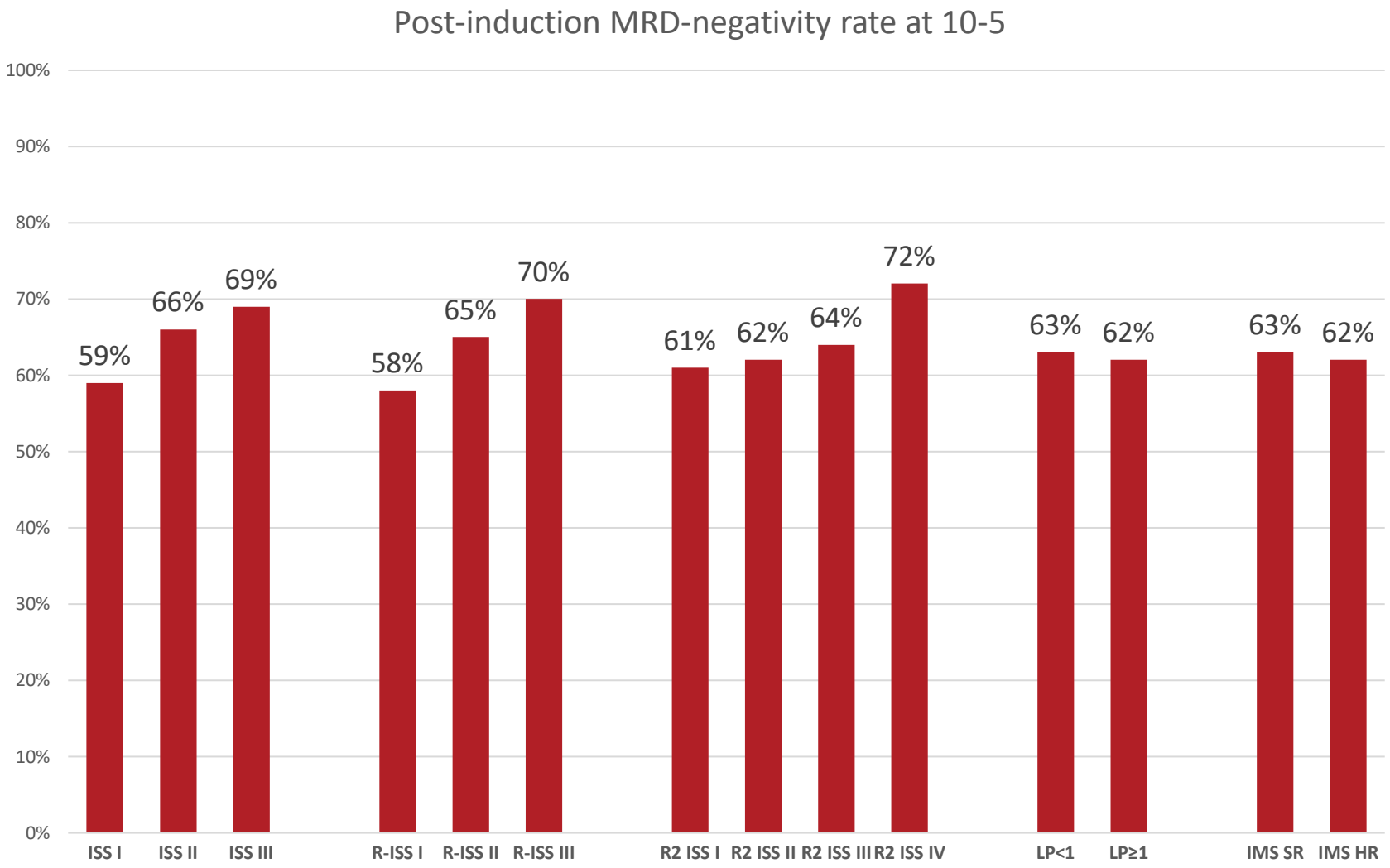


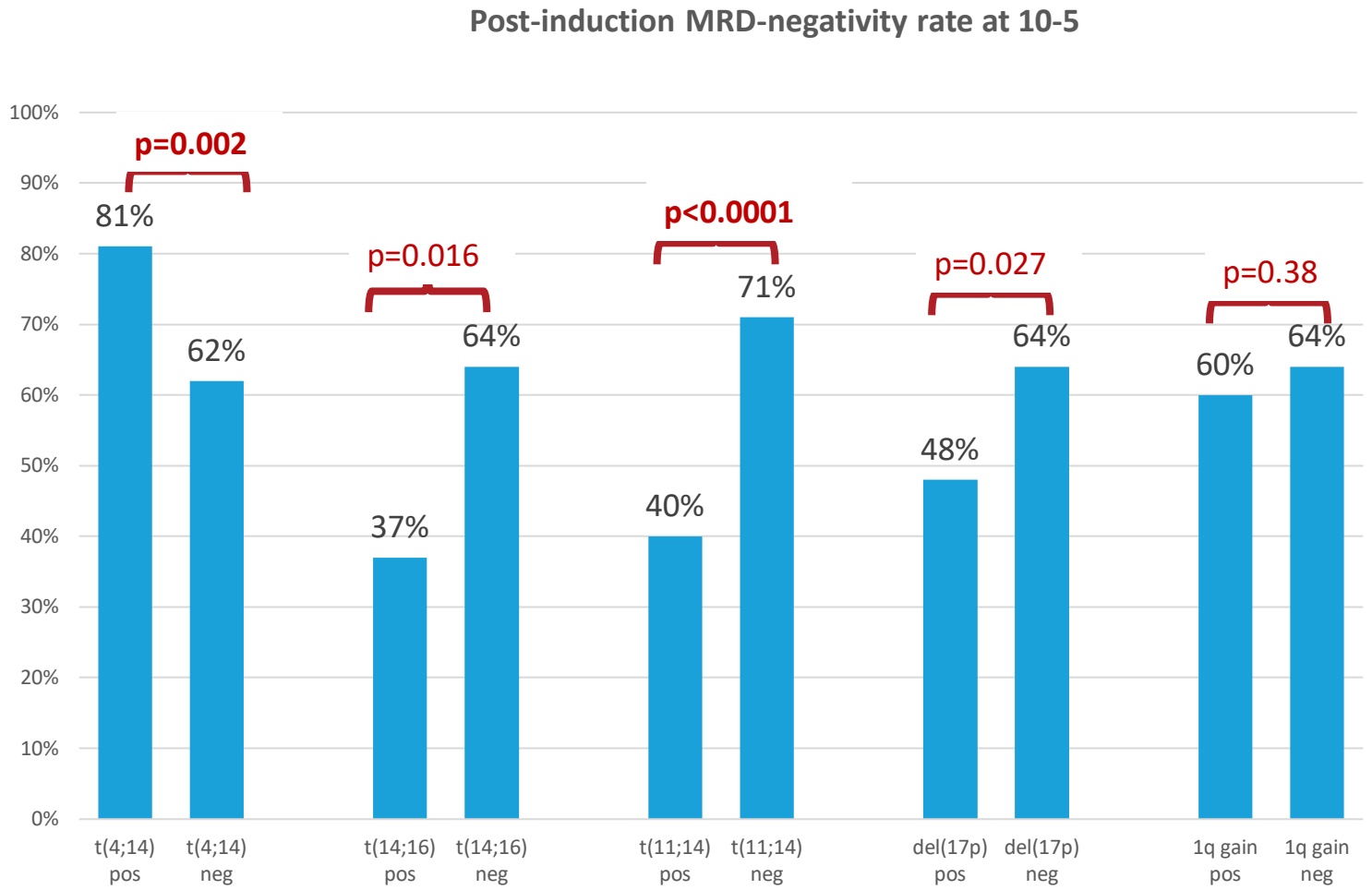
Subgroup analyses of MRD-negativity

Interesting variability across some cytogenetic groups

MRD-negativity rate after induction (sensitivity level 10^{-5}):

- **t(4;14): 81%**
- **t(11;14): 40%**
- **t(14;16): only 7 patients**
- **del(17p): 48%**

Post-consolidation results and kinetics are pending



Safety

Most common AEs and those of particular interest:

	Any grade, N (%)	Grade >2, N (%)
Hematologic		
Anemia	134 (17%)	52 (7%)
Thrombocytopenia	100 (13%)	42 (5%)
Neutropenia	229 (29%)	204 (25%)
Non hematologic		
Gastrointestinal disorders	441 (56%)	22 (3%)
Infections	364 (46%)	54 (7%)
Hepatobiliary disorders	104 (13%)	46 (6%)
Cardiac disorders	49 (6%)	9 (1%)
Peripheral neuropathies	103 (13%)	3 (<1%)
Thrombotic microangiopathy	1 (<1%)	1 (<1%)

No new safety signals were observed with IsaKRD, with a low (<1%) mortality rate.

Conclusion - Perspectives

- **The MIDAS trial was designed to tailor therapy based on MRD status after 6 cycles of IsaKRD**
- **Our findings confirm that six cycles of IsaKRD induce exceptionally high response and MRD-negativity rates, not only at a sensitivity of 10^{-5} but also at 10^{-6}**
- **These rates are the highest reported to date:**
  - **MRD-negativity rate at 10^{-5} = 63%** (35%, 22%, 45% in CASSIOPEIA, GRIFFIN, IsKia trials, respectively)
  - **nCR/CR rate = 64-66%** (41% after GMMG HD7 induction; *Goldschmidt H et al., Lancet Haematol 2022*)
- **MRD status after induction does not appear to align consistently with initial cytogenetic risk**: a longer follow-up is needed to better interpret the significance of achieving MRD-negativity in patients with different cytogenetic abnormalities
- **IsaKRD induction ensures successful stem cell collection, with no new safety signals**
- **Further follow-up of the MIDAS cohort is required to confirm these benefits in the final analysis**

Thanks !

- Patients, families and hospital teams of the 72 French & Belgian investigational centers
- The great MIDAS team, especially Marylaure Gavard (pharmacovigilance), Martine Tching-Sin and Laurent Flet (central pharmacy), Charlotte Avet-Loiseau (central lab), Gaelle Massart (data management), Marie-Odile Petillon and Anis Benkhelouf (medical monitors), Lydia Zerrouk (Lead Project Manager), and Chanaz Louni (IFM Director)
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