New classification for identifying HR Myeloma based on cytogenetics abnormalities

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DISCLOSURES

Honoraria: Janssen, Takeda, Amgen, Sanofi, Bristol Myers Squibb, Pfizer, Adaptive

Consulting or advisory board : None

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Revised International Staging System (R-ISS)

Prognostic Factor	Criteria
ISS stage	
I	Serum β_2-microglobulin < 3.5 mg/L, serum albumin ≥ 3.5 g/dL
II	Not ISS stage I or III
III	Serum β_2-microglobulin ≥ 5.5 mg/L
CA by iFISH	
High risk	Presence of del(17p) and/or translocation t(4;14) and/or translocation t(14;16)
Standard risk	No high-risk CA
LDH	
Normal	Serum LDH < the upper limit of normal
High	Serum LDH > the upper limit of normal
A new model for risk stratification for MM	
R-ISS stage	
I	ISS stage I and standard-risk CA by iFISH and normal LDH
II	Not R-ISS stage I or III
III	ISS stage III and either high-risk CA by iFISH or high LDH

Greipp et al. J Clin Oncol 2005

Palumbo et al. J Clin Oncol 2015

(CA : Chromosomal Abnormalities)

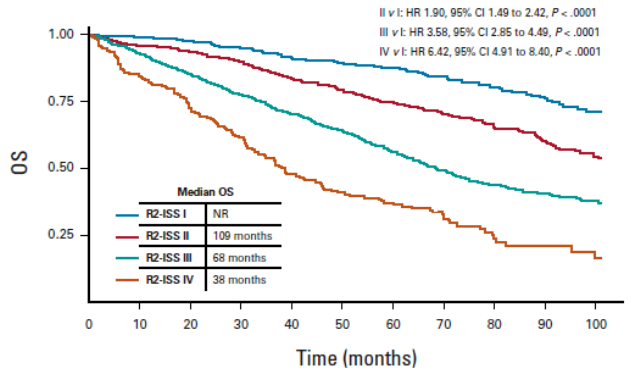
R2-ISS from European Myeloma Network

3340 NDMM patients

TABLE 2. R2-ISS Score Definition on the Basis of the Evaluable Patients Included in the Training Set (n = 2,226)

Risk Feature	OS HR (95% CI)	PFS HR (95% CI)	Score Value[a]
ISS II	1.75 (1.49 to 2.05)	1.43 (1.28 to 1.61)	1
ISS III	2.53 (2.13 to 3.01)	1.76 (1.54 to 2.01)	1.5
del(17p)	1.82 (1.53 to 2.17)	1.43 (1.23 to 1.65)	1
LDH high	1.60 (1.36 to 1.88)	1.37 (1.20 to 1.57)	1
t(4;14)	1.53 (1.29 to 1.81)	1.40 (1.21 to 1.62)	1
1q+	1.47 (1.29 to 1.68)	1.33 (1.20 to 1.48)	0.5

Group	No. (%)	Total Additive Score
Low (I)	428 (19)	0
Low-intermediate (II)	686 (31)	0.5-1
Intermediate-high (III)	917 (41)	1.5-2.5
High (IV)	195 (9)	3-5



D'Agostino et al. J Clin Oncol 2022

Workshop on “Genomics Defining High-Risk Myeloma”

Barcelona July 7-8, 2023

IMS consensus on genomic definition of high risk myeloma

Del17p
in more than 20% of sorted plasma cells

TP53 mut
(no threshold VAF)

Biallelic Del(1p32)

Association of 2 among

- **t(4;14)** or **t(14;16)** or **t(14;20)**
- **Gain/Amp 1q**
- **Monoallelic del(1p32)**

Submitted in J Clin Oncol

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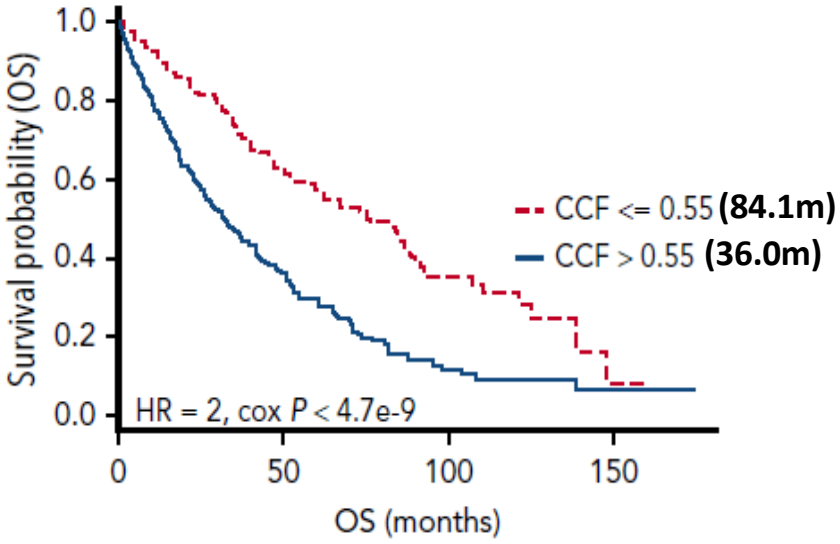
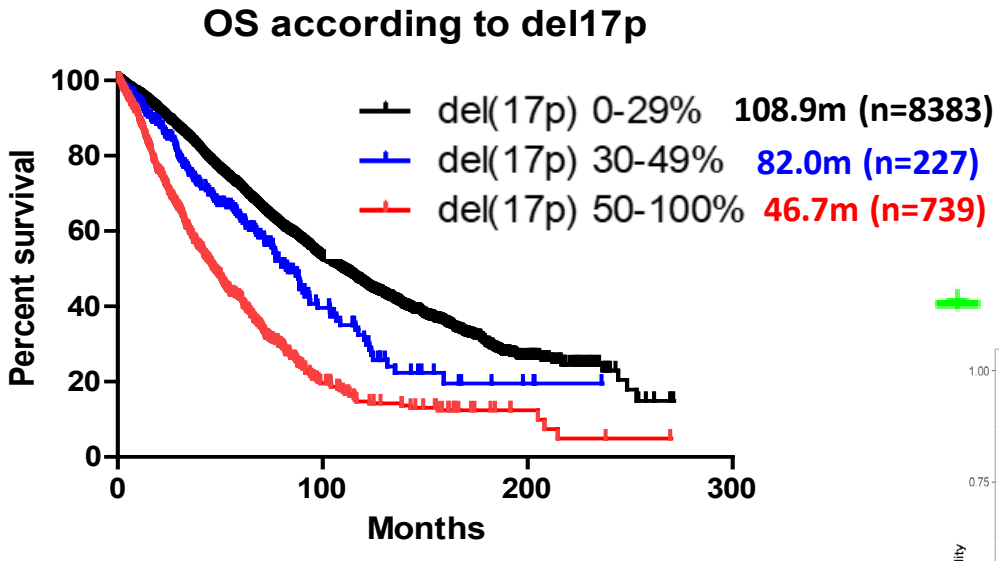
Del17p (8-10% of NDMM) : which prognostic cut off by FISH ?

- *R-ISS : « higher that the cutoff threshold defined by each lab »*
- *R2-ISS : 10 to 20%*
- *IFM : 50-55%*
- *Until 1% in some clinical studies !*

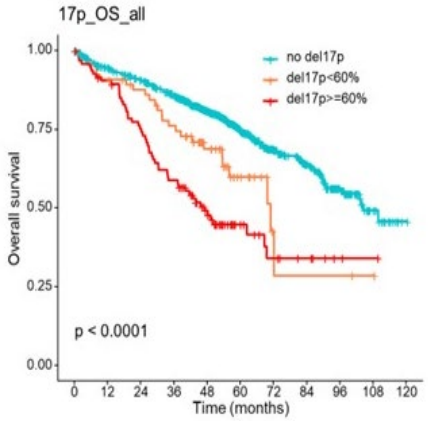
Del17p (8-10% of NDMM) : which prognostic cut off by FISH ?

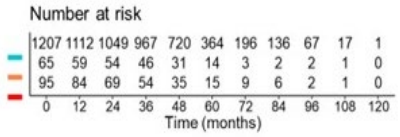


Thakurta et al. Blood 2019

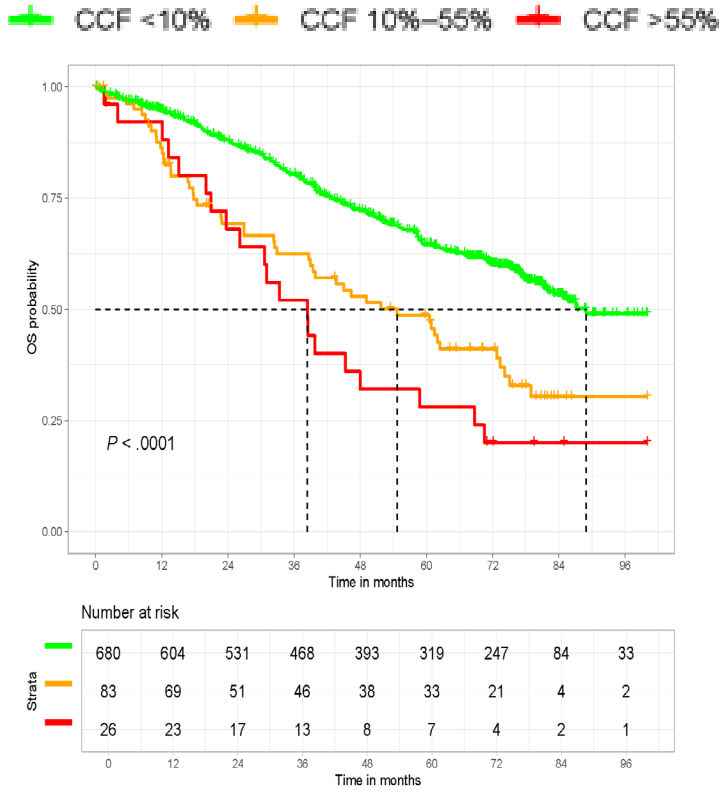


IFM data



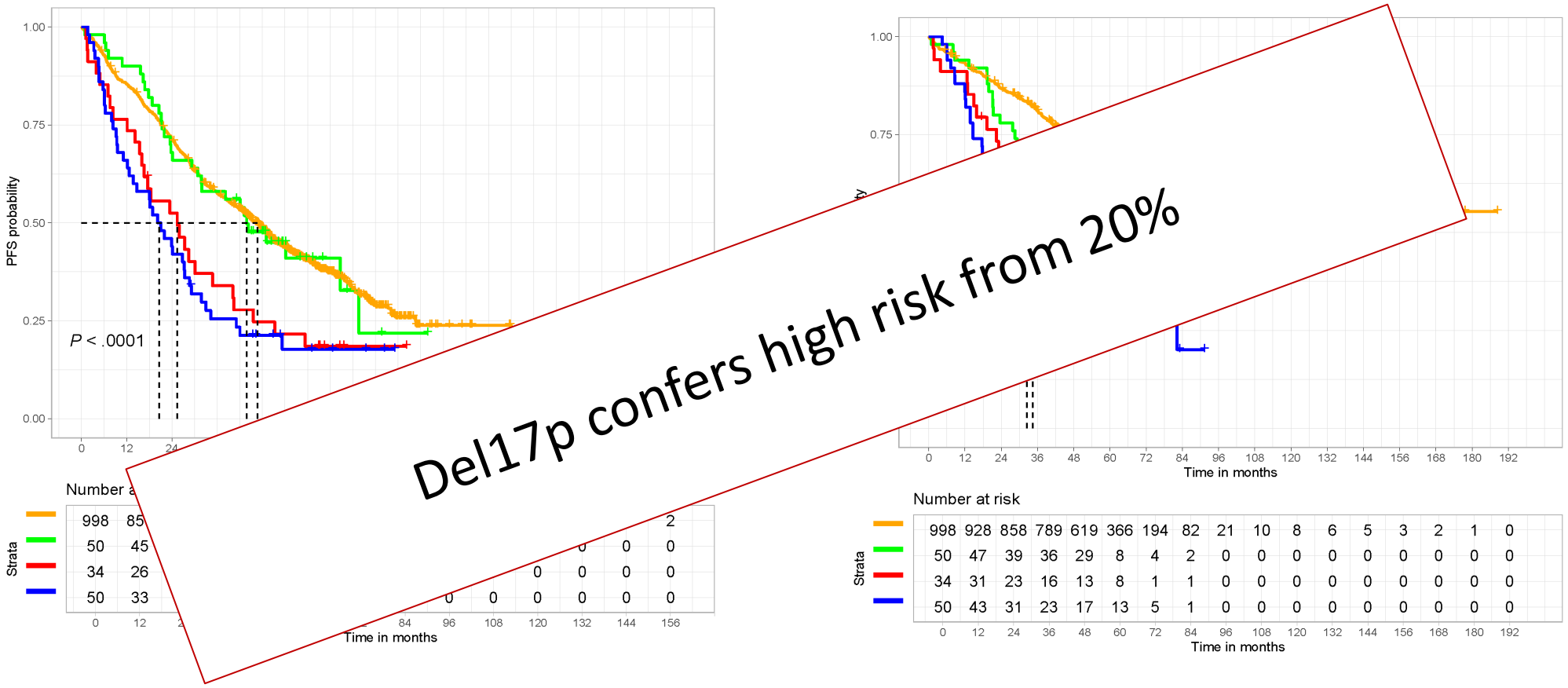


GMMG data



HARMONY dataset

Del17p (8-10% of NDMM) : which prognostic cut off by FISH ?



- **Del17p <10% (998 patients)**
- **Del17p 10%-20% (50 patients)**
- **Del17p 21-50% (34 patients)**
- **Del17p >50% (50 patients)**

Spanish group data

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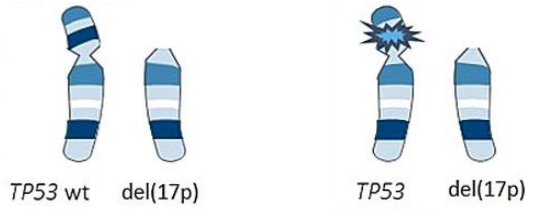
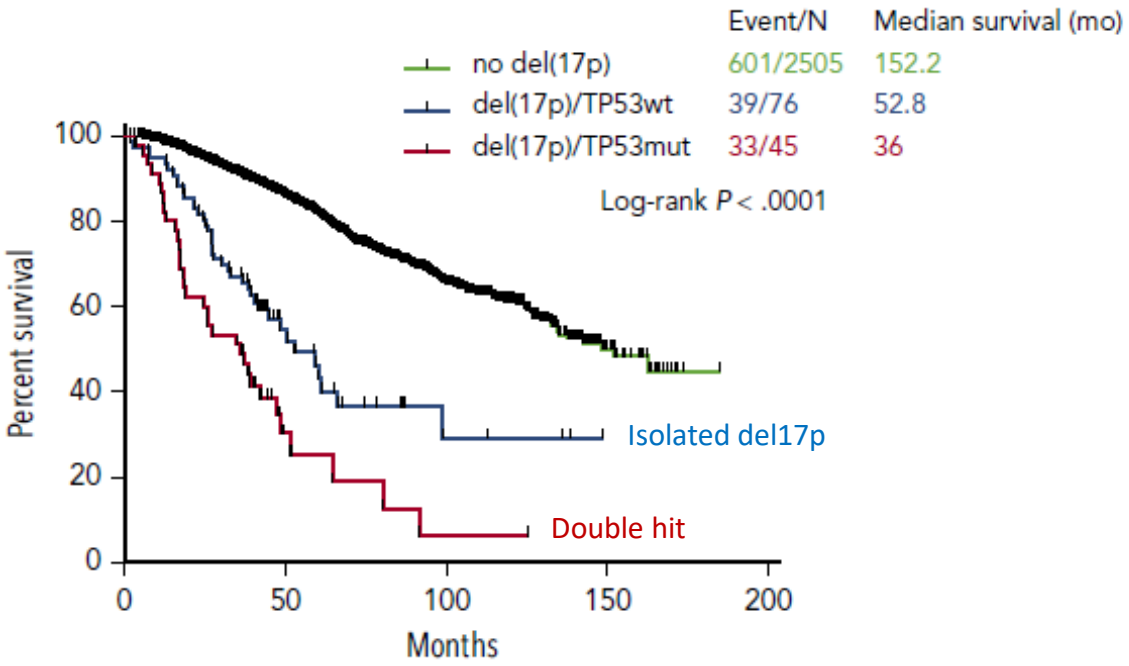
Do we need TP53 mutational status ?





Corre et al. Blood 2021

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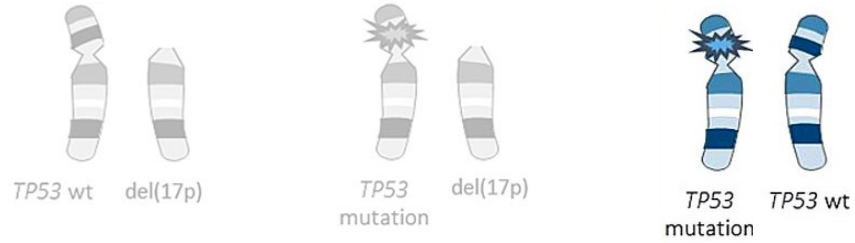

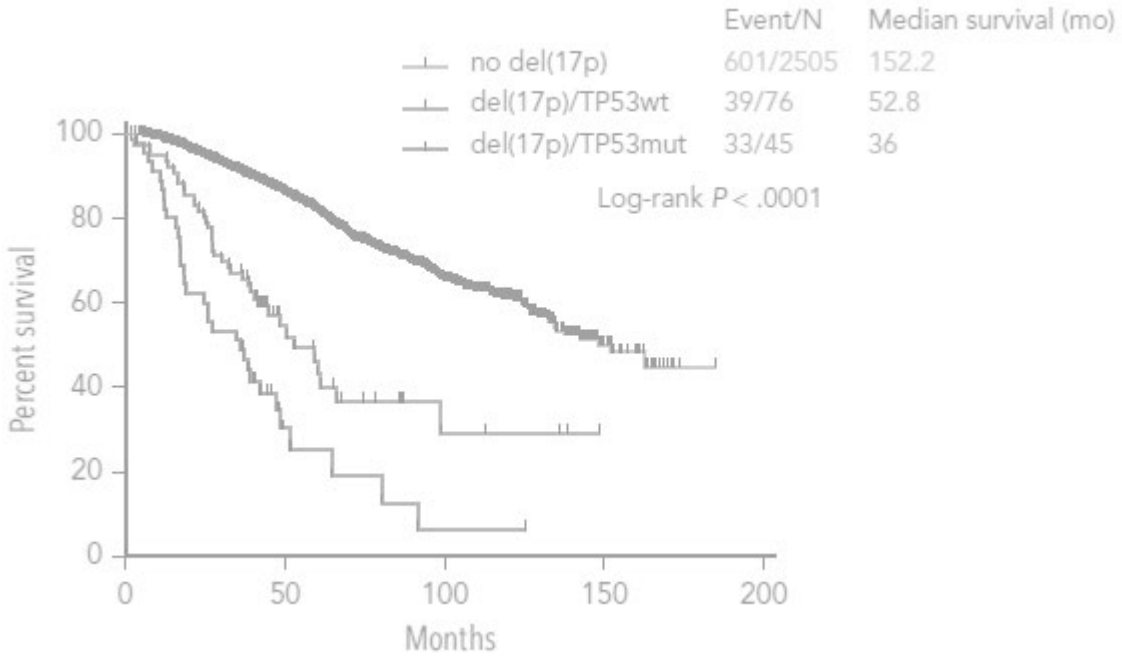

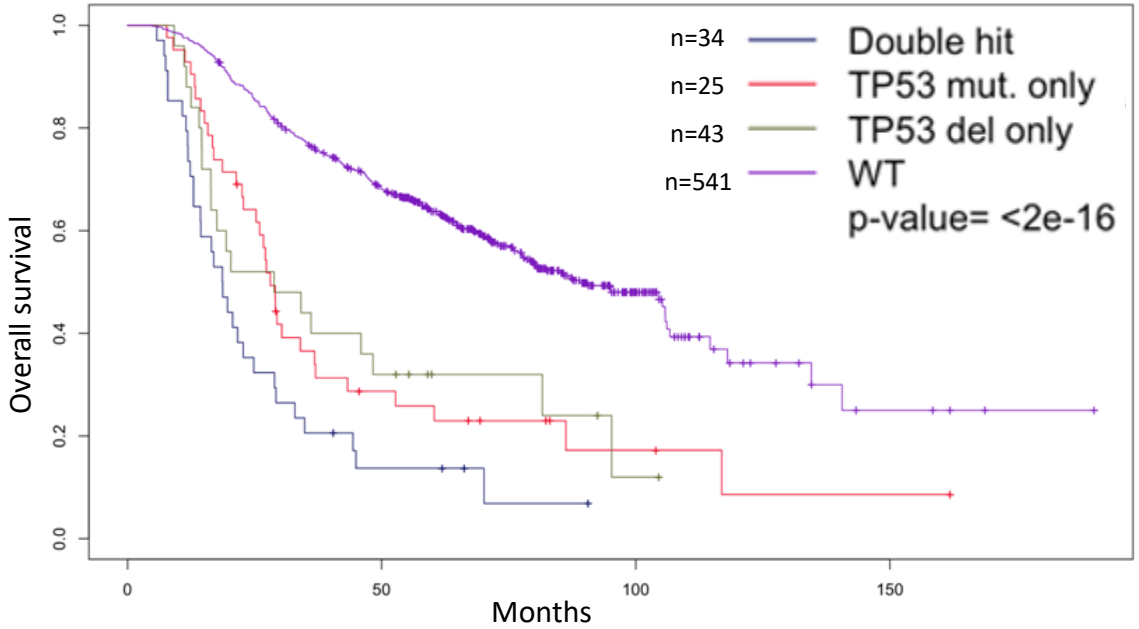

Corre et al. Blood 2021

Manuscript in prep.

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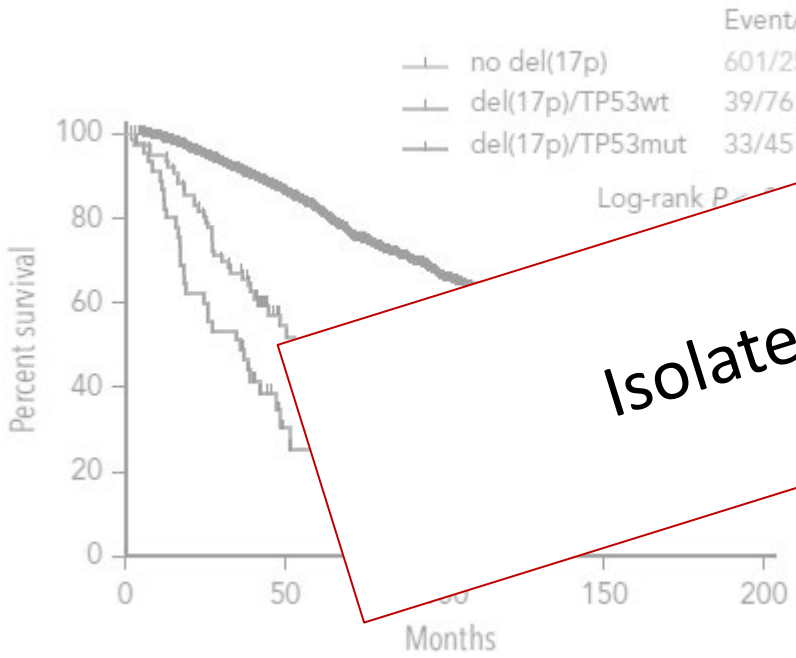

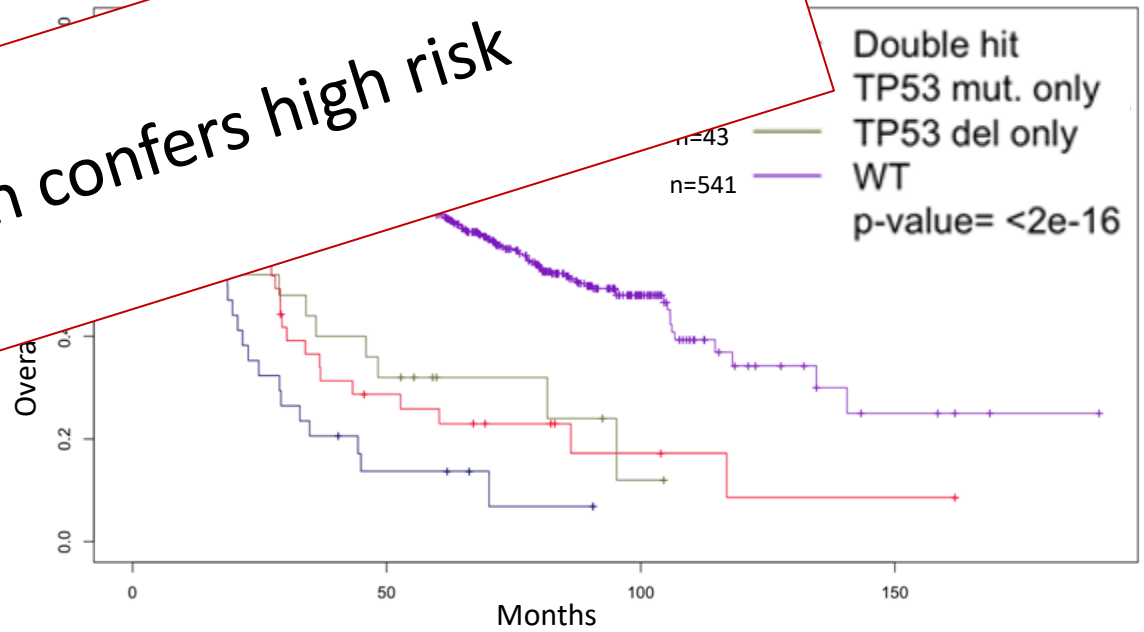

Isolated TP53 mutation confers high risk

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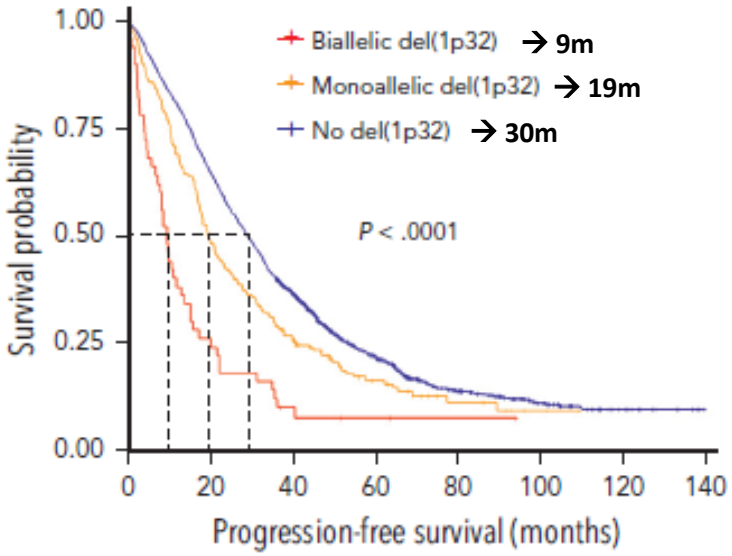
Prognostic impact of del(1p32) : 10% of NDMM, including 1/5 biallelic

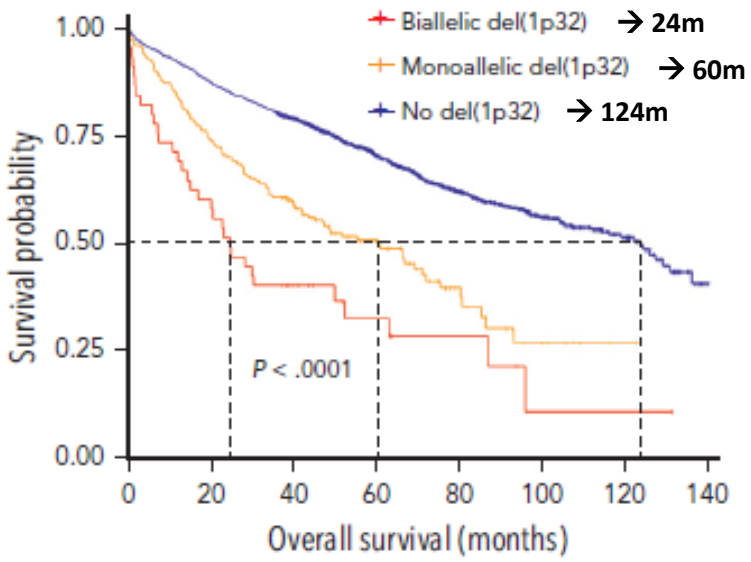
PFS



Number at risk

Biallelic del(1p32)	50	13	4	2	1	0	0	0
Monoallelic del(1p32)	202	99	51	20	7	2	0	0
No del(1p32)	2084	1357	686	276	114	48	14	0

OS

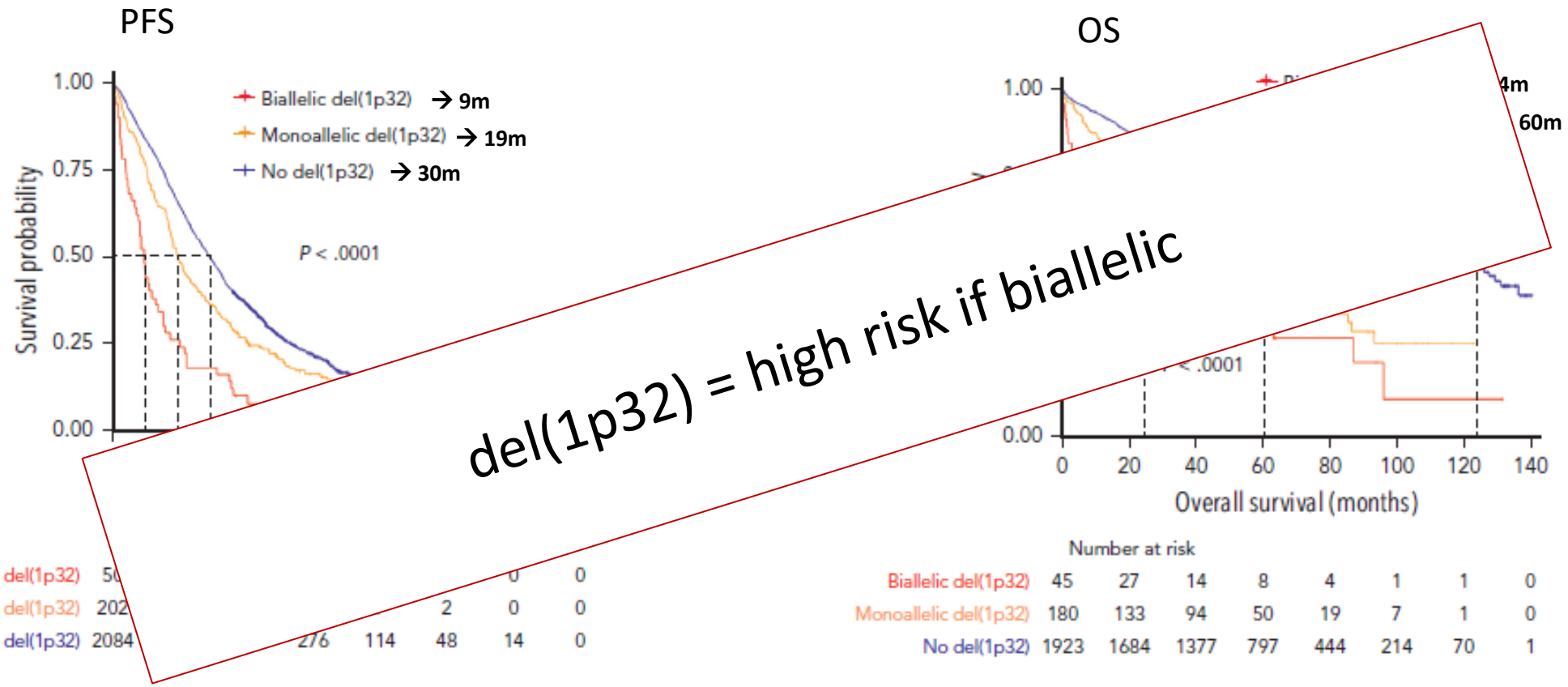


Number at risk

Biallelic del(1p32)	45	27	14	8	4	1	1	0
Monoallelic del(1p32)	180	133	94	50	19	7	1	0
No del(1p32)	1923	1684	1377	797	444	214	70	1

Schavgoulidze et al. Blood 2023

Prognostic impact of del(1p32) : 11% of NDMM, including 1/5 biallelic



del(1p32) = high risk if biallelic

Schavgoulidze et al. Blood 2023

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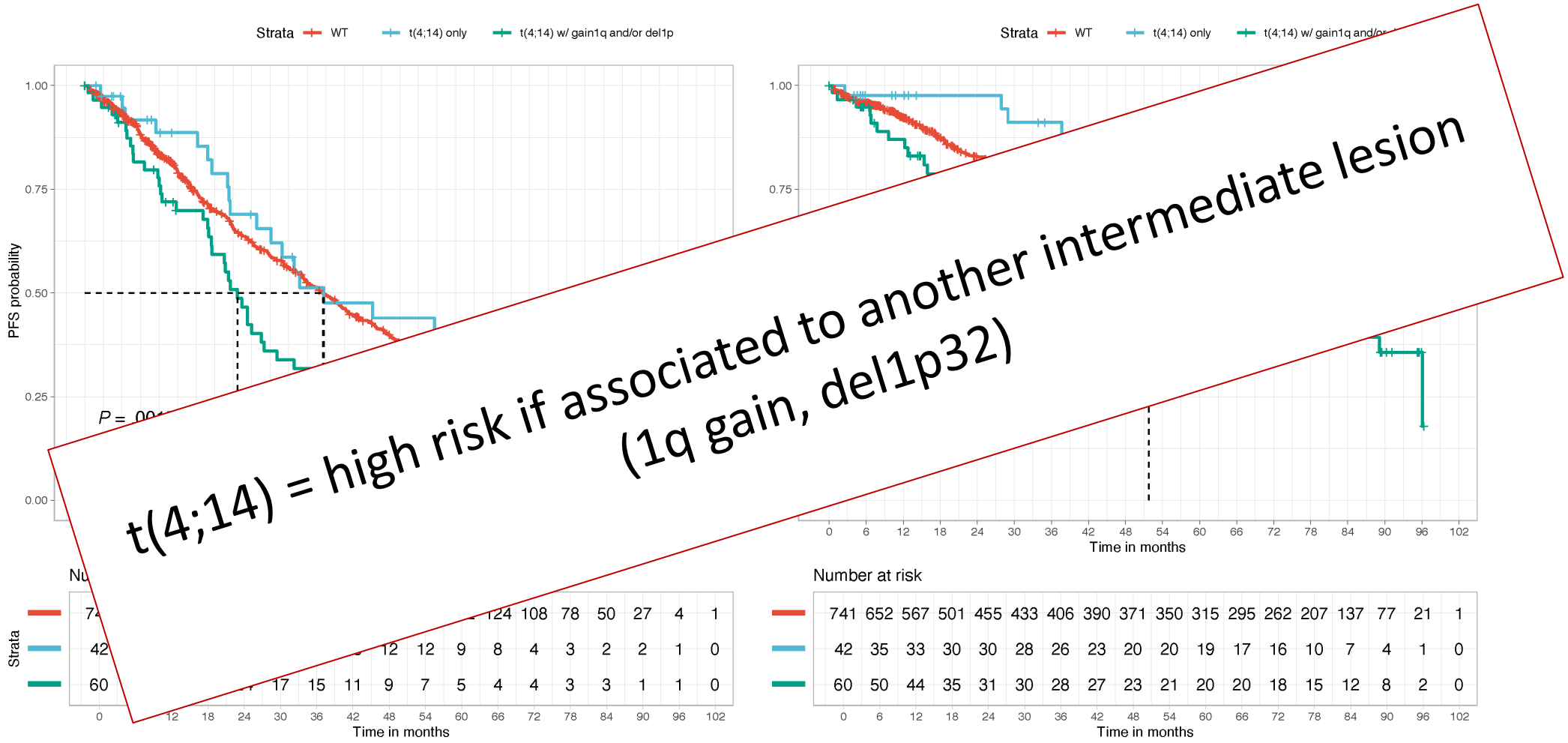
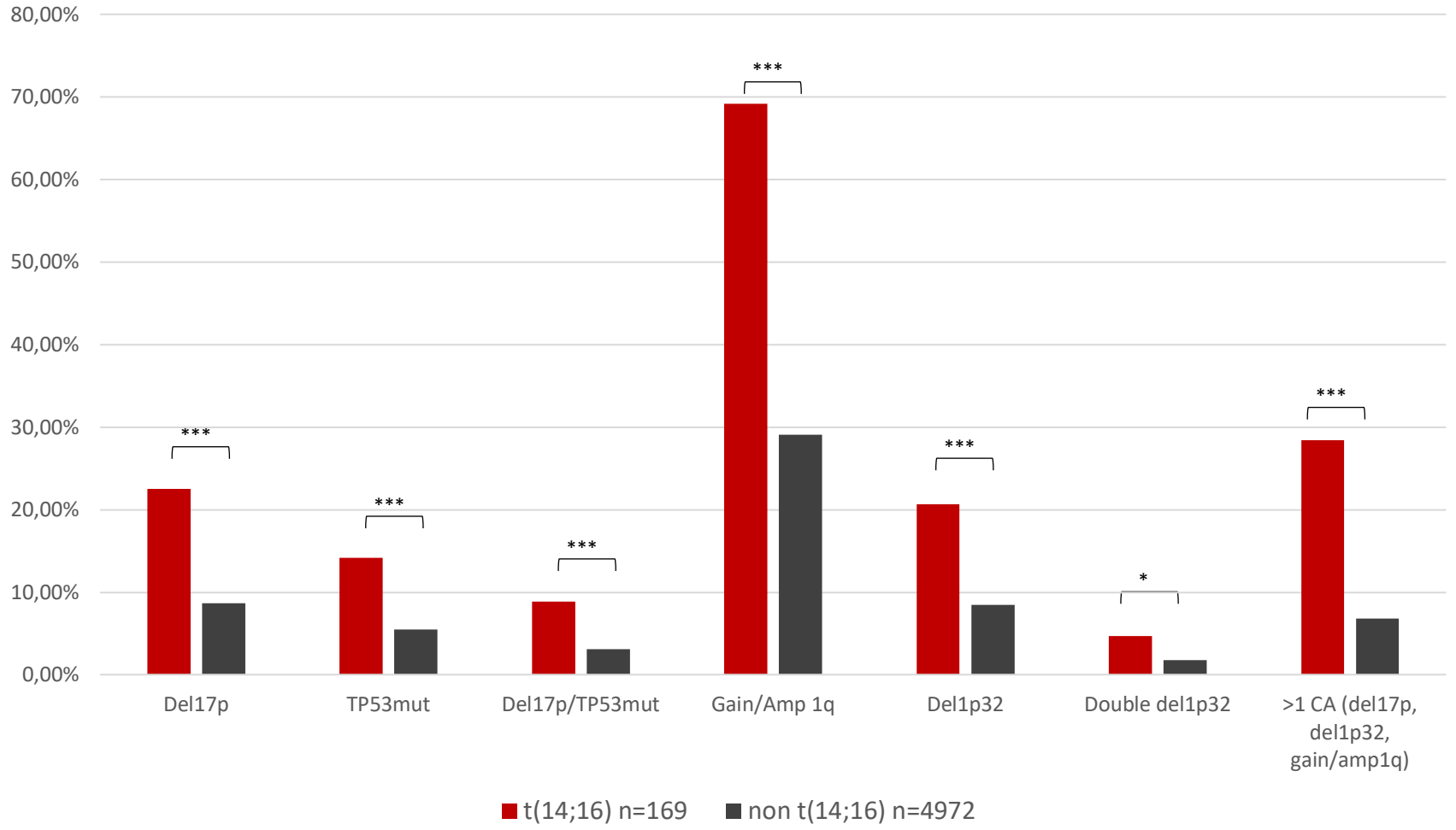
Heterogeneous prognostic impact of t(4;14) : 10-15% of NDMM



CoMMpass dataset[SM]

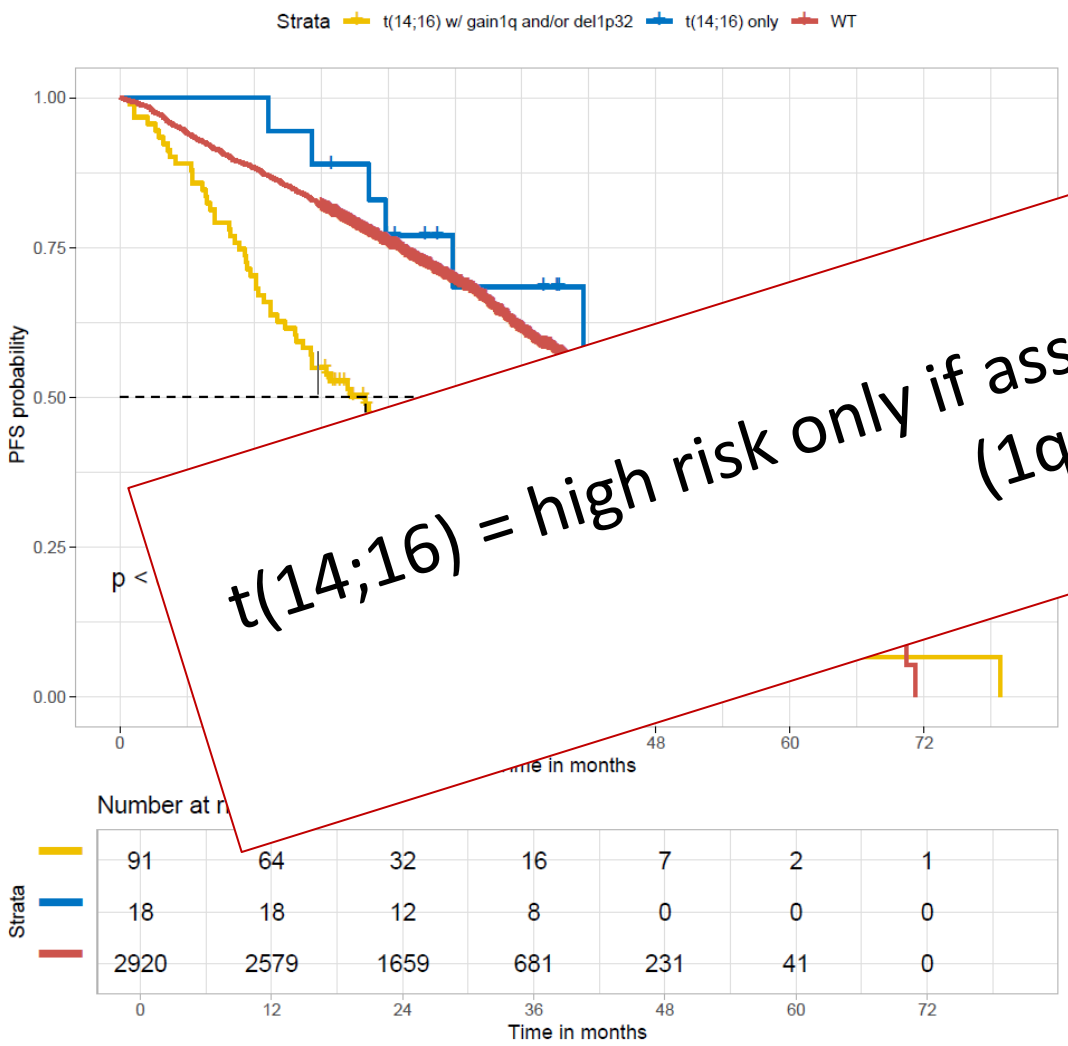
Manuscript in prep

Prognostic impact of t(14;16) : 1-3% of NDMM

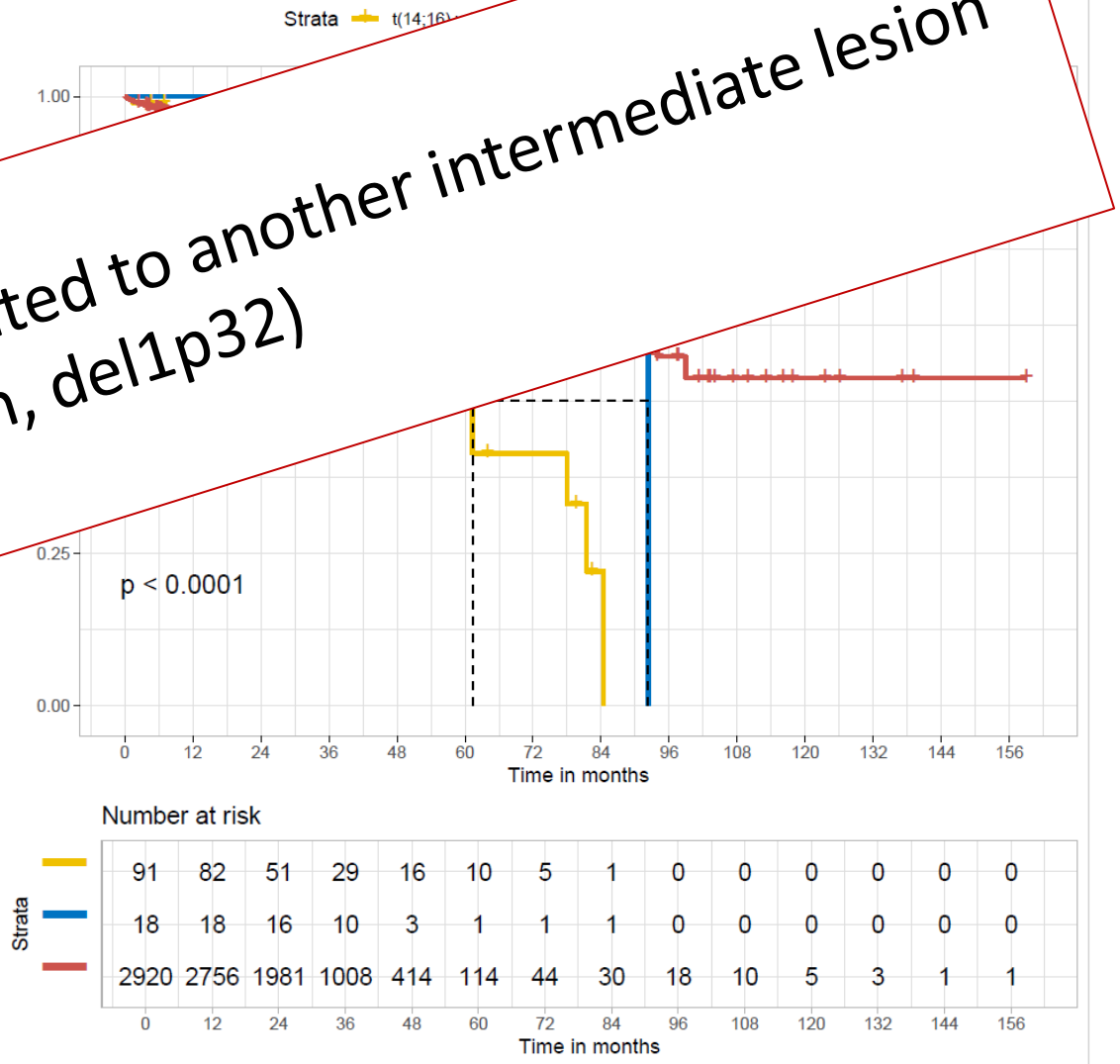


Schavgoulidze et al. Blood Cancer Journal 2023

Prognostic impact of t(14;16)



t(14;16) = high risk only if associated to another intermediate lesion (1q gain, del1p32)



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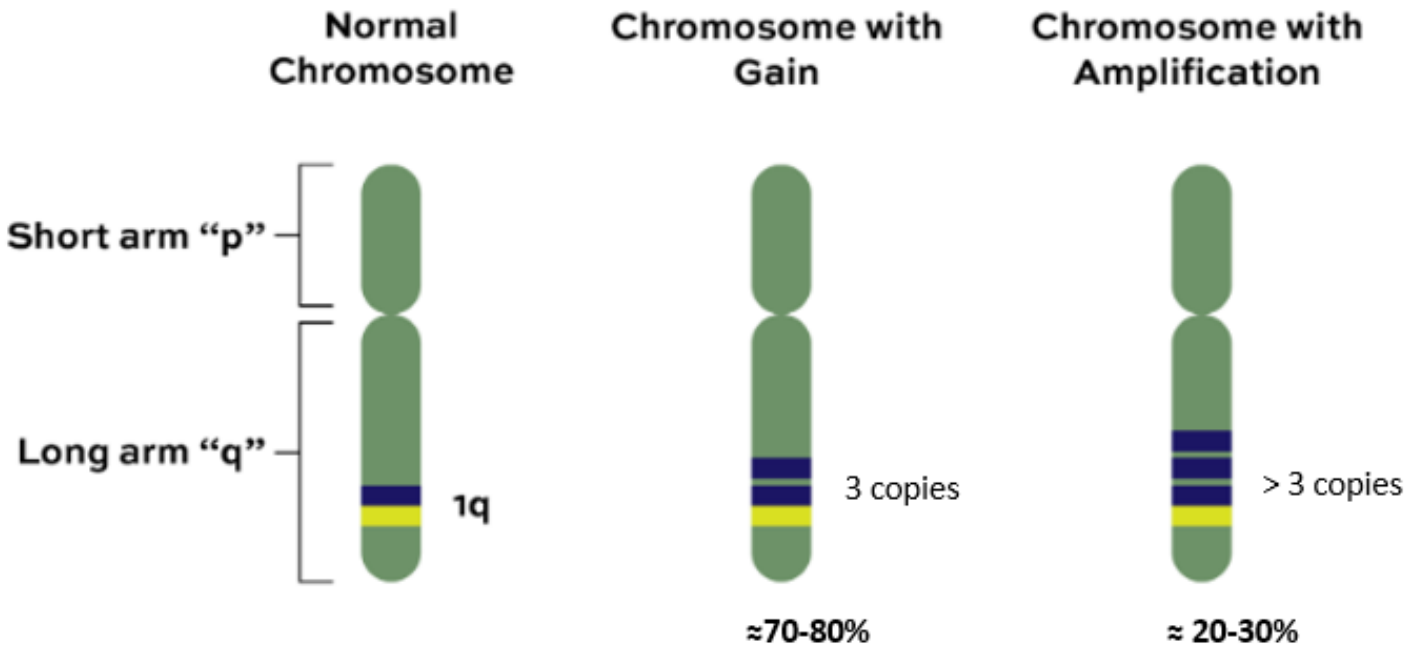
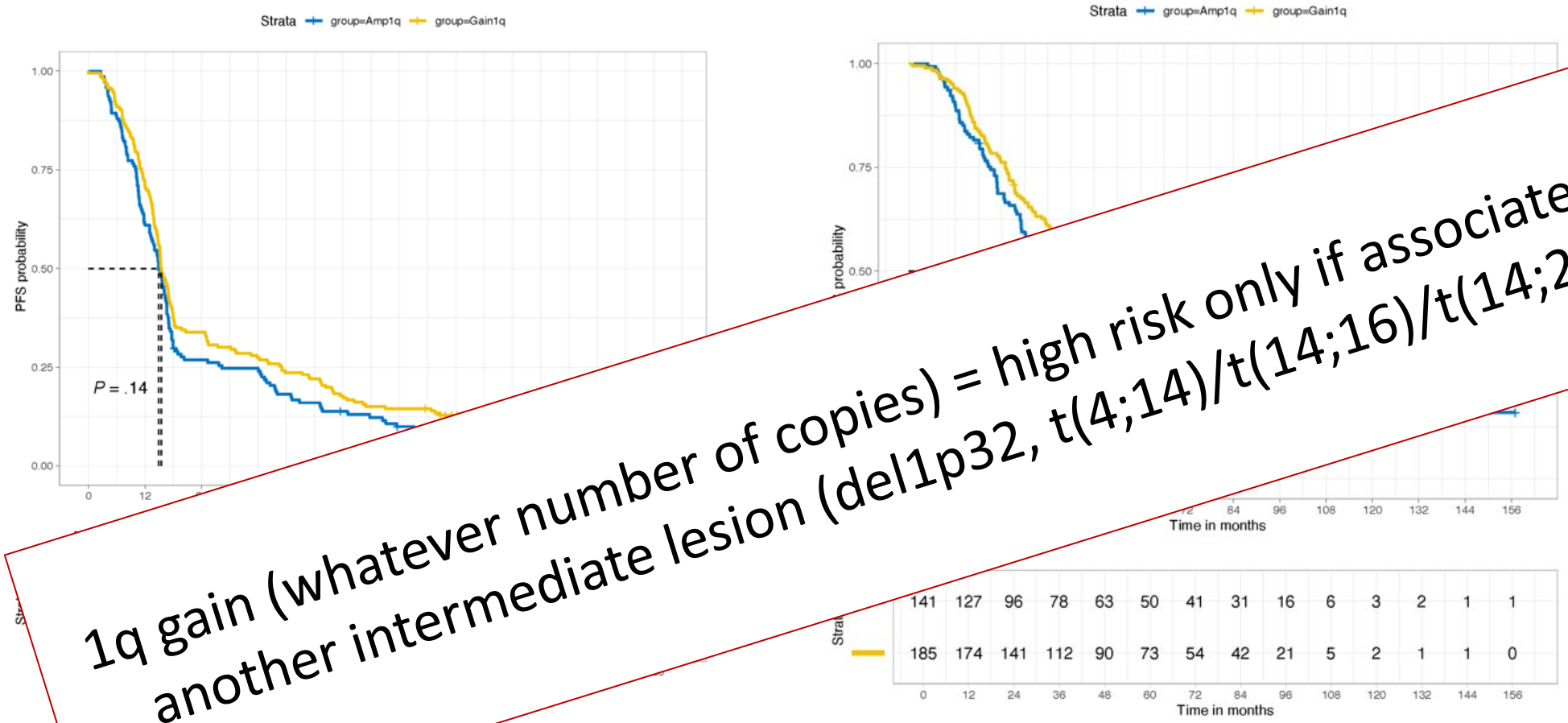
Prognostic impact of Gain 1q : 35% NDMM !



Prognostic impact of Gain 1q : 35% NDMM !



1q gain (whatever number of copies) = high risk only if associated to another intermediate lesion (del1p32, t(4;14)/t(14;16)/t(14;20))

Manuscript in prep

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Manuscript in prep

Conclusion

- The IMS Panel recommends the use of this HRMM definition in all clinical trials going forward and in routine practice.
- The HR subset should represent around 20% of NDMM patients.
- Represents an important step toward risk-stratified therapeutic approaches in routine.
- **We hope that this definition will promote the design and conduct of clinical trials FOCUSED on patients with HRMM**
- NGS-based definition, but available data with FISH (report the cut-offs positivity used)
- *Do we need an ultra high risk definition ?*
- FUTUR : continue to explore GEP, CTC, EMD, APOBEC, chromotrypsis, TSG mutations, GPRC5D/BCMA mutations, number of focal lesions, immune profile …….

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THANKS

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