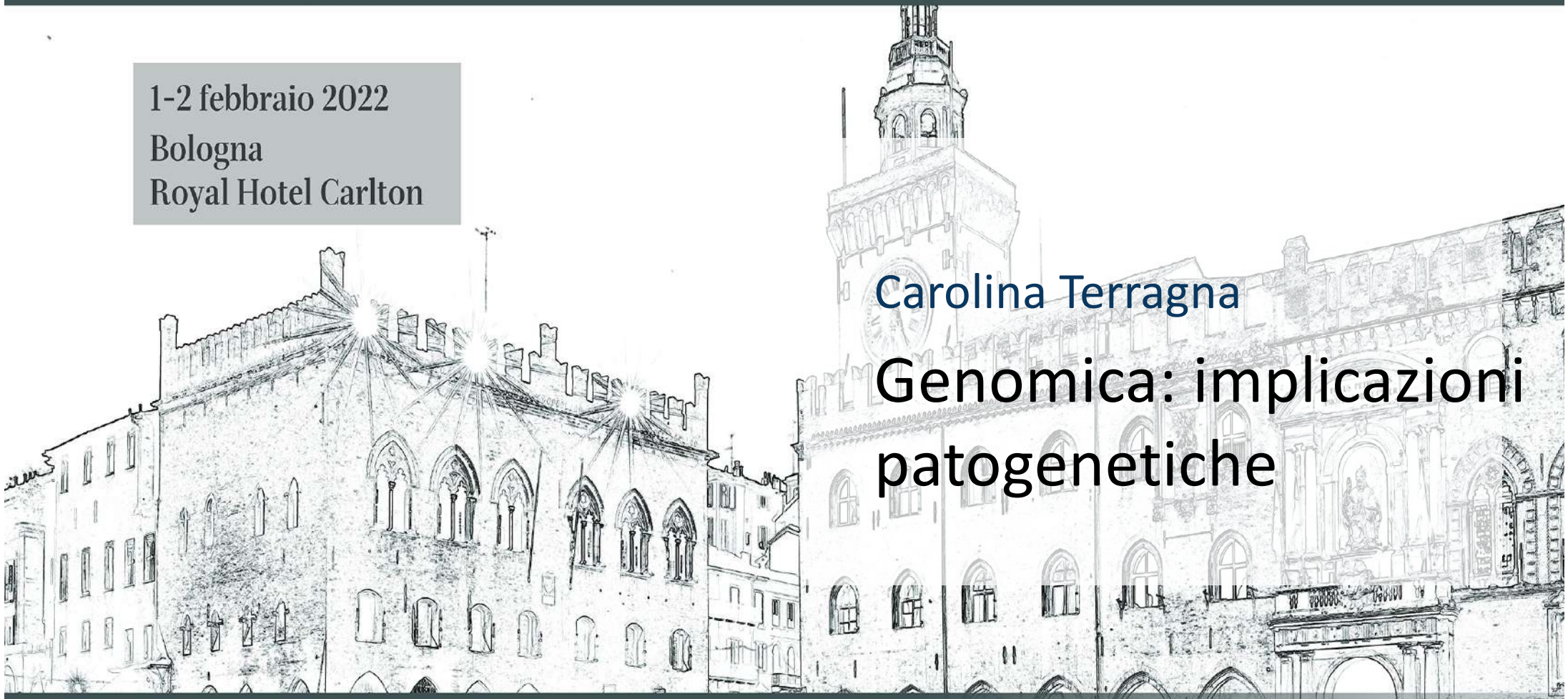
Highlights from IMW 2021

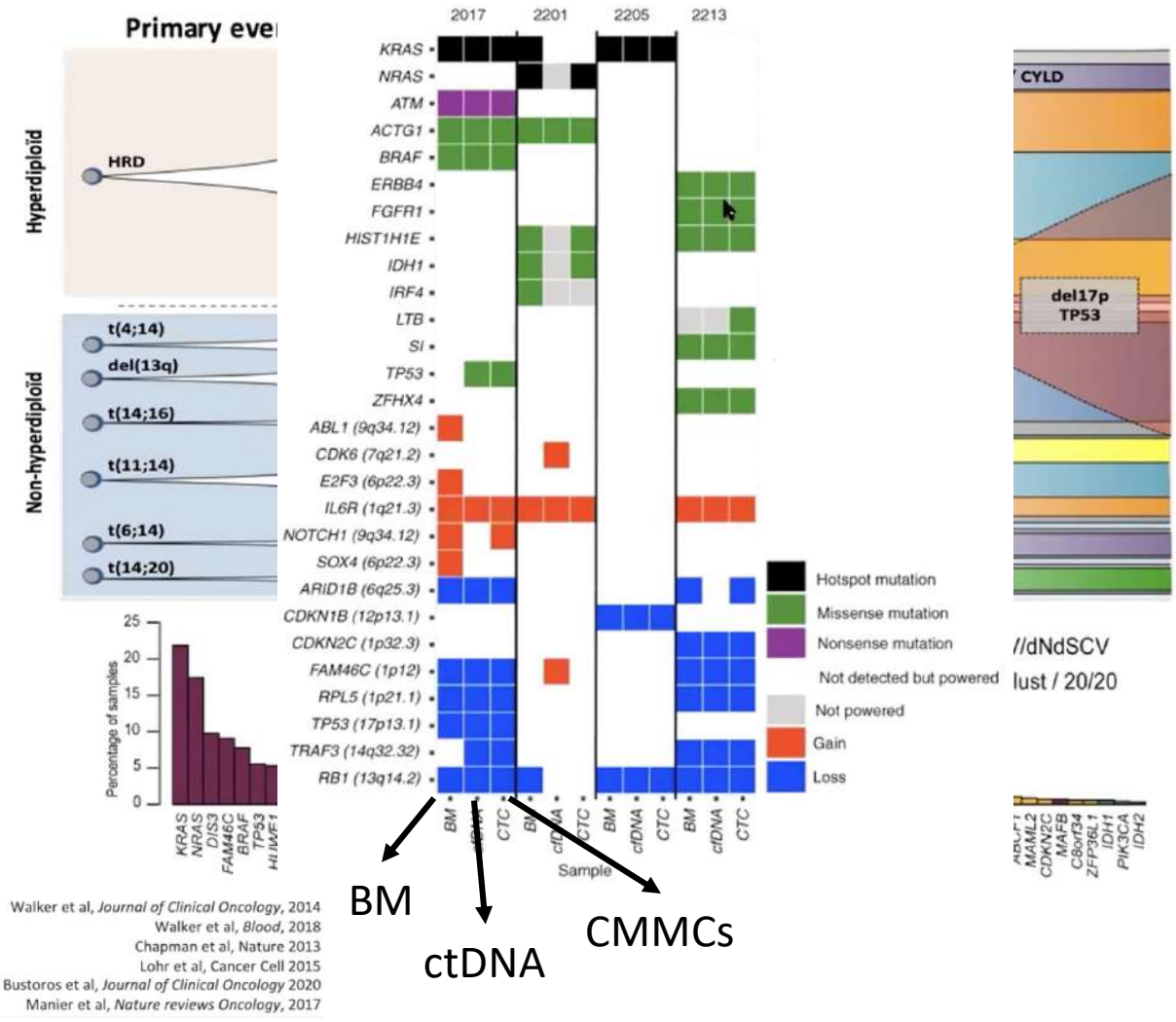
1-2 febbraio 2022
Bologna
Royal Hotel Carlton



Carolina Terragna

Genomica: implicazioni patogenetiche

MM genomic heterogeneity



Walker et al, *Journal of Clinical Oncology*, 2014
Walker et al, *Blood*, 2018
Chapman et al, Nature 2013
Lohr et al, Cancer Cell 2015
Bustoros et al, *Journal of Clinical Oncology* 2020
Manier et al, *Nature reviews Oncology*, 2017

1. molecular aberrations ***CO-occur*** => the genomic landscape is complex

2. molecular aberrations are many and consists in ***CNAs*** (mainly), ***t-IgH*** and ***SNVs***

3. the genomic landscape change ***in time*** & ***in space***

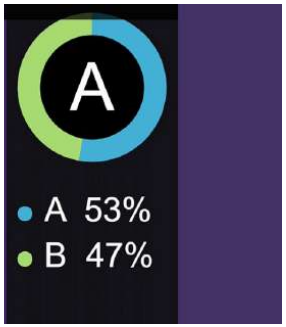
M. Bustoros, IMW 2021

why do we need to know about MM genomic heterogeneity?

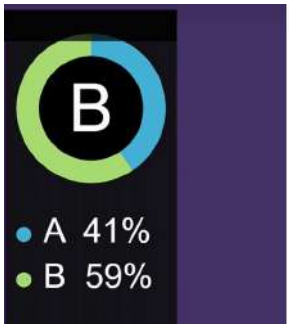
Is stratification based on genomics ready for primetime?

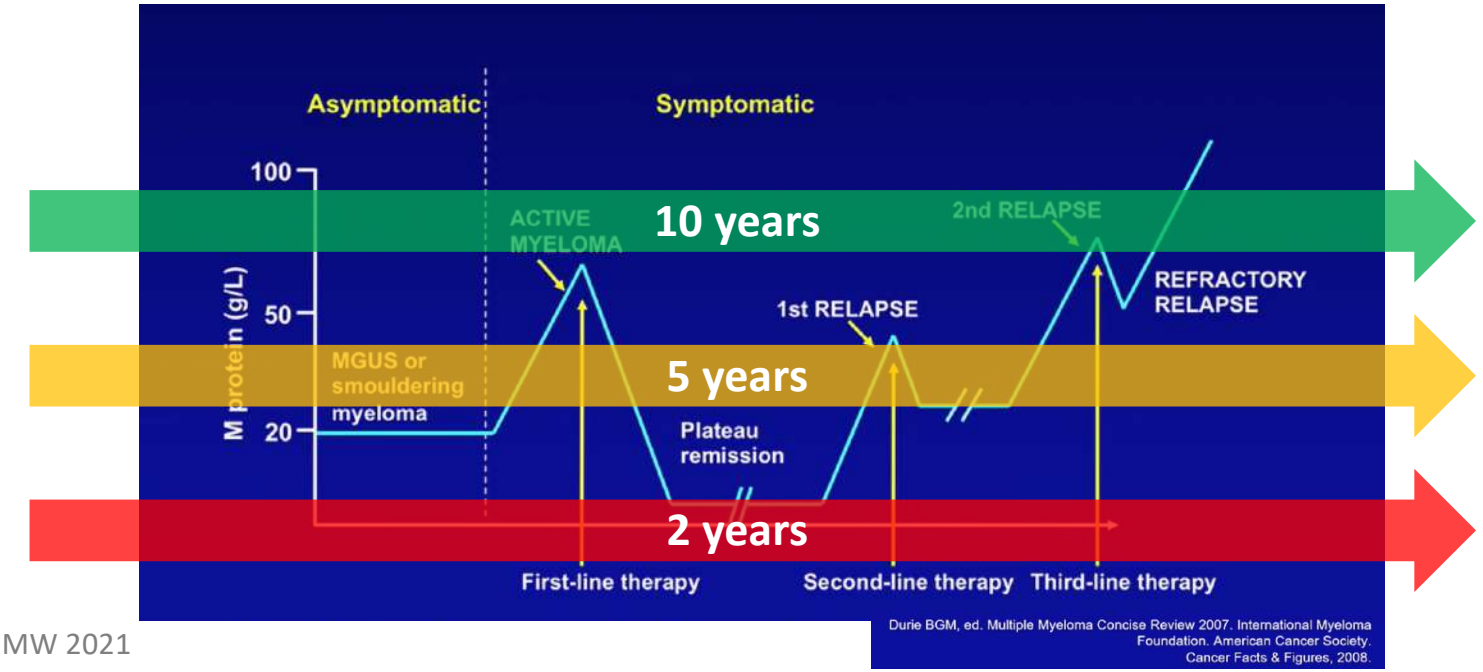
A. Yes
B. No

PRE debate



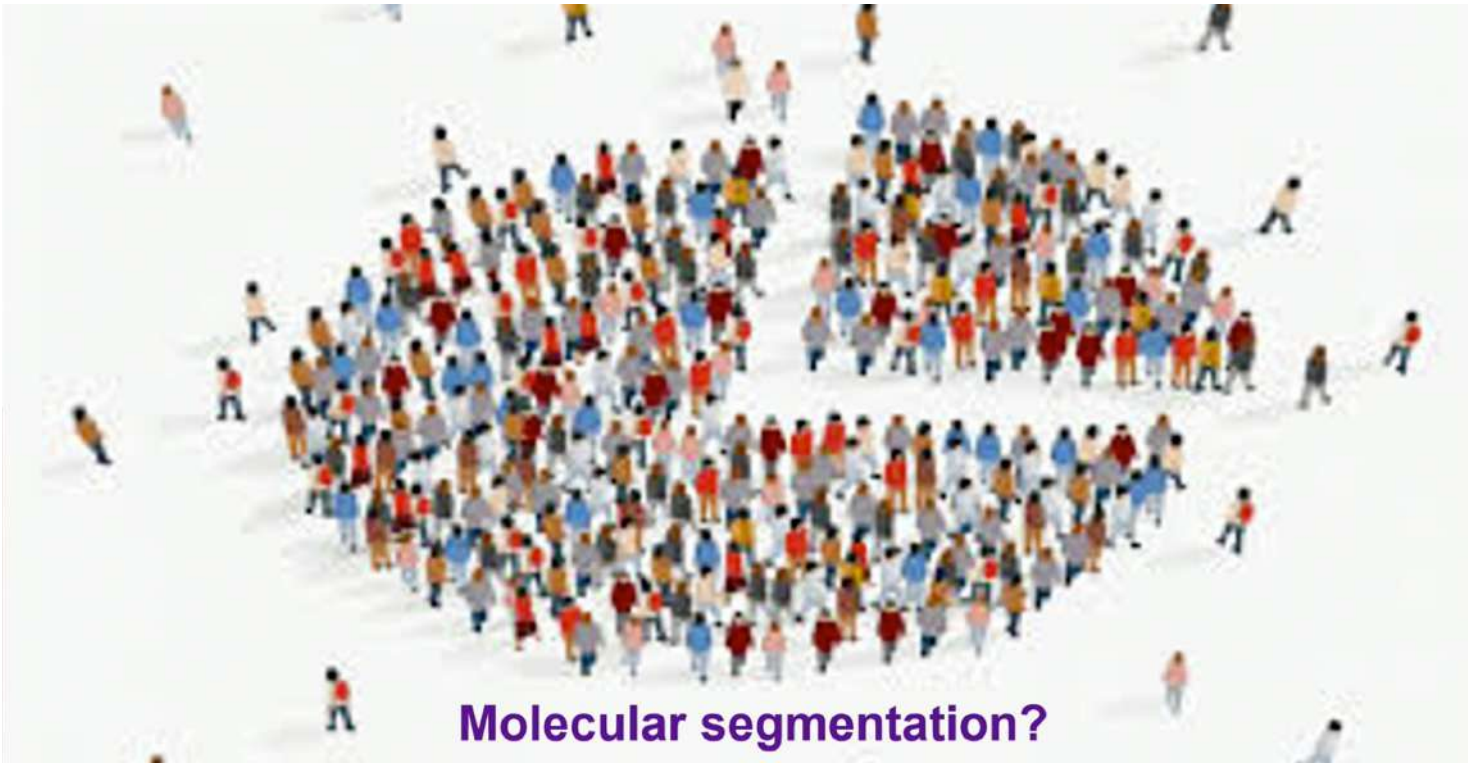
POST debate





G. Morgan & F. Davies, IMW 2021

why *do we need to know about MM genomic heterogeneity?*



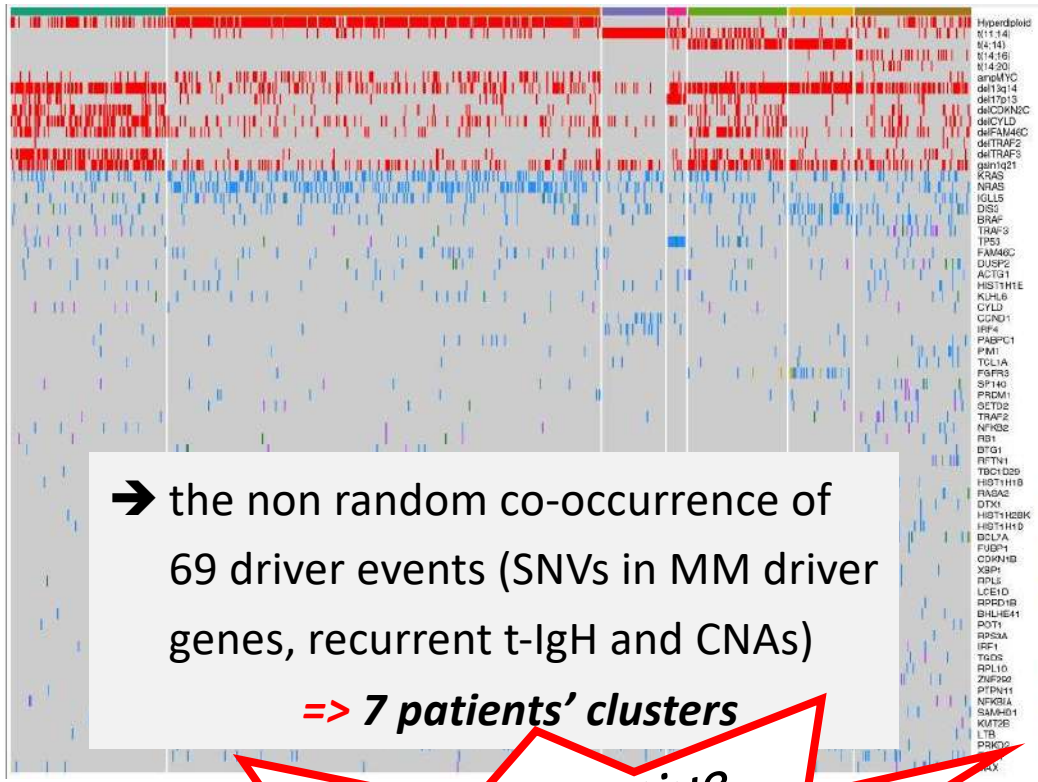
⇒ to target the disease ***biology***

⇒ to ***decrease*** therapy intensity in patients with low-risk features

⇒ to consider ***CURABLE*** a significant fraction of patients

G. Morgan, IMW 2021

genomics' *added value* over FISH



➔ the non random co-occurrence of 69 driver events (SNVs in MM driver genes, recurrent t-IgH and CNAs)

=> 7 patients' clusters

highly informative, though quite **complex**

➔ differ… …ients' segmentation

risk stratifier

- **INTERNATIONAL MYELOMA WORKING GROUP (IMWG)**
  → ISS, FISH (del(17p), t(4;14), t(14;16)), LDH, IgA, histology, cytogenetics, GEP, Labeling Index, MRI/PET scan, SNP/CGH
- **mSMART 3.0 (MAYO)**
  → HIGH: FISH (del(17p), t(4;14), t(14;16), t(14;16), amp1q, TP53 mutations, GEP, R-ISS3, double and triple hit mutations
  → INTERMEDIATE: FISH (t(4;14), cytogenetic del (13q), hypodiploidy, PCLI>3%
- **R-ISS combining ISS with FISH (ESMO2016, EMN, IFM)**
  → ISS, FISH (del(17p), t(4;14)), MRD?
  → "…novel approaches based on molecular technology should be used to achieve a more powerful prediction"
- **ULTRA-HIGH RISK**
  → Presence of multiple HR lesions
- **R-ISS_2 combining ISS with FISH (ESMO2016, EMN, IFM)**
  → ISS, FISH (del(17p), t(4;14), amp(1q)), MRD?

F. Maura et al., Nat Comm 2019
G.Morgan, IMW 2021

definition of "*high-risk*" disease

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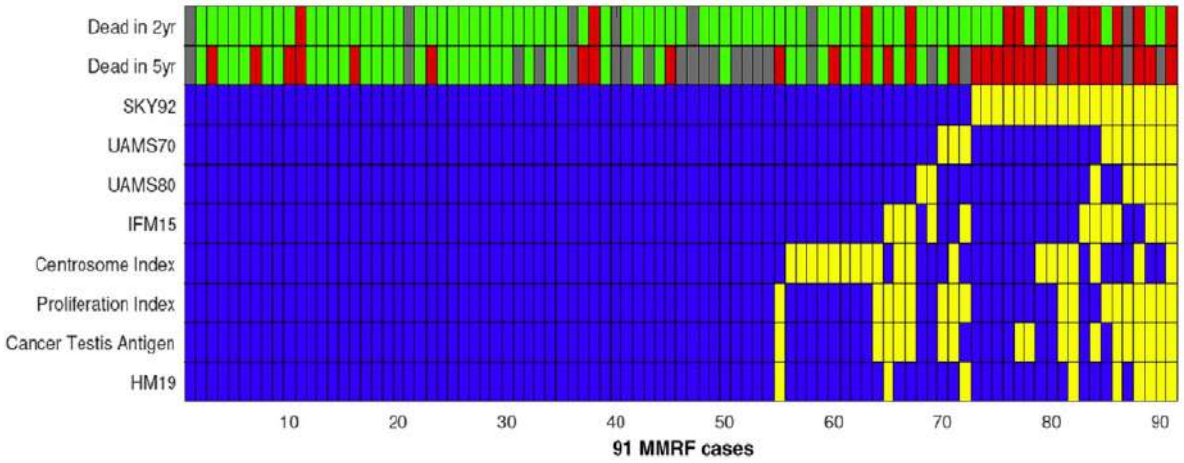
- **GEP70 (UAMS)**
→ expression of 70 genes affecting overlapping functions important for relapse: cell-cycle regulation, angiogenensis, cell adhesion, cell migration and proliferation

- **SKY92/ISS (SkylineDx)**
→ expression of 92 genes both directly and indirectly related to the disease + ISS

- **IFM PI (IFM)**
→ definition of a Prognostic Index (PI) based on the parameter estimates based on the multivariable Cox model computed for del(17p), t(4;14), trisomy 3, trisomy 5, trisomy 21, gain(1q), del(1p32)

- **DOUBLE HIT (UAMS)**
→ bi-allelic inactivation of *TP53* or ISS3 & *CKS1B* amplification (≥4N)

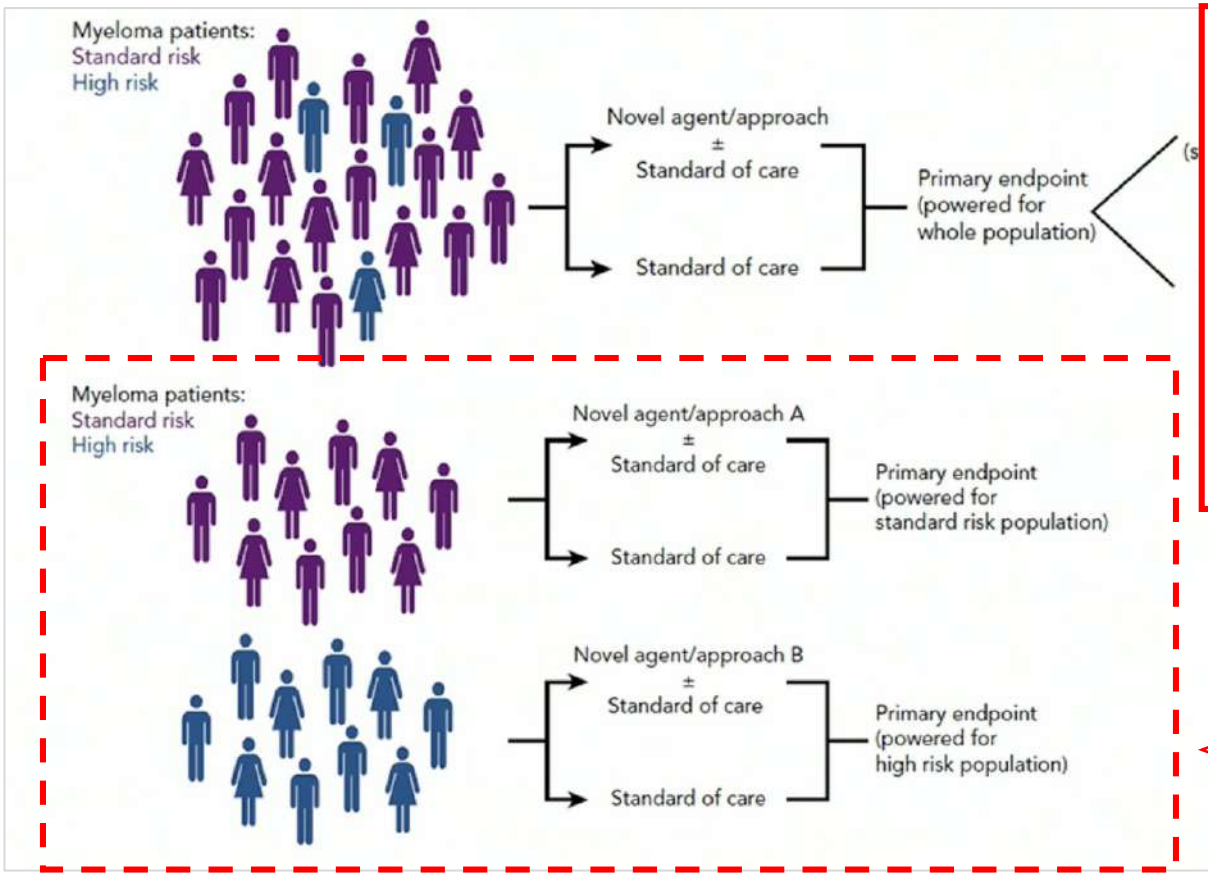


	high-risk (%)	median OS
ISS	33.6%	29 months
IMWG*	20%	35% 4-years OS
R-ISS**	10%	40% 5-years OS
SKY92/ISS	20.9%	50% 2-years OS
IFM PI***	ca. 19%	<50% 2-years OS
double-hit****	6.1%	48% 1.5-years OS

* del(17p) t(4;14) t(14;16)
** ISS del(17p) t(4;14)
*** del(17p) t(4;14) trisomy 3, 5, 21 gain(1q) del(1p32)
**** ISS III bi-allelic TP53 amp1q

Van Biers E.H..et al, Lymphoma & Myeloma International Congress 2017; Pawlyn C. et al., Leukemia 2020

high-risk definition => ***still*** an unmet clinical need



different ***genomic patterns***

↓

different ***expression pathways***

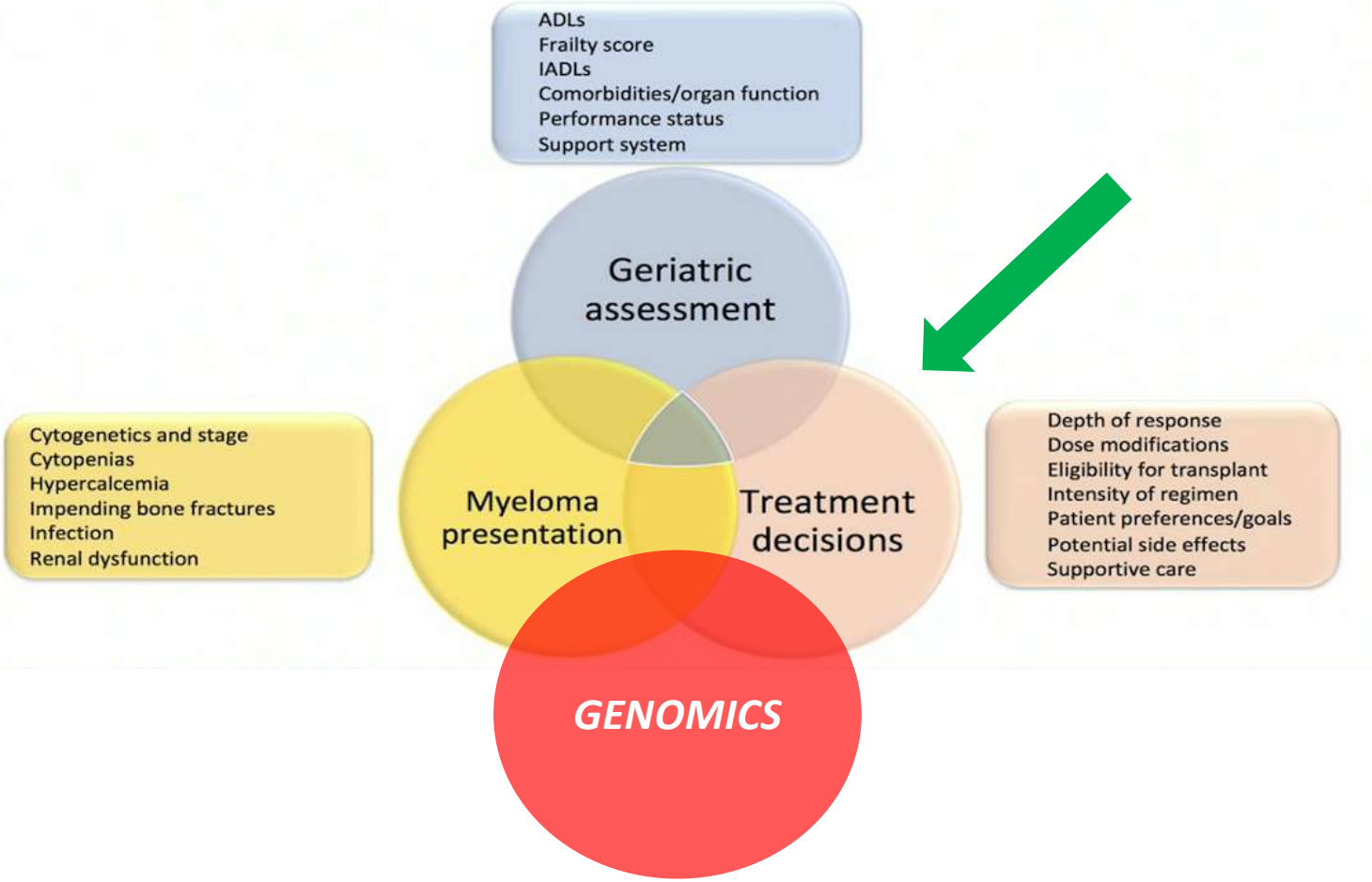
↓

different ***myeloma sub-types***

«trial design for high-risk patietns, who are identified UP-FRONT and entered into dedicated protocols»

F.Davies, IMW 2021

*"informed treatment decision based on **data**"*



G. Morgan, IMW 2021

NGS panel **for the daily clinical practice**

=> ***UMA panel***, NGS Unique Molecular Assay has been designed* to detect all the currently validated and suspected genomic DNA aberrations with prognostic value ***in a single assay*** (all-in-one panel)

- ***CNAs***: pipeline steps and analysis tools that take advantage of off-target reads to compute a whole genome Log2ratio signal precise enough for ARM-level calls
- ***IgH traslocations***: custom design on IgH region to minimize costs
- ***SNV and Indels***: pipelines already validated (Mutect, Strelka, Seurat)

Number	GENE	Mean cov	Min cov	Max cov	Number	GENE	Mean cov	Min cov	Max cov
1	ATM	255	27	816	42	KDM6A	142	4	358
2	ATR	253	11	643	43	KMT2B	168	1	537
3	BAX	167	10	512	44	KRAS	217	33	409
4	BCL7A	161	3	368	45	LEMD2	180	12	522
5	BIRC2	268	26	866	46	LTB	147	48	394
6	BIRC3	243	9	886	47	MAX	164	23	411
7	BRAF	235	13	689	48	MYC	202	65	520
8	BTG1	143	2	303	49	MYD88	241	53	577
9	CARD11	173	22	559	50	NF1	222	4	534
10	CCND1	145	36	607	51	NFKB1	206	9	544
11	CD19	156	25	415	52	NFKB2	156	19	396
12	CD27	150	21	368	53	NFKBIA	169	14	382
13	CD38	196	18	502	54	NOTCH2	199	11	642
14	CDKN1B	194	47	446	55	NRAS	222	83	402
15	CDKN2C	193	43	368	56	PIK3CA	266	13	675
16	CKS1B	188	53	496	57	PRDM1	196	31	533
17	CRBN	233	25	582	58	PRKD2	182	29	601
18	CUL4B	172	6	425	59	PSMB5	227	41	489
19	CYLD	191	10	448	60	PSMD1	218	4	441
20	DDB1	237	32	757	61	PTEN	175	2	417
21	DIS3	183	25	402	62	PTPN11	189	1	450
22	DNAH5	239	10	622	63	RASA2	234	2	599
23	DTX1	138	17	330	64	RB1	173	1	389
24	DUSP2	110	18	239	65	RBX1	209	42	430
25	EGR1	219	60	492	66	RPL10	155	29	434
26	EVI5	185	31	428	67	RPL5	169	26	455
27	FAF1	197	7	441	68	SAMHD1	229	31	479
28	FAM46C	223	92	373	69	SETD2	240	13	715
29	FANCA	181	3	476	70	SF3B1	225	35	467
30	FBXO4	221	15	610	71	SGPP1	133	10	364
31	FGFR3	81	3	312	72	SNX7	176	3	434
32	HIST1H1B	133	29	303	73	SP140	194	1	457
33	HIST1H1D	159	42	367	74	STAT3	218	57	512
34	HIST1H1E	125	47	243	75	TGDS	178	19	413
35	HIST1H4H	278	106	539	76	TNFRSF17	188	42	413
36	IDH1	230	56	454	77	TNFSF12	95	7	373
37	IDH2	190	1	735	78	TP53	144	10	423
38	IGLL5	68	0	344	79	TRAF2	187	16	624
39	IKZF1	227	36	672	80	TRAF3	184	6	421
40	IL6ST	245	28	670	81	XBP1	173	12	389
41	IRF4	229	26	559	82	XPO1	239	66	543

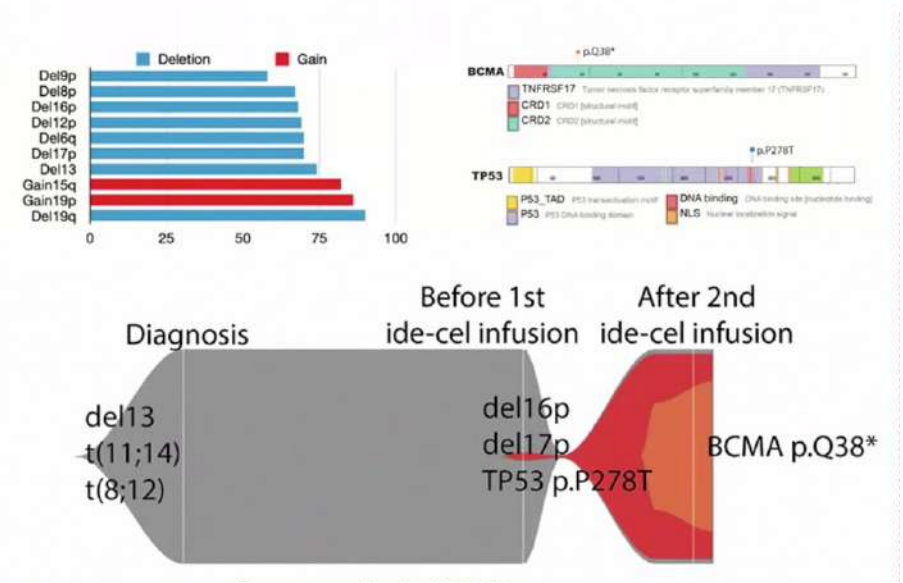
*in collaboration with N. Bolli, UniMi

t(4;14)

1q CN gain

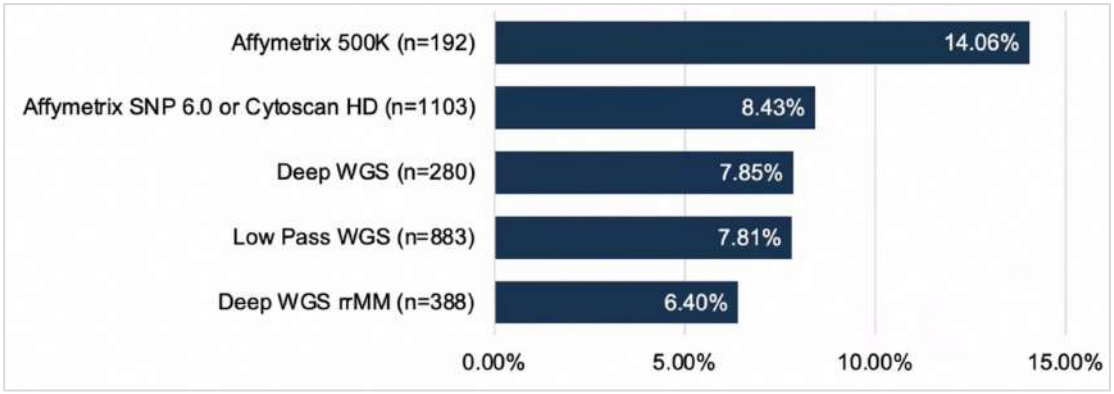
del(17p)

bi-allelic *BCMA* loss after CAR-T cell therapy



M.Samur et al., 2021

M.Da Via et al., 2021



M.Samur, IMW 2021

BO dataset

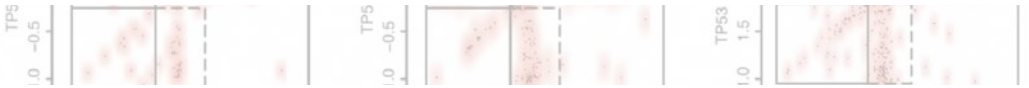
(CNAs profile by SNPs array)

171/471 del16p (36%)

25/471 del *BCMA* (***5%***)

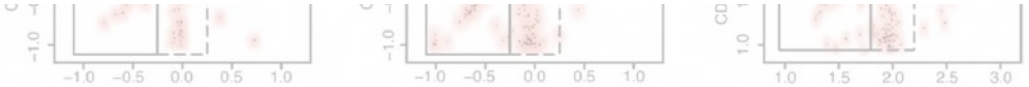
bi-allelic *BCMA* loss co-occurs with other high-risk events

- mono-allelic del(16p) co-occurs with several deletions, mainly del(17p) and del(1p)



- del(16p) extension varies among patients => ***local genomic instability***?

- is del(16p) the ***consequence*** or the ***cause*** of this genomic instability?



- mono-allelic del(16p) at baseline ***do not*** correlate with more frequent relapse after anti-BCMA therapy (but more data are needed)

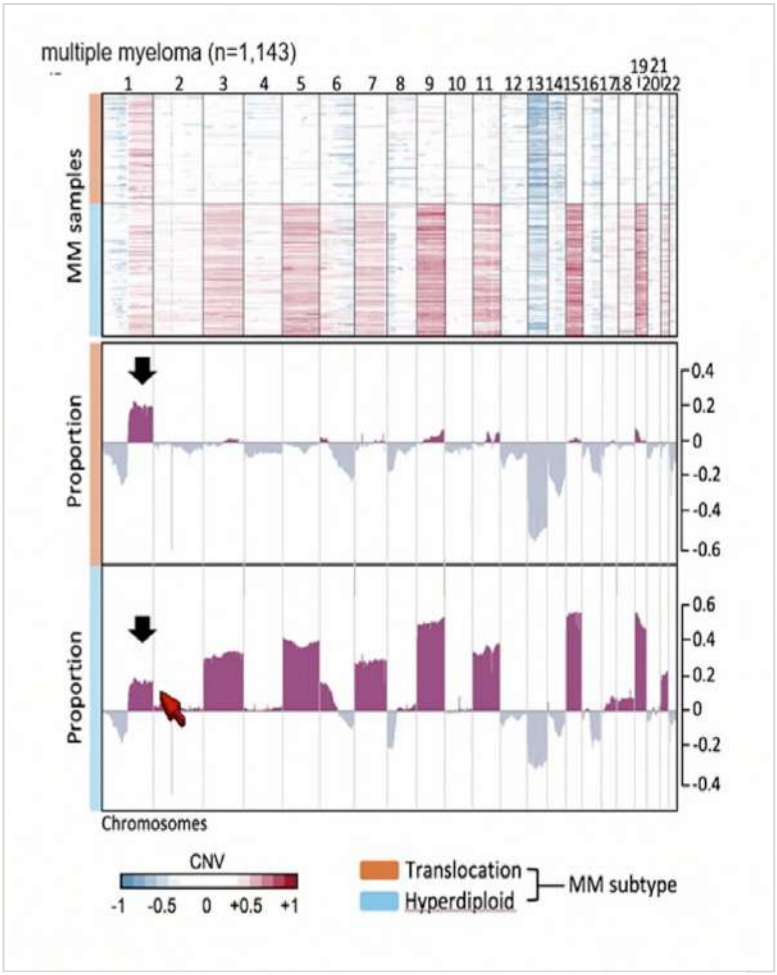
(CNAs profile by SNP's array)

8/25 del *BCMA* & del *TP53* (**44%**)

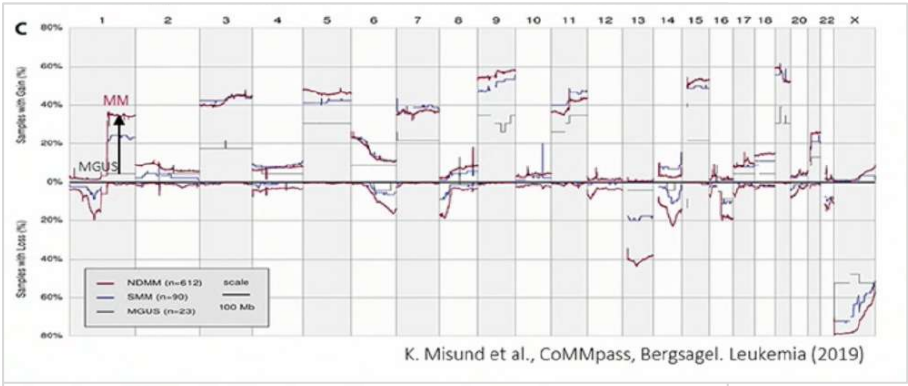
4/25 del *BCMA* & amp *MYC* (16%)

M.Samur, IMW 2021

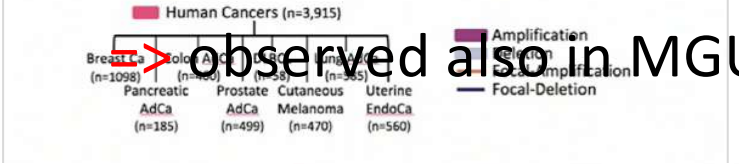
chromosome1q CNAs



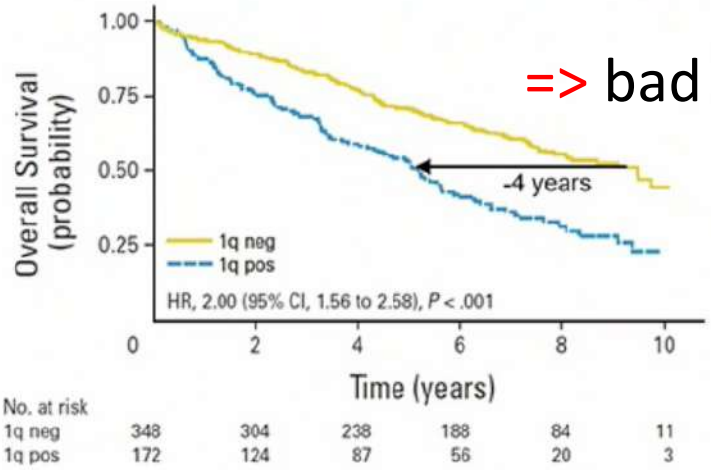
Broad and MMRF COMMPASS data. A. Mahdipour & R. Tiedemann, Unpublished Data, IMW 2021



K. Misund et al., CoMMpass, Bergsagel. Leukemia (2019)



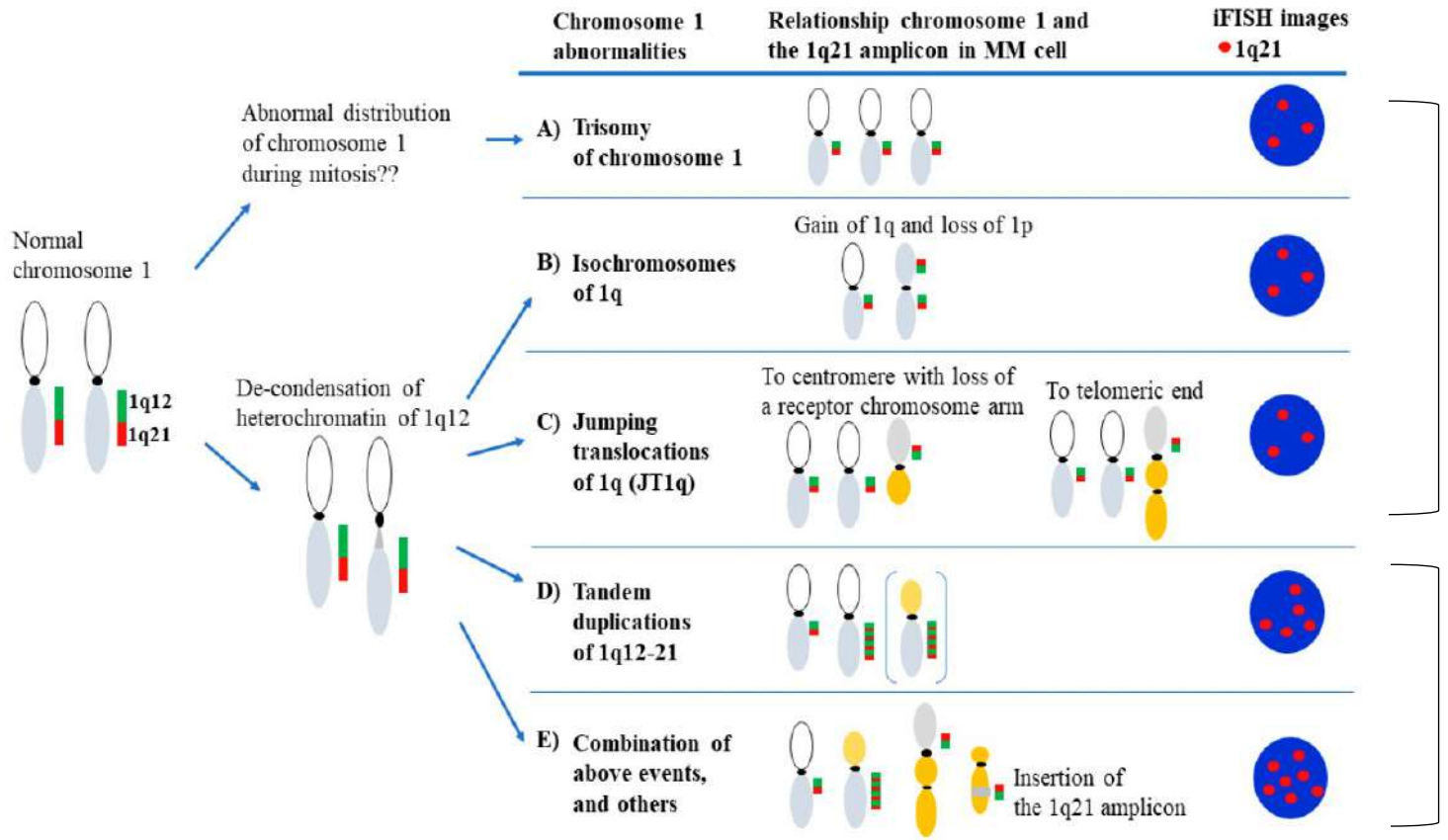
=> observed also in MGUS



=> bad prognosis (?)

H. Avet-Loiseau, JCO (2012) 30, 1949-1952

1q CNAs => frequency



gain1q (***3 copies***)

ca.30% NDMM

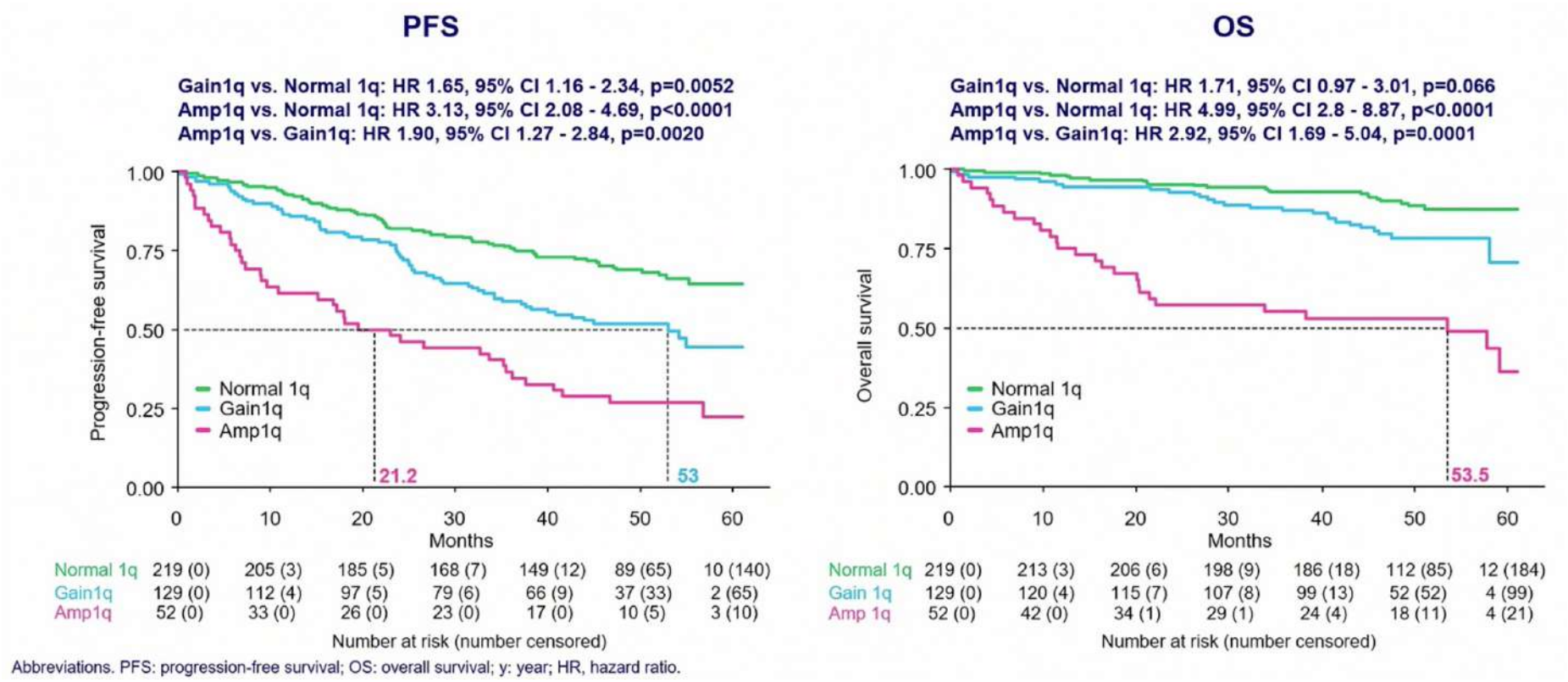
amp (***4 copies***)

ca.8% NDMM

FISH cut-off = 10% (20%)

H. Hanamura, Cancer 2021

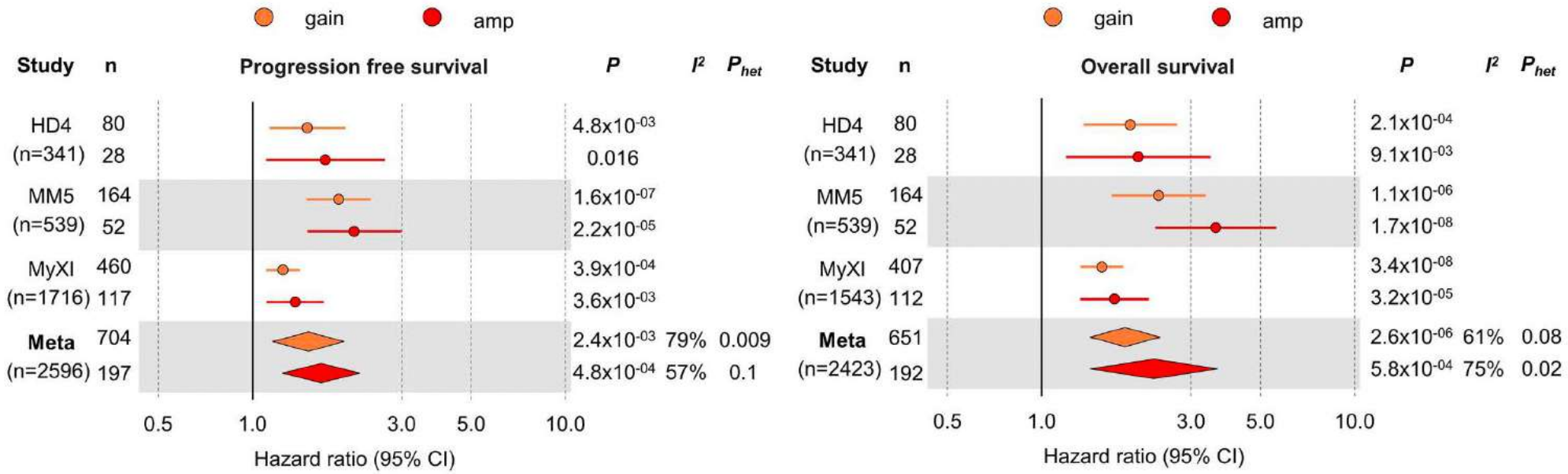
1q CNAs & FORTE trial



Abbreviations. PFS: progression-free survival; OS: overall survival; y: year; HR, hazard ratio.

M. D'Agostino, IMW 2021

1q CNAs & 2,596 trial patients meta-analysis

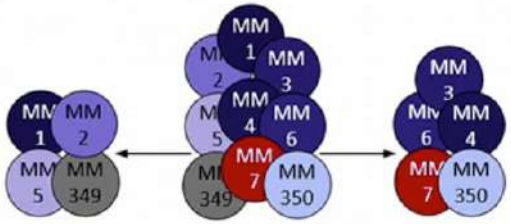


➔ «*..gain(1q) and amp(1q) are independently associated with poor outcome, with no discernible differences…*»

N. Weinhold, Haematologica 2021

gain(1q) => biological significance

UAMS TT3 MM tumor cohort (n=350)



No +1q
+11q22
+11q13
+5q14

Hyperdiploid MM*
t(11;14) MM*

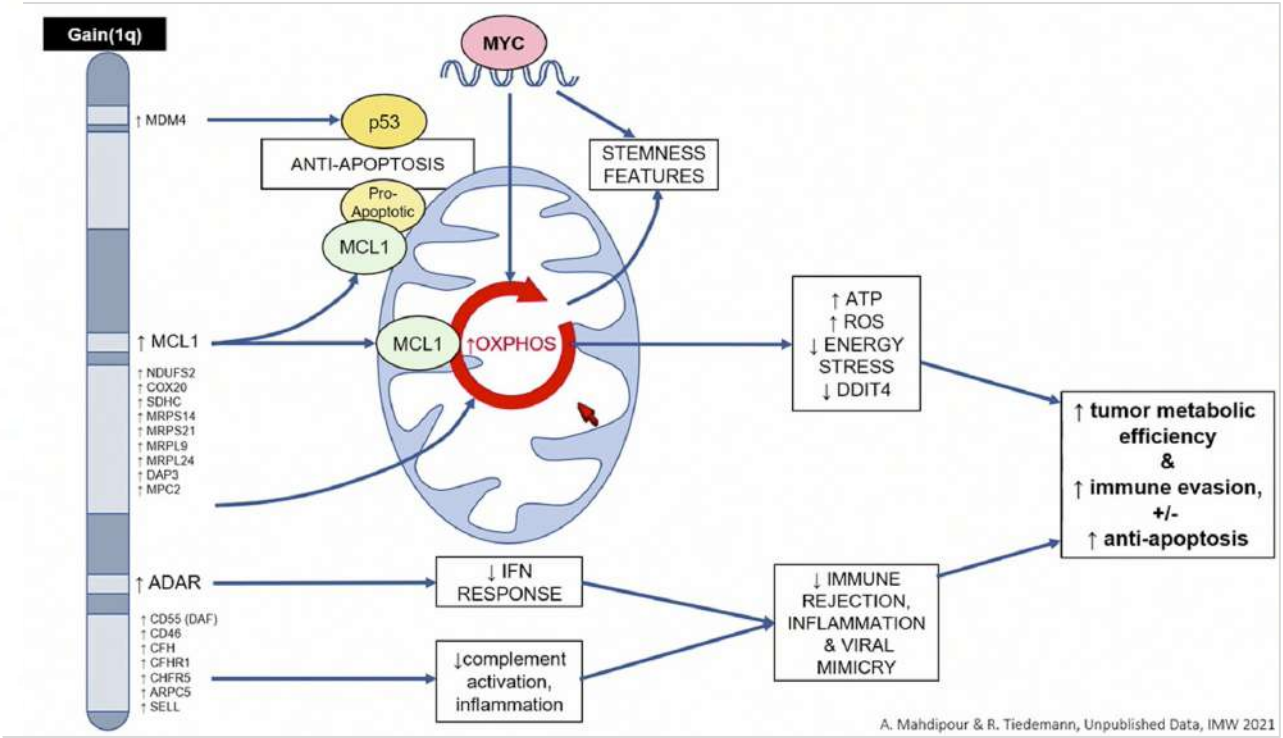
↑ IFNγ response
↑ IFNα response
↑ IL6 JAK STAT3
↑ Inflammatory response

+1q
+1q
-1p22
-13q12
+8q24

Proliferative (PR) MM*
t(4;14) MM*

↑ E2F targets
↑ G2M checkpoint
↑ MYC targets
↑ Mitotic spindle
↑ WNT β-catenin signaling
↑ Estrogen late response
↑ Spermatogenesis
↑ UPR
↑ Oxidative phosphorylation
↑ Cholesterol homeostasis
↑ MCL1

scRNAseq



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1-2 Febbraio 2022
Bologna
Royal Hotel Carlton

take-home message

1. MM genomic heterogeneity needs to be explored (aka, *know your enemy*)

2 . high-risk definition => unmet clinical need (*#more biology, less statistics*)

3. a precise *molecular segmentation* is mandatory to design risk-based clinical trials

4. genomics is *ready for prime-time* (implemented in the daily clinical practice)

thanks

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prof. Michele Cavo

AIT Bologna

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