Highlights from IMW 2019

19-20 novembre 2019
Bologna
Royal Hotel Carlton

Antonino Neri

Dipartimento di Oncologia ed Emato-oncologia
Università di Milano
UOC Ematologia
Fondazione Cà Granda IRCCS Policlinico, Milano

L'evoluzione genomica clonale
Eventi "Double Hit"

Coordinatore Scientifico
Michele CAVO

Comitato Scientifico
Mario BOCCADORO
Michele CAVO
Maria Teresa PETRUCCI

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I have NO financial disclosure or conflicts of interest with the presented material in this presentation.

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PRIMARY and SECONDARY GENETIC EVENTS in MULTIPLE MYELOMA

Primary abnormalities

Trisomies (~45%)
Odd-numbered chromosomes: 3, 5, 7, 9, 11, 15, 19, and 21

IgH translocations (~55%)
Translocations involving the IgH gene locus at 14q32

Translocation;locus;gene
t(4;14);4p16;*FGFR3–MMSET*
t(14;16);16q23;*MAF*
t(14;20);20q12;*MAFB*
t(8;14);8q24;*MAFA*
t(11;14);11q13;*CCND1*
t(6;14);6p21;*CCND3*

MYC dysregulation

Cyclin dysregulation

Secondary abnormalities

Monosomies
Chromosome 13
Chromosome 17
Chromosome 14

Deletions
Chromosome 17p
Chromosome 1p

Amplification
Chromosome 1q gain or amplification

Other genomic alterations
miRNA

Recurrent mutations
KRAS
NRAS
TP53
DIS3
FAM46C
BRAF
TRAF3
ROBO1
CYLD
EGR1
SP140
FAT3
CCND1

KUMAR et al NAT REV ONCOL, 2018

Genetic lesions associated with high-risk multiple myeloma

Class	Lesion	Genes affected	Frequency in NDMM (approx. %)	Change in Frequency at relapse	Identifiable by			
					iFISH	CNA	GEP	NGS
Primary translocations	t(4;14)	MMSET	15	No change, clonal initiating events	Yes	No	Yes	Yes
	t(14;16)	MAF	3					
	t(14;20)	MAFB	1.5					
Secondary translocations	MYC	MYC	20	Increased	Yes	No	No	Yes
	JT1q	BCL9, MCL1, IL6RA, CKS1B, ANP32E and others	Unknown	Increased	Yes	No	No	Yes
Copy number change	Isochromosome formation	Many	Unknown	Unknown	No	Yes	No	Yes
	Hyperhaploidy	Many	Few	Unknown				
	Gain (1q)	Genes located in the 1q transcriptional unit are: BCL9, MCL1, IL6RA, CKS1B, ANP32E and others	Gain: 30 Amp: 10	Increased	Yes	Yes	Yes	Yes
	Del (1p)	Genes lost on 1p are: FAF1, CDKN2C, FAM46C, RPL5 and others	20	Increased				
	Del (17p)	TP53 and others	10	Increased				
Homozygous inactivation of TSGs	Mutation +/− copy number change	RB1	2	Increased	No	Yes, with NGS	No	Yes with CNA
		TP53	4					
		FAM46C	5					
		CYLD	3					
		TRAF3	8					
Genetic changes associated with DNA repair deficiency	Genome-wide LOH	Many	5	Increased	No	No	No	Yes

Pawlyn et al. Nature reviews Cancer 2017, 17:534

COMMON RISK STRATIFICATION APPROACHES IN NEWLY DIAGNOSED MULTIPLE MYELOMA

Staging system	Variables	Stages
International Staging System (ISS)[56]	Serum albumin and β_2m levels	• I: serum albumin ≥3.5 g/dl and β_2m <3.5 mg/dl • II: neither stage I nor III • III: β_2m >5.5 mg/dl
Revised International Staging System (RISS)[8]	Serum albumin, β_2m, and LDH levels, and plasma cell FISH	• I: ISS stage I, LDH normal[a], and standard-risk disease according to FISH • II: neither stage I nor stage III • III: ISS stage III plus abnormal LDH or high-risk disease according to FISH (del 17p and/or t(4;14) or t(14;16))
International Myeloma Working Group (IMWG) risk staging[5]	Serum albumin, β_2m, and LDH levels, and plasma cell FISH	• Low risk: ISS stage I or II, absence of t(4;14), del 17p13 and del 1q21, and <55 years of age • Standard risk: all others • High risk: ISS stage II or III and either t(4;14) or del 17p13
mSMART risk staging[41]	Serum albumin, β_2m and LDH levels, plasma cell FISH, and proliferation index	• Standard risk: trisomies and/or t(11;14) • Intermediate risk: t(4;14) or 1q amplification • High risk: t(14;16), t(14;20), or del 17p
Gene-expression-based signatures[59,118–120]	• UAMS • Skyline 92–HOVON • IFM	Presence of alterations detected by each signature

KUMAR et al NAT REV ONCOL, 2018

17th International Myeloma Workshop | IMS | September 12-15, 2019 Hynes Convention Center Boston, MA, USA

What Are the Critical Unanswered Questions for Multiple Myeloma in 2019?

Meletios A. Dimopoulos, MD
Rector of the National and Kapodistrian University of Athens (N.K.U.A), Chair of the Department of Clinical Therapeutics, N.K.U.A, School of Medicine, Athens, Greece (email: mdimop@med.uoa.gr)

High-risk Myeloma

Need to Improve predictive factors at diagnosis

R-ISS is suboptimal:
Cannot predict early failures in R-ISS-1
Cannot identify R-ISS-3 with good prognosis

- **Additional molecular markers**
  - gene expression classifiers
  - double hit myeloma
  - Immune profiling

What is the best induction treatment for high-risk disease at diagnosis?
KRD+antiCD38 *vs* VRD+antiCD38

	5-Year OS* (%)	5-Year PFS* (%)
R-ISS I	82	55
R-ISS II	62	36
R-ISS III	40	24

*At a median follow-up of 46 months

DOUBLE HIT MYELOMA

Leukemia (2019) 33:159–170
https://doi.org/10.1038/s41375-018-0196-8

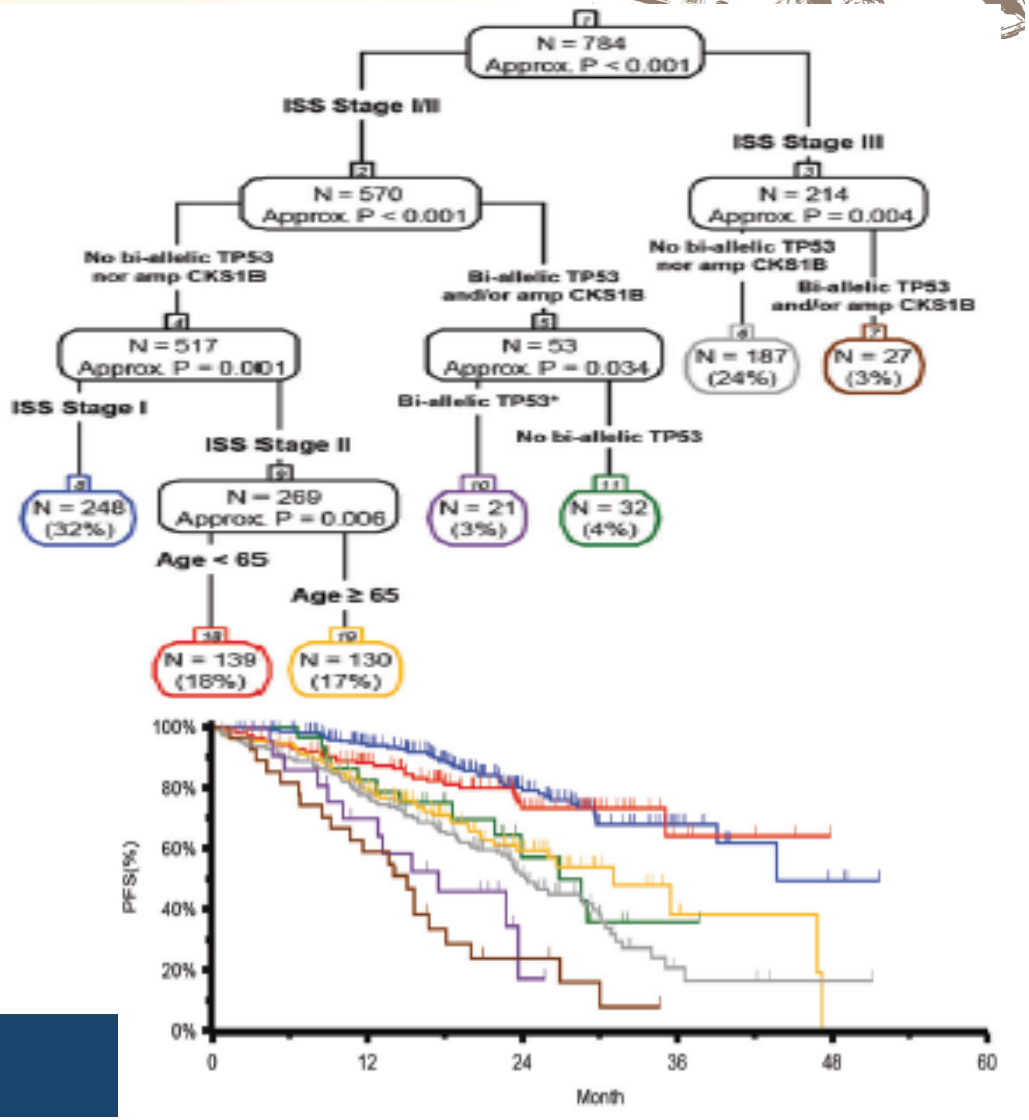
Walker B et al , Leukemia 2018

ARTICLE

Multiple myeloma gammopathies

A high-risk, Double-Hit, group of newly diagnosed myeloma identified by genomic analysis

- Modeled by the Arkansas Myeloma Group
- Whole-genome and exome data from 1273 patients
  - Genetic factors that influenced PFS and OS
- High-risk subgroup identified based on 784 pts using genomic data, ISS and age
  - Bi-allelic TP53 inactivation
    - OR
  - Amplification (>3 copies) of CKS1B (1q21) plus ISS stage 3
- Comprises 6.1% of the population
- PFS 15.4 months, OS 20.7 months
- Poor outcomes despite novel therapies…



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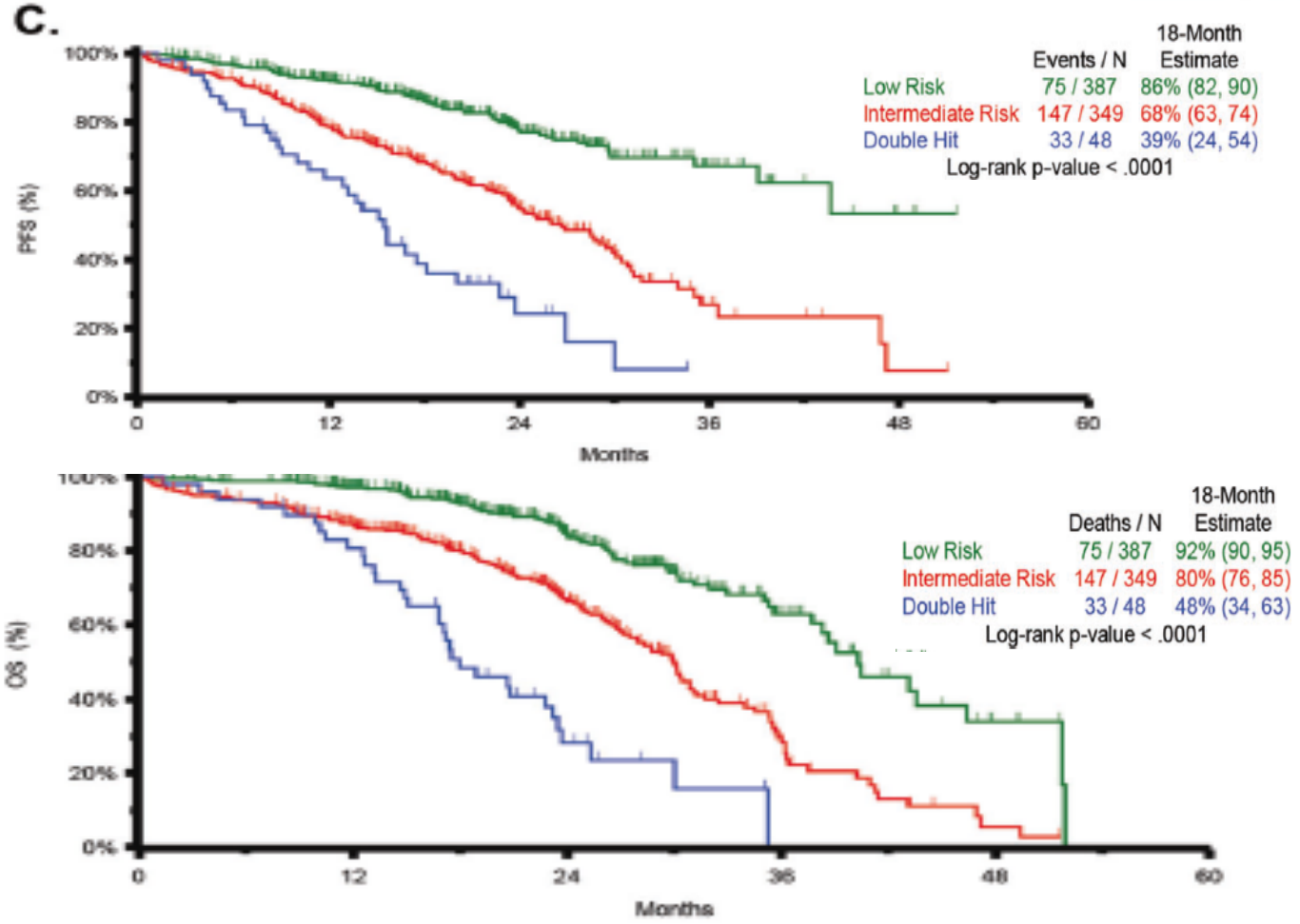
DOUBLE HIT MYELOMA



LOW RISK

No Biallelic loss of TP53 nor 1q gain and ISS I or ISS II and age < 65

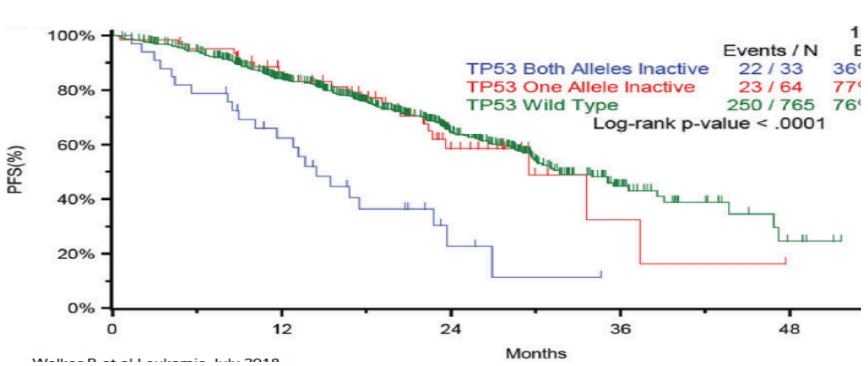
HIGH RISK

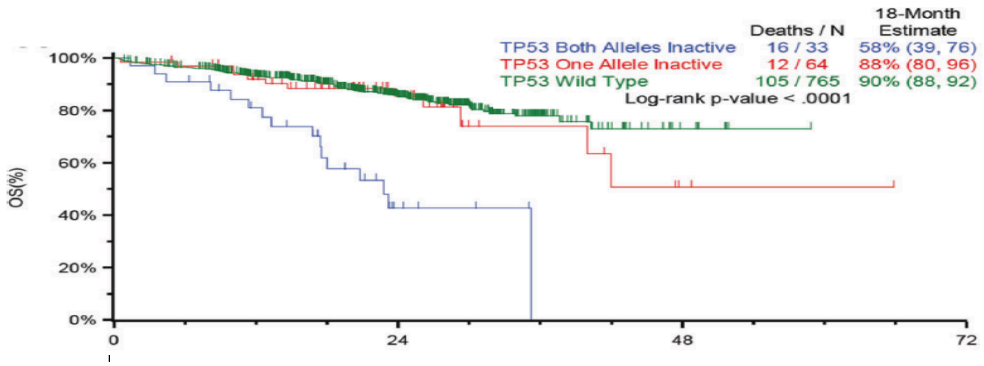
Biallelic loss of TP53 or ISS III and 1q amp

Walker et al. Leukemia, 2018

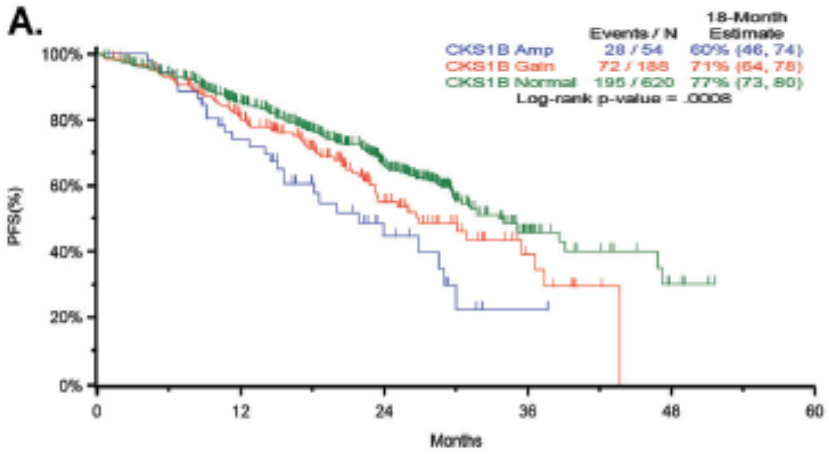
DOUBLE HIT MYELOMA

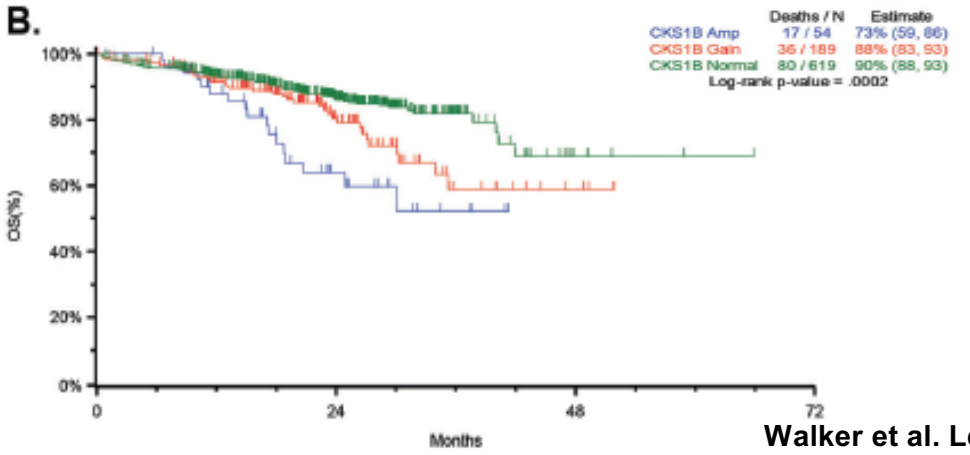
TP53 Mutations and Bi-allelic Inactivation Define Poor Outcome





Amp1q **(>3 copies)** Have A Worse Outcome Compared to Gain1q **(3 copies)**





Walker et al. Leukemia, 2018

DOUBLE HIT MYELOMA

The “Double Hit” group does not replace previous risk markers identified by iFISH but rather it identifies a distinct subgroup of patients at particularly high-risk of early progression and death that are suitable for entry into trials of novel therapies aimed at improving their outcome.

Given the frequency of other mutational events in NDMM it is unlikely that, given our current knowledge of the impact and frequency of mutations, the size of the group will increase substantially unless other driver mechanisms are identified.

In this context we clearly show that despite the size of the study we are missing genetic drivers in a substantial proportion of cases. Such mechanisms may be currently unknown or occur in portions of the genome we have not studied.

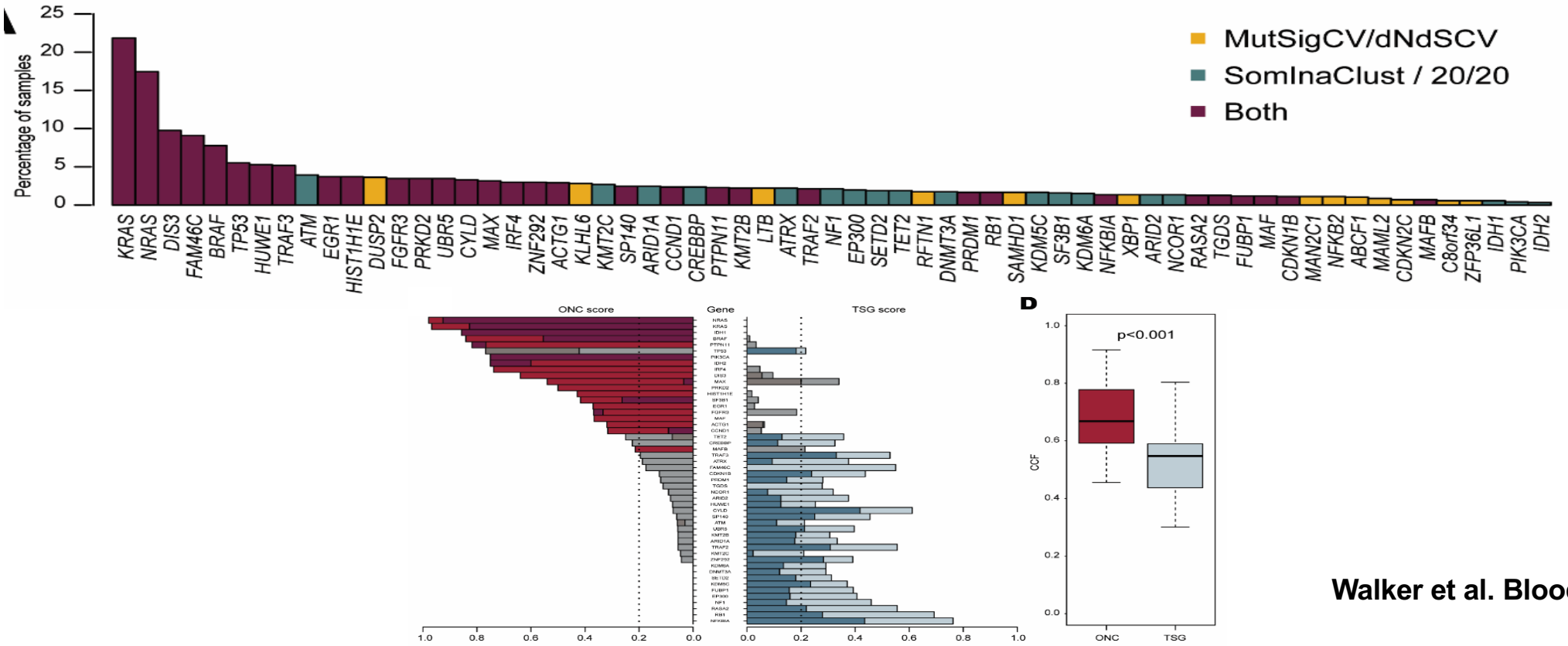
Walker et al. Leukemia, 2018

blood® Regular Article

Mutation Frequencies of 63 Driver Genes

LYMPHOID NEOPLASIA

Identification of novel mutational drivers reveals oncogene dependencies in multiple myeloma

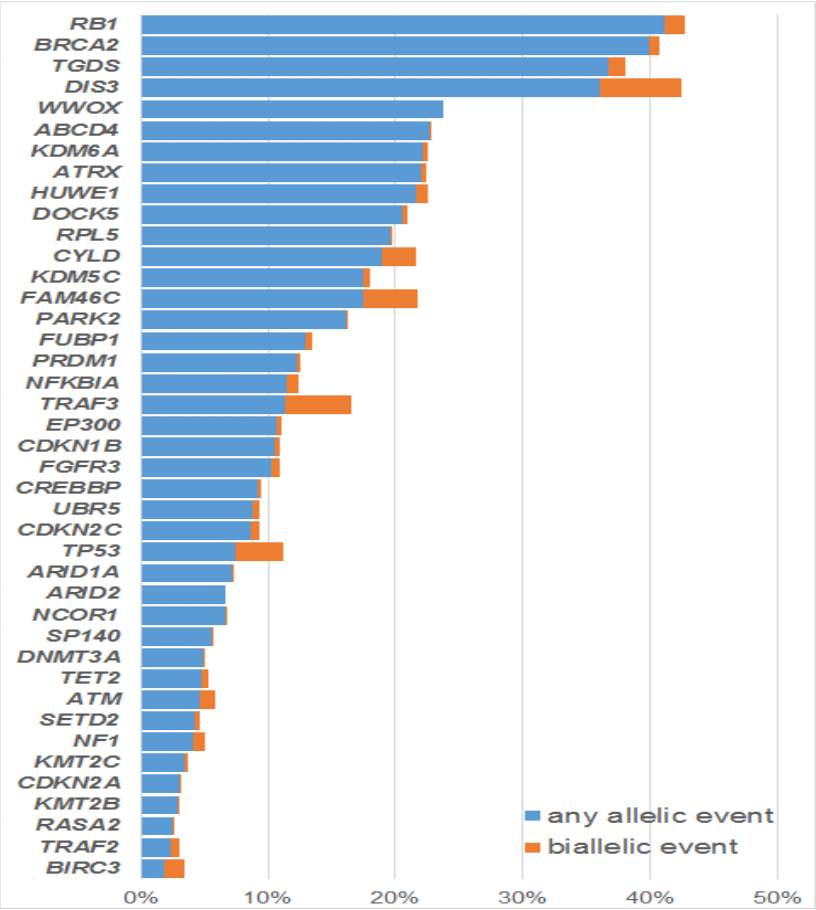


Walker et al. Blood 2018

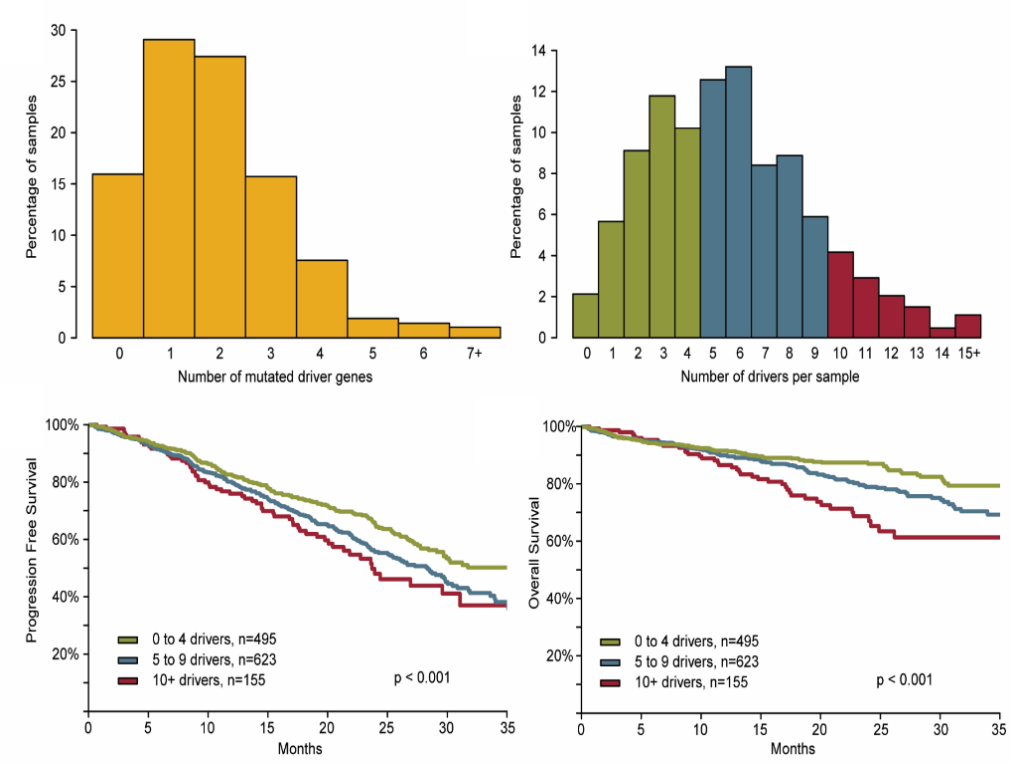
Identification of novel mutational drivers reveals oncogene dependencies in multiple myeloma

Mutation Frequencies of 63 Driver Genes

Recurrent bi-allelic events in driver genes



Increasing Number of Driver Alterations Results in Worse Outcome

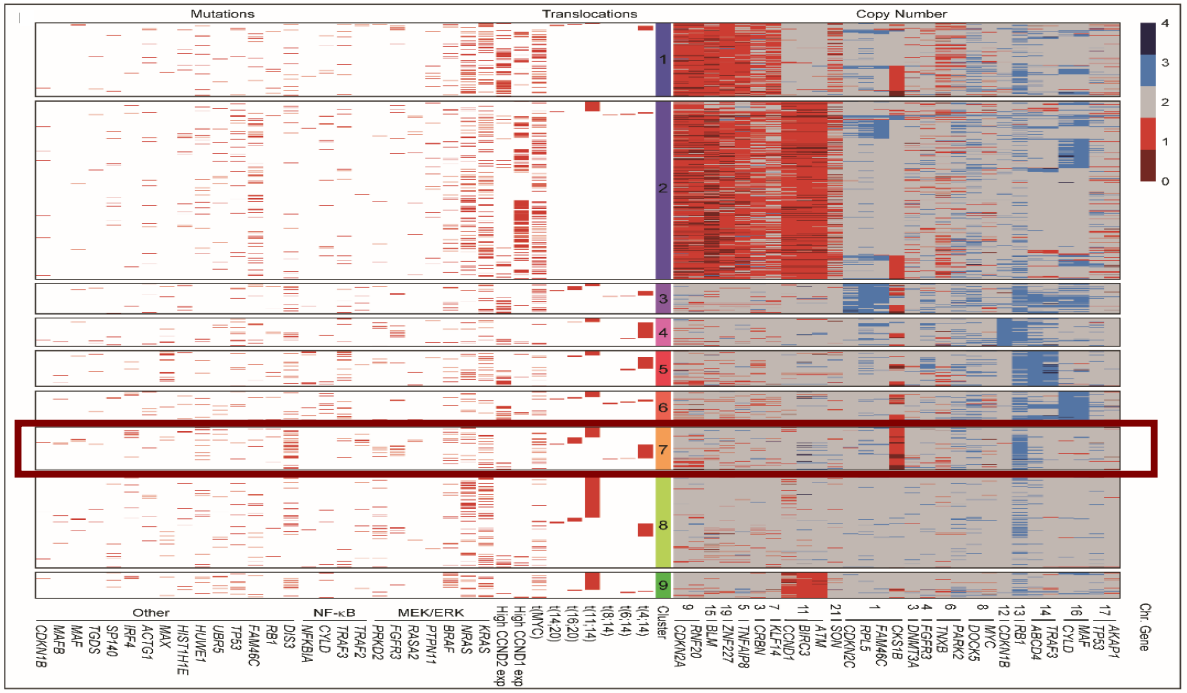


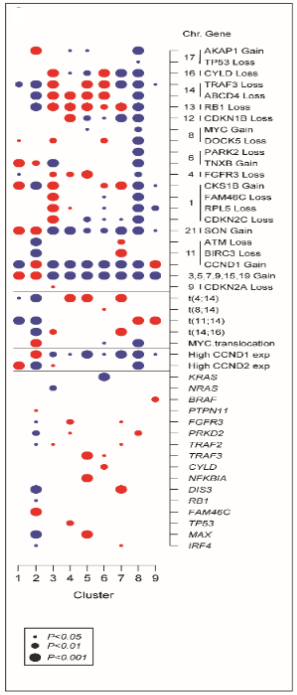
Walker et al. Blood 2018

LYMPHOID NEOPLASIA

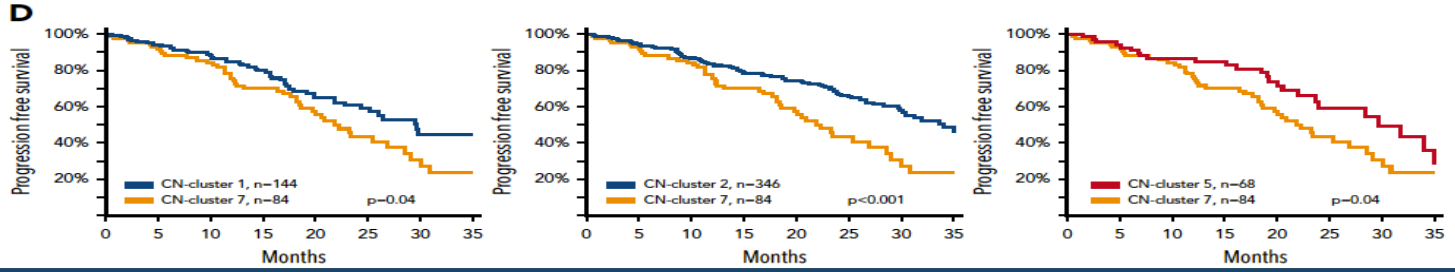
Identification of novel mutational drivers reveals oncogene dependencies in multiple myeloma

Clustering of Copy Number Data Identifies Nine Sub-Groups





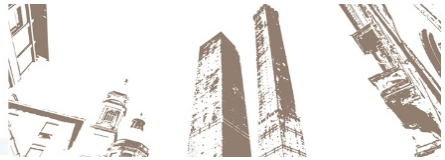
DIS3 mut
t(4;14)
t(14;16)
1q gain
RB1 del
Birc loss



Walker et al. Blood 2018

Transcriptome of malignant plasma cells

Gareth Morgan, NYU



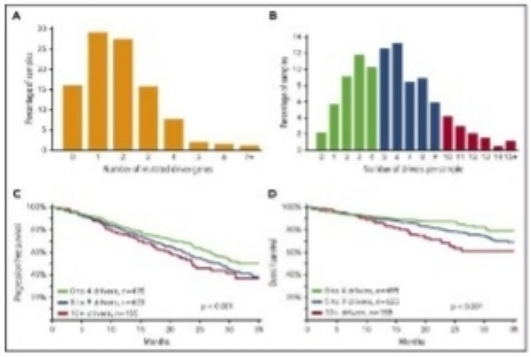
Talk outline.

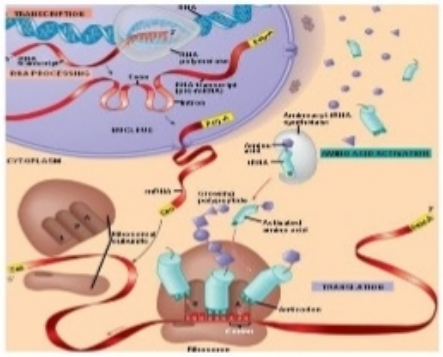
- To improve outcomes we need to understand biology.
- DNA mutations are interesting but the real action is in using RNA and protein to define biology using this to improve disease segmentation and identify new therapeutic targets.
- The importance of RNA processing as an oncogenic mechanism is beginning to emerge.
- Ultimately the transcriptome is controlled by epigenetic events in the nucleus and this is emerging as a critical mechanism which can be manipulated therapeutically.
- It is important to consider multiple myeloma not just as a genetic disease of plasma cells but as a disorder of the bone marrow as an organ.

Transcriptome of malignant plasma cells

Gareth Morgan, NYU

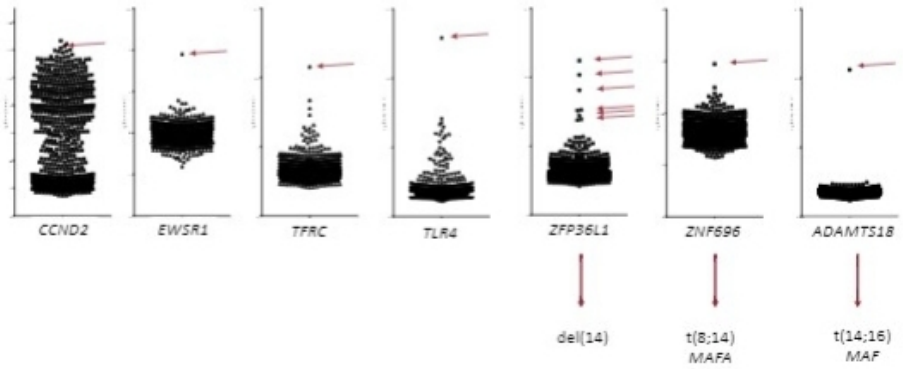
Missing drivers may be explained by abnormalities of the transcriptome.





Transcriptome abnormalities

- Amplification
- Fusion genes
- Gene overexpression by superenhancer rearrangement
- Gene knockout
- Abnormal RNA processing

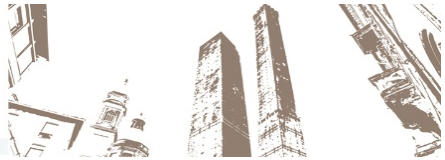


Kinase	Transcription Factor	Others
EML4-ALK	EIF4E3-FOXP1	TBL1XR1-ATR
AGK-BRAF	EIF4E3-FOXP1	ATM-DLG2
GTF2I-BRAF	EIF4E3-FOXP1	MED15-EP300
ESYT2-BRAF	TXNDC5-MYC	KAT6A-EYS
KANK-BRAF	TXNDC5-MYC	MKL1-LTBR
SNX29-FGFR1	TXNDC5-MYC	SLC5A5-MYO18A
ARHGAP27-MAP3K14	FOXO3-MYC	EWSR1-PKDREJ
AKT1-MAPK14	CDC6-RARA	HDAC4-PLEKHM3
HNRNPA2B1-NTRK3	DIP2B-ATF1	ABL1-RBM18
UBE2R2-NTRK3	DUSP22-IRF4	STK11-RTDR1
TSPAN3-ROS1	SS18-FLI1	TBL1XR1-SLC9C1
	ATF1-GALNT6	CREBBP-SLX4
	RUNX1-LINC00160	ST3B-TBL1XR1
		RUNX1T1-TBL1XR1

NYU Langone Health

Transcriptome of malignant plasma cells

Gareth Morgan, NYU



Abnormalities of RNA processing as potential drivers.

TENT5C
- 1p12
- Mutated 10%
- Deleted and translocated
- RNA processing
- Nucleotdyl transferase
- Destabilizes ER response genes

ZFP36L1
- located at 14q
- Interstitial deletion to IgH locus
- 1% NDMM
- Functions to modulate RNA transcripts
- Mutated in marginal zone lymphoma

SF3B1
- Recurrent hot spot mutations
- Rare
- Common MDS AML
- Hot spot mutations impact splicing
- High and low splicing impact biology of MM and is frequent

Splice variation is common in NDMM and high splice variant load is an adverse prognostic factor

NYU Langone Health

Identification and Molecular Characterization of High-Risk Multiple Myeloma Patients from the MMRF CoMMpass Study at Diagnosis and Progression

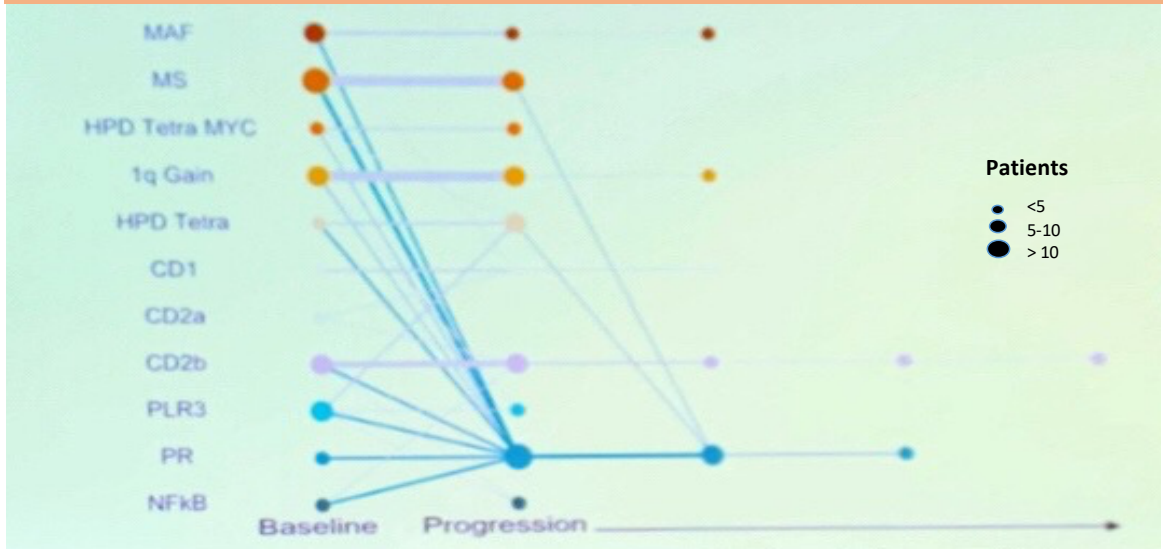
Sheri Skerget 1 , Austin Christofferson 1 , Sara Nasser 1 , Christophe Legendre 1 , Jennifer Yesil 2 , Daniel Auclair 2 , Sagar Lonial 3 , Jonathan Keats 1

[1] Translational Genomics Research Institute (TGen), Phoenix, AZ, [2] Multiple Myeloma Research Foundation (MMRF), Norwalk, CT, 3 Emory University, Atlanta, GA

✓ Analysis of patients from the MMRF CoMMpass Study with 1143 newly diagnosed myeloma patients.

✓ Tumor samples were analyzed using whole genome, exome, and RNA sequencing at diagnosis and each progression event, and clinical parameters were collected at baseline and every three months through the eight-year observation period.

Patients Transition to PR Class at Relapse



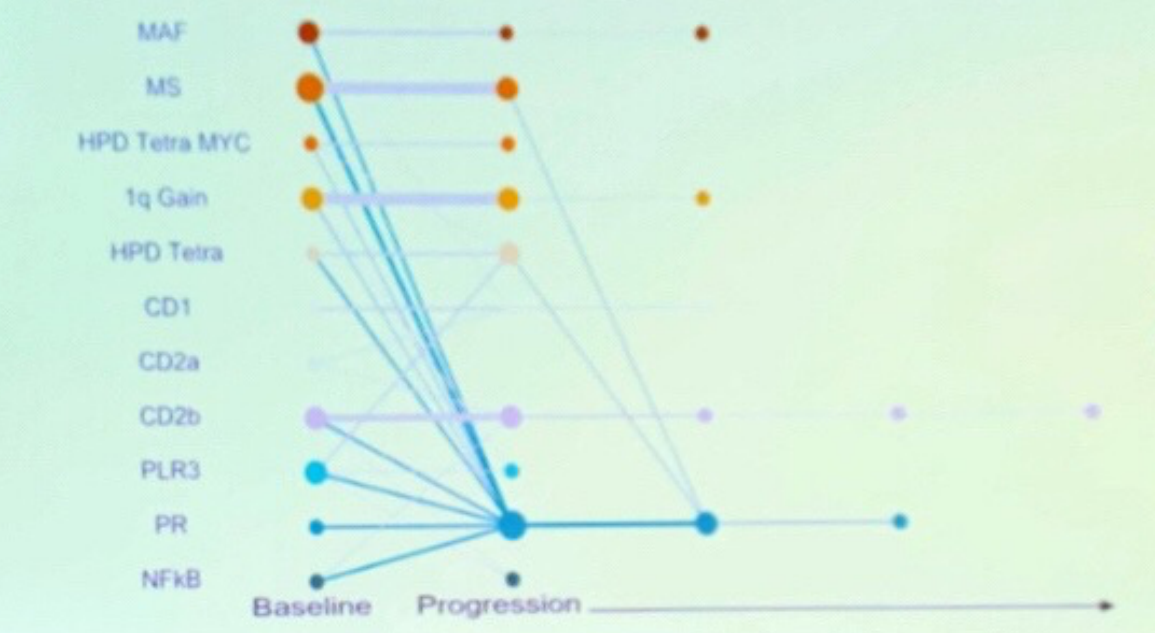
Consensus clustering of RNAseq data from 714 patients at diagnosis identified 12 expression subtypes of myeloma which generally correspond to known genetic subgroups.

Skerget et al. IMW, Boston 2019, Multiple Myeloma Genomics 1, AB420

Identification and Molecular Characterization of High-Risk Multiple Myeloma Patients from the MMRF CoMMpass Study at Diagnosis and Progression

Skerget et al. IMW, Boston 2019,
Multiple Myeloma Genomics 1, AB420

Patients Transition to PR Class at Relapse



The proliferation (PR) subtype comprised 51 patients whose tumors had an array of genetic backgrounds but converged upon a similar gene expression profile
(TP53 signalling, Cell cycle, RNA transport)

PR patients had extremely poor OS (median = 21 months, HR = 3.7, 95% CI = 2.5 - 5.6, $p<0.001$) outcomes compared to patients in other RNA subtypes

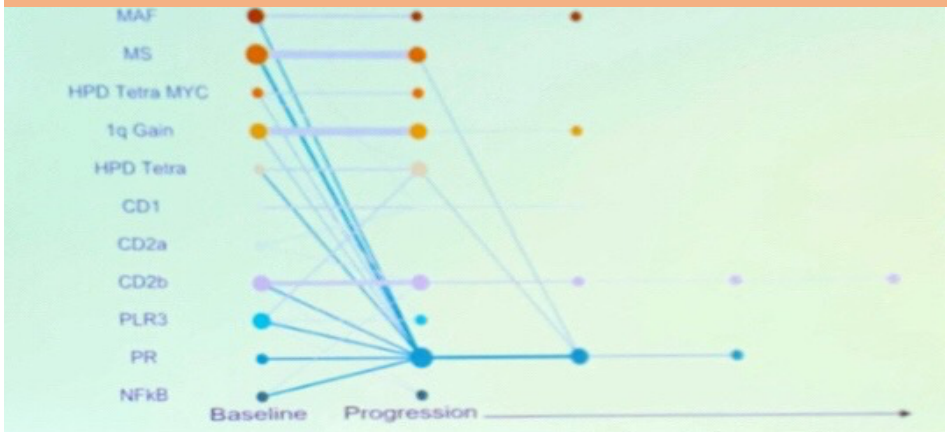
PR patients were enriched for gain of 1q ($p<0.001$), loss of 13q ($p<0.001$), and bi-allelic loss of MAX ($p<0.01$) or RB1 ($p<0.001$).

Although the PR subtype was enriched for patients classified as ISS III ($p<0.001$), 25 were classified as ISS I or II, highlighting that ISS underestimates disease severity in nearly half of high-risk patients.

Identification and Molecular Characterization of High-Risk Multiple Myeloma Patients from the MMRF CoMMpass Study at Diagnosis and Progression

Skerget et al. IMW, Boston 2019,
Multiple Myeloma Genomics 1, AB420

Patients Transition to PR Class at Relapse

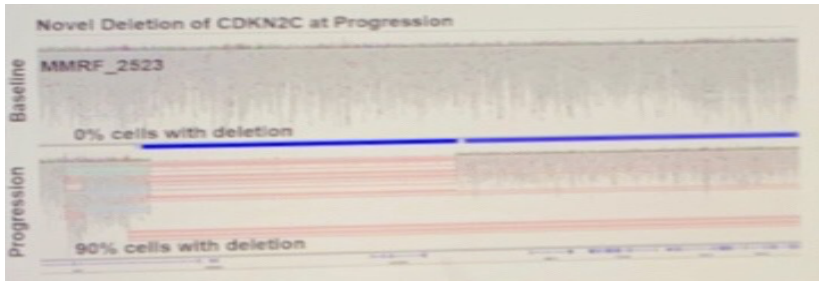


13/55 (28%) patients evaluated at several time points progressed to PR group

OS at progression: 88 days

Acquired LOF / GOF Event	Patients (n = 9)	Percent
CL CDKN2C	2	22%
CL CDKN1B (p27)	1	11%
CL TP53	3	33%

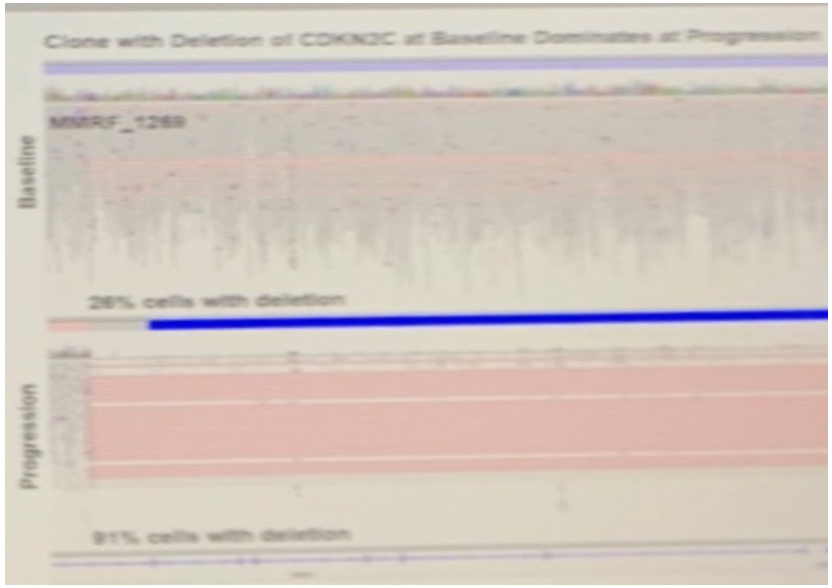
CDKN2C (P18) 1p23



0%

90%

CDKN1B (p27) 12p13



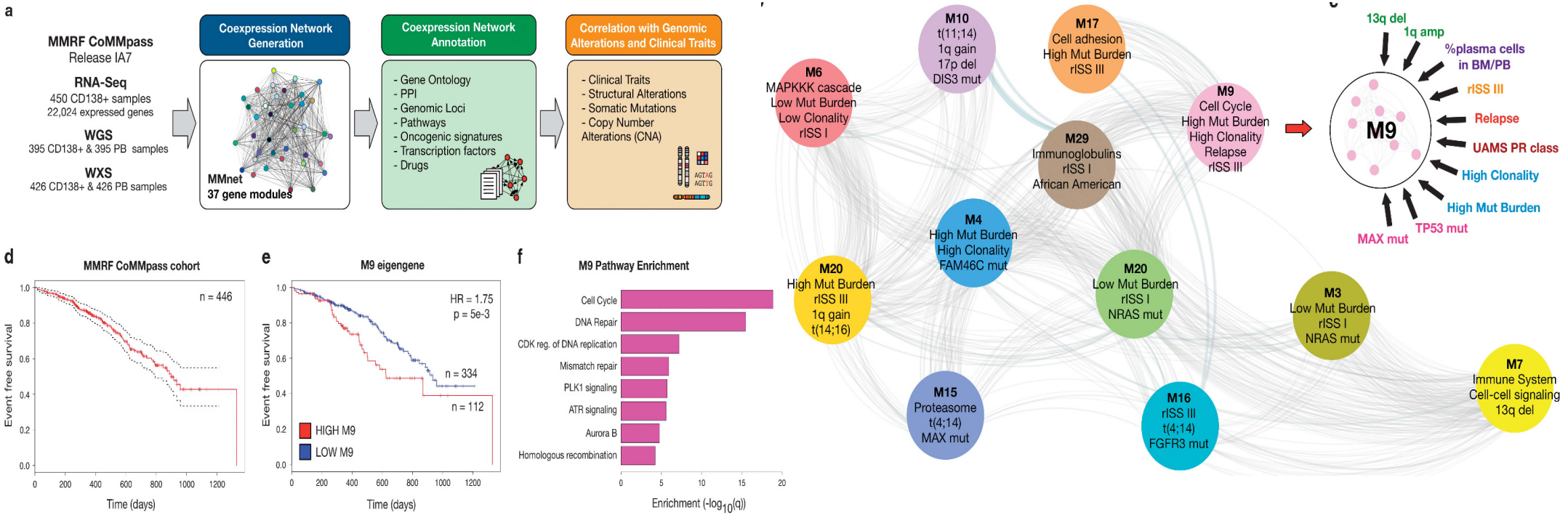
26%

91%

Integrative network analysis identifies novel drivers of pathogenesis and progression in newly diagnosed multiple myeloma

Alessandro Laganà et al Leukemia, 2018

A Laganà[1,2], D Perumal[3], D Melnekoff[1,2], B Readhead[1,2,4], BA Kidd[1,2,4], V Leshchenko[3], P-Y Kuo[3], J Keats[5], M DeRome[6], J Yesil[6], D Auclair[6], S Lonial[7], A Chari[3], HJ Cho[3], B Barlogie[3], S Jagannath[3], JT Dudley[1,2,4] and S Parekh[3,8]



Identification of groups of coexpressed genes significantly correlated with clinical traits and genomic alterations.

Module 9 is correlated with early relapse (< 2 years) and traits associated with high-risk and aggressive MM

Clinical and Biological Early Relapse Predictors in Multiple Myeloma: An Analysis from the MMRF CoMMpass Study

Mattia D'Agostino,[1,2] Gian Maria Zaccaria,[1] Bachisio Ziccheddu,[3] Elisa Genuardi,[1] Francesco Maura,[4] Stefania Oliva,[1] Daniel Auclair,[5] Jennifer Yesil,[5] Andrea Capra,[1] Paola Colucci,[1] Marco Poggiu,[1] Jonathan Keats,[6] Alessandra Larocca,[1] Manuela Gambella,[1] Niccolò Bolli,[3] Mario Boccadoro,[1] Francesca Gay[1]

1. Myeloma Unit, Division of Hematology, University of Torino, Azienda Ospedaliero-Universitaria Città della Salute e della Scienza di Torino, Torino, Italy;
2. Center for Multiple Myeloma, Massachusetts General Hospital Cancer Center, Boston, MA, USA.
3. Università degli Studi di Milano - Fondazione IRCCS Istituto Nazionale per lo Studio e la Cura dei Tumori di Milano, Milano, Italy
4. Myeloma Service, Memorial Sloan Kettering Cancer Center, New York, US;
5. Multiple Myeloma Research Foundation (MMRF), Norwalk, US-CT
6. Translational Genomics Research Institute (TGen), US-AZ

- Characterize patients with early relapse (relapse ≤18 months from start of therapy) after first line therapy with IMiDs and/or 1st-2nd generation PIs
- Define baseline clinical and biological features predicting early relapse
- Addressing the role of different therapy in reducing the risk of early relapse

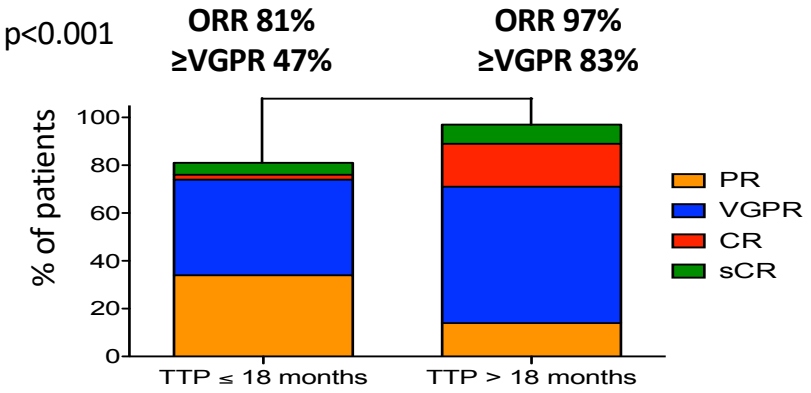
Clinical and Biological Early Relapse Predictors in Multiple Myeloma: An Analysis from the MMRF CoMMpass Study

No relapse
at current follow-up
n = 507 (54.8%)

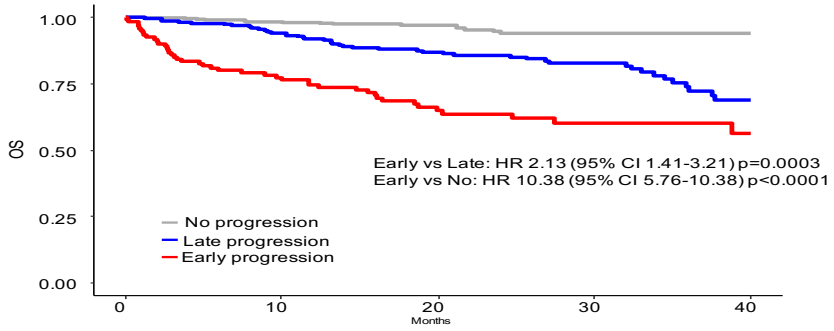
Early relapse (≤18 months)
n = 191 (20.6%)

Late relapse (>18 months)
n = 228 (24.6%)

Response rate

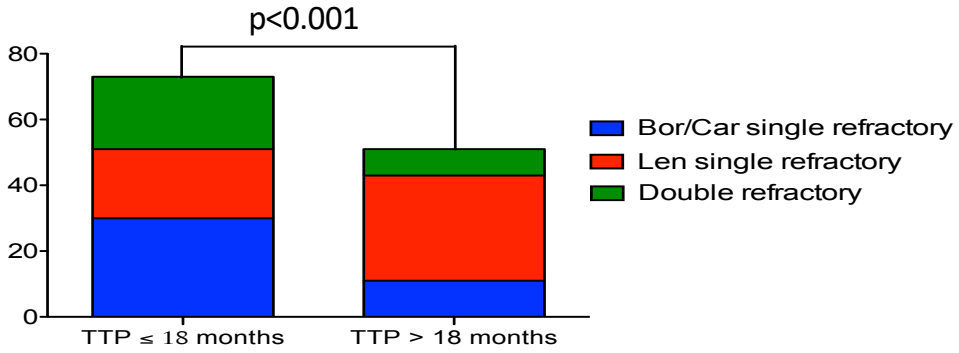


OS : 18-months Landmark analysis



- **MMRF CoMMpass study: 1151 MM patients enrolled**
- **926 patients with available TTP and baseline molecular data**
- **Mixed real-world + clinical trial population.**

Drug refractoriness after 1st line



Mattia D'Agostino: AB359

Clinical and Biological Early Relapse Predictors in Multiple Myeloma: An Analysis from the MMRF CoMMpass Study

Mattia D'Agostino:
AB359

All variables

↓ n = 40

Univariate analysis (p<0.15)

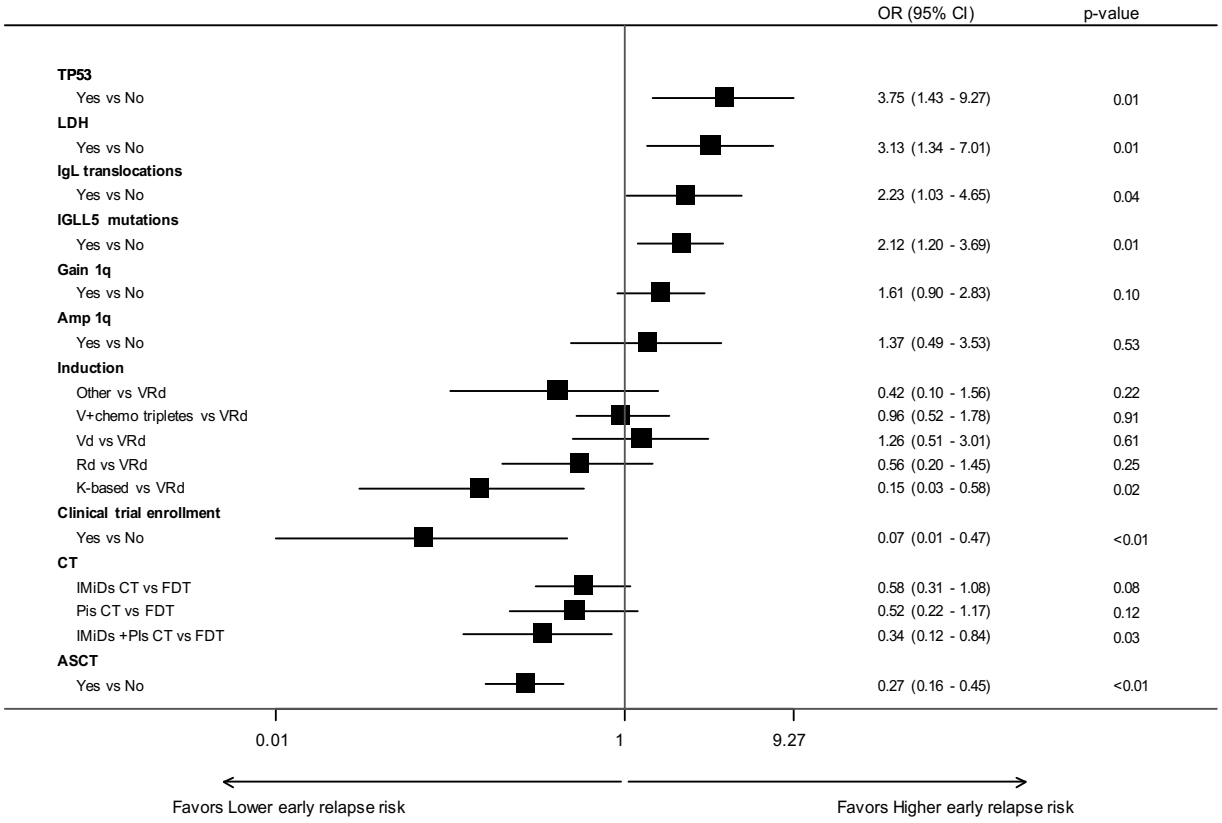
↓ n = 14

Multivariate logistic regression

↓ n = 9

Final model

Risk of early relapse: Multivariate analysis

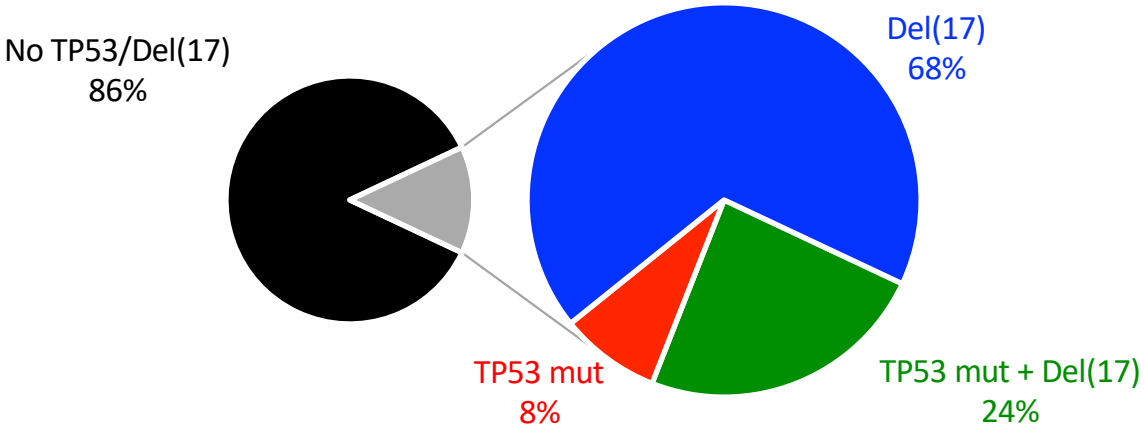


OR: odds ratio; IgL: immunoglobulin lambda chain; LDH: lactate dehydrogenase; V: Bortezomib; d: low dose dexamethasone; chemo: conventional chemotherapy; R: lenalidomide; K: Carfilzomib; ASCT: autologous stem cell transplantation. CT: continuous therapy; FDT: fixed duration of therapy; IMiDs: immunomodulatory drugs; PIs: proteasome inhibitors. Analysis is adjusted for missing values within each variable.

Clinical and Biological Early Relapse Predictors in Multiple Myeloma: An Analysis from the MMRF CoMMpass Study

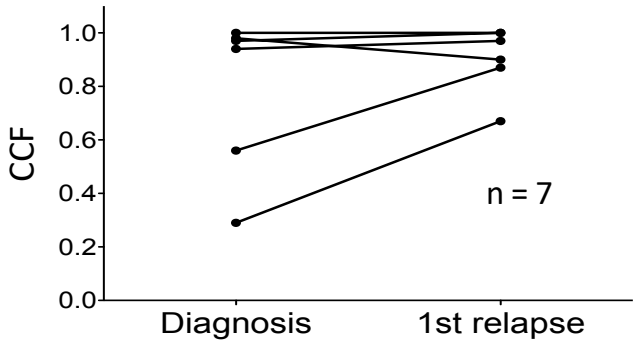
Mattia D'Agostino: AB359

TP53 but not Del(17) is an indipendent predictor of early relapse

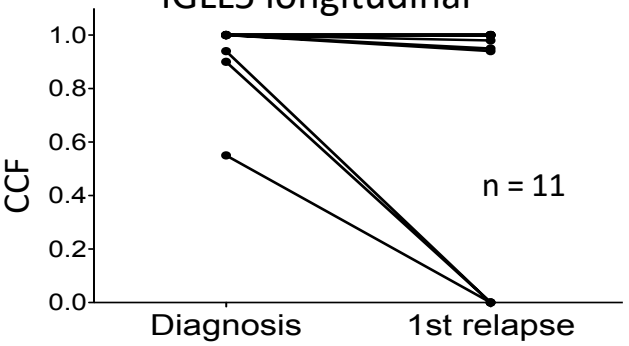


Subpopulation	Early PD n/evaluable (%)
No TP53mut/Del(17p)	146/744 (19.6%)
Del(17p) but not TP53mut	14/82 (17.1%)
TP53mut but not Del(17p)	5/10 (50%)
TP53mut+Del(17p)	12/29 (41.4%)

TP53 longitudinal



IGLL5 longitudinal



White et al. *Blood Cancer Journal* (2018)8:35

FP-022: The adverse double-hit effect of combining cytogenetic abnormalities and ISS stage III on the outcome of patients with newly-diagnosed multiple myeloma

Fengyan Jin 1 , Shaji Kumar 2 , Yun Dai 1

1 The First Hospital of Jilin University, Changchun, Jilin, 2 Mayo Clinic, Rochester, MN

- ✓ *A total of 307 NDMM patients with baseline FISH information and ISS staging who received at least 4 cycles of treatment.*
- ✓ *According to the IMWG 2016 consensus, 1q gain, del(17p), t[4;14], and t[14;16] were defined as HRCA.*
- ✓ *DHMM was defined as co-occurrences of either a) >= 2 HRCAs or b) at least 1 HRCA plus ISS stage III.*

- ➢ Shorter PFS and OS in cases carrying >= 2 HRCAs compared with those carrying only 1 HRCA
  [median PFS: 12.1 versus 32.2 months (p = 0.0004); median OS: 29.3 versus 65.6 months (p = 0.027)]
- ➢ Shorter PFS and OS in cases carrying 1 HRCA plus del(13q14) compared with those carrying only 1 HRCA
  [median PFS: 19.1 versus 32.2 months (p = 0.046); median OS: 29.6 versus 65.6 months (p = 0.055)]
- ➢ Shorter PFS and OS in cases carrying 1q gain plus >=1 additional HRCA compared with those carrying only 1q gain [median PFS: 11.2 versus 30.1 months (p = 0.0009); median OS: 18.9 versus 65.6 months (p = 0.0008)]
- ➢ Shorter PFS and OS in cases carrying both 1q gain and del(17p) compared with those carrying either 1q gain or del(17p) alone, respectively
- ➢ Shorter PFS and OS in ISS III cases carrying >= 1 HRCAs compared to those without HRCA
  [median PFS: 13.2 versus 21 months (p = 0.032; median OS: 15.2 versus 43.8 months (p = 0.057]
- ➢ Shorter PFS and OS in ISS III cases carrying both 1q gain and del(17p) compared to those with only one of these two HRCA (median PFS: 2.3 versus 15.8 months; median OS: 4.5 versus 24.5 months)

FP-022: **The adverse double-hit effect of combining cytogenetic abnormalities and ISS stage III on the outcome of patients with newly-diagnosed multiple myeloma**

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➢ Shorter PFS and OS in cases carrying 1 HRCA plus del(13q14) compared with those carrying only 1 HRCA

Patients either carrying two or more HRCA or at ISS III stage with at least one HRCA (DHMM) have significantly worse outcome (both PFS and OS) than those carrying only one HRCA or at ISS III stage, respectively.

alone, respectively
[PFS: p = 0.008 or p = 0.001; OS: p = 0.001 or p = 0.006]

➢ Shorter PFS and OS in ISS III cases carrying >= 1 HRCAs compared to those without HRCA
[median PFS: 13.2 versus 21 months (p = 0.032; median OS: 15.2 versus 43.8 months (p = 0.057]

➢ Shorter PFS and OS in ISS III cases carrying both 1q gain and del(17p) compared to those with only one of these two HRCA
(median PFS: 2.3 versus 15.8 months; median OS: 4.5 versus 24.5 months)

Synthetic lethality in multiple myeloma harboring double oncogenic hits of 17p13(del) and 1q21(amp) OAB-076

Phaik Ju Teoh 1 , Tae-Hoon Chung 1 , Omer An 1 , Pamela Chng 1 , Anand Jeyasekharan 2 , He Yang 1 , Wee Joo Chng 3
1 National University of Singapore, Singapore, Singapore, 2 National University Cancer Institute, Singapore, Singapore, Singapore, 3 National University Health System, Singapore, Singapore

- ✓ **TP53 maintains the genomic integrity by keeping the double stranded DNA damage (DSB) pathway in check.**
- ✓ **ADAR1 is a critical gene within 1q21 involved in RNA editing events on NEIL1 (base-excision repair- BER) gene causing defective single stranded DNA breaks (SSB) repair, resulting in CHK1 activation.**
- ✓ **CHK1 is a DNA damage marker, overexpressed in DH MM patients according to CoMMpass dataset, suggesting that is could be considered a good therapeutic target in these patients**

AIMS

to elucidate how p53 and NEIL1 aberrancy has potential collaborating role in affecting DNA damage response and their sensitivity to CHK1 inhibitor to identify novel biomarkers for patients with the double oncogenic hits.

RESULTS

Cell lines with DH chromosomal lesions were more sensitive to the pharmacological inhibition of CHK1 as compared to single abnormalities, showing increased amount of unrepaired DSB , cell cycle progression and increased apoptosis.

Could genomic instability serve as the Achilles heel in DH MM patients?

ADAR1

1q21(amp)

RNA editing

NEIL1

Defective

BER pathway

Defective

SSB repair

CHK1 activation

Defective

DNA damage repair

Synthetic lethality

- AZD7762
- VE821

p53

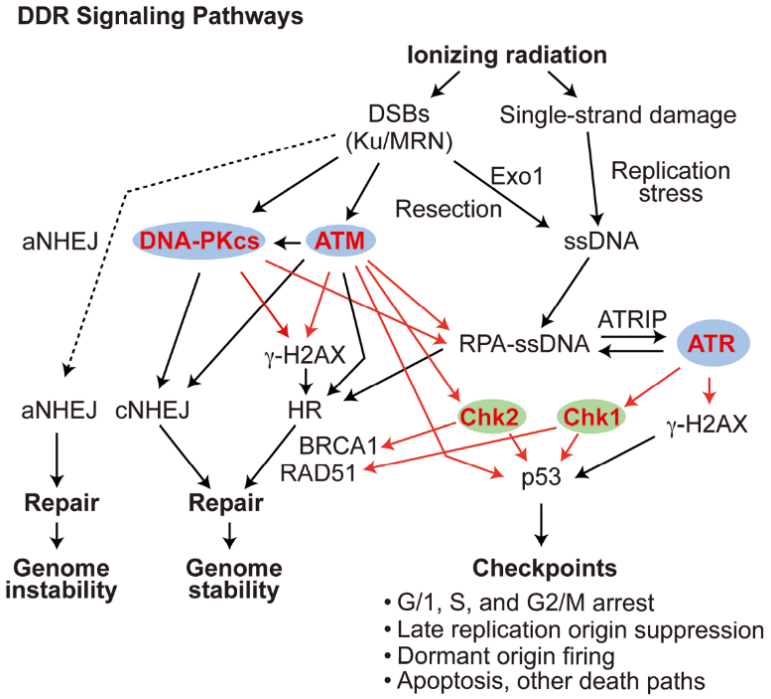
DSB pathway

Defective

Genome integrity

Cell death

17p13(del)



TRIPLE HIT MYELOMA ?

MAYO CLINIC

mSMART 2.0: Classification of

High-Risk 20%	Intermediate-Risk 20%
▪ FISH ▪ Del 17p ▪ t(14;16) ▪ t(14;20) ▪ GEP ▪ High risk signature	▪ FISH ▪ t(4;14)* ▪ Cytogenetic Deletion 13 or hypodiploidy ▪ PCLI ≥3%

Mikhael et al Mayo Clinic Proceedings April 2013

MAYO CLINIC

mSMART 3.0: Classification of Active MM

High-Risk

- High Risk genetic Abnormalities [a,b]
  - t(4;14)
  - t(14;16)
  - t(14;20)
  - Del 17p
  - p53 mutation
  - Gain 1q
- RISS Stage 3
- High Plasma Cell S-phase[c]
- GEP: High risk signature

- Double Hit Myeloma: Any 2 high risk genetic abnormalities
- Triple Hit Myeloma: 3 or more high risk genetic abnormalities

Standard-Risk[a]

All others including:
- Trisomies
- t(11;14)[d]
- t(6;14)

[a] Trisomies may ameliorate
[b] By FISH or equivalent method
[c] Cut-offs vary
[d] t(11;14) may be associated with plasma cell leukemia

Dispenzieri et al. Mayo Clin Proc 2007;82:323-341; Kumar et al. Mayo Clin Proc 2009 84:1095-1110; Mikhael et al. Mayo Clin Proc 2013;88:360-376. v14 //last reviewed August 2018

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