Highlights from IMW 2019

19-20 novembre 2019
Bologna
Royal Hotel Carlton

NICOLA GIULIANI

MIELOMA AD ALTO RISCHIO

- Caratteristiche biologiche e cliniche

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Disclosures of NICOLA GIULIANI

Company name	Research support	Speakers bureau	Advisory board	Other
Celgene	X	X	X	
Janssen Pharmaceutical	X	X	X	X
Millenium Pharmaceutical			X	X
Bristol Mayers Suibb		X		
GSK	X			

Coordinatore Scientifico
Michele CAVO

Comitato Scientifico
Mario BOCCADORO
Michele CAVO
Maria Teresa PETRUCCI

Clinical hallmarks of high-risk multiple myeloma (MM)

- ✓20-30% [1,2]
- ✓Clinical **aggressive** behaviour → Early **relapse** / Treatment **Refractory**
- ✓**PFS** < 18 months or **OS** < 2-3 years[1,2]

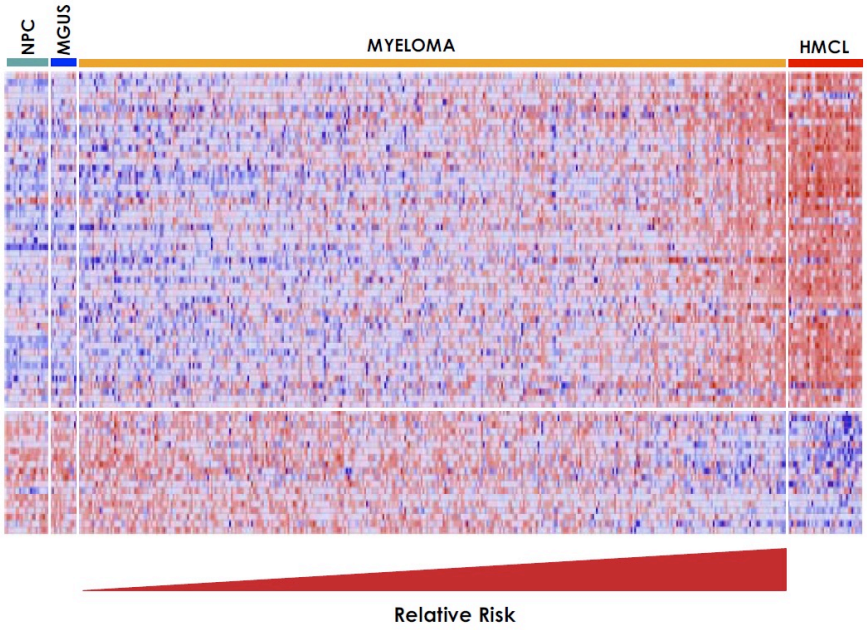
1. Barlogie B et al, Blood 2014; 2. Kumar S et al, Leukemia 2013

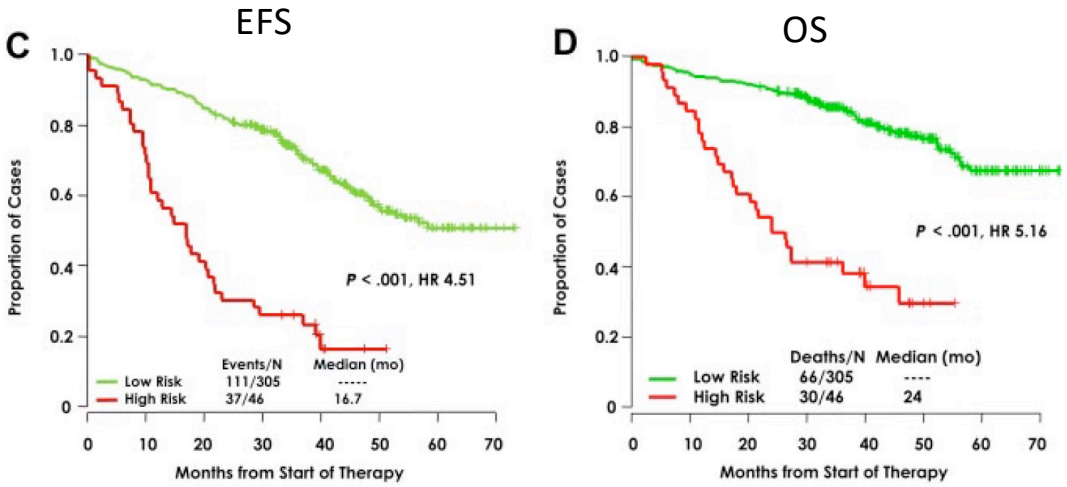
Recognizing high-risk feature in MM

Table 1 A comparison between the genetic and molecular markers in the RISS and mSMART stratification

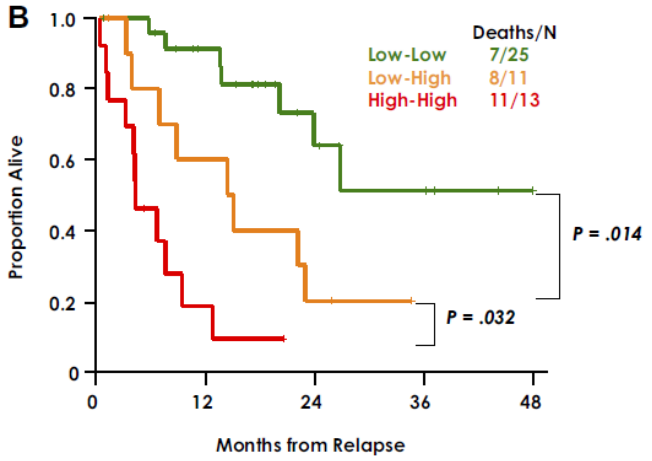
Stage	RISS		mSMART		Risk
I	Serum albumin ≥ 3.5 g dL^{-1} Serum β2M < 3.5 mg L^{-1} No high-risk cytogenetics Normal LDH level	5 year OS 82%	t(11;14) t(6;14)	Median OS 8–10 years	Standard
II	Not fitting stage I or III	5 year OS 62%	t(4;14) del(13) Hypodiploidy PCLI $\geq$ 3%	Median OS 4–5 years	Intermediate
III	Serum β2M > 5.5 mg L^{-1} High-risk cytogenetics: t(4;14), t(4;16), or del(17p) or elevated LDH	5 year OS 40%	del(17p) t(14;16) t(14;20) GEP high-risk signatures	Median OS 3 years	High

Expression-based Definition of Aggressive Disease (GEP70)





Diagnosis-relapse risk



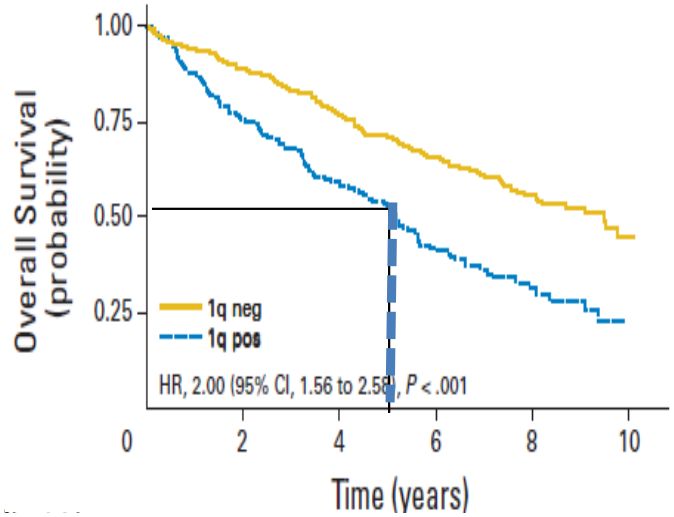
Shaughnessy et al, Blood 2007

Expression-based Definition of Aggressive Disease

	Signature	No of genes	Genes common with 70 Gene	No of Genes common with 92 Gene
1	**UAMS**	**70 genes**	**--**	**2 genes (BIRC5, LTBP1)**
2	**HOVON-65/GMMG-HD4 (EMC92)**	92 genes	2 genes (BIRC5, LTBP1)	--
3	**IFM**	15 genes	None	1 gene (FAM49A)
4	**Chromosome instability signature**	214 genes	7 genes	15 genes
5	**Centrosome index signature (CNTI)**	4 genes	None	None
6	**Cell death signature implicated by homozygous deletion (HZDCD)**	6 genes	None	None
7	**7-gene prognostic signature HMCL MM cell lines study**	7 genes 6 genes	None None	None None
8	**Proliferation signature**	50 genes	3 genes (BIRC5, ASPM, CKS1B)	6 genes (ESPL1, MCM6, NCAPG, SPAG5, ZWINT, BIRC5)

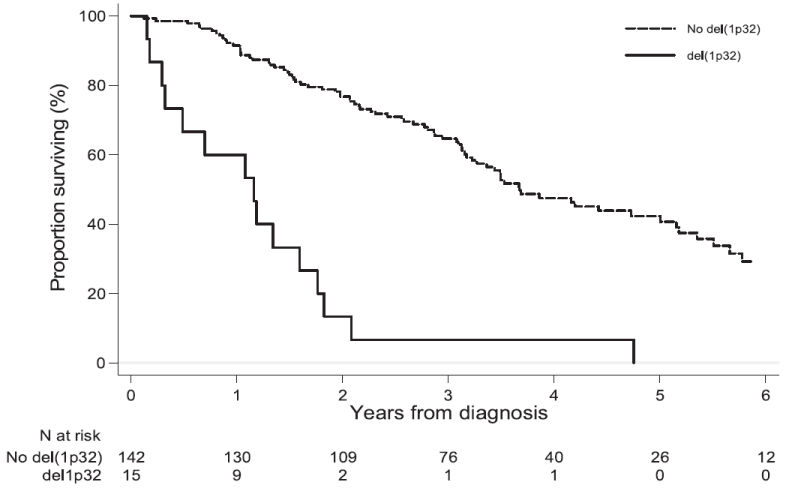
Recognizing high-risk: Chr1 abnormalities?

1q gains: 30-35% of patients



Avet-Loiseau et al, J Clin Oncol 2012

Del(1p32)



Hebraud et al, Blood 2015

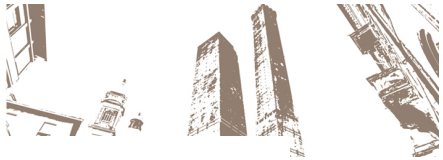
TABLE 4. Mayo Clinic Risk Stratification for Multiple Myeloma

Risk group	Percentage of newly diagnosed patients with the abnormality
Standard risk	75
Trisomies	
t(11;14)	
t(6;14)	
Intermediate risk	
t(4;14)	10
gain(1q)	
High risk	
t(14:16)	
t(14;20)	15
del(17p)	

Adapted from *Am J Hematol.*[2]

Rajkumar et al., Mayo Clin Proc 2016

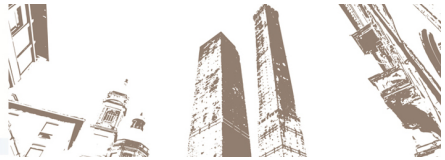
IMW Consensus…



- **Genetic**
  - Any deletion by metaphase
    - possibly any non-hyperdiploid karyotype
  - Any translocation t(4;14), t(14;16), t(14;20), del(17/17p) and (?) gain 1q
  - RISS stage III
  - High risk GEP
- **Clinical**
  - High proliferative features
    - Circulating plasma cells (cPC)
      - Frank plasma cell leukemia (PCL), and possibly if > 400,000 cPC/150,000 MNC
    - Elevated LDH
    - Morphologic features of plasmablastic morphology, increased PCLI, increased Ki67
  - Extramedullary disease
    - Especially clearly, if not bone-based extension, particularly CNS disease

Adopted from Muchtar et al, Leuk Lymph 2016; Dispenzieri Hematology Am Soc Hematol Educ Program. 2016; IMW 2017 Consensus Panel #2

IMW Consensus…



…clinical course may reveal high risk patients

- Primary refractory disease
- Trend or frank progression during even short breaks (i.e. during break for stem cell collection or while recovering from transplant)
- Early relapse post transplant (<12 mo)

…regardless of known cytogenetic and FISH-based risks

High-risk disease characteristic in relapsed MM

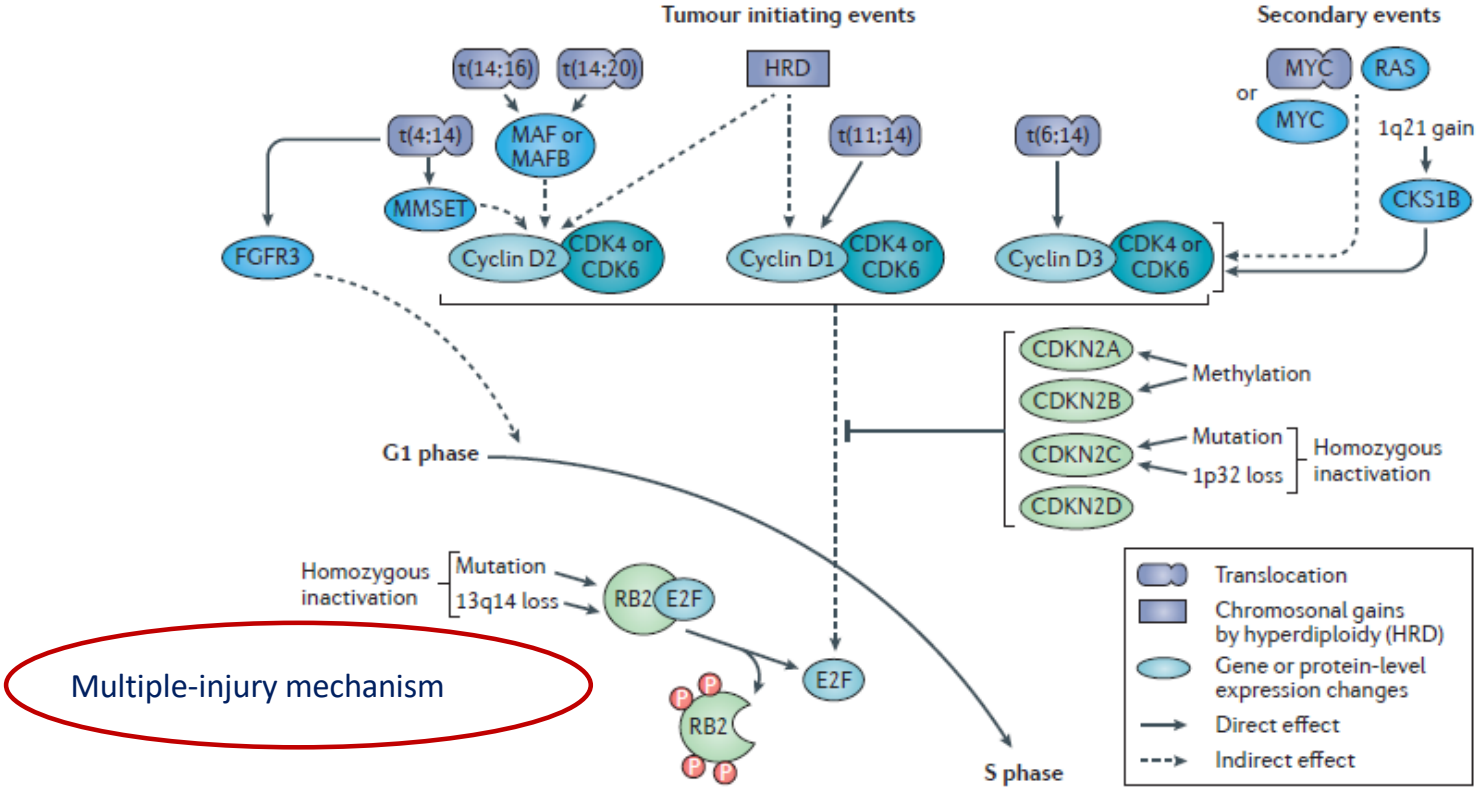
Adverse cytogenetic abnormalities	Del17p, amp 1q21 o t(4;14)	• Dimopoulos et al, *Leukemia 2010* • Smetana et al, *Clin Lymphoma Myeloma Leuk 2013* • Jakuboviak et al, *Leukemia 2013* • Reece et al, *Blood 2009*
Extramedullary disease		• Rasche, *Ann Hematol 2012* • Dimopoulos, *Leukemia 2010* • Papanikolau, *Leuk Lymphoma 2013*
Short remission duration after first treatment		• Sellner L, *Cancer 2013* • Jimenez-Zepeda, *Biol Blood Marrow Transplant 2012*
ISS stage at relapse		• Sellner, *Blood 2014* • Anagnostopoulos, *Leuk Lymphoma 2004*
Isotype transformarion	Light chain escape, hyposecretory disease	• Brioli , *Blood 2015* • Ahn, *Clin Lymphoma Myeloma Leuk 2014*
High LDH levels at relapse		• Dimopoulos, *Leukemia 2010* • Sellner, *Cancer 2013*

Which biological processes drive the high risk phenotype ?

- ✓ Many genetic **drivers** of the high risk disease
- ✓ High potential to acquire **additional changes**
- ✓ Higher ability to **evolve**
  - ✓ High **proliferative** rate
  - ✓ Anti-**apoptosis**
  - ✓ Drug **resistance**
  - ✓ Microenvironment **independency**

1. Barlogie et al, Blood 2014; 2. Kumar et al, Leukemia 2013

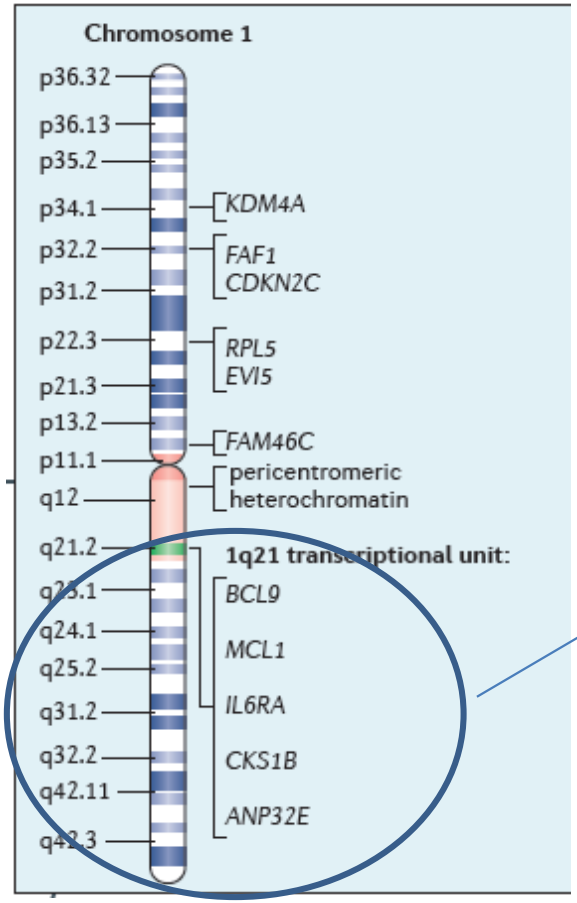
Convergent evolutionary route to high-risk MM via cell cycle dysregulation



Multiple-injury mechanism

Pawlyn et al, Nature Reviews 2017

Copy Number Abnormalities: Chr1



Pawlyn et al, Nature Reviews 2017

amp or gain(1q21)

MCL1
BCL9 → Anti-apoptotic , proliferation

CSK1B → Cellular proliferation through p27 degradation and cyclin-dependent kinases

UMC Utrecht

Multiple myeloma with amplification of chromosome 1q is highly sensitive to MCL-1 targeting

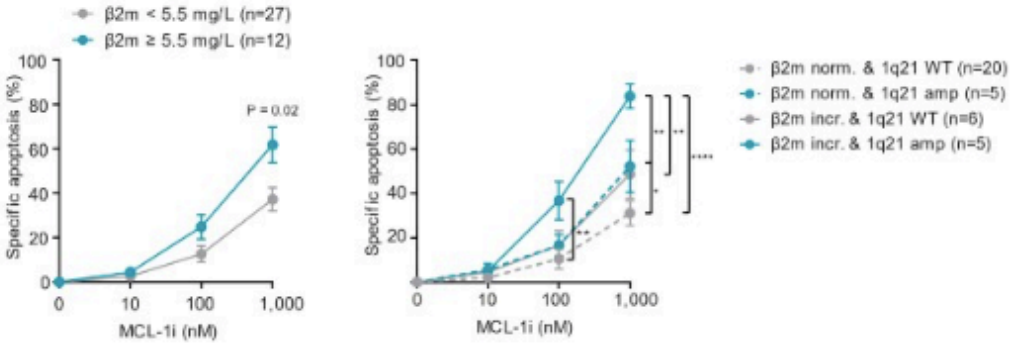
Anne Slomp

PhD student
Center for Translational Immunology
University Medical Center Utrecht, Utrecht, the Netherlands

9-14-2019
17th International Myeloma Workshop
Boston, MA, USA

University Medical Center Utrecht

1q amplification and additional poor prognosis diagnostic markers identify a MM subset that is most sensitive to MCL-1 targeting



- High serum β2m levels are associated with increased MCL-1i sensitivity, partly independent of 1q status
- MM with 1q amp and high β2m is highly sensitive to MCL-1i treatment

Copy Number Abnormalities: del(17p)

✓Whole arm-level **aberrations** and whole-arm **jumping translocations** are associated with **high-risk** myeloma

✓**TP53** gene at the short arm of chromosome 17

Small sub-clones with monoallelic inactivation of TP53 (<20%)

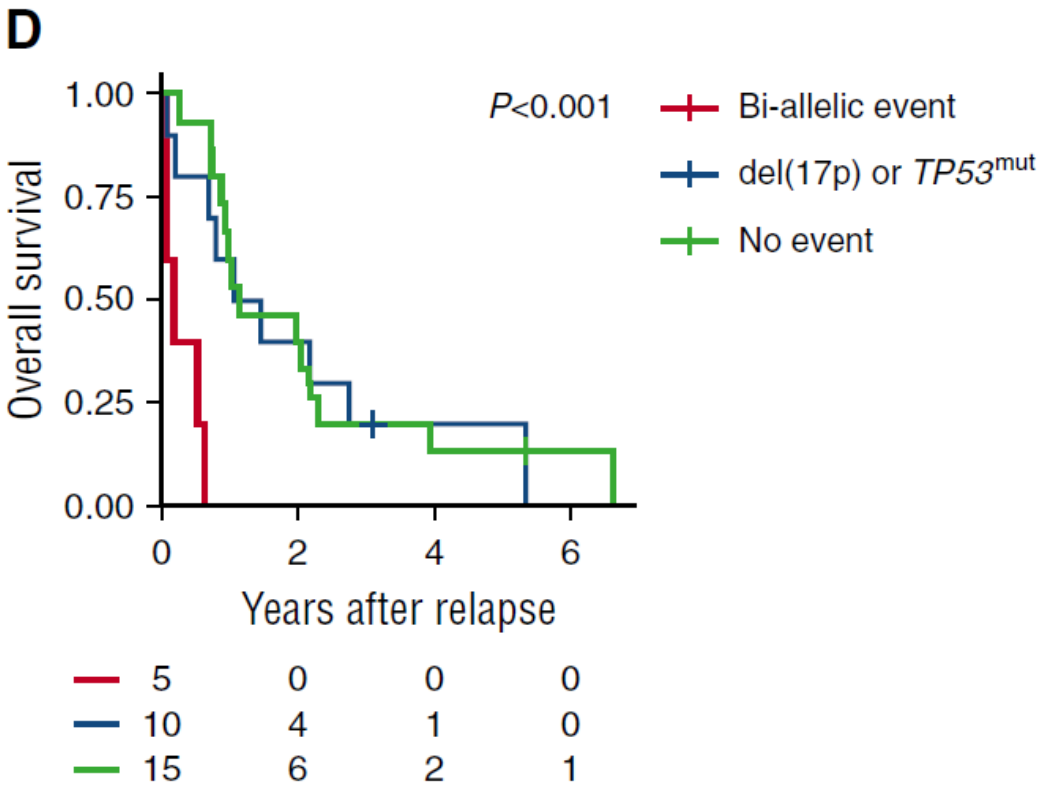
Vs.

Larger clones with monoallelic inactivation of TP53 (50-60%)

→ **High-risk**

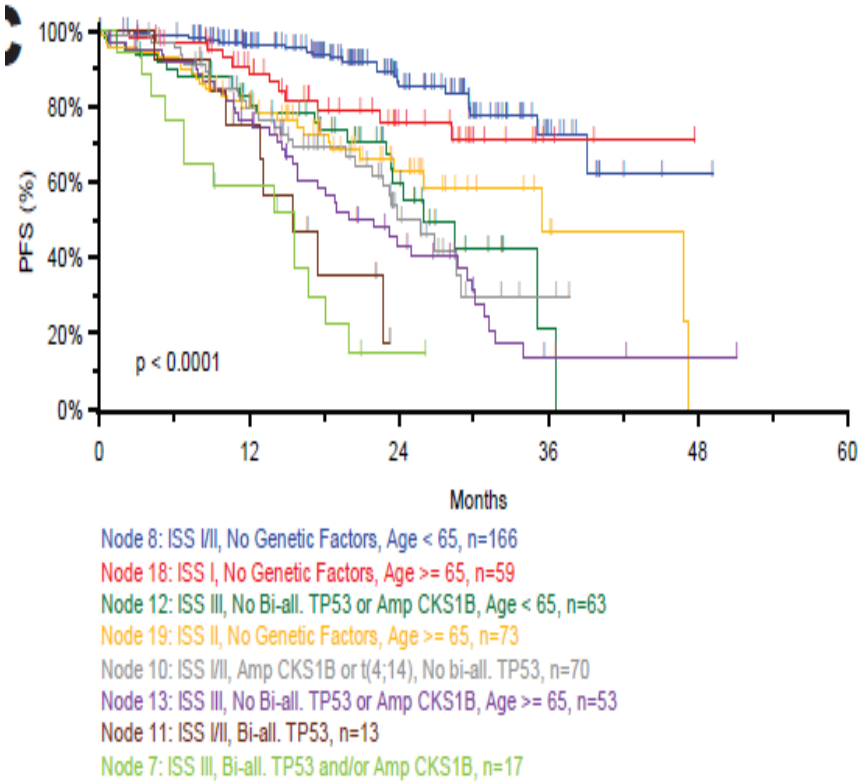
Lionetti et al, Oncotarget 2016; Pawlyn et al, Nature Reviews, 2017

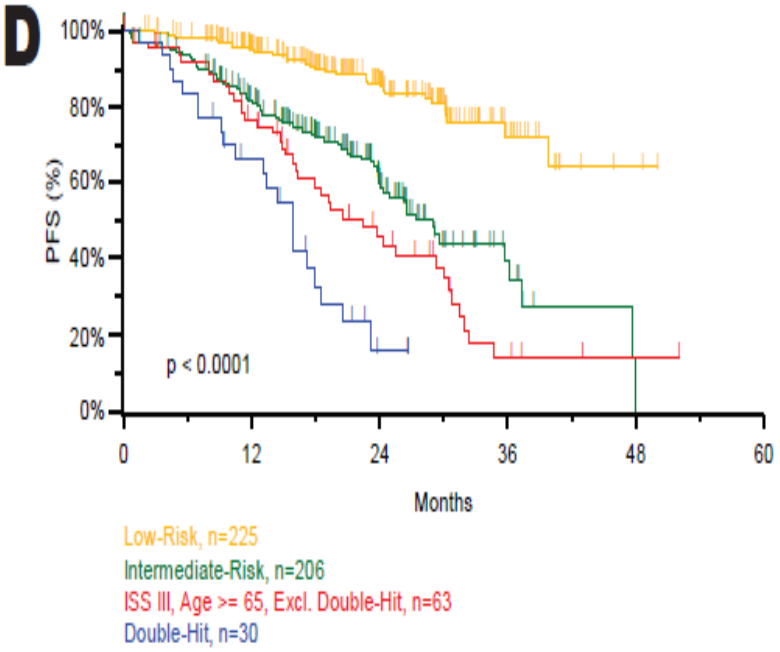
TP53 bi-allelic events identify aggressive course in relapsed MM



Weinhold et al , Blood 2016

Redefining High-risk MM



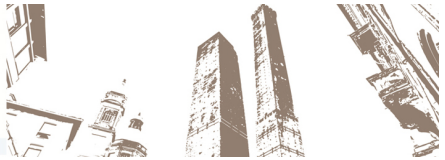


Walker et al. Leukemia 2019

High-risk segment defined by ISS III and either

a) biallelic *TP53* inactivation or

b) amplification of *CKS1B* (1q21)



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MM RF SM MULTIPLE MYELOMA Research Foundation

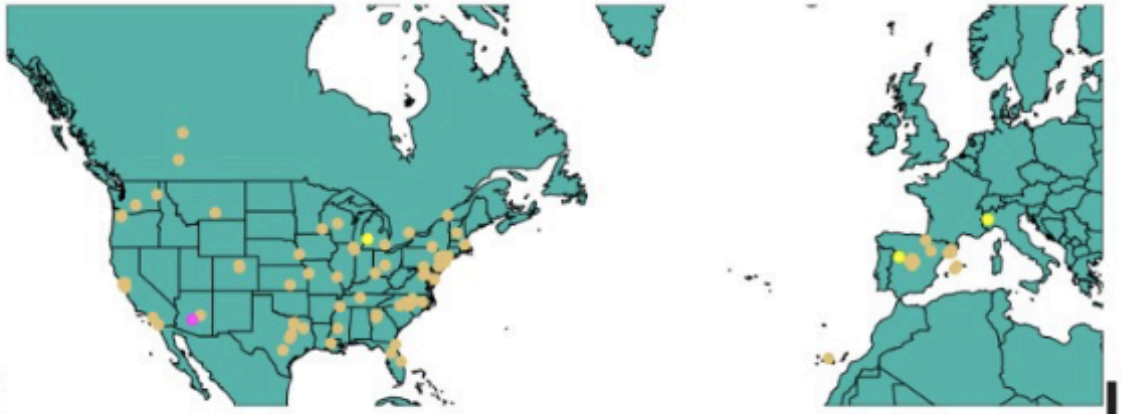
Identification and Molecular Characterization of High-Risk Multiple Myeloma Patients from the MMRF CoMMpass Study at Diagnosis and Progression

Sheri J Skerget, PhD
International Myeloma Workshop
September 13 2019

sskerget@tgen.org | @SheriJS

Overview of the MMRF CoMMpass Study

	Untreated / Newly Diagnosed	Progression Events
Patients / Events	1143 (982 sequenced)	152 / 216 (800 planned)
Molecular Profiling	WES / WGS / RNAseq	WES / WGS / RNAseq
Clinical data	Every 3 months → Minimum 8 years	



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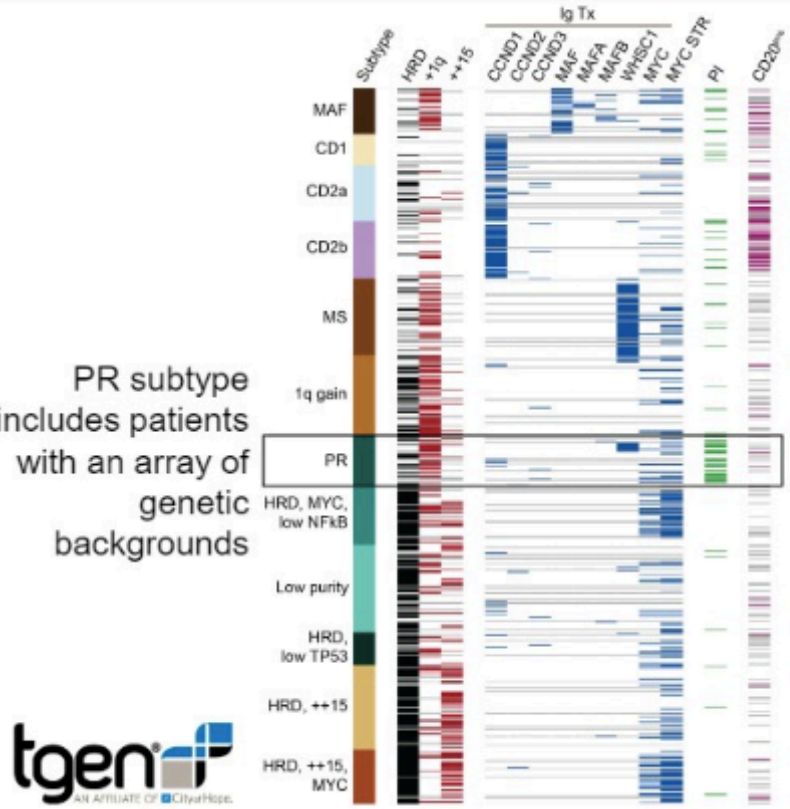
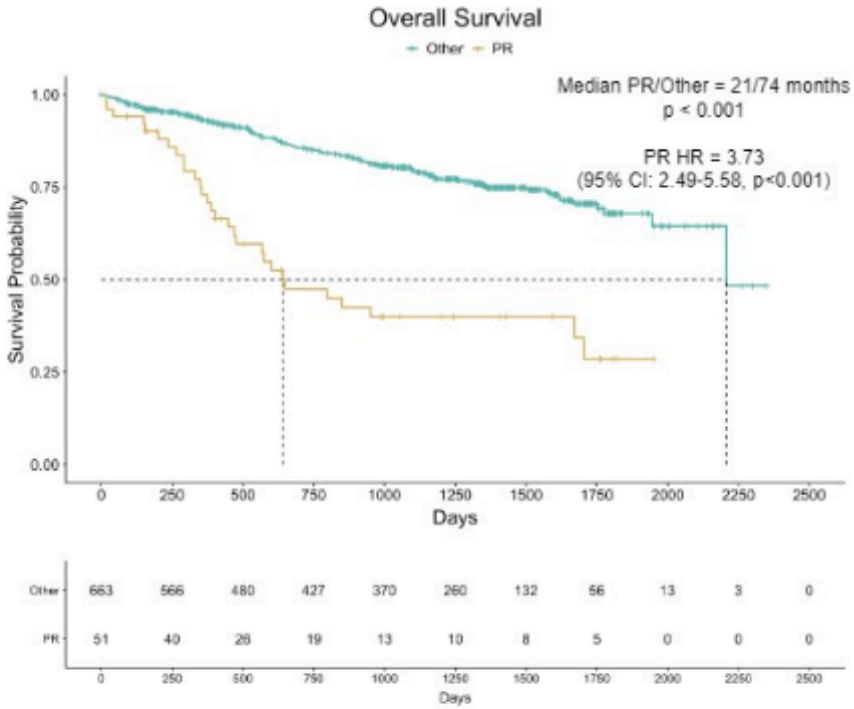
Gene Expression Subtypes in the Baseline Cohort



PR subtype includes patients with an array of genetic backgrounds



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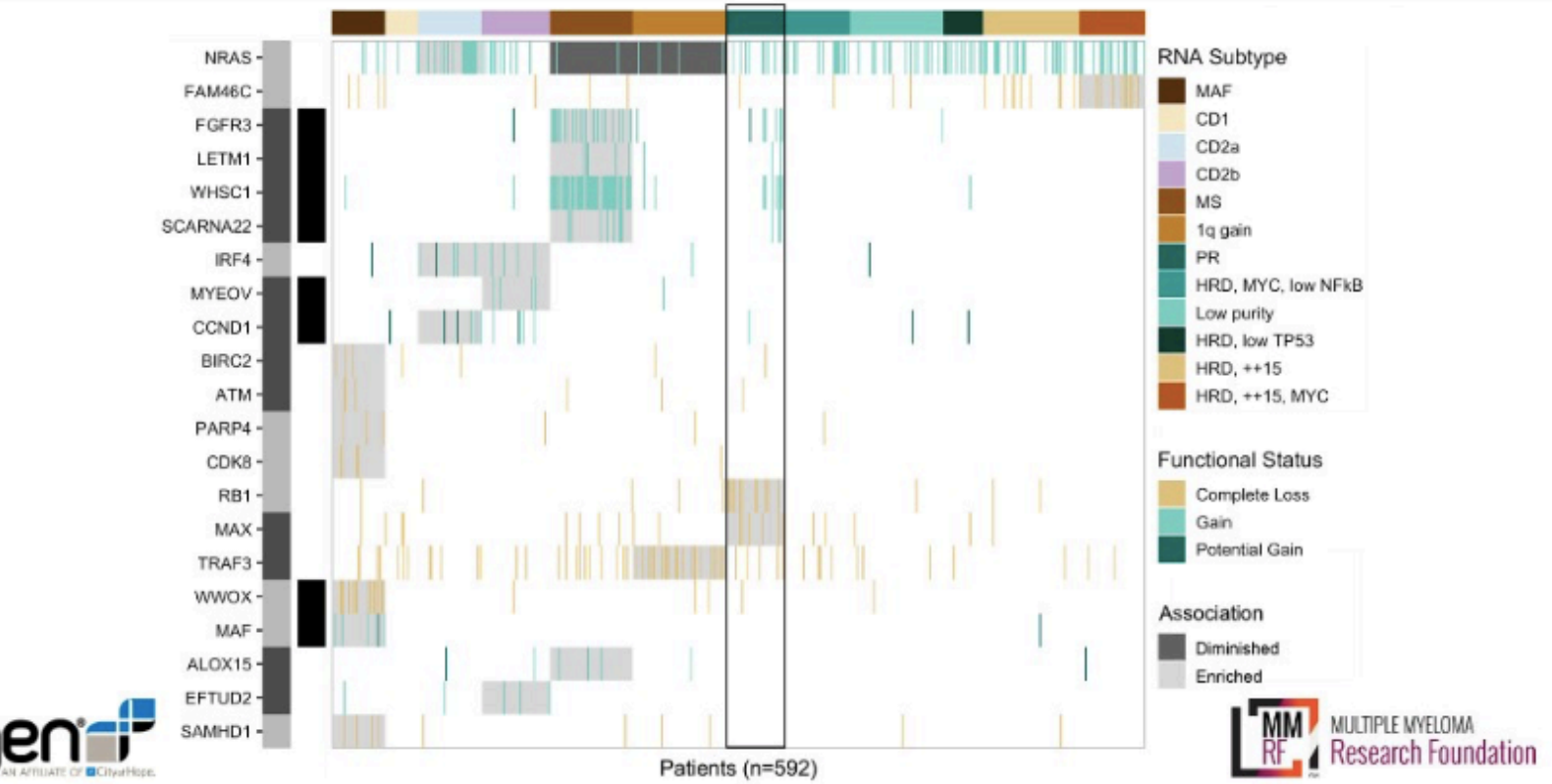
LOF Events in RB1 and MAX Enriched in the PR Subtype



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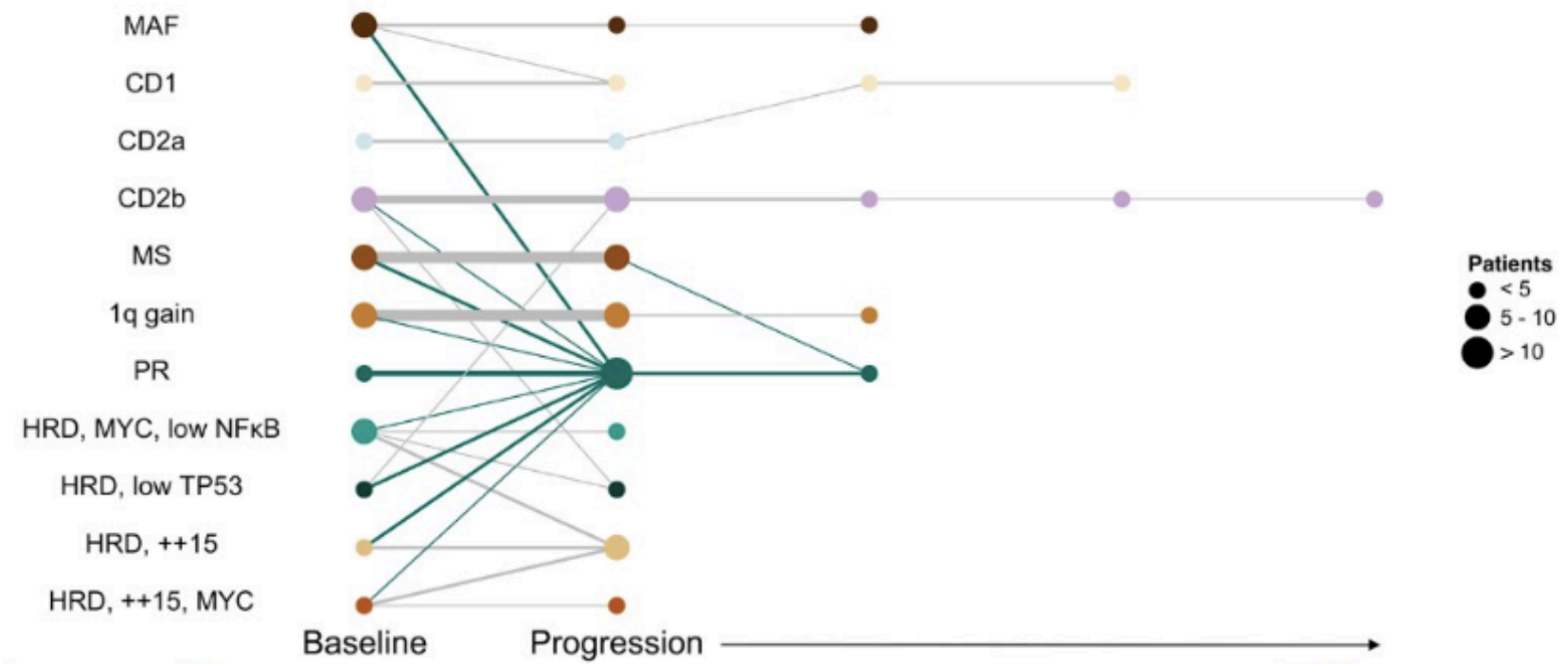
Serial Patients Transition to PR Class at Progression

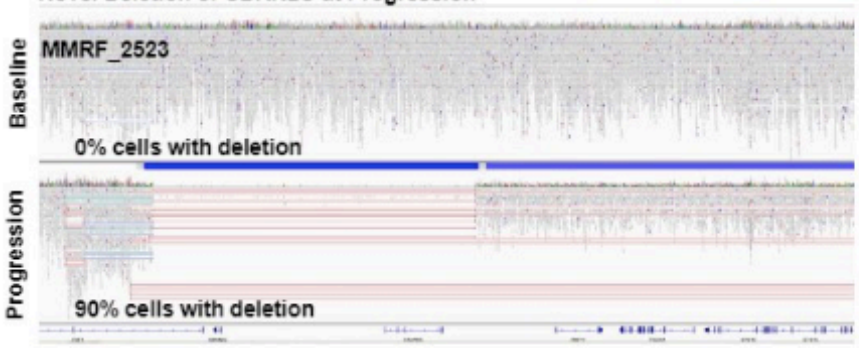


25% of patients transition to PR at progression

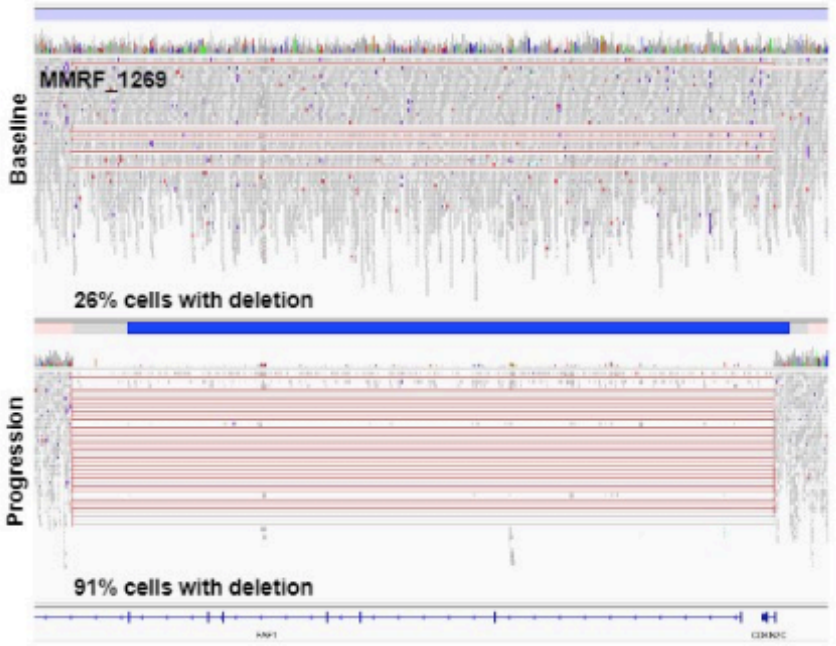
Molecular Events in Patients that Transition to PR

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

Novel Deletion of CDKN2C at Progression

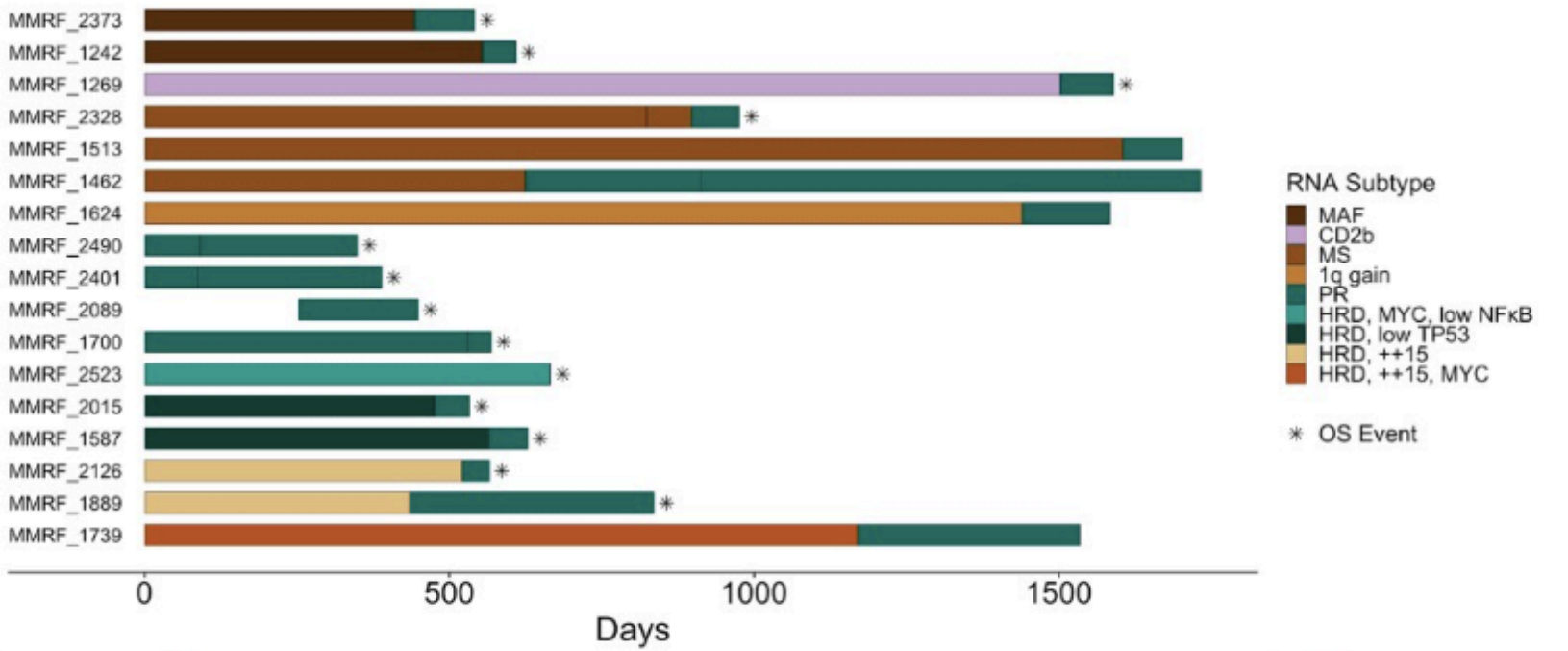


Clone with Deletion of CDKN2C at Baseline Dominates at Progression



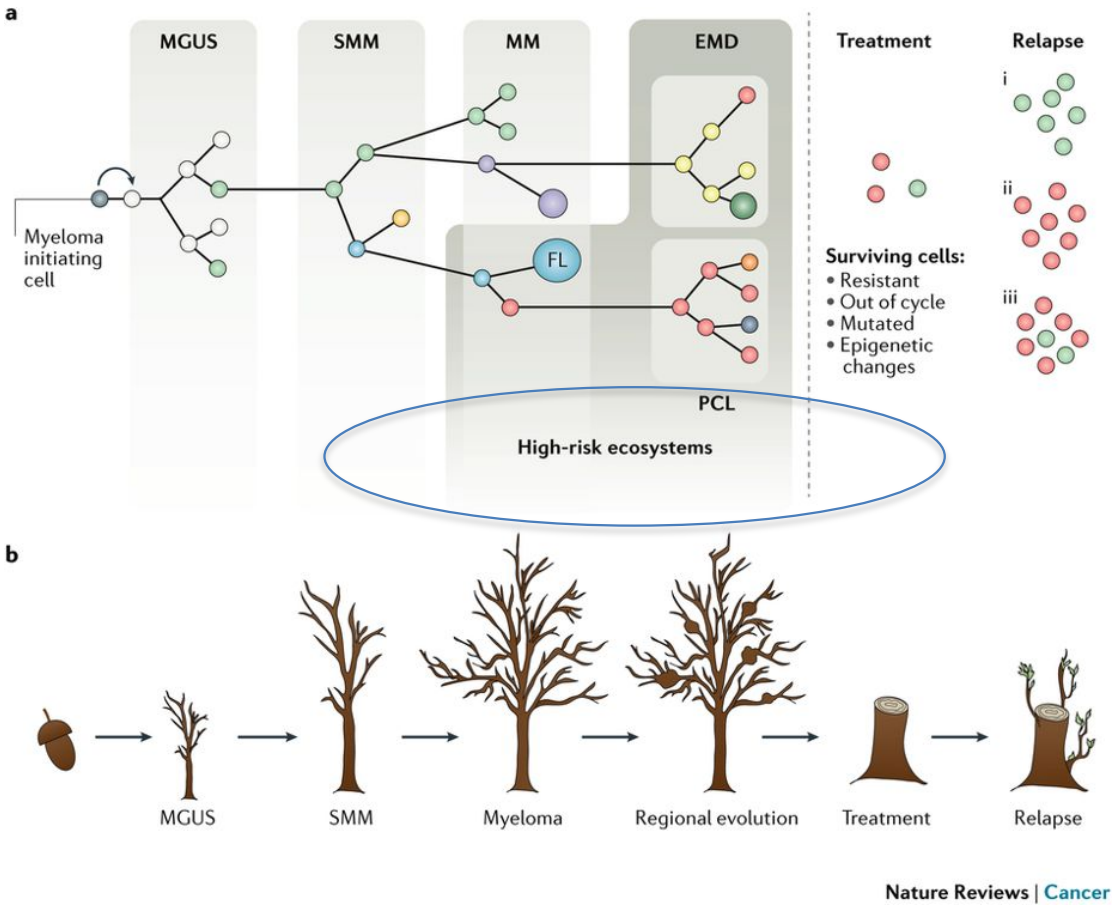
Different events driving the transition to PR in different patients

Patients who Transition to PR Exhibit Poor Survival



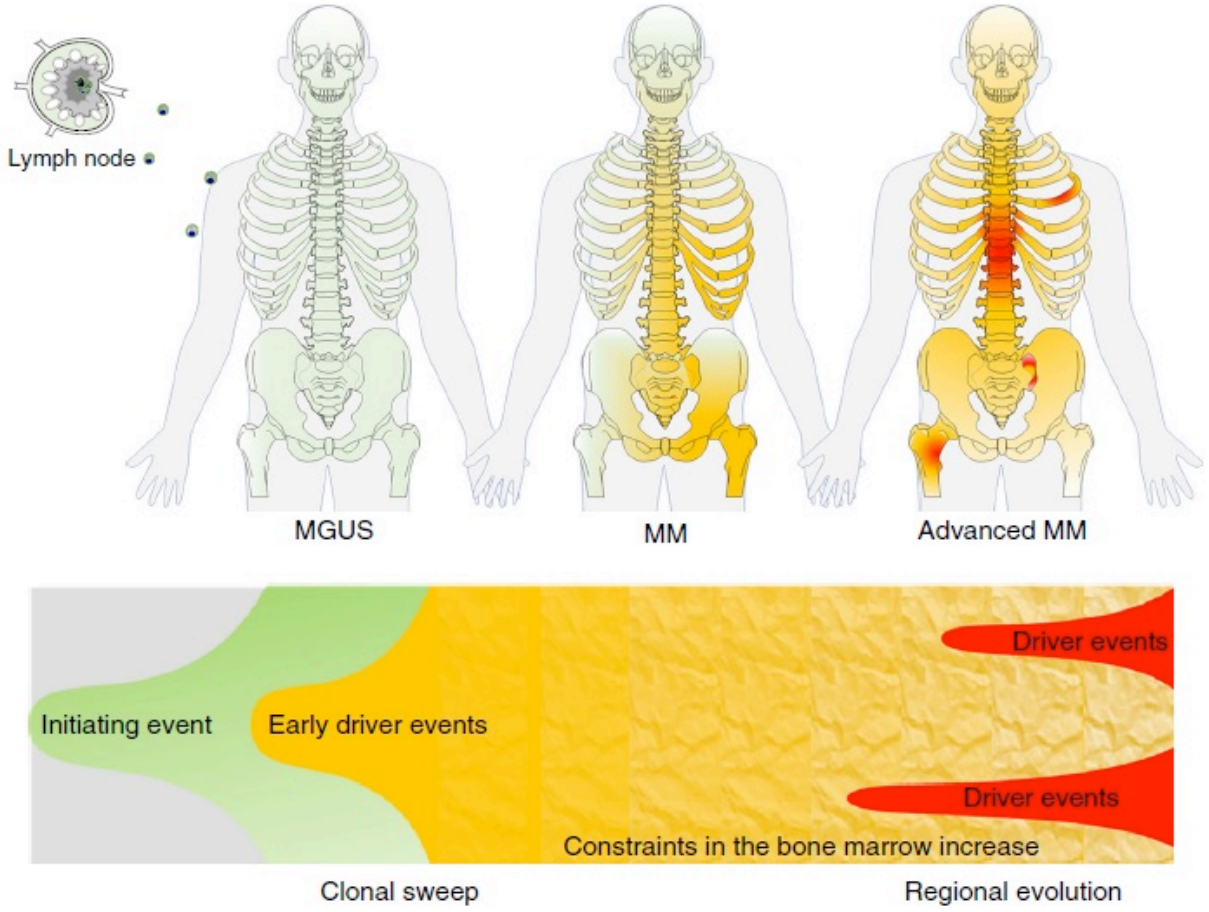
Median OS of 88 days after the PR progression event

Myeloma clonal evolution to high-risk



Pawlyn et al, Nature Reviews 2017

Regional evolution in multiple myeloma

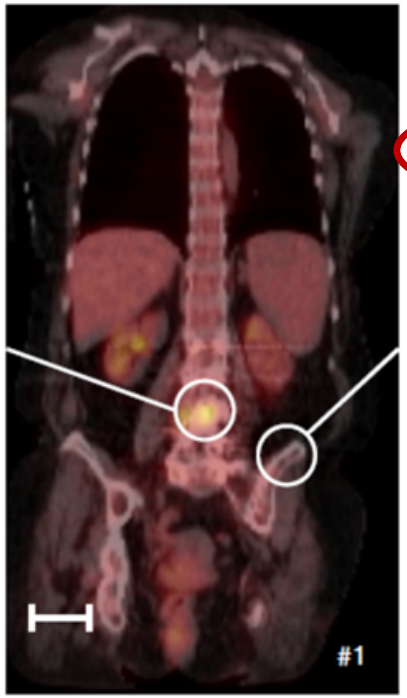


Rasche et al, Nature Comm 2017

Spatial clonal architecture

Focal lesion at 4th lumbal vertebra:

- GEP70 high risk
- Non-Hyperdiploid
- Del(1p12)
- Del(1p32)
- Del(13q)
- Biallelic *TP53* ^{del}



Left liac crest:

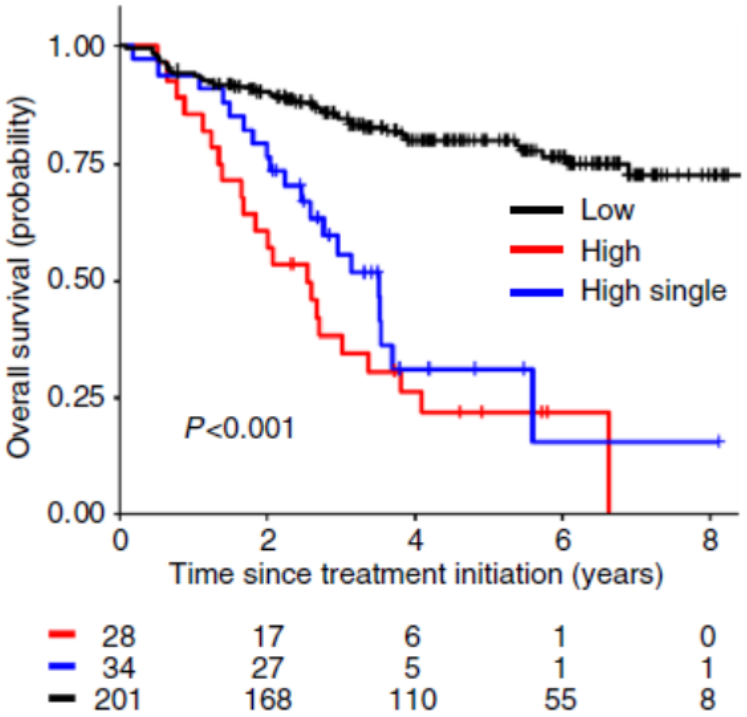
- GEP70 low risk
- Hyperdiploid
- t(MYC)
- BRAF^{V600E}

13 cases

- ✓ Medical imaging frequently shown an **imbalanced distribution** of **MM**
- ✓ Failure to detect clones that drives relapse may be explained by **regionally restricted** evolution
- ✓ Multi-region investigations are critical to understanding **intra-patients heterogeneity** in MM

Rasche et al, Nature Comm 2017

Impact of regional high risk diseas on survival



- ✓ A **worse outcome** for cases with a **non-homogenous** distribution of GEP70 high-risk clones
- ✓ High-risk subclones **drive** prognosis even if they are not ubiquitously distributed

Rasche et al, Nature Comm 2017

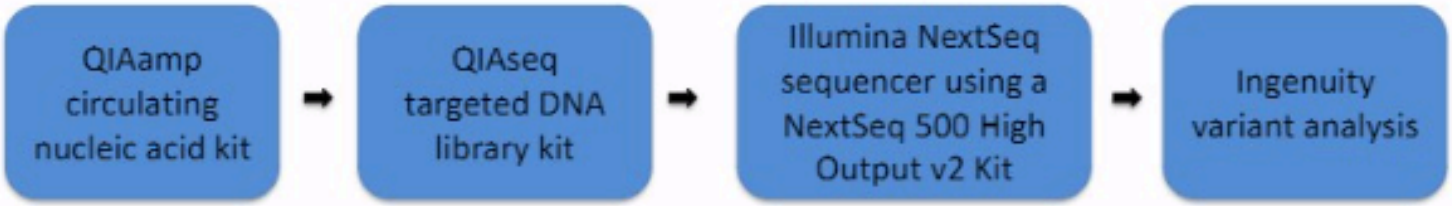
17th International Myeloma Workshop, Boston, September 16-18, 2019

Utilisation of liquid biopsies in functional high-risk myeloma demonstrates a unique mutational pattern and extensive spatial heterogeneity

Andrew Spencer, Kawa Choi, Malgorzata Gorniak, Hang Quach, Noemi Horvath, Ian Kerridge, Edwin Lee, Edward Morris, Flora Yuen, Anna Kalff, Tiffany Khong, Sridurga Mithraprabhu

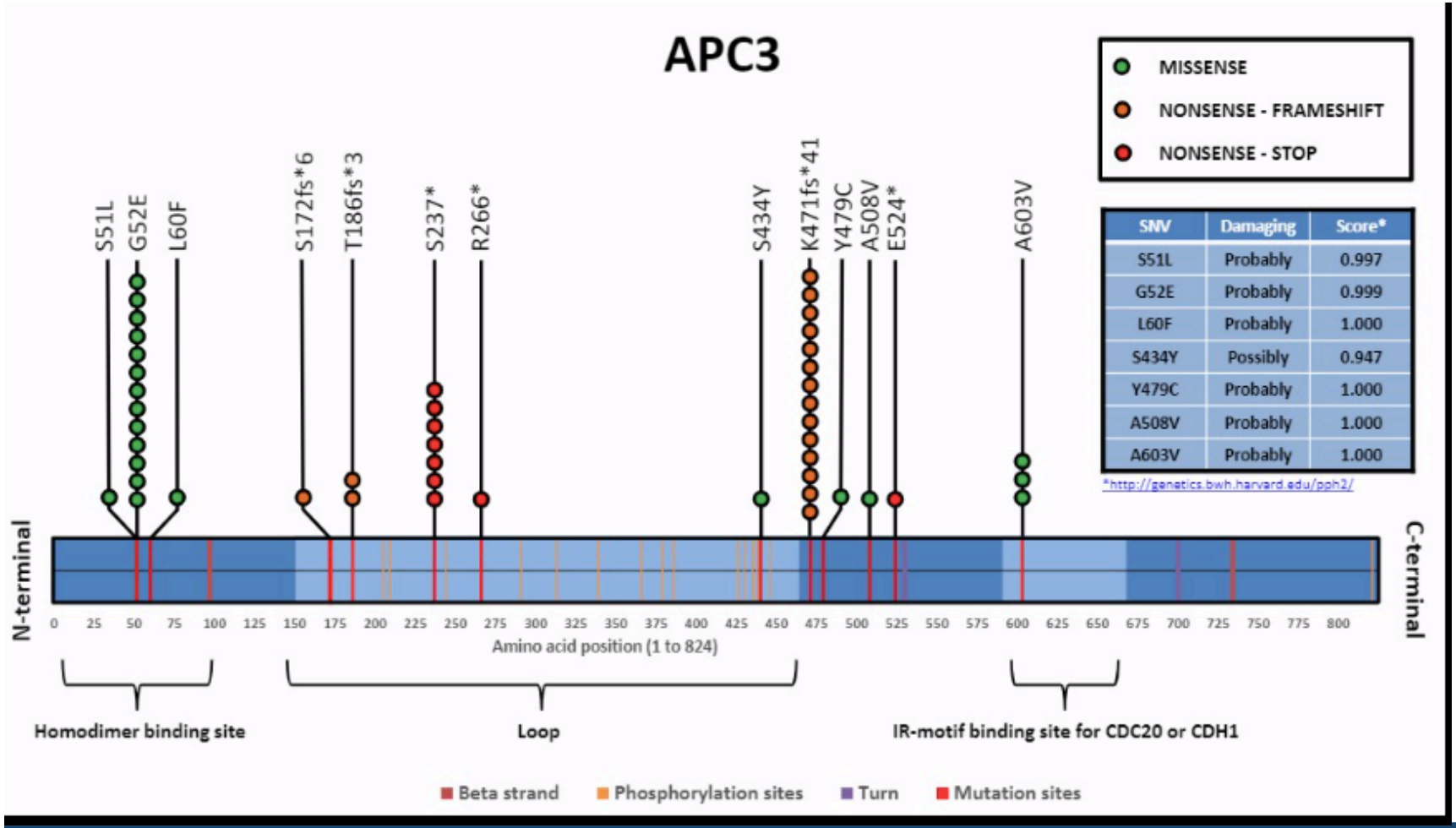
Mutational Characterisation – Targeted Amplicon Sequencing (TAS)

Custom panel with 23 MM specific genes using targeted amplicon sequencing (QIAGEN)



Sensitivity 0.01 – 0.1%

KRAS	EGR1
NRAS	CDC27
DIS3	CCND1
FAM46C	HIST1H1E
BRAF	MAX
TP53	PIK3CA
FGFR3	GNAS
RB1	TMEM14B
IRF4	PRDM1
ATM	CYLD
ATR	TRAF3
ACTG1	



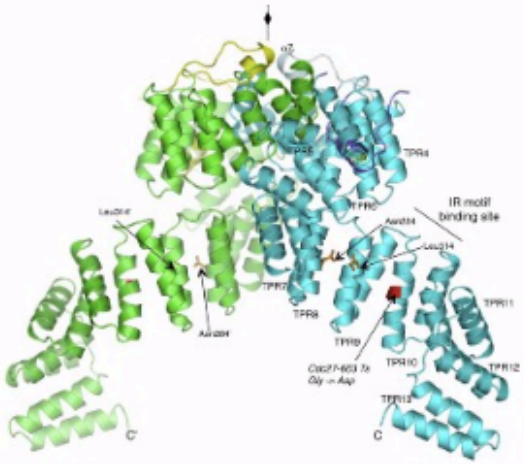
SNV	Damaging	Score*
S51L	Probably	0.997
G52E	Probably	0.999
L60F	Probably	1.000
S434Y	Possibly	0.947
Y479C	Probably	1.000
A508V	Probably	1.000
A603V	Probably	1.000

*http://genetics.bwh.harvard.edu/pph2/

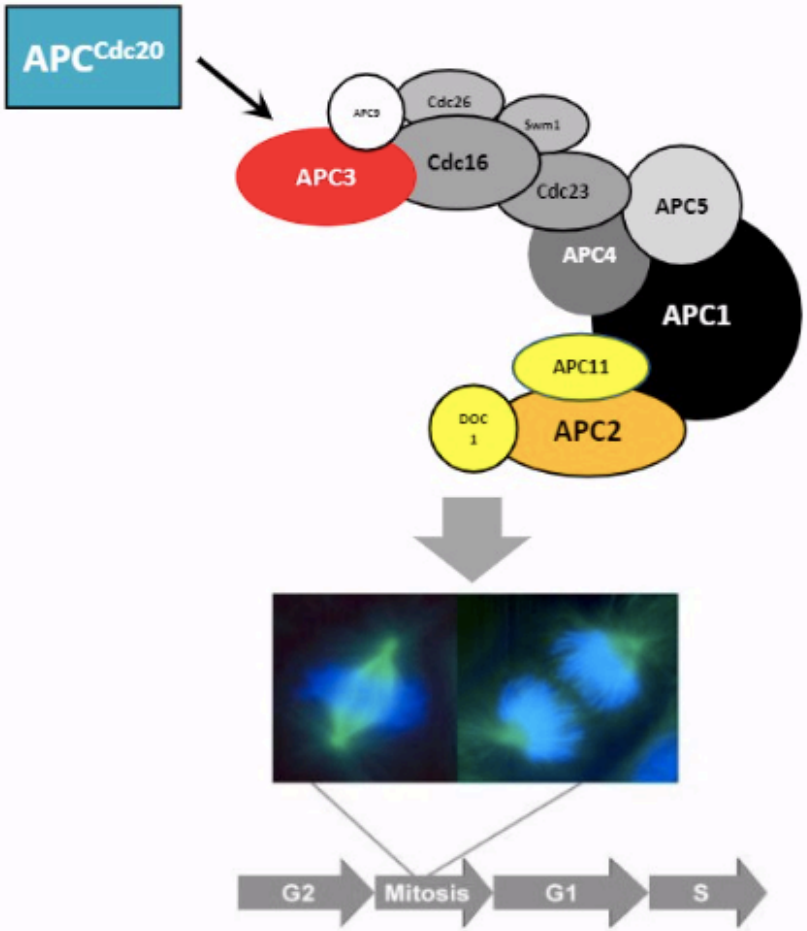
Anaphase-promoting Complex (APC)

Multi-subunit E3 ubiquitin ligase

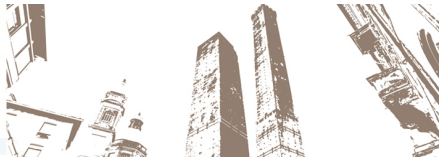
Mitosis & G1/S transition



CDC27 = APC3



RESULTS

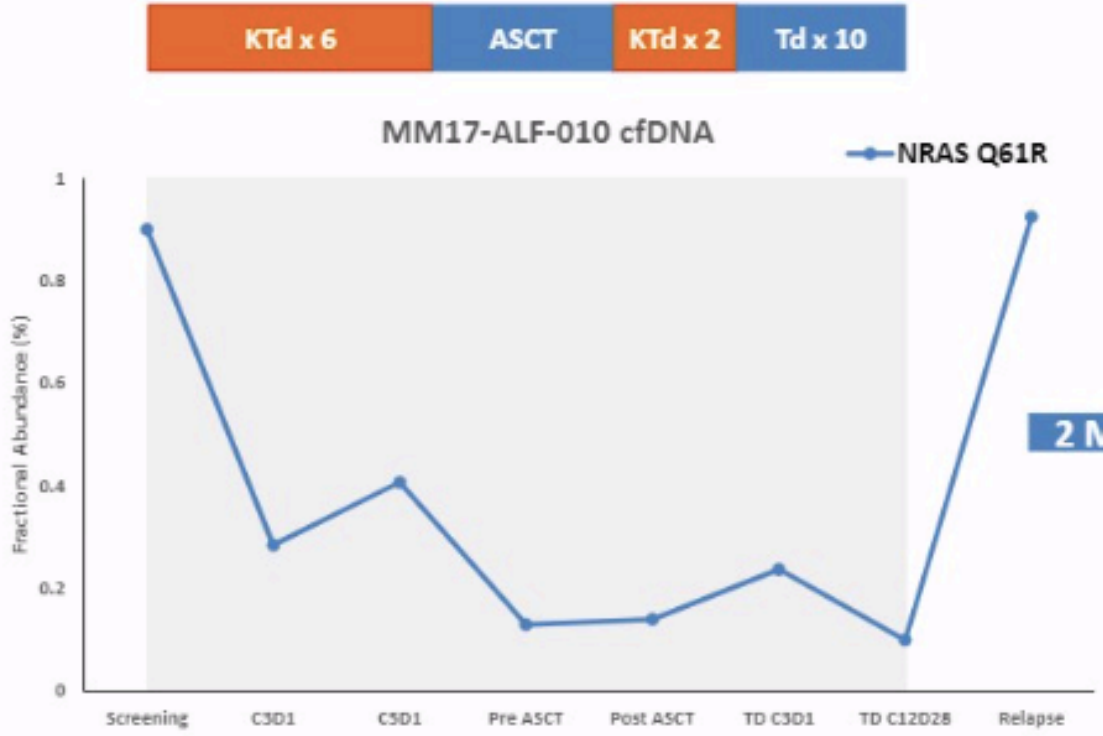


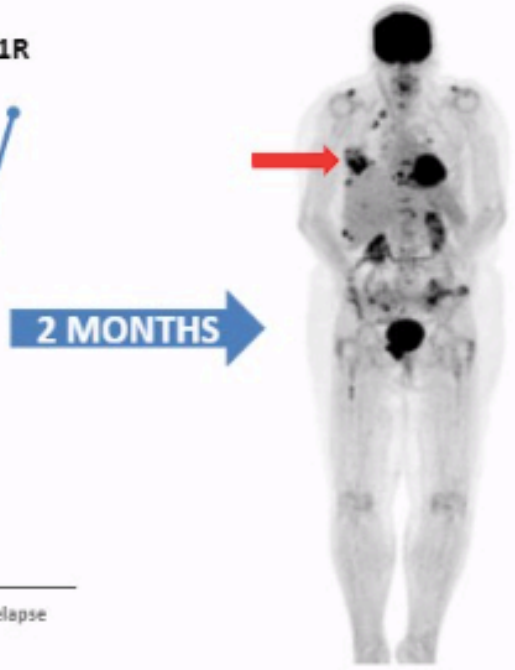
- Patients failing bortezomib-based induction rapidly manifest a unique mutational pattern (c/w newly diagnosed and bortezomib-sensitive patients).

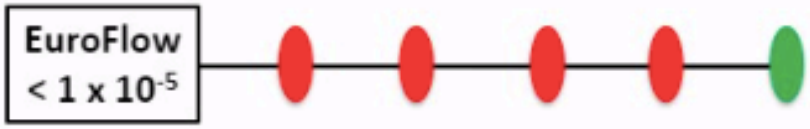
- Loss of function mutations of CDC27 (APC3) may represent a previously unrecognised cause of disease progression and drug resistance. Confirmatory and mechanistic studies are required.

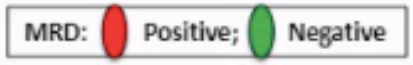
- Patients with functional HR MM display extensive spatial heterogeneity highlighting the limitations of bone marrow evaluation for genomic disease characterisation.

7 patients with ddPCR tracking (5 RAS/2 PIK3CA)
→ 2 with post-ASCT C12D28 discordance - MRD –ve / cfDNA +ve









Circulating Cell Free DNA is a Biomarker for GEP70 Risk Score and Tumor Burden in Myeloma

Shayu Deshpande[1], Yan Wang[1], Ruslana Tytarenko[1], Cody Ashby[1], Eileen Boyle[2], Carolina Schinke[1], Sharmilan Thanendrarajan[1], Maurizio Zangari[1], Faith E. Davies[2], Gareth J. Morgan[2], Frits van Rhee[1] and Brian A. Walker[1]

[1]Myeloma Center, Winthrop P. Rockefeller Cancer Institute, University of Arkansas for Medical Sciences, Little Rock, AR, USA. [2]Department of Medicine, New York University, New York, NY

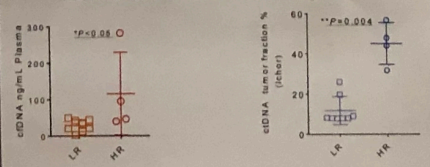
RESULTS

cfDNA Levels Correlate with LDH, κ/λ Ratio, β2-microglobulin Levels and ISS Score

Parameters	Spearman *r*	*P* value
Lactate dehydrogenase (LDH, IU/L)	0.4	***0.0003
Kappa/Lambda light chain ratio	0.25	*0.02
β2-microglobulin (mg/L)	0.33	**0.0032
Albumin (g/dL)	-0.12	ns
M protein (g/dL)	-0.10	ns
ISS score	0.32	**0.0049

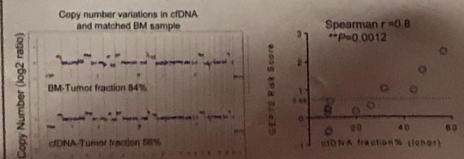
ctDNA Tumor Fraction is Higher in HR and Correlates with GEP70 Risk Score

cfDNA levels and ctDNA levels are higher in HR



✓ In a subset of patients (n=12; LR=8; HR=4) ULP-WGS was performed. cfDNA and ctDNA were significantly higher (Mann Whitney test) in the HR group.

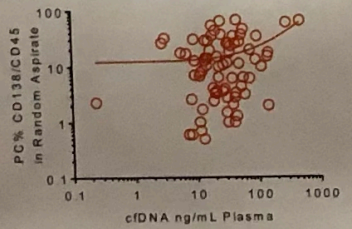
ctDNA fraction correlates with GEP70 risk score



✓ ctDNA tumor fraction strongly correlated with GEP70 score in this patient group.

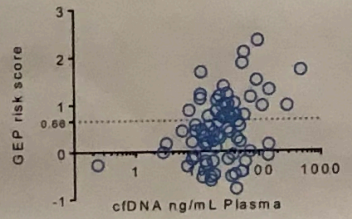
GEP70 Risk Score Correlates with cfDNA Levels and HR Has Higher cfDNA Levels Compared to the LR Subgroup

cfDNA levels increase with increased tumor burden in BM



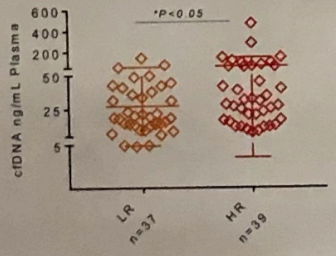
Linear Regression Analysis
r^2=0.157; F=13.8; ***P<0.0004

cfDNA levels correlate with GEP70 risk score



Spearman r =0.26 *P<0.05
Linear regression Analysis:
r^2=0.09; F=7.71 **P<0.01

HR has higher cfDNA levels than LR subgroup

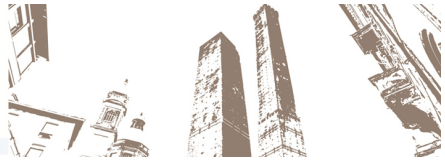


✓ Linear regression analysis showed that cfDNA levels increased with PC percentage.

✓ cfDNA levels correlate with GEP70 risk score by Spearman's test.

✓ cfDNA levels were significantly higher in HR compared to LR (Mann-Whitney test). No significant differences were observed among GEP subgroups or UAMS TC groups.

High-risk MM: take home messages…



- ✓ High-risk disease is define by both clinical and genetic features.
- ✓ Strong negative prognostic role of the double hit p53 mutations and of *GSK1B* amplification
- ✓ No unique pathogenetic biological mechanism defines the high-risk disease.
- ✓ High sensitivity to MCL-1 inhibitor in Amp1q high risk patients
- ✓ High proliferative rate and signature: possible role of LOF of RB1 and MAX at the diagnosis and CDKN1C/CDKN2C at the transition to PR group.
- ✓ A spatial regional genomic heterogeneity of high-risk disease occurs in MM patients with poor prognosis.
- ✓ Identification of possible surrogate markers of high-risk disease by liquid biopsy.

Grazie per l'attenzione…

IMW 2019