Le basi molecolari della resistenza al trattamento nel mieloma multiplo

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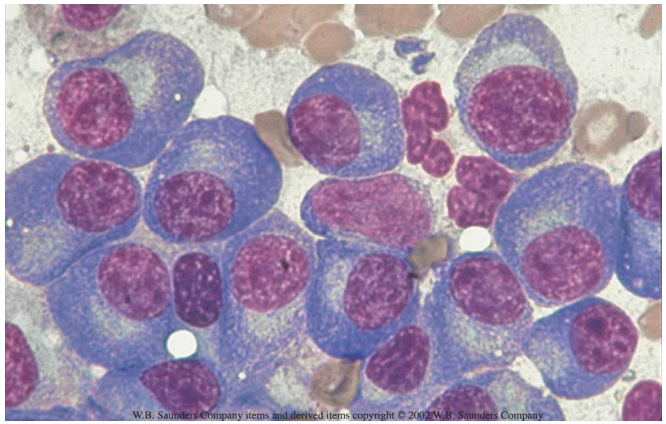
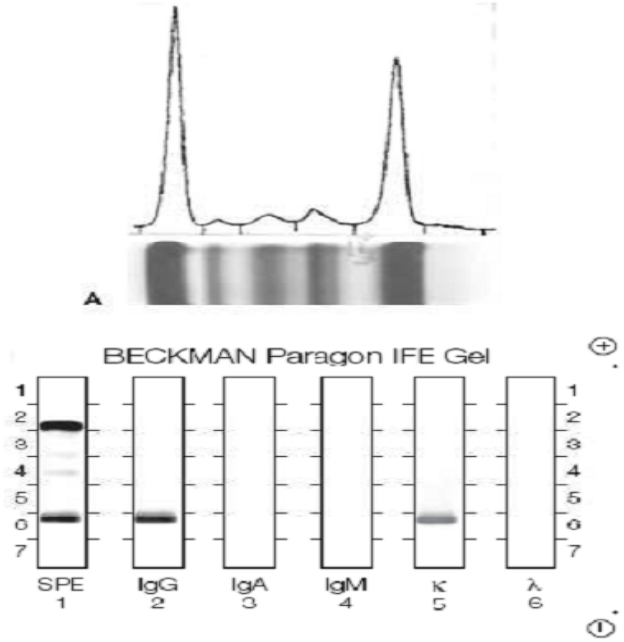
Multiple myeloma: a malignant proliferation of bone marrow plasma cells

Plasma cell: Ig-secreting, heavy-chian class switched, terminally differentiated B-cell





abnormal production of a monoclonal immunoglobulin (M-protein)

- 1% of cancer
- 10% of hematological malignancies
- 2-4 cases/year/100.000
- Uncurable disease_ MS approximately 6 ys

Major issues

- Myeloma looks homogeneous at microscope
- Survival outcome cannot be predicted at presentation
- High molecular heterogeneity

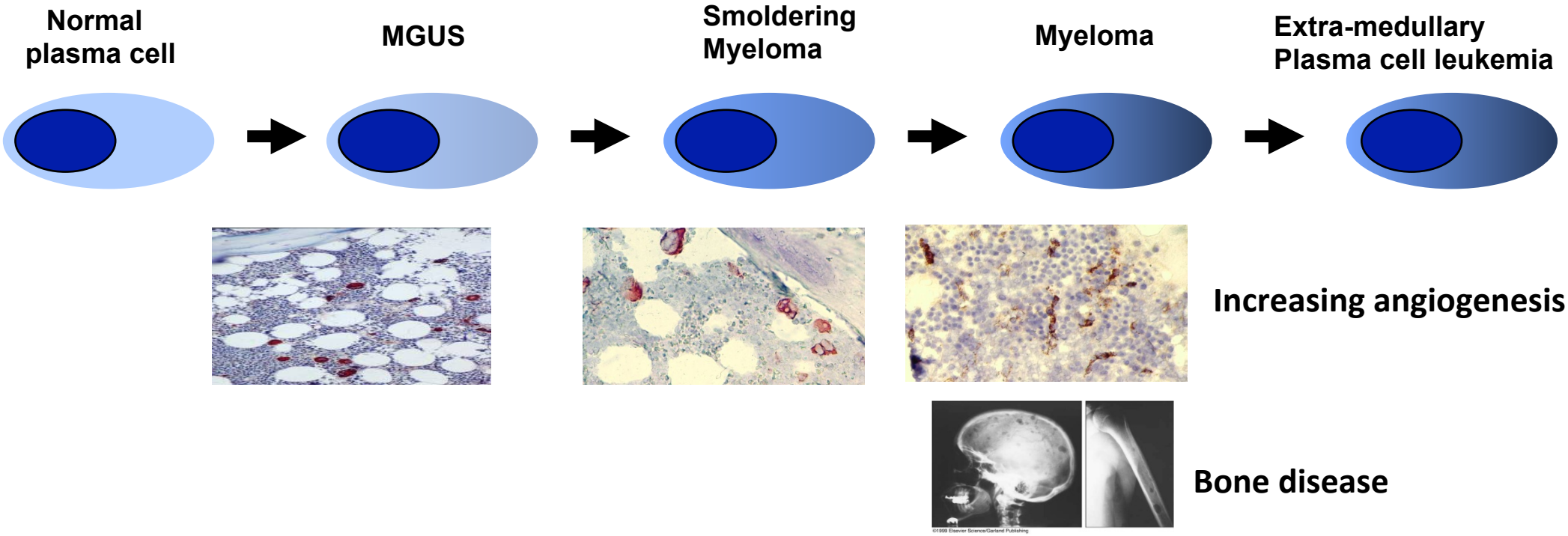
What's the relevance of molecular genetics in the risk stratification and targeting treatments of patients?

Common cytogenetic findings in MM by FISH

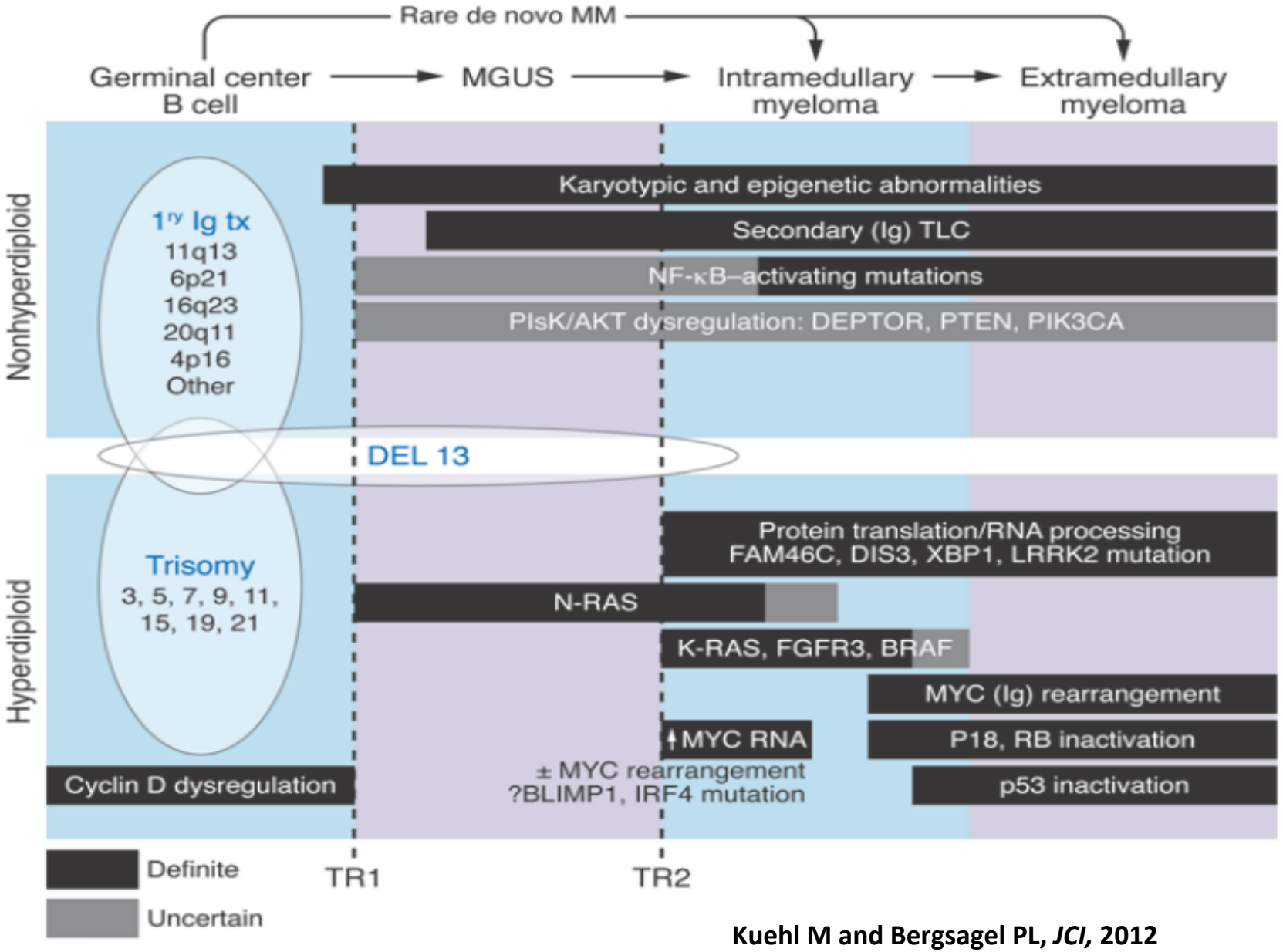
Translocations involving 14q32 ▪ t(11;14) Cyclin D1 ▪ t(4;14) FGFR3-MMSET ▪ t(14;16) MAF ▪ t(14;20) MAFB	▪ ≅40% ▪ 16% ▪ 15% ▪ 5% ▪ 2
Chromosome 13 abnormalities ▪ Monosomy ▪ Deletion 13 ▪ 13q translocations	▪ ≅40-50%
17p deletions	▪ ≅8%
Hyperdiploidy	▪ ≅50% (3,5,7,9,11,15,19,21)
1q amplifications 1p deletions C-MYC alterations (Trx, gain)	• ≅50% • ≅35% • 50%

Fonseca R, et al. Leukemia. 2009; 23: 2210-2221; Bergsagel et al, Blood 2013; Affer et al. Leukemia, 2014

Disease stages and timing of oncogenic events in Multiple Myeloma



Molecular pathogenesis of Multiple Myeloma: two main models



NON-HYPERDIPLOIDY

Class-switch recombination In germinal center

IGH TRX

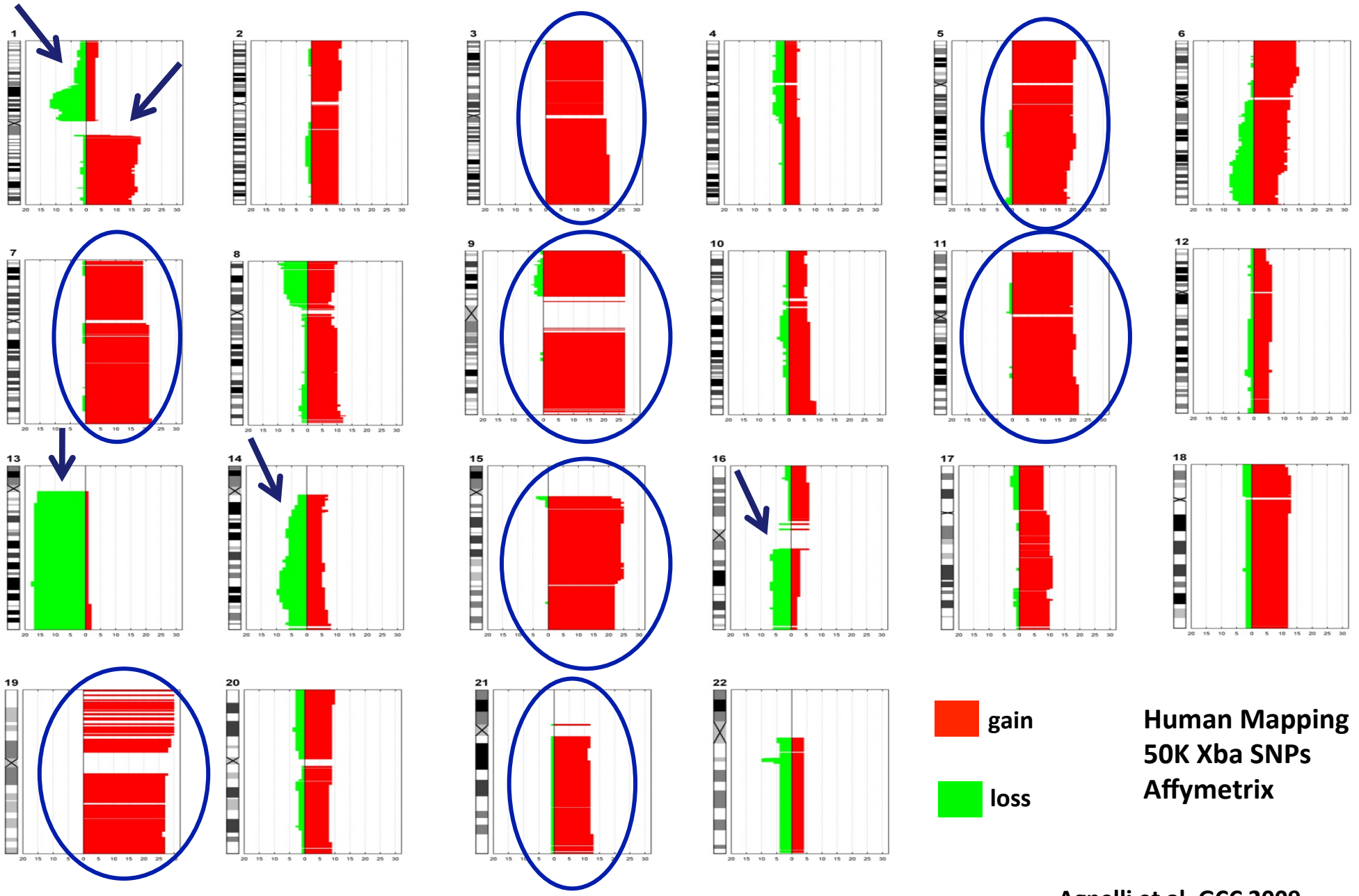
HYPERDIPLOIDY

Mechanisms ???

Trisomies 3,5,7,9,11,15,19,21

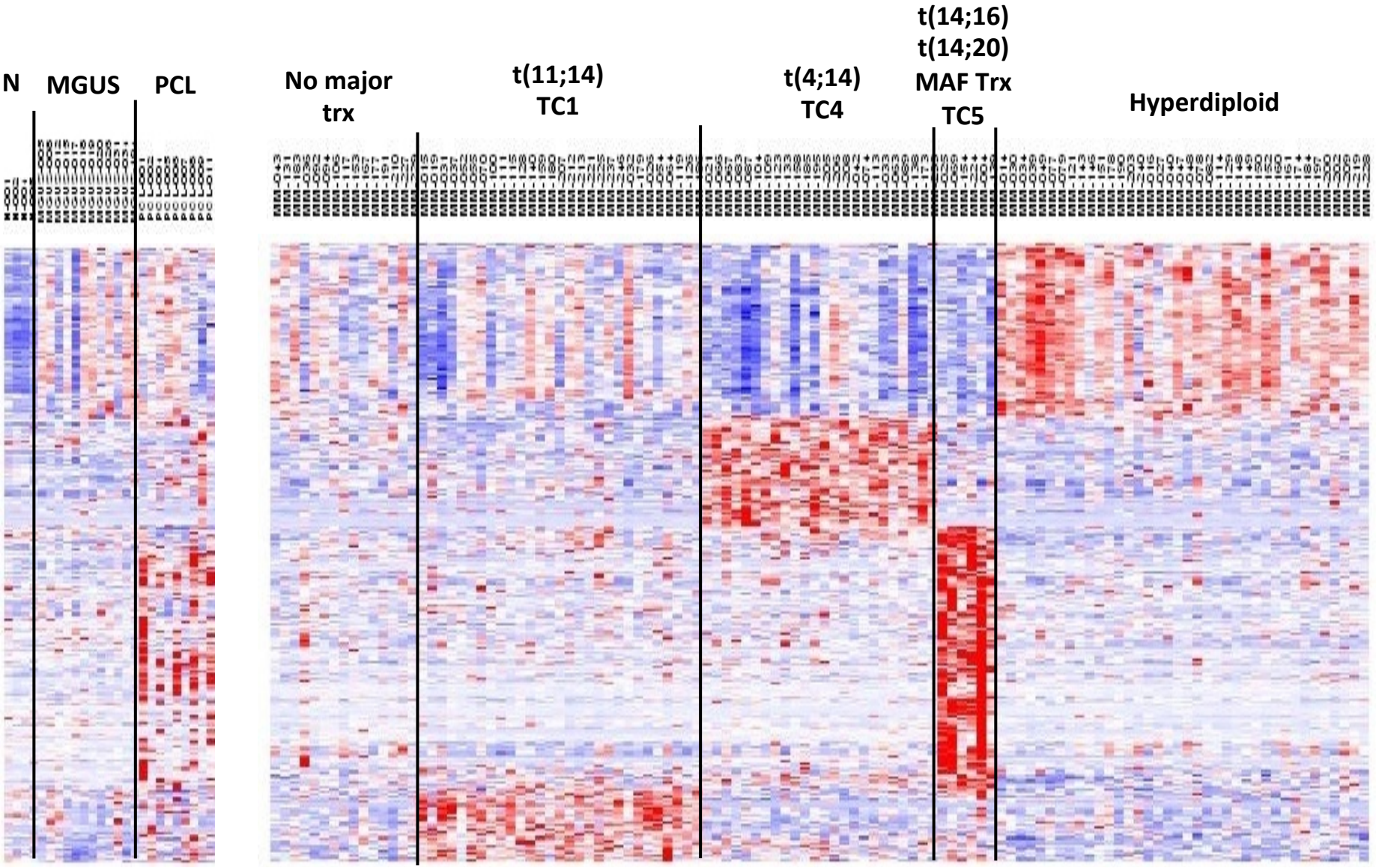
Kuehl M and Bergsagel PL, *JCI,* 2012

Frequency of DNA copy number alterations in MMs by SNP-array



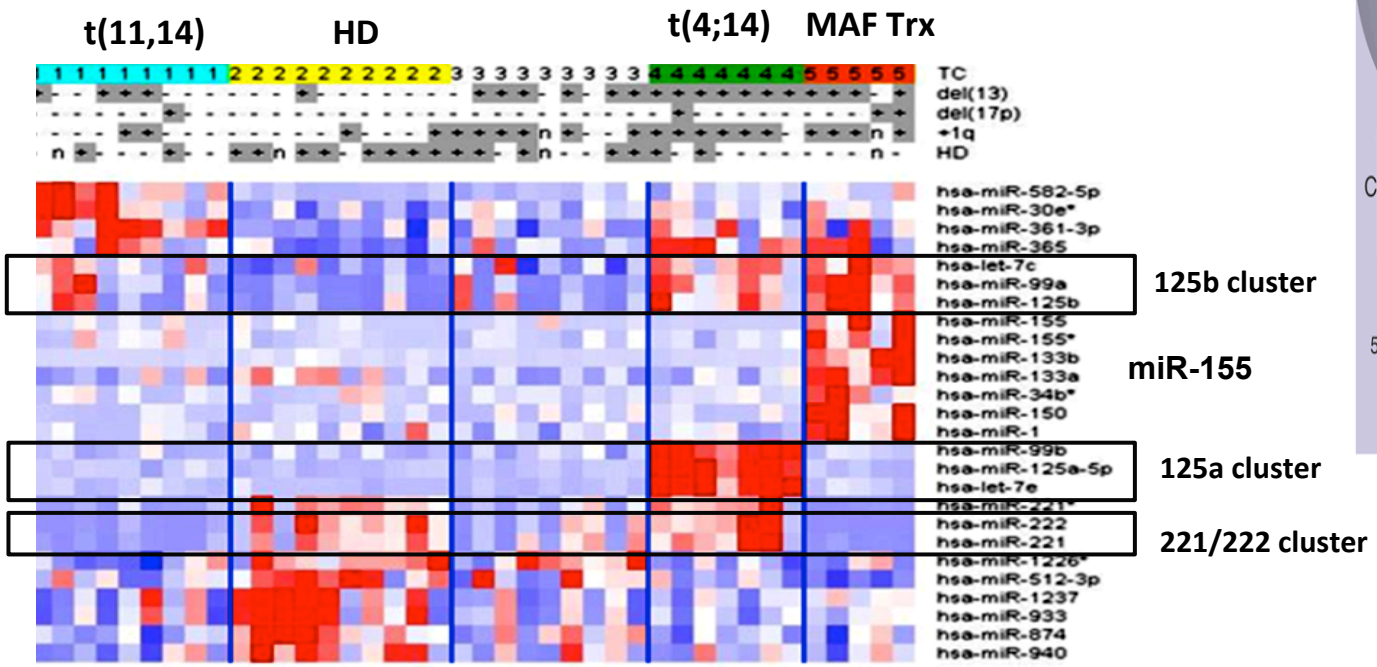
Agnelli et al. GCC 2009

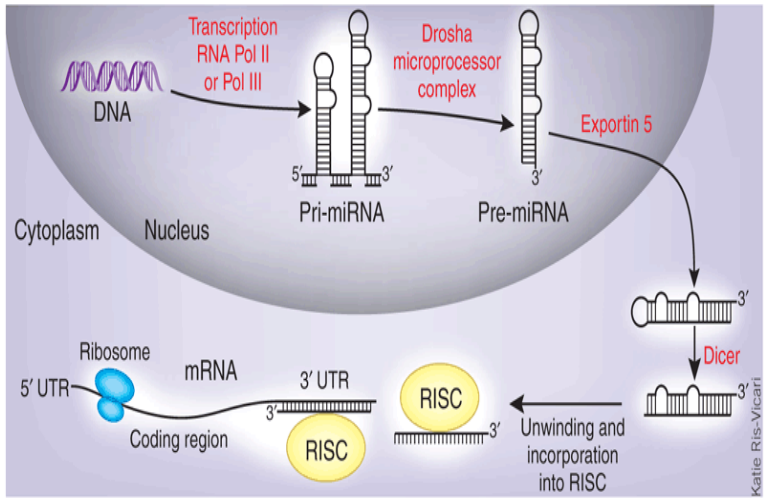
Distinct molecular types of MM are associated with specific RNA expression profiles



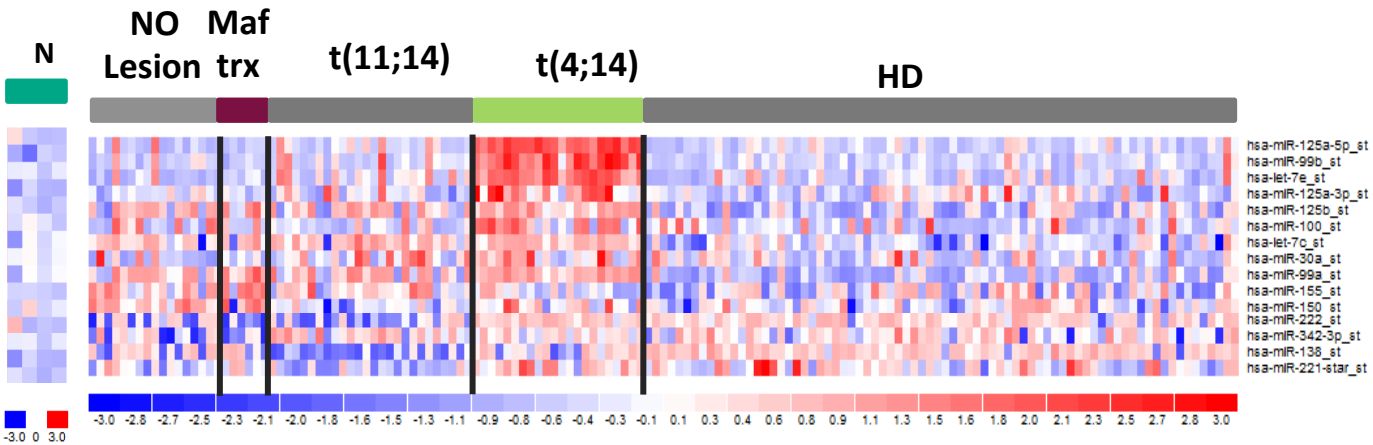
Mattioli et al. *Oncogene*,2005; Agnelli et al. *JCO*,2005

Specific microRNA expression profiles are associated with major molecular MM groups



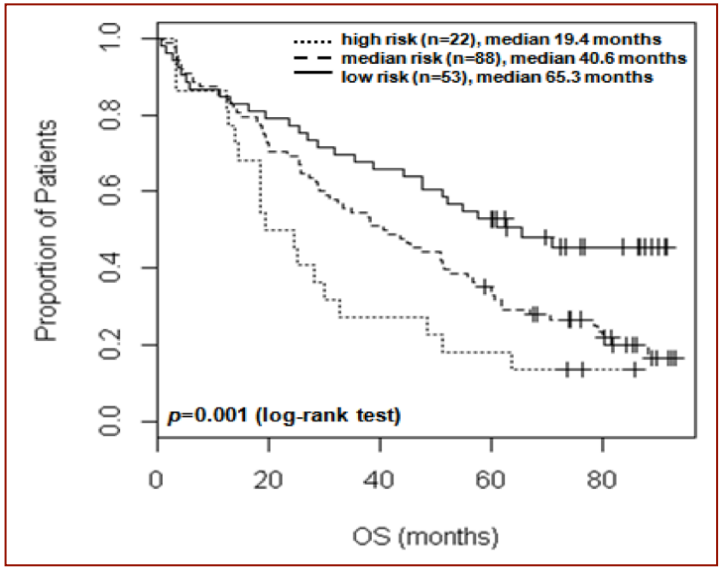


Lionetti M. et al., Blood, 2009



Wu P, Agnelli A. et al. BJH, 2013 MRC Myeloma IX trial

Definition of three prognostic groups based on *miR-17* and *miR-886-5p* expr ession:



www.impactjournals.com/oncotarget/ Oncotarget, February, Vol.4, No 2

In Vitro and in Vivo Anti-tumor Activity of miR-221/222 Inhibitors in Multiple Myeloma

Maria Teresa Di Martino[1,2], Annamaria Gullà[1], Maria Eugenia Gallo Cantafio[1], Marta Lionetti[3], Emanuela Leone[1], Nicola Amodio[1], Pietro Hiram Guzzi[4], Umberto Foresta[1], Francesco Conforti[2], Mario Cannataro[4], Antonino Neri[3], Antonio Giordano[5,6], Pierosandro Tagliaferri[1,2], and Pierfrancesco Tassone[1,2,6]

Clinical Cancer Research

AACR

Targeting miR-21 inhibits in vitro and in vivo multiple myeloma cell growth

Emanuela Leone, Eugenio Morelli, Maria T. Di Martino, et al.

Clin Cancer Res Published OnlineFirst February 27, 2013.

www.impactjournals.com/oncotarget/ Oncotarget, Advance Publications 2012

DNA-demethylating and anti-tumor activity of synthetic miR-29b mimics in multiple myeloma

Nicola Amodio[1], Marzia Leotta[1], Dina Bellizzi[2], Maria Teresa Di Martino[1], Patrizia D'Aquila[2], Marta Lionetti[3], Fernanda Fabiani[1], Emanuela Leone[1], Anna Maria Gullà[1], Giuseppe Passarino[2], Michele Caraglia[4], Massimo Negrini[5], Antonino Neri[3], Antonio Giordano[6], Pierosandro Tagliaferri[1] and Pierfrancesco Tassone[1,6]

[1] Department of Experimental and Clinical Medicine, Magna Graecia University and Medical Oncology Unit, T. Campanella

OPEN

Leukemia (2015), 1–11

www.nature.com/leu

ORIGINAL ARTICLE

Selective targeting of IRF4 by synthetic microRNA-125b-5p mimics induces anti-multiple myeloma activity *in vitro* and *in vivo*

E Morelli[1], E Leone[1], ME Gallo Cantafio[1], MT Di Martino[1], N Amodio[1], L Biamonte[1], A Gullà[1], U Foresta[1], MR Pitari[1], C Botta[1], M Rossi[1], A Neri[2], NC Munshi[3,4], KC Anderson[3], P Tagliaferri[1] and P Tassone[1,5]

Published OnlineFirst on October 3, 2012; DOI:10.1158/1078-0432.CCR-12-1708

Cancer Therapy: Preclinical

Clinical Cancer Research

Synthetic miR-34a Mimics as a Novel Therapeutic Agent for Multiple Myeloma: *In Vitro* and *In Vivo* Evidence

Maria T. Di Martino[1], Emanuela Leone[1], Nicola Amodio[1], Umberto Foresta[1], Marta Lionetti[3], Maria R. Pitari[1], Maria E. Gallo Cantafio[1], Annamaria Gullà[1], Francesco Conforti[2], Eugenio Morelli[1], Vera Tomaino[1], Marco Rossi[1], Massimo Negrini[4], Manlio Ferrarini[5], Michele Caraglia[6], Masood A. Shammas[7,8], Nikhil C. Munshi[7,8], Kenneth C. Anderson[7], Antonino Neri[3], Pierosandro Tagliaferri[1], and Pierfrancesco Tassone[1,9]

www.impactjournals.com/oncotarget/ Oncotarget, Advance Publications 2012

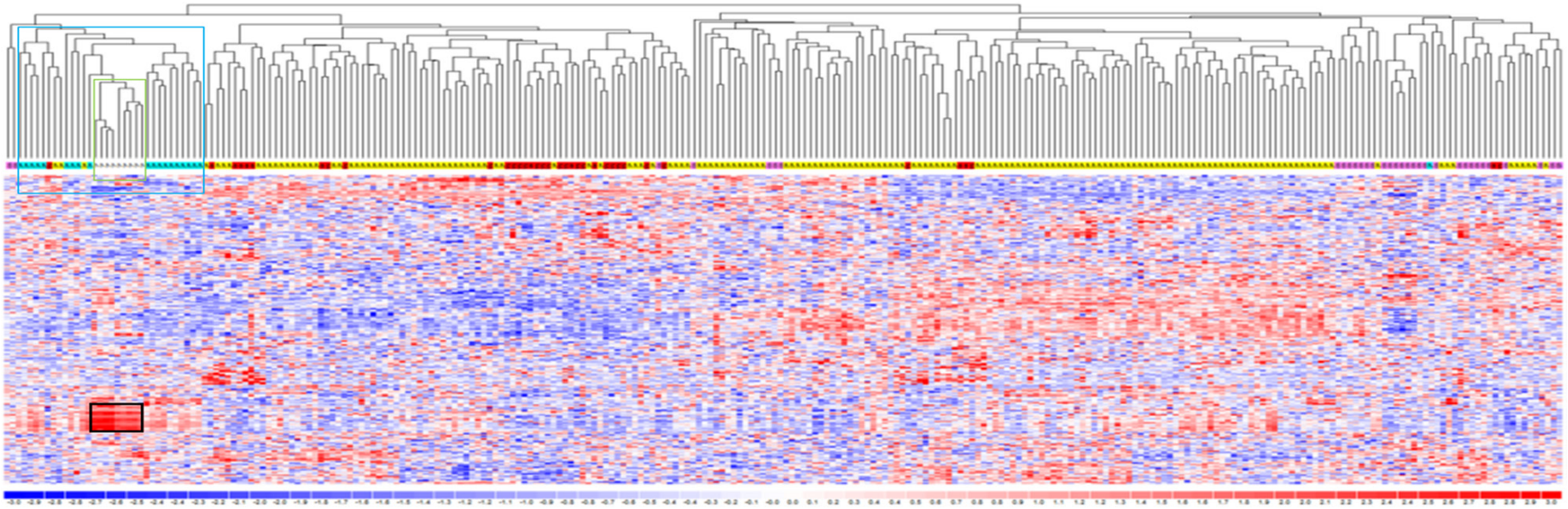
DNA-demethylating and anti-tumor activity of synthetic miR-29b mimics in multiple myeloma

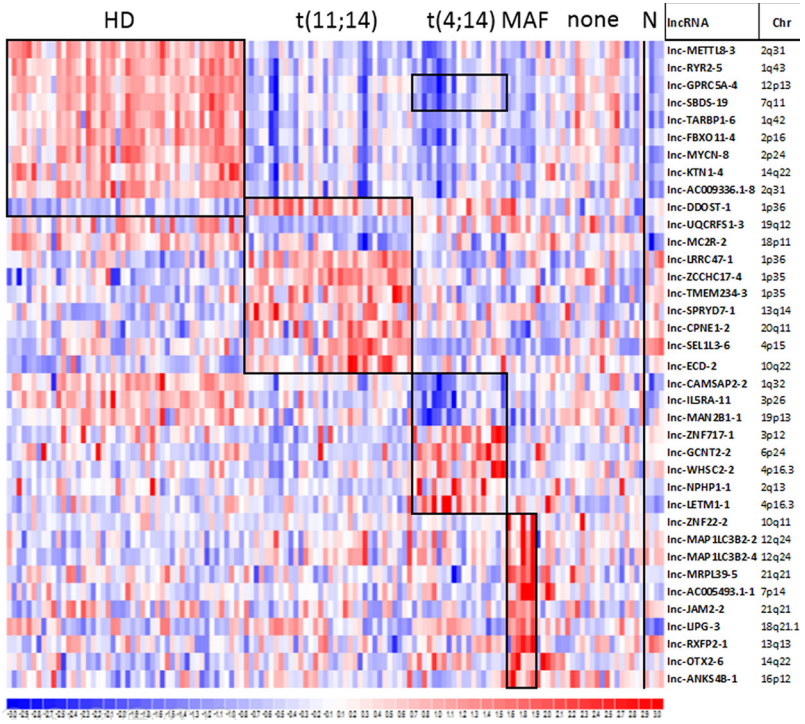
Nicola Amodio[1], Marzia Leotta[1], Dina Bellizzi[2], Maria Teresa Di Martino[1], Patrizia D'Aquila[2], Marta Lionetti[3], Fernanda Fabiani[1], Emanuela Leone[1], Anna Maria Gullà[1], Giuseppe Passarino[2], Michele Caraglia[4], Massimo Negrini[5], Antonino Neri[3], Antonio Giordano[6], Pierosandro Tagliaferri[1] and Pierfrancesco Tassone[1,6]

Cell Cycle 12:23, 3650–3662; December 1, 2013; © 2013 Landes Bioscience

miR-29b induces SOCS-1 expression by promoter demethylation and negatively regulates migration of multiple myeloma and endothelial cells

Nicola Amodio[1], Dina Bellizzi[2], Marzia Leotta[1], Lavinia Raimondi[1], Lavinia Biamonte[1], Patrizia D'Aquila[2], Maria Teresa Di Martino[1], Teresa Calimeri[1], Marco Rossi[1], Marta Lionetti[3,4], Emanuela Leone[1], Giuseppe Passarino[2], Antonino Neri[3,4], Antonio Giordano[5,6], Pierosandro Tagliaferri[1], and Pierfrancesco Tassone[1,6,*]

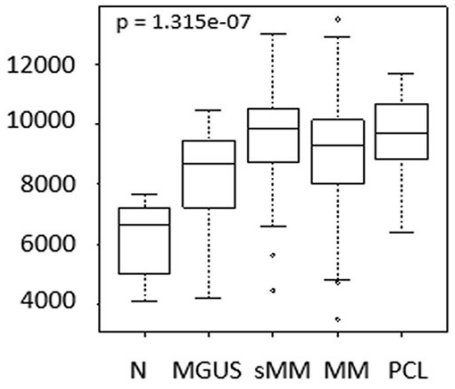


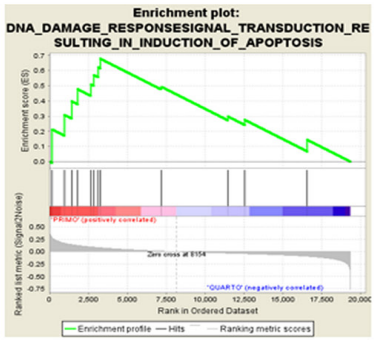


www.impactjournals.com/oncotarget/ Oncotarget, Advance Publications 2016

Distinct lncRNA transcriptional fingerprints characterize progressive stages of multiple myeloma

Domenica Ronchetti[1,2,*], Luca Agnelli[1,2,*], Elisa Taiana[1,2], Serena Galletti[1,2], Martina Manzoni[1,2], Katia Todoerti[3], Pellegrino Musto[3], Francesco Strozzi[4], Antonino Neri[1,2]



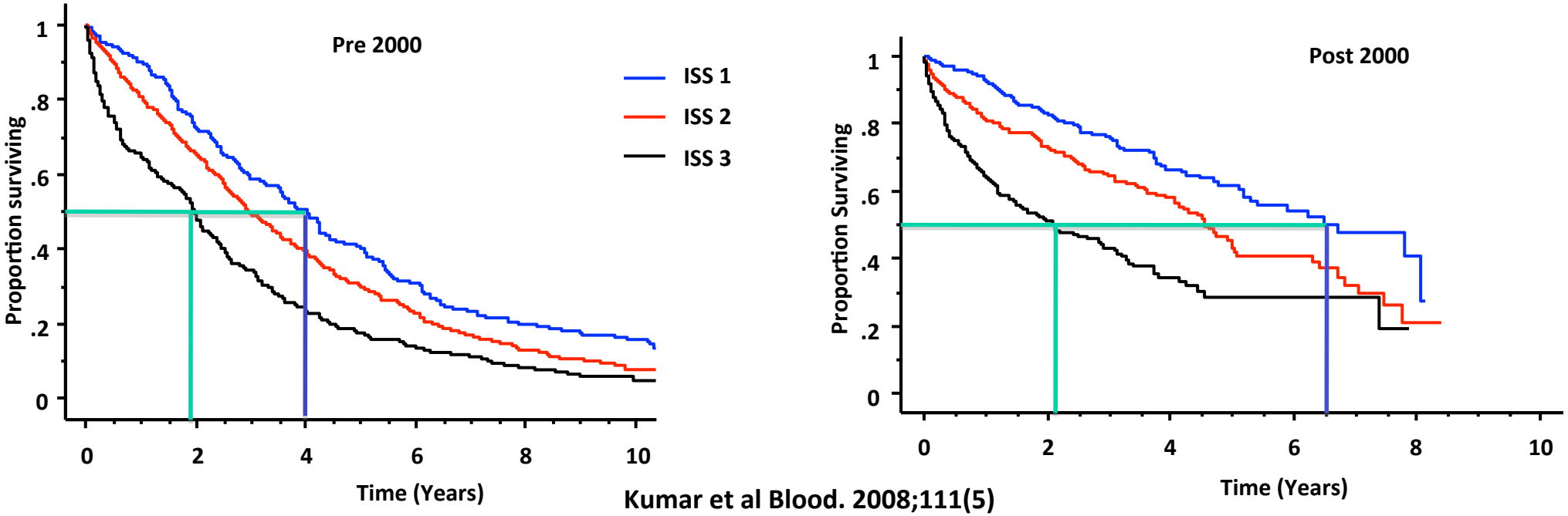


GENE	CORE ENRICHMENT
CIDEB	Yes
TP53	Yes
BCL3	Yes
PCBP4	Yes
BRCA1	Yes
IFI16	Yes
ABL1	Yes
PML	Yes
DYRK2	No
SFN	No
CIDEA	No
TP73	No
CHEK2	No

LncRNA MALAT-1

Survival Has Improved…even for High Risk MM?

ISS Stage	Criteria
I	β_2m < 3.5 mg/L & albumin ≥ 3.5 g/dL
II	Not stage I or III
III	β_2m ≥ 5.5 mg/L



Kumar et al Blood. 2008;111(5)

- How to integrate the molecular genetics for risk stratification and treatment selection

mSMART 2.0: Classification of Active MM

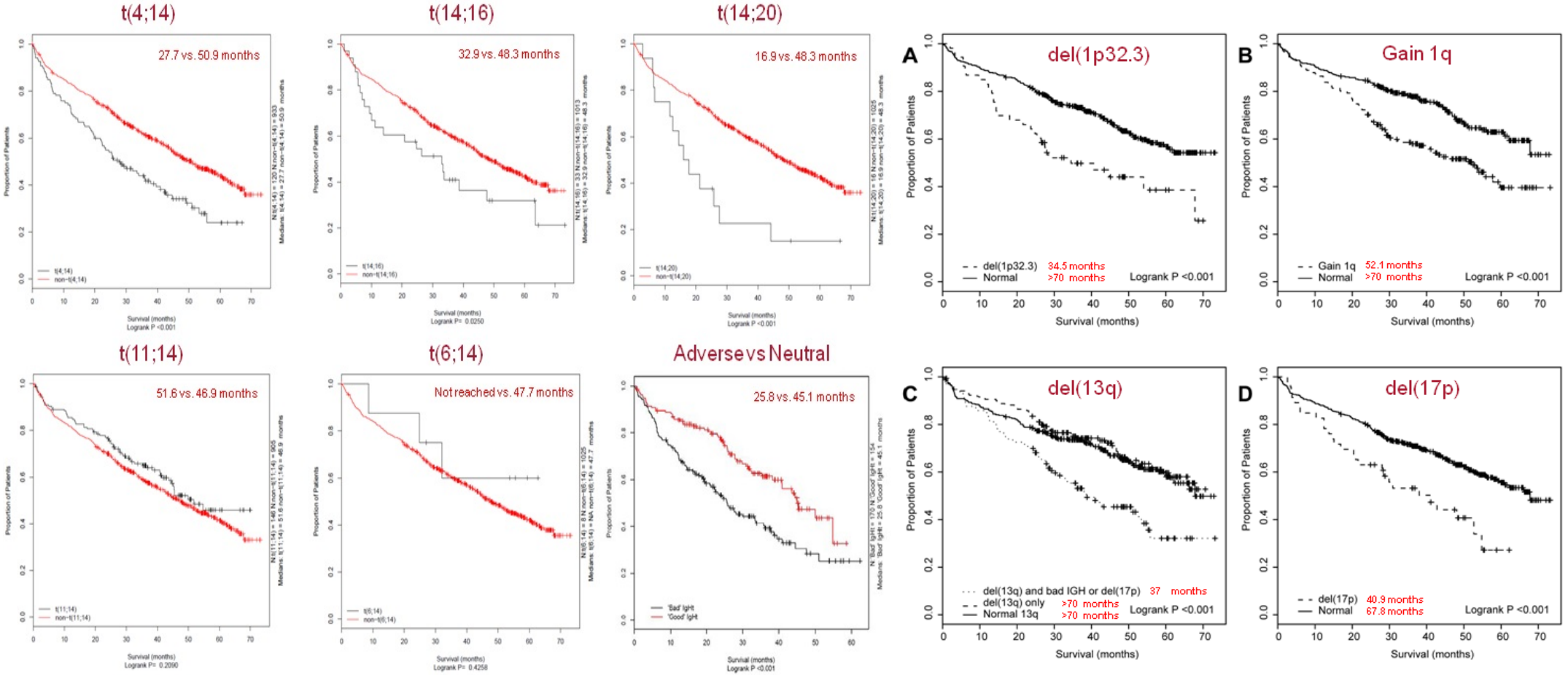
20%	20%	60%
High-Risk	**Intermediate-Risk***	**Standard-Risk*†**
▪ FISH ▪ Del 17p ▪ t(14;16) ▪ t(14;20) ▪ GEP ▪ High risk signature **3 ys**	▪ FISH ▪ t(4;14)‡ ▪ Cytogenetic Deletion 13 or hypodiploidy ▪ PCLI ≥3% **4-5 ys**	All others including: ▪ Hyperdiploid ▪ t(11;14)** ▪ t(6;14) **10 ys**

* Note that a subset of patients with these factors will be classified as high-risk by GEP
† LDH >ULN and beta-2 M > 5.5 may indicate worse prognosis
‡ Prognosis is worse when associated with high beta-2 M and anemia
**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
v8 Revised and updated: Feb 2011

GENETIC PROGNOSTIC MARKERS IN MYELOMA _ MRC MM IX

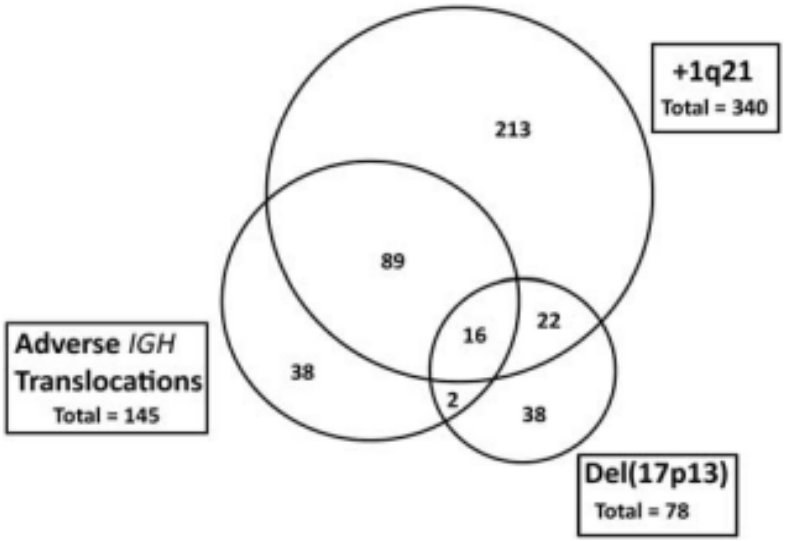
Thalidomide-based regimen

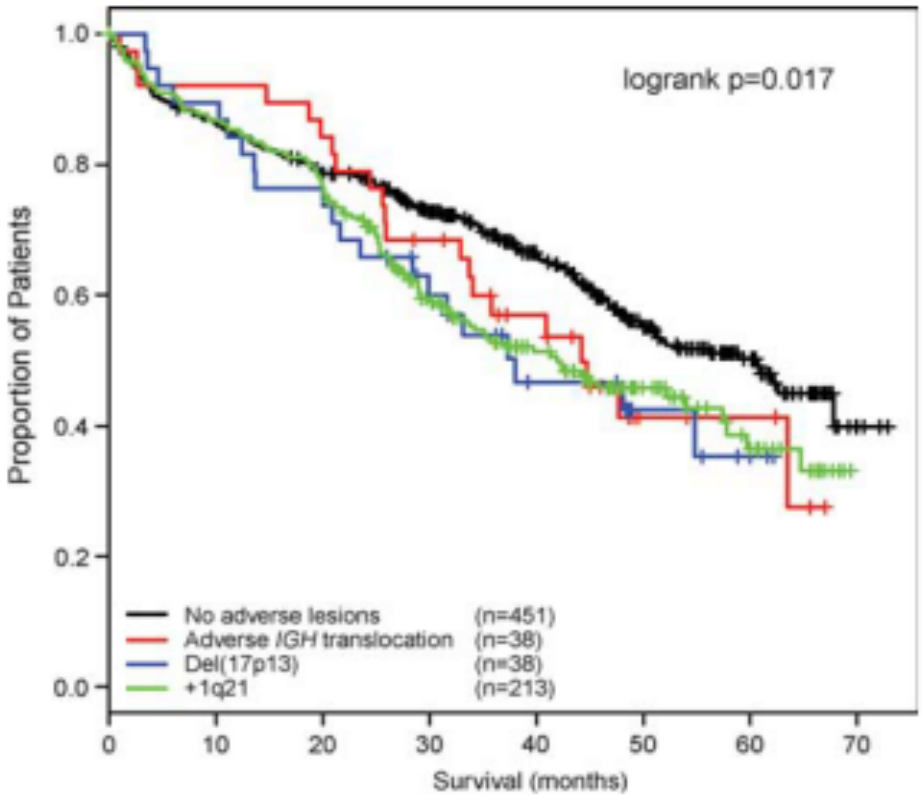


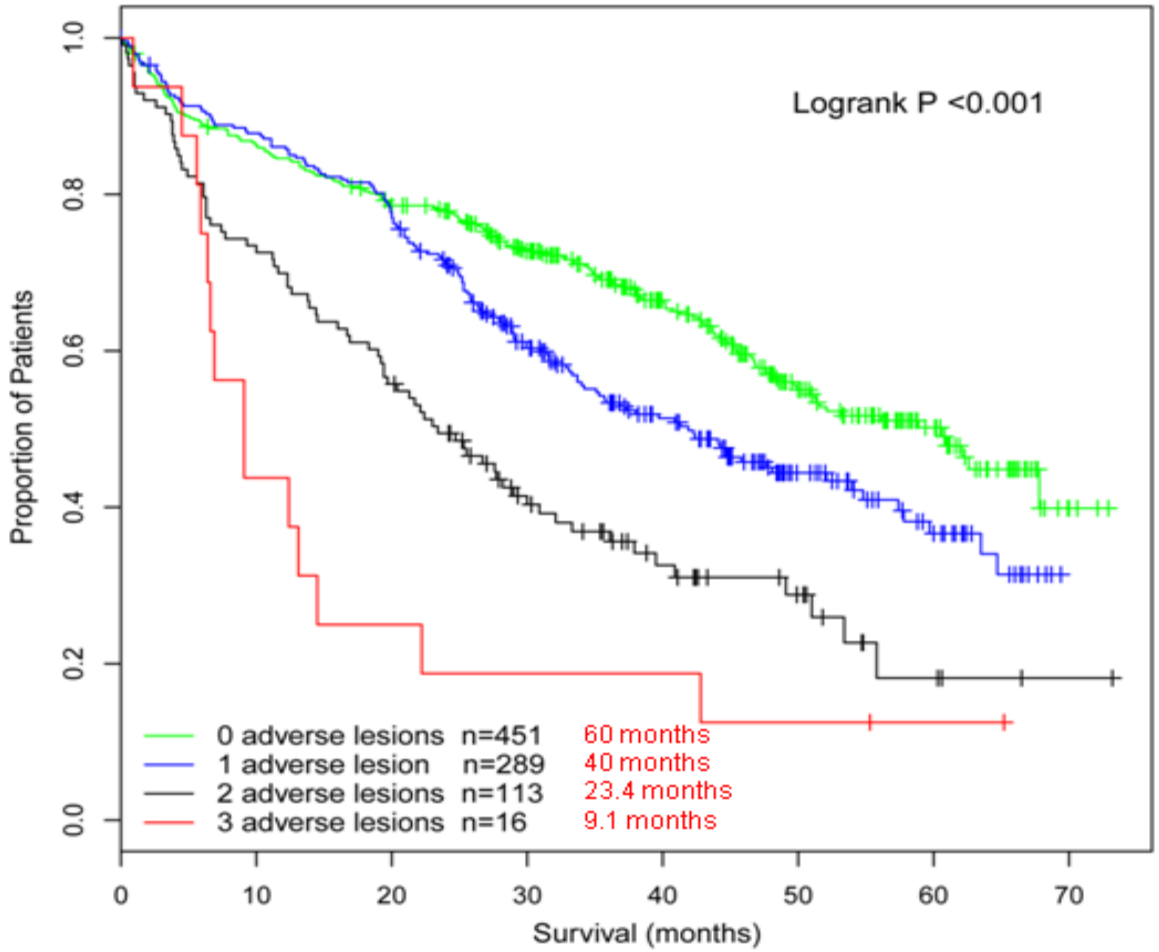
ADVERSE PROGNOSTIC VALUE OF t(4;14), MAF Trx, gain 1q, del1p, del17p

IMPACT OF COMBINED LESIONS

The number of adverse markers has an additive effect on overall survival

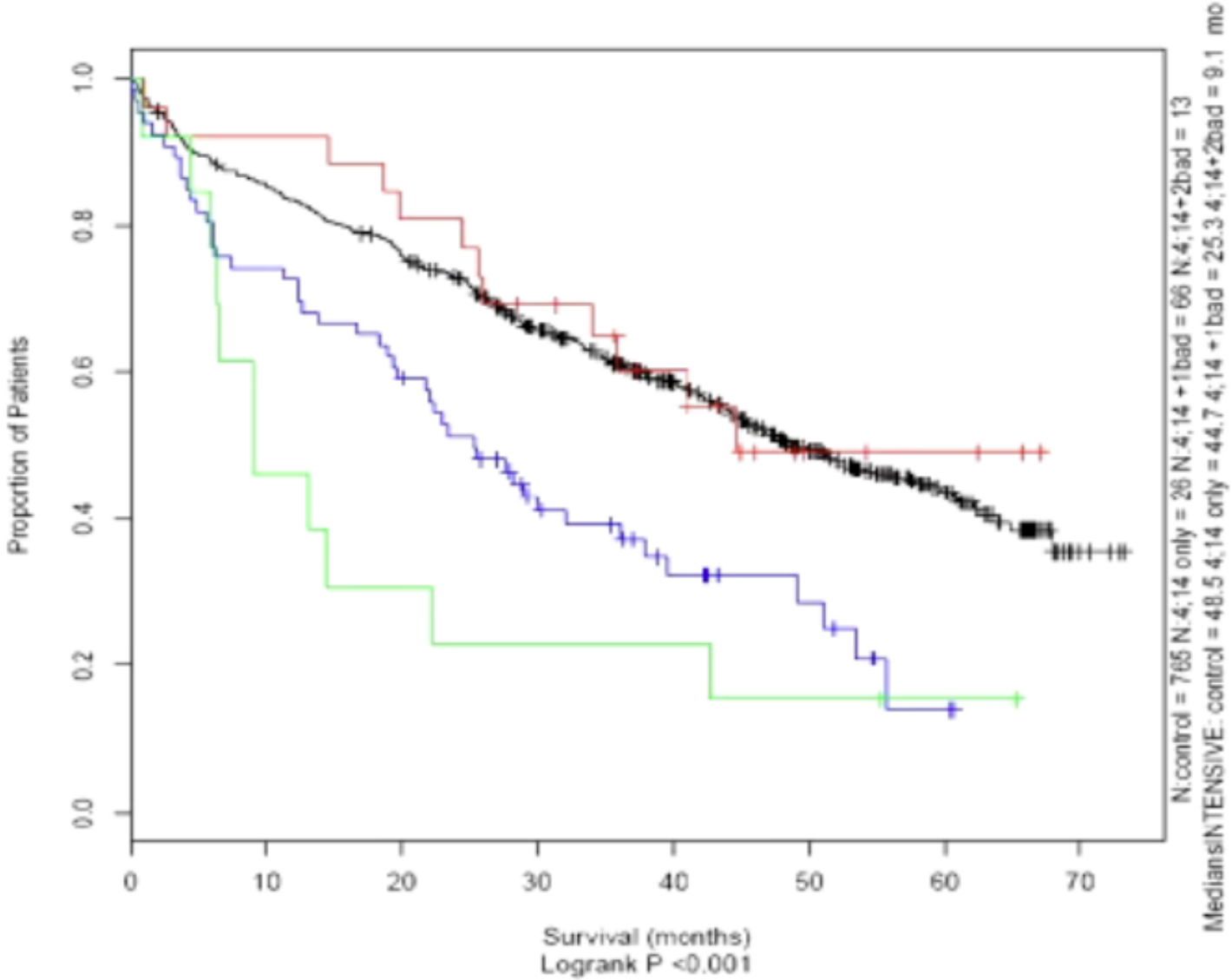






Boyd et al., Leukemia, 2011_MRC IX trial

t(4;14) Are All Bad ?



Black = no 4;14
Red = 4;14 only
Blue = 4;14 + either 17p- or 1q+
Green = 4;14 + 17p- and 1q+

MORGAN G.
IMW Paris, 2011

Leukemia (2009), 1–12

www.nature.com/leu

SPOTLIGHT REVIEW

International Myeloma Working Group molecular classification of multiple myeloma: spotlight review

R Fonseca[1], PL Bergsagel[1], J Drach[2], J. Shaughnessy[3], N Gutierrez[4], K Stewart[1], G Morgan[5], B Van Ness[6], M Chesi[1], S Minvielle[7], A Neri[8], B Barlogie[3], WM Kuehl[9], P Liebisch[10], F Davies[5], S Chen-Kiang[11], BGM Durie[12], R Carrasco[13], Orhan Sezer[14], Tony Reiman[15], Linda Pilarski[16] and H Avet-Loiseau[7]

Table 1 FISH markers and association with outcome for patients with MM

Level	*FISH tests*	*Testing frequency*	*Validation*
Minimal proposed testing (essential testing)			
Established markers	t(4;14)(p16;q32)	Once	Validated by several studies
	t(14;16)(q32;q23)	Once	
	17p13	May be repeated	
Expanded panel			
Markers with modest effects	Hyperdiploidy	Once	Weak effects when used alone. The first two may portend a more favorable outcome
	t(11;14)(q13;q32)	Once	
	Chromosome 13	May be repeated	
Other	Other translocations	Once	Rare events and not routinely tested
Chromosome 1	1q amplification	May be repeated	Although conflicting studies seem to predict outcome
	1p deletion		
aCGH derived markers	12p deletion		
	5q amplification	May be repeated	Data not validated yet

VOLUME 33 · NUMBER 26 · SEPTEMBER 10 2015

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Revised International Staging System for Multiple Myeloma: A Report From International Myeloma Working Group

Antonio Palumbo, Hervé Avet-Loiseau, Stefania Oliva, Henk M. Lokhorst, Hartmut Goldschmidt, Laura Rosinol, Paul Richardson, Simona Caltagirone, Juan José Lahuerta, Thierry Facon, Sara Bringhen, Francesca Gay, Michel Attal, Roberto Passera, Andrew Spencer, Massimo Offidani, Shaji Kumar, Pellegrino Musto, Sagar Lonial, Maria T. Petrucci, Robert Z. Orlowski, Elena Zamagni, Gareth Morgan, Meletios A. Dimopoulos, Brian G.M. Durie, Kenneth C. Anderson, Pieter Sonneveld, Jésus San Miguel, Michele Cavo, S. Vincent Rajkumar, and Philippe Moreau

Author affiliations appear at the end of this article.

Published online ahead of print at www.jco.org on August 3, 2015.

Authors' disclosures of potential conflicts of interest are found in the article online at www.jco.org. Author contributions are found at the end of this article.

Corresponding author: Antonio Palumbo, MD, Azienda Ospedaliero-Universitaria Città della Salute e della Scienza di Torino, Dipartimento di Oncologia ed Ematologia, San Giovanni Battista, Via Genova, 3 - 10126 Torino, Italy; e-mail: appalumbo@yahoo.com.

0732-183X/15/3326w-2863w/$20.00

DOI: 10.1200/JCO.2015.61.2267

ABSTRACT

Purpose
The clinical outcome of multiple myeloma (MM) is heterogeneous. A simple and reliable tool is needed to stratify patients with MM. We combined the International Staging System (ISS) with chromosomal abnormalities (CA) detected by interphase fluorescent in situ hybridization after CD138 plasma cell purification and serum lactate dehydrogenase (LDH) to evaluate their prognostic value in newly diagnosed MM (NDMM).

Patients and Methods
Clinical and laboratory data from 4,445 patients with NDMM enrolled onto 11 international trials were pooled together. The K-adaptive partitioning algorithm was used to define the most appropriate subgroups with homogeneous survival.

Results
ISS, CA, and LDH data were simultaneously available in 3,060 of 4,445 patients. We defined the following three groups: revised ISS (R-ISS) I (n = 871), including ISS stage I (serum β_2-microglobulin level < 3.5 mg/L and serum albumin level ≥ 3.5 g/dL), no high-risk CA [del(17p) and/or t(4;14) and/or t(14;16)], and normal LDH level (less than the upper limit of normal range); R-ISS III (n = 295), including ISS stage III (serum β_2-microglobulin level > 5.5 mg/L) and high-risk CA or high LDH level; and R-ISS II (n = 1,894), including all the other possible combinations. At a median follow-up of 46 months, the 5-year OS rate was 82% in the R-ISS I, 62% in the R-ISS II, and 40% in the R-ISS III groups; the 5-year PFS rates were 55%, 36%, and 24%, respectively.

Conclusion
The R-ISS is a simple and powerful prognostic staging system, and we recommend its use in future clinical studies to stratify patients with NDMM effectively with respect to the relative risk to their survival.

J Clin Oncol 33:2863-2869. © 2015 by American Society of Clinical Oncology

Table 1. Standard Risk Factors for MM and the 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

Abbreviations: CA, chromosomal abnormalities; iFISH, interphase fluorescent in situ hybridization; ISS, International Staging System; LDH, lactate dehydrogenase; MM, multiple myeloma; R-ISS, revised International Staging System.

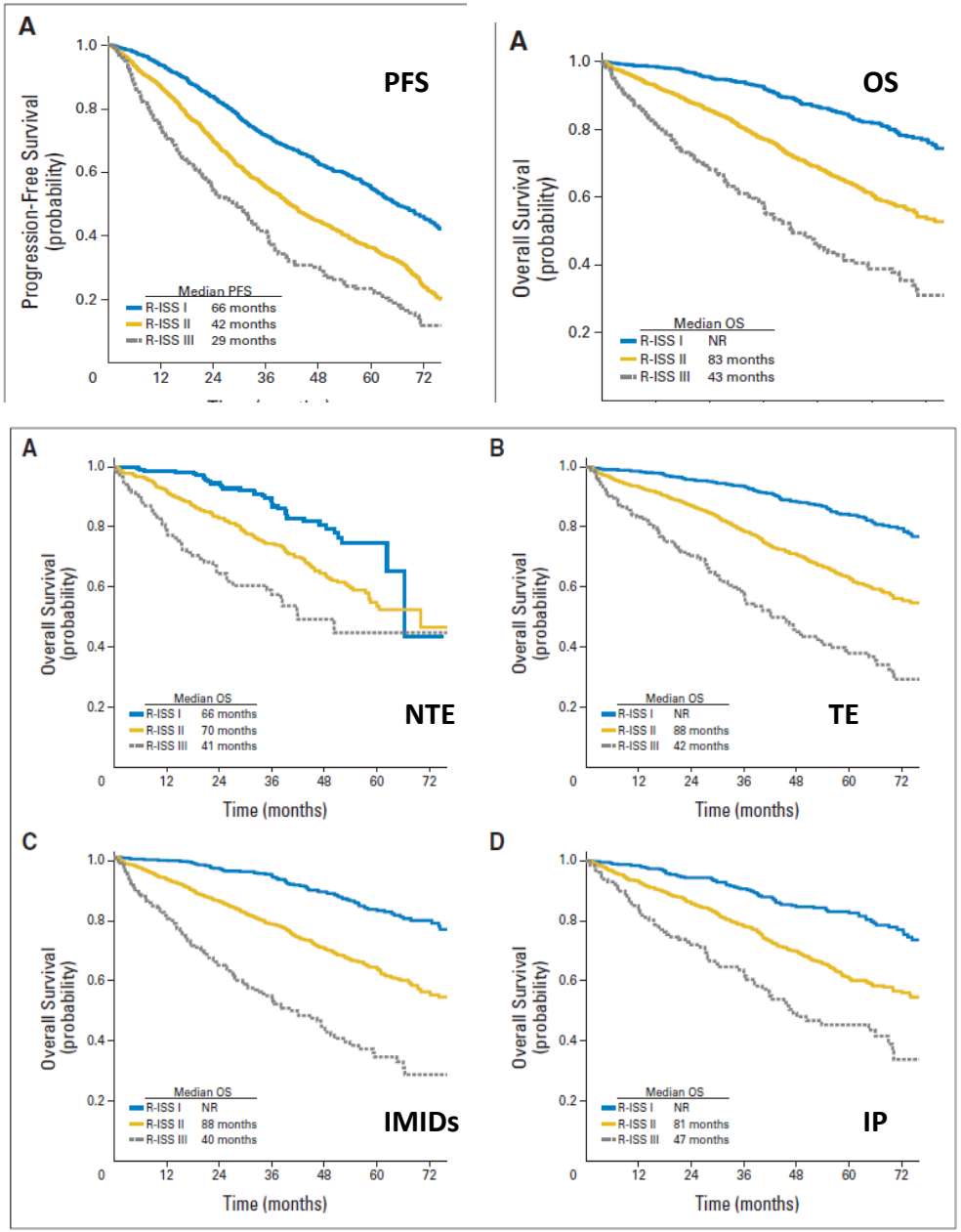
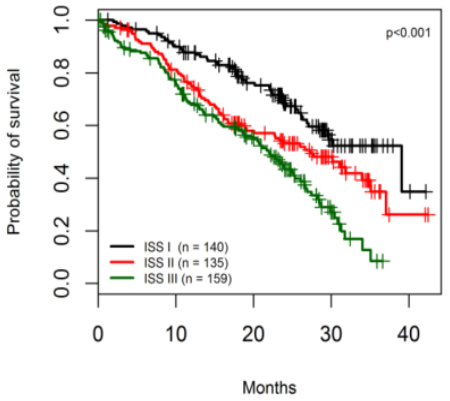


Fig 3. Revised International Staging System (R-ISS) and overall survival (OS) by type of treatment. (A) OS in regimens non–transplantation-based regimens. (B) OS in transplantation-based regimens. (C) OS in immunomodulatory-based regimens. (D) OS in proteasome inhibitor–based regimens. NR, not reached.

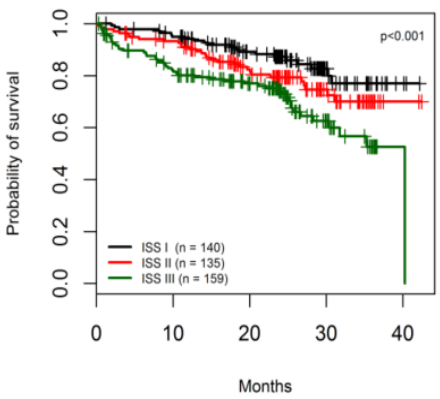
Palumbo et al, J Clin Oncol 2015

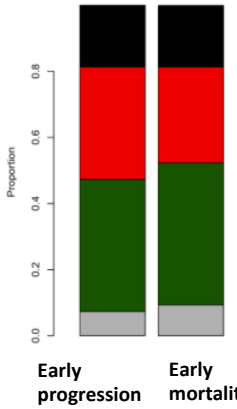
ISS

PFS

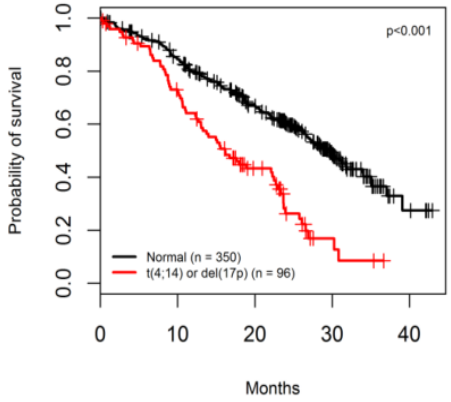


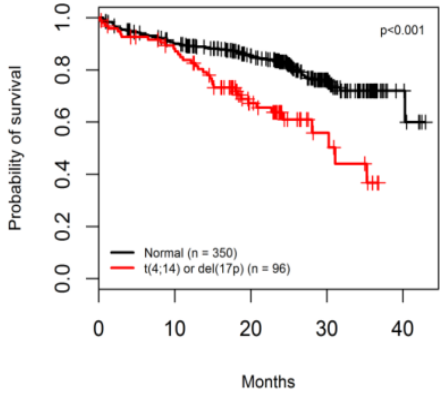
OS

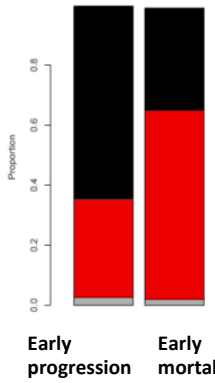




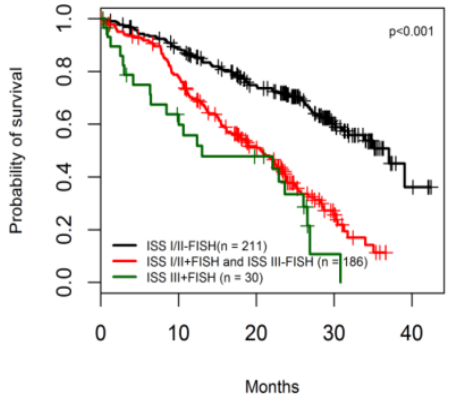
t(4;14) and del(17p)

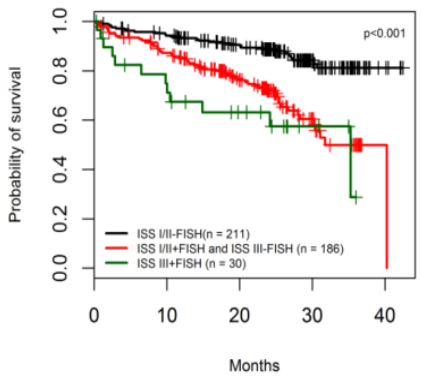


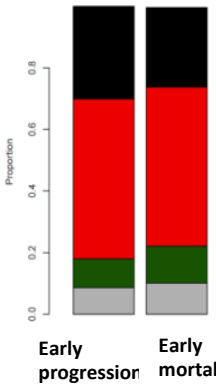




ISS-FISH

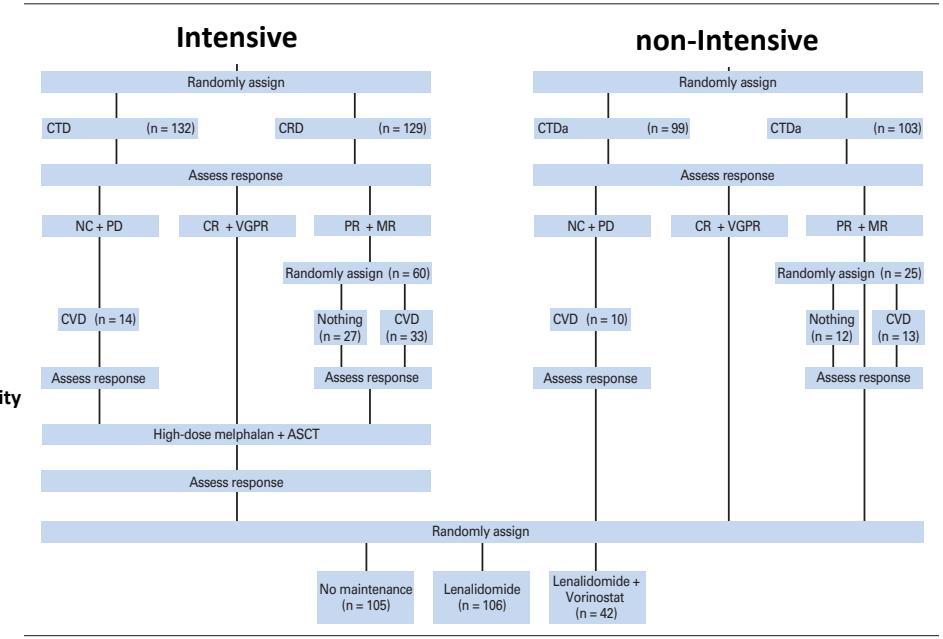






Myeloma XI trial

Randomized CTD vs CRD



Follow-up= 25 mo PFS= 26.6 mo OS 66% at 3 ys

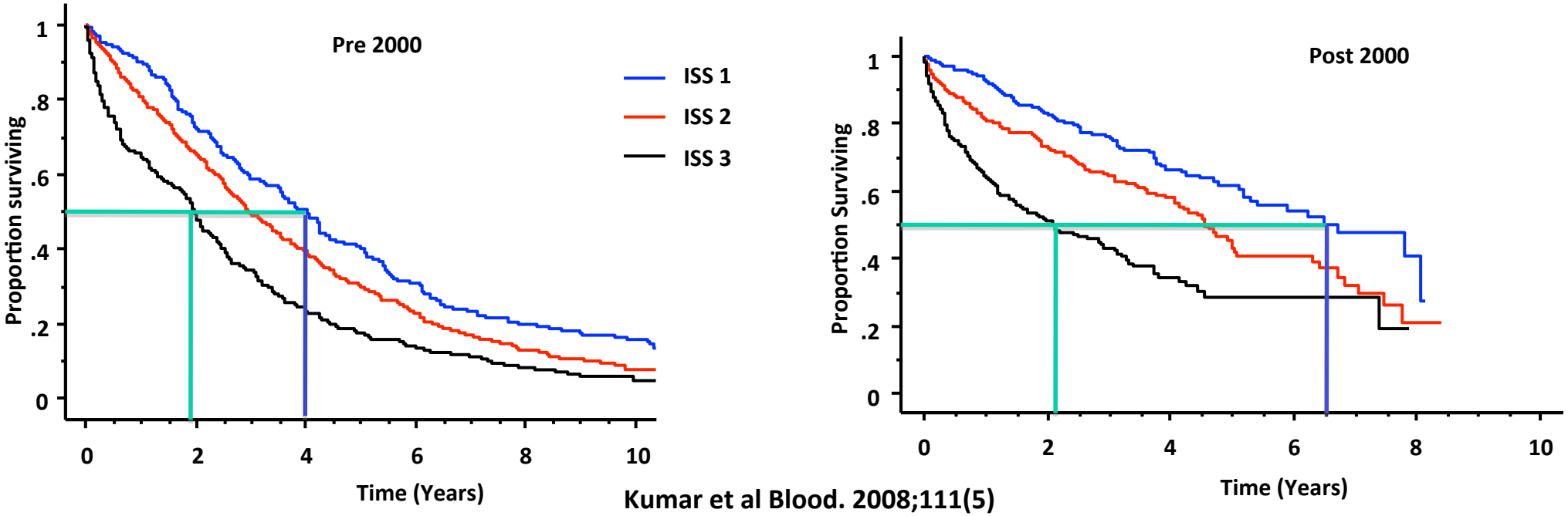
Effect of ISS , t(4;14) and del(17), and ISS-FISH upon PFS and OS and ability to predict early mortality and progression

ISS-FISH improved the sensitivity of t(4;14) and del(17) in predicting early mortality and progression (R)

Walker et al., JCO Aug 17, 2015 Pub ahead

Survival Has Improved…even for High Risk MM?

ISS Stage	Criteria
I	β_2m < 3.5 mg/L & albumin ≥ 3.5 g/dL
II	Not stage I or III
III	β_2m ≥ 5.5 mg/L



Kumar et al Blood. 2008;111(5)

- How to integrate the molecular genetics for risk stratification and treatment selection
- ***What about "novel" agents?***

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2016 127: 2955-2962
doi:10.1182/blood-2016-01-631200 originally published online March 21, 2016

Treatment of multiple myeloma with high-risk cytogenetics: a consensus of the International Myeloma Working Group

Pieter Sonneveld, Hervé Avet-Loiseau, Sagar Lonial, Saad Usmani, David Siegel, Kenneth C. Anderson, Wee-Joo Chng, Philippe Moreau, Michel Attal, Robert A. Kyle, Jo Caers, Jens Hillengass, Jesús San Miguel, Niels W. C. J. van de Donk, Hermann Einsele, Joan Bladé, Brian G. M. Durie, Hartmut Goldschmidt, María-Victoria Mateos, Antonio Palumbo and Robert Orlowski

Thalidomide does not overcome the high risk cytogenetics t(4;14), t(14;20), t(14;16), gain(1q), del(17p), del(1p32) in transplant eligible (TE) patients. Conclusive data for elderly and frail patients are not available.

Lenalidomide partly improves the adverse effect of t(4;14) and del(17p) on PFS, but not OS, in TE patients. In non-TE patients, there are no data suggesting that the drug may improve outcome with HR cytogenetics. Pomalidomide with dexamethasone showed promising results in RRMM with del(17p)

Bortezomib partly overcomes the adverse effect of t(4;14) and possibly del(17p) on CR, PFS, and OS. There is no effect in t(4;14) combined with del(17p) in TE patients. In non-TE patients, VMP may partly restore PFS in HR cytogenetics

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Combining a proteasome inhibitor (Bortezomib) with lenalidomide and dexamethasone greatly reduces the adverse effect of t(4,14) and del(17p) on PFS in newly diagnosed MM patients (NDMM).

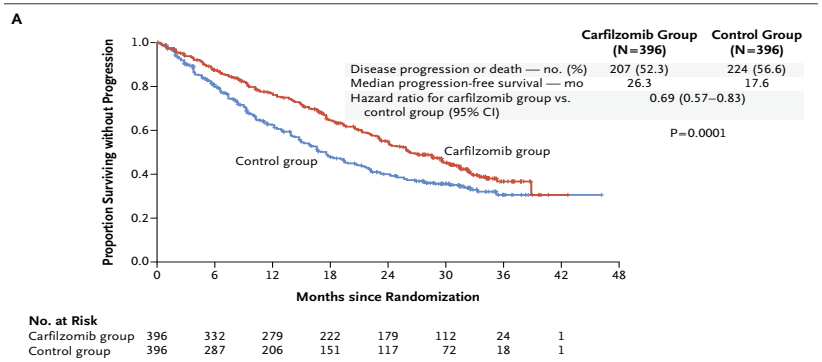
Carfilzomib with lenalidomide and dexamethasone seems effective in patients with HR cytogenetics.However, with a few exception, most data were obtained in non randomized studies and long term follow-up has not been reported.

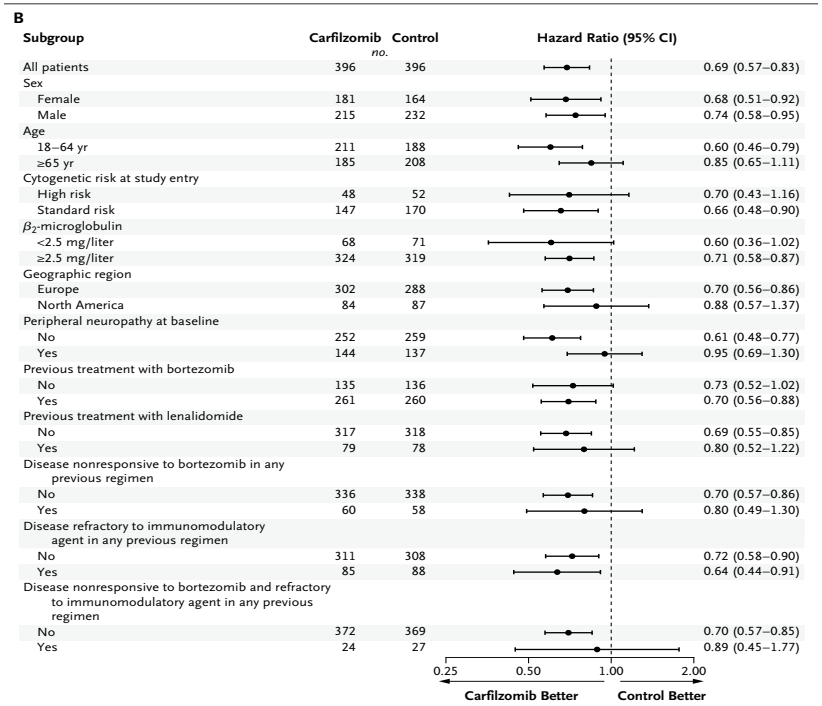
NDMM with HR cytogenetics should be treated with the combination of a proteasome inhibitor with lenalidomide or pomalidomide and dexamethasone

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

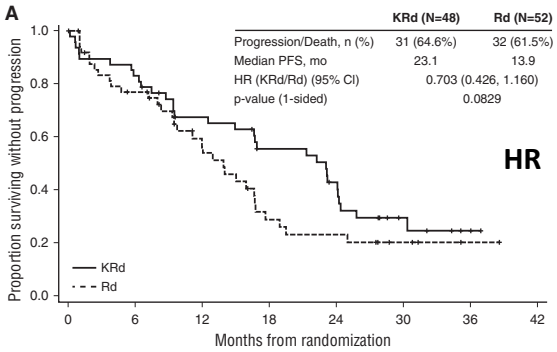
Carfilzomib, Lenalidomide, and Dexamethasone for Relapsed Multiple Myeloma

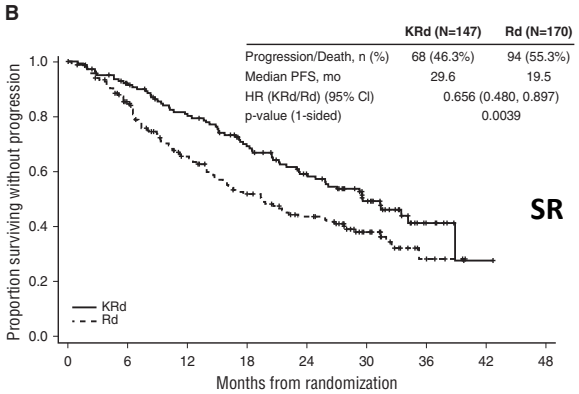




blood®
2016 128: 1174-1180
doi:10.1182/blood-2016-03-707596 originally published online July 20, 2016

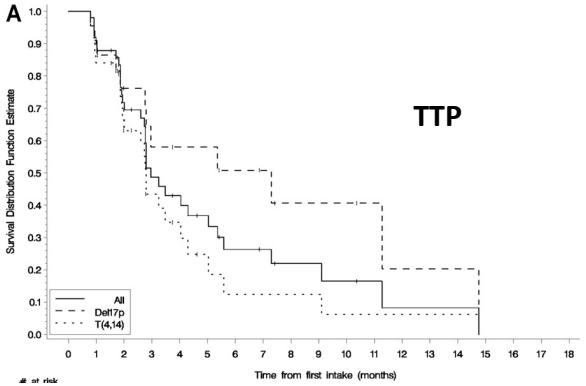
Carfilzomib significantly improves the progression-free survival of high-risk patients in multiple myeloma

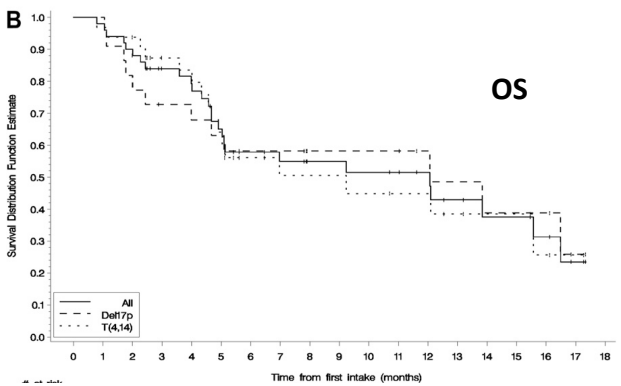




blood®
2015 125: 1411-1417
doi:10.1182/blood-2014-11-612069 originally published online January 9, 2015

Pomalidomide plus low-dose dexamethasone in multiple myeloma with deletion 17p and/or translocation (4;14): IFM 2010-02 trial results





Novel proteasome Inhibitors: IXAZOMIB

Patients (Pts) with Relapsed and/or Refractory Multiple Myeloma_phase 3 study

	ORR, %		≥VGPR, %		≥CR, %		Median OFS, months		
	IRd	Placebo-Rd	IRd	Placebo-Ird	IRd	Placebo-Rd	IRd	Placebo-Rd	HR
All patients	78.3*	71.5	48.1	39	11.7*	6.6	20.6	14.7	0.742*
Standard-risk patients	80	73	51	44	12	7	20.6	15.6	0.640*
All high-risk patients	79*	60	45	21	12*	2	21.4	9.7	0.543
Patients with del(17p)†	72	48	39	15	11*	0	21.4	9.7	0.596
Patients with t(4;14) alone	89	76	53	28	14	4	18.5	12	0.645

*p<0.05 for comparison between regimens. †Alone or in combination with t(4;14) or t(14;18).
Data not included patients with t(14;16) alone due to small numbers (n=7).

- **In the IRd arm, median PFS in high-risk patients was similar to that in the overall patient population and in patients with standard-risk cytogenetics**

Moreau et al. ASH 2015

Initial genome sequencing and analysis of multiple myeloma

Michael A. Chapman[1]†, Michael S. Lawrence[1], Jonathan J. Keats[2,3], Kristian Cibulskis[1], Carrie Sougnez[1], Anna C. Schinzel[4], Christina L. Harview[1], Jean-Philippe Brunet[1], Gregory J. Ahmann[2,3], Mazhar Adli[1,5], Kenneth C. Anderson[3,4], Kristin G. Ardlie[1], Daniel Auclair[3,6], Angela Baker[7], P. Leif Bergsagel[2,3], Bradley E. Bernstein[1,5,8,9], Yotam Drier[1,10], Rafael Fonseca[2,3], Stacey B. Gabriel[1], Craig C. Hofmeister[3,11], Sundar Jagannath[3,12], Andrzej J. Jakubowiak[3,13], Amrita Krishnan[3,14], Joan Levy[3,6], Ted Liefeld[1], Sagar Lonial[3,15], Scott Mahan[1], Bunmi Mfuko[3,6], Stefano Monti[1], Louise M. Perkins[3,6], Robb Onofrio[1], Trevor J. Pugh[1], S. Vincent Rajkumar[3,16], Alex H. Ramos[1], David S. Siegel[3,17], Andrey Sivachenko[1], A. Keith Stewart[2,3], Suzanne Trudel[3,18], Ravi Vij[3,19], Douglas Voet[1], Wendy Winckler[1], Todd Zimmerman[3,20], John Carpten[7], Jeff Trent[7], William C. Hahn[1,4,8], Levi A. Garraway[1,4], Matthew Meyerson[1,4,8], Eric S. Lander[1,8,21], Gad Getz[1] & Todd R. Golub[1,4,8,9]

nature COMMUNICATIONS

ARTICLE

Received 18 Jul 2013 | Accepted 25 Nov 2013 | Published 16 Jan 2014

DOI: 10.1038/ncomms3997 OPEN

Heterogeneity of genomic evolution and mutational profiles in multiple myeloma

Cancer Cell
Article

Widespread Genetic Heterogeneity in Multiple Myeloma: Implications for Targeted Therapy

Jens G. Lohr,[1,2,10] Petar Stojanov,[1,2,10] Scott L. Carter,[1,10] Peter Cruz-Gordillo,[1] Michael S. Lawrence,[1] Daniel Auclair,[1] Carrie Sougnez,[1] Birgit Knoechel,[1,2,3] Joshua Gould,[1] Gordon Saksena,[1] Kristian Cibulskis,[1] Aaron McKenna,[1] Michael A. Chapman,[4] Ravid Straussman,[1] Joan Levy,[5] Louise M. Perkins,[5] Jonathan J. Keats,[6] Steven E. Schumacher,[1,2] Mara Rosenberg,[1] The Multiple Myeloma Research Consortium,[11] Gad Getz,[1,7,12] and Todd R. Golub[1,2,8,9,12,*]

Published Ahead of Print on August 17, 2015 as 10.1200/JCO.2014.59.1503
The latest version is at http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2014.59.1503

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Mutational Spectrum, Copy Number Changes, and Outcome: Results of a Sequencing Study of Patients With Newly Diagnosed Myeloma

No unifying mutation :
highly heterogeneous mutational pattern and clonal variation

RAS genes frequently mutated (50/60%
Other frequently mutated genes up to 10%

Biological pathways analysis required
Histone modification ; RNA processing and protein homeostasis; NF-KB signaling; MAP kinase; DNA damage response

Widespread Genetic Heterogeneity in Multiple Myeloma: Implications for Targeted Therapy

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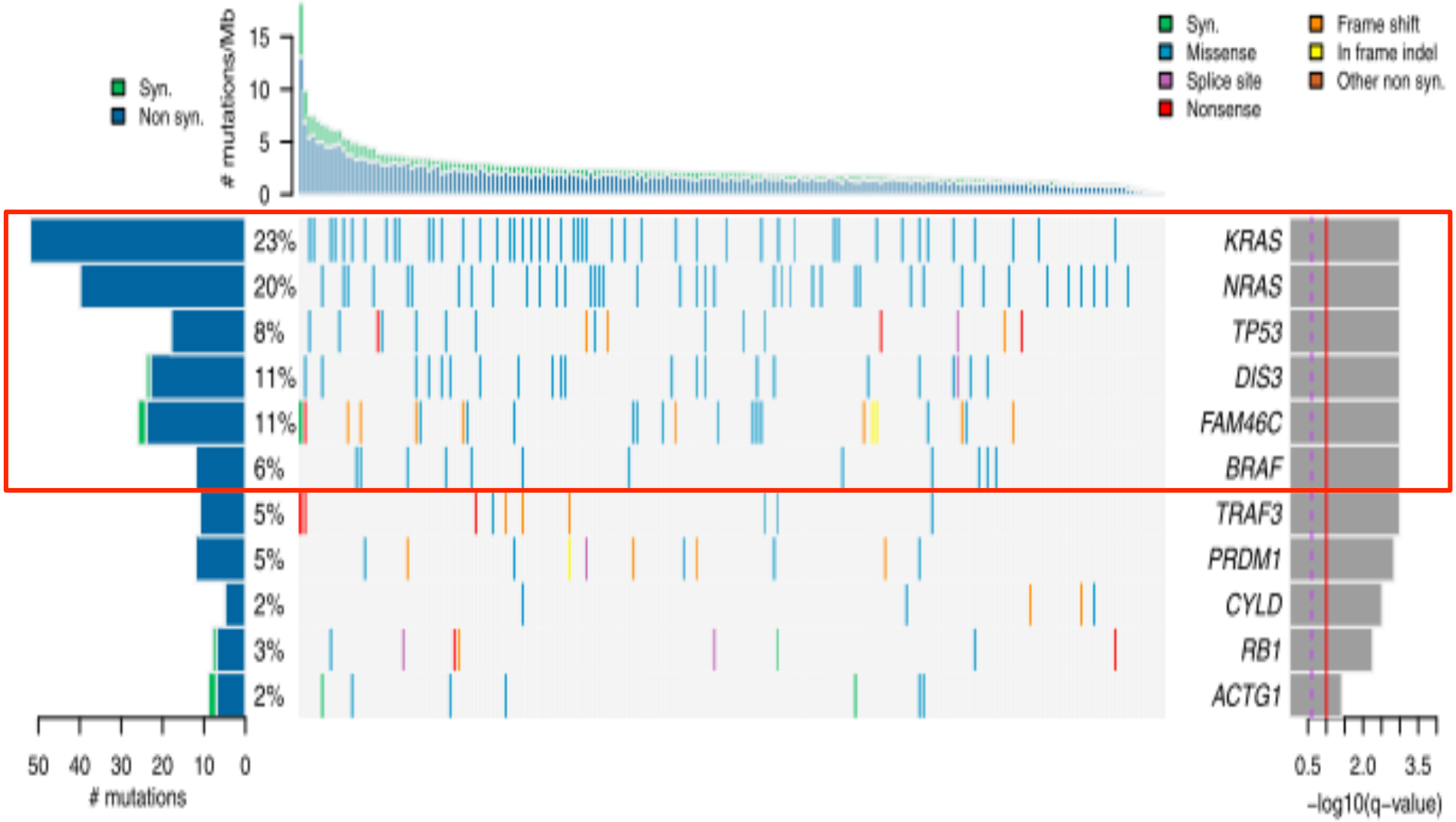

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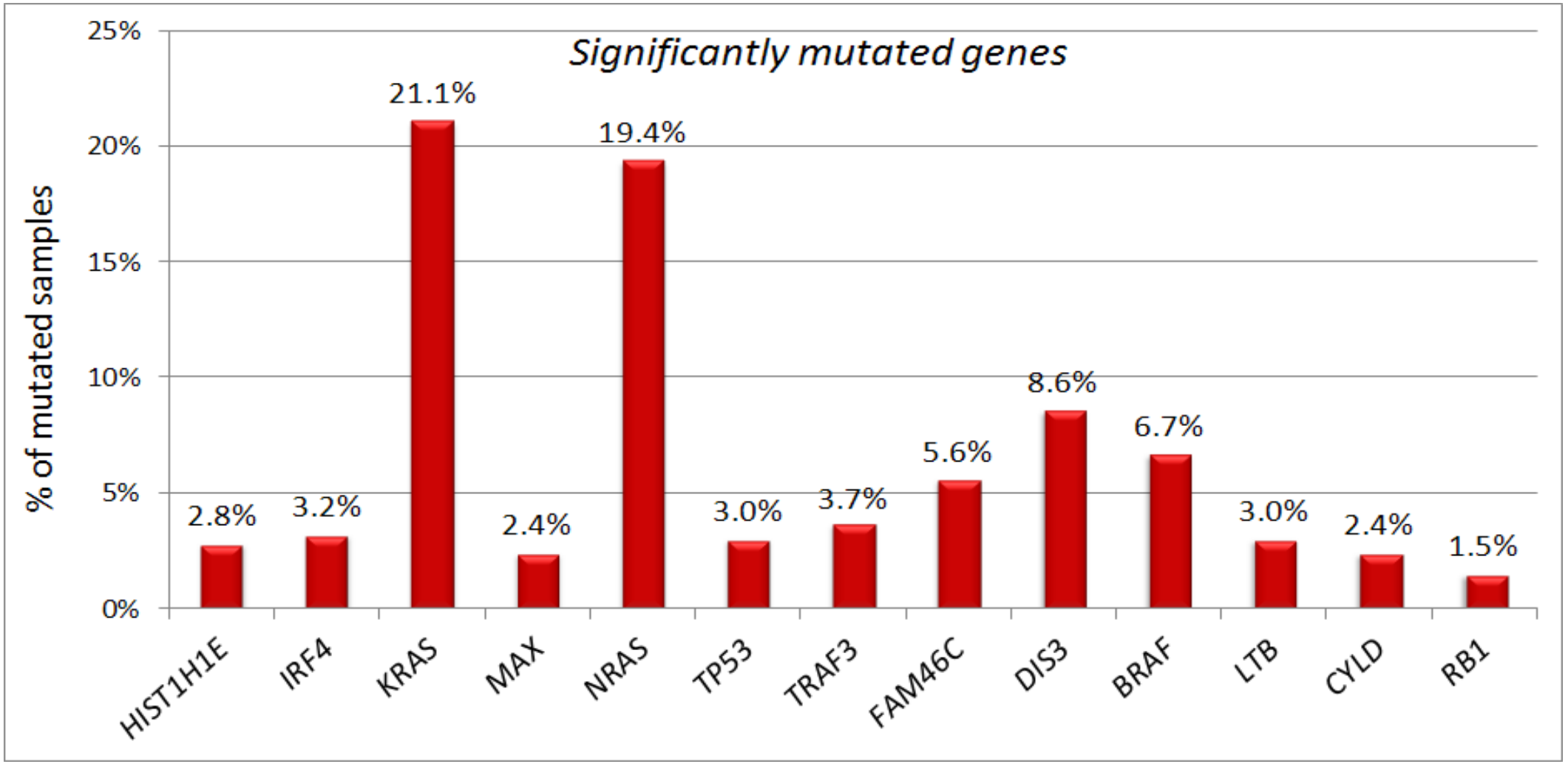
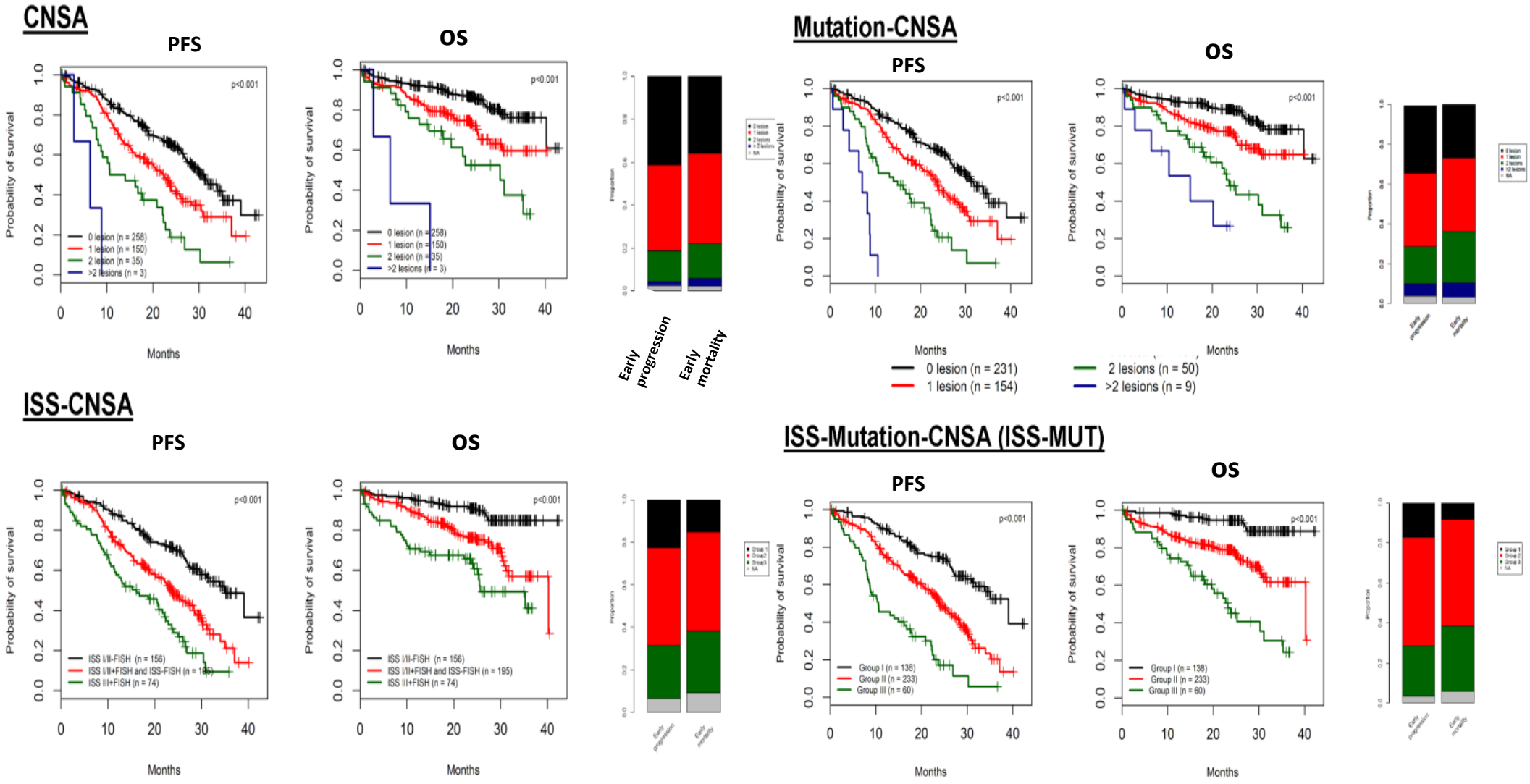
Walker et al., JCO Aug 17, 2015 Pub ahead

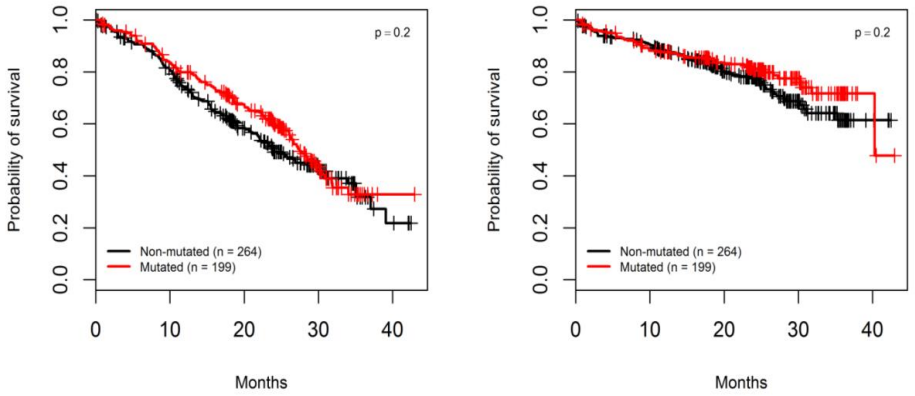


Integration of ISS, copy number/structural alterations (CNSA) and mutations improves the ability to identify early progression and mortality

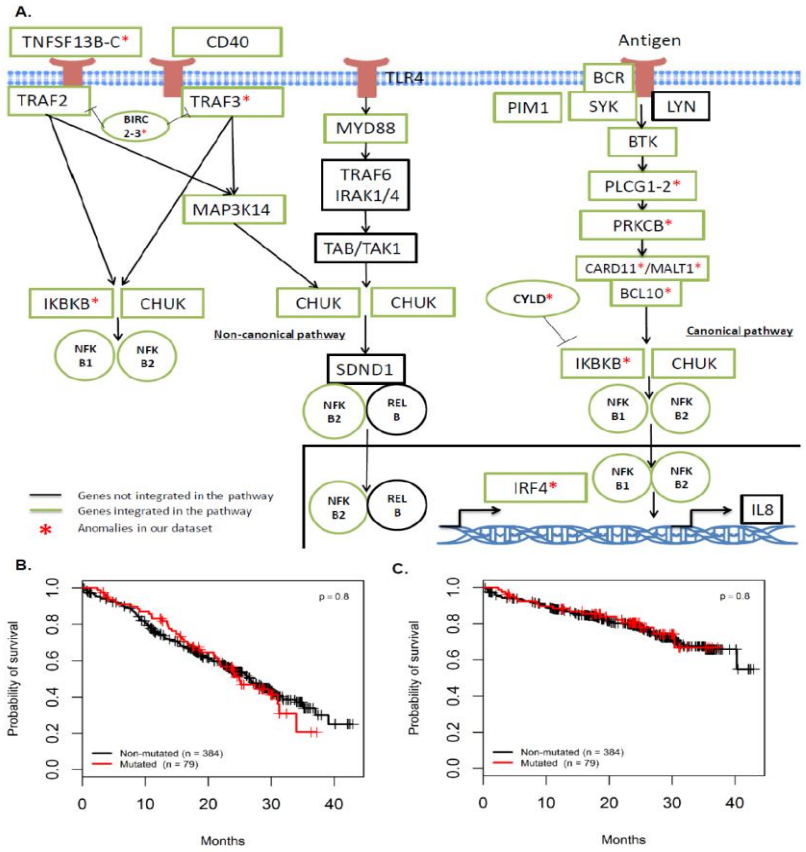


Walker et al., JCO Aug 17, 2015 Pub ahead

RAS/BRAf mutations do not impact on PFS and OS

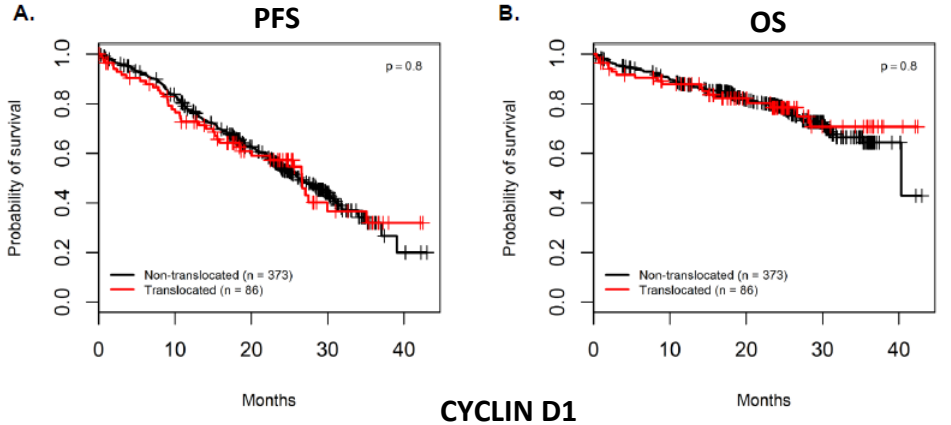


NF-kB gene mutations do not impact on PFS and OS



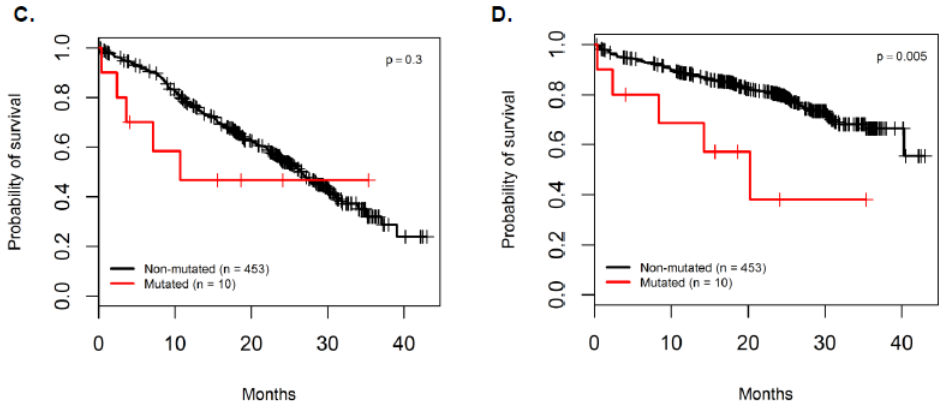
Mutations of Cyclin D1 (4%) impact in OS but not PFS

t(11,14)

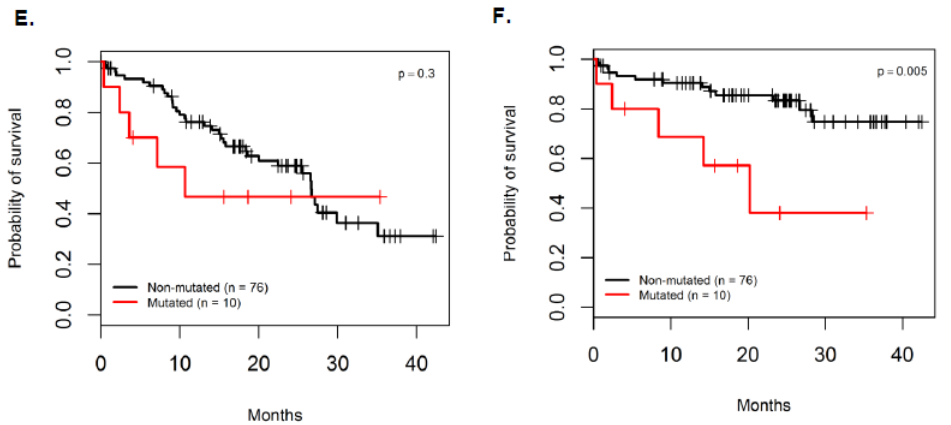


CYCLIN D1

Whole population



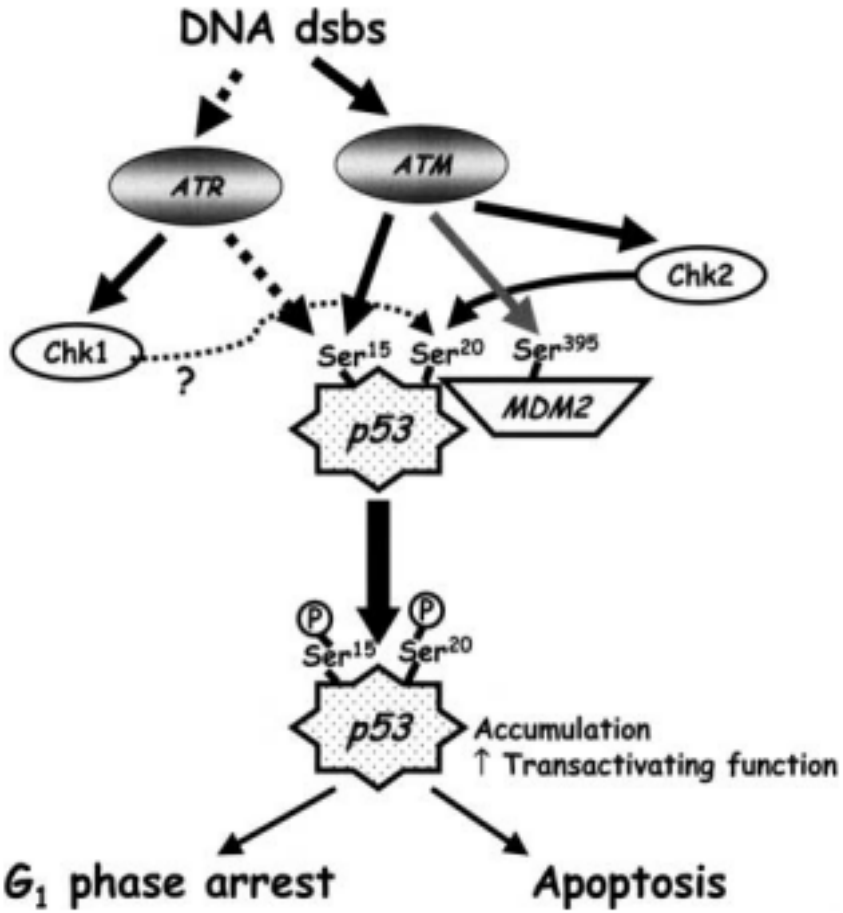
t(11,14)



Walker et al., J Clin Oncol. 2015 aug 17. [Epub ahead of print]

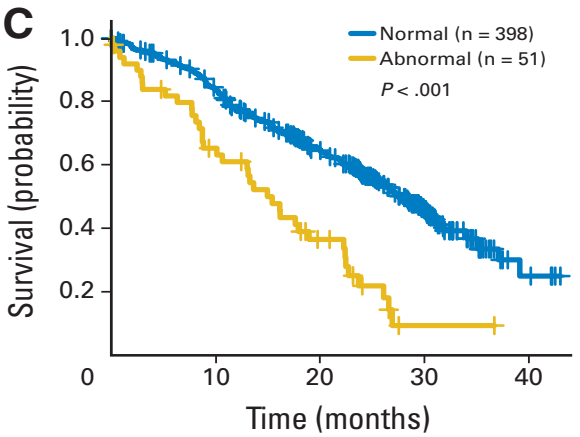
IMPACT OF DNA REPAIR PATHWAY GENES IN MYELOMA

Walker et al., JCO Aug 17, 2015 Pub ahead

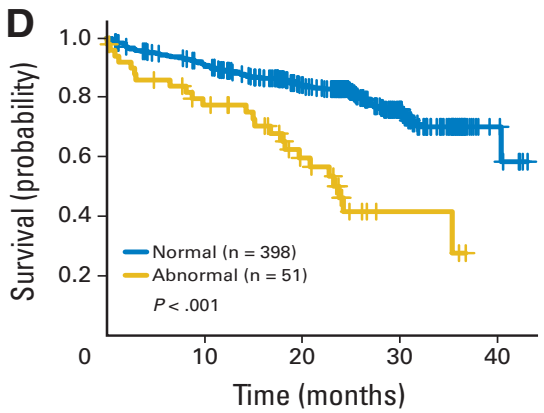


TP53 MUT/DEL

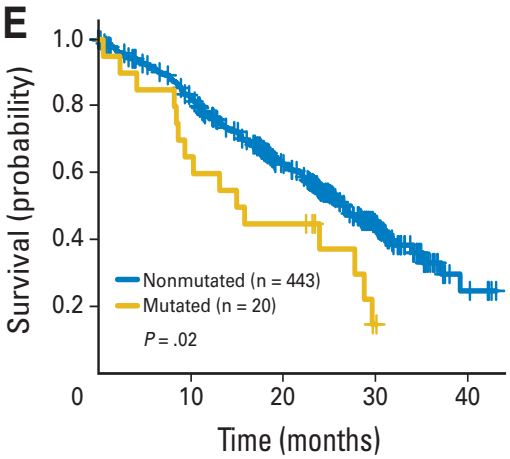
PFS



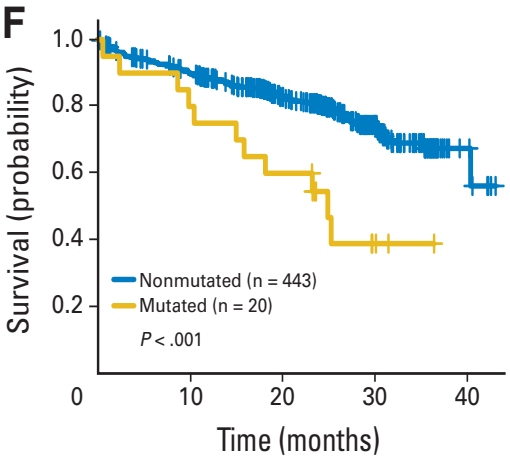
OS



ATM/ATR MUTATIONS



PFS



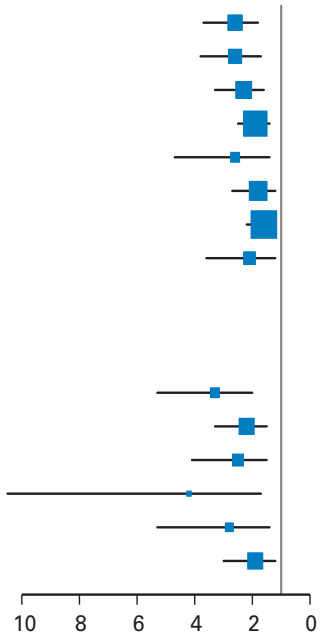
OS

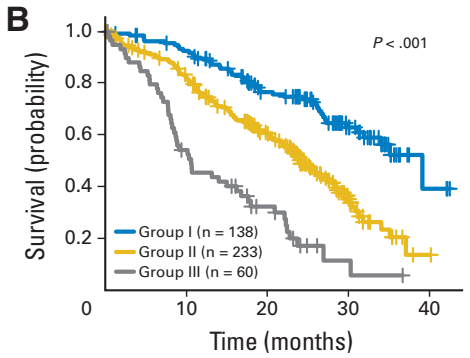
Multivariate analyses of genomic alterations and gene mutations significantly associated with poor prognosis in Myeloma XI trial

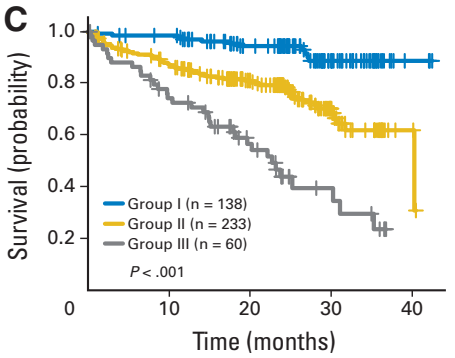
A

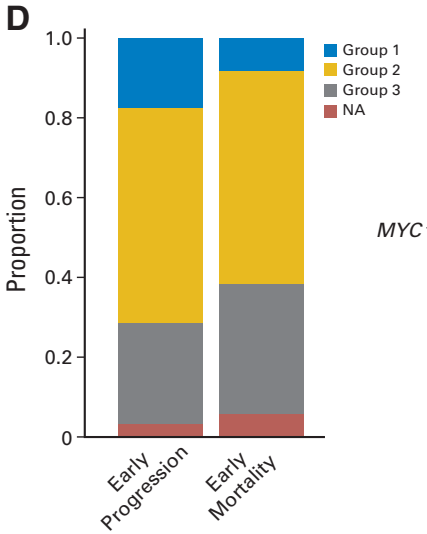
Progression-Free Survival

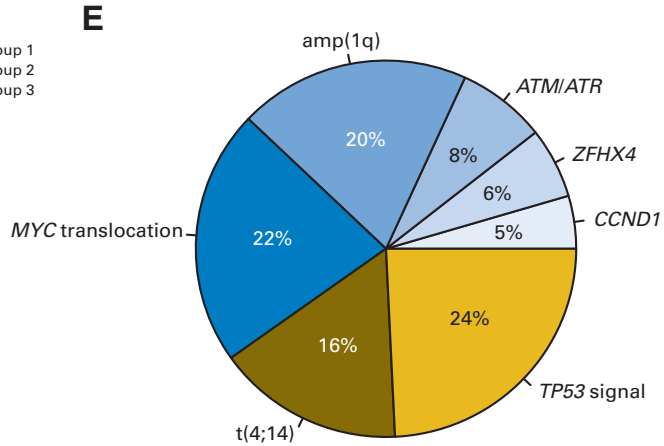
	HR	LCI	UCI	*P*	Sign.
TP53 signal	2.6	1.8	3.7	< .0001	***
ISS III	2.6	1.7	3.8	< .0001	***
t(4;14)	2.3	1.6	3.3	< .0001	***
Age > 70 years	1.9	1.4	2.5	< .0001	***
ZFHX4	2.6	1.4	4.7	< .0001	**
ISS II	1.8	1.2	2.7	.004	**
MYC translocation	1.6	1.2	2.2	.005	**
ATM/ATR	2.1	1.2	3.6	.008	**
Overall Survival					
TP53 signal	3.3	2	5.3	< .0001	***
ISS III	2.2	1.5	3.3	.0001	***
amp(1q)	2.5	1.5	4.1	.0008	***
CCND1	4.2	1.7	10.5	.0025	**
ATM/ATR	2.8	1.4	5.3	.0029	**
MYC translocation	1.9	1.2	3	.0036	**











group 1, ISS I and II with no copy number and structural abnormality [CNSA] or mutation;

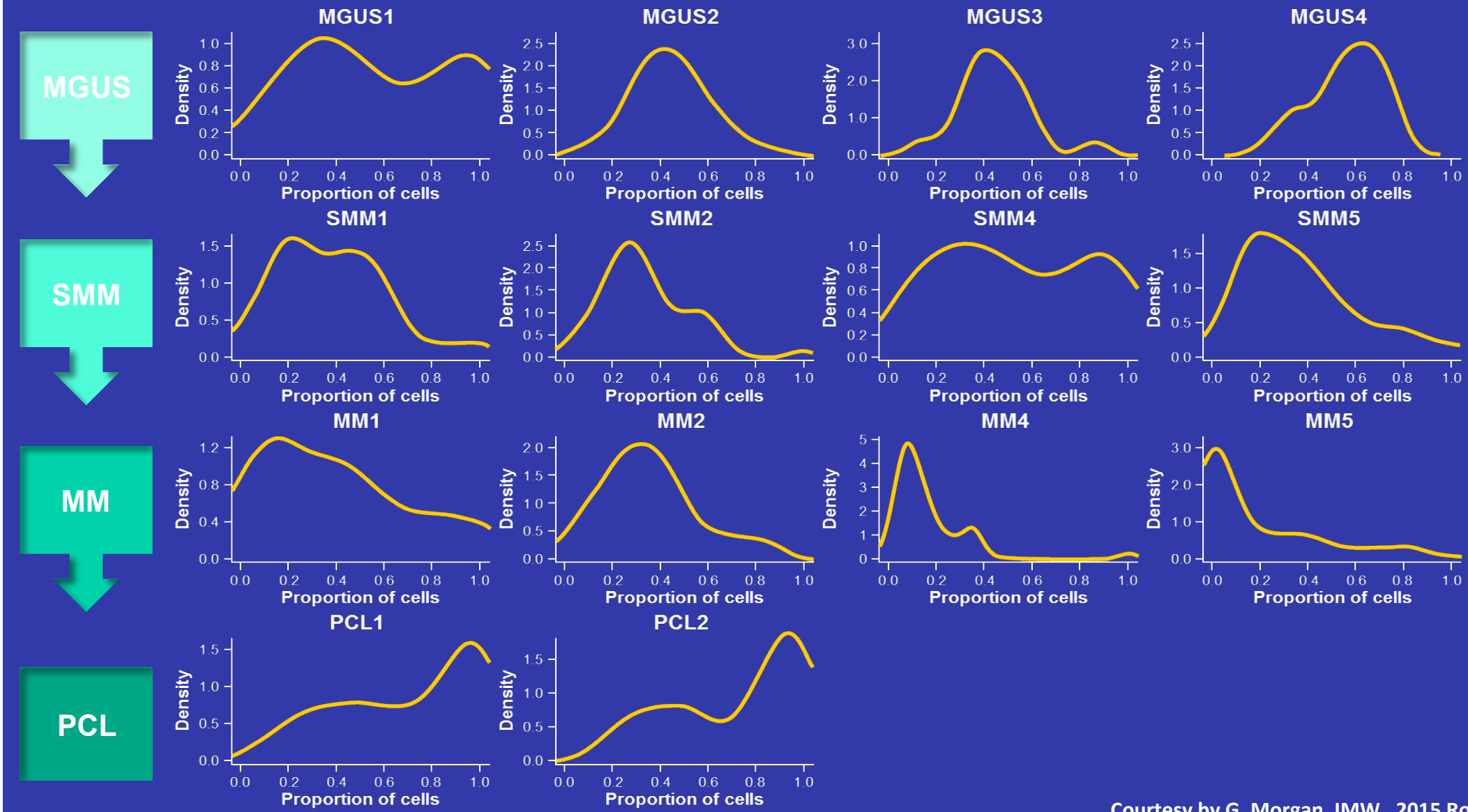
group 2, ISS III with no CNSA or mutation or ISS I, II, and III with one CNSA or mutation

group 3, two CNSAs or mutations regardless of their ISS).

81% and 90% of patients who both experienced relapse and died prematurely are identified by this score

Walker et al., J Clin Oncol. 2015 aug 17. [Epub ahead of print]

Intraclonal diversity arises early in Myeloma

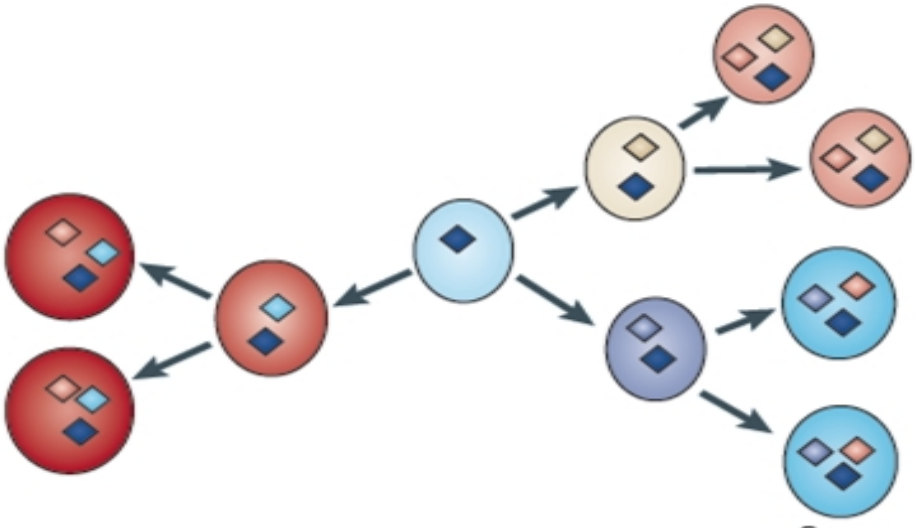


Courtesy by G. Morgan, IMW , 2015 Rome

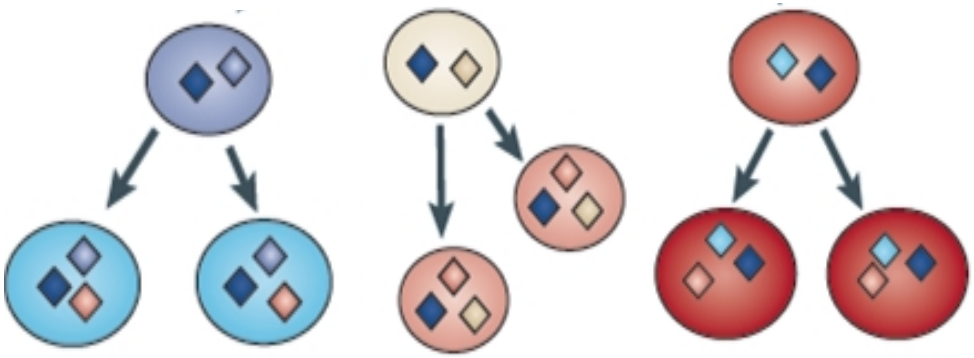
Walker B, et al. *Leukemia*. 2014 28:384–90.

MODEL OF CLONAL EVOLUTION IN CANCER

Linear_ Clonal homogeneity

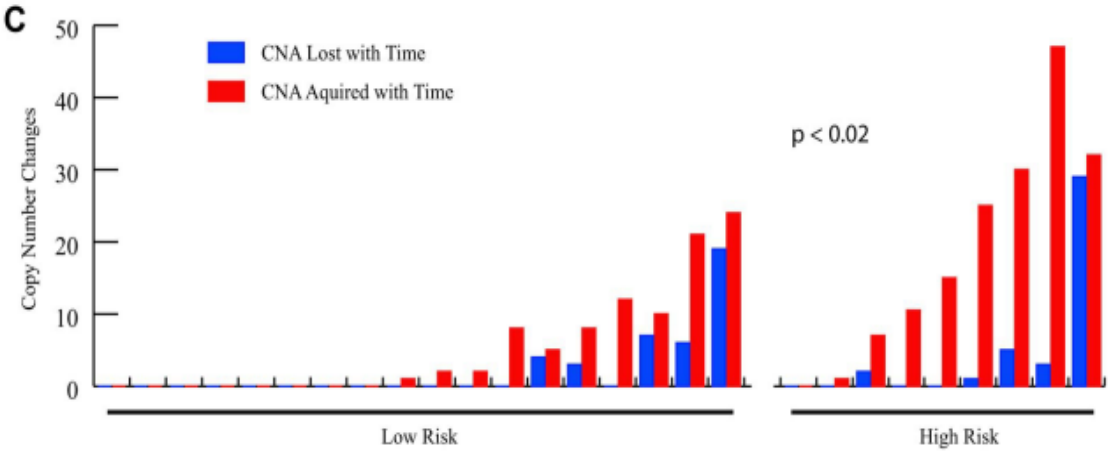


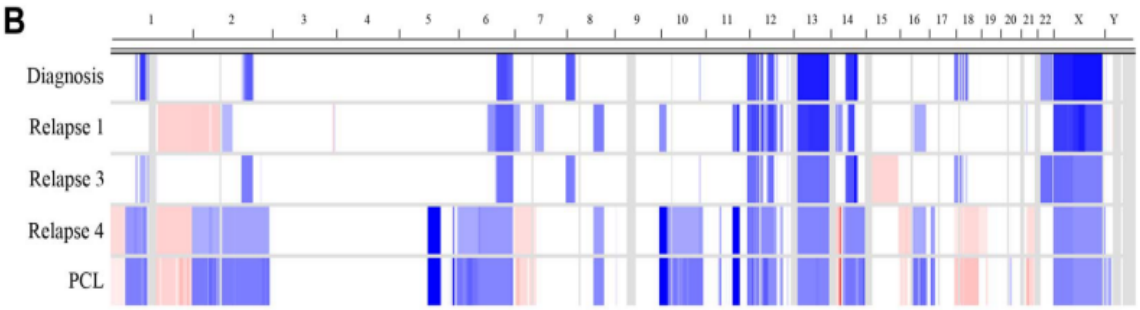
Branching _ Intra-clonal heterogeneity

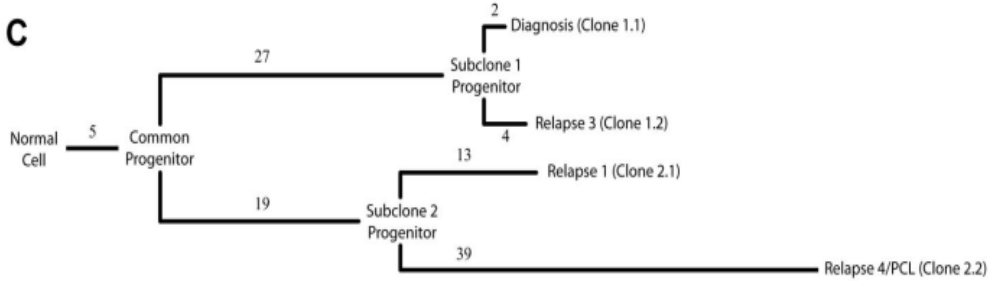


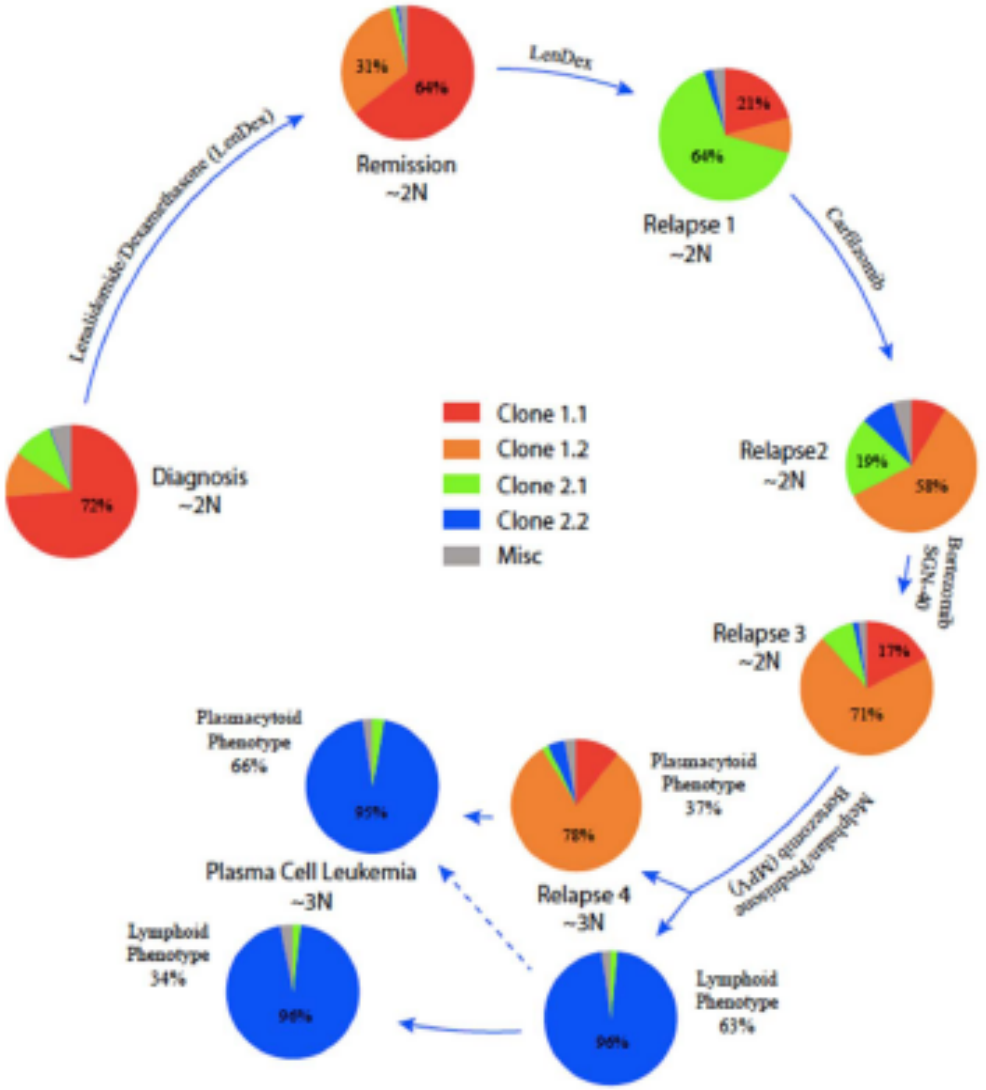
Independent clones _ inter-clonal heterogeneity

Clonal evolution in Myeloma:
implication for high risk disease









Keats J, Blood, 2012

Clonal evolution in Myeloma:

implication for high risk disease

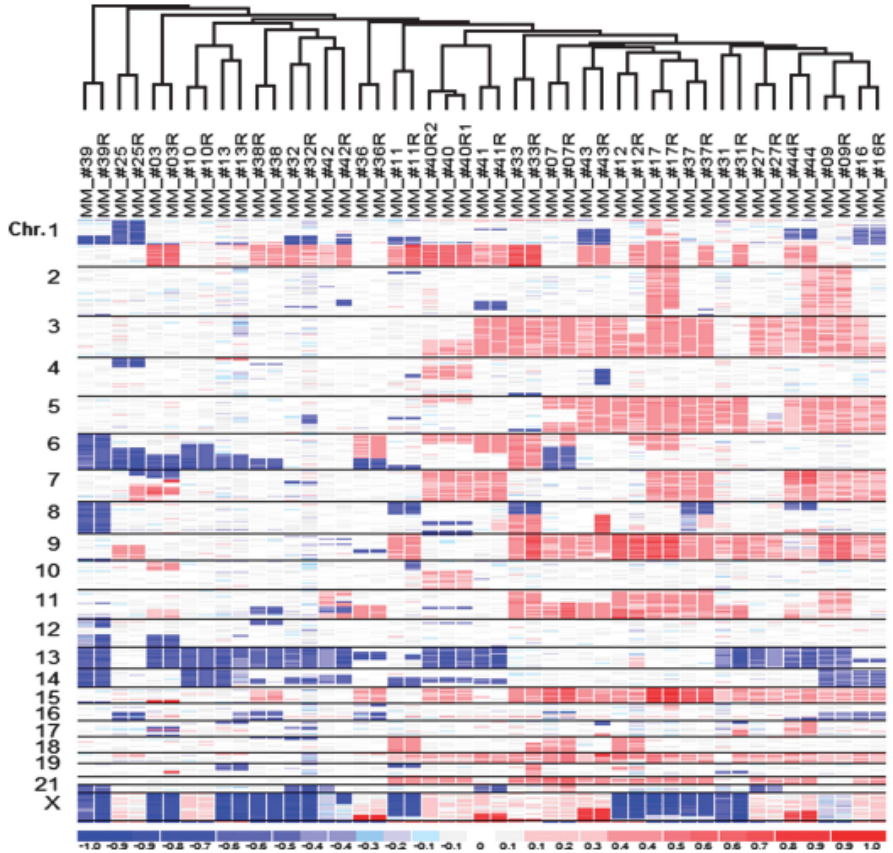
Leukemia (2013) **27**, 473–481

www.nature.com/leu

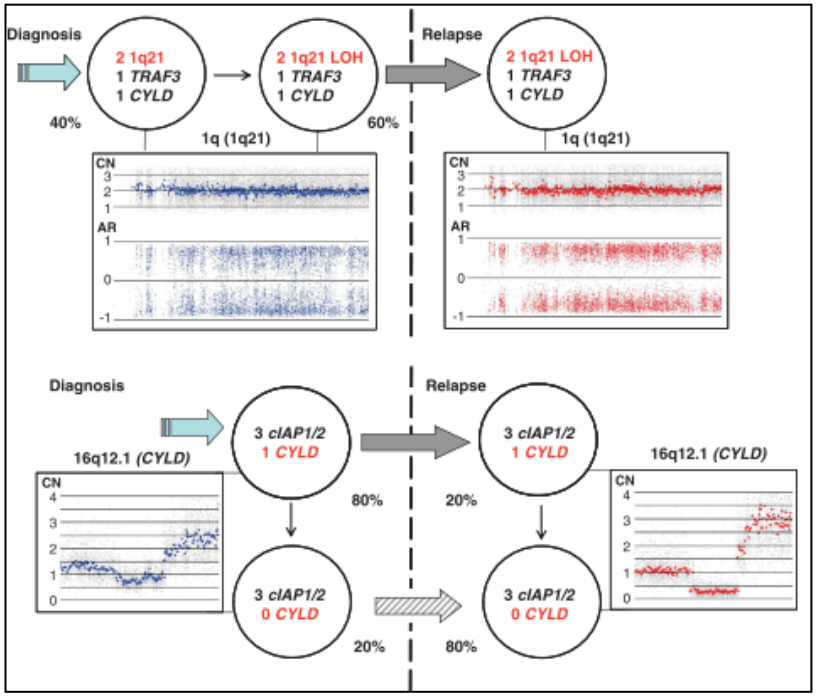
ORIGINAL ARTICLE

Minor clone provides a reservoir for relapse in multiple myeloma

F Magrangeas[1,2], H Avet-Loiseau[2], W Gouraud[1,3], L Lodé[2], O Decaux[1,4], P Godmer[5], L Garderet[6], L Voillat[7], T Facon[8], AM Stoppa[9], G Marit[10], C Hulin[11], P Casassus[12], M Tiab[13], E Voog[14], E Randriamalala[15], KC Anderson[16], P Moreau[1,2], NC Munshi[16,17] and S Minvielle[1,2]

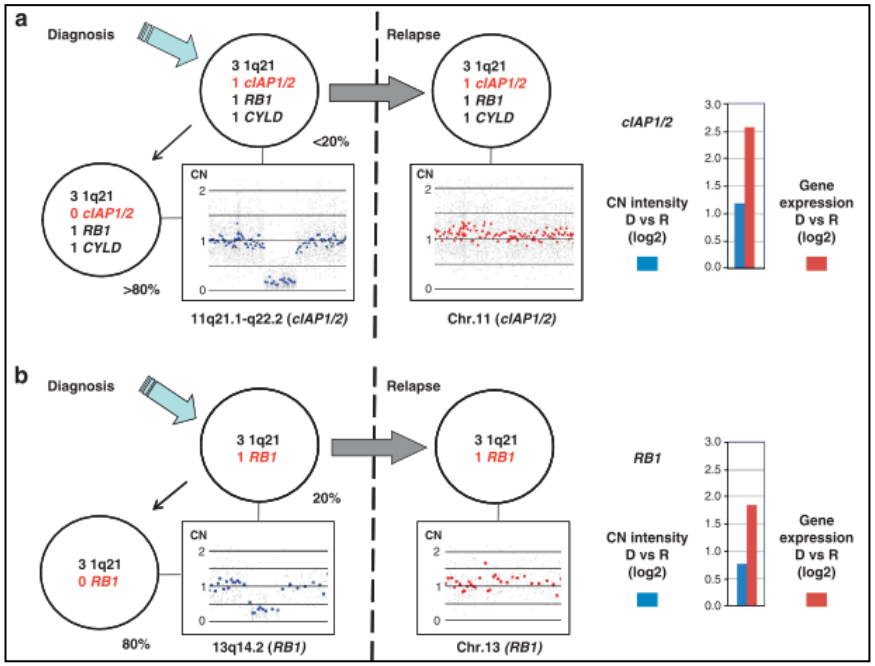


linear subclonal evolution 16/24 MM

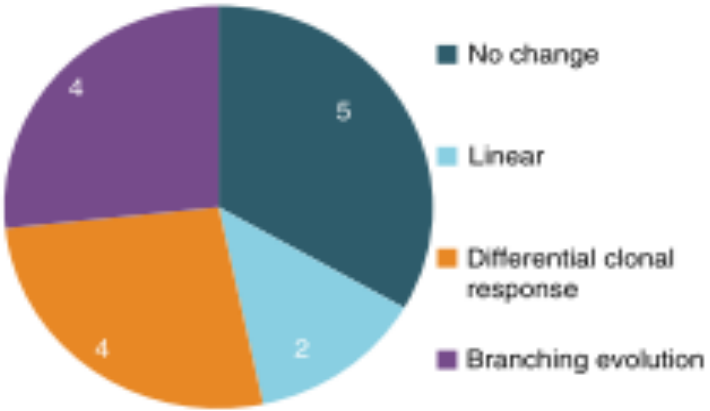


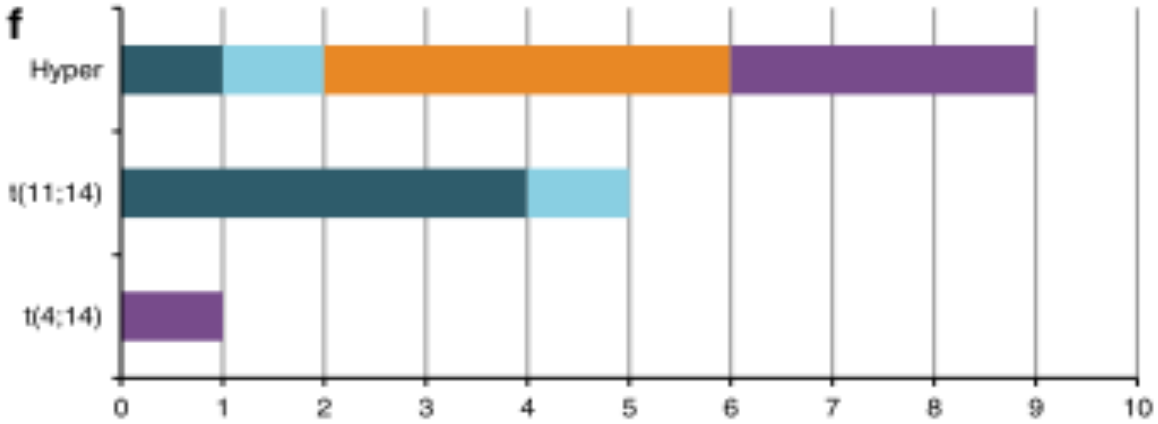
non -linear subclonal evolution 8/24

More frequent in patients treated with bortezomib

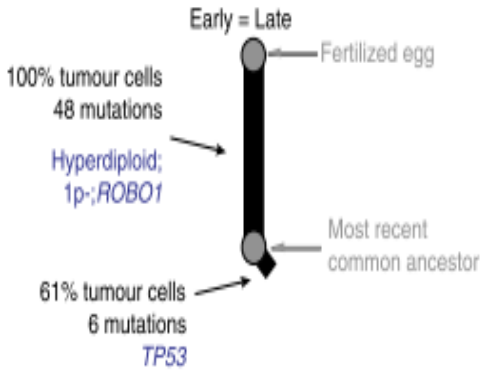


Models of clonal evolution in MM



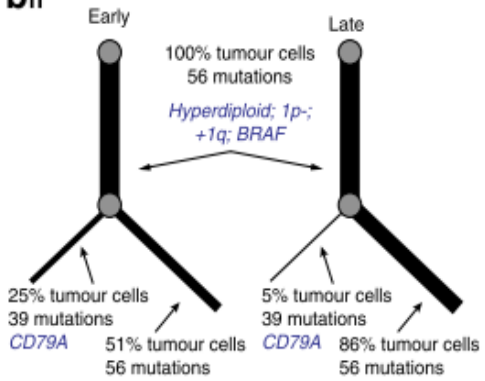


aii



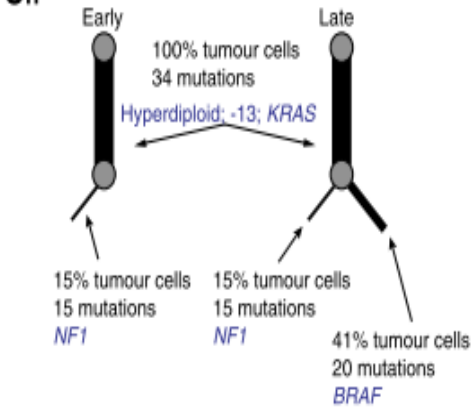
No changes

bii



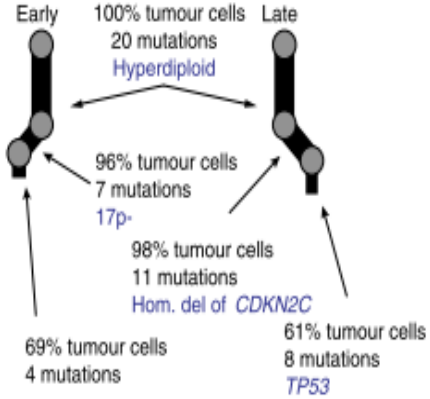
Differential clonal response

cii



Linear evolution

dii



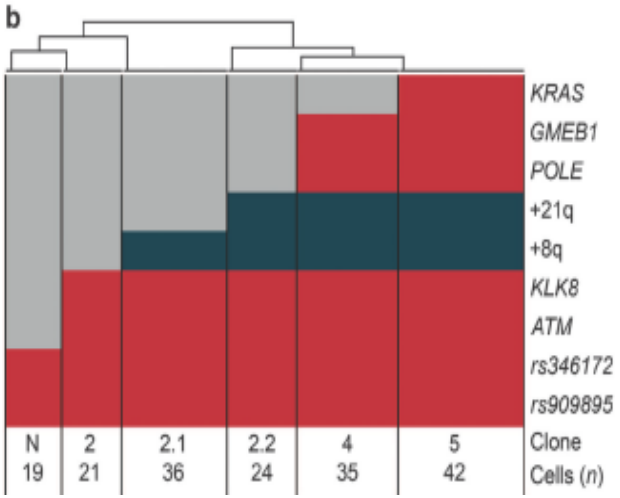
Branching evolution

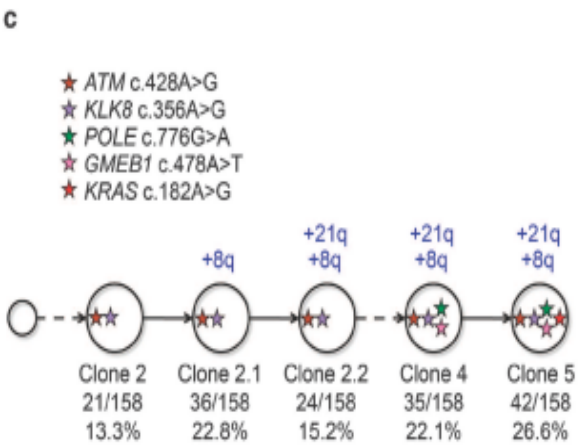
Pattern of genomic evolution could not be predicted by response treatment, interval between sampling or treatment type

Bolli et al., Nature Communications, 2014

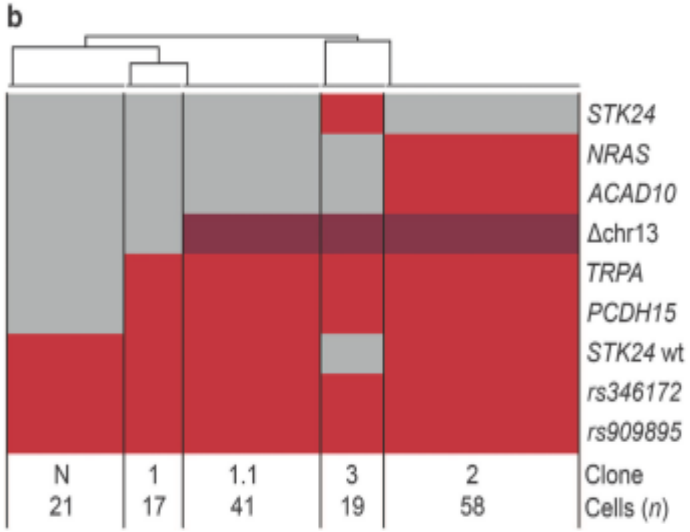
Patterns of Clonal Evolution in Multiple Myeloma:

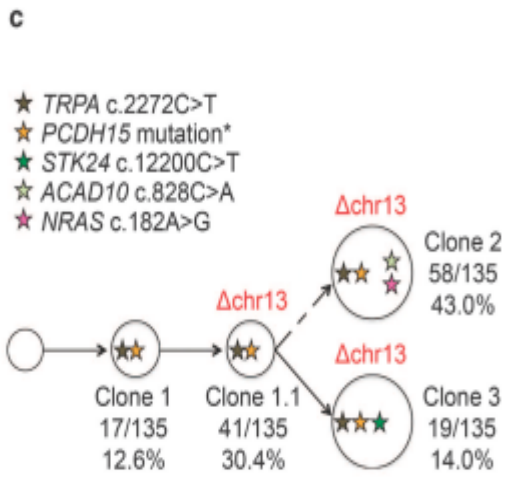
whole-exome sequencing and single-cell genetic analyses





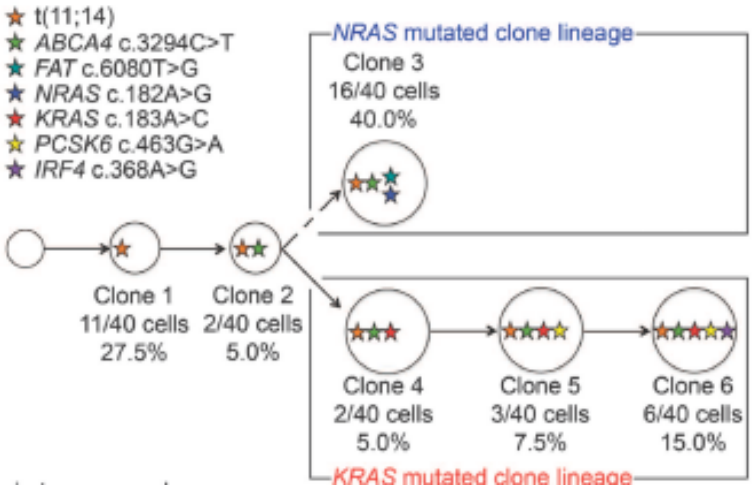
Linear evolution

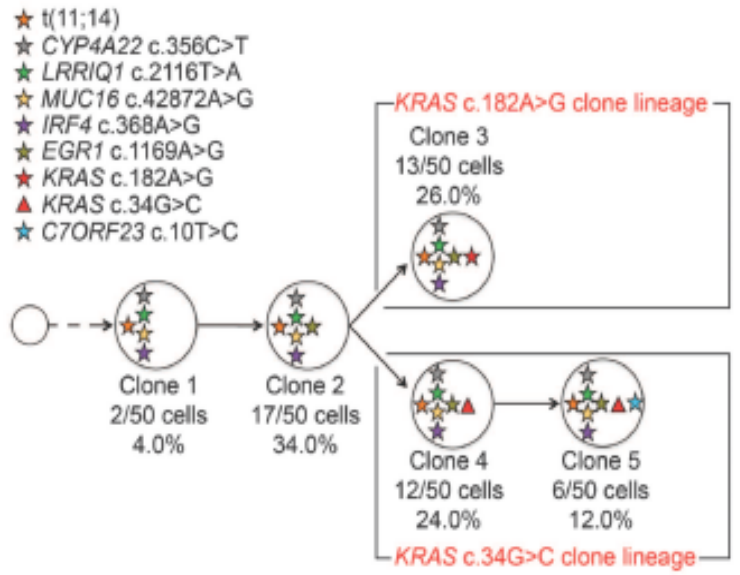




Branching evolution

RAS activation in branching evolution





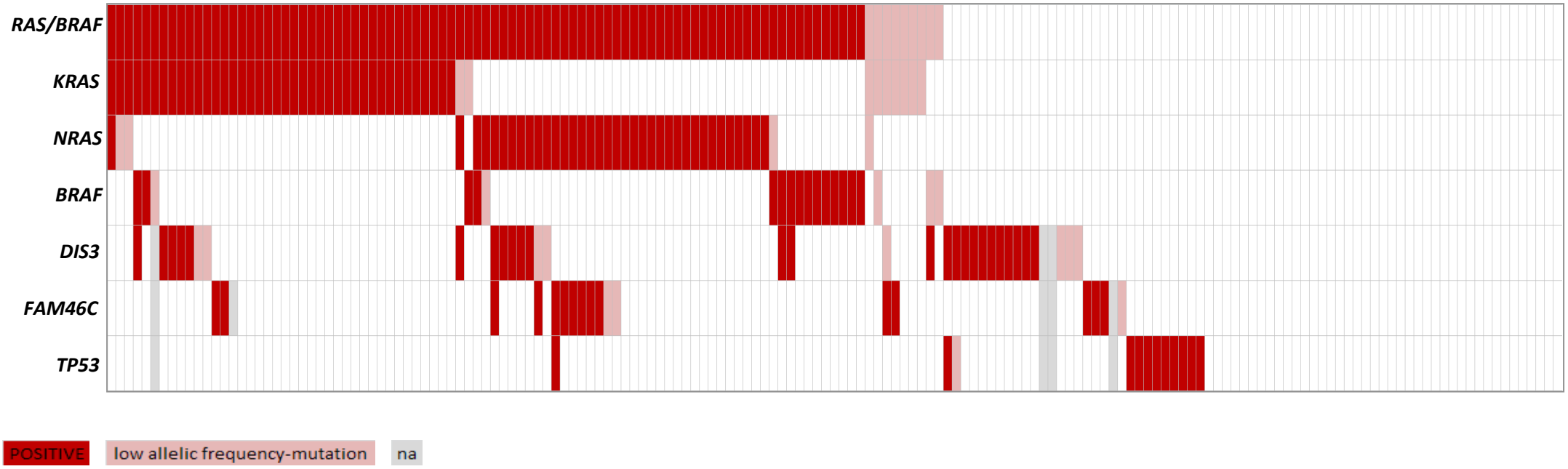
Melchor et al ., Leukemia, 2014

Comparison of *BRAF/NRAS/KRAS/DIS3/TP53/FAM46C* mutation frequencies in MM

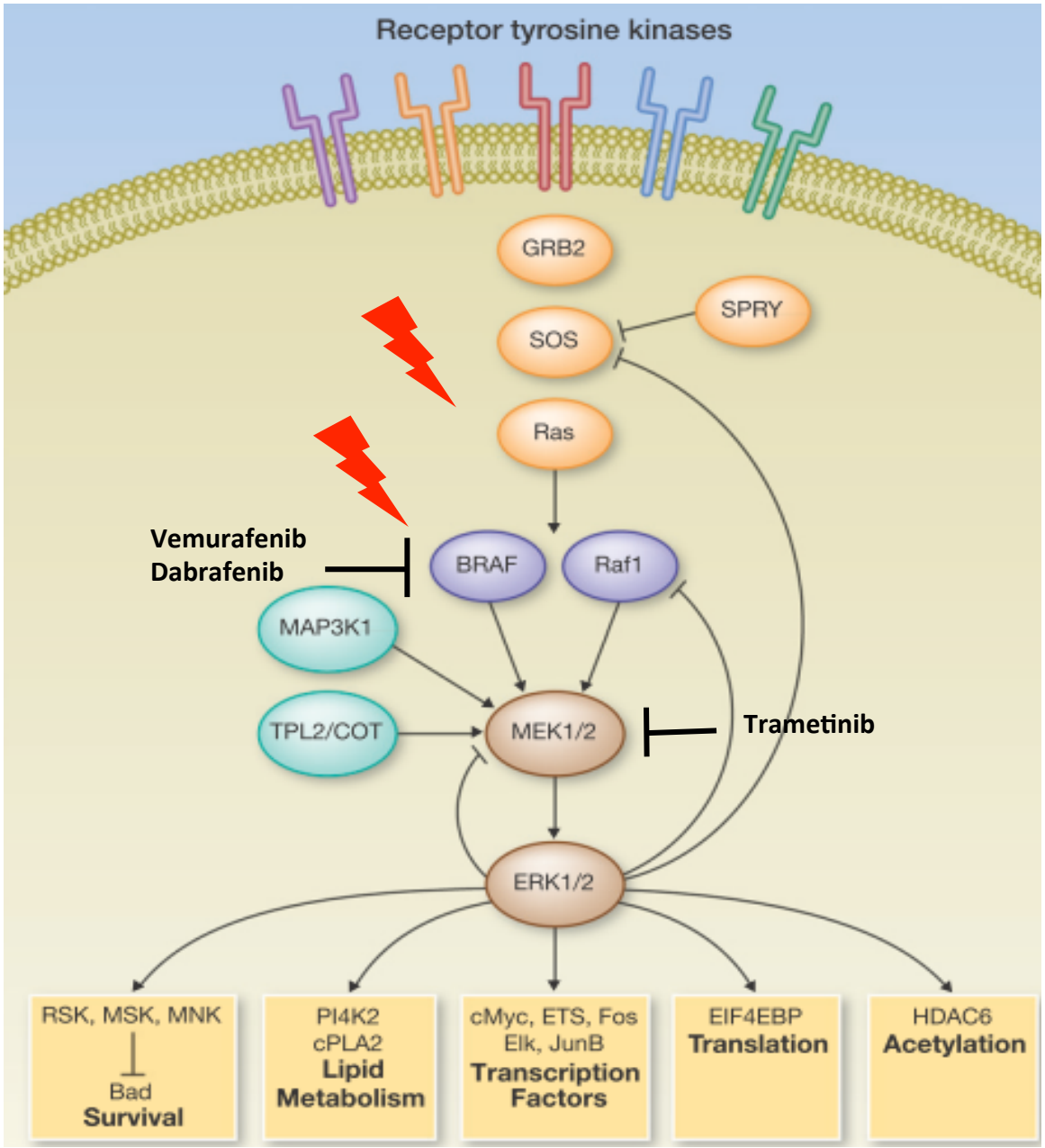
	WES	WES	WES	Targeted sequencing
	Walker (n=463)	**Lohr (n=203)**	**Bolli (n=67)**	**Neri (n=132)**
BRAF	6.7%	6%	14.9%	10.6%
NRAS	19.4%	20%	25.4%	26.5%
KRAS	21.1%	23%	25.4%	32.6%
DIS3	8.6%	11%	1.5%	18.5%
FAM46C	5.6%	11%	11.9%	11.7%
TP53	3.0%	8%	14.9%	3.1%

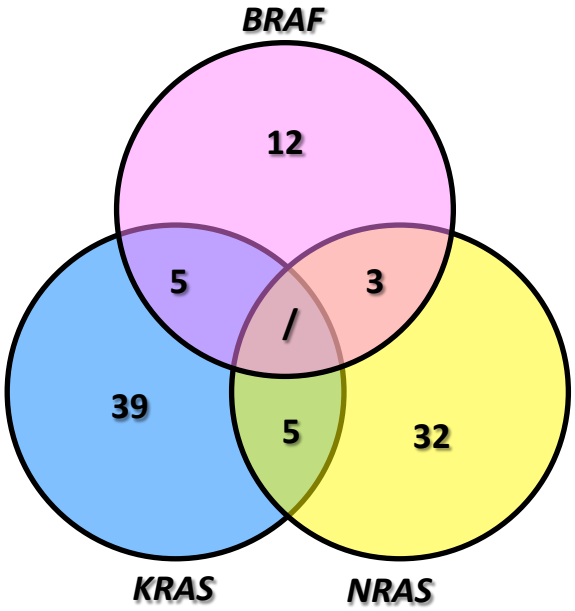
BRAF/NRAS/KRAS/DIS3/TP53/FAM46C mutations [illegible]MM an[illegible]L

	BRAF	*NRAS*	*KRAS*	*DIS3*	13q14 del and/or *DIS3* mut	*TP53*	*TP53* del and/or mut	*FAM46C*
132 MM patients at onset	14/132 **10.6%**	35/132 **26.5%**	43/132 **32.6%**	24/130 **18.5%**	66/130, **50.8%**	4/129 **3.1%** **25% del(17p)**	9/128, **7%**	15/128 **11.7%**
16 MM patients at relapse	0/16 **0%**	3/16 **18.7%**	7/16 **43.7%**	3/16 **18.7%**	8/16, **50%**	1/16 **6.2%**	5/16, **31.2%**	2/16 **12.5%**
24 primary PCL patients at onset	5/24 **20.8%**	1/24 **4.2%**	4/24 **16.7%**	6/24 **25%**	19/24, **79.2%**	6/24 **25%** **67% del(17p)**	9/24, **37.5%**	1/24 **4.2%**
11 secondary PCL patients	1/11 **9.1%**	4/11 **36.4%**	2/11 **18.2%**	3/10 **30%**	6/10, **60%**	2/10 **20%** **100% del(17p**	4/9, **44.4%**	2/10 **20%**

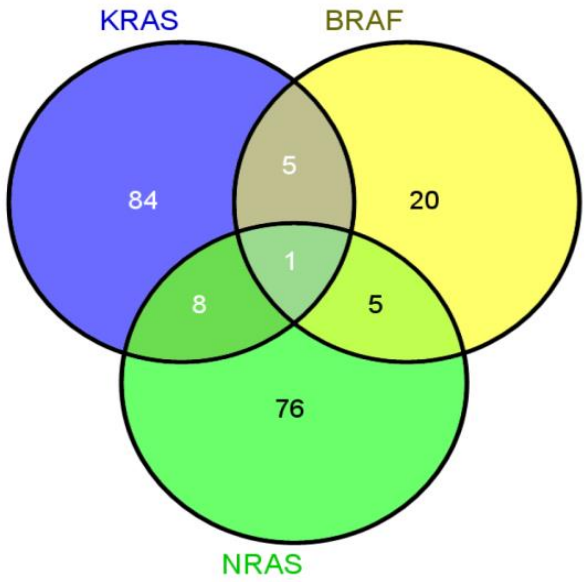


The RAS/MAPK is the most mutated pathway in Multiple Myeloma

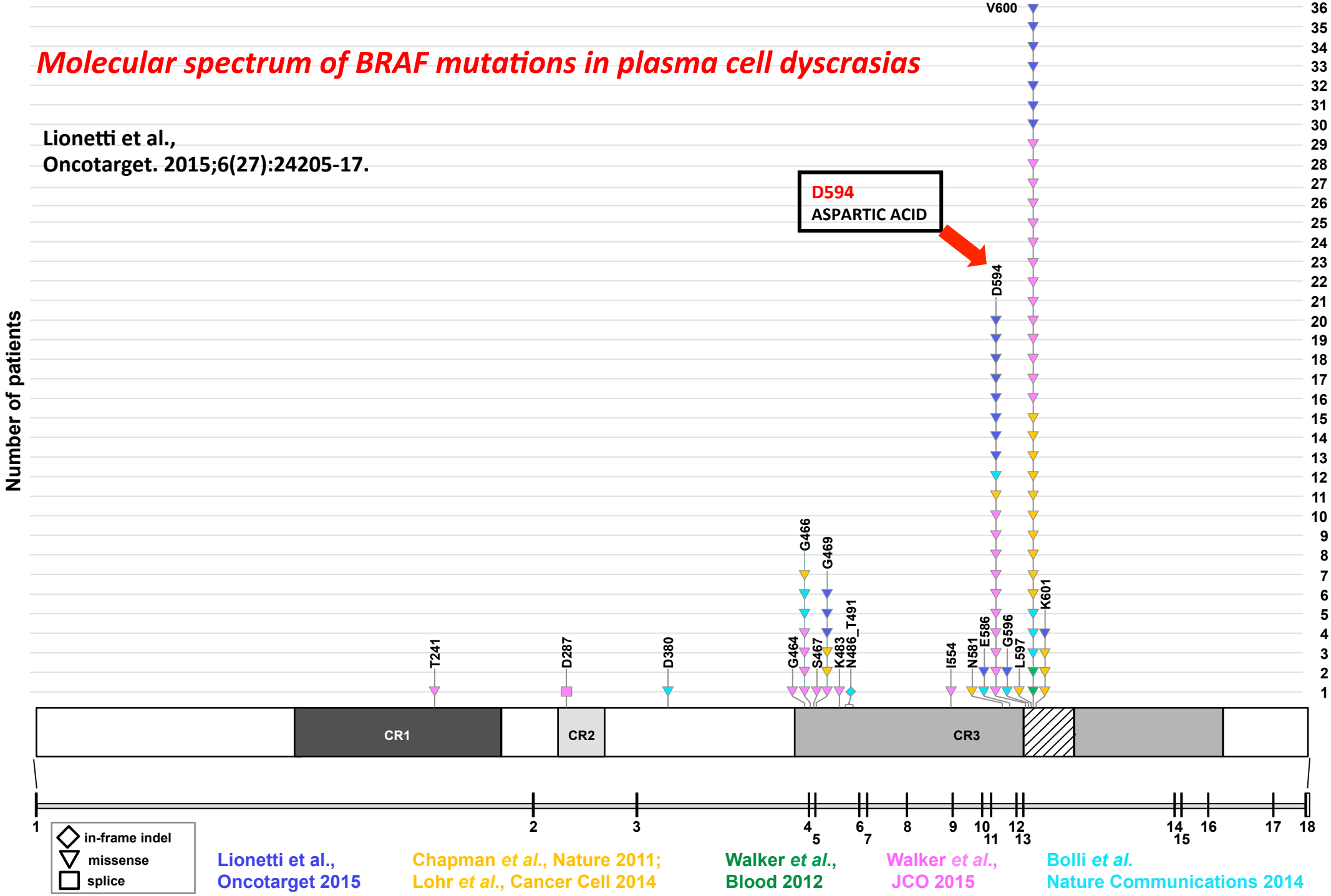




Lionetti et al., Oncotarget. 2015 Jun 10. [Epub ahead of print]

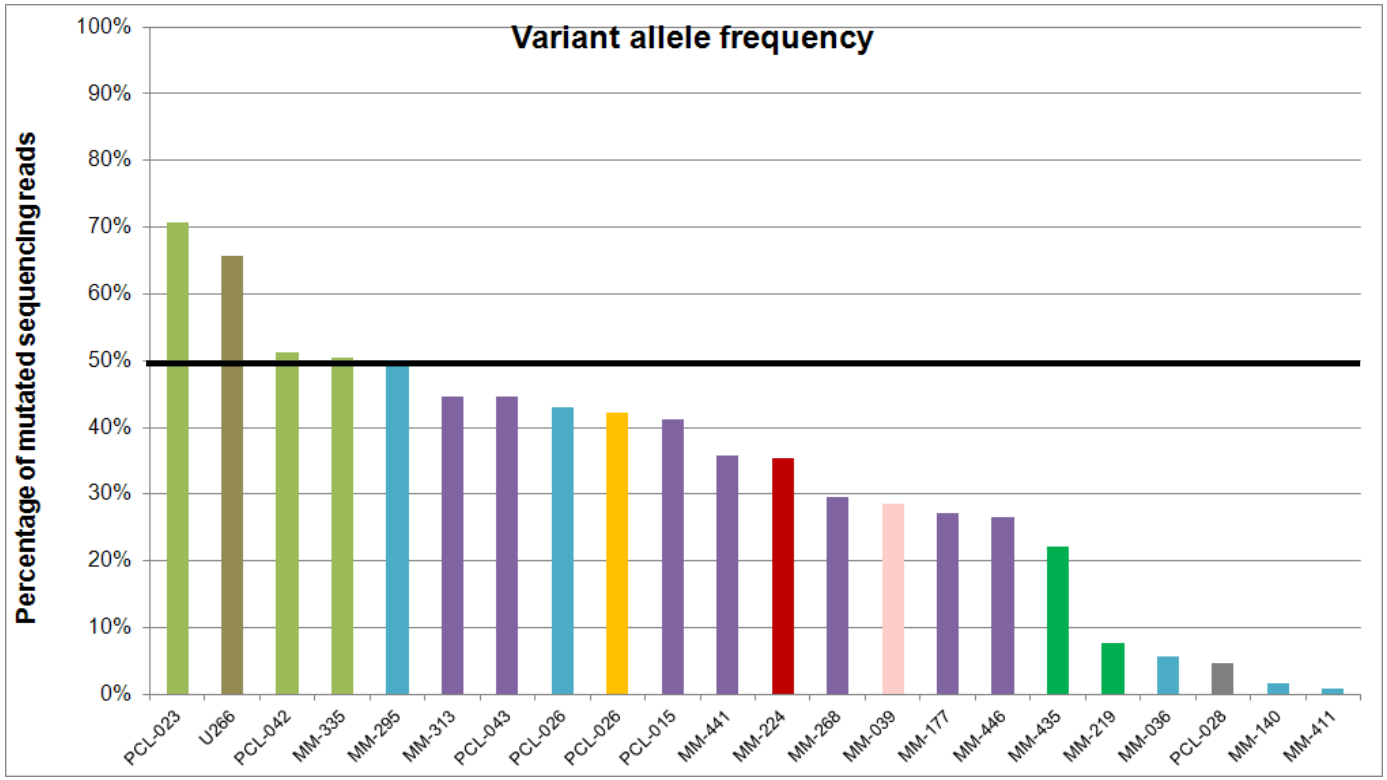


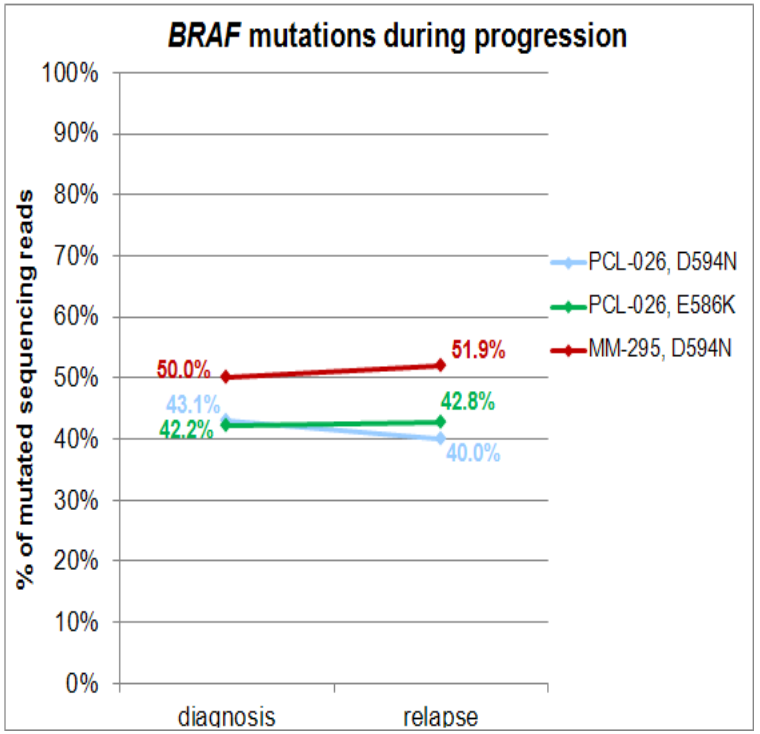
Walker et al., J Clin Oncol. 2015 aug 17. [Epub ahead of print]


Molecular spectrum of BRAF mutations in plasma cell dyscrasias
Lionetti et al.,
Oncotarget. 2015;6(27):24205-17.
D594
ASPARTIC ACID
Number of patients
V600
D594
G466
G469
K601
T241
D287
D380
G464
S467
K483
N486_T491
I554
N581
E586
G596
L597
CR1
CR2
CR3
in-frame indel
missense
splice
Lionetti et al.,
Oncotarget 2015
Chapman et al., Nature 2011;
Lohr et al., Cancer Cell 2014
Walker et al.,
Blood 2012
Walker et al.,
JCO 2015
Bolli et al.
Nature Communications 2014

Variant allelic frequency and sequential analysis of BRAF mutation analysis:

Evidence of mutation in small sublones

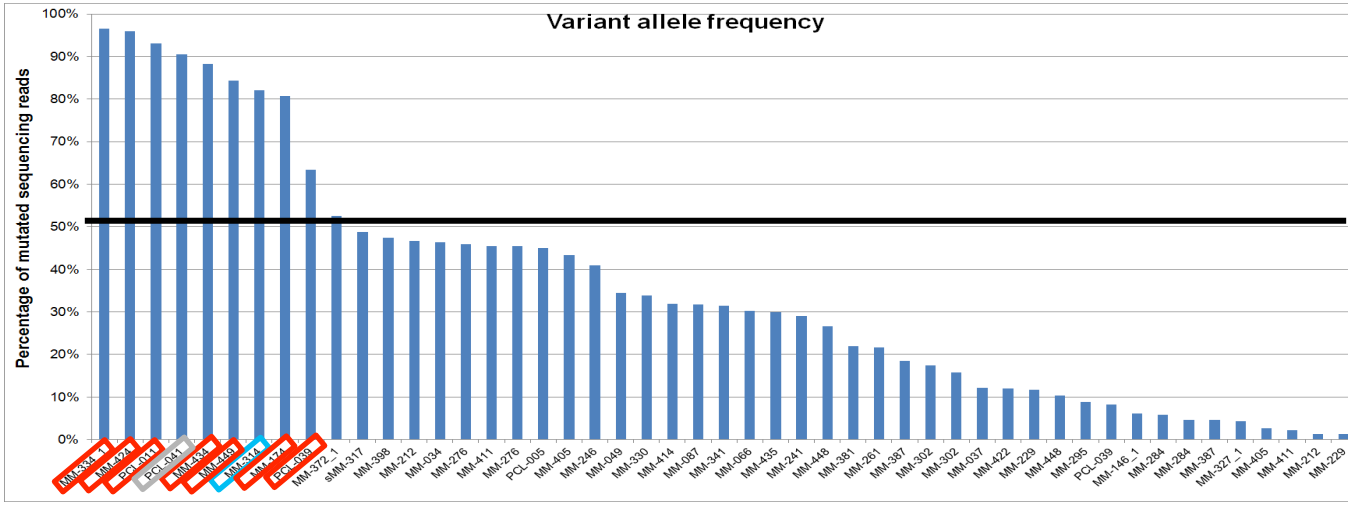




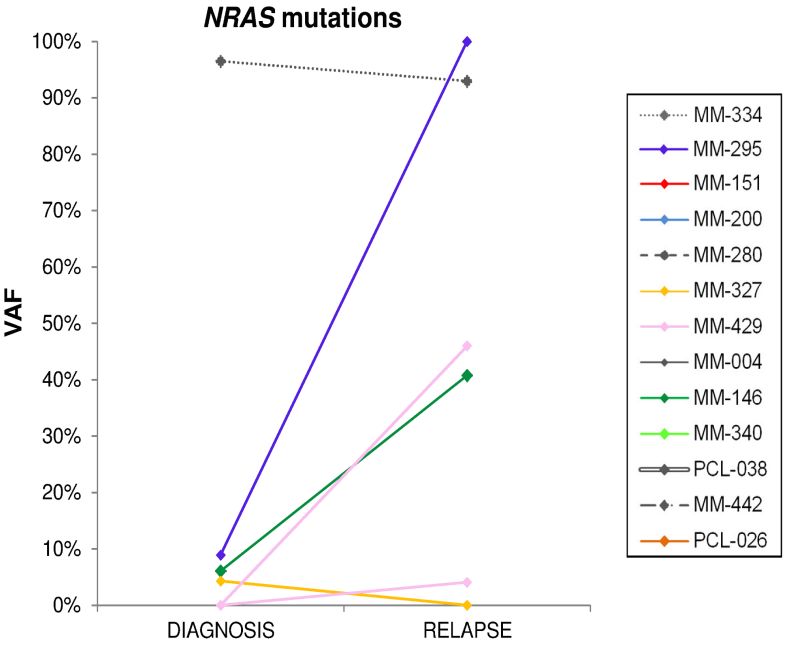
Lionetti et al.,
Oncotarget. 2015;6(27):24205-17.

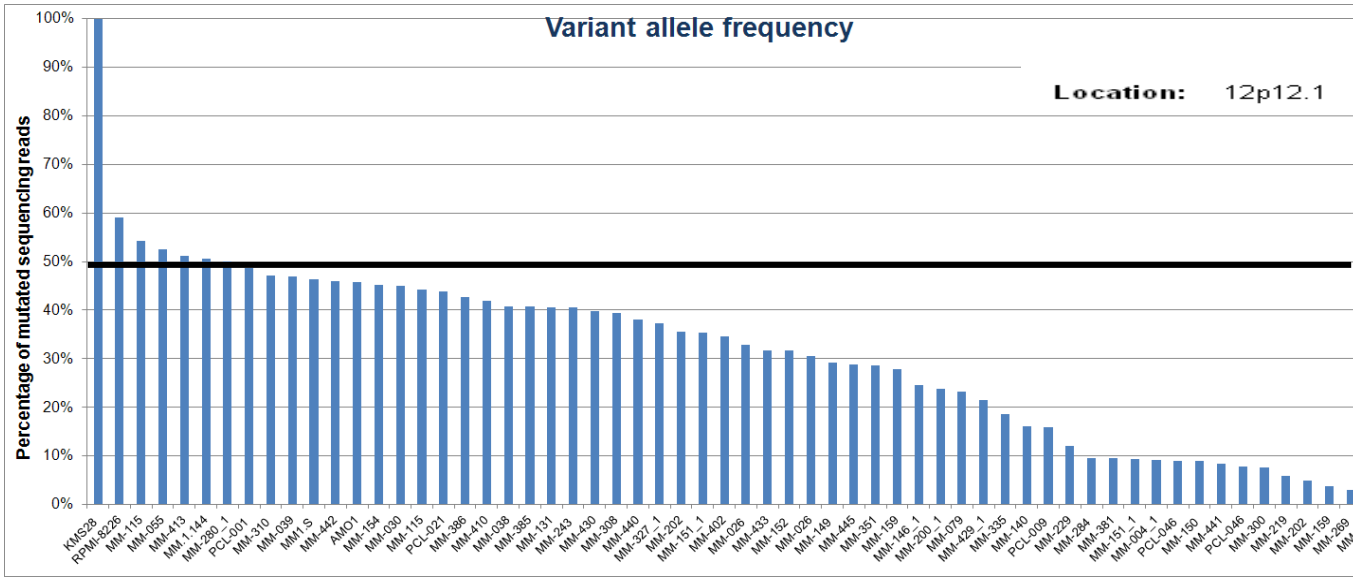
Variant allelic frequency and sequential analysis of RAS mutation analysis:

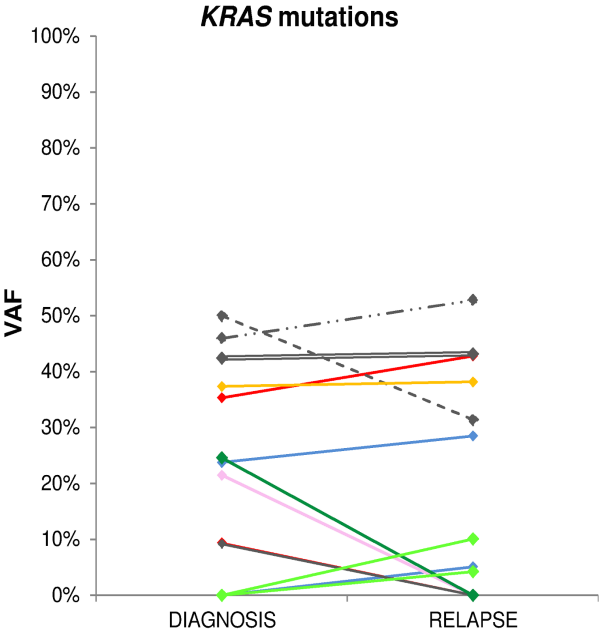
Evidence of mutation in small sublones



Location: 1p13.2 **1p loss** **nd** **1p normal**





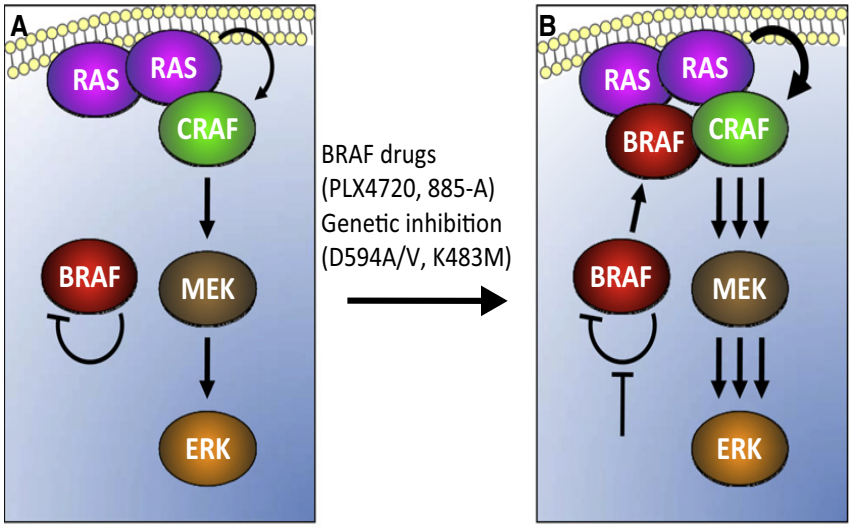


Lionetti et al., Oncotarget. 2015;6(27):24205-17.

Experimental evidence in Melanoma indicates that D594 mut are not able to activate BRAF

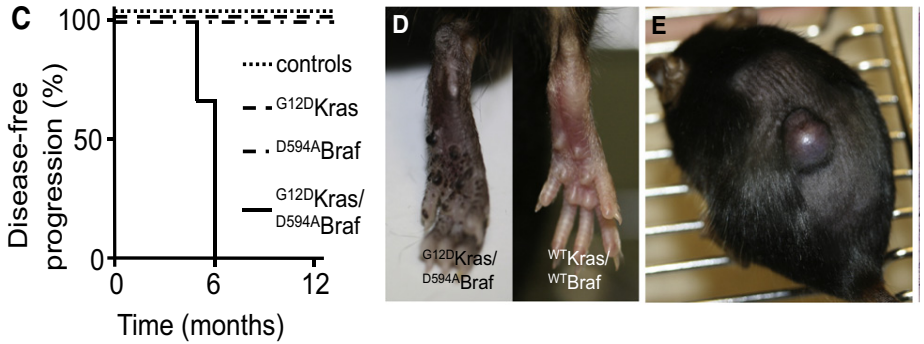
They are defined *Dead Mutations* and reported to be recurrentely concomitant to Ras mutation

Dead-BRAF mutations are able to activate MEK-ERK in a RAS-dependent manner



Sample	BRAF	NRAS	KRAS
MM-295_early	D594N, 50%	**G12D, 8.9%**	wt
MM-295_late	D594N, 51.9%	**G12D, 100%**	wt
MM-435	D594G, 22.2%	**Q61R, 29.9%**	wt
MM-219	D594G, 7.8%	wt	**G13D, 5.9%**
MM-140	D594N, 1.7%	wt	**G12A, 14.8%**
MM-411	D594G, 0.9%	**S87C, 45.5%**	wt
PCL-026_early	D594N, 43.1%/E586K, 42.2%	wt	wt
PCL-026_late	D594N, 40%/E586K, 42.8%	wt	wt
PCL-028	D594E, 4.7%	wt	wt
MM-036	D594N, 5.6%	wt	wt

Oncogenic RAS and Kinase-Dead BRAF Mutation cooperate to induce melanoma in mice

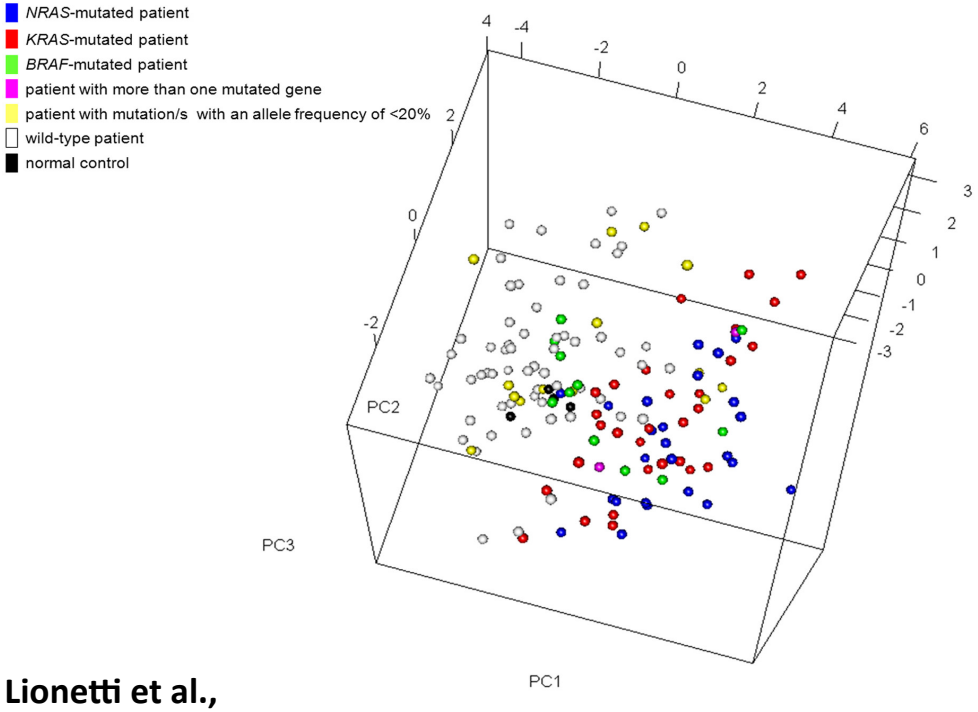


Heidorn et al Cell, 2014

5 out of 8 MM patients carrying a D594 dead-BRAF mutation were mutated for RAS genes.

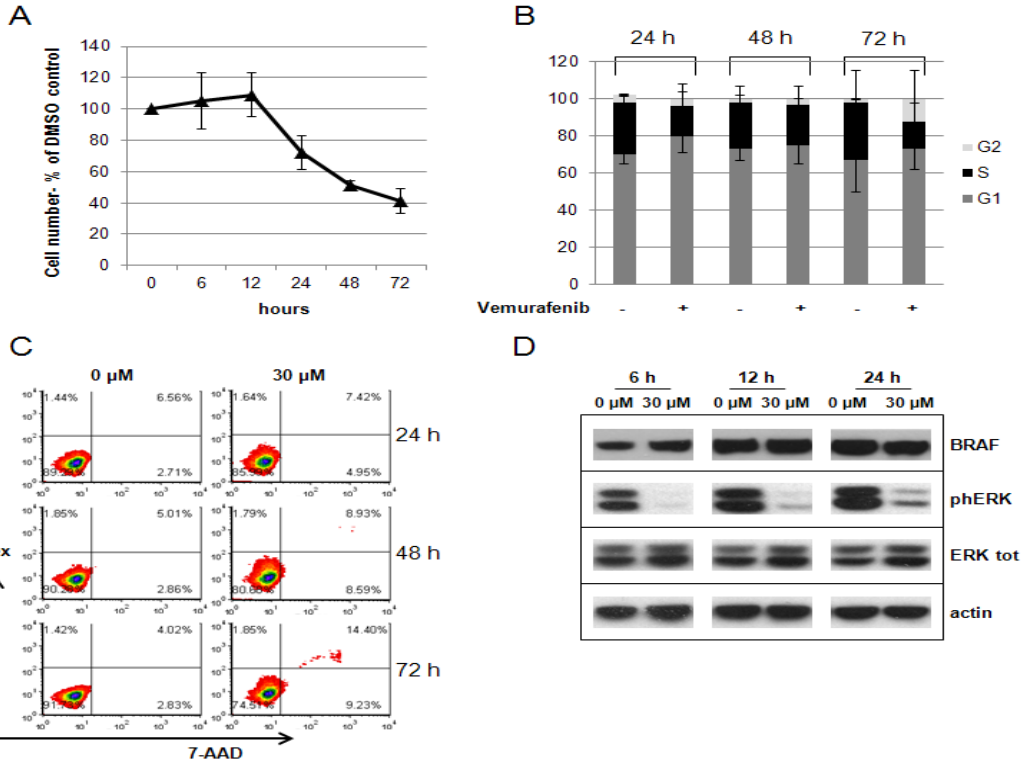
Lionetti et al.,
Oncotarget. 2015;6(27):24205-17.

NRAS, KRAS and BRAF mutated MMs show distinct transcriptional pattern

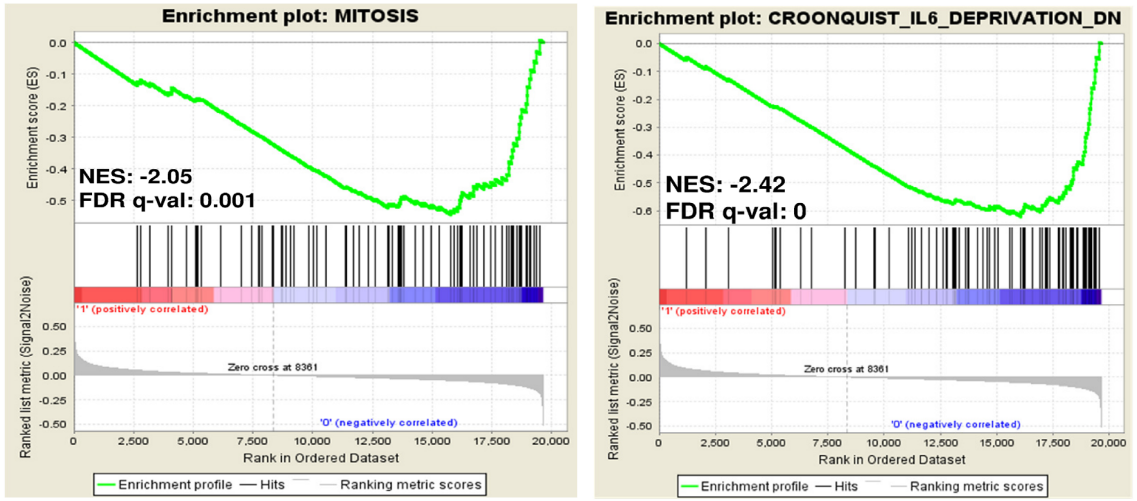


Lionetti et al.,
Oncotarget. 2015;6(27):24205-17.

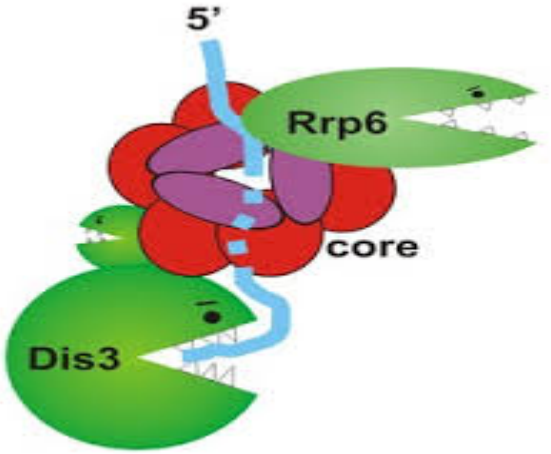
Treatment of Vemurafenib on BRAF mutated U266 myeloma line affects cell proliferation



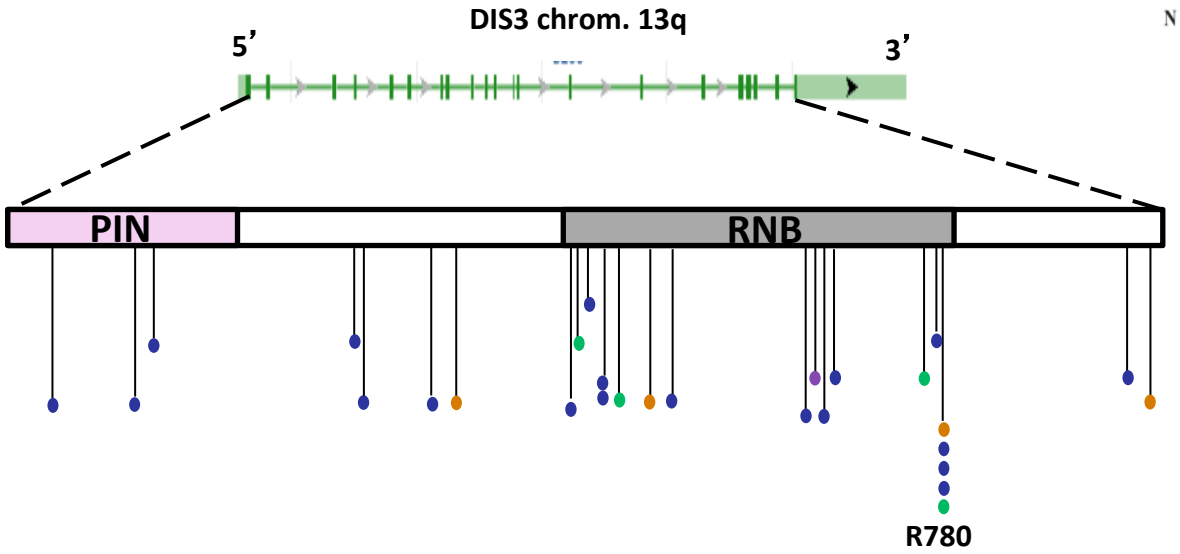
GSEA enrichment plots of U266 vemurafenib-treated cells

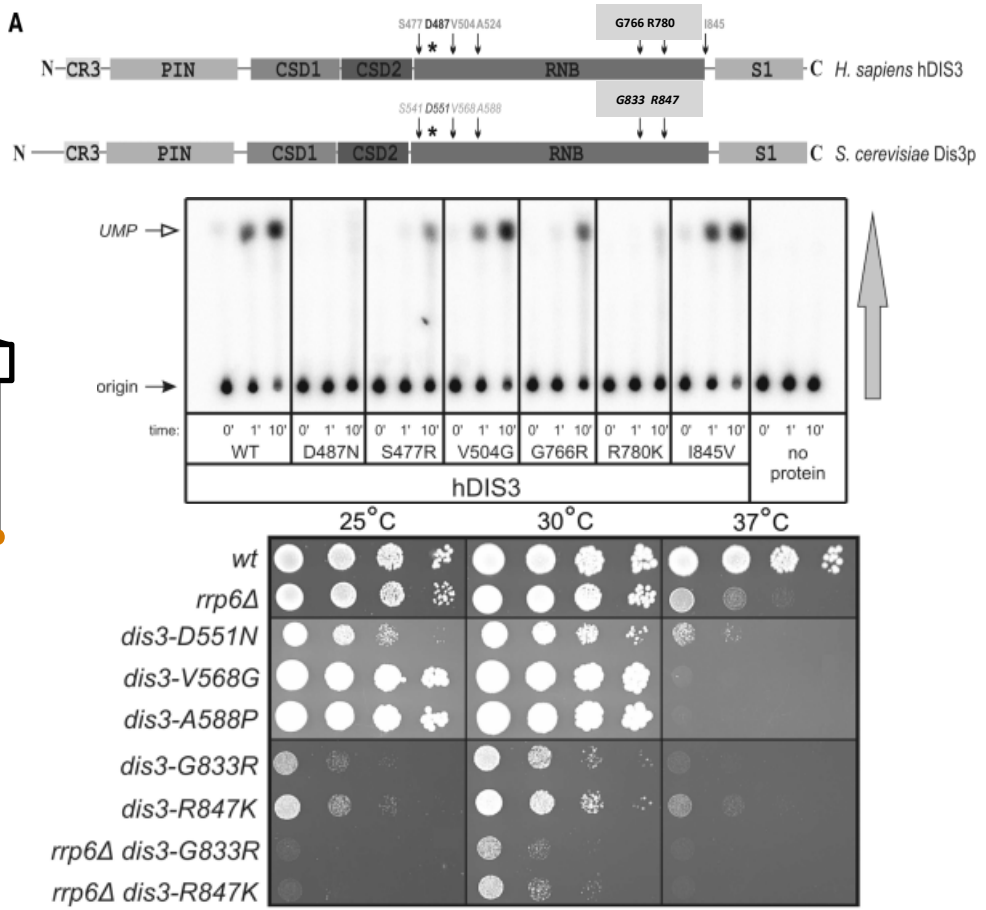


DIS3, a catalytic component of the RNA exosomes



- **DIS3 is the catalytic subunit of the RNA exosome, a macromolecular complex degrading RNA.**
- **The eukaryotic exosome complex is built around a backbone of a 9-subunit ring devoid of any detectable catalytic activity**
- **The RNA decay capability is supplied by two associated hydrolytic ribonucleases, Dis3 and Rrp6.**
- **Dis3 is both a 3'-5' exonuclease and, as recently demonstrated, an endoribonuclease (Lebreton et al. 2008; Schaeffer et al. 2009).**
- **Rrp6 is instead an exonuclease. The functional relationship between Dis3 and Rrp6 is unknown**





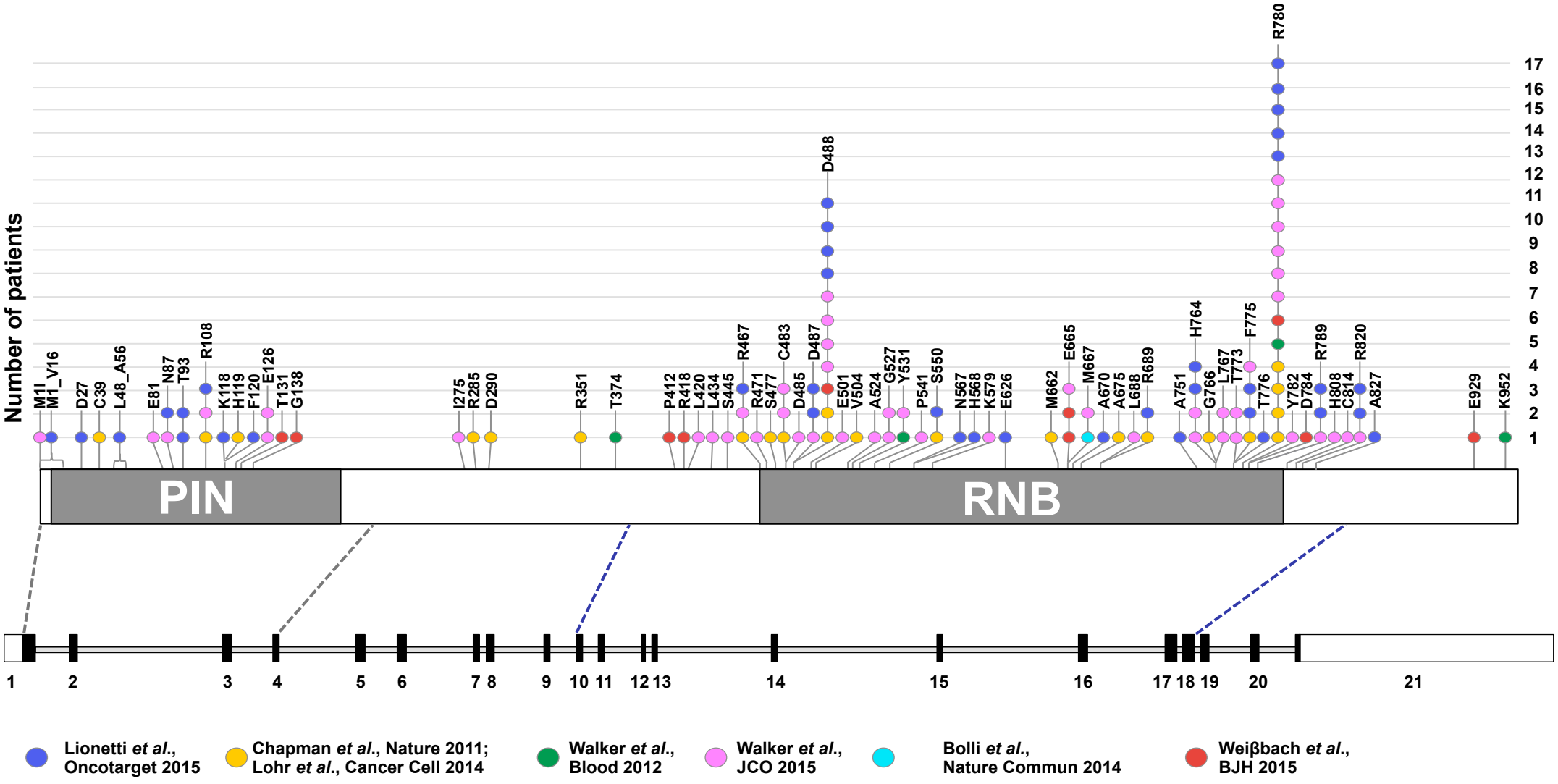
Lohr *et al.*, Cancer Cell 2014

Bolli *et al.*, Nature Comm. 2014

Walker *et al.*, Blood 2012

Chapman *et al.*, Nature 2011

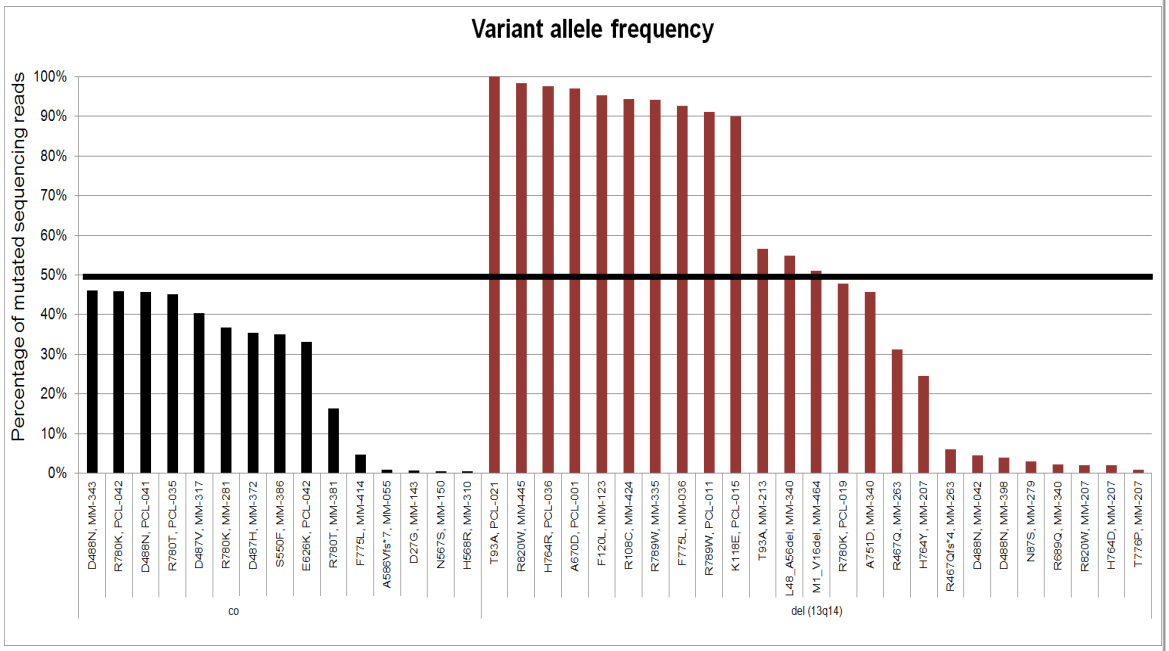
Compendium of DIS3 mutations in plasma cell dyscrasias



Lionetti et al.
Oncotarget. 2015 Sep 22;6(28):26129-41

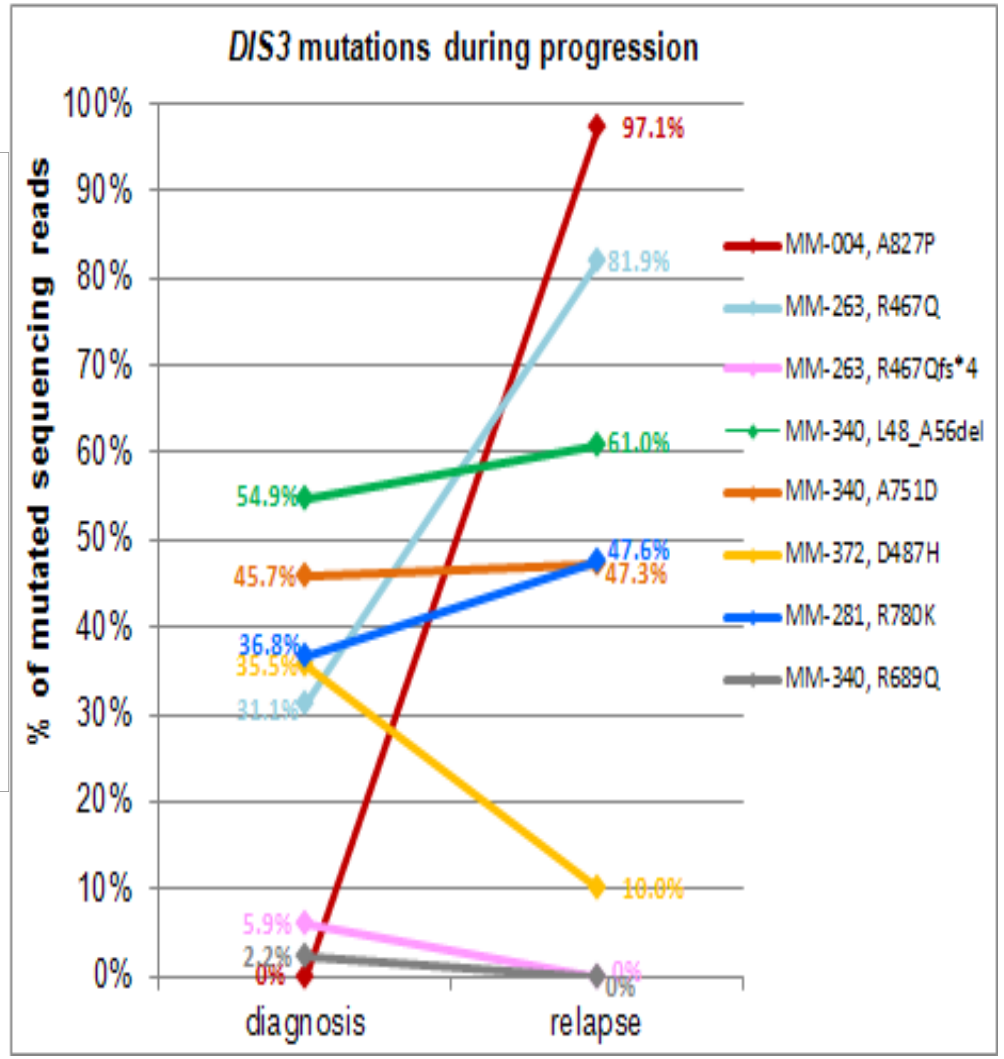
Variant allelic frequency and sequential analysis of DIS3 mutation analysis:

Evidence of mutation in small sublones



copy number chr 13= 2

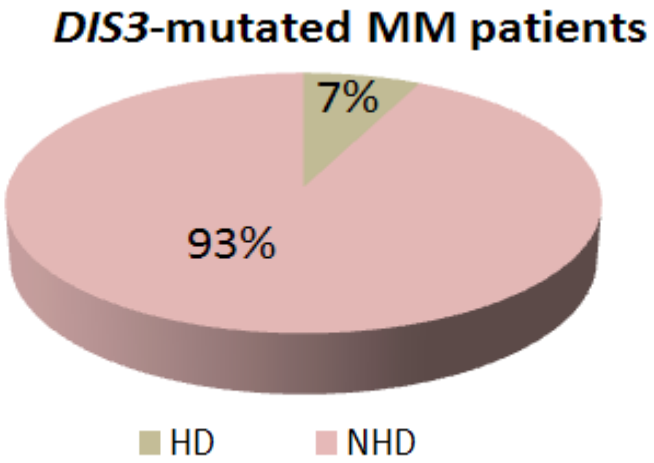
del(13q14)



Lionetti et al.
Oncotarget. 2015 Sep 22;6(28):26129-41

DIS3 mutations and chromosomal abnormalities

Negative/Positive association with Hyperdiplody/non-Hyperdiplody



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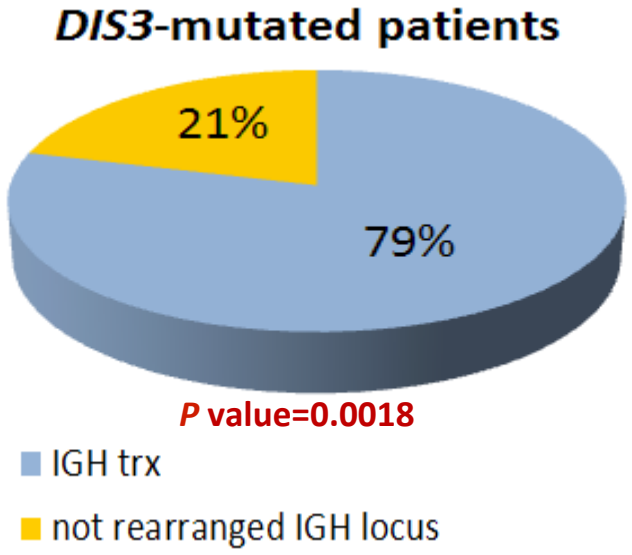

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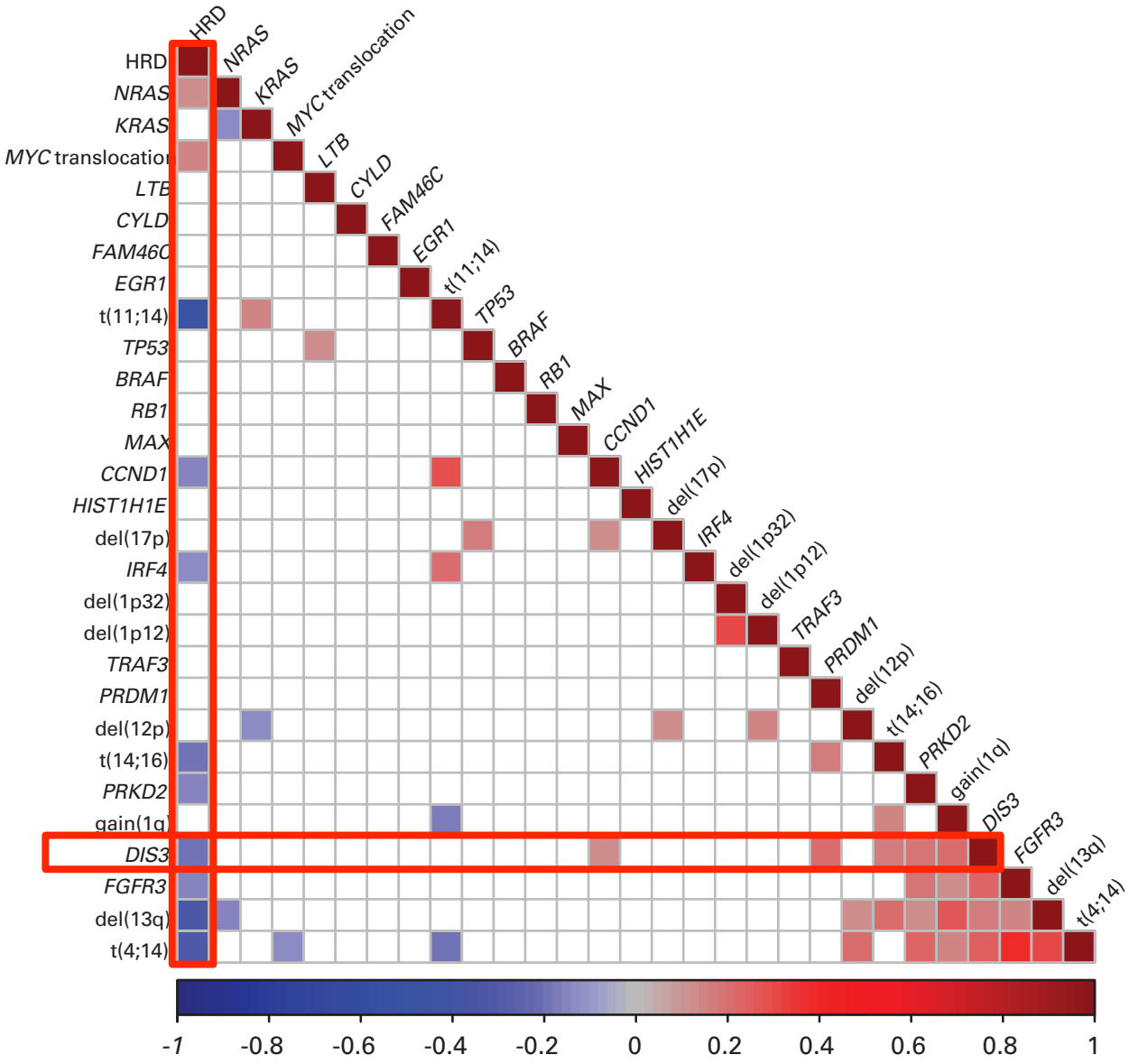


Lionetti et al. Oncotarget. 2015 Sep 22;6(28):26129-41

Walker et al. J Clin Oncology, 2015

Predictive Biomarkers and Personalized Medicine

Clinical Cancer Research

FAM46C putative role in RNA editing and metabolism

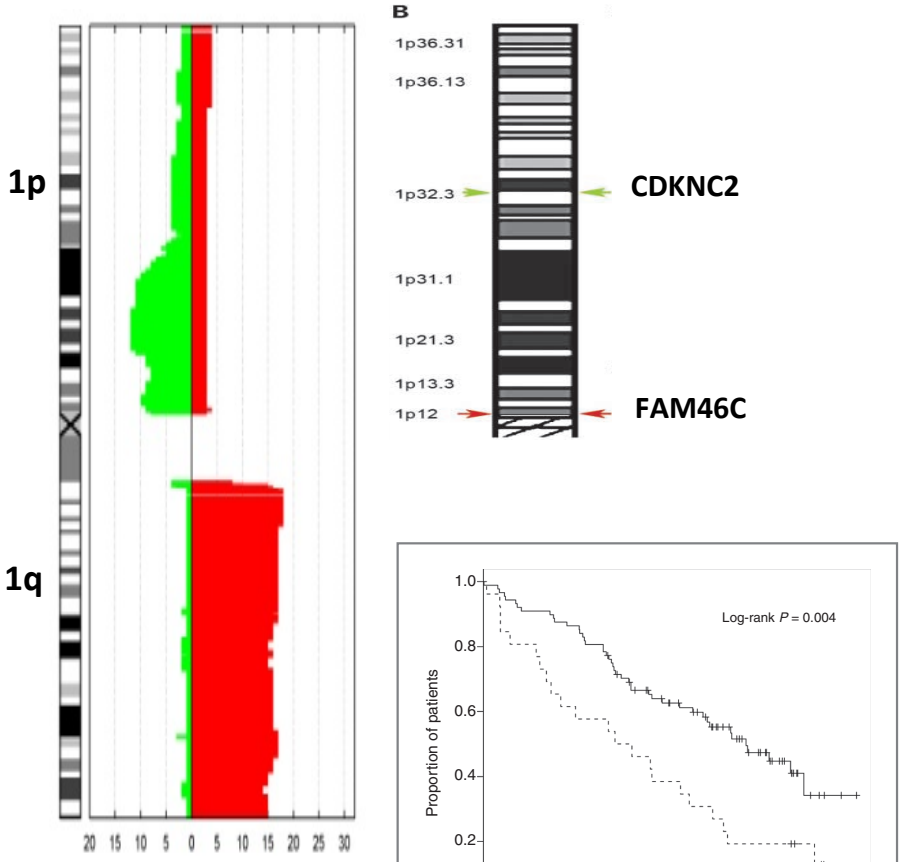
FAM46C (391 aa long) is found on chromosome 1 at the locus 1p12

FAM46C contains one domain of unknown function, DUF1693, and as such has been placed in the DUF1693 protein family.

This protein family has been established as a part of the Nucleotidyltransferase superfamily .

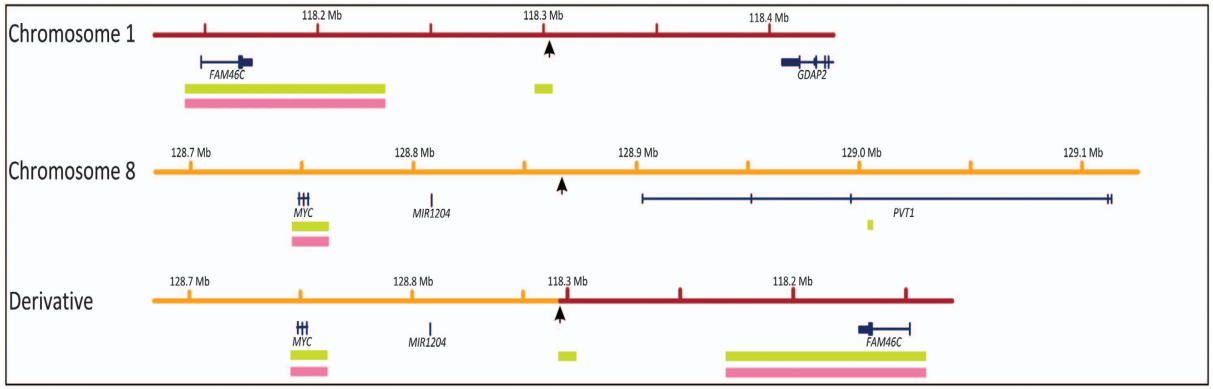
Predicted as a cytosolic protein

Mapping of Chromosome 1p Deletions in Myeloma Identifies *FAM46C* at 1p12 and *CDKN2C* at 1p32.3 as Being Genes in Regions Associated with Adverse Survival



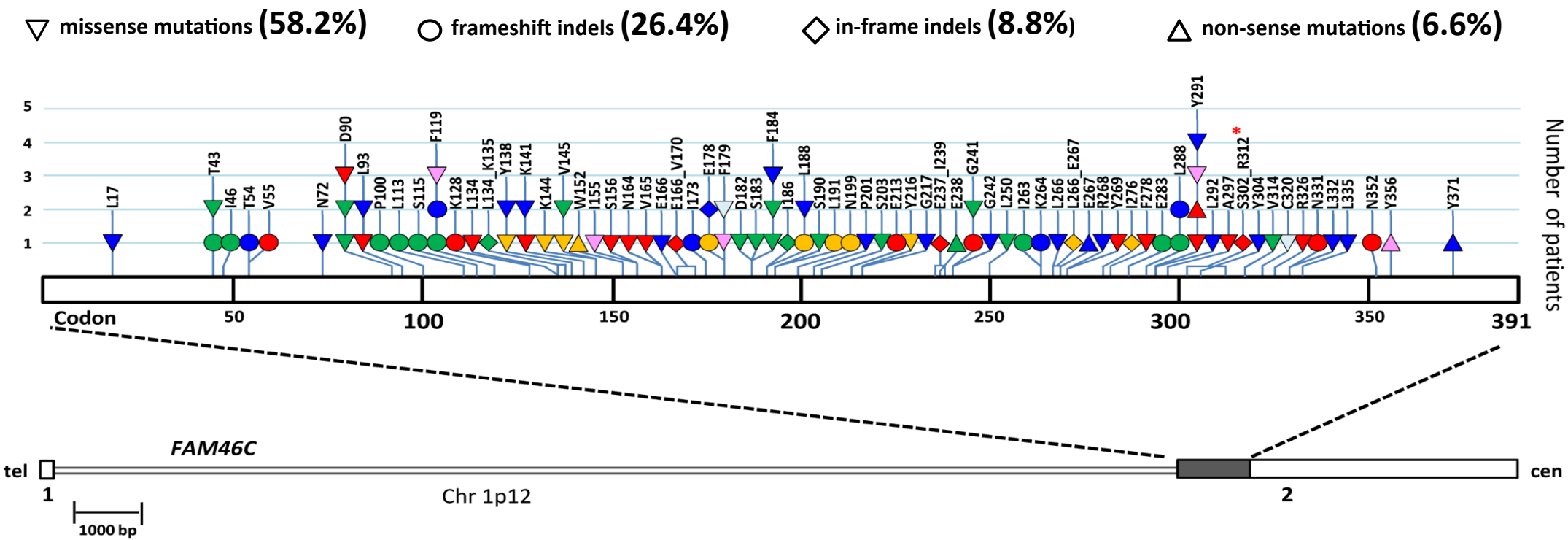
Boyd KD et al. Lin Cancer Res. 2011

FAM46C is recurrently involved in translocation juxtaposing MYC with genes harboring superenhancers with a role in B-cell biology or neoplasia



Walker B. et al. Blood Cancer Journal, 2014
Affer M. et al. Leukemia, 2014

Compendium of FAM46C mutations in plasma cell dyscrasias



Barbieri *et al.*, British Journal of Haematology 2016

Boyd *et al.*, Clinical Cancer Research 2011

Walker *et al.*, Journal of Clinical Oncology 2015

Walker *et al.*, Blood 2012

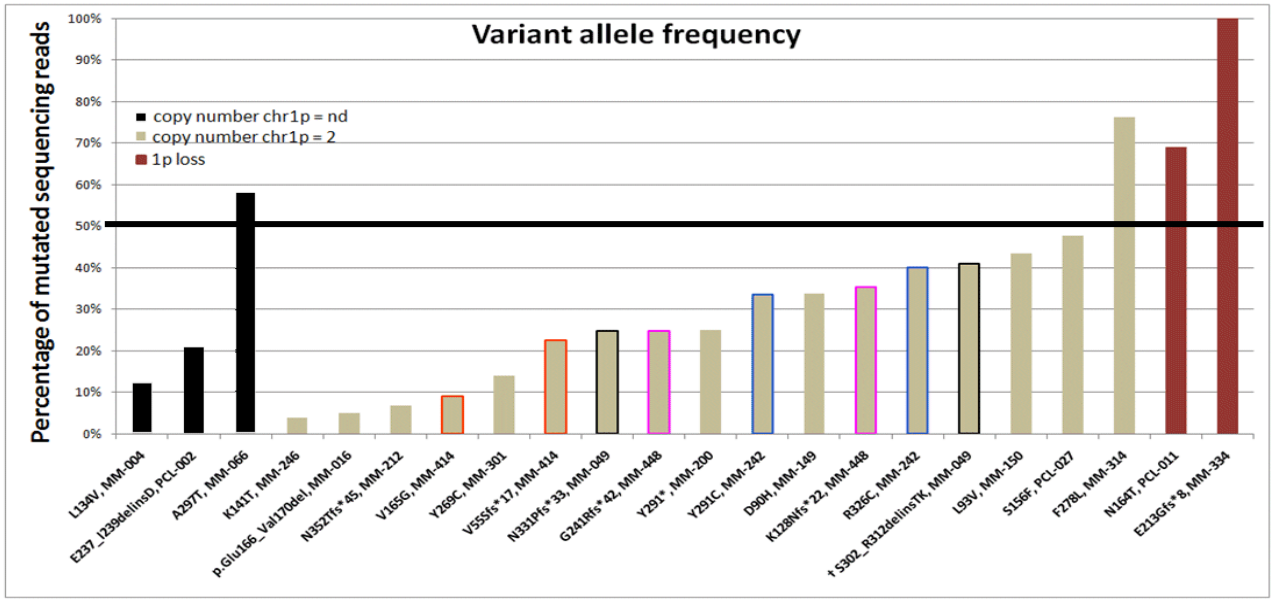
Chapman *et al.*, Nature 2011; Lohr *et al.*, Cancer Cell 2014

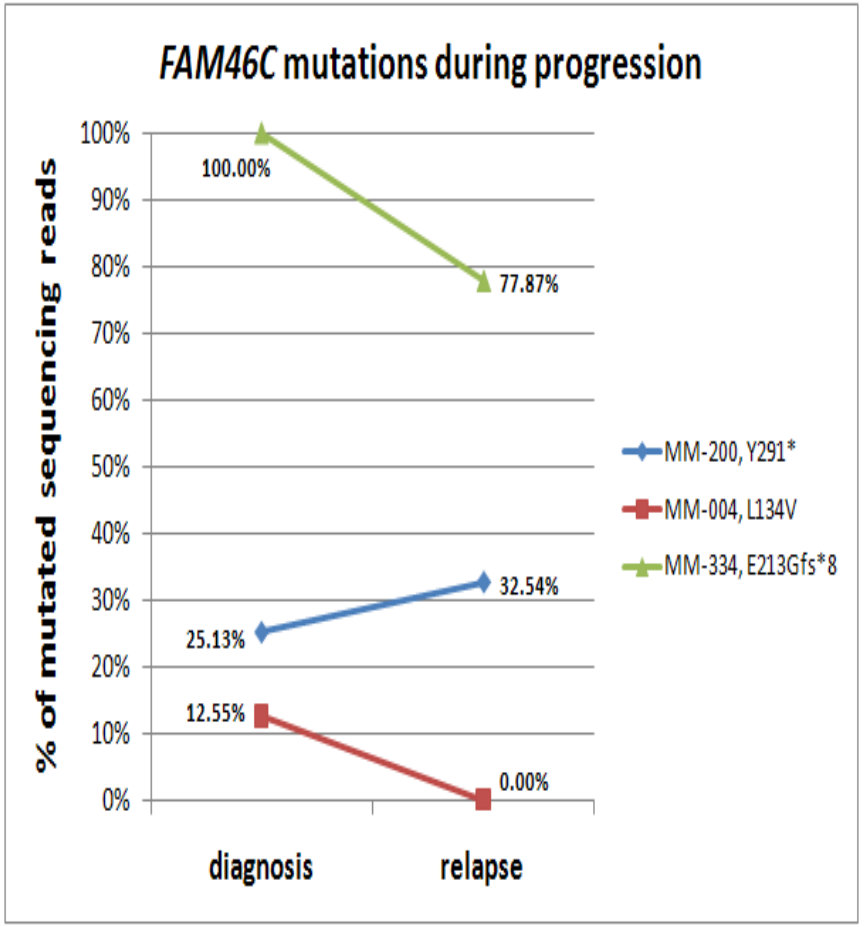
Bolli *et al.*, Nature Communications 2014

Barbieri et al.
Br J Haematol. 2016 Aug;174(4):642-5

Variant allelic frequency and sequential analysis of FAM46C mutation analysis:

Evidence of mutation in small sublones

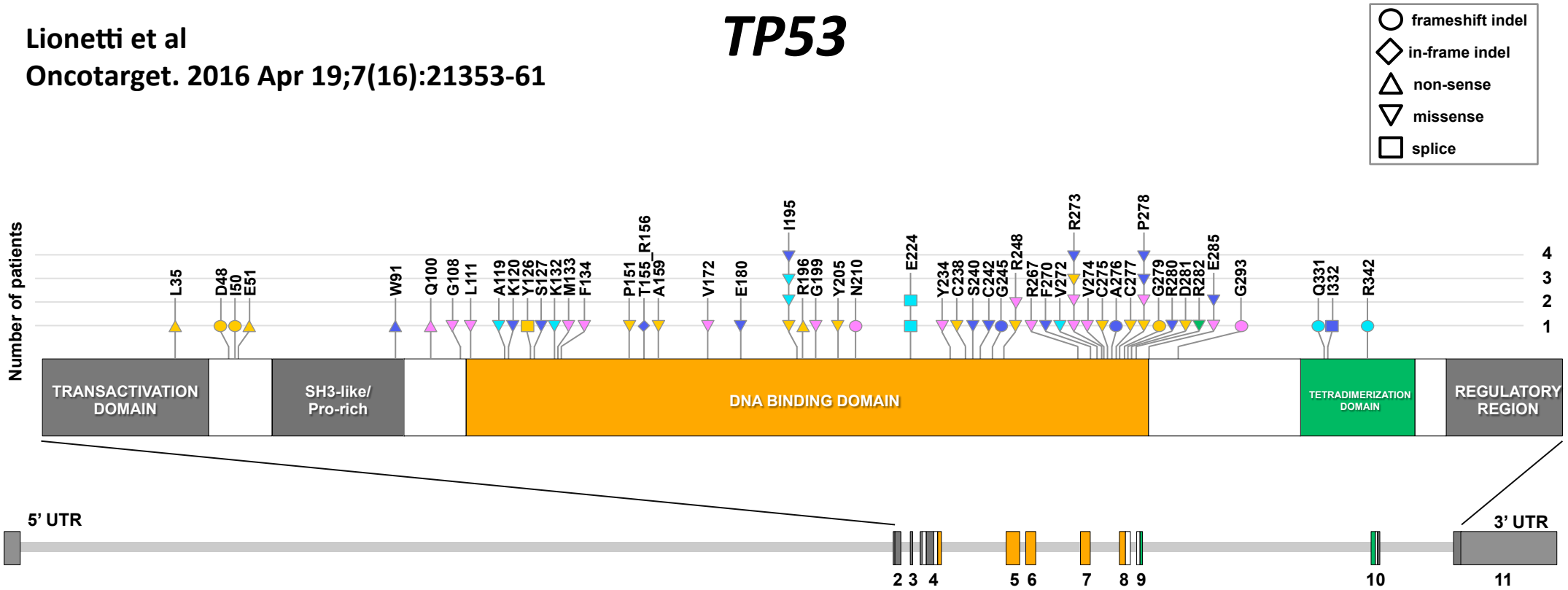




Barbieri et al., BJH. 2016,

Lionetti et al
Oncotarget. 2016 Apr 19;7(16):21353-61

TP53



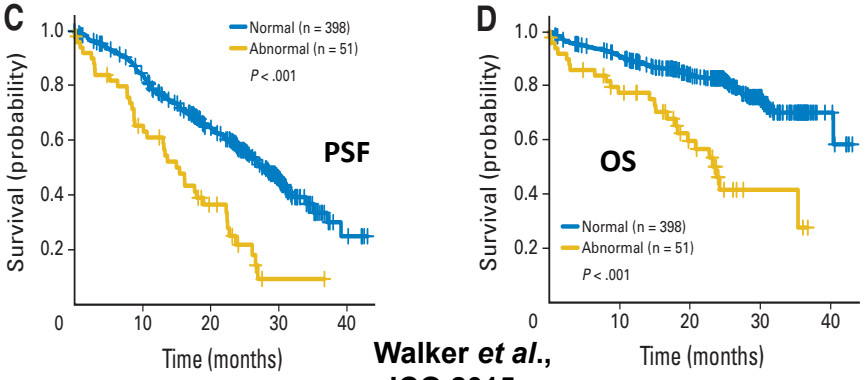
Lionetti et al., Oncotarget, 2016

Chapman *et al.*, Nature 2011;
Lohr *et al.*, Cancer Cell 2014

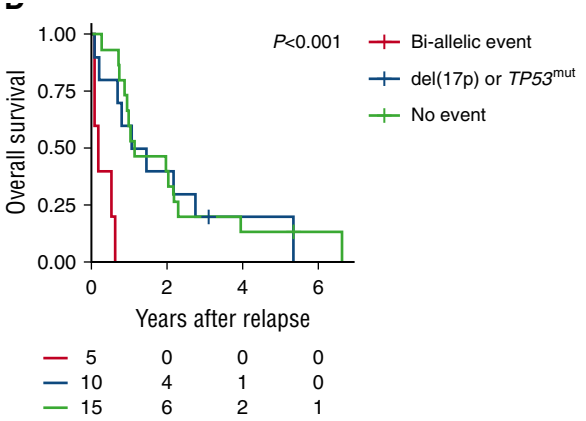
Walker *et al.*,Blood 2012

Walker *et al.*, JCO 2015

Bolli *et al.*
Nature Communications 2014



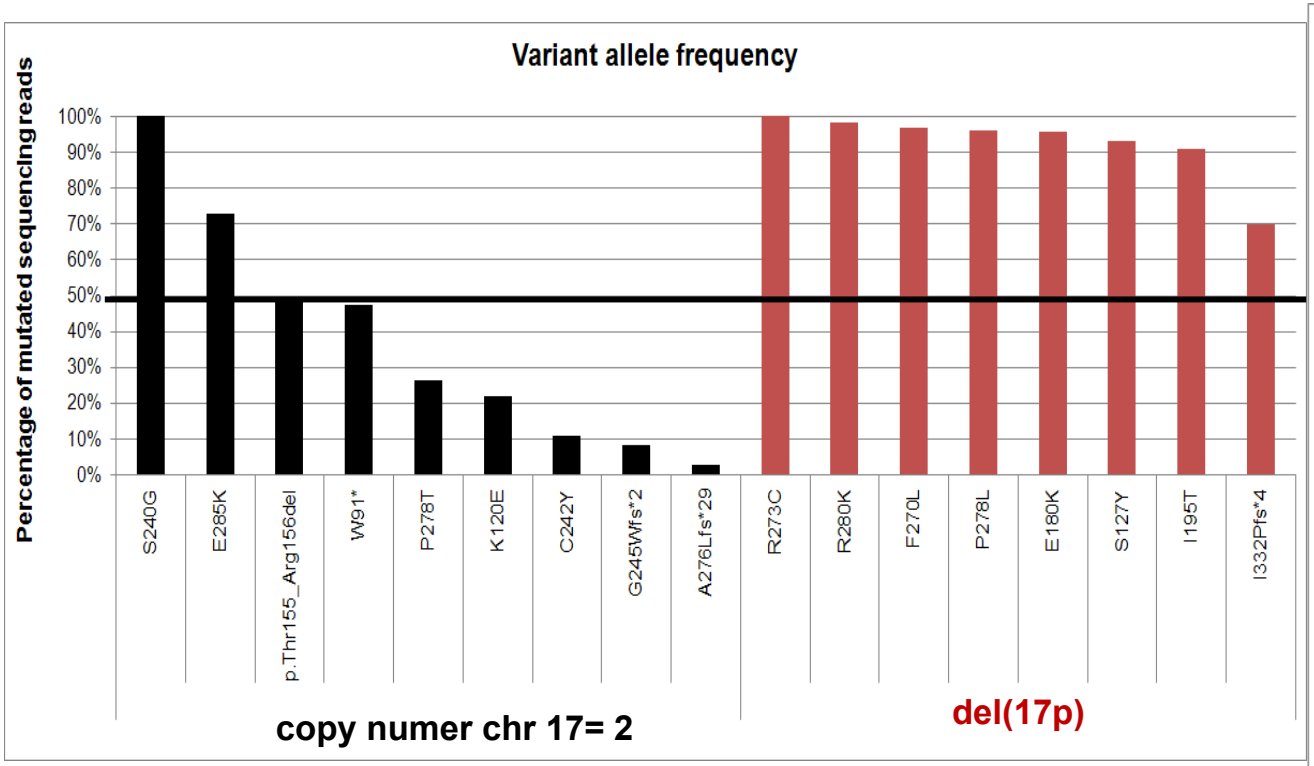
Walker *et al.*, JCO 2015

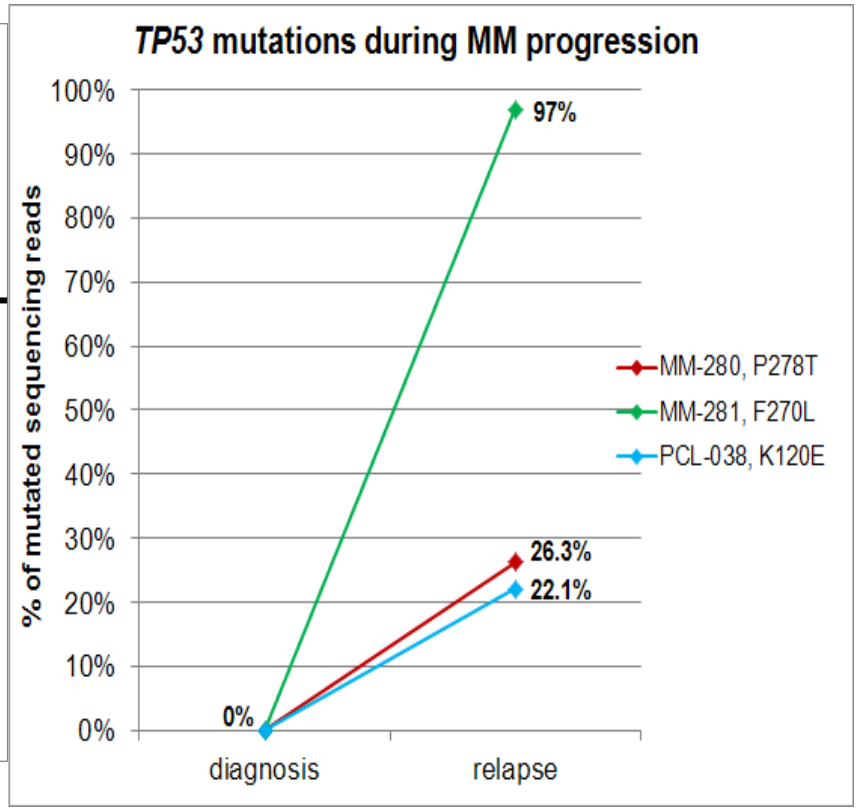


Wheinhold, Blood, sept 2016

Variant allelic frequency and sequential analysis of TP53 mutation analysis:

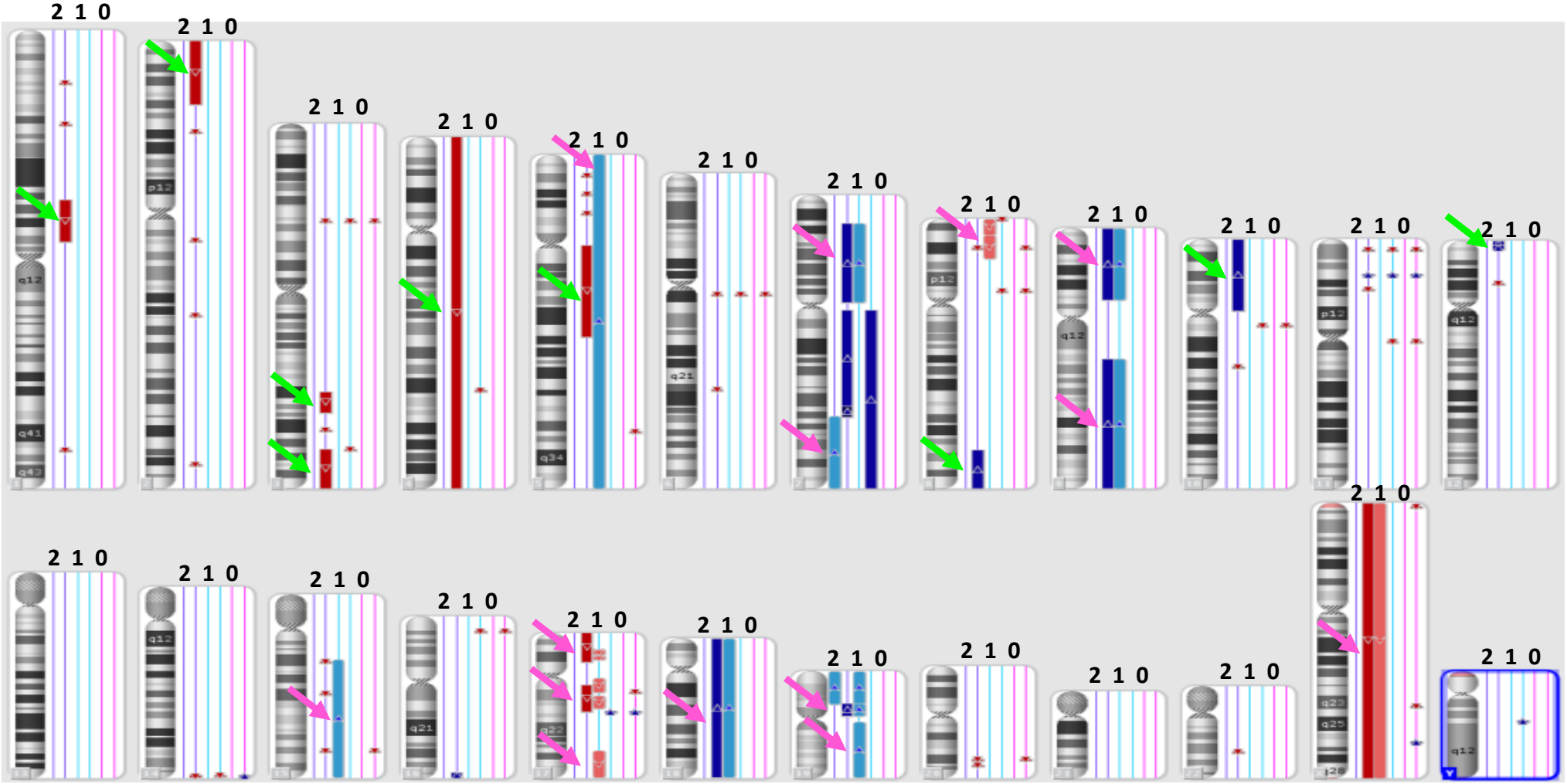
Evidence of mutation in small sublones





Lionetti et al
Oncotarget. 2016 Apr 19;7(16):21353-61

CLONAL EVOLUTION IN MULTIPLE MYELOMA – CytoScan Affy array



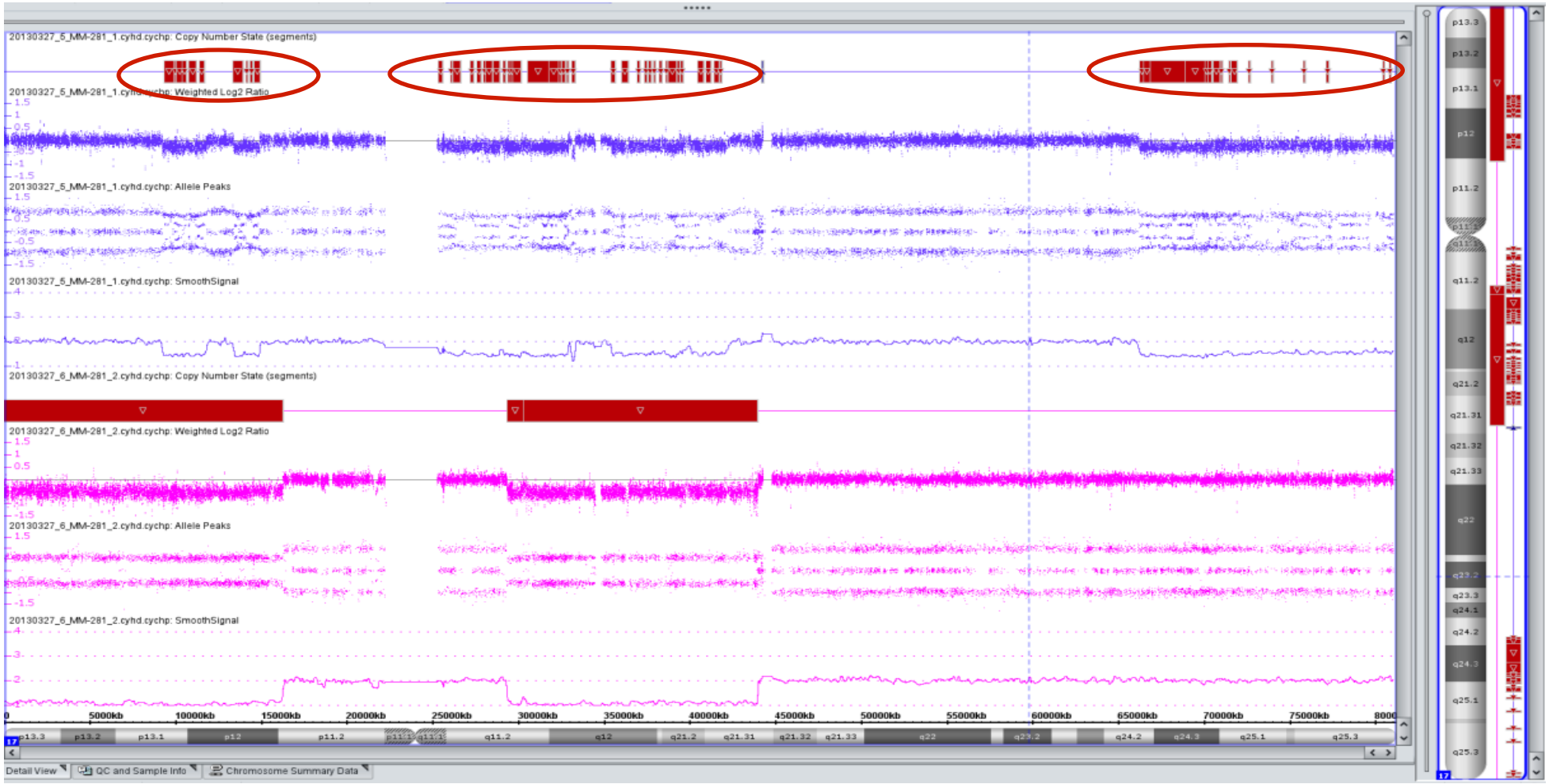
LOSS MOSAICISM
LOSS
GAIN MOSAICISM
GAIN

NEW LESIONS ACQUIRED IN DISEASE PROGRESSION

EVOLVING LESIONS FROM DIAGNOSIS TO PROGRESSION

0= NEGATIVE CONTROL
1= DIAGNOSIS
2= PROGRESSION

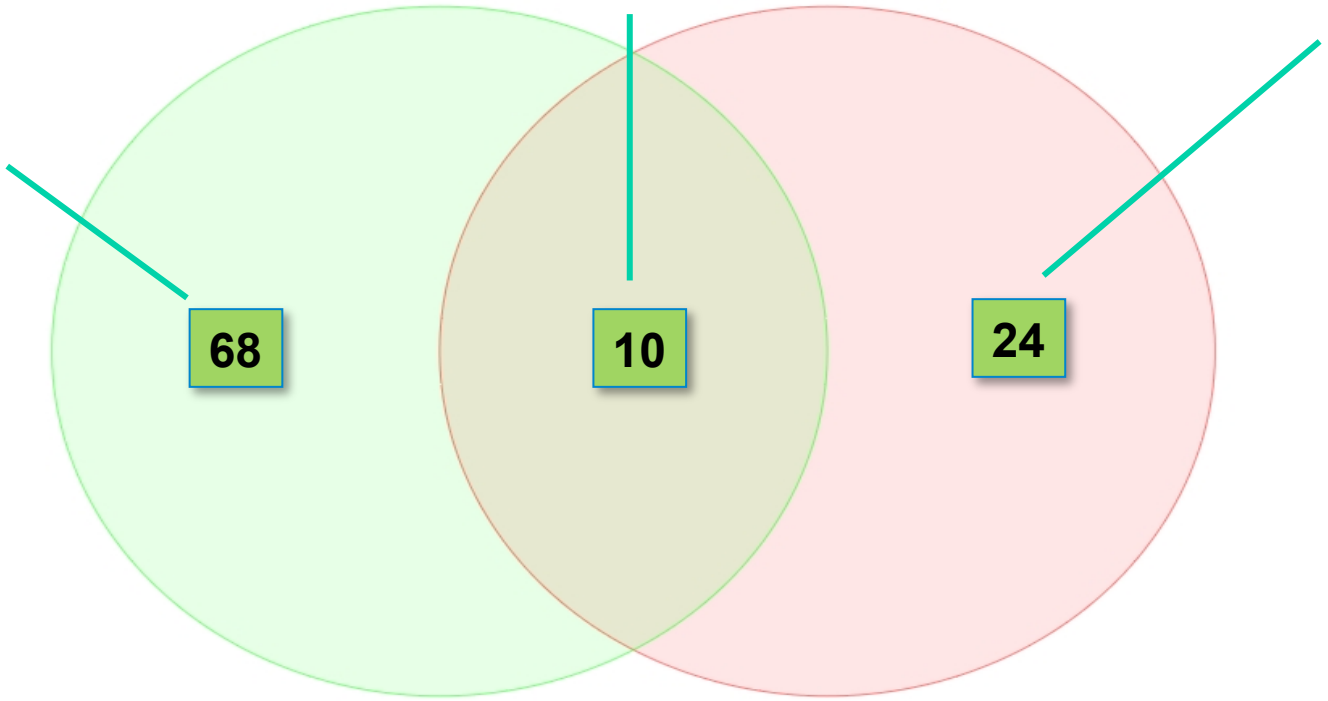
Detailed view of chromosome 17 aberrations in MM - sPCL



- Sub-clonal 17p12-p13.1 loss (2.4 Mb) and 17p12 loss (1.3 Mb)
- TP53 WT

- 17p11.2-p13.3 loss (16.3 Mb)
- TP53 loss (17p13.1) + TP53 mut

WES_ MM-281 : NON-SYN Mutations



AASS
ANKRD31
ANKRD31
ANKRD53
C4orf14
C6orf204
C7orf26
CCDC167
CCDC88A
CD163L1
CD163L1
CEPT1
CNDP1
COL15A1
COL3A1
CYP20A1
DNMT3A
EXO1
FAM115C
FIGNL1
GGT1
KLK10
KRTAP10-7
LRP1B
LRRIQ3
MED15
MTA1
MUC12
MUC12
MUC16

MYH11
MYO7A
NEUROG2
NISCH
OPTC
OR6B1
PAPPA
PARVA
PDZD2
PLCZ1
POLE2
PRDM2
PRKCB
PROM1
PTPRF
RAD50
RASD2
ROS1
SESTD1
SF3A2
SH3RF3
SH3RF3
SLC4A2
SRGAP1
STAT3
TBCK
TCF20
TP53
TTN
VN1R2
XKR5
ZBTB17
ZMYND8
ZNF560
ZNF793
AGGF1
C12orf42
GYPB

CD209
DIS3
GCNT1
HIVEP1
IFIH1
IGF1R
RHPN2
SPTB
WDR72
ZMIZ2

ACADSB
AIM1
CBLB
CCDC121
CIRH1A
DMC1
FAM47C
FCGBP
FTH1
GFRA2
ITGA2
KIAA1109
KIF18A
KRTAP5-1
NBPF10
PSG8
RICTOR
RYR2
SORBS2
TRIM8
TRPC5
UHRF1BP1L
USP32
VPS11

Neri A et al
in preparation

Genomic background in primary PCL

A Pilot Study of Lenalidomide and Dexamethasone in Primary Plasma Cell Leukemia (GIMEMA)

FISH

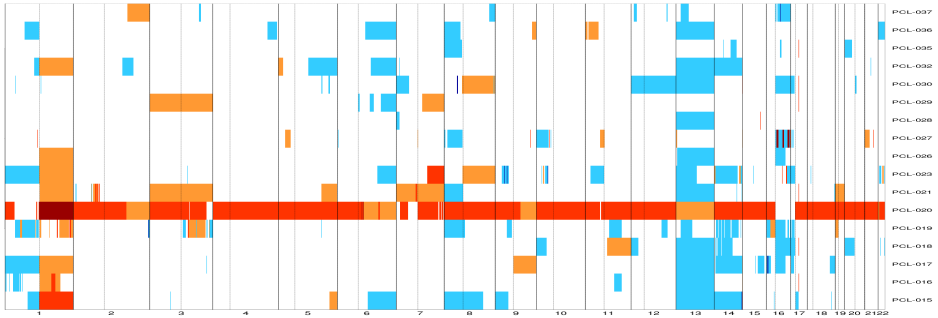
Pos/tested %	t(11;14)	t(4;14)	t(14;16)	del(13q14)	del(17p13)
Mosca AMJ, 2013	9/23 **39%**	3/23 **13%**	7/23 **30%**	17/23 **74%**	8/23 **35%**
Royer JCO, 2016	16/32 50%	2/32 6%	5/32 16%	19/32 59%	9/32 28%

Bortezomib, Doxorubicin, Cyclophosphamide, Dexamethasone Induction Followed by Stem Cell Transplantation for Primary Plasma Cell Leukemia: A Prospective Phase II Study of the Intergroupe Francophone du Myélome

J Clin Oncol 34:2125-2132. © 2016 by American Society of Clinical Oncology

Musto et al. , *Leukemia* 2014
Mosca et al., *Am J Hematol*, 2013
Todoerti et al. , *Clin Cancer Res*, 2013
Lionetti et al. , *Clin Cancer Res*, 2013

absence of hyperdiploid pattern in PPCL



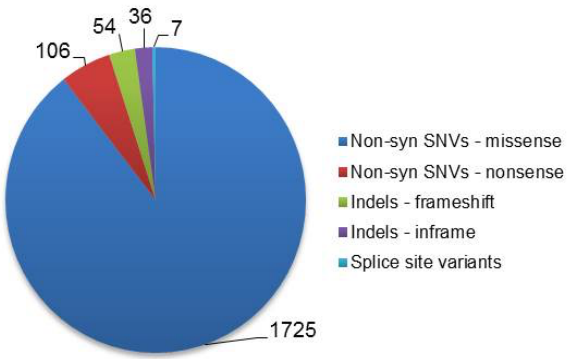
Major genetic lesions do not evidence significant impact in the clinical outcome of PPCL patients enrolled in two recent prospective trials

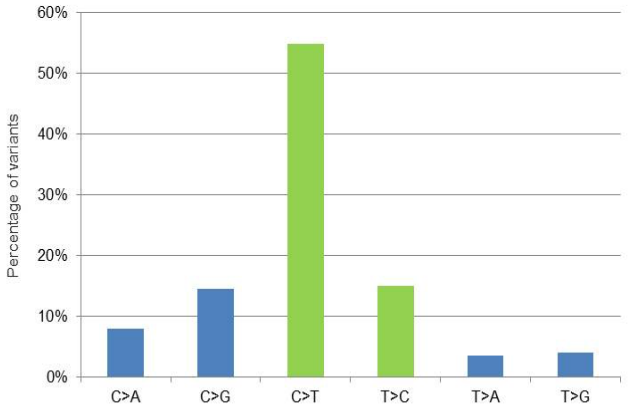
Best outcome observed in transplanted patients

Whole-exome sequencing of primary plasma cell leukemia discloses heterogeneous mutational patterns

CIFOLA et al. Oncotarget, 2015

A

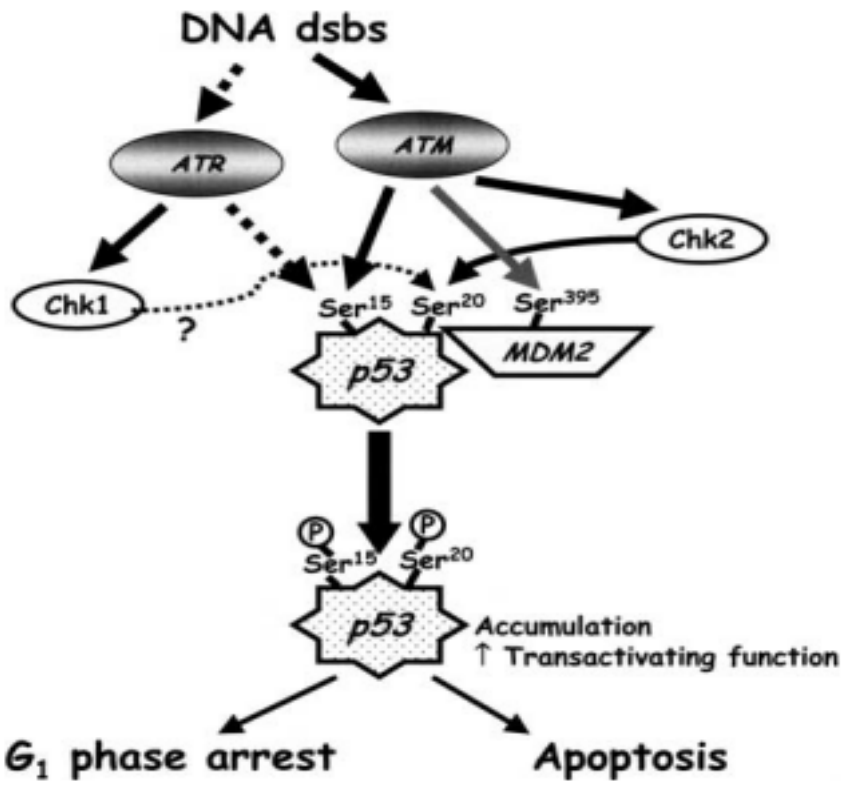




Mutated pathways significantly enriched in mutated genes in pPCL suggest a role in leukemic dissemination

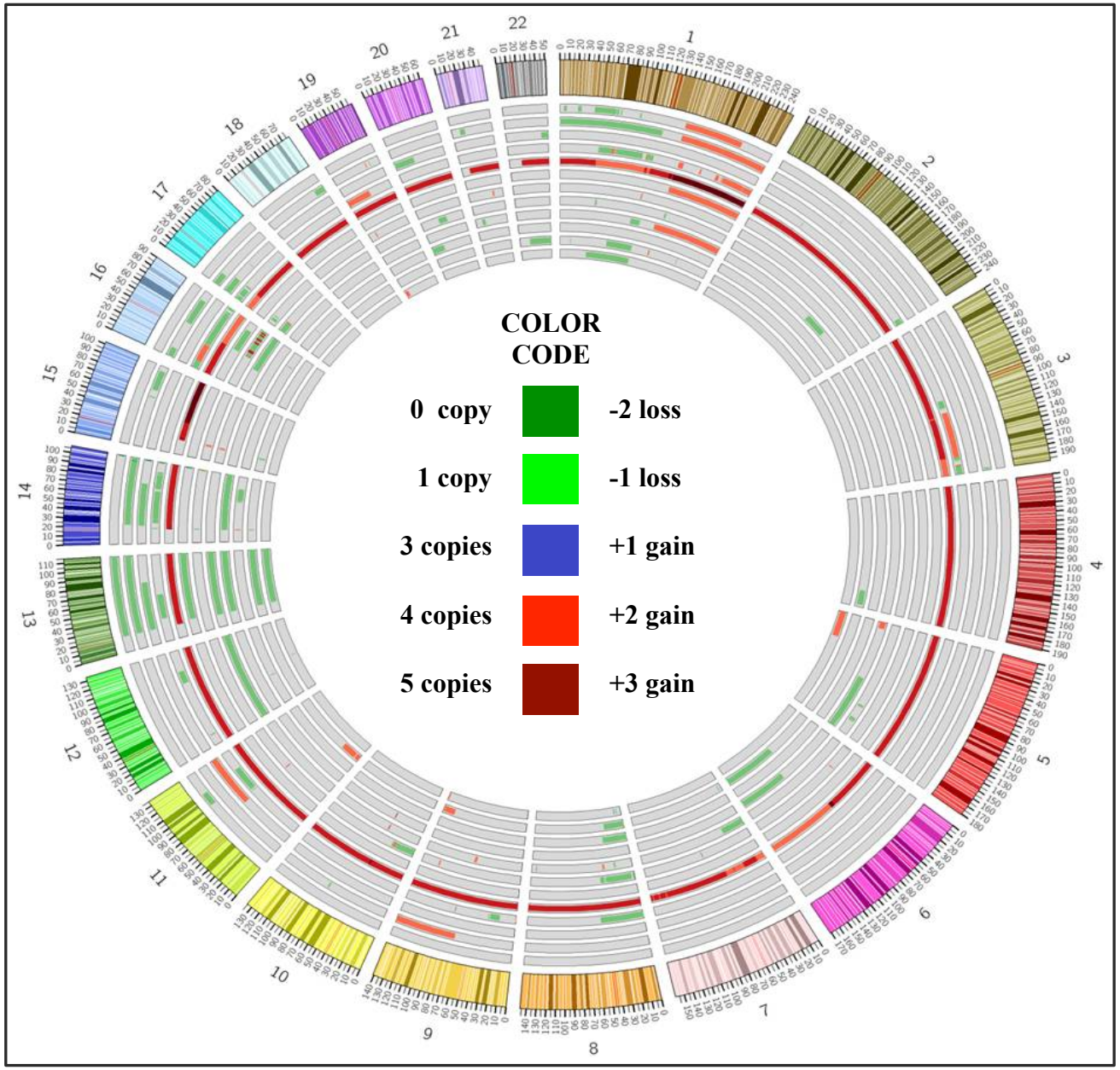
Pathway	*Source*	*p-value*	*Bonferroni q-value*	*No. Damaging/ Total variants*	*Genes*
Cadherin signaling pathway	PantherDB (ID P00012)	1.91E-07	4.69E-04	24/48	PCDH15$^{\Delta}$, FZD6, PCDH7$^{\Delta}$, PCDH20$^{\Delta}$, CDH20$^{\Delta}$, DCHS1$^{\Delta}$, CDH17$^{\Delta}$, CDH4$^{\Delta}$, CDH9$^{\Delta}$, CDH23$^{\Delta}$, CTNNA2, PCDHGB1$^{\Delta}$, PCDHGC5$^{\Delta}$, PCDHGC4$^{\Delta}$, PCDHGA2$^{\Delta}$, PCDHGA1$^{\Delta}$, PCDHA7$^{\Delta}$, PCDHA13$^{\Delta}$, PCDHAC1$^{\Delta}$, PCDHB2$^{\Delta}$, PCDHB3$^{\Delta}$, PCDHB7$^{\Delta}$, PCDHB8$^{\Delta}$, PCDHA2$^{\Delta}$, PCDHA1$^{\Delta}$, PCDHA3$^{\Delta}$, CELSR3$^{\Delta}$, FAT1$^{\Delta}$, FAT2$^{\Delta}$, FER, FZD10, CDHR2$^{\Delta}$, FAT3$^{\Delta}$, YES1, PCDH11X$^{\Delta}$
ECM-receptor interaction	BioSystems: KEGG (ID 83068)	2.66E-06	6.55E-03	9/26	CD36, SV2B, COL1A2°, COL1A1°, COL5A1°, COL6A3°, COL4A2°, DAG1°, COL6A6°, RELN°, TNN°, FN1°, THBS3, TNXB°, HMMR, HSPG2°, ITGA1, LAMB1°, LAMA4°, LAMA5°, LAMA2°, LAMA3°
Cell Cycle G2/M Checkpoint	MSigDB C2: BioCarta (ID M8560)	1.45E-05	3.58E-02	13/20 (*)	ATM, ATR, BRCA1, CDC25A, CDKN1A, PRKDC, EP300, CHEK2, RPS6KA1, TP53
Wnt signaling pathway	PantherDB (ID P00057)	1.60E-05	3.95E-02	36/66 (*)	MYH13, PCDH15$^{\Delta}$, FZD6, PCDH7$^{\Delta}$, MYH7, PCDH20$^{\Delta}$, CDH20$^{\Delta}$, DCHS1$^{\Delta}$, CDH17$^{\Delta}$, CDH4$^{\Delta}$, CDH9$^{\Delta}$, CDH23$^{\Delta}$, PRKCZ, PPP2R5E, PPP3R2, CREBBP, CTNNA2, PLCB4, PCDHGB1$^{\Delta}$, PCDHGC5$^{\Delta}$, PCDHGC4$^{\Delta}$, PCDHGA2$^{\Delta}$, PCDHGA1$^{\Delta}$, DVL3, PCDHA7$^{\Delta}$, PCDHA13$^{\Delta}$, PCDHAC1$^{\Delta}$, PCDHB2$^{\Delta}$, PCDHB3$^{\Delta}$, PCDHB7$^{\Delta}$, PCDHB8$^{\Delta}$, PCDHA2$^{\Delta}$, PCDHA1$^{\Delta}$, PCDHA3$^{\Delta}$, EP300, CELSR3$^{\Delta}$, FAT1$^{\Delta}$, FAT2$^{\Delta}$, SRCAP, FZD10, INO80, TP53, CDHR2$^{\Delta}$, FAT3$^{\Delta}$, PCDH11X$^{\Delta}$, KREMEN1, ITPR2, MYH14, PLCB1
Extracellular matrix organization	BioSystems: REACTOME (ID 576262)	1.71E-05	4.21E-02	22/51	ACTN1, ACAN°, COL6A5°, DDR2, LTBP4°, ADAMTS9°, COL1A2°, COL1A1°, COL15A1°, COL17A1°, COL9A3°, PDGFB, COL9A1°, COL5A1°, COL6A3°, COL4A2°, PLEC, VCAN°, DAG1°, ADAMTS16°, ADAMTS18°, COL6A6°, BCAN°, PSEN1, DSPP°, TNN°, PTPRS, FBN2°, FGA, FN1°, ADAMTS5°, TNXB°, ADAM18, LEPREL1°, HSPG2°, ICAM4, ITGA1, LOXL4, LAMB1°, LAMA4°, LAMA5°, LAMA2°, LAMA3°, FBN3°

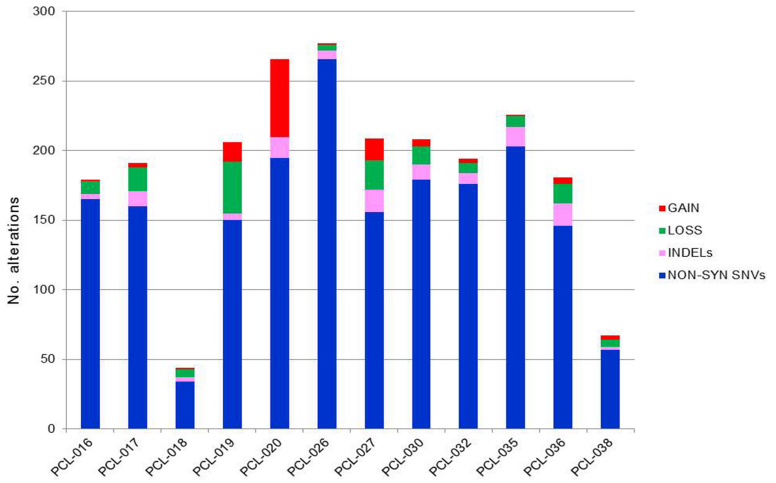
Mutations of DNA repair and cell cycle check-point genes in primary Plasma Cell Leukemia 9/12 (75%)



PCL-017	PCL-018	PCL-019	PCL-020	PCL-026	PCL-027	PCL-030	PCL-032	PCL-035
ATM	TP53	ATR	ATM	ATM	CDKN1A	ATM	BRCA1	ATR
TP53		BRCA1	ATR	EP300	RPS6KA1	CDC25A		CDKN1A
					TP53	CDKN1A		
						CHEK2		
						PRKDC		
						TP53		

Copy Number Alterations in pPCLs: *a WES based approach*



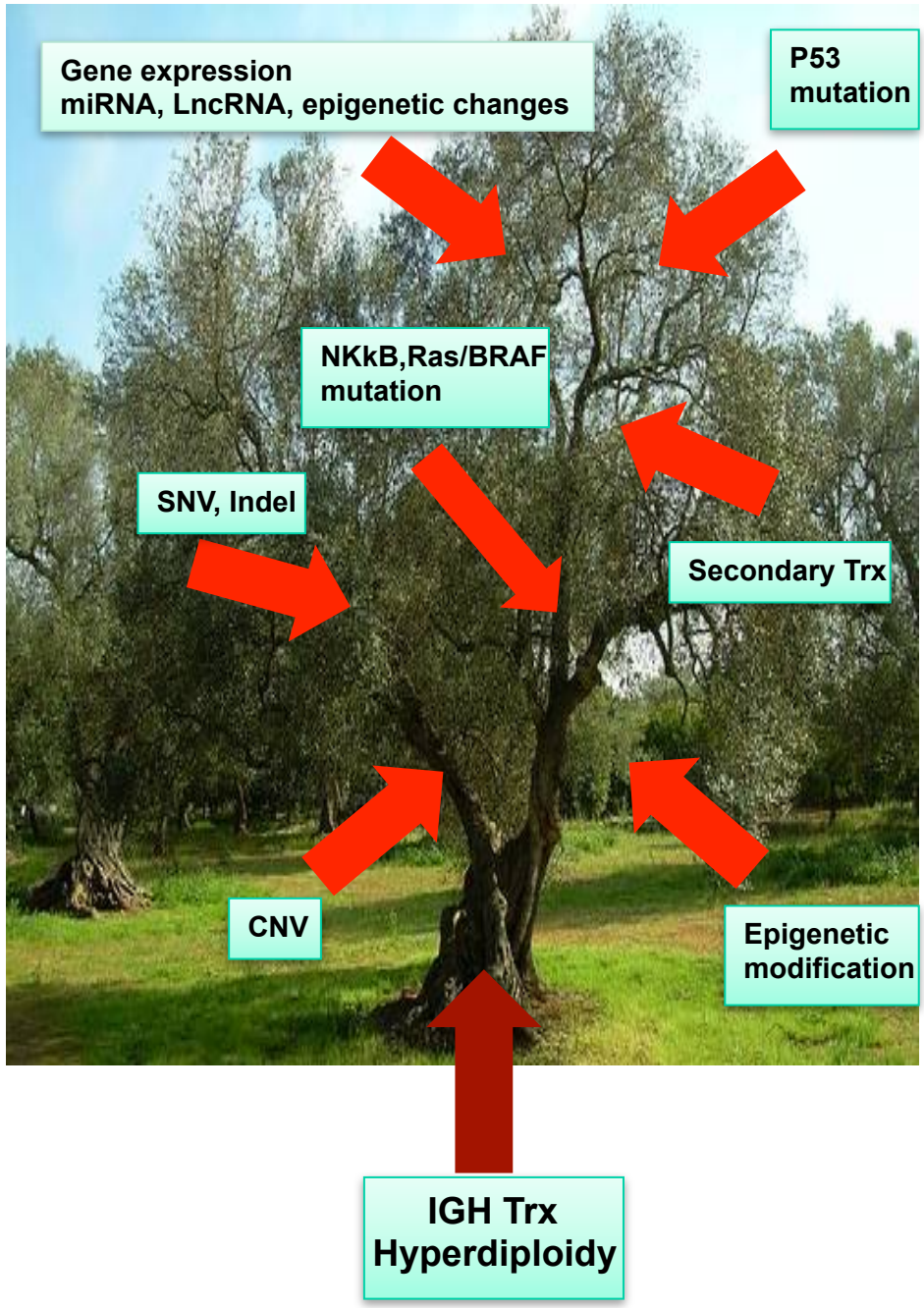


Most frequently biallelically affected genes

Gene	Cytoband	Affected samples			
TP53	17p13.1	PCL-017	PCL-018	PCL-027	PCL-030
DIS3	13q22.1	PCL-019	PCL-036		
MUC4	3q29	PCL-017	PCL-019		
BIRC2	11q22	PCL-019	PCL-016		
TRAF3	14q32.32	PCL-017	PCL-032		

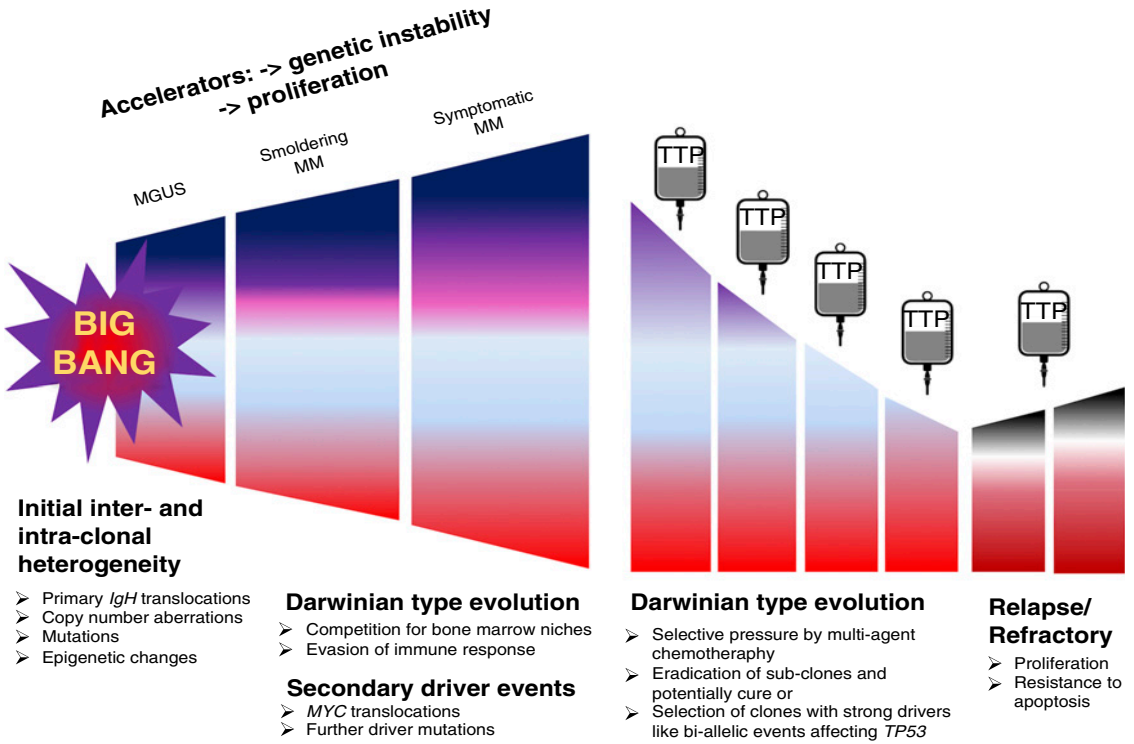
- mutation + deletion
- biallelic deletion

CIFOLA et al. Oncotarget, 2015



Genetic complexity, intraclonal diversity and clonal evolution in Myeloma

Maximise use of current drugs



Adapted from Weinhold et al. BLOOD vol 128, sept, 2016, pag 1735

Acknowledgments

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Sonia Fabris
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