

Building a World Class Myeloma Program

Professor Chng Wee Joo

Provost's Chair Professor

Yong Loo Lin School of Medicine, National University of Singapore (NUS)

Director

National University Cancer Institute of Singapore (NCIS), National University Health System (NUHS)

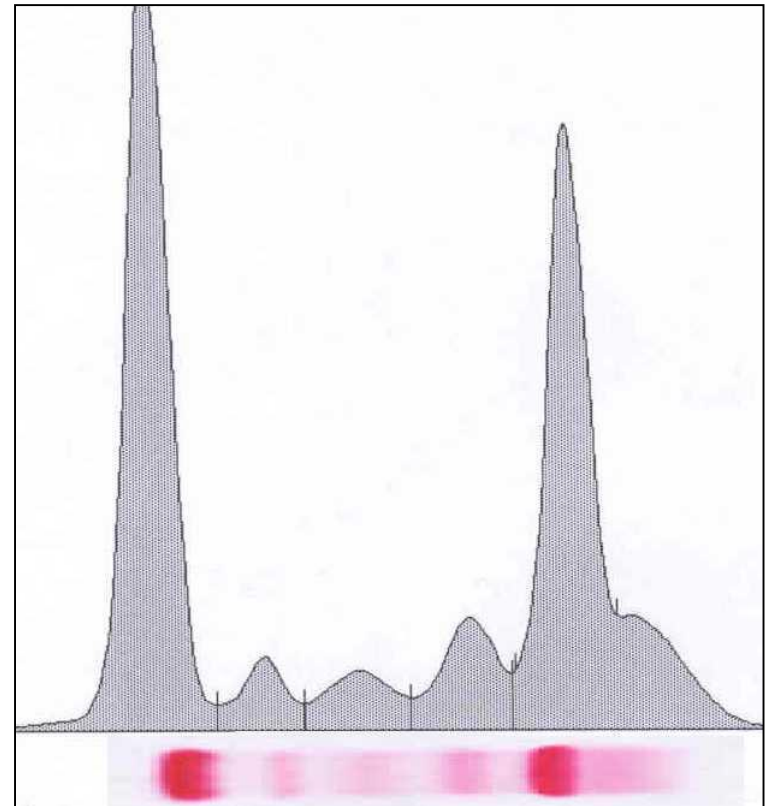
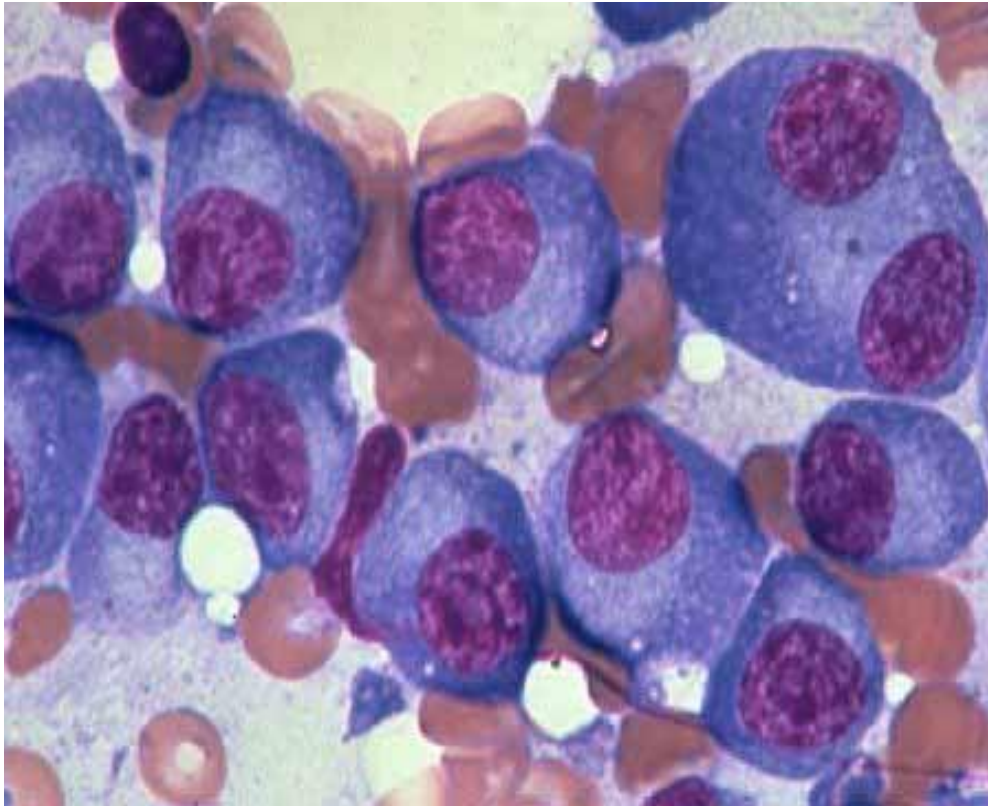
Deputy Director

Cancer Science Institute, Singapore (CSI), National University of Singapore (NUS)

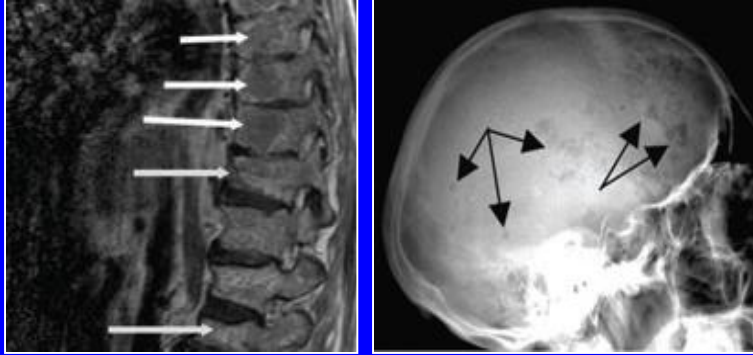
Apr 2018



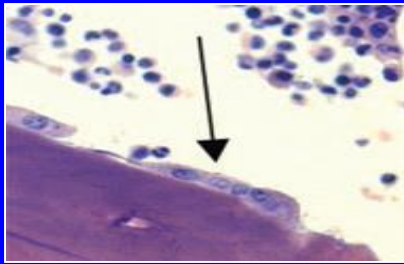
Multiple Myeloma



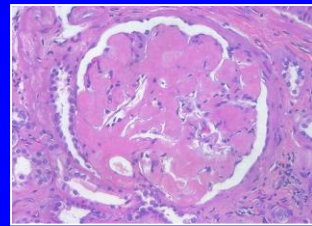
- Neoplastic clonal proliferation of plasma cells
- Production of paraprotein (monoclonal Ig)
- Normal production of Ig impaired (immuneparesis)



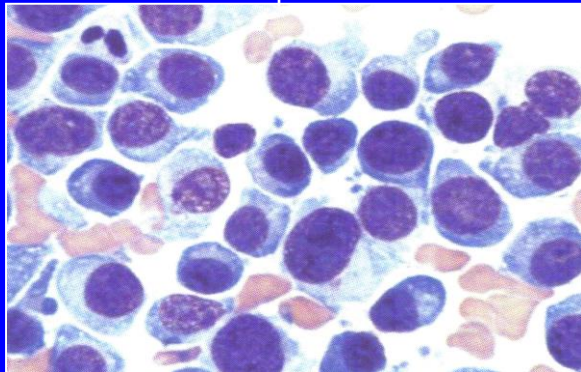
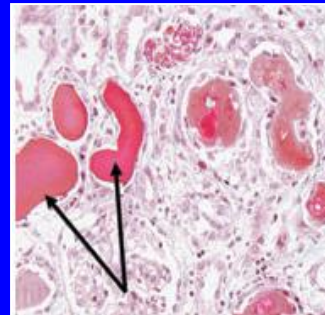
Osteolytic lesions, fractures



Bone Resorption



Deposition of Ig in kidney



Marrow infiltration

Hypercalcemia

Renal impairment

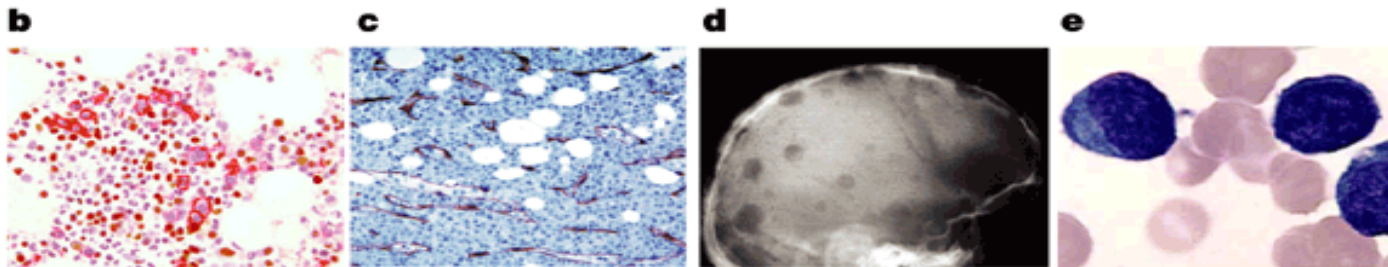
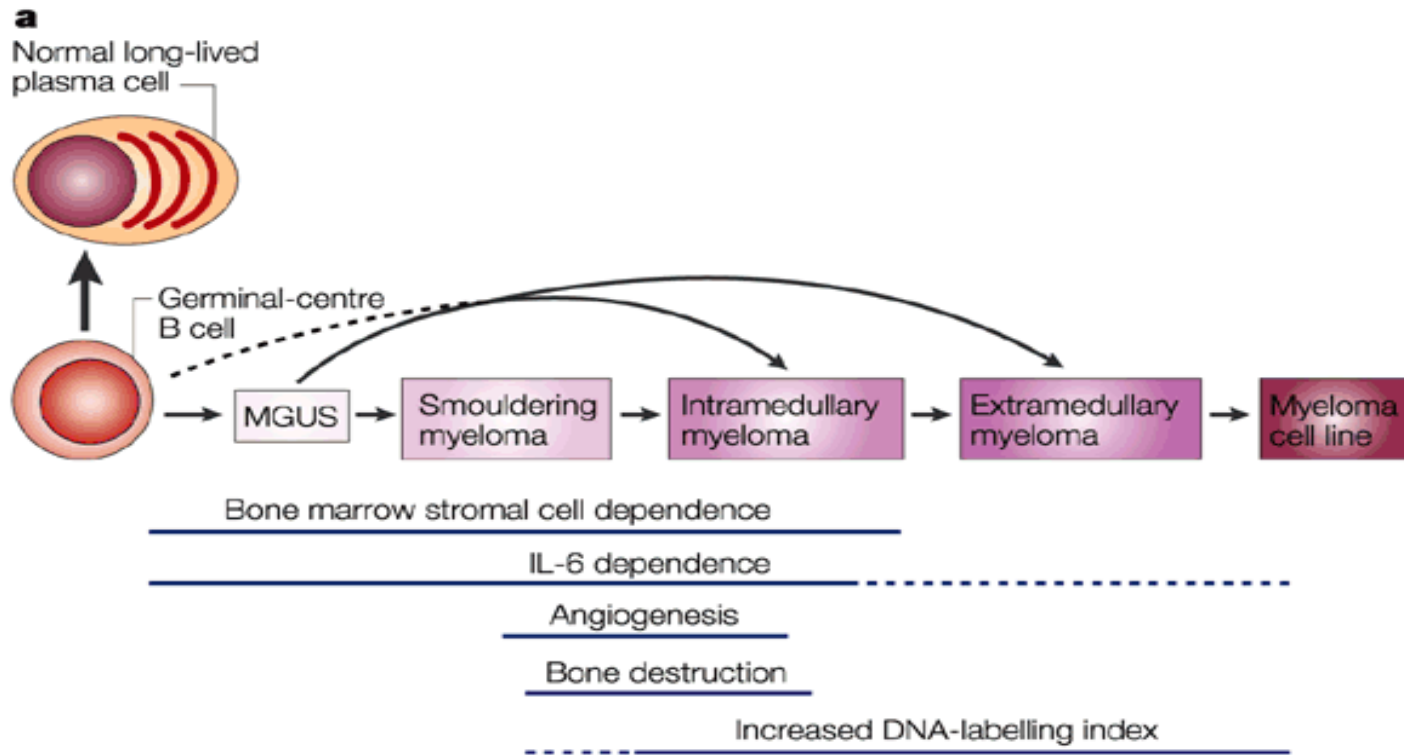
Anaemia

Hyperviscosity syndr

Recurrent infection

Anaemia

Multiple Myeloma - A model Cancer



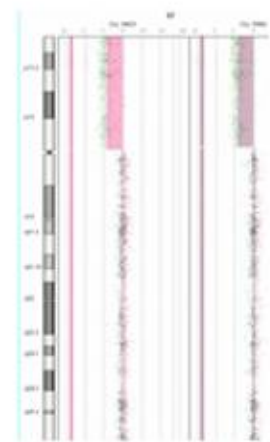
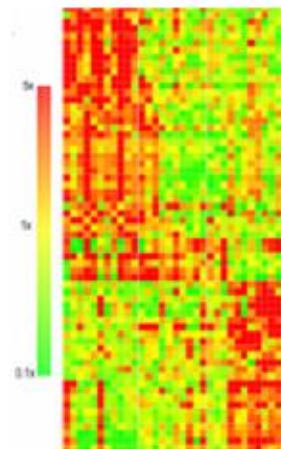
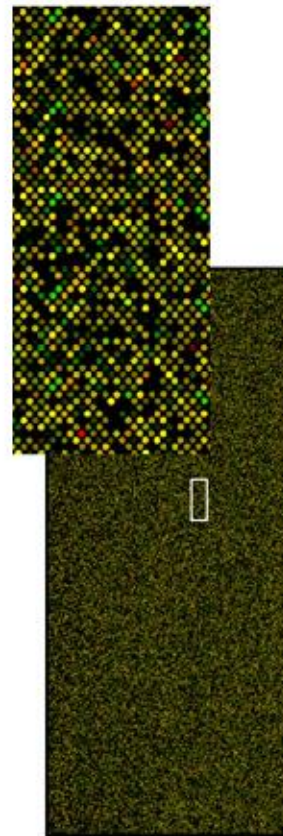
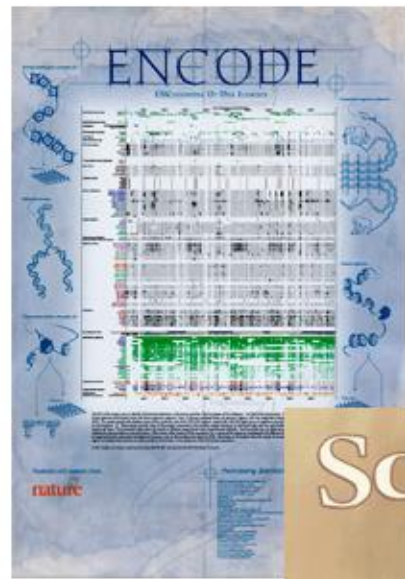
State of Art in 2004

- Median Survival of 3-4 years
- Limited treatment options
 - Stem cell transplant (high dose melphalan)
 - Steroids
 - Thalidomide just starting
 - First reports of Velcade presented with huge fanfare at American Society of Hematology Meeting
- FISH
- Microarray technologies emerging

Funding #1: A*Star International Fellowship



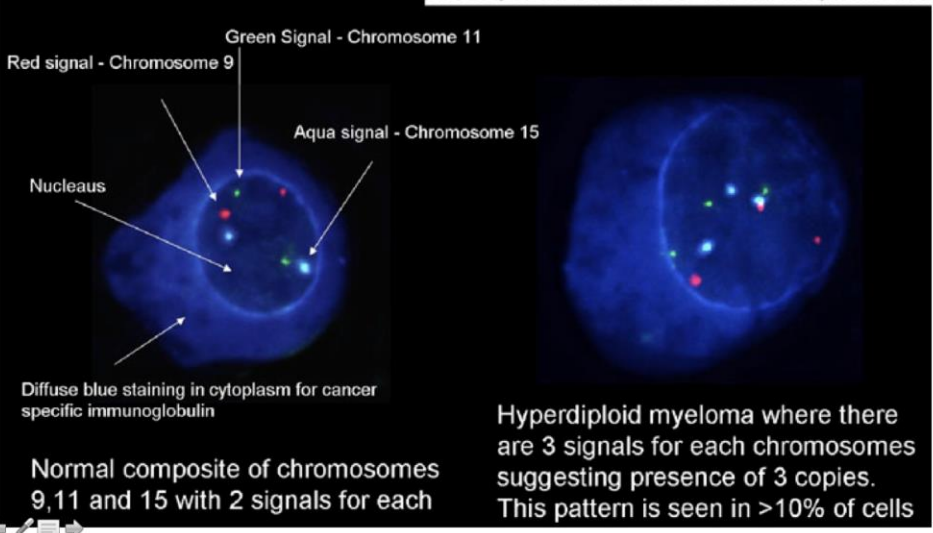
Genomics on a Global Scale



A validated FISH trisomy index demonstrates the hyperdiploid and nonhyperdiploid dichotomy in MGUS

Wee Joo Chng, Scott A. Van Wier, Gregory J. Ahmann, Jerry M. Winkler, Syed M. Jalal, Peter Leif Bergsagel, Marta Chesi, Mike C. Trendle, Martin M. Oken, Emily Blood, Kim Henderson, Rafael Santana-Dávila, Robert A. Kyle, Morie A. Gertz, Martha Q. Lacy, Angela Dispenzieri, Philip R. Greipp, and Rafael Fonseca

BLOOD, 15 SEPTEMBER 2005 • VOLUME 106, NUMBER 6

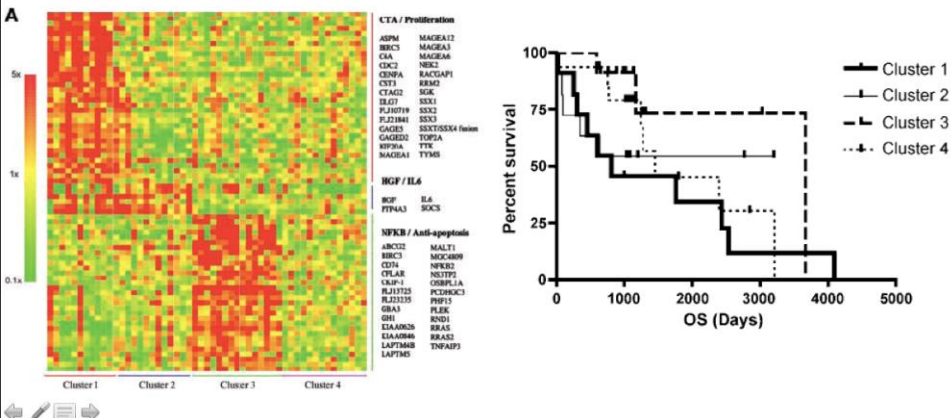


Research Article

Molecular Dissection of Hyperdiploid Multiple Myeloma by Gene Expression Profiling

Wee J. Chng,¹ Shaji Kumar,² Scott VanWier,¹ Greg Ahmann,¹ Tammy Price-Troska,² Kim Henderson,² Tae-Hoon Chung,² Seungchan Kim,^{3,4} George Mulligan,⁵ Barbara Bryant,⁵ John Carpten,³ Morie Gertz,² S. Vincent Rajkumar,² Martha Lacy,² Angela Dispenzieri,² Robert Kyle,² Philip Greipp,² P. Leif Bergsagel,¹ and Rafael Fonseca²

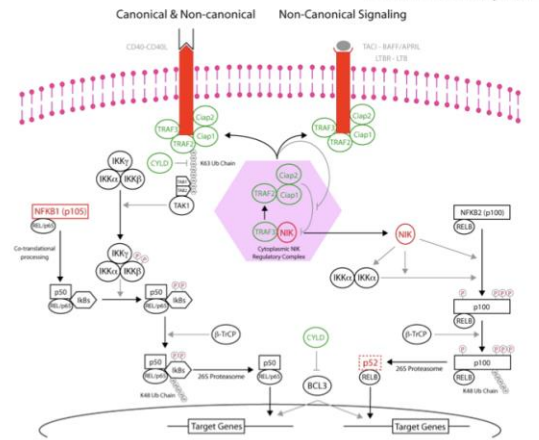
Cancer Res 2007;67(7):2982-9



Promiscuous Mutations Activate the Noncanonical NF-κB Pathway in Multiple Myeloma

Jonathan J. Keats,^{1,7} Rafael Fonseca,^{1,7,*} Marta Chesi,¹ Roelandt Schop,¹ Angela Baker,³ Wee-Joo Chng,¹ Scott Van Wier,¹ Rodger Tiedemann,¹ Chang-Xin Shi,¹ Michael Sebag,¹ Esteban Braggio,¹ Travis Henry,¹ Yuan-Xiao Zhu,¹ Homer Fogle,¹ Tammy Price-Troska,² Gregory Ahmann,¹ Catherine Mancini,³ Leslie A. Brents,⁶ Shaji Kumar,² Philip Greipp,² Angela Dispenzieri,² Barb Bryant,⁵ George Mulligan,⁵ Laurakay Bruhn,⁴ Michael Barrett,³ Riccardo Valdez,¹ Jeff Trent,³ A. Keith Stewart,¹ John Carpten,³ and P. Leif Bergsagel¹

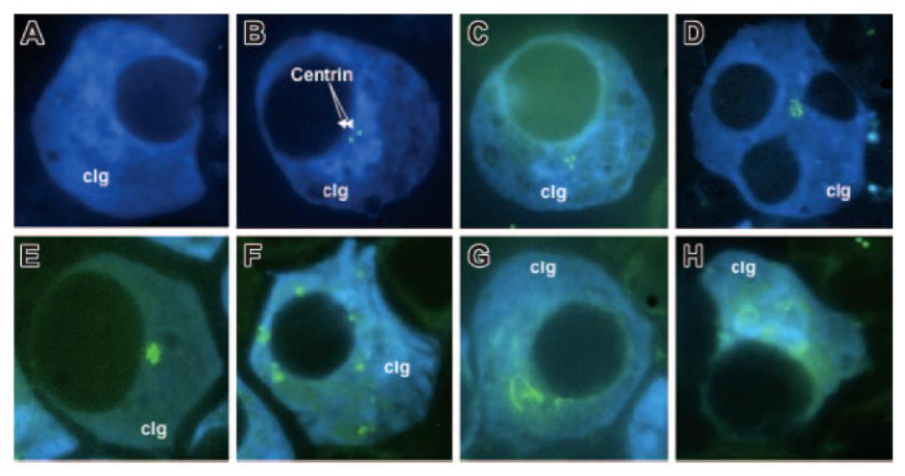
Cancer Cell 12, 131-144, August 2007



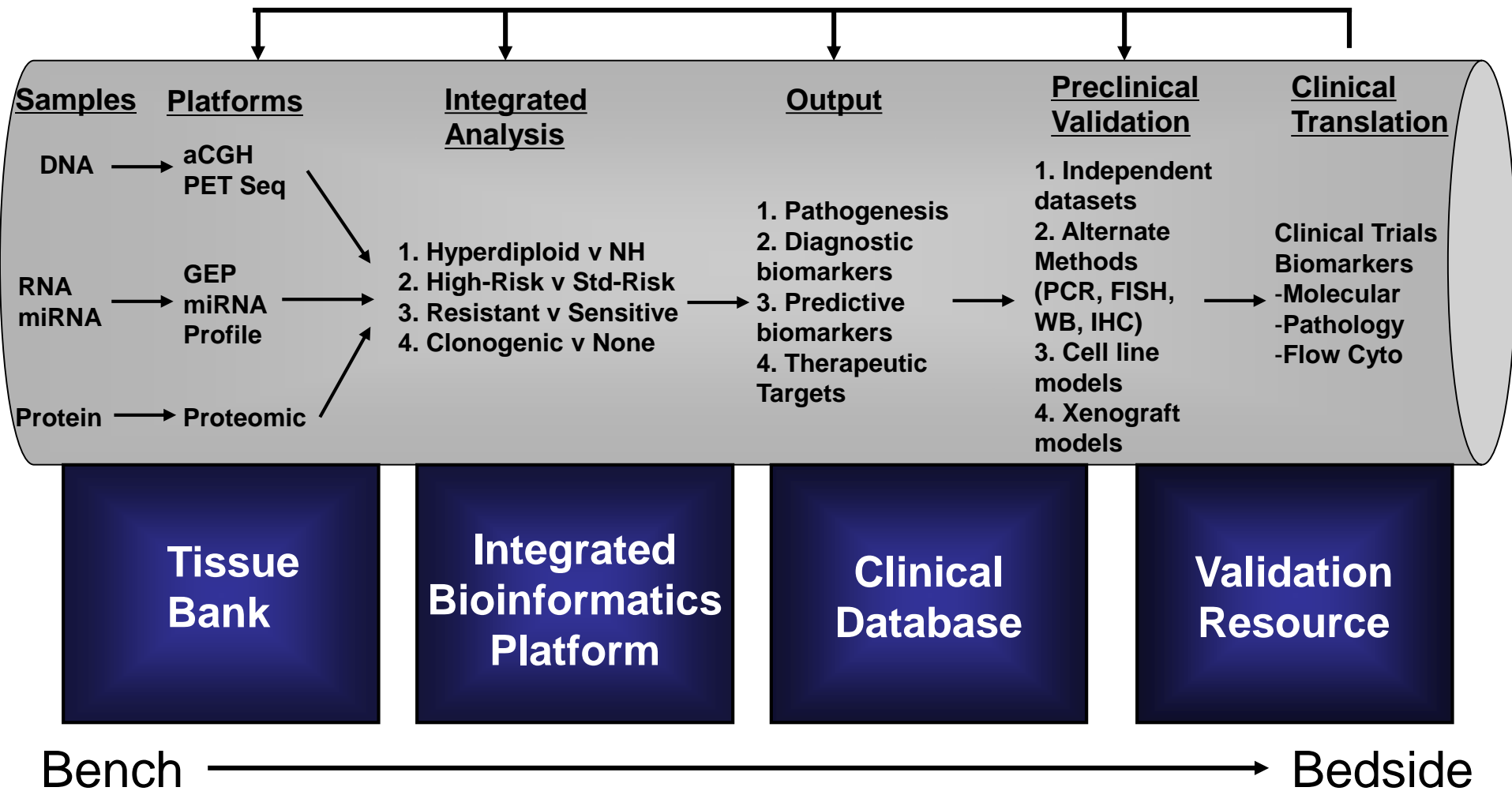
Clinical implication of centrosome amplification in plasma cell neoplasm

Wee J. Chng, Greg J. Ahmann, Kim Henderson, Rafael Santana-Davila, Philip R. Greipp, Morie A. Gertz, Martha Q. Lacy, Angela Dispenzieri, Shaji Kumar, S. Vincent Rajkumar, John A. Lust, Robert A. Kyle, Steven R. Zeldenzust, Suzanne R. Hayman, and Rafael Fonseca

BLOOD, 1 MAY 2006 • VOLUME 107, NUMBER 9



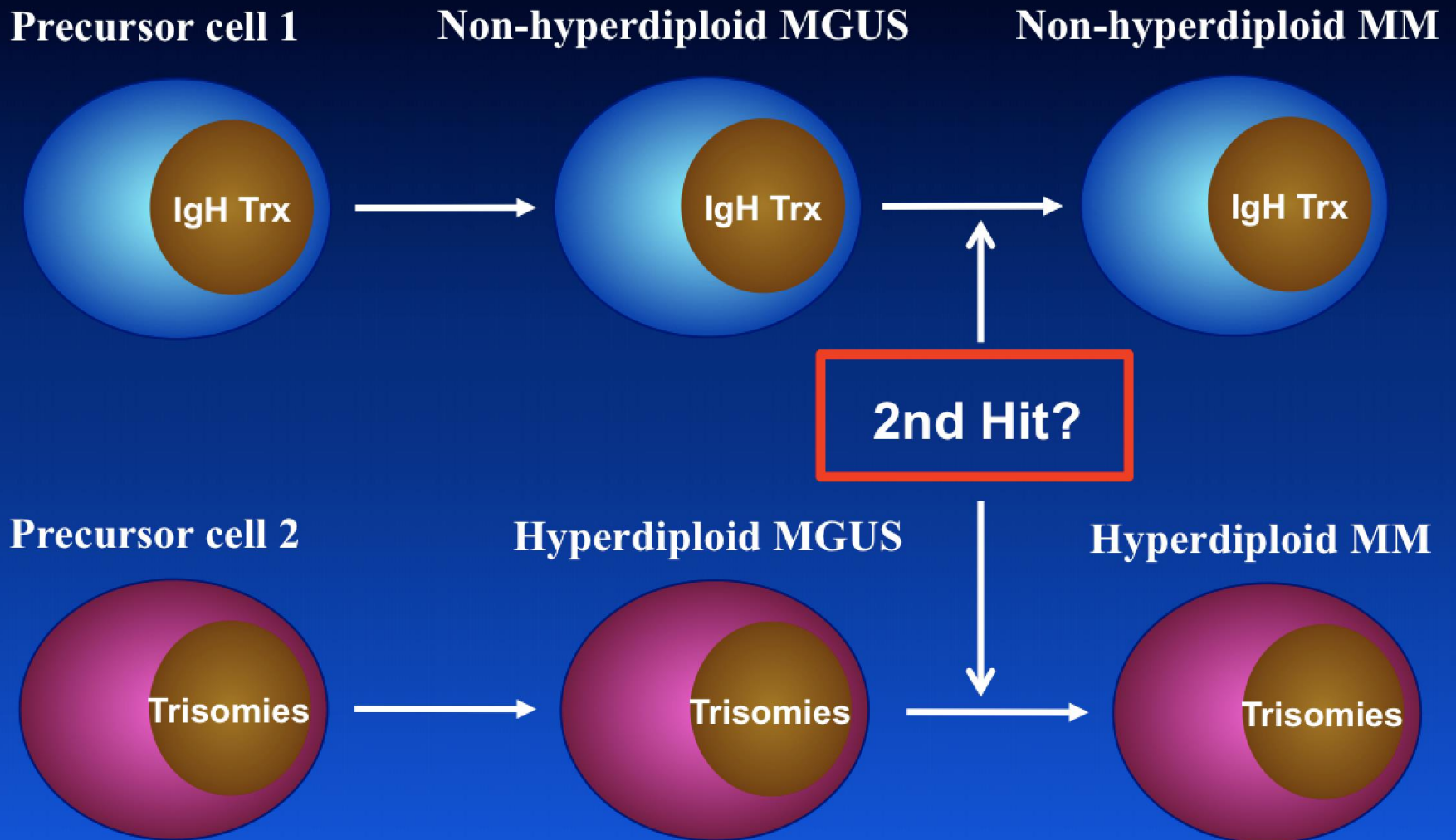
Funding #2: Singapore Cancer Syndicate – Development of Comprehensive Cancer Gene Repository in Multiple Myeloma (2007 – 3 years)



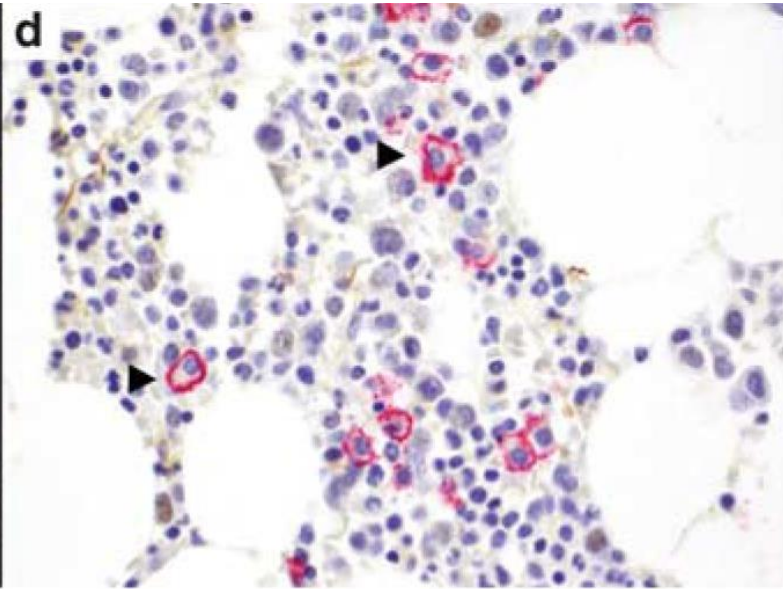
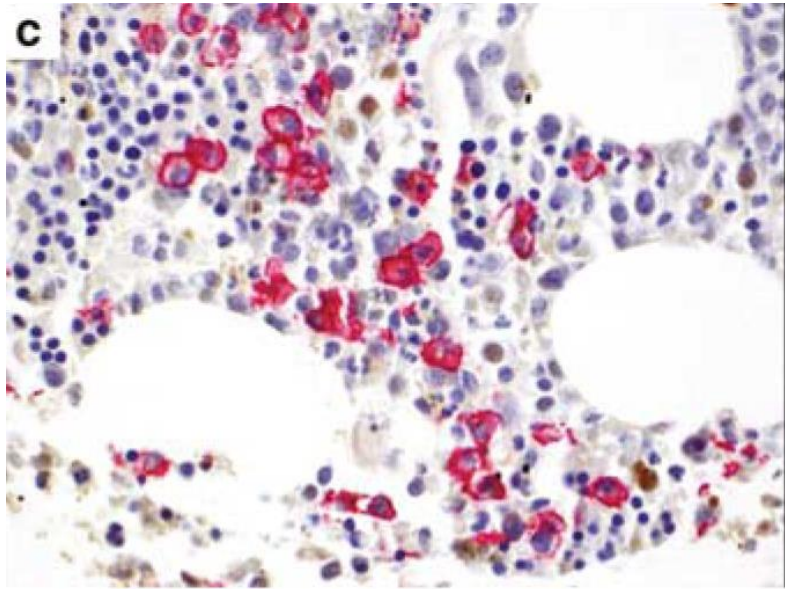
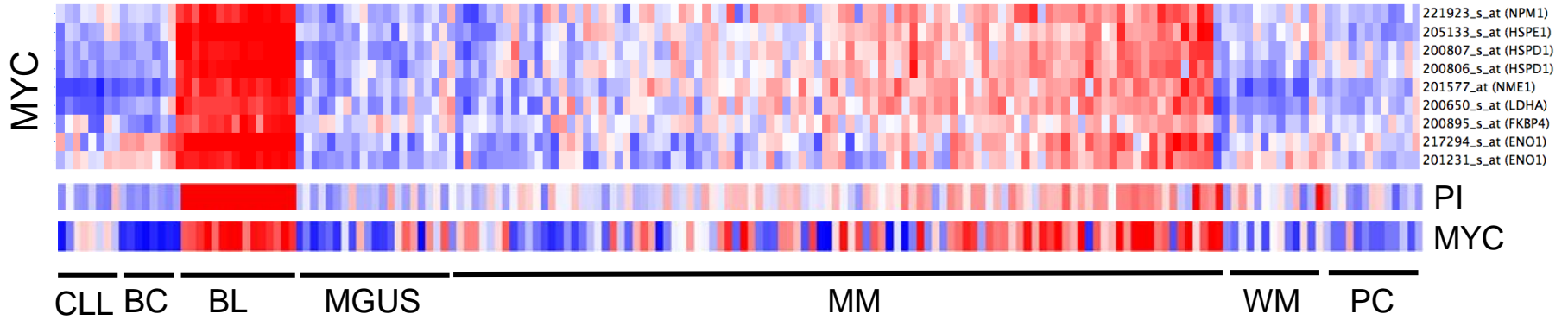
Building the Infrastructure (since 2009)

- Clinical Database (Data since 2000) – 9 Publications
- Cell bank (>500 patients) – 13 Publications
- Bioinformatics Framework – 7 publications

Funding #3: NMRC CSA Inv (junior) – Using unbiased forward genetic screen and comparative genomics in mice to model progression and transformation of multiple myeloma (2008 - 3 yrs)



Exp of MYC signature and protein in MM



Funding #4: NMRC CSA Inv (Senior) – Genomic-based diagnosis, Classification & Targeted Treatment of Multiple Myeloma (2012 – 5 yrs)

Establishing an International Presence
Making an Impact for Patients

Prognostic Signatures

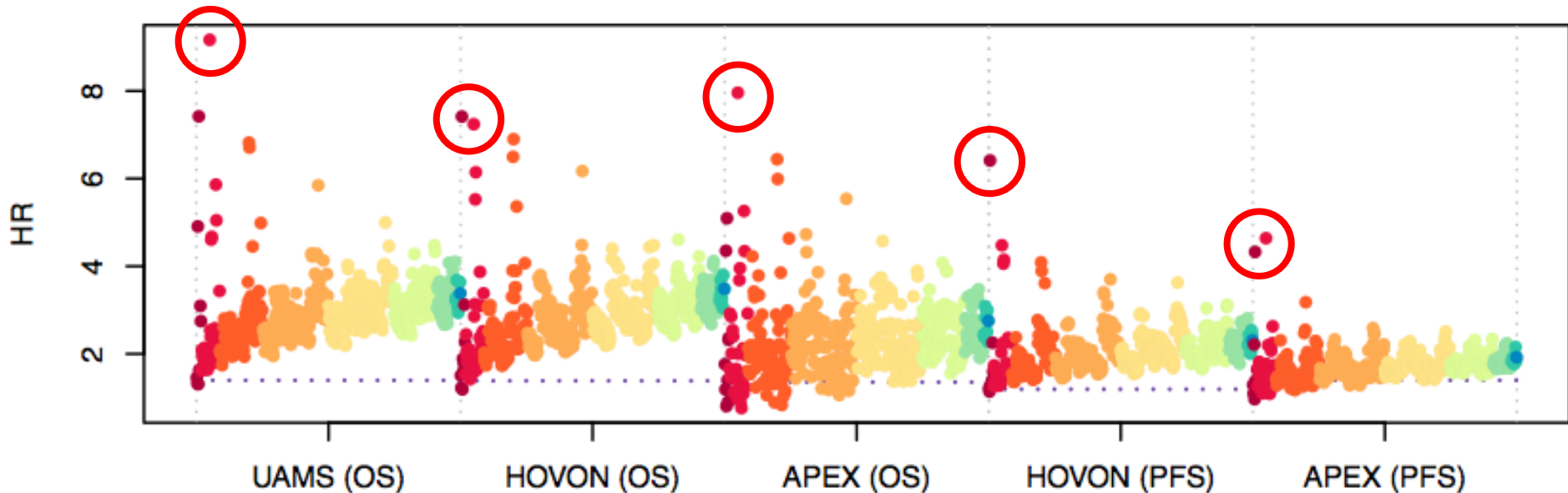
- UAMS 70-gene signature (Shaughnessy JD et al. *Blood* 2007; 109: 2276-2284)
- IFM signature (Decaux O et al. *J Clin Oncol* 2008; 26: 4798-805)
- **Centrosome Index** (Chng WJ et al. *Blood* 2006; 107: 3669-3675; Chng WJ et al. *Blood* 2008; 111: 1603-1609)
- IL6-HMCL signature (Moreaux J et al. *Haematologica* 2011; 96: 574-82)
- HZD Cell Death signature (Dickens NJ et al. *Clin Cancer Res* 2010; 16: 1856-64)
- **CINGEC signature** (Chung TH et al. *PLoS ONE* 2013; 8: e66361)

ORIGINAL ARTICLE

Gene signature combinations improve prognostic stratification of multiple myeloma patients

WJ Chng^{1,10}, T-H Chung^{2,10}, S Kumar³, S Usmani⁴, N Munshi⁵, H Avet-Loiseau⁶, H Goldschmidt⁷, B Durie⁸ and P Sonneveld⁹ on behalf of the International Myeloma Working Group¹¹

Combination of Signature



	Data	Combination	HR	CI:low	CI:high	P
OS	UAMS	EMC92:HZDCD	9.17	4.58	18.34	3.79E-10
		HZDCD	7.42	3.33	16.55	9.77E-07
		EMC92:HZDCD:UAMS70	6.82	4.14	11.24	4.67E-14
		EMC92:HZDCD:UAMS80	6.71	3.74	12.02	1.59E-10
		HZDCD:UAMS70	5.86	3.71	9.28	4.11E-14
		EMC92:HZDCD:UAMS70:UAMS80	5.85	3.61	9.46	6.71E-13
		HZDCD:UAMS80	5.05	2.86	8.90	2.19E-08
		EMC92:HMCL7:HZDCD:UAMS70:UAMS80	5.00	3.20	7.82	1.81E-12
		HZDCD:UAMS70:UAMS80	4.99	3.17	7.83	3.10E-12
	EMC92	4.91	2.88	8.37	5.12E-09	
	HOVON	EMC92	7.42	4.88	11.27	0
		EMC92:HZDCD	7.24	4.27	12.30	2.30E-13
		EMC92:HZDCD:UAMS80	6.90	4.12	11.57	2.30E-13
		EMC92:HZDCD:UAMS70	6.50	4.17	10.12	1.11E-16
		EMC92:HZDCD:UAMS70:UAMS80	6.17	3.92	9.72	4.00E-15
		EMC92:UAMS80	6.14	3.91	9.66	3.55E-15
		EMC92:UAMS70	5.53	3.83	7.98	0
		EMC92:UAMS70:UAMS80	5.36	3.59	8.02	2.22E-16
		CINGECS: EMC92:HMCL7:HZDCD:UAMS70:UAMS80	4.61	3.17	6.69	9.99E-16
	EMC92:HZDCD:PI:UAMS80	4.48	2.99	6.72	3.78E-13	
	APEX	EMC92:HZDCD	7.96	3.98	15.91	4.39E-09
		EMC92:HZDCD:UAMS70	6.44	3.83	10.83	2.08E-12
		EMC92:HZDCD:UAMS80	5.99	3.60	9.97	5.76E-12
		EMC92:HZDCD:UAMS70:UAMS80	5.54	3.53	8.69	9.14E-14
		HZDCD:UAMS70	5.26	3.29	8.40	3.81E-12
		HZDCD	5.10	2.57	10.09	3.02E-06
		CINGECS: EMC92:HZDCD:UAMS70	4.73	3.15	7.11	8.29E-14

IMWG consensus on risk stratification in multiple myeloma

WJ Chng^{1,2,3}, A Dispenzieri⁴, C-S Chim⁵, R Fonseca⁶, H Goldschmidt⁷, S Lentzsch⁸, N Munshi⁹, A Palumbo¹⁰, JS Miguel¹¹, P Sonneveld¹², M Cavo¹³, S Usmani¹⁴, BGM Durie¹⁵ and H Avet-Loiseau¹⁶ on behalf of the International Myeloma Working Group¹⁷

Multiple myeloma is characterized by underlying clinical and biological heterogeneity, which translates to variable response to treatment and outcome. With the recent increase in treatment armamentarium and the projected further increase in approved therapeutic agents in the coming years, the issue of having some mechanism to dissect this heterogeneity and rationally apply treatment is coming to the fore. A number of robustly validated prognostic markers have been identified and the use of these markers in stratifying patients into different risk groups has been proposed. In this consensus statement, the International Myeloma Working Group propose well-defined and easily applicable risk categories based on current available information and suggests the use of this set of prognostic factors as gold standards in all clinical trials and form the basis of subsequent development of more complex prognostic system or better prognostic factors. At the same time, these risk categories serve as a framework to rationalize the use of therapies.

Leukemia (2014) **28**, 269–277; doi:10.1038/leu.2013.247

Keywords: prognosis; treatment; biomarkers

	High-Risk	Std-Risk	Low-Risk
Parameters	ISS II/III and t(4;14) ¹ or 17p13 del	Others	ISS I/II and Absence of t(4;14), 17p13 del and +1q21 and Age <55yrs
Median OS	2 years	7 years	>10 years
% Patients	20%	60%	20%

Funding #5: NMRC STaR – Understanding and Targeting High-Risk Myeloma. (2017 – 5 yrs)

Why monoallelic loss of 17p13 is associated with poor outcome?

ORIGINAL ARTICLE

p53 haploinsufficiency and functional abnormalities in multiple myeloma

PJ Teoh^{1,2}, TH Chung², S Sebastian³, SN Choo⁴, J Yan², SB Ng^{4,5}, R Fonseca³ and WJ Chng^{1,2,6}

How does MMSET mediate its oncogenic function?

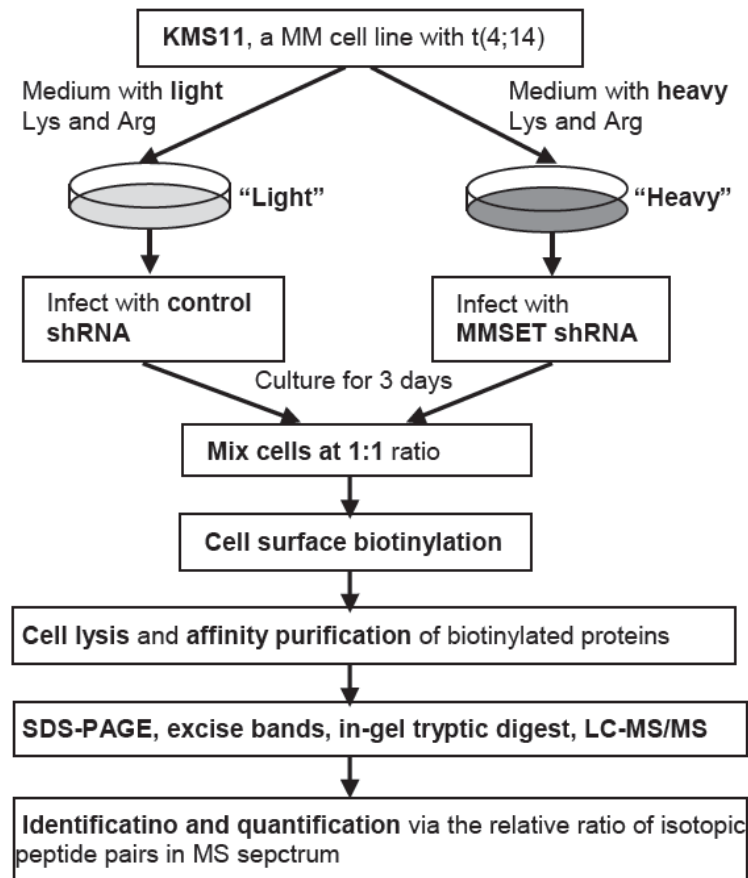
ORIGINAL ARTICLE

MMSET regulates expression of IRF4 in t(4;14) myeloma and its silencing potentiates the effect of bortezomib

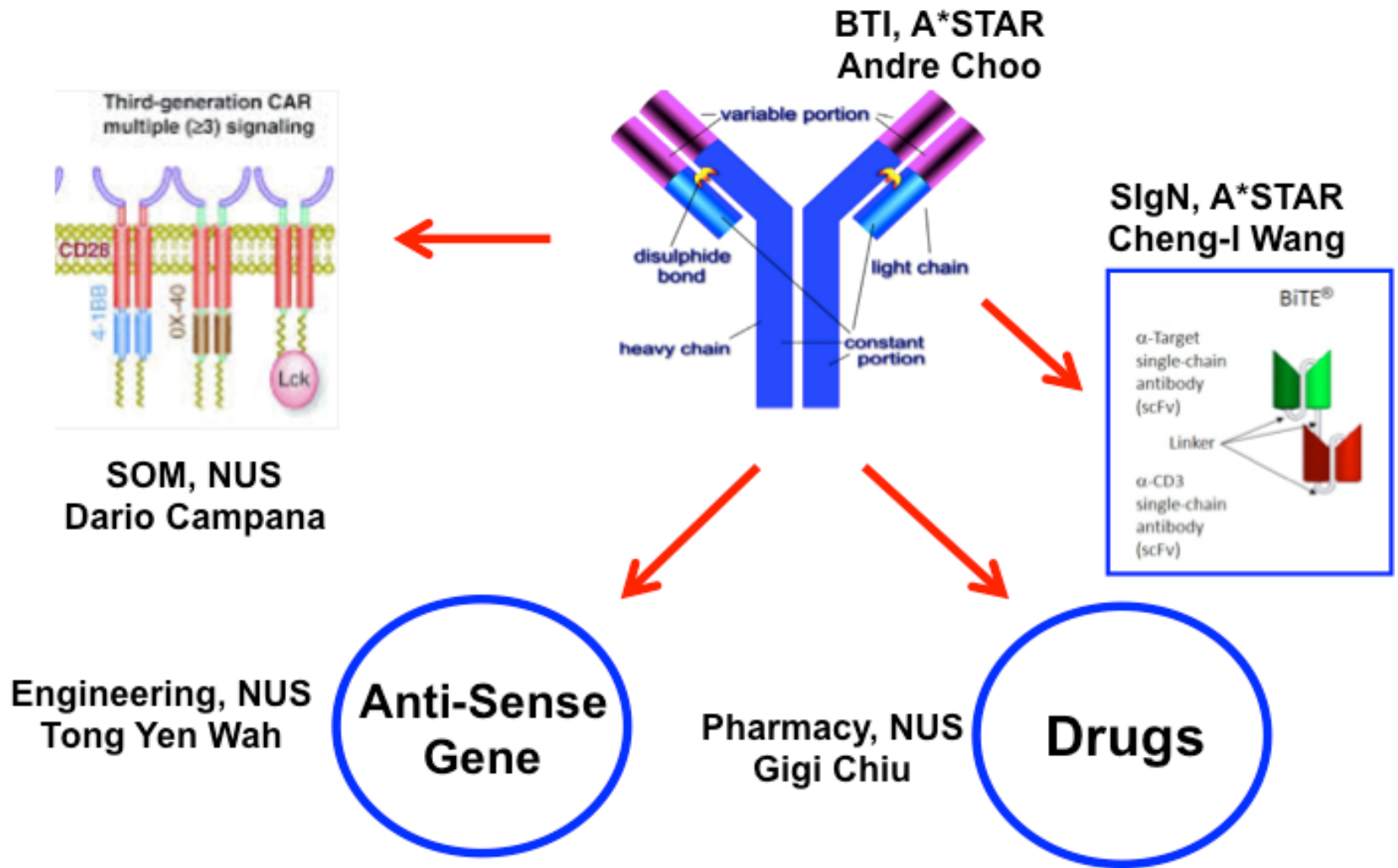
Z Xie¹, C Bi¹, JY Chooi², ZL Chan¹, N Mustafa² and WJ Chng^{1,2,3}

Plasma Membrane Proteomics Identifies Biomarkers Associated with MMSET Overexpression in T(4;14) Multiple Myeloma

Zhigang Xie¹, Jayantha Gunaratne², Lip Lee Cheong³, Shaw Cheng Liu¹, Tze Loong Koh⁴, Gaofeng Huang⁴, Walter P. Blackstock², Wee Joo Chng^{1,3,4}



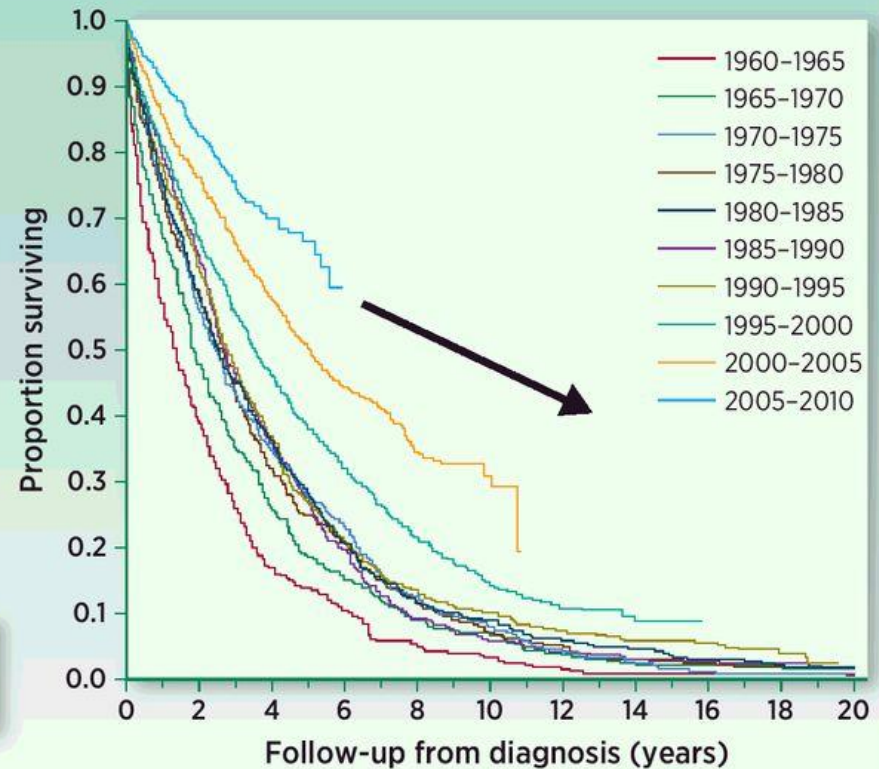
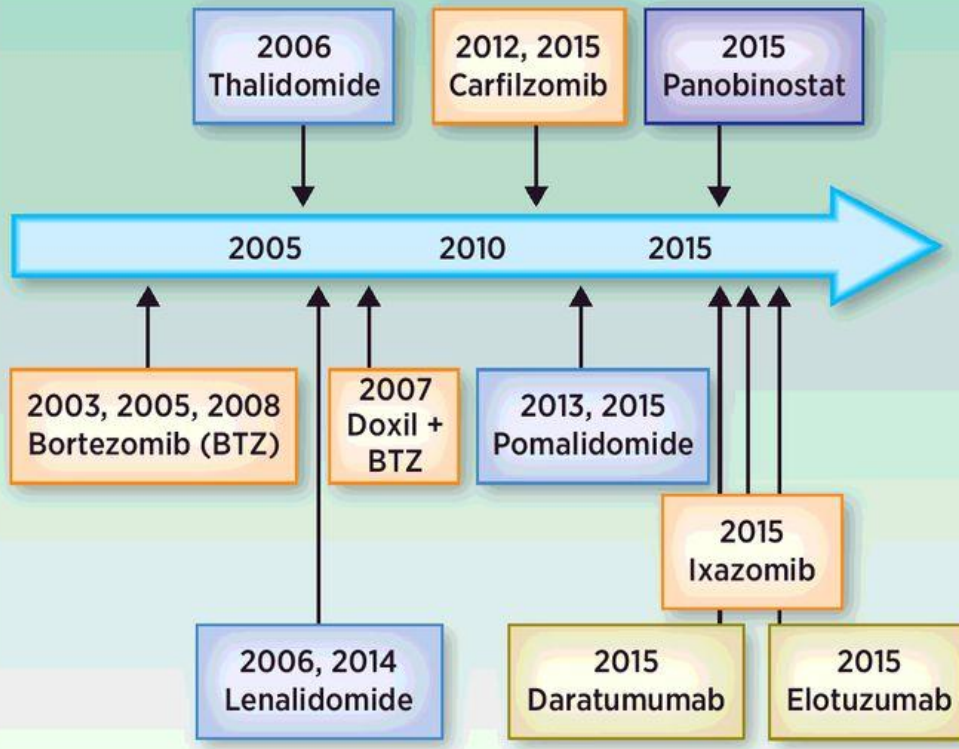
Many ways to skin a cat – High Risk Disease



Making Clinical Impact on the World Stage

Preclinical and clinical studies leading to FDA approvals in MM

Improvement in overall survival from median of 3 to 8-10 years



Immunomodulatory agent

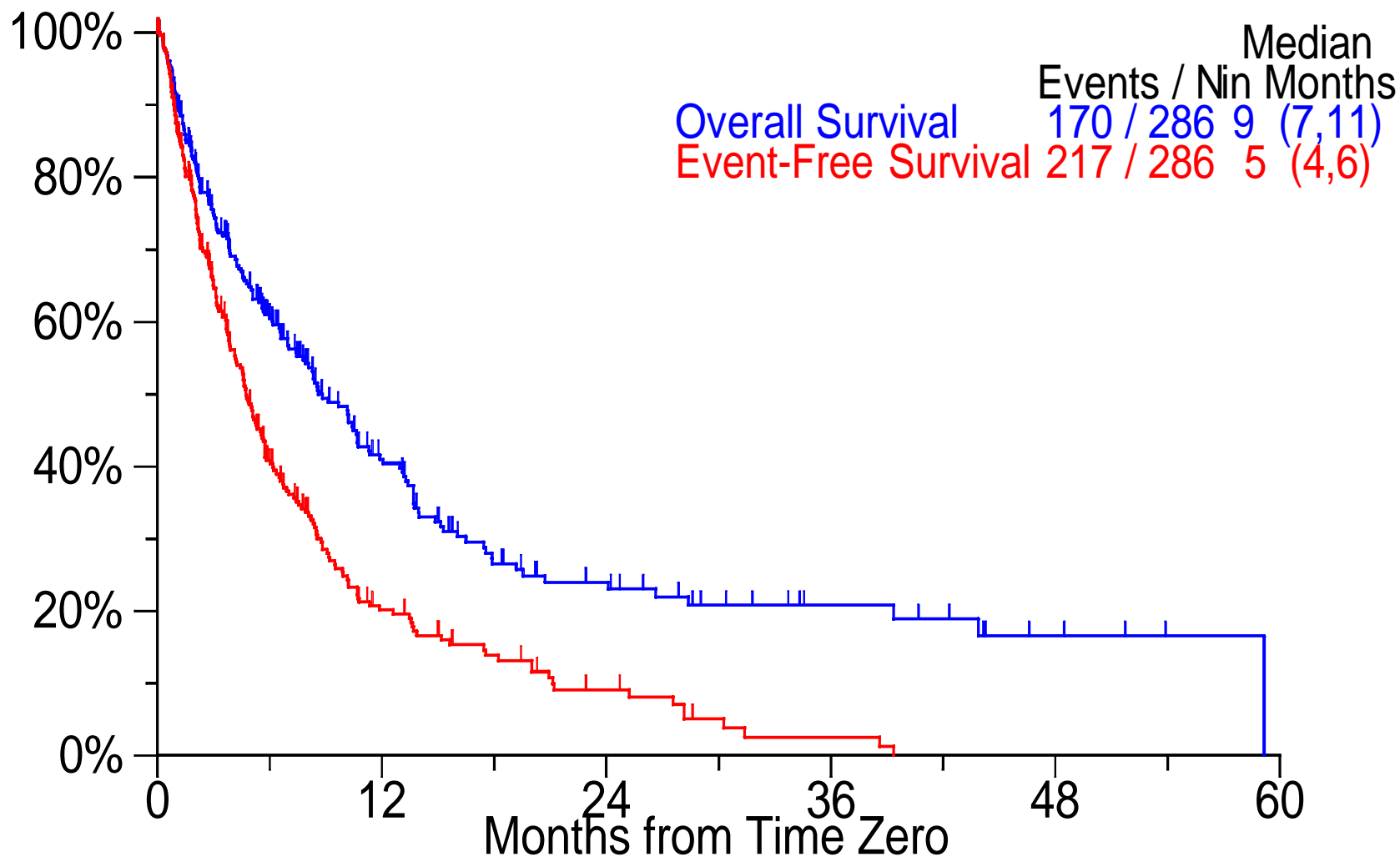
Monoclonal antibody

Proteasome inhibitor

HDAC inhibitor

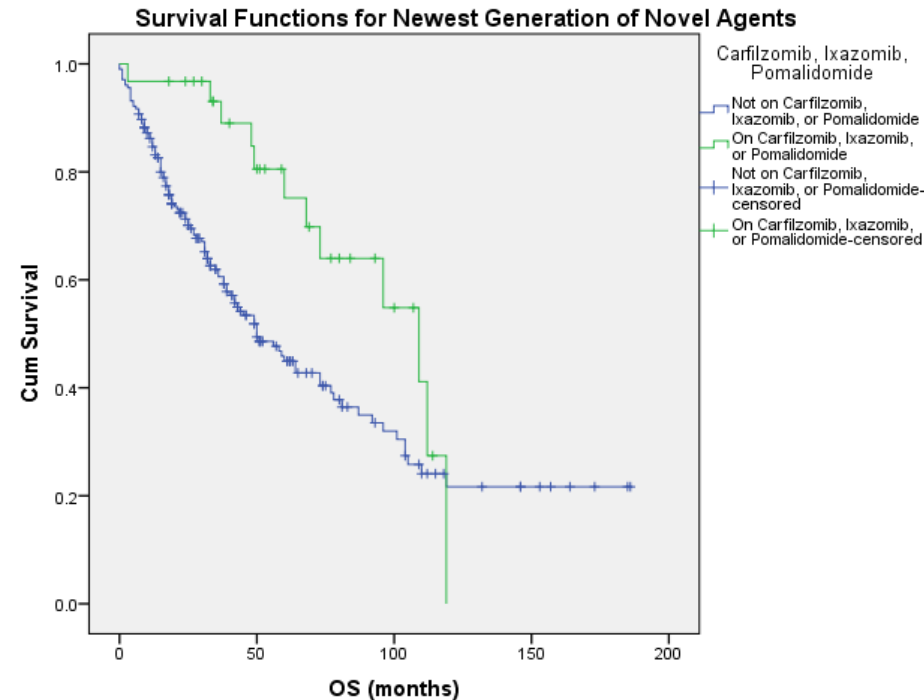
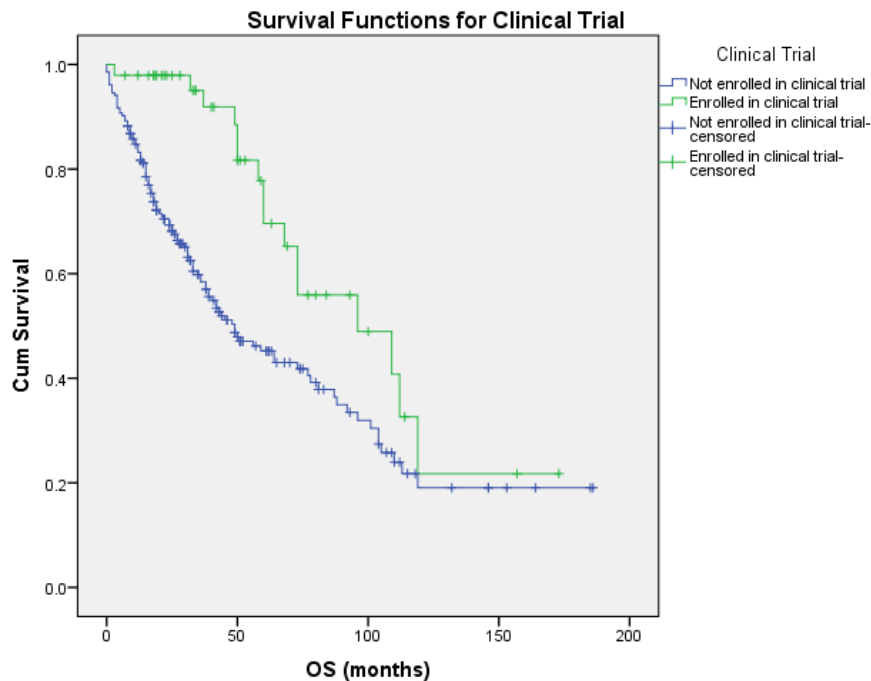
© 2016 American Association for Cancer Research

Survival following relapse after bortezomib and lenalidomide



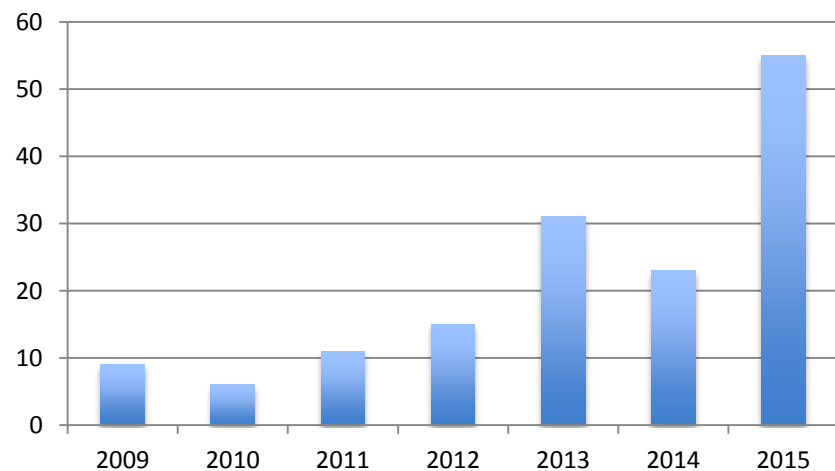
Access to Next Generation Novel Agents through Clinical Trials is important prognostic feature

N=252



Clinical Trials

Patient Recruited to Clinical Trials



Weekly Enrollment
18

Total Enrolled Since 20 June 2012
741 of Target 888

Congratulations to the following investigators and their staff!

This Week's Investigators

- Dr. CHEONG (n=1)
- Dr. CHNG (n=1)*
- Dr. DUECK (n=1)
- Dr. GOPALAKRISHNAN (n=2)
- Dr. HÄNEL (n=1)*
- Prof. HUNGRIA (n=1)
- Dr. KAPLAN (n=1)
- Dr. MATOUS (n=1)*
- Prof. MOREAU (n=1)
- Dr. ORIOL (n=1)*
- Dr. POUR (n=1)*
- Dra. ROSIÑOL (n=1)*
- Dr. ROSSI (n=1)
- Dr. SUVOROV (n=1)
- Dr. SZOMOR (n=1)

To see a complete list of enrolling investigators, [Click here](#).

Top 20 Investigators

- Prof. DIMOPOULOS (n=30)
- Dr. POUR (n=23)
- Dr. ORIOL (n=18)
- Prof. GAIDANO (n=15)
- Prof. PALUMBO (n=15)
- Dr. SUVOROV (n=15)
- Dr. CHNG (n=13)**
- Dr. GORANOVA-MARINOVA (n=12)
- Prof. ŠČUDLA (n=12)
- Dr. ARAUJO (n=11)
- Prof. JOSHUA (n=11)
- Dr. KARLIN (n=11)
- Prof. SCHWARER (n=11)
- Dr. STRAUB (n=11)
- Prof. MOREAU (n=10)



Carfilzomib and dexamethasone versus bortezomib and dexamethasone for patients with relapsed or refractory multiple myeloma (ENDEAVOR): a randomised, phase 3, open-label, multicentre study

*Meletios A Dimopoulos**, *Philippe Moreau**, *Antonio Palumbo*, *Douglas Joshua*, *Ludek Pour*, *Roman Hájek*, *Thierry Facon*, *Heinz Ludwig*, *Albert Oriol*, *Hartmut Goldschmidt*, *Laura Rosiñol*, *Jan Straub*, *Aleksandr Suvorov*, *Carla Araujo*, *Elena Rimashevskaya*, *Tomas Pika*, *Gianluca Gaidano*, *Katja Weisel*, *Vesselina Goranova-Marinova*, *Anthony Schwarzer*, *Leonard Minuk*, *Tamás Masszi*, *Ievgenii Karamanesht*, *Massimo Offidani*, *Vania Hungria*, *Andrew Spencer*, *Robert Z Orlowski*, *Heidi H Gillenwater*, *Nehal Mohamed*, *Shibao Feng*, *Wee-Joo Chng*, for the ENDEAVOR investigators

Summary

Background Bortezomib with dexamethasone is a standard treatment option for relapsed or refractory multiple myeloma. Carfilzomib with dexamethasone has shown promising activity in patients in this disease setting. The aim of this study was to compare the combination of carfilzomib and dexamethasone with bortezomib and dexamethasone in patients with relapsed or refractory multiple myeloma.

Methods In this randomised, phase 3, open-label, multicentre study, patients with relapsed or refractory multiple myeloma who had one to three previous treatments were randomly assigned (1:1) using a blocked randomisation scheme (block size of four) to receive carfilzomib with dexamethasone (carfilzomib group) or bortezomib with dexamethasone (bortezomib group). Randomisation was stratified by previous proteasome inhibitor therapy, previous lines of treatment, International Staging System stage, and planned route of bortezomib administration if randomly assigned to bortezomib with dexamethasone. Patients received treatment until progression with carfilzomib (20 mg/m² on days 1 and 2 of cycle 1; 56 mg/m² thereafter; 30 min intravenous infusion) and dexamethasone (20 mg oral or intravenous infusion) or bortezomib (1.3 mg/m²; intravenous bolus or subcutaneous injection) and dexamethasone (20 mg oral or intravenous infusion). The primary endpoint was progression-free survival in the intention-to-treat population. All participants who received at least one dose of study drug were included in the safety analyses. The study is ongoing but not enrolling participants; results for the interim analysis of the primary endpoint are presented. The trial is registered at ClinicalTrials.gov, number NCT01568866.

Lancet Oncol 2016; 17: 27–38

Published Online

December 5, 2015

[http://dx.doi.org/10.1016/S1470-2045\(15\)00464-7](http://dx.doi.org/10.1016/S1470-2045(15)00464-7)

See [Comment](#) page 2

*Contributed equally

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University of Nantes, Nantes,

France (Prof P Moreau MD);

University of Turin, Turin, Italy

(Prof A Palumbo MD); Royal

Prince Alfred Hospital,

Camperdown, New South

Wales, Australia

(Prof D Joshua MD); University

Hospital Brno, Brno, Czech

Regional Collaboration – Asian Myeloma Network

- Tackle MM In Asia
- Epidemiology of MM (Am J Hem 2015)
- Clinical Trials (AMN001 – Pom Dex, PI – Chng WJ)



Pomalidomide Plus Dexamethasone (Pd) in the Treatment of Asian Patients with Relapsed/Refractory Myeloma (RRMM) Who Are Previously Treated with Bortezomib and Refractory to Lenalidomide – Interim Analysis of a Trial By the Asian Myeloma Network (AMN)

Wee J Chng, MD, MRCP, FRCPATH, PhD¹, Kihyun Kim², Jeffrey Huang^{3*}, Chor Sang Chim, MBChB^{4*}, Hiroshi Kosugi, MD, PhD⁵, Junichi Sakamoto, MD, PhD⁶, Sathish Kumar Gopalakrishnan^{7*}, Yuan Wei^{8*}, Ling Ying Zhuo^{9*}, Je-Jung Lee¹⁰, Sung-Soo Yoon¹¹, Jin Seok Kim^{12*}, Chang-Ki Min^{13*}, Jae-Hoon Lee¹⁴ and Brian G M Durie¹⁵

¹Department of Haematology-Oncology, National University Cancer Institute of Singapore, Singapore, Singapore;

²Sungkyunkwan University, Samsung Medical Center, Seoul, South Korea; ³National Taiwan University, Taipei, Taiwan; ⁴Queen Mary Hospital, Kowloon, CHN; ⁵Department of Hematology, Ogaki Municipal Hospital, Ogaki, Japan;

⁶Tokai Central Hospital, Kakamigahara, Japan; ⁷Singapore General Hospital, Singapore, SGP; ⁸Singapore Clinical Research Institute, Singapore, Singapore; ⁹Singapore Cancer Research Institute, Singapore, Singapore;

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¹¹Seoul National University Hospital, Seoul, Korea, The Republic of; ¹²Severance Hospital, Yonsei University College of Medicine, Seoul, Korea, The Republic of; ¹³Seoul St. Mary's Hospital, Catholic University of Korea, Seoul, Korea, The Republic of; ¹⁴Gachon University Gil Medical Center, Incheon, Korea, The Republic of; ¹⁵Cedars-Sinai Outpatient Cancer Center at the Samuel Oschin Comprehensive Cancer Institute, Los Angeles, CA

AMN Trials

Code	Regimen	New / Relapse	Numbers	Remarks
AMN001	P(C)D	Relapse	136	Complete
AMN002	KTD	Relapse	50	ALLG Collab, commenced
AMN003	PCD vs PD	Relapse	60 ea arm	Commenced
AMN004	Dara-TD	Relapse	100	Soon to be initiated
AMN005	Duvulumab-PCD	Relapse	40	On Hold
AMN006	Dara-VD	New NTE	60	Soon to be initiated
AMN007	Venetoclax-VD	Relapse with Plasmacytoma	25	Concept approved

State of Art 2016

- Clear Understanding of Biology
- Risk stratification
- Many effective drugs available
- Survival on average 8-10 years
- 15% curable

The Future of Myeloma Treatment

- Better treatment for High-Risk Disease
- Better tools for patient selection for different treatments
- Risk and response adapted therapeutic strategies
- Increase cure rate to beyond 30%

Acknowledgements

My Lab



Clinical Team



The Patients



Singapore Myeloma Study Group



Asian Myeloma Network



International Myeloma Study Group



Acknowledgement

- Mayo Clinic, USA
 - Rafael Fonseca
 - Leif Bergsagel
 - Keith Stewart
- BTI, A*STAR
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