



L'EMATOLOGIA "SERÀGNOLI"
E LA SCUOLA EMATOLOGICA BOLOGNESE:
UNA STORIA DI 50 ANNI

Mieloma multiplo e amiloidosi AL Contributi dell'ematologia bolognese

Paola Tacchetti, Elena Zamagni, Carolina Terragna

IRCCS Azienda Ospedaliero-Universitaria di Bologna

Istituto di Ematologia "Seràgnoli"



Disclosures of Paola Tacchetti

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Johnson & Johnson						x	x
Sanofi						x	x
BMS-Celgene						x	x
Amgen						x	x
GSK							x
Takeda							x
Pfizer							x
Menarini Stemline						x	x
Abbvie							x



Allogeneic stem cell transplantation

ALLOGENEIC BONE MARROW TRANSPLANTATION IN MULTIPLE MYELOMA

GÖSTA GAHRTON, M.D., SANTE TURA, M.D., PER LJUNGMAN, M.D., CORALIE BELANGER, M.D., LENA BRANDT, B.Sc., MICHELE CAVO, M.D., THIERRY FACON, M.D., ALBERTO GRANENA, M.D., MARTIN GORE, M.D., ALOIS GRATWOHL, M.D., BOB LÖWENBERG, M.D., JUKKA NIKOSKELAINEN, M.D., JOSY J. REIFFERS, M.D., DIANA SAMSON, M.D., LEO VERDONCK, M.D., AND LIISA VOLIN, M.D., FOR THE EUROPEAN GROUP FOR BONE MARROW TRANSPLANTATION*

Molecular monitoring of minimal residual disease in patients in long-term complete remission after allogeneic stem cell transplantation for multiple myeloma

Michele Cavo, Carolina Terragna, Giovanni Martinelli, Sonia Ronconi, Elena Zamagni, Patrizia Tosi, Roberto M. Lemoli, Monica Benni, Giorgio Pagliani, Giuseppe Bandini, and Sante Tura



BLOOD, 1 JULY 2000 • VOLUME 96, NUMBER 1

*"In conclusion, the data herein reported demonstrate that allo SCT induces **sustained serological and molecular remission** in selected patients with MM. Although a longer follow-up is required to determine if these patients are truly **cured**, it is unusual for relapses to occur more than 5 years after allo BMT"....*



The NEW ENGLAND JOURNAL of MEDICINE

N Engl J Med 1991;325:1267-73.

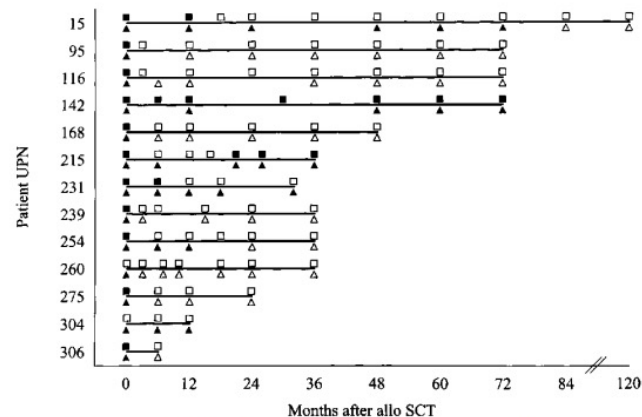


Figure 1. Results of PCR analysis for MRD detection on serial bone marrow samples taken before and after allo SCT. The figure represents positive (■) and negative (□) results of immunofixation analysis and positive (▲) and negative (△) results of the PCR-based assay.

Gahrton G, Tura S et al. NEJM 1991; Cavo M et al. Blood 2000



Autologous stem cell transplantation

HIGH-DOSE MELPHALAN FOR MULTIPLE MYELOMA

L. & A. Seragnoli Institute of Haematology,
S. Orsola University Hospital,
40138 Bologna, Italy;
and Department of Haematology,
University of Trieste

MICHELE CAVO
MICHELE BACCARANI
MARCO GOBBI
SANTE TURA

Prospective, Randomized Study of Single Compared With Double Autologous Stem-Cell Transplantation for Multiple Myeloma: Bologna 96 Clinical Study

Michele Cavo, Patrizia Tosi, Elena Zamagni, Claudia Cellini, Paola Tacchetti, Francesca Patriarca, Francesco Di Raimondo, Ettore Volpe, Sonia Ronconi, Delia Cangini, Franco Narni, Affra Carubelli, Luciano Masini, Lucio Catalano, Mauro Fiacchini, Antonio de Vivo, Alessandro Gozzetti, Antonio Lazzaro, Sante Tura, and Michele Baccarani

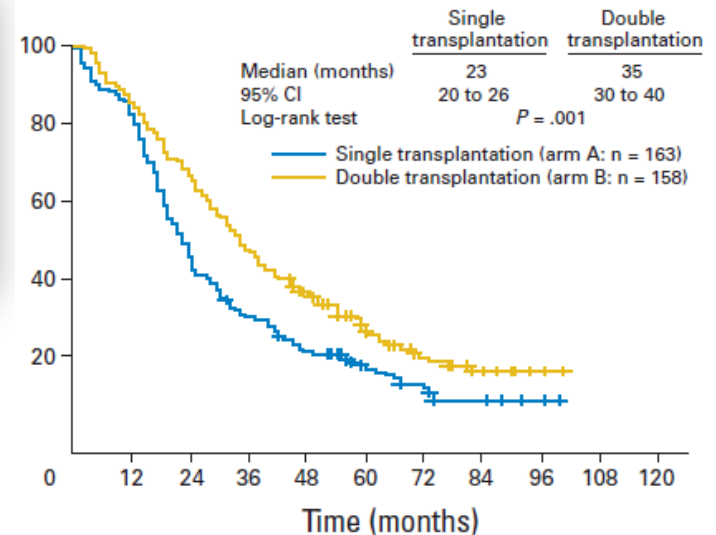
VOLUME 25 · NUMBER 17 · JUNE 10 2007

JOURNAL OF CLINICAL ONCOLOGY

THE LANCET

THE LANCET, NOVEMBER 19, 1983

“The **sensitivity** of multiple myeloma to melphalan makes the use of **higher doses attractive**”...





First-line therapy with thalidomide and dexamethasone in preparation for autologous stem cell transplantation for multiple myeloma

[haematologica]
2004;89:826-831

MICHELE CAVO
ELENA ZAMAGNI
PATRIZIA TOSI
CLAUDIA CELLINI
DELIA GANGINI
PAOLA TACCHETTI
NICOLETTA TESTONI
MICHELA TONELLI
ANTONIO DE VIVO
GUALTIERO PALARETI
SANTE TURA
MICHELE BACCARANI

Aspirin, Warfarin, or Enoxaparin Thromboprophylaxis in Patients With Multiple Myeloma Treated With Thalidomide: A Phase III, Open-Label, Randomized Trial

Antonio Palumbo, Michele Cavo, Sara Brighen, Elena Zamagni, Alessandra Romano, Francesca Patriarca, Davide Rossi, Fabiana Gentilini, Claudia Crippa, Monica Galli, Chiara Nozzoli, Roberto Ria, Roberto Marasca, Vittorio Montefusco, Luca Baldini, Francesca Elice, Vincenzo Callea, Stefano Pulini, Angelo M. Carella, Renato Zambello, Giulia Benevolo, Valeria Magarotto, Paola Tacchetti, Norbert Pescosta, Claudia Cellini, Claudia Polloni, Andrea Evangelista, Tommaso Caravita, Fortunato Morabito, Massimo Offidani, Patrizia Tosi, and Mario Boccadoro

VOLUME 29 · NUMBER 8 · MARCH 10 2011

JOURNAL OF CLINICAL ONCOLOGY

JOURNAL OF CLINICAL ONCOLOGY

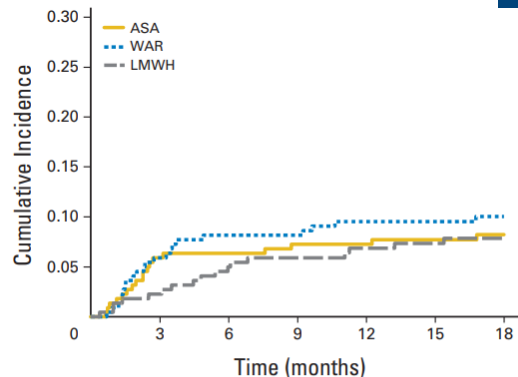
Official Journal of the American Society of Clinical Oncology

To the editor:

Deep-vein thrombosis in patients with multiple myeloma receiving first-line thalidomide-dexamethasone therapy

Michele Cavo, Elena Zamagni, Claudia Cellini, Patrizia Tosi, Delia Cangini, Michela Cini, Lelia Valdrè, Gualtiero Palareti, Luciano Masini, Sante Tura, and Michele Baccarani

BLOOD, 15 SEPTEMBER 2002 · VOLUME 100, NUMBER 6



No. at risk		0	3	6	9	12	15	18
ASA	220	205	203	199	193	185	164	
WAR	220	206	197	195	184	178	161	
LMWH	219	212	205	202	190	183	168	

Cavo M et al. Haematologica 2004; Cavo M et al. Blood 2002; Palumbo A et al. JCO 2011

Superiority of thalidomide and dexamethasone over vincristine-doxorubicin-dexamethasone (VAD) as primary therapy in preparation for autologous transplantation for multiple myeloma

Michele Cavo, Elena Zamagni, Patrizia Tosi, Paola Tacchetti, Claudia Cellini, Delia Cangini, Antonio de Vivo, Nicoletta Testoni, Chiara Nicci, Carolina Terragna, Tiziana Grafone, Giulia Perrone, Michela Ceccolini, Sante Tura, and Michele Baccarani, for the writing committee of the Bologna 2002 study



BLOOD, 1 JULY 2005 • VOLUME 106, NUMBER 1

Table 2. Rates of response

	No. of patients		P
	Thal-Dex, N = 100	VAD, N = 100	
At least PR	76	52	< .001
CR	10	8	—
nCR	3	5	—
VGPR	6	1	—
PR	57	38	—
NR/PROGR	24	48	< .001

At least partial remission (PR) includes complete remission (CR), near complete remission (nCR), very good partial remission (VGPR), and partial remission (PR).

— indicates not applicable; NR/PROGR, no response/progression.

Short-Term Thalidomide Incorporated Into Double Autologous Stem-Cell Transplantation Improves Outcomes in Comparison With Double Autotransplantation for Multiple Myeloma

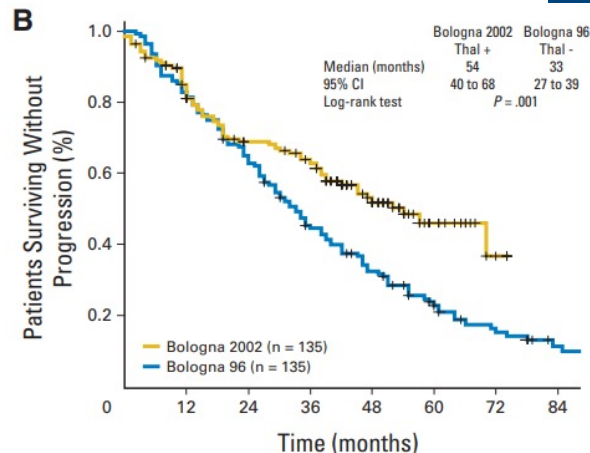
Michele Cavo, Francesco Di Raimondo, Elena Zamagni, Francesca Patriarca, Paola Tacchetti, Antonio Francesco Casulli, Silvestro Volpe, Giulia Perrone, Antonio Ledda, Michela Ceccolini, Catello Califano, Catia Bigazzi, Massimo Offidani, Piero Stefani, Filippo Ballerini, Mauro Fiacchini, Antonio de Vivo, Annamaria Brioli, Patrizia Tosi, and Michele Baccarani

VOLUME 27 • NUMBER 30 • OCTOBER 20 2009

JOURNAL OF CLINICAL ONCOLOGY

JOURNAL OF CLINICAL ONCOLOGY

Official Journal of the American Society of Clinical Oncology





inside **blood**

1 JULY 2005 | VOLUME 106, NUMBER 1

CLINICAL OBSERVATIONS

Comment on Cavo et al, page 35

Multiple myeloma: the death of VAD as initial therapy

S. Vincent Rajkumar MAYO CLINIC

In a matched case-control study of 200 patients, Cavo and colleagues show that thalidomide plus dexamethasone (Thal-Dex) yields significantly higher response rates compared with VAD as pretransplant induction therapy for multiple myeloma.

*“In this issue of Blood, Cavo and colleagues appear to have placed **the final nail in the coffin for VAD**”.....*

Rajkumar SV. Blood 2005; Cavo M & Baccarani M. NEJM 2006



The NEW ENGLAND
JOURNAL of MEDICINE

EDITORIALS N ENGL J MED 354:10 WWW.NEJM.ORG MARCH 9, 2006

The Changing Landscape of Myeloma Therapy

Michele Cavo, M.D., and Michele Baccarani, M.D.

*....“the **concept of targeting the bone marrow microenvironment (the “soil”)** in a way that interferes with the growth of the myeloma “seed” emerged as the rationale for trials of **new agents in combination** with established therapies in an attempt to **enhance cytotoxicity, reverse drug resistance**, and increase the probability of **curing myeloma**”.....*

Bortezomib with thalidomide plus dexamethasone compared with thalidomide plus dexamethasone as induction therapy before, and consolidation therapy after, double autologous stem-cell transplantation in newly diagnosed multiple myeloma: a randomised phase 3 study

Michele Cavo, Paola Tacchetti, Francesca Patriarca, Maria Teresa Petrucci, Lucia Pantani, Monica Galli, Francesco Di Raimondo, Claudia Crippa, Elena Zamagni, Antonio Palumbo, Massimo Offidani, Paolo Corradini, Franco Narni, Antonio Spadano, Norbert Pescosta, Giorgio Lambertenghi Delilieri, Antonio Ledda, Claudia Cellini, Tommaso Caravita, Patrizia Tosi, Michele Baccarani, for the GIMEMA Italian Myeloma Network*

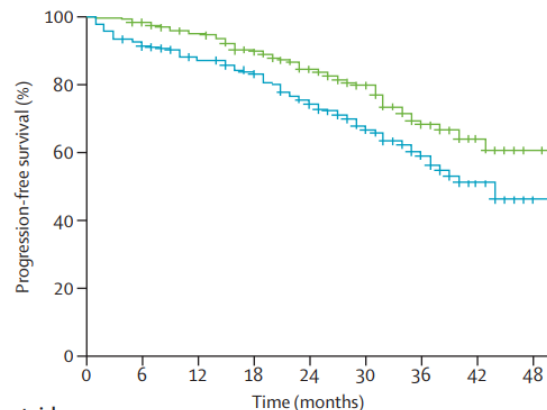
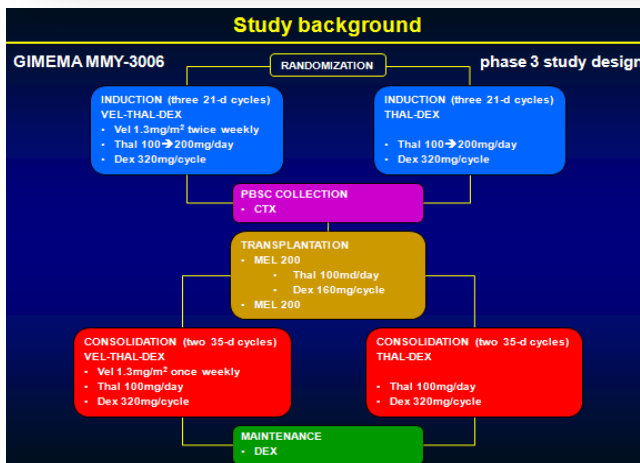
Lancet 2010; 376: 2075-85

Bortezomib-thalidomide-dexamethasone is superior to thalidomide-dexamethasone as consolidation therapy after autologous hematopoietic stem cell transplantation in patients with newly diagnosed multiple myeloma

Michele Cavo,¹ Lucia Pantani,¹ Maria Teresa Petrucci,² Francesca Patriarca,³ Elena Zamagni,¹ Daniela Donnarumma,⁴ Claudia Crippa,⁵ Mario Boccadoro,⁶ Giulia Perrone,¹ Antonietta Falcone,⁷ Chiara Nozzoli,⁸ Renato Zambello,⁹ Luciano Masini,¹⁰ Anna Furlan,¹¹ Annamaria Brioli,¹ Daniele Derudas,¹² Stelvio Ballanti,¹³ Maria Laura Dessanti,¹⁴ Valerio De Stefano,¹⁵ Angelo Michele Carella,¹⁶ Magda Marcatti,¹⁷ Andrea Nozza,¹⁸ Felicetto Ferrara,¹⁹ Vincenzo Callea,²⁰ Catello Califano,²¹ Annalisa Pezzi,¹ Anna Baraldi,²² Mariella Grasso,²³ Pellegrino Musto,²⁴ and Antonio Palumbo,⁶ for the GIMEMA (Gruppo Italiano Malattie Ematologiche dell'Adulto) Italian Myeloma Network

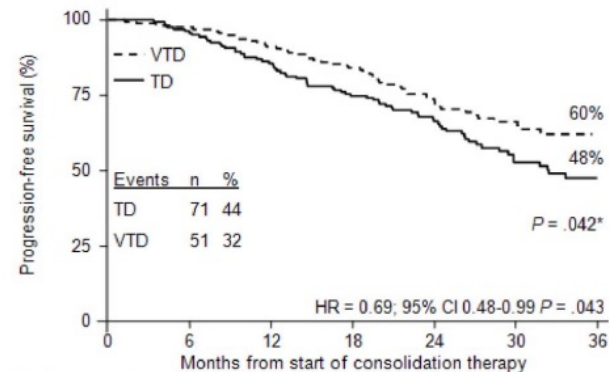
Plenary paper

BLOOD, 5 JULY 2012 • VOLUME 120, NUMBER 1



Number at risk

	0	6	12	18	24	30	36	42	48
VTD	236	230	212	195	159	111	55	21	2
TD	238	218	200	185	158	99	51	13	2



Number at risk

	0	6	12	18	24	30	36
TD	161	153	136	114	84	43	21
VTD	160	154	142	125	86	53	26

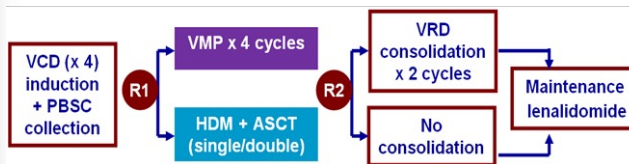


Autologous stem cell transplantation in the era of novel agents

Autologous haematopoietic stem-cell transplantation versus bortezomib-melphalan-prednisone, with or without bortezomib-lenalidomide-dexamethasone consolidation therapy, and lenalidomide maintenance for newly diagnosed multiple myeloma (EMN02/HO95): a multicentre, randomised, open-label, phase 3 study

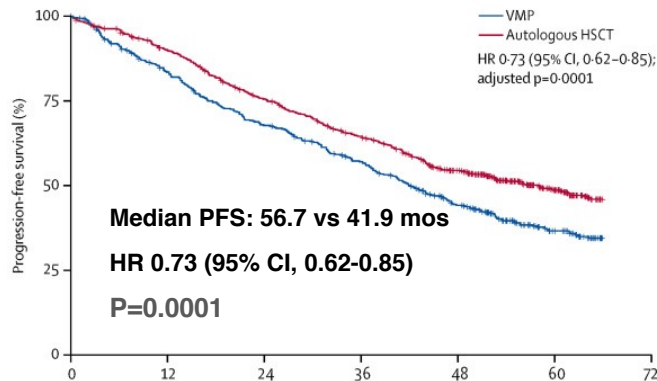
Michele Cavo, Francesca Gay, Meral Beksas, Lucia Pantani, Maria Teresa Petrucci, Meletios A Dimopoulos, Luca Dozza, Bronno van der Holt, Sonja Zweegman, Stefania Oliva, Vincent H J van der Velden, Elena Zamagni, Giuseppe A Palumbo, Francesca Patriarca, Vittorio Montefusco, Monica Galli, Vladimir Maisnar, Barbara Gamberi, Markus Hansson, Angelo Belotti, Ludek Pour, Paula Yrma, Mariella Grasso, Alessandra Crocchietti, Stelvio Ballanti, Massimo Offidani, Iolanda D Vincelli, Renato Zambello, Anna Marina Liberati, Niels Frost Andersen, Annemiek Broijl, Rossella Troia, Anna Pascarella, Giulia Benevolo, Mark-David Levin, Gerard Bos, Heinz Ludwig, Sara Aquino, Anna Maria Morelli, Ka Lung Wu, Rinske Boersma, Roman Hajek, Marc Durian, Peter A von dem Borne, Tommaso Caravita di Toritto, Thilo Zander, Christoph Driessen, Giordina Specchia, Anders Waage, Peter Gimsing, Ulf-Henrik Mellqvist, Marinus van Marwijk Kooy, Monique Minnerma, Caroline Mandigers, Anna Maria Caforio, Angelo Palmas, Susanna Carvalho, Andrew Spencer, Mario Boccadoro, Pieter Sonneveld

EMN02/HO95 phase 3 study



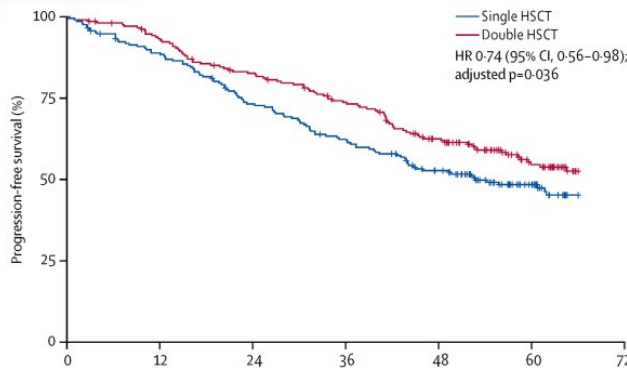
THE LANCET Haematology

Lancet Haematol 2020; 7: e456-68



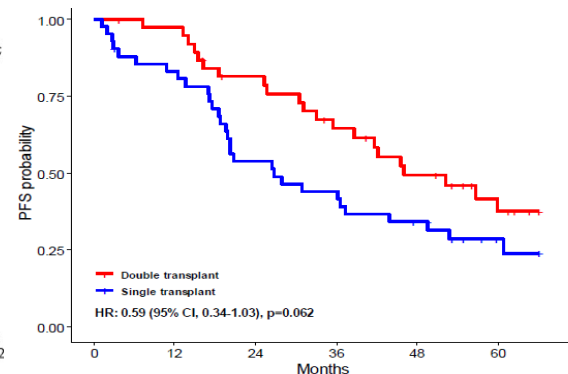
Months of Follow-up

ASCT-1 vs ASCT-2



ASCT-1 vs ASCT-2

PFS: del (17p) and/or t(4;14) and/or t(14;16)



Cavo M et al. Lancet Haematol 2020



Long term survivors and potential cure

Bortezomib, thalidomide, and dexamethasone followed by double autologous haematopoietic stem-cell transplantation for newly diagnosed multiple myeloma (GIMEMA-MMY-3006): long-term follow-up analysis of a randomised phase 3, open-label study

Paola Tacchetti, Lucia Pantani, Francesca Patriarca, Maria Teresa Petrucci, Elena Zamagni, Luca Dozza, Monica Galli, Francesco Di Raimondo, Claudia Crippa, Mario Boccadoro, Simona Barbato, Patrizia Tosi, Franco Narni, Vittorio Montefusco, Nicoletta Testoni, Antonio Spadano, Carolina Terragna, Norbert Pescosta, Giulia Marzocchi, Claudia Cellini, Piero Galleni, Sonia Ronconi, Marco Gobbi, Lucio Catalano, Antonio Lazzaro, Giovanni De Sabbata, Clotilde Cangialosi, Fabrizio Ciambelli, Pellegrino Musto, Francesca Elice, Michele Cavo, for the GIMEMA (Gruppo Italiano Malattie Ematologiche dell'Adulto Italian Myeloma Network)

THE LANCET Haematology

Lancet Haematol 2020;
7: e861-73

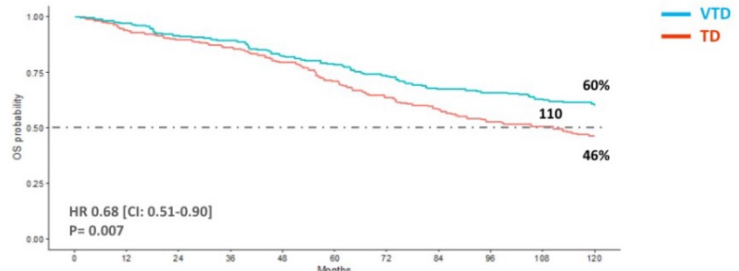
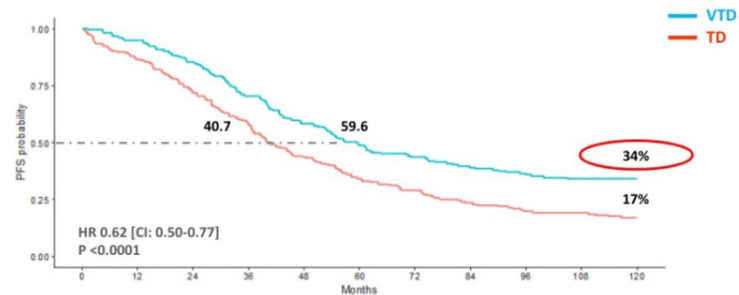
Nuovi «nuovi farmaci» e nuovi meccanismi di azione

Caratterizzazione biologica

Stratificazione del rischio

Monitoraggio malattia minima residua

Terapia personalizzata



Tacchetti P et al. Lancet Haematol 2020



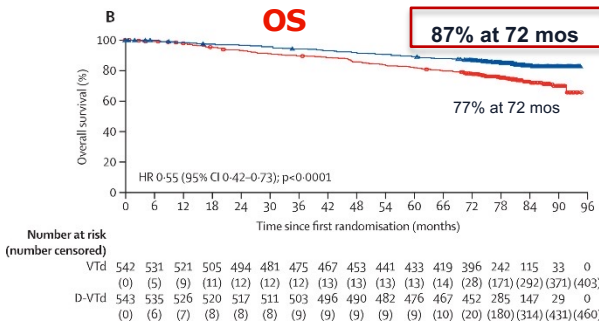
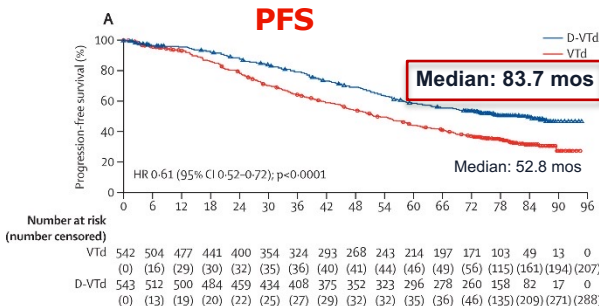
Disclosures of Name Surname

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Janssen						X	X
Sanofi						X	X
Pfizer						X	X
BMS						X	X
Amgen						X	X
GSK						X	X
Oncopeptide						X	X
Menarini- Stemline						X	X



The advent of anti-CD38 MoAbs in 1 line in ND-TE-MM

CASSIOPEIA phase III trial: Dara-VTd vs VTd + ASCT



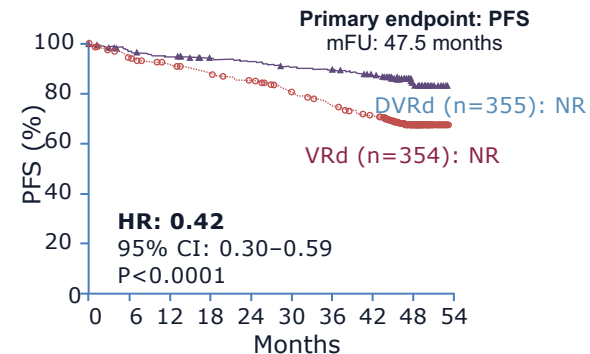
EMN28/PERSEUS phase III trial: Dara-VRd vs VRd + ASCT

The NEW ENGLAND JOURNAL of MEDICINE

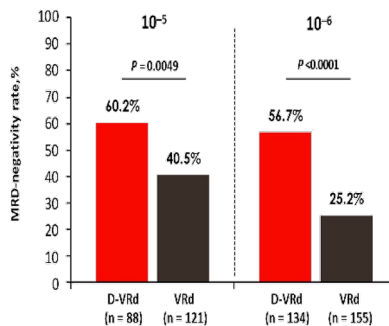
ESTABLISHED IN 1812 JANUARY 25, 2024 VOL. 390 NO. 4

Daratumumab, Bortezomib, Lenalidomide, and Dexamethasone for Multiple Myeloma

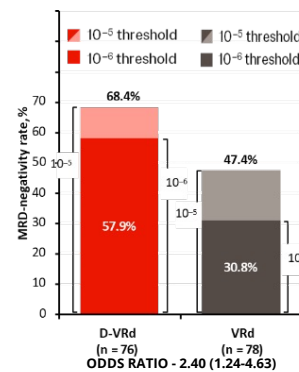
P. Sonneveld, M.A. Dimopoulos, M. Boccadoro, H. Quach, P.J. Ho, M. Beksac, C. Hulín, E. Antonioli, X. Leleu, S. Mangiacavalli, A. Perrot, M. Cavo, A. Belotti, A. Broijl, F. Gay, R. Mina, I.S. Nijhof, N.W.C.J. van de Donk, E. Katodritou, F. Schjesvold, A. Sureda Balari, L. Rosiñol, M. Delforge, W. Roelfszten, T. Szilze, A. Vangsted, H. Einsele, A. Spencer, R. Hajek, A. Jurczyszyn, S. Lonergan, T. Ahmadi, Y. Liu, J. Wang, D. Veyra, E.M.J. van Brummelen, V. Vanquickenbergh, A. Sitthi-Amorn, C.J. de Boer, R. Carson, P. Rodriguez-Otero, J. Bladé, and P. Moreau, for the PERSEUS Trial Investigators*



MRD rate during maintenance



MRDneg in Pts With High-risk



Sonneveld P et al, NEJM 2024
Sonneveld P et al, EHA 2024



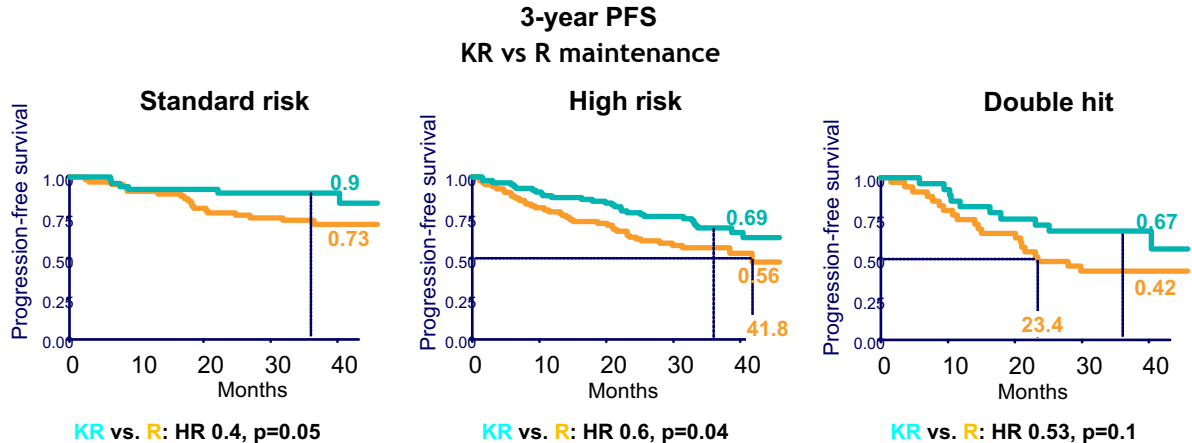
Anti-CD38 Mo Abs + KRd: the treatment for HR patients?

FORTE phase III trial: KRd vs KRd+ASCT vs KCd + ASCT

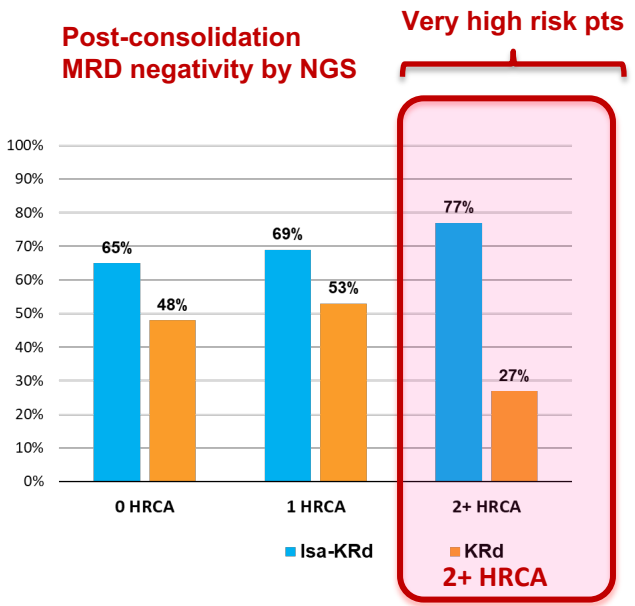
Carfilzomib with cyclophosphamide and dexamethasone or lenalidomide and dexamethasone plus autologous transplantation or carfilzomib plus lenalidomide and dexamethasone, followed by maintenance with carfilzomib plus lenalidomide or lenalidomide alone for patients with newly diagnosed multiple myeloma (FORTE): a randomised, open-label, phase 2 trial



Francesca Gay, Pellegrino Musto*, Della Rota-Scalabrini, Luca Bertamini, Angelo Belotti, Monica Galli, Massimo Offidani, Elena Zamagni, Antonio Ledda, Mariella Grasso, Stelvio Ballanti, Antonio Spadano, Michele Cea, Francesca Patriarca, Mattia D'Agostino, Andrea Capra, Nicola Giuliani, Paolo de Fabritiis, Sara Aquino, Angelo Palmas, Barbara Gamberi, Renato Zambello, Maria Teresa Petrucci, Paolo Corradini, Michele Cavo, Mario Boccadoro*



EMN24/ISKIA phase III trial: Isa-KRd vs KRd + ASCT



Gay F et al, Lancet Oncology 2021
Mina R et al, Lancet Oncology 2023

Gay F et al, ASH 2023, manuscript submitted to JAMA



Immunotherapy moving earlier: CART and bispecifics

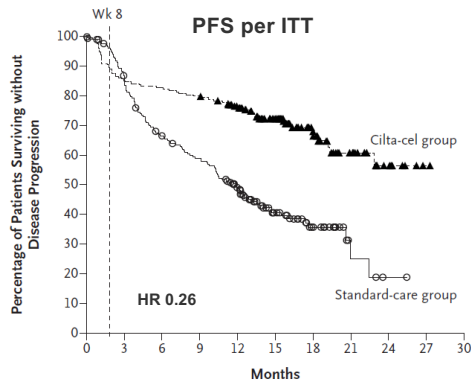
Ide-cel: the first CART in RRMM (2021)

THE NEW ENGLAND JOURNAL OF MEDICINE

ORIGINAL ARTICLE

Idecabtagene Vicleucel in Relapsed and Refractory Multiple Myeloma

Nikhil C. Munshi, M.D., Larry D. Anderson, Jr., M.D., Ph.D., Nina Shah, M.D., Deepu Madduri, M.D., Jesús Berdeja, M.D., Sagar Lonial, M.D., Noopur Rajee, M.D., Yi Lin, M.D., Ph.D., David Siegel, M.D., Ph.D., Albert Oriol, M.D., Philippe Moreau, M.D., Ibrahim Yakoub-Agha, M.D., Ph.D., Michel Delforge, M.D., Michele Cavo, M.D., Hermann Einsele, M.D., Hartmut Goldschmidt, M.D., Katja Weisel, M.D., Alessandro Rambaldi, M.D., Donna Reece, M.D., Fabio Petrocchi, M.D., Monica Massaro, M.P.H., Jamie N. Connors, Ph.D., Shari Kaiser, Ph.D., Payal Patel, Ph.D., Liping Huang, Ph.D., Timothy B. Campbell, M.D., Ph.D., Kristen Hege, M.D., and Jesús San-Miguel, M.D., Ph.D.



No. at Risk	0	3	6	9	12	15	18	21	24	27	30
Cilta-cel group	208	177	172	166	146	94	45	22	9	1	0
Standard-care group	211	176	133	116	88	46	20	4	1	0	0

San Miguel J et al, NEJM 2023

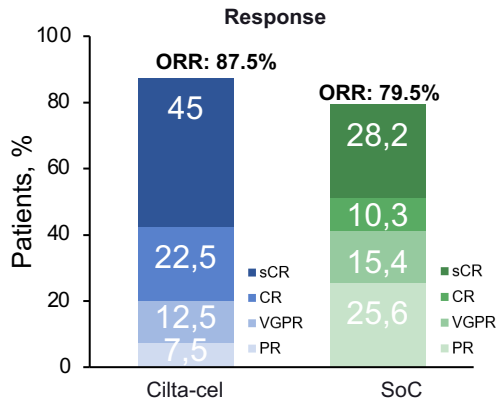
CARTITUDE-4 phase III trial: cilta-cel vs SOC in RRMM 1-3 prior LOT

ORIGINAL ARTICLE

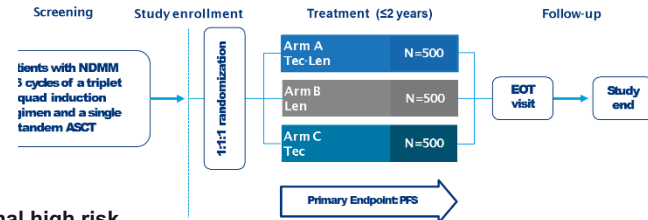
Cilta-cel or Standard Care in Lenalidomide-Refractory Multiple Myeloma

J. San-Miguel, B. Dhakal, K. Yong, A. Spencer, S. Anguille, M.-V. Mateos, C. Fernández de Larrea, J. Martínez-López, P. Moreau, C. Touzeau, X. Leleu, I. Avivi, M. Cavo, T. Ishida, S.J. Kim, W. Roeloffzen, N.W.C.J. van de Donk, D. Dytfeld, S. Sidana, L.J. Costa, A. Oriol, R. Popat, A.M. Khan, Y.C. Cohen, P.J. Ho, J. Griffin, N. Lendvai, C. Lonardi, A. Slaughter, J.M. Schecter, C.C. Jackson, K. Connors, K. Li, E. Zudaire, D. Chen, J. Gilbert, T. Yeh, S. Nagle, E. Florendo, L. Pacaud, N. Patel, S.J. Harrison, and H. Einsele

Results in patients with 1 prior LOT and functional high risk (PD ≤18 months after ASCT or the start of initial therapy in pts with no ASCT)

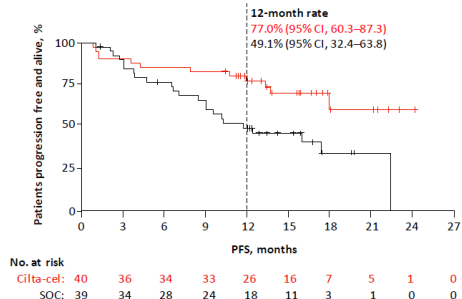


MajesTEC-4: Phase 3 Study Design



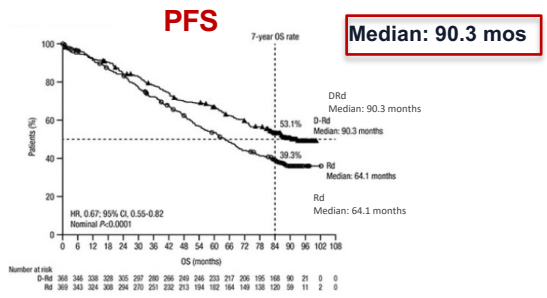
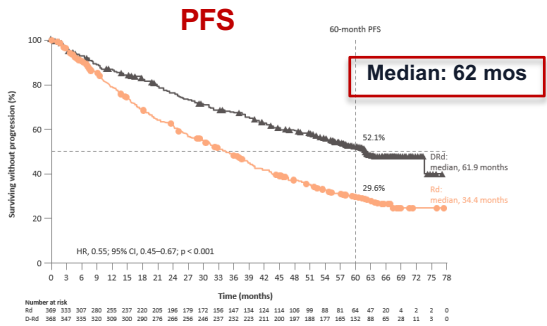
Zamagni E as global PI

	Cilta-cel (n=40)	SOC (n=39)
Median PFS (95% CI), months ^a	NR (18.00-NE)	11.79 (8.44-NE)
HR (95% CI); P value ^{b,c}	0.27 (0.12-0.60); 0.0006	





MAIA phase III trial: Dara-Rd vs Rd



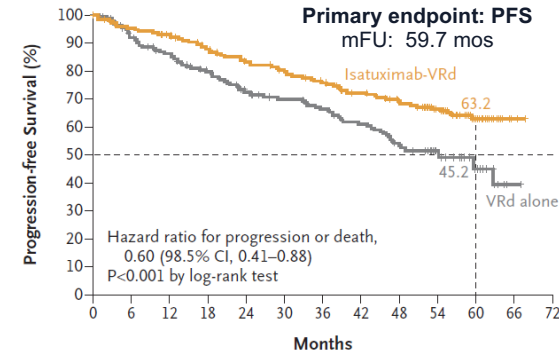
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Isatuximab, Bortezomib, Lenalidomide, and Dexamethasone for Multiple Myeloma

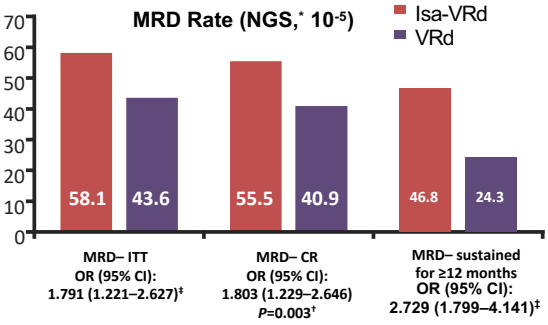
Thierry Facon, M.D., Meletios-Athanasios Dimopoulos, M.D., Xavier P. Leleu, M.D., Meral Bekzac, M.D., Ludek Pour, M.D., Roman Hájek, M.D., Zhuogang Liu, M.D., Jiri Minarik, M.D., Philippe Moreau, M.D., Joanna Romejko-Jarosinska, M.D., Ivan Spicka, M.D., Vladimir I. Vorobyev, M.D., Britta Besemer, M.D., Tadao Ishida, M.D., Wojciech Janowski, M.D., Sevgi Kalayoglu-Besisik, M.D., Gurdeep Parmar, M.D., Pawel Robak, M.D., Elena Zarnagni, M.D., Hartmut Goldschmidt, M.D., Thomas G. Martin, M.D., Salomon Manier, M.D., Mohamad Mohty, M.D., Corina Oprea, M.D., Marie-France Brégeault, M.D., Sandrine Macé, Ph.D., Christelle Berthou, M.S., David Bregman, M.D., Zandra Klippel, M.D., and Robert Z. Orlowski, M.D., for the IMROZ Study Group*

IMROZ phase III trial: Isa-VRd vs VRd



No. at Risk

Isatuximab-VRd	265	243	234	217	201	190	177	164	153	104	43	2	0
VRd alone	181	155	141	121	104	96	89	81	70	51	20	2	0

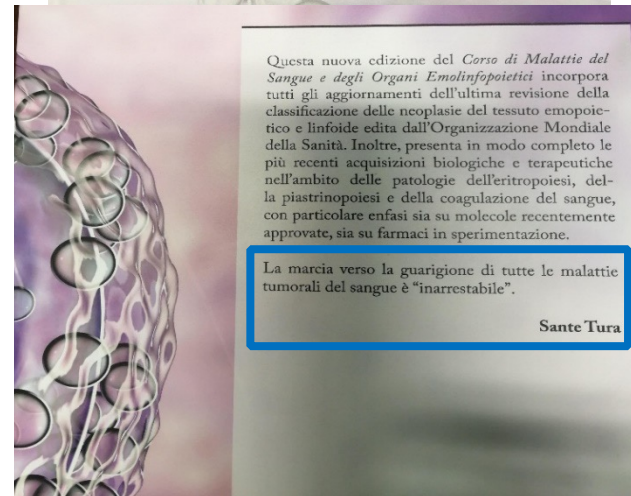
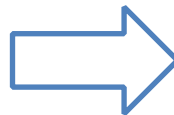
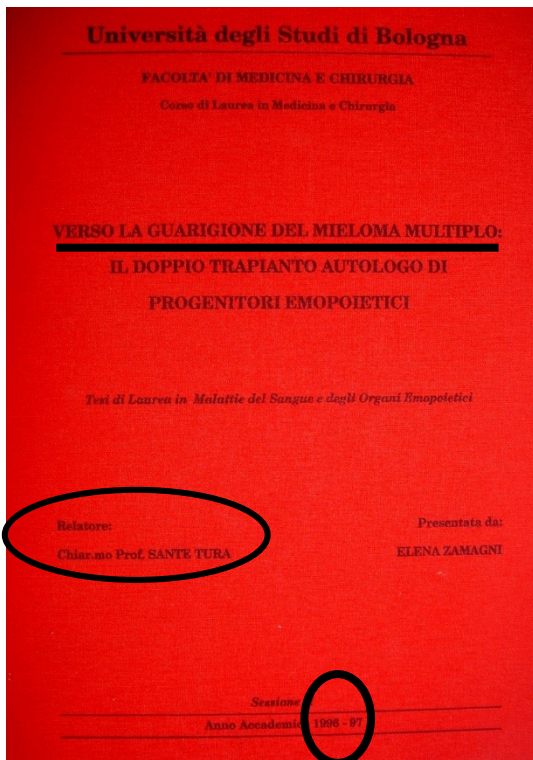


Facon T et al, NEJM 2019
Facon T et al, EHA 2024

Facon T et al, NEJM 2024



Can we considered «cured» a portion of MM patients?



Tura Sante, edizione 2020

Ricerca clinica sul mieloma multiplo presso l' Istituto Seragnoli

- Dal 2001, oltre **150 studi interventistici** (fase I-III), di cui oltre **65 studi *ongoing***
- Dal 2001, oltre **50 studi osservazionali**, di cui oltre **20 studi *ongoing***
- Dal 2014, partecipazione ad oltre **20 studi registrativi** di regimi terapeutici standard (RRMM e NDMM)
- Dal 2018, **6 studi con cellule CAR-T**: KarMMa-1, KarMMa-2, KarMMa-3, CARTITUDE-4, CPHE885B12201, KarMMa-9
- **14 studi con BsAbs**: Teclistamab (MajesTEC-1, MajesTEC-3, MajesTEC-4, MajesTEC-7, MajesTEC-9), Elranatamab (MagnetisMM-5, MagnetisMM-7), Talquetamab (MonumentAL-3, MonumentAL-6), Cevostamab (CAMMA-2, CAMMA-3), Forimtamig (GRACE, GRACE COMBO), M22-947

Strategie terapeutiche innovative nel MM: partecipazione a studi registrativi

FIRST ^{a)}	Lenalidomide and dexamethasone vs Melphalan, Prednisone, thalidomide
ASPIRE ^{b)}	Carfilzomib, lenalidomide, and dexamethasone vs lenalidomide and dexamethasone
ELOQUENT-2 ^{c)}	Elotuzumab, lenalidomide and dexamethasone vs lenalidomide and dexamethasone
CASTOR ^{d)}	Daratumumab, Bortezomib and Dexamethasone vs Bortezomib and Dexamethasone
POLLUX ^{e)}	Daratumumab, lenalidomide, and dexamethasone vs lenalidomide and dexamethasone
ENDEAVOR ^{f)}	Carfilzomib and dexamethasone vs bortezomib and dexamethasone
TOURMALINE-1 ^{g)}	Ixazomib, lenalidomide and dexamethasone vs Placebo, lenalidomide and dexamethasone
ALCYONE ^{h)}	Daratumumab, bortezomib, Melphalan-Prednisone vs bortezomib, Melphalan-Prednisone
ELOQUENT-3 ⁱ⁾	Elotuzumab, pomalidomide and dexamethasone vs pomalidomide and dexamethasone
ICARIA-MM ^{j)}	Isatuximab, pomalidomide and dexamethasone vs pomalidomide and dexamethasone

BOSTON ^{k)}	Bortezomib, selinexor, and dexamethasone (once- vs twice-weekly regimen)
IKEMA ^{l)}	Isatuximab, carfilzomib and dexamethasone vs carfilzomib and dexamethasone
APOLLO ^{m)}	Daratumumab, pomalidomide and dexamethasone vs pomalidomide and dexamethasone
KarMMa ⁿ⁾	Ide-cel in RRMM
MajesTEC-1 ^{o)}	Teclistamab in RRMM
CARTTUDE-4 ^{p)}	Cilta-cel vs Standard Care
PERSEUS ^{q)}	Daratumumab, bortezomib, lenalidomide, and dexamethasone vs bortezomib, lenalidomide, and dexamethasone
DREAMM-7 ^{r)}	Belamaf, bortezomib and dexamethasone vs daratumumab, bortezomib and dexamethasone
DREAMM-8 ^{s)}	Belamaf, pomalidomide and dexamethasone vs bortezomib, pomalidomide and dexamethasone
MajesTEC-4* (...) MagnetisMM-7*	Teclistamab and lenalidomide vs lenalidomide (...) Elranatamab vs Lenalidomide After ASCT

References:

- a) FIRST: *Benboubker, N Engl J Med* 2014
- b) ASPIRE: *Stewart, NEJM* 2015
- c) ELOQUENT-2: *Lonial, NEJM* 2015
- d) CASTOR: *Palumbo, NEJM* 2016
- e) POLLUX: *Dimopoulos, NEJM* 2016
- f) ENDEAVOR: *Dimopoulos, Lancet Oncology* 2016
- g) TOURMALINE-1: *Moreau, NEJM* 2016
- h) ALCYONE: *Mateos, NEJM* 2018
- i) ELOQUENT-3: *Dimopoulos, NEJM* 2018
- j) ICARIA: *Attal, Lancet*, 2019
- k) BOSTON: *Grosicki, Lancet*, 2020
- l) IKEMA: *Moreau, Lancet*, 2021
- m) APOLLO: *Dimopoulos, Lancet Oncol*, 2021
- n) KarMMa: *Munshi, NEJM*, 2021
- o) MajesTEC-1: *Usmani, Lancet*, 2021
- p) CARTTUDE-4: *San-Miguel, NEJM*, 2023
- q) PERSEUS: *Sonneveld, NEJM*, 2024
- r) DreaMM-7: *Hungria, NEJM*, 2024
- s) DreaMM-8: *Dimopoulos, NEJM*, 2024

*Recruiting phase ongoing



• National and international collaborations

- International Myeloma Working Group
- International Myeloma Society
- European Myeloma Network
- European Hematology Association
- European Myeloma Network Italy
- European Society of Medical Oncology
- Società Italiana di Ematologia
- GIMEMA
- Associazione Italiana Oncologia medica



Elena Zamagni current member of the IMS board of director as representative for Europe



The new role of imaging in MM

International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma



S Vincent Rajkumar, Meletios A Dimopoulos, Antonio Palumbo, Joan Blade, Giampaolo Mezzini, María-Victoria Mateos, Shaji Kumar, Jens Hillengass, Efstathios Kastritis, Paul Richardson, Ola Landgren, Bruno Paiva, Angela Dispenzieri, Brendan Weiss, Xavier LeLeu, Sonja Zweegman, Sagar Lonial, Laura Rosinol, Elena Zamagni, Sundar Jagannath, Orhan Sezer, Sigurdur Y Kristinsson, Jo Caers, Saad Z Usmani, Juan José Lahuerta, Hans Erik Johnsen, Meral Beksar, Michele Cavo, Hartmut Goldschmidt, Evangelos Terpos, Robert A Kyle, Kenneth C Anderson, Brian G M Durie, Jesus F San Miguel

From CRAB to MDE (CRAB + SLiM CRAB)

International myeloma working group consensus recommendations on imaging in monoclonal plasma cell disorders

Jens Hillengass, Saad Usmani, S Vincent Rajkumar, Brian G M Durie, María-Victoria Mateos, Sagar Lonial, Cristina Joao, Kenneth C Anderson, Ramón García-Sanz, Eloísa Riva, Juan Du, Niels van de Donk, Jesús G Berdeja, Evangelos Terpos, Elena Zamagni, Robert A Kyle, Jesús San Miguel, Hartmut Goldschmidt, Sergio Giral, Shaji Kumar, Noopur Raje, Heinz Ludwig, Enrique Ocio, Rik Schots, Hermann Einsele, Fredrik Schjesvold, Wen-Ming Chen, Niels Abildgaard, Brea C Lipe, Dominik Dytfeld, Baldeep MonaWirk, Matthew Drake, Michele Cavo, Juan José Lahuerta, Suzanne Lentzsch

Role of ¹⁸F-FDG PET/CT in the diagnosis and management of multiple myeloma and other plasma cell disorders: a consensus statement by the International Myeloma Working Group



Michele Cavo, Evangelos Terpos, Cristina Nanni, Philippe Moreau, Suzanne Lentzsch, Sonja Zweegman, Jens Hillengass, Monika Engelhardt, Saad Z Usmani, David H Vesole, Jesus San-Miguel, Shaji K Kumar, Paul G Richardson, Joseph R Mikhael, Fernando Ledo da Costa, Meletios-Athanasios Dimopoulos, Chiara Zingaretti, Niels Abildgaard, Hartmut Goldschmidt, Robert Z Orłowski, Wee Joo Chng, Hermann Einsele, Sagar Lonial, Bart Barlogie, Kenneth C Anderson, S Vincent Rajkumar, Brian G M Durie, Elena Zamagni

Standardization of ¹⁸F-FDG–PET/CT According to Deauville Criteria for Metabolic Complete Response Definition in Newly Diagnosed Multiple Myeloma

original reports

Elena Zamagni, MD, PhD¹; Cristina Nanni, MD²; Luca Dozza, MS¹; Thomas Carlier, PhD³; Clément Bailly, MD, PhD³; Paola Tacchetti, MD¹; Annibale Versari, MD⁴; Stephane Chauvie, PhD⁵; Andrea Gallamini, MD⁶; Barbara Gamberi, MD⁷; Denis Caillot, MD⁸; Francesca Patriarca, PhD⁹; Margaret Macro, MD¹⁰; Mario Boccadoro, MD, PhD¹¹; Laurent Garderet, MD¹²; Simona Barbato, PhD¹; Stefano Fanti, MD²; Aurore Perrot, MD¹³; Francesca Gay, MD¹¹; Peter Sonneveld, MD, PhD¹⁴; Lionel Karlin, MD¹⁵; Michele Cavo, MD, PhD¹; Caroline Bodet-Milin, MD³; Philippe Moreau, MD, PhD¹⁶; and Françoise Kraeber-Bodéré, MD, PhD³

Active and continuous collaboration with Nuclear Medicine and Radiology of IRCCS S. Orsola-Malpighi

Rajkumar V et al, Lancet Oncology 2014
Hillengass J et al, Lancet Oncology 2019

Cavo M et al, Lancet Oncology 2017
Zamagni E et al, JCO 2021



Beyond conventional CR MRD detection and novel response criteria

International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma



Shaji Kumar, Bruno Paiva, Kenneth C Anderson, Brian Durie, Ola Landgren, Philippe Moreau, Nikhil Munshi, Sagar Lonial, Joan Bladé, Maria-Victoria Mateos, Meletios Dimopoulos, Efsthios Kastritis, Mario Boccadoro, Robert Orłowski, Hartmut Goldschmidt, Andrew Spencer, Jian Hou, Wee Joo Chng, Saad Z Usmani, Elena Zamagni, Kazuyuki Shimizu, Sundar Jagannath, Hans E Johnsen, Evangelos Terpos, Anthony Reiman, Robert A Kyle, Pieter Sonneveld, Paul G Richardson, Philip McCarthy, Heinz Ludwig, Wenming Chen, Michele Cavo, Jean-Luc Harousseau, Suzanne Lentzsch, Jens Hillengass, Antonio Palumbo, Alberto Orfao, S Vincent Rajkumar, Jesus San Miguel, Herve Avet-Loiseau

Response criteria*

IMWG MRD criteria (requires a complete response as defined below)

Sustained MRD-negative	MRD negativity in the marrow (NGF or NGS, or both) and by imaging as defined below, confirmed minimum of 1 year apart. Subsequent evaluations can be used to further specify the duration of negativity (eg, MRD-negative at 5 years)†
Flow MRD-negative	Absence of phenotypically aberrant clonal plasma cells by NGF‡ on bone marrow aspirates using the EuroFlow standard operation procedure for MRD detection in multiple myeloma (or validated equivalent method) with a minimum sensitivity of 1 in 10 ⁵ nucleated cells or higher
Sequencing MRD-negative	Absence of clonal plasma cells by NGS on bone marrow aspirate in which presence of a clone is defined as less than two identical sequencing reads obtained after DNA sequencing of bone marrow aspirates using the LymphoSIGHT platform (or validated equivalent method) with a minimum sensitivity of 1 in 10 ⁵ nucleated cells§ or higher
Imaging plus MRD-negative	MRD negativity as defined by NGF or NGS plus disappearance of every area of increased tracer uptake found at baseline or a preceding PET/CT or decrease to less mediastinal blood pool SUV or decrease to less than that of surrounding normal tissue¶

Standard IMWG response criteria||

Stringent complete response	Complete response as defined below plus normal FLC ratio** and absence of clonal cells in bone marrow biopsy by immunohistochemistry (κ/λ ratio ≤4:1 or ≥1:2 for κ and λ patients, respectively, after counting ≥100 plasma cells)††
Complete response	Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and <5% plasma cells in bone marrow aspirates



L'EMATOLOGIA "SERÀGNOLI"
E LA SCUOLA EMATOLOGICA BOLOGNESE:
UNA STORIA DI 50 ANNI

The biology of Multiple Myeloma

Carolina Terragna

IRCCS Azienda Ospedaliero-Universitaria di Bologna

UNIVERSITÀ DEGLI STUDI
ISTITUTO DI EMATOLOGIA E ONCOLOGIA MEDICA
LORENZO E ARIOSTO SERÀGNOLI

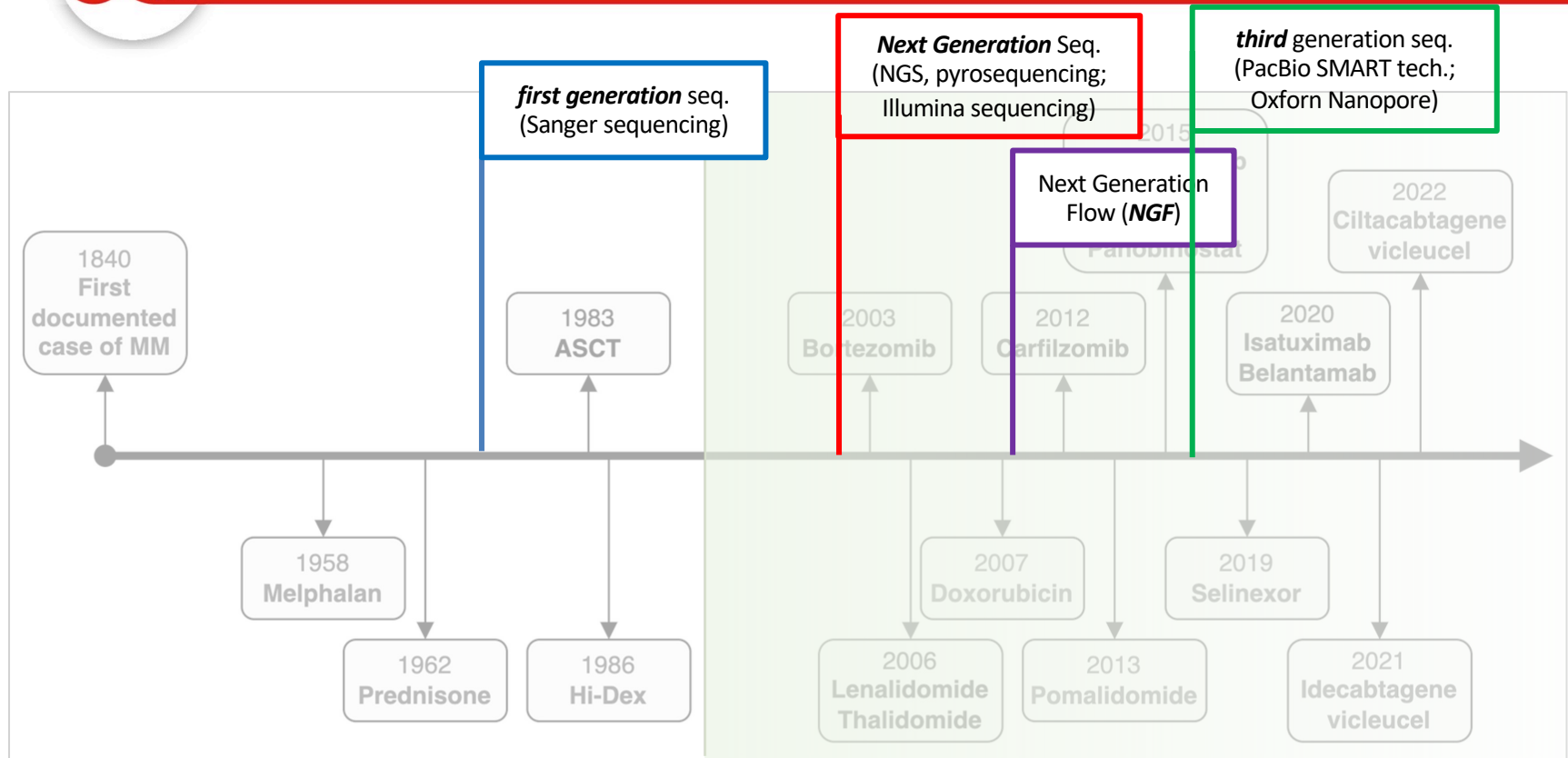


Disclosures of Carolina Terragna

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Janssen	X						
Werfen					X		
Miltenyi					X		



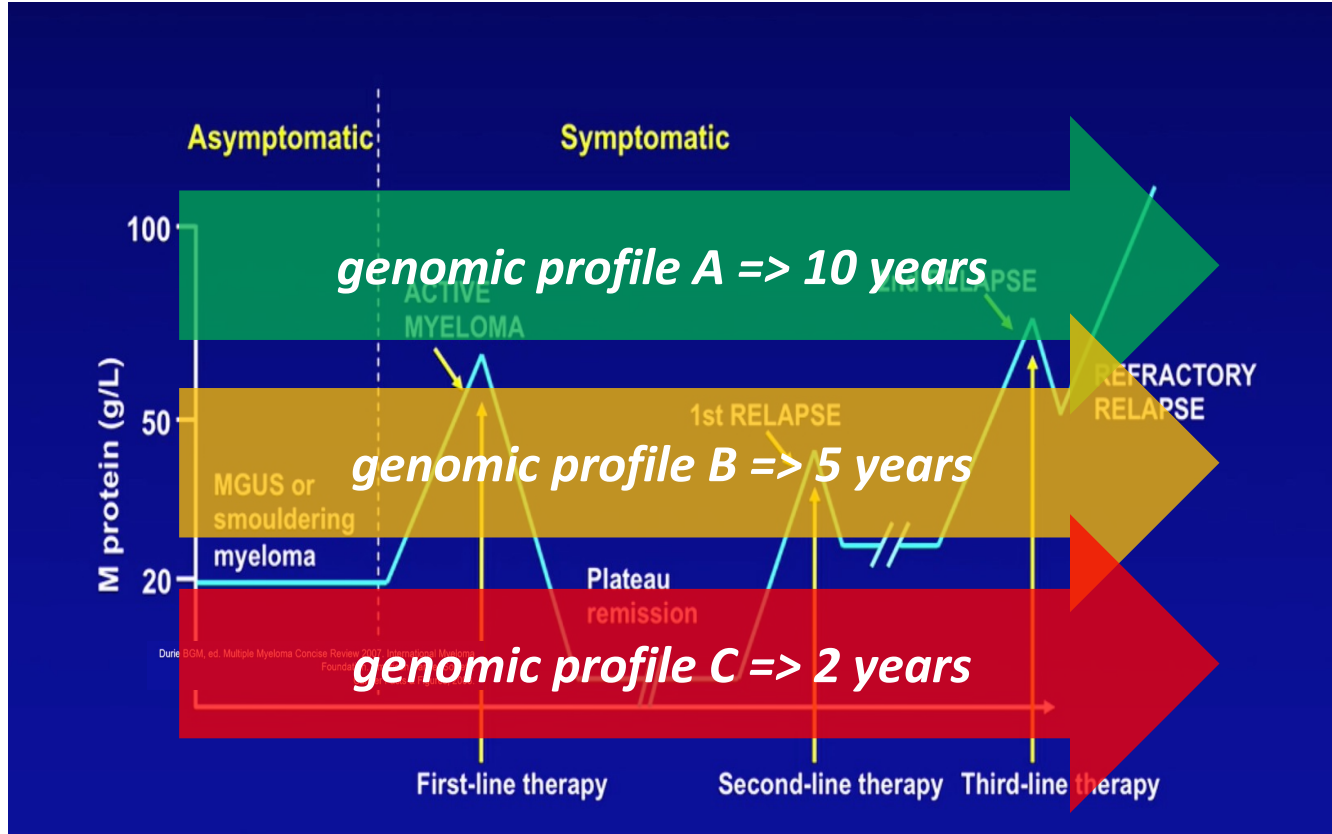
novel drugs & NEXT-gen technologies



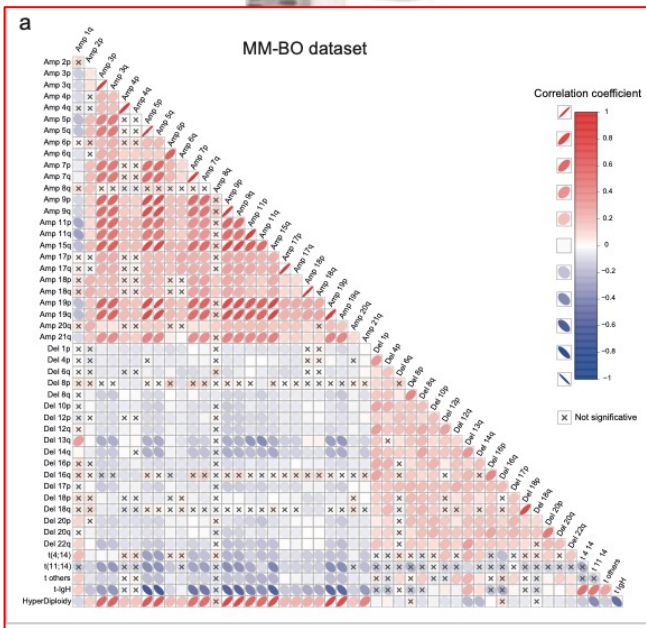
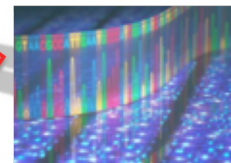
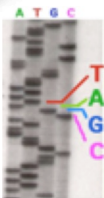
Kumar S, et al. Lancet Oncol 2016;17:e328–46



WHY should we value MM biology

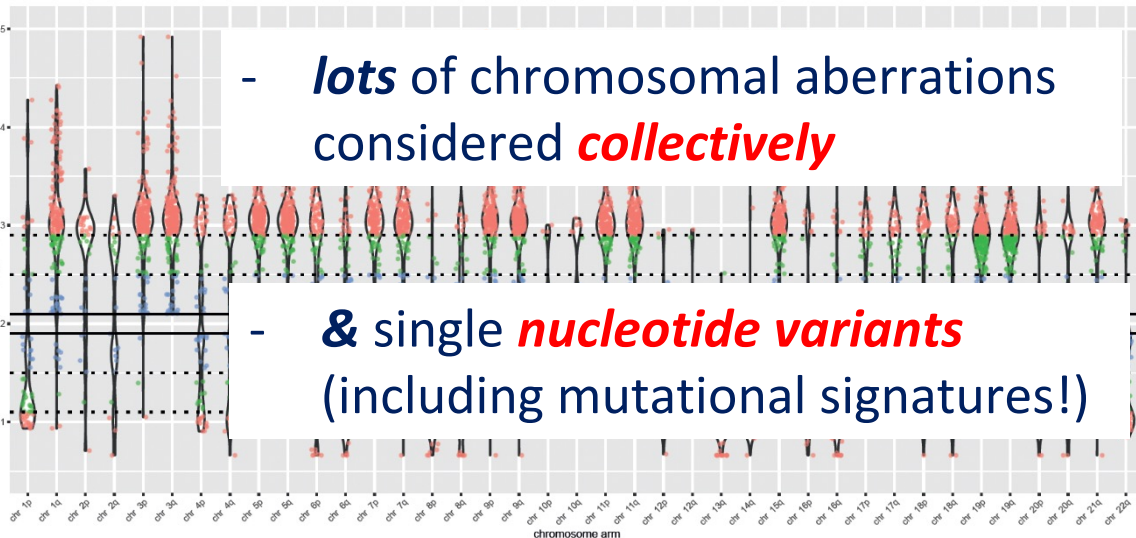


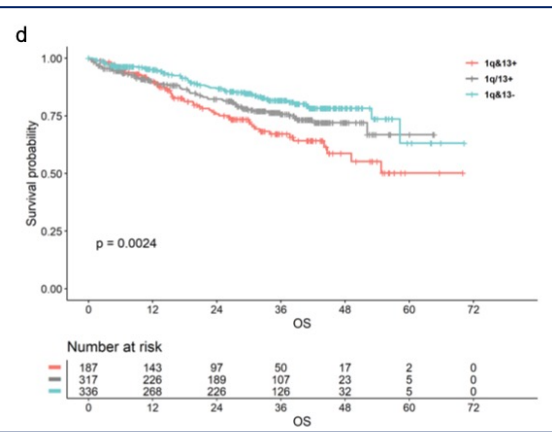
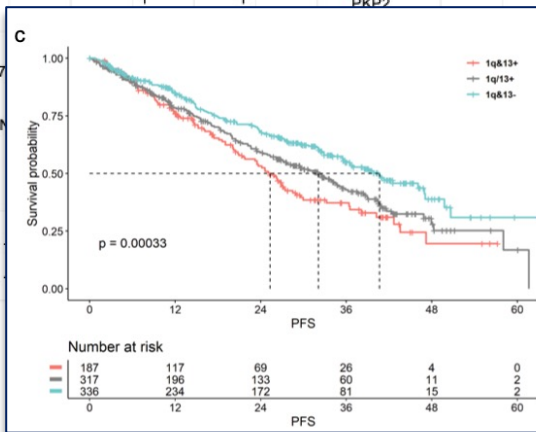
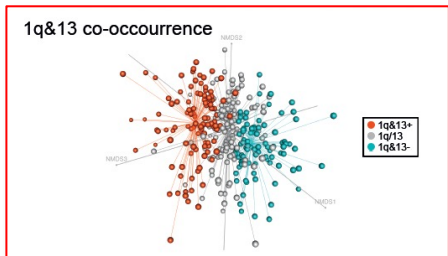
1. MM *genomic* landscape



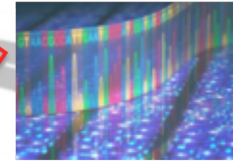
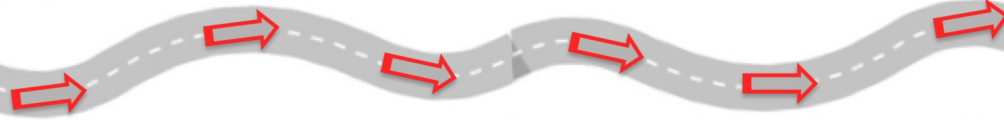
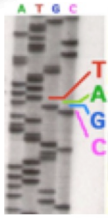
BO dataset

status: ● clonal ● subclonal major ● subclonal minor



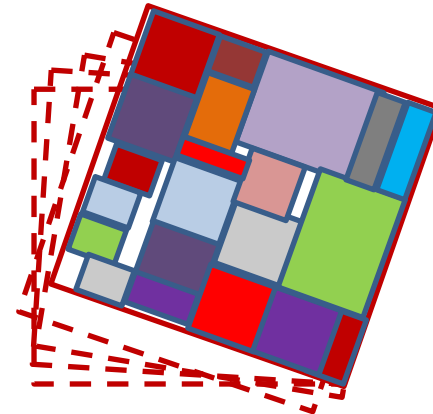
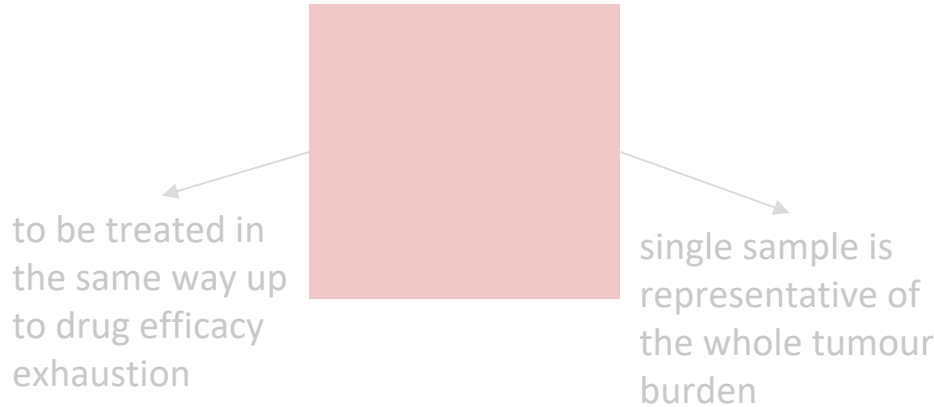


2. MM disease *dynamics*



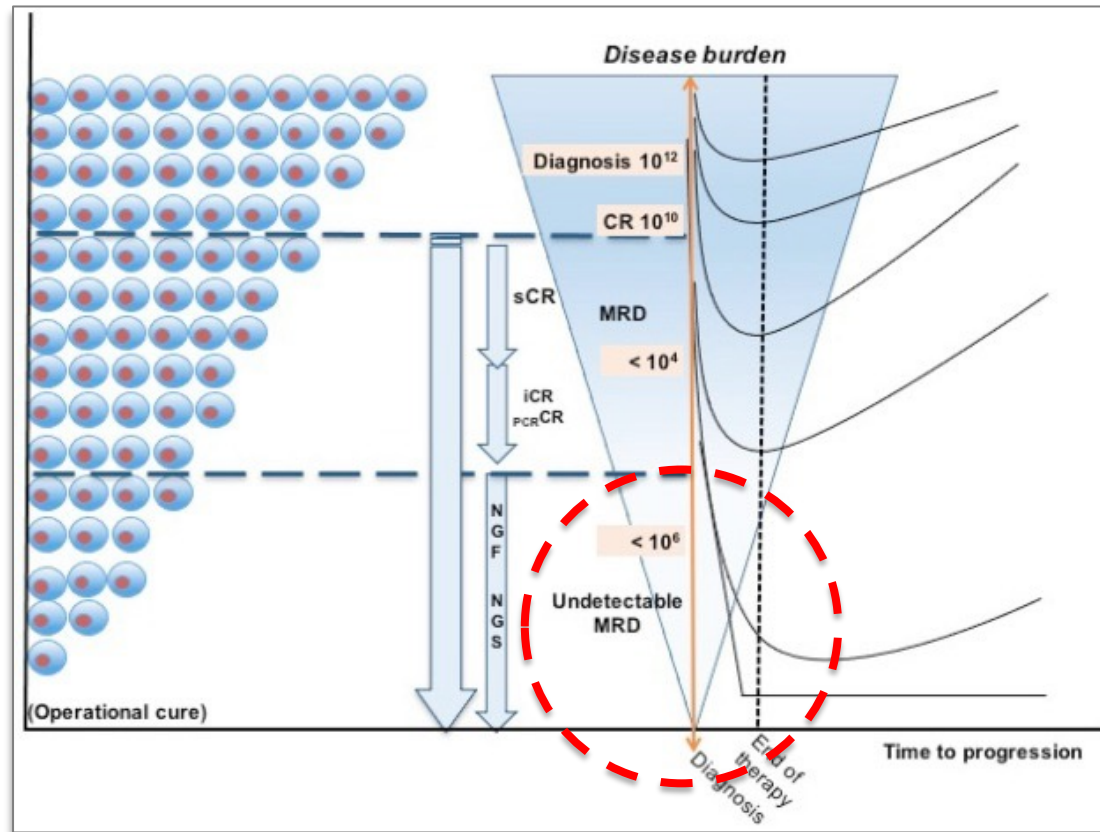
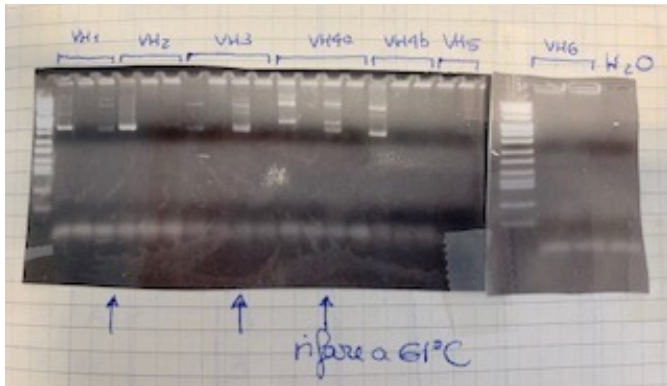
- MM is a **STATIC & HOMOGENEOUS** disease

- MM is a **DYNAMIC & HETEROGENEOUS** disease!!



=> therapy can **SHAPE** the clonal dynamics!!

MRD assessment



Cavo M., Terragna C. et al, Blood, 2000
 Martinelli G., Terragna C. et al, JCO, 2000



MRD assessment



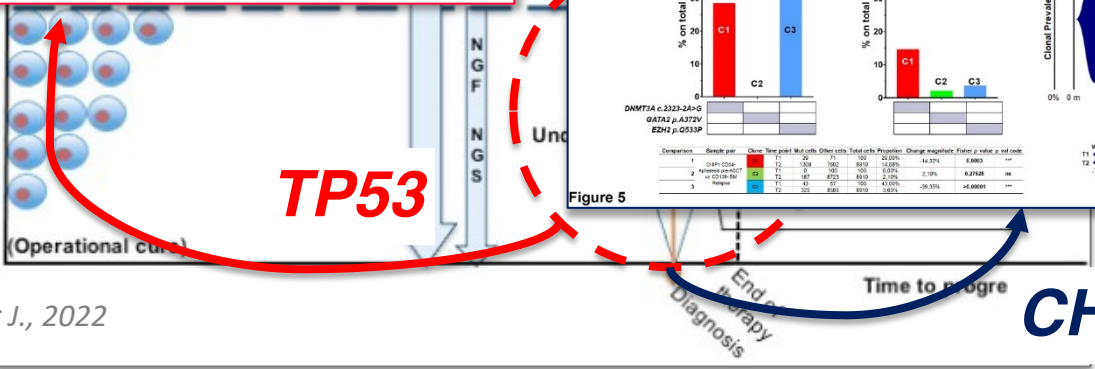
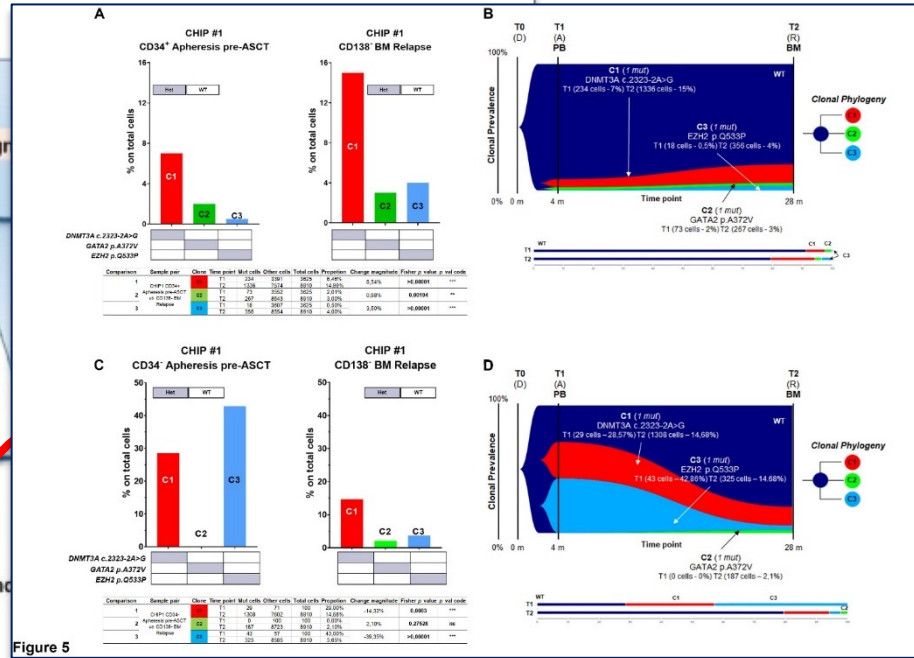
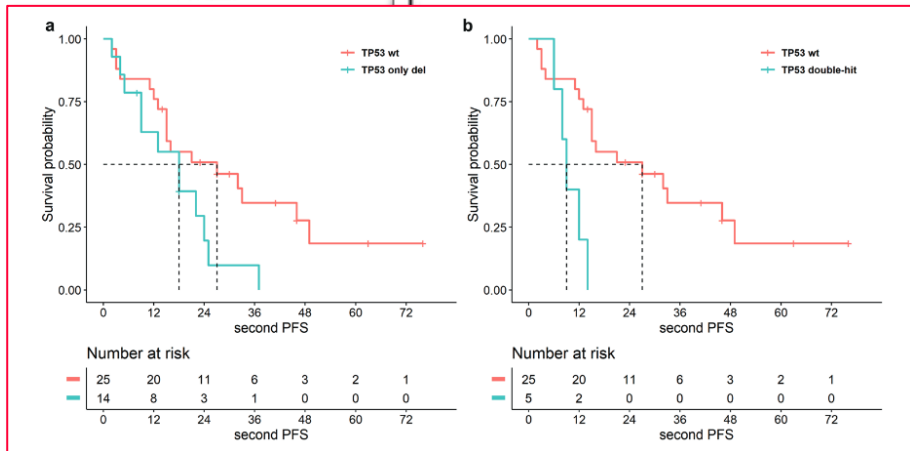
1. FDA-approved method, CE-IVD marked for both clonotype and MRD assessment, either commercially available or tech-transfer; expansive, BUT **10^{-6} sensitivity guaranteed**

=> clinical trials & **daily practice (?)**

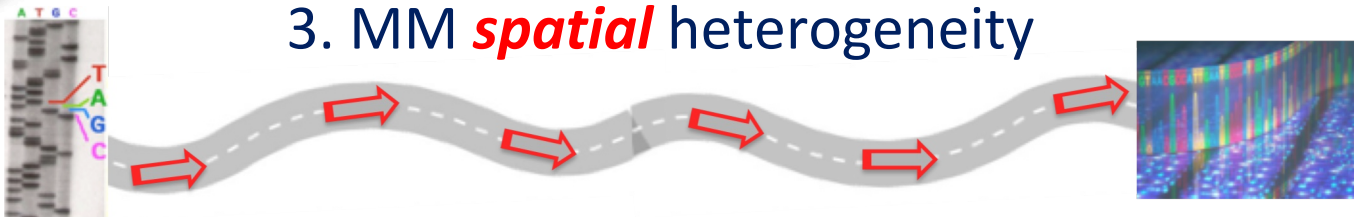
2. unvalidated method, CE-IVD marked for clonotype assessment (MRD assessment is RUO); less expansive at 10^{-5} , sensitivity up to 10^{-6} ; **ongoing validation** in the context of an Italian network

=> **daily practice**

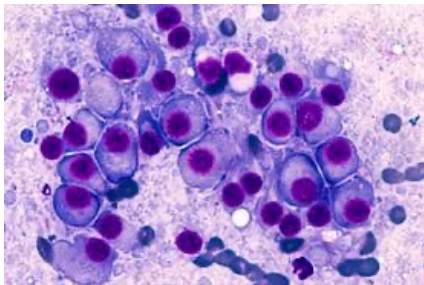




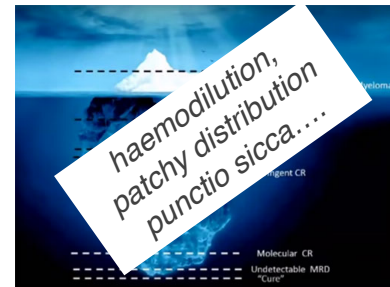
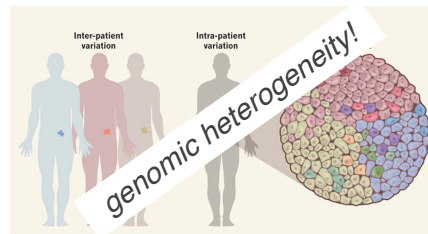
3. MM *spatial* heterogeneity



- just one BM aspirate is representative of the disease: the disease is **HOMOGENEOUS**

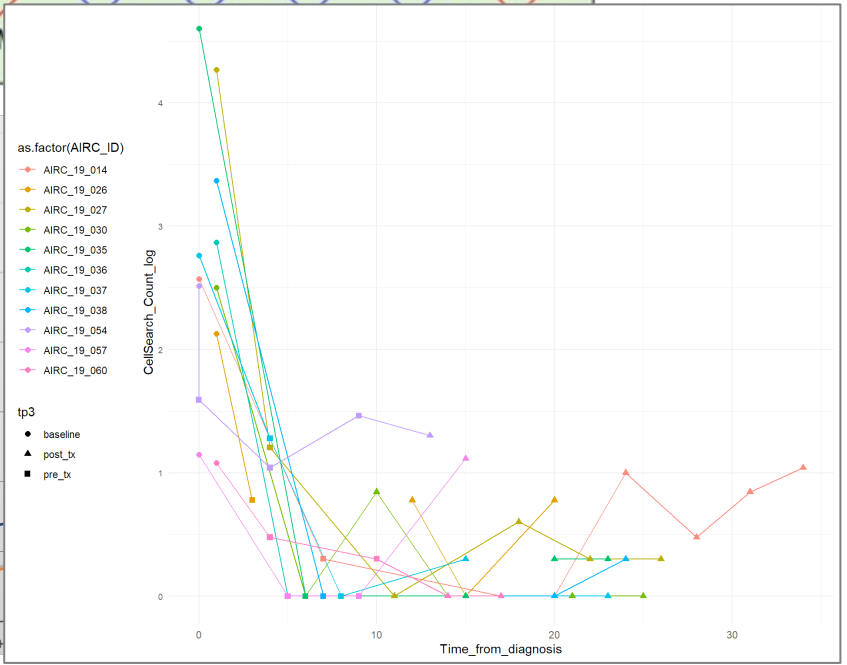
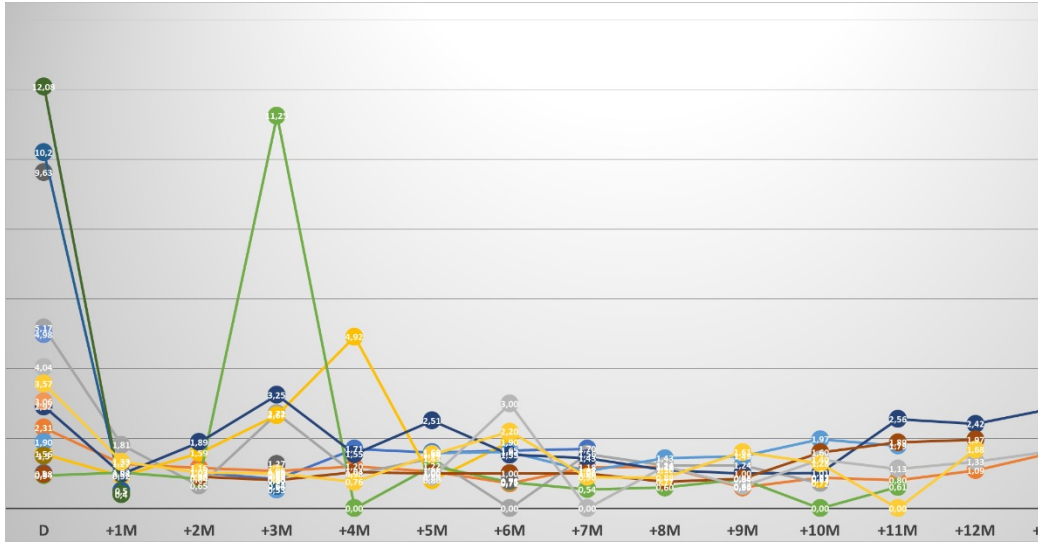
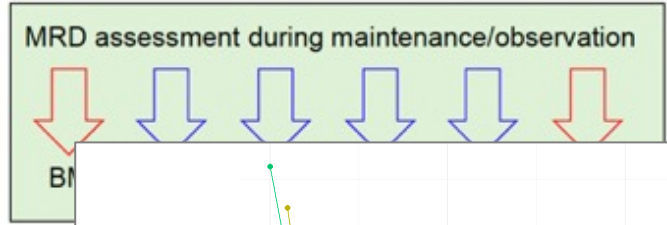
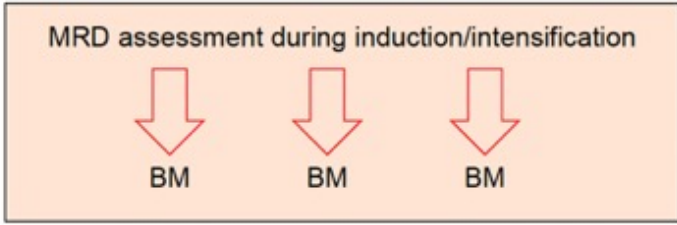


- MM is **HETEROGENEOUS**: a multimodal approach (including *imaging* and *liquid biopsy*) should be implemented to reliably monitor the disease dynamics





MM is (also) in the PB



Martello M. et al, submitted

Vigliotta I. et al, manuscript in prep.



thank's

Multiple Myeloma Research Unit

prof. Michele Cavo



MOL BIOL LAB

Marina Martello, Enrica Borsi, Silvia Armuzzi, Ilaria Vigliotta, Barbara Taurisano, Ignazia Pistis

BIOINFO NERDs

Vincenza Solli, Andrea Poletti, Gaia Mazzocchetti, Viola Vuong Meixian



CLINICAL RESEARCH UNIT

Elena Zamagni, Paola Tacchetti, Lucia Pantani, Katia Mancuso, Ilaria Rizzello, Chiara Sartor, Miriam Iezza, Marco Talarico, Flavia Bigi, Michele Puppi, Enrica Manzato, Ilaria Sacchetti, Simone Masci, Roberta Restuccia

DATA ANALYSIS & MANAGEMENT

Simona Barbato, Giorgia Lazzarini, Alessandra Scatà, Francesca Michela Trombetta, Nicola Parisi, Nicola Paprusso, Federica Di Camillo, Luca Pedrini



thank's



*Sante Tura
Giovanni Martinelli
Roberto Massimo Lemoli
Michele Baccarani*

*Nicoletta Testoni
Vittorio Montefusco
Patrizia Farabegoli
Marilina Amabile
Simonetta Rizzi
Marina Ratta
Ilaria Iacobucci
Daniel Remondini
Gastone Castellani
Giulia Marzocchi
Gaia Ameli*

*Maria Stella Zagarella
Alessandra Vittone
Maura Rossi
Matteo Renzulli
Francesca Chiavaroli
Sandra Durante
Angela Flores Dico
Rosalinda Termini
Chiara Benni
Barbara Santacroce
Mauro Procacci
Luca Cifarelli
Agboyi Emmanuel Lakbo
Ajisi Kanapari*



Conclusion

- The survival outcomes of patients with MM has tripled in the last 10 years, regardless of age
- Current treatment algorithm, along different disease' phases, is based on the combination of the 3 main classes of agents (proteasome inhibitors, IMiDs and anti- CD-38 Mo Abs) (triplets or quadruplets) and on immunotherapy (CARTs, Bispecifics, ADC)
- Newer and highly sensitive tools in the bone marrow, peripheral blood and imaging are routinely available, for prognostication and to drive the treatment
- We are starting the era of «MRD-tailored» and «individualized» treatment
- The cure of Myeloma is possible!



Team clinico

3 medici strutturati
2 RTD-A
1 Post-Doc
2 PhD students
6 MFS
3 collaboratori ricerca sanitaria
5 assegnisti di ricerca
1 amministrativo

Ricerca traslazionale

1 dirigente biologo
1 RTD-A
1 collaboratore
1 ricercatore sanitario
2 Assegnisti di ricerca
1 tecnico di laboratorio
3 bioinformatici
2 statistici