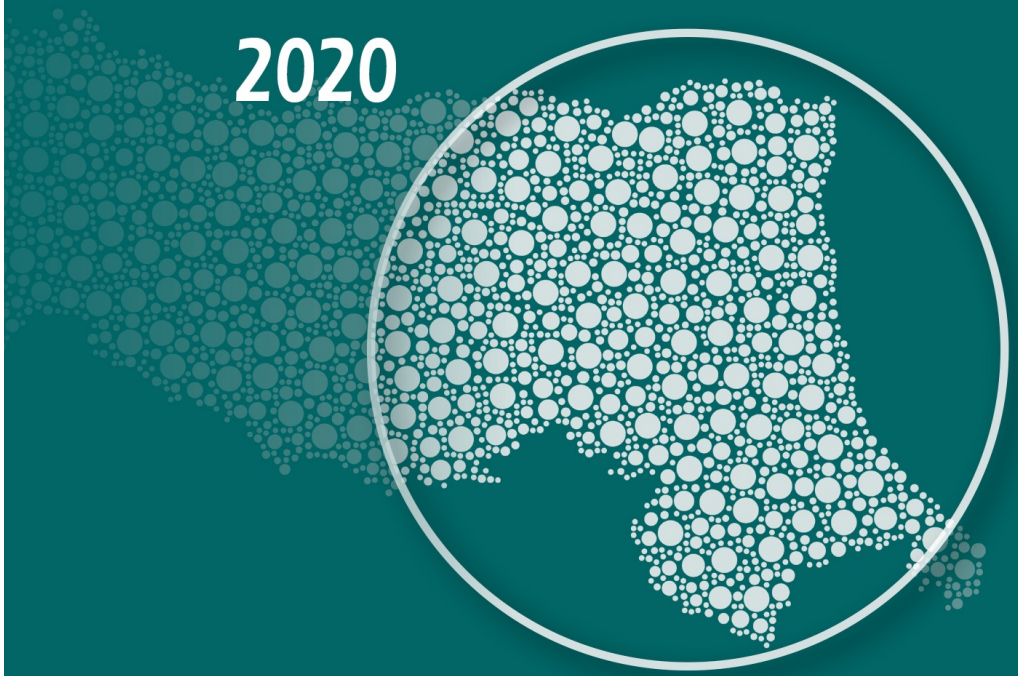


Progetto Ematologia Romagna

Mieloma multiplo: i lunghi sopravviventi

Introduzione

DIPARTIMENTO DI MEDICINA SPECIALISTICA, DIAGNOSTICA E SPERIMENTALE

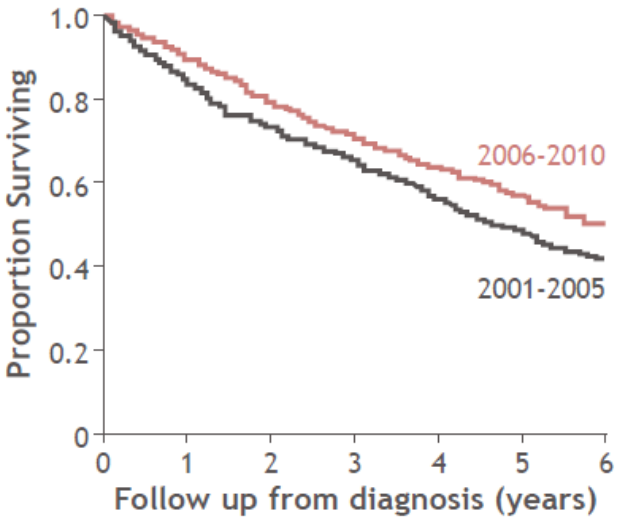
Elena Zamagni

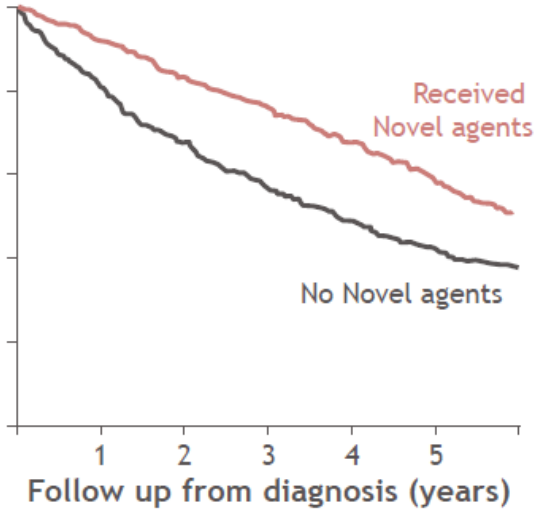
DIPARTIMENTO DI MEDICINA SPECIALISTICA, DIAGNOSTICA E SPERIMENTALE

Azienda Ospedaliero-Universitaria di Bologna; Istituto di Ematologia “Seràgnoli”; Dipartimento di Medicina Specialistica, Diagnostica e Sperimentale; Università degli Studi di Bologna

Improvement in MM outcome: Longer overall survival

- There are 1038 patients grouped into 2001-2005 and 2006-2010 cohorts
- Use of novel agents in treatment regimens improved OS





MM, multiple myeloma.
Kumar SK, et al. *Leukemia* 2014;28:1122-28.

IMWG MRD criteria

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

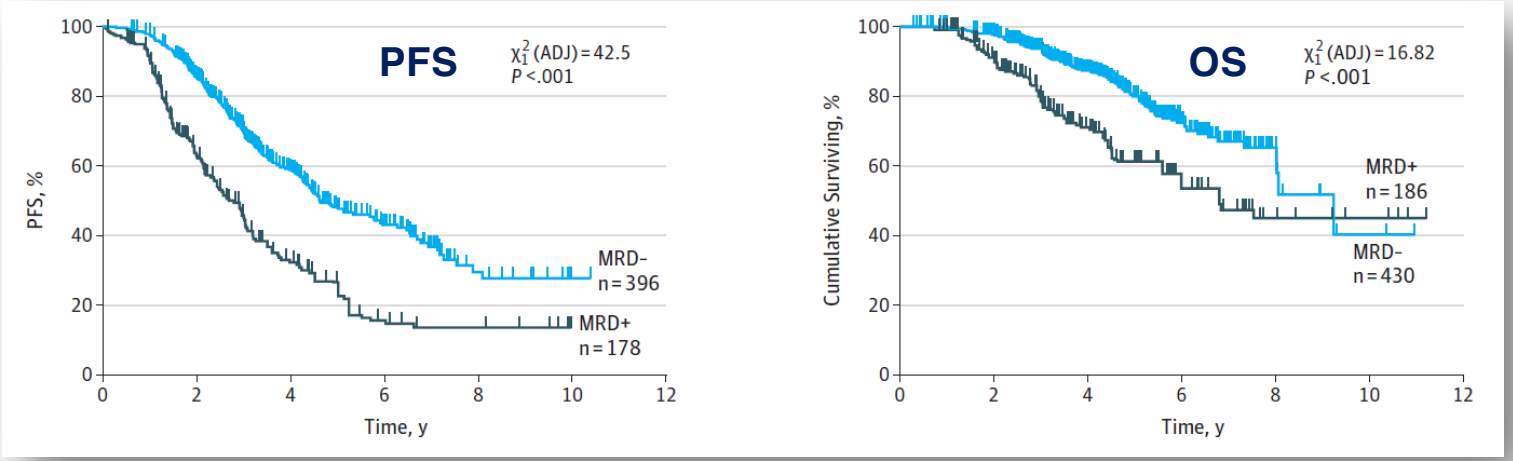
Shaji Kumar, Bruno Paiva, Kenneth C Anderson, Brian Durie, Ola Landgren, Philippe Moreau, Nikhil Munshi, Sagar Lonial, Joan Bladé, Maria-Victoria Mateos, Meletios Dimopoulos, Efstathios Kastritis, Mario Boccadoro, Robert Orlowski, Hartmut Goldschmidt, Andrew Spencer, Jian Hou, Wee Joo Chng, Saad Z Usmani, 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

IMWG MRD negativity criteria
(requires a complete response)

Response SubCategory	Response Criteria
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 positive 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

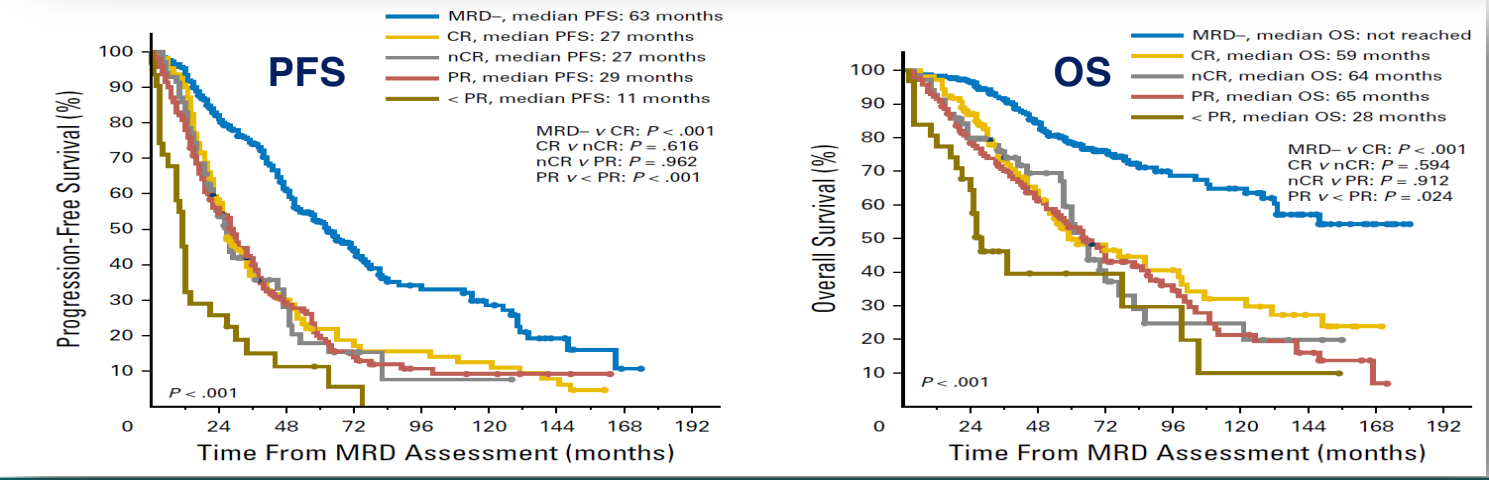
Kumar SK, et al. Lancet Oncology 2016;17(8):e328-e346

MRD is the best biomarker to predict outcome and overseeds CR



Meta-analysis of MRD studies (CR patients)

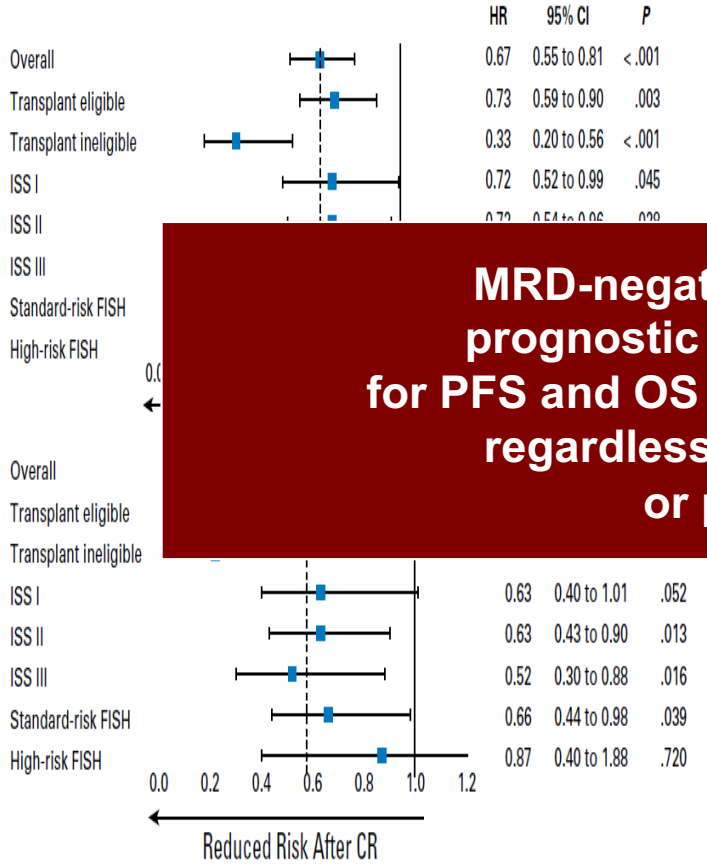
Munshi NC, *et al. JAMA Oncol* 2017;3:28-35



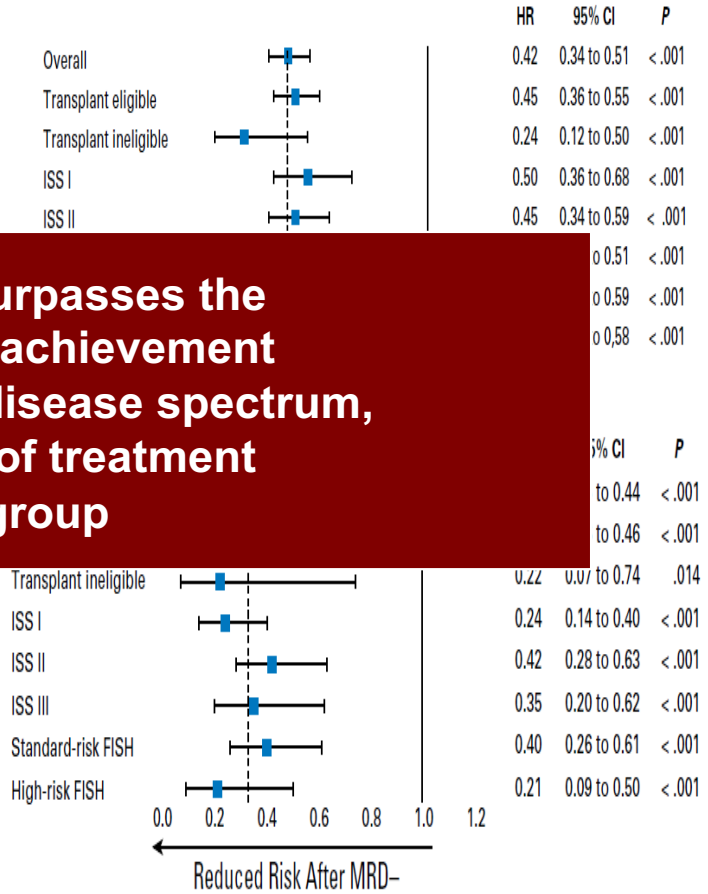
Lahuerta JJ, *et al. JCO* 2017;35:2900-10

Depth of response and survival: importance in different settings

PFS

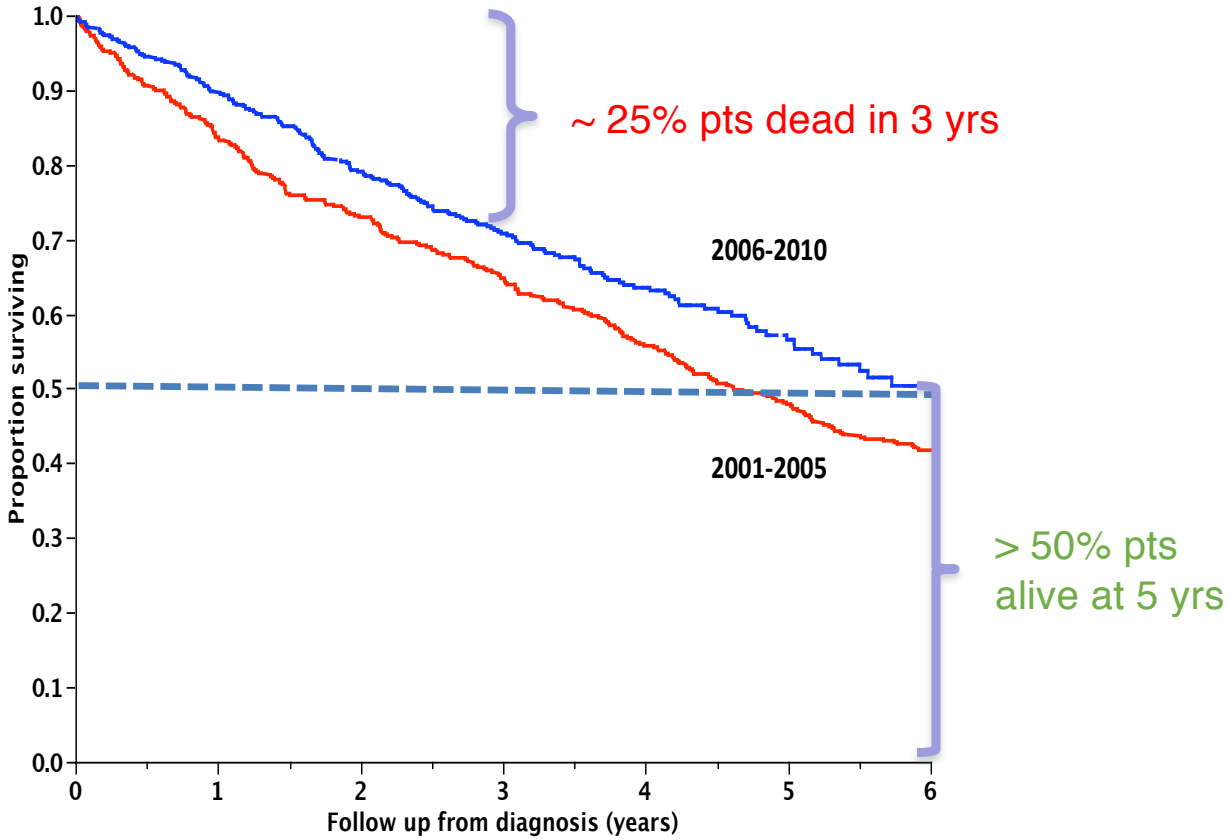


OS



MRD-negative status surpasses the prognostic value of CR achievement for PFS and OS across the disease spectrum, regardless of the type of treatment or patient risk group

Myeloma Is Not One Disease



Kumar SK, et al. Leukemia. 2014;28:1122-1128

Prognostic factors in MM

Patient-related

- Age
- Performance status, comorbidities

Disease-related

- High β_2 microglobulin
- Low albumin
- Renal impairment
- LDH above the upper limit
- Cytogenetic abnormalities
- Gene expression profile
- Circulating plasma cells
- Extramedullary disease
- High proliferation rate

ISS → **Disease burden**

Disease biology

At diagnosis

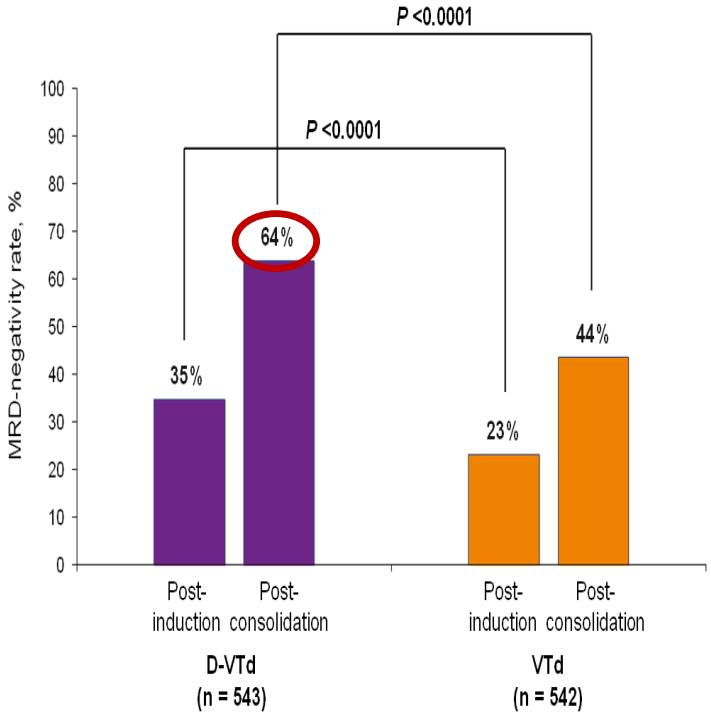
Therapy-related

- Quality of response
- Early relapse

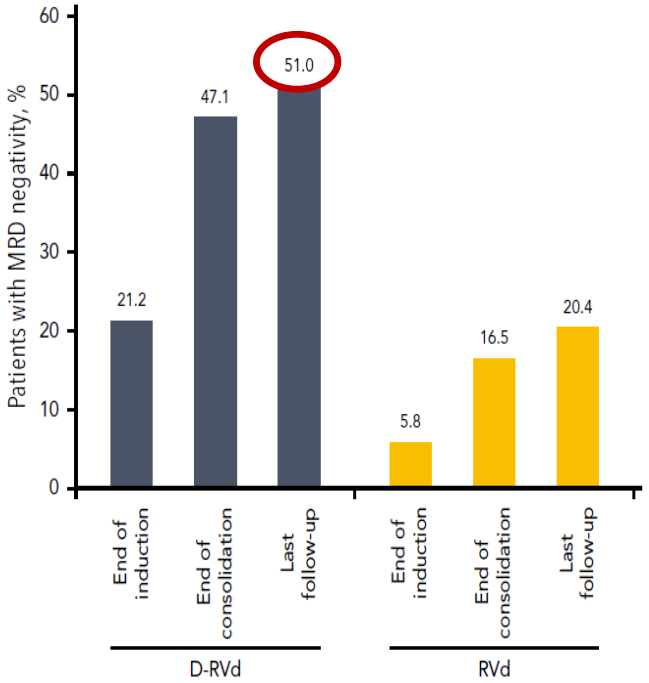
Dynamic Model

Modern induction and post-ASCT consolidation/maintenance therapies are inducing high rates of MRD negativity: MRD data (10^{-5})

CASSIOPEIA study



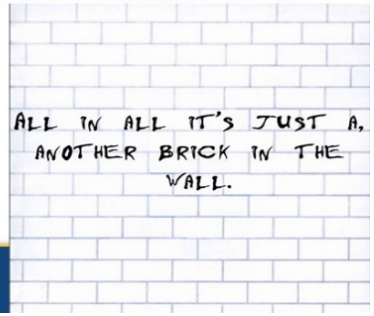
GRIFFIN study



Moreau et al. The Lancet 2019;394:29-38; Avet-Loiseau H, et al. IMW 2019,Oral presentation; Voorhees PM et al., Blood. 2020;136(8):936-945

High-risk MM: ”the black beast of MM”

- Ongoing work needed to standardize and better classify all patients in terms of risk stratification
- Despite marked improvement in outcomes of Myeloma patients; high-risk disease continues to suffer from worse outcomes
- Intensification of induction therapy may be needed to achieve functionally deep remissions (MRD- and beyond) in the high risk population
  - Quadruplet induction strategies **(Weisel, et al. / Usmani, et al.)**
  - Continued benefit of HDM; with some patients benefiting from tandem ASCT **(Hari, et al.)**
- These presentations provide a necessary framework towards the evolution of a risk-adapted treatment algorithm to overcome high-risk disease

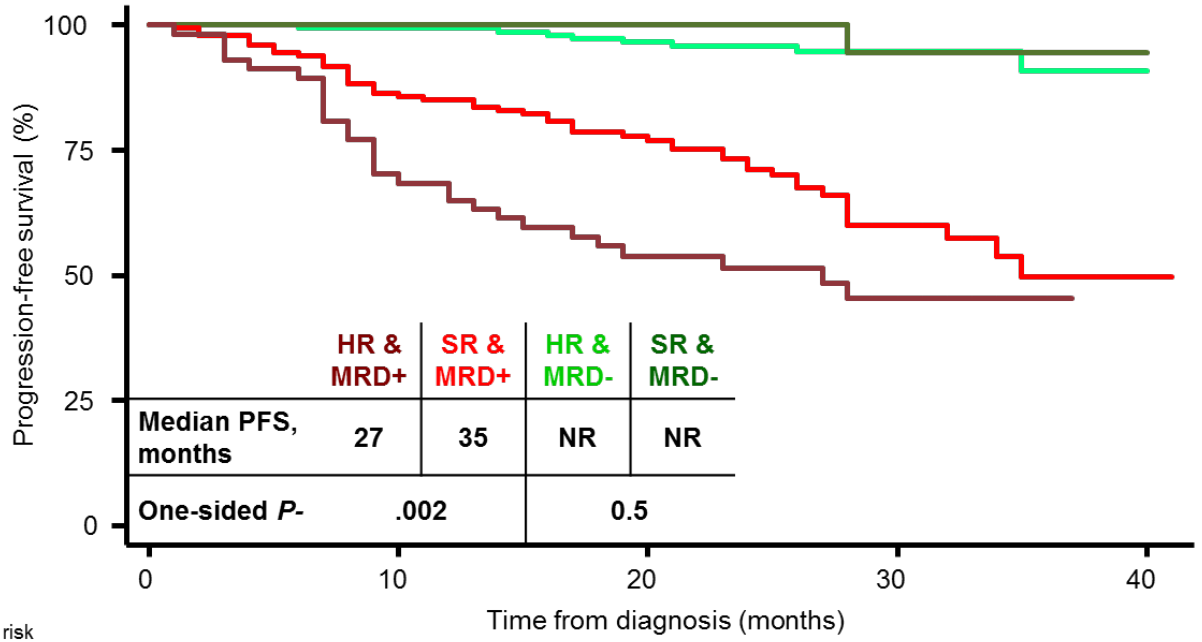


PRESENTED AT: 2020 ASCO ANNUAL MEETING #ASCO20 Slides are the property of the author, permission required for reuse. PRESENTED BY: Joshua Richter, MD

Richter J et al, ASCO 2020 educational session

Relationship between risk and depth of the response

Progression-free survival according to FISH and NGF



Number at risk					
SR FISH & MRD-neg	0	151	122	59	1
HR FISH & MRD-neg	0	33	28	14	2
SR FISH & MRD-pos	300	126	93	31	3
HR FISH & MRD-pos	90	40	27	12	0

HR FISH: t(4;14), t(14;16) and/or del(17p)

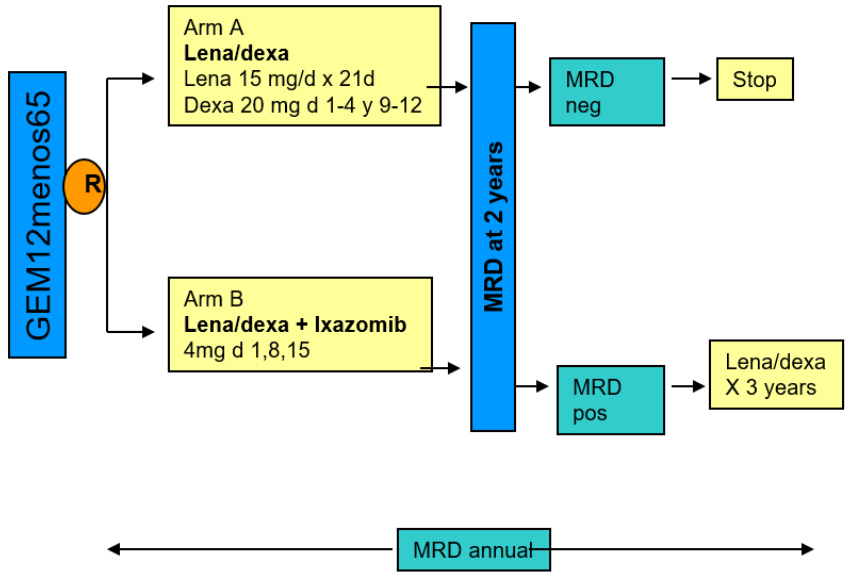
The best pathway to overcome the poor prognosis of HRCA is through the achievement of MRD-negativity

Paiva B et al. ASH 2017

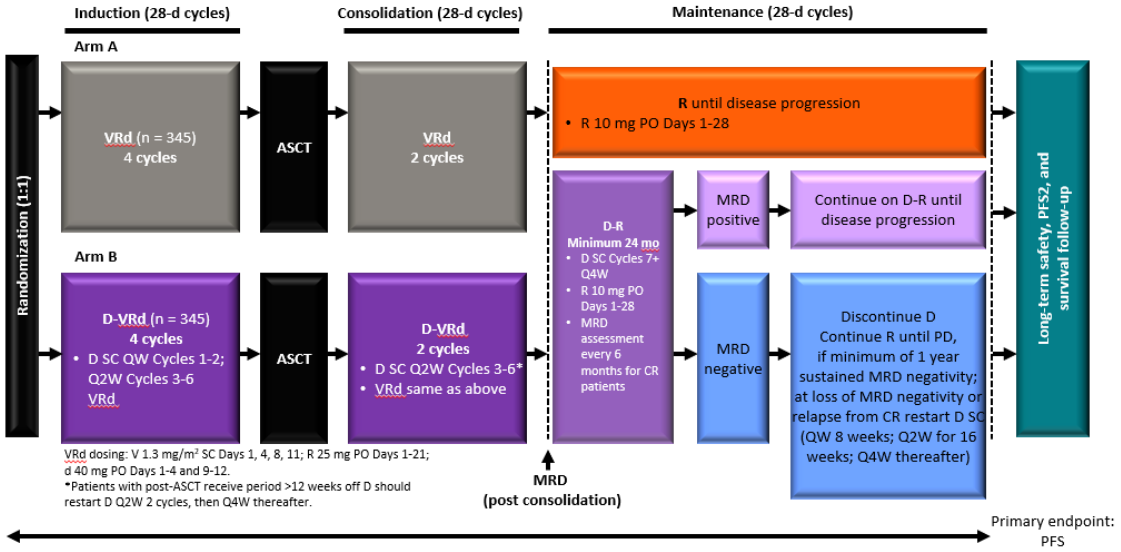
Goicoechea I, *et al. Blood 2020*

Current trials with MRD-driven maintenance

GEM12MENOS65 trial



PERSEUS trial

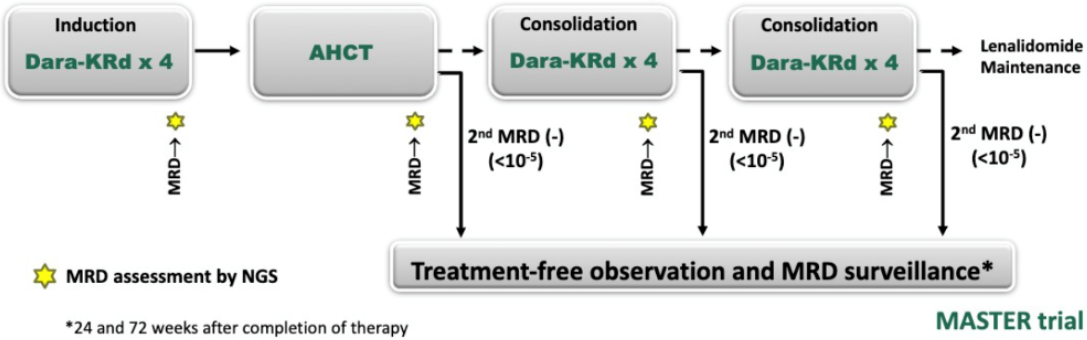


DSC, daratumumab subcutaneous; RVd, lenalidomide/bortezomib/dexamethasone;
ASCT, autologous stem cell transplant; QW, weekly; Q2W, every 2 weeks; Q4W, every 4 weeks; MRD, minimal residual disease; PO, by mouth; PFS2, progression-free survival on next line of therapy.
Protocol EMN17/54767414MMY3014.

wKRdD Induction, ASCT and MRD Response-Adapted Consolidation in NDMM: MASTER trial

Dara-KRd

- Daratumumab 16 mg/m² days 1,8,15,22 (days 1,15 C 3-6; day 1 C >6)
- Carfilzomib (20) 56 mg/m² Days 1,8,15
- Lenalidomide 25 mg Days 1-21
- Dexamethasone 40mg PO Days 1,8,15,22

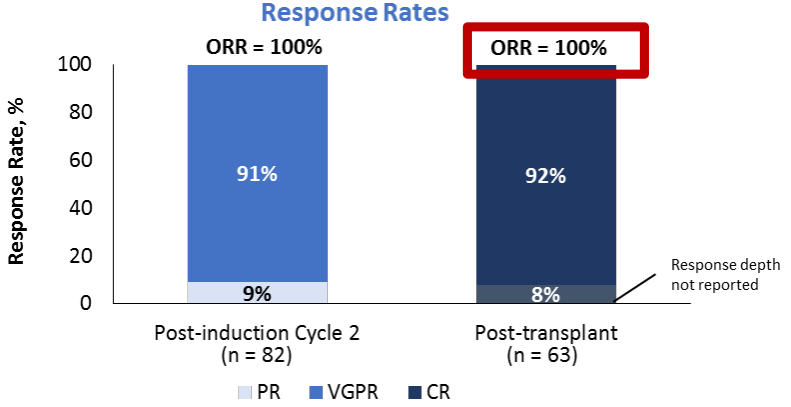


Primary Endpoint: Achievement of MRD-negative remission (< 10^{-5} per IMWG consensus)†

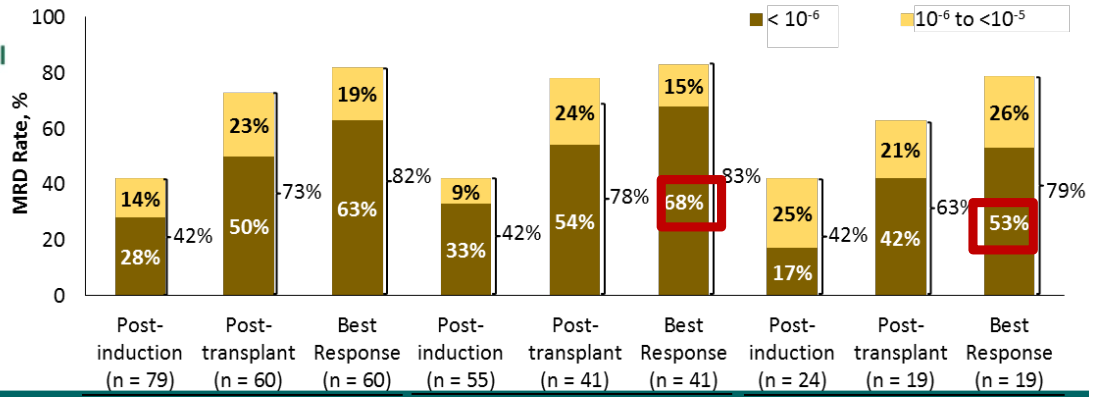
Secondary Endpoints: MRD < 10^{-6}, CR (per IMWG criteria),‡ and rate of imaging plus MRD-negative CR

Costa LJ, et al., EHA 2020; oral presentation

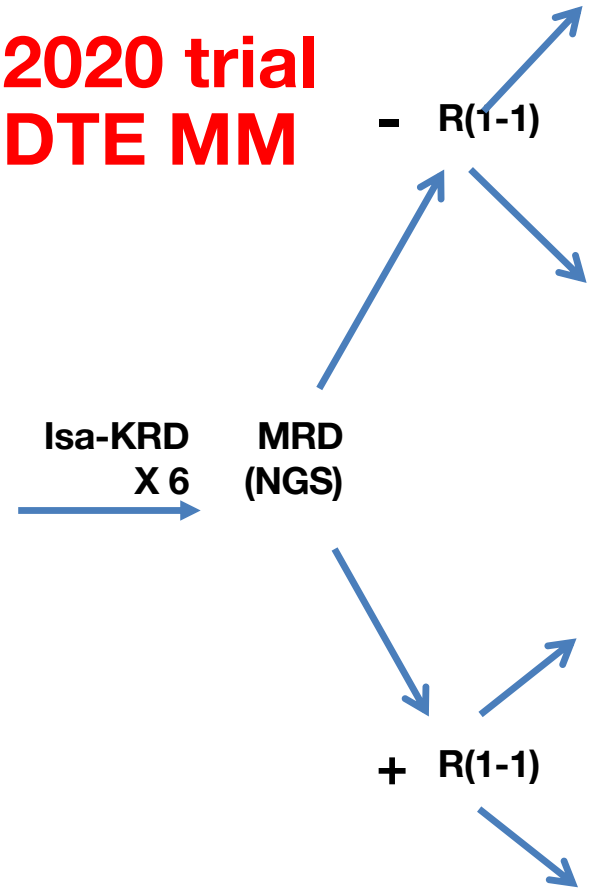
Response Rates



MRD-Negative Rates



IFM 2020 trial for NDTE MM



Arm A:	Isa-KRD X4	Isa-KRD X2	Lenalidomide 3 yrs
Arm B:	HDM	Isa-KRD X2	Lenalidomide 3 yrs
Arm C:	HDM	Isa-KRD X2	Isatux/Iberdomide 3 yrs
Arm D:	HDM	HDM	Isatux/Iberdomide 3 yrs

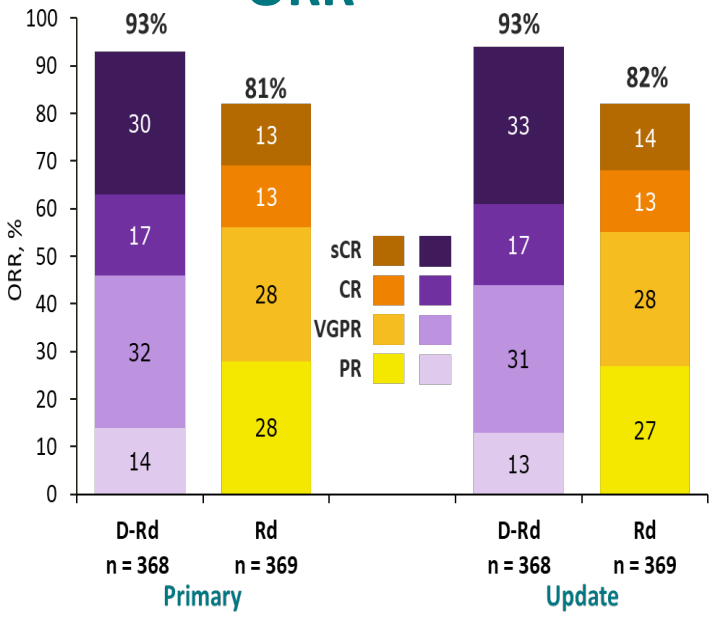
Treatment goals

Younger, fit | Elderly, fit | Intermediate | Frail

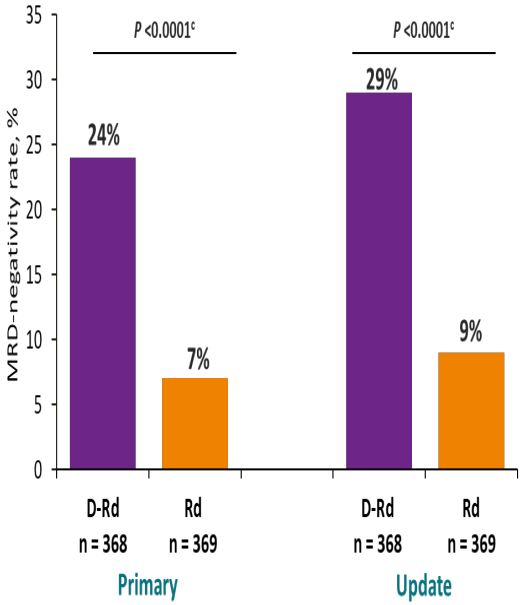
Efficacy: ORR[a] and MRD[b] (NGS; 10^{-5} Sensitivity Threshold)

Median follow-up → Primary: 28.0 mo **Update:** 36.4 mo

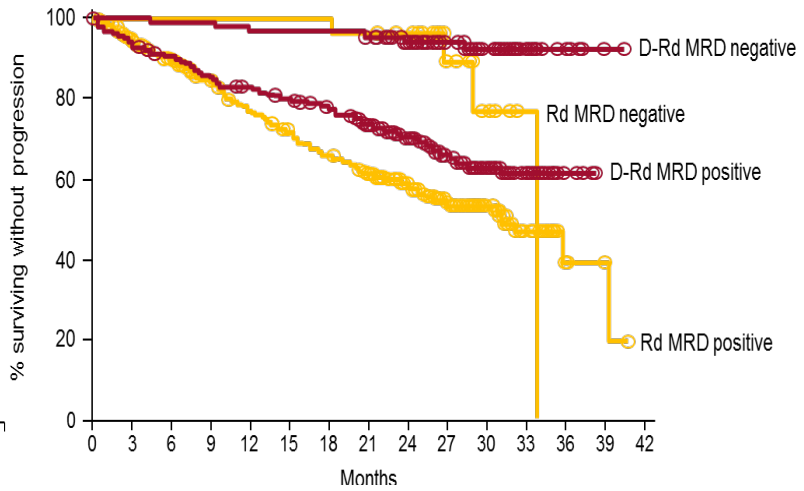
ORR



MRD



PFS



- **Significantly higher ORR, ≥CR rate, ≥VGPR rate, and MRD-negative rate with D-Rd**
- **>3-fold higher MRD negativity achieved with D-Rd**
- **Lower risk of progression or death with MRD negativity**

Facon T et al. ASH 2019

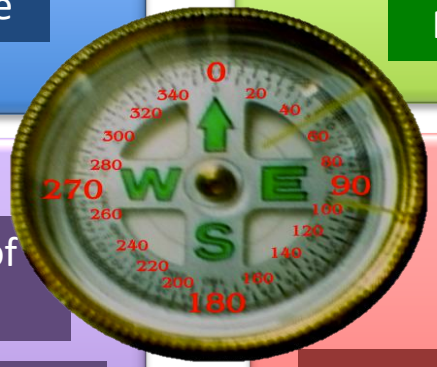
Key clinical considerations at relapse

Patient

- Age
- Co-morbidities
- Support network
- Performance status
- QoL
- Bone marrow reserve
- Oral vs IV

Prior treatment

- ASCT
- PI-based
- IMiD-based
- Alkylators
- Maintenance / Continuous treatment



Disease and molecular assessment

- Extramedullary disease
- Aggressiveness of relapse
- Clinical vs biochemical relapse
- Focal lesions
- Cytogenetic risk status
- Speed paraprotein increase

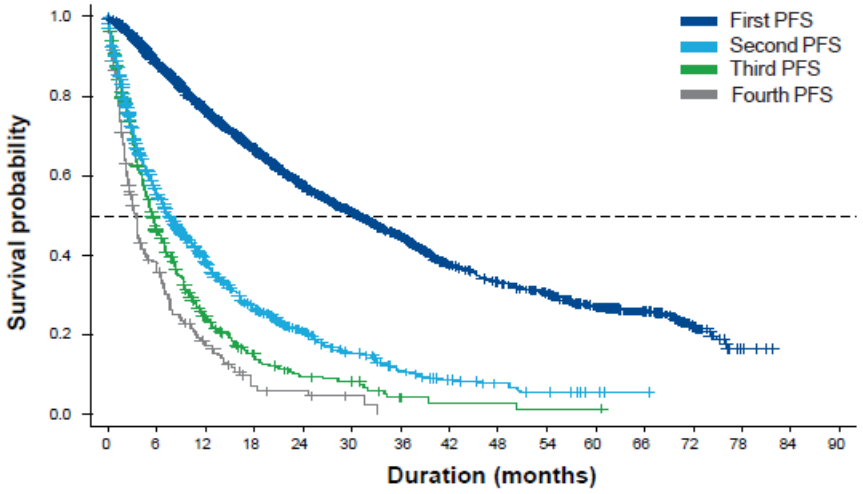
Response and tolerability

- PFS
- Response to prior therapy
- TFI
- Side effects

Importance of choice of second-line treatment

Patients with a confirmed diagnosis of symptomatic MM[1]

- 95% Receive first-line treatment
- 61% **Receive second-line treatment**
- 38% Receive third-line treatment
- 15% Receive fourth-line treatment
- 1% Receive fifth-line treatment, or subsequent treatments



CONNECT®-MM: Median PFS was longest with front-line therapy and decreased with each subsequent line of therapy[2]

MM, multiple myeloma; PFS, progression-free survival.

1. Raab MS, et al. Br J Haematol 2016; 175: 66–76; 2. Jagannath S, et al. Poster presentation at EHA 2018 Abstract PF570 and poster

Options of therapy for RRMM patients

Induction Bortezomib-based combination

↓

ASCT (melphalan 200)

↓

Nothing/Consolidation/Maintenance

Induction Bortezomib-based combo

Lenalidomide-dex

(VRd)

Relapse

PIs based combinations		IMiDs based combinations	
Kd 18.7 m, HR: 0.53 CR 13%	**DaraVD** PFS: 16.7 m, HR: 0.32 CR 30%	**KRd** PFS: 26.3 m, HR: 0.69 CR 32%	**DaraRd** PFS: 44.5 m, HR: 0.44 CR 56%
		EloRd PFS: 19.4 m, HR: 0.71 CR 5%	**IxaRd** PFS: 20.6 m, HR: 0.74 CR 12%

Dimopoulos MA et al, Lancet Oncology 2016; Spencer at al, Haematologica 2018; Stewart AK et al, N Engl J Med 2015; Dimopoulos MA et al, Haematologica 2018; Dimopoulos MA et al, Br J Haematol 2017; Moreau P et al, NEJM 2016; Bahlis NJ et al. Leukemia 2020

Lenalidomide refractoriness: a new unmet medical need?

Moreau et al. *Blood Cancer Journal* (2019)9:38
https://doi.org/10.1038/s41408-019-0200-1

Blood Cancer Journal

CLINICAL TRIALS AND OBSERVATIONS

Comment on Mikhael et al, page 123

Facing lenalidomide-refractory myeloma

Michele Cavo | Bologna University School of Medicine

blood® 11 JULY 2019 | VOLUME 134, NUMBER 2

ARTICLE Open Access

Treatment of patients with multiple myeloma progressing on frontline-therapy with lenalidomide

Philippe Moreau[1], Elena Zamagni[2] and Maria-Victoria Mateos[3]

Abstract

Over the last years, there has been great progress in the treatment of multiple myeloma with many new agents and combinations having been approved and being now routinely incorporated into treatment strategies. As a result, patients are experiencing benefits in terms of survival and better tolerance. However, the multitude of treatment options also presents a challenge to select the best options tailored to the specific patient situation. Lenalidomide is increasingly being used as part of frontline therapy in newly diagnosed multiple myeloma. This agent is typically administered until disease progression. It is currently unclear, how to best manage patients, who relapse while receiving lenalidomide as part of their frontline treatment. We conducted a review to summarize the available evidence in this setting. Our summary shows that there are very few data from current trials testing new combinations based on carfilzomib, pomalidomide, or daratumumab that address this specific patient population. Our review is aimed to summarize the available evidence to assist treatment decision making and to raise awareness of this lack of data to encourage further analyses and the incorporation of sequencing questions in future trial designs.

Treatment of relapse: the changing landscape….

First relapse after IMiD-based induction

- **Doublets**
  Kd / Vd
- **Triplets based on Bortezomib**
  DaraVD or PanoVD or EloVD or VCD

First relapse after Bortezomib-based induction

- **Rd**
- **Triplets based on Rd**
  DaraRd or KRd or IxaRd or EloRd

First relapse after PI and/or IMiD-based induction and len-refractory

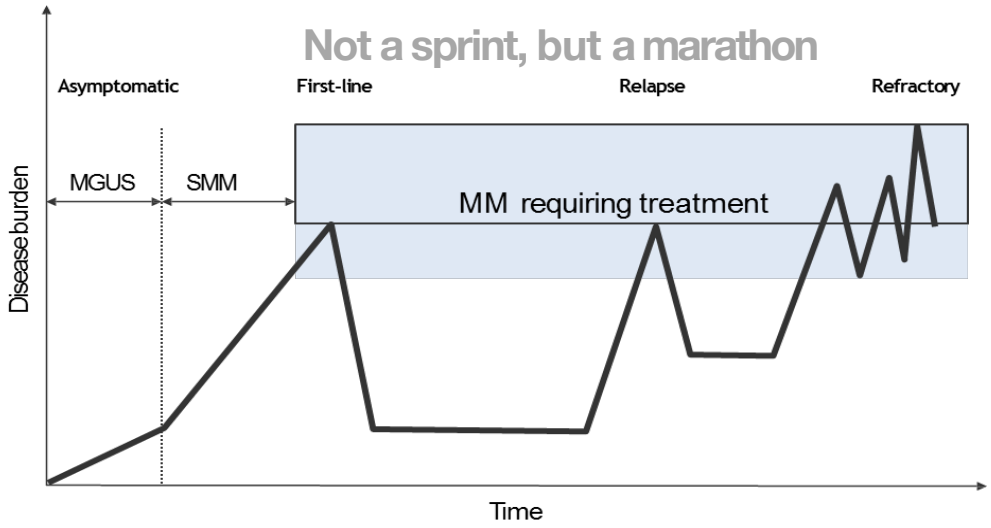
Poma-dex + V
Poma-dex + Cyclo
Poma-dex + Dara
Poma-dex + Isa
Poma-dex + Elo
Poma-dex + K

Kd + Dara
Kd + Isa
Kd + Cyclo
Kd + Venetoclax

Vd + Selinexor
Vd + Venetoclax

Moreau P et al. Ann Oncol 2017;28(suppl_4):iv52-iv61
Facon T EHA 2019

Treating myeloma in 2020 – Upcoming challenges



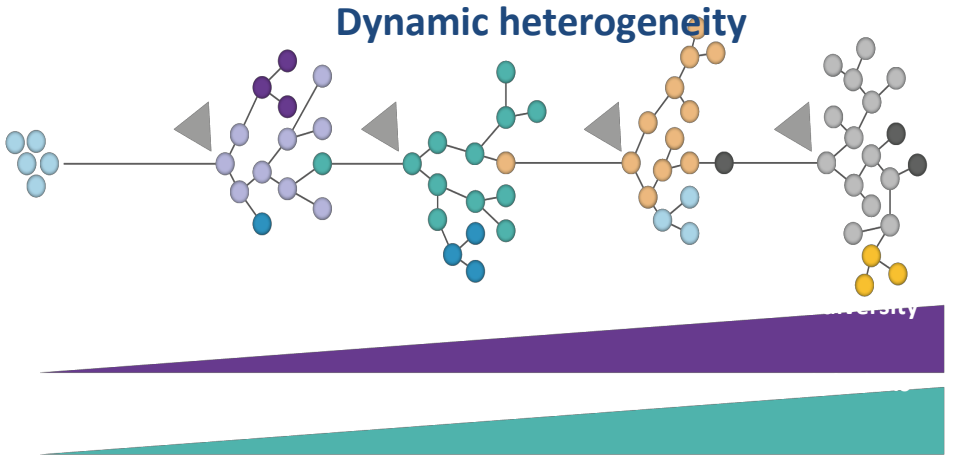
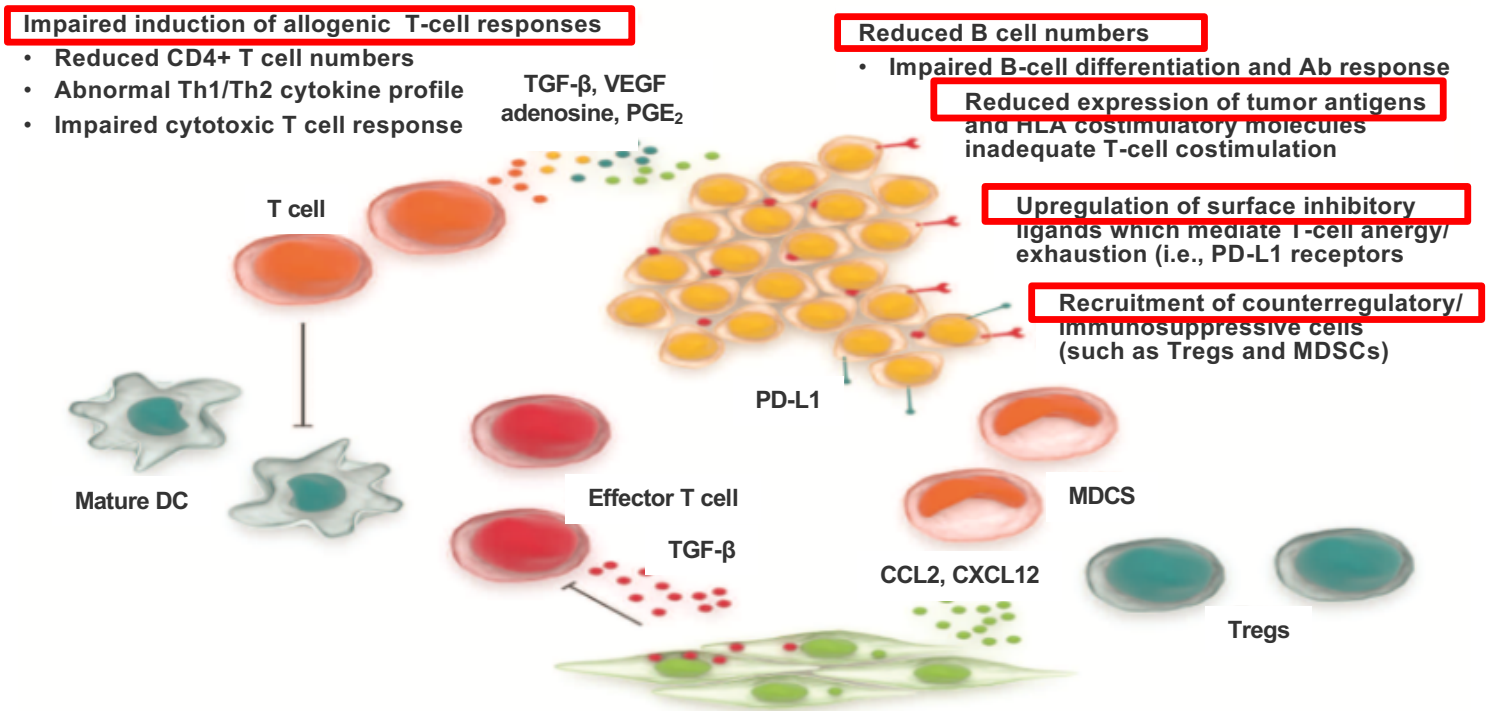


Image adapted from Morgan G et al. Nat Cancer Revs 2012;12:335-348

- There is a trend towards **extended duration of therapy**, and highly active **combinations** being used already in **early lines**
- The population of **refractory** patients is increasing
- **Treatment resistance** is becoming an important and timely consideration in clinical practice

Immune impairment in MM

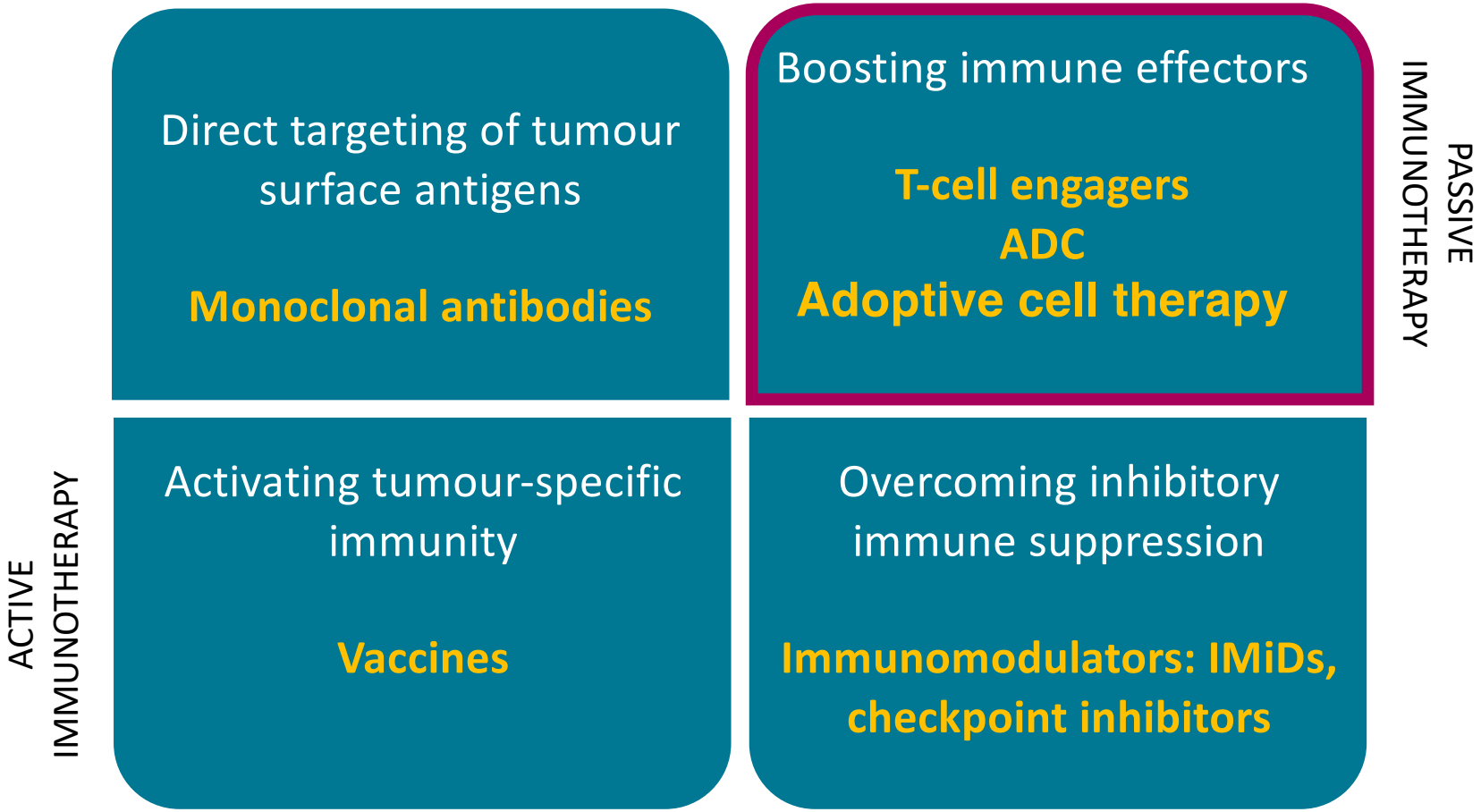
While the immune system is well-equipped to identify and eliminate myeloma cells, they can escape immune-mediated destruction through:



- **Role of graft versus Myeloma after allo-transplant as well as Donor Lymphocytes infusions**
- **Interferon was the first drug to stimulate the immune system**
- **Anti-myeloma effect of the immunomodulatory drugs**

Rodriguez-Otero P, et al. Haematologica. 2017;102(3):423-432

Innovative strategies are needed to overcome refractoriness to conventional drugs

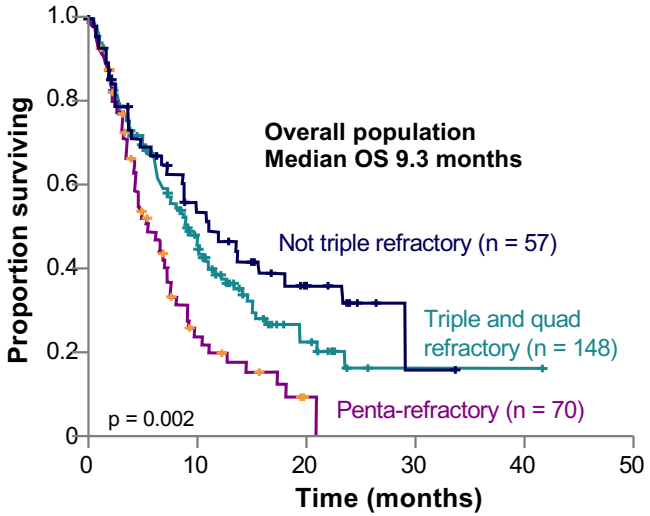


Rodríguez-Otero P, et al. Haematologica. 2017;102:423-32.

MAMMOTH study: suboptimal outcomes in patients refractory to anti-CD38 Mo Abs

275 patients refractory to anti-CD38 mAbs

	Median OS months	
Not triple refractory	11.2	Refractory to 1 CD38 mAb, and not both PI and IMiD
Triple and quad refractory	9.2	Refractory to 1 CD38 mAb + 1 PI + 1 or 2 IMiD compounds, etc.
Penta refractory	5.6	Refractory to 1 CD38 mAb + 2 PIs + 2 IMiD compounds
Overall cohort	8.6	



249 patients received further treatment
ORR 31%
mPFS 3.4 months
mOS 9.3 months

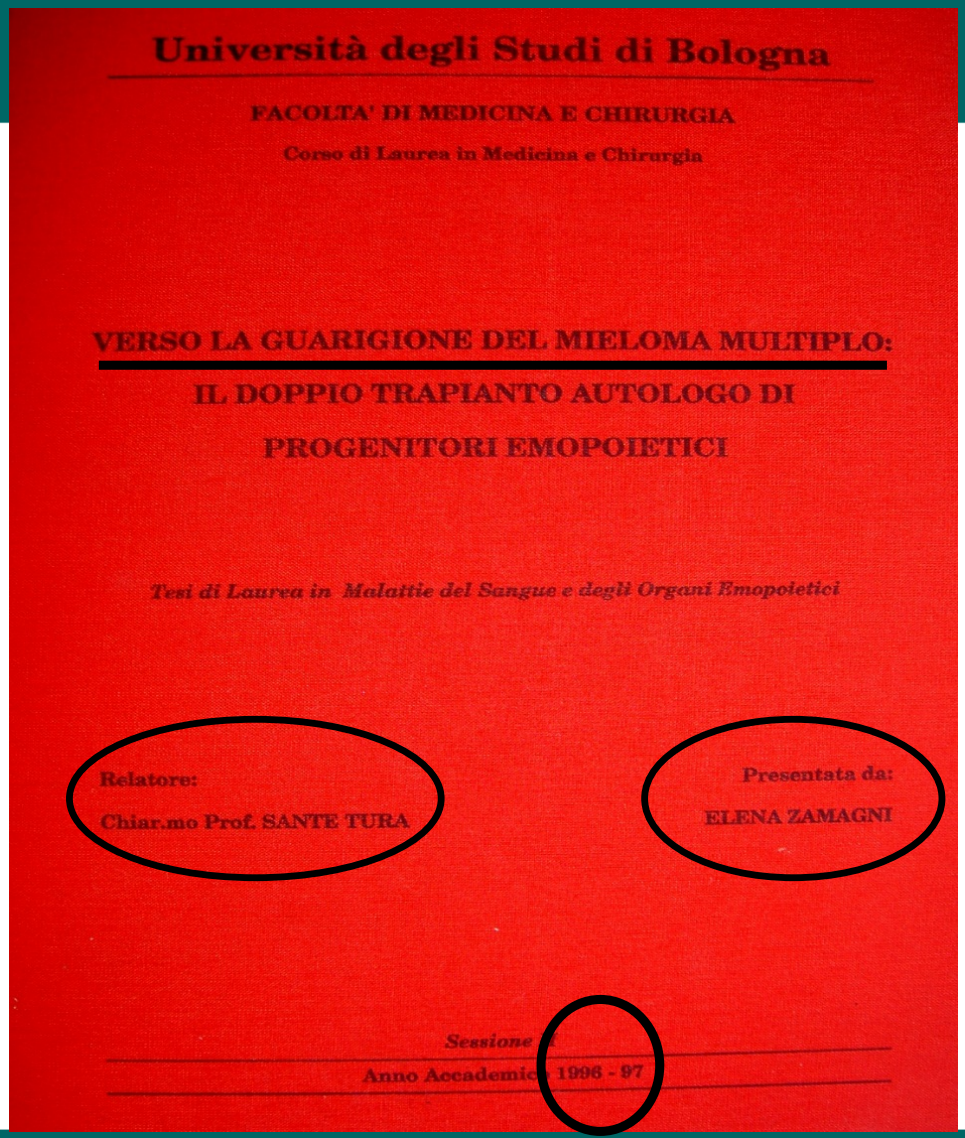
Gandhi UH et al., *Leukemia*. 2019

Efficacy Across BCMA CAR T Trials in RRMM

	KarMMa: Idecabtagene Vicleucel (n = 128)	EVOLVE: Orvacabtagene Autoleucel (n = 62)	CARTITUDE-1: JNJ-4528 (n = 29)
ORR, %	73	92	100
sCR/CR, %	33	36	86
Evaluable patients with MRD neg ≥ 10^5, %	94	84	81
PFS, mos	8.8	NR*	NR†
DoR, mos	10.7	NR	NR
Screened, n	150	--	35
Apheresed, n	140	--	35
Treated, n	128	--	29

*PFS in lowest dose cohort (300 x 10^6 cells/kg): 9.3 mos. †9-mo PFS: 86%.

Patel et al. ASCO 2020



Università degli Studi di Bologna

FACOLTA' DI MEDICINA E CHIRURGIA

Corso di Laurea in Medicina e Chirurgia

VERSO LA GUARIGIONE DEL MIELOMA MULTIPLO:

IL DOPPIO TRAPIANTO AUTOLOGO DI

PROGENITORI EMOPOIETICI

Tesi di Laurea in Malattie del Sangue e degli Organi Emopoietici

Relatore:

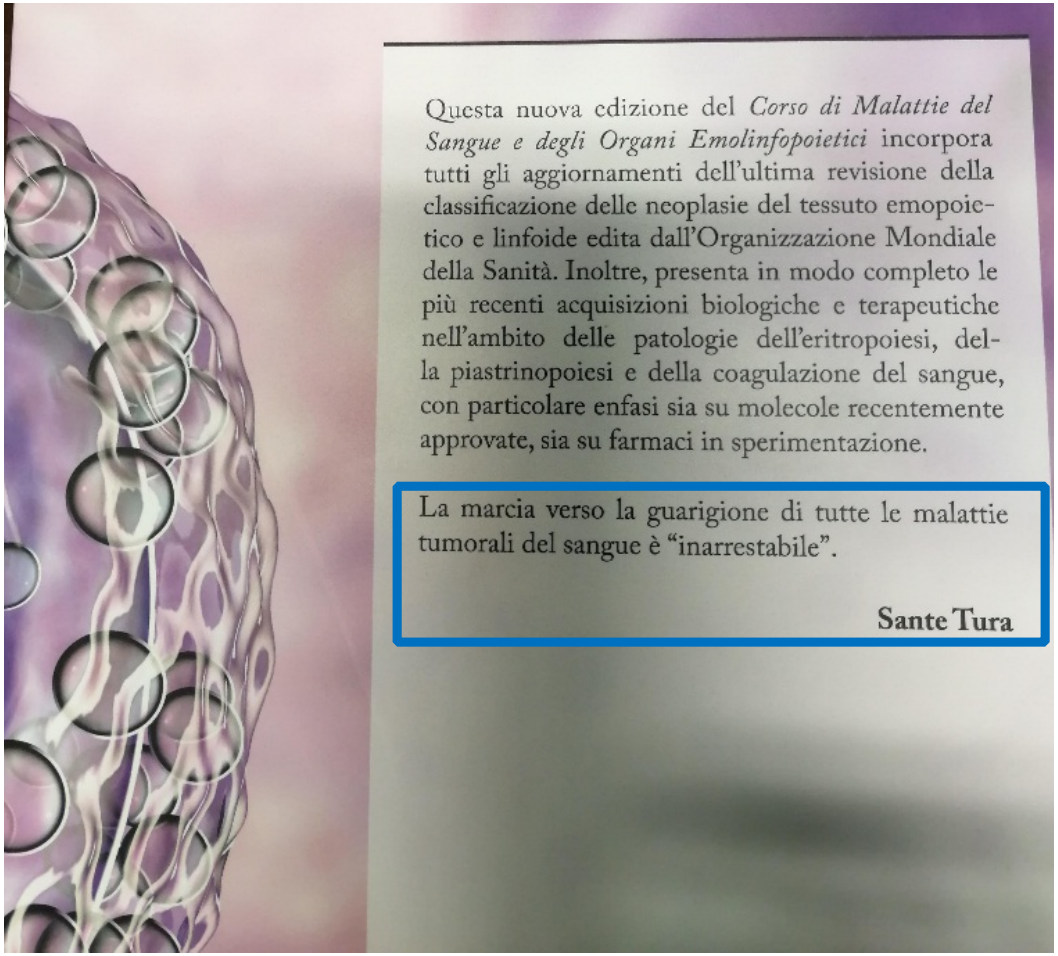
Chiar.mo Prof. SANTE TURA

Presentata da:

ELENA ZAMAGNI

Sessione

Anno Accademico 1996 - 97



Questa nuova edizione del *Corso di Malattie del Sangue e degli Organi Emolinfopoietici* incorpora tutti gli aggiornamenti dell'ultima revisione della classificazione delle neoplasie del tessuto emopoietico e linfoide edita dall'Organizzazione Mondiale della Sanità. Inoltre, presenta in modo completo le più recenti acquisizioni biologiche e terapeutiche nell'ambito delle patologie dell'eritropoiesi, della piastrinopoiesi e della coagulazione del sangue, con particolare enfasi sia su molecole recentemente approvate, sia su farmaci in sperimentazione.

La marcia verso la guarigione di tutte le malattie tumorali del sangue è "inarrestabile".

Sante Tura