Highlights from IMW 2019

19-20 novembre 2019
Bologna
Royal Hotel Carlton

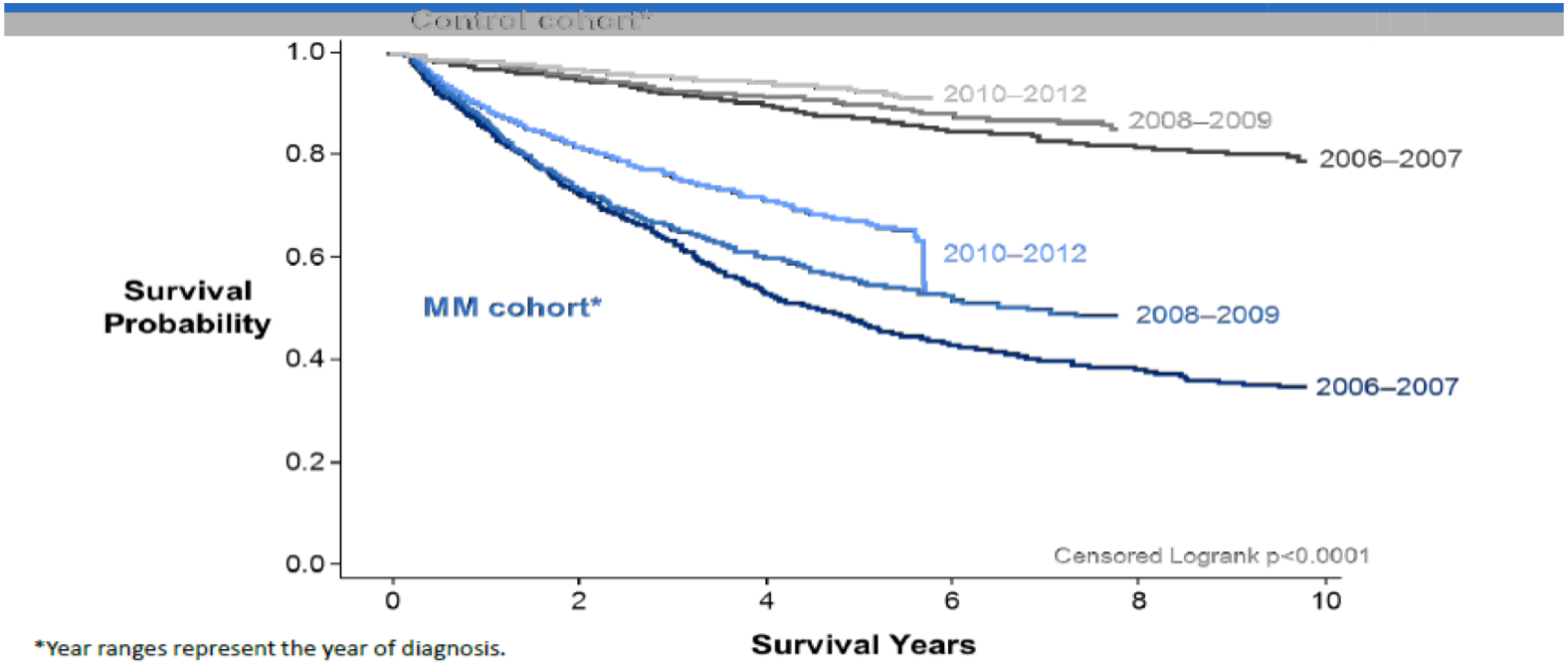
ANTONIO SPADANO

MRD negatività: *endpoint* terapeutico e/o regolatorio?

Disclosure

- I have no actual or potential conflict of interest in relation to this program/presentation.

MM: advances in therapy and outcome



*Year ranges represent the year of diagnosis.

Note: By linking to the SSA Master Death File, survival was measured as time from diagnosis date to the date of death obtained from the SSA, time from diagnosis date to the date of inpatient death, or time from diagnosis date to September 30, 2015; Survival estimates were presented for multiple myeloma patients diagnosed and treated during 2006-2012 (n=9,521).

tgen AN AFFILIATE OF City of Hope

INTERNATIONAL MYELOMA FOUNDATION

The evaluation of response in MM has similarly evolved to parallel advances in therapy and outcome

Complete Response (CR)

- Negative serum and urine immunofixation
- <5% PCs in marrow

Stringent Complete Response (sCR)

- Normal FLC ratio
- No clonal plasma cells in marrow

MRD negative

- Flow negative MRD
- Sequencing negative MRD
- Imaging negative MRD

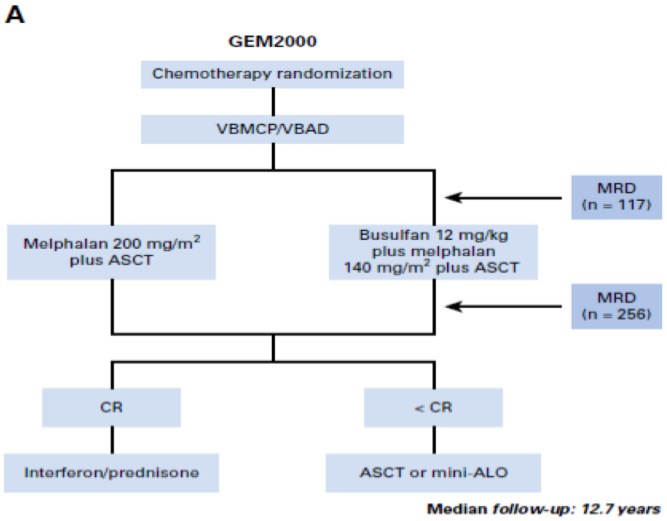
Kumar S. Lancet Oncol, 2016

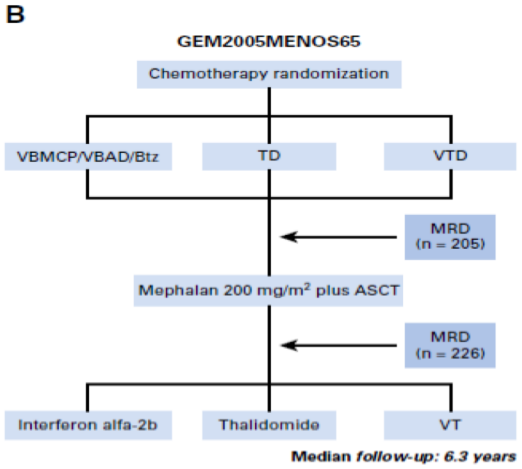
What is the clinical data to date justifying the use of MRD?

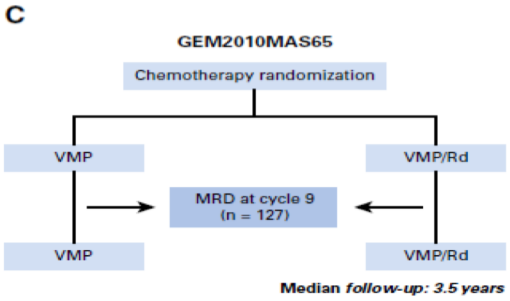
Anderson KC. Blood Adv, 2017

Depth of Response in Multiple Myeloma: A Pooled Analysis of Three PETHEMA/GEM Clinical Trials

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT







Three clinical trials:

609 newly diagnosed pts

- GEM2000 and GEM2005 for transplant-eligible pts
- GEM 2010 for transplant-ineligible pts

Depth of Response in Multiple Myeloma: A Pooled Analysis of Three PETHEMA/GEM Clinical Trials

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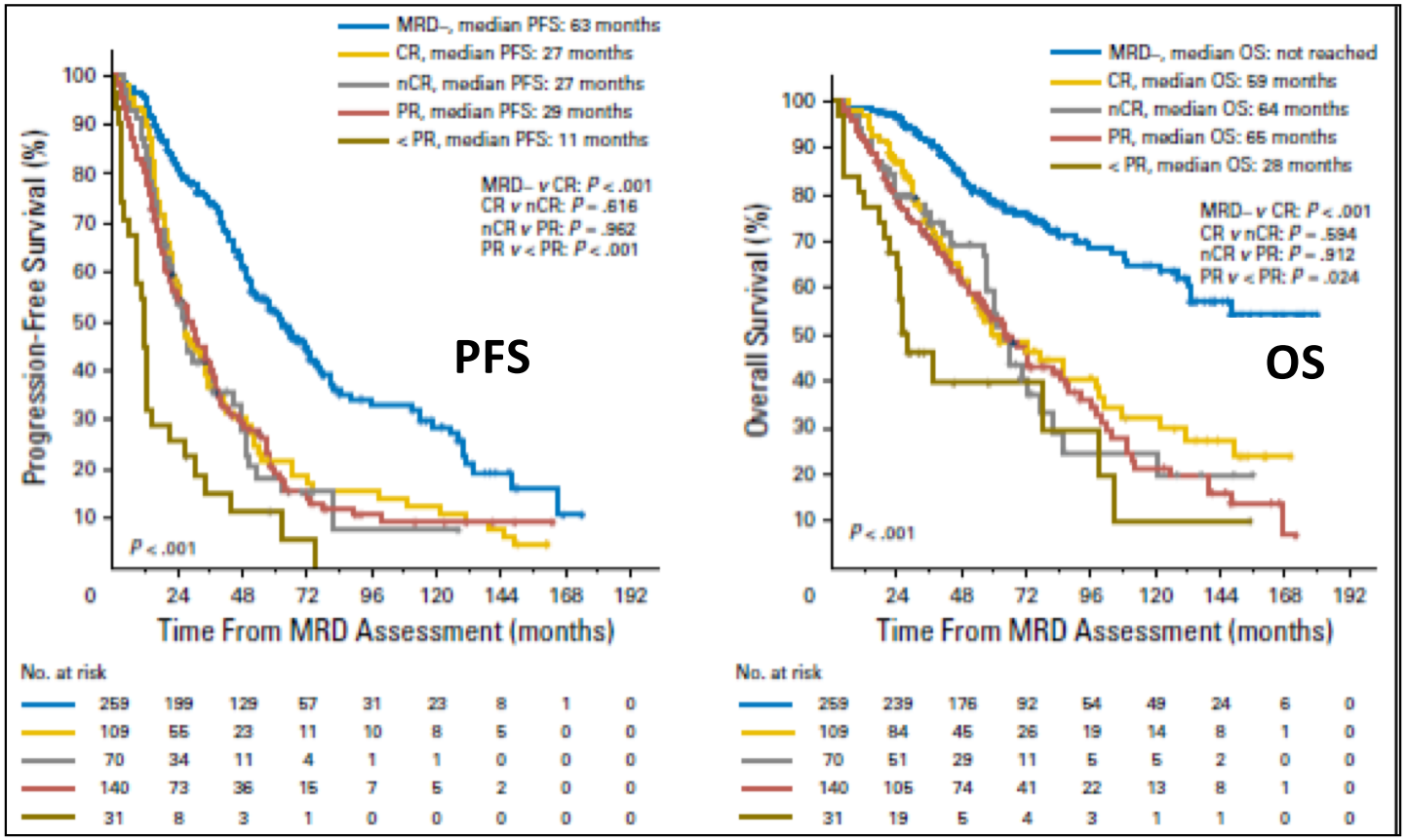

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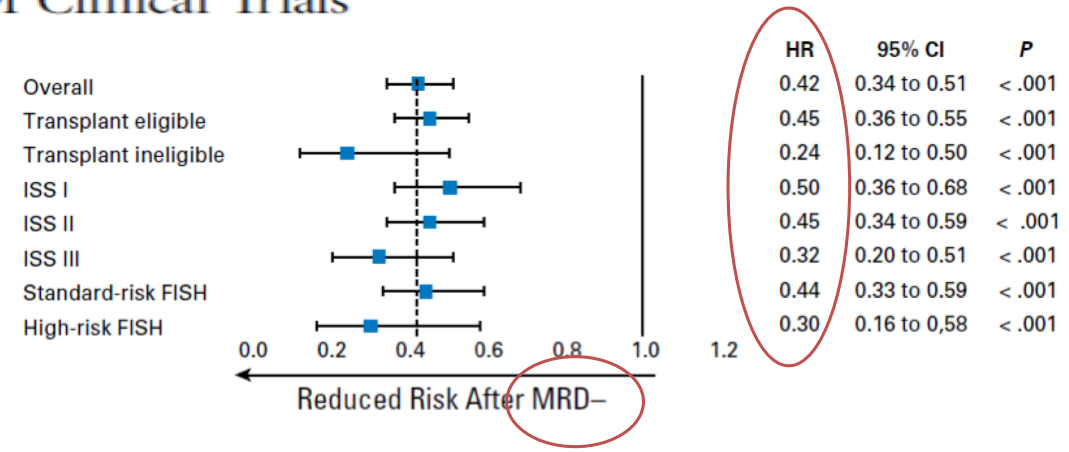
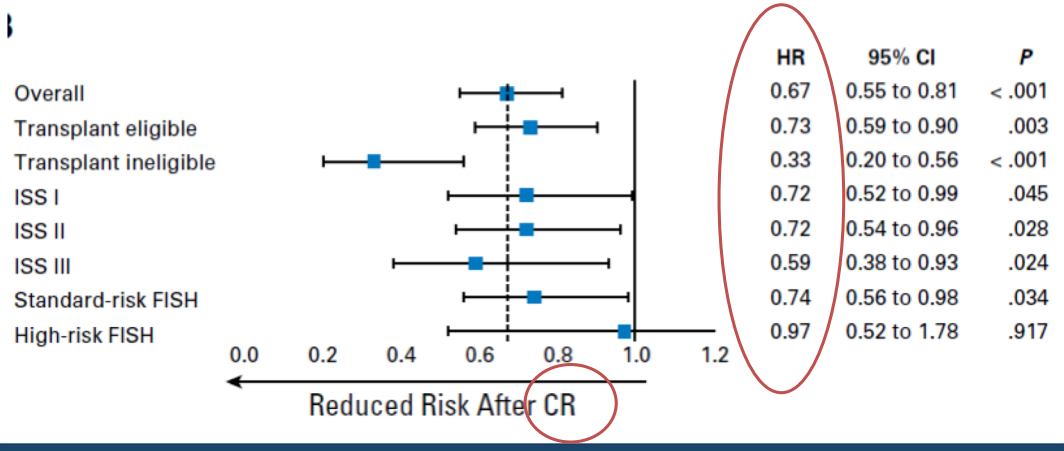
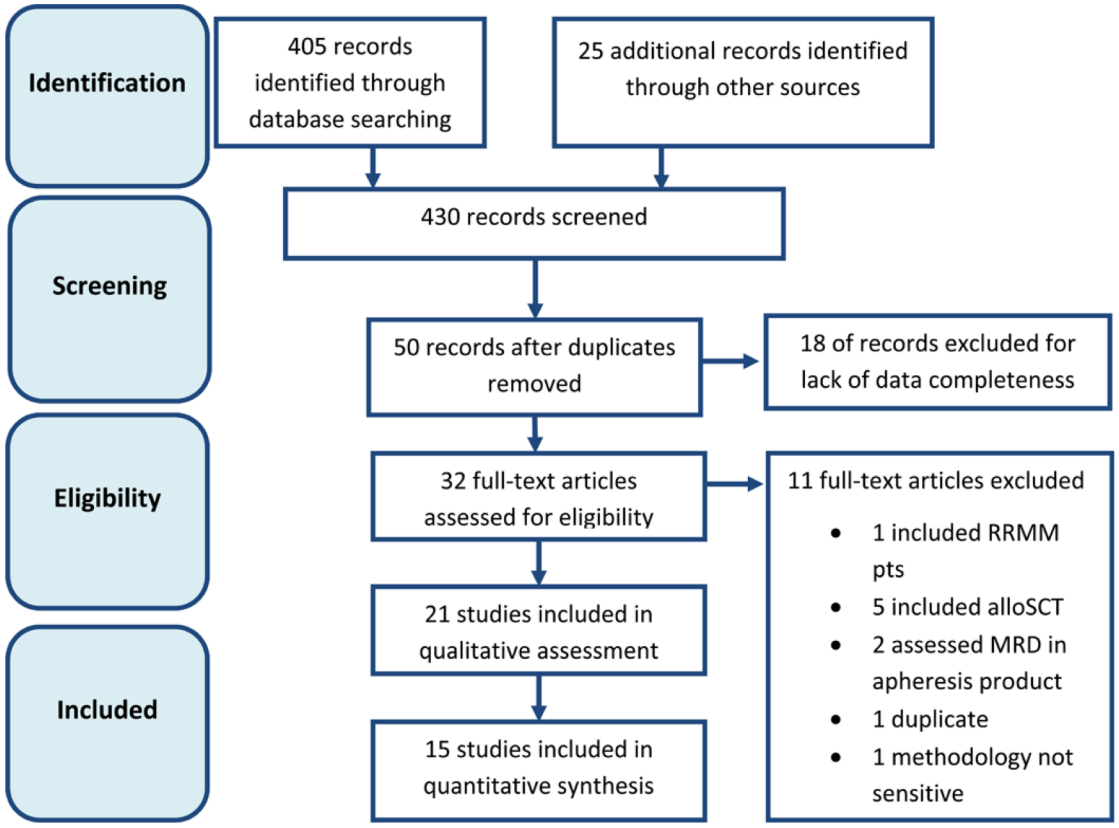




Minimal residual disease predicts superior survival in patients with multiple myeloma: a meta-analysis



[l]Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA

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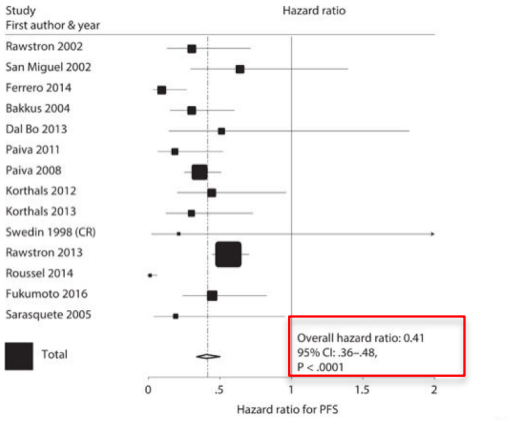
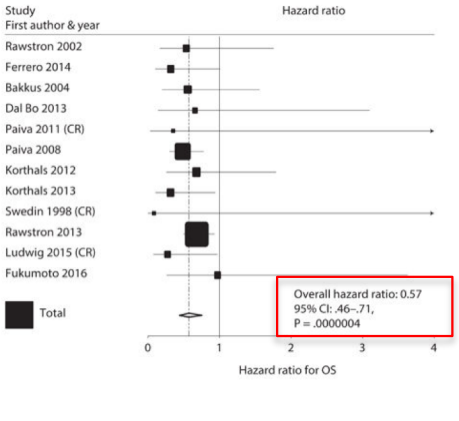
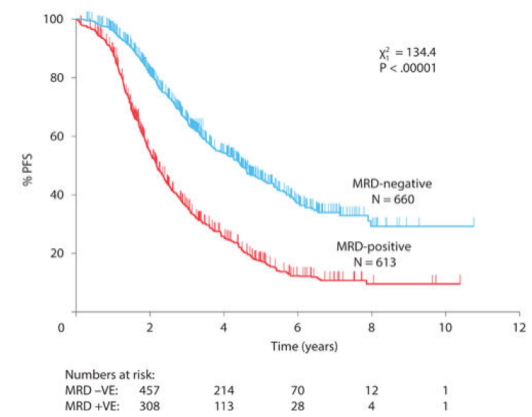




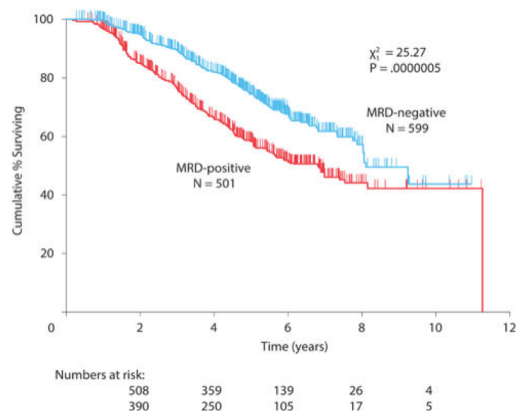
1273 pts
HR 0.41

1100 pts
HR 0.57

PFS



OS



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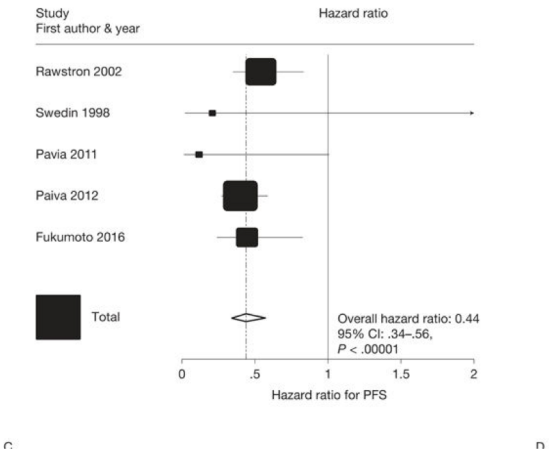
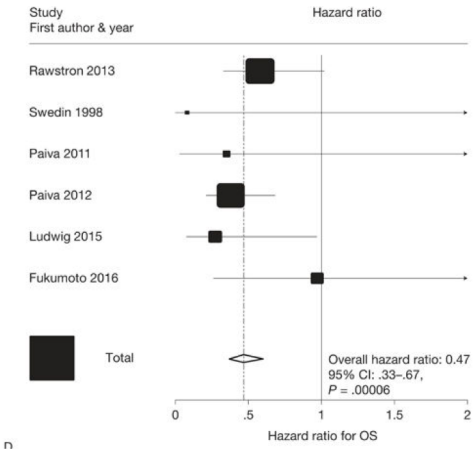
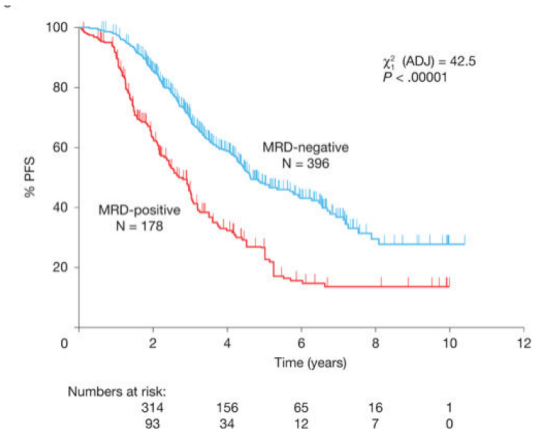


HR 0.44



HR 0.47

PFS



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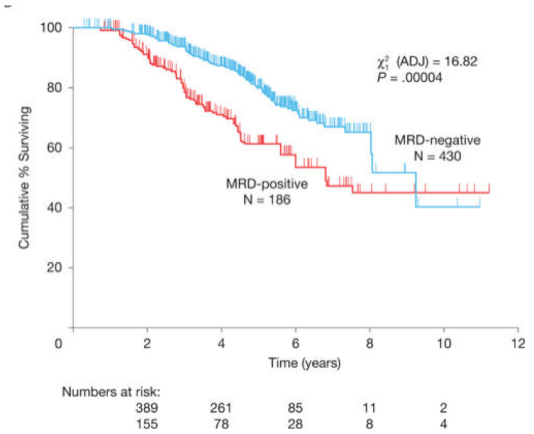

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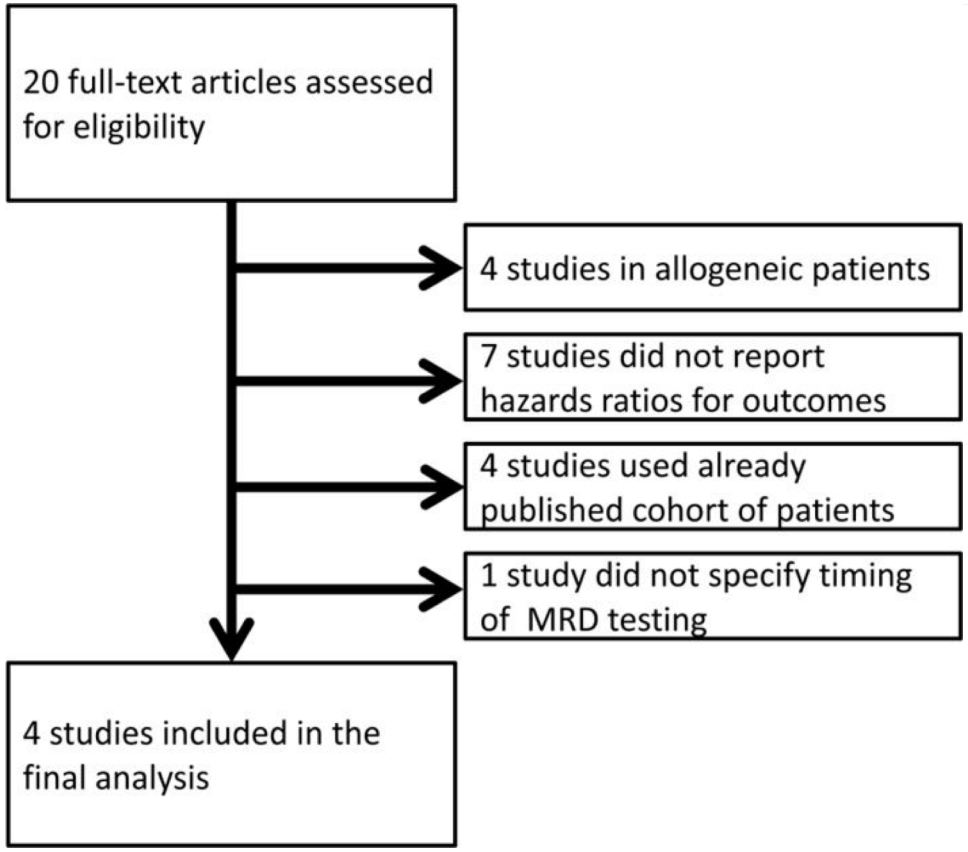
Role of MRD status in relation to clinical outcomes in newly diagnosed multiple myeloma patients: a meta-analysis



Landgren O. BMT, 2017

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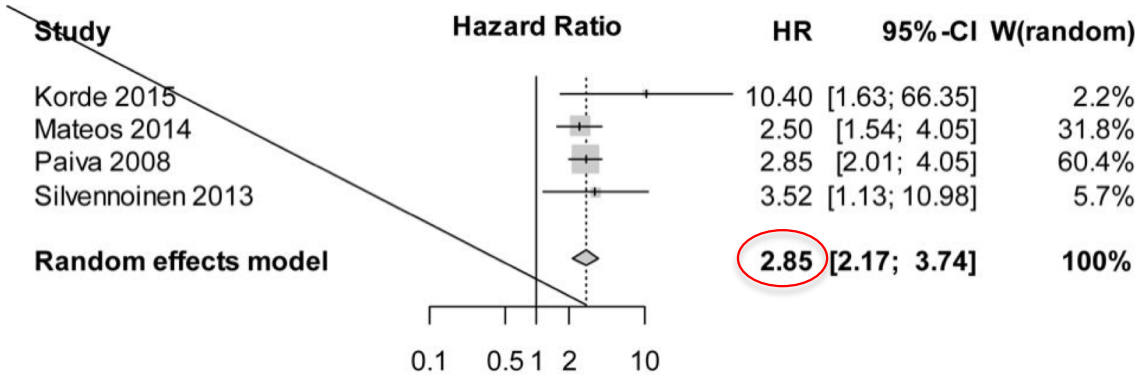

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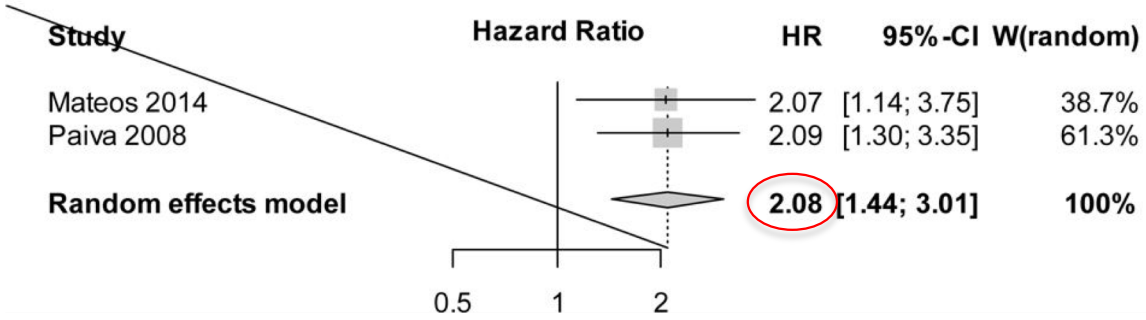
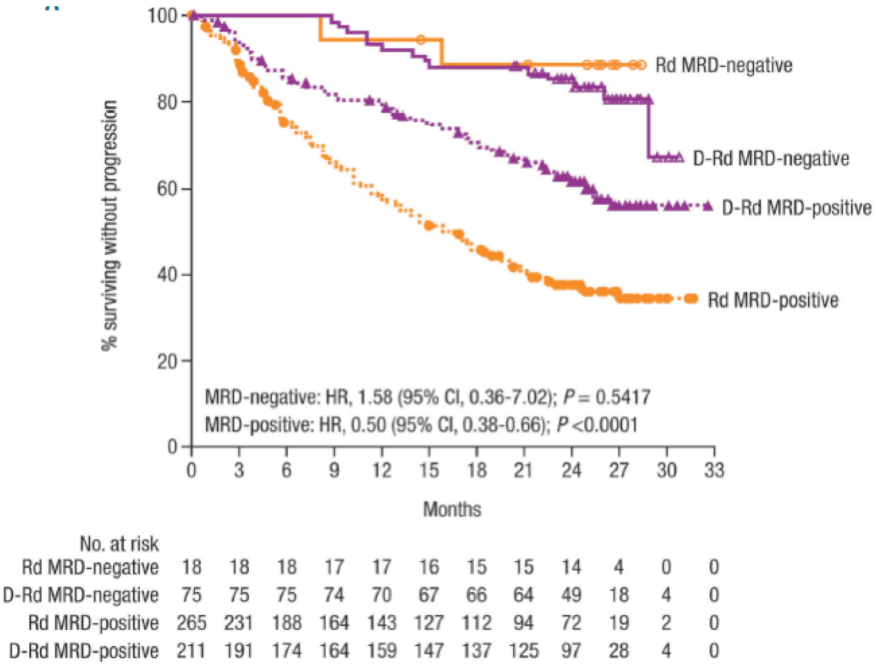


OS

Landgren O. BMT, 2017

MRD: independence from treatment

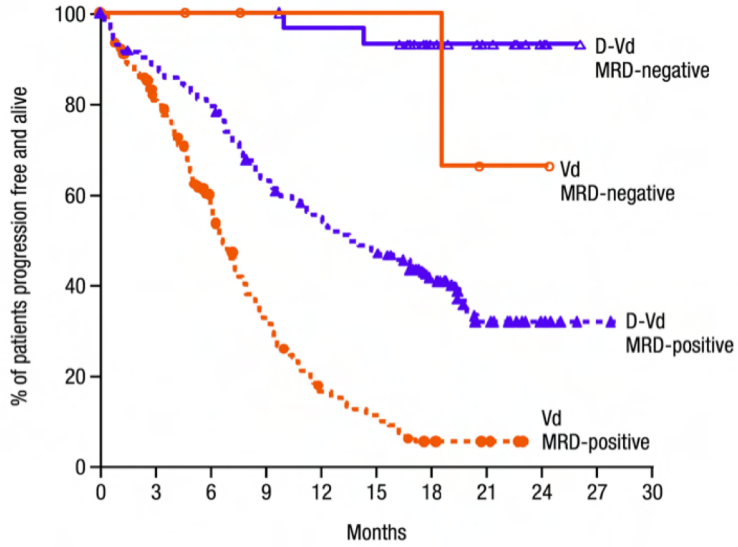
POLLUX



No. at risk												
Rd MRD-negative	18	18	18	17	17	16	15	15	14	4	0	0
D-Rd MRD-negative	75	75	75	74	70	67	66	64	49	18	4	0
Rd MRD-positive	265	231	188	164	143	127	112	94	72	19	2	0
D-Rd MRD-positive	211	191	174	164	159	147	137	125	97	28	4	0

Dimopoulos M. Haematologica, 2018

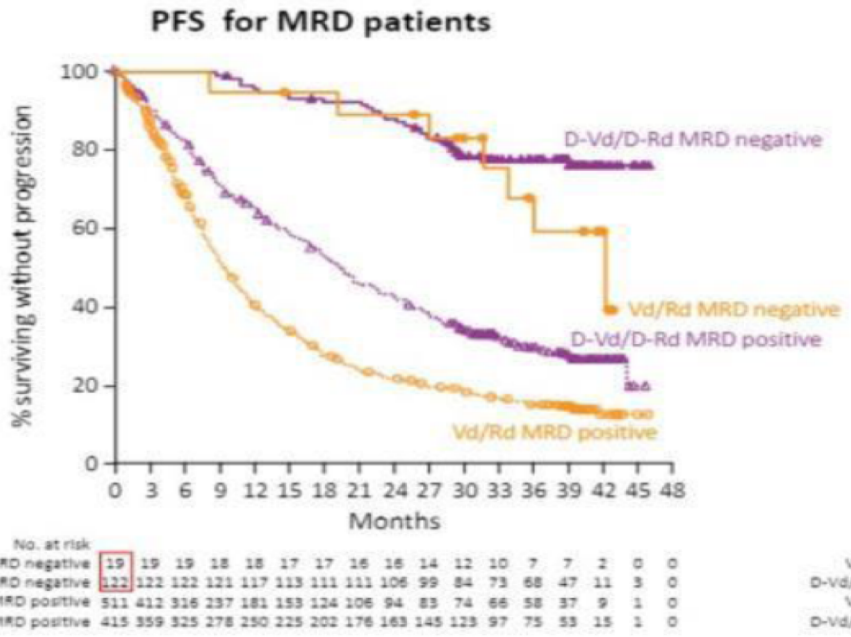
CASTOR

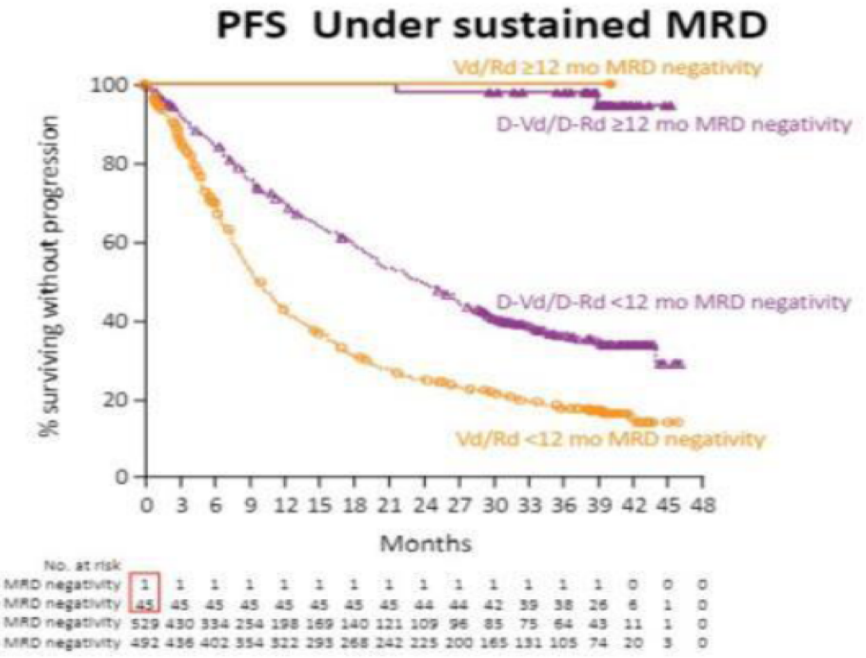


No. at risk											
Vd MRD-neg	6	6	6	6	6	6	5	1	1	0	0
D-Vd MRD-neg	29	29	29	29	27	26	17	11	3	0	0
Vd MRD-pos	241	176	123	68	33	21	6	4	0	0	0
D-Vd MRD-pos	222	186	169	132	111	98	62	19	5	1	0

Spencer A. Haematologica, 2018

MRD: PFS based on sustained MRD negativity



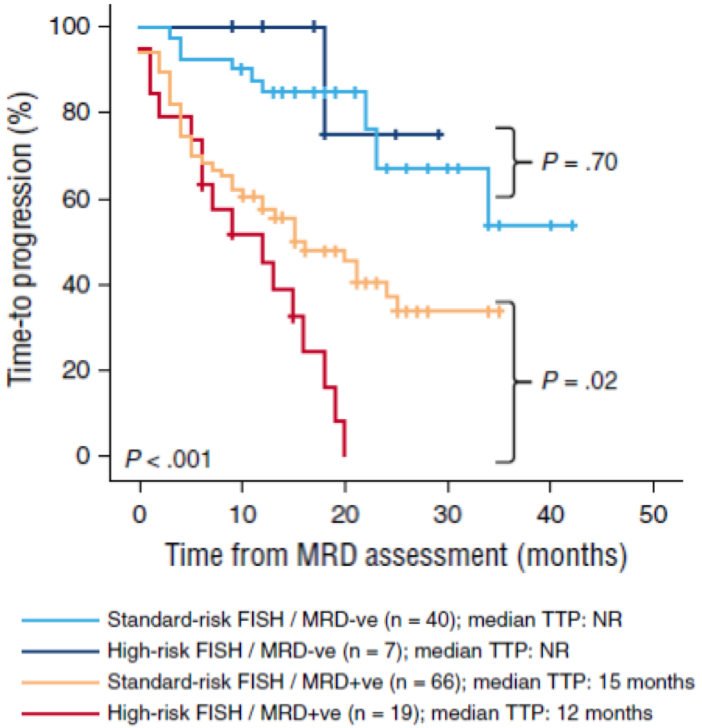


PFS, progression-free survival;; MRD, minimal residual disease; DARA, daratumumab; D-Vd, daratumumab/bortezomib/dexamethasone; D-Rd, daratumumab/lenalidomide/dexamethasone; Vd, bortezomib/dexamethasone; Rd, lenalidomide/dexamethasone.

MRD negativity : 30% on Intention-to-treat; 16% sustained at 6m; 13% at 12m

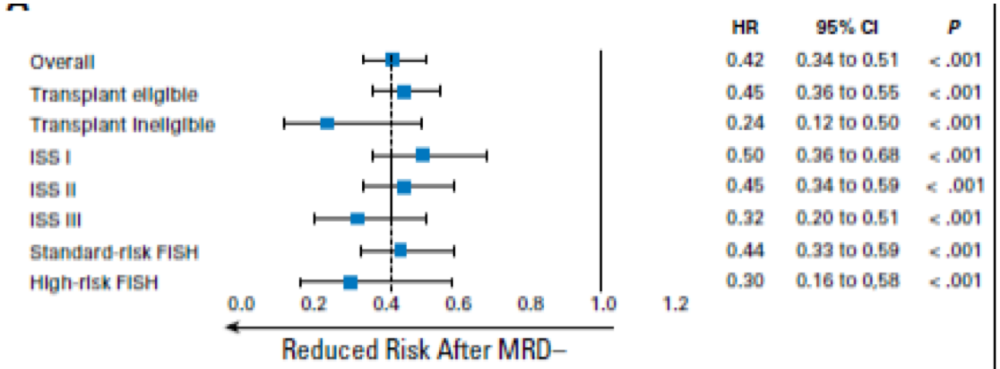
Avet- Loiseau, H ASH 2018 , Poster 3272

MRD in HIGH RISK MM



Paiva B. Blood, 2016

PFS



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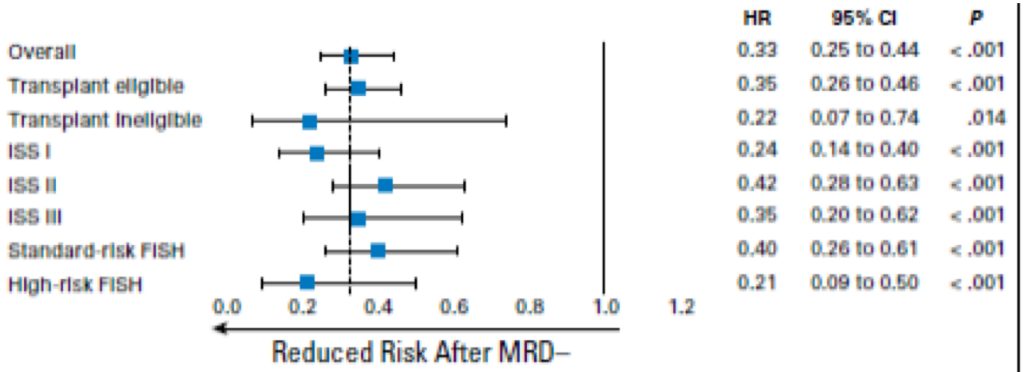
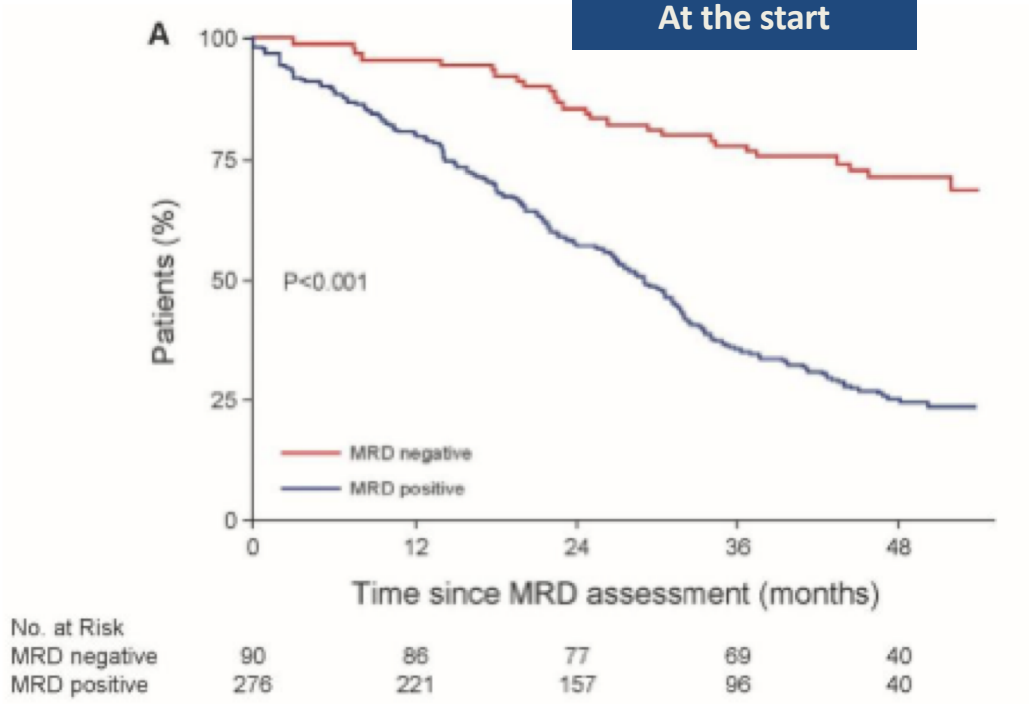


Lahuerta J-J, JCO 2017

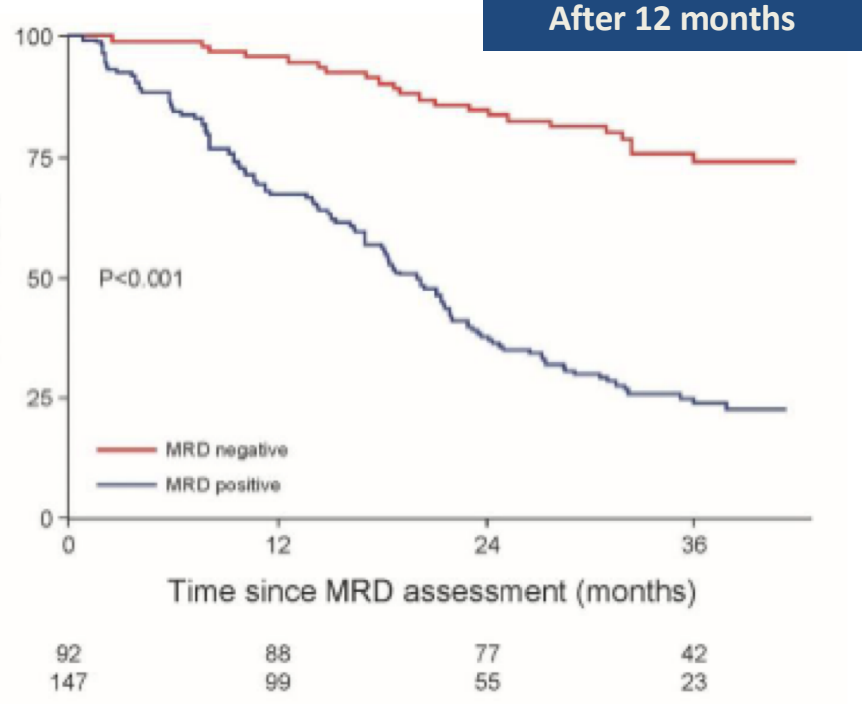
MRD: to evaluate maintenance therapy

At the start



No. at Risk					
MRD negative	90	86	77	69	40
MRD positive	276	221	157	96	40

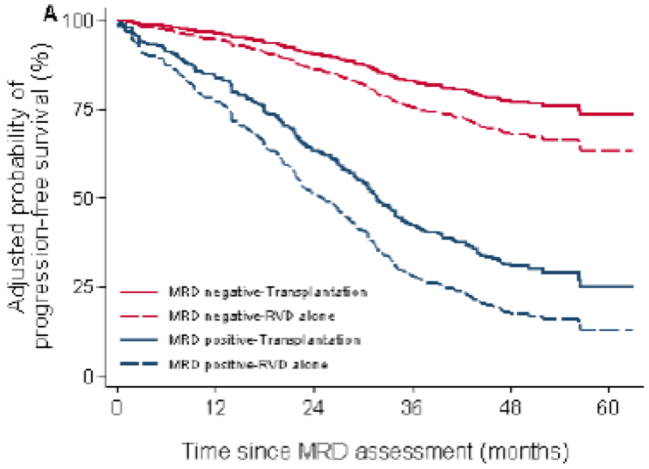
After 12 months

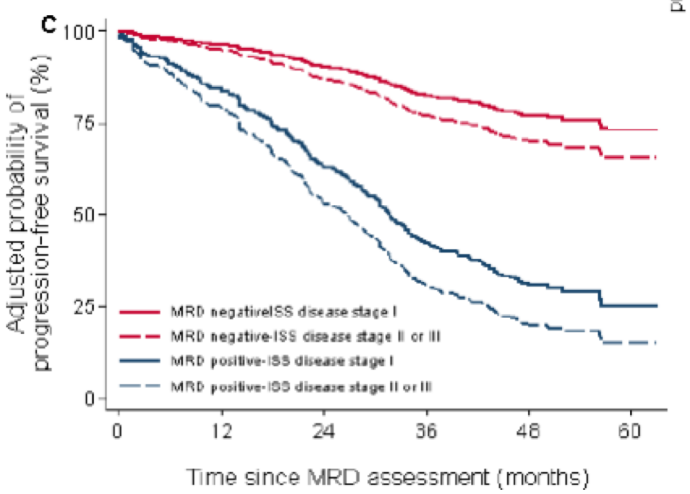


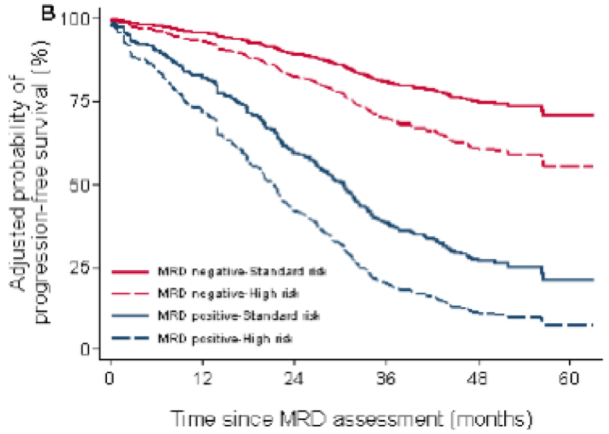
92	88	77	42
147	99	55	23

Perrot A. Blood, 2018

MRD: to evaluate maintenance therapy







Perrot A. Blood, 2018

MRD: potential utility

- Prognostic factor (surrogate endpoint)
- To make treatment decisions
  - *tool for defining the timing of treatment intervention*
- To evaluate treatment efficacy

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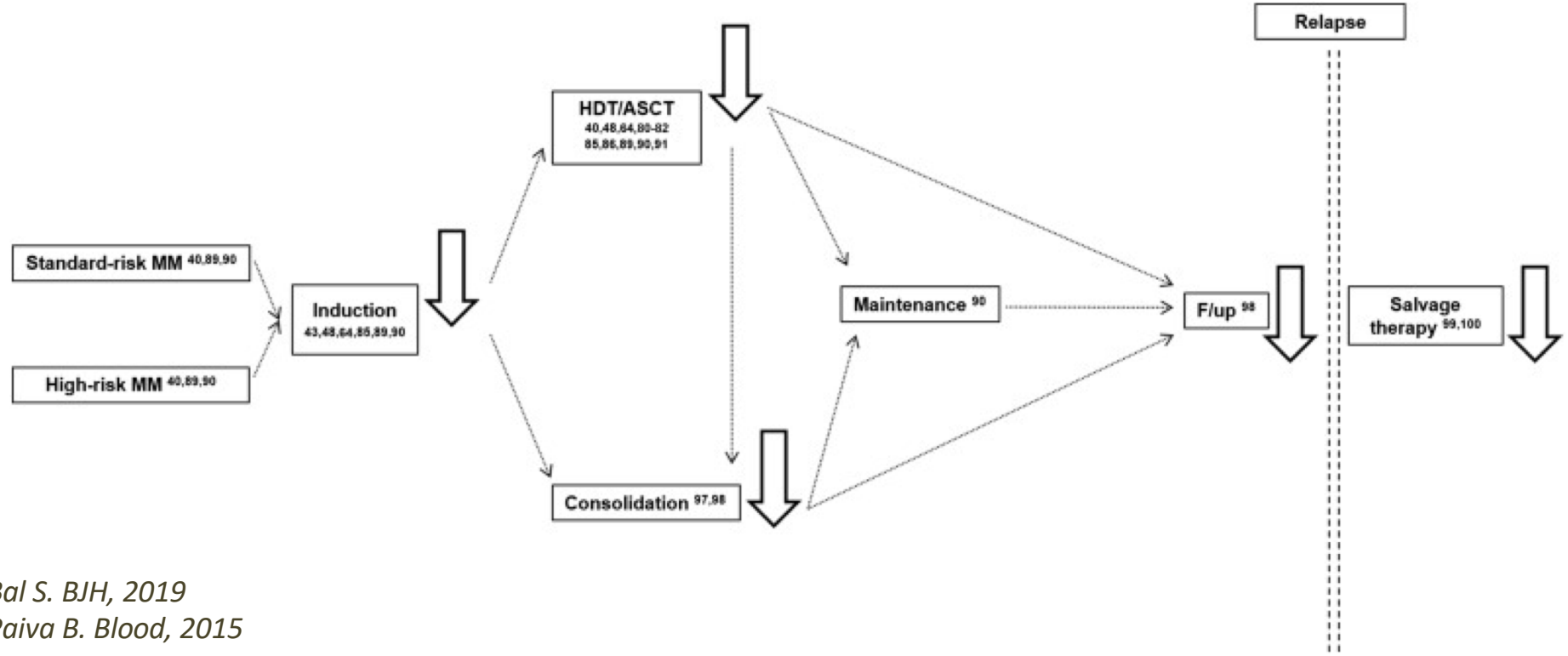
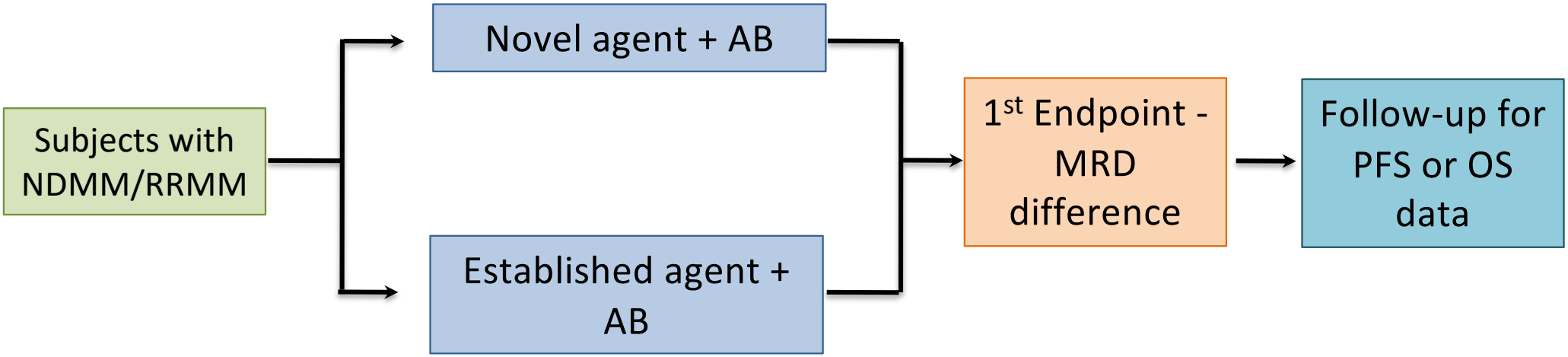
When and how frequently to measure MRD?



Bal S. BJH, 2019
Paiva B. Blood, 2015

MRD: useful as an endpoint for novel agents approval

In a disease with long natural history, the acceptance of MRD as a surrogate endpoint for regulatory purposes would enable much faster comparison between treatments, potentially translating into faster therapeutic development



Bal S. BJH, 2019
Anderson KC. Clin Cancer Res, 2017

Regulatory considerations for use of MRD in development of drug and biological products for treatment

- MRD should be assessed only in patients that are in CR
- The relationship between MRD and clinical benefit will need to be demonstrated in each disease setting (newly diagnosed, nontransplant eligible, relapsed refractory)
- Imaging techniques could be used in combination with MRD to assess response in extramedullary disease

Hematologic malignancies FDA 2018

i²TEAMM

International Independent Team for Endpoint Approval of Myeloma MRD

Objectives

- To evaluate and validate **MRD as a surrogate endpoint** of progression-free survival in multiple myeloma clinical trials through prospectively planned meta-analytic surrogacy analysis based on individual patient data
- To create an integrated **meta-database** (Mayo Clinic as independent Statistics and Data Coordination Center)
- **14 clinical trials**: NDMM, RRMM, young, elderly, MRD after induction, after ASCT, after consolidation, during maintenance, methods: 1st generation flow (10^{-4}), 2nd generation flow (10^{-5}) or NGF (10^{-6}), few studies NGS/ PCR, CR or > VGPR, > PR,

MRD: potential utility

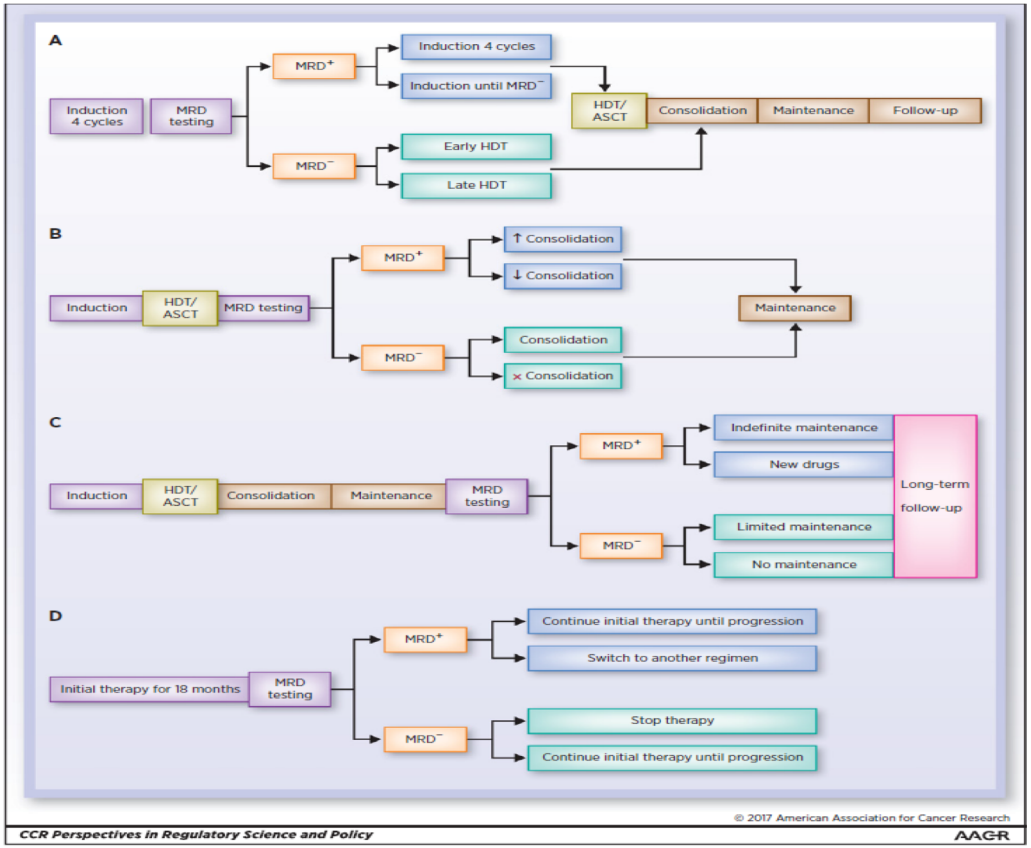
- Prognostic factor (surrogate endpoint)
- To make treatment decisions
  - *tool for defining the timing of treatment intervention*
- To evaluate treatment efficacy

MRD in MM: unanswered question

While elimination of detectable MRD has been shown to be a prognostic marker in MM, therapeutic decision-making based on MRD has NOT been tested in prospective trials and is NOT yet the standard of care

Bal S. BJH, 2019

Using MRD for making treatment decisions



Kenneth C.A. Clin Cancer Res, 2017

Key ongoing or planned studies using MRD as a tool for eligibility or stratification

Study identifier – trial title	Population	Phase	Group/ Sponsor	Planned N	MRD methodology/ threshold	MRD threshold for eligibility	Intervention	Primary endpoint
NCT03901963 – A Study of Daratumumab Plus Lenalidomide vs. Lenalidomide Alone as Maintenance Treatment in Participants with Newly Diagnosed Multiple Myeloma Who Are Minimal Residual Disease Positive After Frontline Autologous Stem Cell Transplant	NDMM post-ASCT	3	Janssen	214	NGS/$<10^{-5}$	MRD- positive after ASCT	Lenalidomide vs. Lenalidomide + subcutaneous daratumumab for 36 cycles	Percentage of patients with MRD $< 10^{-5}$
NCT03697655 – Pre-emptive Daratumumab Therapy of Minimal Residual Disease Reappearance or Biochemical Relapse in Multiple Myeloma	Relapsed	2	Polish Myeloma Consortium	274	MFC/$<10^{-5}$	MRD-negative after last line of therapy with re-appearance of MRD	Daratumumab vs. Observation for MRD reappearance up to 73 weeks	EFS in Daratumumab vs. observation
S1803-Phase III study of Daratumumab/ rHuPH20 (NSC-810307) + Lenalidomide or Lenalidomide as Post Autologous Stem Cell Transplant Maintenance Therapy in Patients with Multiple Myeloma (MM) using Minimal Residual Disease to Direct Therapy Duration (DRAMMATIC study)	NDMM post-ASCT	3	SWOG	TBD	NGS/$<10^{-6}$	MRD-negative after 24 months post-ASCT maintenance therapy	Continue vs. stop maintenance with Lenalidomide or Lenalidomide + Daratumumab/ rHuPH20 (based on initial randomization)	Compare OS between continuation of maintenance therapy vs. discontinuation of maintenance
NCT03490344- Short Course Daratumumab in Patients With Multiple Myeloma	NDMM post induction	2	MSKCC	25	MFC/$<10^{-6}$	MRD-positive after induction (±ASCT) or MRD re-appearance after being MRD negative to prior line of therapy	Daratumumab IV + Lenalidomide for 6 months	MRD negative ($<10^{-6}$) after 6 months of therapy
NCT02969837 – Study of Initial Treatment with Elotuzumab, Carfilzomib, Lenalidomide and Dexamethasone in Multiple Myeloma	NDMM	2	University of Chicago	55	NGS/$<10^{-6}$	MRD positive after induction with Elo-KRd x6	Additional Elo-KRd x6 followed by Elo-Rd maintenance	MRD negative ($<10^{-5}$) after 8 months

Bal S. BJH, 2019

Conclusions

- MRD is a powerful prognostic factor

- MRD is the most appealing candidate as surrogate endpoint for drug development and approval

- Future studies should link MRD to decision points as to how to manage the different phases of treatment

It's time for an MRD-based treatment in MM

grazie