Treatment of Multiple Myeloma In 2018

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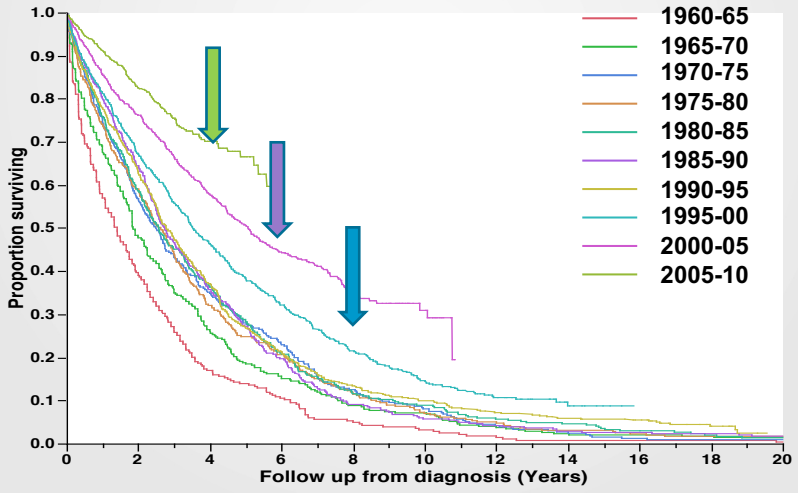
ifm

Multiple Myeloma Survival Improving With New Drugs



Adapted from Kumar et al *Leukemia* 2014

2

When should we start treatment ?
1 MDE or more

Symptomatic Myeloma

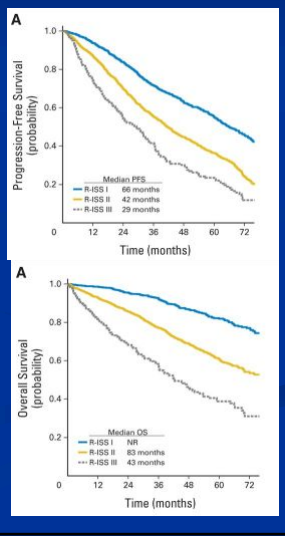
- **C** Calcemia
- **R** Renal insufficiency
- **A** Anemia
- **B** Bone lesions (X ray)

New IMWG Criteria
Rajkumar Lancet Oncol 2014;15:538-548

- ≥60% BMPC
- ≥100 FLC ratio
- >1 MRI focal lesion

New Prognostic Classification
R-ISS
Palumbo A JCO 2015;33:2863-9

Prognostic Factor		Criteria
ISS stage		
	I	Serum β_2-microglobulin < 3.5 mg/L, serum albumin ≥ 3.5 g/dL
	II	Not ISS stage I or III
	III	Serum β_2-microglobulin ≥ 5.5 mg/L
CA by iFISH		
	High risk	Presence of del(17p) and/or translocation t(4;14) and/or translocation t(14;16
	Standard risk	No high-risk CA
LDH		
	Normal	Serum LDH < the upper limit of normal
	High	Serum LDH > the upper limit of normal
A new model for risk stratification for MM		
	R-ISS stage	
	I	ISS stage I and standard-risk CA by iFISH and normal LDH
	II	Not R-ISS stage I or III
	III	ISS stage III and either high-risk CA by iFISH or high LDH



Current treatment of MM
Transplant eligible patients

In the era of « novel » agents
HDT/ASCT
Is no longer just HDT supported by ASCT
But is a part of a complex multistep prodedure

Induction therapy	ASCT	Consolidation	Maintenance
3-4 CYCLES « novel » agents	Melphalan 200 mg/m^2	2-3 CYCLES « novel» agents Or Second ASCT	Lenalidomide Bortezomib

Induction therapy with novel agents

- Induction should contain Bortezomib [1,2]
- Triple Combination > Double Combination
  - VTD > TD [3,4]
  - vTD > VD [5]
- Triplets should contain 1 IMId and 1 PI
  - VTD >VCD [6]

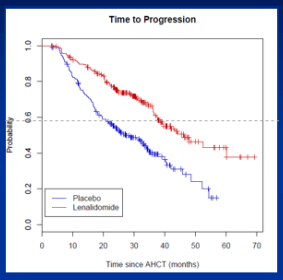
VTD is the standard induction regimen

- But VRd is better tolerated
  - and may be prescribed longer (6 cycles) [7]
  - No randomized comparison VTd vs VRd

1 Avet Loiseau H JCO 2010;28:4630 2 Sonneveld P JCO 2013;31:3279 3 Cavo M Lancet 2010;376:2075 4 Rosinol L Blood 2012;120:1589 5 Moreau P Blood 2011;118:5752 6 Moreau P (Blood 2016;127:2569-2574) 7 Rosinol L (ASH 2017)

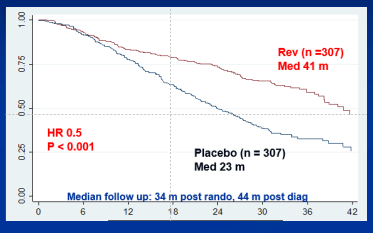
LENALIDOMIDE MAINTENANCE

Four randomized trials show a dramatic improvement of PFS



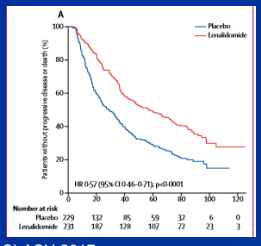
HR 0.37

McCarthy P (CALGB) NEJM 2012; 366:1770



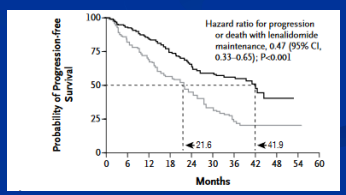
HR 0.5

Attal M (IFM) NEJM 2012;366:1778



HR 0.57

Jackson G (MRC) ASH 2017



HR 0.47

Palumbo A NEJM 2014;371:895

Consolidation Therapy

- Currently 2-3 cycles of combination therapy (usually the same as induction therapy)
- Or Second ASCT (high-risk patients) [1]
- With the objective of increasing the rate of Complete Remission
- And of upgrading the level of response
  - stringent CR (sCR) (normal FLC ratio)
  - <0 minimal residual disease (MRD)

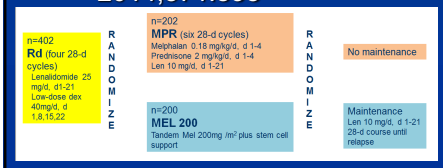
1 Cavo ASH 2017

Is frontline ASCT still standard of care ?

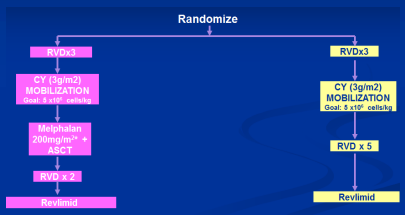
- Non-intensive therapies (triple combinations) are well-tolerated and yield high response rates and long PFS
  (SWOG Study RVd vs Rd Durie BG Lancet 2017)
- Therefore the question is no longer is ASCT> non-intensive therapies ?
- But does ASCT add to non-intensive therapies ?

Four Randomized Trials addressed this question

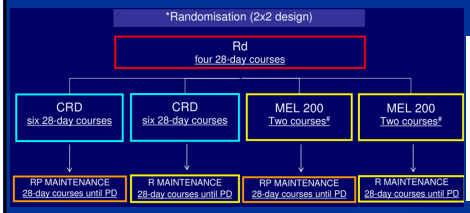
- Palumbo A et al NEJM 2014;371:895



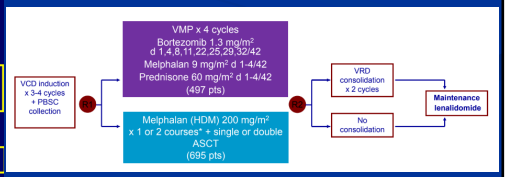
- Attal M NEJM 2017;376:1311



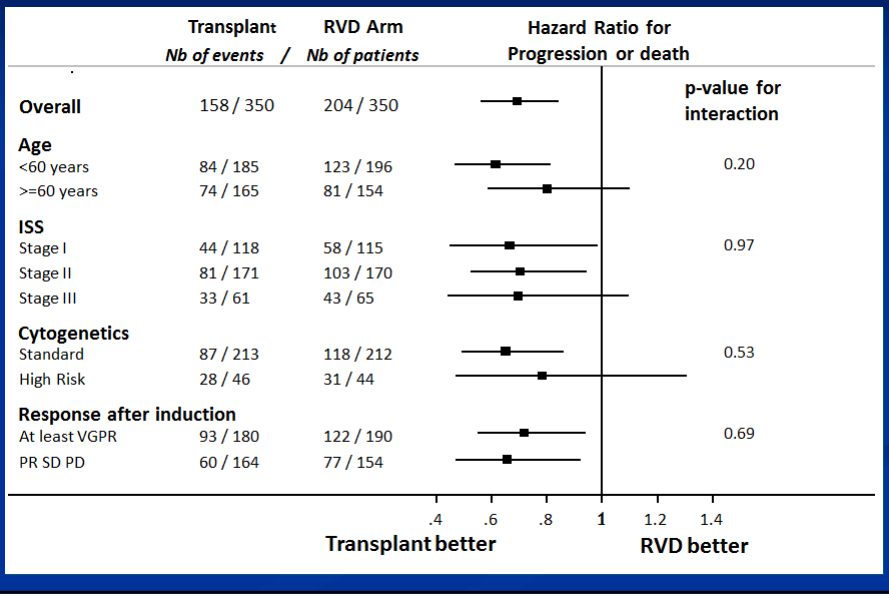
- Gay P Lancet Oncol 2015;16:1617



- EMN02/HO95 Cavo M ASH 2017



IFM 2009 : PFS is improved in all prognostic subgroups

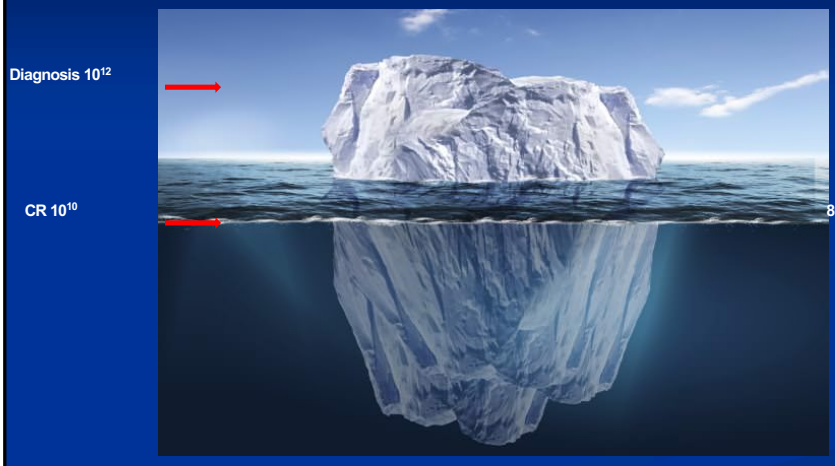


IFM 2009 Response rate

	RVD 5 courses + ASCT	RVD 8 courses	*P*
CR	59 %	48 %	0.006
post maintenance CR+ VGPR	88 %	76%	< 0.002
post maintenance <0 MRD	79 %	65 %	< 0.001

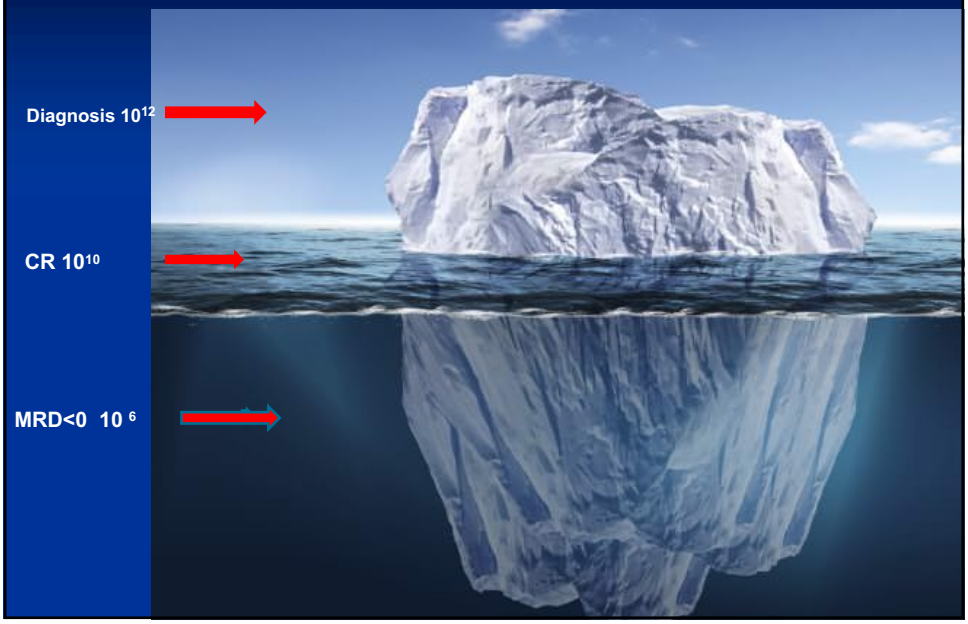
Attal M NEJM 2017;376:1311

Why to assess MRD in Myeloma?



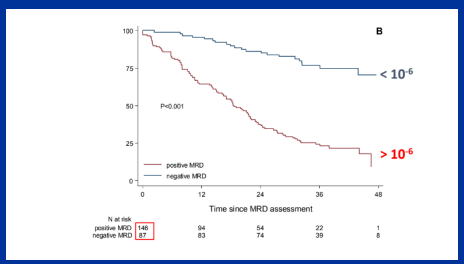
CR was the objective of clinical trials in MM
CR is now achieved in up to 80% of patients treated with ASCT plus novel agents
But most of them will utlimately relapse

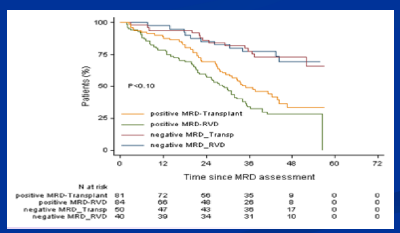
What does Minimal Residual Disease Mean ?



Prognostic value of MRD negativity in the IFM 2009 trial (NGS)

- Much longer PFS if MRD is <0 (10^{-6})
- Prognostic value is the same in both arms
- But more <0 MRD in the ASCT arm



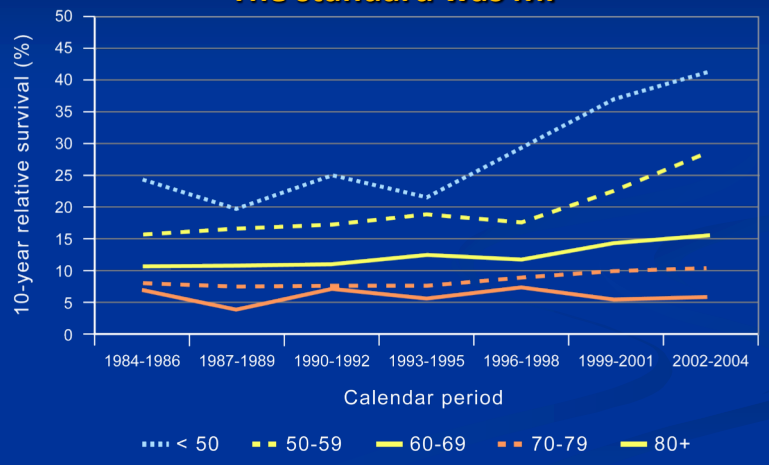


Conclusions

- Frontline ASCT remains the standard of care
  - higher CR rate
  - higher proportion of MRD<0
  - Longer PFS in all prognostic subgroups
- And is included in all ongoing trials in Europe
- However due to excellent results of RVd and to the use of ASCT in relapse, OS may be comparable and delayed ASCT is a possible alternative (mostly in the US)

Current treatment in transplant non-eligible patients

No improvement in the 10-Year OS in patients>70 years of age before introduction of new agents The standard was MP



Brenner et al; Blood 2008; 111:2521-26

MPT Becomes a New Standard of Care

Melphalan and prednisone plus thalidomide versus melphalan and prednisone alone or reduced-intensity autologous stem cell transplantation in elderly patients with multiple myeloma (IFM 99-06): a randomised trial

Lancet 2007; 370: 1209–18

Thierry Facon, Jean Yves Mary, Cyrille Hulin, Lotfi Benboubker, Michel Attal, Brigitte Pegourie, Marc Renaud, Jean Luc Harousseau, Gaelle Guillerm, Carine Chaleteix, Mamoun Dib, Laurent Voillat, Hervé Maisonneuve, Jacques Troncy, Véronique Dorvaux, Mathieu Moncanduit, Claude Martin, Philippe Casassus, Jérôme Jaubert, Henry Jardel, Chantal Doyen, Brigitte Kolb, Bruno Anglaret, Bernard Grosbois, Ibrahim Yakoub-Agha, Claire Mathiot, Hervé Avet-Loiseau, on behalf of the Intergroupe Francophone du Myélome

blood

2011 118: 1239-1247
Prepublished online June 13, 2011;
doi:10.1182/blood-2011-03-341669

Thalidomide for previously untreated elderly patients with multiple myeloma: meta-analysis of 1685 individual patient data from 6 randomized clinical trials

Peter M. Fayers, Antonio Palumbo, Cyrille Hulin, Anders Waage, Pierre Wijermans, Meral Beksaç, Sara Bringhen, Jean-Yves Mary, Peter Gimsing, Fabian Termorshuizen, Rauf Haznedar, Tommaso Caravita, Philippe Moreau, Ingemar Turesson, Pellegrino Musto, Lotfi Benboubker, Martijn Schaafsma, Pieter Sonneveld, Thierry Facon and on behalf of the Nordic Myeloma Study Group, Italian Multiple Myeloma Network, Turkish Myeloma Study Group, Hemato-Oncologie voor Volwassenen Nederland, Intergroupe Francophone du Myélome, and European Myeloma Network

Facon T, et al. Lancet. 2007;370:1209-18. Fayers PM, et al. Blood. 2011;118: 1239-47.

Currently :Two standards in Europe

VMP (VISTA trial) VMP>MP The NEW ENGLAND JOURNAL of MEDICINE 2008

Bortezomib plus Melphalan and Prednisone for Initial Treatment of Multiple Myeloma

Jesús F. San Miguel, M.D., Ph.D., Rudolf Schlag, M.D., Nuriet K. Khuageva, M.D., Ph.D., Meletios A. Dimopoulos, M.D., Ofer Shpilberg, M.D., Ph.D., Martin Kropff, M.D., Ivan Spicka, M.D., Ph.D., Maria T. Petrucci, M.D., Antonio Palumbo, M.D., Olga S. Samoilova, M.D., Ph.D., Anna Dmoszynska, M.D., Ph.D., Kudrat M. Abdulkadyrov, M.D., Ph.D., et al., for the VISTA Trial Investigators*

Rd continuous >MPT (PFS and OS) The NEW ENGLAND JOURNAL of MEDICINE 2014

Rd continuous > **Rd 18** (PFS) (FIRST trial)

ORIGINAL ARTICLE

Lenalidomide and Dexamethasone in Transplant-Ineligible Patients with Myeloma

Lotfi Benboubker, M.D., Meletios A. Dimopoulos, M.D., Angela Dispenzieri, M.D., John Catalano, M.D., Andrew R. Belch, M.D., Michele Cavo, M.D., Antonello Pinto, M.D., Katja Weisel, M.D., Heinz Ludwig, M.D., Nizar Bahlis, M.D., Anne Banos, M.D., Mourad Tiab, M.D., et al., for the FIRST Trial Team*

HOW TO IMPROVE ?

- **Combine IMId and PI**

-simultaneously Ex :VMPT (Gimema)

RVd (SWOG) standard in the US

-sequentially Ex : VMP-Rd (Pethema)

- **Induction plus Maintenance**

Bortezomib Ex :VMPT +VT (Gimema)

VMP+ VT or VP (Pethema)

Lenalidomide Ex : MRC XI trial

Current treatment in Relapsed Myeloma

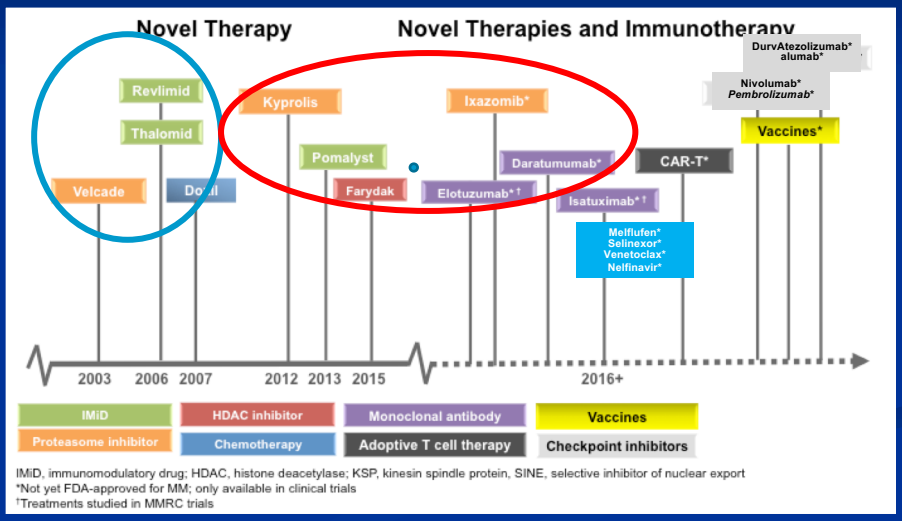
The objectives of Clinical Trials in Newly Diagnosed Patients

- Achieving MRD negativity is a new end-point of MM treatment
- Starting treatment at earlier stages (high-risk smoldering myeloma) to cure patients
- Improving PFS by increasing the % of MRD<0 at the 10^{-6} level

→ Introduce 2nd generation agents

- 2nd generation PI (carfilzomib, ixazomib)
- Anti CD-38 Antibodies (daratumumab, isatuximab)

Myeloma Drug Development



IMiD, immunomodulatory drug; HDAC, histone deacetylase; KSP, kinesin spindle protein, SINE, selective inhibitor of nuclear export
*Not yet FDA-approved for MM; only available in clinical trials
†Treatments studied in MMRC trials

Second generation new agents further improve results in RRMM

(Rajkumar SV NEJM 2016)

Trial and Regimen†	Complete Response	Median Progression-free Survival	Hazard Ratio for Disease Progression or Death (95% CI)	P Value
	% of patients	mo		
Lenalidomide-based regimen				
TOURMALINE-MM1[6]			0.74 (0.59–0.94)	0.01
Lenalidomide–dexamethasone	7	14.7		
Ixazomib–lenalidomide–dexamethasone	12	20.6		
ELOQUENT-2[7]			0.70 (0.57–0.85)	<0.001
Lenalidomide–dexamethasone	7	14.9		
Elotuzumab–lenalidomide–dexamethasone	4	19.4		
ASPIRE[4]			0.69 (0.57–0.83)	<0.001
Lenalidomide–dexamethasone	14	17.6		
Carfilzomib–lenalidomide–dexamethasone	32	26.3		
POLLUX[10]			0.37 (0.27–0.52)	<0.001
Lenalidomide–dexamethasone	19	18.4		
Daratumumab–lenalidomide–dexamethasone	43	NR		
Bortezomib-based regimen				
PANORAMA1[5]			0.63 (0.52–0.76)	<0.001
Bortezomib–dexamethasone	6	8.1		
Panobinostat–bortezomib–dexamethasone	11	12.0		
CASTOR[9]			0.39 (0.28–0.53)	<0.001
Bortezomib–dexamethasone	9	7.2		
Daratumumab–bortezomib–dexamethasone	19	NR		

26

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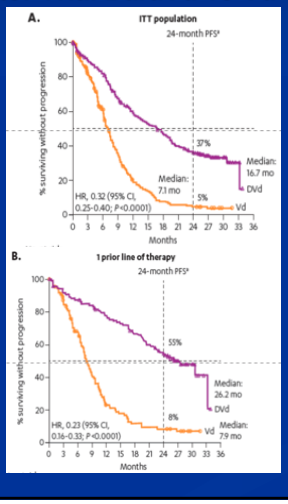
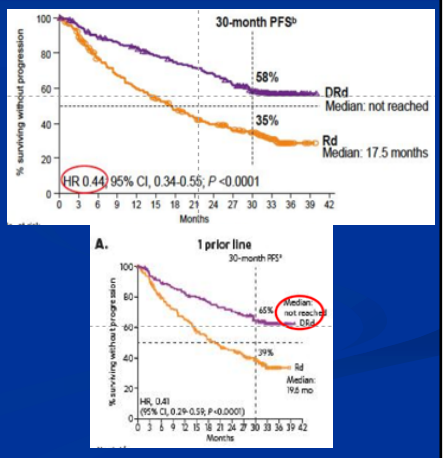
27

Daratumumab (anti-CD38) in combination with Vd or Rd in Relapsed MM:Best results ever achieved

Castor Trial DaraVd vs Vd PFS



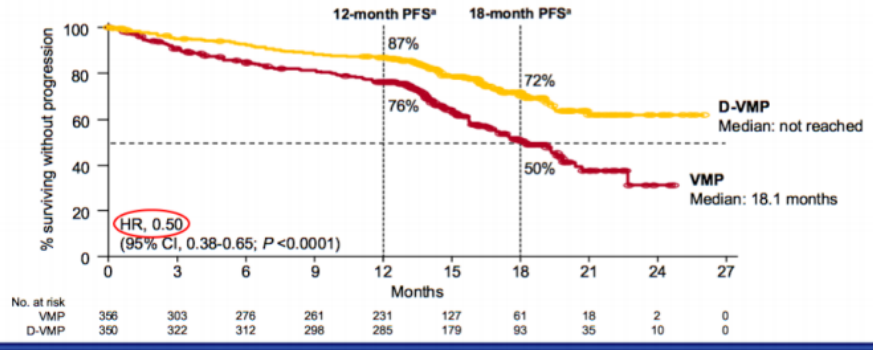
Pollux trial DaraRd vs Rd PFS



ALCYONE TRIAL

PFS

- Median (range) follow-up: 16.5 (0.1-28.1) months



50% reduction in the risk of progression or death in patients receiving D-VMP

MATEOS M.V., NEJM 2018; 378 : 548-28

29

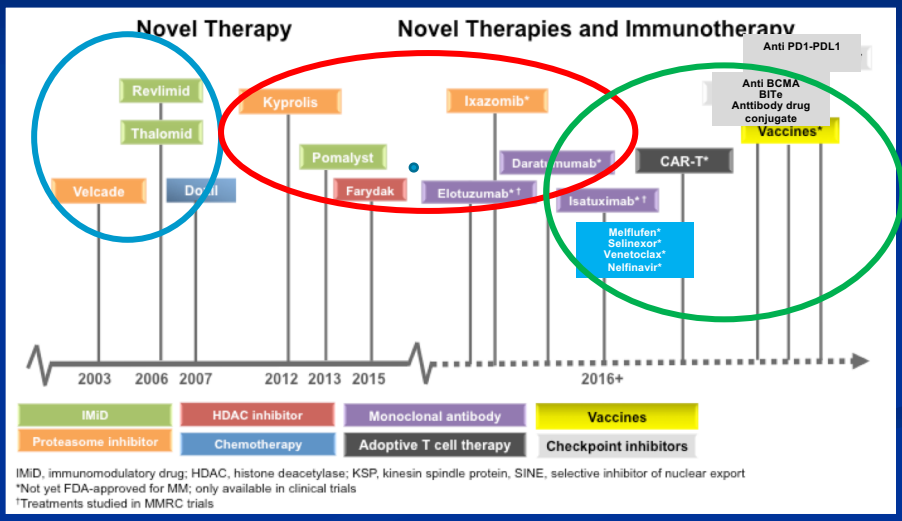
The objectives of Clinical Trials in Newly Diagnosed Patients

- Achieving MRD negativity is a new end-point of MM treatment
- Increasing the proportion of patients with MRD<0 at the 10^{-6} level
- Tailoring treatment (risk-adapted therapy)

→ to initial prognostic factors
- Fit/frail elderly patients
- High-risk cytogenetics

→ to MRD assessment

Treatment of relapsed MM
What are the newer agents?

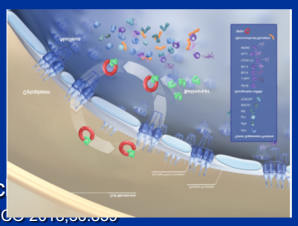


IMiD, immunomodulatory drug; HDAC, histone deacetylase; KSP, kinesin spindle protein, SINE, selective inhibitor of nuclear export
*Not yet FDA-approved for MM; only available in clinical trials
†Treatments studied in MMRC trials

Third generation new agents

SELINEXOR

- Selinexor is the first-in-class of the Selective Inhibitor of Nuclear Export (SINE) which are XPO1- inhibitors
- XPO1 transport tumor-suppressor genes from the nucleus to the cytoplasm

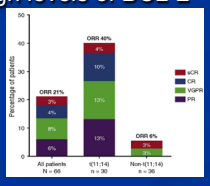


- In c

Vogl DT JC
Chen C Blood 2018;131:855

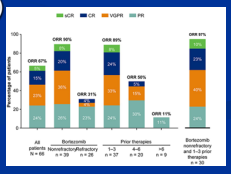
VENETOCLAX (anti-BCL-2)

- Targeted therapy in t(11;14) MM With high levels of BCL-2



Kumar S Blood 2017;130:2401

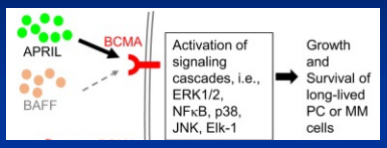
- In combination with BTZ (to target MCL-1)



Moreau P Blood 2017;130:2392

Targeting BCMA in MM

- B-cell Maturation antigen
- Is expressed on normal and MM PC
- New anti-BCMA Immunotherapies
  - Bispecific T-cell engagers (BiTE)
  - Antibody Drug Conjugate



First in Human Study with GSK2857916, an Antibody Drug Conjugated to Microtubule–Disrupting Agent Directed Against B-Cell Maturation Antigen (BCMA) in Patients with Relapsed/Refractory Multiple Myeloma (MM): Results from Study BMA117159 Part 1 Dose Escalation

Adam D. Cohen, Rakesh Popat, Suzanne Trudel, Paul G Richardson, Ed N. Libby III, Nikoletta Lendvai, Larry D. Anderson Jr., Heather J. Sutherland, Stephen DeWall, Catherine E Ellis, Zangdong He, Jolly Mazumdar, Catherine Wang, Joanna B. Opalinska, and Peter M. Voorhees

Blood 2016 128:1148

- Anti BCMA CAR T-cells

CAR-T cells in MM

Review on CAR T cells June CH NEJM 2018

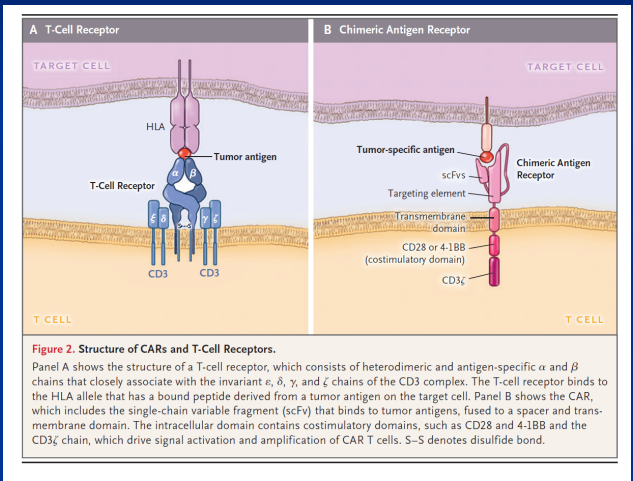
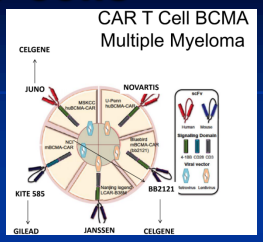


Figure 2. Structure of CARs and T-Cell Receptors.
Panel A shows the structure of a T-cell receptor, which consists of heterodimeric and antigen-specific α and β chains that closely associate with the invariant ε, δ, γ, and ζ chains of the CD3 complex. The T-cell receptor binds to the HLA allele that has a bound peptide derived from a tumor antigen on the target cell. Panel B shows the CAR, which includes the single-chain variable fragment (scFv) that binds to tumor antigens, fused to a spacer and transmembrane domain. The intracellular domain contains costimulatory domains, such as CD28 and 4-1BB and the CD3ζ chain, which drive signal activation and amplification of CAR T cells. S–S denotes disulfide bond.

Targets — CD19, **BCMA** SLAM F7

Anti-BCMA CAR T cells



- CAR T cells in development
- High response rate
- Tumour response related to the dose , not to BCMA expression
- Response duration (median 1 year in heavily pre-treated patients; 17 months in <0 MRD patients)
- Toxicity - Cytokine Release Syndrome
  - Neurotoxicity
- Logistics - limited access
  - long preparation process
  - cost

Fan ASCO 2017,Cohen A ASH 2017,Raje N ASH 2017,Brudno JCO 2018