



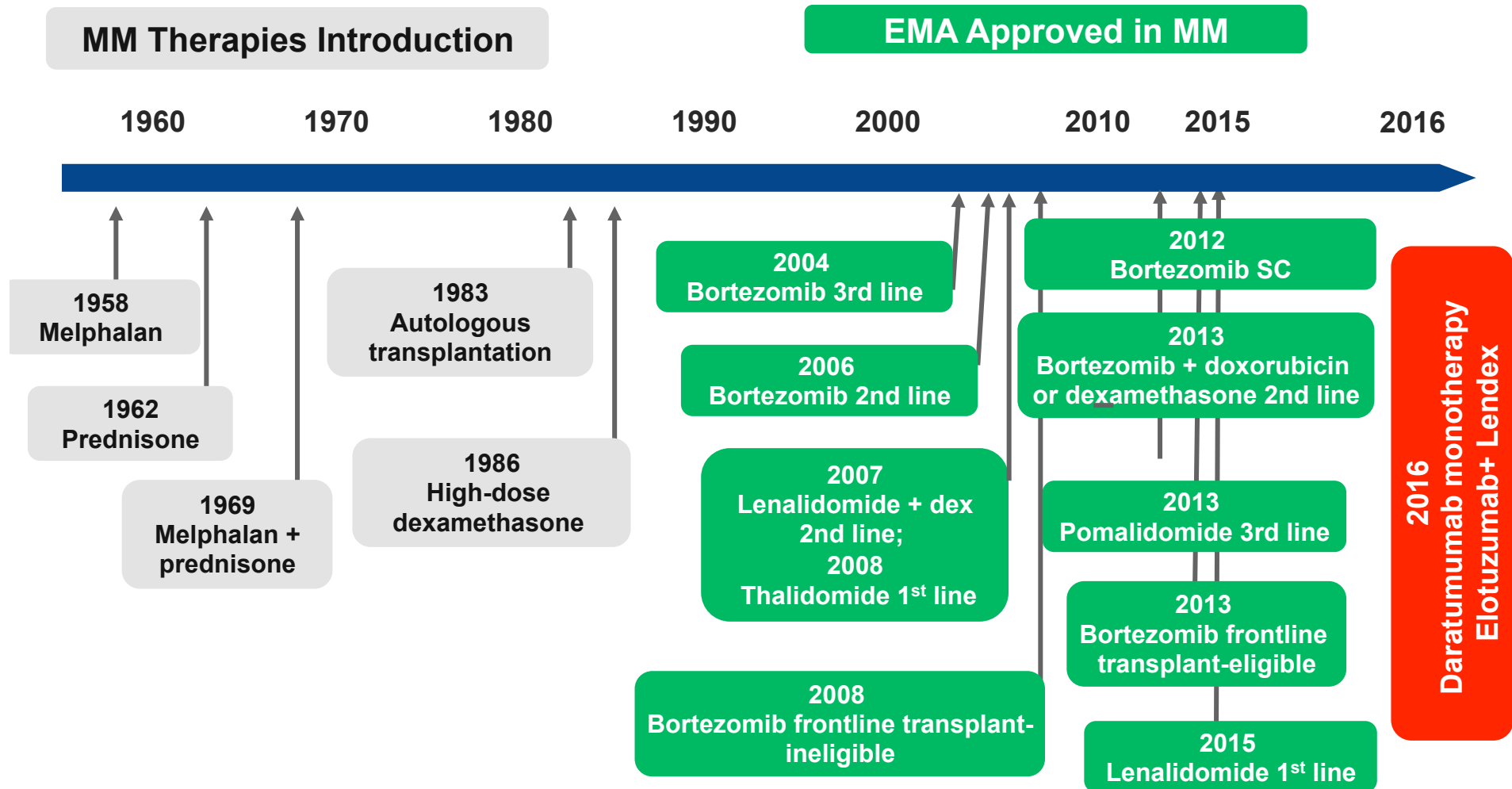
La terapia del mieloma multiplo: 20 anni di successi

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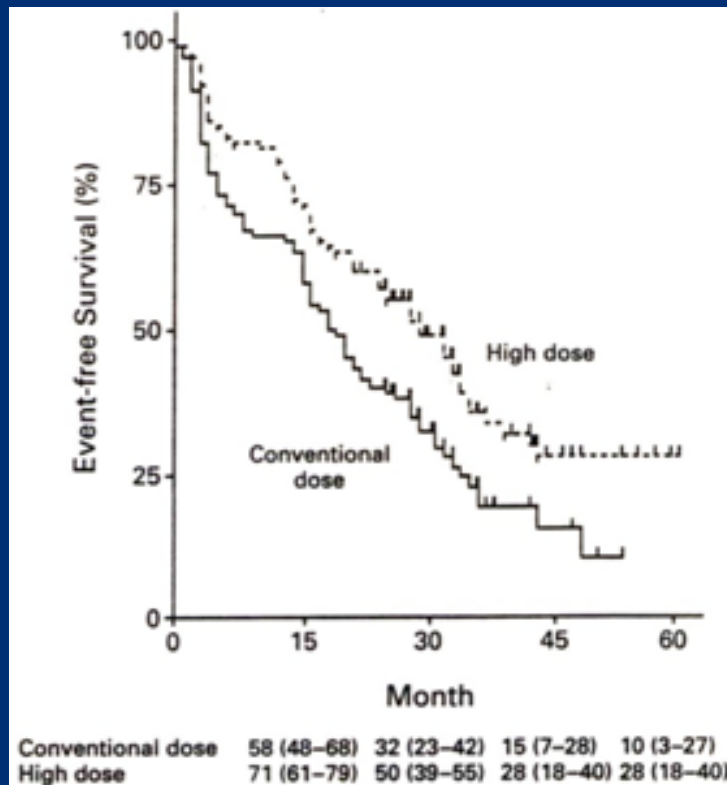
Ravenna, 15 Ottobre, 2016

Increased Approved Treatment Options in MM



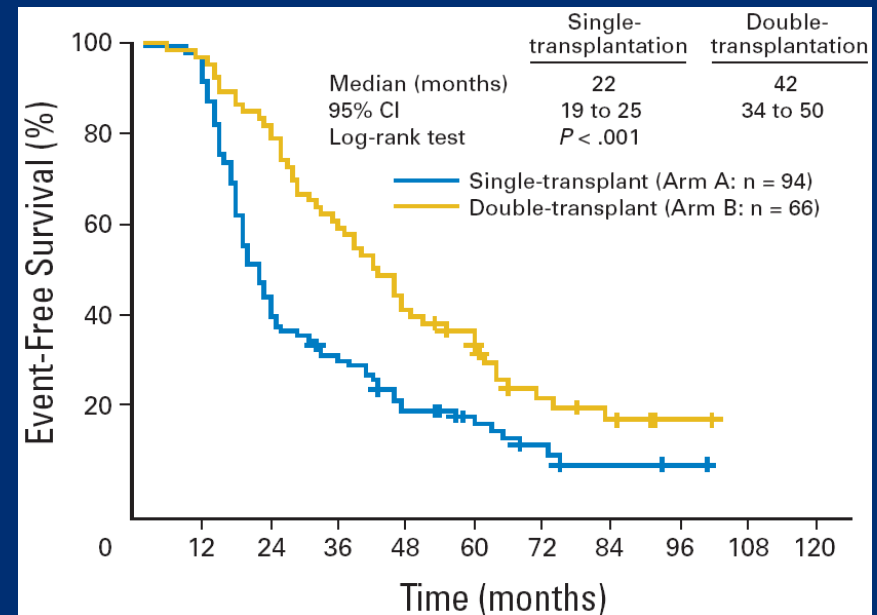
ASCT as Consolidation Therapy

Single ASCT vs CHT



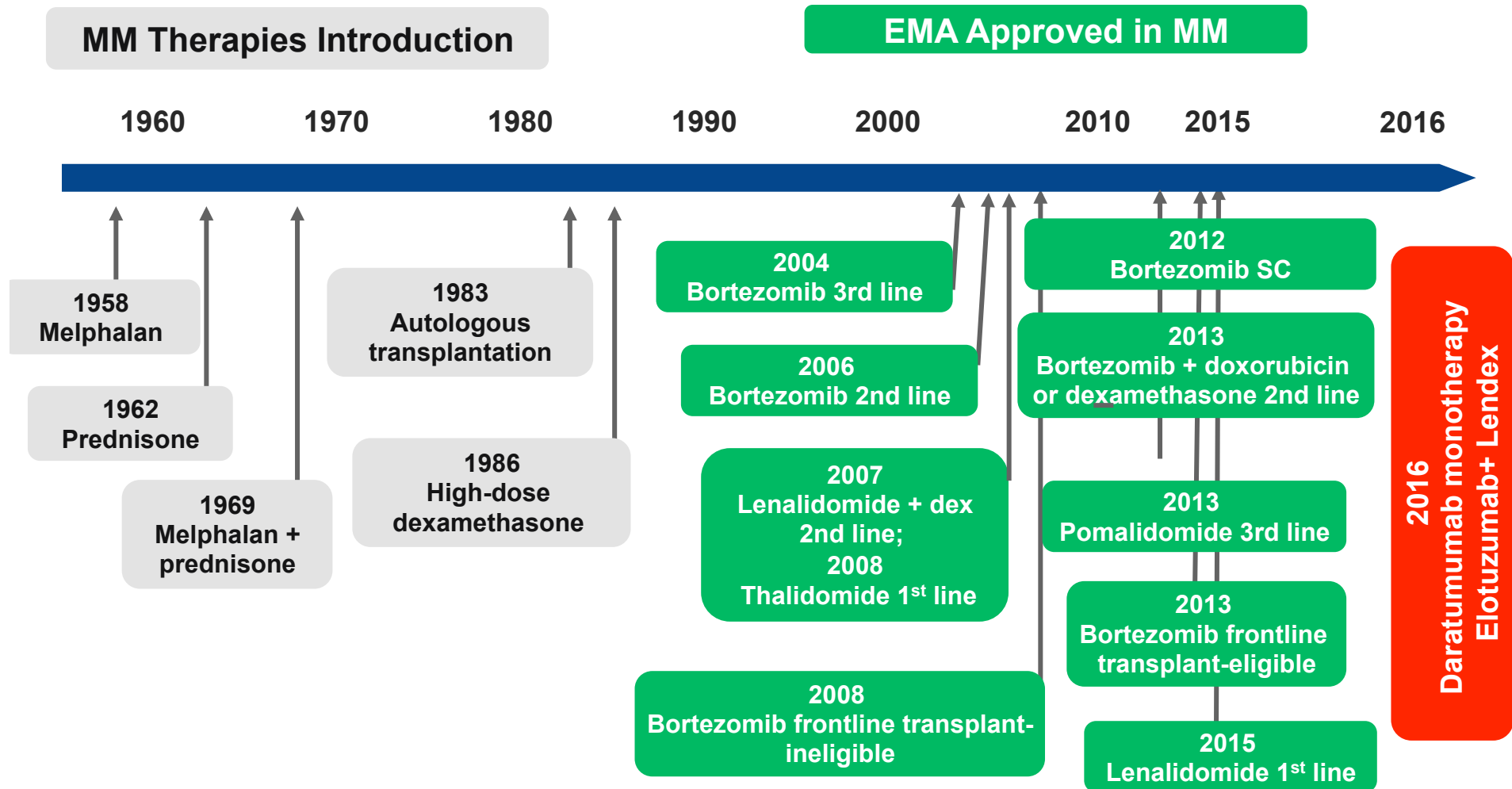
Attal M. et al, *NEJM* 1996

Single vs Double ASCT



Cavo M. et al, *J Clin Oncol* 2007

Increased Approved Treatment Options in MM



Novel Agent–Based Induction Therapies for Patients Eligible for a Transplant

blood

2005 106: 35-39
Prepublished online March 10, 2005;
doi:10.1182/blood-2005-02-0522

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

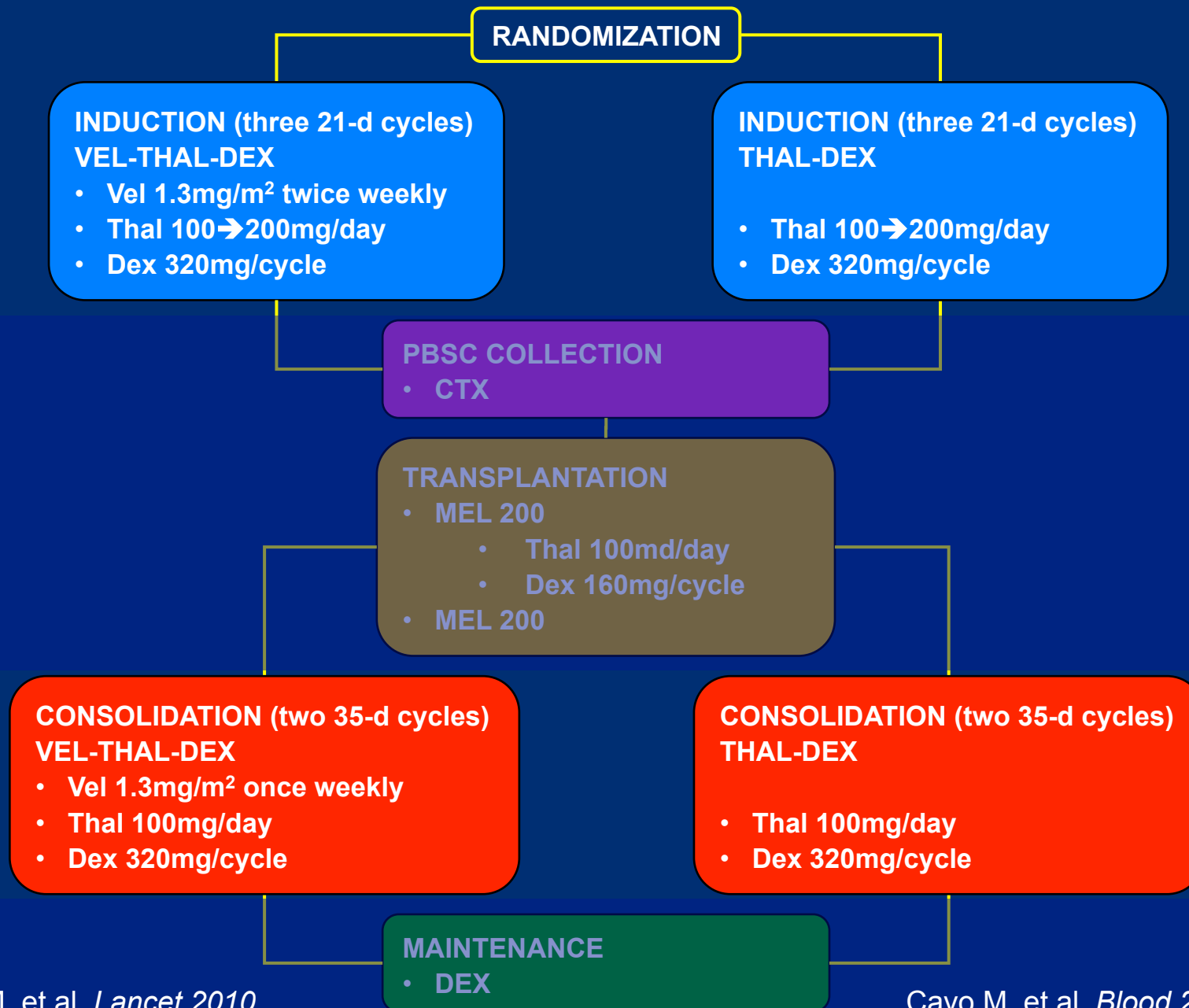
Rate of Response

	No. of patients		<i>P</i>
	Thal-DEX, N = 100	VAD, N = 100	
≥PR	76	52	<0.001
CR + nCR	13	13	
≥VGPR	19	14	
PR	57	38	
NR/PROG	24	48	<0.001

PR, partial response; NR, no response; PROG, progression

Cavo M et al. *Blood*. 2005;106:35.

GIMEMA MMY-3006 Phase III Study Design

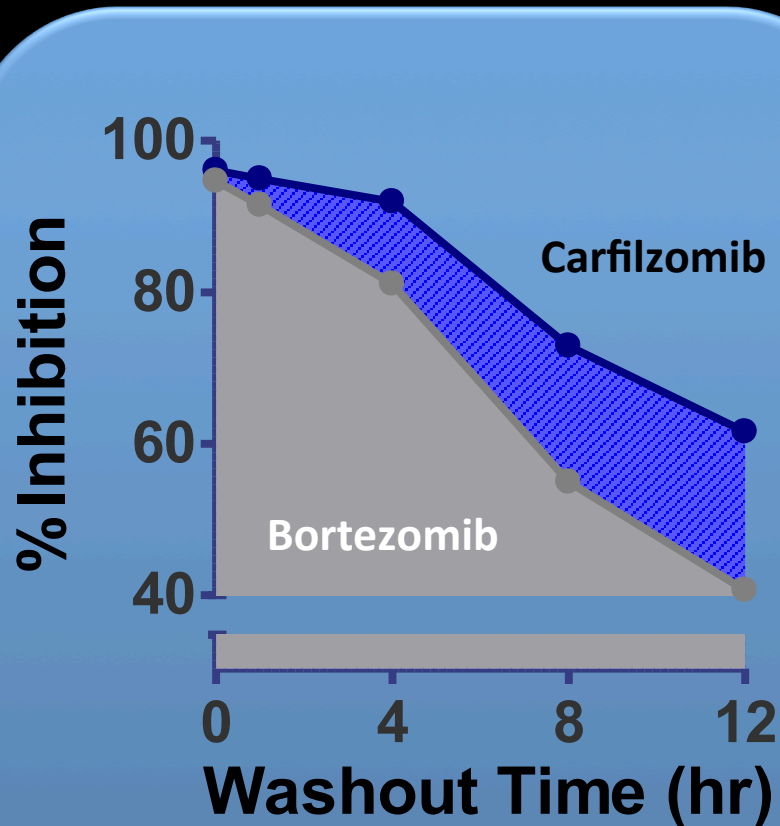


Multiple Myeloma treatment evolution

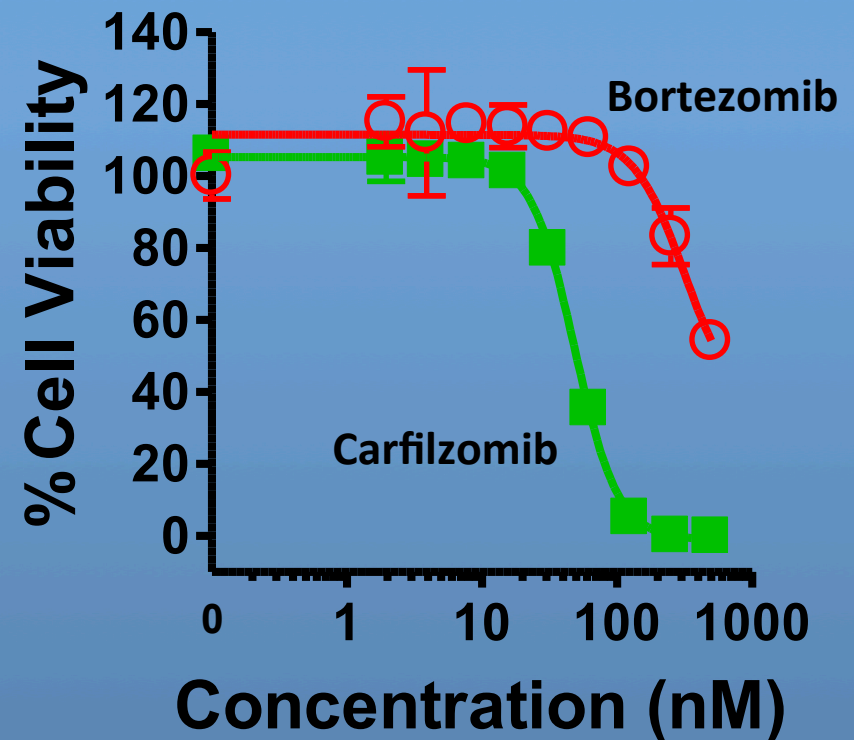
Drug Class	Name
Alkylating agents	Melphalan
	Cyclophosphamide
Proteasome inhibitor	Bortezomib
	Carfilzomib
	Ixazomib
Immunomodulatory agents	Thalidomide
	Lenalidomide
	Pomalidomide
Monoclonal Antibodies	Daratumumab
	Elotuzumab

Carfilzomib Induces Prolonged Proteasome Inhibition: Increased Anti-Tumor Activity

Target Inhibition¹



Myeloma Cell Survival²



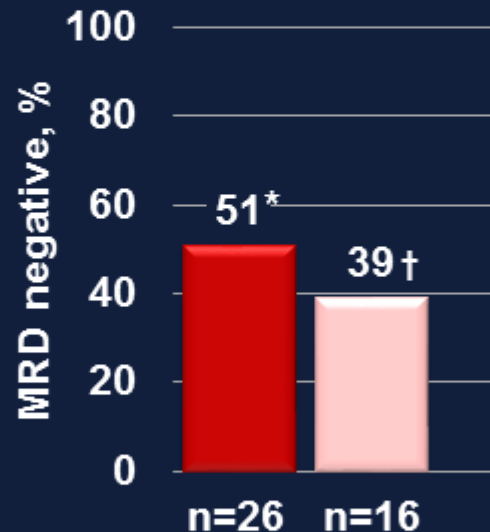
1. Suzuki et al. (PLoS 2011). 2. Demo et al. (Can. Res. 2007).

MRD Evaluation

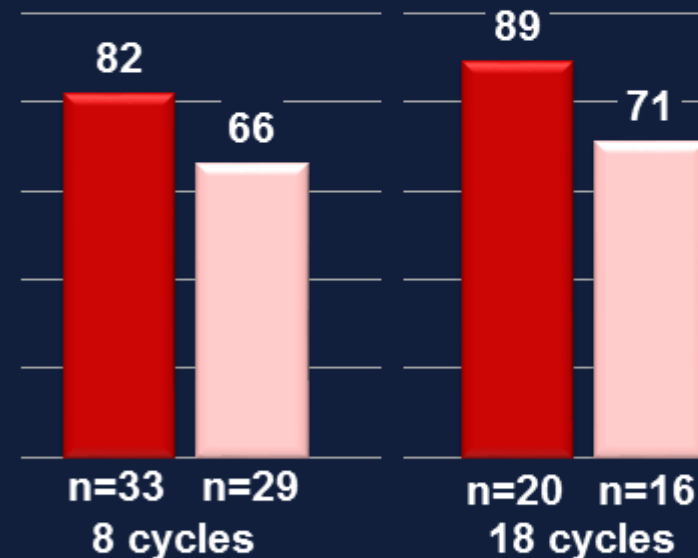
Multiparameter Flow Cytometry (MFC)
10 color
Sensitivity: 10^{-4} – 10^{-5}

Next generation sequencing (NGS)
Adaptive Biotechnologies
Sensitivity: 10^{-6}

KRd w/o ASCT
At CR



KRd + ASCT‡
At landmark time points



*Estimated rate based on 23 of 26 evaluated pts assessed for MRD by flow cytometry at CR/ suspected CR

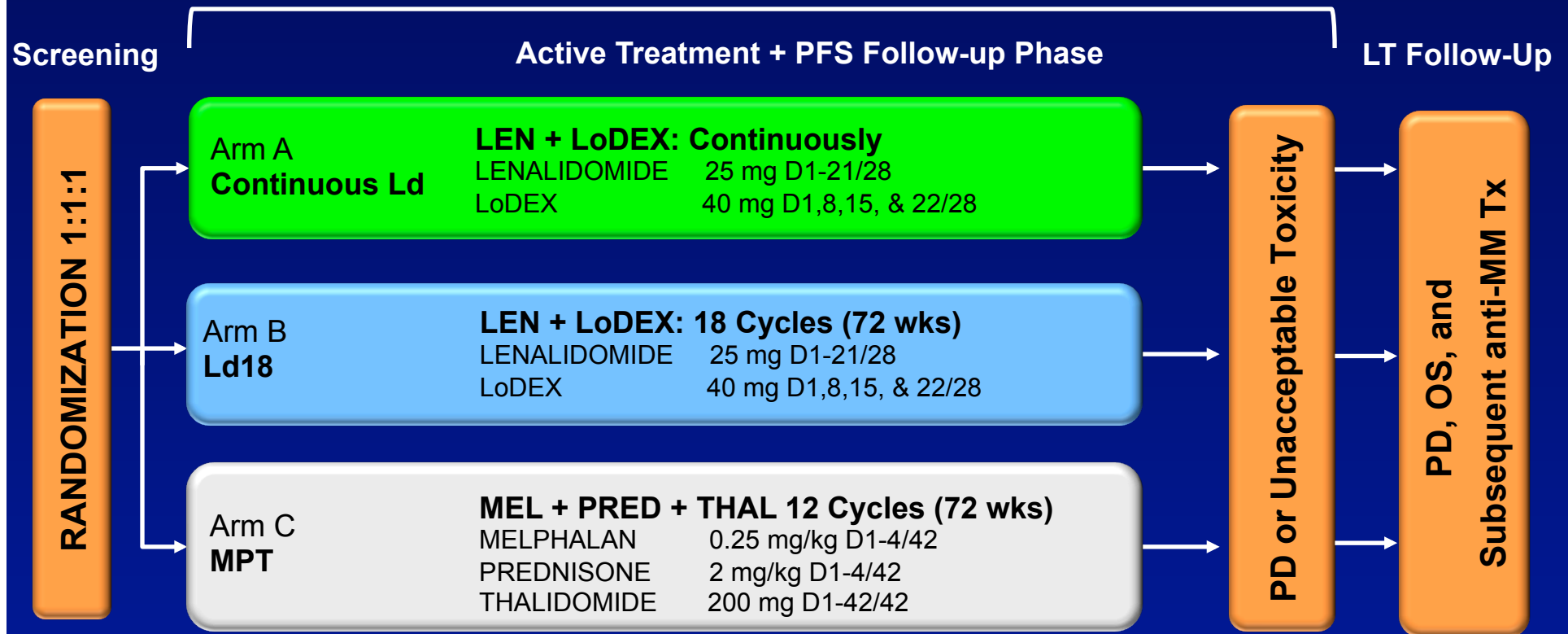
†Estimated rate based on percentage of 13 pts in CR/sCR negative by NGS

‡ Actual MRD rates in subgroup of pts evaluated for MRD at the end of 8 and 18 cycles as per new IMWG MRD criteria (**pts were considered MRD – negative only if in CR/sCR**)

Multiple Myeloma treatment evolution

Drug Class	Name
Alkylating agents	Melphalan
	Cyclophosphamide
Proteasome inhibitor	Bortezomib
	Carfilzomib
	Ixazomib
Immunomodulatory agents	Thalidomide
	Lenalidomide
	Pomalidomide
Monoclonal Antibodies	Daratumumab
	Elotuzumab

FIRST Trial: Study Design



Pts > 75 yrs: Lo-DEX 20 mg D1, 8, 15 & 22/28; THAL (100 mg D1-42/42); MEL 0.2 mg/kg D1-4

- Stratification: age (≤ 75 y vs. > 75 y), country, and ISS stage (I or II vs. III)
- Thromboprophylaxis was mandatory

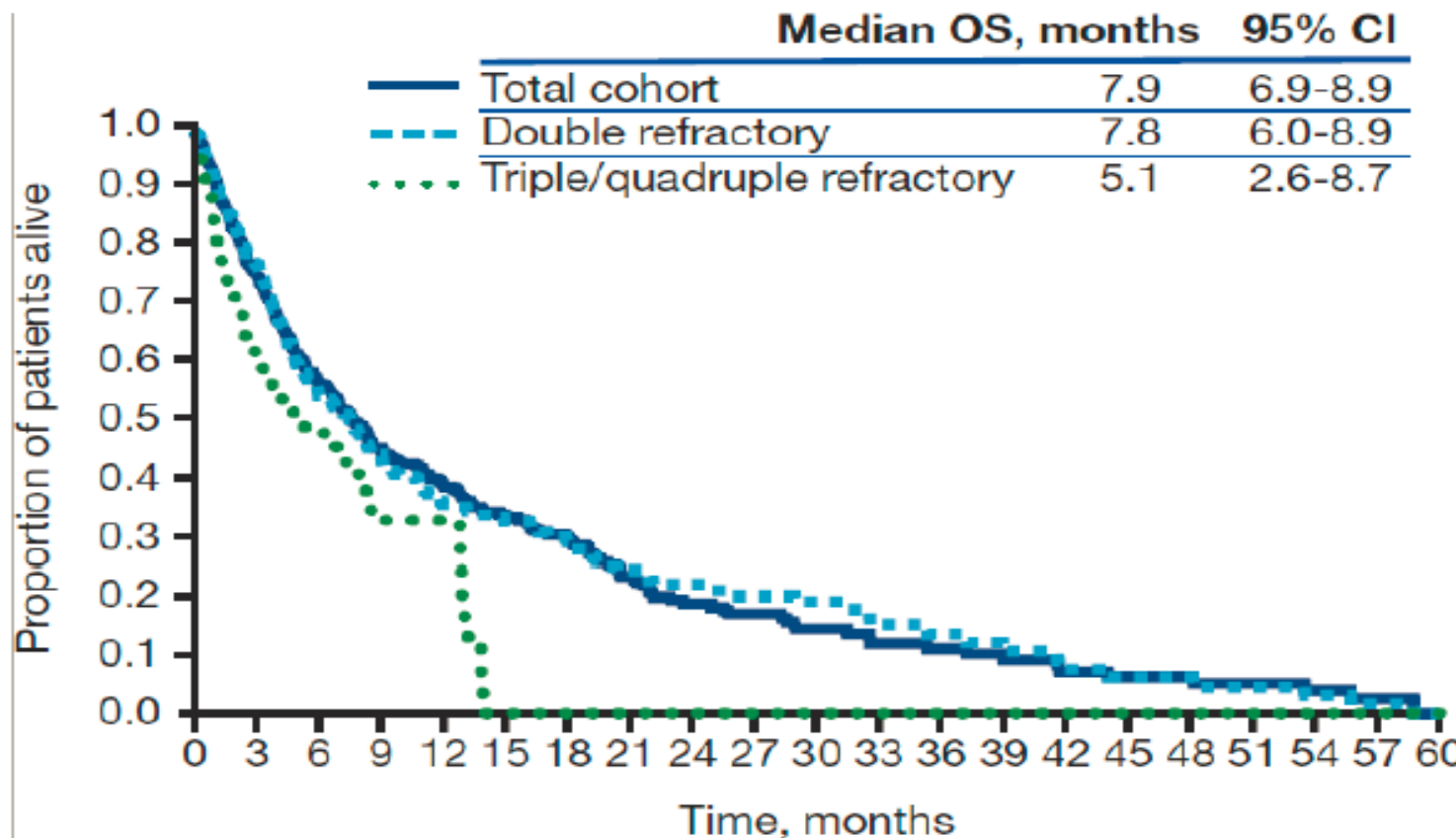
FIRST, Frontline Investigation of Revlimid and Dexamethasone versus Standard Thalidomide; ISS, International Staging System; Ld, lenalidomide plus low-dose dexamethasone; Ld18, lenalidomide plus low-dose dexamethasone for 18 cycles; LEN, lenalidomide; LoDEX, low-dose dexamethasone; LT, long-term; MEL, melphalan; MM, multiple myeloma; MPT, melphalan, prednisone, thalidomide; OS, overall survival; PD, progressive disease; PFS, progression-free survival; Pred, prednisone; pt, patient; THAL, thalidomide; Tx, treatment.

Multiple Myeloma treatment evolution

Drug Class	Name
Alkylating agents	Melphalan
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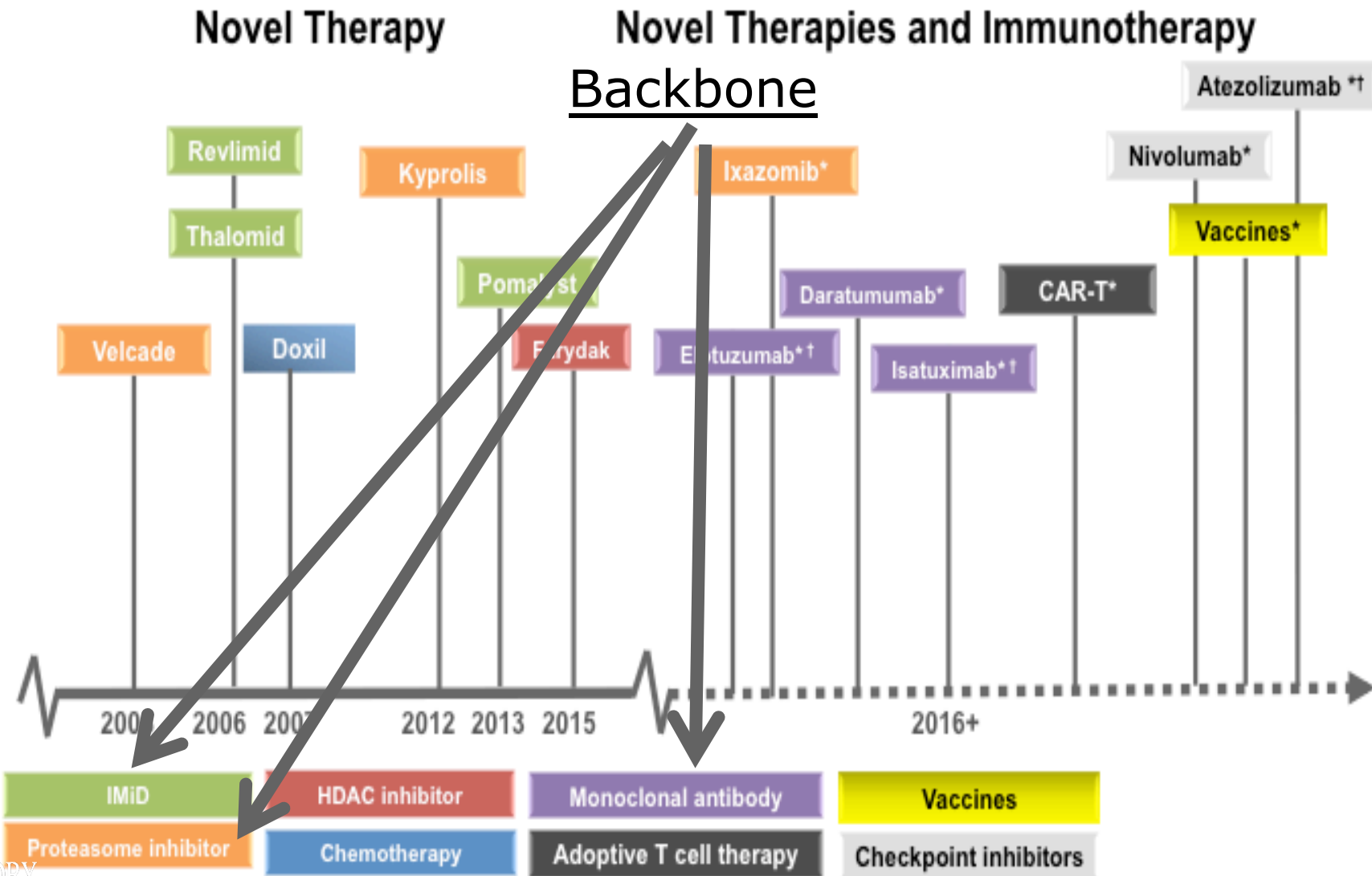
Median overall survival for RRMM patients

Recent review of real world data found outcomes remain poor for patients with relapsed MM despite the approval of carfilzomib and pomalidomide.



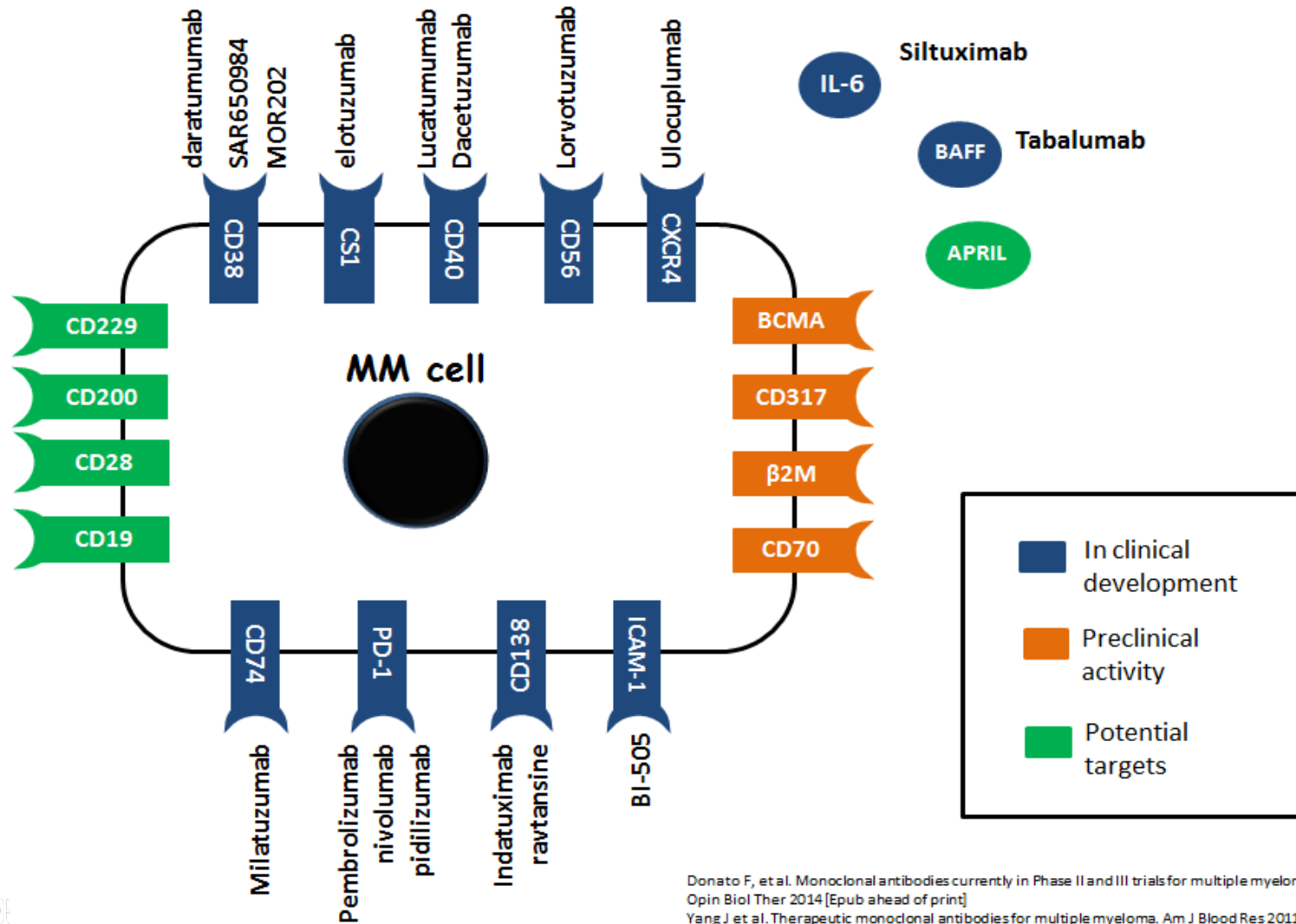
1. Usmani S *et al.* (2015). EHA Annual Congress. Vienna, Austria. Abstract No. E1256. (Poster).
2. Published Ahead of Print on August 2, 2016 as 10.1634/theoncologist.2016-0104.

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

Targets for MoABs in MM



Donato F, et al. Monoclonal antibodies currently in Phase II and III trials for multiple myeloma. Expert Opin Biol Ther 2014[Epub ahead of print]
 Yang J et al. Therapeutic monoclonal antibodies for multiple myeloma. Am J Blood Res 2011;1:22-33
 Mateo G, et al. Prognostic value of immunophenotyping in multiple myeloma: A study by the PETHEMA/GEM Cooperative study groups on patients uniformly treated with high-dose therapy
 Atanackovic D, et al. Surface molecule CD229 as a novel target for the diagnosis and treatment of multiple myeloma. Haematologica 2014;96:1512-20.

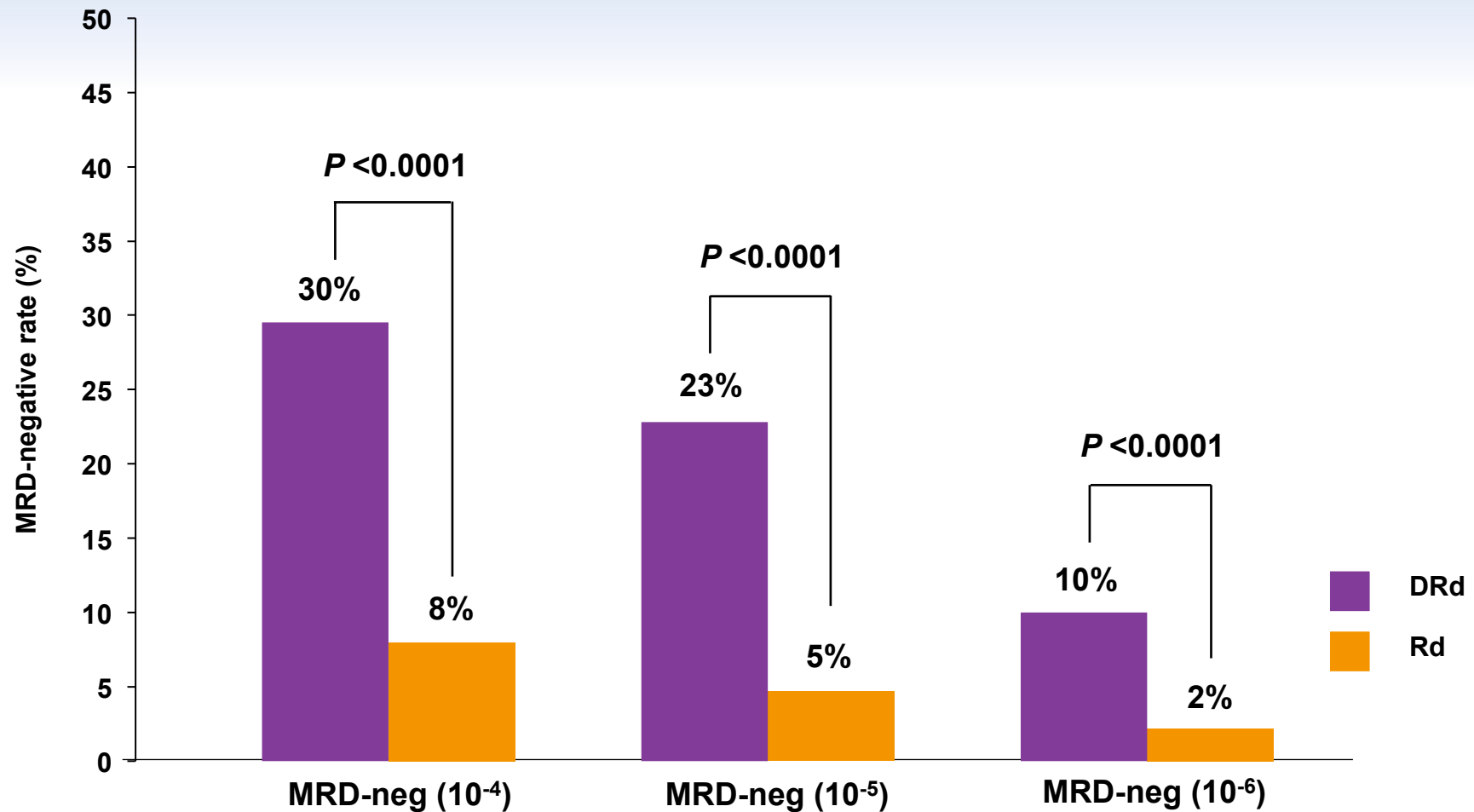
Lonial et al, Leukemia 2015

Lenalidomide-based Studies

	POLLUX Dara-Rd vs Rd	ASPIRE KRd vs Rd¹	ELOQUENT-2 Elo-Rd vs Rd^{2,3}	TOURMALINE-MM1 Ixa-Rd vs Rd⁴
PFS HR (95% CI)	0.37 (0.27-0.52)	0.69 (0.57-0.83)	0.73 (0.60-0.89)	0.74 (0.59-0.94)
ORR	93%	87%	79%	78%
≥VGPR	76%	70%	33%	48%
≥CR	43%	32%	4%	14%
Duration of response, mo	NE	28.6	20.7	20.5
OS HR (95% CI)	0.64 (0.40-1.01)	0.79 (0.63-0.99)	0.77 (0.61-0.97)	NE

1. Stewart AK, et al. *N Engl J Med.* 2015;372(2):142-152.
2. Lonial S, et al. *N Engl J Med.* 2015;373(7):621-631.
3. Dimopoulos MA, et al. *Blood.* 2015;126(23):Abstract 28.
4. Moreau P, et al. *N Engl J Med.* 2016;374(17):1621-1634.

MRD-negative Rate



Significantly higher MRD-negative rates for DRd vs Rd

Immunotherapy targets in MM.

