Why Do We Recommend Additional Therapy After Autologous Transplant for Multiple Myeloma ?

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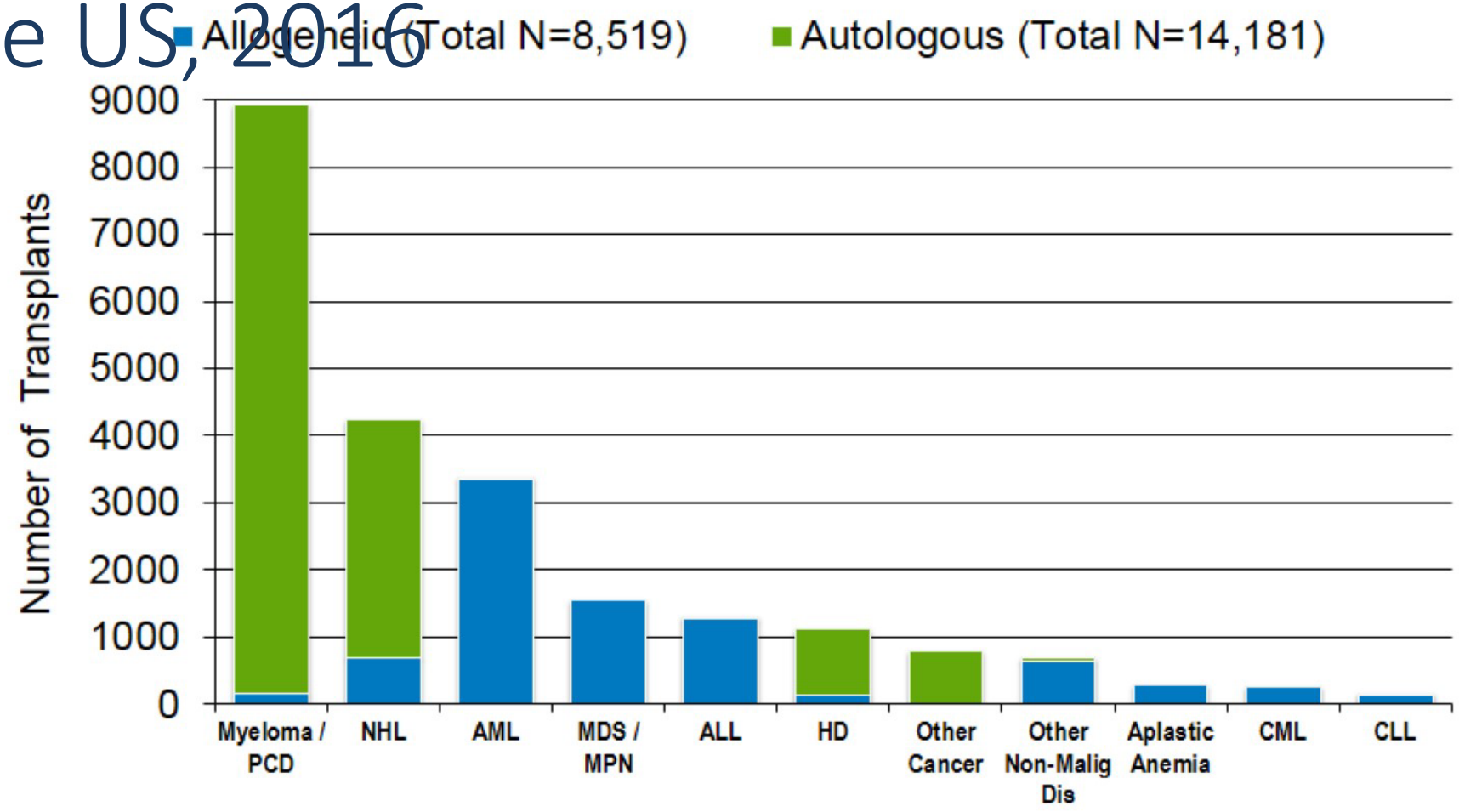
Disclosures

- Discussion of multiple off label use of FDA approved drugs
- Research funding
  - Seattle Genetics, Merck, Sharpe and Dohme Inc, Genzyme/Sanofi, Millennium-Takada, Bristol Meyers Squibb, Celgene, Juno
- Consultant
  - Jazz and NCCN
- Royalty
  - Up-To-Date

Indications for Hematopoietic Cell Transplant in the US, 2016



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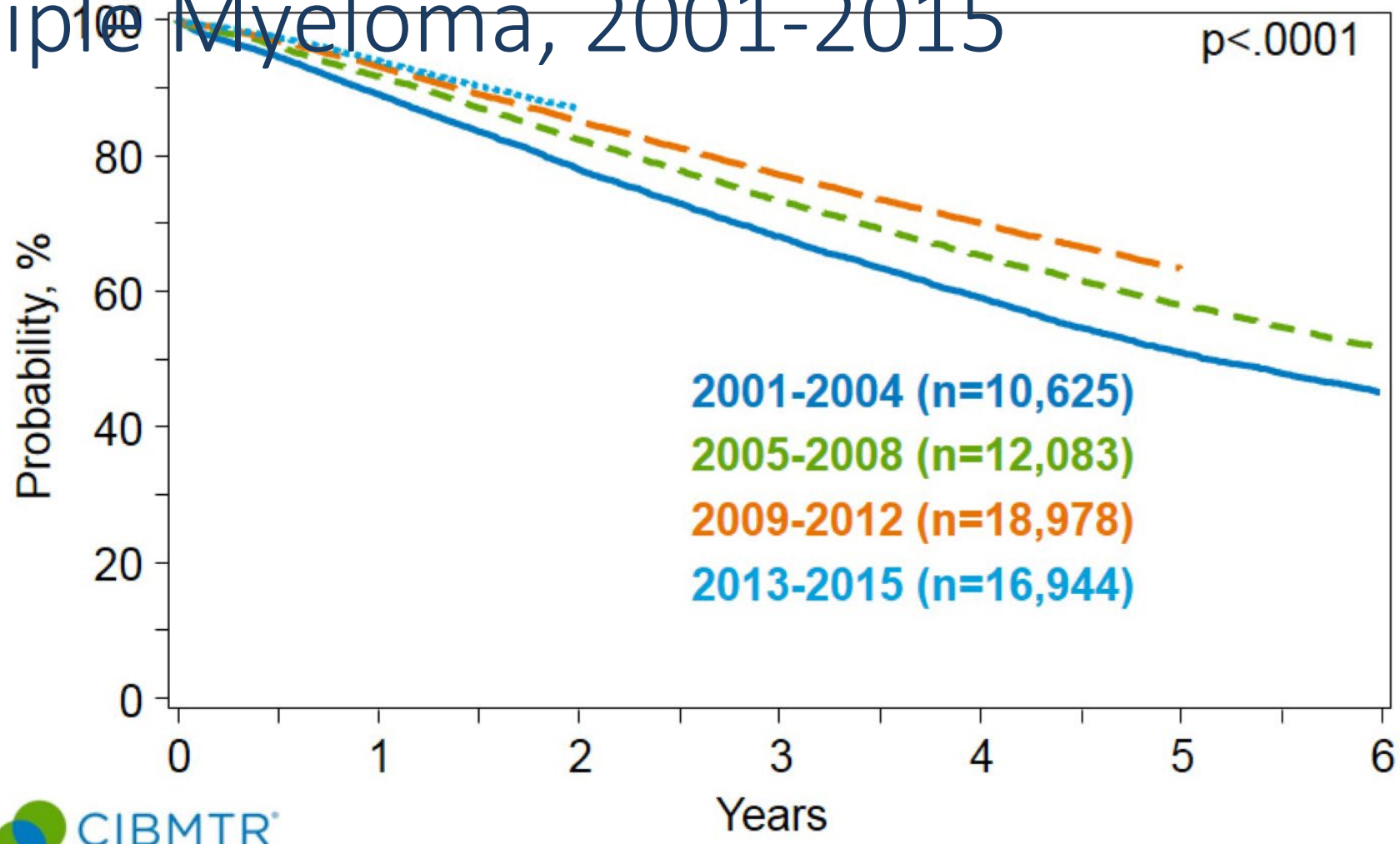
Trends in Survival after Autologous HCT for Multiple Myeloma, 2001-2015



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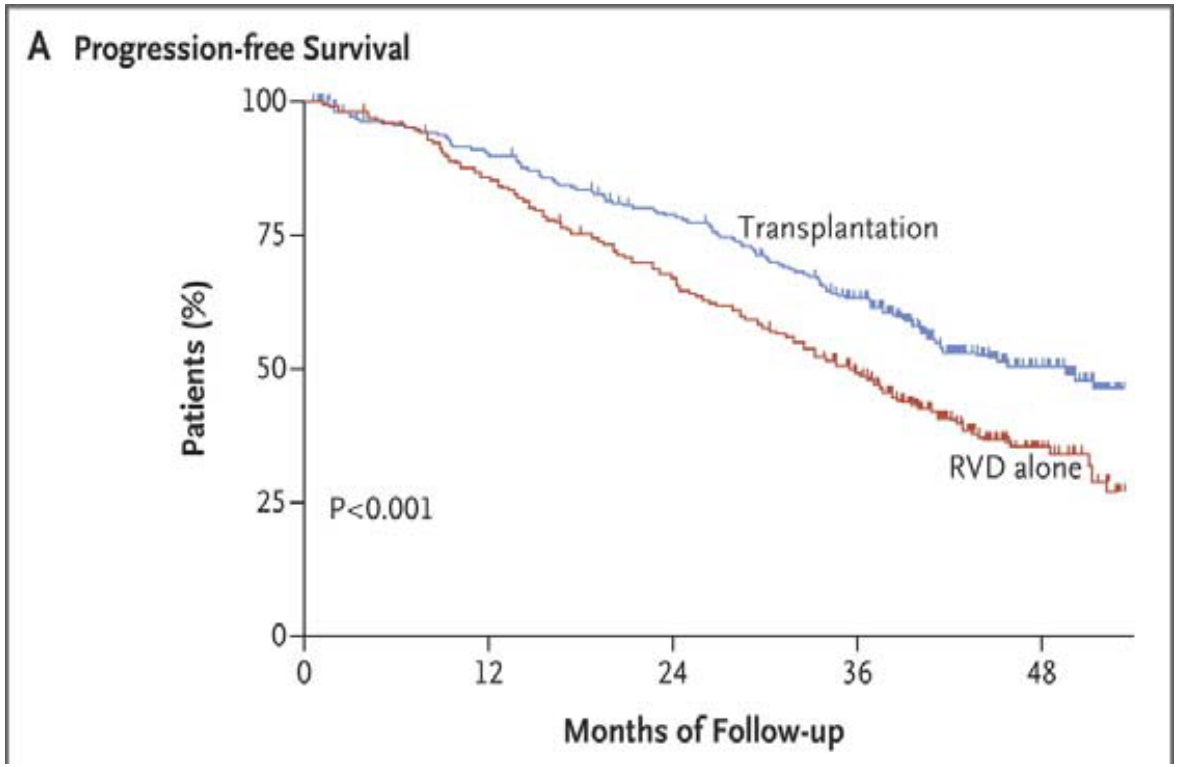
Attal et al study (ref NEJM 336, 1311, 2017)



ASCT is a Platform…

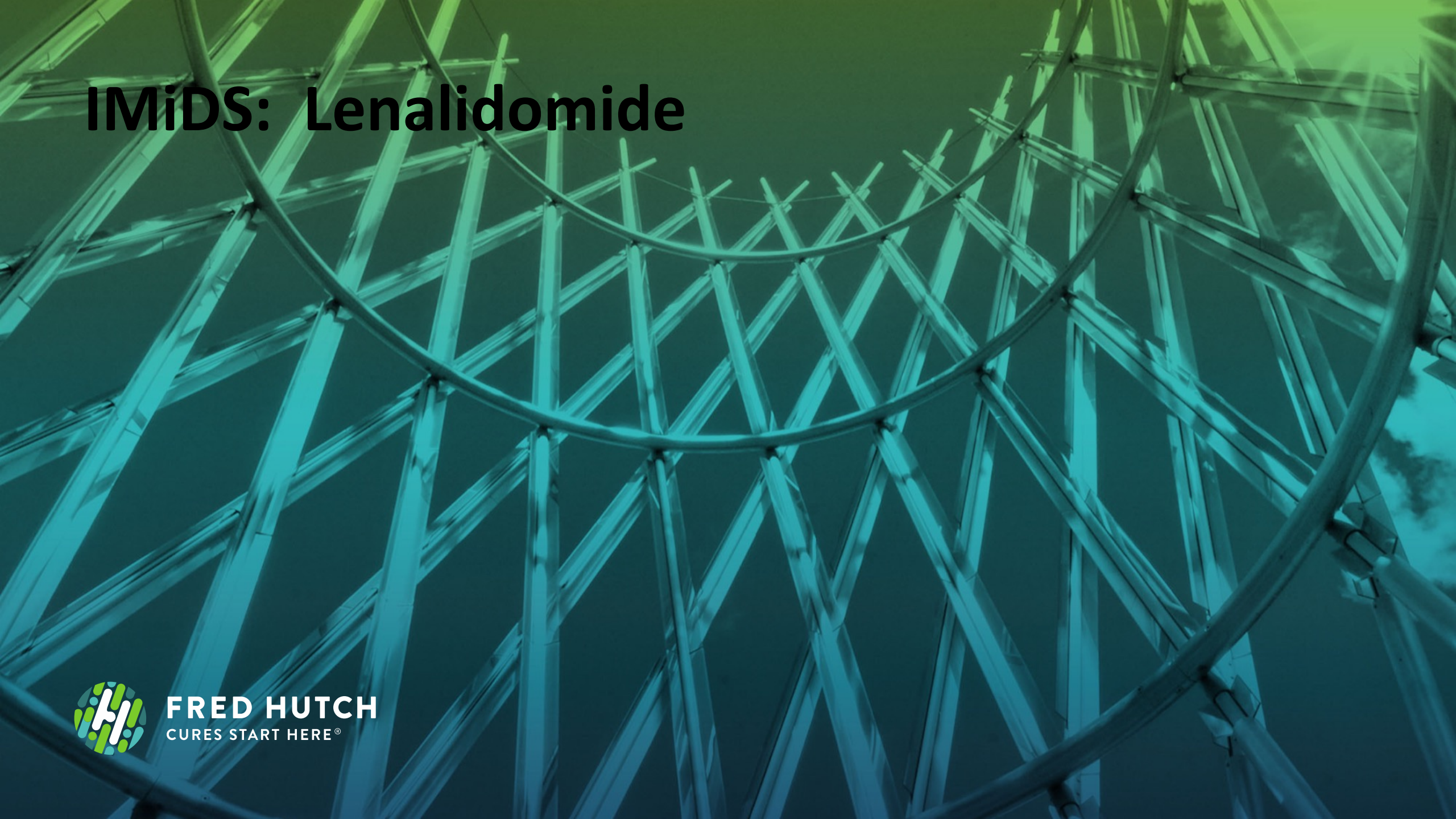
…to build on in which you can add additional therapy post ASCT to amplify the disease response in setting of reduced disease burden and changed immune system in order to prolong the duration of the response.

… to try to buy more time as in future new therapy options will exist.

Maintenance therapy

- Effective
- Well tolerated with easily manageable toxicity
- Simple administration
- Ability to administer long term
- Lower doses than standardly given

IMiDS: Lenalidomide



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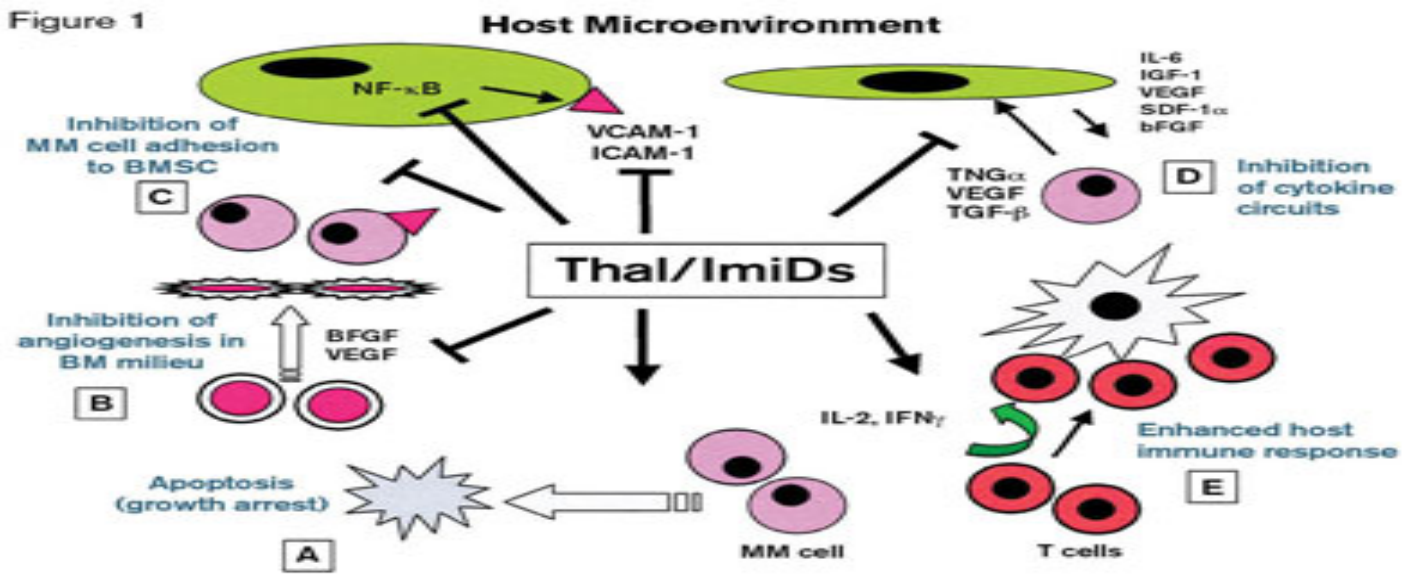
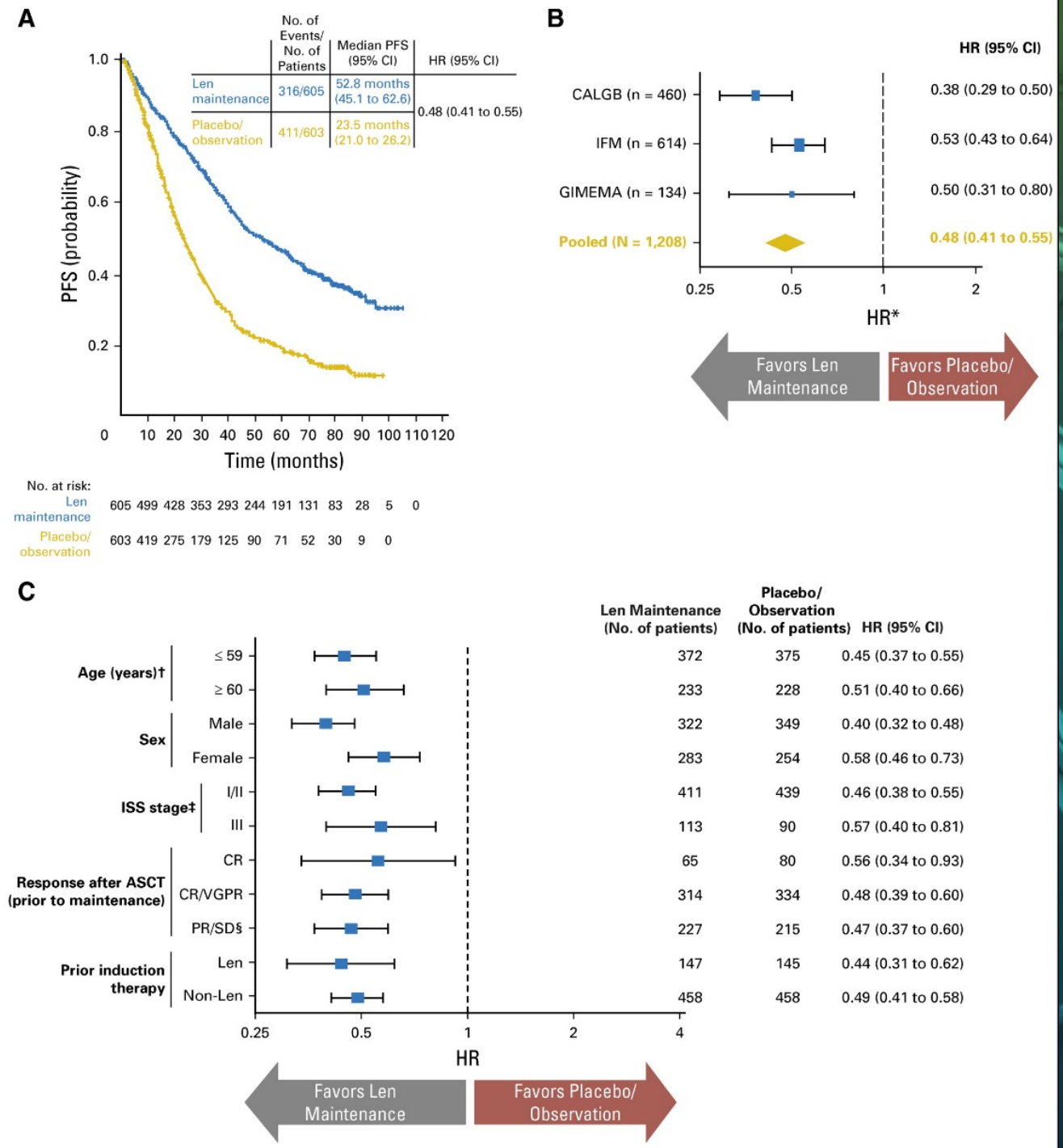
IMiDS



Richardson, P et al: Immunomodulatory analogs of thalidomide: an emerging new therapy in myeloma. J Clin Oncol. Vol. 22 (16), 2004:3212-3214.

Meta-Analysis of Overall PFS and S after Len maintenance after ASCT

- Three trials (IFM 2005, CALGB 100104 and GIMEMA RV-209)
- Total of 1029 patients randomized
  - Len n=605 10 mg/day days 1-21/28 (GIMEMA) or days 1-28/28 (IFM and CALGB)
    - ❖ Meta-analysis was published McCarthy et al JCO 35:3279-89, 2017



Lenalidomide Maintenance After ASCT
A Meta-Analysis

Studies Included in the Meta-Analysis

CALGB 100104	Accrual 8/2005 to 11/2009 United States
IFM 2005-02	Accrual 6/2006 to 8/2008 France
GIMEMA (RV-MM-PI-209)	Accrual 11/2007 to 7/2009 Italy

- All studies enrolled patients who had an ASCT
- All studies examined the role of lenalidomide or placebo as posttransplant maintenance therapy

	Lenalidomide	Placebo	HR; *P* value
7-y OS, %	62	50	
Median OS, mo	NE	86	0.74; .001

- Lenalidomide maintenance resulted in a benefit for all subgroups analyzed except patients with high-risk cytogenetics (HR=1.18)

Attal M, et al. *J Clin Oncol*. 2016;34(suppl). Abstract 8001.

Results (cont)

- All studies favored significantly Lenalidomide maintenance therapy for PFS .
- PFS2 (time after second progression) was also prolonged with lenalidomide maintenance vs placebo 73.3 months vs 56. 7months i.e. 28% reduction in risk of a PFS2 event.
- 20% into CR after one year of maintenance therapy.
- Toxicity seen as 29% d/c Lenalidomide therapy. Toxicity commonly seen include: cytopenia, fatigue, diarrhea, constipation, muscle ache, infections and rare blood clots.
- Len use post High dose melphalan ASCT led though to an increased cumulative incidence of hematological (HR 2.33, p=.015) and solid tumor (HR 1.71, p=.032) cancers. Second cancers (SPM) were seen in Len 5.3% vs 0.8% with placebo pre relapse (most early after ASCT) and after relapse MM 6.1% vs 2.2%.

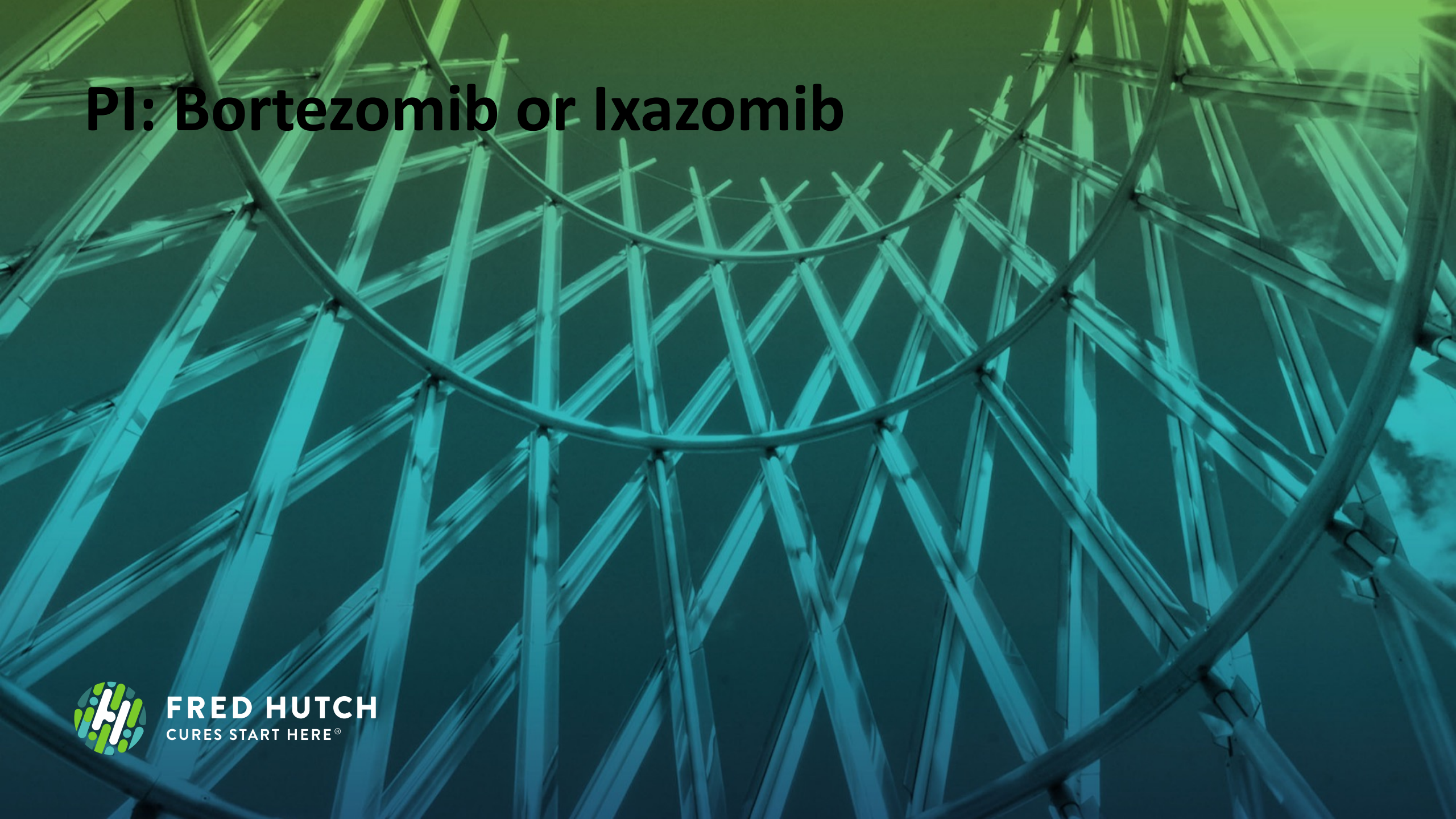
Results (cont)

- Overall there was 23% reduction in death if got Len maintenance. Most favorable OS was in those already received induction Len. No improvement in OS if high risk cytogenetics (not all patients had cytogenetics at Dx).
- Maintenance lenalidomide PFS and survival benefits outweigh the risk of getting a second cancer. Resulting in overall 2.5 year increase in median OS after ASCT.
- Lenalidomide maintenance after ASCT thus has Category 1 NCCN recommendation and Lenalidomide is FDA approved for this use.
- Based on CALGB study done in NA standardly give Lenalidomide drug as long as tolerated until disease progression ie. (1 yr < 2 yr< than >3 yr)

Benefit of Lenalidomide Maintenance in MRD-

- Did not have MRD status in these studies.
- Jackson et al Myeloma XI study showed in small group of patients that MRD-patients had a PFS benefit with maintenance therapy. Arguing that Lenalidomide maintenance with chemo-sensitive disease and high quality responses already will increase or maintains the depth of response. Thus, getting deep response and maintaining response is important.
- Utilization of MRD in the future is only as good as testing results and validation of MRD testing including imaging needs to be done in clinical trials before can use MRD status to determine who should get maintenance therapy and how long should treat.

PI: Bortezomib or Ixazomib



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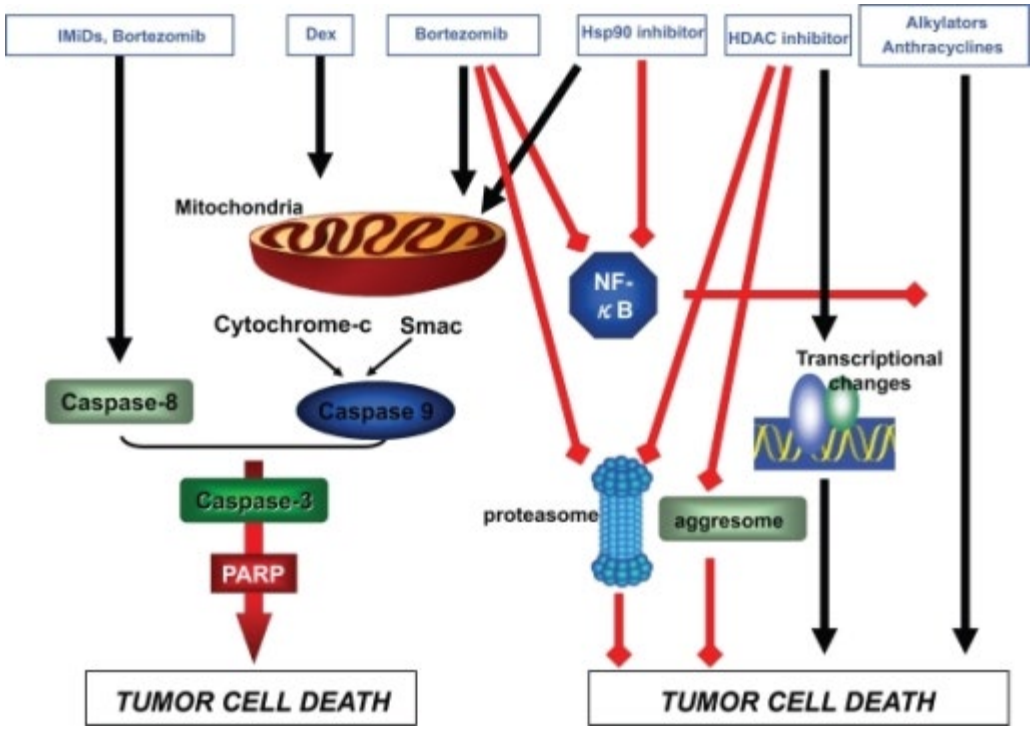
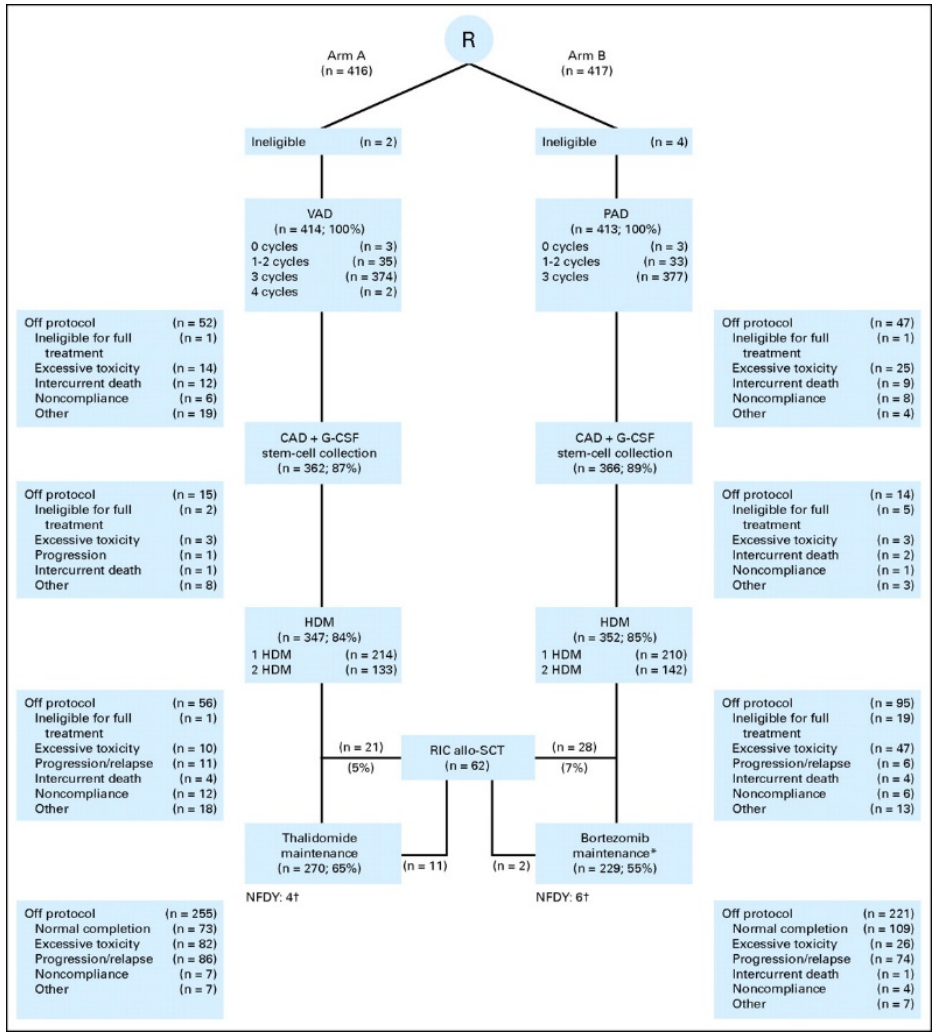
Tumor Cell Death

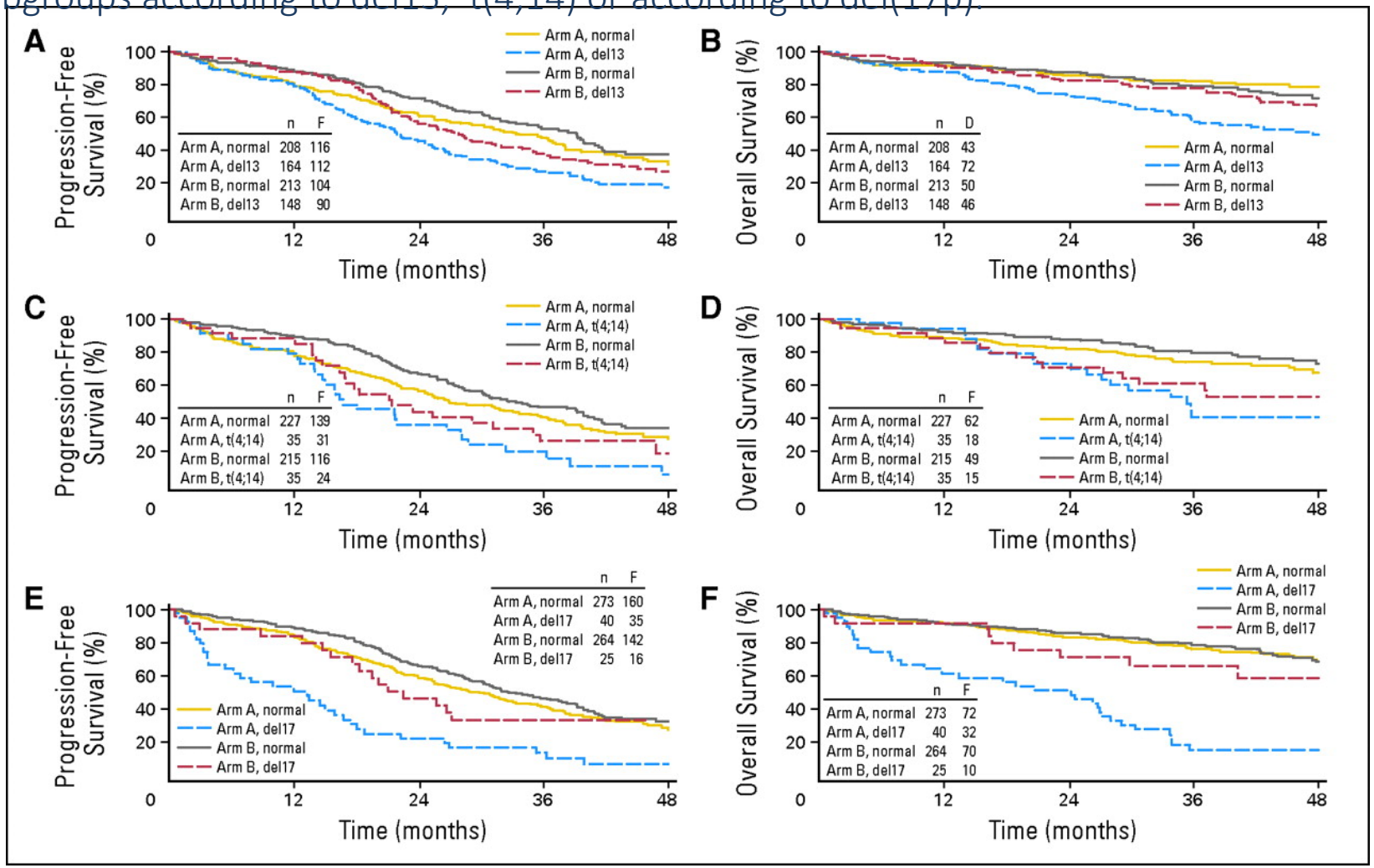


CONSORT diagram of 827 adult patients with multiple myeloma (MM) in the Dutch-Belgian Hemato-Oncology Group 65/German Multicenter Myeloma Group HD4 (HOVON-65/GMMG-HD4) study by treatment arm. allo-SCT, allogeneic stem-cell transplantation; CAD, cyclophospha...



Sonneveld P et al. JCO 2012;30:2946-2955

Kaplan-Meier survival curves of progression-free survival (PFS) and overall survival (OS) according to treatment arm within subgroups according to del13, t(4;14) or according to del(17p).



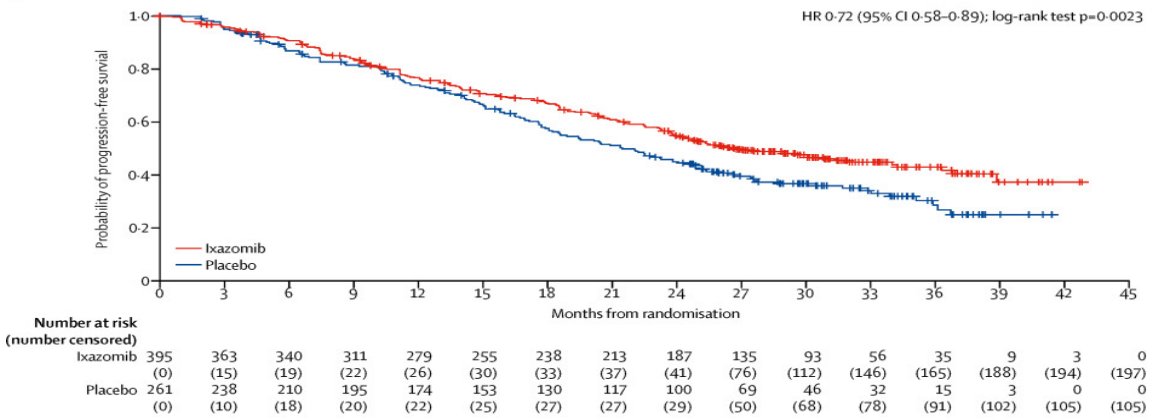
Sonneveld P et al. JCO 2012;30:2946-2955

Hovan study Summary

- If adjust in multivariate analysis, OS at 3 yrs improved for all in PAD arm, p=.049. Peripheral neuropathy 2-4 in PAD arm 40% in induction and 5% during maintenance therapy (IV velcade).
- Patients with poor risk cytogenetics benefited especially del 17p13 and t 4,14.
- Both induction and maintenance had bortezomib so not know if need both to have benefit and since improved induction response not sure how much that led to end results.

Tourmaline - MM3 (Ixazomib)

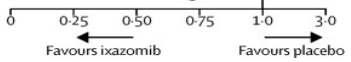
- A



Number at risk (number censored)																
Ixazomib	395	363	340	311	279	255	238	213	187	135	93	56	35	9	3	0
	(0)	(15)	(19)	(22)	(26)	(30)	(33)	(37)	(41)	(76)	(112)	(146)	(165)	(188)	(194)	(197)
Placebo	261	238	210	195	174	153	130	117	100	69	46	32	15	3	0	0
	(0)	(10)	(18)	(20)	(22)	(25)	(27)	(27)	(29)	(50)	(68)	(78)	(91)	(102)	(105)	(105)

B

	Events/patients		HR (95% CI)
	Ixazomib (n=395)	Placebo (n=261)	
All subjects (n=656)	**198/395**	**156/261**	**0·72 (0·58–0·89)**
Pre-induction ISS stage (local)			
I (n=242)*	68/146	56/96	0·70 (0·49–1·01)
II or III (n=414)	130/249	100/165	0·73 (0·56–0·95)
Response after transplant			
Complete or very good partial (n=509)	142/305	118/204	0·71 (0·56–0·91)
Partial (n=147)*	56/90	38/57	0·74 (0·48–1·12)
Induction regimen			
Immunomodulatory drug and proteasome inhibitor (n=196)	61/118	41/78	0·97 (0·65–1·44)
Proteasome inhibitor without immunomodulatory drug (n=389)	120/234	97/155	0·67 (0·51–0·87)
Proteasome inhibitor exposed (n=585)	181/352	138/233	0·75 (0·60–0·94)
Immunomodulatory drug without proteasome inhibitor (n=71)	17/43	18/28	0·50 (0·25–0·97)
Age			
<60 years (n=356)	118/229	74/127	0·84 (0·62–1·12)
≥60 years and <75 years (n=300)	80/166	82/134	0·66 (0·48–0·91)
Race			
White (n=528)	148/315	126/213	0·65 (0·51–0·83)
Asian (n=95)	36/59	25/36	0·86 (0·50–1·47)
Region			
EMEA (n=518)	150/306	129/212	0·72 (0·56–0·91)
APAC (n=121)	44/76	26/45	0·86 (0·52–1·44)
Pre-induction ISS stage			
I (n=245)*	69/151	55/94	0·68 (0·47–0·98)
II (n=221)	76/129	55/92	0·88 (0·61–1·26)
III (n=190)	53/115	46/75	0·66 (0·44–1·00)
Response at study entry			
Complete (n=225)	56/132	47/93	0·88 (0·59–1·31)
Very good partial (n=294)	93/179	73/115	0·69 (0·50–0·94)
Partial (n=137)*	49/84	36/53	0·69 (0·44–1·09)
Cytogenetic risk			
High risk (n=115)	38/61	38/54	0·62 (0·38–1·02)
Corresponding standard risk (n=404)	118/252	90/152	0·65 (0·49–0·86)
Unclassifiable (n=137)	42/82	28/55	1·13 (0·68–1·85)
Renal function based on baseline creatinine clearance			
<60 mL/min (n=58)	14/38	10/20	0·71 (0·24–2·09)
≥60 mL/min (n=595)	184/355	146/240	0·74 (0·59–0·92)



Tourmaline - MM3 (ASH 2018)

- Post ASCT Ixazomib or placebo, 28 days/cycle, 3 mg /dose increased after cycle 4 to 4 mg /dose days 1, 8 and 15 for 26 cycles . N=656
- Median f/u 31 months
- 28% reduction in relapse or death in Ixazomib arm.
- Median PFS 26.5 months vs. 21.3 months, p= .0023

Consolidation Therapy (usually followed by maintenance Therapy)

- Standard therapy dosing
- Accept more toxicity
- Limited time use
- Effective
- Need not be simple to administer

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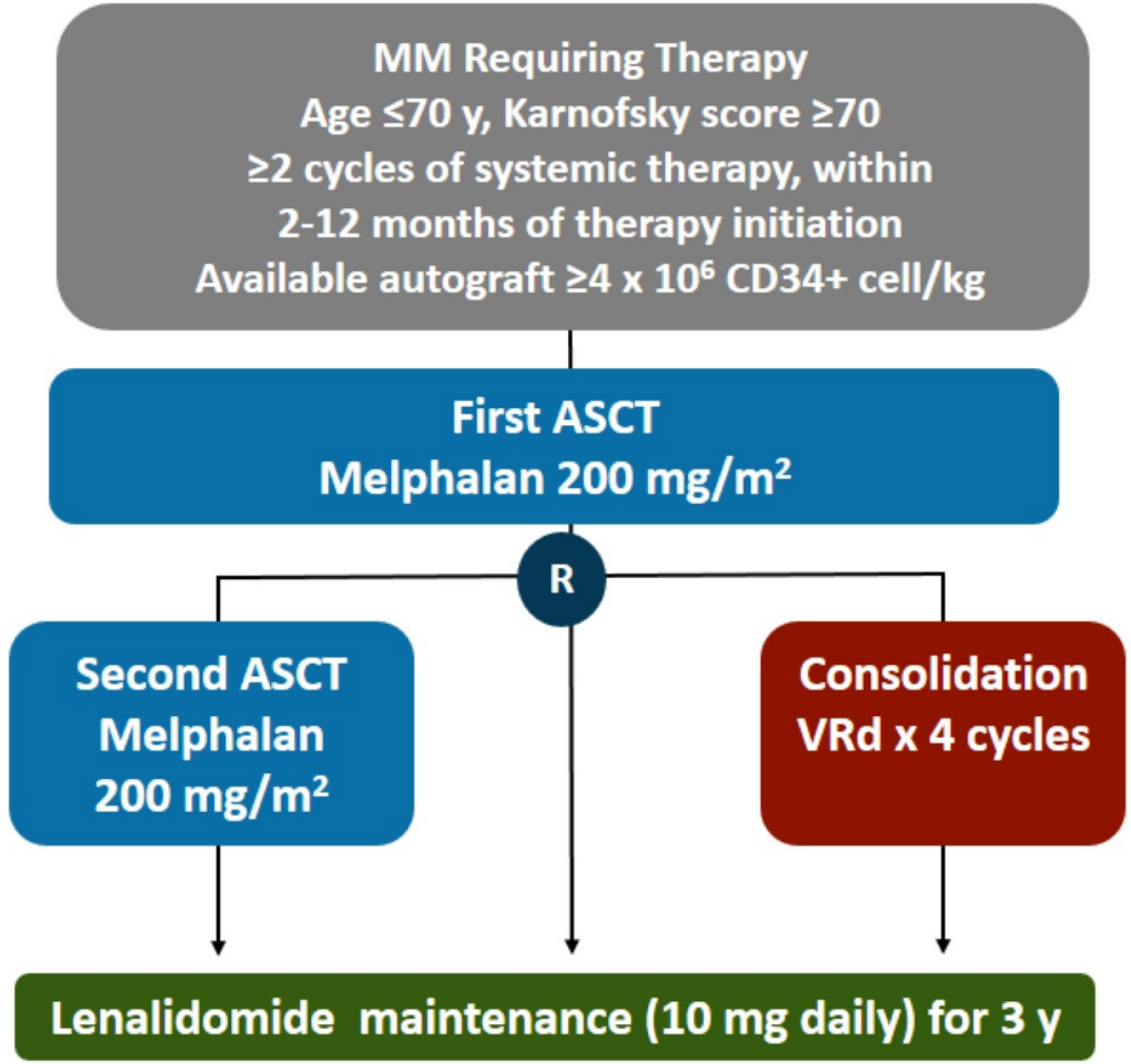
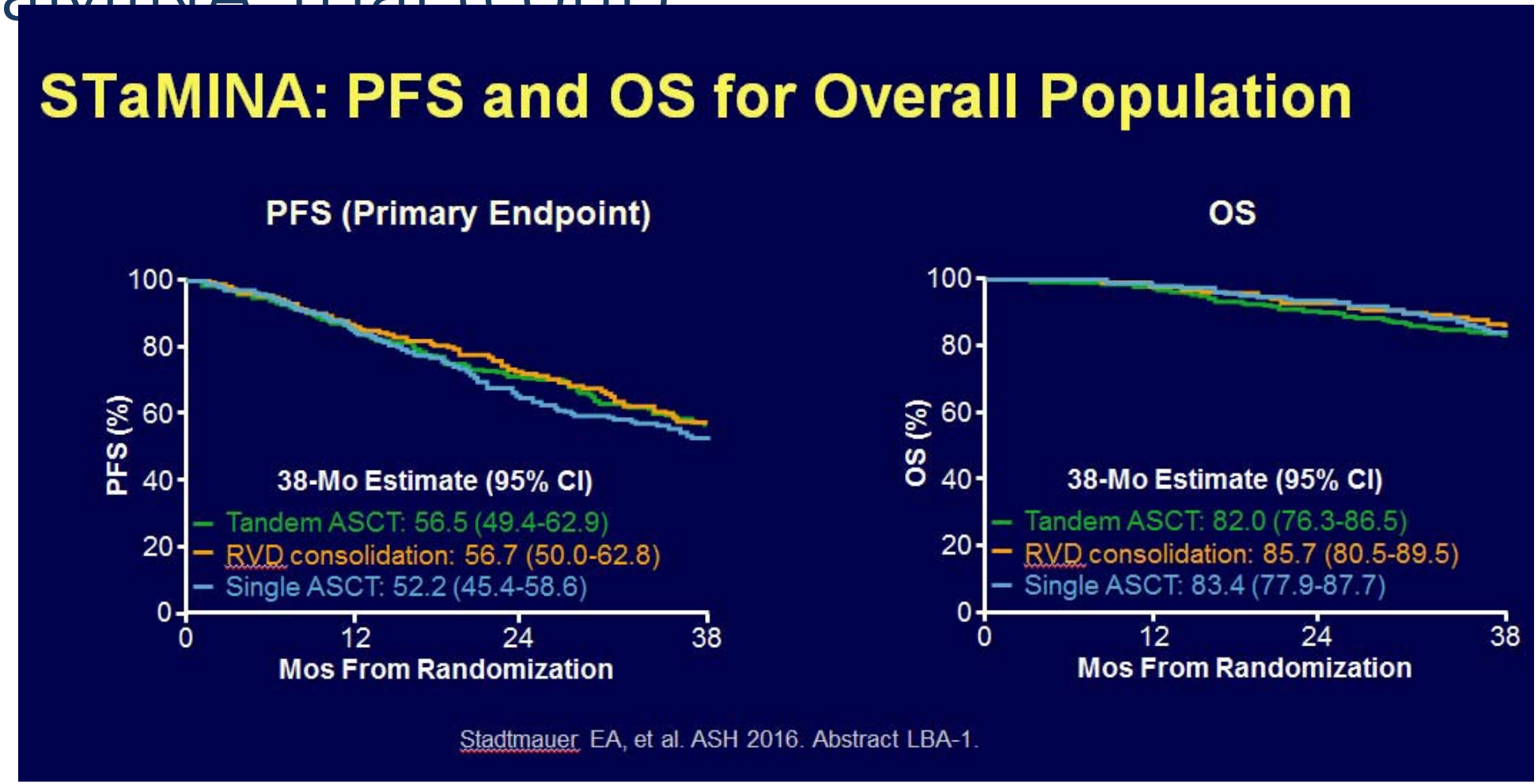
STaMINA Trial
BMT CTN 0702

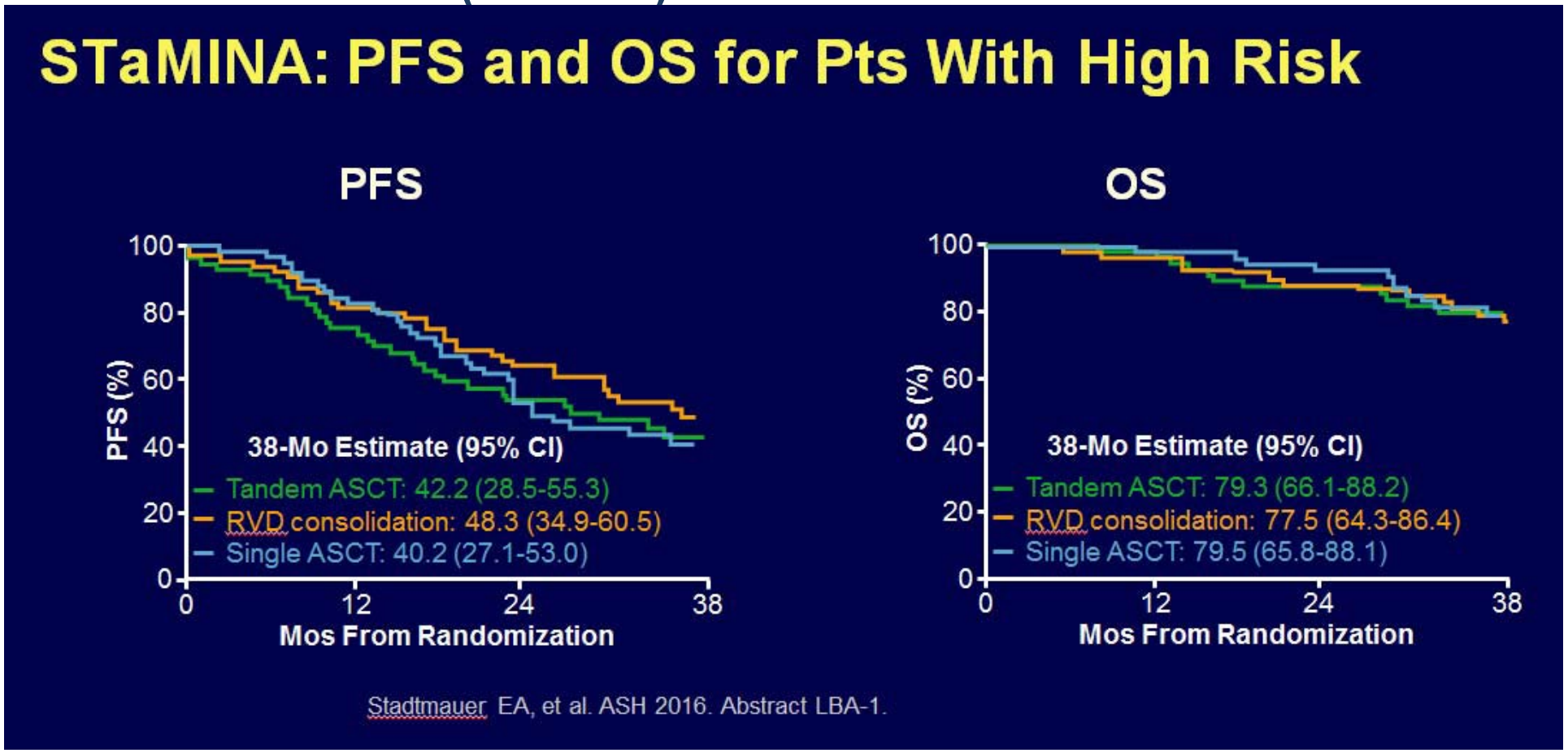


ClinicalTrials.gov. NCT01109004.

STaMINA Trial (cont)



STaMINA Trial (cont)



Emory Highest Risk MM (ref: Nooka et al Leukemia 2014)

- N=45 , 34% PCL, 42% del 17p
- RVD, ASCT, RVD (lite) for 3 years, then single agent lenalidomide
- 96%> VGPR
- PFS =32 months (historically expect OS about 2 years)

Conclusions for now

- Standard risk MM without high risk cytogenetics: lenalidomide maintenance post ASCT if previous sensitive and treat as long as tolerated or to disease progression. MRD with imaging status in the future may change the duration of maintenance therapy but still may not get rid of need for maintenance therapy post ASCT but need validate this from large phase III trials before do.
- High risk or resistant Lenalidomide MM: Bortezomib maintenance for 2 years post ASCT. Question if MRD status in future will change duration of therapy.
- Very high risk, like double hit ie. Del 17 and t14,16 : clinical trial best options. If off trial treating, can consider consolidation therapy followed by maintenance therapy.
- New studies ongoing to address different agents post ASCT like daratumumab, Carfilzomib, drug combinations and drug sequencing, MM fusion vaccines, CARS etc.
- When discuss post ASCT therapy with your oncologist, you need to balance risk and benefits of therapy including type of MM, cost, duration of therapy and side effects to make decision right for you.