Immunotherapy for Myeloma

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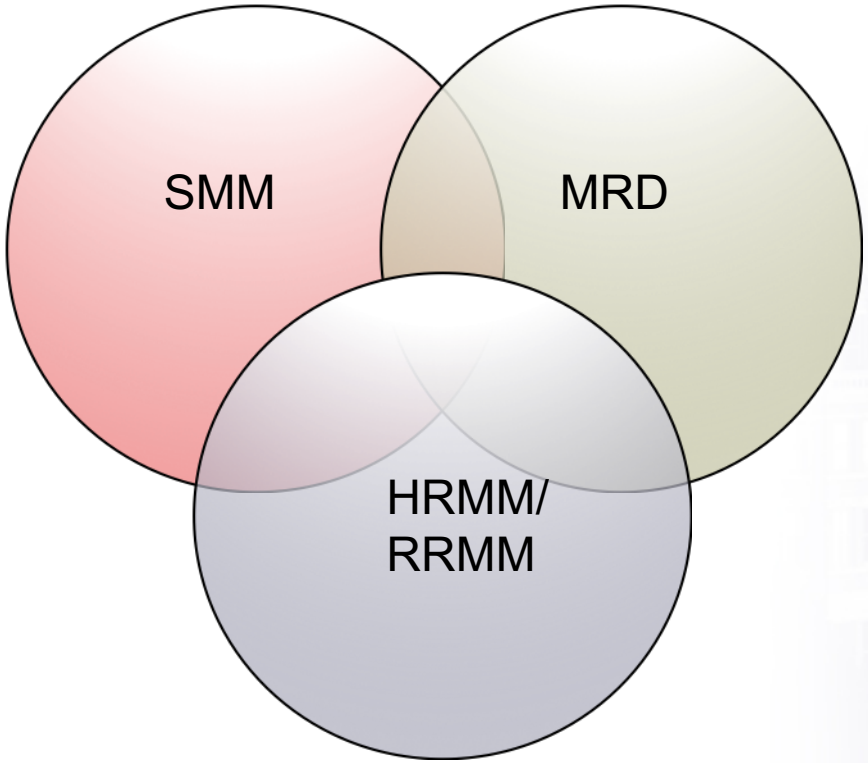
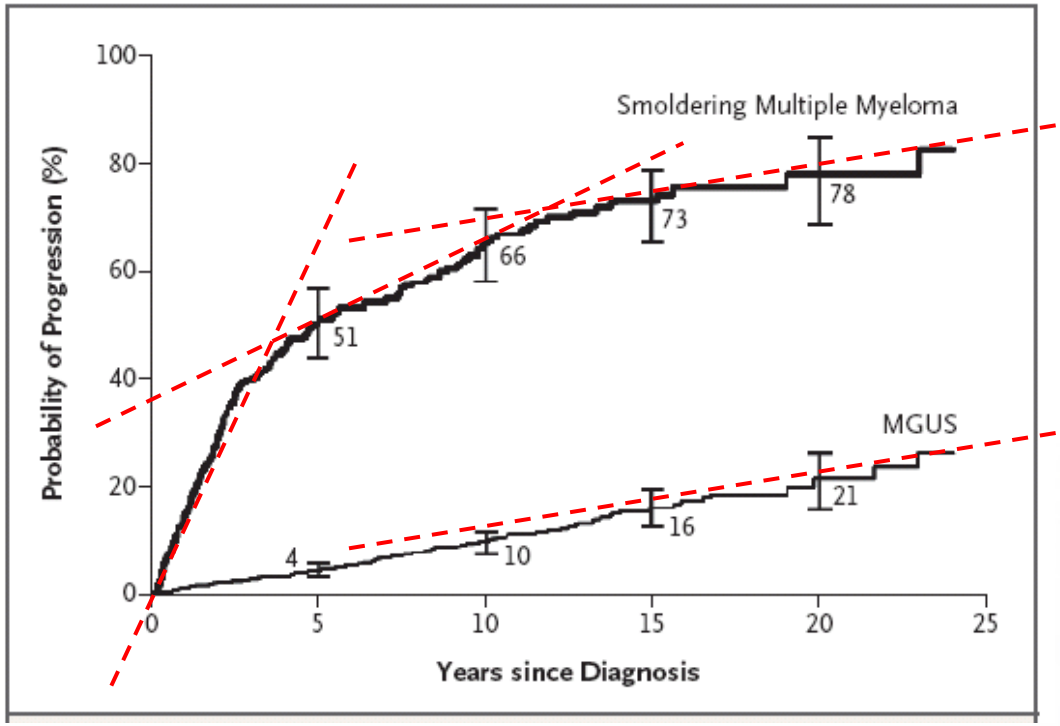
Disease Settings for Immunotherapy in Myeloma



Smoldering myeloma (SMM): the Mayo Clinic experience



- 276 SMM patients diagnosed 1970-1995
- 163 (59%) progressed
  - 158 multiple myeloma
  - 5 amyloidosis
- Overall risk of progression (per year):
  - 10% the first 5 years
  - 3% the next 5 years
  - 1% the last 10 years

Kyle et al. *NEJM 2007*

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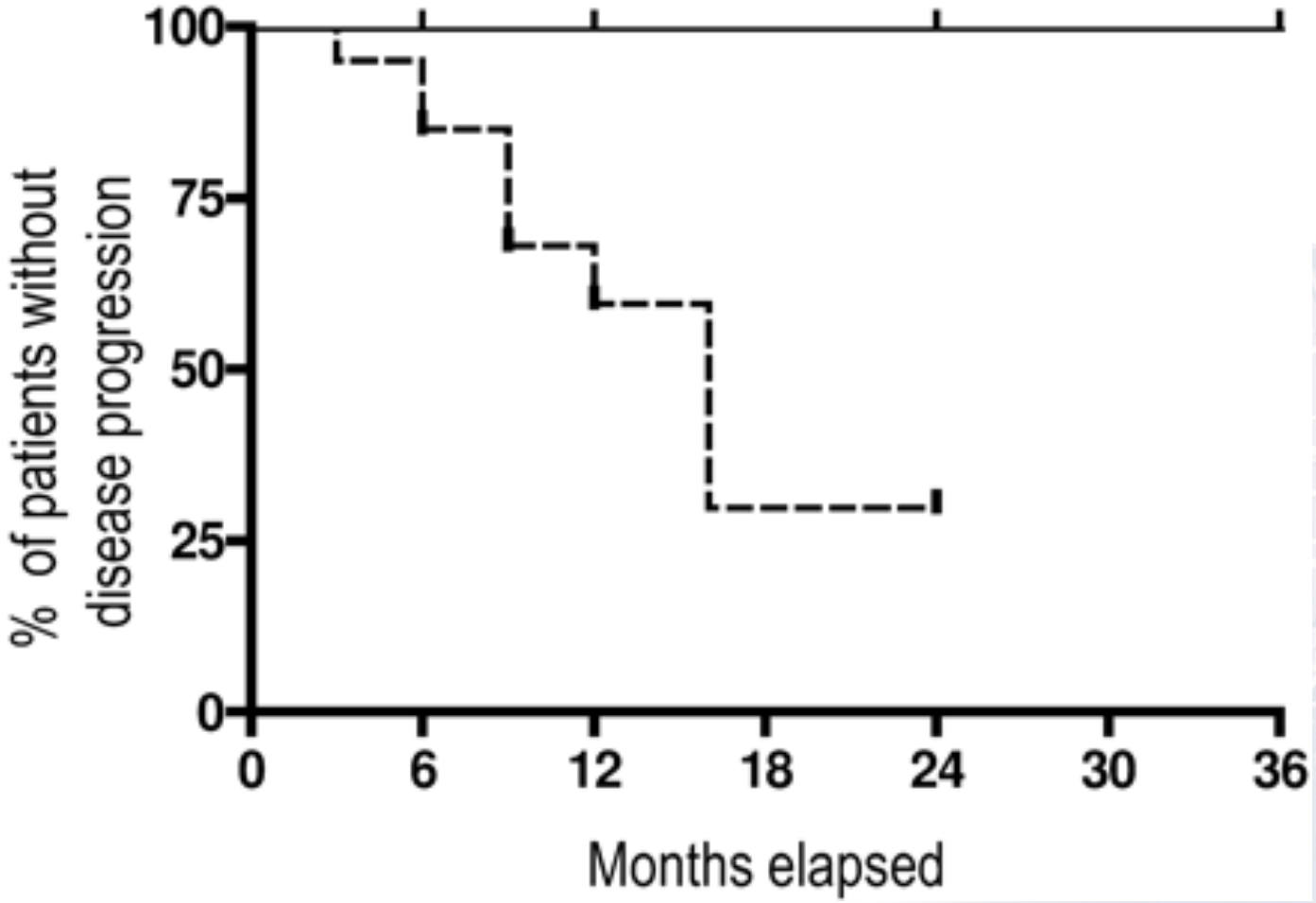
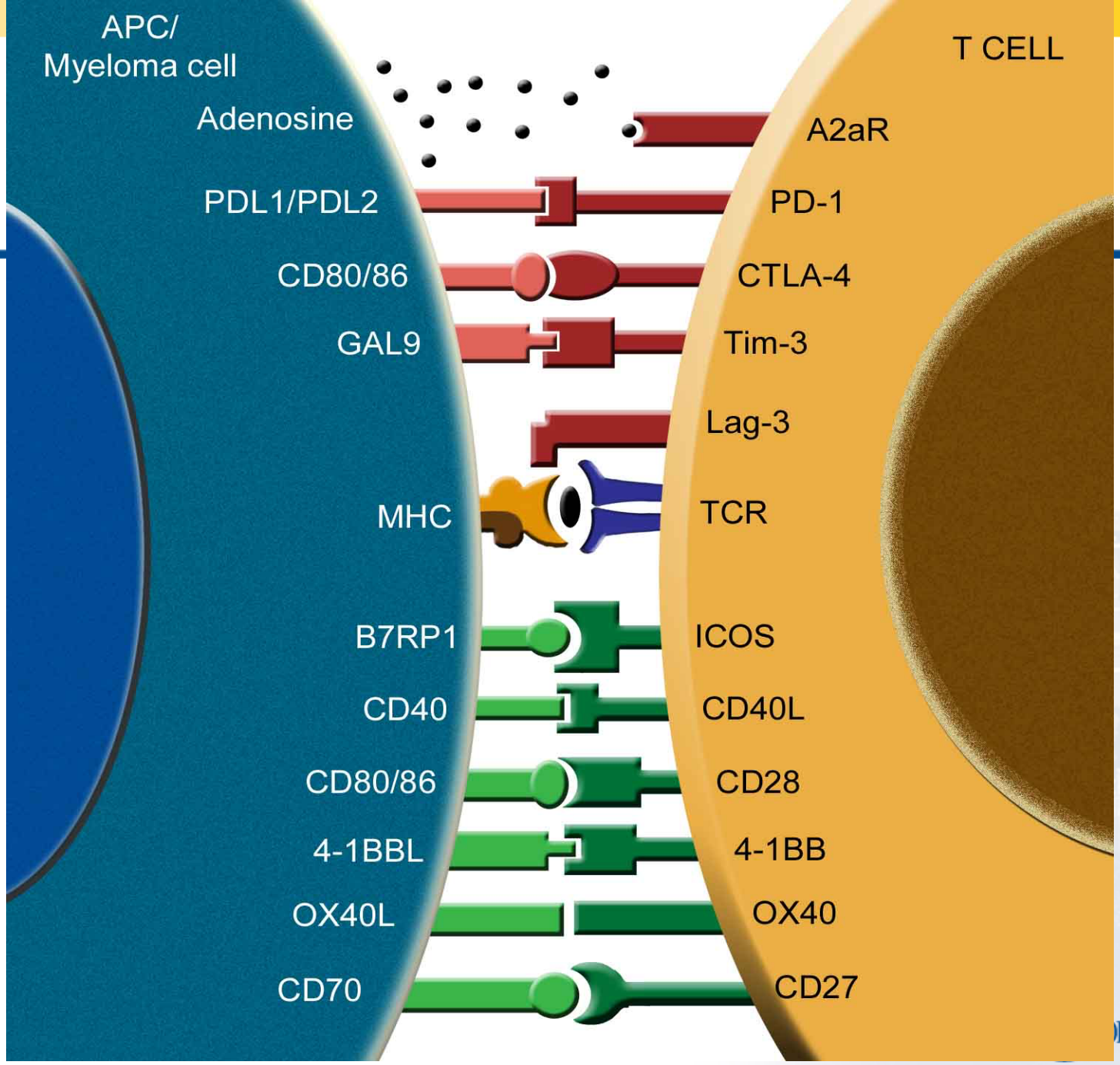
SOX2+ T cells Prevent Disease Progression in SMM



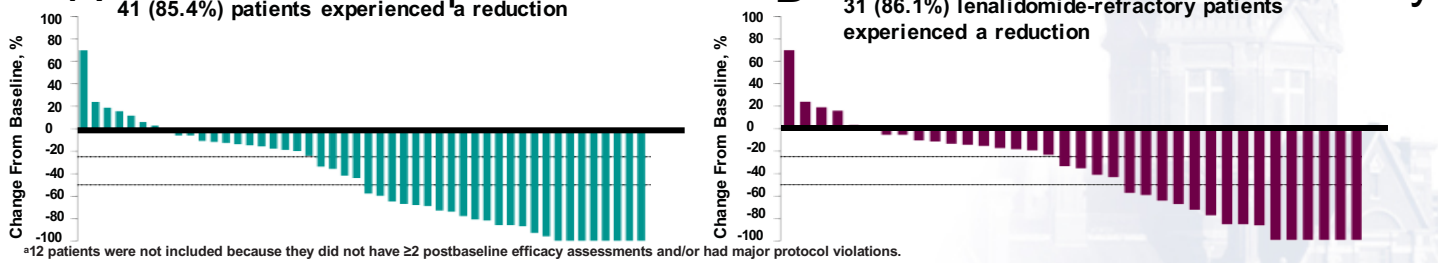
Spisek et al JEM 2007



Hoyos and Borrello Blood 2016

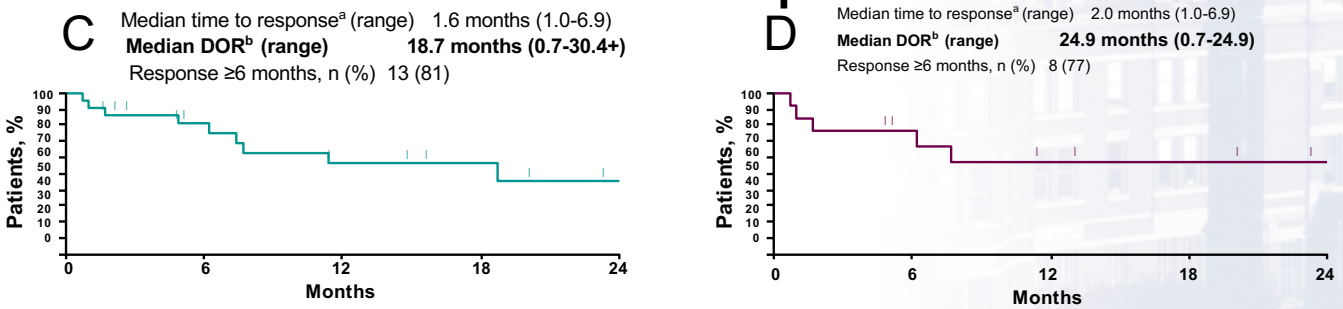
Pembrolizumab (Anti-PD-1) + Lenalidomide / Dex in Relapsed MM

Change from Baseline Disease Burden



[a]12 patients were not included because they did not have ≥2 postbaseline efficacy assessments and/or had major protocol violations.

Duration of Response



C. All responders (n = 22).
D. Lenalidomide-refractory responders (n = 13)

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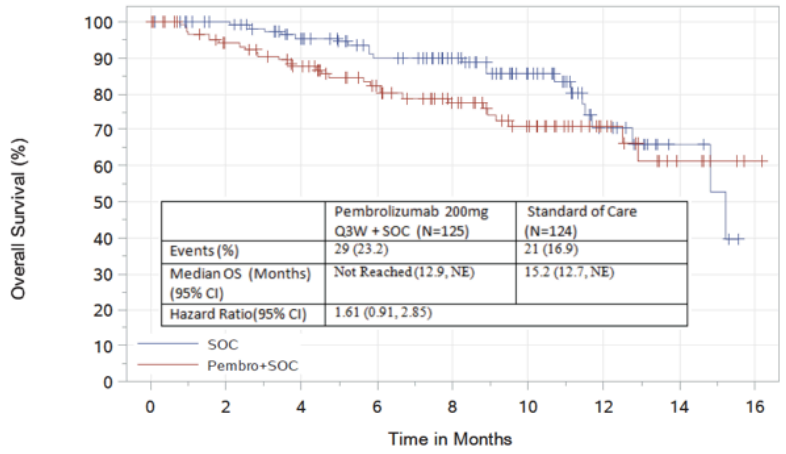
Pembrolizumab in Combination with IMiDs Increases Risk of Death in MM

FDA Alerts Healthcare Professionals and Oncology Clinical Investigators about Two Clinical Trials on Hold Evaluating KEYTRUDA® (pembrolizumab) in Patients with Multiple Myeloma

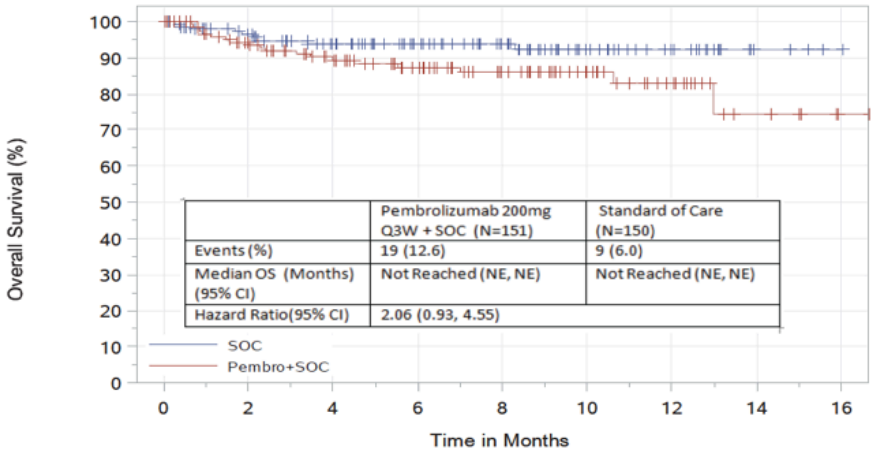
[August 31, 2017] Based on data from two recently halted clinical trials, the U.S. Food and Drug Administration today is issuing this statement to inform the public, health care professionals, and oncology clinical investigators about the risks associated with the use of KEYTRUDA® (pembrolizumab) in combination with dexamethasone and an immunomodulatory agent (lenalidomide or pomalidomide) for the treatment of patients with multiple myeloma. KEYTRUDA® (pembrolizumab) is not approved for treatment of multiple myeloma.

Relapsed & Refractory & 2+ Prior Lines of Therapy



	Pembrolizumab 200mg Q3W + SOC (N=125)	Standard of Care (N=124)
Events (%)	29 (23.2)	21 (16.9)
Median OS (Months) (95% CI)	Not Reached (12.9, NE)	15.2 (12.7, NE)
Hazard Ratio (95% CI)	1.61 (0.91, 2.85)	

Newly Diagnosed & Ineligible for Transplant



	Pembrolizumab 200mg Q3W + SOC (N=151)	Standard of Care (N=150)
Events (%)	19 (12.6)	9 (6.0)
Median OS (Months) (95% CI)	Not Reached (NE, NE)	Not Reached (NE, NE)
Hazard Ratio (95% CI)	2.06 (0.93, 4.55)	

Standard of Care (SOC): Dex + IMiD

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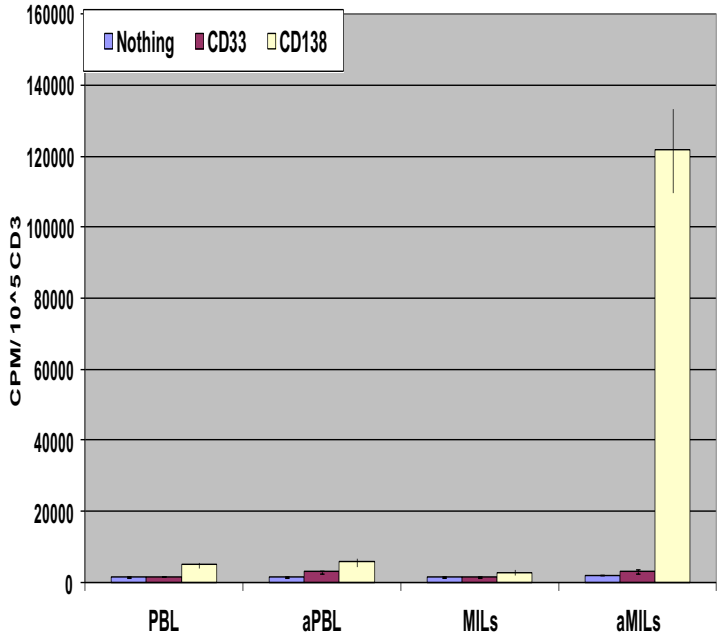
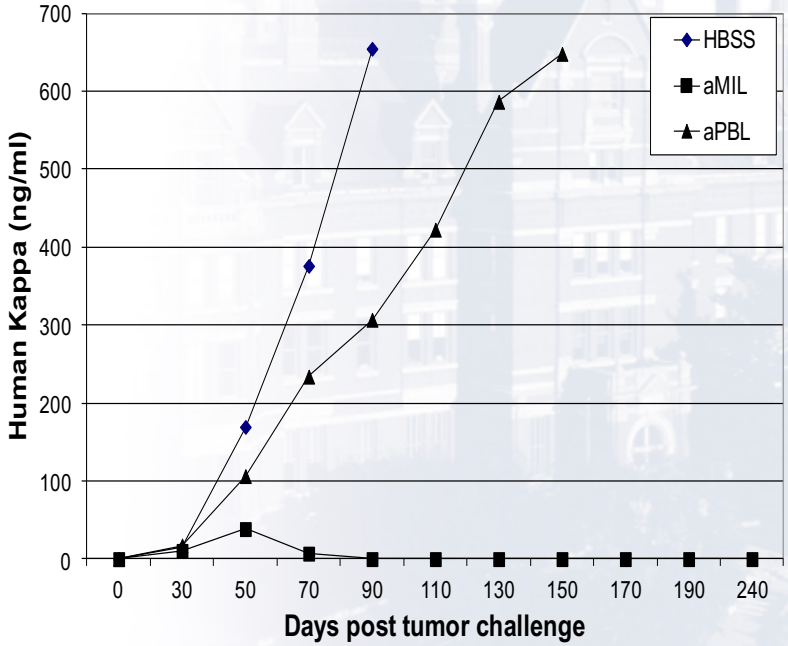
Marrow Infiltrating Lymphocytes

MILs Exhibit Significant Anti-Myeloma Specificity



MILs Results in Complete Myeloma Clearance



Noonan et al. Cancer Res. 2005 Mar 1;65(5):2026-34

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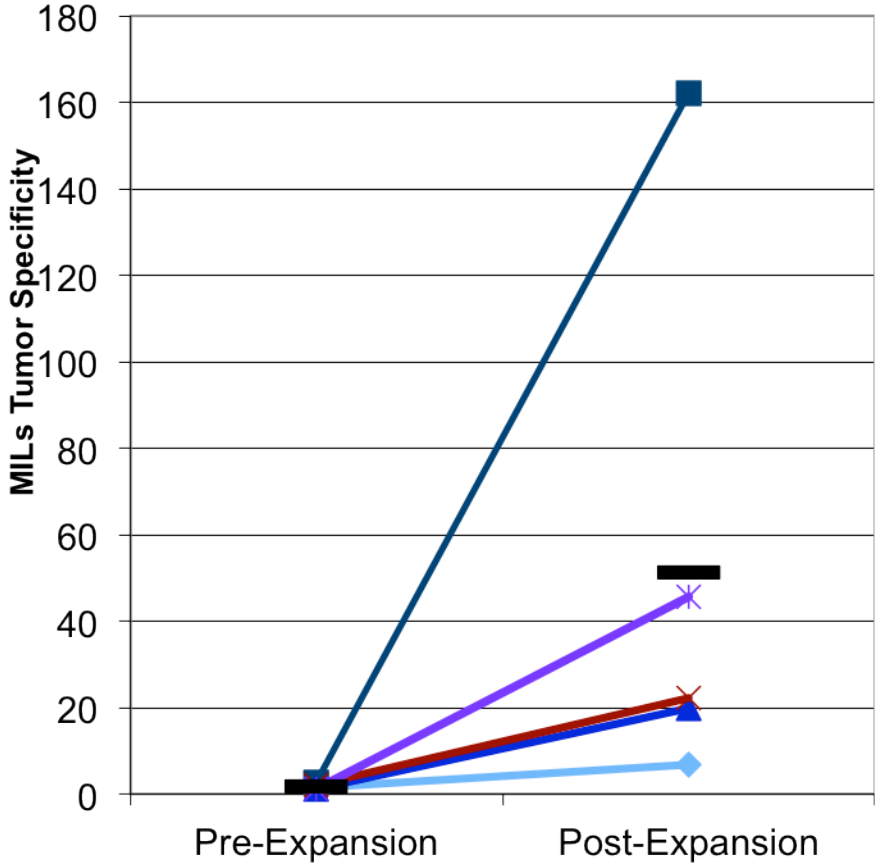
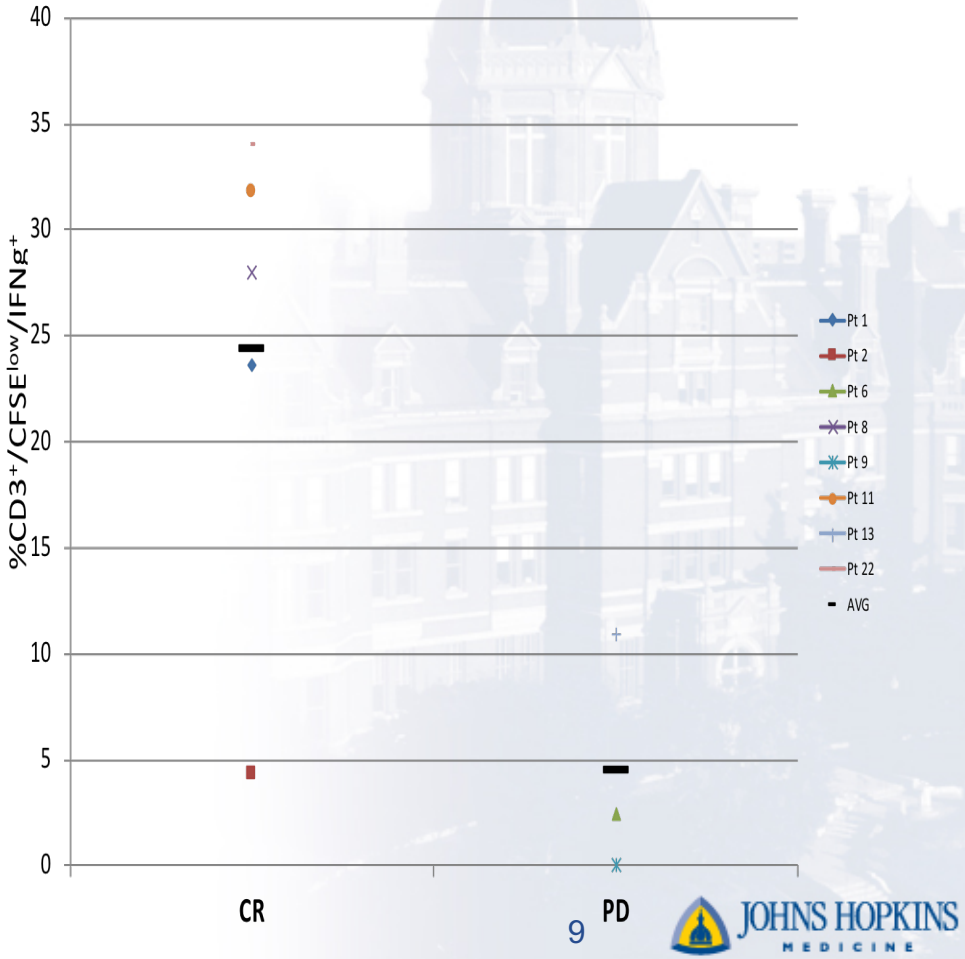
Tumor specificity of the MILs Product





Noonan et al Sci Trans Med 2015

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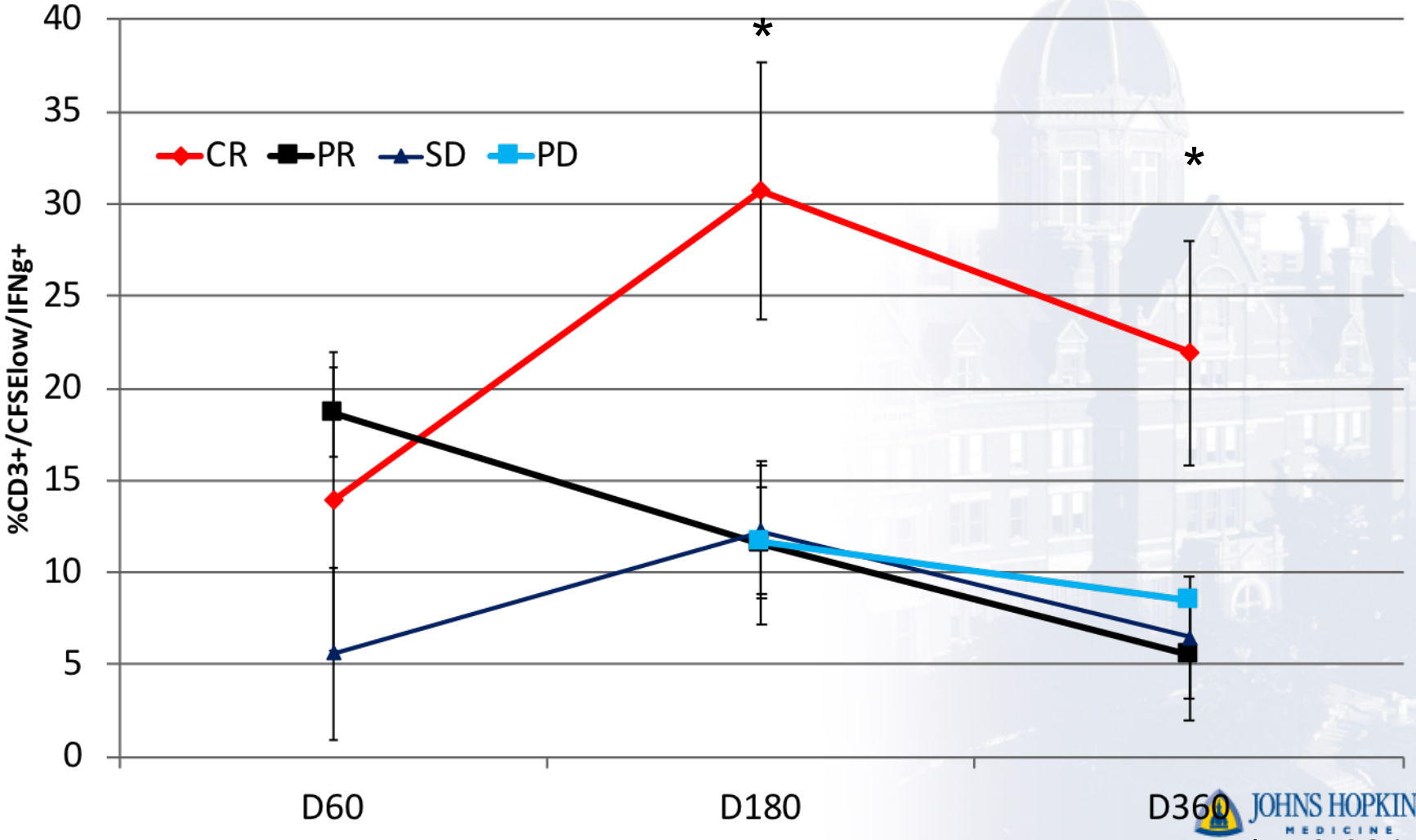
Correlation of Anti-tumor Immunity and Clinical Outcomes



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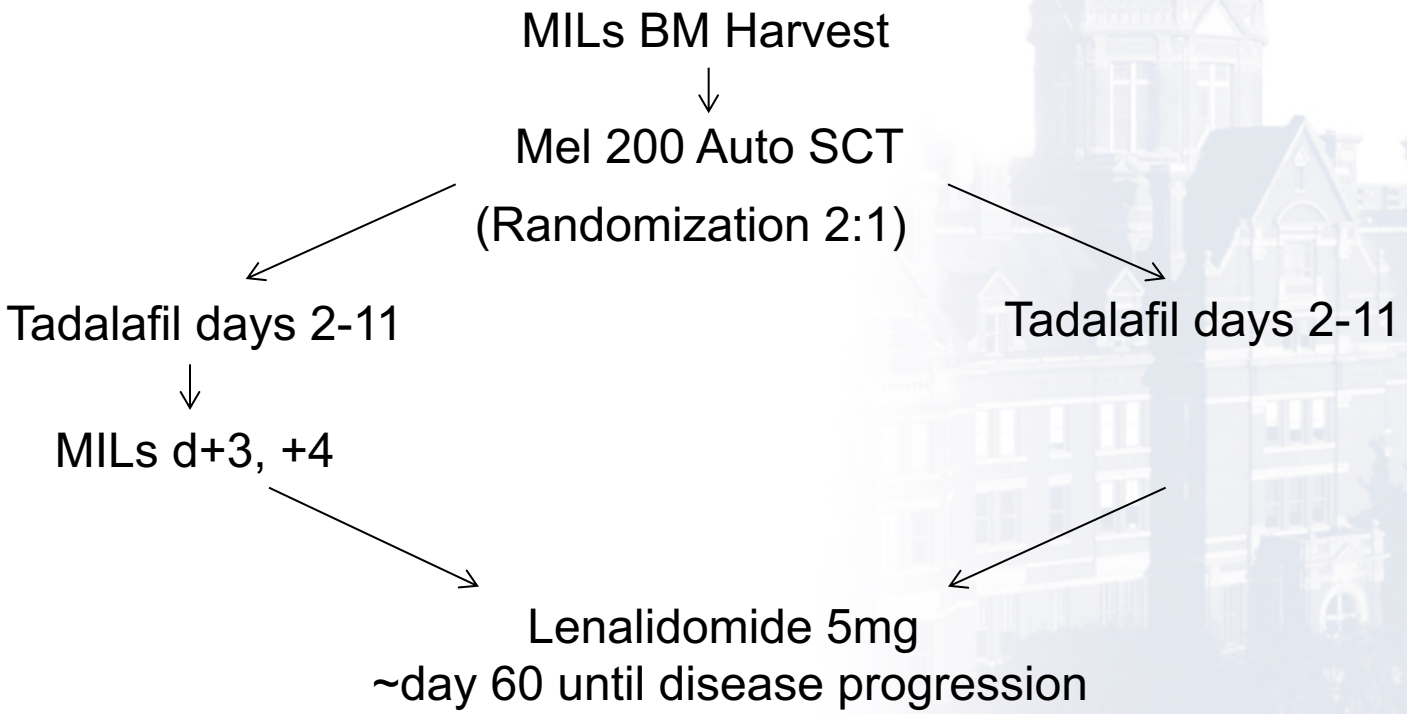
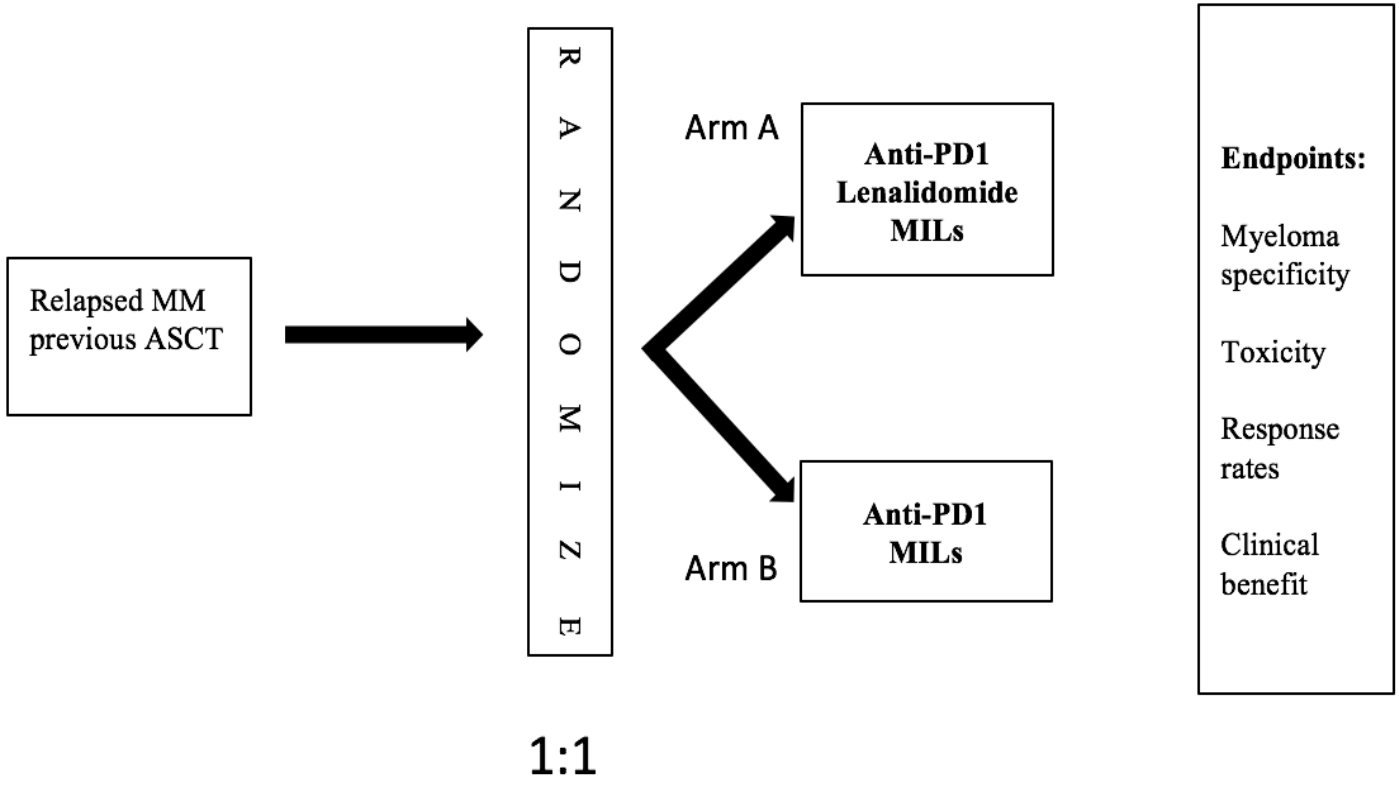
*p<0.001

MILs Trial for High Risk Myeloma J1343 (n=90)



MILs + Anti-PD-1 in Relapsed MM



Phil Imus PI

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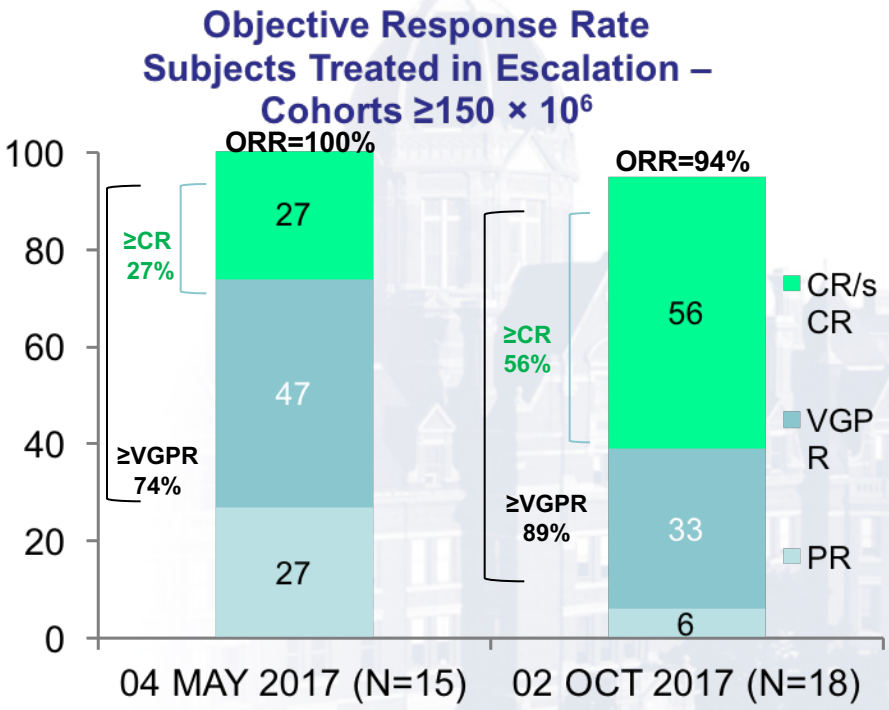
BCMA CAR-T (bb2121) Clinical Responses

Dose Escalation: Cohorts ≥150 × 10^6 CAR+ T Cells (N=18)

Median duration of follow up 40 weeks (min, max: 6.6, 69.1)

Efficacy Parameter	Statistic	Result
Time (months) to First Response	Median (min, max)	1.02 (0.5, 3.0)
Time (months) to Best Response	Median (min, max)	3.74 (0.5, 13.7)
Time (months) to Complete Response	Median (min, max)	3.84 (0.5, 13.7)
Duration of Response	Median (min, max)	NR
Progression free survival	Median (min, max)	NR
Progression free survival rate @ 6 mos	%	81%
Progression free survival rate @ 9 mos	%	71%

NR, not reached



Note: Objective Response defined as attaining Stringent Complete Response, Complete Response, Very Good Partial Response, or Partial Response. Including unconfirmed responses.

Berdeja et al ASH 2017

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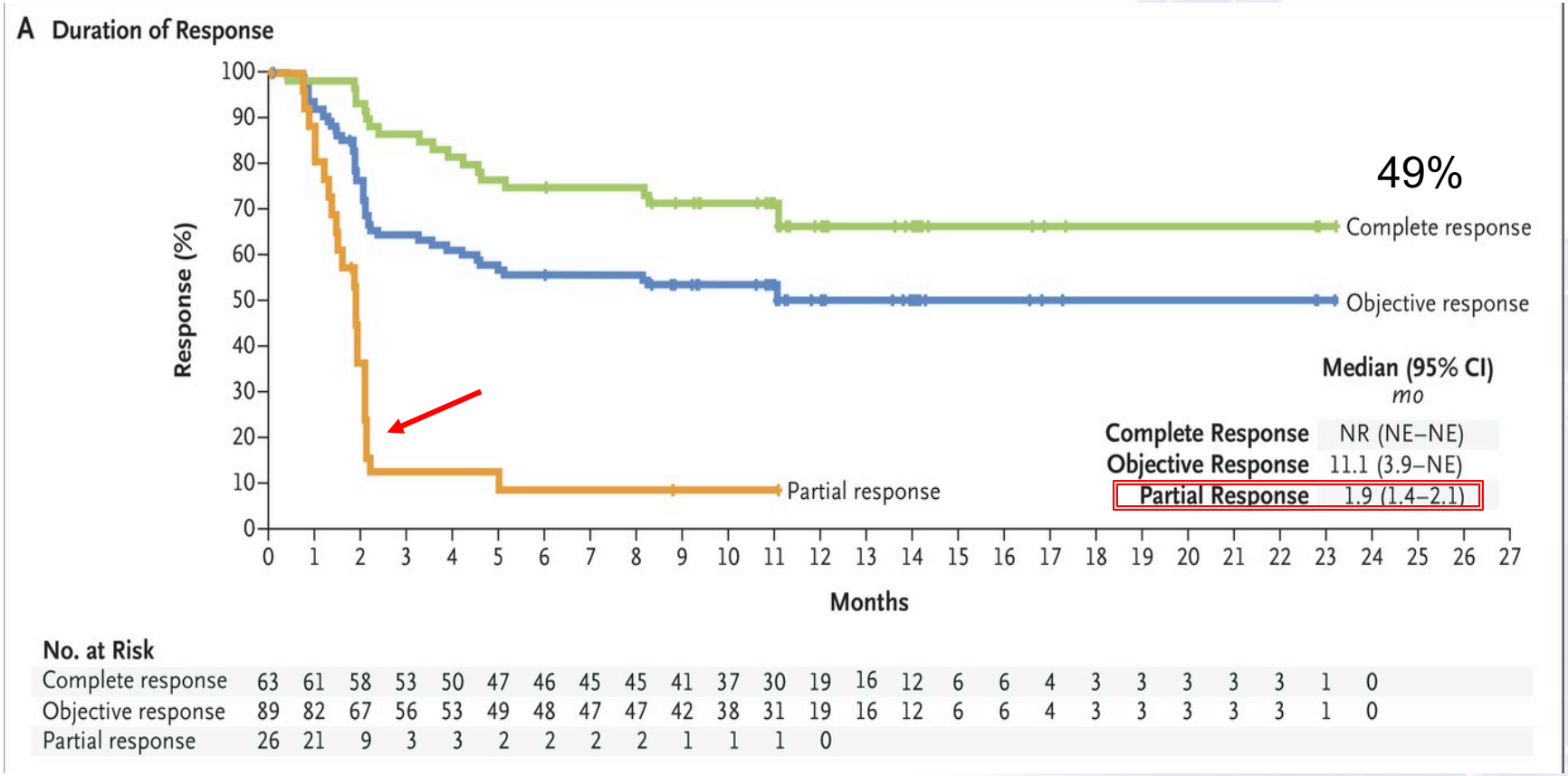
Current Benefits and Challenges with CAR-T Therapy

- Benefits
  - Effective in patients with advanced disease
  - Achieve rapid tumor clearance
  - High response rate
- Challenges
  - Cost: $300K – $700K/pt
  - Cytokine release syndrome
  - Lack of durable responses especially for patients that do not achieve a CR
  - Relapses associated with antigen escape variants of the tumor

Clinical Efficacy of CD19 CAR-T Therapy in DLBCL Not Achieving a CR



Neelapu et al 2017;377:2531-44

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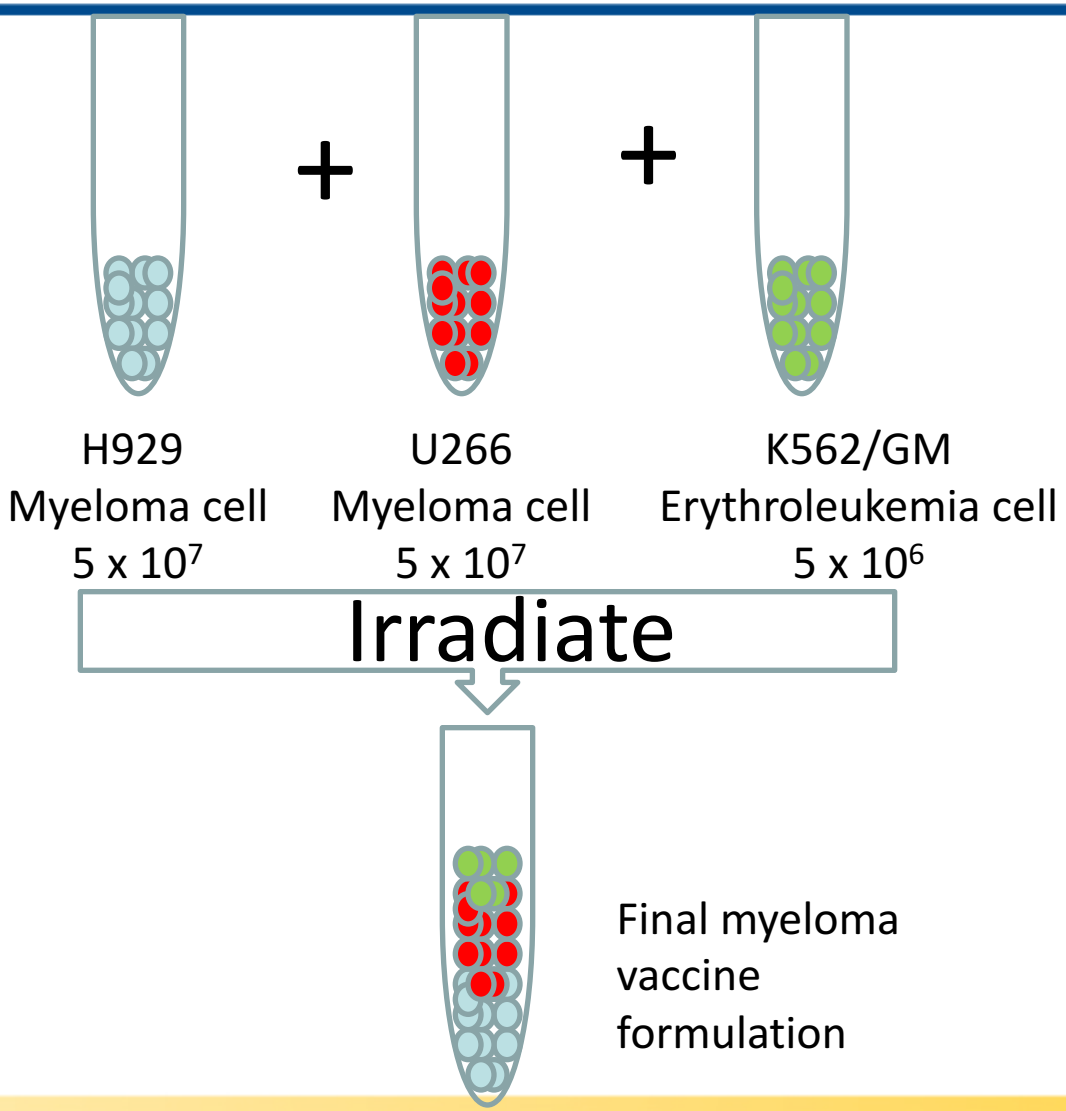
Allogeneic myeloma vaccine



Changes to Vaccine Formulation

- Developed an allogeneic vaccine
- Reduced the concentration of GM-CSF production in the vaccine formulation
- Increased the antigen dose
- Final formulation 20:1

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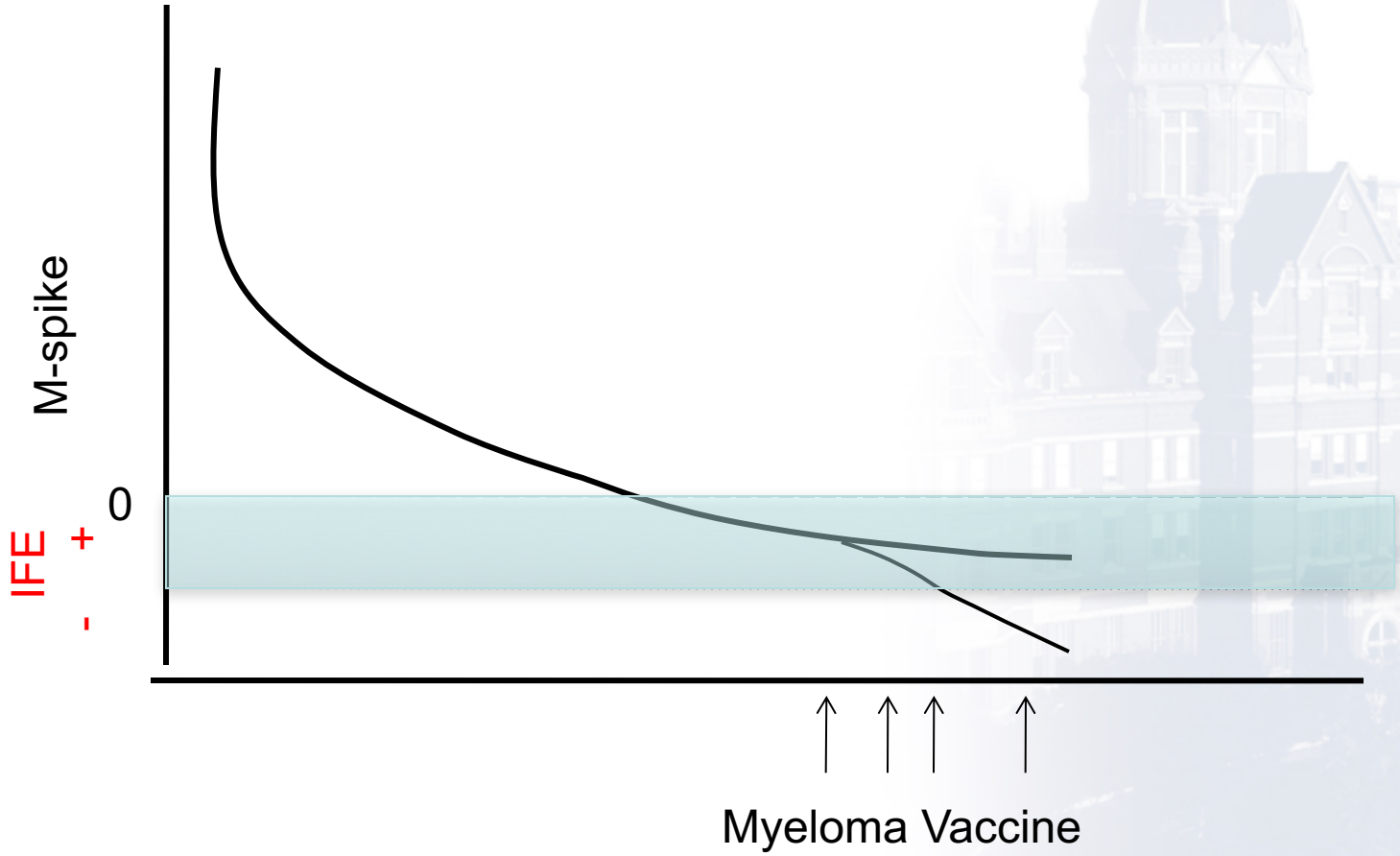
Targeting MRD with Myeloma Vaccine



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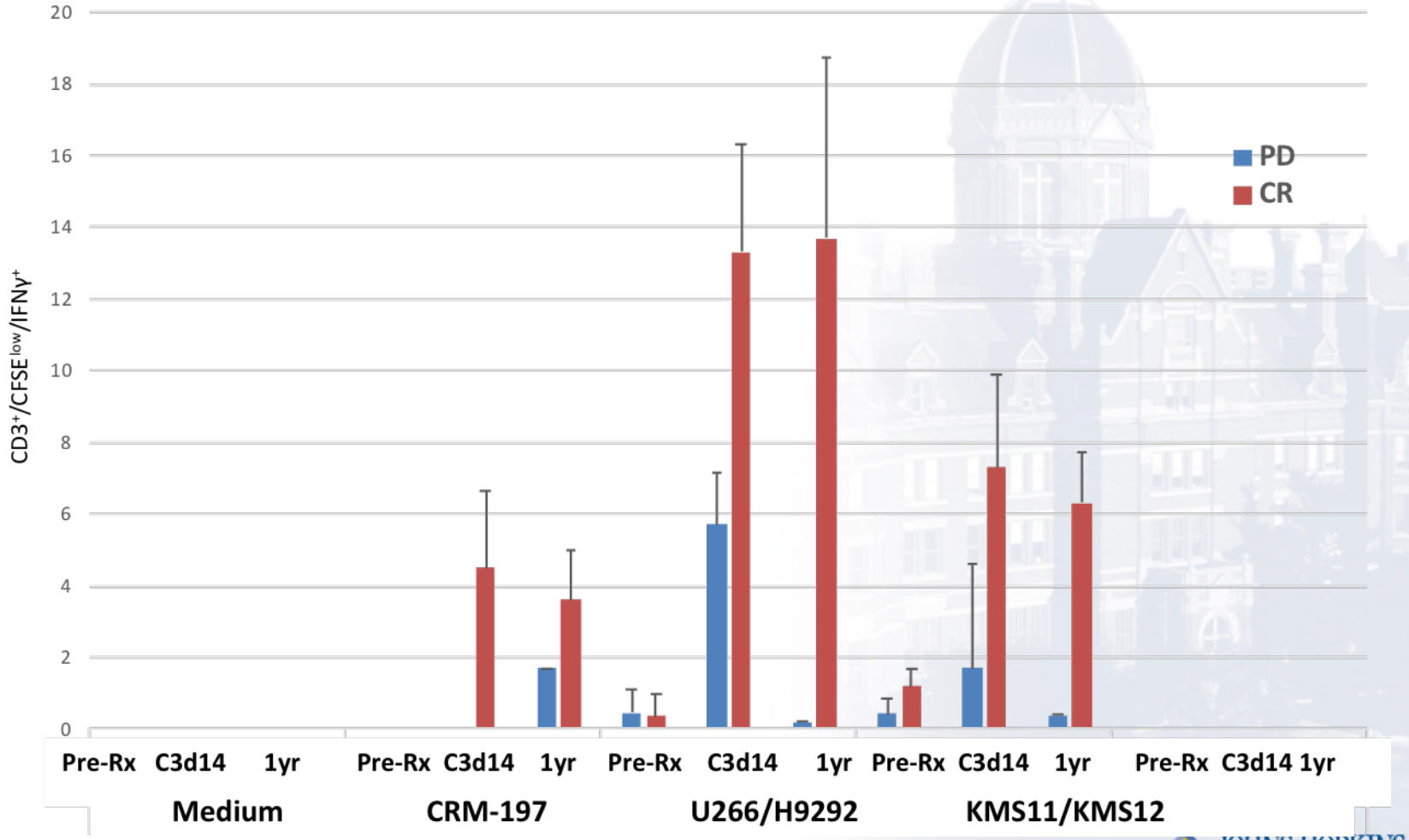
Patient Characteristics

	Vaccinated (n=15)	Observation (n=15)
Age	66 (45-81)	65.7 (40-83)
FISH high risk	0%	0%
ISS III	2 (16%)	2 (16%)
Pre-enrollment IFE neg	0 (0%)	7 (46%)
Prior Therapies	1.8 (1-4)	1.8 (1-3)
Prior ASCT	5 (33%)	4 (26%)

GVAX + Len Enhances Potent and Durable Tumor Immunity



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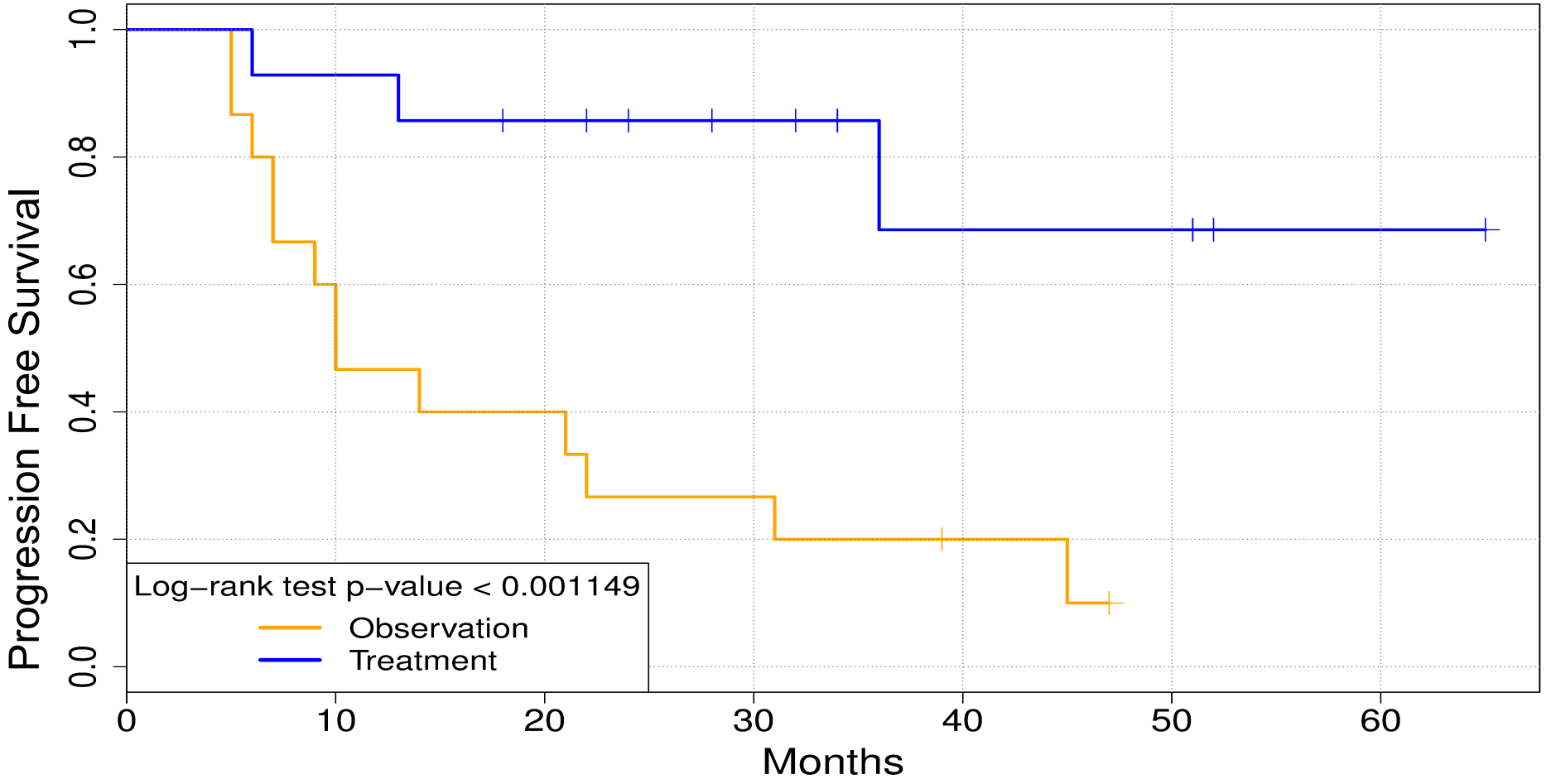
GVAX Significantly Prolongs PFS in Patients in a nCR



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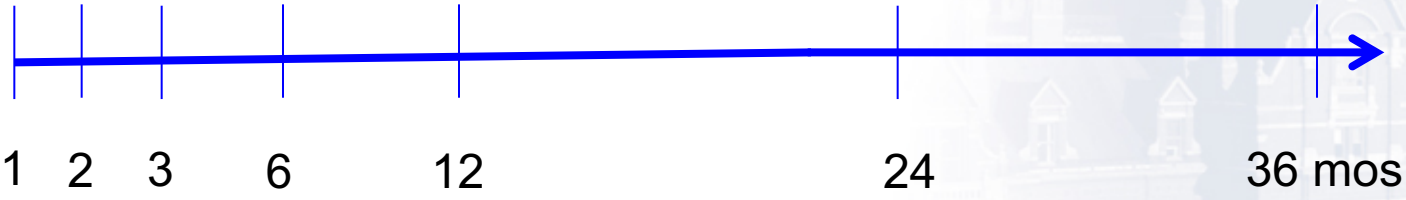
Trial Design
-Schema-

Randomization n=40 (1:1)

GVAX



Placebo

- Continue on same Lenalidomide dose if 15mg or less
- Vaccines administered on d14 of each Len-cycle
- Offer vaccine to patients on control arm at relapse

Conclusions

- Immunotherapy represents an additional treatment option for MM patients
- CAR-T cells show significant activity but durability is still unclear and must be balanced with cost
- Vaccines offer the possibility of preventing disease relapse
- Anti-PD-1 showed significant activity but further studies need to be done to address the safety concerns