



MULTIPLE MYELOMA
Research Foundation

Multiple Myeloma Highlights From the 2015 ASH Annual Meeting

January 13, 2016

Welcome and Introductions



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FDA Approvals in 2015

Drug	FDA Approval
Panobinostat (Farydak [®])	February 23
Daratumumab (Darzalex [™])	November 16
Ixazomib (Ninlaro [®])	November 20
Elotuzumab (Empliciti [™])	November 30

Multiple Myeloma Update From the 2015 ASH Annual Meeting

Faculty



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Smoldering Multiple Myeloma



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Smoldering Multiple Myeloma

- How do we identify smoldering myeloma?
 - CRAB criteria
 - Plasma cell infiltration
 - Free light chain assay
 - PET/CT scan imaging
- Who really is a smolderer?
- What are the risk factors for progression

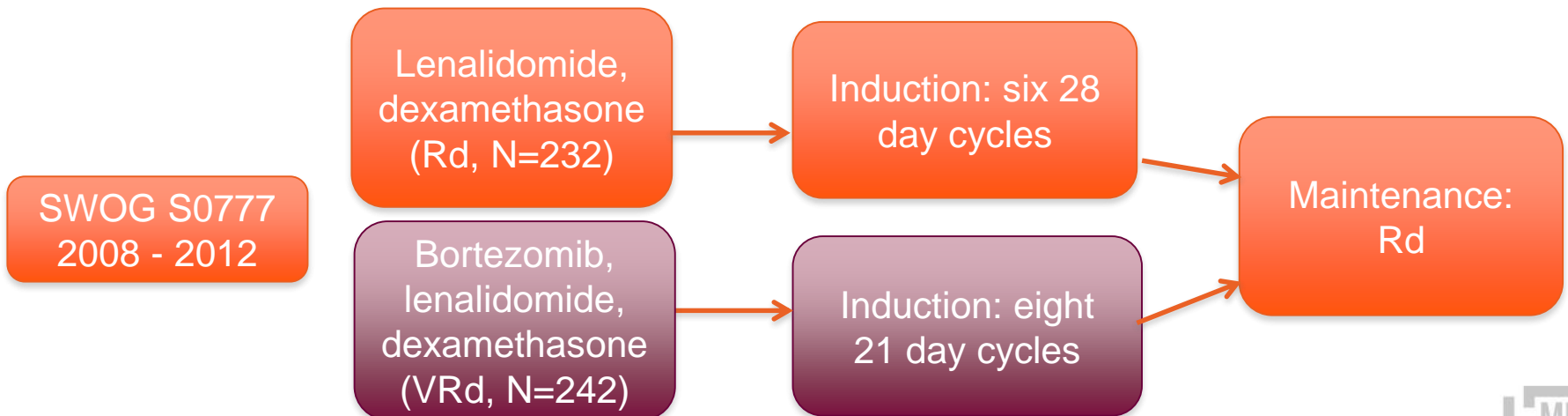
Upfront Therapy



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SWOG S0777 Update – Newly Diagnosed Multiple Myeloma

- The Southwest Oncology Group (SWOG) ongoing clinical trial compares 2 combination therapies for patients with newly diagnosed multiple myeloma (eligible or not eligible for transplant)
 - Revlimid[®] (lenalidomide), Velcade[®] (bortezomib), and dexamethasone (RVd)
 - Revlimid and dexamethasone (Rd)



SWOG S0777 Update – Newly Diagnosed Multiple Myeloma (cont)

- Results show that over the course of 72 months, overall survival was greater for newly diagnosed patients who received triplet therapy (RVd) than those who received Rd

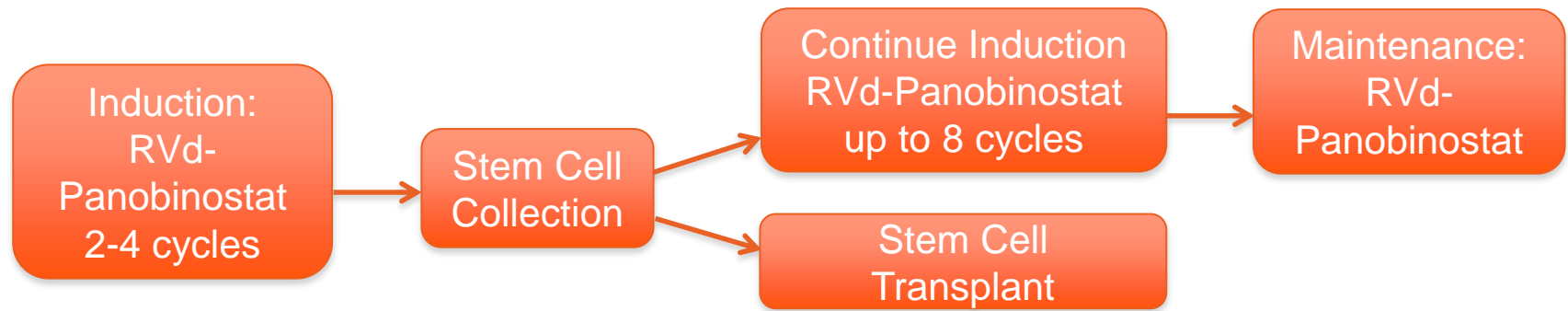
Endpoint	RVd	Rd
Median PFS	43 months	31 months
Median OS	Not reached	63 months
ORR	71%	63%

RVd, Revlimid® (lenalidomide) -Velcade® (bortezomib) -dexamethasone; Rd: Revlimid (lenalidomide)®-dexamethasone
ORR, overall response rate; OS, overall survival; PFS, progression-free survival; SWOG, Southwest Oncology Group.

Newly Diagnosed Patients: RVd-Panobinostat

Phase I/II clinical trial at MD Anderson Cancer Center

- Combining (Farydak[®]) panobinostat with Revlimid[®] (lenalidomide), Velcade[®] (bortezomib) and dexamethasone (RVd)



- Conclusions:
 - Panobinostat (10 mg) can be safely combined with full dose RVd
 - Some patients achieved very deep responses after 4 cycles of panobinostat-RVd

Quadruplet vs Triplet Therapy

- This clinical trial reviewed adding Kyprolis™ (carfilzomib) to cyclophosphamide, Revlimid® lenalidomide and dexamethasone (KCRd) as initial therapy
 - 1/2 of the patients received
 - Cyclophosphamide, lenalidomide and dexamethasone (CRd) or
 - Cyclophosphamide, thalidomide and dexamethasone (CTd) prior to Autologous Stem Cell Transplant (ASCT)
 - The other 1/2 received
 - Only CRd or CTd then ASCT
 - All patients received maintenance therapy after ASCT
- Patients receiving quadruplet therapy achieved deep responses

ASCT: autologous stem cell transplantation; VGPR: very good partial response

1. Pawlyn C, et al.. *Blood*. 2015;126(23):189.

Transplant Ineligible Newly Diagnosed Multiple Myeloma

- The availability of new drugs are driving regimens for transplant-eligible and transplant-ineligible patients close
- For patients who are not eligible for transplant, new classes of drugs (ie, more selective classes of drugs) may be able to be used in combination(s) and may be easier for these patients to tolerate
- Treatment regimens can be optimized for patient fitness and/or frailty

All Oral Regimen for Newly Diagnosed Patients – Not Eligible for Transplant

- In November 2015, the FDA approved ixazomib (NINLARO[®]), an oral proteasome inhibitor (PI) for the treatment of relapsed/refractory multiple myeloma
- Dr. Dimopoulos and colleagues looked at an all oral regimen, including ixazomib
 - Combined with cyclophosphamide (at 2 doses) and dexamethasone (called Icd)
 - For newly diagnosed multiple myeloma patients



All Oral Regimen for Newly Diagnosed Patients – Not Eligible for Transplant

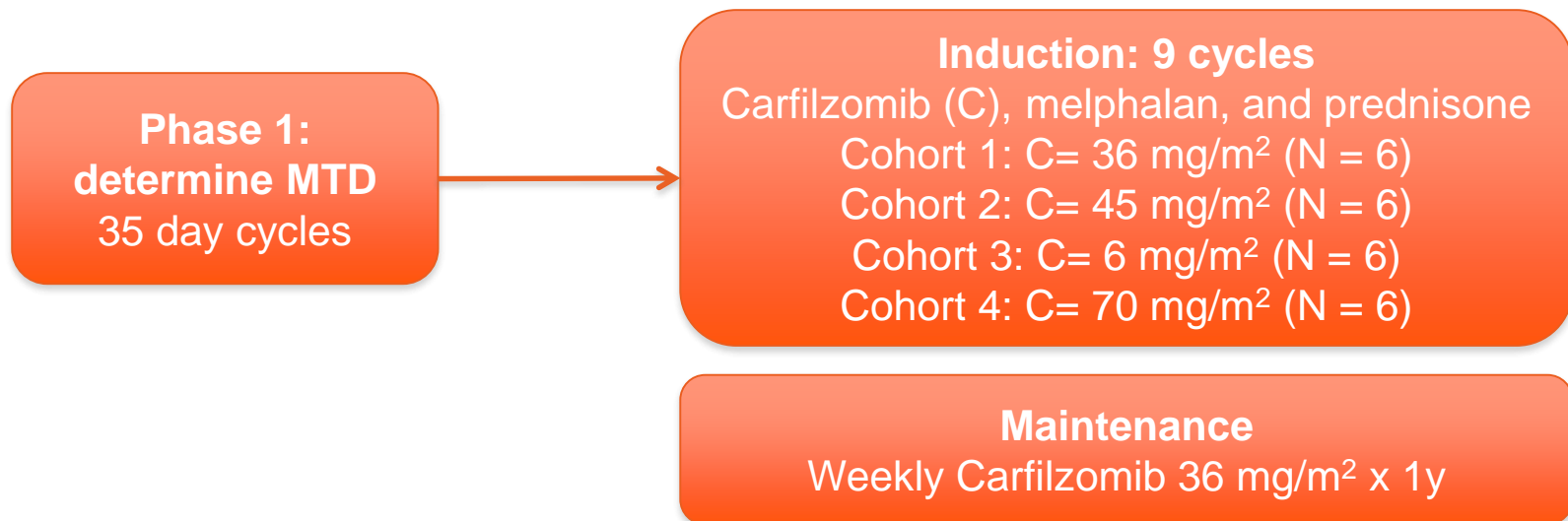
- The majority of patients responded well to this new combination therapy
 - 70% of patients who received ixazomib and the lower dose of cyclophosphamide achieved a partial response
 - The overall response rate for these patients was 80%

Response, n (%)	lcd-300	lcd-400
CR	3 (10)	3 (10)
PR	21 (70)	19 (63)
VGPR	5 (17)	4 (13)
CR + VGPR	8 (27)	7 (23)
ORR (CR + VGPR + PR)	24 (80)	22 (73)
SD	6 (20)	8 (27)

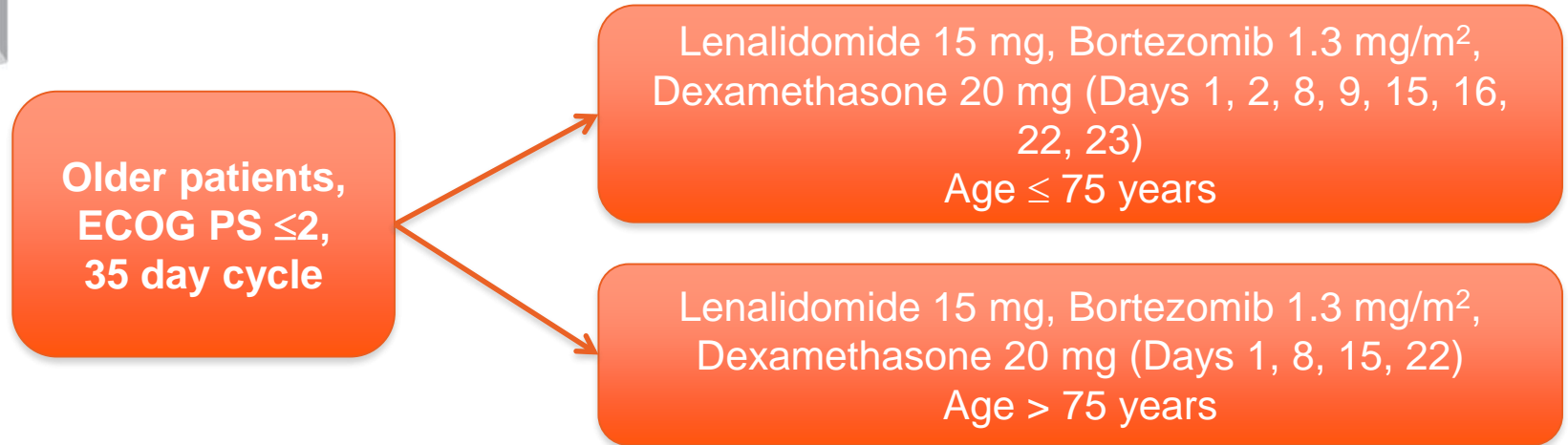
lcd: ixazomib, cyclophosphamide, dexamethasone; CR: complete response; PR: partial response; VGPR; very good partial response; ORR: overall response rate; SD: stable disease

Carfilzomib + MP in Elderly Newly Diagnosed Multiple Myeloma

- Dr. Leleu and colleagues conducted a clinical trial assessing the addition of increasing doses of carfilzomib, to melphalan and prednisone (MP)
 - MP is an old combination which is used mostly outside USA
- The observed maximum tolerated dose of carfilzomib was 70 mg/m²



RVD-lite – Alternate Dosing for Patients Younger or Older than 75 years



Interim Response (4 cycles)	
ORR of \geq PR (N=40)	90%
CR (n)	10
VGPR	14
PR	12
SD	4

PR: partial response; CR: complete response; VGPR: very good partial response; SD: stable disease

1. O'Donnell EK, et al.. *Blood*. 2015;126(23):4217.

Relapsed/Refractory Disease and Immune Therapies



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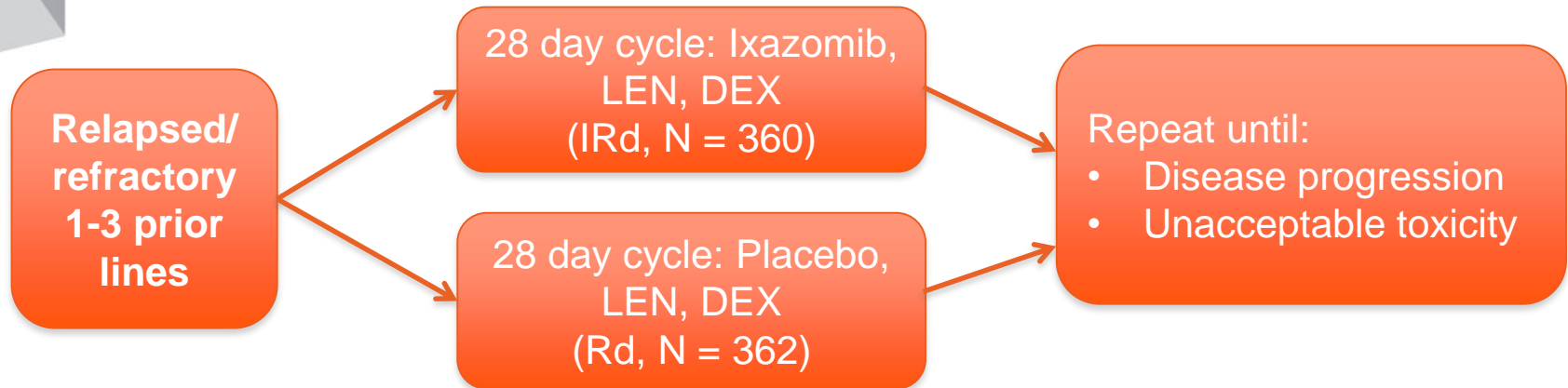


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All Oral Triplet Therapy (With a Proteasome Inhibitor and an IMiD)

- Ixazomib (NINLARO®), an oral proteasome inhibitor (PI), combined with lenalidomide and dexamethasone is FDA approved for patients with multiple myeloma who received ≥ 1 prior therapy
- This all-oral therapy combines a PI and an immunomodulatory drug (IMiD) and is approved for use in early stage relapsed myeloma

All Oral Triplet Therapy (With a Proteasome Inhibitor and an IMiD)



Response	IRd	Rd
Median PFS (mo)	20.6	14.7
Confirmed ORR, %	78.3	71.5
CR	11.7	6.6
≥ VGPR	48.1	39.0
Median time to 1 st response (mo)	1.1	1.9
Median duration of response (≥ PR, mo)	20.5	15.0

CR: complete response; DEX, dexamethasone, IMiD, immunomodulatory drug; LEN, lenalidomide; PI: proteasome inhibitor; PFS: progression free survival; ORR: overall response rate; VGPR: very good partial response

1. Moreau P, et al. *Blood*. 2015;126(23):727.

Other Ninlaro[®] (ixazomib) Trials for Relapsed/Refractory Disease

The results of other clinical trials which looked at ixazomib were presented at ASH 2015

- Ixazomib, pomalidomide, dexamethasone (compared to pomalidomide, dex)
 - Patients who received ≥ 2 prior lines of therapy and were refractory to an IMiD and a proteasome inhibitor
 - 13 patients completed >1 cycle; best ORR = 62% (7 PR, 1 VGPR)

Other Ninlaro® (ixazomib) Trials for Relapsed/Refractory Disease (cont)

- Ixazomib monotherapy at 2 doses (ie, 4 mg vs. 5.5 mg) with weekly dex for patients with relapsed MM (who had not received a proteasome inhibitor previously)
 - Early results (median follow up of 10 mos) –the overall response rate is better for the 5.5 mg ixazomib group (51%) than the 4 mg group (31%)
 - Disease progressed in 17 (49%) patients in 4 mg ixazomib group and 19 patients (54%) in 5.5 mg ixazomib group

Other Novel Agents

Drug	Class	Drug	Class
Oprozomib	Oral proteasome inhibitor	Ibrutinib	Oral Bruton tyrosine kinase inhibitor
Selinexor (KPT-330)	Oral SINE XPO1/CRM1 antagonist	Isatuximab (SAR650984)	Anti-CD38 monoclonal antibody
MDV9300	Anti-PD-1 monoclonal antibody	Filanesib	Kinesin spindle protein inhibitor

1. Martin, T, et al.. *Blood*. 2015;126(23):509;
2. Efebra YA, et al.. *Blood*. 2015;126(23):1838;
3. Shaj JJ, et al.. *Blood*. 2015;126(23):376;
4. Chari A, et al.. *Blood*. 2015;126(23):377;
5. Shah J, et al.. *Blood*. 2015;126(23):378;
6. Jakubowiak A, et al.. *Blood*. 2015;126(23):4223.

Immune Paralysis and Multiple Myeloma

- Low levels of antibodies increase risk of infection
- MM cells lack of stimulatory signals that drive T cell responses
- Cells in the bone marrow microenvironment suppress immune responses
- Increased expression of molecules like PDL1 which inhibit immune responses
- T cells and NK cells, the killers of the immune system are ineffective

Immune Therapies for Multiple Myeloma

- Antibodies directly target the MM cells inducing cell death or marking them for killing by immune cells like NK cells
 - Daratumumab, Elotuzumab
- PD-1 blockade breaks a critical pathway for immune escape
 - Pembrolizumab + Lenalidomide
- CAR T cells are engineered T cells that are activated and bind a target using an antibody
 - CAR T cells targeting BCMA
- Cancer vaccines reeducate the patient's immune system to see MM cell as foreign
 - DC/MM Fusion Vaccine and PD-1 blockade

Elotuzumab Update

- Empliciti™ (elotuzumab) is a monoclonal antibody that recognizes a protein (SLAMF7) that myeloma and natural killer cells produce
- It is approved by the US FDA for the treatment of multiple myeloma as combination therapy (ELd, elotuzumab, Revlimid® (lenalidomide), dexamethasone) in patients who have received 1 to 3 prior therapies

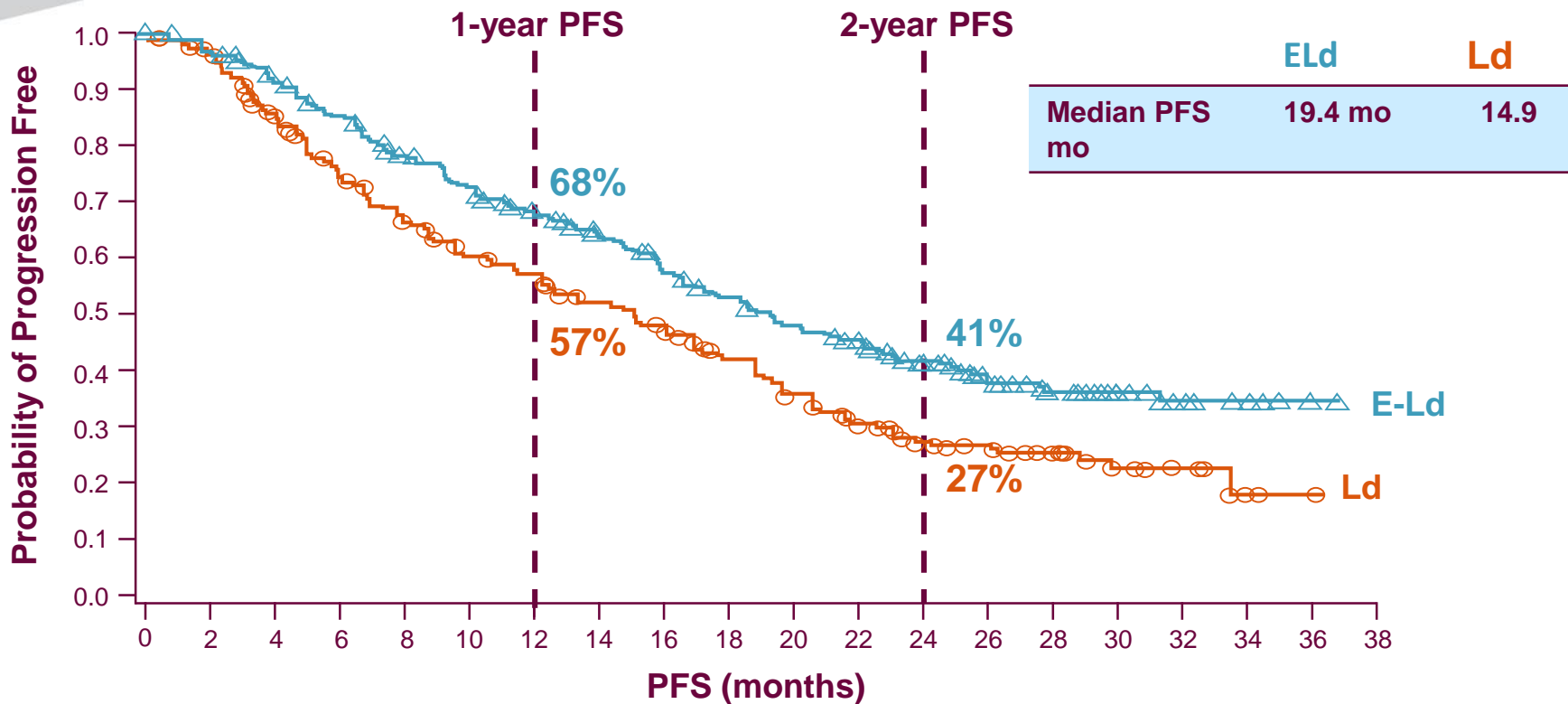
ELOQUENT-2 Update

- The ELOQUENT-2 trial compared the effectiveness of elotuzumab, lenalidomide, and dexamethasone (ELd) with lenalidomide and dexamethasone (Ld) in patients with relapsed, refractory multiple myeloma
 - Three year follow-up data were presented at ASH 2015
- Patients receiving ELd had a 30% reduction in the risk of disease progression or death compared with those treated with Ld

ELd: elotuzumab plus lenalidomide/dexamethasone; Ld: lenalidomide/dexamethasone

1. Lonial S, et al. *N Engl J Med*. 2015;373:621-631. 2. Dimopoulos MA, et al. *Blood*. 2015;126(23):28.

ELOQUENT-2 Update Progression-Free Survival



ELd-treated patients had a 30% reduction in the risk of disease progression or death vs Ld; treatment difference at 1 and 2 years was 11% and 14%, respectively

Eld, elotuzumab plus lenalidomide/dexamethasone; Ld, lenalidomide/dexamethasone

1. Lonial S, et al. *N Engl J Med*. 2015;373:621-631. 2. Dimopoulos MA, et al. *Blood*. 2015;126(23):28.

Daratumumab Monotherapy in Heavily Treated RRMM

- Daratumumab is a novel humanized monoclonal antibody which targets CD-38
 - Received FDA indication for previously treated, relapsed/refractory myeloma patients
- Current approved use for daratumumab:
 - Patients who have had ≥ 3 lines of treatment
 - Patients who are refractory to a proteasome inhibitor (PI) and an immunomodulatory drug (IMiD)
 - Approved for use as a single therapeutic agent

RRMM, relapsed/refractory multiple myeloma.

1. Usmani S, et al.. *Blood*. 2015;126(23):29.

Daratumumab Monotherapy in Heavily Treated RRMM (cont)

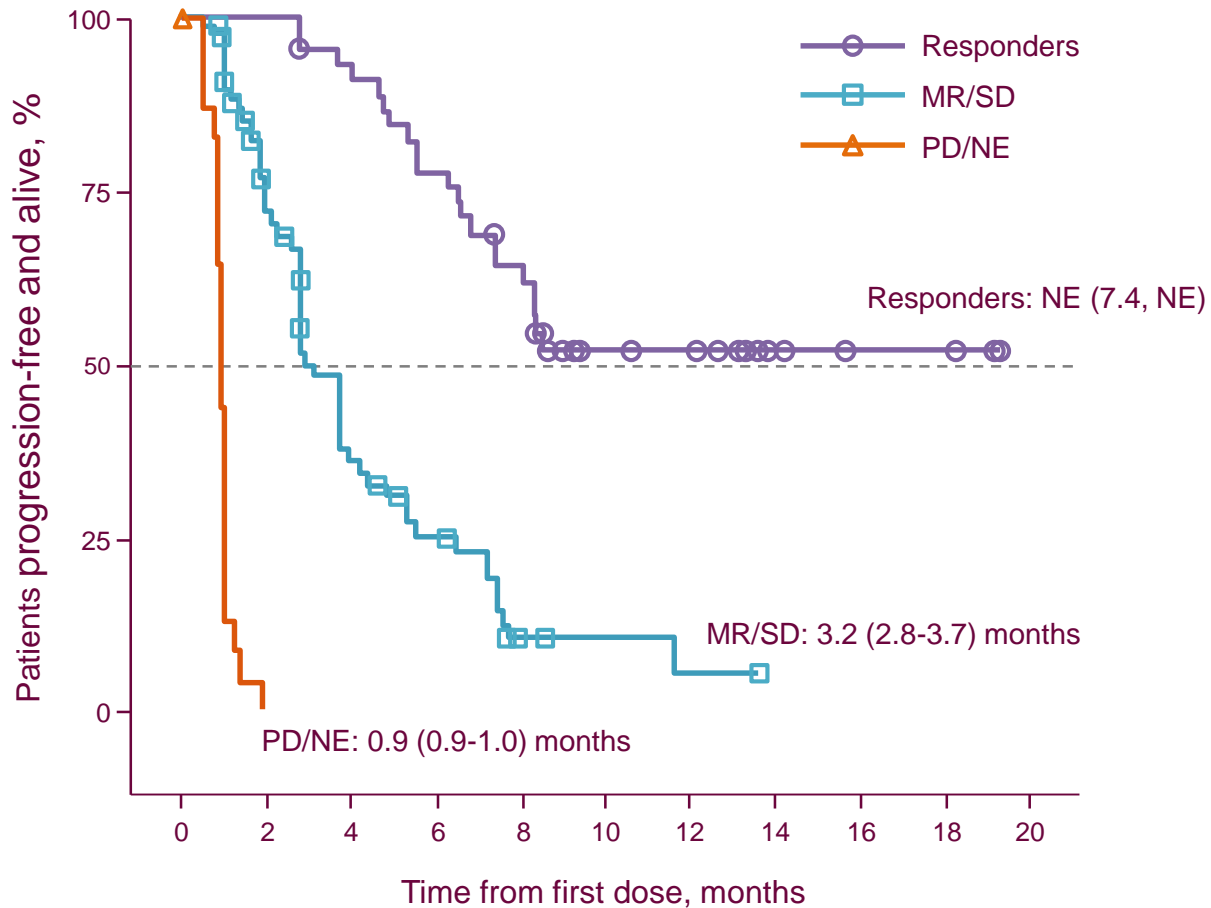
- Dr. Usmani summarized the results of a trial of daratumumab used as a monotherapy
 - 16 mg/kg: n=148 from GEN501 and SIRIUS Trial
- In the combined dataset of early data (median duration of treatment = 3.4 months, median number of treatments = 12, median follow-up = 14.8 months),
 - The overall response rate was 31%
 - The median duration of response was 7.6 months
 - Overall survival was 19.9 months
- Since this is a monoclonal antibody, patients with underlying comorbidities need to be monitored closely

RRMM, relapsed/refractory multiple myeloma.

1. Usmani S, et al.. *Blood*. 2015;126(23):29.

Daratumumab Monotherapy in Heavily Treated RRMM (cont)

Progression Free Survival



MR, minimal response; NE, not evaluable; PD, progressive disease; RRMM, relapsed/refractory multiple myeloma; SD, stable disease.

1. Usmani S, et al.. *Blood*. 2015;126(23):29.

Other Immuno-Oncology Trials for Relapsed/Refractory Disease

Studies investigating immunotherapy and checkpoint inhibitors were presented at ASH 2015

- Pembrolizumab is a highly selective humanized monoclonal antibody directed against the cell surface receptor programmed cell death-1 (PD-1), allowing the immune system to attack tumor cells
- An early trial studied the combination of pembrolizumab and lenalidomide in patients who previously did not respond to a proteasome inhibitor and immunomodulatory drug
 - 13 of 17 patients responded to this combination treatment: 4 achieved a very good partial response and 9 achieved a partial response

Other Immuno-Oncology Trials for Relapsed/Refractory Disease (cont)

- In a Phase 2 trial, pembrolizumab was combined with pomalidomide and dexamethasone to treat patients who had previously received proteasome inhibitors (Pis) and immunomodulatory drugs (IMiDs)
 - 75% of these patients were double refractory to IMiDs and PIs, and 21% refractory to lenalidomide
 - Early; objective responses from 22 patients show that 3 achieved a near complete response; 2 a very good partial response; 6 a partial response; 3 a minimal response; 6 achieved stable disease; and 2 progressed

Chimeric Antigen Receptor (CAR)-Modified T Cells

- A chimeric antigen receptor (CAR) is derived from an antibody which has a specific target and is fused with T-cell signaling domains
- The CAR target is usually restricted to antigens which
 - Are present on the surface of tumor cells surface
 - Are absent from T-cells
- T-cells which are engineered to produce a CARs (CAR-T-cells) specifically interact with the CAR target
- Researchers at University of Pennsylvania developed CAR-T-cells targeting CD19 B-cell maturation antigen
 - Although only a small numbers of patients were treated, these patients showed strong and durable responses
- The experts noted that long-term follow up and more studies are needed

Chimeric Antigen Receptor (CAR)-Modified T Cells (cont)

- Researchers at the NCI (National Cancer Institute), NIH (National Institute of Health), and MD Anderson Cancer Center developed a CAR-T cell which targets anti-B-cell maturation antigen (BCMA)
- The phase 1 trial of this anti-B-cell maturation antigen (BCMA) CAR (CAR-BCMA) looked at 4 dosing levels of CAR-BCMA in patients who had received prior therapies
 - Results are encouraging but very preliminary

Maintenance and Vaccine Therapy

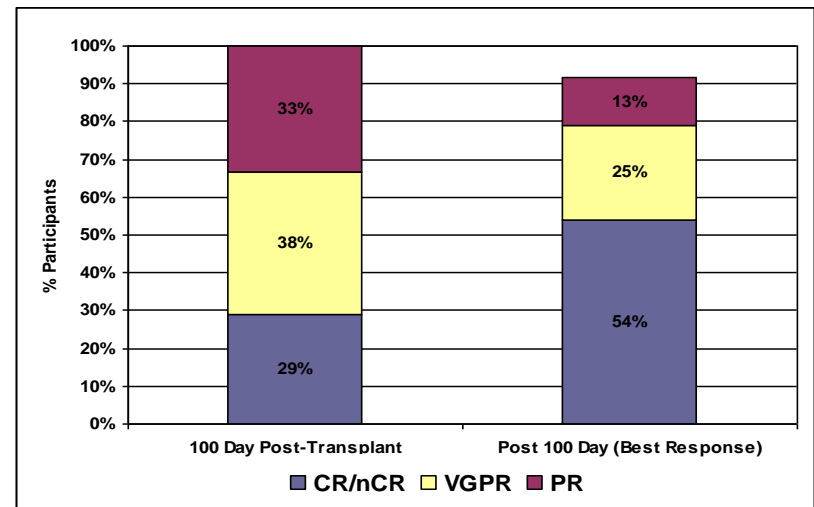
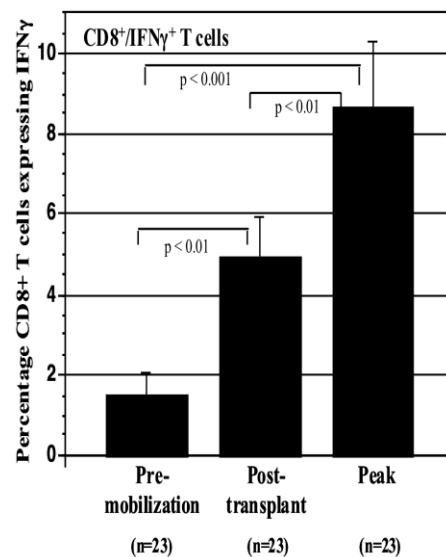
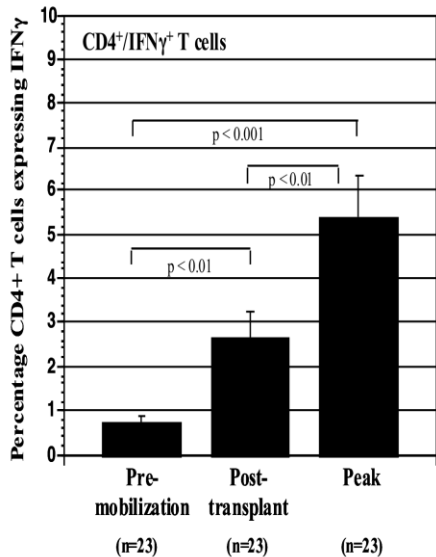
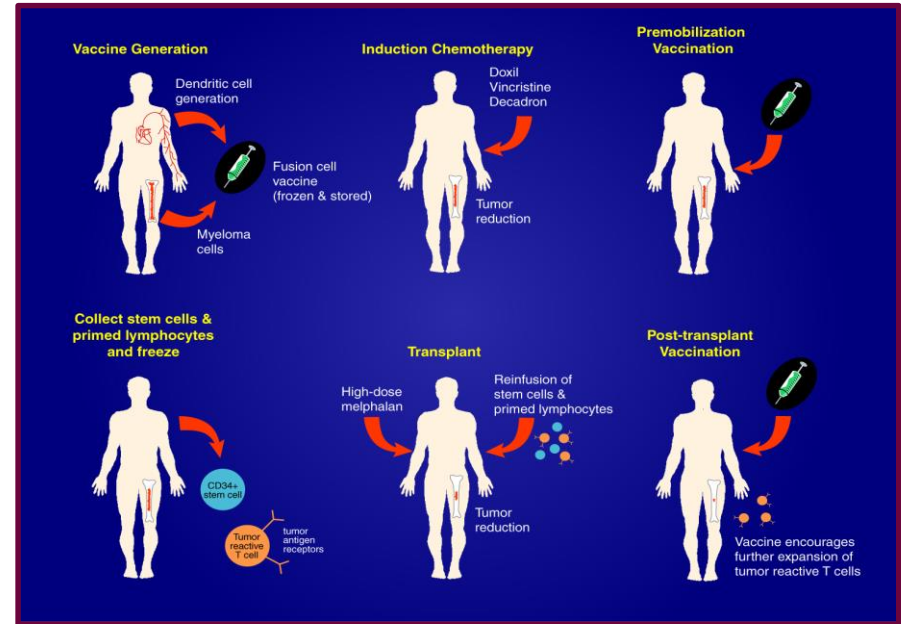
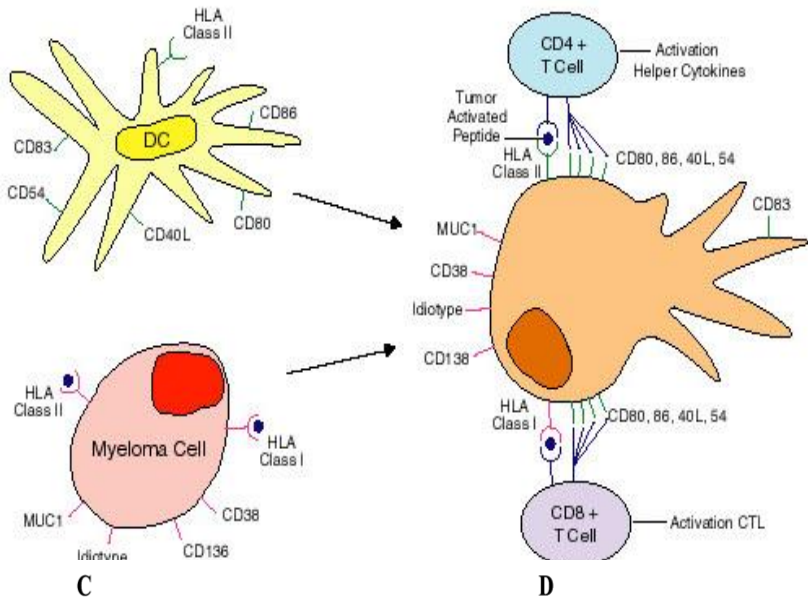


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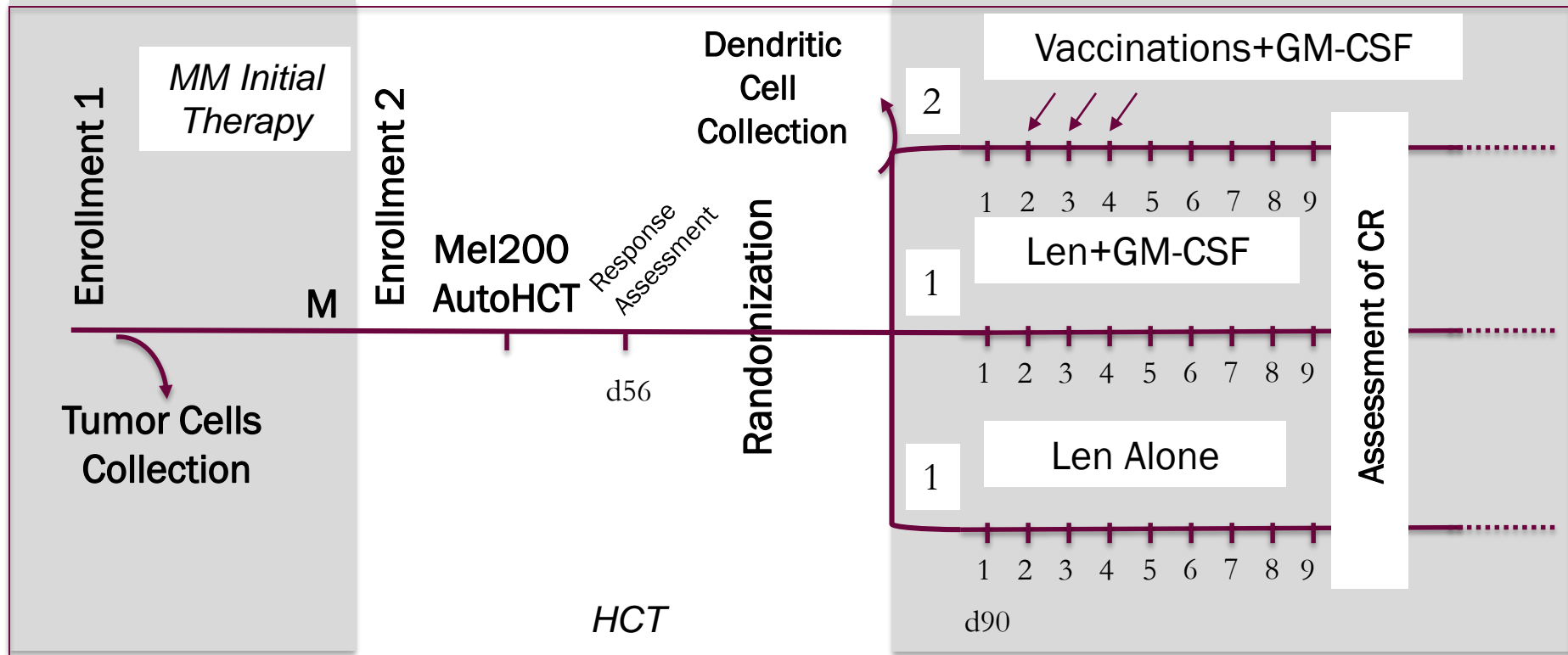
Maintenance Therapy

- Is there a common approach to maintenance therapy in the United States?
- New oral proteasome inhibitors and immunomodulatory drugs (IMiDs) provide future options for maintenance
- Maintenance approaches for patients with high-risk disease are needed
- Toxicity and quality of life are key factors to consider when selecting therapy
- Patients on maintenance therapy should be monitored carefully for toxicity

Vaccination with Whole Tumor Antigens: DC/MM Fusion Vaccination Post-transplant



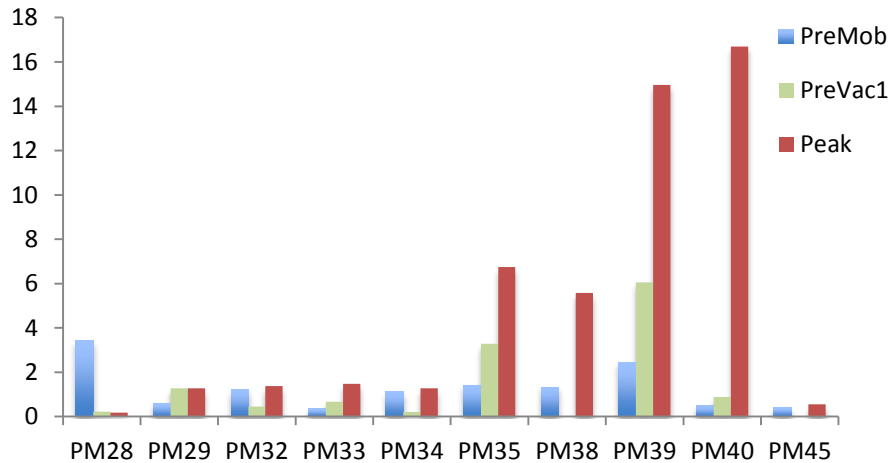
BMT CTN Protocol 1401 – Phase II Multicenter Trial of Post-transplant Lenalidomide Maintenance with or without Vaccination with Dendritic Cell (DC)/Myeloma Fusions (MY T VAX)



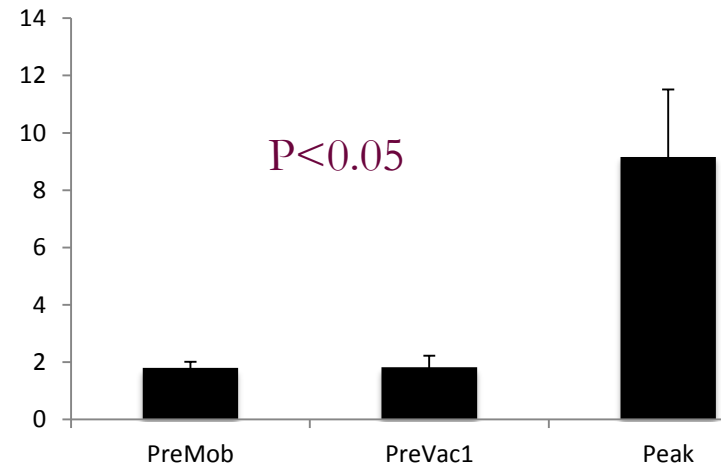
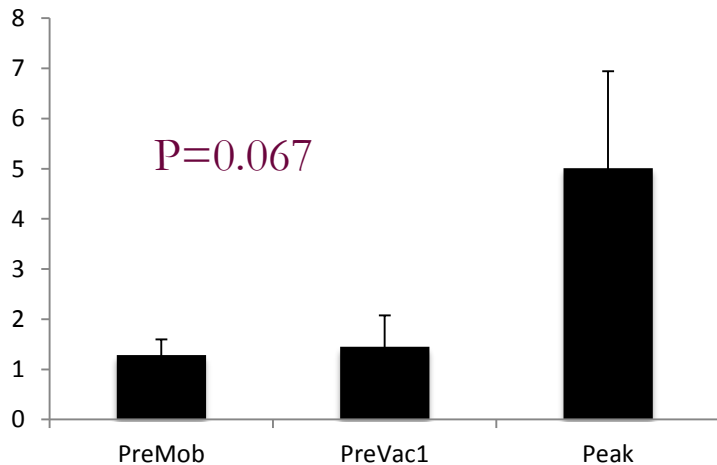
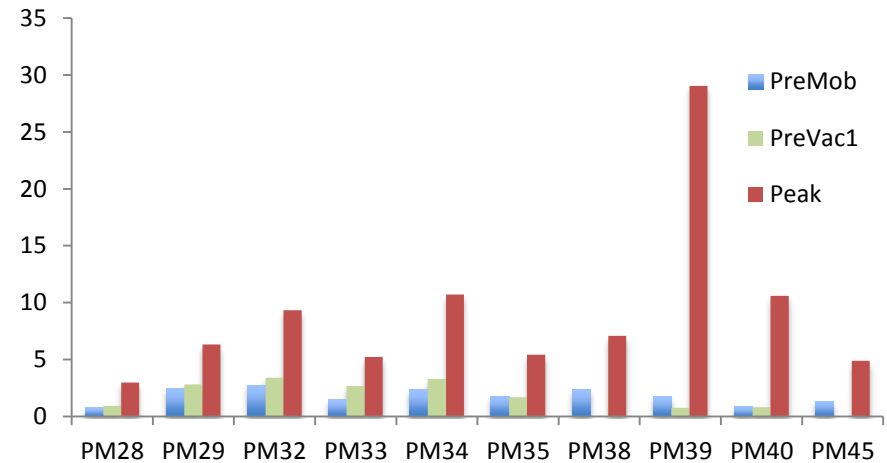
- Accrual targets 188 patients to be enrolled with a target of 132 patients to be randomized
- Assuming about 30% of patients are unable to proceed with post-transplant immunotherapy.
 - Arm A: Maintenance lenalidomide + vaccine + GM-CSF (n=66)
 - Arm B: Maintenance lenalidomide + GM CSF (n=33)
 - Arm C: Maintenance lenalidomide alone (n=33)
- Patients will be stratified according to disease status at time of randomization between
- CR and sCR and VGPR/PR/Stable disease.

Immune Response to Vaccine + Pidilizumab

CD4+IFN γ



CD8+IFN γ



Minimal Residual Disease



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Testing for Minimal Residual Disease

- Many patients are achieving deep and complete responses with new myeloma therapies
- Minimal residual disease (MRD) are the myeloma cells that remain after achieving a complete response
- In order to advance towards a cure, more sensitive methods are needed to identify and measure these remaining myeloma cells
- Two methods that are being looked at are
 - Flow cytometry (FCM) analysis
 - Sensitivity of 10^{-4} – 10^{-5} (1 in 10,000 or 100,000)
 - Next generation sequencing (NGS) analysis
 - Sensitivity of $< 10^{-6}$ (1 in 1,000,000)

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Question & Answer



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Closing Remarks



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