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IMF Chairman of the Board

Pre-ASH

What Myeloma Patients &
Caregivers Need to Know

Thursday, November 17, 2016

4:00 pm Pacific / 5:00 pm Mountain/
6:00 pm Central / 7:00 pm Eastern

Duration: 60 minutes (including Q&A)

with support from:

AMGEN



Bristol-Myers Squibb



janssen





ASH 2016



58th ASH[®] Annual Meeting and Exposition

San Diego Convention Center • San Diego, California

MEETING: DECEMBER 3-6, 2016

EXPOSITION: DECEMBER 3-5, 2016

Myeloma Related

| | |
|---------------------------|------------|
| Oral Presentations | 114 |
|---------------------------|------------|

| | |
|----------------|------------|
| Posters | 573 |
|----------------|------------|

Total = 687





Bottom Line Takeaways from ASH 2016

- New Genetics confirm old ideas
- MRD: strong support for “Black Swan” concepts
- Nelfinavir: AIDS drug works in myeloma
- Venetoclax: drug for t(11;14) myeloma
- Selinexor: data for “unmet need”
- CASTOR/ POLLUX: dara combo updates
- CAR-T: status of immune therapy
- Amyloid: carfilzomib (Kyprolis®) active
- Diet and MGUS
- Clinical Pearls: knowledge for day-to-day care





Initial Molecular Oral Session

Abstracts #115 - #120

New data confirm old ideas

- #115: Little Rock (Morgan): **MyC oncogene** active in 54.8% of MM
- #116: Dana Farber (Munshi): **B Cell genome mutator** linked to active MM (AID: signature #9)
- #117: Little Rock (Walker): **Fusion genes** rare, but linked to RAS
- #118: Pamplona (Kulis): **Histone modification**/ gene activation common
- #120: Canada (Bahlis): **Cereblon splicing** linked to IMiD resistance





Smoldering Myeloma (SMM) Oral Session

Abstracts #235 - #240

Confirming the pattern of change over time

#235 Heidelberg Group

- Patients with MGUS/ SMM/ MM
- Progression linked to:
 - Myeloma stage at diagnosis
 - Rate of change
 - Molecular changes at diagnosis
- Main genes affected:
 - NRAS and KRAS
 - P53 and histones



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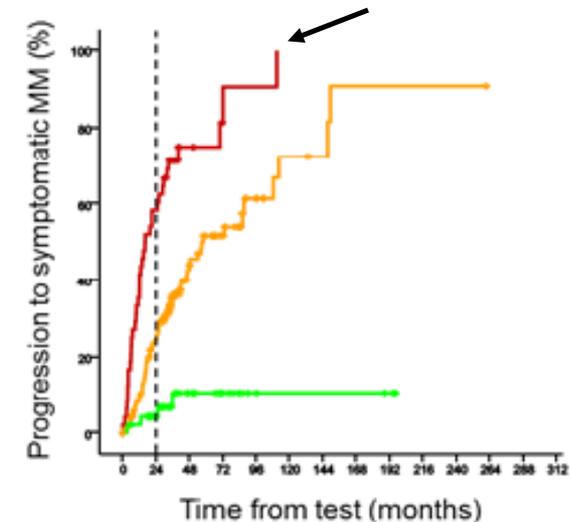
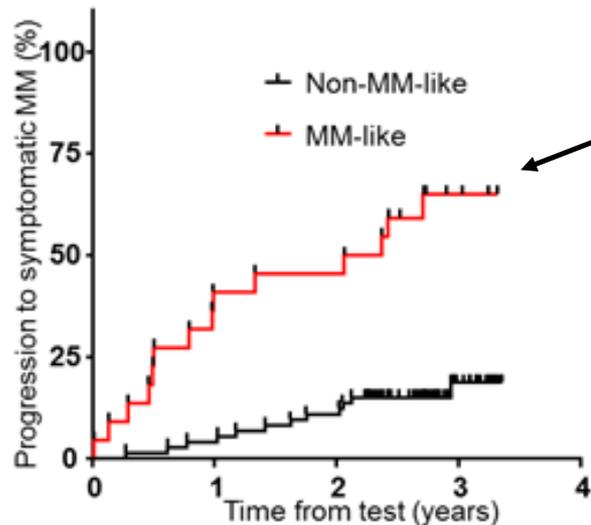
Diagnosis of HRSMM using NGF

Abstract #373



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- Bruno Paiva and Pamplona team
- 270 SMM patients: ½ Spain, ½ Little Rock



of events/N

Median TTP

| | | |
|--------|--------------|----|
| 4/47 | MGUS-like | |
| 76/175 | Intermediate | 56 |
| 38/48 | MM-like | 16 |





MDS at MM diagnosis

Abstract #357



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- Bruno Paiva and Pamplona team
- 312 newly diagnosed MM
- CD 56 positive abnormal monocytes indicated MDS
- Occurs in ~6.5% of patients
- Have low blood counts and poor survival:
 - PFS = 24 versus 37 months
 - OS = 47 versus 73 months





Comparison of NGF/ NGS and PET/ CT

Abstract #377

- Little Rock team
- 100 patients with \geq VGPR
- 50% are MRD positive
- Maximum chance of MRD negative during maintenance
- PET/ CT crucial during long term monitoring





Prognostic value of PET/ CT in NDMM

Abstract #992

- Zamagni et al: Bologna team
- 718 patients with serial monitoring; transplant eligible
- Evaluated: number of lesions; location (BM/EMD); SUV; bone destruction
- PET/ CT “Pre-Maintenance” most predictive
 - 66% negative; 44% positive
 - PFS and OS improved if negative





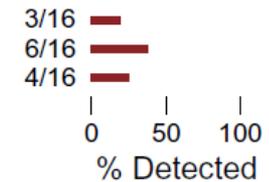
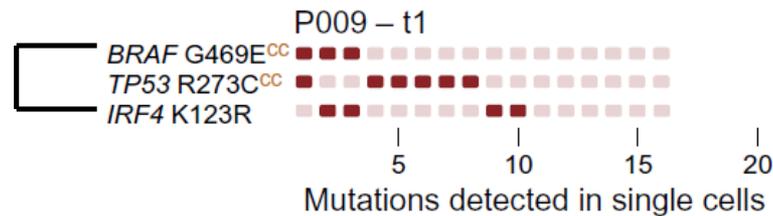
Single cell analyses of circulating plasma cells

Abstract #800

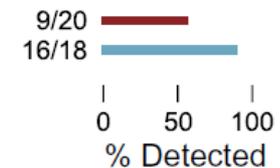
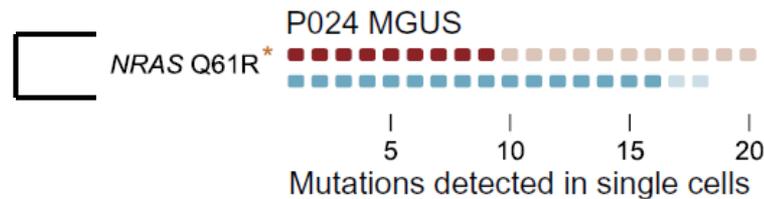
- Lohr et al: Boston team
- 24 MM/ MGUS samples

Specific mutations

A



B



- CTC
- Bone marrow
- ^{CC} CLIA confirmed
- * CLIA test not performed





NGF and genetic testing of circulating myeloma cells: “liquid biopsy”

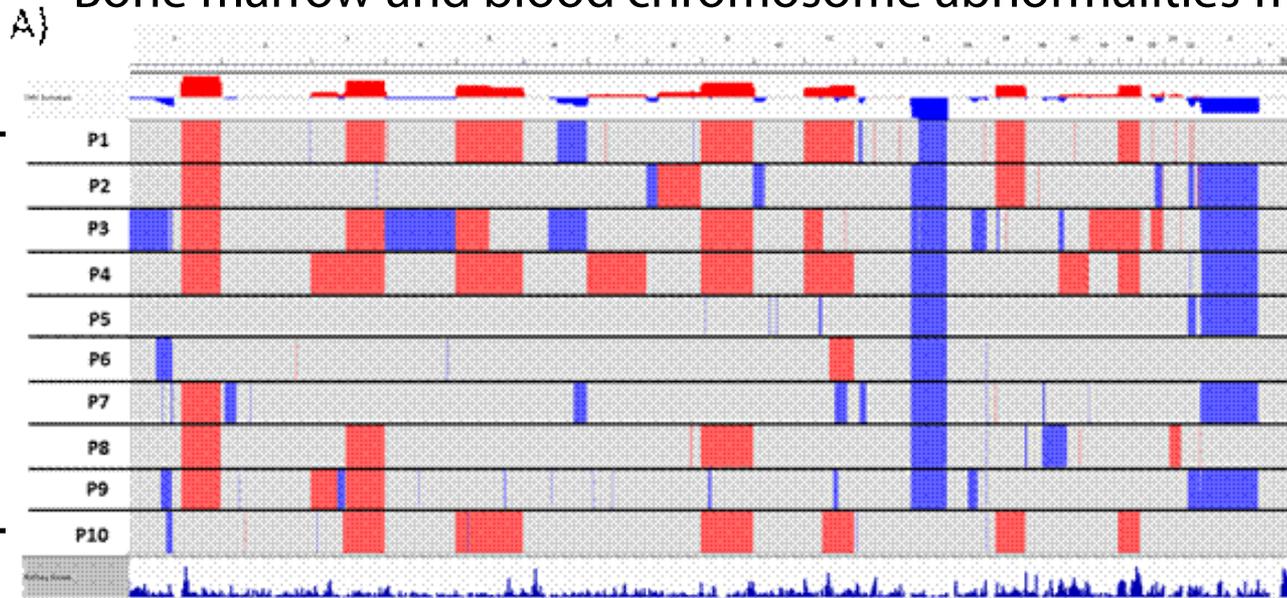
Abstract #801



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- Pamplona/ Madrid teams
- Myeloma cells present: MGUS 60%; MM 87%

Bone marrow and blood chromosome abnormalities match





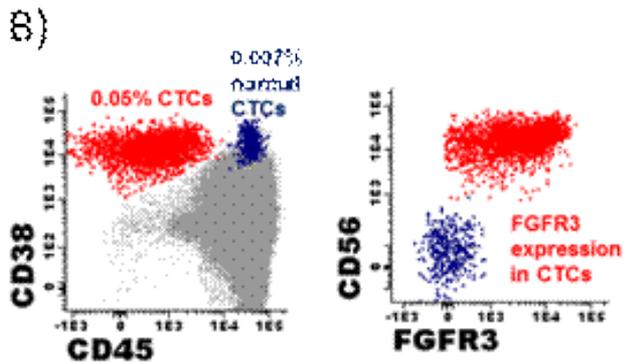
NGF and genetic testing of circulating myeloma cells: "liquid biopsy"

Abstract #801

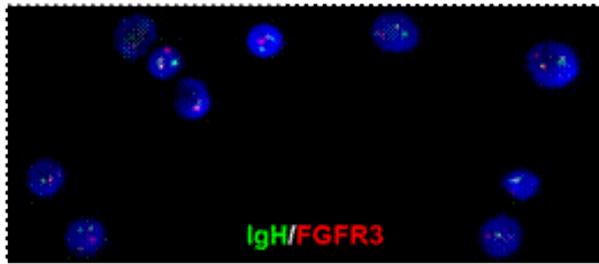


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blood

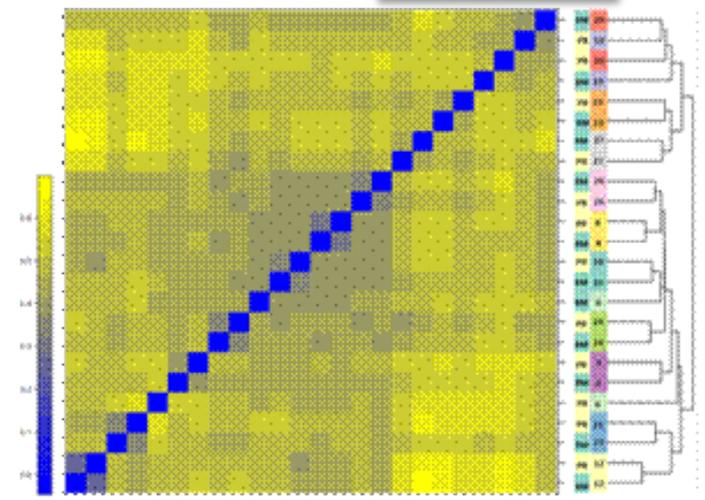


bone marrow



blood

bone marrow



t(4;14)

GEP: Gene Expression Profiling





New Myeloma Therapy combination with AIDS drug

Abstract #487

- St. Gallen, Switzerland team
- 34 patients; resistant to Velcade[®]
- Nelfinavir (NFV); oral; overcomes Velcade[®] resistance
- Combo = NFV + Velcade/ Dex; well tolerated
- Relapse/ Refractory patients
- ORR (PR or better) = 65%

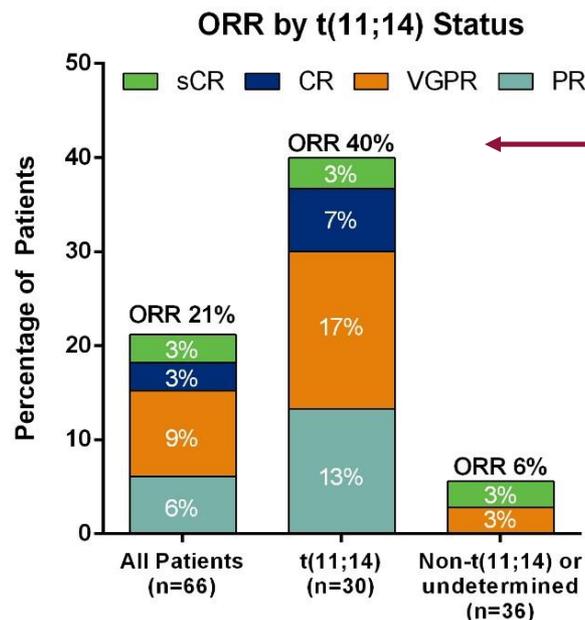




Venetoclax: BCL-2 Inhibitor Therapy

Abstract #488

- Shaji Kumar; AbbVie Inc. (Genentech) study
- 66 patients; relapse/ refractory disease
- Acceptable safety profile



t(11;14)

40%



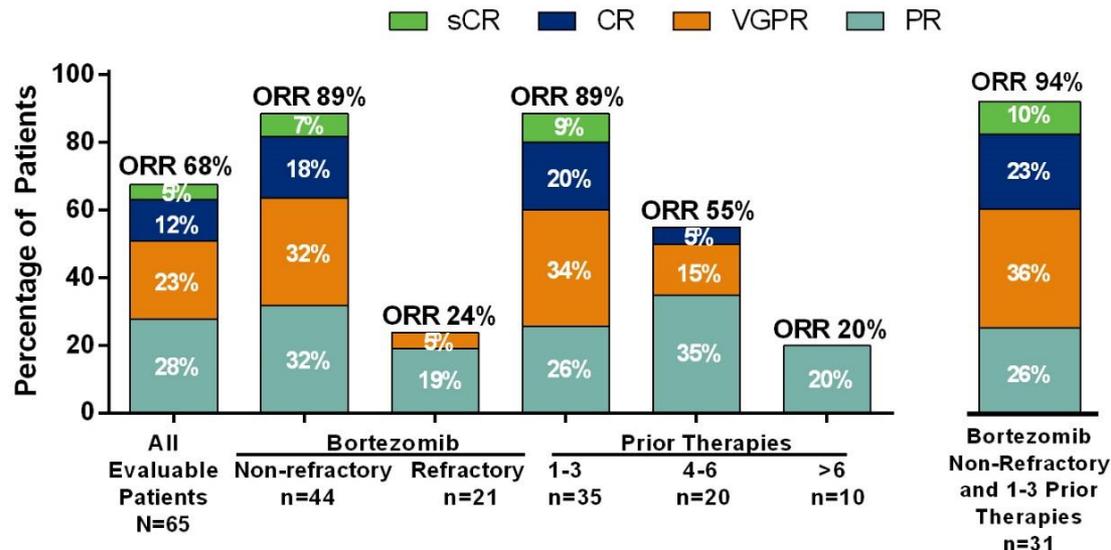


Venetoclax + bortezomib/ dex in Relapse/ Refractory Myeloma

Abstract #975

- Philippe Moreau; AbbVie Inc. (Genentech) study
- 66 patients; relapse/ refractory disease

Objective Responses Rates for Patients with R/R MM



Numbers are based on evaluable patients per subgroups.



Selinexor/ Dex in Relapse/ Refractory Myeloma

Abstract #491

- Dan Vogl: Karyopharm **“STORM” Trial**
- 79 patients:
 - 48 – quad (4) refractory: Rev/ Pom/ Velcade/ Kyprolis
 - 31 – penta (5) refractory: + dara → “unmet need group”
- ORR (\geq partial response) = 21% (quad); 20% (penta)
- Median DOR = 5 months
OS = 9.3 months
- Main toxicities: platelets ↓ ; GI ; fatigue





Selinexor/ Velcade/ Dex Combo

Abstract #977

- Bahlis; Karyopharm **“STOMP” Trial**
- 22 patients; PI refractory; well tolerated

| Prior PI Status | N | ORR (%) | CR (%) | VGPR (%) | PR (%) | MR (%) | SD (%) | PD (%) |
|--------------------------------------|----|----------------|--------|----------|---------|---------|--------|--------|
| Refractory (7 Bort, 3 Car, 2 Ixa) | 12 | 7 (58%) | 1 (9%) | -- | 6 (50%) | 3 (25%) | 1 (8%) | 1 (8%) |
| Bort - Exposed | 7 | 7 (100%) | -- | 5 (71%) | 2 (29%) | -- | -- | -- |

Table 1: Best Response by Prior Proteasome Inhibitor (PI) Treatment Status

Also, Abstract #330: Selinexor/ Pom/ dex

Abstract #973: Selinexor/ car/ dex

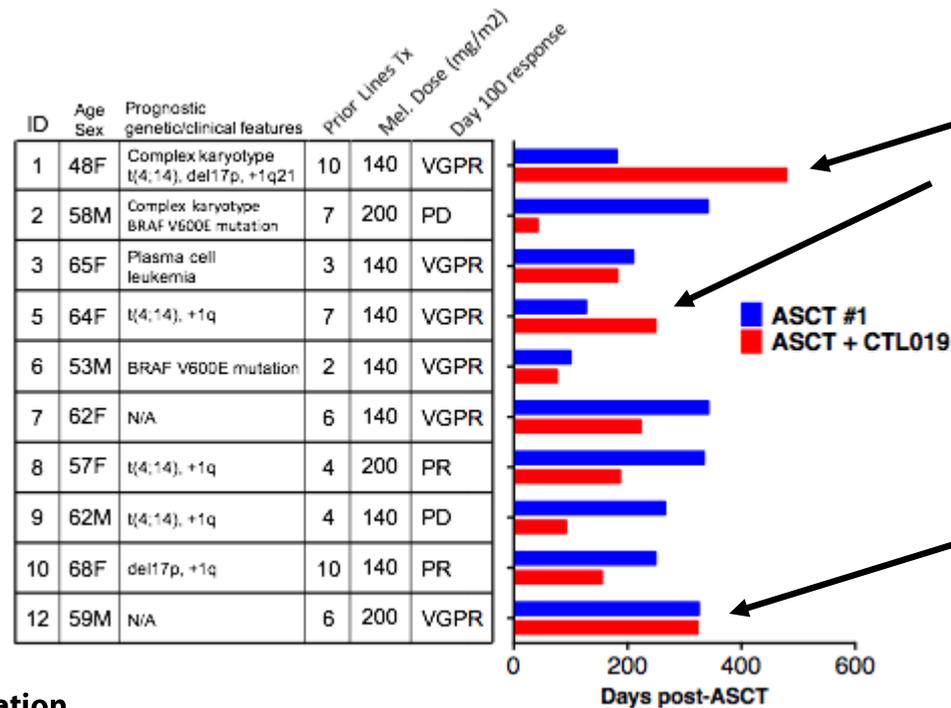




Anti CD19 CAR-T Cell Therapy

Abstract #974

- U Penn Team
- 10 patients treated; post-ASCT; safe



**3
long
VGPRs**





BCMA CAR-T Therapy

Abstract #1147

- BCMA = B Cell Maturation Antigen
- Adam Cohen and U Penn team
- 6 patients treated
- Cytokine release syndrome (CRS) and neurotoxicity a concern
- Also second Abstract #1148
Anti-BCMA monoclonal antibody with evidence of efficacy

| Peak CART expansion in blood: qPCR [#] | Best <u>Heme</u> response | DOR (mos.) |
|---|---------------------------|------------|
| 174110 | SCR | 7+ |
| 6160 | MR | 2 |
| 220081 | VGPR | 5 |
| 240 | SD | 2 |
| 302 | PD | - |
| 5801 | MR* | 1+ |



Amyloid Studies

Abstracts #643 - #648

Table: Hematologic response data

| Carfilzomib dose cohort | | | | |
|-----------------------------|-------------|--------------|-------------|--------------|
| Best Hematologic response | 20/27 (n=3) | 20/36 (n=21) | 20/45 (n=4) | Total (n=28) |
| CR | 0 | 3 | 0 | 3 |
| VGPR | 2 | 4** | 2 | 8 |
| PR | 0 | 3 | 1* | 4 |
| SD | 1 | 7** | 1† | 9 |
| Not evaluable/ too early | 0 | 4 | 0 | 4 |

**ORR
15/28
(54%)**

➤ Abstract #645

**Carfilzomib
(Kyprolis)
monotherapy**

- Adam Cohen: AMyC Consortium
- 28 patients: relapsed/refractory amyloid

*Dex added. **2 had dex added. †Never escalated above 20mg/m2



DIET and MGUS

Abstract #3257

- University of Iceland team
- 5,764 Individuals: 352 with MGUS

| | MGUS combined ^a n = 352 OR (95% CI) | MGUS n = 300 OR (95% CI) | LC-MGUS n = 52 OR (95% CI) | Progression ^b n = 18 HR (95% CI) | Progression ^c n = 28 HR (95% CI) |
|--------------------|--|--------------------------------|----------------------------------|---|---|
| Adolescence | | | | | |
| early | Pattern I | 0.89 (0.79-1.00) | 0.90 (0.80-1.02) | 0.80 (0.59-1.09) | - |
| | Pattern II | 0.99 (0.88-1.11) | 1.02 (0.90-1.15) | 0.81 (0.57-1.13) | - |
| | Pattern III | 1.02 (0.91-1.15) | 1.05 (0.92-1.19) | 0.87 (0.64-1.20) | - |
| | Pattern IV | 0.91 (0.81-1.02) | 0.91 (0.81-1.03) | 0.90 (0.67-1.20) | - |
| Midlife | | | | | |
| middle | Pattern I | 0.90 (0.80-1.02) | 0.92 (0.81-1.04) | 0.80 (0.59-1.10) | - |
| | Pattern II | 0.99 (0.88-1.11) | 1.03 (0.91-1.17) | 0.72 (0.52-1.00) | - |
| | Pattern III | 0.88 (0.79-0.98) | 0.92 (0.81-1.03) | 0.70 (0.53-0.91) | - |
| | Pattern IV | 1.11 (0.98-1.25) | 1.12 (0.98-1.27) | 1.04 (0.76-1.42) | - |
| Late life | | | | | |
| late | Pattern I | - | - | 0.64 (0.48-1.14) | 0.73 (0.48-2.64) |
| | Pattern II | - | - | 0.73 (0.40-1.31) | 0.91 (0.58-1.43) |
| | Pattern III | - | - | 0.78 (0.47-1.30) | 0.93 (0.63-1.38) |
| | Pattern IV | - | - | 0.72 (0.40-1.27) | 1.01 (0.66-1.52) |
| | Pattern V | - | - | 0.96 (0.58-1.58) | 1.03 (0.68-1.57) |
| | Pattern VI | - | - | 1.34 (0.80-2.26) | 1.84 (1.22-2.75) |

Abbreviations; MGUS = monoclonal gammopathy of undetermined significance, LC-MGUS = light chain monoclonal gammopathy of undetermined significance, OR = odds ratio, HR = hazard ratio, CI = confidence interval.

^aMGUS and LC-MGUS cases analyzed together. ^bProgression from MGUS and LC-MGUS combined to MM.

^cProgression from MGUS and LC-MGUS combined to MM and other lymphoproliferative diseases.



Clinical Pearls

- **Dara combos very active:** CASTOR/ POLLUX updates
Abstracts #489; #492 (Dara Pd); #1150; #1151; #3313; #4517
- **Dara effective for cardiac amyloid:** Abstract #4525
- **Dara can be given by subcutaneous injection (versus IV):** Abstract #1149 (Usmani)
- **Pembrolizumab** (checkpoint inhibitor) combos also active:
Abstract #490 (Badros)
- **Elo/ Rd:** safe and active for HRSMM: Abstract #976
- **Freelite and Hevylite** useful for monitoring:
Abstracts #376; #3245; #4428; #4633 (IFM & Oxford)





Clinical Pearls

- **High uptake on PET** is poor risk: Abstract #3260 (Denmark)
- **Carfilzomib (Kyprolis) combinations** (Thalidomide; Revlimid; Pomalidomide) all very active: Abstracts #1141; #1142; #1145
- **Racial disparities and HLA type/ plus presentation management and outcomes:** Abstracts #3250 and #3544 (Ailawadhi; Mayo)
- **High cut-off (HCO) dialysis improves renal failure:** Abstract #978 (Ferland/ Paris)





Support



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