Disclosures of: M.H. van Vliet
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# Proteasome Inhibitor Treatment Response can be Predicted by Gene Expression Profiling in Multiple Myeloma

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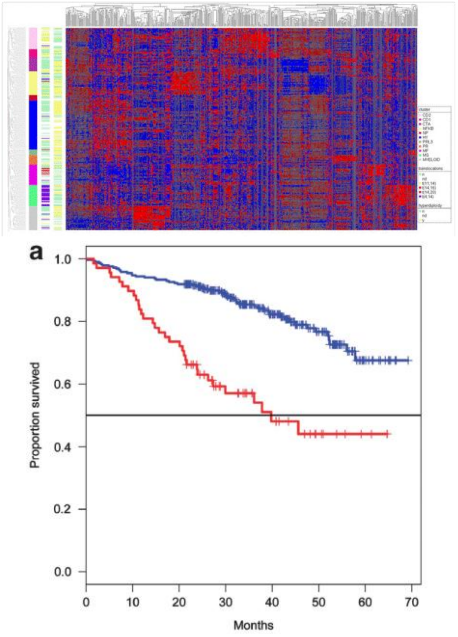
Abstract S1286
Sunday, June 15, 8:15-8:30, Room Gold

# Introduction

Not a single disease




- Multiple Myeloma (MM)
  - Is a not a single disease
  - Outcome varies per subtype
  - Clinical, ISS and genetic markers
  - Gene Expression Profiling (GEP) “risk stratification” is powerful and robust[1-4]
  - Guideline: *“GEP signatures may be capable of discerning prognosis and helping rational therapeutic decisions.”*[5]

- Utility of the markers in the Clinic → Personalized Medicine
  - Prognostic markers may be used for Risk Stratified Treatment (RST)
  - Predictive markers should help in Marker Stratified Treatment (MST)


1 Zhan et al., Neoplasia 2006
2 Broyl et al., Blood 2008
3 Kuiper et al., Leukemia 2012
4 van Vliet et al., EHA 2013, abstract S580
5 NCCN v1.2014

# Predictive Potential of GEP Markers Underexplored

- Indications for predictive use of iFISH markers
  - t(4;14), gain(1q), del(17p) have OS benefit from Bortezomib[1,3]

- Indications for predictive use of a GEP marker
  - Cereblon: low expression is a predictor for IMiD resistance[4-6]

A wealth of GEP data is available from clinical research, and therefore many more GEP markers can be evaluated for their predictive potential


1 Avet-Loiseau *et al.,* JCO 2010
2 Goldschmidt *et al.,* ASH 2010, abstract 305
3 Sonneveld *et al.,* JCO 2012
4 Zhu *et al.,* Blood 2011
5 Broyl *et al.,* Blood 2013
6 Shuster *et al.,* Leuk Res 2014

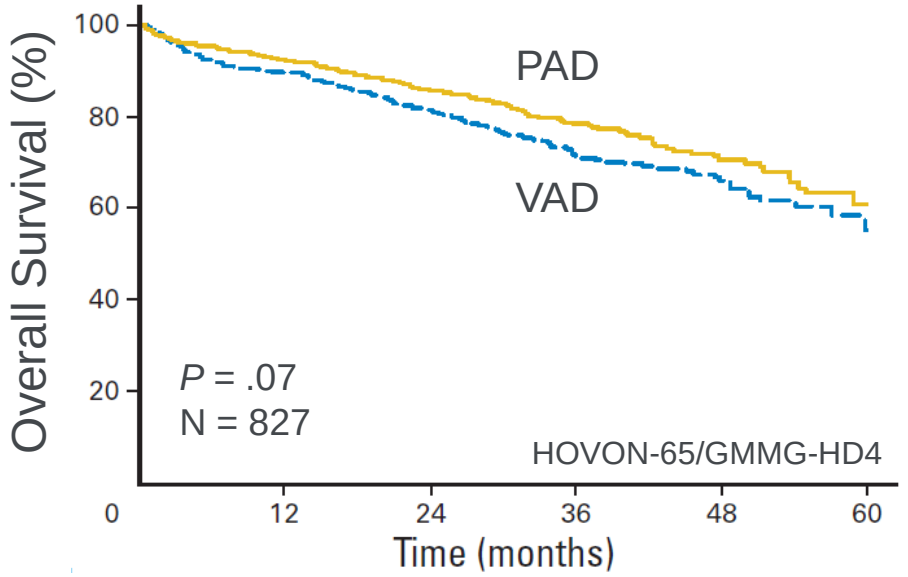
# Research Question

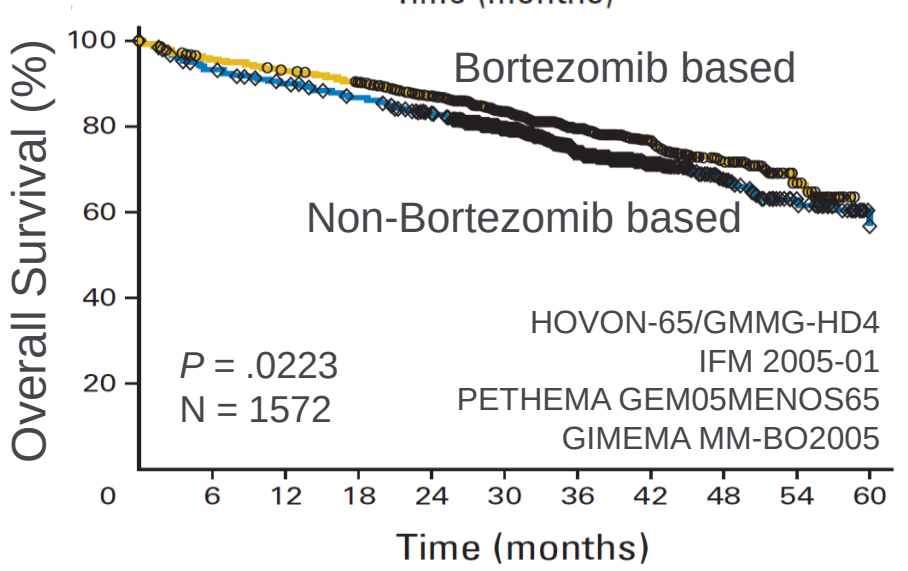
Can GEP Markers Predict Outcome to Proteasome Inhibitor Treatment?

# PAD/Bortezomib Improves Overall Survival

- HOVON-65/GMMG-HD4[1,2]
  - Phase 3 trial, 2 arms:
    VAD (Vincristine, Dox, Dex)
    PAD (Bortezomib, Dox, Dex)
  - Improved OS for PAD/Bortezomib[3,4]

- Subtype assessment using GEP markers
  - GEP data available for 329 patients
  - Cox proportional hazards model using OS and treatment arm (VAD/PAD)

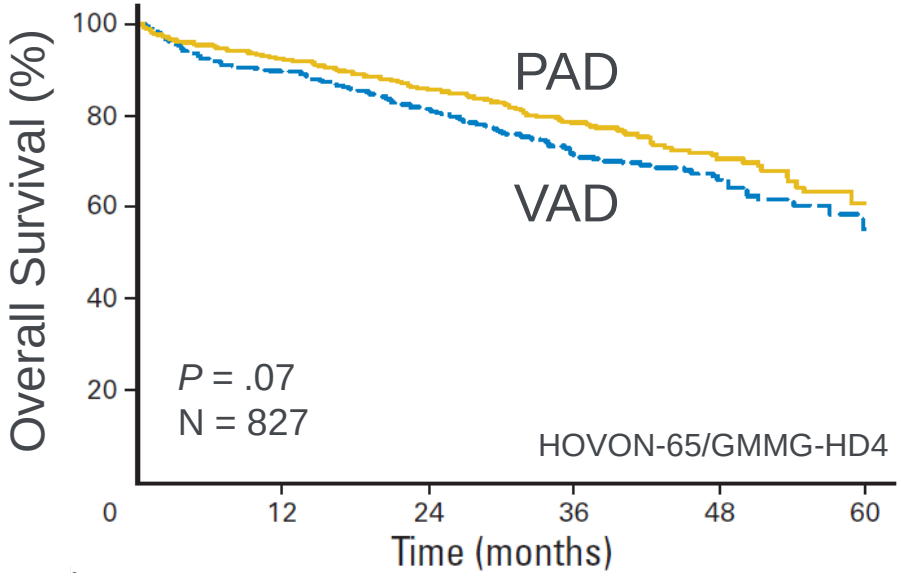




1 Broyl *et al.,* Blood 2008
2 Sonneveld *et al.,* ASH 2013, abstract 404
3 Sonneveld *et al.,* JCO 2012
4 Sonneveld *et al.,* JCO 2013

# Who Benefits from Treatment?




Small benefit for all?

Large benefit for subtype(s)?

# 20 GEP Markers Explored for Their Predictive Potential

- Each patient is assessed for each of the following 20 GEP markers
- Assess survival difference between treatment arms in each subtype

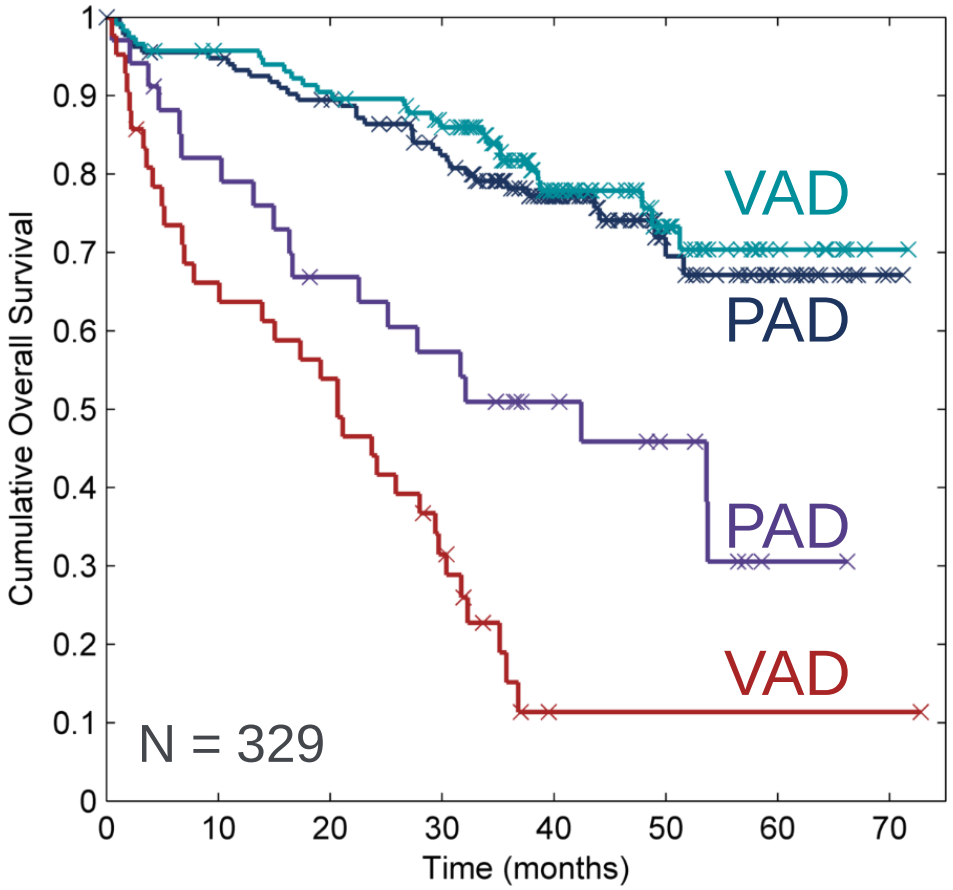
| High risk signature[1] |
| --- |
| EMC92/SKY92 |

| Virtual Karyotyping[2] |
| --- |
| Virtual t(4;14) |
| Virtual t(11;14) |
| Virtual t(14;16)/t(14;20) |
| Virtual del(13q) |
| Virtual gain(1q) |
| Virtual Hyperdiploid |
| Virtual del(17p) |

| Cluster Classifiers[2] |
| --- |
| Cluster MS |
| Cluster MF |
| Cluster CD2 |
| Cluster CD1 |
| Cluster CTA |
| Cluster NFKB |
| Cluster NP |
| Cluster HY |
| Cluster PRL3 |
| Cluster PR |
| Cluster LB |
| Cluster Myeloid |

1 Kuiper *et al.*, Leukemia 2012
2 van Vliet *et al.,* EHA 2013, abstract P234

# EMC92/SKY92 Predictive for Bortezomib Treatment Outcome




Standard Risk

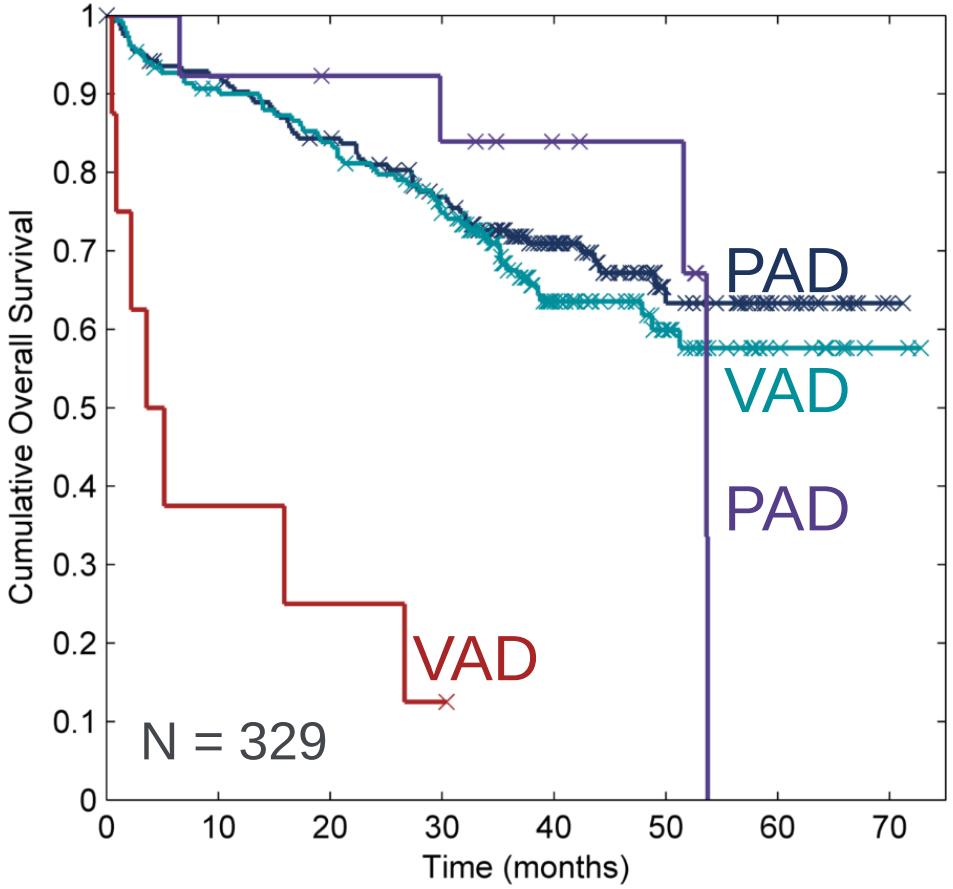
77% of patients
HR=0.9; p=0.58

High Risk

23% of patients
HR=2.2; p=0.0072

- ✓ EMC92/SKY92 predictive for Bortezomib treatment outcome
- ✓ Large benefit for subtype

# MF Cluster Predictive for Bortezomib Treatment Outcome




Negative

93.6% of patients
HR=1.2; p=0.42

Positive

6.4% of patients
HR=12.9; p=0.002

- ✓ MF Cluster predictive for Bortezomib treatment outcome
- ✓ Large benefit for subtype

# Five GEP Markers predictive for Proteasome Inhibition Outcome

| High risk signature | HR | p |
|---|---|---|
| **EMC92/SKY92** | **2.21** | **0.007** |

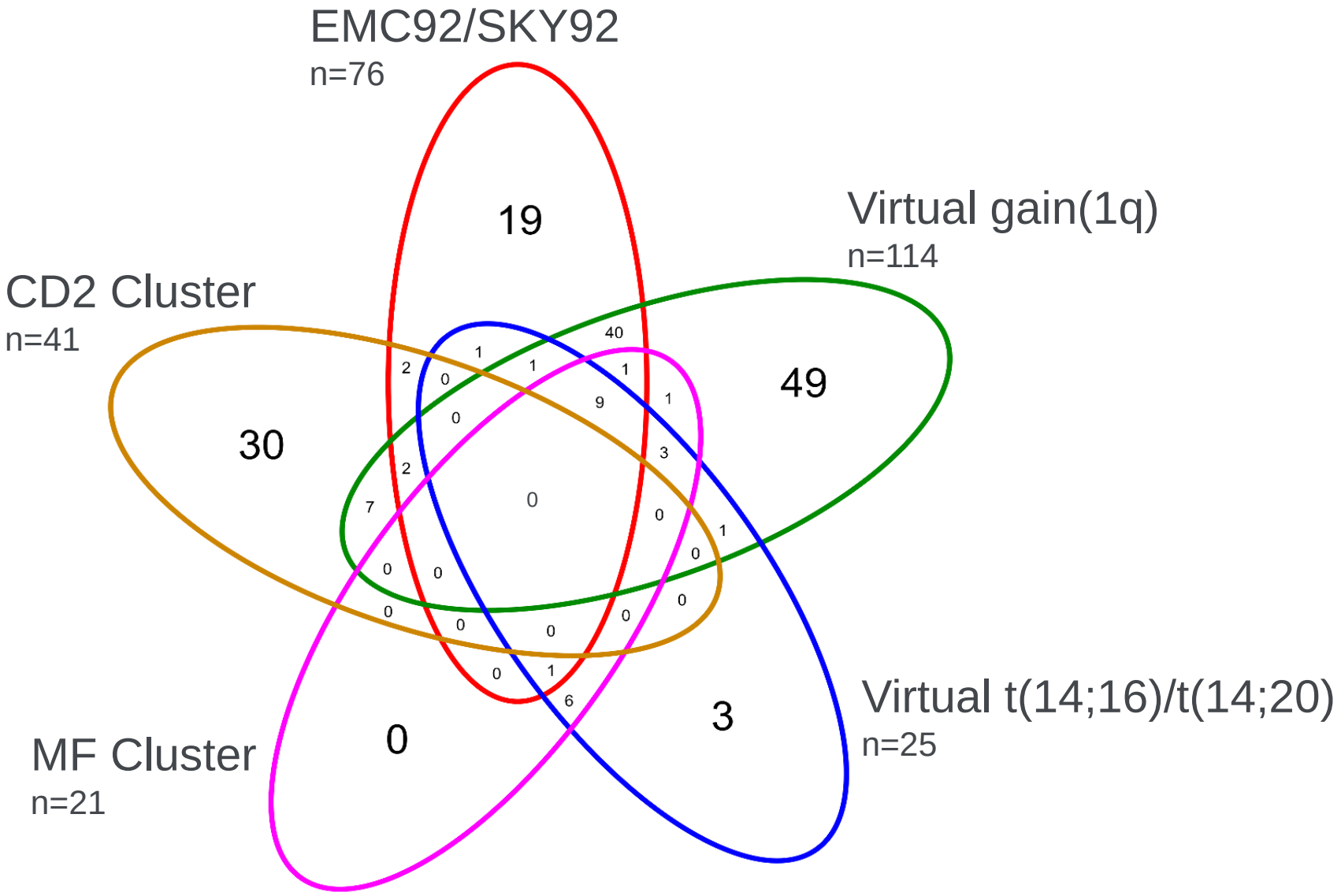
| Virtual Karyotyping | HR | p |
|---|---|---|
| Virtual t(4;14) | 1.83 | 0.146 |
| Virtual t(11;14) | 2.06 | 0.100 |
| **Virtual t(14;16)/t(14;20)** | **7.86** | **0.003** |
| Virtual del(13q) | 1.57 | 0.075 |
| **Virtual gain(1q)** | **2.49** | **0.002** |
| Virtual Hyperdiploid | 1.05 | 0.876 |
| Virtual del(17p) | 1.44 | 0.146 |

**Red: p<0.05**

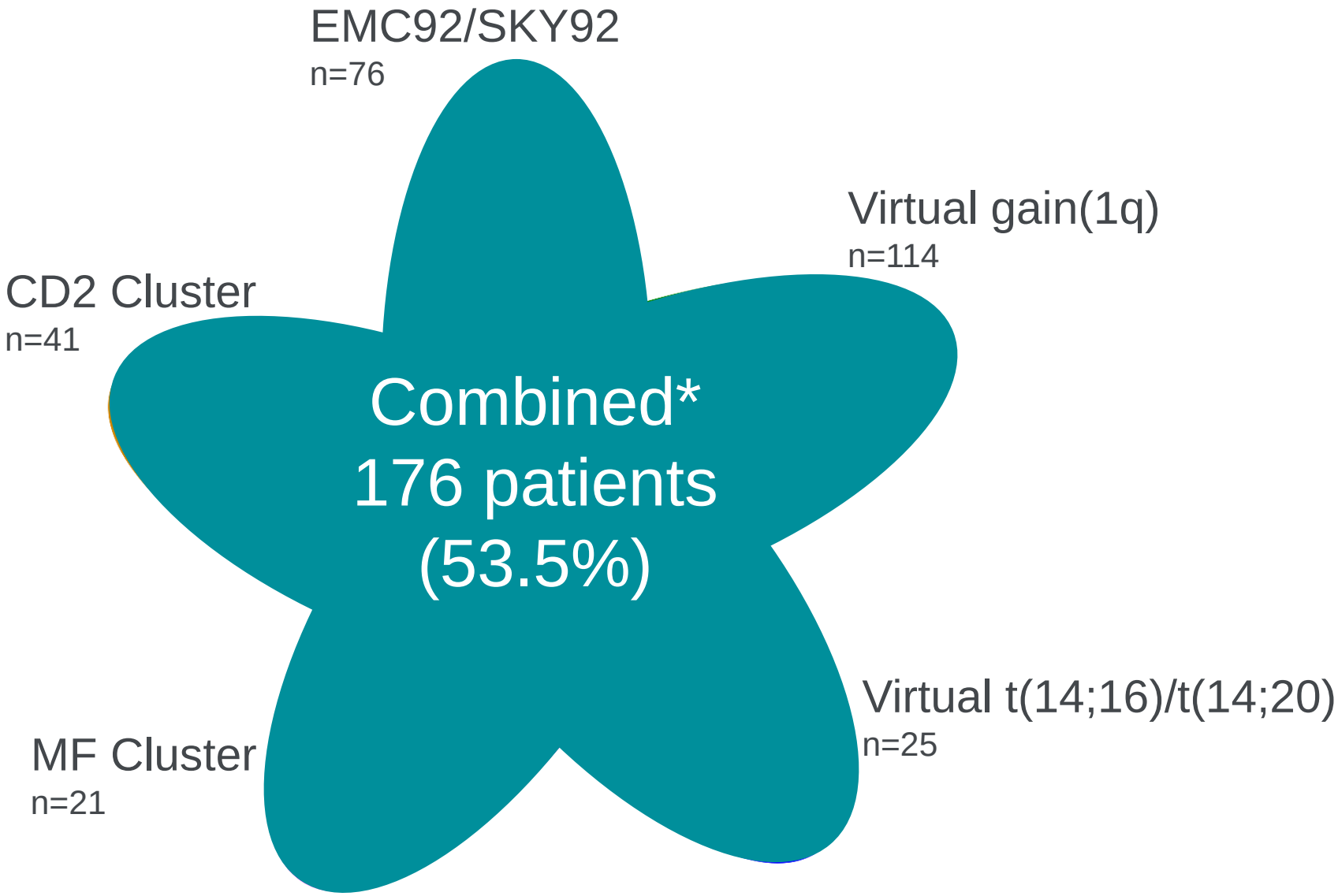
| Cluster Classifiers | HR | p |
|---|---|---|
| Cluster MS | 1.63 | 0.281 |
| **Cluster MF** | **12.88** | **0.002** |
| **Cluster CD2** | **4.42** | **0.015** |
| Cluster CD1 | 1.44 | 0.141 |
| Cluster CTA | 1.38 | 0.701 |
| Cluster NFKB | 2.31 | 0.121 |
| Cluster NP | 1.61 | 0.102 |
| Cluster HY | 0.84 | 0.673 |
| Cluster PRL3 | 1.07 | 0.818 |
| Cluster PR | 0.96 | 0.920 |
| Cluster LB | 3.31 | 0.301 |
| Cluster Myeloid | 0.72 | 0.523 |

- ✓ Five GEP markers predict significantly longer OS on PAD
- ✓ Preliminary data for other proteasome inhibitors

# The Five GEP Markers Identify Overlapping and Unique Patients

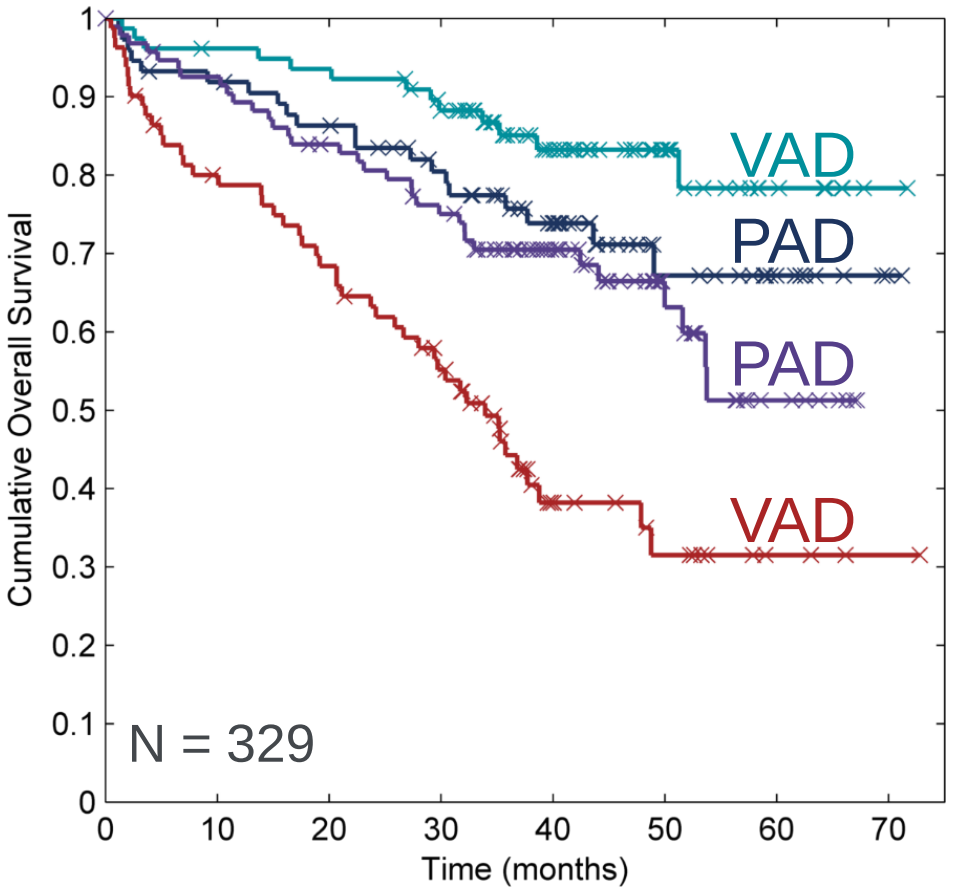


# The Five GEP Markers Identify Overlapping and Unique Patients




* positive for one or more of the five GEP markers

# Combined Predictive for Bortezomib Treatment Outcome




Rest

46.5% of patients
HR=0.6; p=0.11

Combined

53.5% of patients
HR=2.2; p=0.00006

# Conclusions

- ✓ Specific GEP markers can predict outcome to proteasome inhibitor treatment in MM
- ✓ No treatment benefit for all, but large benefit for subtypes

# Future Perspectives

- ✓ Validation planned using EMN-02 trial
- ✓ Clinical trials should incorporate and evaluate GEP markers for prediction of treatment effectiveness

# Acknowledgements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# Thank you