Use of plasma cell immunophenotype as prognostic markers in patients with systemic AL amyloidosis

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Background - 1

- Amyloidosis is a disorder of protein misfolding
- AL amyloidosis
  - Associated with underlying B cell clonal disroder, mainly plasma cell dyscrasias
  - >60% of patients seen at NAC
  - Median OS 2.2 years

Background - 2

- Prognosis driven by advanced organ dysfunction
- Measurement of cardiac biomarkers at presentation is vital
- ***Dispenzieri et al. 2004 – Mayo staging***
  - Troponin T <0.035 mcg/L
  - NT-proBNP <332 pg/mL

Stage	Incidence	Median survival (m)
I	33%	26.4
II	30%	10.5
III	37%	3.5

Background - 3

- Prognosis driven by advanced organ dysfunction
- Measurement of cardiac biomarkers at presentation is vital
- *Dispenzieri et al. 2004*
  - Troponin T <0.035 mcg/L
  - NT-proBNP <332 pg/mL
- ***Kumar et al. 2012 – Revised staging system***
  - FLC-diff 18 mg/dL
  - cTnT 0.025 ng/mL
  - NT-ProBNP 1,800 pg/mL

Stage	Incidence	Median survival (m)
1	25%	94.1
2	27%	40.3
3	25%	14
4	23%	5.8

Background - 4

- Prognosis driven by advanced organ dysfunction
- Measurement of cardiac biomarkers at presentation is vital

- *Dispenzieri et al. 2004*
  - Troponin T <0.035 mcg/L
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- *Kumar et al. 2012*
  - FLC-diff 18 mg/dL
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- ***Dispenzieri et al. 2013***
  - 'Patients with AL amyloidosis who have more than 10% BMPCs have a poor prognosis, similar to that of patients with AL-CRAB...'

Background - 5

- Contribution of underlying PC clone to prognosis unknown

- Paiva et al. 2011
  - Quantification of bone marrow plasma cells (BMPCs) by MFC immunophenotyping is a significant prognostic factor for overall survival

  - >5% normal PCs at diagnosis prolonged OS (2-year rates of 88% vs 37%, P .01)

Aim and Methods

- Aim
  - Understand the plasma cell phenotype in AL amyloidosis
  - Study the role of plasma cell phenotype on refining prognostic assessment in patients with AL amyloidosis

- Method
  - Prospective bone marrow study on newly diagnosed systemic AL amyloidosis patients
  - 8 colour multiparameter flow cytometry
  - Markers tested - CD138, CD38, CD56, CD117, CD28, CD20, CD27, CD19, CD81 and kappa and lambda light chains

Analysis

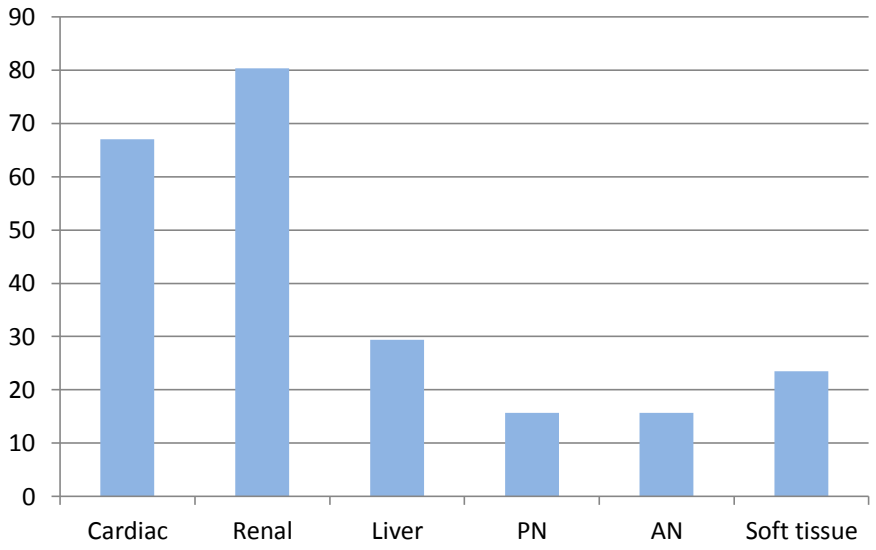
- Disease assessment
  - Organ involvement by consensus criteria (2010)
  - Organ involvement on SAP scintigraphy
- Outcome assessment
  - Overall survival
  - Haematological response to first line treatment
- In the context of PC phenotype

Results

- 51 consecutive patients
- Median follow up 8.5 months (0.7-24.8 months)
- Aberrant plasma cells:
  - CD38+ CD138+ CD19-

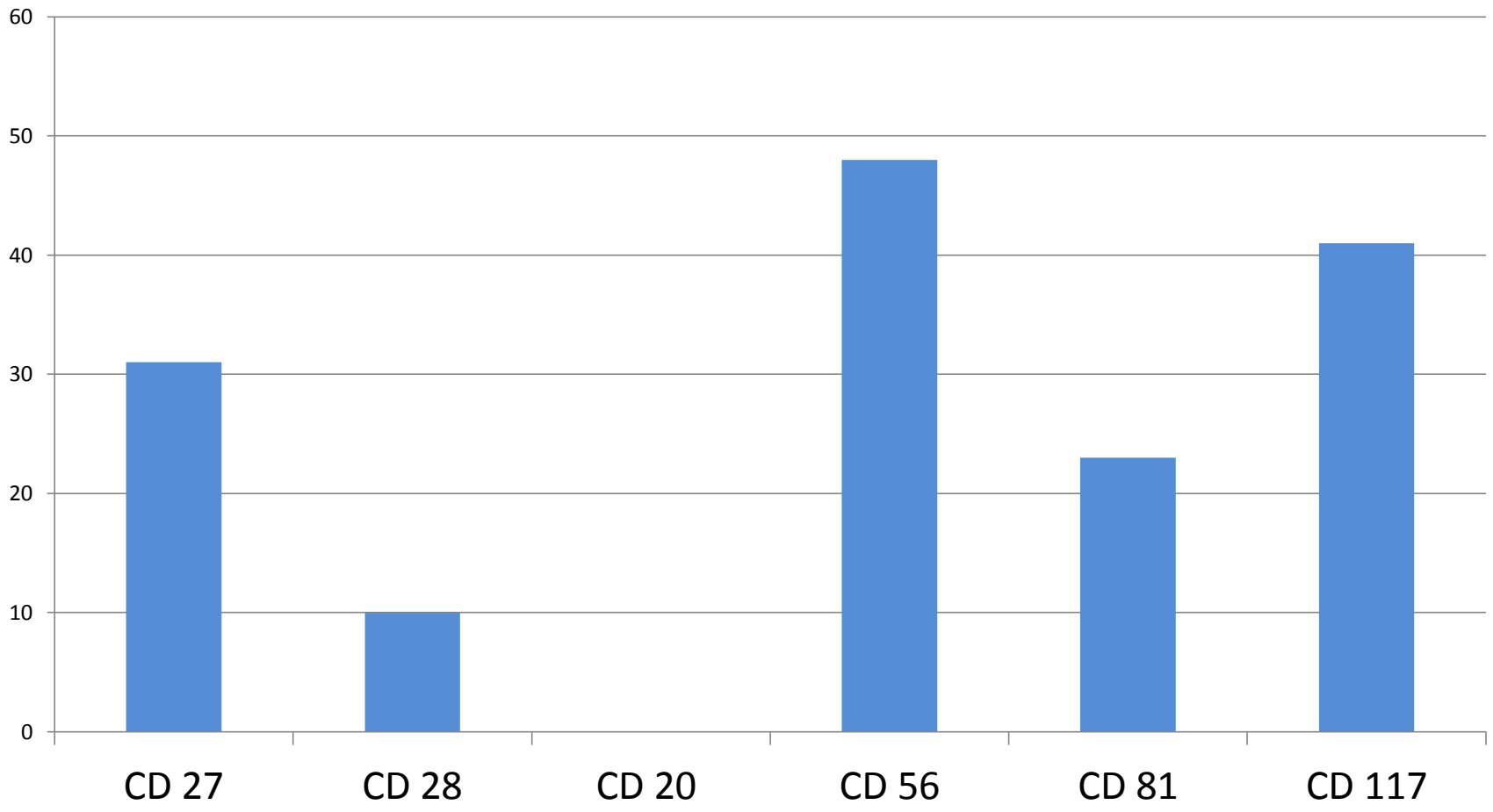
Patient characteristics

	Median (range)	No of patients (%)
Age (years)	63.9 (38.5-83.3)	
Sex (Male: Female ratio)	2.4:1	
Monoclonal type		
• IgG		15 (29)
• IgA		3 (6)
• IgM		1 (2)
• IgD		1 (2)
• Light chain		31 (61)
Baseline Kappa	609 (41-4040)	13 (25)
Baseline Lambda	199 (46-2527)	38 (75)



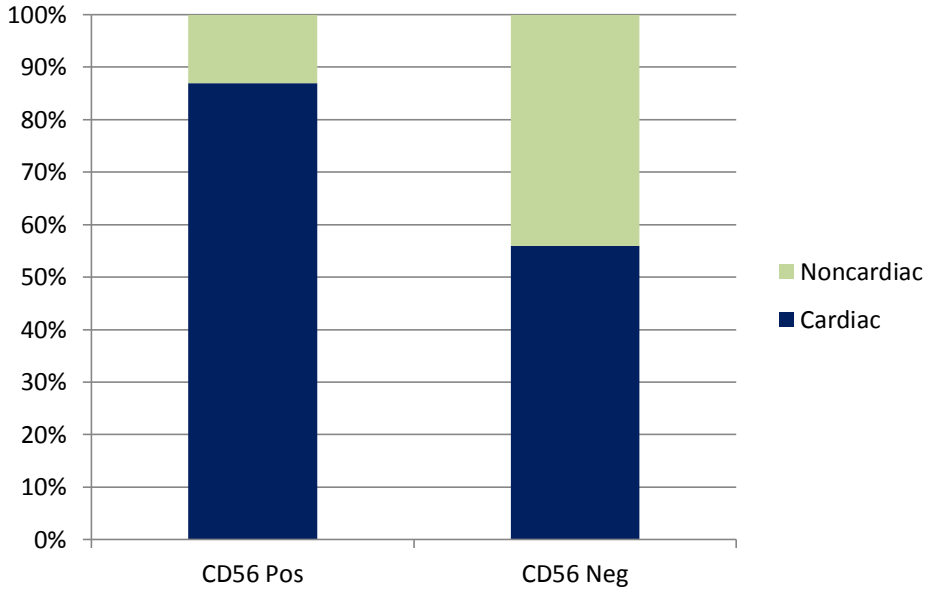
Mayo stage	No of patients (%)
1	9 (18)
2	17 (33)
3	25 (49)

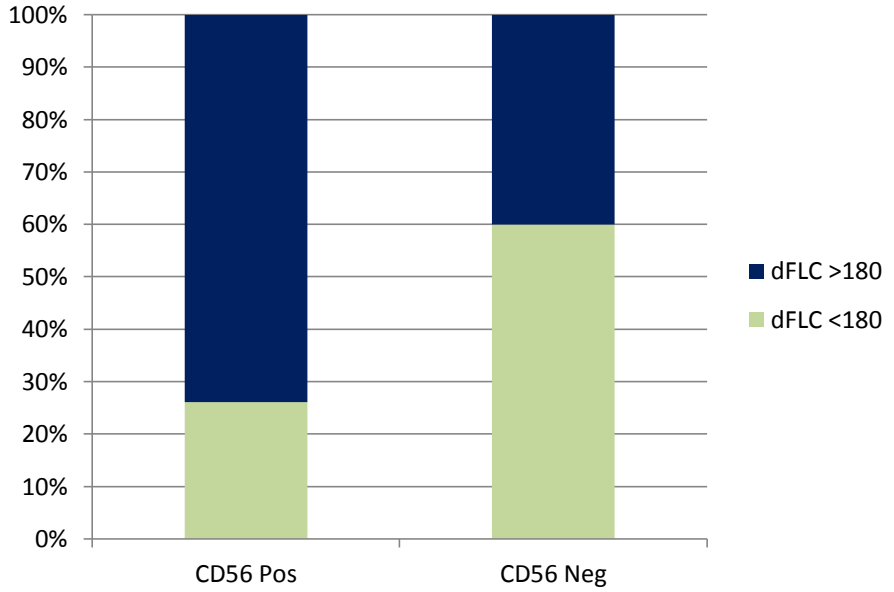
Phenotypes of aberrant PCs



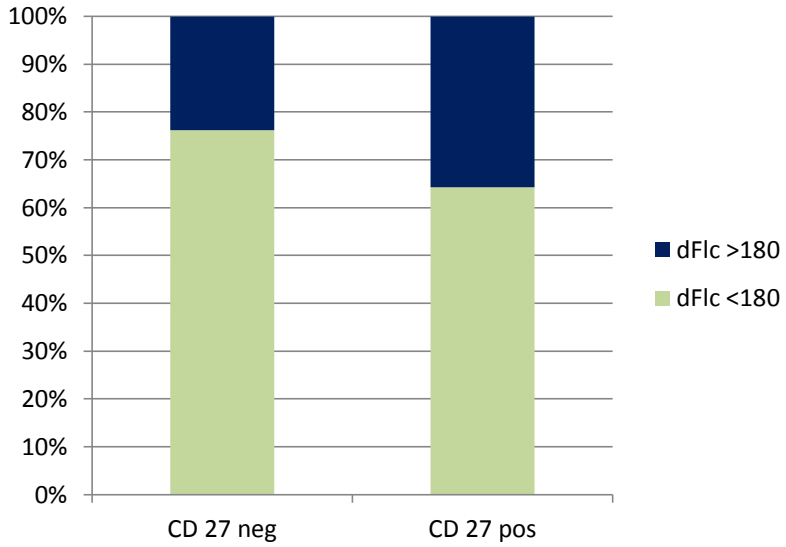
- Expression of CD56 appeared to correlate with both cardiac involvement and dFLC >180mg/L

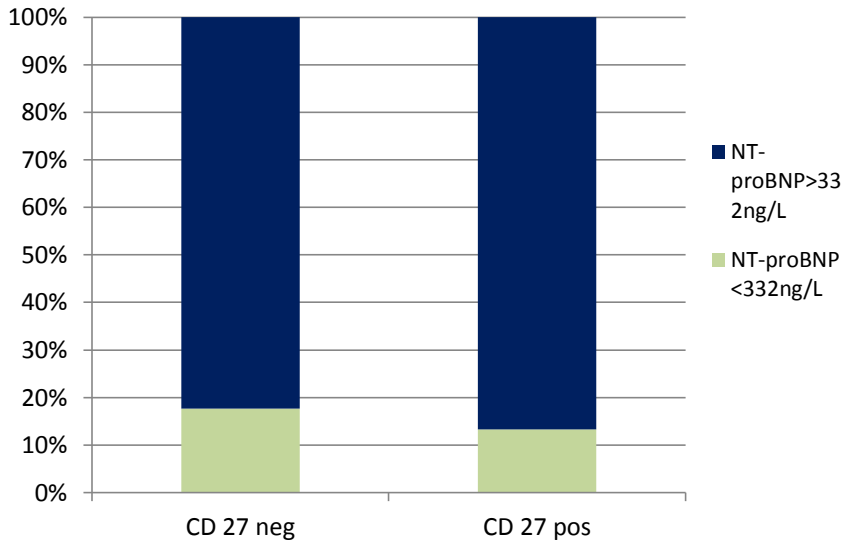
(spearman's correlation coefficient, 0.340, p=0.018 and 0.342, p=0.018 respectively)





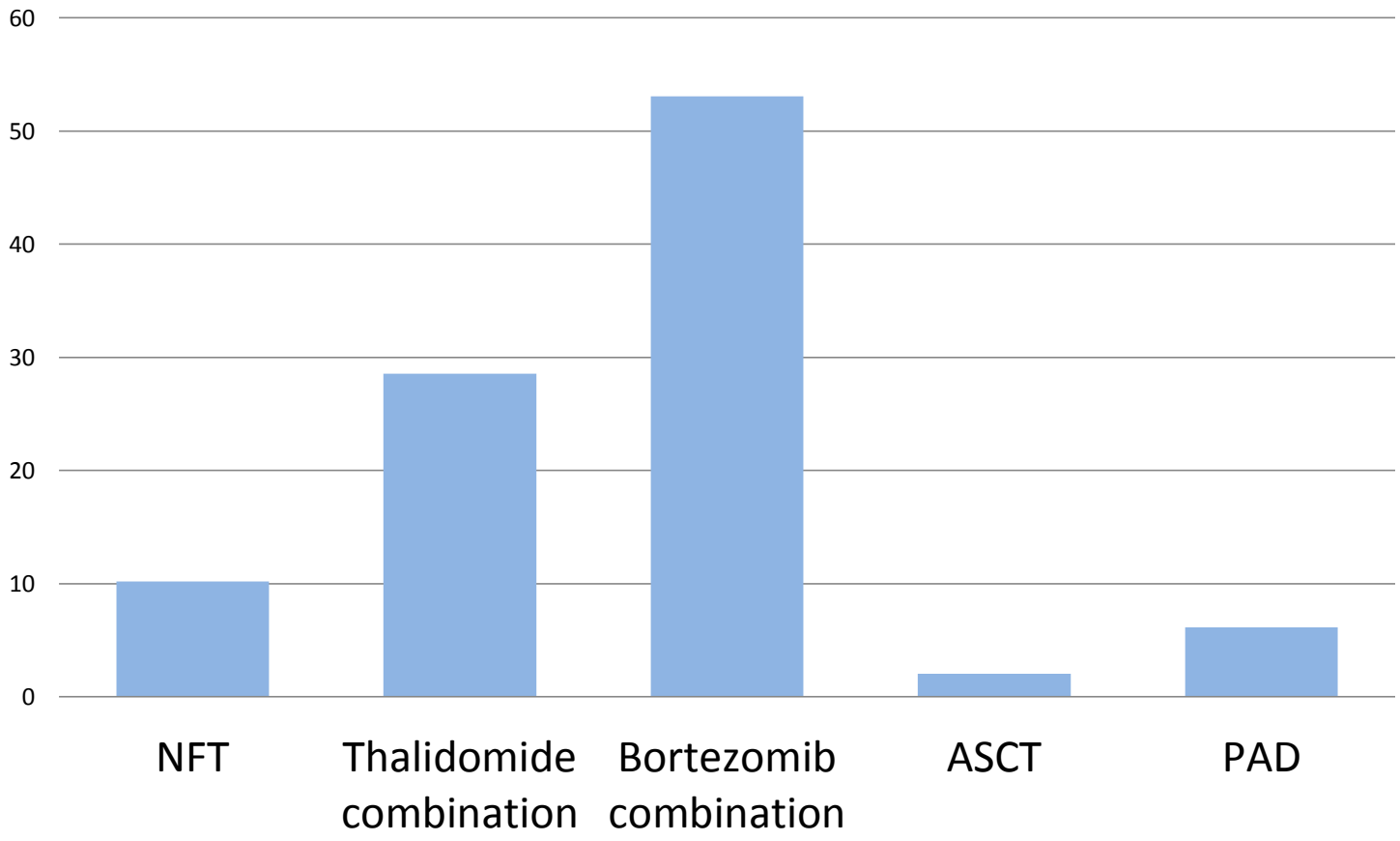
- There was no correlation between CD27 expression and NT-proBNP or dFLC





Spearman correlation: 0.128, p=0.381 and 0.054, p=0.714

Treatment and response



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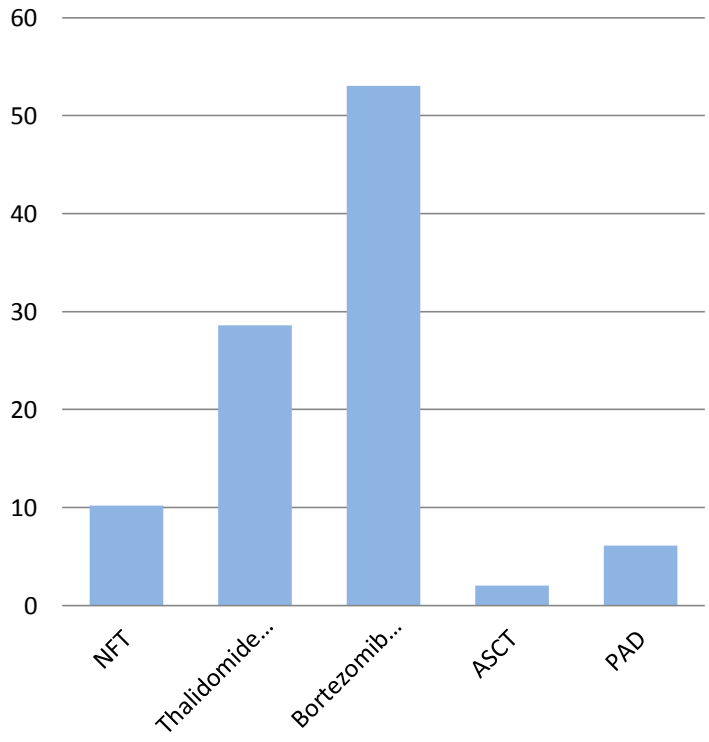

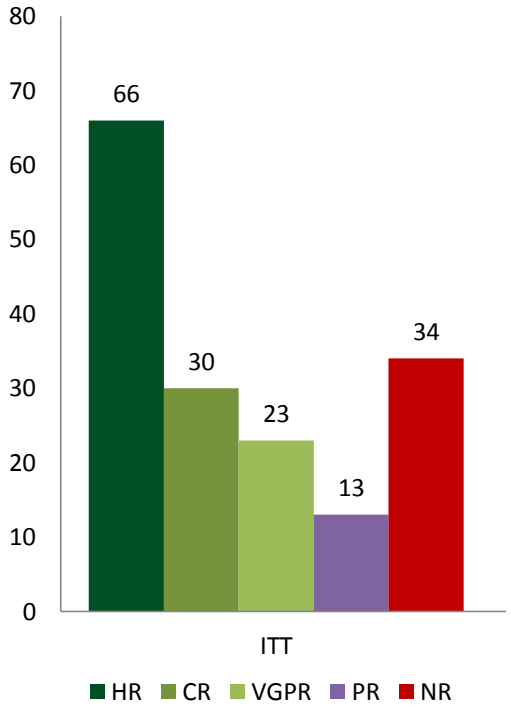

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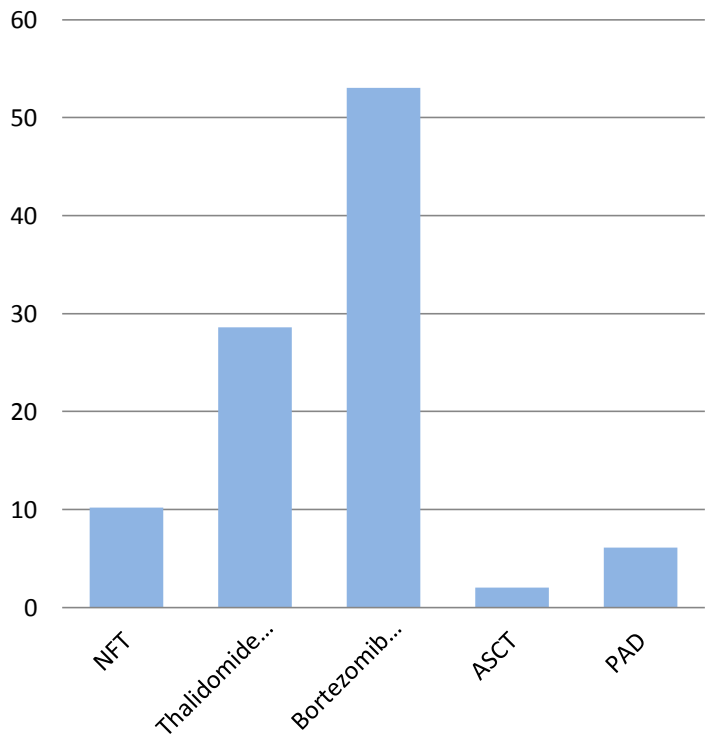
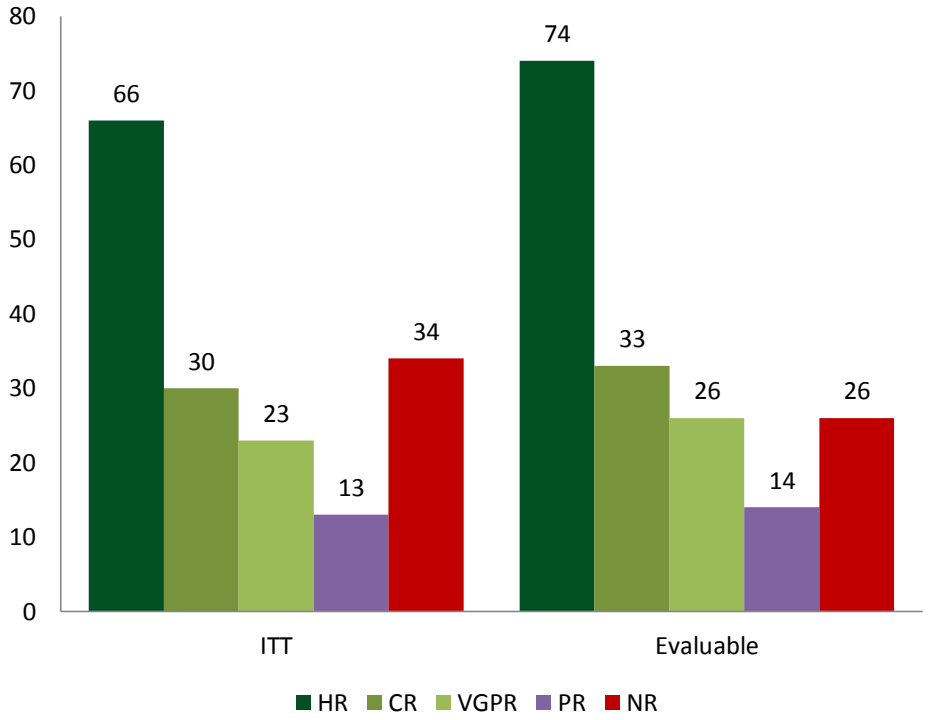
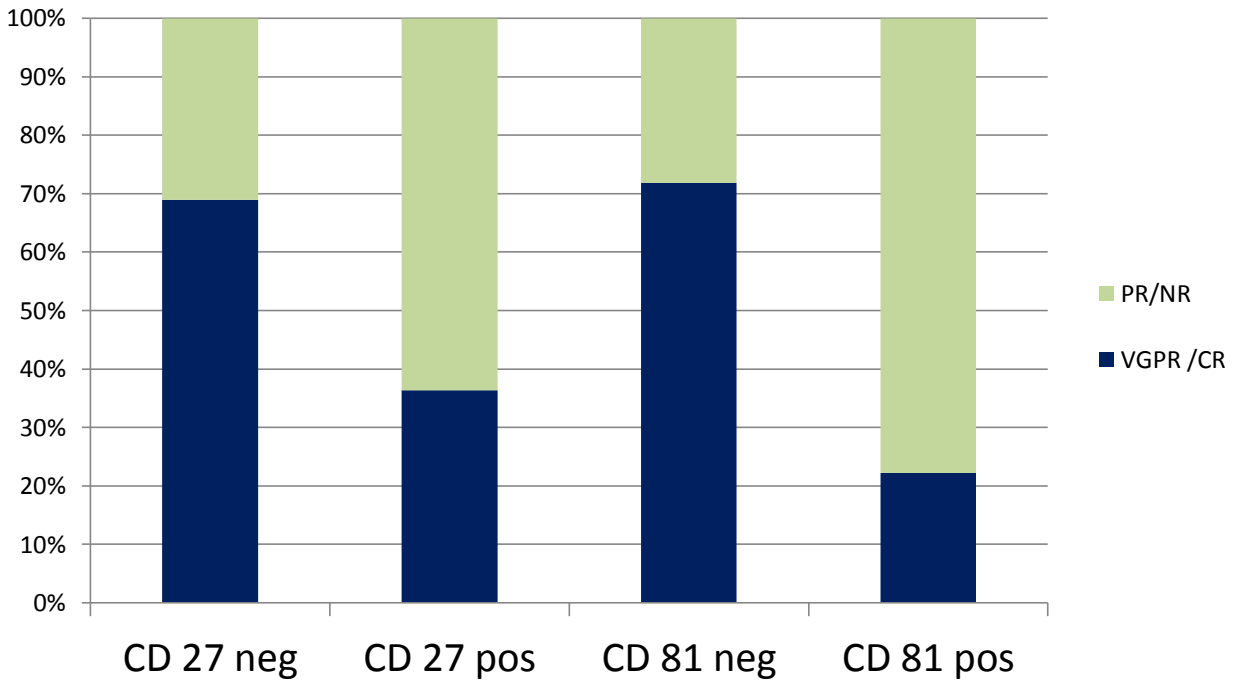




Response in the context of PC phenotype

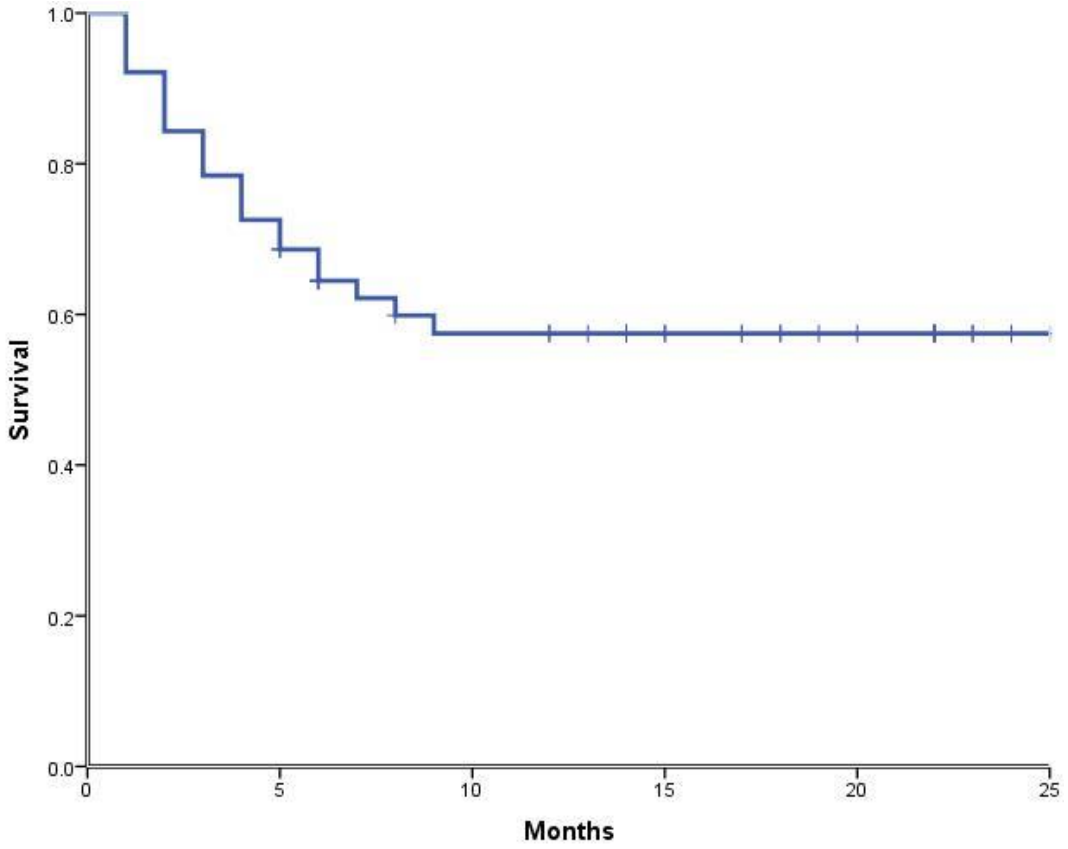
- The lack of CD27 or CD81 expression correlated with a higher rate of VGPR or better response

(spearman's correlation coefficient = 0.300 and 0.409, p=0.060 and p=0.010 respectively)



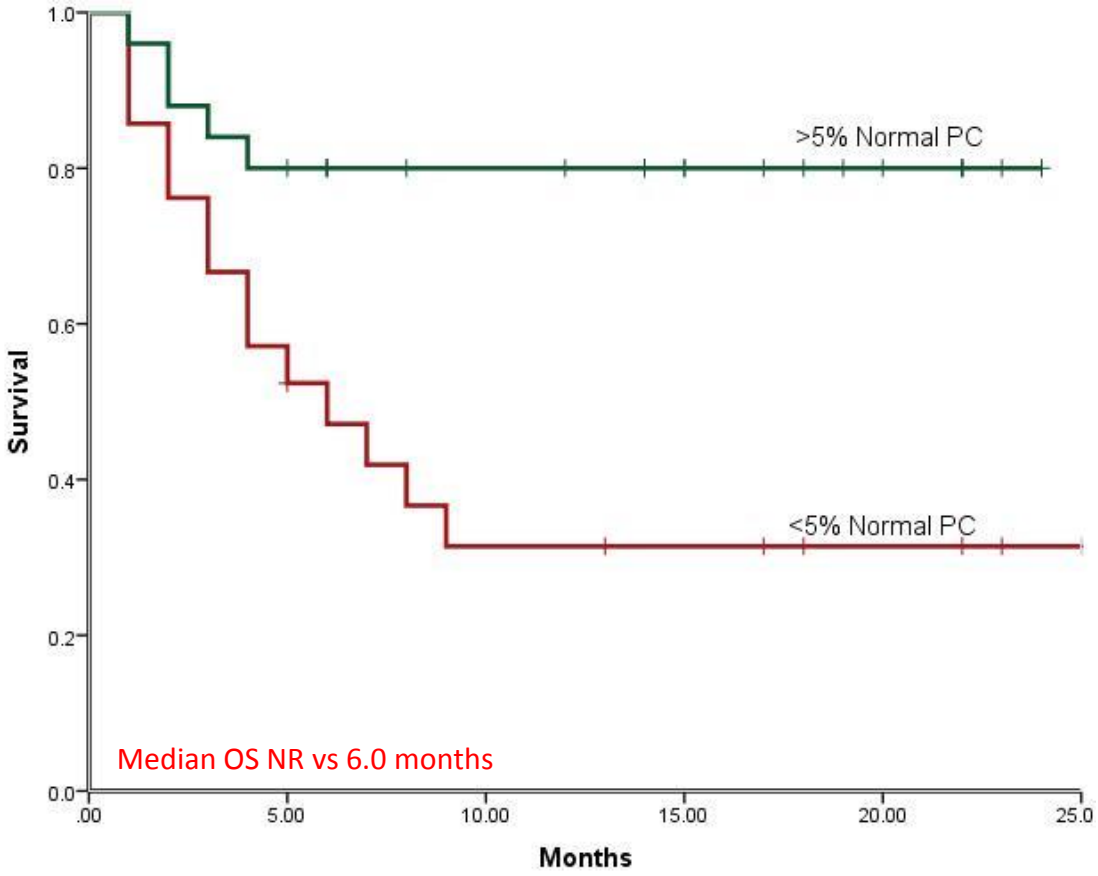
Survival analysis

- Median overall survival (OS) was not reached (NR)



Significance of normal PCs

- Better survival in the presence of >5% of normal phenotype (CD38+CD138+CD19+) plasma cells
- The 2 year OS in patients with >5% normal plasma cells was 74% vs 45% in those with <5% normal plasma cells



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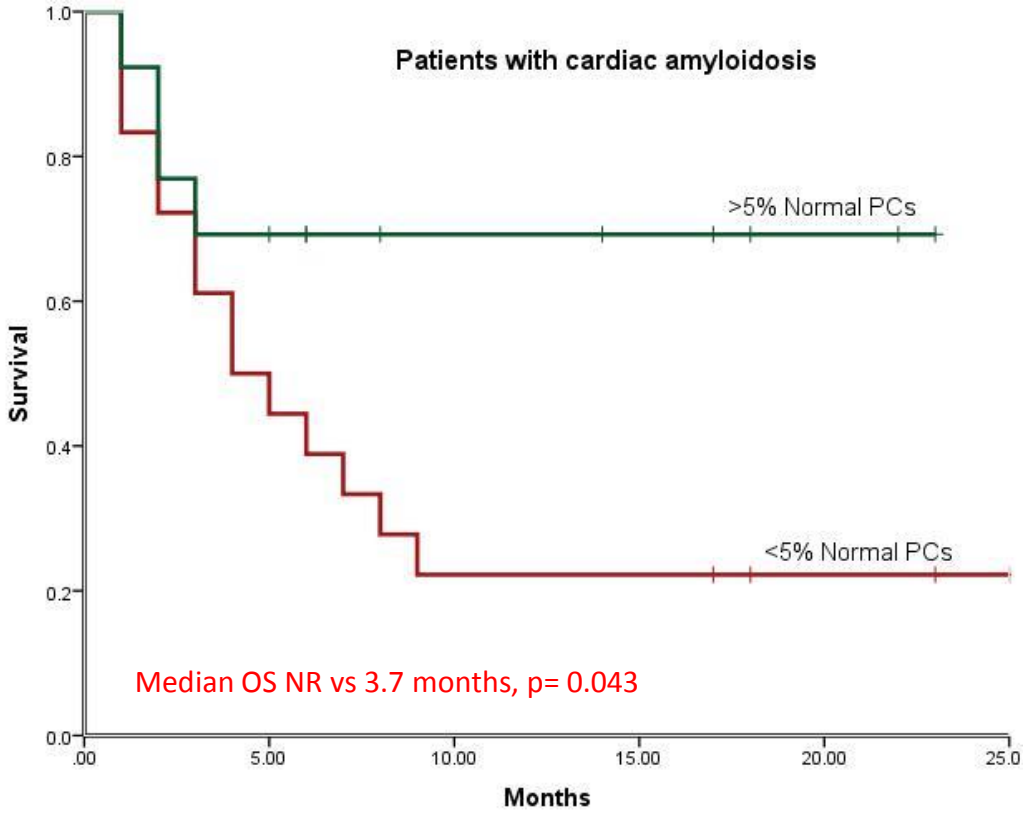
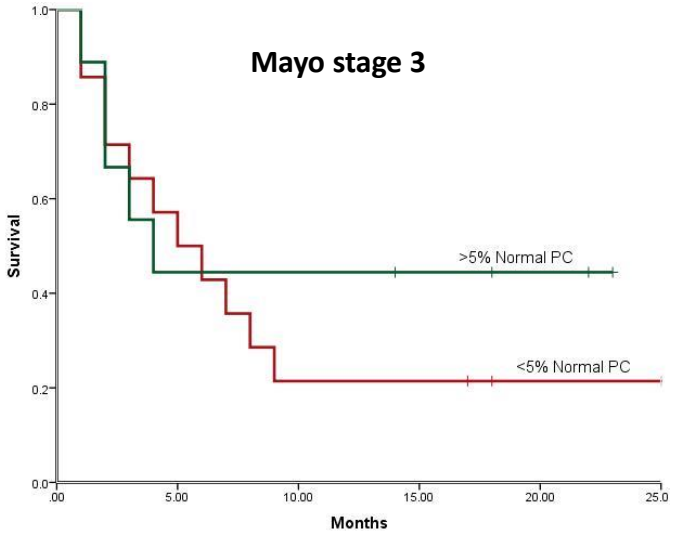
- Better survival in the presence of >5% of normal phenotype (CD38+CD138+CD19+) plasma cells
- The 2 year OS in patients with >5% normal plasma cells was 74% vs 45% in those with <5% normal plasma cells
- Remains significant within high risk group

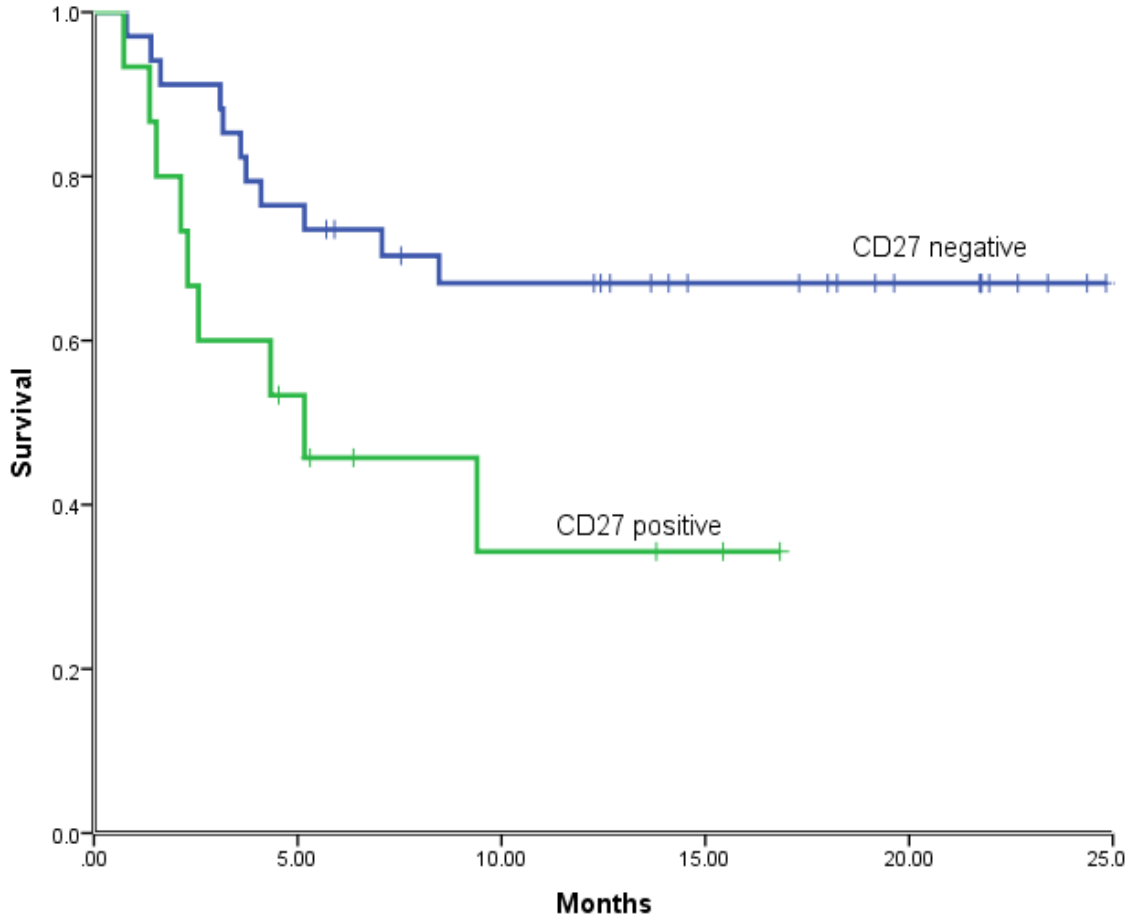


Median OS NR vs 3.7 months, p= 0.043



Survival in the context of PC phenotype

- Expression of CD27 had a significantly worse OS
  (5.0 months vs NR, p=0.037)



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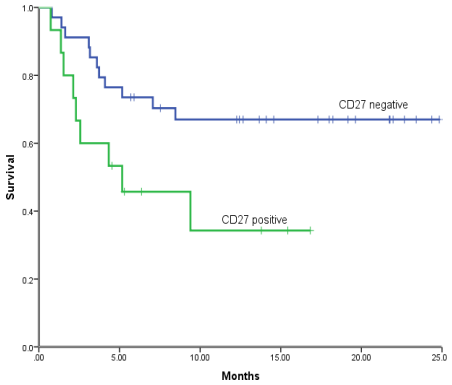
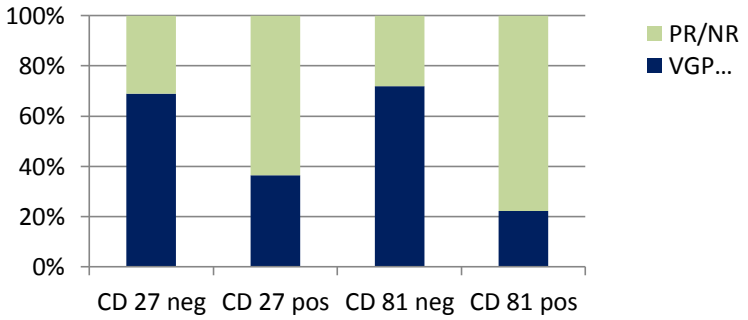
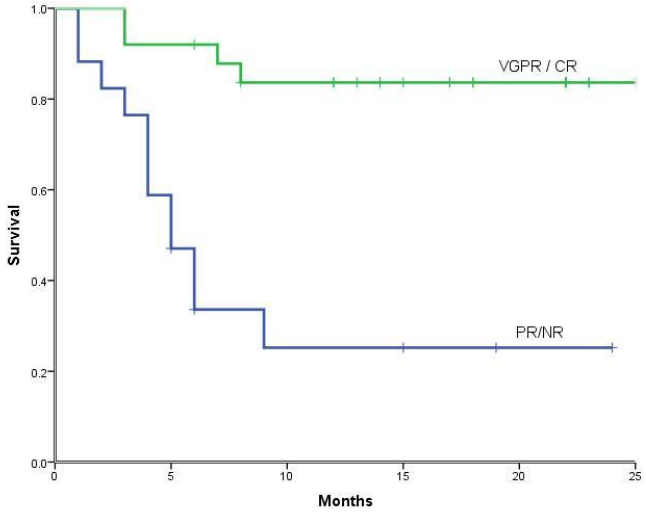
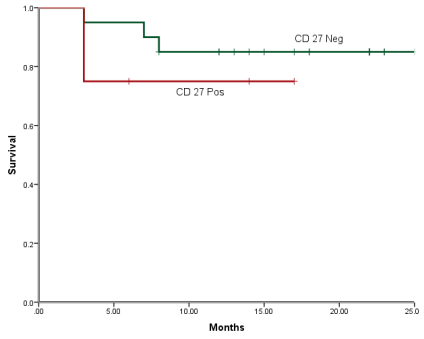


? Reflecting Haematological response

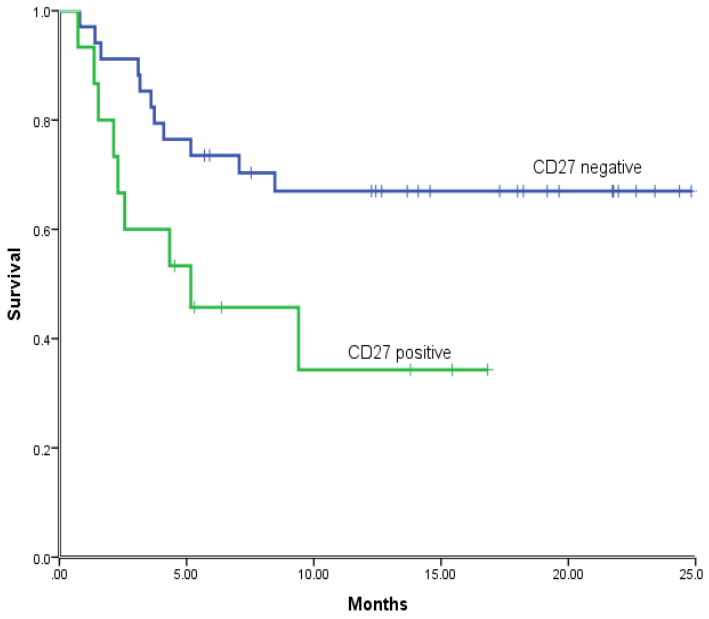






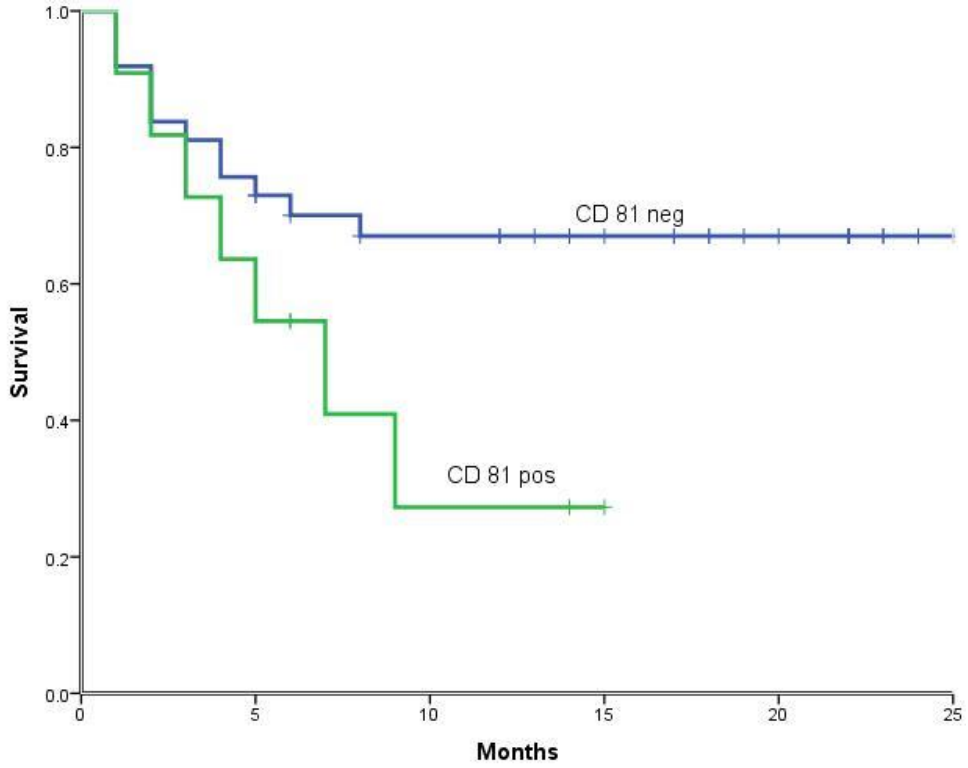
Survival in the context of PC phenotype - 2

- Expression of CD27 had a significantly worse OS
  (5.0 months vs NR, p=0.037)



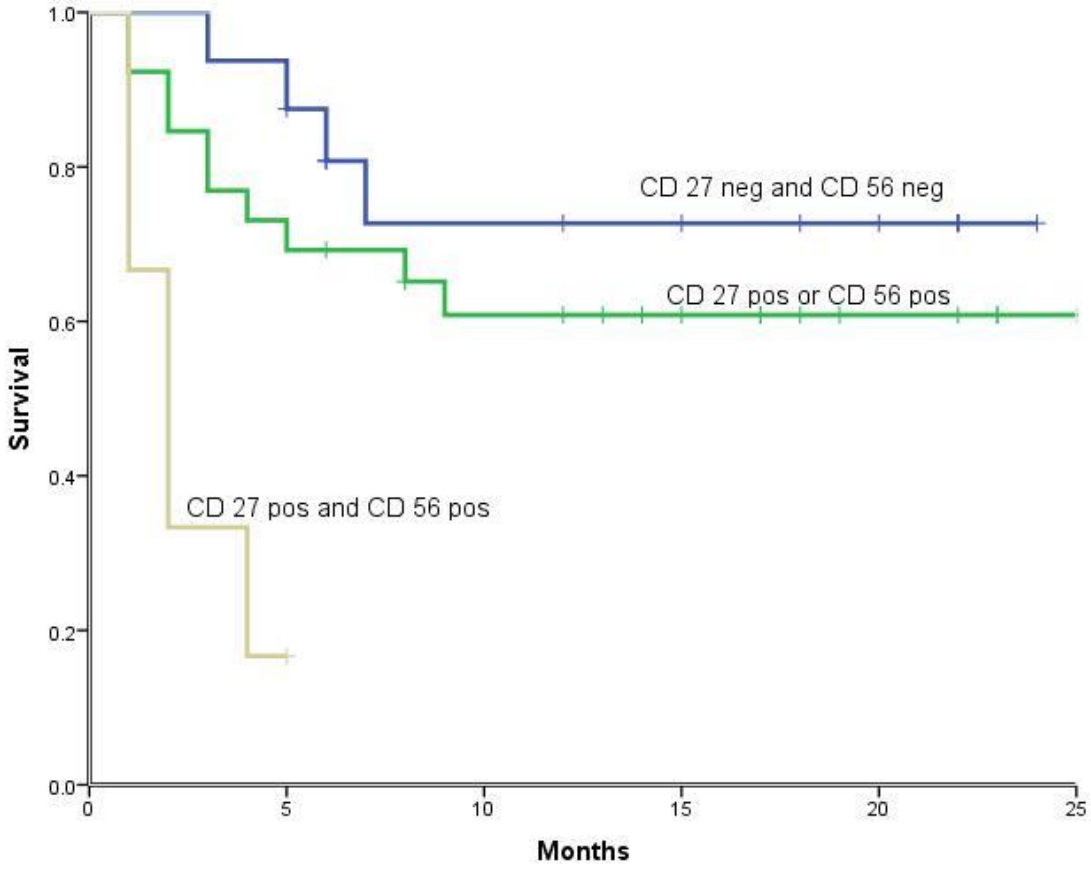
Expression of CD81 had a worse OS

7.0 months vs NR, p= 0.069



Survival in the context of PC phenotype - 3

- Those expressing CD27+CD56+ had an OS of 2.0 months compared to OS NR in the CD27+CD56- group (p=0.001). OS was NR in either CD27-CD56- or CD27-CD56+ patients



Summary

- >5% of normal phenotype PCs correlated with superior survival
- CD 56 expression appears to correlate with cardiac involvement and high dFLC at presentation
- CD27 and CD81 expression correlated with poor response to treatment
- Better survival rates seen with CD27 and CD81 negative PCs - ?reflecting response to treatment
- Co-expression of CD27 and CD56 resulted in worse outcome

Limitations

- Small cohort of patients
  - ?selection bias - M>F, 50% Mayo stage 3
- Variation in method of analysis
- Other markers involved but not tested?
- Heterogeneity of AL amylodosis

Conclusion

- The presence of CD56+CD27+ appears to define a particularly poor prognostic cohort of patients
- Plasma cell immunophenotype may help to refine the current staging of AL amyloidosis and response to treatment
- Further validation in larger studies is vital

Thank you

Acknowledgements

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