National Cancer Institute
Center for Cancer Research

Serum Heavy-Light Chains (HLC) and Free-Light Chains (FLC) As Predictors For Early CR In Newly Diagnosed Myeloma Patients Treated With Carfilzomib, Lenalidomide, and Dexamethasone

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Background

- Good clinical response to anti-myeloma therapy is associated with improved PFS and OS

- Inferior clinical response is a key factor to revise treatment strategy in myeloma patients

Background (contd.)

- In other malignancies “on-treatment early indicators” are being explored in clinical trials (such as HL, ALL, CML)

- Currently, no established markers to predict response in relation to anti-myeloma therapy

Study objective

Evaluate if early normalization of serum heavy-light chains (HLC) and free light chains (FLC) is predictive of rapid and deep response to anti-myeloma therapy

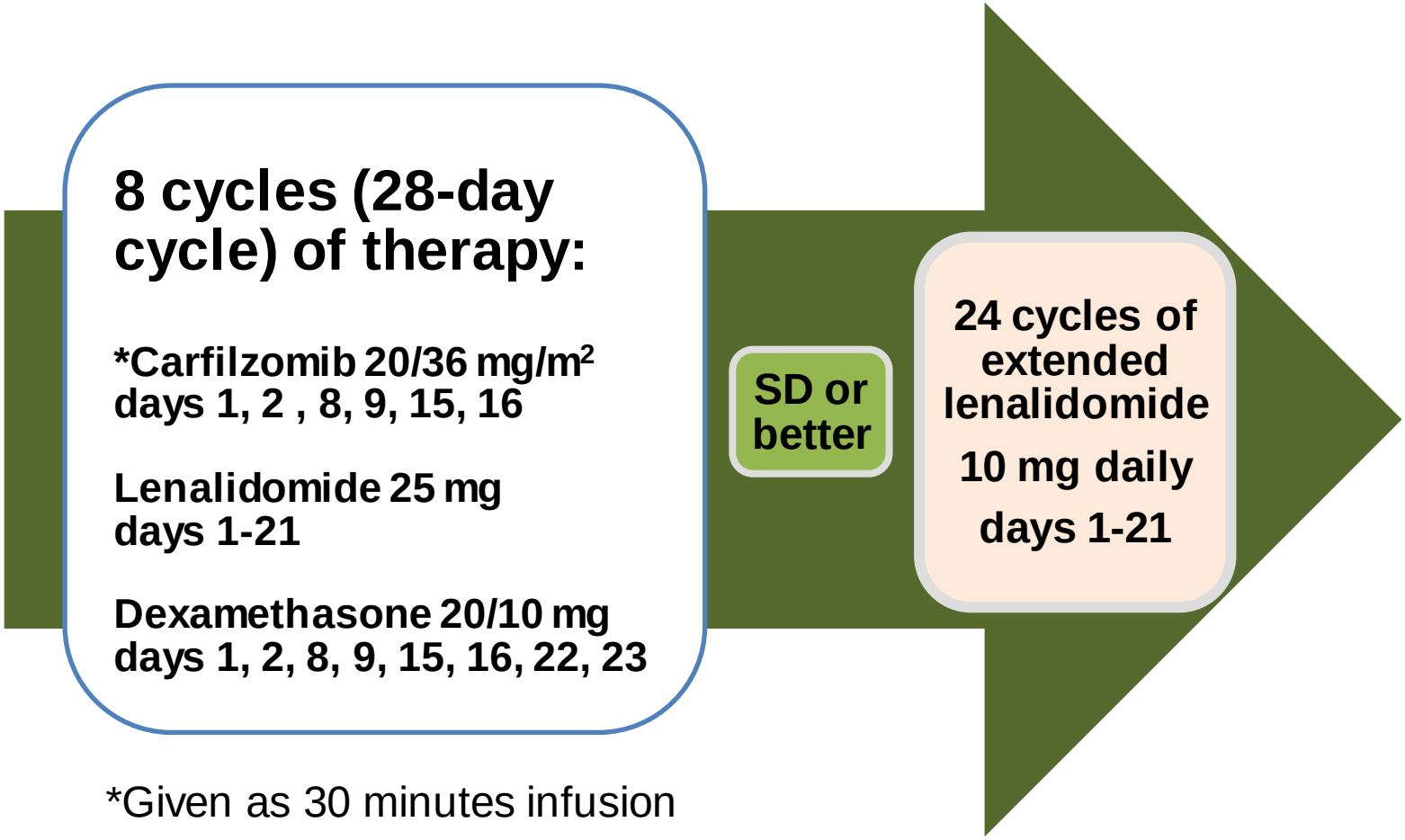
Patients

50 newly diagnosed patients enrolled on two ongoing NCI clinical trials using carfilzomib, lenalidomide, and dexamethasone:

- 38 multiple myeloma[1]
- 12 high-risk smoldering myeloma[2]

[1]Korde et al. ASH Abstract # 538, Monday, Dec 9, 2013
[2]Landgren et al. ASH Abstract # 1939, Saturday, Dec 7, 2013

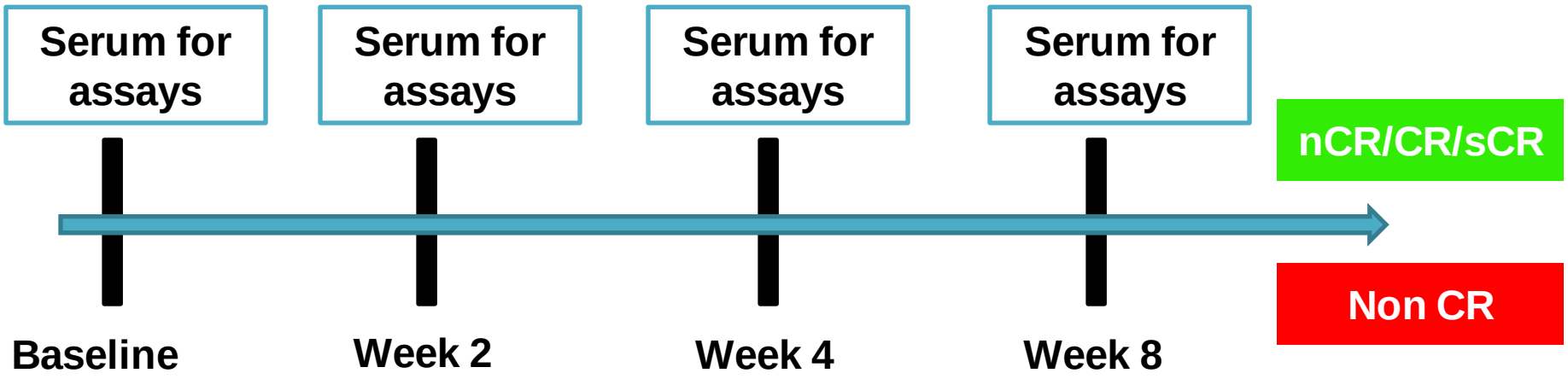
Dosing schedule[1,2]



*Given as 30 minutes infusion

[1]Korde et al. ASH Abstract # 538, Monday, Dec 9, 2013
[2]Landgren et al. ASH Abstract # 1939, Saturday, Dec 7, 2013

Study design

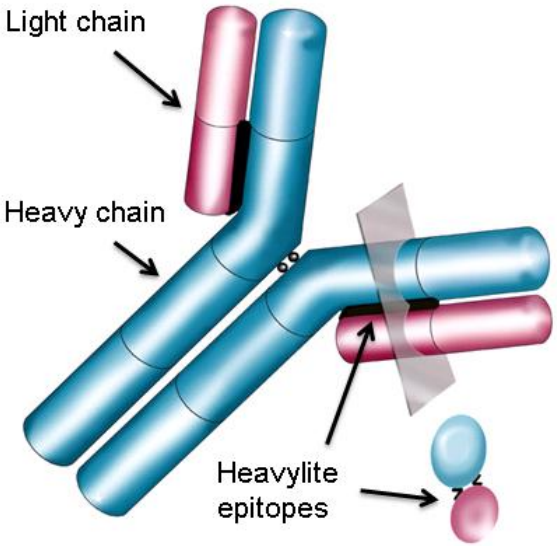


Clinical responses evaluated by standard criteria

Classified as: early (cycles 1-4) vs. late (cycle 5+)

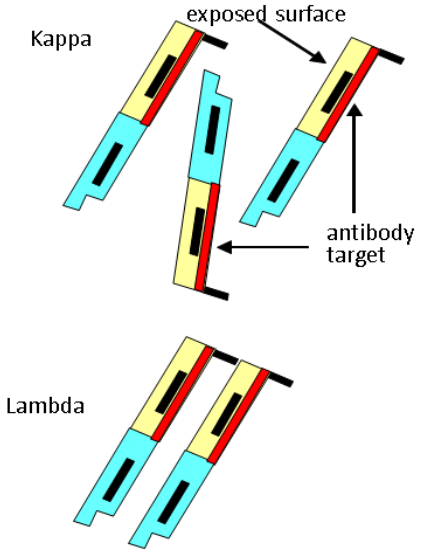
Immunoassays

Serum HLC assay (Hevylite®)



- Involved minus uninvolved pair = HLC-difference
- IgGκ/IgGλ & IgAκ/IgAλ = HLC-ratio

Serum FLC assay (Freelite®)



- Involved minus uninvolved = FLC-difference
- κ/λ = FLC-ratio

Patients' characteristics at baseline (N=50)

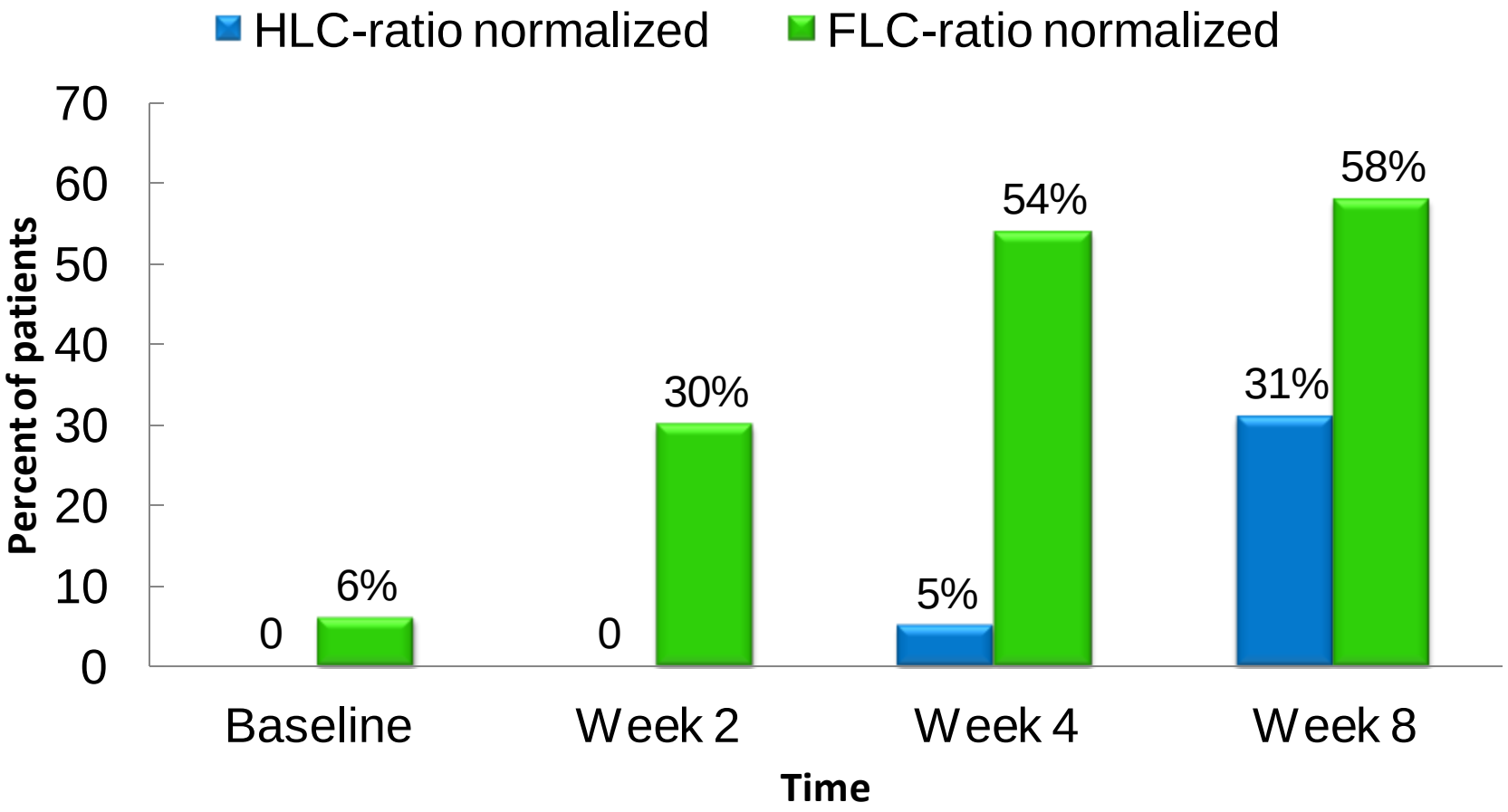
Characteristic	Distribution, n (%)
Systemic immunoparesis	46 (92)
Myeloma isotype	
IgGκ	28 (56)
IgGλ	9 (18)
IgAκ	5 (10)
Ig Aλ	2 (4)
Light chain	6 (12)
Abnormal HLC-ratio	43* (100)
Abnormal FLC-ratio	47 (94)

* HLC performed in 43 patients

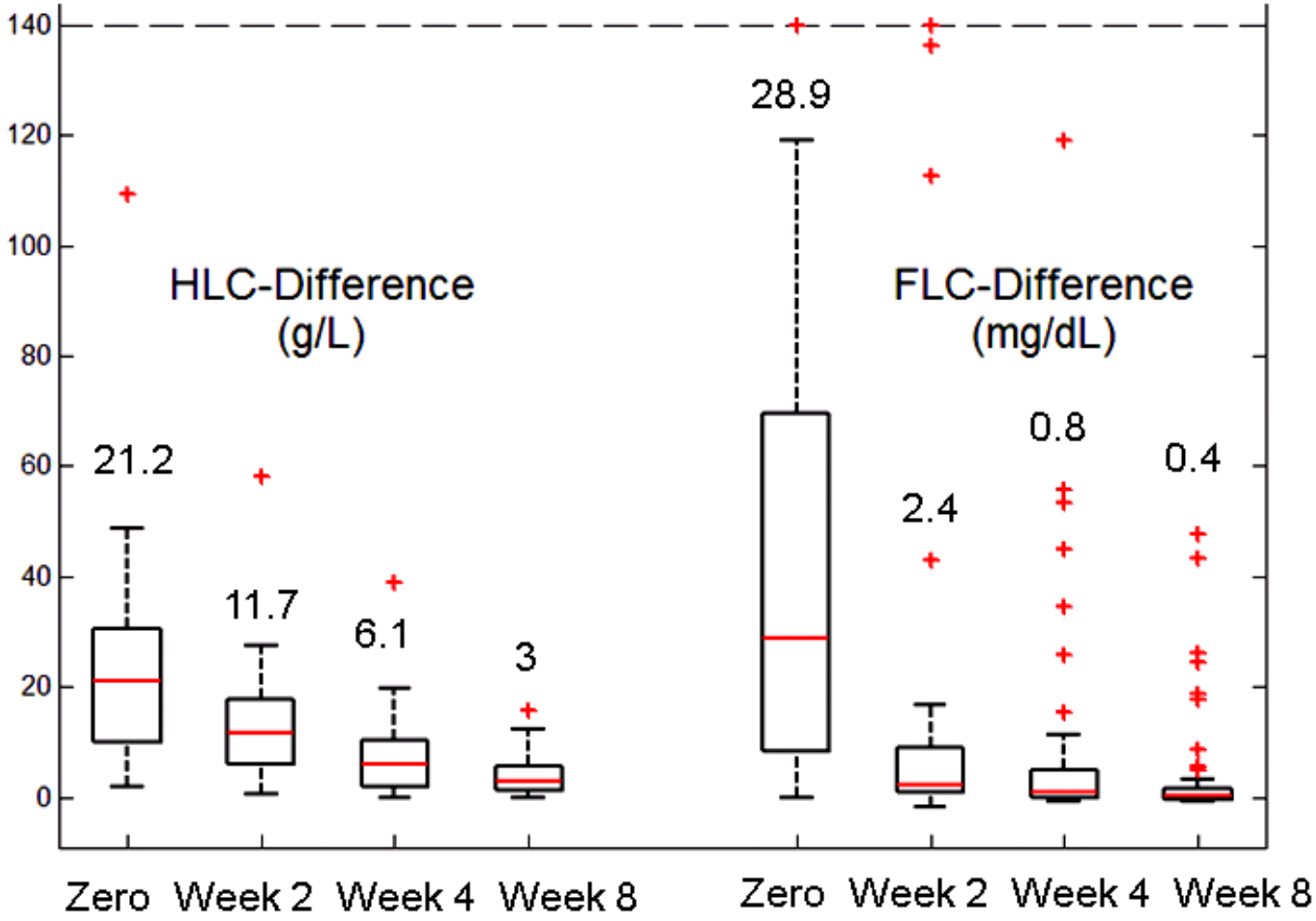
Results: Immunoassays at baseline

Marker	Median (range)	Reference
HLC-difference, g/L	21.29 (1.85-109)	
HLC-ratio	35.44 (0.00-1547)	1.12-3.21
FLC-difference, mg/dL	28.94 (–0.06-1620)	
FLC-ratio	40.43 (0.01-12462)	0.26-1.65
M spike, g/dL	2.5 (0-7.7)	

Normalization of HLC- and FLC-ratios in relation to therapy



Decreased difference of involved minus uninvolved HLC and FLC in relation to therapy



Patients' response to therapy[1,2]

- 39/50 obtained nCR/CR/sCR:
  - 77% sCR, 5% CR and 18% nCR
- Time to complete response (median 5 cycles):
  - 1-4 cycles: 12 patients
  - 5-8 cycles: 19 patients
  - 9-17 cycles: 8 patients
- 37/39 (95%) patients were MRD negative by multicolor flow cytometry of the bone marrow

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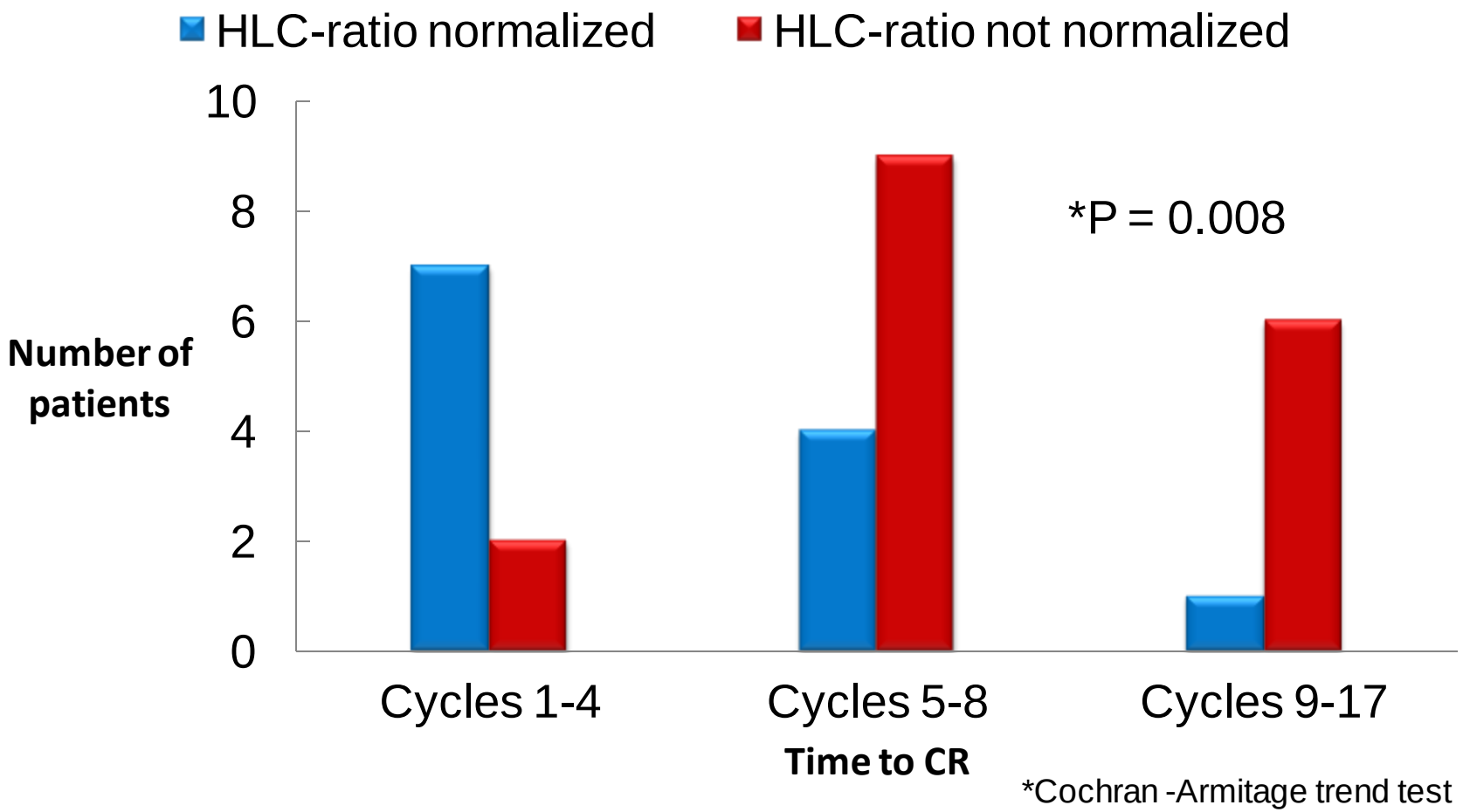
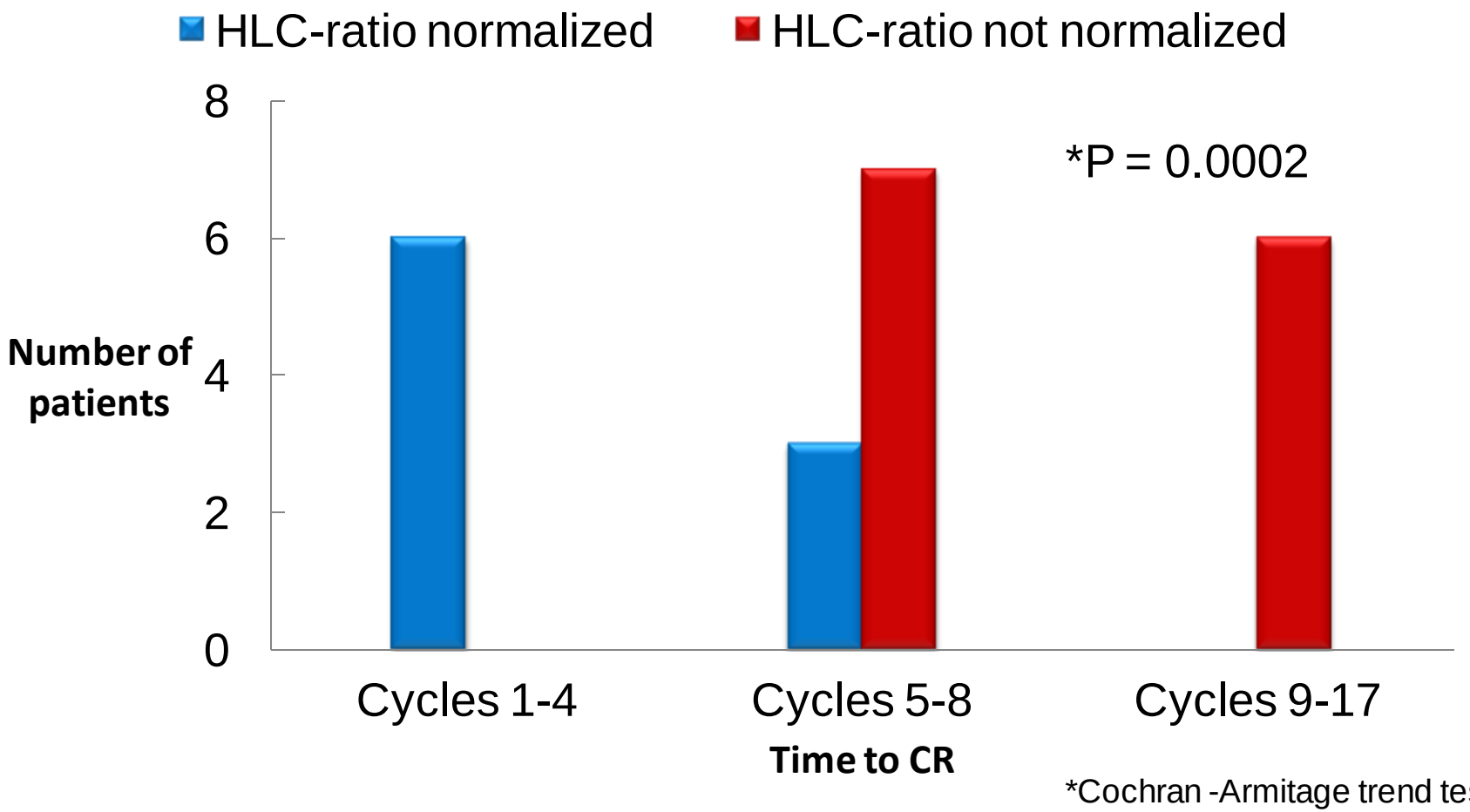
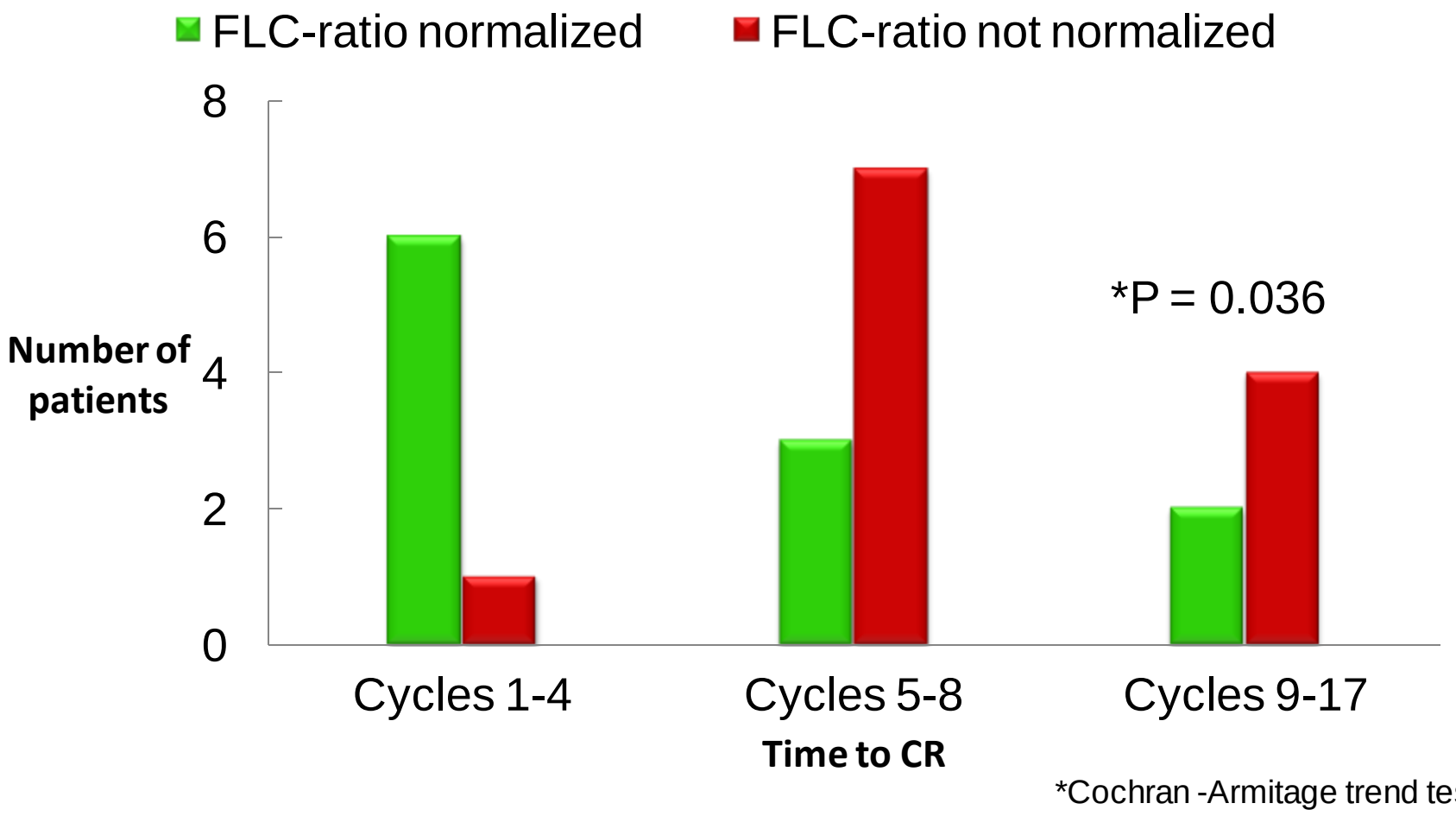
Normalized HLC-ratio at week 8 and sCR/CR/nCR



Normalized HLC-ratio at week 8 and sCR



Normalized FLC-ratio at week 2 and sCR



*Cochran -Armitage trend test

Predictors of early (cycle 1-4) vs. late (cycle 5+) complete response*

Variable	Univariate (p-value)	Multivariable (p-value)
HLC-difference at week 8	0.0002	**0.0089
HLC-difference at week 4	0.013	N.S.
Normalized HLC-ratio at week 8	0.014	N.S.
Normalized FLC-ratio at week 2	0.021	N.S.
M spike at baseline	0.0051	N.S.

*nCR/CR/sCR

**HLC-difference (involved minus uninvolved) <1.8 g/L vs. ≥ 1.8 g/L

Summary and conclusions

- Early normalization of serum heavy-light chains is an independent “on-treatment early indicator” of rapid and deep response to anti-myeloma therapy

- Future larger clinical trials are needed to validate our findings of heavy-light chains in myeloma patients

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