

T cell receptor diversity evaluation to predict patient response to ipilimumab in metastatic melanoma

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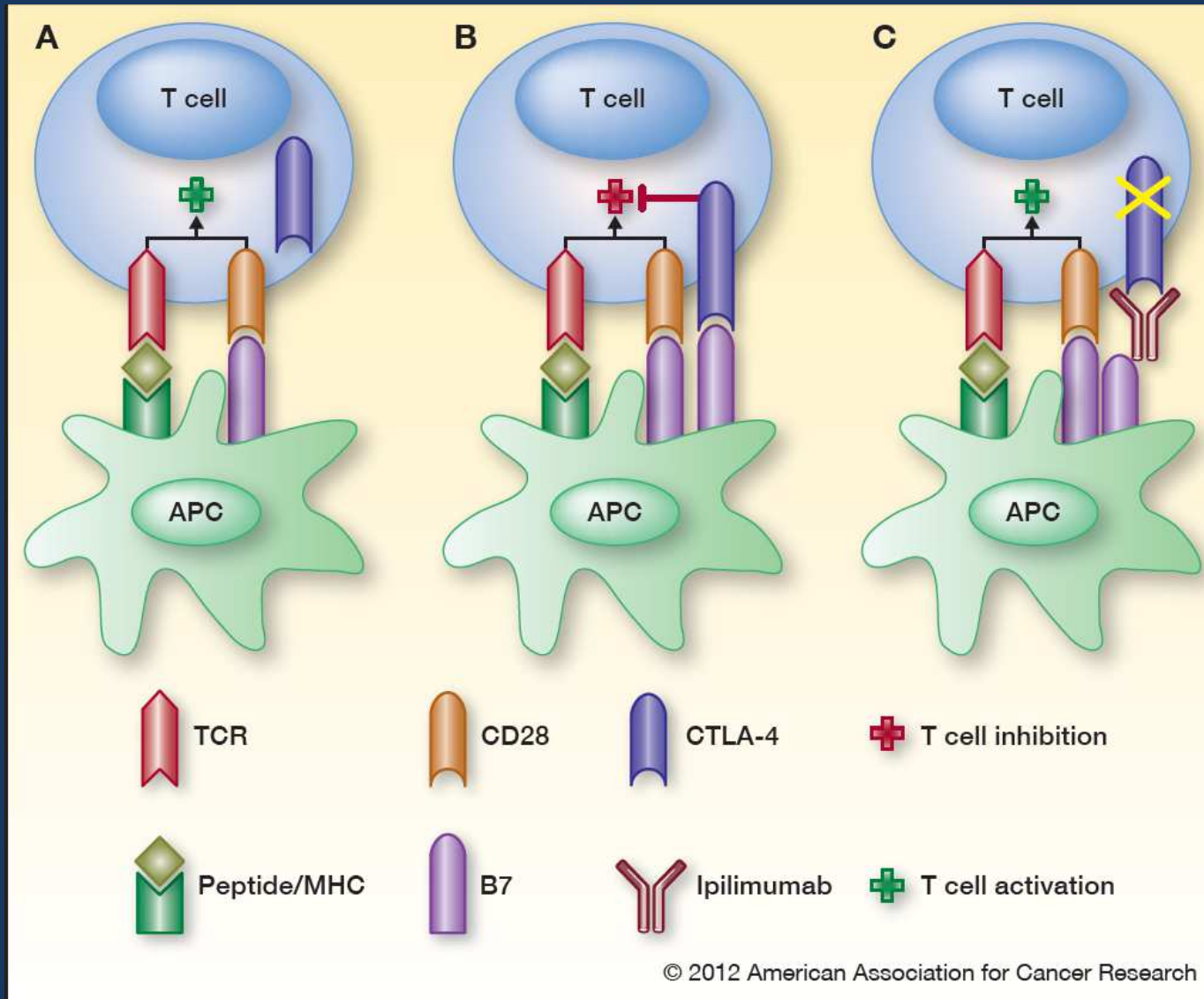
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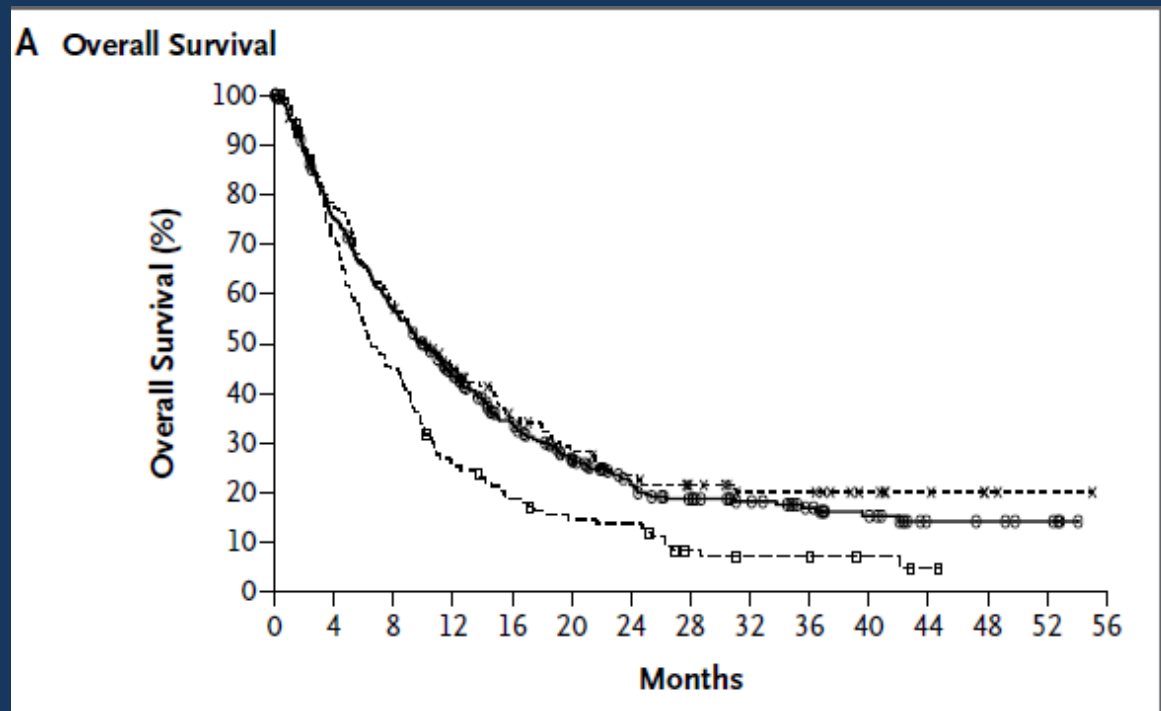
The following relationships exist related to this presentation:

BRISTOL-MYERS SQUIBB, Research Grant, unrelated to this study

CTLA-4 as an immune “checkpoint”



Ipilimumab confers OS benefit to gp100 vaccine in phase III study

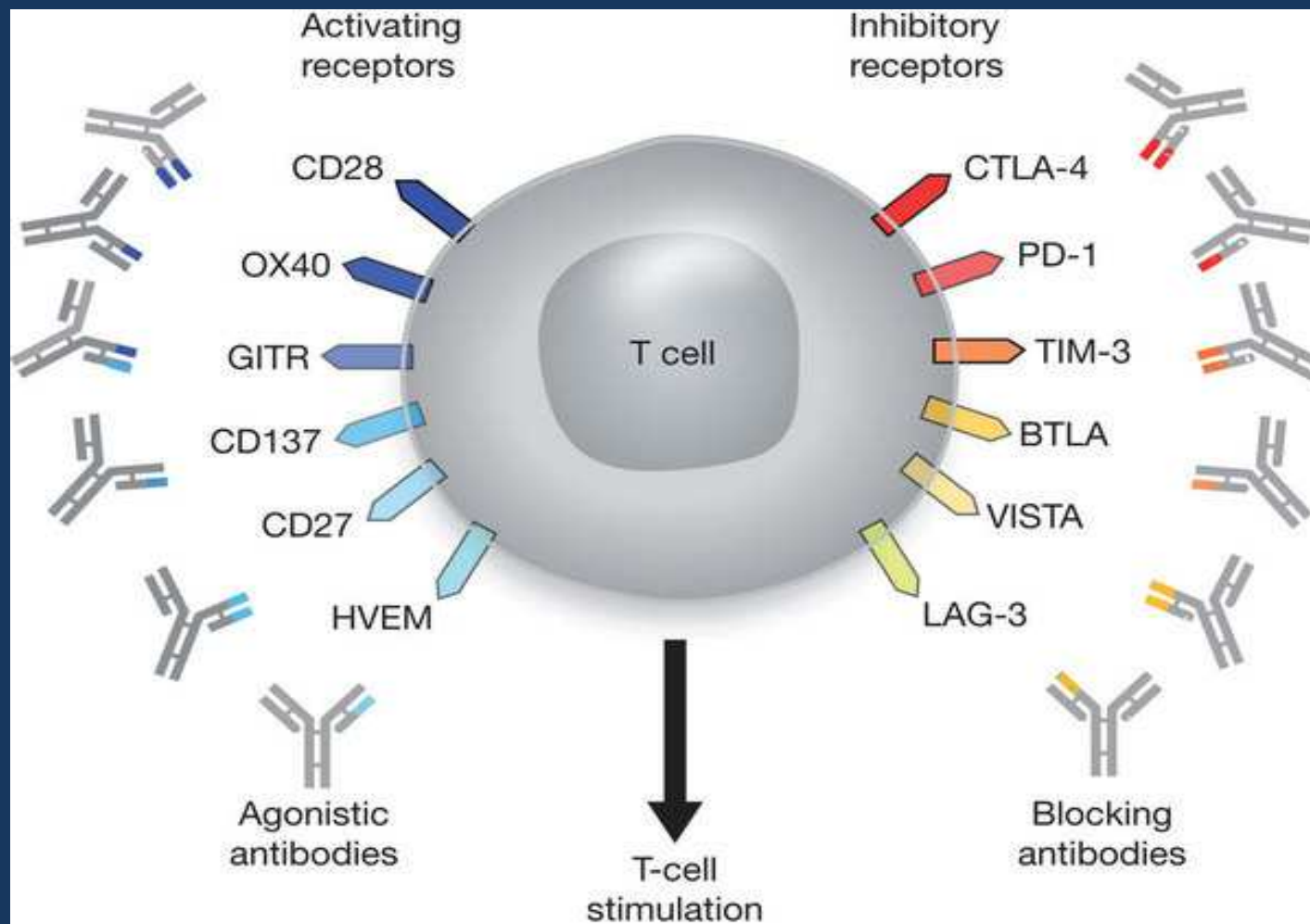


Median OS
10.1 mos

24% alive at 2
years

Response rate of 10.9%

The target is the lymphocyte



T cell receptor diversity

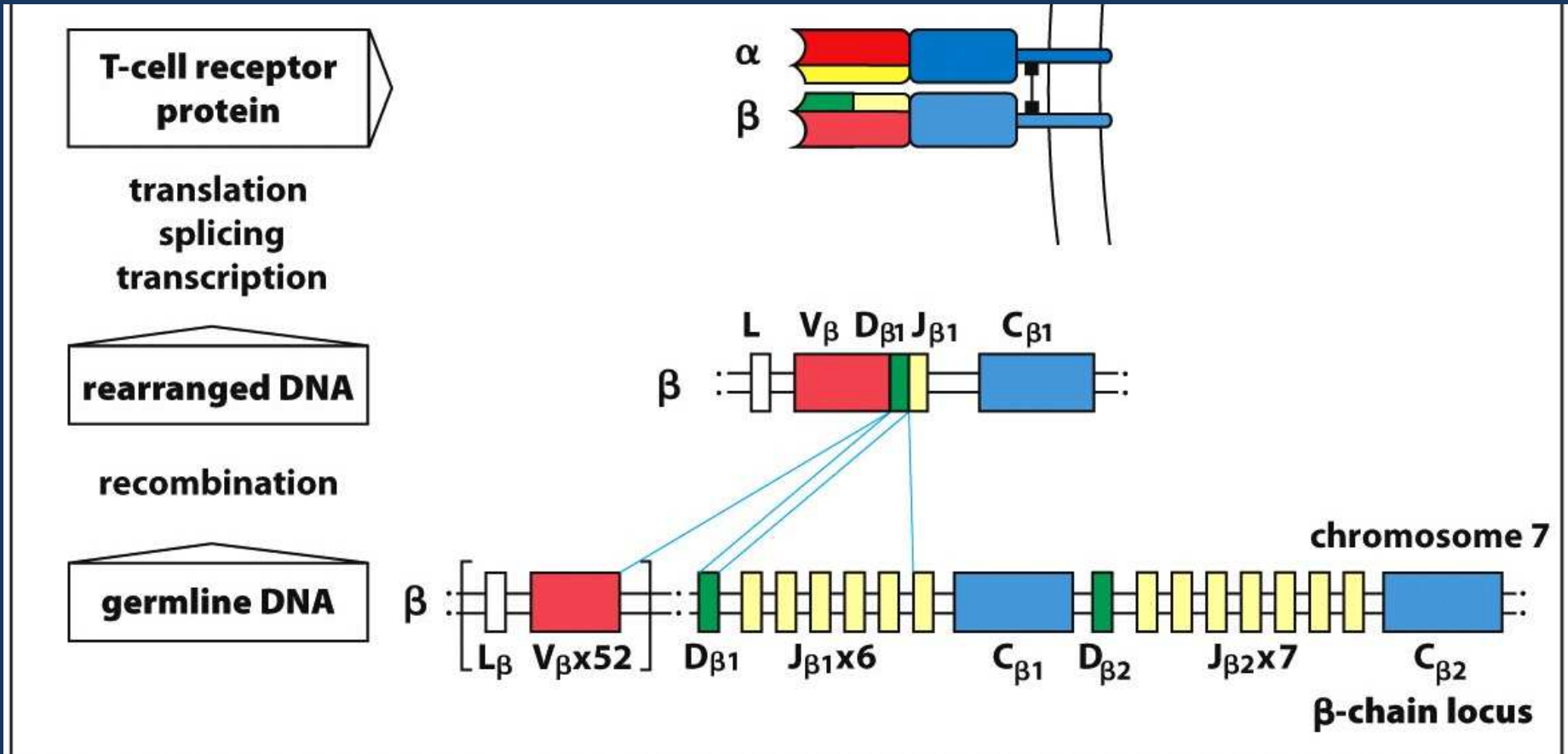


Figure 5.3 The Immune System, 3ed. (© Garland Science 2009)

Investigations of the T cell repertoire

- CTLA-4 blockade broadens the peripheral T cell repertoire which is associated with side effects. [1]
- Maintenance of high frequency TCR clones was associated with overall survival. [2]

[1] Robert L., et al. *Clin Cancer Res* 2014

[2] Cha E., et al. *Sci Transl Med* 2014

Pilot Study Objectives

1. To investigate T cell repertoire diversity in peripheral blood of patients with melanoma treated with ipilimumab using a PCR based assay.
2. To determine if T cell repertoire diversity was associated with clinical outcomes.

Methods

12 patients with stage IV melanoma treated with 3mg/kg of ipilimumab

Under institutional IRB approved correlative protocol, peripheral blood collected at baseline

DNA extracted and diversity assessed by investigators blinded to clinical outcome

Two components of TCR diversity

1. Richness

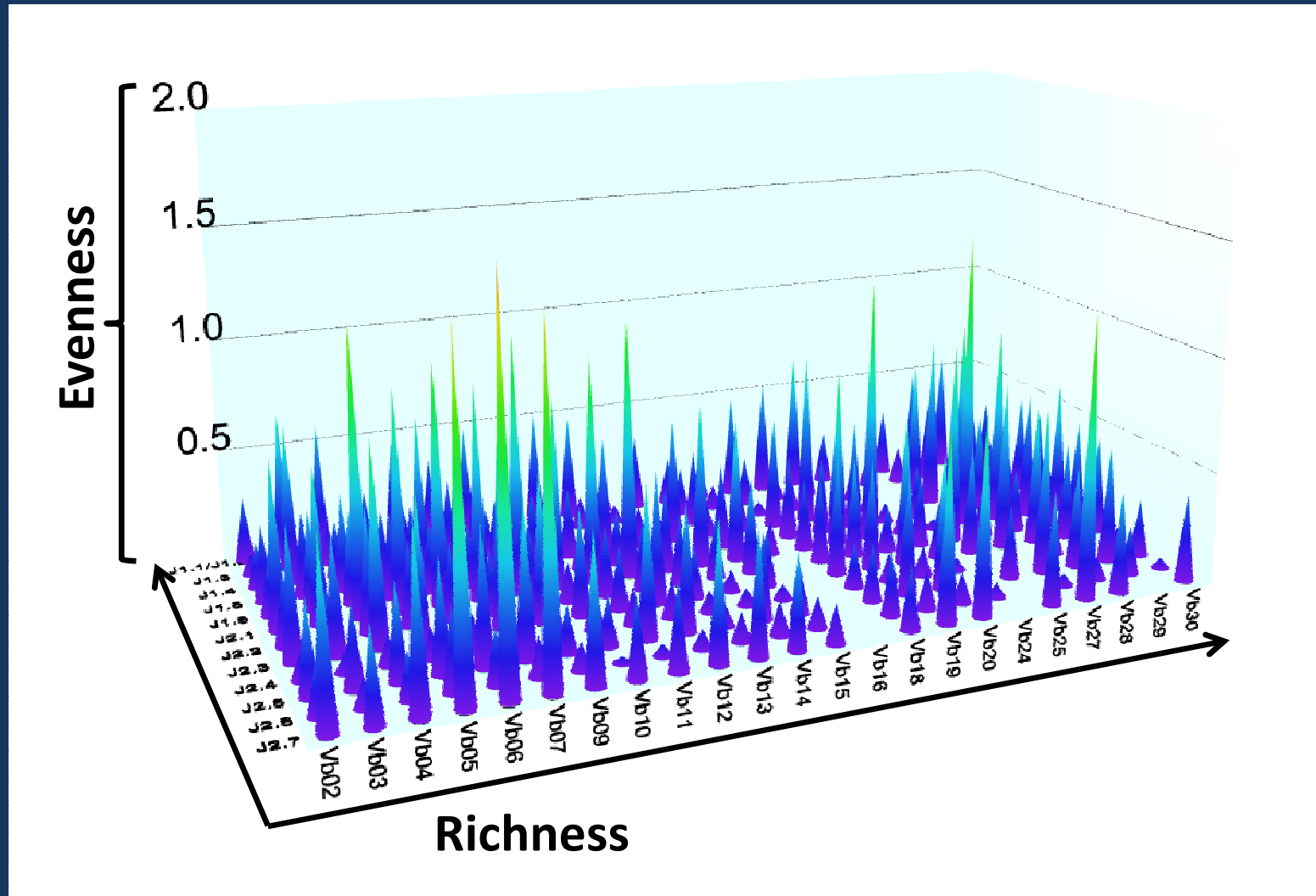
- Observed / Theoretical rearrangements
- “How many buildings?”

2. Evenness

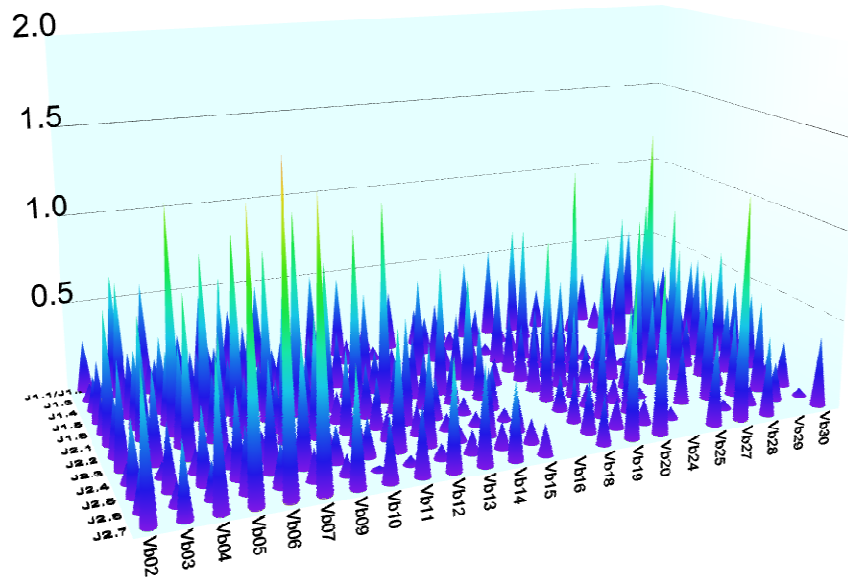
- How similar are the frequencies of rearrangements
- “How similar are the heights of each building?”



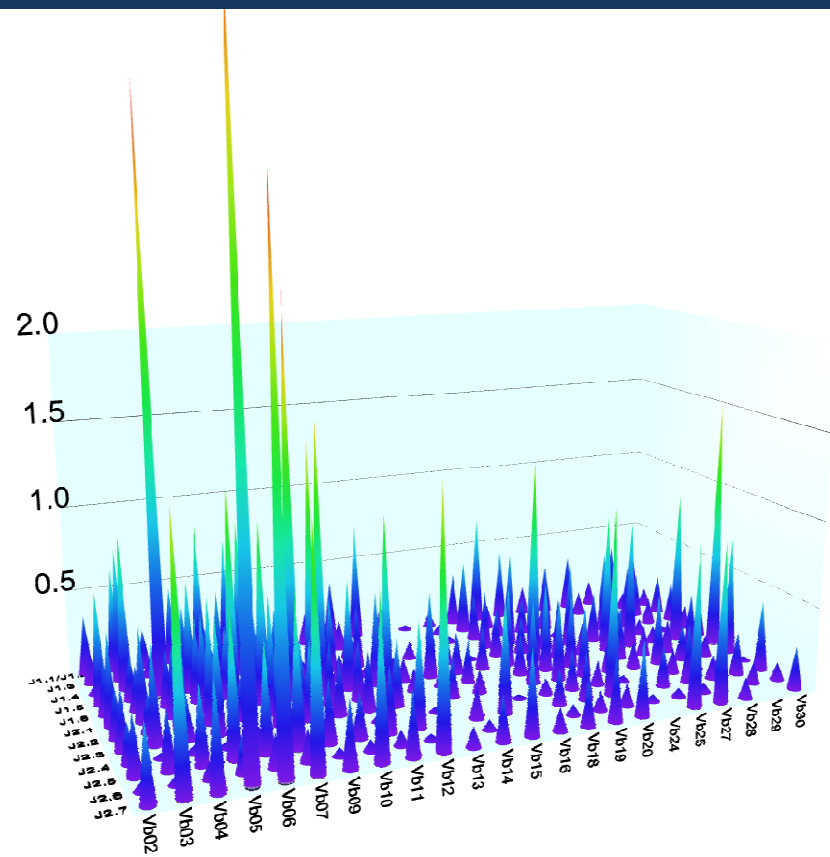
Example patient



Immune Profiles at Baseline



High evenness



Low evenness

Patient Characteristics

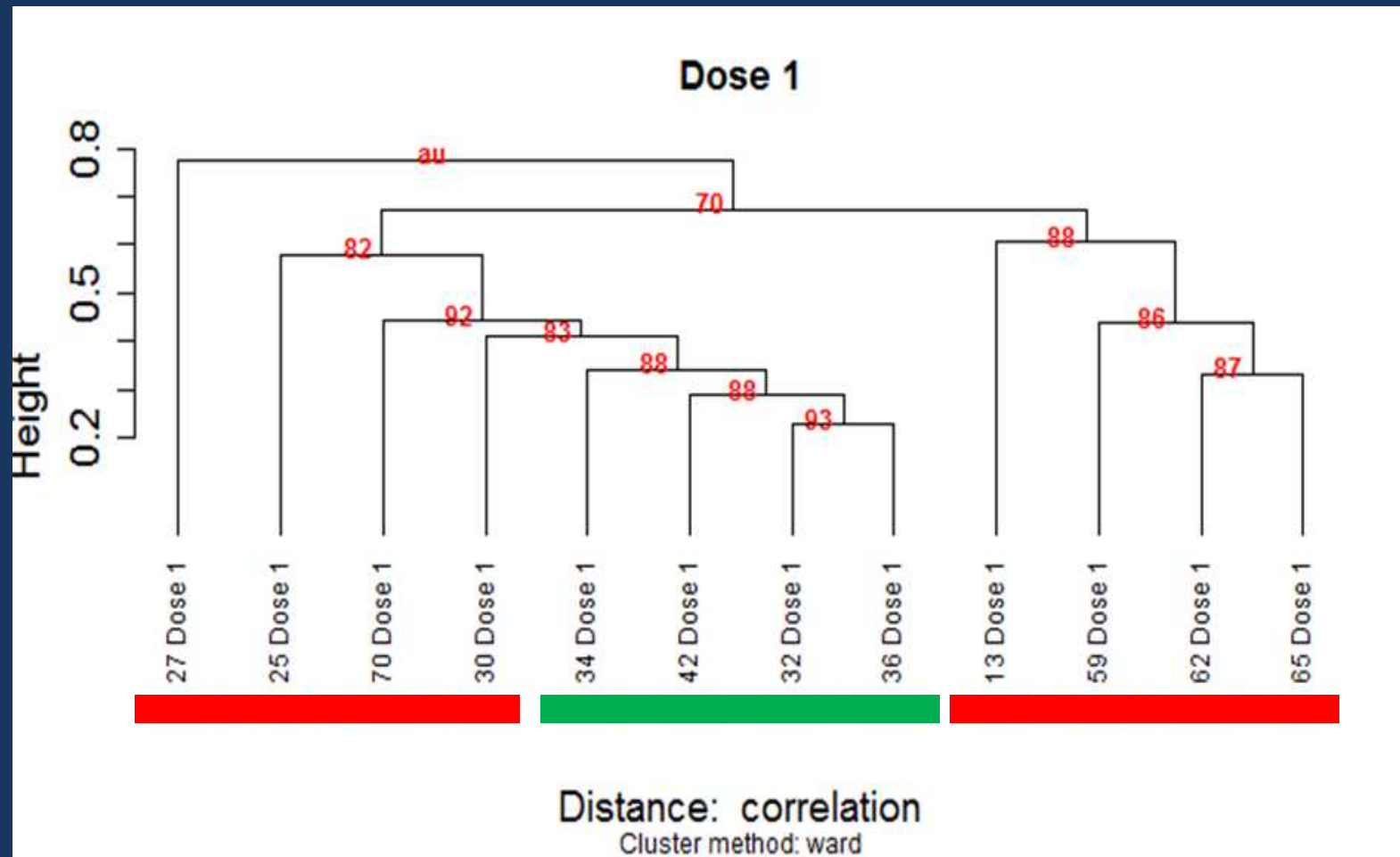
	Responders (n=4)*	Non-Responders (n=8)*
Median age (range)	57 (38-78)	67 (52-77)
Sex	1 female 3 male	3 female 5 male
M-stage	0 M1A 2 M1B 2 M1C	2 M1A 0 M1B 6 M1C
Median baseline LDH	156**	211 (183-438)
Karnofsky Performance	90 (90-100)	90 (90-100)

* Responders = patients with tumor shrinkage or stability lasting >9 months

* Non-Responders = patients with progressive disease

** Only one patient had LDH evaluated

TCR repertoire clustering at baseline

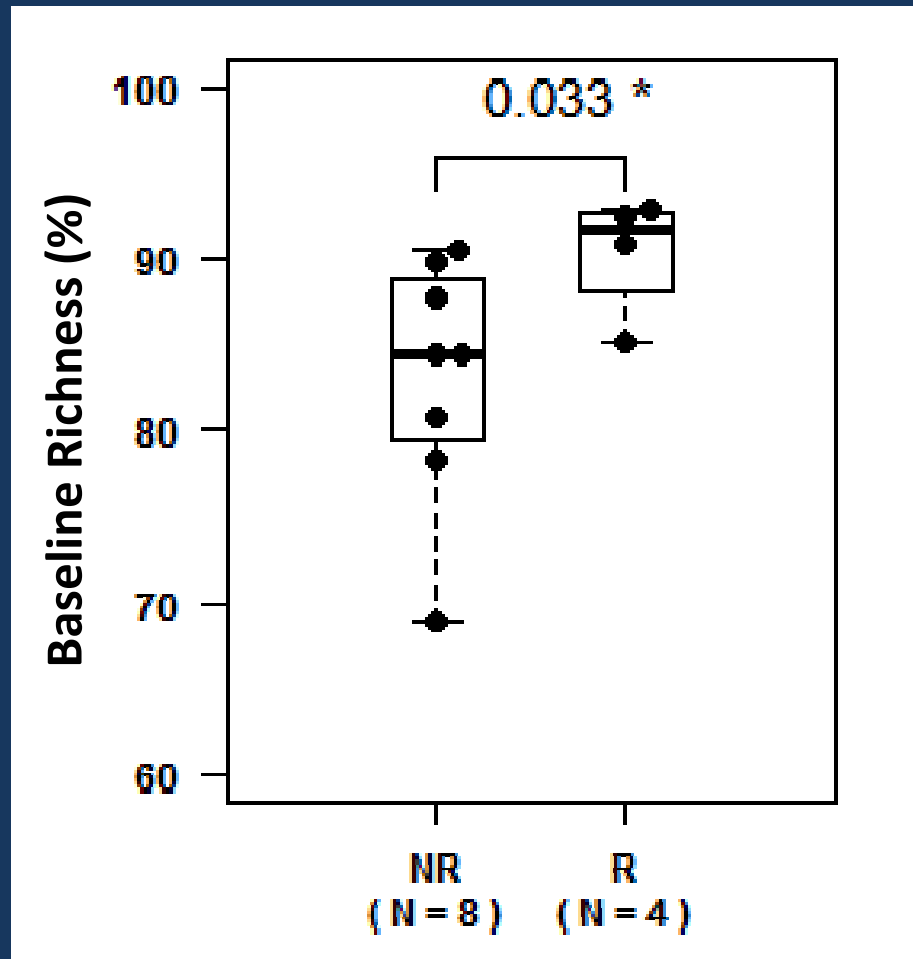


Orange= Non-responder

Green= Responder

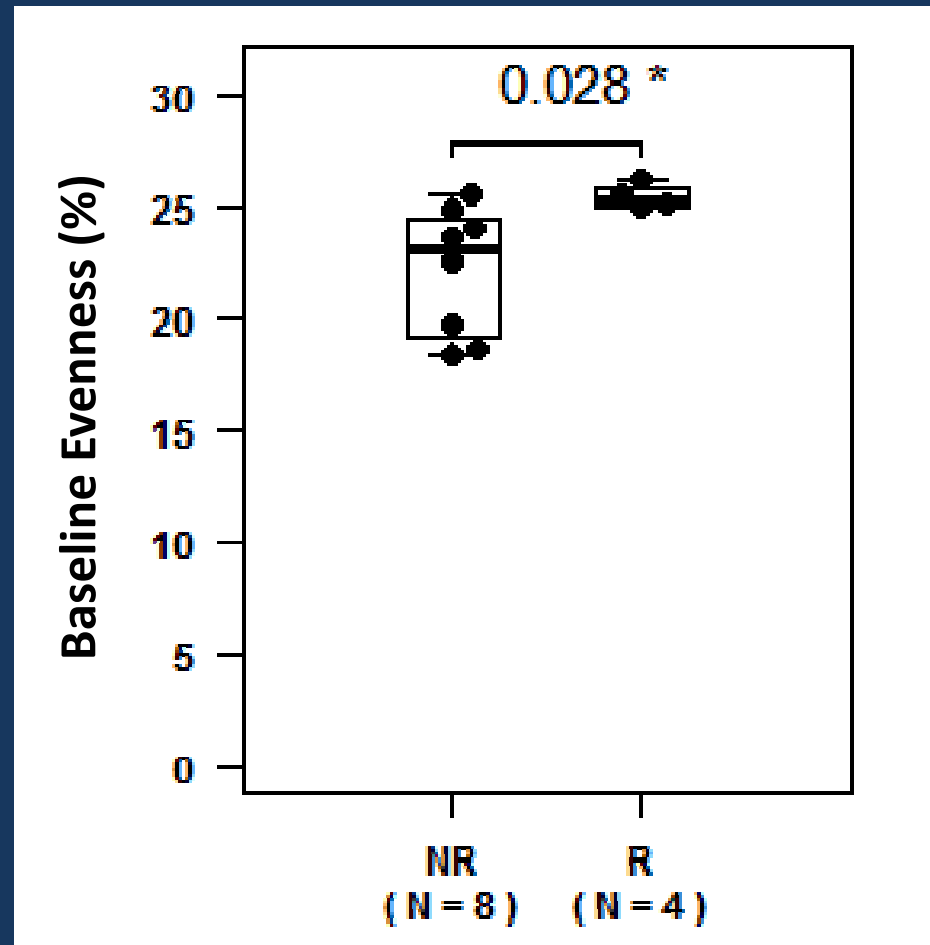
AU (red)= Approximately unbiased probability values

Significant difference in richness at baseline between responders and non-responders



Wilcoxon rank sum test, p-value=0.033

Significant difference in evenness at baseline between responders and non-responders

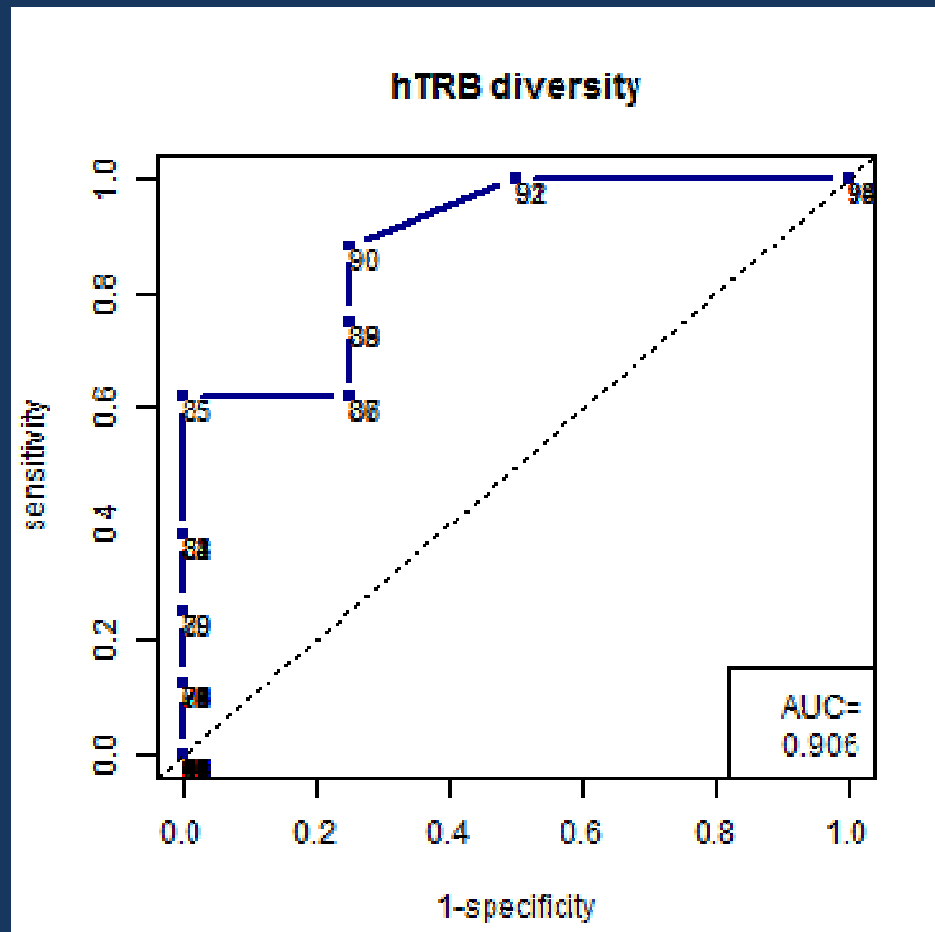


Wilcoxon rank sum test, p-value=0.028

Dichotomized analyses

Receiver operating characteristic (ROC) curves suggested exploratory thresholds for high vs. low groups

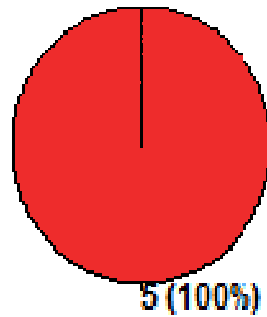
Baseline richness of $\geq 85\%$ proposed as threshold



Baseline richness and patient response

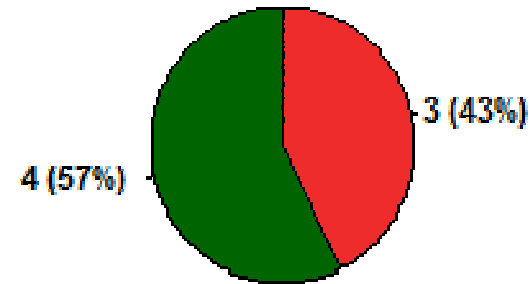
Response	Baseline Richness < 85%	Baseline Richness ≥ 85%
Non-Responder	5	3
Responder	0	4

Richness <85%



■ Non responder

Richness ≥85%

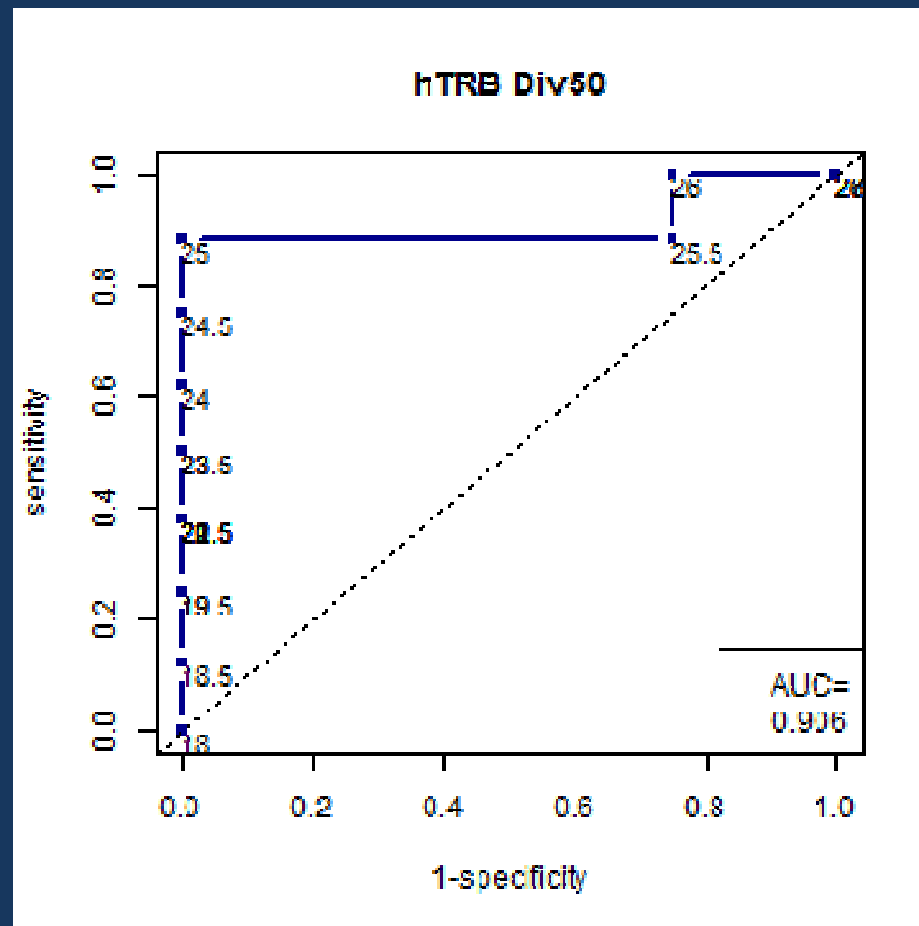


■ Non responder ■ Responder

Fisher test: $p=0.081$

There was no difference in OS

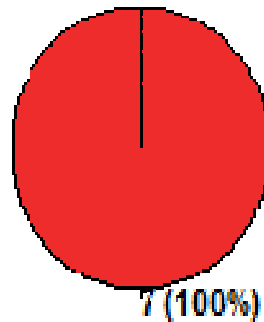
Baseline evenness of $\geq 25\%$ proposed as threshold



Significant association between baseline evenness and patient response

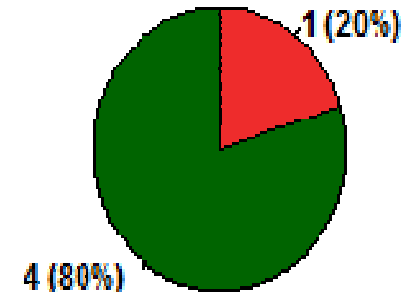
Response	Baseline Evenness < 25%	Baseline Evenness ≥ 25%
Non responder	7	1
Responder	0	4

Evenness <25%



■ Non responder

Evenness ≥25%



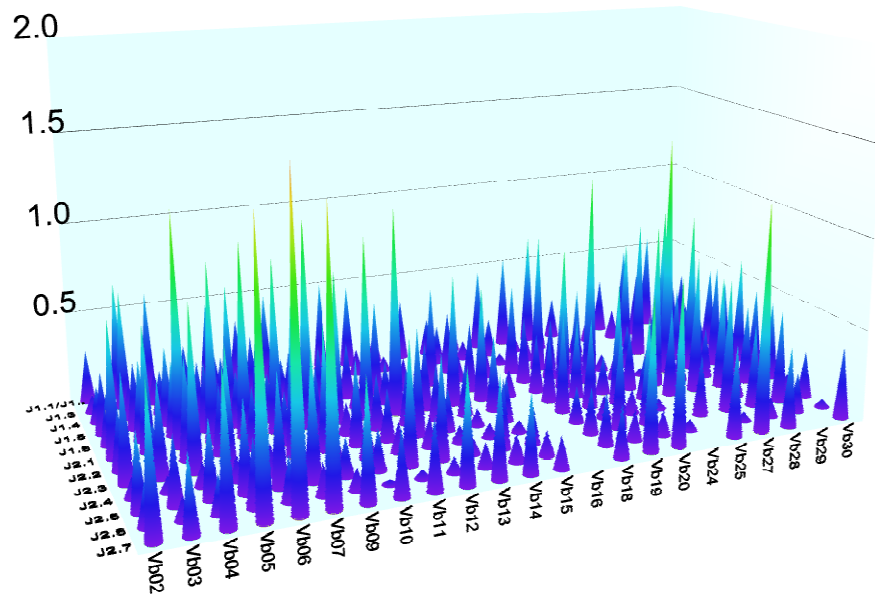
■ Non responder ■ Responder

Fisher test: $p=0.01$

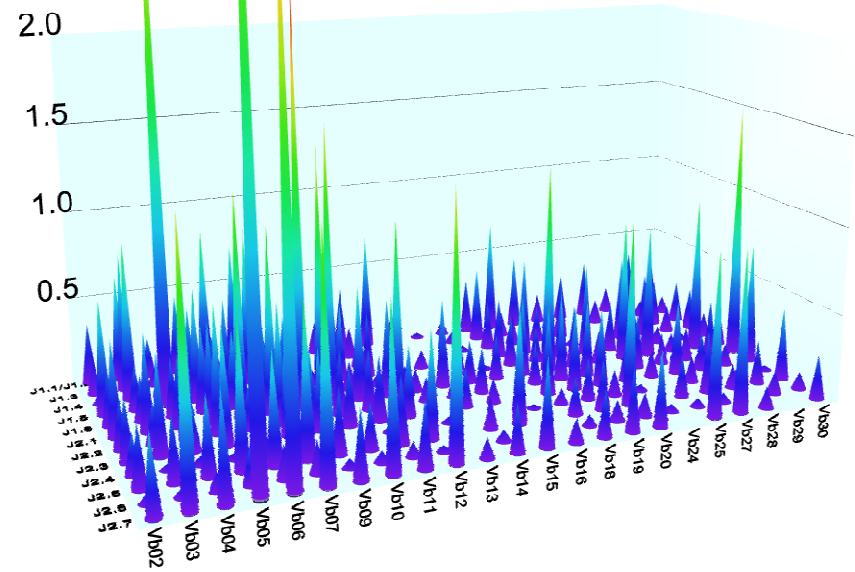
There was no difference in OS

Immune Profiles at Baseline

Responder



Non-Responder



Richness \geq 85%, Evenness \geq 25%

Richness $<$ 85%, Evenness $<$ 25%

Summary

- In a small group of patients with melanoma, diversity of the T cell repertoire (richness and evenness) at baseline was associated with clinical responses to ipilimumab.
- Additional study in a larger sample set is ongoing.

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