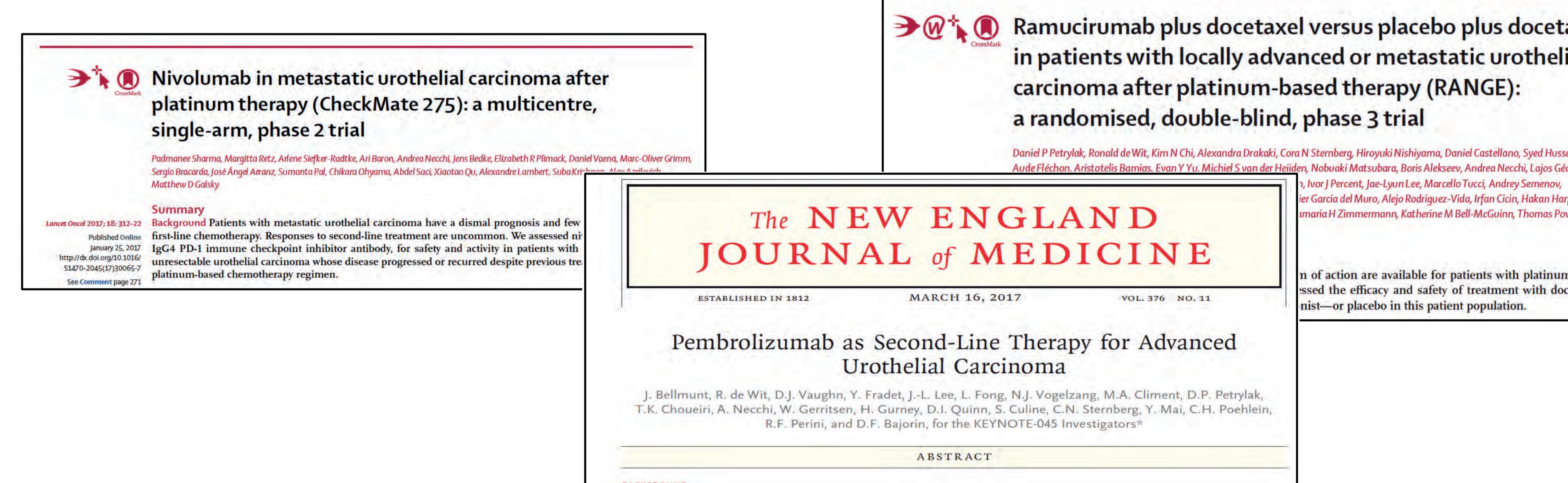


# Plasticity in the biological response to neoadjuvant chemotherapy in muscle-invasive bladder cancer

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## Background

### Emerging evidence for second-line treatment options in muscle-invasive bladder cancer not responding to cisplatin based chemotherapy



### Cisplatin-resistant bladder cancer

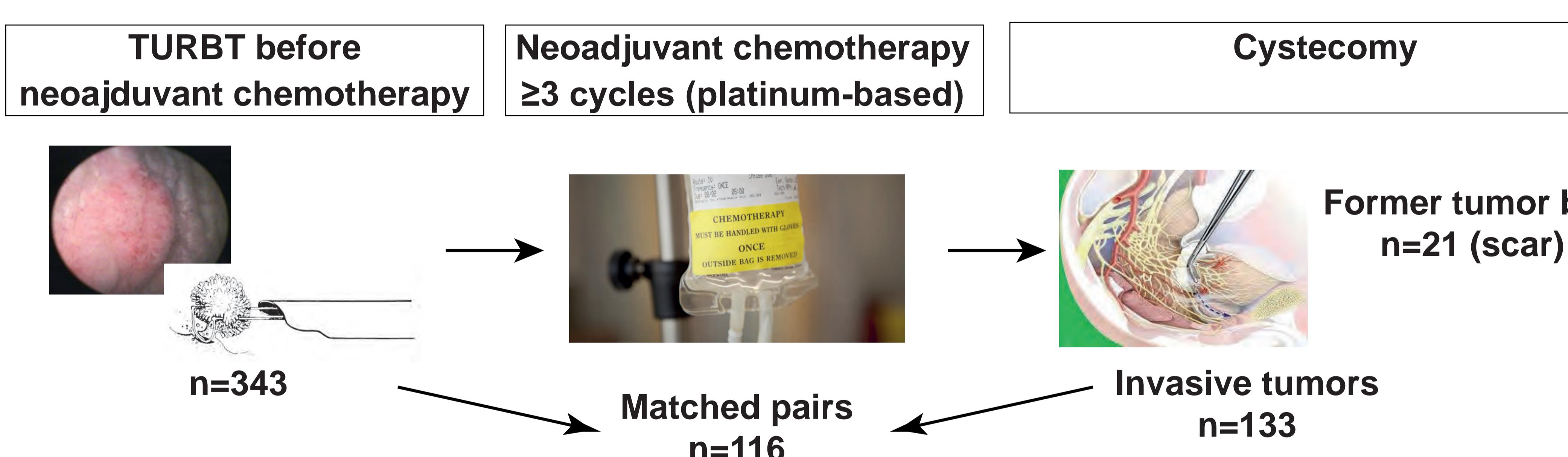
- Molecular alterations induced by chemotherapy are poorly characterized
- Early data available on alterations on genome and transcriptome level<sup>1,2</sup>

### Aim of the present study:

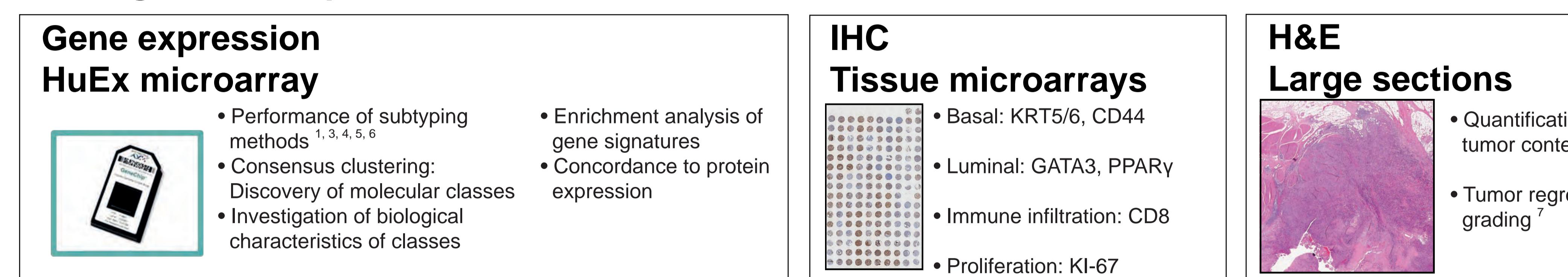
#### Molecular characterization of cisplatin-resistant bladder cancer

## Material & Methods

### Dataset pre- and post-neoadjuvant chemotherapy

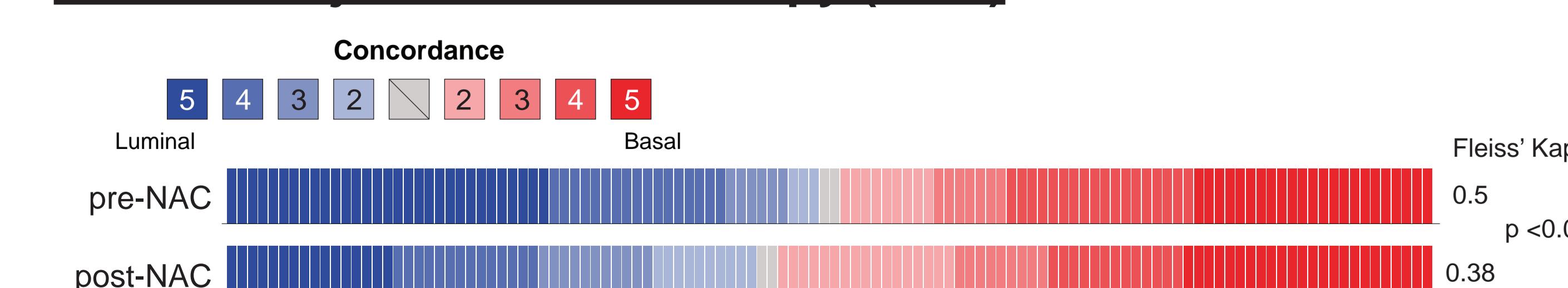


### Investigations of specimens in this dataset



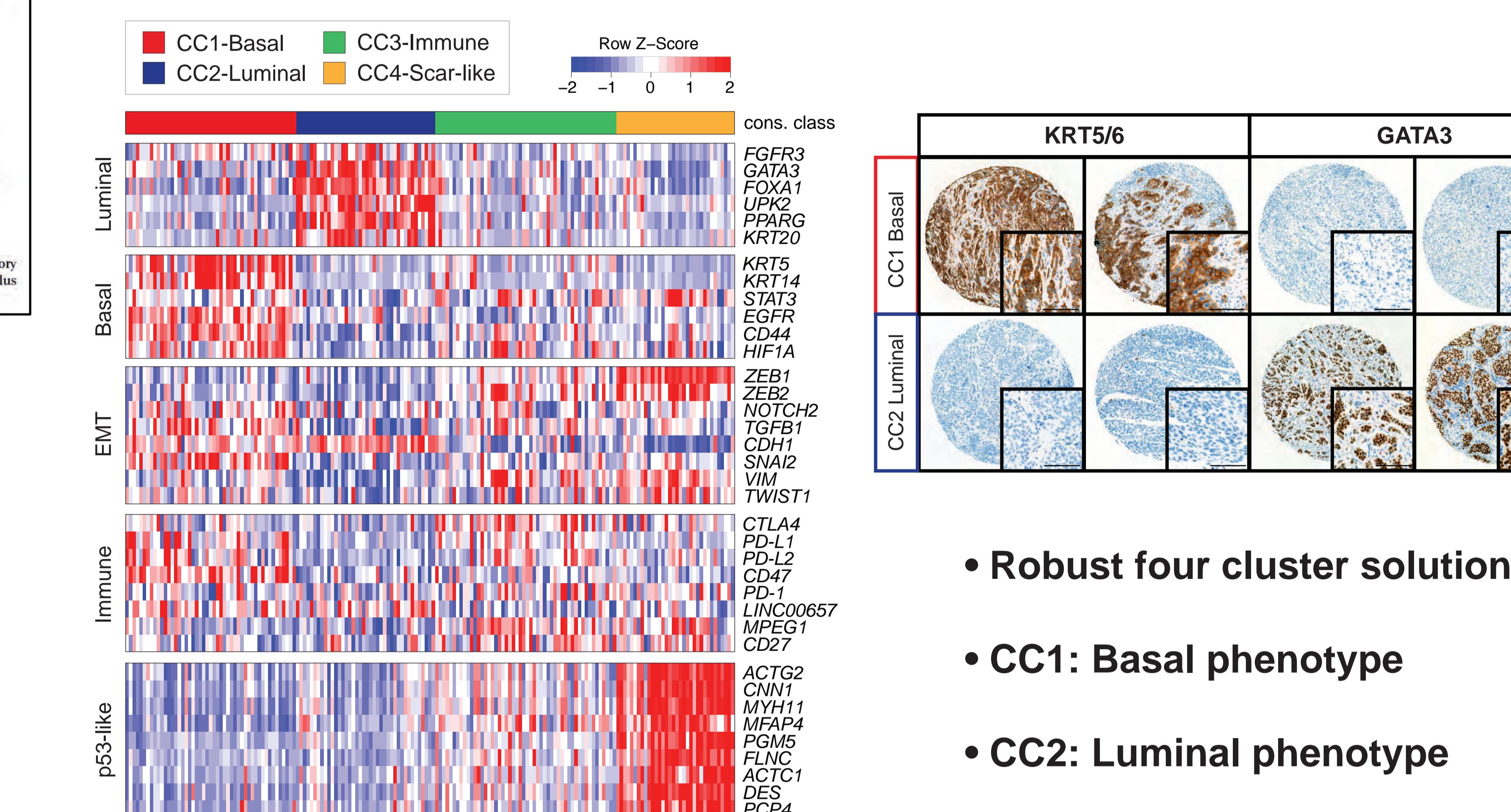
## Results

### Performance of published subtyping methods in invasive bladder cancer after neoadjuvant chemotherapy (NAC)



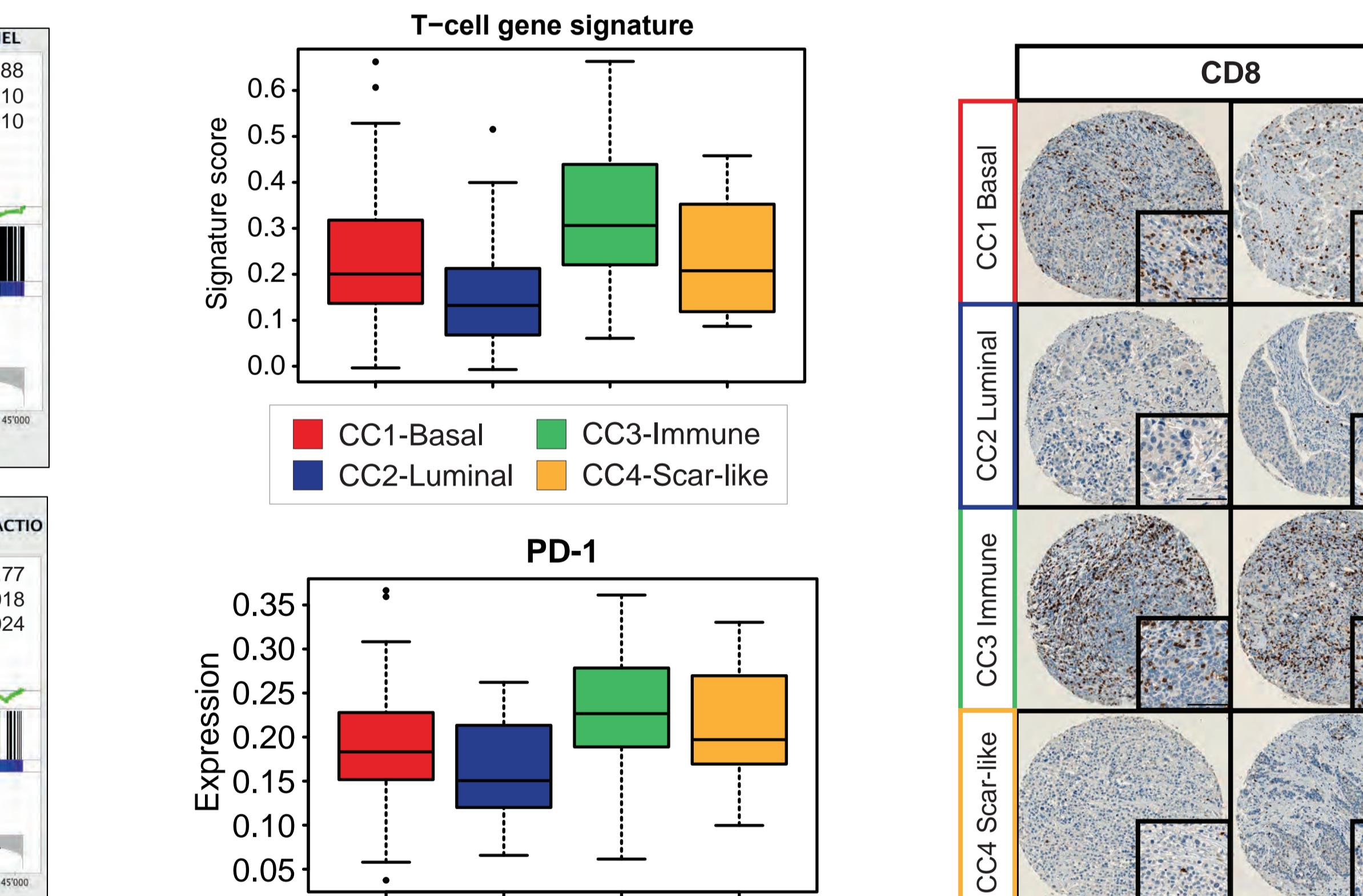
### Lower concordance across different subtyping methods

### Discovery of molecular classes in invasive bladder cancers after neoadjuvant chemotherapy

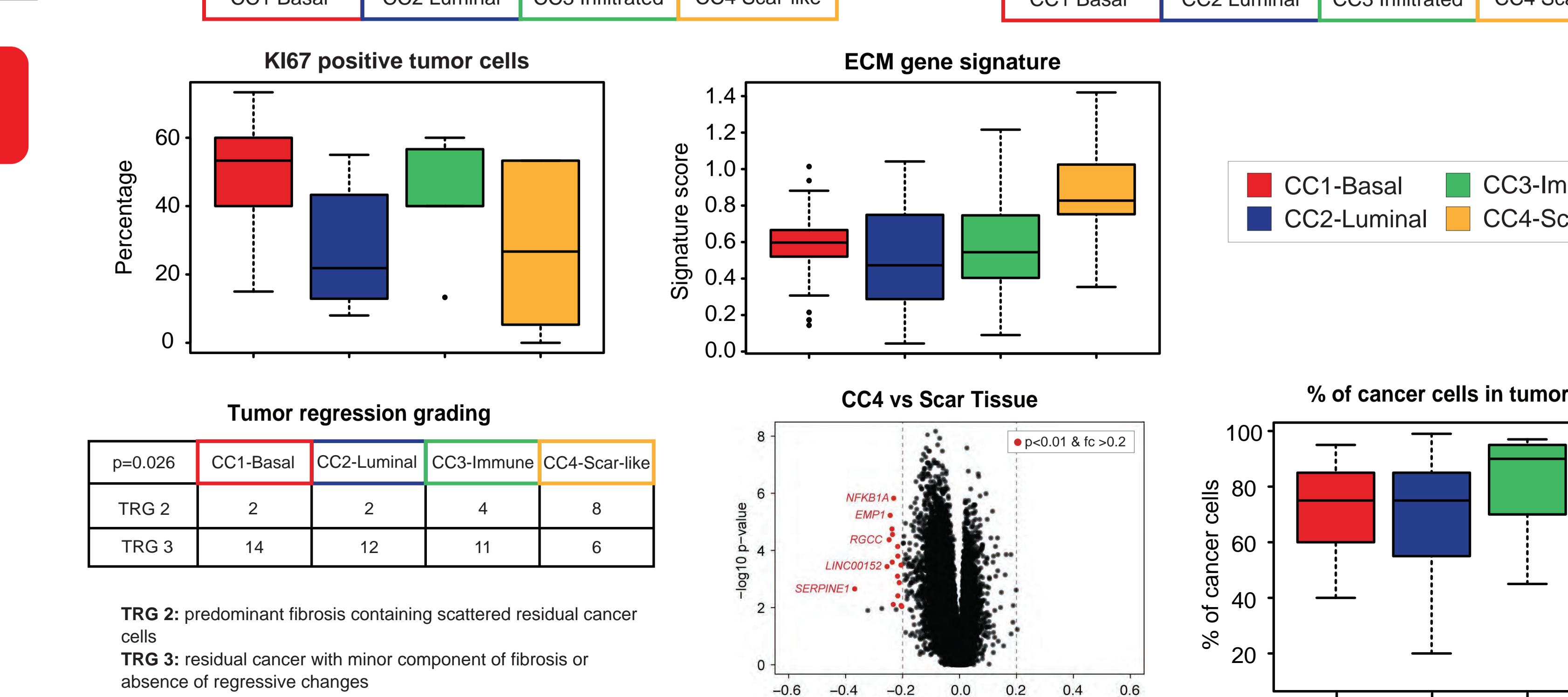
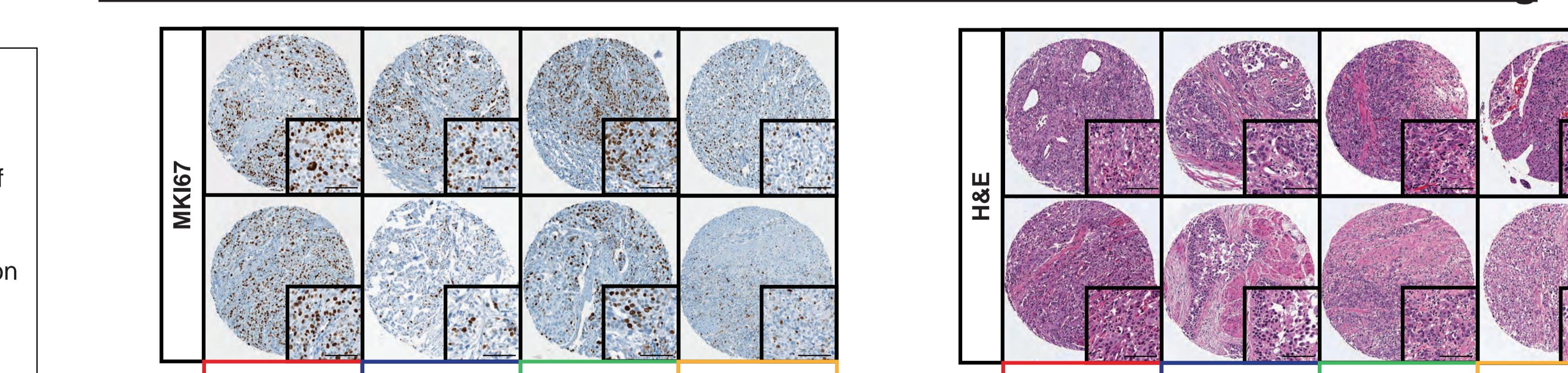


- Robust four cluster solution
- CC1: Basal phenotype
- CC2: Luminal phenotype

### Consensus cluster 3: Strong immune signature and loss of basal/luminalness

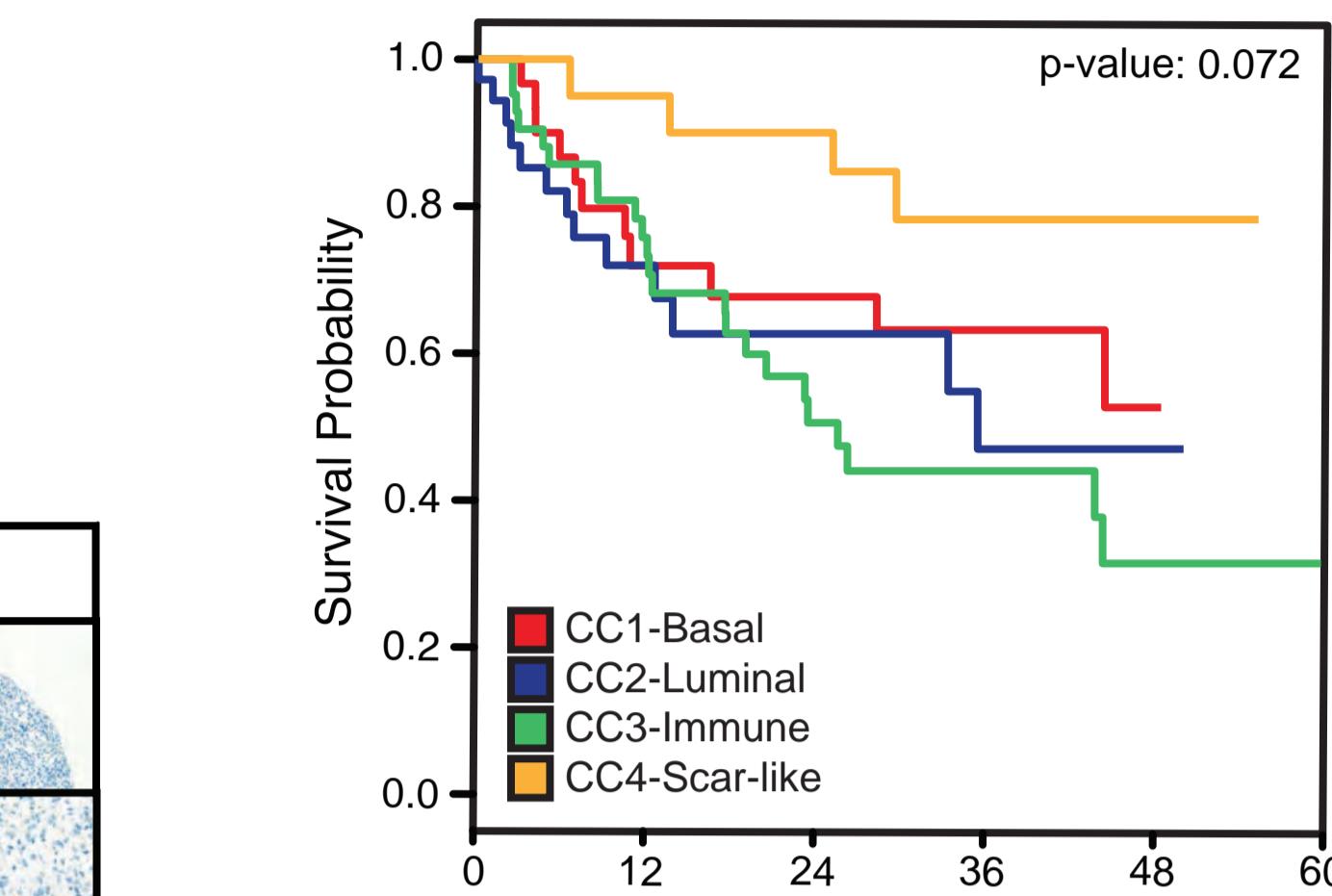


### Consensus cluster 4: Characteristics of scarring and wound healing



## Results

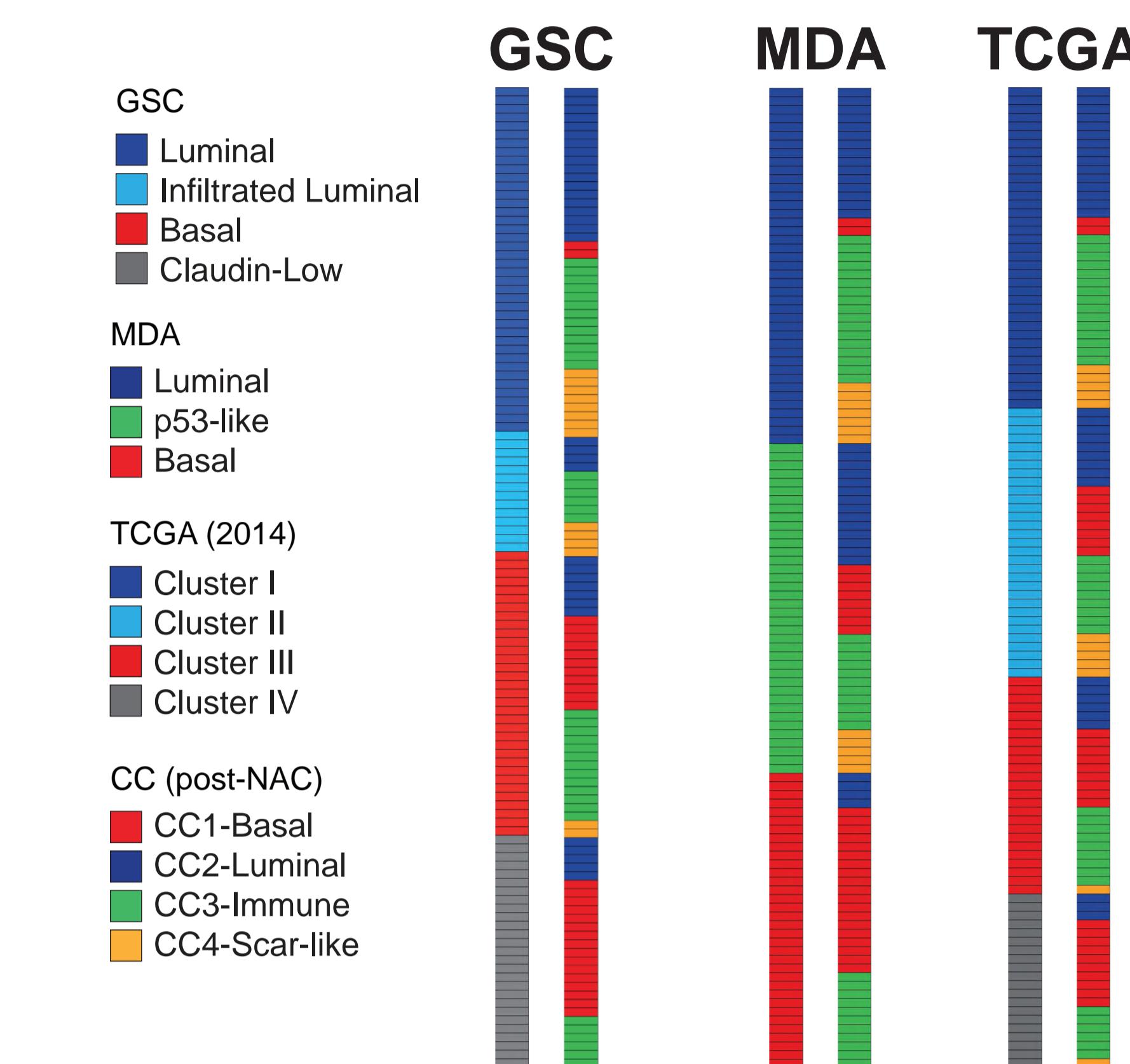
### Univariable survival analysis



### Multivariable survival analysis

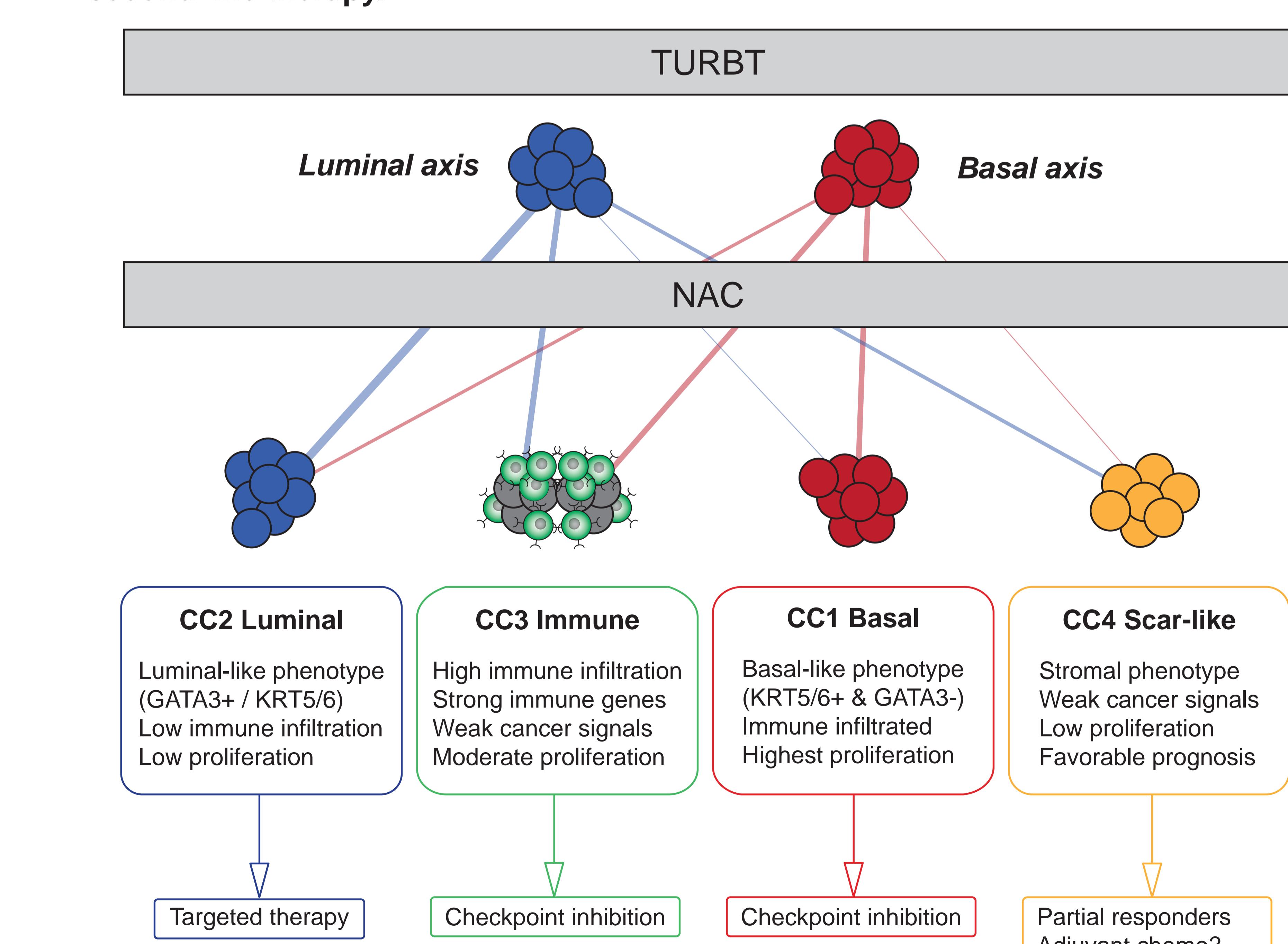
| Variables           | HR   | CI 95%    | p-value |
|---------------------|------|-----------|---------|
| Age                 | 1.01 | 0.98-1.03 | 0.54    |
| RC Stage T3-4 (ref) | 1    | -         | -       |
| RC Stage T1         | 0.3  | 0.07-1.31 | 0.11    |
| RC Stage T2         | 0.18 | 0.07-0.47 | <0.001  |
| LNI positive        | 1.68 | 0.94-3.02 | -       |
| CC3-Immune (ref)    | 1    | -         | -       |
| CC1-Basal           | 0.46 | 0.22-0.98 | 0.045   |
| CC2-Luminal         | 0.93 | 0.46-1.90 | 0.85    |
| CC4-Scar-like       | 0.36 | 0.14-0.94 | 0.038   |

### Pre to post neoadjuvant chemotherapy



## Conclusions

- Existing molecular subtypes are not readily applicable to post-chemotherapy bladder cancer.
- Two post-chemotherapy subtypes (CC3/CC4) lack clear basal or luminal gene expression.
- Two post-chemotherapy subtypes (CC1/CC3) are highly immune infiltrated.
- CC4: Gene expression resembles tumor bed scar and patients show favourable prognosis.
- Further investigation will determine whether these subtypes can be used to guide second line therapy.



## References

- Choi, Cancer Cell, 2014; 2. Faltas, Nature Gen 2016; 3. Daumrauer, PNAS, 2014; 4. Kardos, JNCI; 5. TCGA, Nature, 2014; 6. Sjödahl, Clin Cancer Res, 2012; 7. Fleischmann, Am J Surg Pathol, 2014