

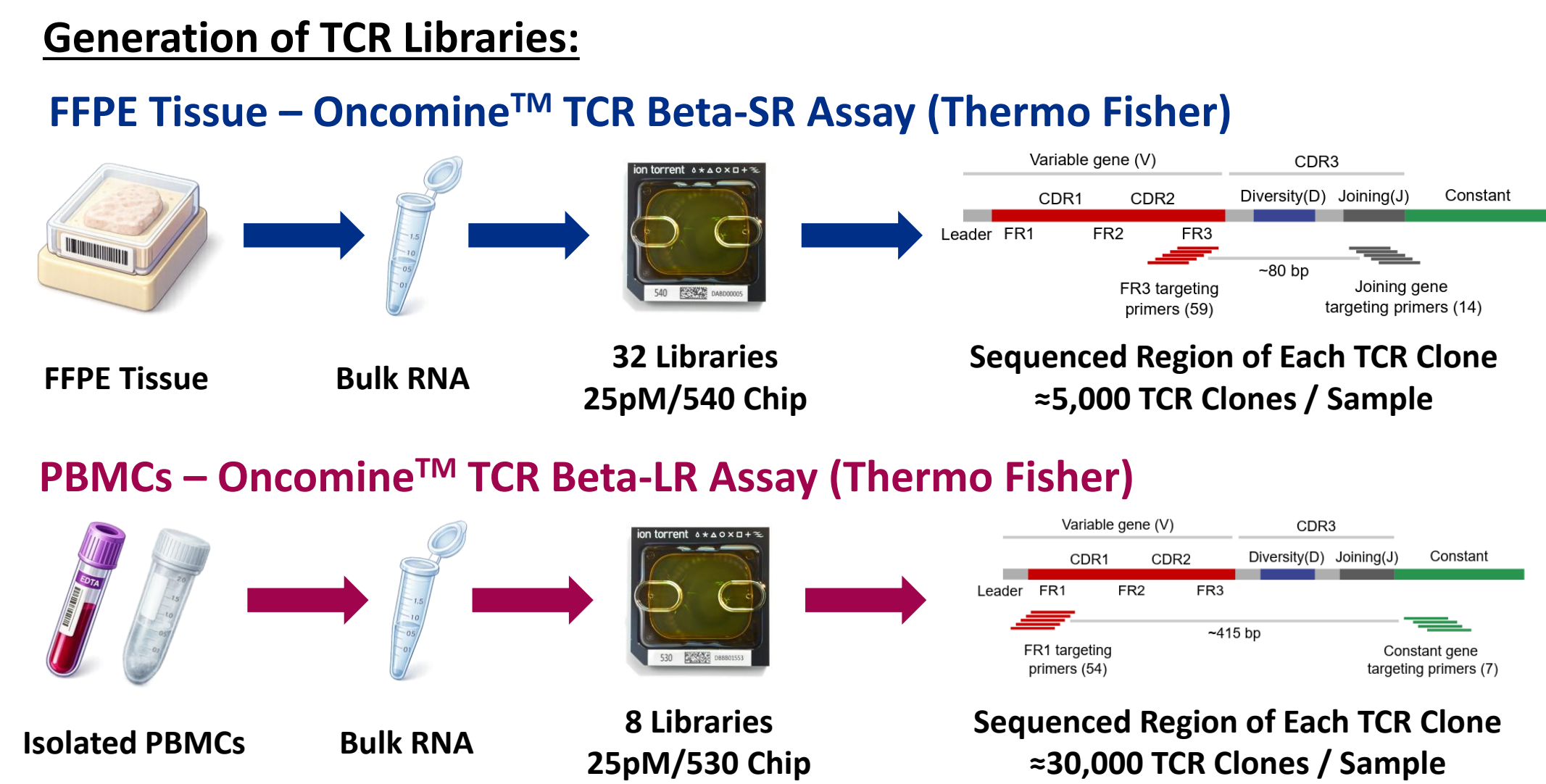
INTRODUCTION

Although **perioperative chemoimmunotherapy** has increased **complete pathological response (CPR)** rates in **potentially resectable stage non-small cell lung cancer (NSCLC)**, not all patients benefit from this approach.

T cell receptor (TCR) repertoire clonality and higher abundance of **Top 1% baseline tissue clones** has been associated with complete pathological responses (CPR) and improved survival after perioperative chemoimmunotherapy in NSCLC. However, their **systemic dynamics** throughout treatment remain unknown.

Objective: Track Top 1% baseline tissue clones to assess their longitudinal behavior in tissue and blood according to pathological response.

METHODS



DISCUSSION AND CONCLUSION

The top 1% baseline tissue clones associated with pathological response can be monitored across following tissue and blood samples.

These clones maintain a consistently higher presence, and a greater selective expansion, in patients achieving CPR throughout neoadjuvant and adjuvant treatment.

REFERENCES AND ACKNOWLEDGEMENTS

- Casarrubios M, Cruz-Bermúdez A, Nadal E, et al. Pretreatment Tissue TCR Repertoire Evenness Is Associated with Complete Pathologic Response in Patients with NSCLC Receiving Neoadjuvant Chemoimmunotherapy. *Clin Cancer Res.* 2021;27(21):5878-5890. doi:10.1158/1078-0432.CCR-21-1200
- Provencio M, Nadal E, Insa A, et al. Perioperative chemotherapy and nivolumab in non-small-cell lung cancer (NADIM): 5-year clinical outcomes from a multicentre, single-arm, phase 2 trial. *Lancet Oncol.* 2024;25(11):1453-1464. doi:10.1016/S1470-2045(24)00498-4
- Provencio M, Nadal E, González-Larriba JL, et al. Perioperative Nivolumab and Chemotherapy in Stage III Non-Small-Cell Lung Cancer. *N Engl J Med.* 2023;389(6):504-513. doi:10.1056/NEJMoa2215530

We would like to thank the patients, their families, all the participating clinical teams, and all the Spanish Lung Cancer Group, BMS, for making this study possible.

Presenting Author: Cristina Martínez Toledo (cmartinez@idiphim.org)
Corresponding Authors: Alberto Cruz-Bermúdez (alberto.cruz.bermudez@gmail.com)
Mariano Provencio (mprovenciop@gmail.com)

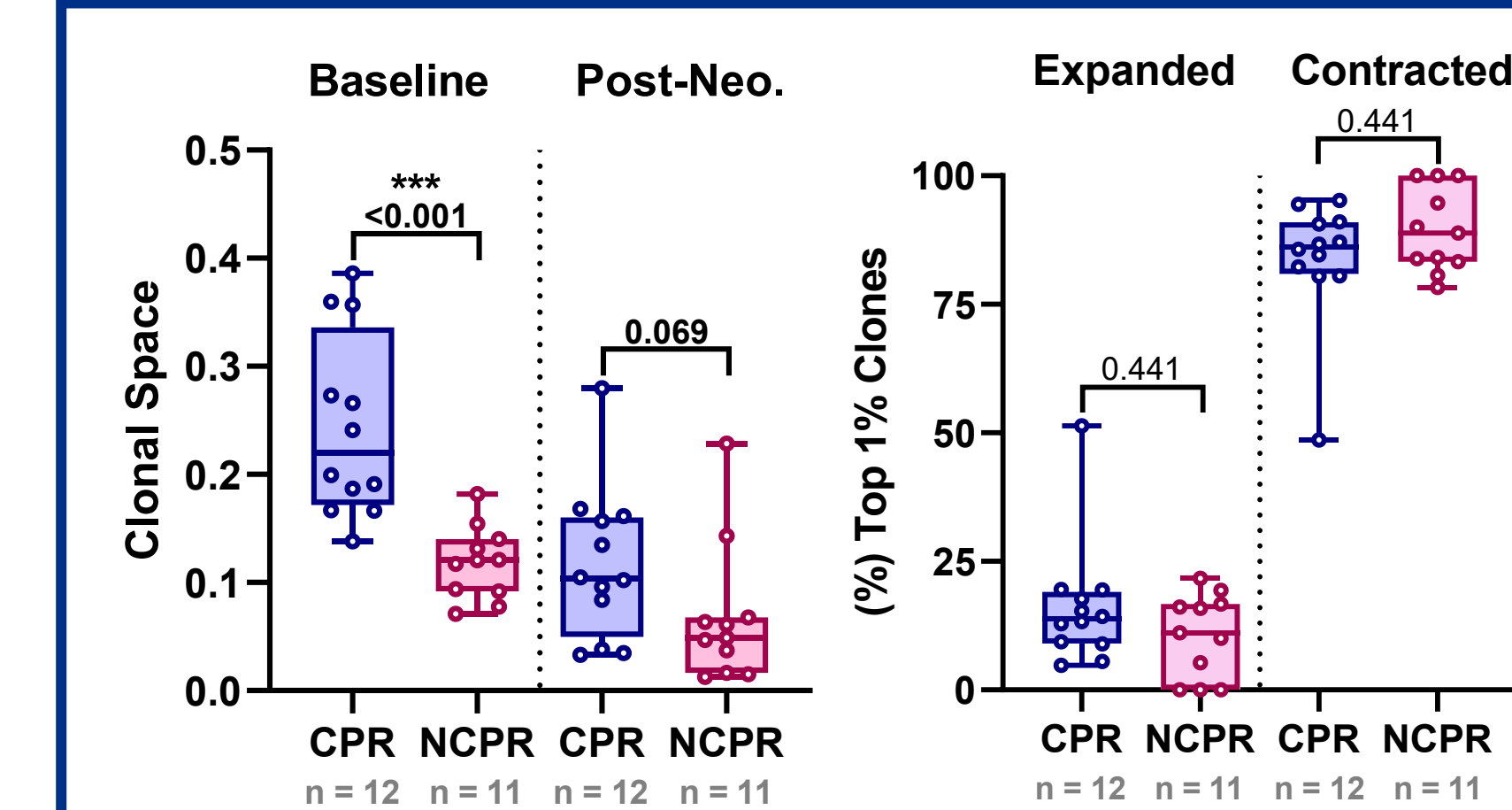
FUNDING: This study was funded by Bristol-Myers Squibb, Instituto de Salud Carlos III (ISCIII); grants PI19/01652, PI22/01223 and PI23/01054; contracts CP23/00044 and FI24/00270), the European Union's Horizon 2020 research and innovation programme (PERME190002RODR and AC19/0026), Scientific Foundation of Spanish Association Against Cancer, Spanish Ministry of Science and Innovation (RTC-2017-6502-1, RTC-2019-007359-1 and CPP2022-009545), Comunidad de Madrid (PIPF-2022/SAL-GL-25283, PEJ-2023-AI/SAL-GL-27634) and IDIPHISA.

AI Disclosure: AI tools were only used for the generation of icons in the methods section.

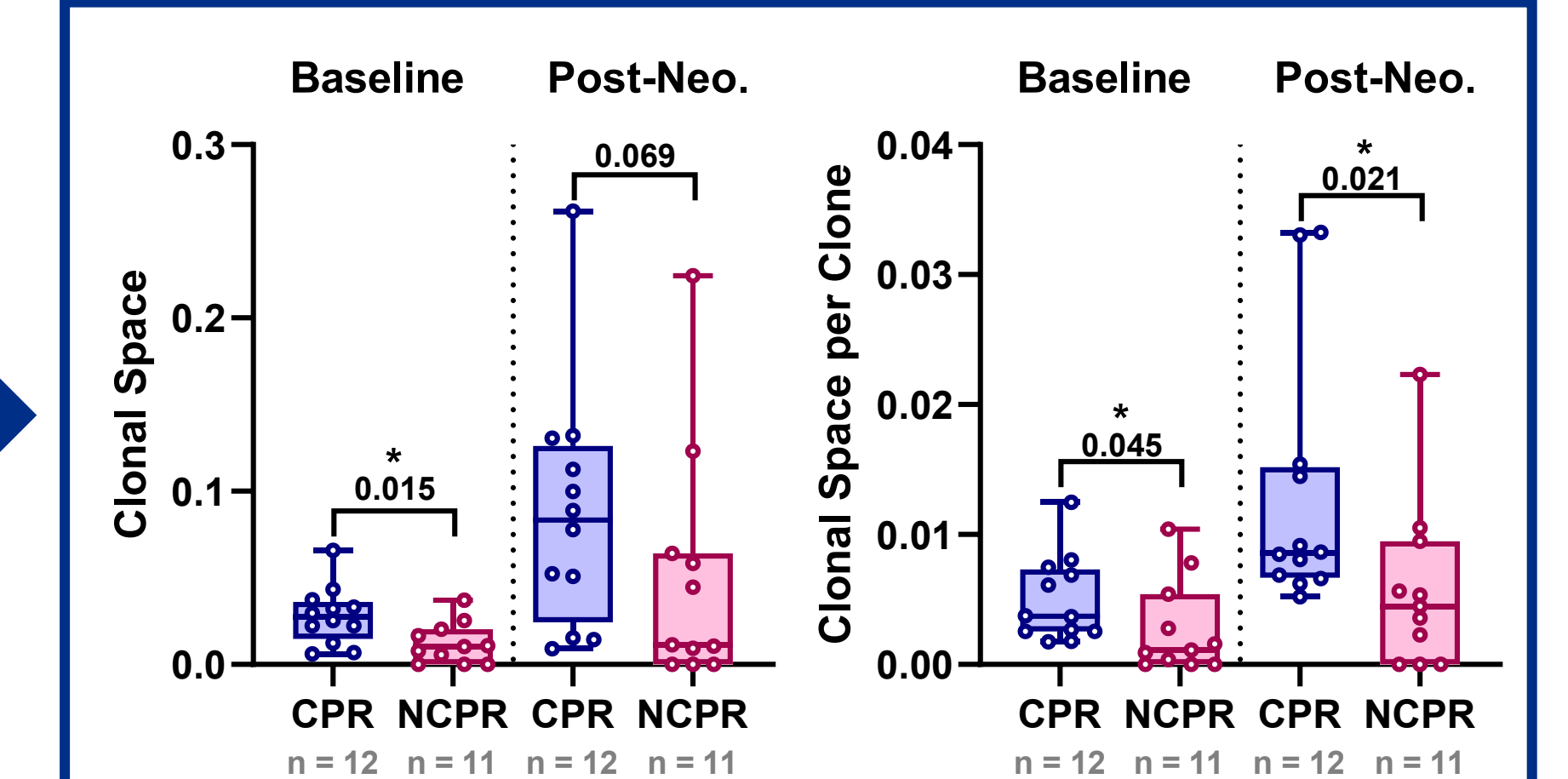
RESULTS

Tissue Samples

Figure 1. A) All Clones



B) Expanded Clones



C) Contracted Clones

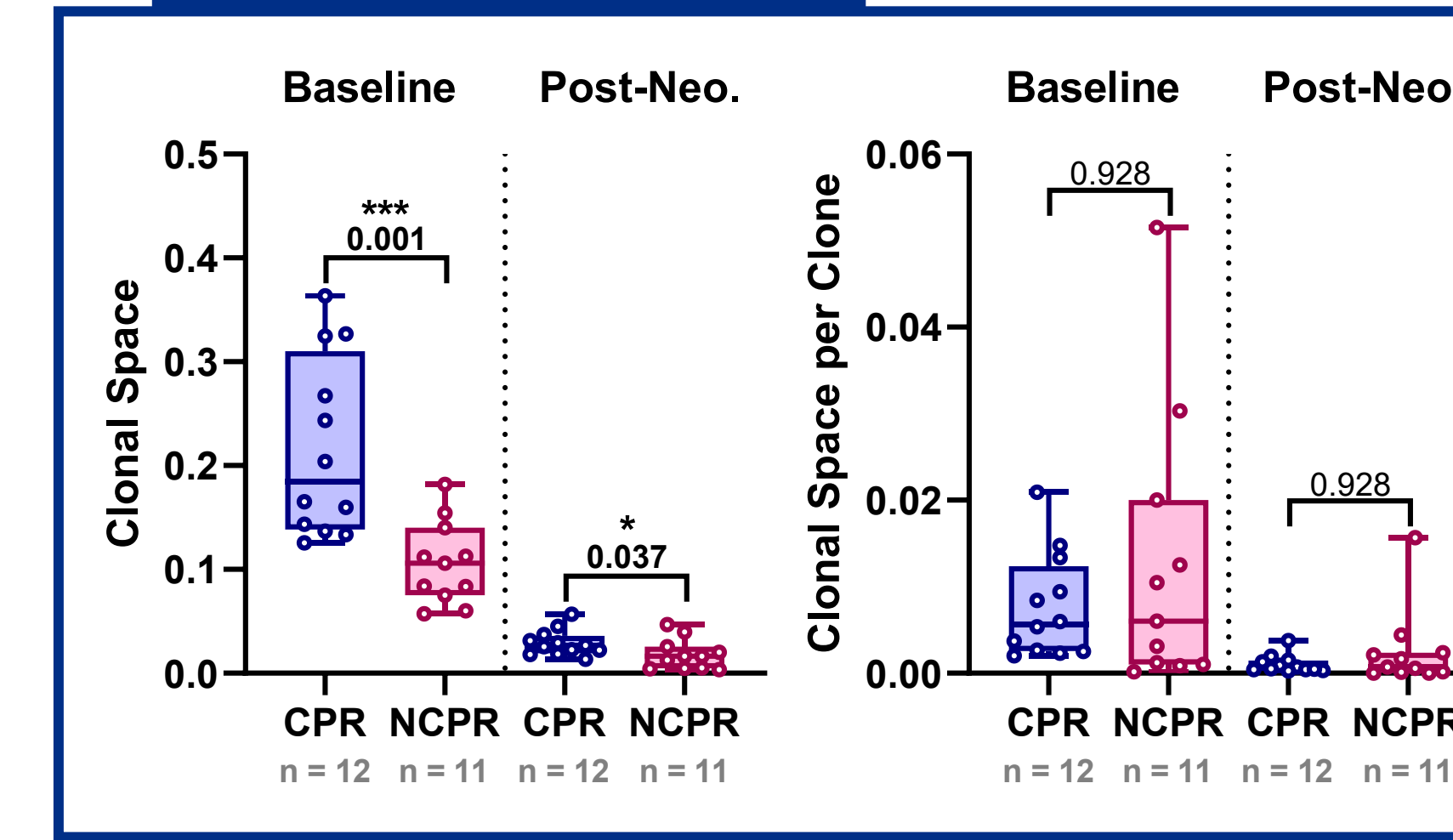


Figure 1. Tissue Dynamics of the Top 1% Baseline Tissue TCR Clones Following Neoadjuvant Treatment. (A) After neoadjuvant treatment, the differences in the clonal space (CS) occupied by the top 1% baseline tissue clones between CPR and NCPR tumors became less pronounced, due to an overall reduction after the neoadjuvant treatment. Nevertheless, CPR tumors retained these clones at approximately 10% of the total CS (median 10.35%; IQR 4.96%–16.03%), whereas in NCPR tumors they accounted for only 5% (median 4.91%; IQR 1.66%–6.77%). **(B)** Among expanded clones, both the overall and the normalized CS per clone were higher in the CPR tumors, indicating a greater contribution of each individual expanded clone to the overall repertoire. **(C)** In contrast, for contracted clones, these differences were observed only in the overall CS.

Blood Samples

Figure 2. A) All Clones

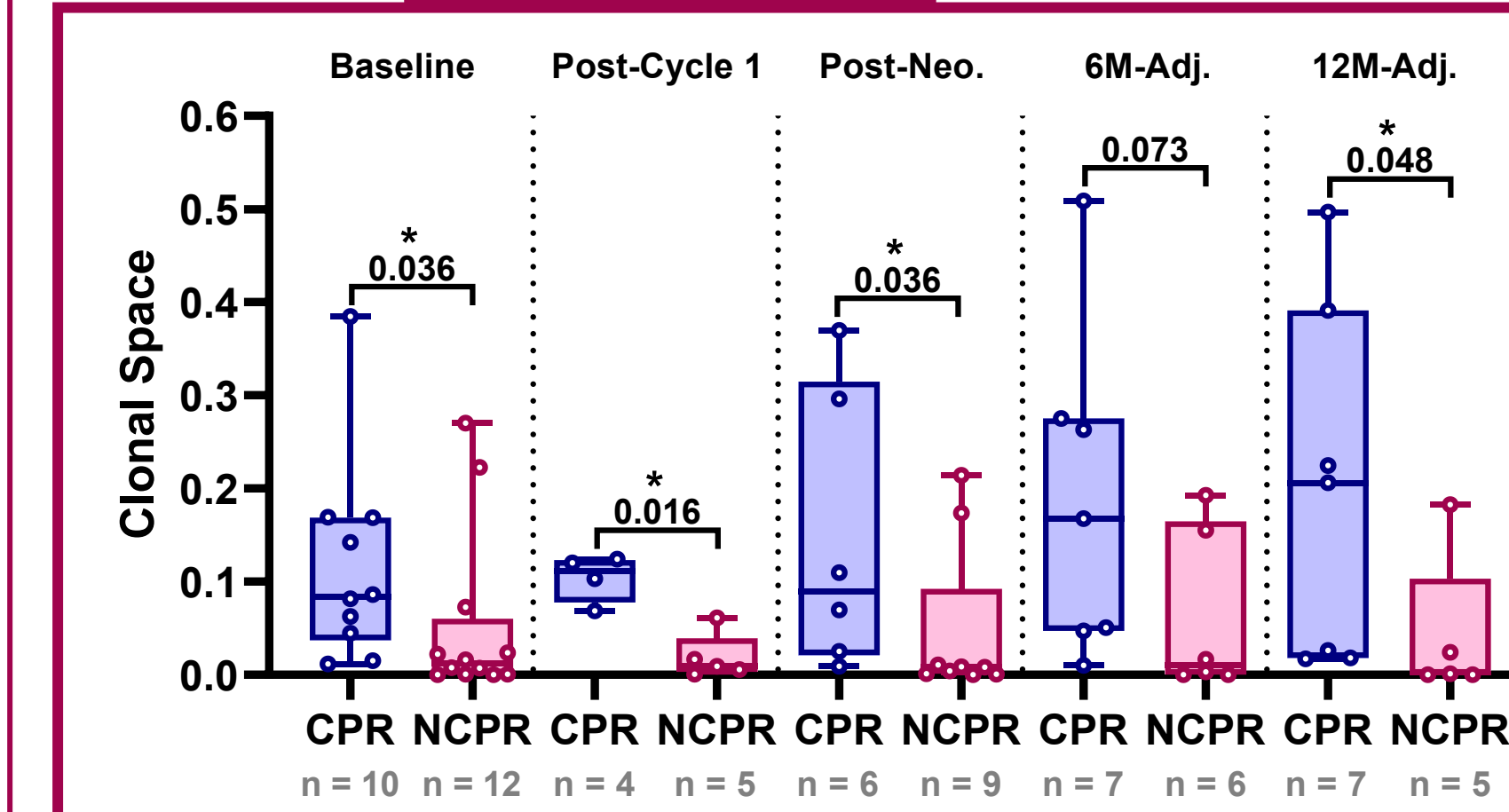
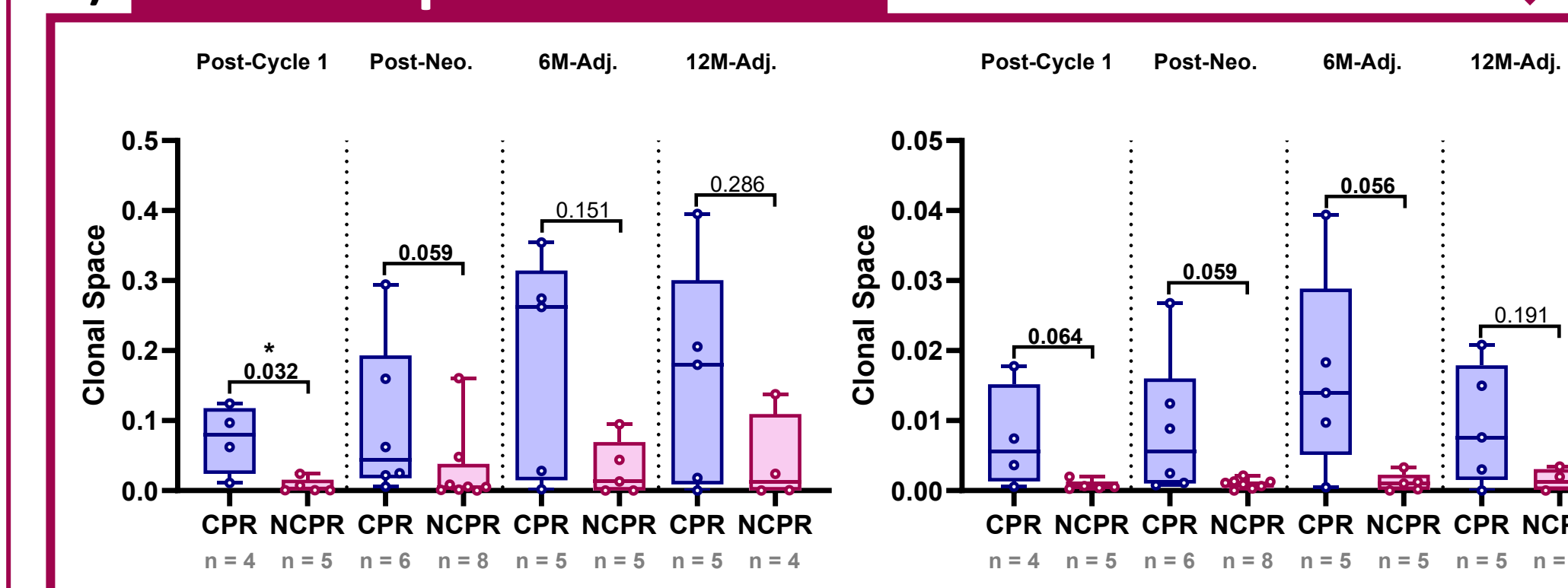


Figure 2. Blood Dynamics of the Top 1% Baseline Tissue TCR Clones Following Neoadjuvant Treatment. (A) The top 1% baseline tissue clones remained detectable in peripheral blood throughout treatment, with a consistently higher representation in patients achieving CPR. In these patients, the clones occupied approximately 11% of the total blood clonal space (CS) (median 11.19%; IQR 2.35%–28.04%), whereas in NCPR patients they accounted for less than 1% (median 0.84%; IQR 0.08%–4.27%) across all treatment time points. **(B)** Tracking the dynamics of these top 1% tissue clones from the baseline blood revealed that expanded blood clones tended to occupy a greater CS in patients with CPR at multiple treatment time points. **(C)** On the contrary, contracted blood clones showed no differences according to treatment response.

B) Blood Expanded Clones



C) Blood Contracted Clones

