

Abstract # 35472

B014

Sean Santos¹, Emma Darlington², Laura Woodhouse², Niamh Peters², Erin Peat², Assunta De Rienzo¹, Rob Smale³, Shawn Watson¹, Stephen Blakemore¹, Louise Carter^{2,4}, Carly Campbell¹

1. Bicycle Therapeutics, Cambridge, MA. 2. Experimental Cancer Medicine Team, The Christie NHS Foundation Trust, Manchester, United Kingdom. 3. Neogenomics, Fort Meyers, FL. 4. Division of Cancer Sciences, The University of Manchester, Manchester, United Kingdom.

INTRODUCTION

- ▶ Nectin-4, a cell adhesion molecule from the Nectin-like family, is a validated tumor target overexpressed on the surface of cells in several cancers¹.
- ▶ Using Bicycle peptides, a novel class of fully synthetic, short, constrained peptides, we are developing Bicycle Toxin Conjugates[®] (BTCs) and Bicycle Tumor-Targeted Immune Cell Agonists (Bicycle TICAs) that target Nectin-4 expressing tumors.
- ▶ BT8009 is a BTC[™] which consists of a bicyclic peptide targeting Nectin-4 linked to the cytotoxin monomethyl auristatin E (MMAE) via a molecular spacer and cleavable linker.
- ▶ BT7480 is a Bicycle TICA[™] that binds Nectin-4 on tumor cells and CD137 on immune cells to induce CD137 mediated immune agonism.
- ▶ Both BT8009 and BT7480 are currently under investigation in clinical trials, BT8009-100 (NCT04561362) and BT7480-100 (NCT05163041), respectively.
- ▶ To identify tumors expressing Nectin-4, we previously developed a proprietary Nectin-4 monoclonal antibody to measure its protein expression in an immunohistochemistry (IHC) assay².

METHODS

- ▶ In collaboration with The Christie Hospital & The Manchester Cancer Research Centre Biobank (MCRC), we performed Nectin-4 IHC on tissue microarrays (TMAs) created by the MCRC from samples provided by The Christie consisting of tumor biopsies from 59 non-small cell lung cancer (NSCLC) patients, including 4 longitudinal pairs, and 10 synchronous primaries with an average of 4 cores per tissue.
- ▶ A Nectin-4 IHC assay was developed to CAP/CLIA standards on the Leica platform using a proprietary rabbit monoclonal α -Nectin-4 primary antibody YMW-1-58 (Abcam, Burlingame CA) and the BOND Polymer Refine detection kit.
- ▶ A pathologist manually scored the TMAs for Nectin-4, evaluating tumor proportion score (TPS), which is the percentage of viable tumor cells showing staining at any intensity, independently in the tumor cell membrane and tumor cytoplasm. If tumor membrane or cytoplasm is not specified, TPS refers to the greater of the two metrics.
- ▶ Using a validated cutoff of TPS > 1, Nectin-4 positivity was defined as TPS > 1 in either the tumor membrane or tumor cytoplasm, in at least 1 core.

RESULTS

Demographics:
▶ Median age: 68.1

Sex:
▶ 57.6% Male (n = 34)
▶ 42.4% Female (n = 25)

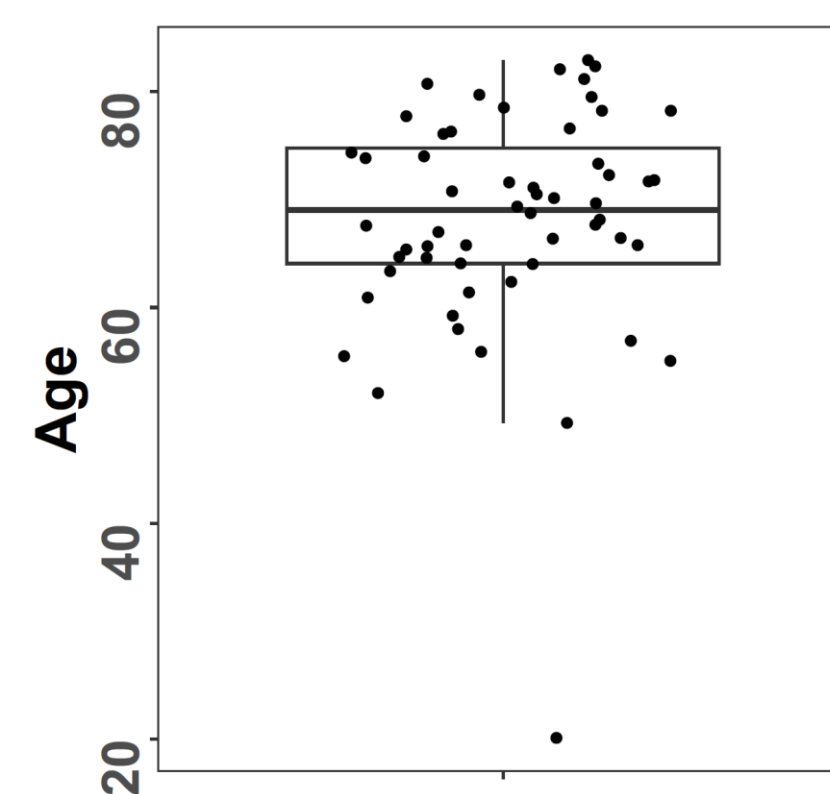
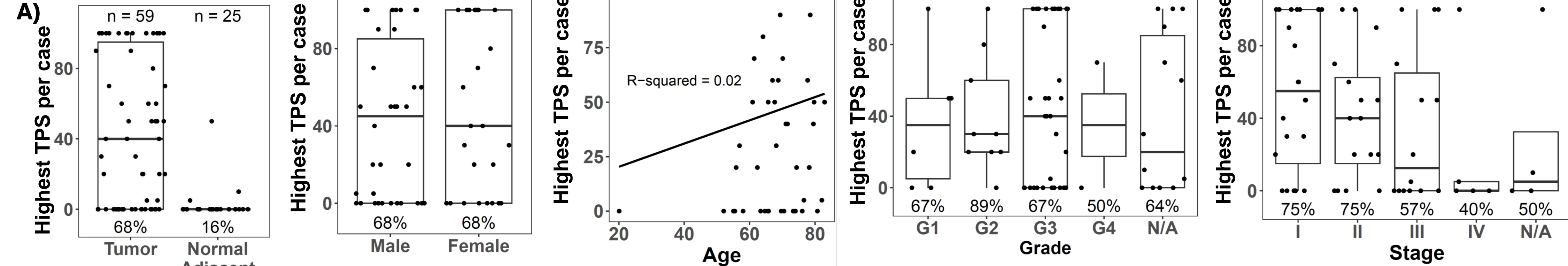


Figure 1. Distribution of patient age at baseline.

RESULTS



Category 1	Category 2	P-value
Adeno carcinoma	SqCC	0.55
Grade 2	Grade 3	0.25
Stage I	Stage 3	0.30
KRAS	No mutation	0.70

Figure 2. High Nectin-4 positivity in NSCLC. Highest TPS per case characterized by A) tumor and normal adjacent tissue, B) sex, C) age at baseline, D) grade, E) stage, F) morphology, G) mutational status. The total number of cases in each category is shown at the top and percent Nectin-4 positivity (see methods) at bottom.

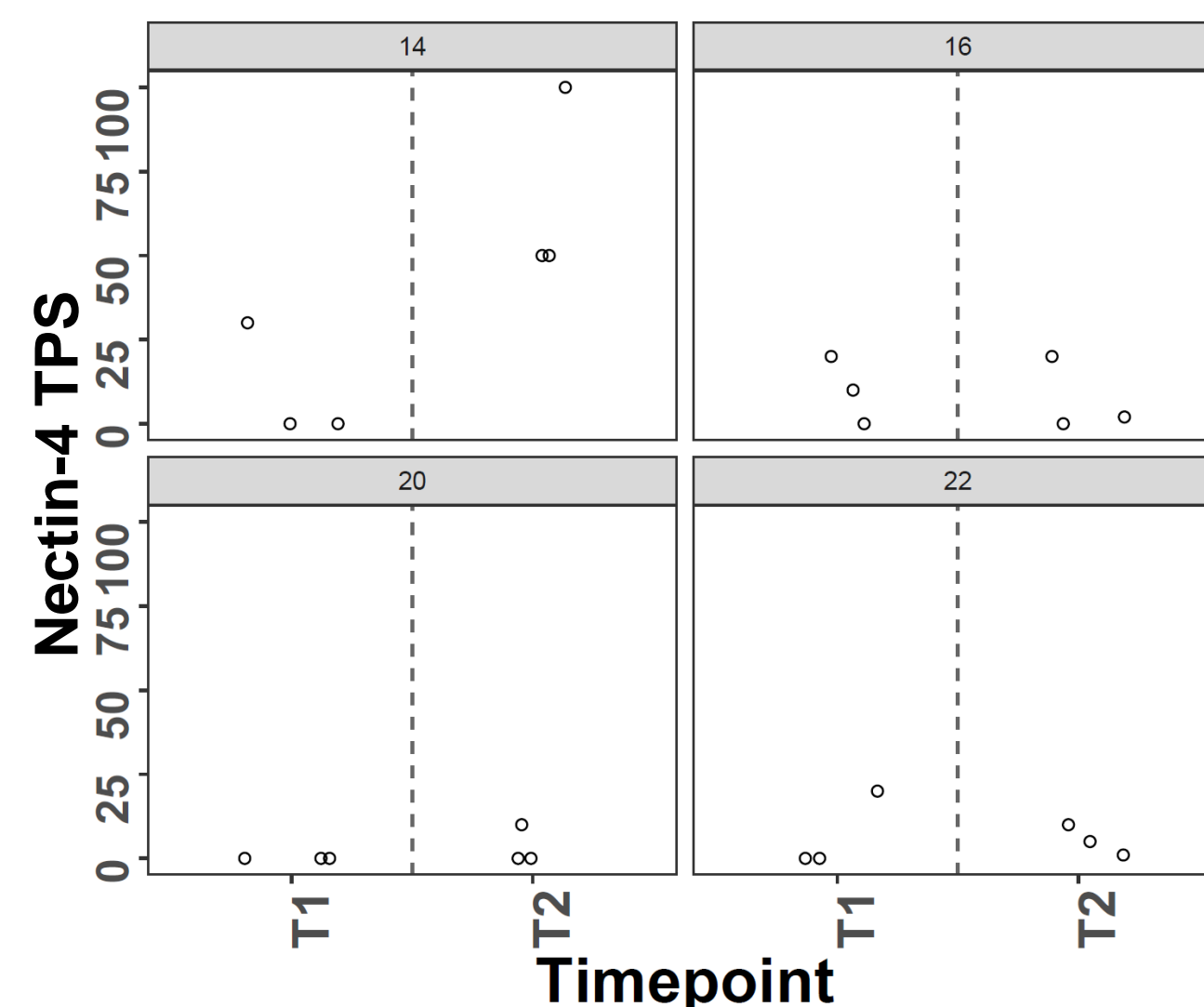
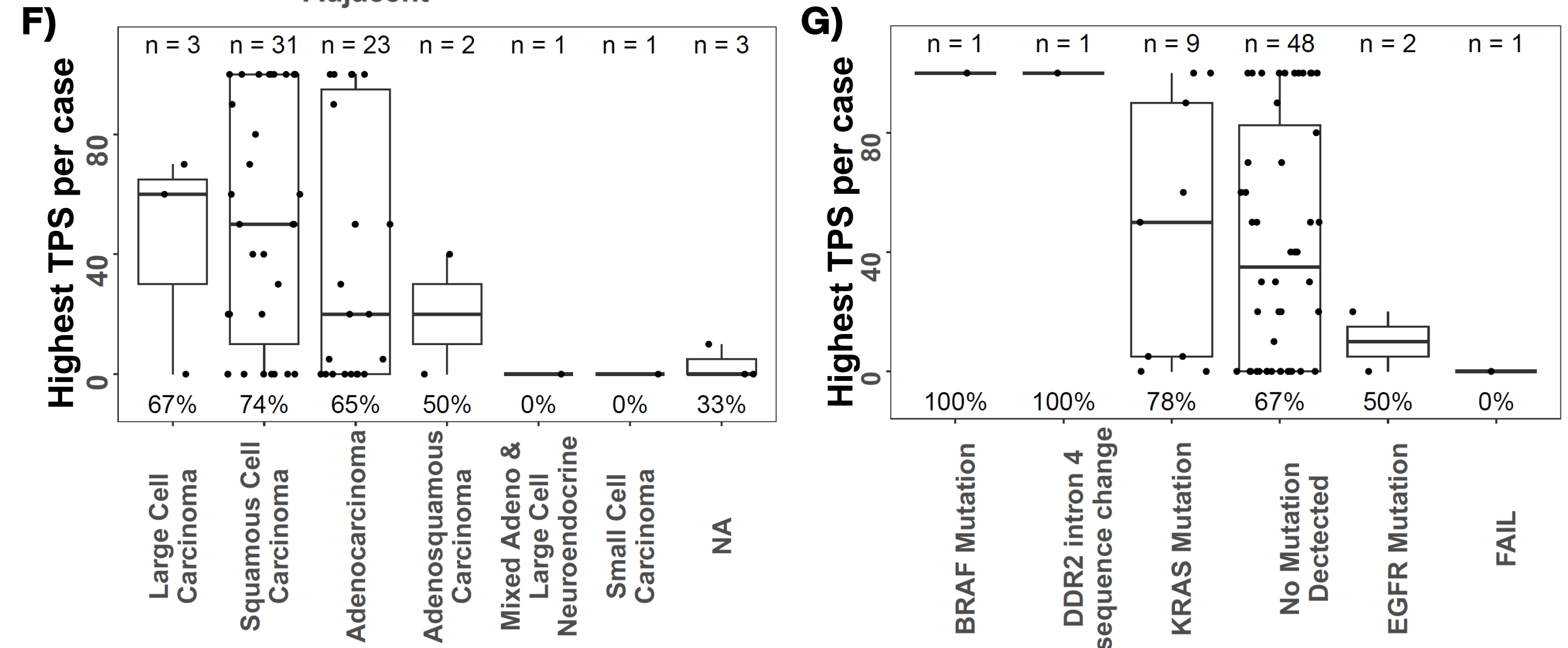


Figure 3. Nectin-4 TPS in longitudinal pairs. TPS in individual cores for the first (T1) or second (T2) timepoint for longitudinal pairs. Individual boxes represent the four patients with longitudinal pairs. 3/4 patients had Nectin-4 positivity at the first time point, and 4/4 at the second time point.

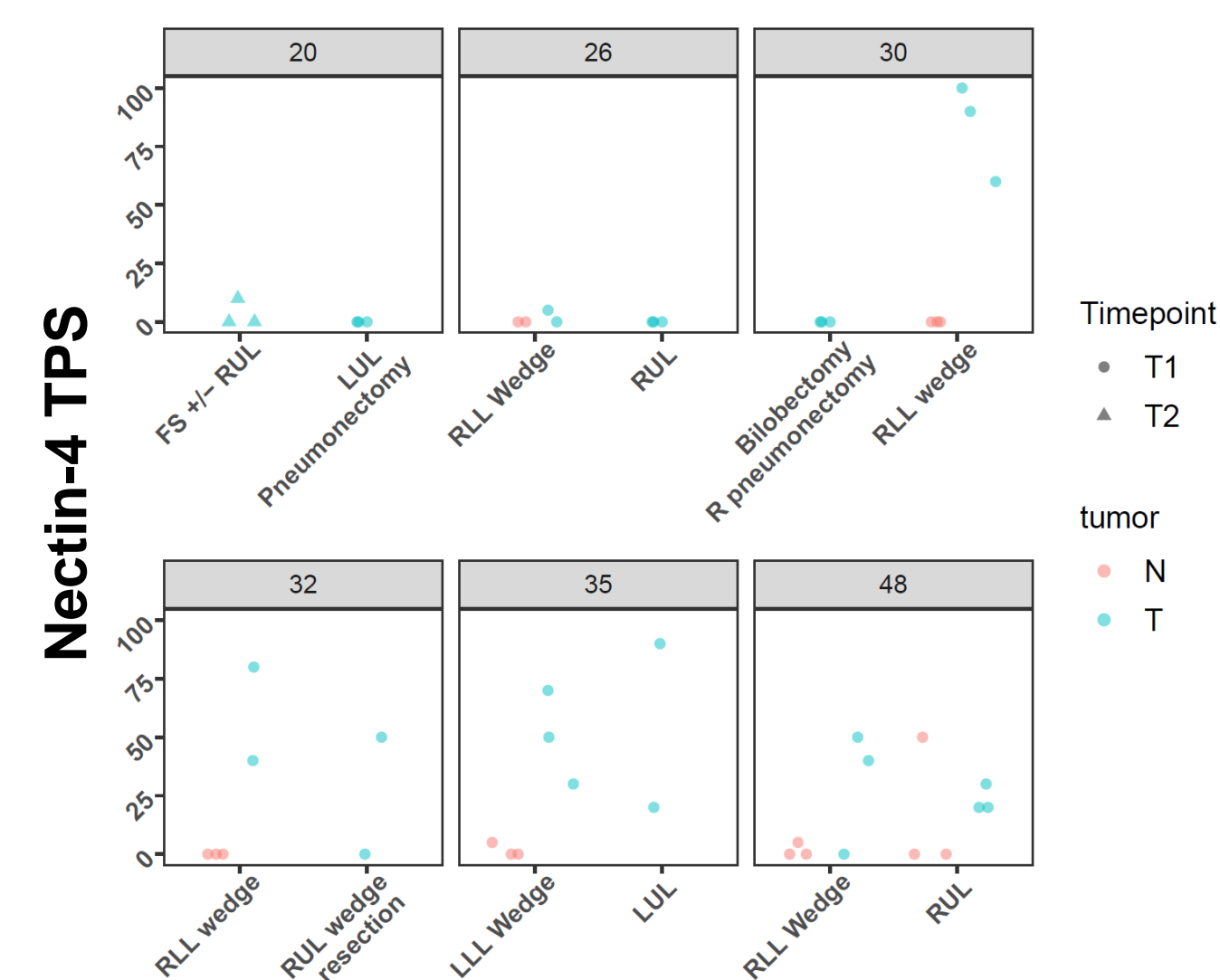


Figure 4. Heterogeneity in Nectin-4 TPS from select synchronous primaries. TPS is represented in individual cores for six synchronous primaries. Individual boxes represent six selected patients with synchronous primaries. Shape represents the first (T1) or second (T2) timepoint, and color represents normal adjacent (N) or tumor (T) tissue.

In some cases, samples taken from different locations met criteria for multiple categories and were considered separately (e.g. the total n may exceed total number of patients for these cases). H) Select category comparisons for Nectin-4 percent positivity using Fisher's exact test. SqCC = squamous cell carcinoma. *some percentages in figures have small differences compared to the abstract which included adjacent tissue in Nectin-4 percent positivity calculations in categorical groups, and are not included here except in A.

SUMMARY

- ▶ ~68% of NSCLC patients had Nectin-4 staining in at least one core from a biopsy taken at baseline.
- ▶ A similarly high rate of Nectin-4 positivity is observed in several NSCLC subcategories.
- ▶ The high percent of Nectin-4 positivity observed in NSCLC supports the inclusion of this indication in Bicycle's BT8009-100 and BT7480-100 studies.

REFERENCES

1. Challita-Eid, P. et al. Cancer Research. 2016; 76(10): 3003-13.
2. Campbell, C. et al. AACR Annual Meeting 2021. Poster #1197.

Bicycle Therapeutics, Inc.
35 Cambridgepark Drive, Suite 350
Cambridge, MA 02140
USA
T. +1 617-945-8155

BicycleTx Limited
Portway Building
Grantia Park, Cambridge
CB21 6GS, UK
T. +44 (0)1223 261503
Company number 11036101.
Registered in England.
bicycletherapeutics.com

