

Clinical Impact of NGS Testing and Targeted Therapy Treatment Across Histologic Subtypes of Advanced NSCLC

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BACKGROUND

- Molecular testing for driver identification and first-line (1L) therapy selection is a guideline-recommended practice for the treatment of advanced NSCLC (aNSCLC).
- Adenocarcinoma (LUAD) comprises the majority of NSCLC, and the prevalence of driver alterations and associated outcomes in other histological subtypes has not been as thoroughly assessed.
- We examined the clinical impact of comprehensive genomic profiling (CGP) and targeted therapy (TT) treatment in aNSCLC across histologic subtypes.

METHODS

- The US-based deidentified Flatiron Health-Foundation Medicine (FH-FMI) NSCLC Clinico-Genomic Database (CGDB), in which clinical data from the FH Research Database¹ were linked to genomic data derived from FMI's CGP tests by de-identified, deterministic matching², was queried to assess the distribution of NCCN drivers and treatment patterns in patients with aNSCLC.
- The cohort included 11,862 patients with aNSCLC (diagnosed between January 2011 and September 2025) who underwent tissue-based CGP (FoundationOne®CDx).
- The cohort included the following histological subtypes: LUAD (N=8,738), squamous cell carcinoma (LUSC; N=2,951), adenosquamous carcinoma (ASC; N=87), pulmonary sarcomatoid carcinoma (PSC; N=52), and large cell carcinoma (LCC; N=34).
- NCCN drivers were categorized into those associated with 1L approved matched targeted therapy (mTT) (ALK rearrangements [REs], BRAF V600E, EGFR mutations [mut], ERBB2 muts, MET exon 14 skipping alterations [METex14], NTRK fusions, RET RE, ROS1 RE), mTTs approved for previously treated (2L+) patients (KRAS G12C, ERBB2 amplifications [amps] and MET amps), or associated with investigational therapies (KRAS non-G12C muts).
- mTT receipt was assessed for targetable driver-positive (driver+) tumors associated with an approved TT at the time of 1L treatment.
- Real-world overall response rate (rwORR) was summarized for driver+ patients treated with a mTT. rwORR was based on abstracted real-world response (rwR), defined as the clinician assessment of change in disease burden following radiographic imaging. rwR assessments within 30 days of a line start were excluded.

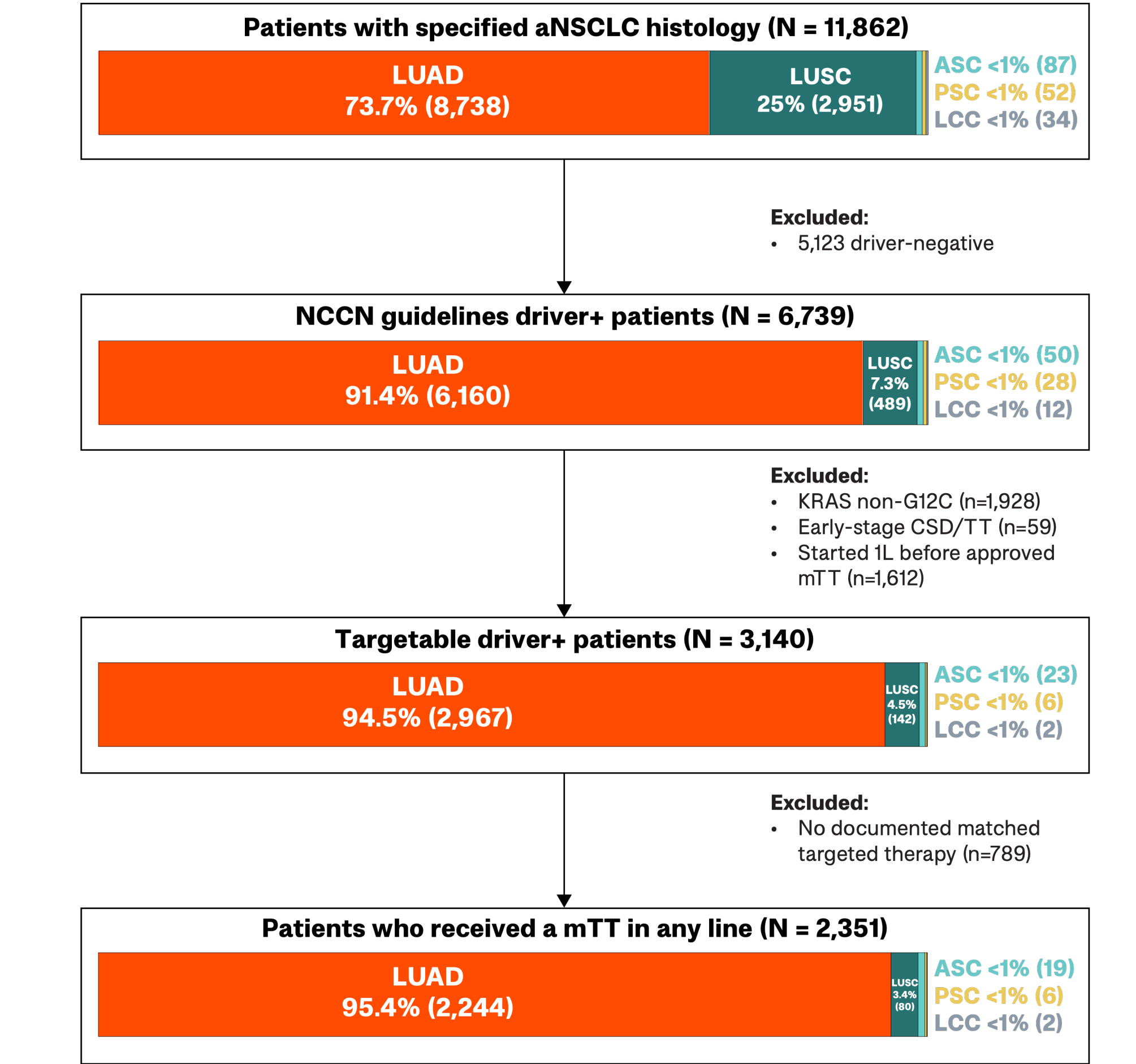


FIGURE 1: Consort diagram

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RESULTS: CGP Testing Timing for Patients with aNSCLC by Histology

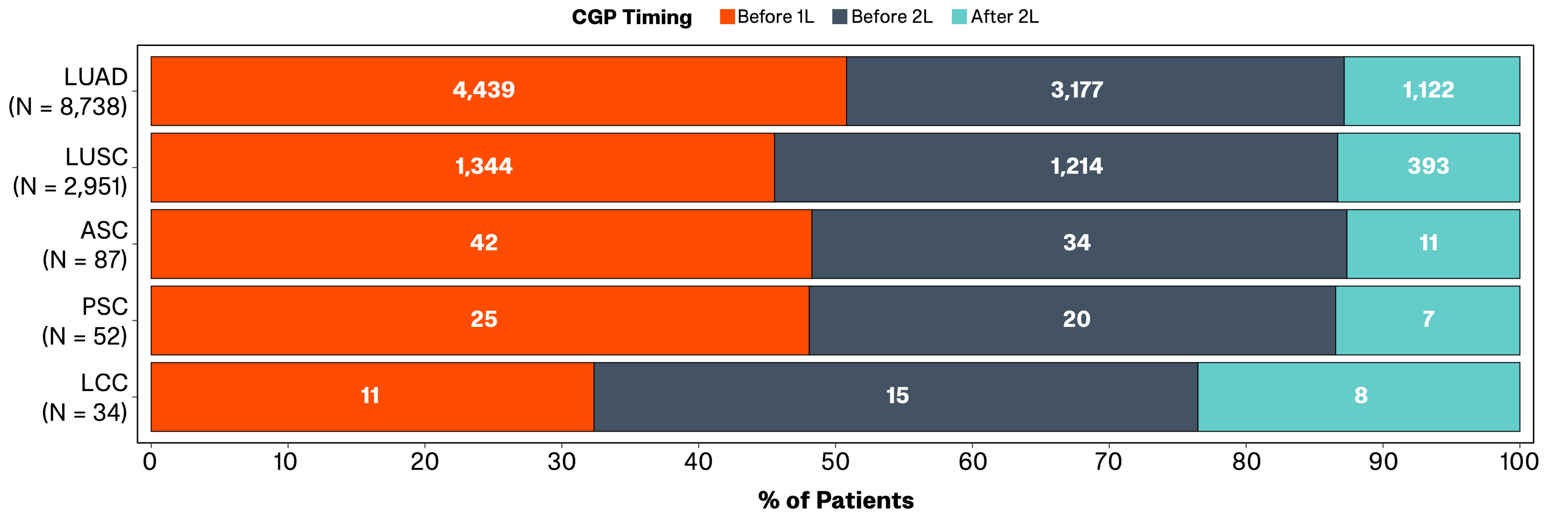


FIGURE 2. Timing of CGP testing. Distribution of FMI CGP testing timing stratified by histology.

- Among patients with aNSCLC, approximately half of those with LUAD (51%), ASC (48%), and PSC (48%) underwent CGP testing before 1L therapy start, compared to 46% of patients with LUSC and 32% of patients with LCC.

RESULTS: Driver Prevalence by Histology

- Among all patients with aNSCLC:**
- 6,739 (57%) patients harbored an NCCN genomic driver alteration. LUAD cases had the highest driver prevalence (70%), followed by ASC (57%), PSC (54%), LCC (35%) and LUSC (17%).
- Among driver+ cases:**
- EGFR L858R/ex19del comprised 14-20% of all drivers in ASC, LCC, and LUAD, compared to 6-7% in PSC and LUSC (p<0.001).
 - KRAS non-G12C mutations were overrepresented in LUSC and PSC compared to other histologies (32-39% vs. 25-28% of driver+ cases, p=0.04), while the relative prevalence of KRAS G12C remained consistent across histologies (14-22%, p = 0.93).
 - METex14 alterations represented a high relative proportion of drivers in PSC (29%) and ASC (14%) compared to other histologies (0-6%, p<0.001), whereas MET amps had a higher relative prevalence in LCC (25%) and LUSC (6%) compared to other histologies (0-2%, p<0.001).
 - ERBB2 amplifications were additionally overrepresented in LUSC (15%) and LCC (8%) compared to other histologies (0-3%, p<0.001).

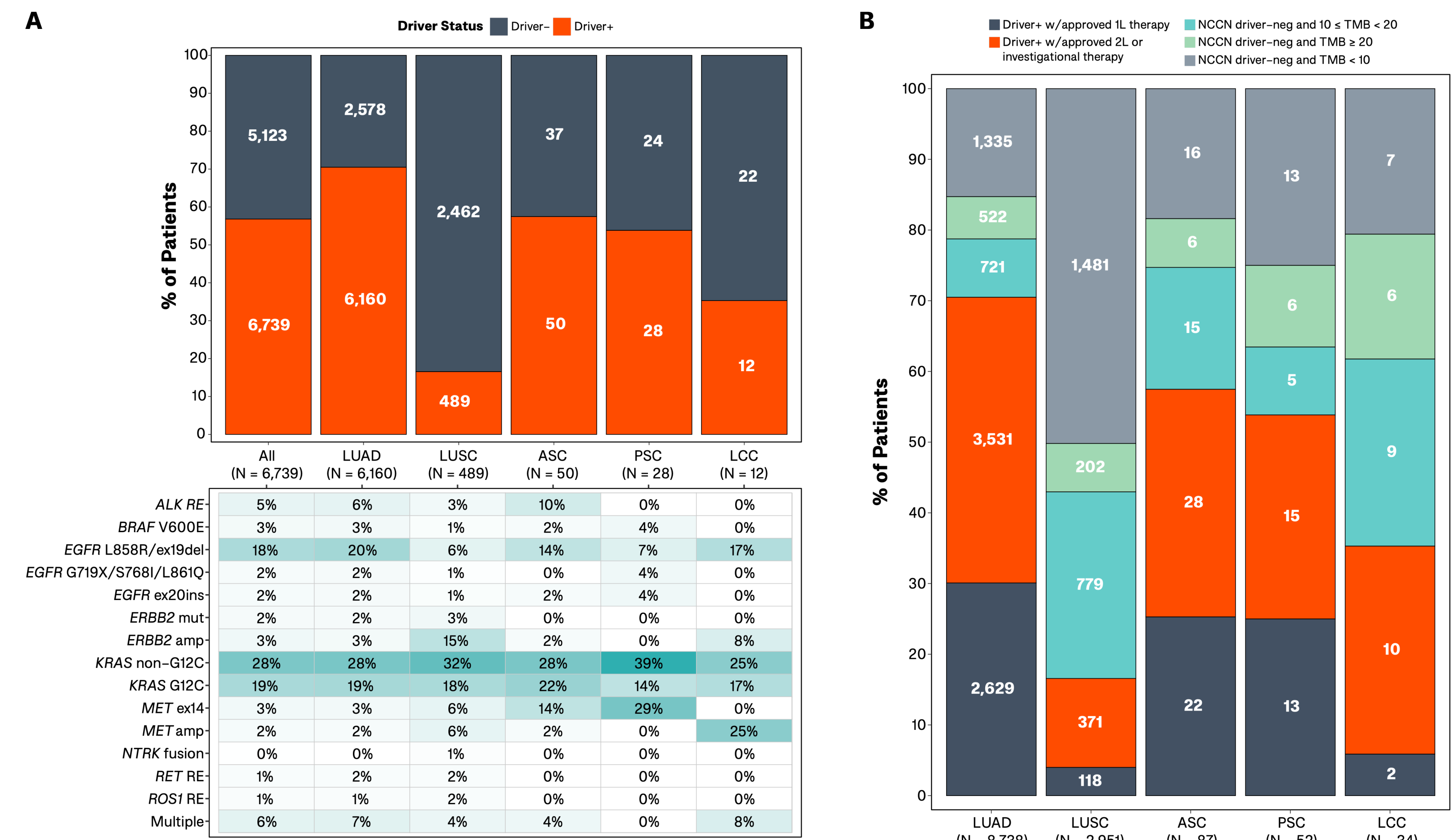


FIGURE 3. Driver prevalence and distribution across histologic subtypes. (A) Prevalence of NCCN-drivers across histologies and distribution of drivers within driver+ samples across histologies. (B) Prevalence of targetable alterations by histology, including tumor mutational burden (TMB). Approximately, 50% of patients in LUSC and 80% in the remaining histologies, harbored a targetable genomic driver or high TMB.

RESULTS: mTT Receipt and Clinical Outcomes

- Among the 3,140 patients positive for a driver associated with an approved mTT:**
- 76% (2,244/2,967) of LUAD patients received a mTT (70% in 1L) compared to 56% (80/142) of LUSC (60% in 1L) (p<0.001).
 - Additionally, 83% (19/23) of ASC, 100% of PSC (6/6), and 100% of LCC (2/2) also received a mTT.

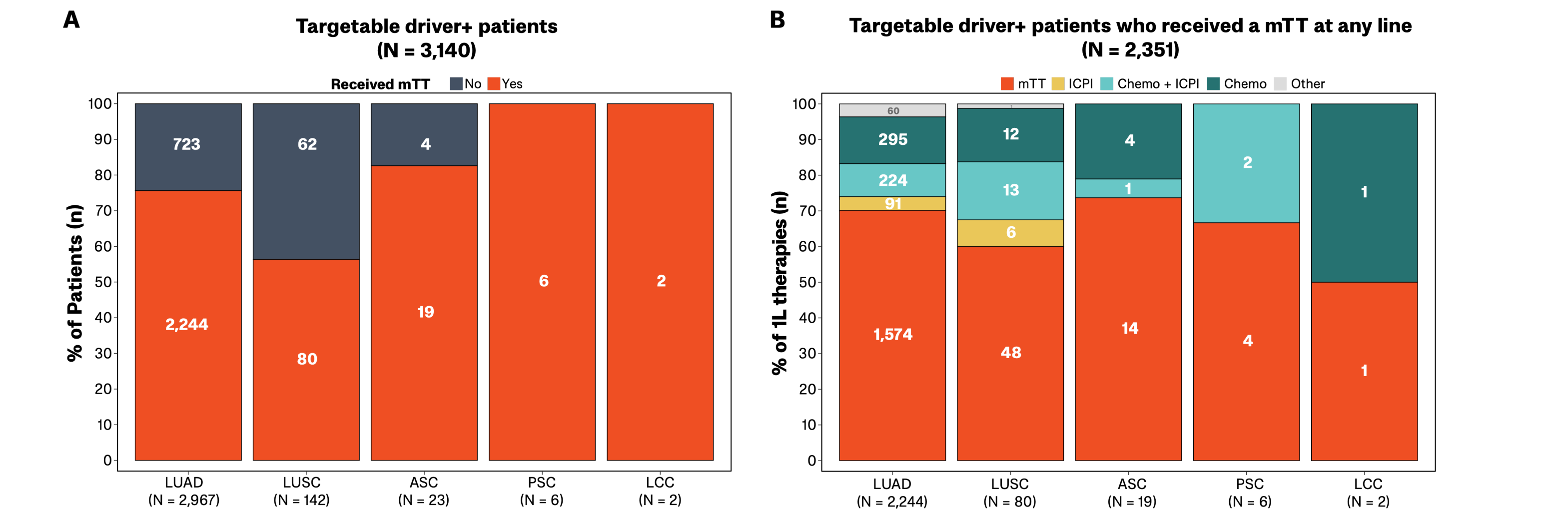


FIGURE 4 Treatment patterns. (A) Rate of mTT receipt (in any line) among patients positive for a targetable driver, stratified by histology. (B) Distribution of 1L therapies among patients who received a mTT at any line, by histology.

- In driver+ patients who received a 1L mTT with documented rwR (1,165 LUAD, 32 LUSC, 11 ASC, 4 PSC, 1 LCC):**
- The rwORR was 71% for LUAD and 68.8% for LUSC.
 - For the remaining ASC, PSC, and LCC patients, the combined rwORR was 44% (7/16).

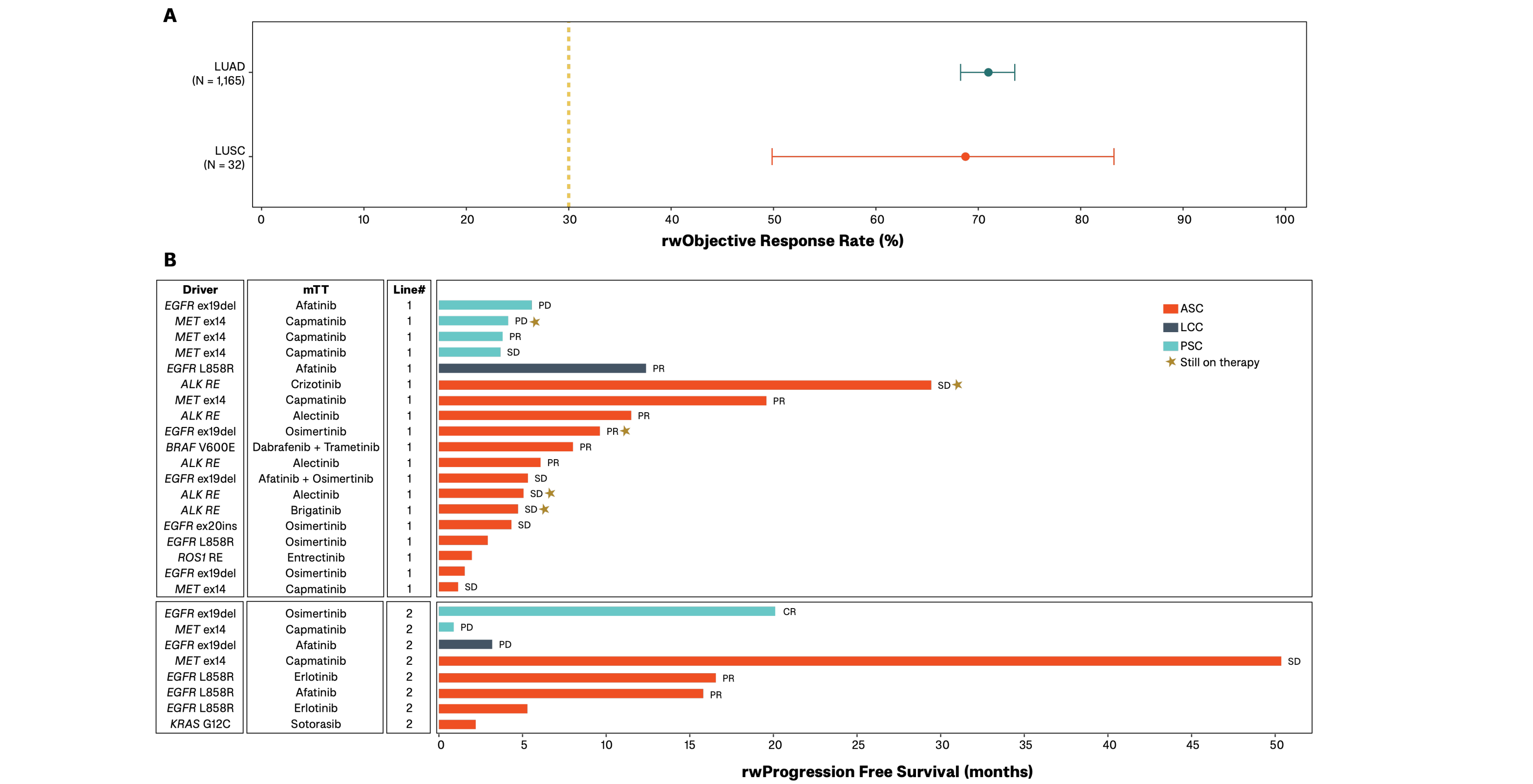


FIGURE 5. Clinical outcomes. (A) rwORR in LUAD and LUSC, demonstrating response rates that exceeded the literature-reported benchmark of 30% for chemotherapy³ (yellow line). (B) rwPFS and best observed rwR for patients with ASC, PSC, and LCC. Driver alterations, mTT received, and mTT line number are also shown.

CONCLUSIONS

- Targetable drivers were identified across all histologic subtypes of aNSCLC with histology-specific variation in driver enrichment.
- In all histologies except for LCC, approximately half of patients underwent CGP prior to 1L treatment.
- Fewer patients with LUSC tumors received mTT than those with LUAD, even though ORRs were comparable among driver+ patients treated with 1L mTT in both histologies. Responses were likewise seen in driver+ ASC, PSC, and LCC patients who received 1L mTT.
- These findings suggest that expanding CGP uptake may increase identification of patients eligible for targeted therapies and improve delivery of precision oncology across the spectrum of aNSCLC histologies.

REFERENCES

- Flatiron Health. Database Characterization Guide. Flatiron.com. Published March 18, 2025. Accessed August 19, 2026. <https://flatiron.com/database-characterization>
- Singal G, Miller PG, Agarwala V, et al. Association of patient characteristics and tumor genomics with clinical outcomes among patients with non-small cell lung cancer using a clinicogenomic database. JAMA. 2019;321(14):1391-1399. doi:10.1001/jama.2019.3241
- Li G, Greene SB, Kaur B, et al. Clinical utility of companion diagnostic biomarker results below the limit of detection in comprehensive genomic profiling of patients with advanced non-small cell lung cancer. The Oncologist. 2025;30(6):oyaf159.