

# Poorer outcomes in *EGFR* L858R-driven NSCLC treated with osimertinib may be addressed with novel combination of BLU-945 and osimertinib

Poster Number  
LB123

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## Background

- Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) are used to treat patients with *EGFR* mutant non-small cell lung cancer (NSCLC), including those with activating *EGFR* exon 19 deletions (ex19del) and L858R mutations
- Osimertinib, a 3<sup>rd</sup>-generation *EGFR* TKI, is the standard of care in treatment-naïve patients with advanced *EGFR* mutant NSCLC<sup>1</sup>
  - In the phase 3 FLAURA study, patients with *EGFR* ex19del had a median progression-free survival (mPFS) of 21.4 months, while patients with *EGFR* L858R mutations had a mPFS of 14.4 months<sup>2</sup>
  - While an increased overall survival (OS) benefit was observed in patients with *EGFR* ex19del treated with osimertinib versus 1<sup>st</sup>-generation TKIs, no OS benefit was seen with osimertinib in the *EGFR* L858R subset of the FLAURA study<sup>1</sup>
- Poorer outcomes for *EGFR* L858R mutations have also been reported with other 3<sup>rd</sup>-generation TKIs<sup>3</sup>
- BLU-945 is an investigational, next-generation, reversible, oral *EGFR* TKI that selectively targets common *EGFR* activating (L858R, ex19del) as well as T790M and C797X resistance mutations, while sparing *EGFR* wild-type (WT)<sup>4,5</sup>
- BLU-945 in combination with osimertinib could potentially provide superior inhibition of *EGFR* L858R in treatment-naïve patients, while preventing osimertinib on-target resistance mutations such as *EGFR* C797X
- BLU-945 in combination with osimertinib is an all oral novel combination that projects to have a differentiated tolerability profile from other studied combinations, including chemotherapy and amivantamab
- Here, we explored outcomes of patients with *EGFR* L858R-driven NSCLC using real-world datasets, analyzed potential contributors to poorer outcomes, and report a preclinical proof of concept for combination treatment BLU-945 with osimertinib, further validating prior data<sup>6</sup>

## Methods

### Real-world analyses

- Survival outcomes were assessed in front-line osimertinib-treated patients with *EGFR* ex19del or L858R from MD Anderson Cancer Center (MDACC; n=122; data cutoff: February 1, 2023)
- Clinical outcomes measured by time to treatment discontinuation (TTD), as well as prognosis factors, were assessed in front-line osimertinib-treated patients with *EGFR* ex19del or L858R from the clinical-genomic Guardant INFORM database (*EGFR* ctDNA baseline positive; n=1386; data cutoff: September 30, 2022)
- TTD was calculated as the time between front-line osimertinib initiation and discontinuation of osimertinib or death while on therapy. Patients who were lost to follow-up while on therapy were censored at last active date
- Inherent limitations of endpoints derived from administrative claims must be considered, including the extent of missing clinical information that is not routinely reported. Moreover, in real-world setting, reasons for treatment discontinuation can include cancer progression; however, it may also include adverse events, access barriers, patient choice, etc

### Cellular potency/synergy analyses

- Cellular half maximal inhibitory concentrations (IC<sub>50</sub>s) of osimertinib on *EGFR* mutations and WT were determined in Ba/F3 cells
- The *in vitro* analysis of additivity or antagonism between BLU-945 and osimertinib was performed in Ba/F3 cells expressing *EGFR* L858R. Cells were co-treated with a matrix of concentrations of BLU-945 and osimertinib, and tested by CellTiter-Glo® (72 hours treatment) and phosphorylated-EGFR (pEGFR) by AlphaLISA® (4 hours treatment)

### Cellular potency/synergy analyses continued

- Loewe synergy scores were calculated using SynergyFinder<sup>7</sup> and graded as follows:
  - Less than -10: likely to be **antagonistic**
  - From -10 to 10: likely to be **additive**
  - Larger than 10: likely to be **synergistic**

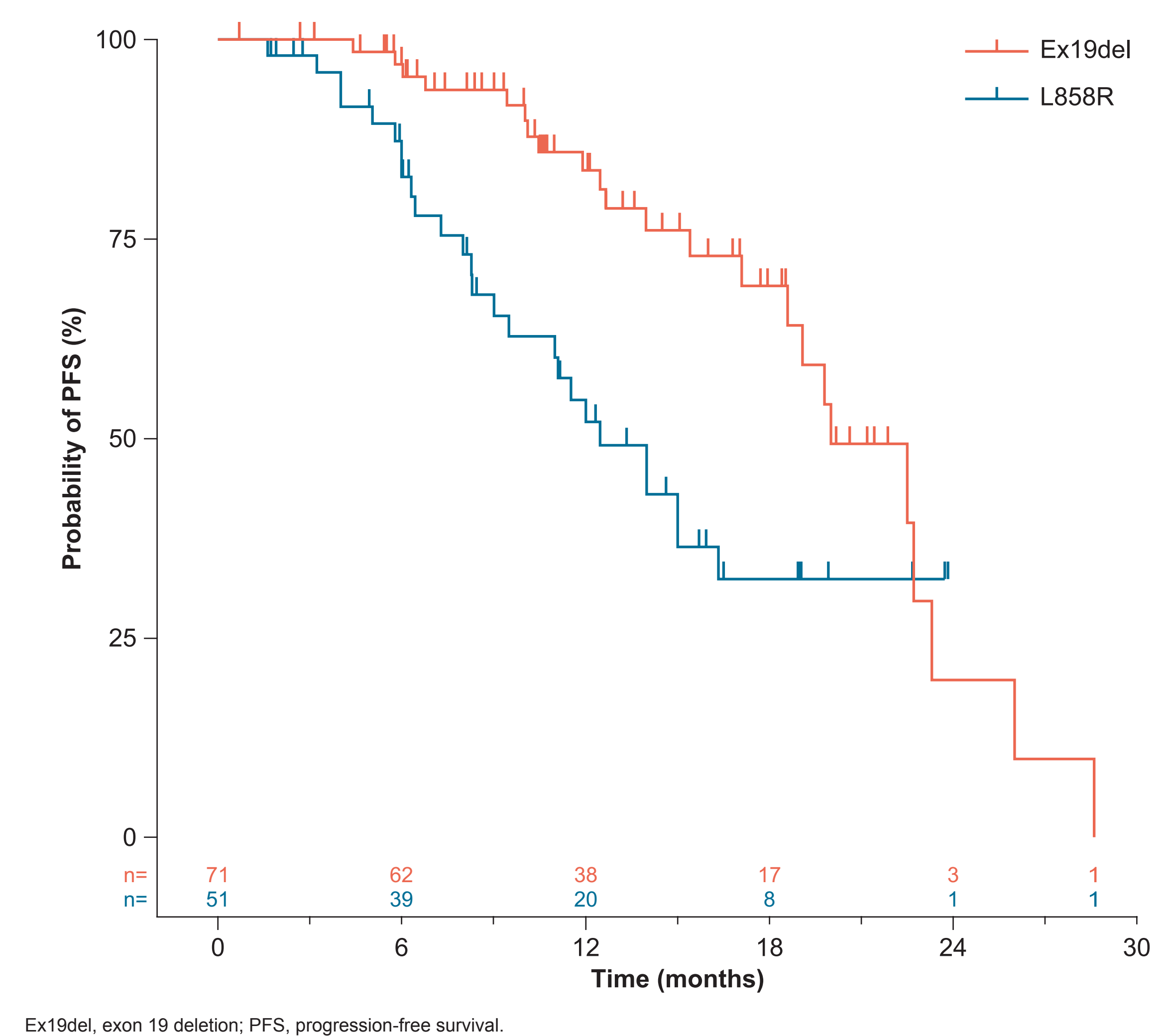
### *In vivo* antitumor activity of BLU-945 in combination with osimertinib

- The *in vivo* antitumor activities of BLU-945 75 mg/kg twice a day (BID) and osimertinib 5 mg/kg once a day (QD) as single agents and in combination were evaluated in a Ba/F3 cell line-derived xenograft (CDX) tumor model expressing *EGFR* L858R-mutant protein

## Results

- In the MDACC real-world data set, the 12-month PFS rate was 52% for L858R (n=51) versus 84% for ex19del (n=71); mPFS was 12.47 months for L858R versus 20 months for ex19del (Figure 1)
- Osimertinib exhibited most clinical and cellular activity on ex19del, followed by L858R, then G719X, and then exon 20 insertions (Figure 3)
- No antagonism was observed when combining BLU-945 and osimertinib in *in vitro* cellular proliferation assays (CellTiter-Glo) (Figure 4D) and pEGFR assays (Figure 4H)

**Figure 1: Poorer probability of PFS was observed in front-line osimertinib-treated patients with *EGFR* L858R versus *EGFR* ex19del from the MDACC cohort**

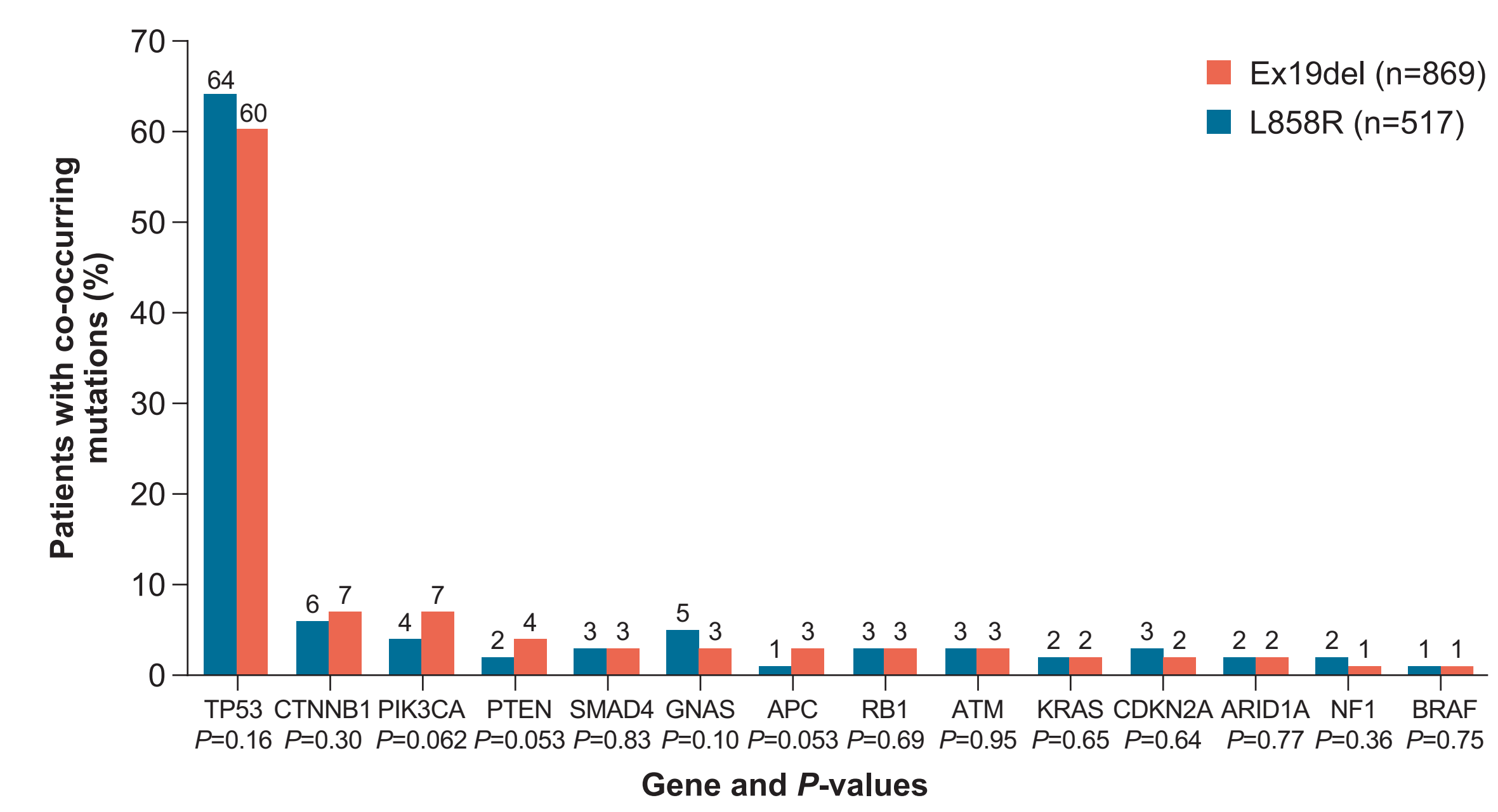


**Table 1: Shorter median time to treatment discontinuation was observed in front-line osimertinib-treated patients with *EGFR* L858R versus *EGFR* ex19del from the Guardant INFORM cohort**

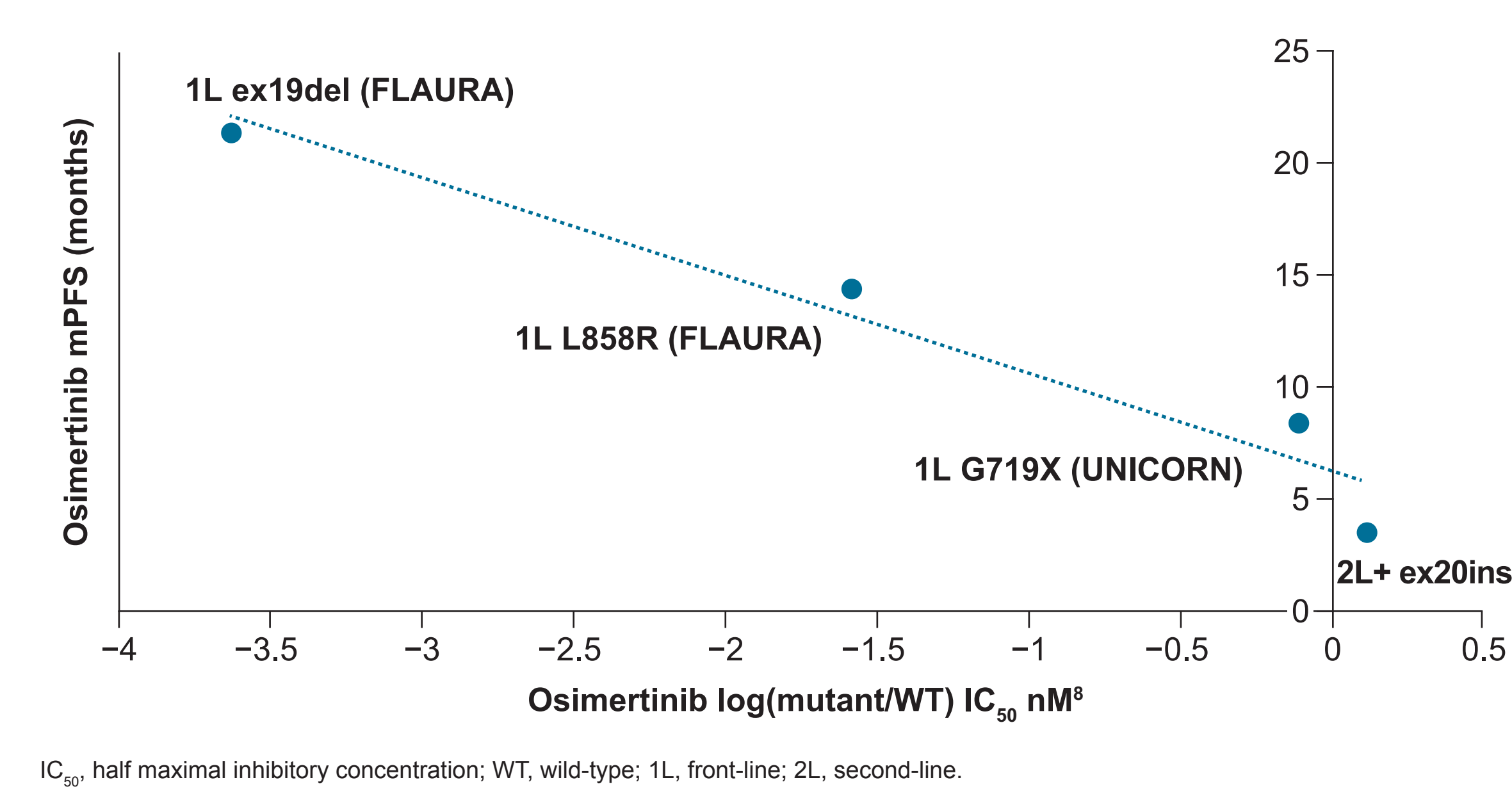
<i>EGFR</i> mutation	Patients	Event	Censored	Median TTD, month (95% CI)	Log-rank P-value
Ex19del	869	556	313	11.4 (9.6–12.8)	0.0026
L858R	517	338	179	8.0 (7.0–9.3)	

CI, confidence interval; *EGFR*, epidermal growth factor receptor; TTD, time to treatment discontinuation.

**Figure 2: Poor prognosis factors (including TP53 mutations and co-mutation number) were not significantly different between *EGFR* L858R and *EGFR* ex19del in the Guardant INFORM cohort; both had a similar number of off-target mutations in pre-osimertinib samples**

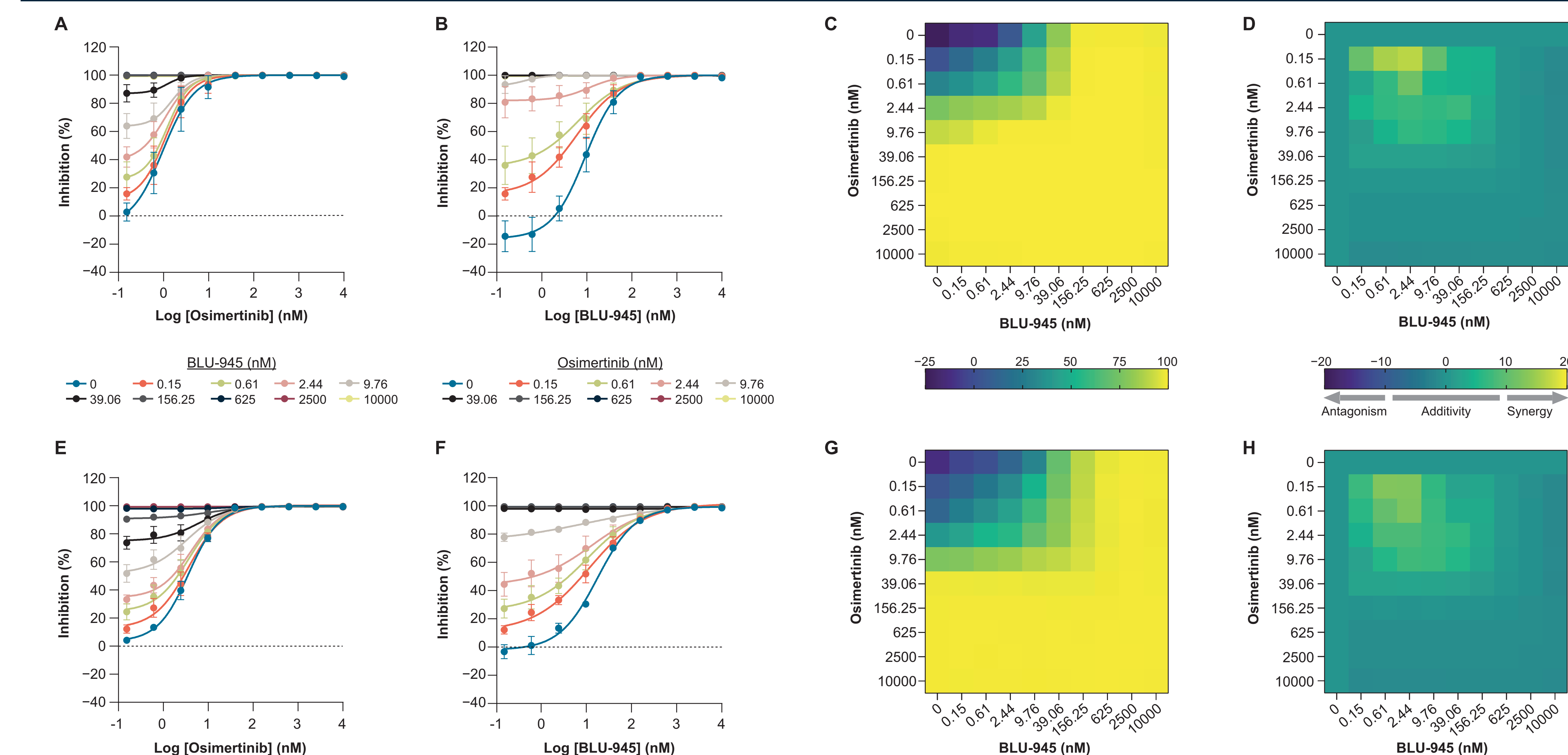


**Figure 3: A strong association was found between osimertinib cellular IC<sub>50</sub> and osimertinib clinical trial outcomes (mPFS) in osimertinib-treated patients with *EGFR* mutations**

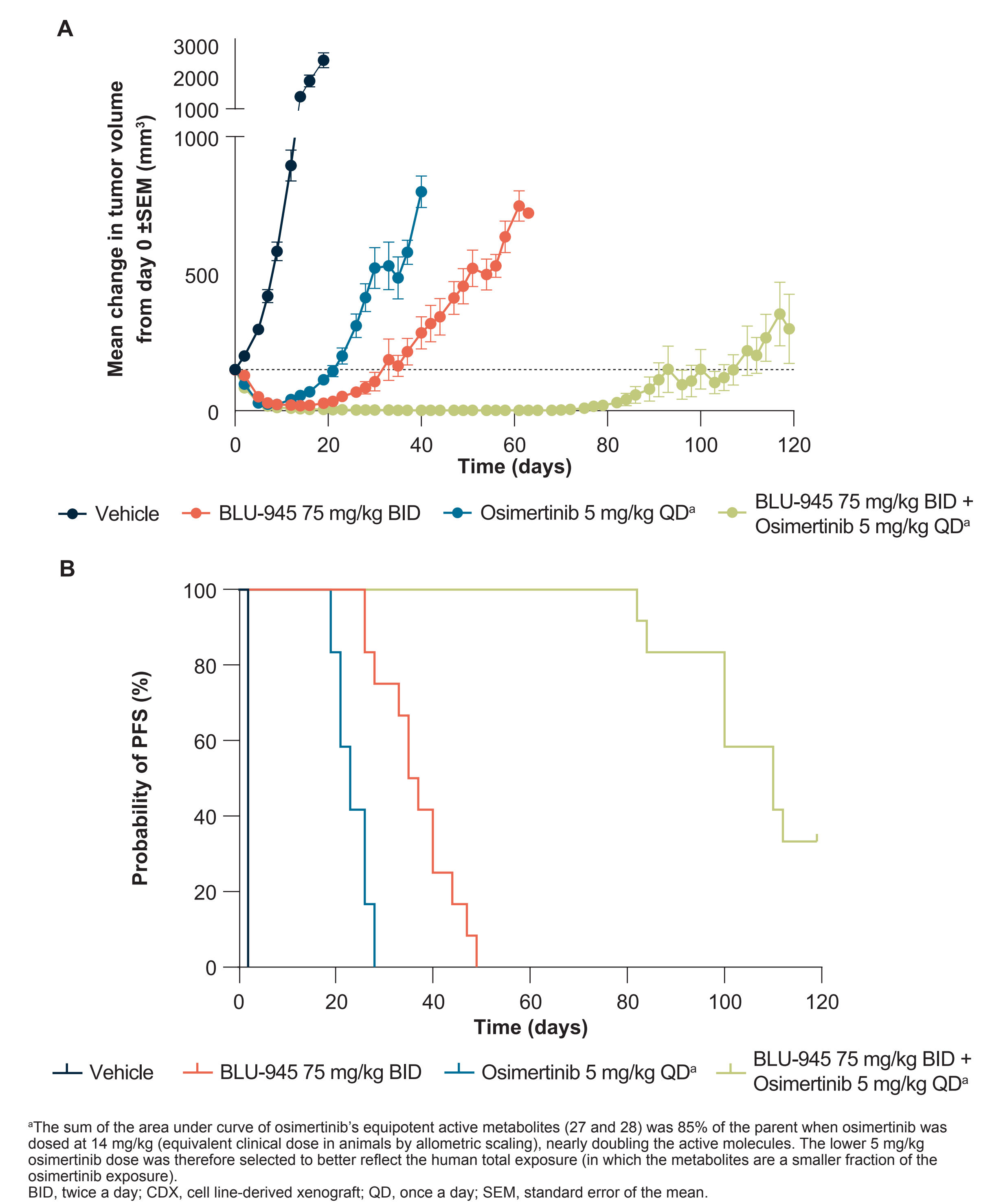


IC<sub>50</sub>, half maximal inhibitory concentration; WT, wild-type; 1L, front-line; 2L, second-line.

**Figure 4: *In vitro* cellular proliferation assay (A, B, and C) and *in vitro* cellular pEGFR assay (E, F, and G) showed additivity of BLU-945 and osimertinib in Ba/F3 *EGFR* L858R cell lines. No antagonism was observed when combining the 2 agents (D and H)**



**Figure 5: Administration of BLU-945 in combination with osimertinib resulted in tumor regression and prolonged durability of response in *EGFR* L858R-driven treatment-naïve Ba/F3 CDX model (A), and prolonged survival (B)**



\*The sum of the area under curve of osimertinib's equipotent active metabolites (27 and 28) was 85% of the parent when osimertinib was dosed at 14 mg/kg (equivalent clinical dose in animals by allometric scaling), nearly doubling the active molecules. The lower 5 mg/kg osimertinib dose was therefore selected to better reflect the human total exposure (in which the metabolites are a smaller fraction of the osimertinib exposure).

## Conclusions

- BLU-945 is an investigational, reversible, selective, and orally available TKI designed to target common activating and osimertinib-resistant mutations in *EGFR*-mutated NSCLC
- In both real-world datasets, front-line osimertinib-treated patients with *EGFR* L858R-driven NSCLC had poorer outcomes versus *EGFR* ex19del, further confirming the results from the phase 3 FLAURA study
- Poor prognosis factors were not significantly different between *EGFR* L858R and *EGFR* ex19del, with a similar number of off-target mutations
- Cellular IC<sub>50</sub> correlates closely with clinical PFS outcome. Together these data suggest that poorer outcomes in patients with *EGFR* L858R mutations is associated with weaker inhibition with osimertinib monotherapy
- BLU-945 and osimertinib bind to the ATP-binding pocket of *EGFR*. *In vitro* combination of BLU-945 and osimertinib showed additivity in Ba/F3 L858R cell lines, and no antagonism was observed when the 2 molecules were added simultaneously to cells
- In an *EGFR* L858R-driven Ba/F3 CDX model, BLU-945 monotherapy led to significant tumor growth inhibition, and BLU-945 in combination with osimertinib increased *EGFR* L858R inhibition further, resulting in more durable antitumor activity and longer survival in L858R xenografts versus osimertinib alone. This supports the rationale for combination treatment in treatment-naïve patients with *EGFR* L858R-driven NSCLC
- These data highlight the potential clinical application of combination BLU-945 and osimertinib in improving outcomes of patients with *EGFR* L858R-driven NSCLC in front-line settings. This combination therapy is being evaluated in treatment-naïve patients with NSCLC driven by *EGFR* L858R mutations in the SYMPHONY study (NCT04862780)

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