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

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Yasir Y. Elamin,[1] Tyler Rouskin-Faust,[2] Nicole Zhang,[3] Teresa Green,[2] Aditya Dhande,[2] Brenton G. Mar,[2] John V. Heymach,[1] Chiara Conti[2]

[1]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [2]Blueprint Medicines Corporation, Cambridge, MA, USA; [3]Guardant Health, Palo Alto, CA, USA

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 3rd-generation EGFR TKI, is the standard of care in treatment-naïve patients with advanced *EGFR* mutant NSCLC[1]
  - 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[2]
  - While an increased overall survival (OS) benefit was observed in patients with *EGFR* ex19del treated with osimertinib versus 1st-generation TKIs, no OS benefit was seen with osimertinib in the EGFR L858R subset of the FLAURA study[1]
- Poorer outcomes for *EGFR* L858R mutations have also been reported with other 3rd-generation TKIs[3]
- 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)[4,5]
- 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[6]

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_{50}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+[7] 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**

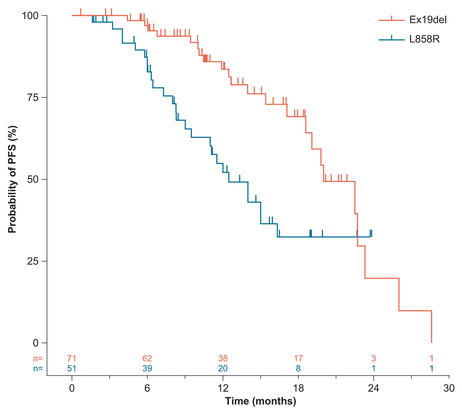
In vivo antitumor activity of BLU-945 in combination with osimertinib

- 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



Ex19del, exon 19 deletion; PFS, progression-free survival.

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

EGFR 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

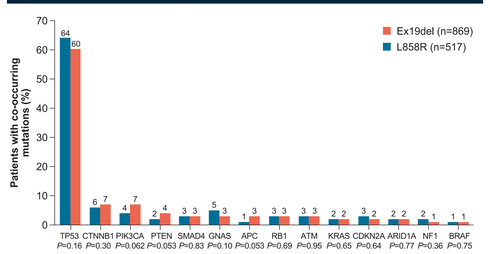
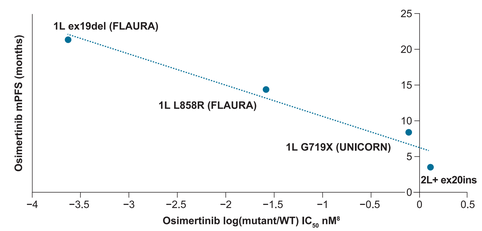
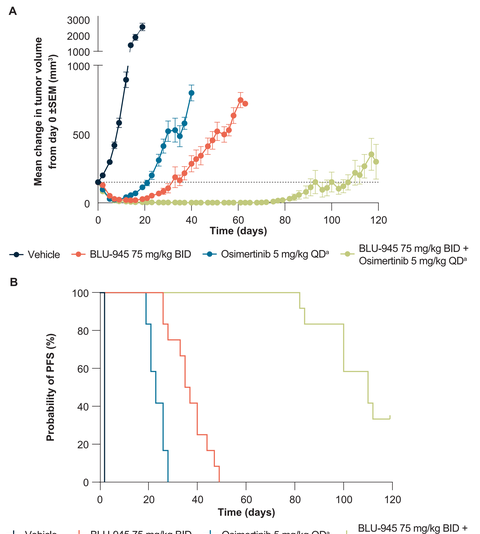


Figure 3: A strong association was found between osimertinib cellular IC_{50} and osimertinib clinical trial outcomes (mPFS) in osimertinib-treated patients with *EGFR* mutations



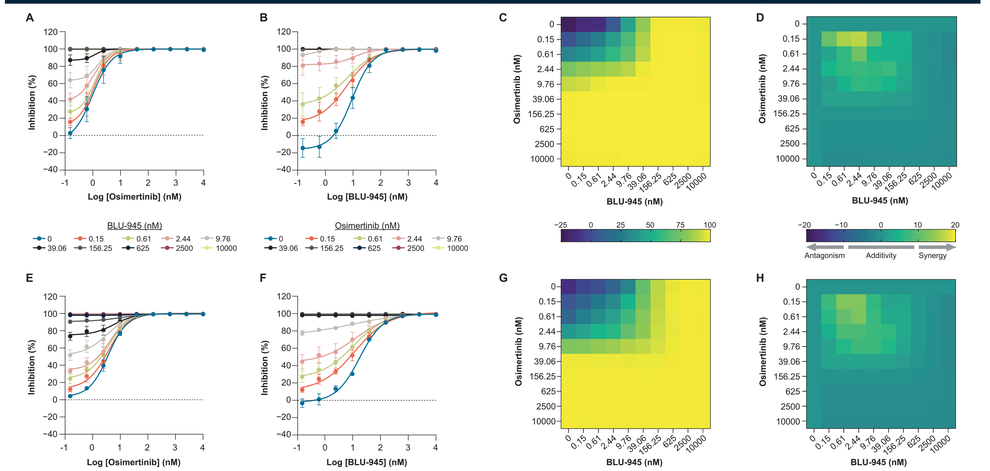
IC_{50}, half maximal inhibitory concentration; WT, wild-type; 1L, front-line; 2L, second-line.

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)



[a]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).
BID, twice a day; CDX, cell line-derived xenograft; QD, once a day; SEM, standard error of the mean.

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)



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_{50} correlates closely with clincial 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)

References

1. Ramalingam SS et al. *N Engl J Med*. 2020;382:41–50.
2. Soria JC et al. *N Engl J Med*. 2018;378:113–125.
3. Lu S et al. *J Clin Oncol*. 2022;40:3162–3171.
4. Lim SM et al. *Cancer Res*. 2021;81:1467–1467.
5. Tavera L et al. *AACR* 2022. 3328.
6. Tavera L et al. *Eur J Cancer*. 2022;174:S63.
7. Zheng S et al. *Genomics Proteomics Bioinformatics*. 2022;20:587–596.
8. Robichaux JP et al. *Nature*. 2021;597:732–737.

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For all author disclosures, please contact medinfo@blueprintmedicines.com.

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