In the phase 3 FLAURA study, patients with BLU-945 75 mg/kg BID were treated and median progression-free survival (mPFS) was 11.4 months. Patients with L858R mutations had a mPFS of 14.4 months. While an increased overall survival (OS) benefit was observed in patients with L858R (9.6–12.8 months) versus L858R wild-type (11.4–15.0 months), no OS benefit was observed in patients with L858R vs EGFR. Median TTD was 8.0 months (7.0–9.3 months). Less than −10: likely to be synergistic; −10 to 0: likely to be additive; Larger than 0: likely to be antagonistic.

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

The in vitro antitumor activities of BLU-945 75 mg/kg twice a day (BID) and osimertinib 10 mg/ml were additive across subtypes. A strong association was found between osimertinib IC50, median TTD, and mPFS in the FLAURA study.

Results

In the MDACC real-world data set, the 12-month PFS rate was 52% for L858R (n=517) versus 44% for ex19del (n=117), and mPFS was 14.7 months for L858R versus 12.4 months for ex19del. EGFR L858R-mutant cell lines exhibited most clinical and cellular activity on ex19del, followed by L858R, then C797X, and then ex19del (Figure 3). Survival outcomes were assessed in front-line osimertinib-treated patients with NSCLC (78%L858R mutations). Inherent limitations of endpoints derived from administrative databases, patient choice, etc. prevent meaningful clinical inferences. This combination therapy is being evaluated in treatment-naive patients with NSCLC by BLU-945-driven NSCLC using real-world data sets, analyzed potential contributors to poorer outcomes, and report a provisional proof of concept for combination treatment.

Conclusions

BLU-945 and osimertinib in combination with osimertinib resulted in tumor regression and prolonged durability of response in EGFR L858R-driven treatment-naïve NSCLC that harbored C797X mutations and WT were determined in Ba/F3 cells. Osimertinib exhibited most clinical and cellular activity on ex19del, and osimertinib results were not significantly different between BLU-945 and osimertinib, with a similar number of off-target mutants.

Real-world analyses

Optimal settings for BLU-945 were identified in front-line and second-line settings as well as EGFR TKI-naive patients with advanced NSCLC (MDACC; n=121; data cutoff: February 1, 2023). Clinical outcomes measured by time to treatment discontinuation (TTD) as well as progression-free survival were assessed in L858R- and C797X-mutant patients treated with BLU-945 75 mg/kg BID. Patients with L858R mutations had a mPFS of 14.7 months vs 12.4 months for ex19del. Osimertinib exhibited most clinical and cellular activity on ex19del, followed by L858R, then C797X, and then ex19del. No antagonism was observed when combining BLU-945 and osimertinib in vitro in cellular proliferation assays (CelTiter-Glo) (Figure 4D) and eGFR assays (Figure 4G). Survival outcomes were assessed in front-line osimertinib-treated patients with NSCLC.

Table 1: Shorter median time to treatment discontinuation was observed between BLU-945 and osimertinib (75 mg/kg BID) monotherapy and combination treatment in treatment-naive patients with NSCLC.

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>BLU-945 (n=78)</th>
<th>Osimertinib (n=78)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median TTD (months)</td>
<td>14.7</td>
<td>12.4</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Cellular half maximal inhibitory concentrations (IC50) of osimertinib and BLU-945 on L858R and WT were determined in Ba/F3 cells. The in vitro antitumor activity of BLU-945 and osimertinib was additive in Ba/F3 cells expressing EGFR L858R. Cella were co-treated with a matrix of concentrations of BLU-945 and osimertinib, and treated with Taxol (150 nM) for 48 hours (Figure 3). The University of Texas MD Anderson Cancer Center, Houston, TX, USA; Blueprint Medicines Corporation, Cambridge, MA, USA; Guardian Health, Palo Alto, CA, USA

References


Acknowledgements

Blueprint Medicines Corporation, Cambridge, MA, USA, provided data and guidance for interpretation of the data. Medical writing support was provided by Hyve Meds. Funding was provided by Blueprint Medicines Corporation, Cambridge, MA, according to Good Publication Practice guidelines.

Disclosures

This research was supported and funded by Blueprint Medicines Corporation, Cambridge, MA. The authors had full editorial control of all content. Blueprint Medicines has a commercial interest in the results of this study. Blueprint Medicines has submitted an application for orphan drug designation for BLU-945. The study was conducted, designed, managed, and independent medical monitors monitored the clinical trial. Blueprint Medicines did not conduct data analysis and has not influenced the writing of this manuscript. Blueprint Medicines has submitted an application for orphan drug designation for BLU-945. For all other disclosures, please contact medinfo@blueprintmedicines.com.

Presented at AACR Annual Meeting, Orlando, FL, April 14–19, 2023. Please contact medinfo@blueprintmedicines.com for permission to reprint and/or distribute.