BLU-945 monotherapy and in combination with osimertinib in previously treated patients with advanced *EGFR*-mutant NSCLC in the phase 1/2 SYMPHONY study

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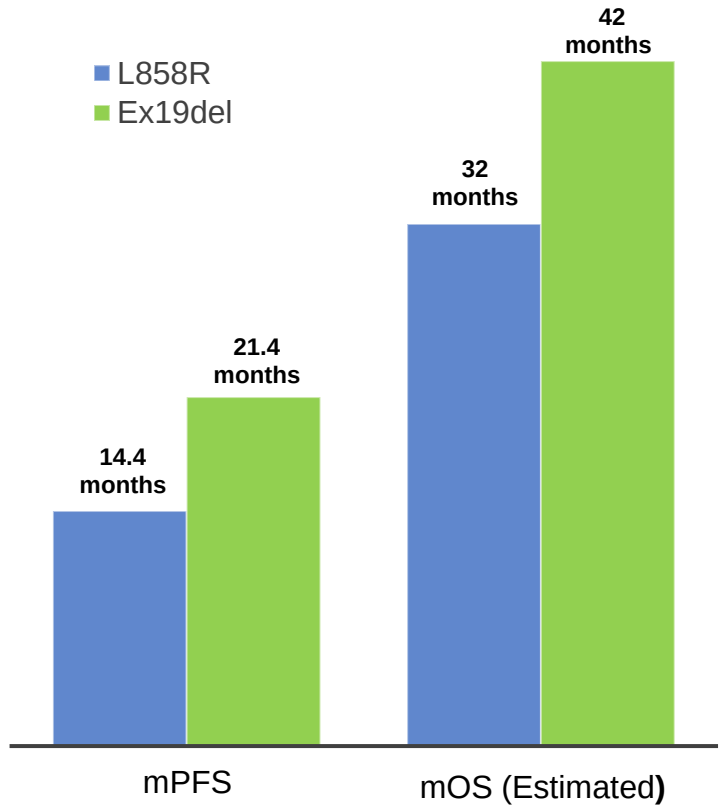
Introduction

- In EGFRm-positive NSCLC, on-target and off-target treatment resistance eventually develops with third generation EGFR TKIs, presenting a patient population that is challenging to treat
- Optimization of EGFR pathway inhibition with combination treatment is likely to be more successful in front-line due to patient genomic homogeneity
- While EGFR TKI-TKI combinations have been explored, a high rate of EGFR WT toxicity has limited their clinical utility[1]
- **BLU-945 is an investigational, next-generation, oral TKI uniquely selective against EGFR WT:**
  - nM potency on EGFR-activating (L858R, ex19del) and T790M and C797X resistance mutations
  - Large EGFR WT window makes BLU-945 a combination partner with reduced risk for unacceptable EGFR WT toxicity

Osimertinib outcomes in first-line treatment of NSCLC[2,3]



EGFR, epidermal growth factor receptor; ex19del, exon 19 deletion; mOS, median overall survival; mPFS, median progression free survival; NSCLC, non-small cell lung cancer; TKI, tyrosine kinase inhibitor, WT, wild type.

1. Rotow J, et al. *J Clin Oncol.* 2020;38(15):9507-9507. **2**. Souria JC, et al. *New Engl J Med*. 2018;378:113-125. **3.** Ramalingam SS, et al. *J Thorac Oncol.* 2022:17(9):S67-S68.

SYMPHONY (NCT04862780) study design and patient characteristics

Key eligibility criteria

- **Adults with metastatic *EGFR*m NSCLC**
- **No other known oncogenic tumor drivers**
- **ECOG status 0-1**
- **Prior treatment with ≥1 EGFR TKI with activity against T790M; progression on osimertinib as last therapy (part 1B only)**

Phase 1 (dose escalation)

Part 1A (N=112)
BLU-945 monotherapy
BOIN design
Starting dose: 25 mg QD[a]
Initiated May 2021

Part 1B (N=55)
BLU-945 + osimertinib (80 mg)
Starting dose:
BLU-945 200 mg QD[a]
Initiated June 2022

All combination patients received osimertinib as last line of therapy without a washout period

Primary endpoints
MTD, RP2D, safety

Characteristic	BLU-945	
	Monotherapy[b] (n=112)	Combination[c] (n=55)
Age, years, median (min, max)	63 (34, 84)	62 (28, 87)
Age group, n (%)		
<65 years	63 (56.3)	32 (58.2)
≥65 years	49 (43.8)	23 (41.8)
Female, n (%)	74 (66.1)	34 (61.8)
CNS metastases at baseline, n (%)	43 (38.4)	17 (30.9)
Prior LOT, median (min, max)	3.5 (1, 13)	2 (1, 7)

- Patients enrolled in the phase 1 dose escalation were heavily pretreated
- 94% of monotherapy and 89% of combination patients had an additional EGFR and/or detectable additional genetic alteration
- Combination dose escalation is ongoing

[a]BID dosing was also evaluated. [b]25–600 mg QD; 100–300 mg BID. [c]200–400 mg QD;100–200 mg BID with OSI 80 mg QD.
BID, twice daily; BOIN, Bayesian optimal interval; ECOG PS, Eastern Cooperative Oncology Group performance status; ex19del, exon 19 deletion; LOT, line of therapy; MTD, maximum tolerated dose; QD, every day; RP2D, recommended phase 2 dose; TKI, tyrosine kinase inhibitor.

BLU-945 monotherapy was generally well tolerated

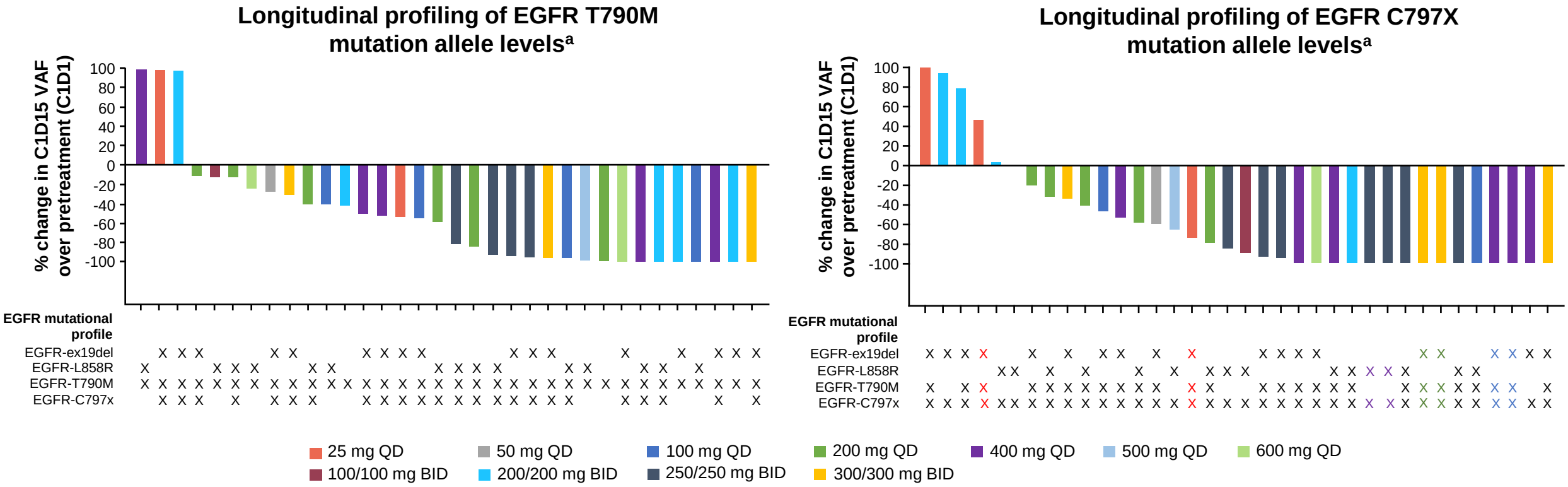
TRAEs, N=112		
TRAEs, n (%) Safety population	**Any grade**	**Grade ≥3[a]**
Any TRAE	86 (76.8)	37 (33.0)
EGFR-related TRAEs (all patients)		
Rash	11 (9.8)	0
Diarrhea	7 (6.3)	0
Dry skin	4 (3.6)	0
Paronychia	2 (1.8)	0
TRAEs in ≥25% of patients		
ALT	41 (36.6)	25 (22.3)
Nausea	38 (33.9)	3 (2.7)
AST	37 (33.0)	12 (10.7)
Headache	31 (27.7)	0
Vomiting	30 (26.8)	1 (>1)

- Majority of TRAEs were low grade (NCI CTCAE Grade 1–2)
- There were 12 patients with DLTs across 400 mg–600 mg total daily doses (QD and BID), with the most common DLTs being Grade 3 ALT and AST elevation
- EGFR-WT associated AEs were low grade and infrequent (<10%)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BID, twice daily; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; DLT, dose limiting toxicity; EGFR, epidermal growth factor receptor; QD, once daily; TRAE, treatment-related adverse event; WT, wild type.

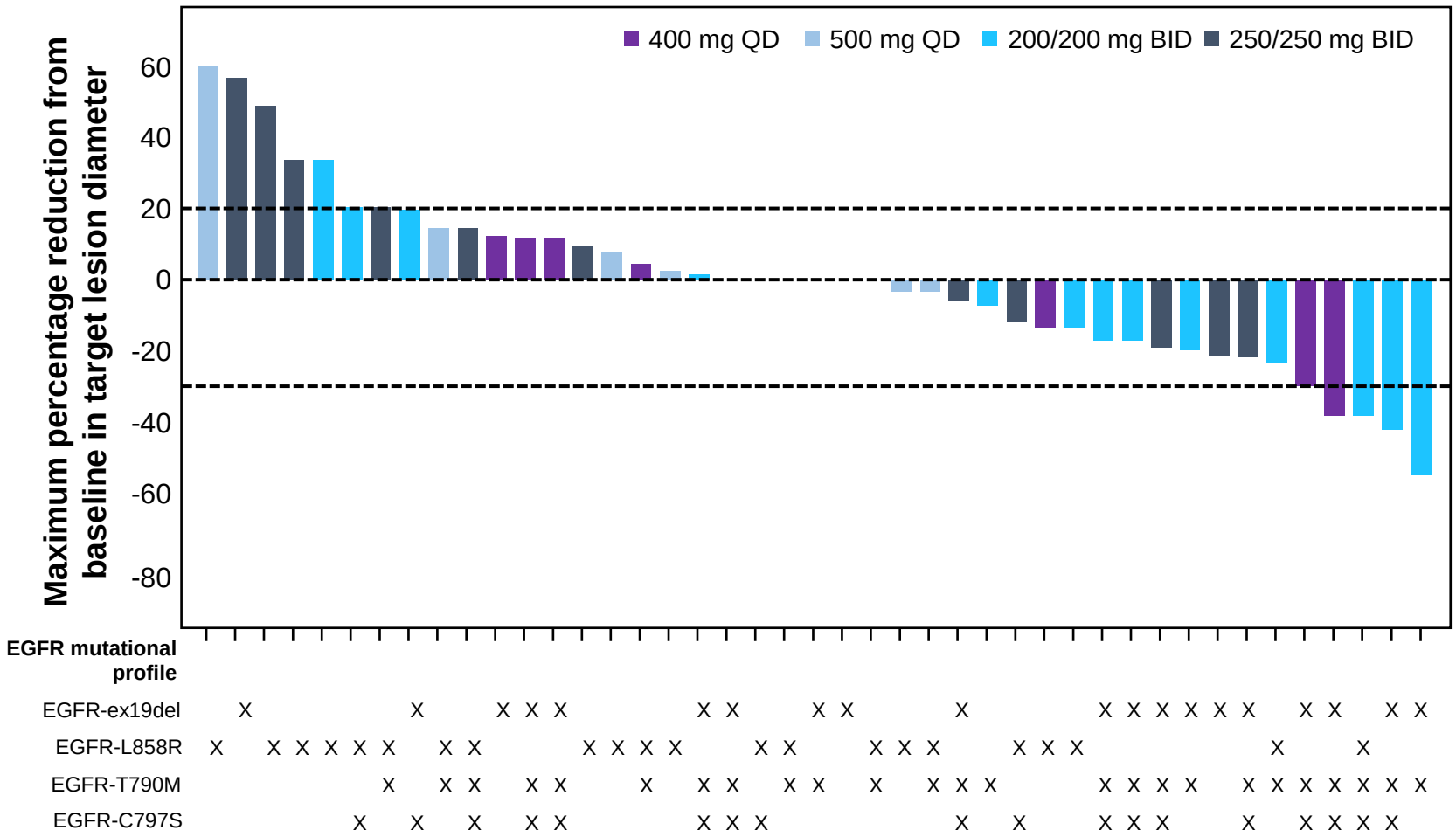
[a]Two patients (1.8%) experienced Grade 5 AE possibly related to BLU-945 as assessed by an investigator: pneumonitis at 300 mg BID and intracranial bleeding at 100 mg BID in a patient with suspected brain metastases.

BLU-945 monotherapy resulted in dose-dependent reduction and clearance of EGFR T790M and EGFR C797X ctDNA at Cycle 1 Day 15



[a]Percent change greater than 100% are displayed as 100% in the figure. EGFR mutational profile based on results from Foundation One Liquid CDx (F1CDx) baseline (C1D1) analysis
Note: Patient with multiple mutations for EGFR C797S in the same specimen are shown as a different colored X in the EGFR mutational profile.
BID, twice daily; EGFR, epidermal growth factor receptor; QD, once daily

BLU-945 monotherapy antitumor activity[a]



- Heavily pretreated population resulting in disease heterogeneity
- Tumor reduction and two confirmed partial responses were observed at higher dose levels of BLU-945 monotherapy
- Limited durability of clinical benefit observed, likely due to late-line disease heterogeneity and off-target resistance

[a]Patients with EGFR-mutant positive NSCLC were enrolled based on local mutation assessment of tumor biopsy or blood ctDNA (displayed) with a follow-up central ctDNA assessment at C1D1. Patients were counted only once.
BID, twice daily; EGFR, epidermal growth factor receptor; PD, progressive disease; PR, partial response; QD, once daily; SD, stable disease.

BLU-945 + osimertinib combination is well tolerated with limited EGFR WT AEs

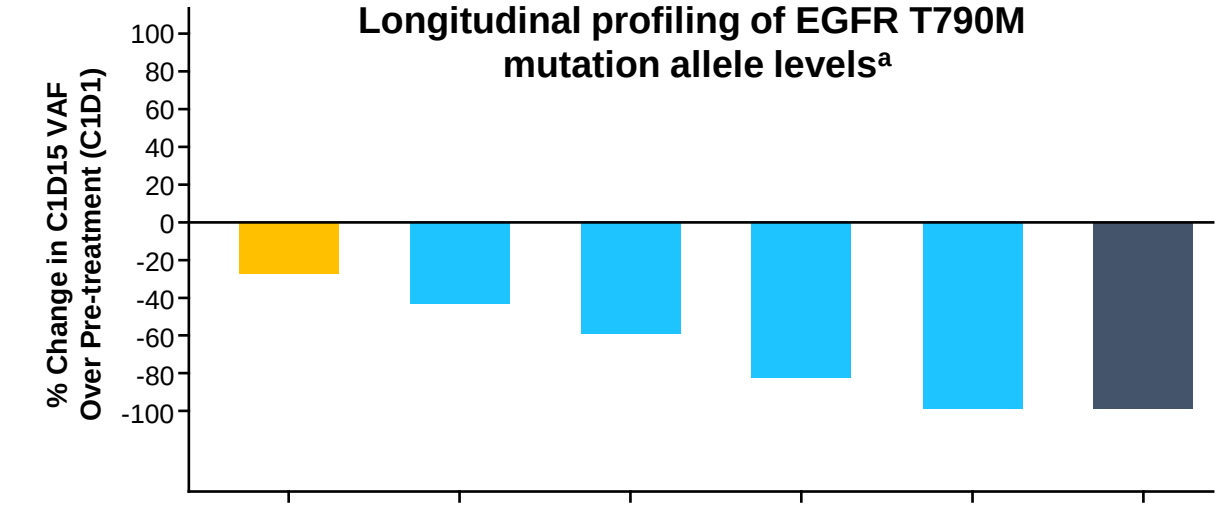
TRAEs, (N=55)		
TRAEs, n (%) Safety population	**Any grade**	**Grade ≥3**
Any TRAEs	52 (94.5)	6 (10.9)
EGFR-associated TRAEs		
Diarrhea	16 (29.1)	0
Dry skin	9 (16.4)	0
Dermatitis acneiform	8 (14.5)	1 (1.8)
Paronychia	6 (10.9)	0
TRAEs in ≥10% of patients		
Headache	19 (34.5)	0
Nausea	19 (34.5)	0
Fatigue	12 (21.8)	1 (1.8)
Decreased appetite	7 (12.7)	0
Vomiting	6 (10.9)	0

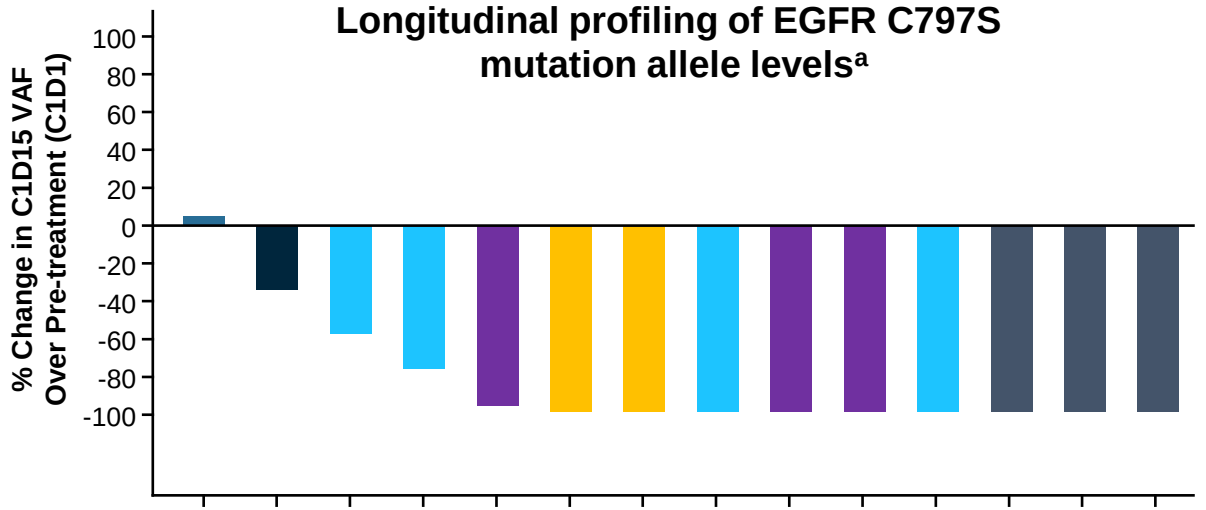
- Exposure of BLU-945 and osimertinib when coadministered are comparable to PK data from BLU-945 given alone and published osimertinib data[1,2]
- EGFR-WT associated AEs were infrequent, and the majority were Grade 1
- Three patients had DLTs across 200 – 400 mg total daily doses
  - 100 mg BID + 80 mg osi, Grade 3 acute respiratory failure
  - 300 mg QD + 80 mg osi - Grade 4 pneumonitis
  - 400 mg QD + 80 mg osi- Grade 3 dermatitis acneiform
- Two patients (3.6%) discontinued due to TRAEs
- There were no treatment-related deaths
- Dose escalation is on-going with MTD/RP2D yet to be determined

AE, adverse event; BID, twice daily; DLT, dose limiting toxicity; EGFR, epidermal growth factor receptor; MTD, maximum tolerated dose; QD, once daily; RP2D, recommended phase 2 dose; TRAE, treatment-related adverse event; WT, wild type.

1. Brown K, et al. Br J Clin Pharmacol. 2017;83(6):1216-1226. **2.** Planchard D, et al. Cancer Chemother Pharmacol. 2016;77: 767-776.

BLU-945 + osimertinib combination therapy resulted in dose-dependent reduction of EGFR T790M and EGFR C797S mutant allele levels at Cycle 1, Day 15

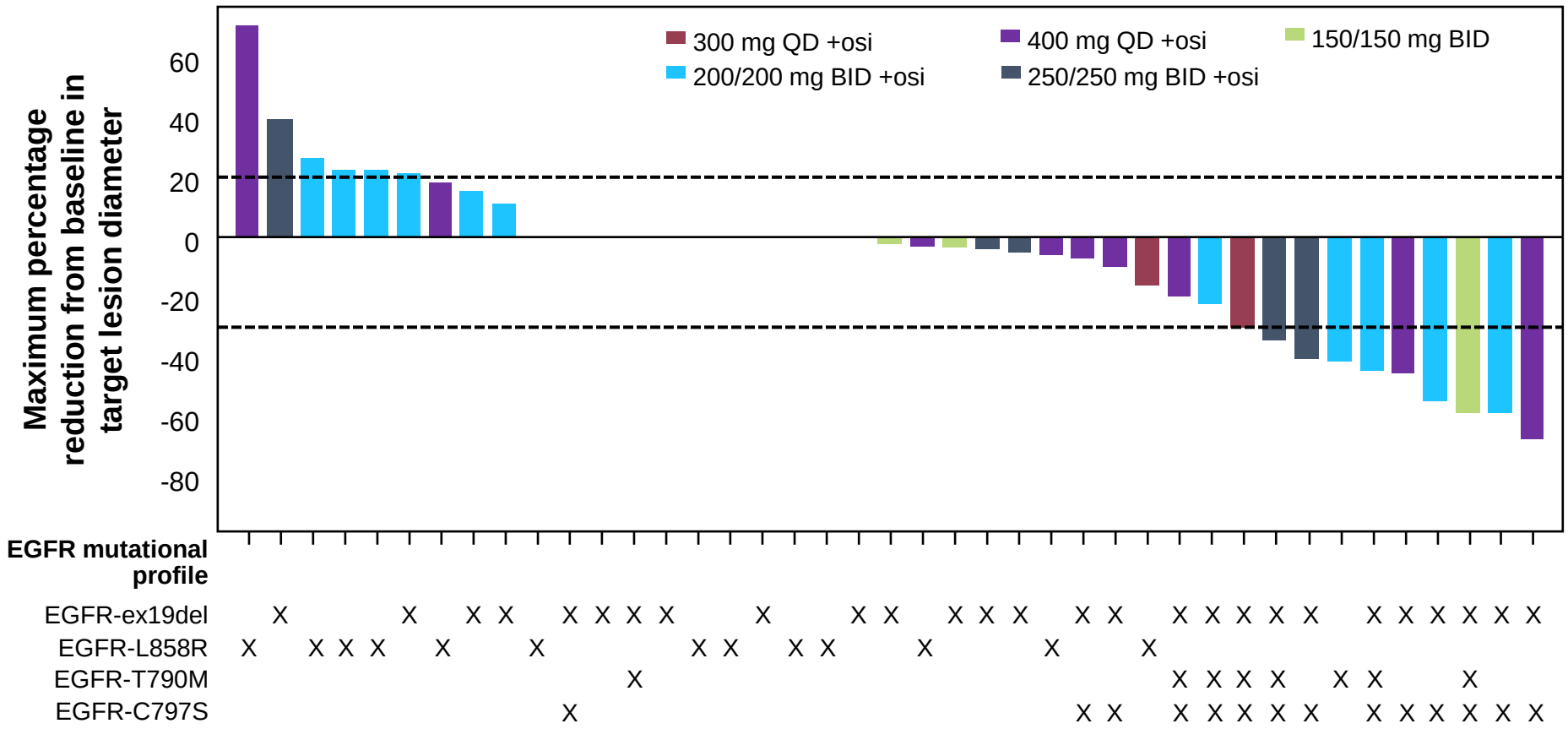




200 mg QD +osi
300 mg QD +osi
400 mg QD +osi
100/100 mg BID +osi
150/150 mg BID +osi
200/200 mg BID + osi
250/250 mg BID +osi

[a]Percent change greater than 100% are displayed as 100% in the figure. EGFR mutational profile based on results from Foundation One Liquid CDx baseline (C1D1) analysis.
Note: Patient with multiple mutations for EGFR C797S in the same specimen are shown as a different colored X in the EGFR mutational profile.

Early BLU-945 + osimertinib antitumor activity[a]



- In the ongoing dose-escalation, tumor shrinkage, including 4 confirmed PRs, was observed in patients who had progressed on osimertinib as the last therapy line

[a]Patients with EGFR-mutant positive NSCLC were enrolled based on local mutation assessment of tumor biopsy or blood ctDNA with a follow-up central ctDNA assessment at C1D1. Patients were counted only once.
BID, twice daily; EGFR, epidermal growth factor receptor.

Conclusions

- In heavily pretreated EGFR-mutant NSCLC patients, BLU-945 monotherapy was active and well-tolerated; however, due to genomic heterogeneity, responses were not durable
- Emerging BLU-945 + osimertinib combination data demonstrated clinical activity post progression on osimertinib and was well tolerated with infrequent EGFR WT toxicity
- A correspondence between reduction of the resistance mutation alleles by ctDNA and tumor shrinkage was observed in both cohorts
- Phase 1 data support BLU-945 + osimertinib as a differentiated, fully oral, novel combination for treatment of EGFR-mutant NSCLC, warranting further clinical development
    - Combination escalation is ongoing with RP2D/MTD yet to be established

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EGFR, epidermal growth factor receptor; MTD, maximum tolerated dose; NSCLC, non-small cell lung cancer; RP2D, recommended phase 2 dose; WT, wild type.

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