EP671 OUTCOMES BEFORE AND AFTER DOSE REDUCTION IN PATIENTS WITH NEWLY DIAGNOSED CHRONIC MYELOID LEUKEMIA RECEIVING BOSUTINIB OR IMATINIB. M. W. Deininger 1,*, T. H. Brümmendorf 2 , D. Milojkovic 3 *, F. Cervantes 4* , F. Huguet 5 , A. Viqueira 6 , E. Leip 7 , S. Purcell 8 , J. E. Cortes 9 1 University of Utah Health Care, Salt Lake City, United States, 2 Universitätsklinikum RWTH Aachen, Aachen, Germany, 3 Hammersmith Hospital, London, United Kingdom, 4 Hospital Clinic, IDIBAPS, University of Barcelona, Barcelona, Spain, 5 Institut Universitaire du Cancer, Toulouse, France, 6 Pfizer SLU, Madrid, Spain, 7 Pfizer Inc, Cambridge, United States, 8 Pfizer Ltd, London, United Kingdom, 9 Georgia Cancer Center, Augusta, United States

Background: Bosutinib is approved for patients with Philadelphia chromosome-positive chronic myeloid leukemia (CML), at a starting dose of 400mg once daily (QD) in newly diagnosed patients in chronic phase (CP). Aims: This analysis evaluated the impact dose reduction has on the outcomes of bosutinib and imatinib in patients with CP CML.

Methods: In the open-label BFORE trial, 536 patients with newly diagnosed CP CML were randomized to receive 400mg QD bosutinib (N=268) or imatinib (N=268; 3 untreated). Dose could be reduced to 300mg QD for toxicity. Following sponsor approval, dose reduction to bosutinib 200mg QD was permitted for 4 weeks maximum; after this time, dose escalation or treatment discontinuation was required. Maintenance of response after dose reduction was defined as having a response >6 months after the first reduction. Database lock: June 12, 2020, 5 years after the last patient enrolled. Results: In the bosutinib arm, dose reduction to 300 (without further reduction) or 200mg QD was seen in 82 (31%) and 33 (12%) patients, and median time to dose reduction was 85 and 205 days. In the imatinib arm, 50 (19%) patients had a dose reduction to 300mg QD, and median time to dose reduction was 92 days. Most common (≥2% of patients) treatment-emergent adverse events (TEAEs) leading to dose reduction were increased alanine aminotransferase (8%), thrombocytopenia (7%), diarrhea (7%), increased lipase (6%), increased aspartate aminotransferase (4%), nausea (4%), neutropenia (3%), rash (3%) and abdominal pain (2%) with bosutinib, and neutropenia (4%) with imatinib. Of the patients who remained on 400mg QD bosutinib (n=153) or imatinib (n=214), respectively, 120 (78%) and 139 (65%) achieved major molecular response (MMR). Among patients who had a bosutinib dose reduction to 300mg QD, 51/82 (62%) had MMR >6 months after dose reduction: 14 (17%) maintained MMR before and after dose reduction and 37 (45%) achieved MMR for the first time after dose reduction. Seven (9%) patients had MMR before dose reduction but discontinued treatment before the next >6 months assessment. In the imatinib arm, 32/50 (64%) patients had MMR >6 months after dose reduction: 9 (18%) maintained MMR before and after dose reduction and 23 (46%) achieved MMR for the first time after dose reduction. One (2%) patient had MMR before dose reduction but discontinued treatment before the next >6 months assessment and 1 (2%) patient lost a previously attained MMR after dose reduction. Among patients who had a bosutinib dose reduction to 200mg QD, 12/33 (36%) had MMR >6 months after dose reduction: 7 (21%) maintained MMR before and after dose reduction and 5 (15%) achieved MMR for the first time after dose reduction. Six (18%) patients had MMR before dose reduction but discontinued treatment before the next >6 months assessment. Similar trends were seen for complete cytogenetic response. Summary/Conclusion: Management of TEAEs through bosutinib or imatinib dose reduction

enabled patients to continue treatment, with a substantial number of patients achieving MMR for the first time after dose reduction.

Background: Bosutinib is approved for patients with Philadelphia chromosome–positive (Ph+) chronic myeloid leukemia (CML) resistant/ intolerant to prior therapy and newly diagnosed Ph+ chronic phase (CP) CML. In a phase 1/2 study, second-line bosutinib showed durable efficacy and manageable toxicity in patients with imatinib-resistant (IM-R) or imatinib-intolerant (IM-I) Ph+ CP CML. Aims: The final efficacy and safety analysis of this phase 1/2 study and its extension study (NCT00261846 and NCT01903733) is presented.

Methods: Patients with Ph+ CP CML who received bosutinib starting at 500mg/day after prior treatment with imatinib only were included. This analysis was based on ≥10 years of follow-up. Results: 19% of patients were on treatment with bosutinib at year 10, and 13% were still receiving bosutinib at study completion after ≥10 years; 19% completed ≥10 years of follow-up. Median duration of treatment and follow-up were 26 and 54 months, respectively. Median (range) dose intensity was 436 (87–599) mg/day. The most common primary reasons for permanent treatment discontinuation were lack of efficacy (unsatisfactory response or disease progression; 27%) and adverse events (AEs; 26%). In patients with a valid baseline assessment, cumulative complete cytogenetic response (CCyR), major molecular response (MMR) and MR4 rates were 50%, 42% and 37%, respectively (Table). Responses were durable, with estimated probabilities of maintaining CCyR, MMR and MR4 >50% after ≥10 years (Table). At 10 years, cumulative incidence of on-treatment progression/death was 24% and Kaplan-Meier (K-M) overall survival 72% (Table). 55 deaths (IM-R: n=41; IM-I: n=14) occurred on study; causes of death were disease progression (n=30), AEs (n=16; none bosutinib-related), other (n=5) and unknown (n=4). Any grade treatment-emergent AEs (TEAEs) occurring in ≥40% of patients were diarrhea (86%), nausea (46%) and thrombocytopenia (42%). Pleural effusion, cardiac and vascular TEAEs occurred in 13%, 12% and 11% of patients, respectively. 28% of patients had AEs leading to permanent treatment discontinuation; the most common (≥2% of patients) were thrombocytopenia (6%), neutropenia (2%) and alanine aminotransferase increased (2%).

Outcome after ≥10 years[a]	IM-R N=195	IM-I N=89	Total N=284
Patients with CCyR, n/N	88/182	42/80	130/262
Cumulative CCyR rate, % (95% CI)	48 (41–56)	53 (41–64)	50 (43–56)
Probability of maintaining CCyR, % (95% CI)[b,c]	61 (49–73)	52 (32–73)	58 (48–69)
Patients with MMR, n/N	58/127	25/70	83/197
Cumulative MMR rate, % (95% CI)	46 (37–55)	36 (25–48)	42 (35–49)
Probability of maintaining MMR, % (95% CI)[b,c]	55 (39–70)	54 (15–93)	56 (41–71)
Patients with MR[4], n/N	50/127	23/70	73/197
Cumulative MR[4] rate, % (95% CI)	39 (31–48)	33 (22–45)	37 (30–44)
Probability of maintaining MR[4], % (95% CI)[b,c]	55 (38–73)	52 (8–96)	56 (39–72)
Cumulative incidence of on-treatment progression/death, % (95% CI)	29 (23–36)	14 (8–23)	24 (20–30)
Overall survival, % (95% CI)[b]	71 (63–79)	73 (60–87)	72 (64–79)

Molecular data not on International Scale and not available for patients in China, Russia, South Africa and India.
CCyR imputed from MMR in extension study if valid cytogenetic assessment not available on a specific date.
[a] Outcomes reported after ≥10 years; few events (e.g., initial response, loss of response and death) occurred after year 10.
[b] K-M estimates.
[c] Among responders.

Summary/Conclusion: These 10-year data are consistent with prior results of durable efficacy and manageable toxicity with second-line bosutinib and support long-term bosutinib use in patients with CP CML after imatinib failure.