In Reply

We agree with Badaoui et al. [1] that, in addition to the previously published detailed safety report [2], some additional data regarding dose omissions and the association between early-onset adverse events by grade and progression-free survival (PFS) may be useful.

For abemaciclib-treated patients, although 256 of 441 (58.0%) in MONARCH 2 and 214 of 327 (65.4%) in MONARCH 3 had one or more dose omissions, only 93 (21.1%) and 87 (26.6%) patients experienced at least three dose omissions in MONARCH 2 and 3, respectively. As previously reported, dose reductions had no impact on abemaciclib efficacy in either study [2]. Regarding dose omissions, the median maximum number of days a dose was omitted was short (10 days, MONARCH 2; 11 days, MONARCH 3) relative to the median duration of abemaciclib treatment in each trial (52 weeks, MONARCH 2; 67 weeks, MONARCH 3). Given the low proportion of omitted doses overall (median percentage 6.5%, MONARCH 2; 6.1%, MONARCH 3), and the minimal impact of dose omissions on dose intensity, dose omissions are not expected to influence PFS.

We previously investigated the difference in PFS between patients who experienced any-grade diarrhea within the first 7 days of treatment, versus patients who did not experience diarrhea within 7 days, and found that patients received PFS benefit irrespective of early-onset diarrhea [2]. Here, we examined PFS in patients who experienced diarrhea within the first 7 days of treatment by grade (no diarrhea, grade 1, or grade 2/3 diarrhea; no patients experienced grade 4). There were small numerical differences in the estimated median PFS according to grade, but the variability around the estimates was high, particularly among patients with an early onset of grade 2/3 diarrhea, where the number of events was small. Overall, considering the variability, median PFS was consistent for all patients

Table 1. Median progression-free survival by the occurrence of early-onset diarrhea, by grade

Occurrence	MONARCH 2	MONARCH 3
Abemaciclib with no early onset of diarrhea		
Number of patients	213	183
Number of events	114	80
Median PFS (95% CI)	14.7 (13.0–17.7)	29.1 (20.8–NC)
Abemaciclib with early onset of grade 1 diarrhea		
Number of patients	137	106
Number of events	76	48
Median PFS (95% CI)	16.1 (13.9–19.3)	27.5 (21.9–NC)
Abemaciclib with early onset of grade 2/3 diarrhea		
Number of patients	78	28
Number of events	32	10
Median PFS (95% CI)	NC (15.2–NC)	31.1 (21.7–NC)
Endocrine therapy alone		
Number of patients	218	159
Number of events	157	108
Median PFS (95% CI)	9.3 (7.4–11.4)	14.8 (11.2–19.2)

Abbreviations: CI, confidence interval; NC, not calculable; PFS, progression-free survival.

Table 2. Median progression-free survival by the occurrence of early-onset neutropenia, by grade

Occurrence	MONARCH 2	MONARCH 3
Abemaciclib with no early onset of neutropenia		
Number of patients	96	96
Number of events	48	37
Median PFS (95% CI)	17.7 (13.2–NC)	31.1 (23.1–NC)
Abemaciclib with early onset of grade 1/2 neutropenia		
Number of patients	219	163
Number of events	117	65
Median PFS (95% CI)	15.0 (14.0–17.5)	29.1 (27.5–NC)
Abemaciclib with early onset of grade 3/4 neutropenia		
Number of patients	98	41
Number of events	46	24
Median PFS (95% CI)	24.0 (16.1–NC)	17.5 (12.3–NC)
Endocrine therapy alone		
Number of patients	202	149
Number of events	141	99
Median PFS (95% CI)	10.8 (7.9–12.7)	15.6 (14.0–21.9)

Abbreviations: CI, confidence interval; NC, not calculable; PFS, progression-free survival.

receiving abemaciclib, regardless of early-onset diarrhea and grade. Results are presented in Table 1.

We previously investigated the difference in PFS between patients who experienced early-onset grade ≥ 2 neutropenia within the first 56 days of treatment, versus all other patients, and found clinical efficacy, as measured by PFS, favored the abemaciclib arm regardless of grade ≥ 2 neutropenia [2]. Here, we examined PFS in patients who experienced neutropenia within the first 56 days of treatment by grade (no neutropenia, grade 1/2, or grade 3/4). Although there were numerical differences in the estimated median PFS according to the presence of early-onset neutropenia, by grade, there was no consistent trend between studies. Given the small number of events, particularly among patients with an early onset of grade 3/4 neutropenia, results should be interpreted with caution. Results are presented in Table 2.

Overall, additional data presented here suggest dose omissions made up a low proportion of doses overall and were of short duration relative to treatment duration. Therefore, the potential impact on PFS is likely to be minimal. Similarly, despite the small number of events in some subgroups, analyses indicated median PFS was generally consistent for all abemaciclib-treated patients, irrespective of experiencing early diarrhea or neutropenia at any grade. Collectively, results suggest that all patients, even those who experience the most common adverse events early in their treatment or who require a dose omission, can benefit from the addition of abemaciclib to endocrine therapy.

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Disclosures

Hope S. Rugo: Pfizer, Novartis, Eli Lilly & Co., Genentech/Roche, MacroGenics, Merck, Eisai, Odonate Therapeutics, Daiichi Sankyo, Seattle Genetics, Immunomedics, Astra Zeneca, Sermonix, Boehringer Ingelheim, Polyphor (RF), Puma, Samsung (H), PUMA Biotechnology, Mylan, Amgen, AstraZeneca, Daiichi Sankyo, Merck, MacroGenics, Pfizer (other); **Jens Huober:** Eli Lilly & Co., Novartis, Roche, Pfizer, AstraZeneca, Merck Sharp & Dohme, Celgene, Eisai, Abbvie (H), Eli Lilly & Co., Novartis, Roche, Pfizer, Hexal, AstraZeneca, Merck Sharp & Dohme, Celgene, Abbvie (C/A), Roche, Pfizer, Novartis, Celgene, Daiichi (travel expenses), Celgene, Novartis, Hexal (RF); **José A. García-Sáenz:** Eli Lilly & Co., Novartis, Pfizer, Celgene, Daiichi Sankyo, Eisai, AstraZeneca (C/A), AstraZeneca (RF), Roche-Genentech (other); **Norikazu Masuda:** Chugai, AstraZeneca, Pfizer, Eli Lilly & Co., Eisai, Takeda (H), Chugai, AstraZeneca, Kyowa-Kirin, Merck Sharp & Dohme, Novartis, Pfizer, Eli Lilly & Co., Eisai, Daiichi Sankyo (RF—to institution); **Valerie A.M. Andre:** Eli Lilly & Co. (E, OI); **Susana Barriga:** Eli Lilly & Co. (E, OI); **Joanne Cox:** Eli Lilly & Co. (E); **Matthew Goetz:** Eli Lilly & Co., Pfizer, Sermonix (RF), Eli Lilly & Co., Pfizer, Novartis, Sermonix, Biovica, Context Therapeutics (C/A). Joo Hyuk Sohn indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

References

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http://dx.doi.org/10.1002/onco.13782