

**1. Abraxane (Nab-Paclitaxel) – Dose reduction after induction chemotherapy:**

The Phase II SNAP trial was designed to evaluate the efficacy of alternative chemotherapy schedules for prolonged administration in HER2-negative metastatic breast cancer (MBC), after a short induction at conventional doses. Between April 2013 and August 2015, 258 women untreated with chemotherapy for their HER2- MBC were randomly assigned to receive three different maintenance chemotherapy schedules after three cycles of identical induction chemotherapy: Arm A, nab-paclitaxel 150 mg/m<sup>2</sup> days 1 and 15 Q28; Arm B, nab-paclitaxel 100 mg/m<sup>2</sup> days 1, 8 and 15 Q28; Arm C, nab-paclitaxel 75 mg/m<sup>2</sup> days 1, 8, 15 and 22 Q28. Induction was three cycles nab-paclitaxel 150/125 mg/m<sup>2</sup>, days 1, 8 and 15 Q28. The primary objective was to evaluate the efficacy of each maintenance schedule in terms of progression-free survival (PFS) as compared with the historical reference of 7-month median PFS reported by previous studies with first-line docetaxel. Median PFS in Arm A was 7.9 months; Arm B was 9.0 months, and Arm C was 8.5 months. Grade ≥2 sensory neuropathy was reported in 37.9%, 36.1% and 31.2% of the patients in arm A, B and C, respectively. <https://www.ncbi.nlm.nih.gov/pubmed/29228091/?i=5&from=/26712590/related>

In the BOLERO-2 trial, 77 patients were started on 10mg daily, 29 patients were started on 7.5mg daily, and 31 patients were started on 5mg daily. There was no significant difference in PFS between starting the recommended dose or a lower dose. Patients initiated on lower doses were less likely to require dose reductions or discontinue due to toxicity even with later dose increases. This data suggests that progression may not be limited by initiating lower, less toxic doses of everolimus. Therefore, if oncologists are more comfortable starting a lower dose, survival may not be adversely affected and patients may be more compliant, deriving a prolonged benefit from the combination. [https://ascopubs.org/doi/abs/10.1200/JCO.2016.34.15\\_suppl.e12058](https://ascopubs.org/doi/abs/10.1200/JCO.2016.34.15_suppl.e12058)

**2. Afinitor (Everolimus) – Varying starting dosages:**

MBC patients treated with the combination of everolimus and exemestane at Moffitt Cancer Center were subdivided into 3 groups: 77 patients were started on 10mg daily, 29 patients were started on 7.5mg daily, and 31 patients were started on 5mg daily. There was no significant difference in PFS between starting the recommended dose or a lower dose. Patients initiated on lower doses were less likely to require dose reductions or discontinue due to toxicity, even with later dose increases. If oncologists are more comfortable starting a lower dose, survival may not be adversely affected and patients may be more compliant, deriving a prolonged benefit from the combination. [https://ascopubs.org/doi/abs/10.1200/JCO.2016.34.15\\_suppl.e12058](https://ascopubs.org/doi/abs/10.1200/JCO.2016.34.15_suppl.e12058)

68 HR+, HER2- MBC patients were given 5mg of Afinitor with Aromasin. After a median follow up of 14 months, PFS was 5.3 months and OS was immature. 16 patients (23.5%) were at the first or second-line and 52 (76.5%) were at third line or later. PFS for the first and second-line was significantly longer than that for the third-line or later (12.9 months vs. 4.6 months). 11 patients (16.2%) achieved partial response, 42 patients (61.7%) had stable disease, and 15 patients (22.1%) reported progressive disease. The ORR and CBR were 16.2%, 35.2%, respectively. As per the BOLERO-2 trial which combined 10 mg of Afinitor with Aromasin in the second-line setting, the average PFS for patients taking the combination was 7.8 months. <http://sabcs18.posterview.com/nosl/p/P5-04-29>

**3. Ibrance (Palbociclib) – Randomization with standard vs. lower dose at start of treatment; Results after dosage lowered upon AE:**

A Phase II study that randomized 72 HR+ HER2- MBC patients to receive Ibrance in either a 125 mg or 100 mg dose in combination with physician's choice of fulvestrant or tamoxifen concluded that the 100 mg dose was associated with a lower rate of grade 3 or 4 neutropenia. Furthermore, both Progression Free Survival and clinical benefit were the same in both groups. Dr Hope Rugo was the lead investigator. <https://www.targetedonc.com/news/reduced-palbociclib-dose-associated-with-lower-rate-of-neutropenia-in-hr-metastatic-breast-cancer>

In a slide entitled, “PALOMA-3: Effect on PFS of Dose Reductions due to Neutropenia” presented by Dr. Sara Hurvitz at Clinical Care Options Oncology on June 18, 2020, it was reported that the PFS observed between patients who had ≥ 1 Ibrance dose reduction vs. no dose reduction due to neutropenia was identical at 9.5 months.

**4. Kisqali (Ribociclib) Dose Reduction after AE:** As per SABCS 2018 Poster P6-18-06 on the next page: Conclusion: “The results from across the MONALEESA program suggest that the efficacy of ribociclib was maintained regardless of dose intensity,” and that patients’ Overall Response Rates and Clinical Benefit Rates were superior on the reduced dosages.

**5. Xeloda (Capecitabine) – Support of starting patients at lower dosages:**

An analysis of dose modification and outcomes from four Phase II capecitabine monotherapy trials, one Phase III capecitabine/docetaxel combination trial, and an analysis of consecutive MBC patients who received capecitabine outside of a clinical trial concluded that reduced capecitabine doses were associated with a lower incidence of treatment-related adverse events, specifically hand-foot syndrome, diarrhea, and stomatitis. Furthermore, time to disease progression and overall survival were similar, or even slightly longer, among patients who received lower vs. full-dose capecitabine in all of the studies reviewed. Together, these data support the practice of dose-reducing capecitabine, including the possibility of starting at a lower dose (<1250 mg/m<sup>2</sup> twice daily), to reduce the incidence of adverse events without compromising efficacy. [https://www.clinical-breast-cancer.com/article/S1526-8209\(11\)00111-X/fulltext](https://www.clinical-breast-cancer.com/article/S1526-8209(11)00111-X/fulltext)

At the University of Southern California (USC) hospitals, capecitabine is routinely prescribed at dosages as low as 600 mg/m<sup>2</sup> twice daily, with a majority of MBC patients receiving a flat dosage (not adjusted for BSA) of 1000 mg twice daily. In a review of 84 patients who received a median capecitabine dosage of 565 mg/m<sup>2</sup> twice daily, the median PFS among the 62 patients with measurable disease was 4.1 months, which was similar to the median PFS values (4.4 months; 4.2 months) for single agent capecitabine reported in the two major trials with similar eligibility criteria. Furthermore, only 2 patients (2.4%) discontinued capecitabine due to toxicity, supporting our hypothesis that starting treatment at low dosages minimizes side effects while preserving efficacy. <https://www.gotoper.com/publications/ajho/2015/2015feb/efficacy-of-very-low-dose-capecitabine-in-metastatic-breast-cancer>

**6. Verzenio (Abemaciclib) Randomized lower starting dose:**



**Piqray (Alpelisib):** In the Phase 3 SOLAR-1 trial, the median progression-free survival (PFS) for patients taking Piqray with Faslodex was 12.5 months for Piqray doses greater than or equal to 248 mg/day, and 9.6 months for Piqray doses less than 248 mg/day. (Note: The Maximum Tolerated Dose/starting dose of Piqray is currently 300 mg daily, the first allowed lower dose is 250 mg. daily, and the second allowed lower dose is 200 mg. daily). <https://www.practiceupdate.com/content/management-of-adverse-events-with-apelisib-plus-fulvestrant-in-patients-with-hr-advanced-breast-cancer/100780>