DOSAGE-RELATED STUDIES

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/m2 days 1 and 15 Q28; Arm B, nab-paclitaxel 100 mg/m2 days 1, 8 and 15 Q28; Arm C, nab-paclitaxel 75 mg/m2 days 1, 8, 15 and 22 Q28. Induction was three cycles nab-paclitaxel 150/125 mg/m2, 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to evaluate the efficacy of each maintenance schedule in terms of progression-free survival (PFS) as compared with the historical reference of 7-month median PFS reported by previous studies with first-line docetaxel.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/m/pubmed/29228091/?i=5&from=/26712590/related*

2. Afinitor (Everolimus) – Varying starting dosages:

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*

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. *https://ascopubs.org/doi/abs/10.1200/JCO.2018.36.15_suppl.e13035*

3. Ibrance (Palbociclib) – Randomization with standard vs. lower dose at start of treatment; Results after dosage lowered due to Adverse Events:

The Phase II TBCRC035 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.researchgate.net/publication/335048396_Abstract_CT128_Palbociclib_in_combination_with_fulvestrant_or_tamoxifen_as_treatment_for_hormone_receptor_positive_metastatic_breast_cancer_with_prior_chemotherapy_for_advanced_disease_TBCRC_035_A_Pha

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 Adverse Events:

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. Trodelvy (Sacituzumab Govitecan) Dose Reduction after Adverse Events:

Efficacy outcomes for patients with dose reduction or interruption in the Sacituzumab Govitecan arm of the Phase 3 ASCENT study were similar to those for the overall population. Patients who had dose reductions with Sacituzumab Govitecan had a median Progression Free Survival of 8.3 months, which was similar to the overall study (median PFS, 5.6 months). Similarly, although dose reductions were more frequent in patients 65 and older, no considerable impact on efficacy outcomes were observed. *https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8488774/*

6. 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 2 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*

At the University of Southern California (USC) hospitals, capecitabine is routinely prescribed at dosages as low as 600 mg/m2 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/m2 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://e-syllabus.gotoper.com/publications/ajho/2015/2015Feb/Efficacy-of-Very-Low-Dose-Capecitabine-in-Metastatic-breast-Cancer*

At MDA, clinical data were available for 113 patients (105 for response, 106 for toxicity). The mean capecitabine starting dose was 2220 mg/m2/day. Forty per cent of all patients required capecitabine dose reductions; fewer patients treated with 2000 mg/m2/day required dose modification (28%). Patients started at the lowest doses of capecitabine did not have poorer response rates or shorter time to progression. This retrospective analysis supports a starting dose of 2000 mg/m2/day because of its superior therapeutic index. *https://www.sciencedirect.com/science/article/pii/S092375341954947X*

7. Verzenio (Abemaciclib) Randomized lower starting dose:

The Phase 2 nextMONARCH study enrolled 234 HR+, HER2- MBC patients who had previously received 2 or more chemotherapy regimens (1 or 2 of which had been received in the metastatic setting). Patients were randomized to receive either: Verzenio at 150 mg twice daily plus Tamoxifen once daily (arm A), 150 mg of Verzenio twice daily (arm B), or 200 mg of Verzenio twice daily (arm C), which is currently the FDA-approved Verzenio dose when taken as a monotherapy. Results showed a median Overall Survival of 24.2 months with the combination of Verzenio and Tamoxifen (arm A), 20.8 months for the 150 mg twice daily monotherapy dose (arm B), and 17.0 months for the 200 mg twice daily monotherapy dose (arm C). Treatment-related Adverse Events (AEs) were slightly lower on the Verzenio 150-mg monotherapy dose (97.5%) than on the 200 mg monotherapy dose (98.7%). **From:** *https://www.onclive.com/view/abemaciclib-tamoxifen-shows-os-benefit-in-hr-her2-metastatic-breast-cancer?fbclid=IwAR2C9gFP-XTtvE6cAqeRMp4X07hexSRr5bvnJlZkJMvJOsFgJBXLX2JoRnc*

MULTI-TRIAL DOSAGE ANALYSES OF LOWER STARTING DOSES

MD Anderson:

An analysis of 24 trials treating 683 cancer patients at MDA between 2004 and 2008 evaluated patients assigned to various targeted therapy dose levels: Low (≤25% MTD), Medium (25-75% MTD), or High (≥75% MTD). Groups were then compared for Response Rate, TTTF, PFS, and OS. In no case did the Low-dose group have a less desirable outcome than the Medium- or High-dose groups. *https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2822881/*

Meta-analysis of chemo drugs:

A meta-analysis of six randomized controlled studies (RCTs) provided data for low-dose chemotherapy versus conventional-dose chemotherapy for 838 cases and 833 cases, respectively. Chemotherapeutic agents included bleomycin, capecitabine, cisplatin, cyclophosphamide, docetaxel, doxorubicin, fluorouracil, oxaliplatin, tosedostat, vinblastine, and vincristine. The analysis concluded that low-dose chemotherapy achieved the same desired potency as conventional-dose chemotherapy, with no differences in pooled Objective Response Rate (ORR) and a reduction in Severe Adverse Events (SAEs). *https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5454746/*

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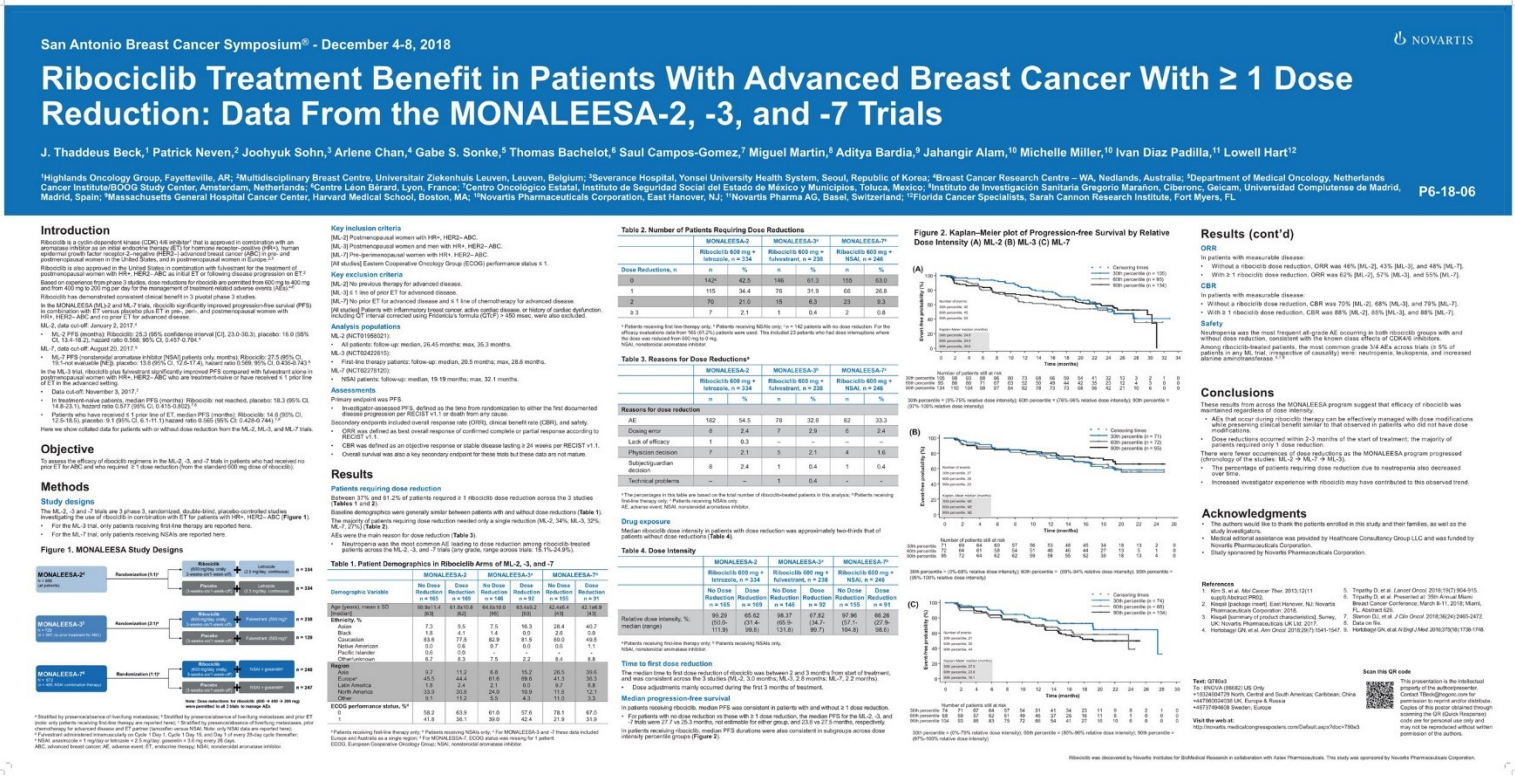

Studies Where a Lower Dose was Less Effective Than a Higher Dose:

Faslodex:

After Faslodex 250 mg was approved as treatment in postmenopausal women with advanced hormone receptor–positive breast cancer that had progressed or recurred after prior antiestrogen therapy, it was determined that a higher, 500 mg dose, was more effective. The randomized, double-blind CONFIRM Phase 3 trial of 736 women comparing the 250 mg dose with the 500 mg dose found that the median Overall Survival for the 500 mg dose was 26.4 months vs. 22.3 months for the 250 mg dose. As a result, the approved dosage was changed in 2010 from 250 mg to 500 mg. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3906991/

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-alpelisib-plus-fulvestrant-in-patients-with-hr-advanced-breast-cancer/100780