Neo-adjuvant chemotherapy has become standard practice in the management of large operable breast cancers with high expectation of response and improvement in cosmesis in for women with oestrogen receptor negative breast cancers. The prognostic implications of pathological complete response have led to its use as surrogate of longer-term recurrence outcomes in trials of novel early breast cancer systemic therapy regimens and as an endpoint for rapid marketing approval of such regimens conditional upon establishment of impacts on survival. While this complete pathological response endpoint remains a point of discussion there is little doubt that the presence of extensive viable residual disease at the end of neoadjuvant chemotherapy identifies a population of patients with oestrogen receptor negative breast cancer that has significant early distant recurrence risk. The identification of the molecular drivers of this chemotherapy resistant disease, and its relationship with that of the metastatic site, has become a priority with some data now been published that begin to address this. The potential impact of such work include the identification of targets and drugs that can be tested as post-surgical adjuvant therapy in this high risk post-neoadjuvant residual disease population using classical recurrence free survival endpoints. A small number of trials have been designed in this setting but few have yet reported results as outcome data are awaited. The landscape of this type of important post neoadjuvant second adjuvant therapy trial context will be reviewed. The pace of progress in optimising therapy for this high risk group will still be limited by the need to await recurrence outcome data at 3 years and the lack of ability to monitor response. An ideal scenario would allow hypotheses around resistance pathway activities, optimal target identification and target combination strategies to be studied driven by pharmacodynamic and short term efficacy biomarker endpoints in accessible residual disease tissue and in blood. Trial designs and platform approaches that are in development to address this will be discussed.

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