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Supplementary information

Systemic therapy for early-stage breast cancer: learning from the past to build the future

In the format provided by the authors and unedited

Supplementary Table 1 | Essential information of the main clinical trials reported in the manuscript.

Study name	Hypothesis	Population	Study design	Treatments	Main results
ALTTO [1]	Does dual HER2-blockade with trastuzumab (T) and lapatinib (L) improve DFS compared to adjuvant trastuzumab alone?	HER2-positive early breast cancer	Randomized, phase III N=8381	4 anti-HER2 treatment arms (+ chemotherapy): - T alone - L alone - T+L - T→L	Adjuvant treatment that includes L did not significantly improve DFS compared with T alone and added toxicity. One year of adjuvant T remains standard of care.
APHINITY [2]	Does dual HER2-blockade with trastuzumab (T) and pertuzumab (P) improve invasive DFS compared to adjuvant trastuzumab alone?	Node-positive or high-risk, node-negative HER2-positive operable breast cancer	Randomized, phase III N=4805	2 anti-HER2 treatment arms (+ chemotherapy): - T + P - T alone	P significantly improved invasive DFS among patients with HER2-positive, operable breast cancer when it was added to T and chemotherapy.
BEATRICE [3]	Does the addition of bevacizumab to adjuvant chemotherapy improve survival?	Early TNBC	Randomized, phase II N=2591	2 arms: - Bevacizumab (1 year) + chemotherapy - Chemotherapy alone	No significant survival improvement with the addition of bevacizumab.
CREATE-X [4]	Does post-neoadjuvant capecitabine improve survival in patients with residual disease after neoadjuvant chemotherapy?	HER2-negative breast cancer, with residual invasive disease after neoadjuvant chemotherapy	Randomized, Phase III N=910 (TNBC, N=286)	2 arms: - Capecitabine (6-8 cycles) - Control (no treatment)	Adjuvant capecitabine improves disease-free survival and overall survival
D-CARE [5]	Does adjuvant denosumab improve survival in early breast cancer?	Stage II-III early breast cancer	Randomized, Phase III N=4509	2 arms: - Denosumab - Placebo	Denosumab did not improve disease-related outcomes for women with high-risk early breast cancer
GeparNuevo [6]	Does the addition of durvalumab to neoadjuvant	Early TNBC	Randomized, Phase II N=174	2 arms (+ neoadjuvant chemotherapy): - Durvalumab - Placebo	Durvalumab was associated with no significant improvement in pCR, but with significant improvement in survival endpoints

	chemotherapy improve patient outcomes?				
KATHERINE [7]	Does post-neoadjuvant T-DM1 improve survival in patients with residual disease after neoadjuvant chemotherapy, compared to adjuvant trastuzumab?	HER2-positive breast cancer, with residual invasive disease after neoadjuvant chemotherapy	Randomized, Phase III, N=1486	2 arms of adjuvant treatments: - T-DM1 - Trastuzumab	T-DM1 reduced the risk of recurrence of invasive breast cancer or death compared to trastuzumab
KEYNOTE-522 [8,9]	Does the addition of pembrolizumab to neoadjuvant chemotherapy improve outcomes in patients with early TNBC?	Stage II-III early TNBC	Randomized, Phase III N=1174	2 arms (+ neoadjuvant chemotherapy): - Pembrolizumab (neo + adjuvant phase) - Placebo	Pembrolizumab was associated with significant improvement in pCR and EFS
MonarchE [10,11]	Does the addition of abemaciclib to adjuvant endocrine therapy improve outcomes in high-risk HR-positive, HER2-negative early breast cancer?	High-risk, node-positive, HR-positive, HER2-negative early breast cancer	Randomized, Phase III N=5637	2 arms: - Abemaciclib + endocrine therapy - Endocrine therapy alone	Abemaciclib combined with ET is demonstrated a significant improvement in IDFS
NeoSphere [12]	Does dual-blockade with pertuzumab and trastuzumab in addition to neoadjuvant chemotherapy improve outcomes compared to trastuzumab alone?	Locally advanced, inflammatory, or early-stage HER2-positive breast cancer	Randomized, Phase II N=417	4 arms: - trastuzumab + docetaxel (group A) - pertuzumab and trastuzumab plus docetaxel (group B) - pertuzumab and trastuzumab (group C) - pertuzumab and docetaxel (group D)	Neoadjuvant pertuzumab was beneficial when combined with trastuzumab and docetaxel.
OLYMPIA [13]	Does adjuvant olaparib improve outcomes in patients with BRCA-	HER2-negative, early breast cancer with BRCA1 or BRCA2	Randomized, Phase III N=1836	2 arms: - Adjuvant olaparib (1 year) - Placebo	Olaparib was associated with significantly longer survival free of invasive or distant disease and overall survival than placebo

	mutated early breast cancer?	germline mutation and high-risk clinicopathological factors who had received local treatment and neoadjuvant or adjuvant chemotherapy			
PALLAS [14]	Does the addition of palbociclib to adjuvant endocrine therapy improve outcomes in high-risk HR-positive, HER2-negative early breast cancer?	Stage II-III HR-positive, HER2-negative early breast cancer	Randomized, Phase III, N=5760	2 arms: - Palbociclib (2 years) + endocrine therapy - endocrine therapy	The addition of 2 years of adjuvant palbociclib to adjuvant endocrine therapy did not improve invasive disease-free survival compared with adjuvant endocrine therapy alone.

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