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Small HER2 Positive Breast Cancer: When is Enough?

Small node negative HER2 Positive tumors are defined as T1 (<2 cm) and N0 (node negative). The above cohort is increasing with more awareness and acceptance of mammography screening. This group in itself is a heterogeneous population such as T1a/b versus T1c, Grade I versus II/III and estrogen receptor (ER) positive versus negative tumours. The role of adjuvant therapy for these women is a long-standing dilemma for clinicians due to the lack of prospective randomized trials and a poor representation of this group in pivotal trials. Even guidelines are inconsistent on chemotherapy regimen and the duration of trastuzumab for this subset.

There is increasing evidence from several retrospective studies for an inferior outcome in these patients with recurrence rates as high as 15%–30% after 5–10 years.[1] In a British Columbia data set[2] of N0 breast cancers, positive HER2 status was an independent predictor of breast cancer death in 10 years in a multivariable model, with odds ratio (OR) of 2.03 (P = 0.003) and in a European Institute of Oncology[3] population of pT1abN0 breast cancers, it was an independent predictor of 5 years disease-free survival (DFS) with OR of 2.5 (95% confidence interval [CI]: 0.9-6.5; P = 0.09). The available evidence for the efficacy of trastuzumab for these patients has limitations such as subgroup analysis of large randomized trials, retrospective nature, small numbers, few events in trials, and differing end points or durations of follow up. Five large randomized Phase III multicenter studies have shown that the addition of trastuzumab to chemotherapy results in decreased recurrence and better overall survival (OS). The proportion of TIN0 tumors and their survival outcome (subgroup analyses) compared to the overall group is depicted in Table 1.

Deescalation of Chemotherapy

The APT trial[9] was the first prospective investigation of a reduced intensity adjuvant treatment regimen (weekly paclitaxel and trastuzumab [TH] for 12 weeks, followed by completion of 1 year of trastuzumab [H]) in small, node-negative HER2+ disease following standard breast surgery. Majority of the patients in this trial were T1N0 with 8.9% of these had T size 2–3 cm. Survival free from invasive disease, the primary end point of the trial, was 98.7% (95% CI: 97.7%–99.8%) at 3 years, supporting TH as a highly effective regimen in this patient population. Another prospective, single-arm Phase II trial[10] has looked at a more intensive regimen in early stage HER2+ breast cancer. In this trial, patients were treated in the adjuvant setting with four cycles of docetaxel/cyclophosphamide/trastuzumab, followed by every 3 week trastuzumab to complete a year of therapy. The primary endpoint was DFS at 2 years, but follow-up was long enough to calculate 3-year survival estimates. Overall 3-year DFS and OS were 96.9% and 98.7%, respectively. Among node-negative patients with primary tumor size less than or equal to 1 cm, 3-year DFS and OS were both 100%.

Deescalation of Trastuzumab Duration

Adjuvant trastuzumab is approved across the globe for 1 year duration as standard treatment. There have been attempts at reducing this duration [Table 2]. The arguments for a shorter duration of exposure may be supported by

Table 1: Overview of the major trials on the benefit of the major trials in HER2+ breast cancer

Study	Patient population	*n*	ER+ and or PgR positive (%)	Node negative (%)	pT 1 tum (%)	HR for DFS (95% CI)	HR for OS (95% CI)
HERA[4]	HER2+N + HER2+ N− >pT1b	3387	45	32	40	Overall: 0.54 (0.43-0.67) N−tum 0.51 (0.30-0.87)	0.76 (0.47-1.23)
Fin Her[2,5]	N+ N− and >pT1c and PgR <10%	1010	72	11	44	0.42 (0.21-0.83)	0.55 (0.27-1.11)
Intergroup N9831, NSABP-B31[4,8,6]	HER2+ N + HER2+ N+ >pT1c ER + HER2+ N− >Pt1b ER-	3969	52	6	39	0.49 (0.41-0.58)	0.62 (0.49-0.81)
BCIRG 006[7]	HER2+ N+ HER2+ N− and risk factors	3222	54	29	40	Overall; 0.49 (ACTH), 0.61 (TCH) N-negative tumors: 0.32 (0.17-0.62) Pt1c tumors: 0.6 (0.4-1.0)	0.63 (0.48-0.81) for ACTH: 0.77 (0.60-0.99) for TCH
PACS-04[8]	HER2+ N+	3010	10	None	32	0.86 (0.61-1.22)	1.27 (0.68-2.38)

HR given for the additional benefit for adjuvant trastuzumab compared with no such treatment. HR – Hazard ratio; CI – Confidence interval; DFS – Disease-free survival; OS – Overall survival; ER – Estrogen receptor; ACTH – Docetaxel and trastuzumab

Table 2: Trials looking at shorter duration trastuzumab

9 weeks versus 12 months
Sold
Doc + Tras → FEC
Doc + Tras → FEC → Tras
Short-HER
EC/AC → Doc + Tras → Tras
Doc+Tras → FEC
6 months versus 12 months
Persephone-sequential
Chemotherapy → Tras
Chemotherapy → Tras
Persephone-concurrent
Doc + Tras → FEC → Tras
Doc + Tras → FEC → Tras
PHARE
Chemotherapy → Tras
Chemotherapy → Tras
Hellenic
FEC → Doc + Tras → Tras
FEC → Doc + Tras → Tras

PHARE – Protocol of Herceptin Adjuvant with Reduced Exposure

cardiac safety and cost effectiveness and especially relevant for this subset of patients.

FINHER approach reported by Joensuu *et al*.[5] showed that a brief course of trastuzumab administered concomitantly with docetaxel is safe and effective, but the study cohort included patients who were either node positive or had T size >2 cm high-risk node negative tumors. The Protocol of Herceptin Adjuvant with Reduced Exposure trial[11] evaluated the efficacy of 6 versus 12 months of trastuzumab treatment. In this noninferiority trial, 3400 patients who had started trastuzumab were randomly assigned at 6 months to complete the standard 12 months of therapy or to stop therapy at the 6-month time point. The 95% CI hazard ratio (HR) for noninferiority was set at 1.15. However, 6 months of trastuzumab did not meet this threshold, with an HR of 1.28 (P = 0.029). Of note, although statistical noninferiority of 6-month duration was not established, the absolute benefit of longer duration in DFS and OS was small. Subsequently, a subgroup analysis of this study was published. In this analysis, there was a suggestion that in patients with very low risk (T <2 cm and N0) and low-risk (T ≤2 cm or 1–3 nodes) 6 months and 12 months of trastuzumab did not result in markedly different outcomes.[12] Hellenic Oncology Research Group conducted a randomized study to compare the efficacy of 12 versus 6 months of adjuvant trastuzumab administered concurrently with dose-dense chemotherapy in women with node-positive or high-risk node-negative early breast cancer. Although this trial also failed to demonstrate the noninferiority of 6 versus 12 months administration, it had many limitations such as small sample size and a relatively high noninferiority margin of 8%.[13] Results of other trials of shorter trastuzumab duration are forthcoming.

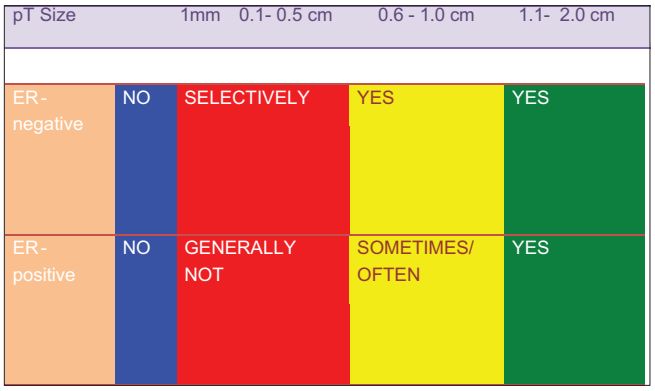

Figure 1: Proposed schema for adjuvant therapy of Stage 1 HER2+ breast cancer

The proposed schema for Adjuvant therapy of Stage 1 HER2+ breast cancer is shown in Figure 1.

In summary, both retrospective and meta-analysis data suggest a benefit to trastuzumab treatment in small and/or node-negative HER2+ tumors. The questions of "how low and how much" and tumor size thresholds remain open to debate. Available data also suggests that, although durations shorter than 1 year are not clearly noninferior to 1 year of adjuvant trastuzumab, the absolute benefits of longer duration are small and may not exist in small, node negative tumors. Thus, durations shorter than 1 year may be appropriate in resource constrained settings. The potential role of novel HER2 directed therapies in this cohort is not clear. Greater integration of translation research and gene signatures may provide further insight for this subset in the future.

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