Residual Disease Management In HER2+ve Early Breast Cancer Setting : Case Discussion

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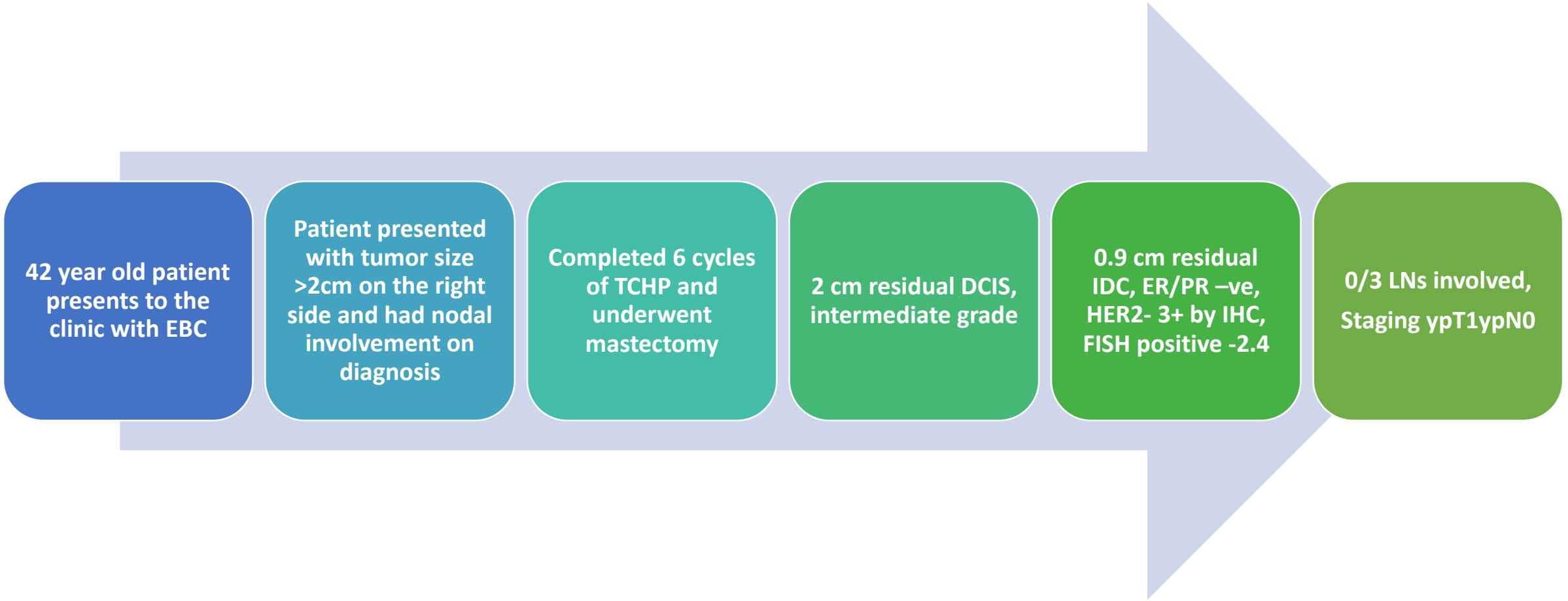
Background of the case



https://www.targetedonc.com/view/case-1-adjuvant-treatment-for-residual-disease-in-early-stage-her2-breast-cancer

Discussion

- *What % of your patients achieve pCR after NACT?*
- *What are the risk factors for having residual disease in HER2+ve EBC setting?*

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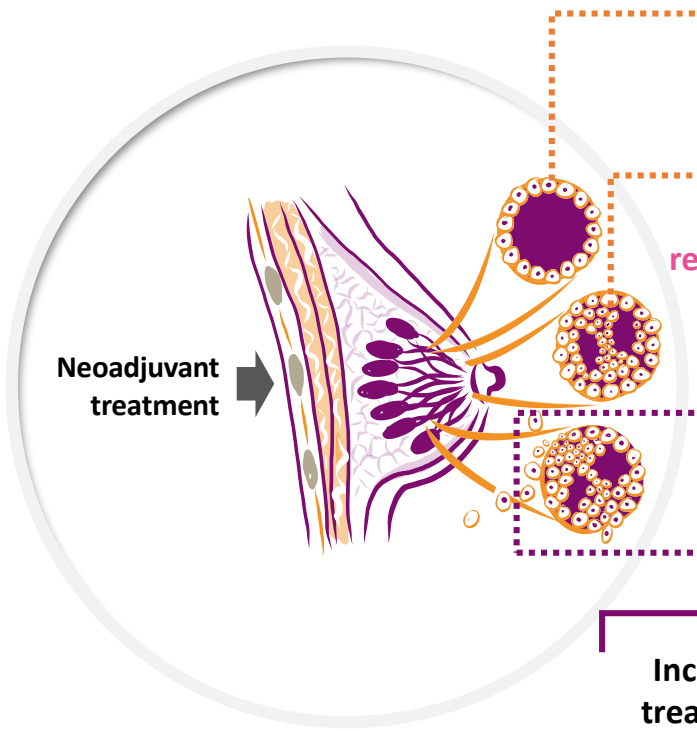
Outcomes of neoadjuvant therapy: Pathological complete response (pCR) or residual disease[1,2]

Outcomes of neoadjuvant therapy are evaluated using pathological samples taken at the time of surgery



No disease

In situ residual disease

tpCR

No malignant cells found on pathological examination of the breast and axilla

Responsive to treatment;
still at risk of recurrence or death

Residual invasive disease

Incomplete response to treatment and **significant** risk of breast cancer recurrence or death[3–5]

Residual macroscopic or microscopic disease present in the breast and axilla

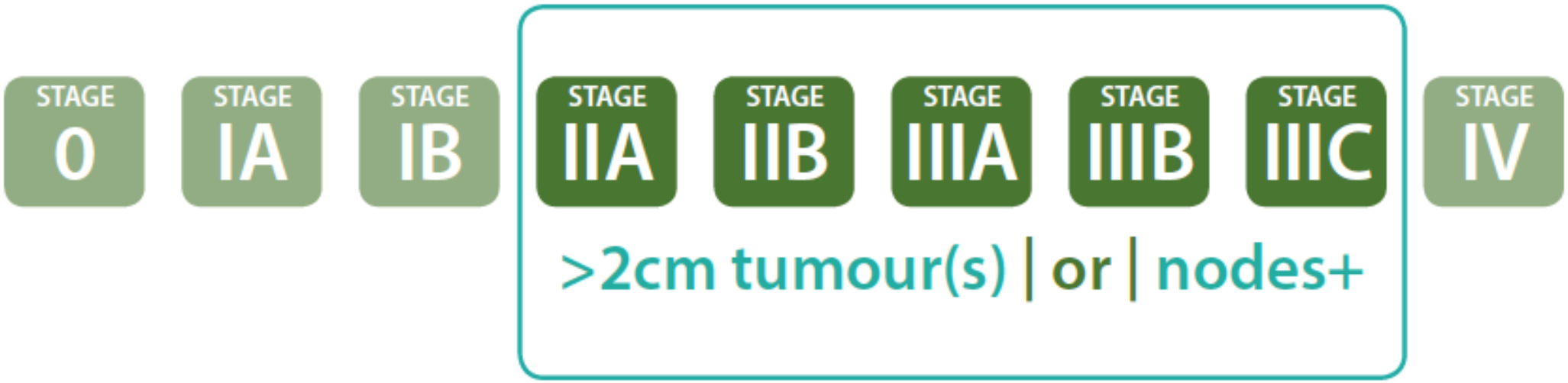
Even a trace of residual invasive disease requires adaptation of continued therapy

tpCR, total pathological complete response

1. Rose BS, *et al. J Clin Oncol* 2016; 2. Caparica R, *et al. Ther Adv Med Oncol* 2019;
3. Gianni L, *et al. Lancet Oncol.* 2016; 4. Cortazar P, *et al. Lancet* 2014; 5. Schneeweiss A, *et al. Eur J Cancer* 2018.

High-risk HER2-positive eBC tumours are >2 cm or node-positive

Treatment guidelines define high risk in the context of neoadjuvant treatment:[1,2]



In early-stage breast cancer, tumour size, grade, hormone receptor status and lymph node metastases should be taken into account[3]

1. Coates AS, *et al. Ann Oncol* 2015; **26:**1533–1546;
2. AJCC Breast Cancer Staging Manual. 7th Ed. 2010;
3. PERJETA (pertuzumab) Summary of Product Characteristics, 2016.

The non-pCR population is heterogeneous: Burden of disease

The Residual Cancer Burden (RCB) Index can also predict outcome after neoadjuvant therapy

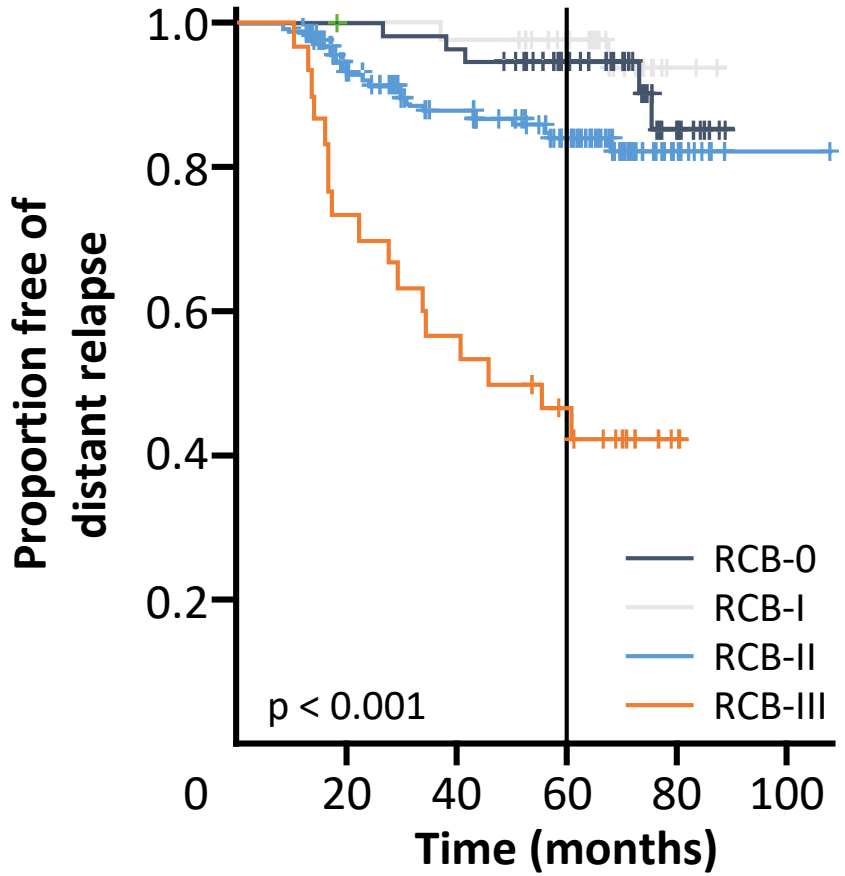
Parameters considered:

- Primary tumour dimensions
- Cellularity of tumour bed
- Number of positive nodes
- Size of largest nodal metastasis

RCB groups:

- RCB-0: pCR
- RCB-I: minimal residual disease
- RCB-II: moderate residual disease
- RCB-III: extensive residual disease

Prognosis



No. at risk

RCB-0	55	55	54	43	14	1
RCB-I	42	42	41	35	4	1
RCB-II	114	106	99	78	13	2
RCB-III	30	23	18	13	2	1

Fraser Symmans W, et al. J Clin Oncol 2007; 25:4414–4422.

Current risk stratification markers

Anatomic features

- ***Size, LN***

Molecular features

- ***ER, grade***
- ***Intrinsic subtype***
- ***TILs***
- ***HER2 levels***
- ***Heterogeneity***
- ***Mutation status (eg PIK3CA)***

Response to neoadjuvant therapy

Discussion

- *Do you retest for hormone receptor status after finding residual disease in the surgery specimen?*
- *Do you rely on the baseline HER2 status or the post surgical HER2 status?*
- *What additional workup would you advise to this patient?*

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Discussion

- *What would you give to this patient?*
- *What is the real world IDFS in your clinical practice for patients with residual disease?*
- *Which parameters are taken into account while deciding treatment for patients with residual disease?*
- *What are your opinions about the Katherine trial?*

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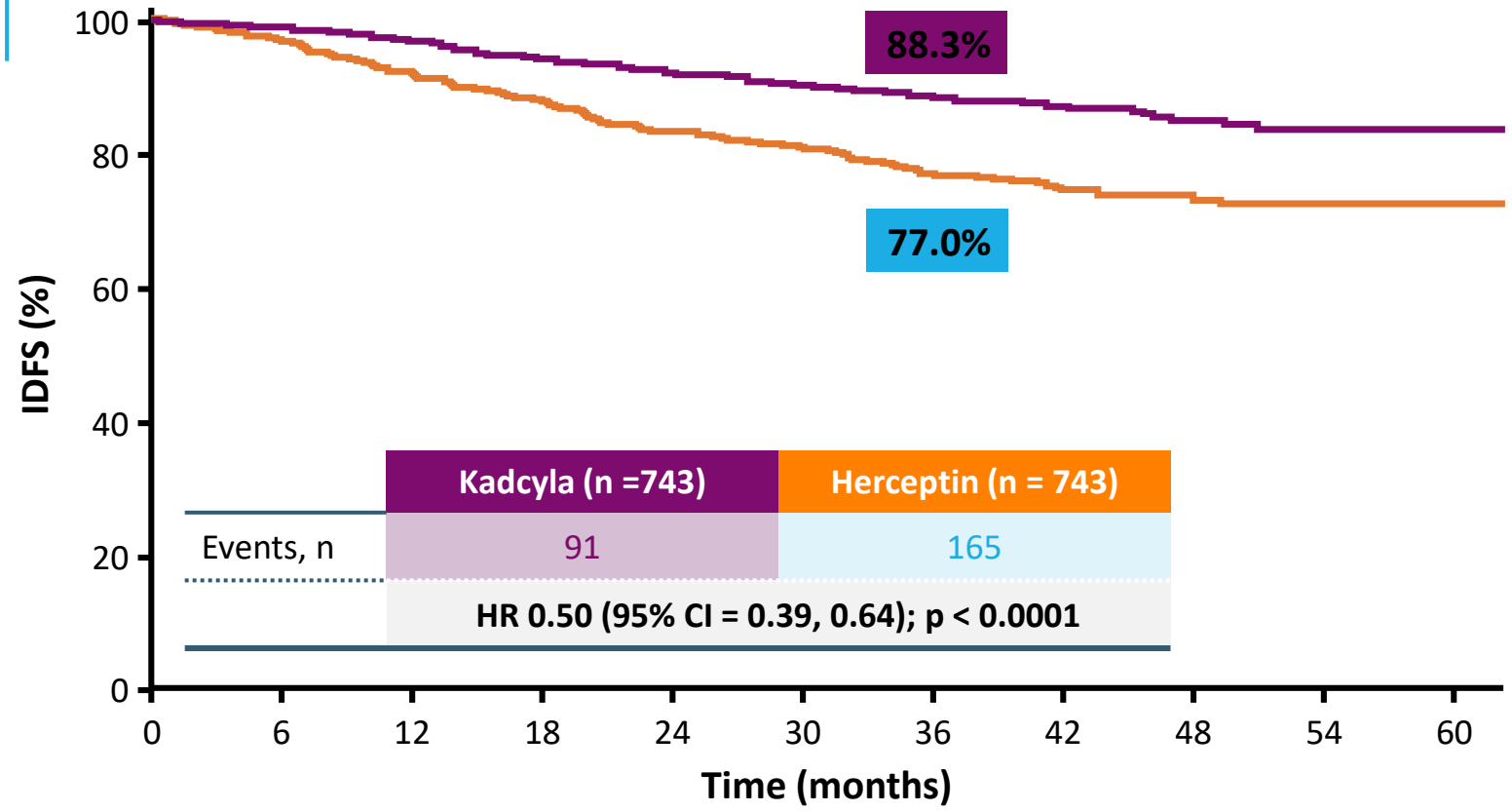
Primary Analysis: IDFS



Kadcyla	743	707	681	658	633	561	409	255	142	44	4
Herceptin	743	676	635	594	555	501	342	220	119	38	4

Kadcyla reduced the risk of an IDFS event by 50% compared with Herceptin at a median follow-up of 41 months

Kadcyla increased the 3-year IDFS rate from 77.0% to 88.3%

CI, confidence interval; HR, hazard ratio IDFS, invasive disease-free survival.

von Minckwitz G, *et al. N Engl J Med*; 2019

KATHERINE: OVERALL SUMMARY

KATHERINE is the first trial to demonstrate a significant benefit with a therapy optimisation by changing to targeted chemotherapy in patients with residual disease after neoadjuvant therapy in HER2-positive BC

Study met its primary objective, with a 50% reduction of the risk of an IDFS event with Kadcyla vs. Herceptin
(HR 0.50; 95% CI = 0.39, 0.64; $p < 0.0001$)

Safety profile of Kadcyla was consistent with previous trials

Magnitude of IDFS benefit was consistent across all subgroups, including HR status, nodal status and prior dual HER2 blockade

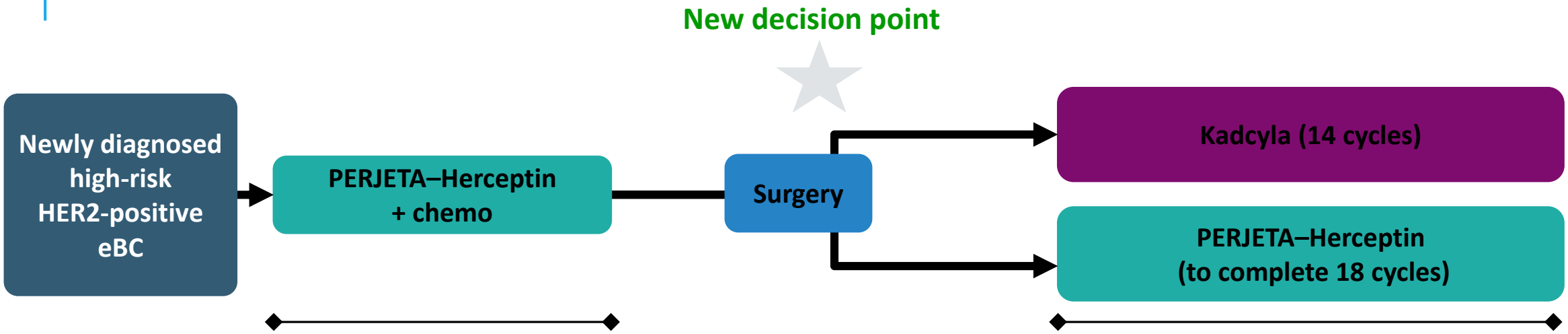
These results will likely form the foundation of a new SoC in this population

The benefit:risk of Kadcyla is transformative for patients with HER2-positive eBC who have residual disease following completion of neoadjuvant therapy

BC, breast cancer; CI, confidence interval; eBC, early breast cancer; HR, hazard ratio; IDFS, invasive disease-free survival.

Roche, data on file.

Presence Of Residual Disease As A New Decision Point



- **Following approval, patients who have residual disease should receive 14 cycles of Kadcyla in the adjuvant setting[1]**
- Patients who have a pCR following neoadjuvant treatment and surgery can continue therapy with PERJETA–Herceptin to complete 18 cycles[2–4]

eBC, early breast cancer; pCR, pathological complete response.

1. Geyer CE, *et al.* SABCS 2013 (Abstract P3-04-02; poster presentation);
2. Curigliano G, *et al. Ann Oncol* 2017; **28**:1700–1712; 3. NCCN Breast Cancer Guidelines Version 3 – 2018 (October 2018); 4. AGO guidelines (accessed October 2018).

Guidelines Recommend Changing Treatment To T-DM1 In The Adjuvant Setting For Patients With Residual Invasive Disease

NCCN Guidelines® Recommended Option[1]

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) recommend ado-trastuzumab emtansine (KADCYLA) monotherapy for the adjuvant treatment of patients with HER2+ breast cancer with residual invasive disease after neoadjuvant treatment (category 1, preferred)†1

NCCN Guidelines recommend treatment with ado-trastuzumab Emtansine (KADCYLA) for 14 cycles in this setting

†Category 1: Based upon high-level evidence, there is uniform National Comprehensive Cancer Network® (NCCN®) consensus that the intervention is appropriate. NCCN makes no warranties of any kind whatsoever regarding their content, use, or application and disclaims any responsibility for their application or use in any way.

American Society of Clinical Oncology (ASCO)® Guideline Recommendation[2]

Eligible patients† should be offered 14 cycles of adjuvant ado-trastuzumab emtansine, unless there is disease recurrence or unmanageable toxicity, per the American Society of Clinical Oncology®.13

†Patients with pathological invasive residual disease at surgery after standard preoperative chemotherapy and HER2-targeted therapy

Category 2A NCCN Other Recommended Regimen Option[1]

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) recommend ado-trastuzumab emtansine (KADCYLA) monotherapy as a category 2A, other recommended regimen option for the treatment of all eligible patients with HER2+ metastatic breast cancer following treatment with trastuzumab and a taxane.*[1]

*Category 2A: Based upon lower-level evidence, there is uniform National Comprehensive Cancer Network® (NCCN®) consensus that the intervention is appropriate. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

References
1. The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Breast Cancer V4.2022.
2. Denduluri N, Somerfield MR, Chavez-MacGregor M, et al. Selection of Optimal Adjuvant Chemotherapy and Targeted Therapy for Early Breast Cancer: ASCO Guideline Update. J Clin Oncol. 2021;39(6):685-693.

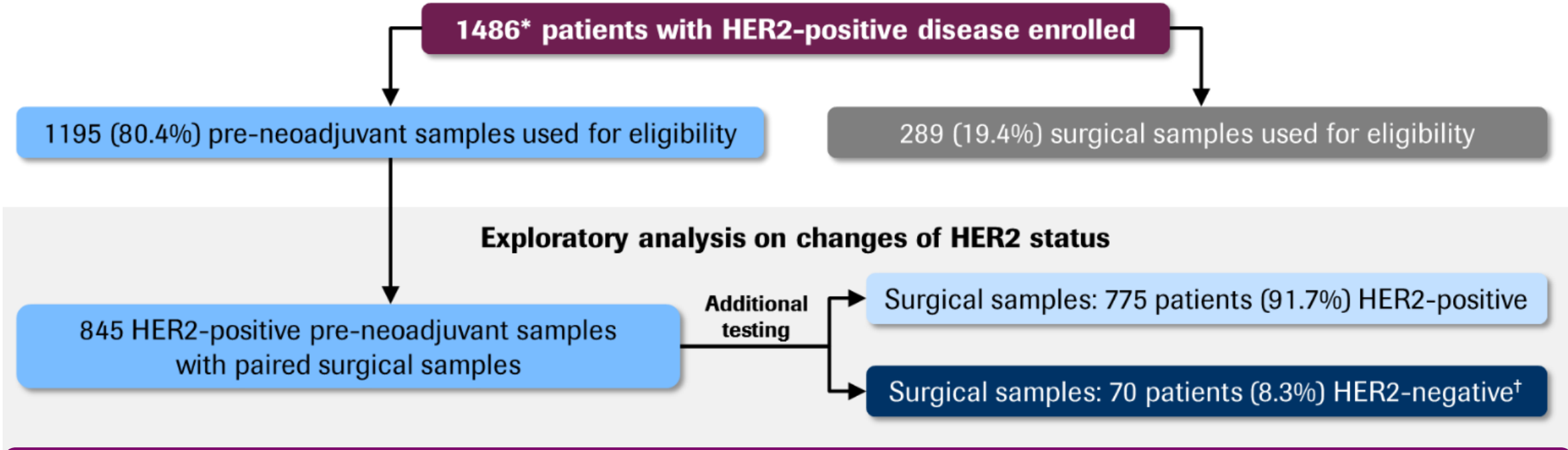
Discussion

What % of your patients experience HER2 loss after surgery/NACT in EBC setting?

Does the treatment change if patient undergoes HER2 loss post surgery or initial NACT?

https://www.targetedonc.com/view/case-1-adjuvant-treatment-for-residual-disease-in-early-stage-her2-breast-cancer

HER2-negative status after neoadjuvant therapy did not impact the efficacy of T-DM1



In the 70 patients with HER2-negative disease after re-testing of surgical samples:

- There were no IDFS events in patients randomised to the Kadcyla arm (n = 28)
- There were 11 IDFS events in patients randomised to the Trastuzumab arm (n = 42)

These data should be interpreted with caution due to the small sample size

Kadcyla® trastuzumab emtansine

* Two patients (both in the Trastuzumab arm) were not included in this analysis: One did not have centrally confirmed HER2-positive disease and one was inadvertently randomised twice.
† 53 HER2-negative and 17 HER2-unknown by IHC 0-1+/ISH unknown
IDFS, invasive disease-free survival.
Loibl S, *et al.* ESMO Breast 2020 (Abstract 96O and oral presentation).

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http://bit.ly/Roche_Kadcyla_PI

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