KEYRICHED-1: A PROSPECTIVE, MULTICENTER, OPEN LABEL, NEOADJUVANT PHASE II SINGLE ARM STUDY WITH PEMBROLIZUMAB IN COMBINATION WITH DUAL ANTI-HER2 BLOCKADE WITH TRASTUZUMAB AND PERTUZUMAB IN EARLY BREAST CANCER PATIENTS WITH MOLECULAR HER2-ENRICHED INTRINSIC SUBTYPE

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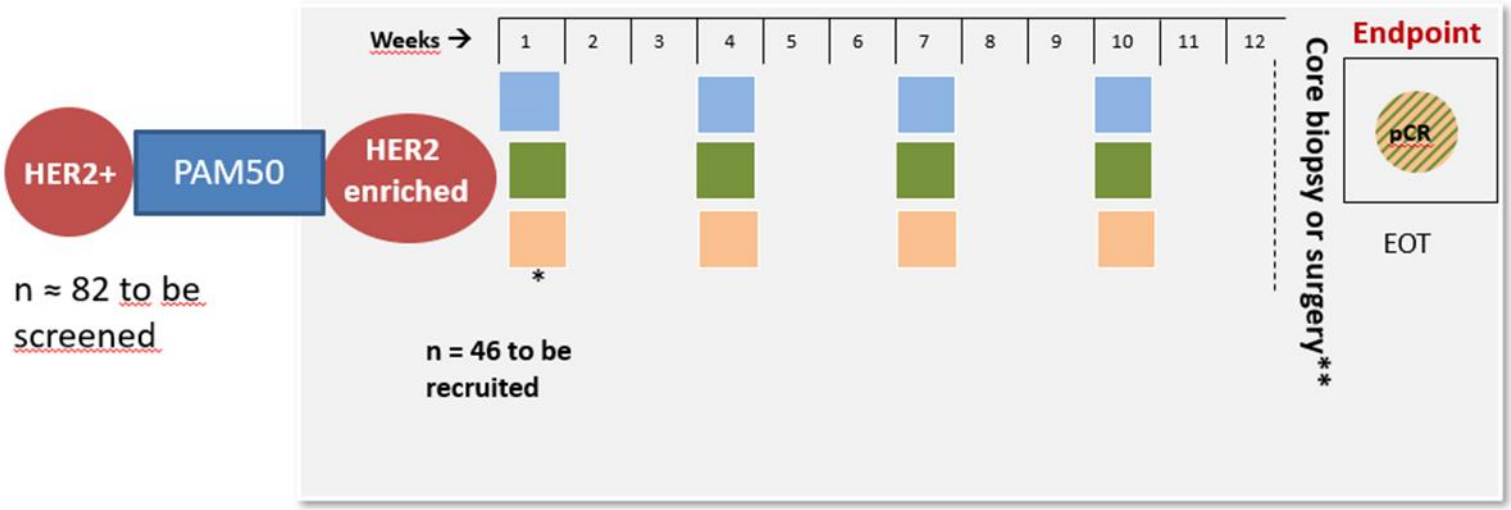
BACKGROUND

- HER2-positive (HER2+) early breast cancer (EBC) is a highly heterogeneous disease that can be subdivided into several molecular subtypes based on the PAM50 gene expression signature.
- Several studies point to increased expression of pro-immune factors and/or tumor-infiltrating lymphocytes as markers for improved prognosis. (PANACEA-Trial, Lois S et al., Lancet Oncol. 2019, 20:371–382; KATE 2-Trial, Emens AL et al., Lancet Oncol. 2020, 21:1283–1295)
- De-escalation strategies seem to be promising in HER2+ EBC and chemotherapy-free therapies are therefore of central importance.
- Initial studies with dual antibody-based HER2 blockade alone have achieved pCR rates of 20-40%, not quite approaching the pCR rates achieved with concurrent chemotherapy. (ADAPT $HER2^+/HR^+$: Harbeck N et al., ESMO 2020; ADAPT $HER2^+/HR^-$: Nitz U et al., Ann Oncol 2017, 28(11): 2768-72)
- Therefore, the prospective, single-arm, hypothesis-generating phase II KEYRICHED-1 trial (NCT03988036) evaluated pCR rates in patients with HER2-enriched EBC receiving chemotherapy-free dual anti-HER2 blockade in combination with the checkpoint inhibitor pembrolizumab with the objective to achieve pCR rates comparable to standard chemotherapies by adding appropriate molecular selection and immuno-oncology.

KEYRICHED-1: STUDY DESIGN



* Cycle 1: C1D1 pembrolizumab only, C1D2 trastuzumab and pertuzumab Cycles 2-4: D1 pembrolizumab, trastuzumab and pertuzumab

** Core biopsy (in case of present residual tumor burden) is only sufficient in case of non-pCR

KEYRICHED-1: METHODS

- This single-arm phase II trial enrolled premenopausal and postmenopausal patients with newly diagnosed HER2 2+ (ISH+) or HER2 3+ EBC (stage I-III) and HER2 enriched (HER2-E) subtype by PAM50 analysis.

- Primary endpoint was centrally confirmed pCR (ypT0/is, ypN0). The trial was planned as a Simon's two-Stage design (null and alternative pCR were 40% and 60%); interim analysis after 16 patients had to show a pCR rate of at least 50% to continue recruitment.

- sTILs (stromal tumor infiltrating lymphocytes) were measured according to international consensus recommendations (Salgado R et al., Ann Oncol 2015, 26(2): 259-271)

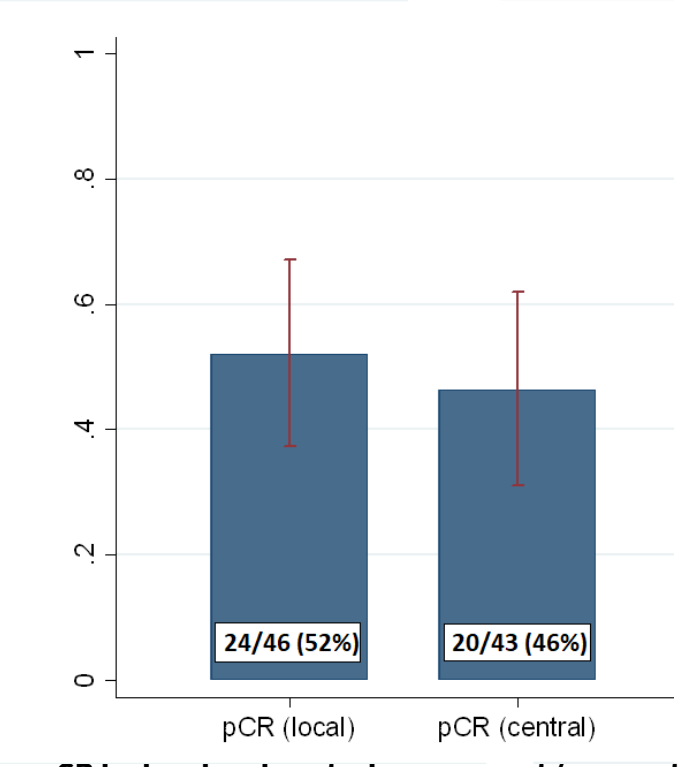
KEYRICHED-1: PATIENT CHARACTERISTICS

	Variable	Frequency	%
Age (years)	Median (range)	57	28-83
	Average (st.deviation)	55.0	11.2
Tumor size	T1c	15	34.88
	T2	25	58.14
	T3	3	6.98
Noda status	N0	30	69.77
	N1	9	20.93
	N2	4	9.30
Menopausal status	postmenopausal	25	58.14
	premenopausal	16	37.21
	unclear	2	4.65
HER2 central	2+	4	9.30
	3+	39	90.70
ER central	negative	17	39.53
	positive	26	60.47
PR central	negative	29	67.44
	positive	14	32.56
GRADING	G2	18	41.86
	G3	25	58.14

- 55% of screened tumors (local HER2 IHC 2+, ISH+ or 3+) had HER2-E subtype
- 65% had tumors $\geq$ 2 cm and 30% positive lymph node status.

KEYRICHED-1: RESULTS I

pCR by local and central assessment (per protocol, pp population)



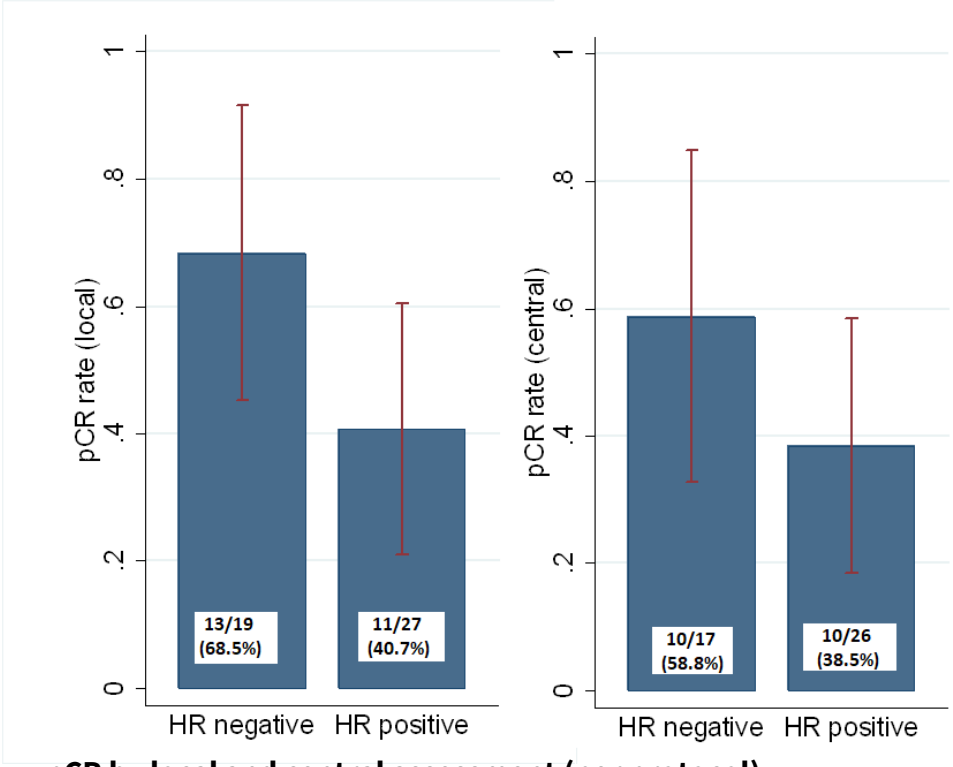
pCR by local and central assessment (per protocol)

- Centrally confirmed pCR rate in surgical specimens was 46% (95% CI 0.31-0.62) in the 43 patients of the pp population, and 52% (95%CI 0.37-0.67) in all 46 evaluable patients (local assessment; two pCRs verified only by core biopsy) (p=0.22 and p=0.06 for null hypothesis, respectively).

- Despite HER2-E subtype, no pCR was observed in the 4 patients with immunohistochemical (IHC) HER2 2+/ISH+ status in contrast to 20/39 (51.2%) pCRs in IHC HER2 3+ tumors.

KEYRICHED-1: RESULTS II

pCR by local and central (per protocol) assessment according to HR status

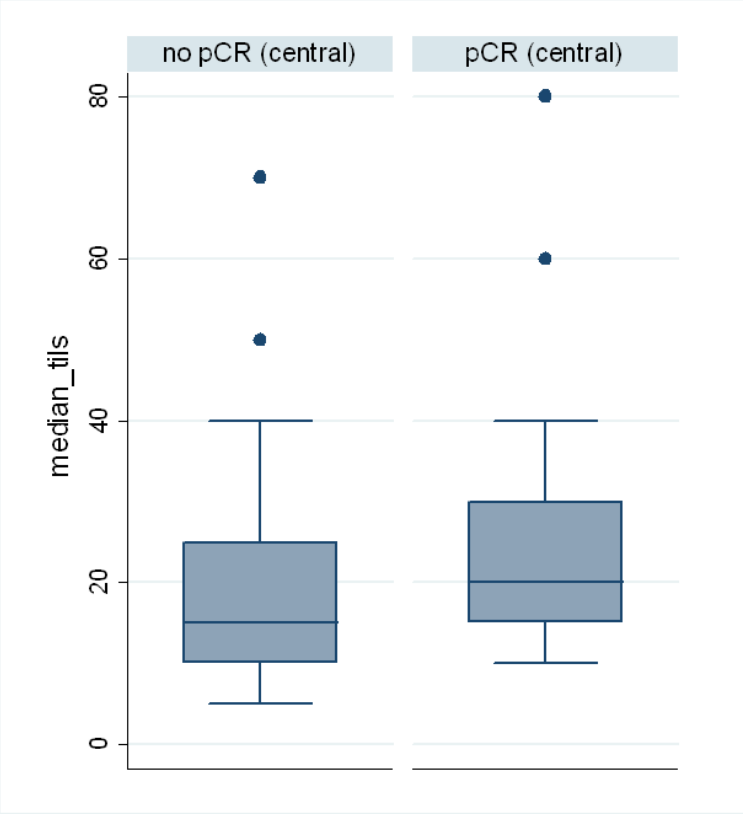


pCR by local and central assessment (per protocol)

- Of all investiagted markers only negative PR status (n=12) was a significant predictor for pCR (p=.027).

KEYRICHED-1: RESULTS III

sTIL‘s by pCR status



- sTILs were measured in 40 patients. Tumors which achieved pCR had higher median baseline sTIL values compared to non-pCR cases (central: 20% vs. 15%, p=.10, and local 20 vs. 12.5, p=0.022).
- Ten patients had sTIL's ≥30%; seven of them had a pCR (local assessment)

KEYRICHED-1: SUMMARY

- Centrally confirmed pCR rate in surgical specimens was 46% in the pp population and 52% (95%CI 0.37-0.67) in all 46 evaluable patients (local assessment; two pCRs verified only by core biopsy).

- Centrally confirmed pCR rate in HR+/HER2+ tumors was 38.5% compared to 58.8% in HR-/HER2+ tumors.

- Negative PR status (n=12) was a significant predictor for pCR (p=.027).

- Despite HER2-E subtype, no pCR was observed in the 4 patients with immunohistochemical (IHC) HER2 2+/ISH+ status in contrast to 20/39 (51.2%) pCRs in IHC HER2 3+ tumors.

- Ten patients had sTIL's ≥30%; seven of them had a pCR (local assessment)

KEYRICHED-1: CONCLUSION

- WSG KEYRICHED-1 provides the first results of neoadjuvant chemotherapy-free 12-week anti-HER2 de-escalation therapy with trastuzumab and pertuzumab in combination with the PD-1 inhibitor pembrolizumab in HER2-E EBC.

- No new safety signals were observed.

- In addition, KEYRICHED-1 demonstrates that using appropriate molecular patient selection, clinically meaningful pCR rates can be achieved by a chemotherapy-free regimen that compare favorably with those achieved by longer, more toxic chemotherapy regimens.