

Expanding options for HER2 advanced breast cancer: Taking trial data to the clinic

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Expert panel



Dr Laura Biganzoli (Chair)

Acting Director of the Division of Medical Oncology and Director of the Breast Centre, Department of Oncology, Hospital of Prato, Prato, Italy



Dr Peter Fasching

Associate Professor of Gynaecology and Obstetrics Translational Medicine, University Hospital Erlangen and Comprehensive Cancer Center, Erlangen-EMN, Friedrich-Alexander University Erlangen-Nuremberg, Erlangen, Germany



Dr Sonia Pernas

Head of Breast Cancer Unit, Catalan Institute of Oncology, Barcelona; Associate Professor Faculty of Medicine, University of Barcelona, Barcelona, Spain



Agenda

Progress with HER2-targeted therapies in advanced breast cancer

Maintaining HER2-targeted therapies: How to manage adverse events

Novel HER2-directed approaches: Implications for future practice

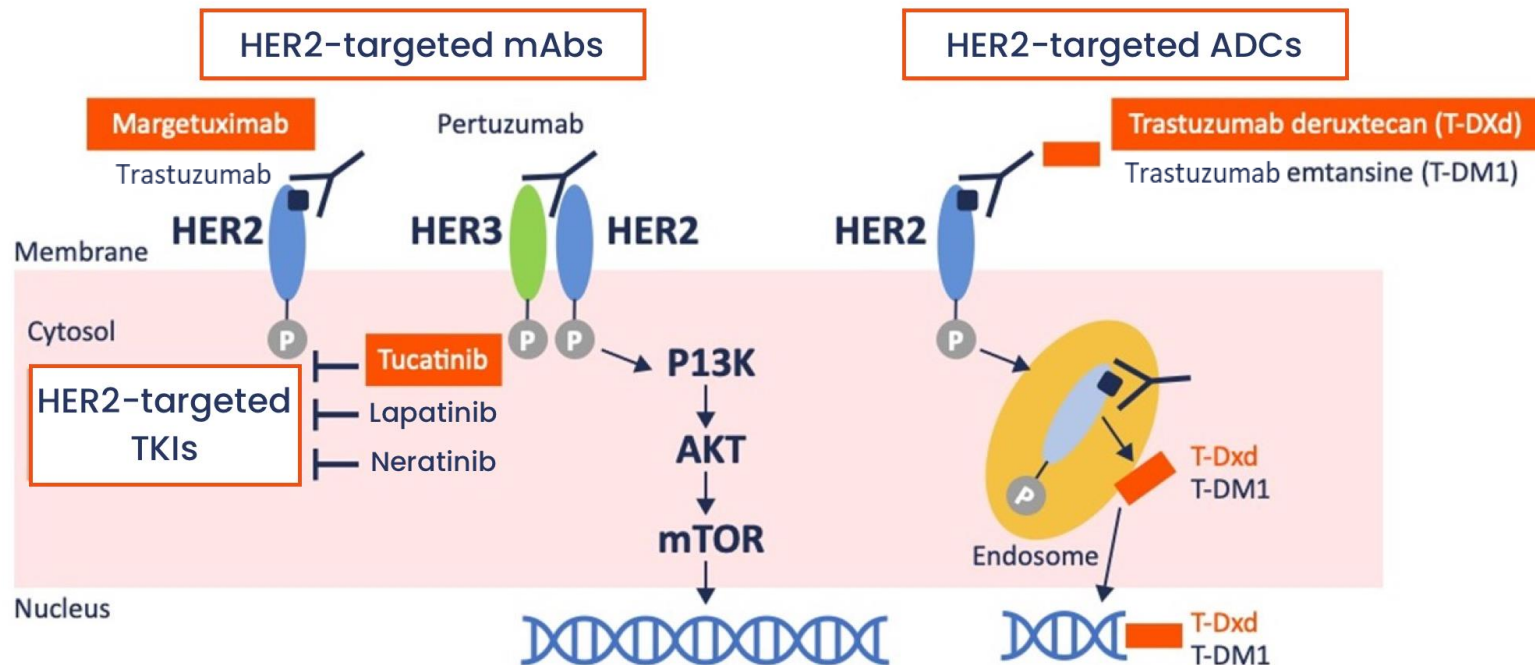
Progress with HER2-targeted therapies in advanced breast cancer

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Targeted therapies for HER2+ ABC



Adapted from Gajria D and Chandarlapaty S. *Expert Rev Anticancer Ther.* 2011.

ABC, advanced breast cancer; ADC, antibody-drug conjugate; AKT, protein kinase B; HER, human epidermal growth factor receptor; mAb, monoclonal antibody; mTOR, mechanistic target of rapamycin; P13K, phosphoinositide 3-kinase; T-DM1, trastuzumab emtansine; TKI, tyrosine kinase inhibitor; T-DXd, trastuzumab deruxtecan.

1. Gajria D, Chandarlapaty S. *Expert Rev Anticancer Ther.* 2011;11:263–75; 2. Martínez-Sáez O, Prat A. *JCO Oncol Pract.* 2021;DOI:10.1200/OP.21.00172.

Recent efficacy data for emerging agents



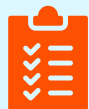
DESTINY-Breast03¹ Trastuzumab deruxtecan



HER2CLIMB^{2,3} Tucatinib



SOPHIA⁴ Margetuximab



Phase III, randomized, open-label
Trastuzumab deruxtecan vs T-DM1

Phase II, randomized
Tucatinib vs placebo, both +
trastuzumab and capecitabine

Phase III, randomized, open-label
Margetuximab + chemotherapy vs
trastuzumab + chemotherapy



Patients with HER2+ MBC,
previously treated with
trastuzumab and a taxane (N=524)

Patients with HER2+ ABC, including
those with brain metastases
(N=612); prior capecitabine and
HER2 TKIs were not allowed

Patients with HER2+ ABC (N=536)
Disease progression on ≥ 2 prior
HER2 therapies; 1–3 prior lines of
treatment for MBC



mPFS was not reached for
trastuzumab deruxtecan;
mPFS=6.8 months with TDM-1
(HR=0.28)

mOS at ~ 30 months follow-up was
5.5 months longer with tucatinib vs
placebo (HR=0.73); in those with
brain metastases, HR=0.60

Significant improvement in PFS
with margetuximab +
chemotherapy
(5.8 vs 4.9 months; HR=0.76)

ABC, advanced breast cancer; HER, human epidermal growth factor receptor; HR, hazard ratio; MBC, metastatic breast cancer; mOS, median overall survival; mPFS, median progression-free survival; T-DM1, trastuzumab emtansine; TKI, tyrosine kinase inhibitor.

1. Cortés J, et al. *Ann Oncol*. 2021;32(Suppl. 5):S1283–346; 2. Curigliano G, et al. *J Clin Oncol*. 2021;39(Suppl. 15):1403; 3. ClinicalTrials.gov. NCT02614794.

Available at: clinicaltrials.gov/ct2/show/NCT02614794 (accessed 7 October 2021); 4. Rugo H, et al. *JAMA Oncol*. 2021;7:573–84.

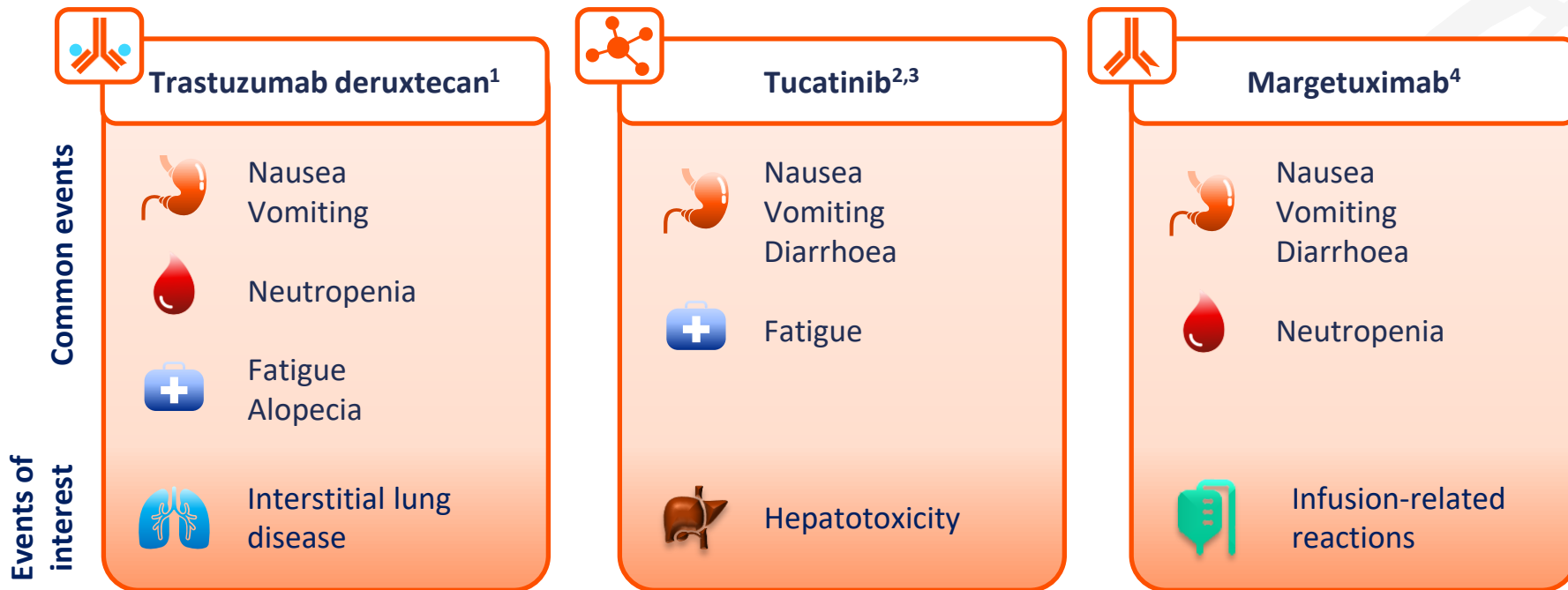
Maintaining HER2-targeted therapies: How to manage adverse events

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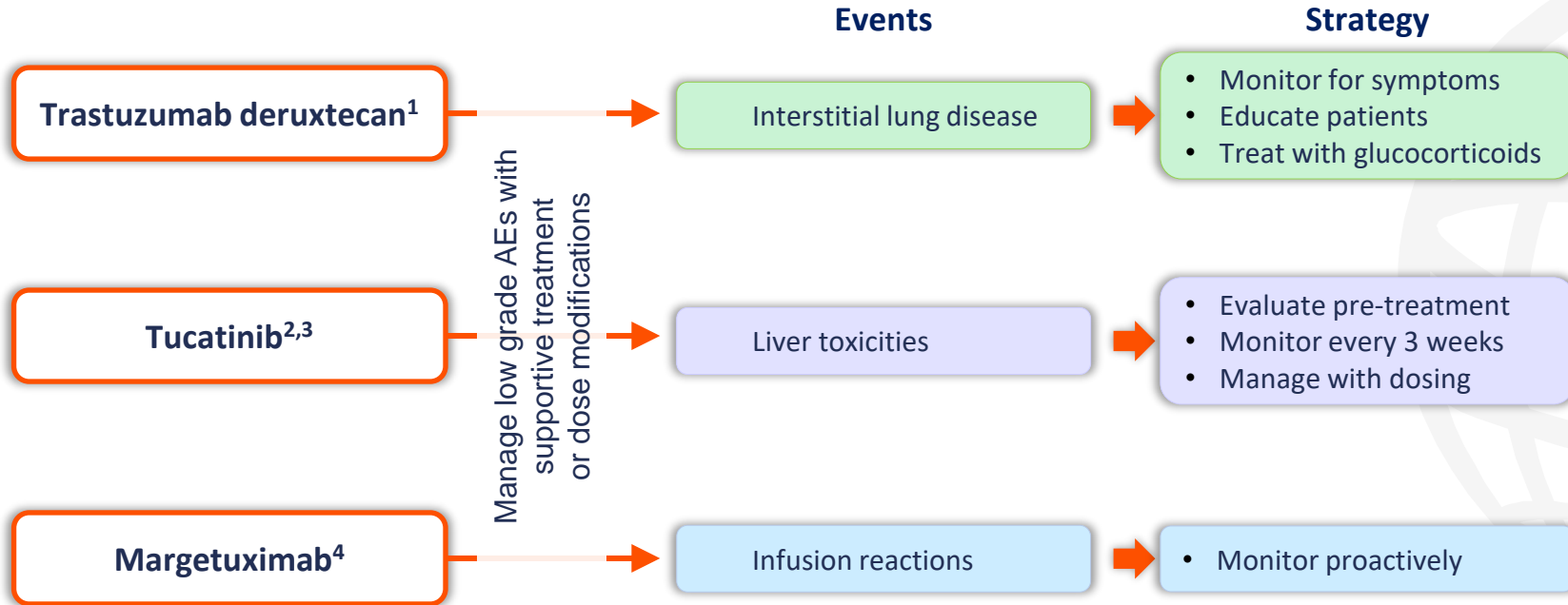
Adverse events with emerging HER2-targeted therapies



HER, human epidermal growth factor receptor.

1. Modi S, et al. *N Engl J Med.* 2020;382:610–21; 2. Murthy R, et al. *N Engl J Med.* 2020;382:597–609; 3. Curigliano G, et al. *J Clin Oncol.* 2021;39(Suppl. 15):1403; 4. Margetuximab. Risk assessment and risk mitigation review. 2020. Available at: www.accessdata.fda.gov/drugsatfda_docs/nda/2020/761150Orig1s000RiskR.pdf (accessed 24 September 2021).

Adverse event management and monitoring



AE, adverse event.

1. Modi S, et al. *N Engl J Med*. 2020;382:610–21; 2. Tucatinib. Highlights of prescribing information. 2020. Available at: www.accessdata.fda.gov/drugsatfda_docs/label/2020/213411s000lbl.pdf (accessed 27 September 2021); 3. Tucatinib. Summary of product characteristics. 2021. Available at: www.ema.europa.eu/en/documents/product-information/tukyasa-epar-product-information_en.pdf (accessed 27 September 2021); 4. Margetuximab. Highlights of prescribing information. 2020. Available at: www.accessdata.fda.gov/drugsatfda_docs/label/2020/761150s000lbl.pdf (accessed 27 September 2021).

Novel HER2-directed approaches: Implications for future practice

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Novel approaches to HER2-targeting

Challenges remain in the management of HER2+ advanced breast cancer

More specific targeted treatments

Treatment resistance

Several strategies are in development



Novel ADCs¹



Activated T cells²



CDK4/6i in HR+/HER2+³



Identification of HER2-low^{4,5}

ADC, antibody–drug conjugate; CDK4/6i, cyclin-dependent kinase 4 or 6 inhibitor; HER, human epidermal growth factor receptor; HR+, hormone receptor-positive.

1. Banerji U, et al. *Lancet Oncol.* 2019;20:1124–35; 2. NCT03272334. Available at: www.clinicaltrials.gov/ct2/show/NCT03272334 (accessed 12 October 2021); 3. Tolaney SM, et al. *Lancet Oncol.* 2020;21:763–75; 4. Marchiò C, et al. *Semin Cancer Biol.* 2021;72:123–35; 5. Dieci MV, et al. *Cancer Treat Rev.* 2020;88:102064.

Latest developments with novel approaches



Trastuzumab duocarmazine

TULIP trial:¹ Trastuzumab duocarmazine vs physician's choice

- Phase III, randomized in HER2+ ABC ≥ 2 prior MBC regimens (N=437)
- mPFS, 7.0 months with trastuzumab duocarmazine; 4.9 months with physician's choice (HR=0.64)
- The most common AEs were conjunctivitis (38.2%), keratitis (38.2%) and fatigue (33.3%), ILD/pneumonitis occurred in 7.6% patients (two grade 5 events)



CDK4/6i in HER2+

monaCHER trial:² Abemaciclib + trastuzumab and fulvestrant

- Phase II, open-label in HR+/HER2+ ABC ≥ 2 prior HER2 therapies (N=237)
- PFS improved (HR=0.67) with abemaciclib + trastuzumab and fulvestrant (8.3 months) vs standard of care chemotherapy + trastuzumab (5.7 months)
- Neutropenia was the most common grade 3 or 4 AE in both arms (~25%)



Ongoing clinical development in HER2-low

Ongoing clinical trials

DESTINY-Breast04 (NCT03734029; phase III)³

- Efficacy and safety of trastuzumab deruxtecan vs physician's choice in HER2-low MBC patients

DEBBRAH (NCT04420598; phase II)⁴

- Efficacy and safety of trastuzumab deruxtecan in HER2+ and HER2-low MBC patients with brain metastases and/or LMC

ABC, advanced breast cancer; AE, adverse event; CDK4/6i, cyclin-dependent kinase 4 and 6 inhibitor; HER, human epidermal growth factor receptor; HR+, hormone receptor-positive; HR, hazard ratio; ILD, interstitial lung disease; LMC, leptomeningeal carcinomatosis; MBC, metastatic brain cancer; m, median; PFS, progression-free survival.

1. Manich SM, et al. *Ann Oncol.* 2021;32(Suppl. 5):S1283–346; 2. Tolane SM, et al. *Lancet Oncol.* 2020;21:763–75; 3. Modi S, et al. *Cancer Res.* 2020;80(Suppl. 4):Abstract nr OT1-07-02;

4. Batista MV, et al. *Ann Oncol.* 2021;32(Suppl. 5):S457–515.