Evidence Accumulates Against Sequencing Topo1-ADCs in HER2-Low Metastatic Breast Cancers: Results from International, retrospective, real-world ADC-Low-Europe cohort.

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Introduction

- According to current recommendations and likely future approvals, **all patients with a HER2-negative metastatic breast cancer (MBC) may be candidate for sequential Antibody-drug conjugates** with a Topoisomerase-1 inhibitory payload (Topo1-ADC).
- However, this population is **poorly represented in pivotal trials** leading to approval of Topo1—ADC, since **prior exposition to Topo1-ADC was an exclusion criteria for most phase II/III trials**.
- Prior exposition to Topo1-ADC in **TROPION-PanTumor01** trial was associated with **reduced progression-free survival (PFS)** in Triple Negative (TNBC) subgroup[1].
- Results from our **previous national retrospective ADC-LOW cohort**[2] and other real-world series raise concerns about **possible common resistance mechanisms upon progression with a first ADC** (ADC1), exposing to reduced efficacy of a second Topo1-ADC (ADC2).

Methods

- **ADC-LOW-EUROPE** is an **European**, **retrospective** series including patients with HER2-low and TNBC or Hormone Receptor positive (HR+) MBC treated sequentially with **Sacituzumab Govitecan** (**SG**) and **Trastuzumab Deruxtecan** (**T-DXd**), or vice-versa.
- Primary objective: Evaluate the efficacy with the second ADC in the overall population.
- Primary endpoint: Progression-Free survival of ADC2 (PFS-ADC2) in the overall population.
- Secondary endpoints: **PFS-ADC2 according to pre-specified subgroups** (HR subgroups, ADC sequence, early administration of ADC2, use of intermediary cytotoxic between ADC1 and ADC2) and the **Progression-free interval (PFI) of the first cytotoxic used after ADC1**.

Population

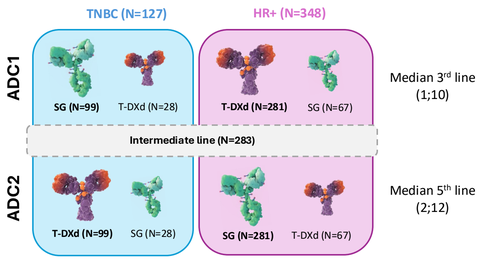
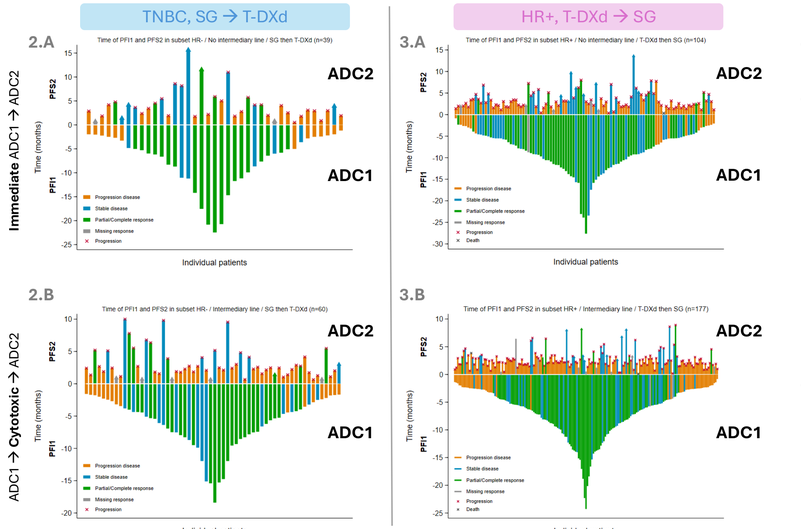


Figure 1: ADC sequence in patients with TNBC or HR+/HER2-Low MBC.

Results



Figures 2 and 3: Icebergplots representing intra-individual efficacy of ADC1 and ADC2 within TNBC (Fig 2) and HR+ (Fig 3.) sub-groups and consecutive use of ADCs (Fig 2A and 3A) or not (Fig 2B and 3B).

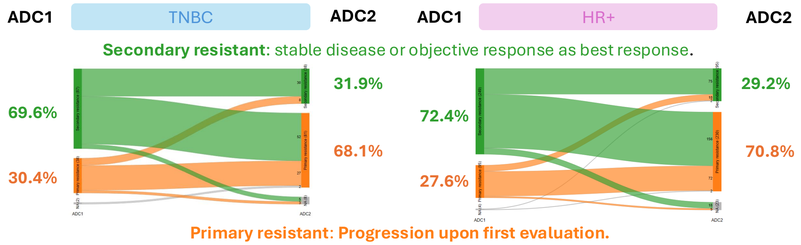


Figure 4: Sankey diagrams representing intra-individual dynamic of best response between ADC1 and ADC2.

Table1: Estimation of PFS-ADC2 according to pre-specified subgroups.

Median PFS-ADC2 (mPFS-ADC2, months) in overall population (HR+ and HR- MBC)			
Early ADC2 (2nd or 3rd Line)	2.9 [2.1; 3.3]	2.6 [2.5; 2.7]	Late ADC2 (4th Line or more)
Stopped ADC1 for Toxicity	2.7 [2.0; 5.2]	2.6 [2.5; 2.8]	Stopped ADC1 for Progression
Objective response ADC1	2.7 [2.4; 3.0]	2.5 [2.1; 2.7]	Primary resistant ADC1
Consecutive ADCs	3.0 [2.7; 3.3]	2.5 [2.3; 2.6]	No consecutive ADCs
HR+	2.6 [2.5; 2.8]	2.6 [2.4; 2.9]	HR-
T-DXd	2.9 [2.6; 3.8]	2.5 [2.2; 2.7]	SG

Neither the **early administration of ADC2** nor the **quality of the response to ADC1** can **predict** which patients will derive a **clinically relevant benefit from ADC2.**

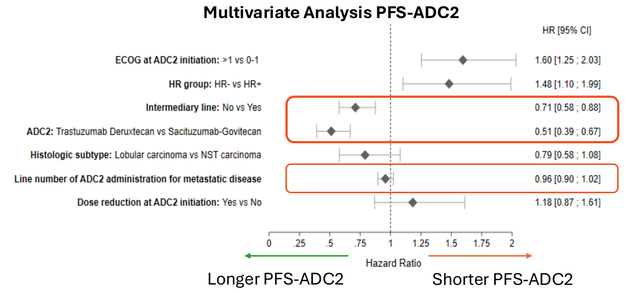


Figure 5: Forest Plot of multivariate analysis of PFS-ADC2.

Focus on Intermediary Treatments

Table2: Type of systemic treatments between ADC1 and ADC2.

Intermediary line	N (%)
Eribuline	101 (35.7)
Capecitabine	44 (15.5)
Anthracycline-based	38 (13.4)
Paclitaxel	34 (12)
Clinical trial	8 (2.8)
iPARP	4 (1.5)
Others	54 (19.1)

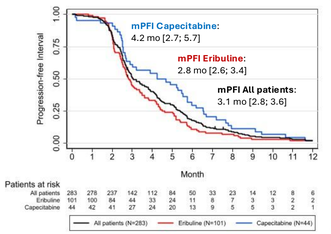


Figure 6: Kaplan-Meier estimation of Progression-Free interval in the overall population and Capecitabine or Eribuline subgroups.

Discussion and conclusions

- Herein, we report the **largest real-world series to date** investigating the efficacy of ADC sequences in HER2-Low MBC. Although we included patients with heavily pre-treated MBC, our results are **consistent with several real-world series** investigating efficacy of ADC-sequences[3] and report **poor outcome** when use of a second Topo1—ADC in patients with HER2-Low MBC.
- Moreover, there was **no differential effect of ADC2 whether it was administered early or late in the metastatic setting**. These results suggest that **prior exposure to a first Topo1-ADC is the main cause of poor outcomes rather than selection bias**.
- Indeed, a vast **majority of patients (70%) will progress upon first evaluation** when exposed to a second Topo1-ADC, irrespectively of the **duration and quality of the response with ADC1 and early administration of ADC2.** Therefore, biomarkers are urgently needed to identify the minority (30%) of patients likely to benefit from a second ADC.
- **Although numerical benefit was reported in some sub-groups,** the **absolute PFS-ADC2 benefit** seems **clinically marginal**.
- **T-DXd, when used as an ADC2,** seems to be associated with a **longer PFS-ADC2** compared to SG. Whether this result is due to the **therapeutic sequence** or the **intrinsic activity of T-DXd** remains **unknown.**
- Finally, compared with an ADC2, the **use of non-targeted cytotoxics after an ADC1** seems to offer a **similar benefit** and should therefore be considered as an option, given their **distinct toxicity profiles**.

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