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Assessing Patient Risk, Benefit, and Outcomes in drug development: Over a Decade of Ado-Trastuzumab Clinical Trials.

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INTRODUCTION

Drug development and approval for use through the Food and Drug Administration (FDA) is both costly and time consuming. The process can take up to 15 years, costing an average of 2.6 billion dollars. Cost estimates can differ depending on therapeutic drug class with cancer drugs being the most expensive to develop. Reasoning for disapproval is most often due to lack of clinical efficacy and unmanageable drug toxicity.

Characterizing a drug's risk/benefit profile may help optimize future drug development research in reducing cost, improving outcomes, and maintaining patient safety. To our knowledge, no study has examined the risk/benefit profile of ado-trastuzumab emtansine (T-DM1) - an FDA approved drug to treat human epidermal growth factor-2 (HER-2) positive breast cancer in patients that have previously been treated with a taxane and trastuzumab. Our primary objective was to examine the risk/benefit profiles of all published clinical trials assessing the efficacy of T-DM1. Secondarily, we aim to examine if there is an excessive risk to patients based on the drug's risk/benefit portfolio.

METHODS

On May 26th, 2023, investigators conducted a literature search for clinical trials using T-DM1 as monotherapy or combination with other therapies for cancer treatment. Inclusion criteria for study extraction included clinical trials published in English, containing adult subjects, involving solid tumors. Screening and data extraction was performed in masked, duplicate fashion.

Search returns were uploaded into Rayyan for literature screening. Two investigators (LT and MC) screened titles and abstracts for potential inclusions in a masked duplicate fashion. Author GH was available to resolve any discrepancies. Reasons for exclusion were documented in the screening process and shown in the flowchart in Figure 1. Data extraction was performed in the same fashion.

In each eligible study, we gathered trial characteristics, adverse event data, progression-free survival (PFS), overall survival (OS), and objective response rate (ORR). Trial outcome was considered positive when meeting primary endpoint and safety, indeterminate (safe but no prespecified primary endpoint), or negative, when not meeting either criteria.

RESULTS

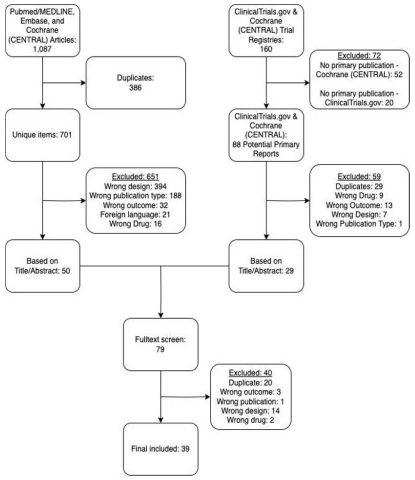

Figure 1: Flow diagram for study inclusion. Thirty-nine studies were included for final analysis.

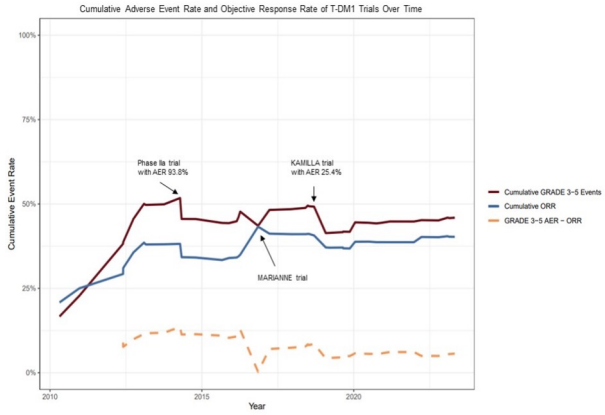

Figure 2: Risk versus Benefit Profile for T-DM1 Clinical Trials. Average adverse event rates per trial-year vs. average ORR per trial-year are plotted over time. Δ[AER-ORR] represents the absolute difference between cumulative adverse event rate (AER) and cumulative ORR. Time points included all trials with results published in a given year.

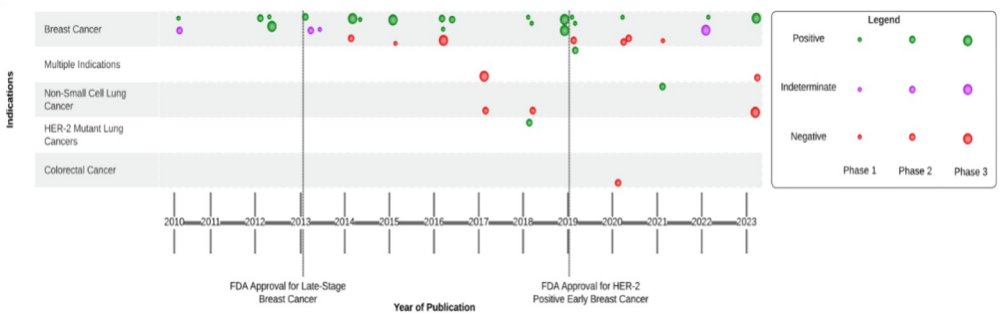

Figure 3: Accumulating Evidence and Research Organization (AERO) diagram T-DM1 trials are categorized by indication and visualized by the date of publication. Positive results are represented by green points, negative results by red points, and indeterminate results by purple points. Phase 1 trials are indicated by small circles, phase 2 trials by medium circles, and phase 3 trials by large circles. FDA approval from the KATHERINE trial in 2019 was not included in our sample.

CONCLUSION

In this study, we assessed the drug development portfolio of T-DM1 clinical trials and its efficacy within its indications. The risk/benefit profile showed an increase in AER and ORR in early years, but then stabilized and leveled off. While T-DM1 on breast cancer has a trend of positive outcomes, all other indications fail to follow that trend. We recommend rigorous scientific and clinical rationale be applied before continuing clinical trial testing of T-DM1 outside its FDA approved indications.

REFERENCES

AFFILIATIONS

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