Real-time monitoring for drug-induced interstitial lung disease with Trastuzumab Deruxtecan and Rilvegostomig combination therapy prevents persistent, symptomatic disease: Safety insights from the I-SPY 2.2 platform trial

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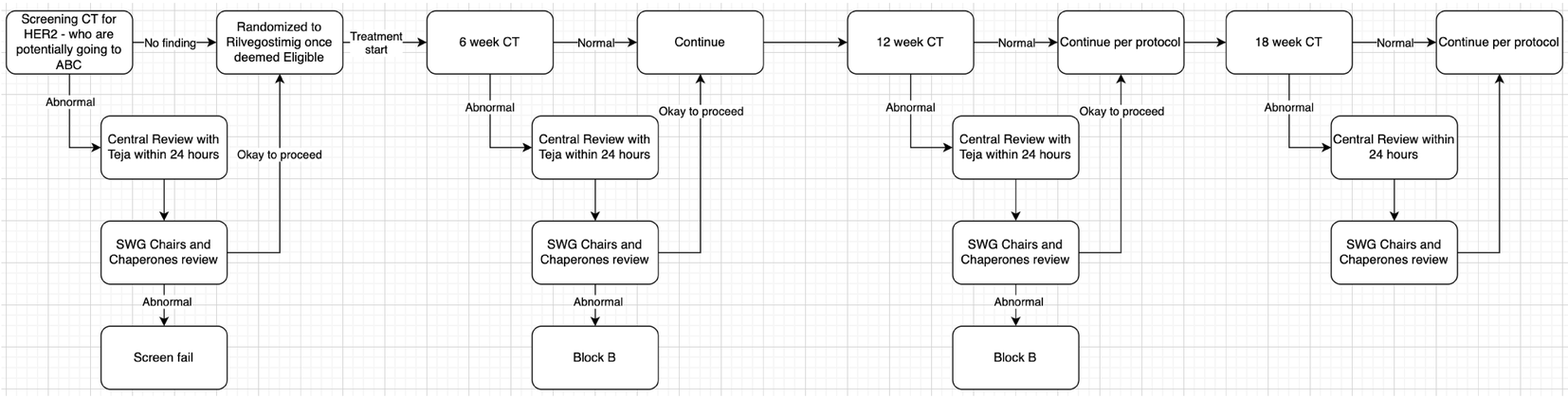
Introduction

- Combinations of antibody-drug conjugates and immunotherapy, such as trastuzumab deruxtecan (T-DXd) and rilvegostomig (rilve), respectively, offer promising efficacy but are associated with increased risk of drug-induced interstitial lung disease (ILD)/pneumonitis (5-10%).
- ILD incidence was approximately 5% in the recently published DESTINY-Breast11 study.
- These ILD events can take several days to resolve, particularly with higher grade events and can rarely be fatal.
- Early detection and management are critical for optimizing patient safety, yet there are no standard protocols for real-time evaluation.
- We hypothesized that vigilant monitoring would enable early detection, prevent symptoms, and minimize the chance of treatment delays while testing novel therapeutic combinations that have a potential risk of ILD for patients with breast cancer.

Methods

- We tested the combination of T-DXd and rilve administered every 3 weeks for 4 cycles in the I-SPY2.2 phase 2 platform trial (NCT01042379), which enrolls patients with clinical stage II/III breast cancer commencing neoadjuvant systemic therapy.
- Given the potential risk of overlapping pulmonary toxicity of these two agents, we added rigorous monitoring with pulmonary function tests (PFTs), six-minute walk test (6MWT), and high-resolution chest CT (HRCT) scanning pretreatment and every 6 weeks thereafter.
- A real-time safety workflow was implemented, with pre-specified criteria for halting treatment and escalation to the next block of treatment (Figure 1).
- All abnormal findings reported on chest CT by site radiologist were centrally reviewed in real time by the study pulmonologist (T.K.) and cases of suspected ILD were adjudicated promptly by a safety committee consisting of the pulmonologist and several medical oncologists, enabling early study drug interruption and therapeutic interventions.
- CT scans were considered abnormal if new ground-glass opacities, nodules, infiltrates, or fibrotic changes were present.
- Per protocol, a diagnosis of pneumonitis (any grade) prompted transition to Block B upon confirmation of resolution of CT findings and symptoms off T-DXd and rilve.
- **Study cohort**: Toxicity data were evaluated in the first 51 patients treated with T-DXd plus rilve and presented here.
- A preplanned hold was initiated until safety was ascertained by the data and safety monitoring board; study has since resumed recruitment.

Figure 1:Real-time study workflow



Real-time study workflow in a study of combination of trastuzumab deruxtecan and rilvegostomig administered every 3 weeks in the I-SPY2.2 phase 2 platform trial. CT scans were considered abnormal if new ground-glass opacities, nodules, infiltrates, or fibrotic changes were present. Per protocol, a diagnosis of pneumonitis (any grade) prompted transition to Block B upon confirmation of resolution of CT findings and symptoms. HRCT: High resolution computed tomography; PFTs: Pulmonary Function Test; 6MWT: Six-minute Walk test

Results

- Safety data were evaluated in the first 51 patients receiving T-DXd plus rilve.
- Eight ILD events were confirmed (15.68% incidence): 5 grade 1, 2 grade 2, and 1 grade 3.
- All cases were identified by HRCT scans; one patient had an early chest CT scan because of dyspnea.
- PFTs and 6MWT did not enhance early detection and were subsequently dropped from the monitoring protocol.
- No patient was symptomatic for more than 24 hours.
- Radiographic findings resolved within 14–55 days.
- Early treatment escalation to the subsequent block of therapy occurred in 4 patients who had received<4 cycles of T-DXd and rilve; all patients were subsequently able to receive appropriate therapy.

Table 1: Characterization of patients with ILD

Patient number	Grade	Time to ILD onset (days)	Symptoms	Steroid	Time to resolution (days)	# Cycles Rilve and T-DXd
1	Grade 1	33	None	No	23	2
2	Grade 1	35	None	No	21	2
3	Grade 3	77	Dyspnea	Yes	14	4
4	Grade 2	62	Dyspnea and chest pain	Yes	55	3
5	Grade 2	84	Dry cough	Yes	23	4
6	Grade 1	87	None	No	52	4
7	Grade 1	77	None	No	30	4
8	Grade 1	45	None	No	20	2

Conclusions

- Real-time, centralized monitoring and adjudication allowed for early detection and prompt management of ILD, which both mitigated severity and supported timely therapeutic management.
- Among the monitoring tools studied, HRCT scanning performed every 6 weeks proved most effective for early ILD identification; PFT and 6MWT did not enhance early detection.
- This approach offers a potential framework for future studies assessing pulmonary safety in regimens combining agents that have a known risk for inducing ILD.

COI

TK: ILD adjudication committee for AstraZeneca, Daichi Sankyo and Merck. CS: participation on advisory boards for AstraZeneca. KK: advisor to AstraZeneca. HR: received research support to UCSF from Astra Zeneca and Daichi Sankyo for the conduct of clinical trials. RN: consulted for AZ and DS. LS: funding from Merck & Co.; participation on an advisory board for Blue Cross Blue Shield; and personal fees from UpToDate; unpaid board member of QLHC. DY: reports research funding from NIH, consulting fees from Martell Diagnostics. NH: reports institutional research funding from NIH. PP: institutional research funding from Genentech/Roche, Fabre-Kramer, Advanced Cancer Therapeutics, Caris Centers of Excellence, Pfizer, Pieris Pharmaceuticals, Cascadian Therapeutics, BOLT, Byondis, Seagen, Orum Therapeutics, Carisma Therapeutics; consulting fees from Personalized Cancer Therapy, OncoPlex Diagnostics, Immunonet BioSciences, Pfizer, HERON, Puma Biotechnology, Sirtex, CARIS Lifesciences, Juniper, Bolt Biotherapeutics, Abbvie; honoraria from Dava Oncology, OncLive/MJH Life Sciences, Frontiers - Publisher, SABCS, ASCO; Speakers' Bureau: Genentech/Roche (past); patents United States Patent no. 8,486,413, United States Patent no. 8,501,417, United States Patent no. 9,023,362, United States Patent no. 9,745,377; uncompensated roles with Pfizer, Seagen and Jazz. Other authors: None.