Incidence and Management of Adverse Events Associated with HER2-Targeted Therapy

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Neratinib

NALA Study: Safety and Tolerability

Treatment-Emergent AEs Occurring in ≥10% of Patients in the Safe Population

Adverse event	N + C (n = 303)		L + C (n = 311)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Diarrhea	252 (83.2)	74 (24.4)	206 (66.2)	39 (12.5)
Nausea	161 (93.1)	13 (4.3)	132 (42.4)	9 (2.9)
PPE syndrome	139 (45.9)	29 (9.6)	179 (96.3)	39 (11.3)
Vomiting	138 (49.9)	12 (4.0)	97 (31.2)	6 (1.9)
Decreased appetite	107 (35.3)	8 (2.6)	67 (21.5)	7 (2.3)
Fatigue	104 (34.3)	9 (3.0)	97 (31.2)	10 (3.2)
Constipation	94 (31.0)	4 (1.3)	41 (13.2)	1 (0.3)
Stomatitis	62 (20.5)	6 (2.0)	83 (26.7)	8 (2.6)
Weight decreased	60 (19.8)	1 (0.3)	41 (13.2)	2 (0.6)
Rash	30 (9.9)	0	69 (22.2)	2 (0.6)
Anemia	45 (14.9)	6 (2.0)	3! (16.4)	11 (3.5)
Dizziness	43 (14.2)	1 (0.3)	31 (10.0)	2 (0.6)
Cough	37 (12.2)	0	34 (10.9)	0
Abdominal pain	36 (11.9)	3 (1.0)	45 (14.5)	6 (1.9)
Asthenia	36 (11.9)	8 (2.6)	36 (11.6)	9 (1.6)
Hypokalemia	39 (11.6)	14 (4.6)	44 (141)	20 (6.4)
Paronychia	35 (11.6)	2 (0.7)	49 (15.8)	3 (1.0)
Pyrexia	33 (10.9)	0	32 (10.3)	1 (0.3)
Headache	32 (10.6)	1 (0.3)	o1 (16.4)	3 (1.0)

Saura C, et al. *J Clin Oncol*. 2020;38(27):3138-3149.

**Neratinib + capecitabine is off-label in HER2+ mBC.*

Diarrhea Grades

Gastrointestinal disorders					
CTCEA term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Diarrhea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 to 6 stools per day over baseline; moderate increase in ostomy output compared to baseline: limiting instrumental activities of daily living (ADLs)	Increase of ≥7 stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care ADLs	Life-threatening consequences; urgent intervention indicated	Death

CONTROL: Incidence of Treatment-Emergent Diarrhea By Worst Grade

- **All preventive strategies reduced incidence of grade ≥3 diarrhea compared with historical control of 40%, without grade 4 diarrhea**
- **Dose escalation: Neratinib at a daily dose of 120 mg for week 1, followed by a daily dose of 160 mg for week 2, and a 240-mg daily dose for week 3 and thereafter for the duration of treatment**

Treatment-Emergent Diarrhea Incidence, n (%)	Loperamide (n = 137)	Budesonide + Loperamide (n = 64)	Colestipol + Loperamide (n = 136)	Colestipol + Loperamide PRN (n = 104)	Neratinib Dose Escalation (n = 60)
No diarrhea	28 (20)	9 (14)	23 (17)	5 (5)	1 (2)
Grade 1	33 (24)	16 (25)	38 (28)	34 (33)	25 (42)
Grade 2	34 (25)	21 (33)	47 (35)	32 (31)	25 (42)
Grade 3	42 (31)	18 (28)	28 (21)	33 (32)	9 (15)
Grade 4	0	0	0	0	0

Barcenas. Ann Oncol. 2020;31:1223. Chan. Lancet Oncol. 2016;17:367. Neratinib (full prescribing information) 2021.

AE Management with Neratinib

Consider & Discuss with Patients:	Prevention & Management of AEs

• May cause severe diarrhea including dehydration, hypotension, renal failure, and death
• In combination with capecitabine and without prophylaxis:
  • Median time to first onset of grade ≥3 diarrhea: 11 days
  • Median duration of grade ≥3 diarrhea: 3 days
• May cause severe hepatotoxicity
	• Antidiarrheal prophylaxis should be given to all patients and should be initiated with the first dose of neratinib
	  • If diarrhea occurs despite prophylaxis, patients should receive additional antidiarrheals, fluids, and electrolytes as clinically indicated
	  • Permanently discontinue neratinib in patients experiencing grade 4 diarrhea or grade ≥2 diarrhea that occurs after maximal dose reduction
	• Alternate: **use 2-week dose-escalation schedule to initiate treatment**
	• Monitor liver function tests for the first 3 months of treatment and then every 3 months while on treatment and as clinically indicated
	  • Permanently discontinue neratinib in patients with grade ≥4 liver abnormalities

Neratinib (full prescribing information) 2021.

Tucatinib

HER2CLIMB Study: Safety and Tolerability

Adverse events summary

TEAEs	Tucatinib combination (N = 404) n (%)	Placebo combination (N = 197) n (%)
Any TEAE	401 (99.3)	191 (97.0)
Grade ≥3 TEAE	245 (60.6)	101 (51.3)
Any serious TEAE	123 (30.4)	58 (29.4)
Death due to TEAE	6 (1.5)	5 (2.5)
Discontinued any study treatment due to TEAE	52 (12.9)	23 (11.7)
Discontinued tucatinib/ placebo due to TEAE	24 (5.9)	8 (4.1)
Discontinued capecitabine due to TEAE	47 (11.6)	22 (11.2)
Discontinued trastuzumab due to TEAE	17 (4.2)	7 (3.6)

Adverse events reported in ≥20% of patients in the tucatinib arm

Adverse event	Tucatinib combination (N = 404) n (%)		Placebo combination (N = 197) n (%)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Any adverse event	401 (99.3)	245 (60.6)	191 (97.0)	101 (51.3)
Diarrhea	331 (81.9)	**53 (13.1)**	106 (53.8)	**17 (8.6)**
Palmar-plantar erythrodysesthesia syndrome	264 (65.3)	**57 (14.1)**	105 (53.3)	**18 (9.1)**
Nausea	243 (60.1)	16 (4.0)	88 (44.7)	7 (3.6)
Fatigue	193 (47.8)	22 (5.4)	87 (44.2)	8 (4.1)
Vomiting	152 (37.6)	13 (3.2)	51 (25.9)	8 (4.1)
Decreased appetite	105 (26.0)	3 (0.7)	41 (20.8)	0
Stomatitis	105 (26.0)	10 (2.5)	28 (14.2)	1 (0.5)
Headache	96 (23.8)	3 (0.7)	40 (20.3)	3 (1.5)
Aspartate aminotransferase increased	89 (22.0)	19 (4.7)	22 (11.2)	1 (0.5)
Anemia	88 (21.8)	17 (4.2)	24 (12.2)	5 (2.5)
Alanine aminotransferase increased	85 (21.0)	23 (5.7)	13 (6.6)	1 (0.5)
Blood bilirubin increased	81 (20.0)	4 (1.0)	21 (10.7)	5 (2.5)

Curigliano G, et al. *Ann Oncol.* 2022;33:321-329.

AE Management of Tucatinib

Be Aware:	Management of AEs
• May cause severe diarrhea including dehydration, hypotension, acute kidney injury, and death • Can cause severe hepatotoxicity	• If diarrhea occurs, administer antidiarrheal treatment as clinically indicated – Perform diagnostic tests as clinically indicated to exclude other causes of diarrhea – Based on the severity of the diarrhea, interrupt dose, then dose reduce or permanently discontinue • Monitor ALT, AST, and bilirubin prior to starting tucatinib, every 3 weeks during treatment, and as clinically indicated • Management of AEs may require temporary interruption, dose reduction, or discontinuation

T-DXd

ILD Grading

Grade	
1	Asymptomatic, radiographic findings only
2	Symptomatic, not interfering with activities of daily living
3	Symptomatic, interfering with activities of daily living or oxygen indicated
4	Life-threatening or ventilator support required
5	Fatal

Skeoch S, et al. *J Clin Med*. 2018;7(10):356.

DESTINY-Breast01 Adverse Events of Special Interest: Interstitial Lung Disease

	Patients who received T-DXd 5.4 mg/kg (N = 184)					
Preferred term, n (%)	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**	**Any grade/ total**
Interstitial lung disease	20 (10.9%)		1 (0.5)	0	4 (2.2)	**25 (13.6)**

All events 15.8% and grade 5 in 5 (2.7%) at update (ESMO 2021)

Among the 25 total events

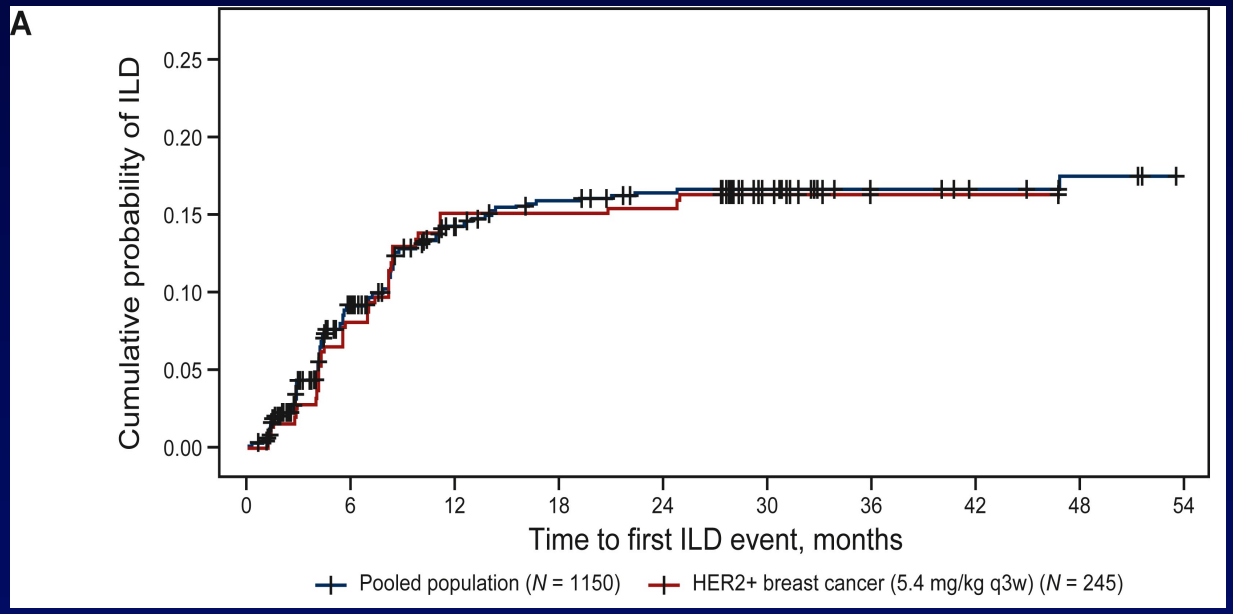
- Median time to investigator-reported onset was 193 days (range, 42-535 days)
- Of the 4 fatal cases, onset was from 63 to 148 days, 3 patients received steroids as part of treatment, and death occurred 9 to 60 days after diagnosis

Recommendations: Monitor for symptoms. Hold T-DXd, and start steroids as soon as ILD is suspected.

Krop IE, et al. SABCS 2019; Abstract GS1-03. Modi S, et al. *N Engl J Med.* 2020;382:610-621.

Pooled analysis of drug-related interstitial lung disease and/or pneumonitis in nine trastuzumab deruxtecan monotherapy studies

A



B

Potential risk factor	Patients, *n* (*N* = 1150)	Hazard ratio[a] (95% CI)
Age group		
<65 years	754	1.56 (1.02-2.38)
≥65 years	396	Ref
Country		
Japan	506	2.08 (1.45-2.98)
Non-Japan	644	Ref
Lung comorbidities[b]		
Yes	81	1.75 (1.03-2.98)
No	1069	Ref
Baseline renal function[c,d]		
Normal	470	Ref
Mild decrease	458	1.24 (0.83-1.84)
Moderate/severe decrease	196	2.73 (1.65-4.52)
Time since disease diagnosis[c]		
0 to ≤4 years	624	Ref
>4 years	403	1.82 (1.20-2.75)
Dose		
5.4 mg/kg q3w	315	Ref
6.4 mg/kg q3w	808	1.30 (0.85-1.99)
>6.4 mg/kg q3w	27	2.92 (1.32-6.42)
Baseline SpO_2[c]		
≥95%	1080	Ref
<95%	57	2.14 (1.11-4.13)

Time to first adjudicated drug-related ILD/pneumonitis event. Among 177 patients who had ILD, 154 (87.0%) had a first ILD/pneumonitis event within 12 months of starting treatment. Median time onset: 5.4 months (range, <0.1-46.8 months).

Powell CA et al. *ESMO Open* 2022 7DOI: (10.1016/j.esmoop.2022.100554)

DESTINY-Breast03: Drug Related AEs and ILD/Pneumonitis

Table 2. Most Common Drug-Related Adverse Events and Adjudicated Drug-Related Interstitial Lung Disease or Pneumonitis.

Event	Trastuzumab Deruxtecan (N=257)		Trastuzumab Emtansine (N=261)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number of patients (percent)			
Most common drug-related adverse events				
Blood and lymphatic system disorders				
Neutropenia*	110 (42.8)	49 (19.1)	29 (11.1)	8 (3.1)
Anemia†	78 (30.4)	15 (5.8)	37 (14.2)	11 (4.2)
Leukopenia‡	77 (30.0)	17 (6.6)	20 (7.7)	1 (0.4)
Thrombocytopenia§	64 (24.9)	18 (7.0)	135 (51.7)	65 (24.9)
Gastrointestinal disorders				
Nausea	187 (72.8)	17 (6.6)	72 (27.6)	1 (0.4)
Vomiting	113 (44.0)	4 (1.6)	15 (5.7)	1 (0.4)
Diarrhea	61 (23.7)	1 (0.4)	10 (3.8)	1 (0.4)
Constipation	58 (22.6)	0	25 (9.6)	0
General disorders				
Fatigue¶	115 (44.7)	13 (5.1)	77 (29.5)	2 (0.8)
Investigations				
Aspartate aminotransferase increased	60 (23.3)	2 (0.8)	97 (37.2)	13 (5.0)
Alanine aminotransferase increased	50 (19.5)	4 (1.6)	71 (27.2)	12 (4.6)
Metabolism and nutrition disorders				
Decreased appetite	67 (26.1)	3 (1.2)	33 (12.6)	0
Skin and subcutaneous tissue disorders				
Alopecia‖	93 (36.2)	1 (0.4)	6 (2.3)	0
Adjudicated drug-related interstitial lung disease or pneumonitis**	27 (10.5)	2 (0.8)	5 (1.9)	0

Nausea most common event!
>70%

Grade 3/4 neutropenia 19%

All grade ILD 10.5%
No grade 4 or 5 ILD events

Cortes J…Hurvitz S, et al. *N Engl J Med.* 2022;386.

DESTINY-Breast04 Adverse Events

Table 3. Most Common Drug-Related Adverse Events (in ≥20% of Patients) in the Safety Analysis Set.*

Event	Trastuzumab Deruxtecan (N=371)		Physician's Choice of Chemotherapy (N=172)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
	number of patients (percent)			
Blood and lymphatic system disorders				
Neutropenia†	123 (33.2)	51 (13.7)	88 (51.2)	70 (40.7)
Anemia‡	123 (33.2)	30 (8.1)	39 (22.7)	8 (4.7)
Thrombocytopenia§	88 (23.7)	19 (5.1)	16 (9.3)	1 (0.6)
Leukopenia¶	86 (23.2)	24 (6.5)	54 (31.4)	33 (19.2)
Gastrointestinal disorders				
Nausea	271 (73.0)	17 (4.6)	41 (23.8)	0
Vomiting	126 (34.0)	5 (1.3)	17 (9.9)	0
Diarrhea	83 (22.4)	4 (1.1)	31 (18.0)	3 (1.7)
Constipation	79 (21.3)	0	22 (12.8)	0
Investigations: increased aminotransferase levels‖	87 (23.5)	12 (3.2)	39 (22.7)	14 (8.1)
General disorders: fatigue**	177 (47.7)	28 (7.5)	73 (42.4)	8 (4.7)
Metabolism and nutrition disorders: decreased appetite	106 (28.6)	9 (2.4)	28 (16.3)	2 (1.2)
Skin and subcutaneous tissue disorders: alopecia	140 (37.7)	0	56 (32.6)	0

Nausea most common event! >70%

Grade 3/4 neutropenia ~14%

All grade ILD 12.1%
Grade 5 ILD events in 3 patients (0.8%)

Modi S, et al. *N Engl J Med.* 2022;387

Strategies to Manage ILD Associated With *HER2*-Directed ADCs

Monitor

Suspected ILD

Urge patients to immediately report cough, dyspnea, fever, and/or new or worsening pulmonary symptoms

- Monitor patients for signs/symptoms of ILD
- Promptly investigate evidence of ILD
- Evaluate patients with suspected ILD by radiographic imaging and assess as follows

Confirm

Assessments should include

- High-resolution CT
- Pulmonologist consult
- Blood culture and CBC; other blood tests as needed
- Consider bronchoscopy and bronchoalveolar lavage (BAL) if indicated and feasible
- Pulmonary function tests (PFTs) and pulse oximetry
- Arterial blood gases, if indicated
- As soon as ILD suspected, collect 1 blood sample for pharmacokinetics (PK) assessment, if feasible
- Rule out other causes of ILD (eg, progression, infection, other drugs, radiotherapy)
- All ILD events should be followed until resolution and after drug discontinuation

Manage

- **Grade 1 T-DXd:** Hold until resolved to Grade 0; consider corticosteroids (0.5 mg/kg/day prednisolone), then
  - *If resolved ≤28 days from onset:* Maintain dose
  - *If resolved >28 days after onset:* Reduce dose by 1 level
- **Grade 1 T-DM1:** Permanently discontinue
- **Grades 2-4:** Permanently discontinue treatment and promptly initiate systemic corticosteroid treatment (eg, ≥1 mg/kg/day prednisolone or equivalent for ≥14 days followed by taper for ≥4 weeks)

Ado-trastuzumab emtansine PI 2022 (https://www.gene.com/download/pdf/kadcyla_prescribing.pdf). Fam-trastuzumab deruxtecan-nxki PI 2022 (https://daiichisankyo.us/prescribing-information-portlet/getPIContent?productName=Enhertu&inline=true). URLs accessed 9.2.2022. Tarantino P, et al. *JAMA Oncol*. 2021;7(12):1873-1881.

T-DXd Related Nausea

	BEFORE T-DXd	Days 2-4	Days 5-21	Dose delays/ modifications
First cycle	5-HT3 receptor antagonist (RA) (**palonosetron**) + DEX	DEX ± 5-HT3 RA **OR** metoclopramide	**Olanzapine** or metoclopramide ± DEX	
Subsequent cycles, *if treatment in Cycle 1 not adequate*	NK1 receptor antagonist **(aprepitant)** ± 5-HT3 RA + DEX ± olanzapine	NK1 RA + 5-HT3 RA ± DEX **OR** DEX ± metoclopramide ± olanzapine	Same as above	Grade 3: delay dose until resolved to grade ≤1 If >7 days until resolution, reduce dose by 1 level

DEX = dexamethasone.

Rugo, Bianchini et al, 2022., slide courtesy of Julie LaBarbera, NP