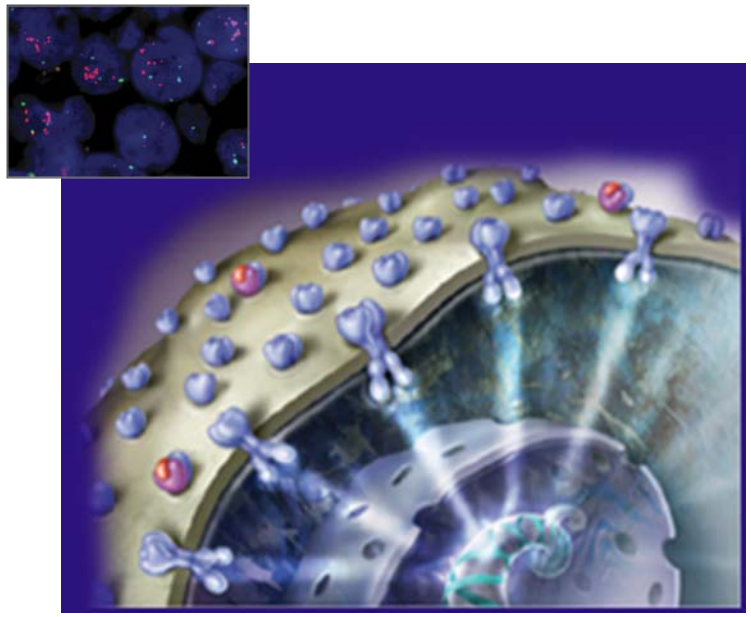
Incidence and Management of Adverse Events Associated with Her2-Targeted Therapy

Virginia F. Borges, MD. MMSc

Objectives

- Dose escalation and other available strategies to reduce the gastrointestinal (GI) toxicities associated with neratinib
- Incidence of interstitial lung disease observed with T-DXd in the DESTINY-Breast01 and DESTINY-Breast03 studies; recommendations for monitoring, prevention and management
- Spectrum, incidence, severity and management of other toxicities reported with T-DXd
- Incidence, prevention and management of GI toxicity and other clinically relevant AEs associated with tucatinib
- Comparative side-effect profiles of margetuximab/chemotherapy and trastuzumab/chemotherapy in the SOPHIA study

Today's Options in Her2 Targeted Therapy



Overexpressed HER2

1998-2020

- trastuzumab
- pertuzumab
- ado-emtansine-trastuzumab [T-DM1]
- trastuzumab-deruxtecan [T-DXd]
- margetuximab
- lapatinib
- neratinib
- tucatinib

Comparative select toxicities overview

drug	neuropathy	neutropenia	thrombocytopenia	diarrhea	LFTs	pulmonary
trastuzumab	-	-	-	+	-	+
pertuzumab	+	-	-	+	-	-
T-DM1	+	+	+	+	+	+
T-DXd	-	+	+	+	+	+
margetuximab	-	-	-	+	-	-
lapatinib	-	-	-	+		-
neratinib	-	-	-	+	+	-
tucatinib	-	-	-	+	+	-

Comparative select toxicities overview

drug	neuropathy	neutropenia	thrombocytopenia	diarrhea	LFTs	pulmonary
trastuzumab	-	-	-	+	-	+
pertuzumab	+	-	-	+	-	-
T-DM1	+	+	+	+		+
T-DXd	-	+	+	+	+	+
margetuximab	-	-	-	+	-	-
lapatinib	-	-	-	+		-
neratinib	-	-	-	+	+	-
tucatinib	-	-	-	+	+	-

Reducing GI toxicity of neratinib

Adjuvant therapy for HR+/Her2+ Node+ BC

ExteNET

Neratinib for Early Stage Her2+ BC

- HR+/≤ 1-year population (n=1334)
  - absolute improvements seen:
    iDFS 5.1%, dDFS 4.7% , OS 2.1%
  - 4 versus 12 CNS events for neratinib v placebo
  - neoadjuvant/non-pCR population (n=295)
    - iDFS 7.4%, dDFS 7.0%, OS 9.1%

Chan et al. Clin Breast Can 2021 doi.org/10.1016/j.dbc.2020.09.014

ExteNET

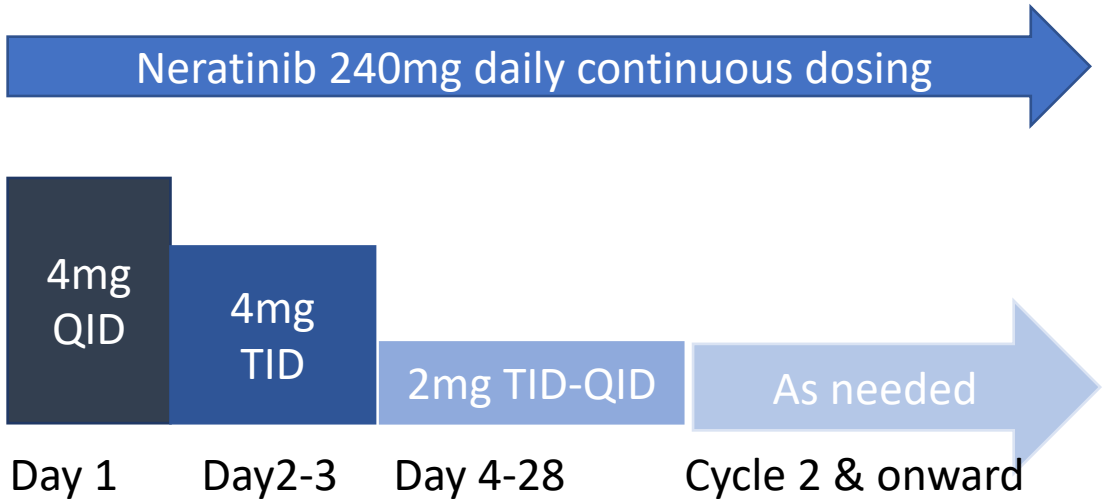
Neratinib for Early Stage Her2+ BC

- Neratinib is a pan-HER TKI
- Unmitigated neratinib at recommended 240mg dosing has 40% incidence grade 3 diarrhea
  - Median onset 8 days
  - Majority occur in the first 2 months

Chan et al. J Clin Oncol. 2014

Mitigating neratinib induced diarrhea

Intensive Loperamide Prophylaxis



Loperamide scheduled dosing schema

Results:

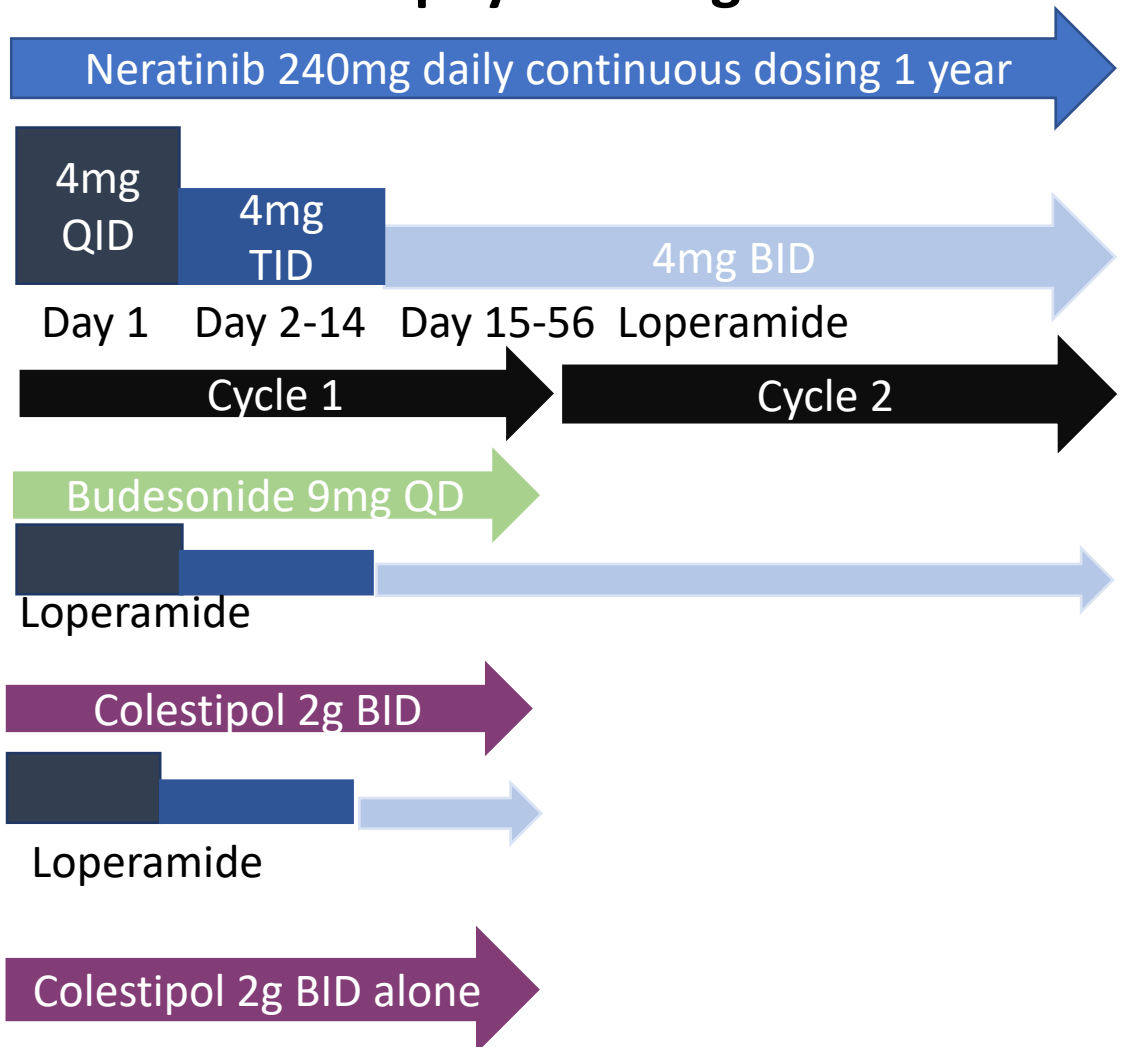
- Grade 3 diarrhea reduced to 0-17%
  - Compliance rates affected success
    - NSABP FB-8 NCT01423123 (0%)
    - 10-005 NCT01111825 (17%, 57% ncmp)

Jankowitz, et al. *Cancer Chemother Pharmacol.* 2013

CONTROL Trial

NCT02400476

Prevention Prophylaxis Regimens



Results:

Grade 3 diarrhea/Diarrhea related drug discontinuation

Loperamide: 31%/20%

Budesonide and L: 28%/8%

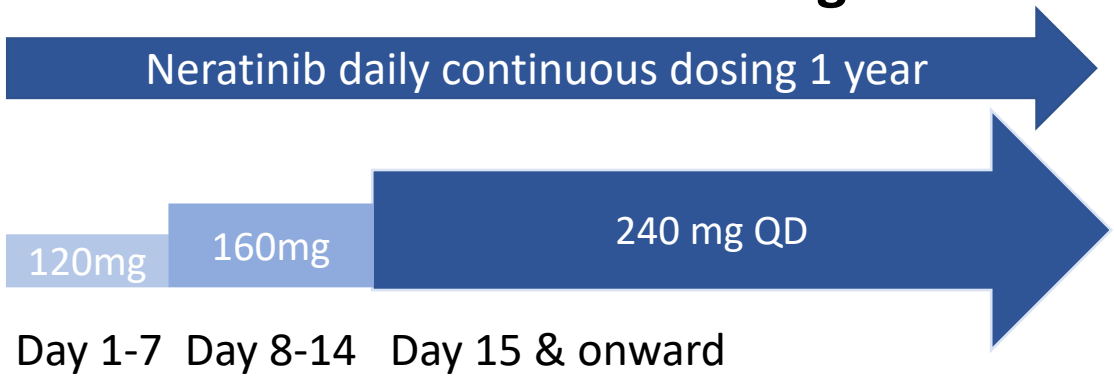
Colestipol and L: 21%/4%

Colestipol with L as prn: 32%/8%

CONTROL Trial

NCT02400476

Dose Escalation Prevention Regimens



Loperamide given 2-16mg daily as needed

Results:

Grade 3 diarrhea:

15%

Improvement in constipation (33%)

Diarrhea related drug discontinuation 3%

Barcenas, Hurvitz, et al. *Annal of Oncol*. 2020

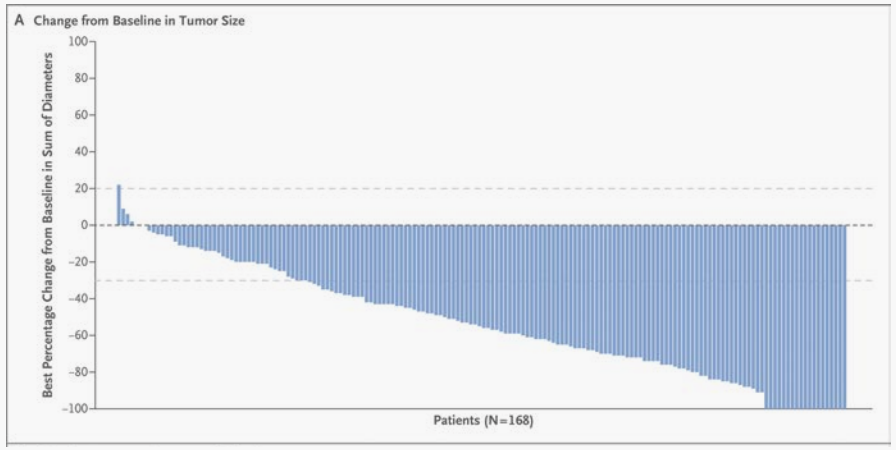
Interstitial Lung Disease and Other Toxicities of T-DXd

MBC therapy for HR any/Her2+ BC

DESTINY-01:
Trastuzumab Deruxtecan in Previously Treated HER2+ Positive Breast Cancer

Single-agent Phase II (n=184)
Median prior therapies for MBC was 6 (2-27)

ORR 60.9%, 6% CR
Median time to response 1.6months
Clinical benefit rate 76.1%
Median PFS 16.4 months



Modi, et al. *NEJM*. 2020 doi:10.1056/NEJMoa1914510

DESTINY-01:
Trastuzumab Deruxtecan in Previously Treated HER2+ Positive Breast Cancer

Adverse Events	Any Grade %	Grade 3 %	Grade 4 %
Neutropenia	34.8	19.6	1.1
Anemia	29.9	8.2	0.5
Thrombocytopenia	21.2	3.8	0.5
Alopecia	48.4	0.5	0
Fatigue/Asthenia	49.5	6.0	0
Nausea	77.7	7.6	0
Vomiting	45.7	4.3	0
Diarrhea	29.3	2.7	0

DESTINY-01:
Trastuzumab Deruxtecan in Previously Treated HER2+ Positive Breast Cancer

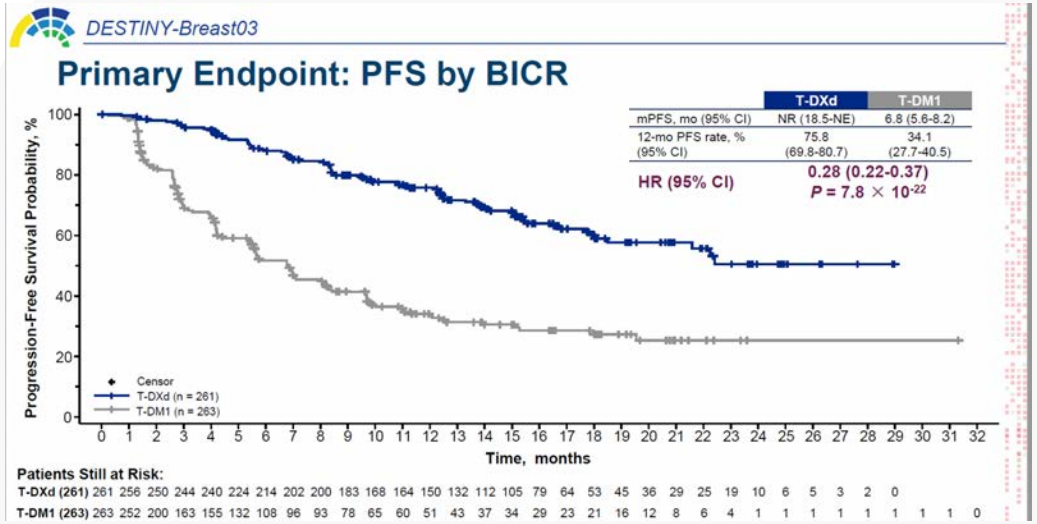
Adverse Events	Any Grade %	Grade 3 %	Grade 4 %
Interstitial Lung Disease	13.6	0.5	0 (4 pts- grade 5)
Prolonged QT	4.9	1.1	0
LVEF decline	1.6	0.5	0

DESTINY-03:
T-DXd v. T-DM1 in Previously Treated HER2+ Positive Breast Cancer

Randomized Phase III (n=524)

mPFS T-DXd not yet reached
mPFS T-DM1 6.8 months

12-month PFS 75.8% T-DXd
12-months PFS 34.1% T-DM1



Cortes, et al. ESMO Congress 2021

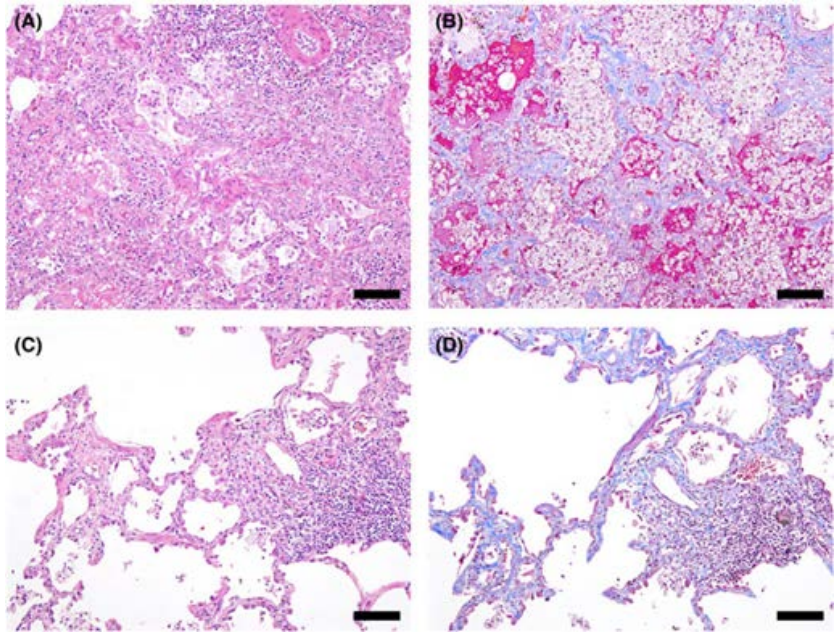
DESTINY-03:
Trastuzumab Deruxtecan in Previously Treated HER2+ Positive Breast Cancer

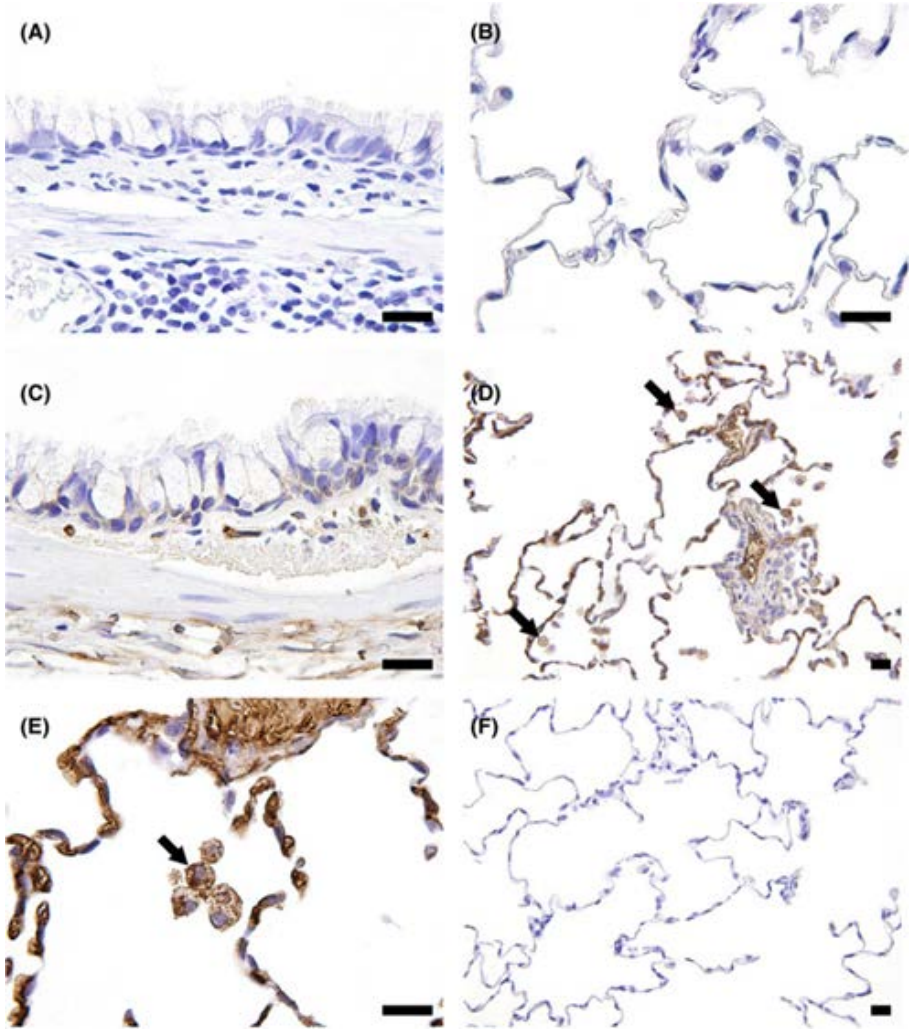
Adverse Events	Any Grade %	Grade 3 %
Neutropenia	42.8	19.1
Anemia	30.4	5.8
Thrombocytopenia	24.9	7.0
Alopecia	36.2	0.4
Fatigue/Asthenia	44.7	5.1
Nausea	72.8	6.6
Vomiting	44.0	1.6
Diarrhea	23.7	0.4

DESTINY-03:
Trastuzumab Deruxtecan in Previously Treated HER2+ Positive Breast Cancer

Adverse Events	Any Grade %	Grade 3 %	Grade 4 or 5 %
Interstitial Lung Disease	10.5	0.8	0
LVEF decline	2.7	0.4	0

T-DXd induces dose dependent and dose-frequency dependent interstitial pneumonitis





Kumagi, et al. *Cancer Sci.* 2020 doi: 10.1111/cas.14686

SOPHIA trial: Toxicities and management

MBC therapy for HR any/Her2+ BC

SOPHIA trial

margetuximab v. trastuzumab

in combination with chemotherapy for Her2+ MBC

536 pts, 1:1 randomization, ~100% prior tras/pertuzumab, 91% prior T-DM1

Chemo partners: capecitabine, eribulin, gemcitabine, vinorelbine

Efficacy: median PFS 5.8 months v 4.9 months

SOPHIA trial gastrointestinal toxicity

	Margetuximab +chemo		Trastuzumab +chemo	
Adverse Reaction	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Nausea	33	1.1	32	0.4
Diarrhea	25	2.3	25	2.3
Vomiting	21	0.8	14	1.5
Constipation	19	0.8	17	0.8
Abdominal pain	17	1.5	21	1.5
LFT increases:				
ALT	32	2	30	0.8
AST	23	2	22	0.8
Alk phos	21	0	23	0.8

Adverse Reaction (>10%) in SOPHIA

	Margetuximab +chemo		Trastuzumab +chemo	
Adverse Reaction	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Fatigue/Asthenia	57	7	47	4.5
Neuropathy	16	1.1	15	2.3
Alopecia	18	0	15	0
PPE	13	0	15	3
Arthralgia/Myalgia	14	0.4	12	0.8
Fever	19	0.4	14	0.4
Headache	19	0	16	0
Infusion Reactions	13	1.5	3	0

Adverse Reaction (>10%) in SOPHIA

	Margetuximab +chemo		Trastuzumab +chemo	
Adverse Reaction	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Fatigue/Asthenia	57	7	47	4.5
Neuropathy	16	1.1	15	2.3
Alopecia	18	0	15	0
PPE	13	0	15	3
Arthralgia/Myalgia	14	0.4	12	0.8
Fever	19	0.4	14	0.4
Headache	19	0	16	0
Infusion Reactions	13	1.5	3	0

margetuximab infusion rxns

Sx: fever, chills, arthralgias, cough, dizziness, fatigue, nausea, vomiting, HA, diaphoresis, tachycardia, hypotension, rash, pruritus, urticaria, dyspnea

margetuximab

- 13% (grade 3, 1.5%) SOPHIA
- Administer over 120 min first dose

trastuzumab

- fever and chills, nausea, vomiting, pain (in some cases at tumor sites), headache, dizziness, dyspnea, hypotension, rash, and asthenia
- In post-marketing reports, serious and fatal infusion reactions have been reported, which include bronchospasm, anaphylaxis, angioedema, hypoxia, and severe hypotension.

Tucatinib: GI toxicities and Other Adverse Reactions

Incidence, prevention, and management

Adverse Reactions in HER2CLIMB

Table 2. Most Common Adverse Events.*

Event	Tucatinib-Combination Group (N = 404)		Placebo-Combination Group (N = 197)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number of patients (percent)			
Any adverse event	401 (99.3)	223 (55.2)	191 (97.0)	96 (48.7)
Diarrhea	327 (80.9)	52 (12.9)	105 (53.3)	17 (8.6)
PPE syndrome	256 (63.4)	53 (13.1)	104 (52.8)	18 (9.1)
Nausea	236 (58.4)	15 (3.7)	86 (43.7)	6 (3.0)
Fatigue	182 (45.0)	19 (4.7)	85 (43.1)	8 (4.1)
Vomiting	145 (35.9)	12 (3.0)	50 (25.4)	7 (3.6)
Stomatitis	103 (25.5)	10 (2.5)	28 (14.2)	1 (0.5)
Decreased appetite	100 (24.8)	2 (0.5)	39 (19.8)	0
Headache	87 (21.5)	2 (0.5)	40 (20.3)	3 (1.5)
Aspartate aminotransferase increased	86 (21.3)	18 (4.5)	22 (11.2)	1 (0.5)
Alanine aminotransferase increased	81 (20.0)	22 (5.4)	13 (6.6)	1 (0.5)

* Listed are adverse events that were reported in at least 20% of the patients in the tucatinib-combination group. Safety analyses included all the patients who received at least one dose of any trial drug or placebo. Data are reported according to preferred terms in the *Medical Dictionary for Regulatory Activities*, version 22.0. PPE denotes palmar–plantar erythrodysesthesia.

Modi et al, NEJM, 2020

HER2CLIMB Updated Safety Analysis

Treatment-Emergent Adverse Events (TEAEs)	TUC+Tras+Cape (N=404) n (%)	Pbo+Tras+Cape (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)
TEAE leading to death	8 (2.0)	6 (3.0)
Pts who discontinued any study treatment due to TEAE	52 (12.9)	23 (11.7)
Pts who discontinued tucatinib/placebo due to TEAE	24 (5.9)	8 (4.1)
Pts who discontinued capecitabine due to TEAE	47 (11.6)	22 (11.2)
Pts who discontinued trastuzumab due to TEAE	17 (4.2)	7 (3.6)

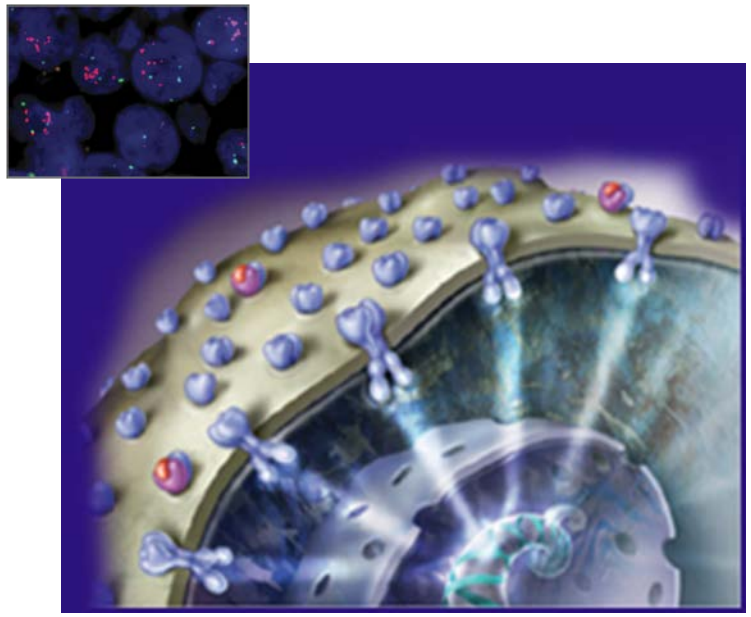
Curigliano et al, ASCO 2021, Abstract 1043

HER2CLIMB Updated Safety Analysis: Most Common AEs (≥20% in tucatinib arm)

	TUC+Tras+Cape (N=404) n (%)		Pbo+Tras+Cape (N=197) n (%)	
Preferred Term	Any grade	Grade ≥3	Any grade	Grade ≥3
Patients with any 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 erythrodysaesthesia 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 et al, ASCO 2021, Abstract 1043

Today's Options in HER2 Targeted Therapy



Overexpressed HER2

1998-2020

- trastuzumab
- pertuzumab
- ado-emtansine-trastuzumab [T-DM1]
- trastuzumab-deruxtecan [T-DXd]
- margetuximab
- lapatinib
- neratinib
- tucatinib

Thank you
for
being here!