Adverse Events (AEs) associated with HER2 targeted therapies

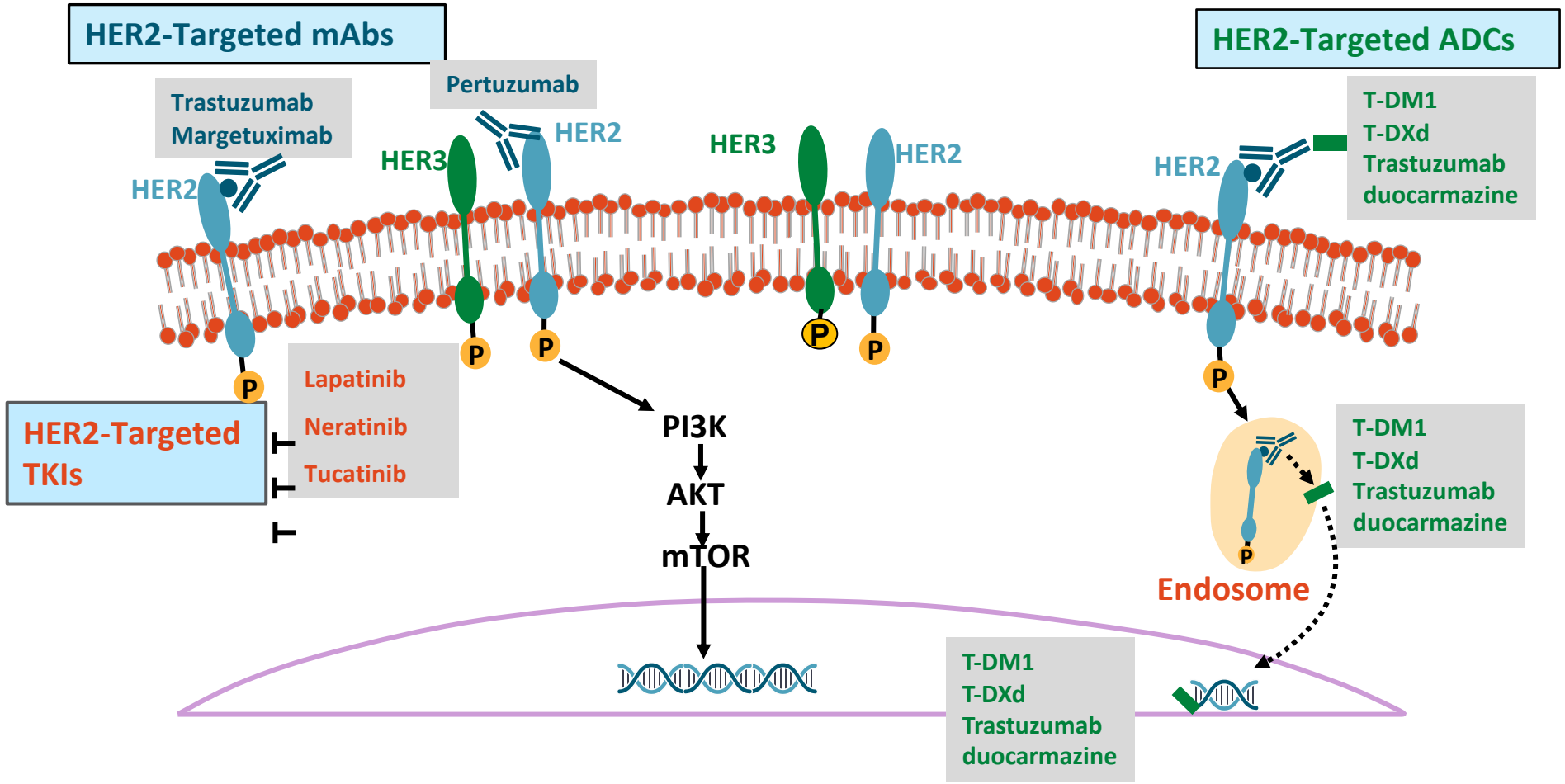
Erika Hamilton, MD

Director, Breast and Gynecological Research

Sarah Cannon Research Institute/Tennessee Oncology

SARAH CANNON

Targeted therapies for HER2+ breast cancer



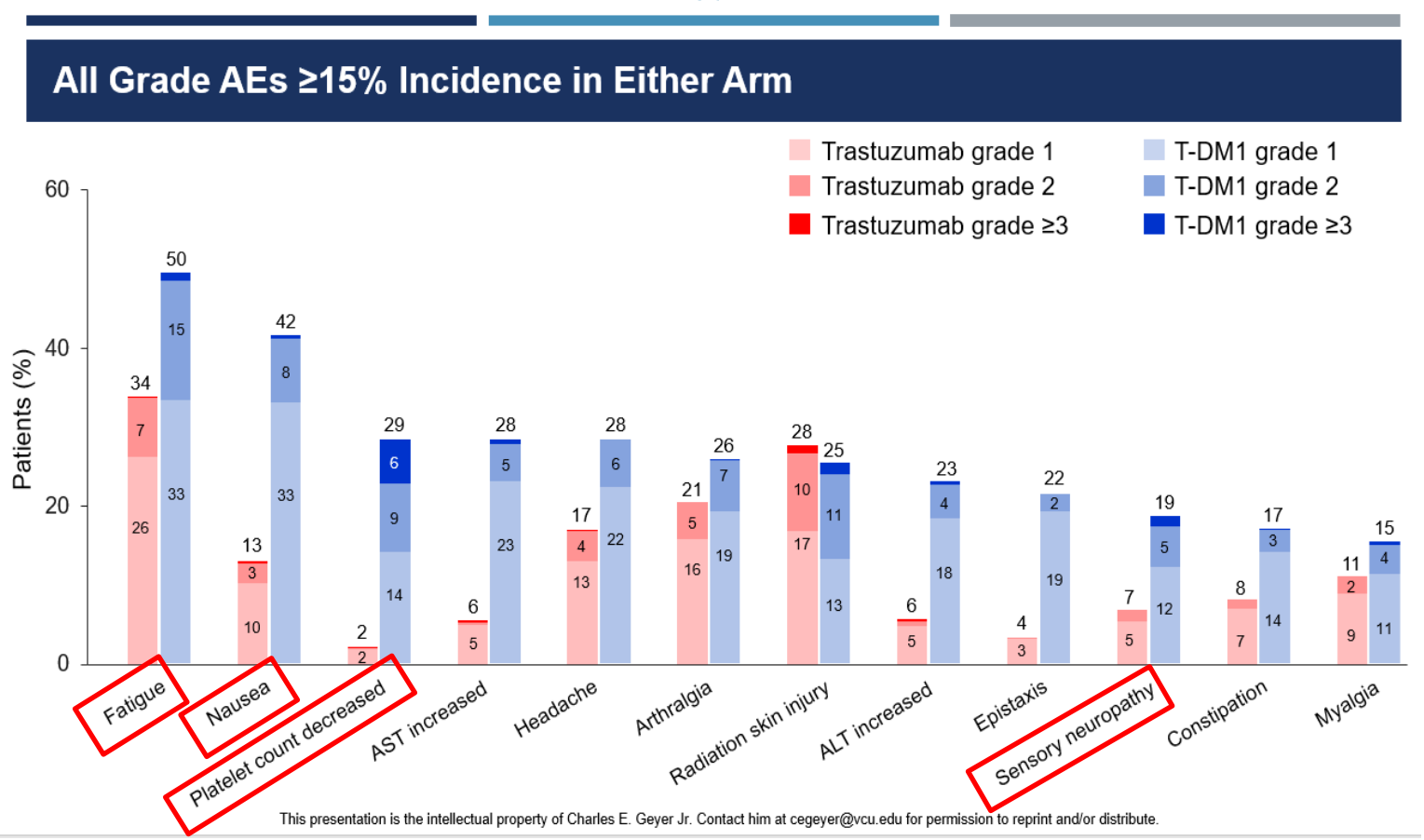
@ErikaHamilton9

SARAH CANNON

Courtesy of Erika Hamilton, MD

Gajria. Expert Rev Anticancer Ther. 2011; Pernas. Ther Adv Med Oncol. 2019

KATHERINE Trial (Trastuzumab vs T-DM1): Adverse event profile



Number of patients	Trastuzumab n=720	T-DM1 n=740
Grade ≥3 AEs	111 (15.4)	190 (25.7)
Serious AEs	58 (8.1)	94 (12.7)
AEs leading to tx discontinuation	15 (2.1)	133 (18.0)
AE with fatal outcome*	0	1 (0.1)

*Fatal AE was intracranial hemorrhage after a fall associated with T-DM1–induced thrombocytopenia

@ErikaHamilton9

Geyer C et al SABCS 2018

SARAH CANNON

Courtesy of Erika Hamilton, MD

KATHERINE: Dose reductions and Treatment discontinuations

Dose reductions

	Trastuzumab (n=720)	T-DM1 (n=740)
Cycles of trastuzumab/T-DM1 completed, n (%)		
7 cycles	664 (92.2)	637 (86.1)
14 cycles	583 (81.0)	528 (71.4)
Patients with a dose reduction, n (%)		
No dose reduction	N/A	634 (85.7)
One dose level reduction (3.0 mg/kg)	N/A	77 (10.4)
Two dose level reductions (2.4 mg/kg)	N/A	29 (3.9)

Treatment discontinuations

	Trastuzumab n=720	T-DM1 n=740
Patients discontinuing due to adverse events	15 (2.1%)	133 (18.0%)
Platelet count decreased	0	31 (4.2%) ✓
Blood bilirubin increased	0	19 (2.6%)
Aspartate aminotransferase (AST) increased	0	12 (1.6%)
Alanine aminotransferase (ALT) increased	0	11 (1.5%)
Peripheral sensory neuropathy	0	11 (1.5%) ✓
Ejection fraction decreased	10 (1.4%)	9 (1.2%)

Geyer C et al SABCS 2018

Courtesy of Erika Hamilton, MD

ATEMPT Trial (T-DM1 vs. TH): Adverse event profile

Treatment related AEs Grade ≥2 by Arm

	T-DM1 (n = 383)	TH (n = 114)
Fatigue	84 (22%)	26 (23%)
Neuropathy	44 (11%)	27 (24%)
Neutropenia	13 (3%)	15 (13%)
Thrombocytopenia	43 (11%)	1 (1%)
Nausea	39 (10%)	8 (7%)
Hypertension	35 (9%)	7 (6%)
ALT increase	33 (9%)	5 (4%)
Headache	24 (6%)	4 (4%)
Bilirubin increase	21 (5%)	1 (1%)
Infusion related reaction	19 (5%)	12 (11%)
Arthralgia	18 (5%)	2 (2%)
Anemia	18 (5%)	2 (2%)

Tolaney S et al SABCS 2019

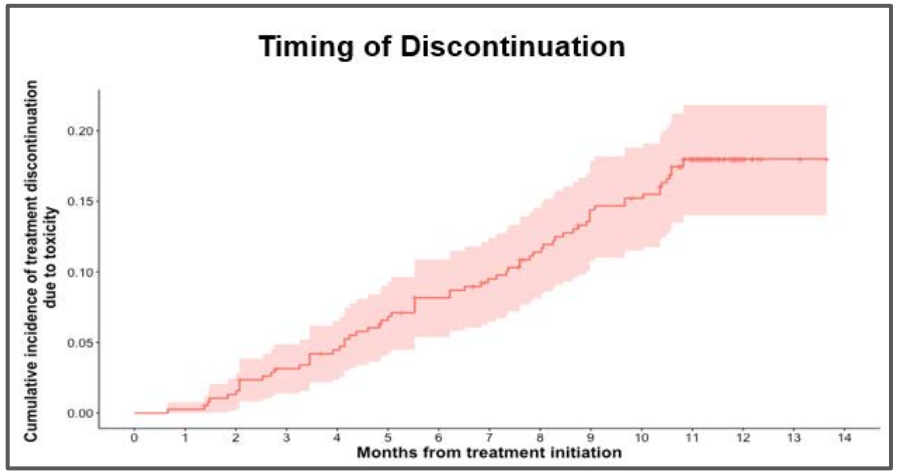
Courtesy of Erika Hamilton, MD

ATEMPT: Toxicities and treatment discontinuations

Clinically Relevant Toxicity	T-DM1 (n = 383) N (%)	TH (n = 114) N (%)
Grade ≥3 non-hematologic toxicity	37 (10%)	13 (11%)
Grade ≥ 2 neurotoxicity	42 (11%)	26 (23%)
Grade ≥4 hematologic toxicity	4 (1%)	0 (0%)
Febrile neutropenia	0 (0%)	2 (2%)
Any toxicity requiring dose delay	106 (28%)	30 (26%)
Any toxicity requiring early discontinuation	67 (17%)	7 (6%)
Total	176 (46%)	53 (46%)

p=0.91

T-DM1



Probability of discontinuing T-DM1 within 6 months: 8.2%
Probability of discontinuing T-DM1 within 6-12 months:10.7%

Discontinuations for toxicity that were protocol mandated: 9%

- Common toxicities leading to T-DM1 discontinuation include elevation of liver enzymes or bilirubin, neuropathy and thrombocytopenia

Tolaney S et al SABCS 2019

SARAH CANNON

Courtesy of Erika Hamilton, MD

Tyrosine kinase inhibitors

Diarrhea seen with neratinib across trials

Trial	EXTENET				NALA				TBCRC 022	
Patient population	HER2+ EBC after adjuvant trastuzumab therapy				HER2+ MBC after ≥2L of anti HER2 therapy				HER2+ MBC with brain mets	
Treatment	Neratinib (N=1408)		Placebo (N=1408)		Neratinib+Cape (N=303)		Lapatinib+Cape (n=311)		Neratinib+Cape (N=49)	
Grade	G1-2	G3	G1-2	G3	All grade	G3-4	All grade	G3-4	G2	G3
Treatment related diarrhea, % of pts	55	40	34	2	83	24	66	13	33	29

Δ38%

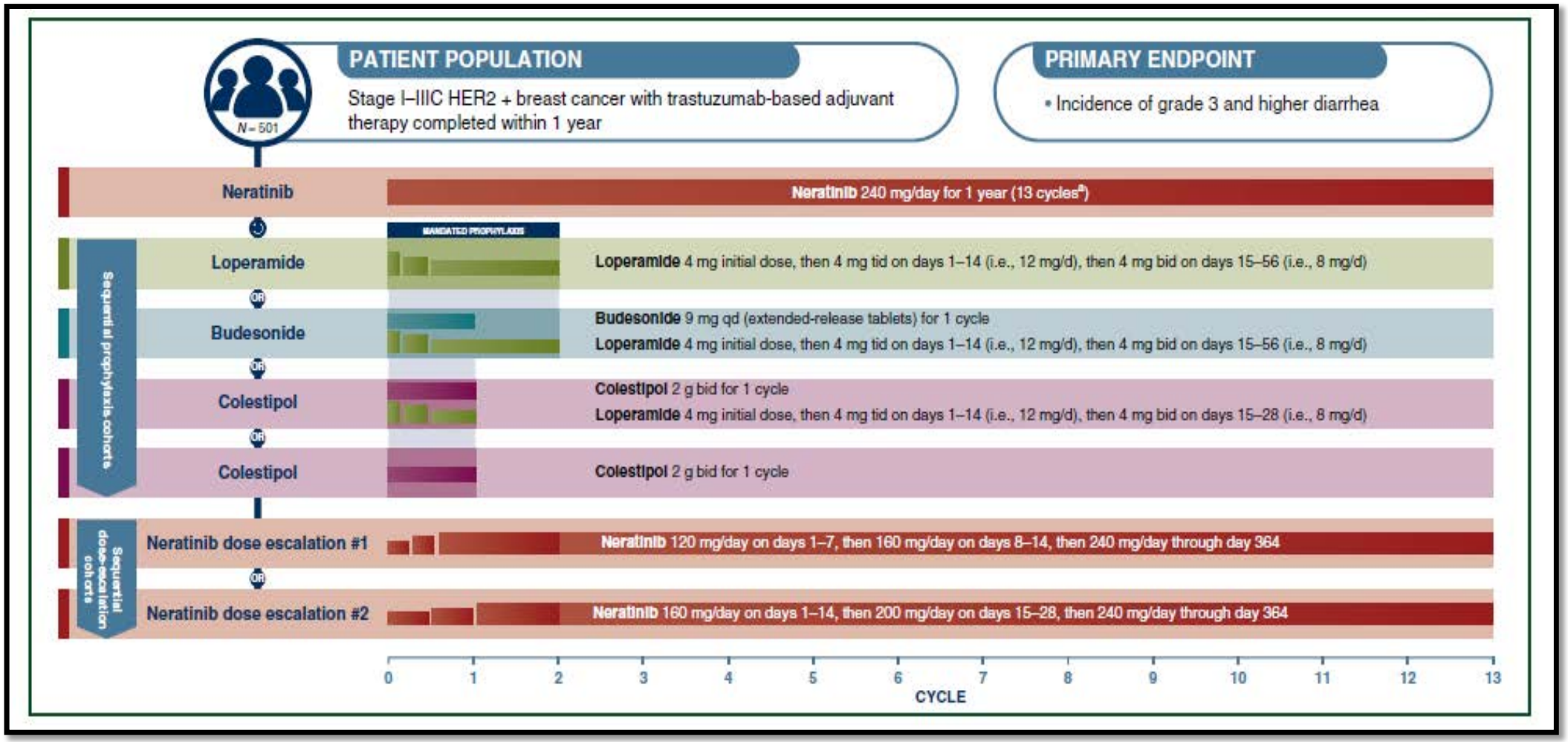
Δ11%

Martin Met al. NEJM 2017
Saura C et al ASCO 2019
Freedman RA et al JCO 2019

Courtesy of Erika Hamilton, MD

CONTROL Trial: Improving tolerability of Neratinib in EBC

Treatment schedules by CONTROL cohort



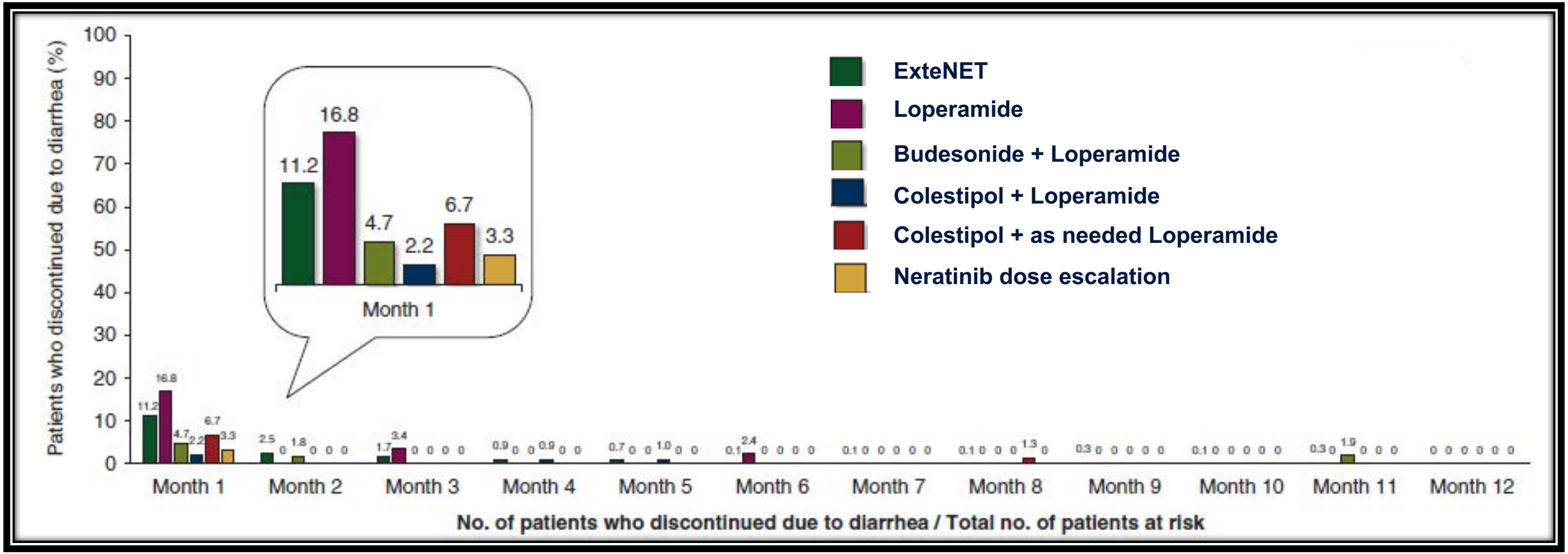
Barcenas CH et al 2020

@ErikaHamilton9

SARAH CANNON

Courtesy of Erika Hamilton, MD

CONTROL: Treatment discontinuations d/t diarrhea



FDA label for Neratinib includes data on the use of prophylactic loperamide plus budesonide

@ErikaHamilton9

Barcenas CH et al 2020

SARAH CANNON

Courtesy of Erika Hamilton, MD

Prophylaxis for diarrhea with Neratinib

Dose management for EBC

Dose management for MBC

Neratinib 240mg once a day daily

Capecitabine twice a day for 14days and 7days off

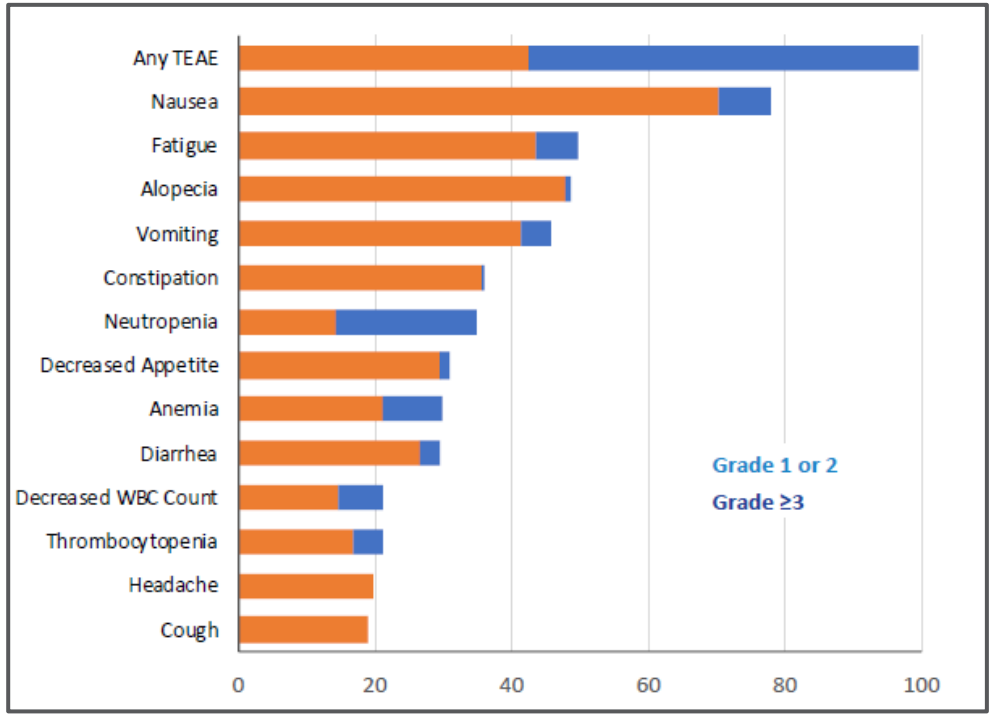
An antidiarrheal should be taken with Neratinib for the first 2 months (EBC & MBC)

Courtesy of Erika Hamilton, MD

Newly approved anti-HER2 therapies

DESTINY Breast-01 Trial: Adverse events with TDxd

Treatment-emergent Adverse Events in >15% of Patients[a]



a Patients who received T-DXd 5.4 mg/kg.

Interstitial Lung Disease

Median time from the first infusion of T-DXd to onset of ILD was 27.6 weeks (range, 6-76 weeks)

Preferred Term, n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade/ Total
Interstitial lung disease	5 (2.7)	15 (8.2)	1 (0.5)	0	4 (2.2)	**25 (13.6)**

- Serious TEAEs, 22.8% (drug related, 12.5%)
- TEAEs associated with discontinuation, 15.2% (drug related, 14.7%); **the majority were due to pneumonitis/ILD (8.7%)**

@ErikaHamilton9

Krop I et al SABCS 2019

SARAH CANNON

Courtesy of Erika Hamilton, MD

Symptom identification for diagnosis of ILD

Talk to your patients about their symptoms….

- ✓ Have you been coughing recently? Is it a dry cough?
- ✓ Have you had any shortness of breath, especially during or after physical activity?
- ✓ Have you experienced any new breathing or respiratory problems?
- ✓ If you already have respiratory problems, have they gotten worse?
- ✓ Have you had a fever?
- ✓ Have you been feeling tired?
- ✓ Have you lost weight?

Symptom identification is vital to identification of ILD/pneumonitis!

Courtesy of Erika Hamilton, MD

Management of ILD with Trastuzumab deruxtecan

Severity	Description (NCI-CTCAE[a] grading)
Grade 1	Asymptomatic, clinical or diagnostic observations only
Grade 2	Symptomatic, limiting instrumental activities of daily living
Grade 3	Severe symptoms, limiting self-care activities of daily living; oxygen indicated
Grade 4	Life-threatening respiratory compromise
Grade 5	Death

[a]Toxicity grades are in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03 (NCI-CTCAE v.4.03).

For asymptomatic ILD (Grade 1)

- Consider corticosteroid treatment (e.g., ≥0.5 mg/kg prednisolone or equivalent)
- Interrupt trastuzumab deruxtecan until resolved to Grade 0, then:
  - If resolved in 28 days or less from date of onset, maintain dose
  - If resolved in greater than 28 days from date of onset, reduce dose one level. See Dose Modifications for Adverse Events

For symptomatic ILD (Grade 2 or greater)

- Promptly initiate corticosteroid treatment (e.g., ≥1 mg/kg prednisolone or equivalent)
- Upon improvement, follow by gradual taper (e.g., 4 weeks)
- Permanently discontinue trastuzumab deruxtecan in patients who are diagnosed with any symptomatic ILD

Courtesy of Erika Hamilton, MD

Management of neutropenia with Trastuzumab deruxtecan

- ✓ Monitor CBC prior to starting treatment with trastuzumab deruxtecan and prior to each dose, and as clinically indicated
- ✓ Based on severity of neutropenia, manage through dose interruptions or discontinuations

Dose modifications for neutropenia[1]

Severity	Treatment Modification
Grade 3 (less than 1.0 to 0.5 x 10^9/L)	• Interrupt trastuzumab deruxtecan until resolved to Grade 2 or less, then maintain dose
Grade 4 (less than 0.5 x 10^9/L)	• Interrupt trastuzumab deruxtecan until resolved to Grade 2 or less • Reduce dose by one level (see Dose Modifications for Adverse Reactions on page 11)

Toxicity grades are in accordance with the National Cancer Institute – Common Terminology Criteria for Adverse Events Version 4.03 (NCI-CTCAE v.4.03).

Dose modifications for febrile neutropenia[1]

Severity	Treatment Modification
Absolute neutrophil count of less than 1.0 x 10^9/L and temperature greater than 38.3°C or a sustained temperature of ≥38°C for more than 1 hour	• Interrupt trastuzumab deruxtecan until resolved • Reduce dose by one level (see Dose Modifications for Adverse Reactions on page 11)

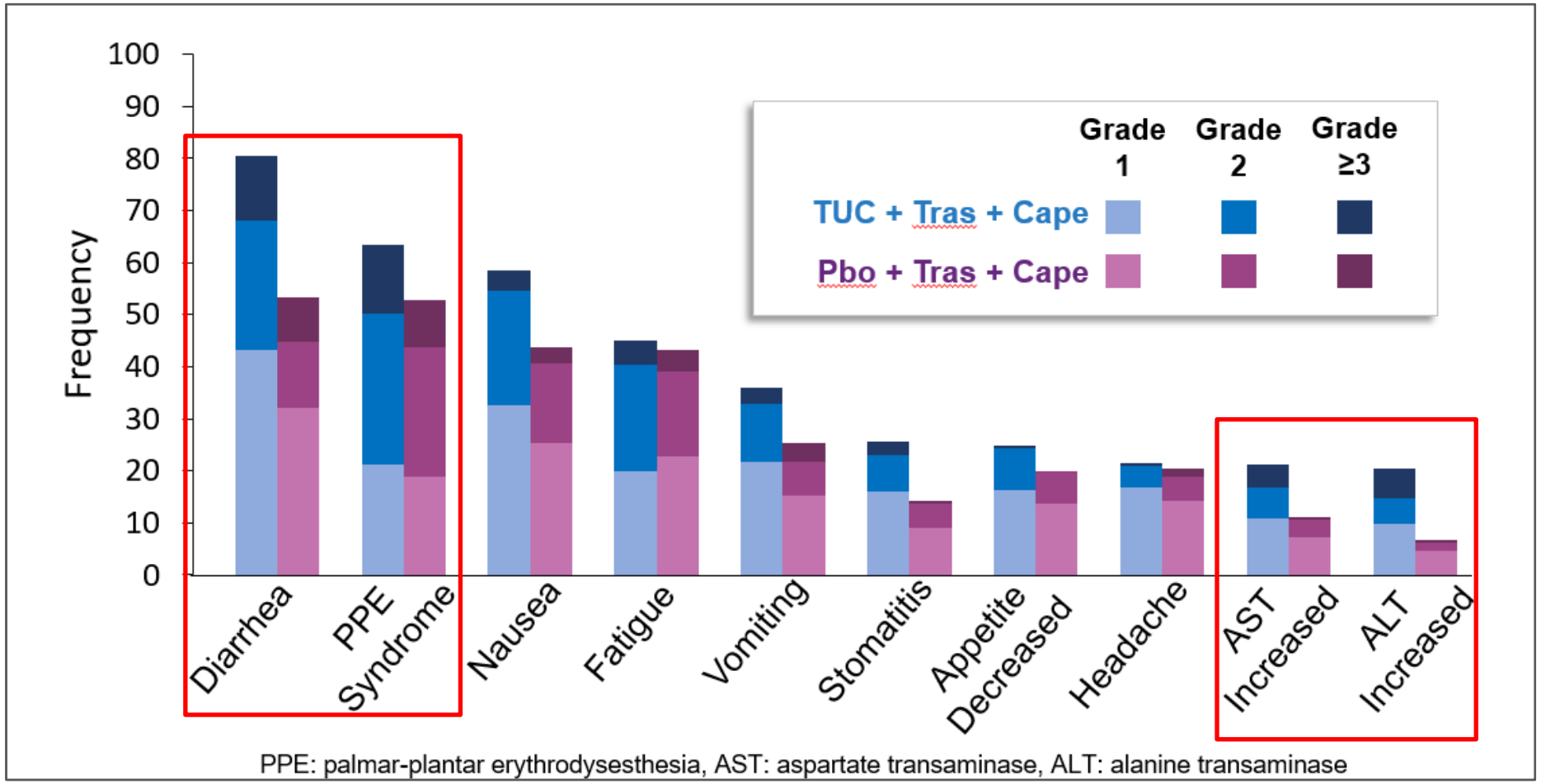
Toxicity grades are in accordance with the National Cancer Institute – Common Terminology Criteria for Adverse Events Version 4.03 (NCI-CTCAE v.4.03).

@ErikaHamilton9

SARAH CANNON

Courtesy of Erika Hamilton, MD

HER2CLIMB Trial (Tucatinib or Placebo + Capecitabine/Trastuzumab) - Most common AEs (≥20% in the Tucatinib arm)



PPE: palmar-plantar erythrodysesthesia, AST: aspartate transaminase, ALT: alanine transaminase

@ErikaHamilton9

Courtesy of Erika Hamilton, MD

Murthy R et al. SABCS 2019

SARAH CANNON

Murthy R et al. SABS 2019

Management of toxicities with Tucatinib

Diarrhea

- Antidiarrheal prophylaxis not required
- 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, consider dose reductions of capecitabine and possibly tucatinib

Hepatotoxicity

- Monitor ALT, AST and bilirubin prior to starting Tucatinib, q 3weeks during treatment and as clinically indicated
- Based on the severity of the hepatotoxicity, interrupt dose, then dose reduce or permanently discontinue tucatinib and/or capecitabine

PPE syndrome

- Side effect of capecitabine
- Support care per standard capecitabine (emollients, topical creams, altered schedule, dose reductions)

Courtesy of Erika Hamilton, MD

PPE: Palmar plantar erythrodysesthesia

Management of hepatotoxicity with Tucatinib

Adverse reaction and severity*	Tucatinib dose modification
G2 bilirubin (>1.5 to 3 x ULN)	Hold until recovery to ≤ G1, then resume Tucatinib at the same dose level
G3 ALT or AST (>5 to 20 x ULN)	Hold Tucatinib until recovery to ≤ G1, then resume Tucatinib at the next lower dose level
G3 bilirubin (>3 to 10 x ULN)	Hold Tucatinib until recovery to ≤ G1, then resume Tucatinib at the next lower dose level
G4 ALT or AST (> 20 x ULN)	Permanently discontinue Tucatinib
G4 bilirubin (> 10 x ULN)	Permanently discontinue Tucatinib
ALT or AST >3 x ULN AND Bilirubin >2 x ULN	Permanently discontinue Tucatinib

* Grades based on NCI CTCAE v4.0

Courtesy of Erika Hamilton, MD

Case 1: trastuzumab deruxtecan

- 69 yo F with HER2-amplified breast cancer
  - Oct 2008 L breast biopsy, ER-, PR -, HER2 3+ L4 biopsy + metastatic carcinoma c/w breast
  - Kyphoplasty and XRT L4
  - For roughly 10 years received 13 lines of HER2-directed therapy including T-DM1, pertuzumab, margetuximab, lapatinib, etc and most chemo backbones with trastuzumab
  - Metastatic disease to liver, bone and even epidural tumor in spine
  - Received trastuzumab deruxtecan
    - C3D1 -26.8% SD
    - C5D1 -55% PR
    - C7D1 -68% PR

Courtesy of Erika Hamilton, MD

Case 1 continued

- At C16D1 presents to clinic feeling unwell, 99% RA, on questioning has subtle SOB on stairs and some cough when lying flat at night
  - Scans ordered and show pneumonitis
  - Steroids started at 1mg/kg and symptoms improve, wean off steroids over 4 weeks
  - Several weeks later symptoms return and she goes back on steroids with hospitalization with prolonged taper over 2 months
  - Remained off therapy for 10 months with no progression

Courtesy of Erika Hamilton, MD

Case 2

- A 44 year old female with HER2-amplified ER/PR negative metastatic breast cancer
  - Feb 2015 presented w/ suspicious mammogram in UOQ R breast
  - Biopsy reveals invasive mammary carcinoma, ER 0, PR 0, HER2 FISH amplified ratio of 6.9, copy number 14.4
  - R axillary node biopsy +, tumor appears to be 4 cm in breast on MRI
  - Enrolls on clinical trial in 2015 and receives T-DM1 + pertuzumab
  - Post-treatment MRI shows resolution of enhancement in breast, decrease in size of R axillary adenopathy
  - Aug 2015 bilateral mastectomies – only 2mm residual invasive disease in breast, but 2/7 + nodes with largest node having 0.8mm disease
  - Completes adjuvant radiation and continues T-DM1/pertuzumab in June 2016 per trial

Courtesy of Erika Hamilton, MD

Case 2 continued

- Undergoes bilateral expander placement
- Has R breast erosion and ultimately has R breast TRAM flap reconstruction and L implant
- Does well for 1 year 3 months post completion of adjuvant therapy

- …
- September 26, 2017 presents with headaches and personality changes
- Brain MRI shows 3.7 cm parietal lesion with 6 mm midline shift

Courtesy of Erika Hamilton, MD

Case 2 continued

- Undergoes resection and post-op tumor bed irradiation
- November 2017 - Initiation of THP chemotherapy
  - April 2018 paclitaxel omitted due to worsened neuropathy
- September 6, 2018 surveillance brain imaging reveals 3 parenchymal brain lesions ~5mm
- April 2019 - Enrolls on HER2CLIMB study
  - October 16, 2019 dose reduction of capecitabine for G2 hand/foot
  - March 2020 unblinding of HER2CLIMB, receiving tucatinib
  - November 2020 – 2nd dose reduction of capecitabine
  - Remains on the combination of capecitabine, tucatinib, trastuzumab

Courtesy of Erika Hamilton, MD

Thank You

SARAH CANNON