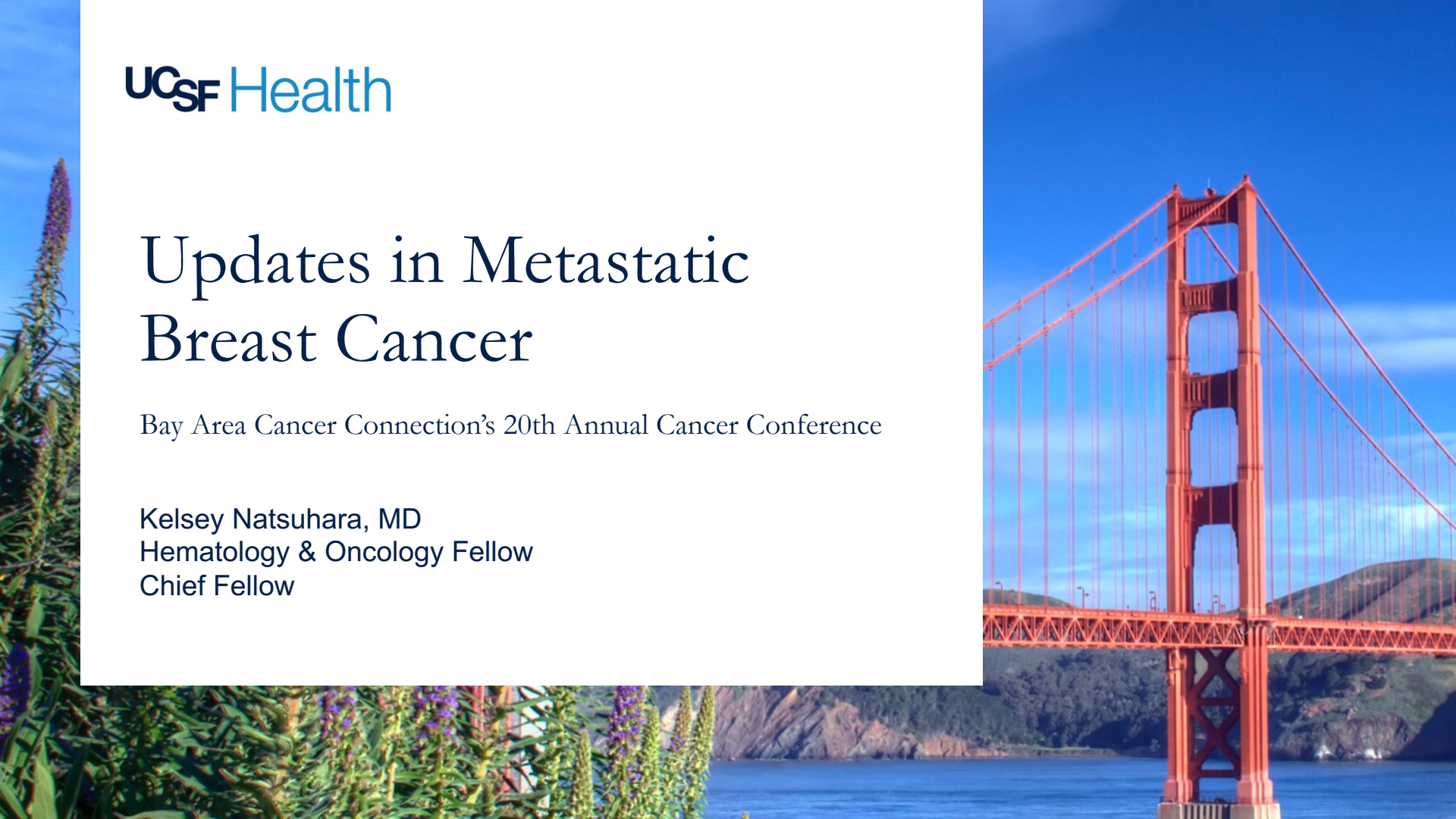
UCSF Health

Updates in Metastatic Breast Cancer

Bay Area Cancer Connection's 20th Annual Cancer Conference

Kelsey Natsuhara, MD
Hematology & Oncology Fellow
Chief Fellow



Disclosures

I have no disclosures or conflicts of interest.

Roadmap

- Living with Metastatic Cancer
- Treatment Updates
  - Hormone positive disease
  - HER2+
  - Triple negative breast cancer
- Clinical Trials
- Questions

UCSF Health

Living with Metastatic Breast Cancer (MBC)

- Unlikely to be cured
- BUT there is reason for hope!
  - Newer systemic therapies have improved outcomes
- Choosing treatment
  - Intermittent vs continuous treatment
  - Symptom management is critical

Goal: help patients live longer and better lives

UCSF Health

Managing Symptoms

- **Neuropathy**
  - Gabapentin, SNRIs (duloxetine, venlafaxine)
- **Hot flashes**
  - **New medication fezolinetant or “Veozah” approved in May 2023!**
  - FDA approved to treat hot flashes from menopause
- **Nausea**
  - Olanzapine (Zyprexa) 2.5-5 mg at bedtime
- **Hand foot syndrome** (from capecitabine or Xeloda)
  - Diclofenac gel (“Voltaren”) decreased incidence and severity of hand foot syndrome!
  - Study presented at ASCO 2023 (Santhosh et al)

Treatment Updates

Treatment Basics

Information we need to know to choose the best treatment for you

- **Receptor Status**
  - Confirming ER / PR / HER2 at time of diagnosis
  - Tumors can “lose” their ER/PR status or change markers
- **Mutation testing** (PD-L1, ESR1, PIK3CA)
  - Testing off biopsy tissue
  - “Liquid biopsy” – peripheral blood test that tests fragments of tumor DNA that are shed into the blood
- **Disease history**
  - Previous therapies you’ve received
  - Where is there disease?

Hormone positive disease (ER/PR+)

Hormone positive MBC (ER/PR+)

An exciting year in research!

- Novel hormone therapies
  - Elacestrant for ESR1 mutations
- New antibody drug conjugates (ADCs)
  - Trastuzumab-Deruxtecan (Enhertu)
  - Sacituzumab-Govitecan (Trodelvy)

New hormone therapy options for HR+ MBC

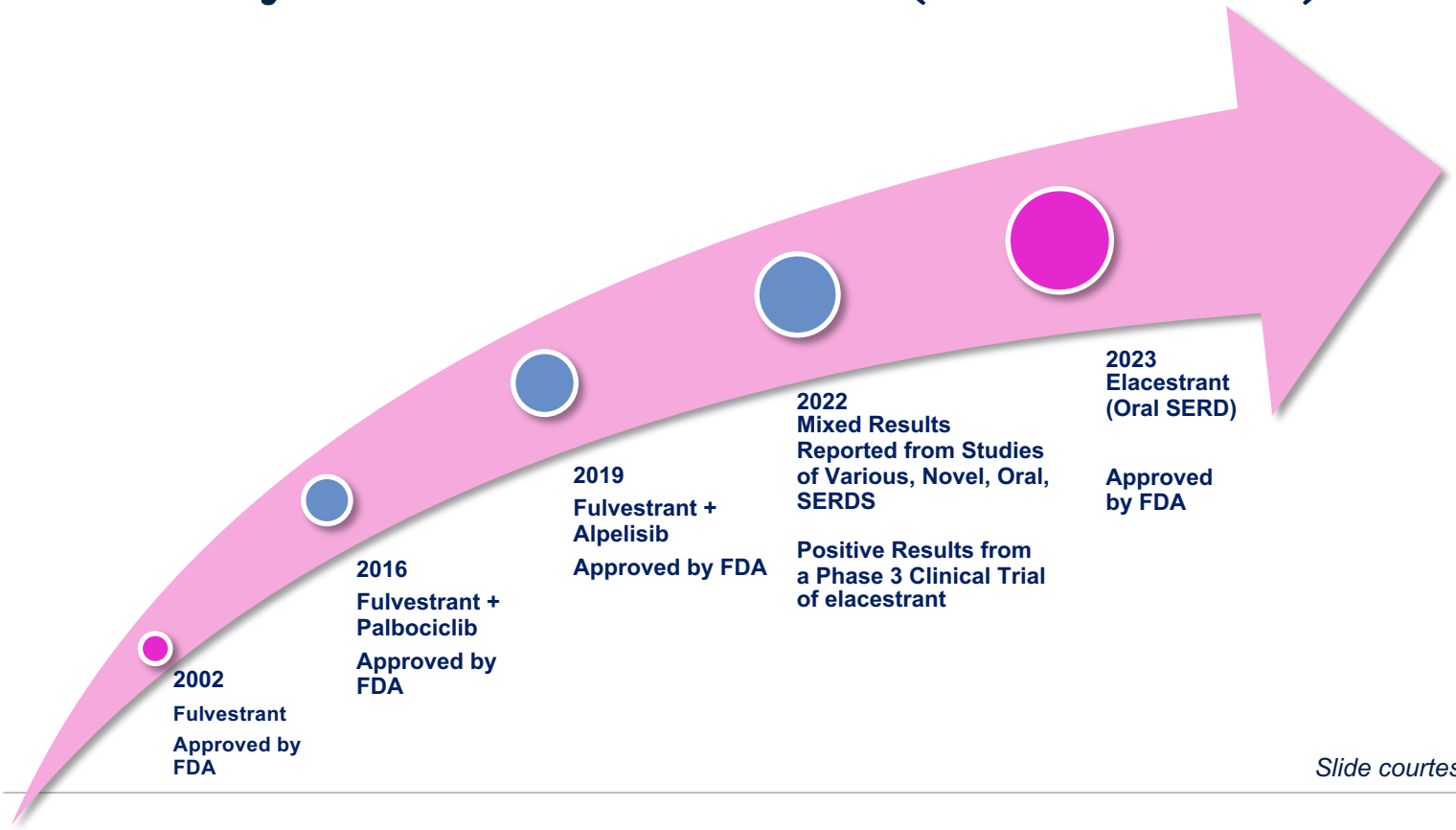
- Patients with HR+ disease can develop resistance to standard endocrine therapy (aromatase inhibitors or AI)

- After progressing on an AI → faslodex or “Fulvestrant”
  - Class of medication called a SERD
  - Only comes as a monthly intramuscular injection

- Patients with an ESR1 mutation can now take an oral pill!

SERD = Selective estrogen receptor down regulator

History of the SERDs (2002-2023)



Slide courtesy of Dr. Laura Huppert

FDA, Food and Drug Administration
SERD, selective estrogen receptor downregulator

UCSF Health

New hormone therapy options for HR+ MBC

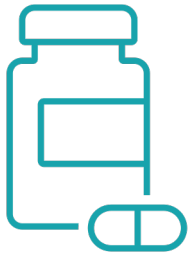
- **Elacestrant** or “Orserdu”
- **EMERALD** trial: Phase III randomized trial
  - ER+ / HER2- metastatic breast cancer
  - Progressed on previous endocrine therapy + CDK 4/6 inhibitor
  - Randomized to elacestrant vs standard of care monotherapy
- **ESR1 mutations** are known to cause resistance to aromatase inhibitors
  - For patients with an ESR1 mutation, their disease was controlled for longer (3.8 vs 1.9 mos)

ESR1 = Estrogen Receptor 1

Bidard, F, et al., JCO 2022; 40(28):3246-3256.

New hormone therapy options for HR+ MBC

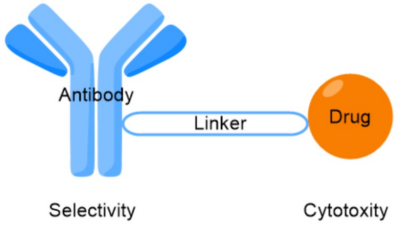
- **Elacestrant is approved for HR+ / HER2- MBC with ESR1 mutation**
  - *After progression on 1+ lines of endocrine therapy + CDK4/6 inhibitor*
  - *Not yet approved for patients without an ESR1 mutation, but hopefully options coming soon*



- **How is it given?** Once a day pill!
- **Common side effects:** nausea, GI upset, diarrhea, lack of appetite

Antibody-Drug Conjugates

Antibody drug conjugates (ADCs) are a novel class of anti-cancer medications

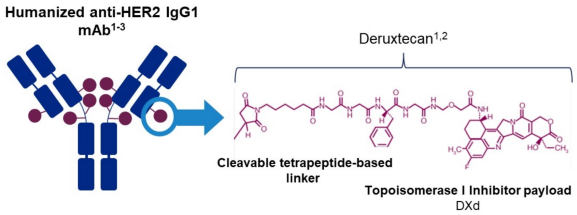


Goal: to deliver chemotherapy in a more targeted way

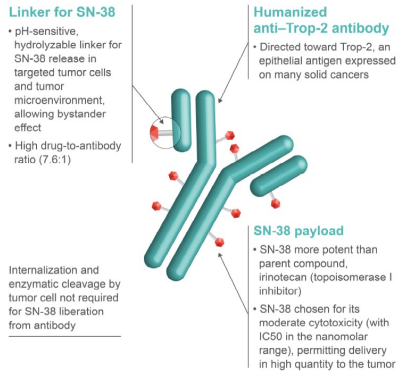
Composed of three parts:

1) *A targeted antibody (provides selectivity)*
2) *A linker*
3) *A cytotoxic payload (therapeutic)*

Trastuzumab-deruxtecan (TDxd)

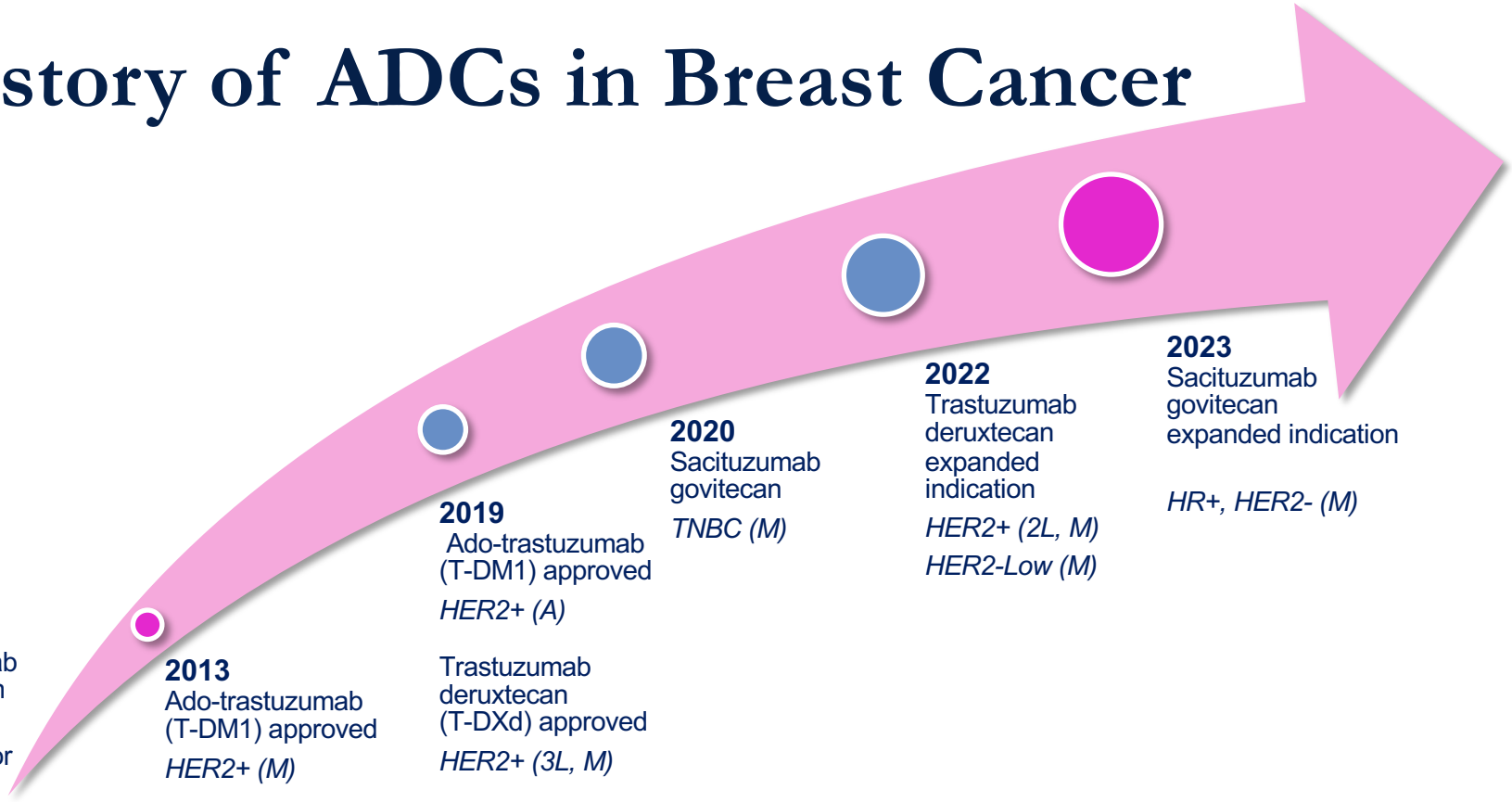


Sacituzumab-govitecan (SG)



UCSF Health

History of ADCs in Breast Cancer



2000
Gemtuzumab ozogamicin

First ADC approved for AML

2013
Ado-trastuzumab (T-DM1) approved

HER2+ (M)

2019
Ado-trastuzumab (T-DM1) approved

HER2+ (A)

Trastuzumab deruxtecan (T-DXd) approved

HER2+ (3L, M)

2020
Sacituzumab govitecan

TNBC (M)

2022
Trastuzumab deruxtecan expanded indication

HER2+ (2L, M)

HER2-Low (M)

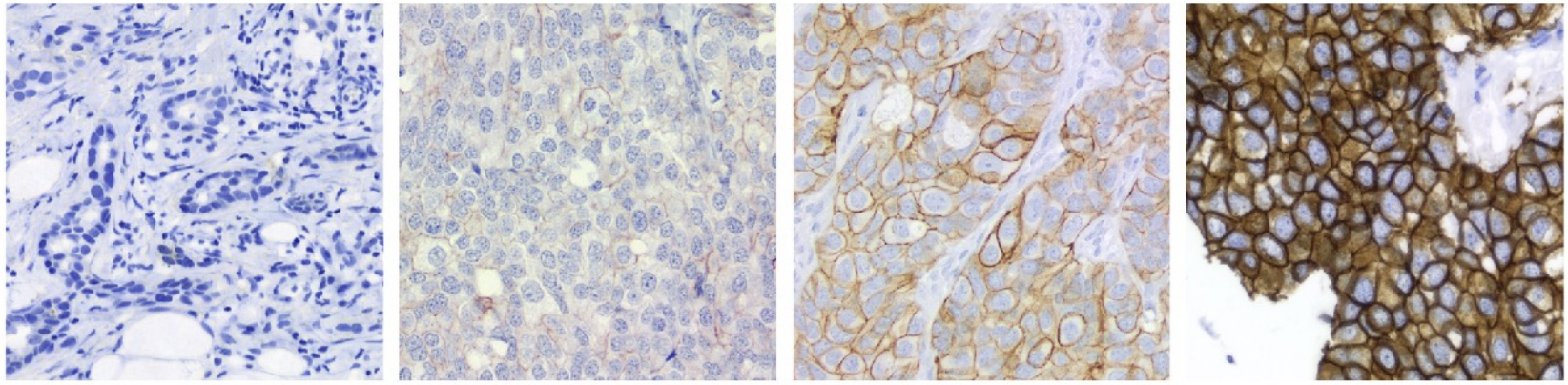
2023
Sacituzumab govitecan expanded indication

HR+, HER2- (M)

Slide courtesy of Dr. Laura Huppert

A, adjuvant; M, metastatic.

HER2-Low Breast Cancer



Adapted from DOI:10.1016/j.semcancer.2020.02.016

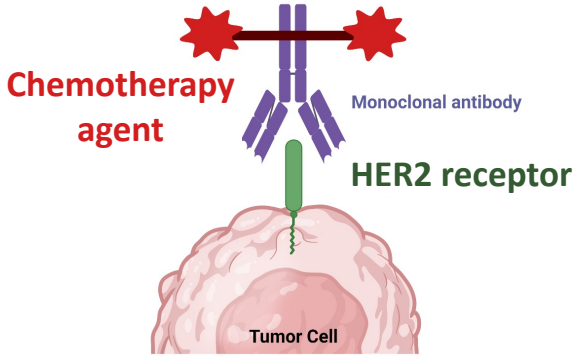
UCSF Health

Trastuzumab-Deruxtecan (T-Dxd)

"Enhertu"

- **HER2-low breast cancer** is defined as breast cancers that express low-levels of HER2
  - IHC scores 1+ or 2+
  - 60% of HER2-negative breast cancers are HER2-low!

- T-DXd is an ADC that targets tumor cells that express low levels of HER2
  - AND delivers its potent cytotoxic payload to neighboring tumor cells that may not express HER2

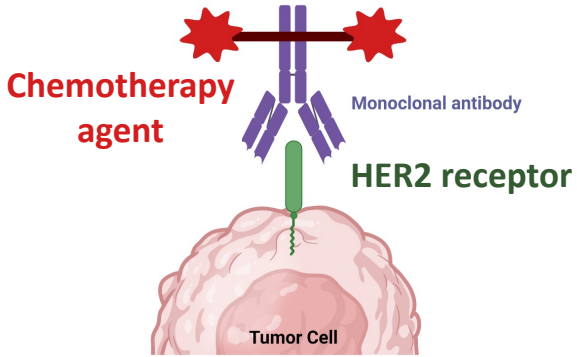


IHC = immunohistochemistry

Trastuzumab-Deruxtecan (T-Dxd)

- **DESTINY-Breast 04:** Phase III randomized trial
  - HER2-low patients with metastatic breast cancer
  - HR positive or HR negative
  - 1-2 prior lines of chemotherapy
  - HR+ disease that progressed on endocrine therapy

- Randomized to T-DXd vs treatment of physician's choice



Modi S, et al. *N Engl J Med*. 2022;387:9-20.
Modi S, et al. ASCO 2022. Abstract LBA3.

UCSF Health

DESTINY-Breast04: Baseline Characteristics

	All patients	
	T-DXd (n = 373)	TPC (n = 184)
Age, median (range), years	58 (32-80)	56 (28-80)
Female, n (%)	371 (99)	184 (100)
Region, n (%)		
Europe + Israel	166 (45)	85 (46)
Asia	147 (39)	66 (36)
North America	60 (16)	33 (18)
HER2 status (IHC), n (%)		
1+	215 (58)	106 (58)
2+/ISH−	158 (42)	78 (42)
ECOG performance status, %		
0	200 (54)	105 (57)
1	173 (46)	79 (43)
Hormone receptor,[a] n (%)		
Positive	333 (89)	166 (90)
Negative	40 (11)	18 (10)
Brain metastases at baseline, n (%)	24 (6)	8 (4)
Liver metastases at baseline, n (%)	266 (71)	123 (67)
Lung metastases at baseline, n (%)	120 (32)	63 (34)

TPC = Treatment of Physician's Choice

Modi S, et al. *N Engl J Med*. 2022;387:9-20.
Modi S, et al. ASCO 2022. Abstract LBA3.

UCSF Health

Trastuzumab-Deruxtecan (T-Dxd)

- **DESTINY-Breast04** showed:
  - Patients' cancer was controlled for longer on T-Dxd (10 vs 5 months)
  - Patients lived longer on T-DXd! (24 vs 17 months)

T-Dxd now approved for HER2-low metastatic breast cancer!

- **How is it given?** IV Infusion every 3 weeks
- **Common side effects:** nausea, hair loss, low blood counts
- **Rare but serious side effect:** interstitial lung disease or "ILD"
  - Requires close monitoring (CT chest every 2-3 months)
  - STOP T-DXd and give steroids

Modi S, et al. *N Engl J Med*. 2022;387:9-20.
Modi S, et al. ASCO 2022. Abstract LBA3.

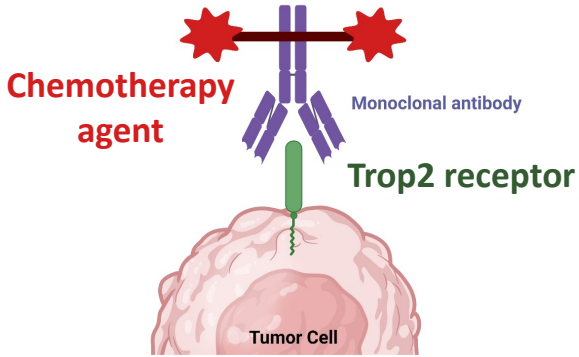
UCSF Health

Sacituzumab-Govitecan

"Trodelvy"

ADC #2

- SG is an ADC that targets **Trop 2**
  - **Trop 2:** cell surface antigen expressed on most breast cancer cells
- SG already approved for triple negative breast cancer



UCSF Health

Sacituzumab-Govitecan

- **TROPICS-02:** Phase III randomized trial
  - Included HR+ HER2- patients with metastatic breast cancer
  - Randomized to SG vs treatment of physician's choice
- Patients who received SG lived longer! (14.5 vs 11 months)

Sacituzumab-govitecan now approved for HR+ HER2- MBC!

- **How is SG given?** IV infusion weekly (2 weeks on, 1 week off)
- **Common Side Effects:** low blood counts, diarrhea, nausea, hair loss
  - Often given with growth factor (Zarxio, Neupogen)

Rugo, HS, et al. Lancet 2023; 402(10411)

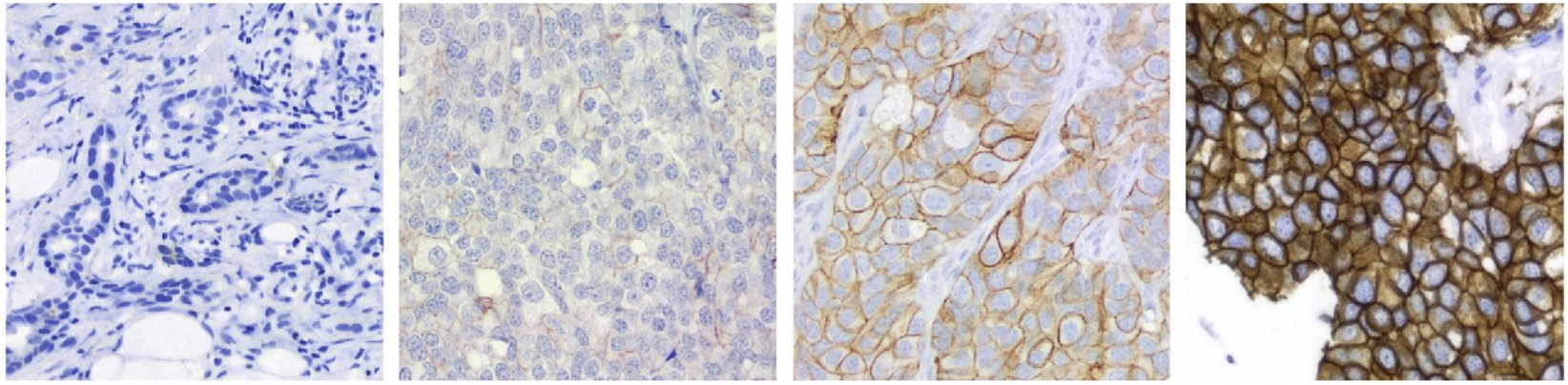
Summary: Hormone positive MBC

- Elacestrant for ESR1 mutations
- New antibody drug conjugates (ADCs)
  - Trastuzumab-Deruxtecan for HER2-low breast cancer
  - Sacituzumab-Govitecan for HR+ metastatic breast cancer

UCSF Health

HER2+ Metastatic Disease

HER2-Positive Breast Cancer



Adapted from DOI:10.1016/j.semcancer.2020.02.016

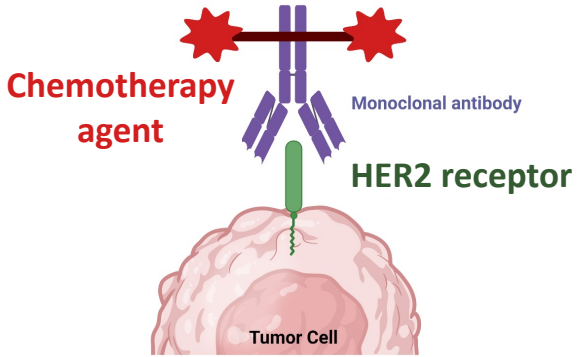
UCSF Health

Trastuzumab-Deruxtecan (T-Dxd)

"Enhertu"

- T-Dxd first used in HER2+ disease

- **DESTINY-Breast03 Trial**
  - Phase III trial of patients with HER2+ metastatic breast cancer
  - Approx 50% HR+ and 50% HR-
  - Randomized to T-DXd vs Trastuzumab-Emtansine (T-DM1, an older ADC)



Cortez et. al. NEJM 2022; 386:1143-1154
Hurvitz et. al., Lancet 2023; 401(10371)

UCSF Health

Trastuzumab-Deruxtecan (T-Dxd)

"Enhertu"

- **For patients on T-DXd vs T-DM1:**
  - More patients responded: 80 vs 35%
  - Patients' disease was controlled for longer: 29 vs 7 months
  - AND patients lived longer!
    - At 2 years, 78% of patients in the T-DXd arm were alive vs 70% in the T-DM1 group

T-DXd approved for HER2+ MBC and is now 2nd line therapy!

- **Subgroup analysis: patients with brain metastases**
  - Intracranial response rate ~70%

Cortez et. al. NEJM 2022; 386:1143-1154
Hurvitz et. al., Lancet 2023; 401(10371)

UCSF Health

Summary: HER2+ MBC

- Trastuzumab-Deruxtecan approved for HER2+ MBC in the 2nd line!
- Excellent intracranial response rates

UCSF Health

Triple Negative Metastatic Disease

Metastatic Triple Negative Breast Cancer

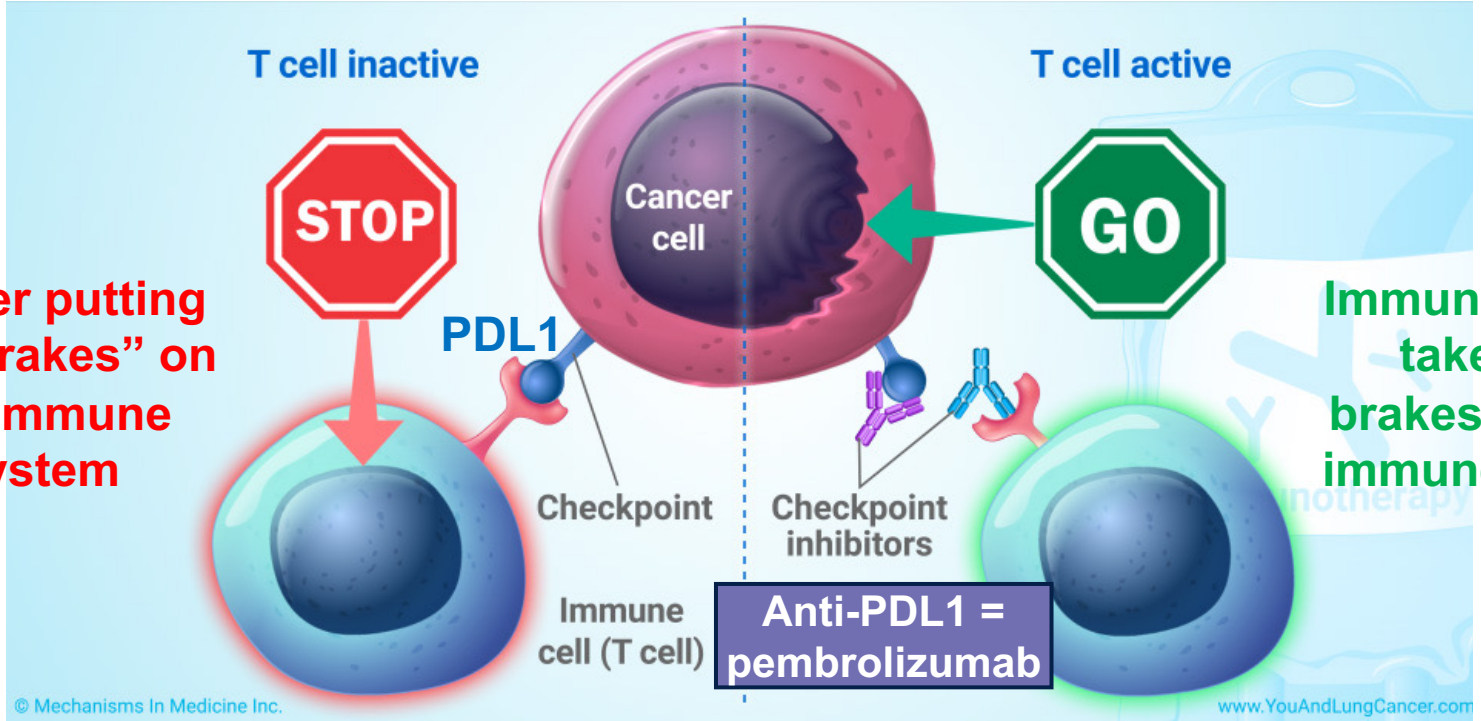
"mTNBC"

- **Why is triple negative breast cancer so hard to treat?**
  - Previously, we have not had good treatment targets
  - E.g. estrogen receptor or the HER2 receptor

- **Now we are finding targets to make treatments better!**
  - Immunotherapy: KEYNOTE 355 Trial
  - Sacituzumab-Govitecan: ASCENT trial
  - Trastuzumab-Deruxtecan in DESTINY-Breast 04

What is immunotherapy?

Cancer putting the "brakes" on the immune system



Immunotherapy takes the brakes OFF the immune system

UCSF Health

Pembrolizumab for mTNBC

"Keytruda"

- **KEYNOTE 355**: Phase III Trial for mTNBC
  - Randomized to chemotherapy +/- pembrolizumab
  - Pembrolizumab is an anti-PDL1 antibody treatment
  - Expression of PD-L1 protein measured with a "CPS score"
- **Patients with more PD-L1 expression benefitted most (CPS≥10)**
  - Patients' cancer was controlled for longer (10 vs 6 months)
  - Patients lived longer (23 vs 16 months)

Pembrolizumab + Chemotherapy now approved as 1st line treatment for mTNBC if CPS≥10!

CPS = Combined Positivity Score

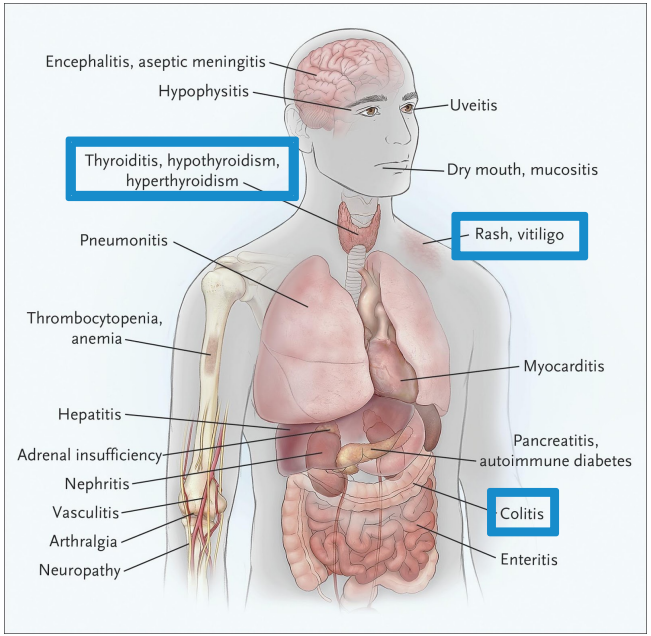
Cortes, J, et. al. NEJM 2022; 387:217-226

UCSF Health

Pembrolizumab for mTNBC

- **How is it given?** IV infusion every 3 weeks

- **Side effects:** immune related side effects
  - Common: fatigue, joint aches, rash, diarrhea, thyroid problems, liver test abnormalities
  - Less common, but severe: adrenal insufficiency, Type 1 diabetes, inflammation of heart, lungs, or other organs
  - Need to be closely monitored, sometimes drug needs to be stopped and steroids needed



Postow *NEJM* 2018

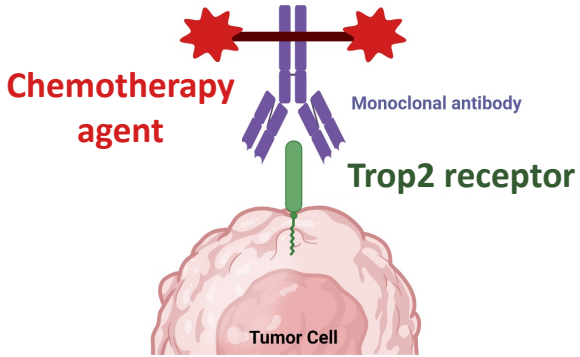
UCSF Health

Sacituzumab-Govitecan

"Trodelvy"

- SG was first approved in mTNBC based on data from the ASCENT trial

- SG is an antibody drug conjugate that targets **Trop 2** a cell surface antigen expressed by most breast cancer cells



UCSF Health

Sacituzumab-Govitecan

- **The ASCENT trial**: Phase III trial
  - Randomized patients with mTNBC to SG vs chemotherapy of physician's choice
- More patients had their cancer shrink (35 vs 5%)
- Patients' cancer was controlled for longer with SG (5.6 vs 1.7 months)
- Patients lived longer! (12 vs 7 months)

Sacituzumab-govitecan approved for metastatic TNBC!

Bardia, et al. *N Engl J Med*. 2021; 384:1529-1541.

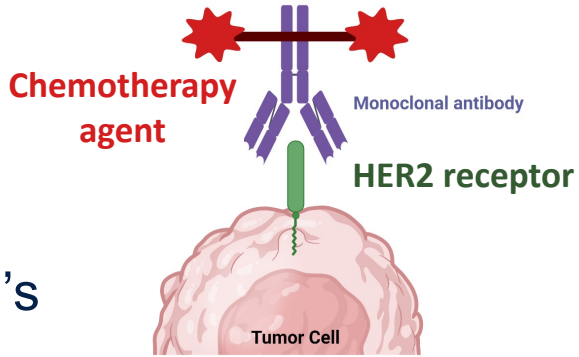
Trastuzumab-Deruxtecan (T-Dxd)

Remember back to our HR+ section of the talk…

HER2 low + HR neg = TNBC

- **DESTINY-Breast 04:** Phase III randomized trial
  - **HER2-low patients** with metastatic breast cancer
  - HR positive or **HR negative**
  - 1-2 prior lines of chemotherapy

- Randomized to T-DXd vs treatment of physician's choice



Modi S, et al. *N Engl J Med*. 2022;387:9-20.
Modi S, et al. ASCO 2022. Abstract LBA3.

UCSF Health

DESTINY-Breast04: Baseline Characteristics

	All patients	
	T-DXd (n = 373)	TPC (n = 184)
Age, median (range), years	58 (32-80)	56 (28-80)
Female, n (%)	371 (99)	184 (100)
Region, n (%)		
Europe + Israel	166 (45)	85 (46)
Asia	147 (39)	66 (36)
North America	60 (16)	33 (18)
HER2 status (IHC), n (%)		
1+	215 (58)	106 (58)
2+/ISH−	158 (42)	78 (42)
ECOG performance status, %		
0	200 (54)	105 (57)
1	173 (46)	79 (43)
Hormone receptor,[a] n (%)		
Positive	333 (89)	166 (90)
Negative	40 (11)	18 (10)
Brain metastases at baseline, n (%)	24 (6)	8 (4)
Liver metastases at baseline, n (%)	266 (71)	123 (67)
Lung metastases at baseline, n (%)	120 (32)	63 (34)

Small number of TNBC patients included

TPC = Treatment of Physician's Choice

Modi S, et al. *N Engl J Med*. 2022;387:9-20.
Modi S, et al. ASCO 2022. Abstract LBA3.

UCSF Health

Trastuzumab-Deruxtecan (T-Dxd)

- **Regardless… given the study showed:**
  - Patients' cancer was controlled for longer on T-Dxd (10 vs 5 months)
  - Patients lived longer on T-DXd! (24 vs 17 months)

T-Dxd is approved for HER2-low metastatic breast cancer!
Including mTNBC

Modi S, et al. *N Engl J Med*. 2022;387:9-20.
Modi S, et al. ASCO 2022. Abstract LBA3.

UCSF Health

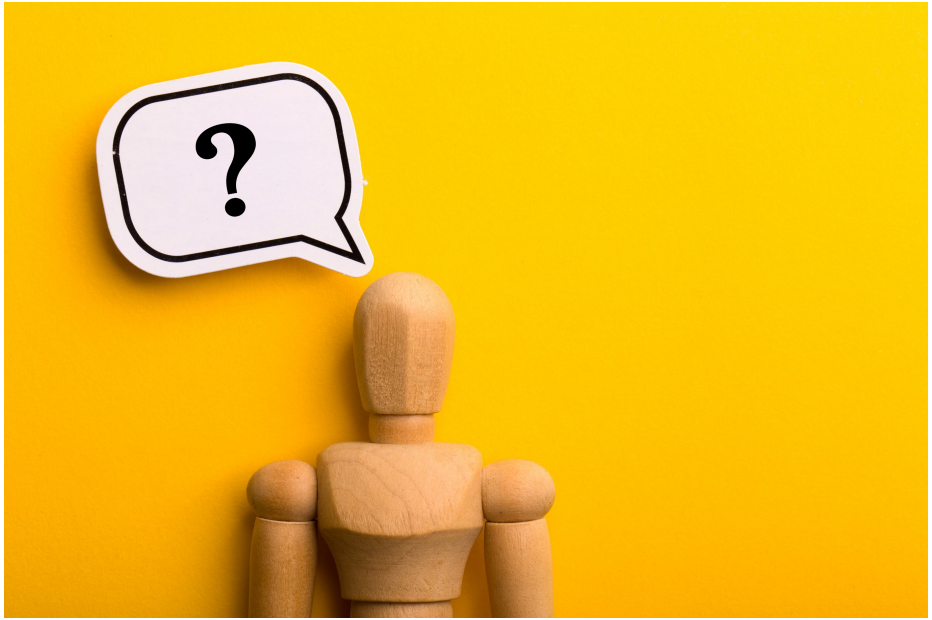
Summary: mTNBC

- Pembrolizumab + chemotherapy approved for 1st line treatment of mTNBC for PD-L1 CPS score ≥10
- Sacituzumab-govitecan approved for mTNBC
- Trastuzumab-deruxtecan approved for HER2 low metastatic disease

UCSF Health

What about clinical trials?

(And where can I find them?)



UCSF Health

What about clinical trials?

(And where can I find them?)

- Trials can be considered at any point in your treatment!

- **Things to consider:**
  - Access to treatments not yet approved
  - Contributing to science
  - Drugs are not *proven* yet
  - May require more visits, repeat biopsies or imaging

- Trial eligibility requirements:
  - # of previous treatments
  - Previously received chemotherapy
  - Sites of metastatic disease
  - Need for repeat biopsies or imaging
  - Takes time to screen and enroll on to a trial

Clinical Trial Resources

Where can I find trials?

- BreastCancerTrials.org
- Susan G. Komen Foundation: www.komen.org/clinical-trials
- ClinicalTrials.gov
- UCSF Bay Area Breast Cancer Forum
- Bay Area Cancer Connection
- Talk to your oncologist!

Summary: Updates in MBC

- **Elacestrant** for ESR1 mutations in HR+ MBC
- **Trastuzumab-Deruxtecan** for HER2-low breast cancer (HR+/-) and HER2+ MBC
- **Sacituzumab-Govitecan** for HR+ and triple negative metastatic breast cancer
- **Pembrolizumab** + Chemo approved for mTNBC

Just the tip of the iceberg!

Future Directions

- **Novel endocrine therapies**
  - Pill form with fewer side effects
  - Approvals for patients without ESR1 mutations
- **New antibody drug conjugates**
  - Datopotamab-deruxtecan
- **Expansion of immunotherapy**
  - Currently approved only for TNBC
  - Recent data for early stage HR+ breast cancer

Thank You!

- To the Bay Area Cancer Connection for inviting me to speak
- To my phenomenal UCSF Breast Mentors: Drs. Hope Rugo, Jo Chien, Laura Huppert, and Michelle Melisko
- To all of you for attending and advocating for breast cancer patients

Questions?

UCSF Health