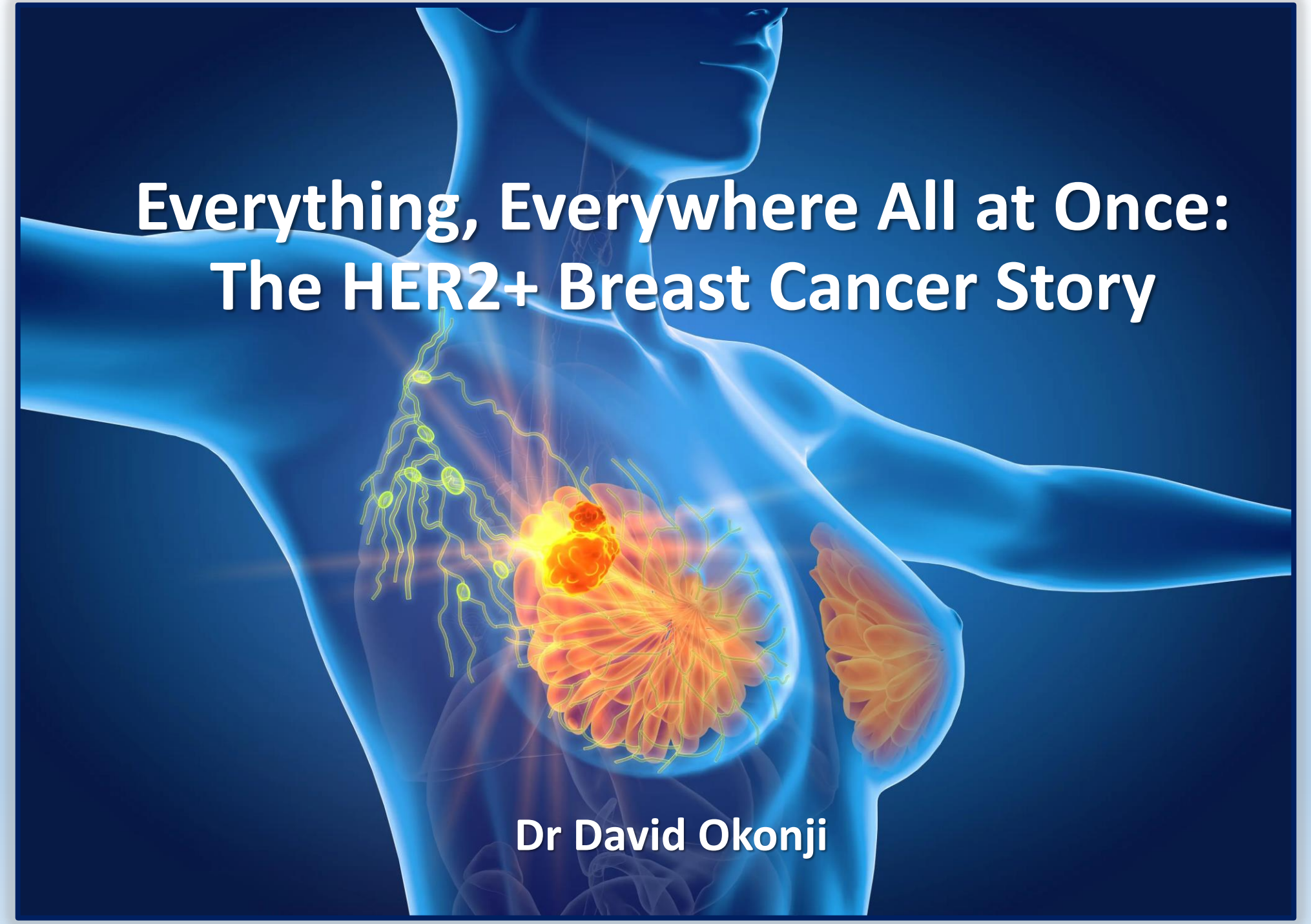

Everything, Everywhere All at Once:
The HER2+ Breast Cancer Story
Dr David Okonji


COMING SOON

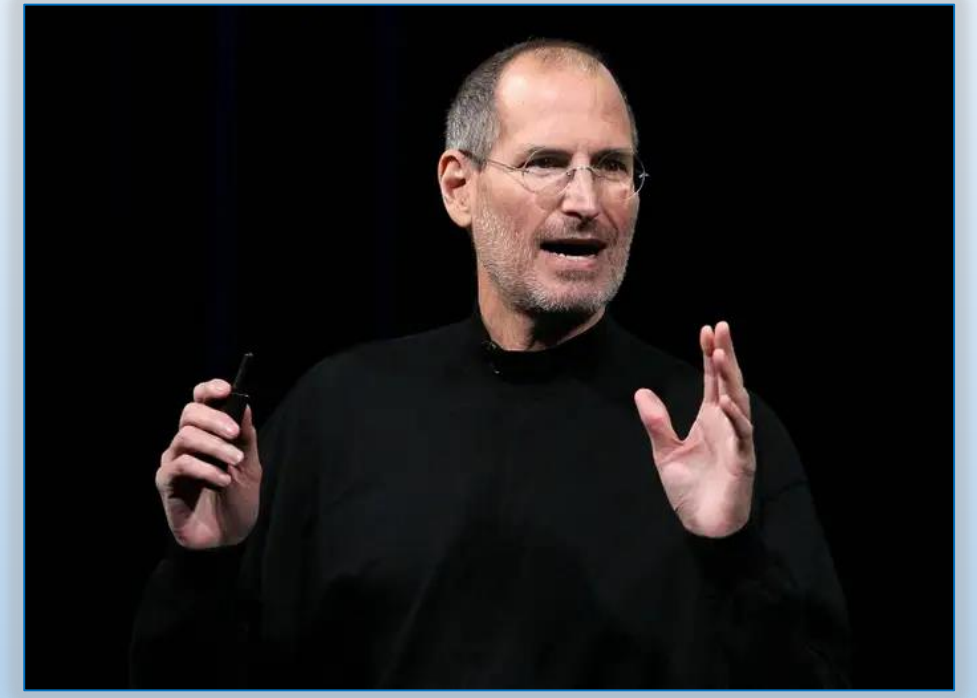
Disclosures

- Honoraria: Pfizer, MSD, Astra Zeneca, Novartis, BMS
- Consulting or Advisory Role: Pfizer, MSD, Astra Zeneca, Novartis, BMS
- Travel/Accommodation grants: Roche, Pfizer, Astra Zeneca

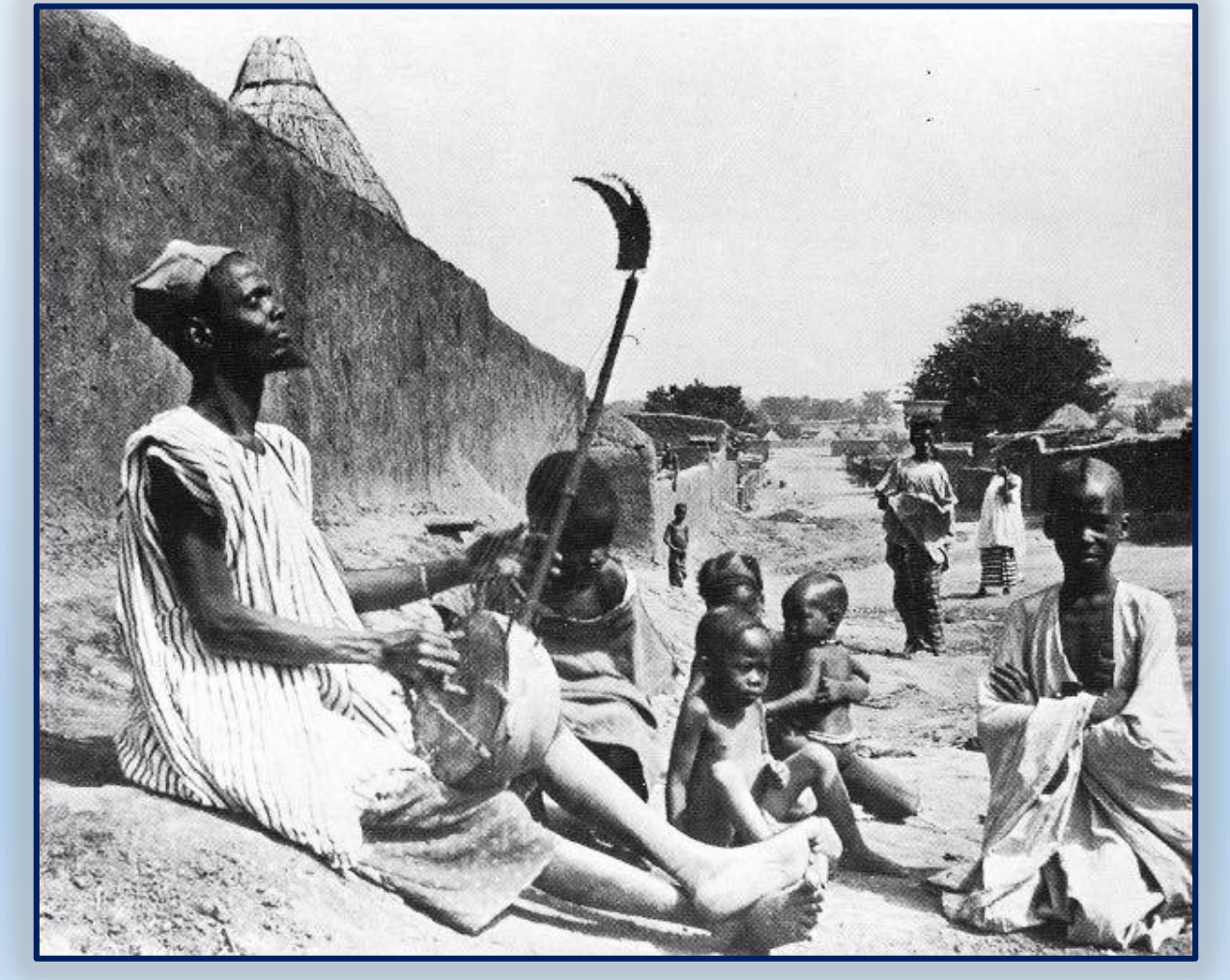
Those who do not have power over the story that dominates their lives, power to retell it, to rethink it, deconstruct it, joke about it, and change it as times change, truly are powerless, because they cannot think new thoughts.

1981 Booker Prize Winner Sir Salman Rushdie

Story Telling:



"The most powerful person in the world is the storyteller. The storyteller sets the vision, values, and agenda of an entire generation that is to come."



Safeguarding Old and New Stories

"A griot was a person in Africa who was charged with keeping the stories of the village. Everyone would tell a griot their stories and the griot would remember them all so that they could tell future generations. When they got old, they'd tell them to someone else. And they say in Africa, when a griot dies it's like a library was burned down."

Dave Chapelle- Mark Twain Prize Acceptance Speech (2019)

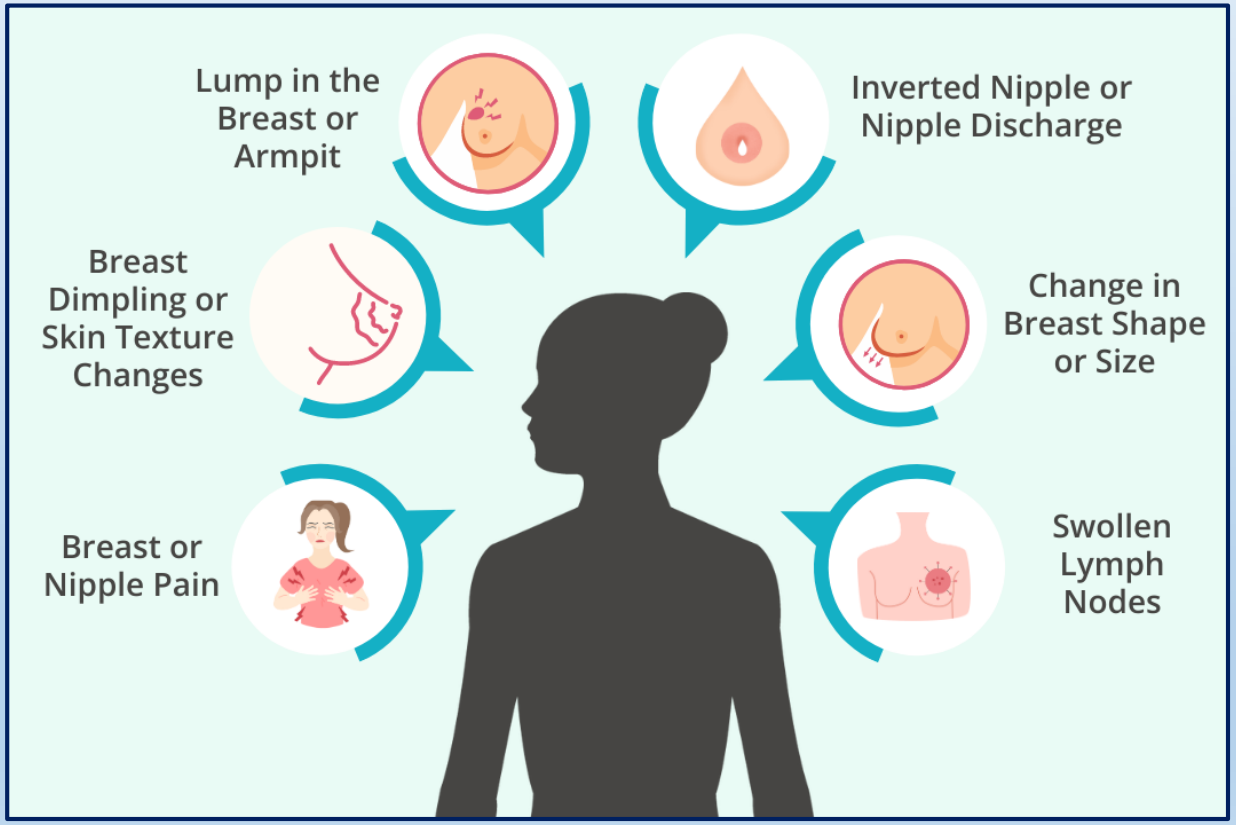
Outline

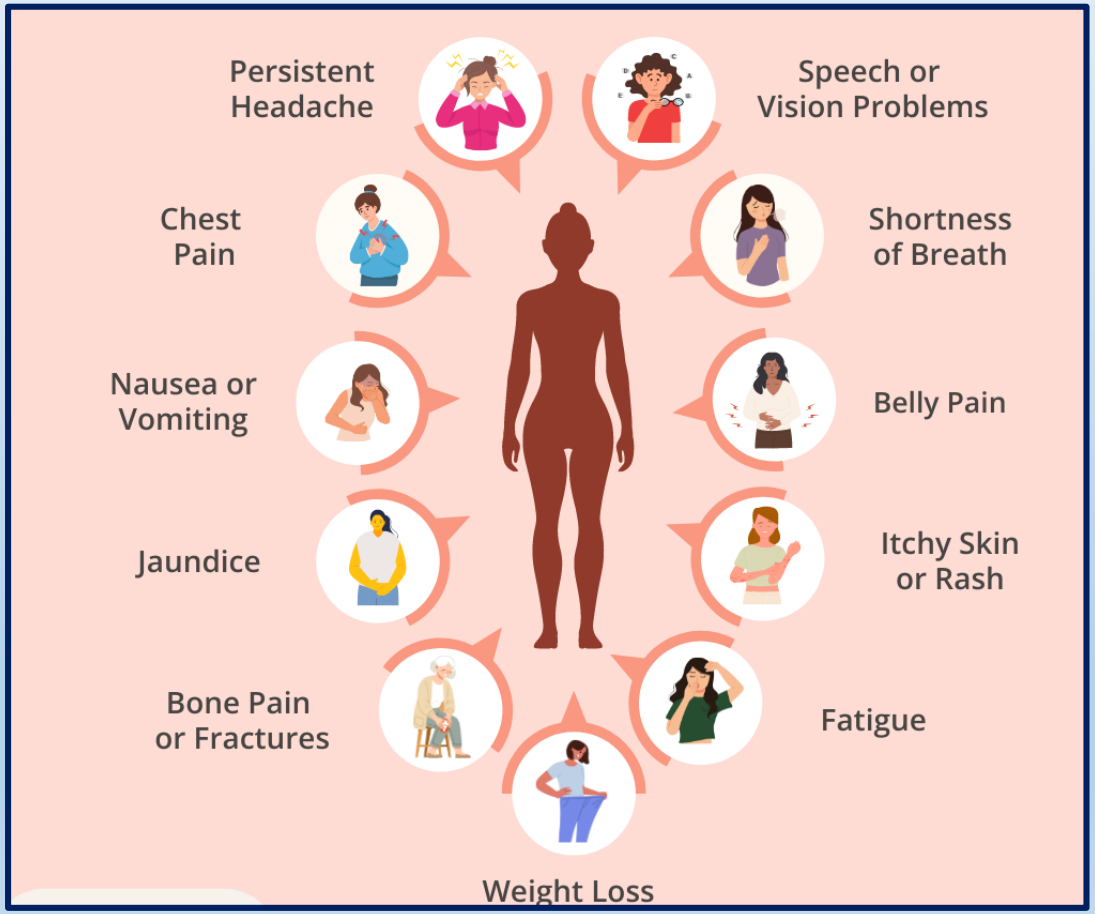
- HER2+ Breast Cancer: What is it?
- Symptoms
- Treating HER2 positive metastatic breast cancer
- The Trastuzumab Story
- How to make Trastuzumab
- The Trastuzumab Biosimilar Story
- Pertuzumab
- Trastuzumab Emtansine
- Trastuzumab Deruxtecan
- HER2-directed therapies: Have they made a difference?
- The Future

The “HER2” & HER2 positive Breast Cancer- What is it?

- The HER2 protein is involved in cell growth and division
- HER2 testing is crucial for determining the most effective treatment in this breast cancer sub-type
- A type of breast cancer where cells have an overabundance of the HER2 protein.
- Approximately 15% to 20% of all breast cancer cases are HER2-positive
- HER2+ breast cancers tend to be more aggressive and grow faster than other types of breast cancers

HER2+ Breast Cancer: Symptoms

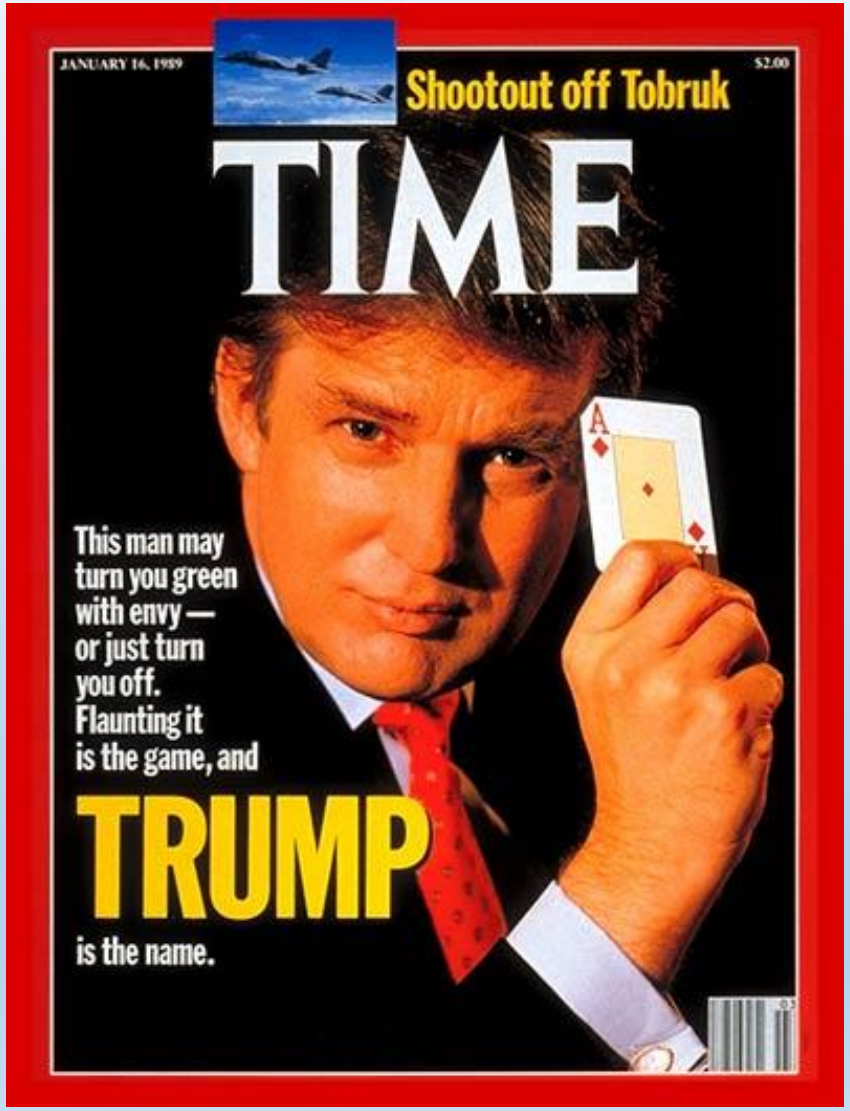




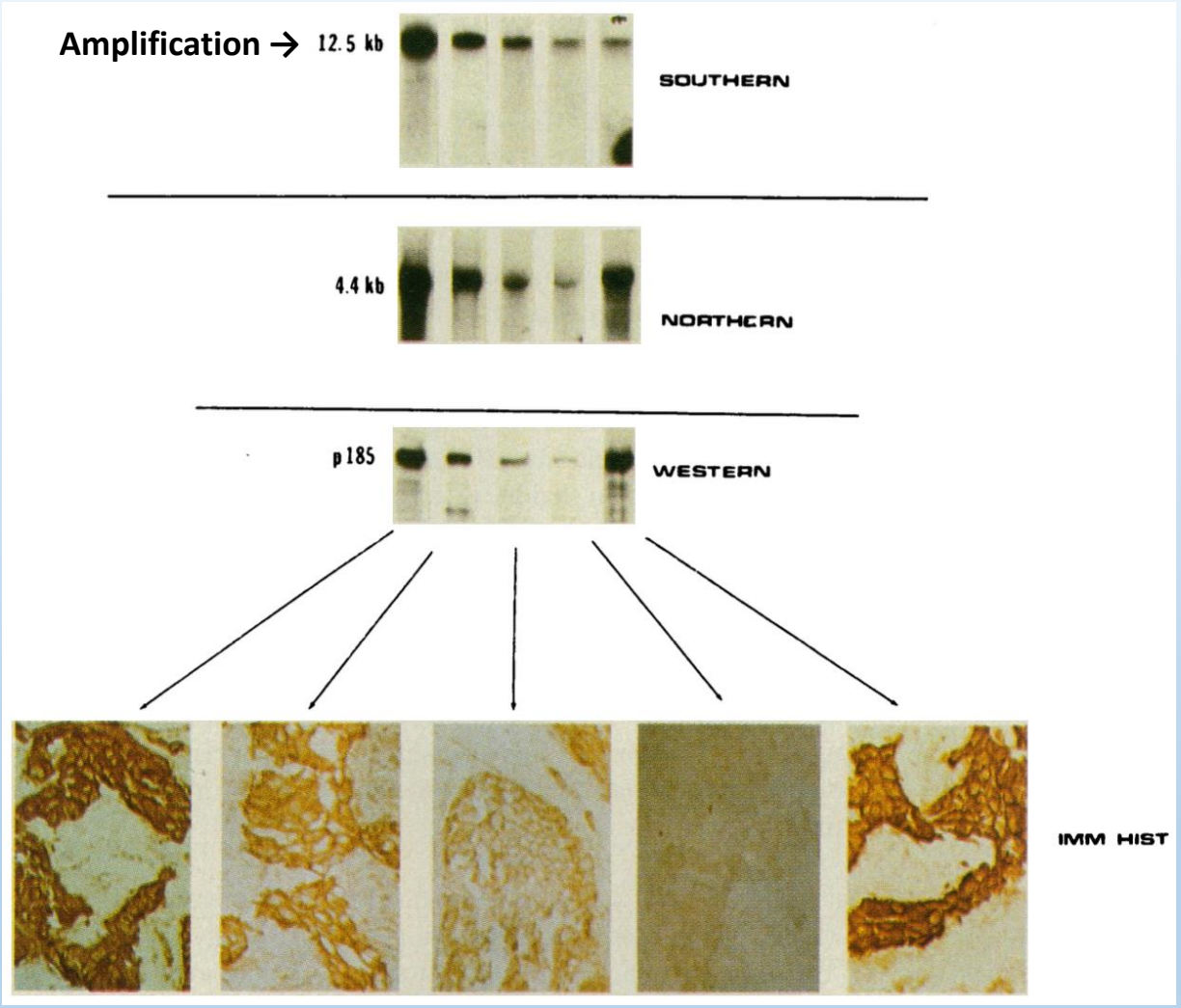
The Trastuzumab Story (Herceptin©)

It all began in 1989

"1989"- Explores the feelings that come after a major move or life change, focusing on freedom, fun, and flirtation.



Correlation Between HER-2/*neu* Gene Amplification and Expression

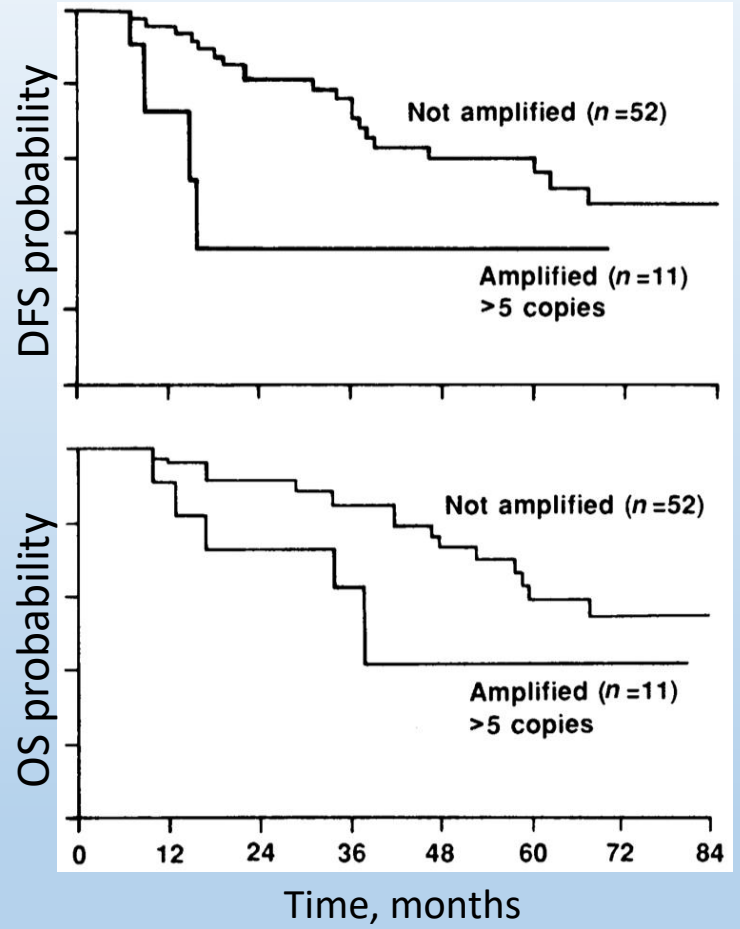


Southern blot analyses show the 12.5-kb HER-2/*neu* band seen with Eco RI cut DNA.

Northern blot analyses show the 4.5-kb HER-2/*neu* transcript.

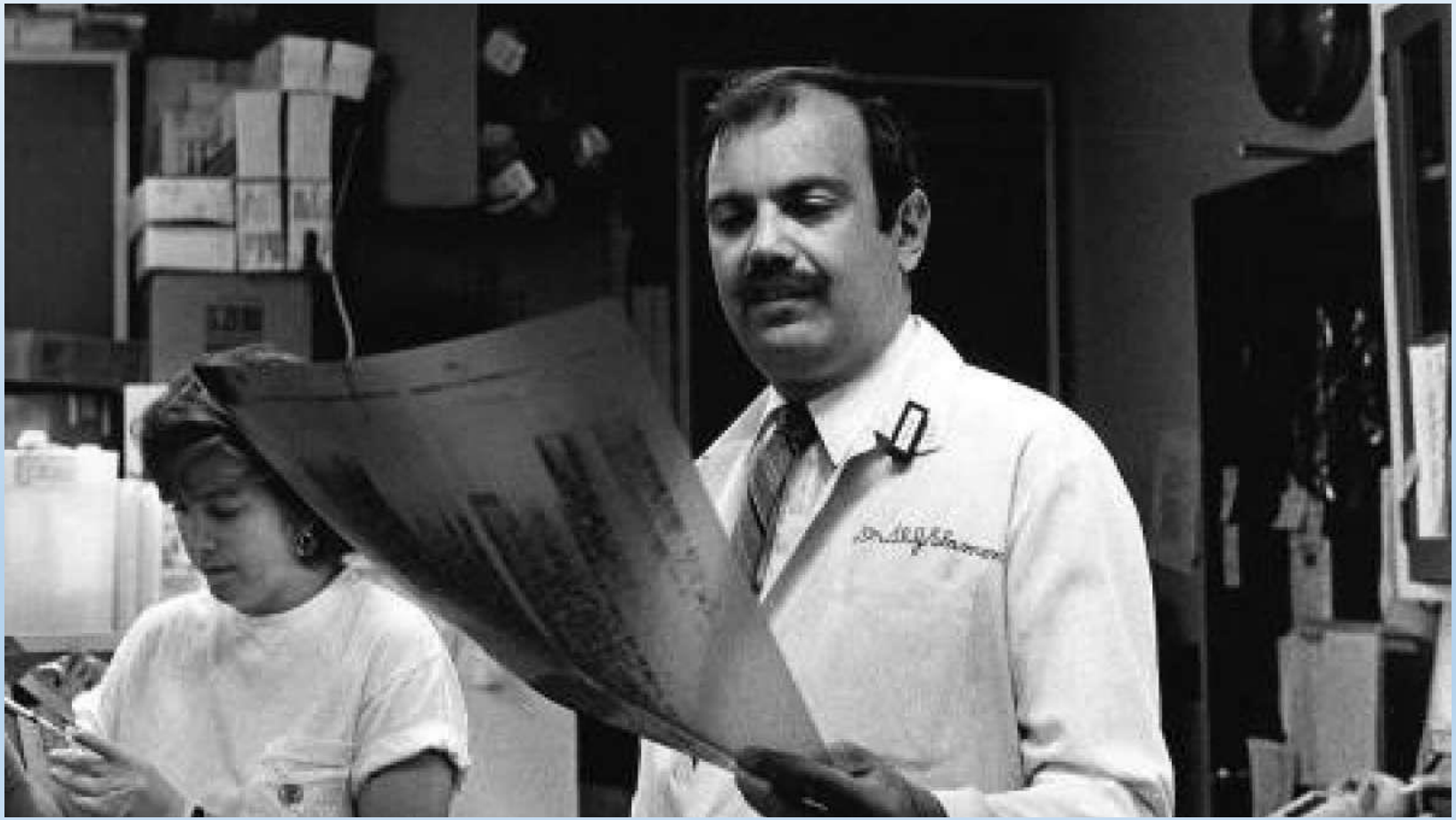
Western blot analyses show the 185-kD HER-2/*neu* protein band.

"Immunohistochemical analysis was done with the anti-HER-2/*neu* specific antibody on frozen sections. Tissues were scored and placed in one of the four staining categories shown on the basis of the relative level of specific staining as judged by microscopic examination as follows: negative to weak, 1+, 2+, and 3 +".



Slamon DJ, *et al*. Science. 1989; 244(4905):707-12.

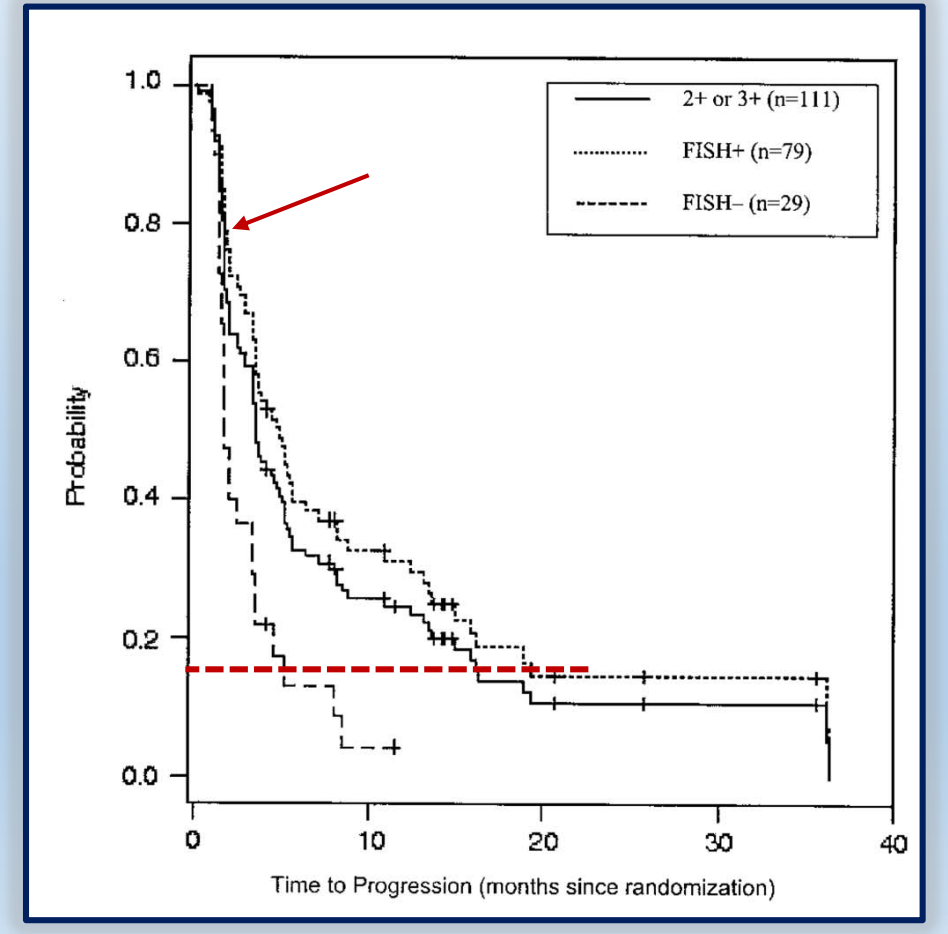
Trastuzumab: Testing the drug- First in human studies



Trastuzumab: Is it safe? Does it work?

Efficacy and Safety of Trastuzumab as a Single Agent in First-Line Treatment of *HER2*-Overexpressing Metastatic Breast Cancer

By Charles L. Vogel, Melody A. Cobleigh, Debu Tripathy, John C. Gutheil, Lyndsay N. Harris, Louis Fehrenbacher, Dennis J. Slamon, Maureen Murphy, William F. Novotny, Michael Burchmore, Steven Shak, Stanford J. Stewart, and Michael Press



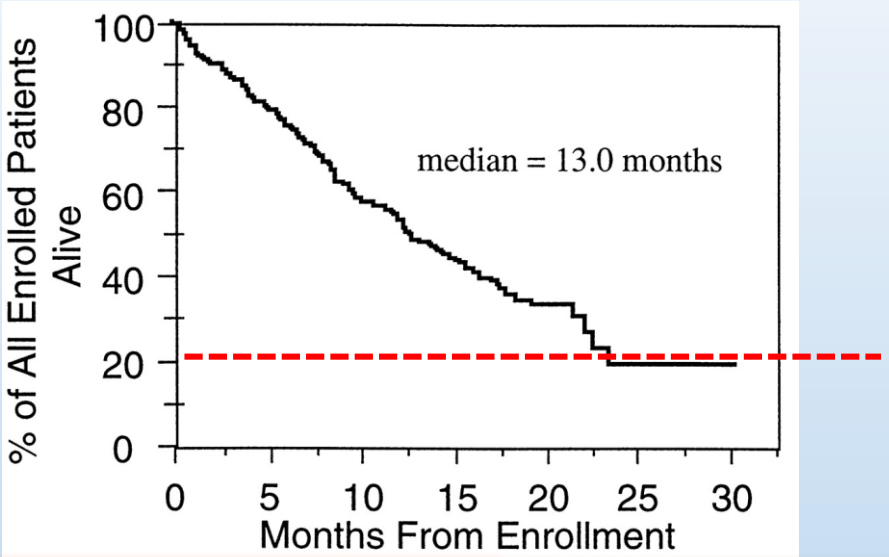
Vogel et al, 2002. JCO 20:719-726

Trastuzumab- Practice Changing

Clinical Trial > J Clin Oncol. 1999 Sep;17(9):2639-48. doi: 10.1200/JCO.1999.17.9.2639.

Multinational study of the efficacy and safety of humanized anti-HER2 monoclonal antibody in women who have HER2-overexpressing metastatic breast cancer that has progressed after chemotherapy for metastatic disease

M A Cobleigh [1], C L Vogel, D Tripathy, N J Robert, S Scholl, L Fehrenbacher, J M Wolter, V Paton, S Shak, G Lieberman, D J Slamon

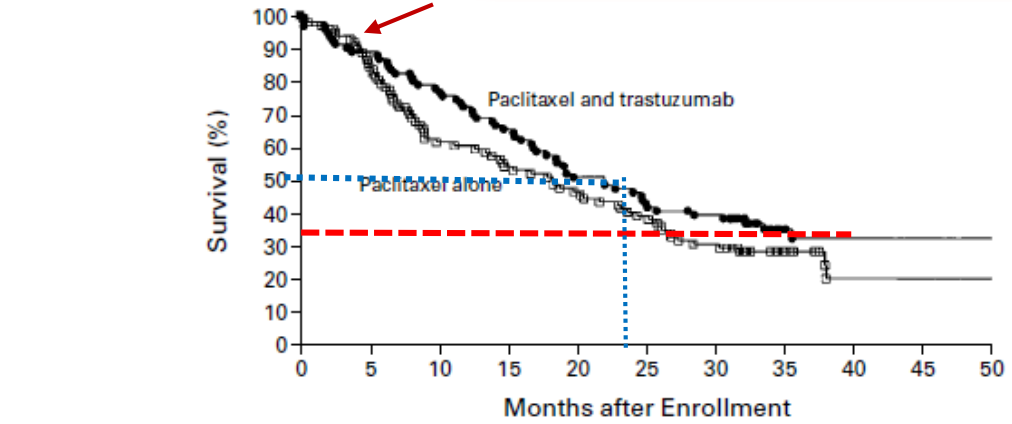


The New England Journal of Medicine

VOLUME 344 MARCH 15, 2001 NUMBER 11

USE OF CHEMOTHERAPY PLUS A MONOCLONAL ANTIBODY AGAINST HER2 FOR METASTATIC BREAST CANCER THAT OVEREXPRESSES HER2

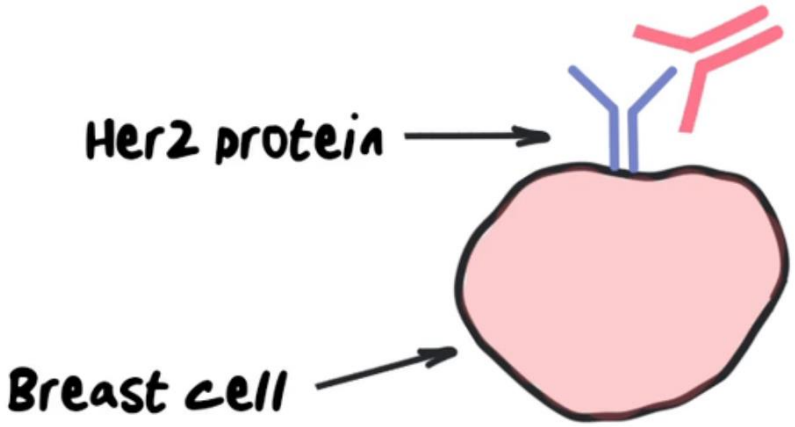
DENNIS J. SLAMON, M.D., PH.D., BRIAN LEYLAND-JONES, M.D., STEVEN SHAK, M.D., HANK FUCHS, M.D., VIRGINIA PATON, PHARM.D., ALEX BAJAMONDE, PH.D., THOMAS FLEMING, PH.D., WOLFGANG EIERMANN, M.D., JANET WOLTER, M.D., MARK PEGRAM, M.D., JOSE BASELGA, M.D., AND LARRY NORTON, M.D.*



"[Without] a paclitaxel arm, Trastuzumab could not be in the market today,"

Trastuzumab: Novel drug with a new target and new mechanism of action

Her2 Targeted Therapies



Herceptin

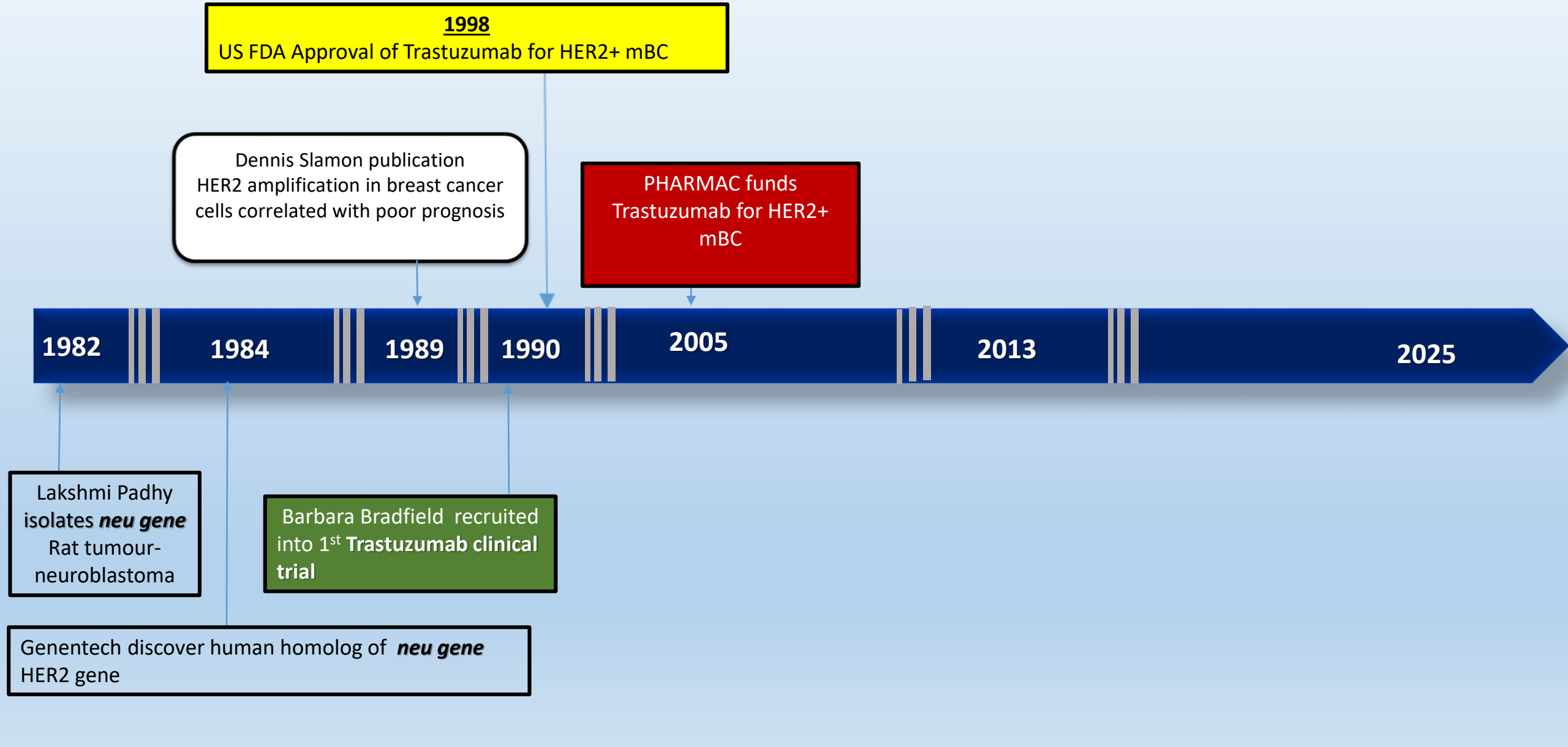
Trastuzumab

Binds Her2 receptor

Blocks growth

Immune attack

A Brief History anti-HER2 therapy (1982-2025)

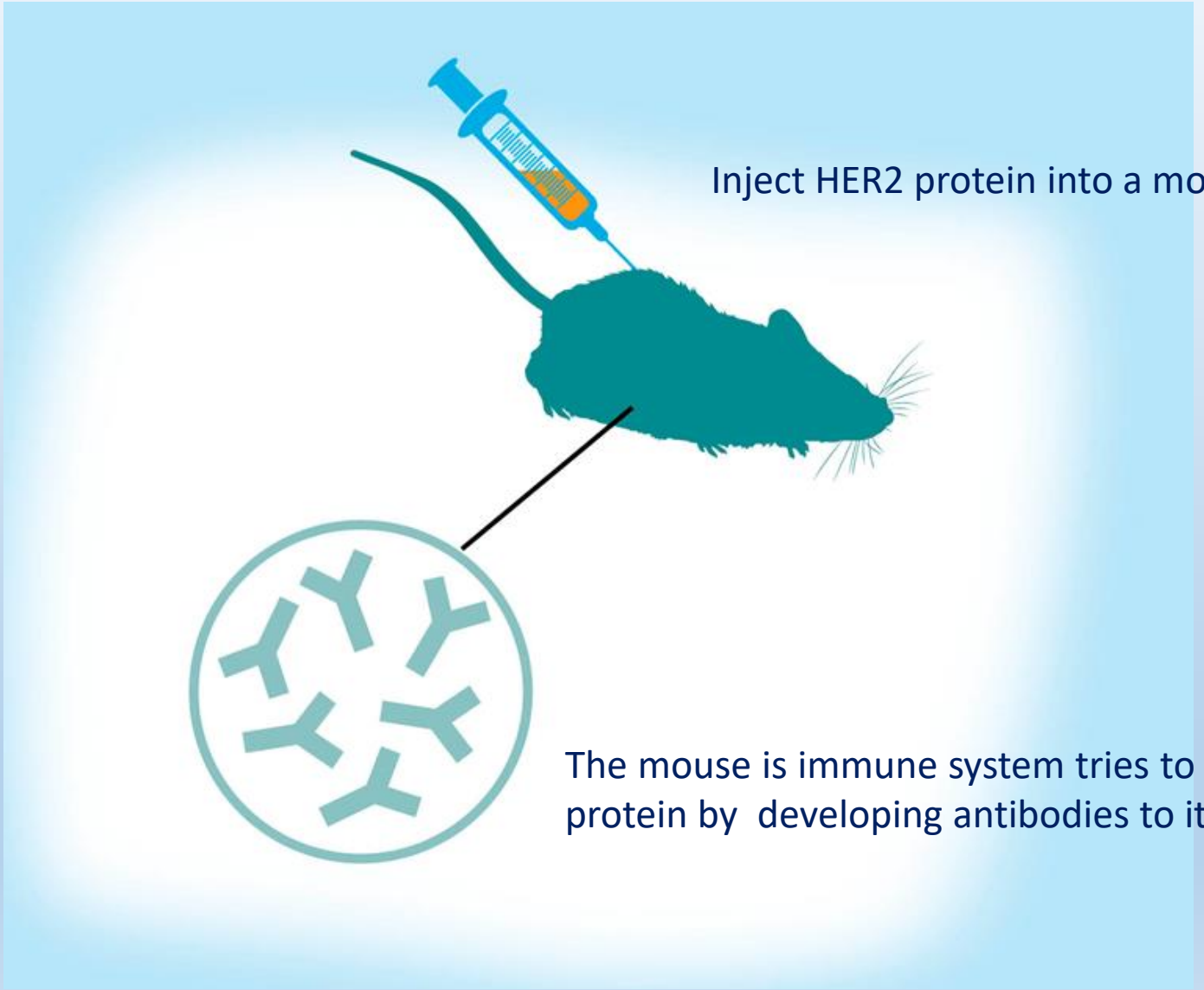


HER2+ breast cancer- a quick re-cap

- Approx. 20% of all Breast cancers are HER-2 positive
- This is manifest as:
  - over-expression of HER2 receptor
  - gene amplification of HER2receptor
- HER2 receptor positivity confers a more aggressive phenotype with poorer prognosis.
- Taxane + Trastuzumab superior to Taxane alone in 1st line treatment of patients with HER-2 positive metastatic breast cancer (The M77001 Study Group, 2005)

HER2 positive Breast Cancer: How to make Trastuzumab

Step 1: Develop the antibody



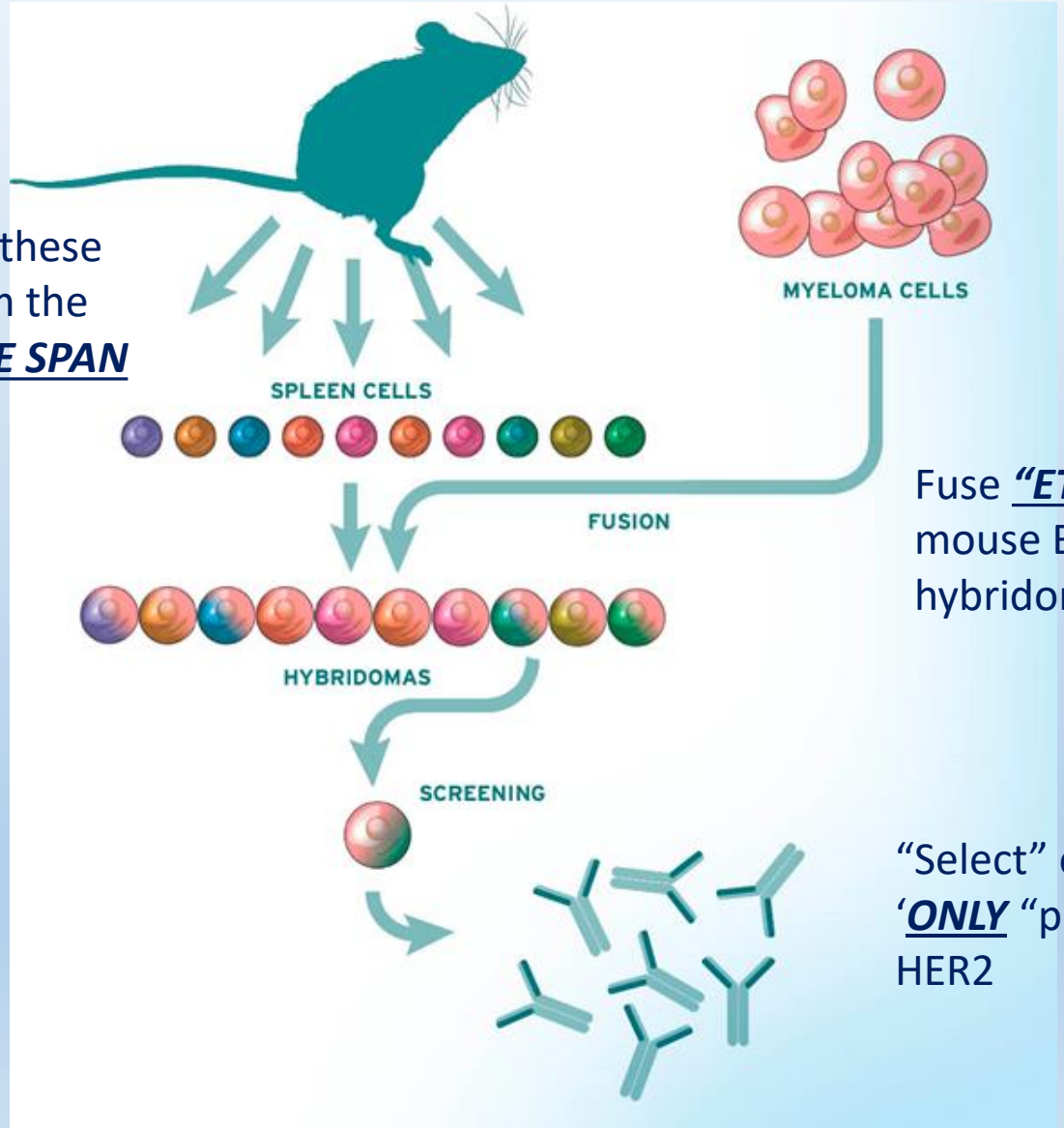
Inject HER2 protein into a mouse

The mouse is immune system tries to get rid of the HER2 protein by developing antibodies to it

Images derived from https://www.understandinganimalresearch.org.uk/human-diseases/cancer/breast-cancer-treatment [Accessed 21 Jul 2025]

Step 2: Select out and mass produce specific antiHER2 antibodies

The B-cells that manufacture these antibodies are extracted from the mouse's spleen- ***LIMITED LIFE SPAN***

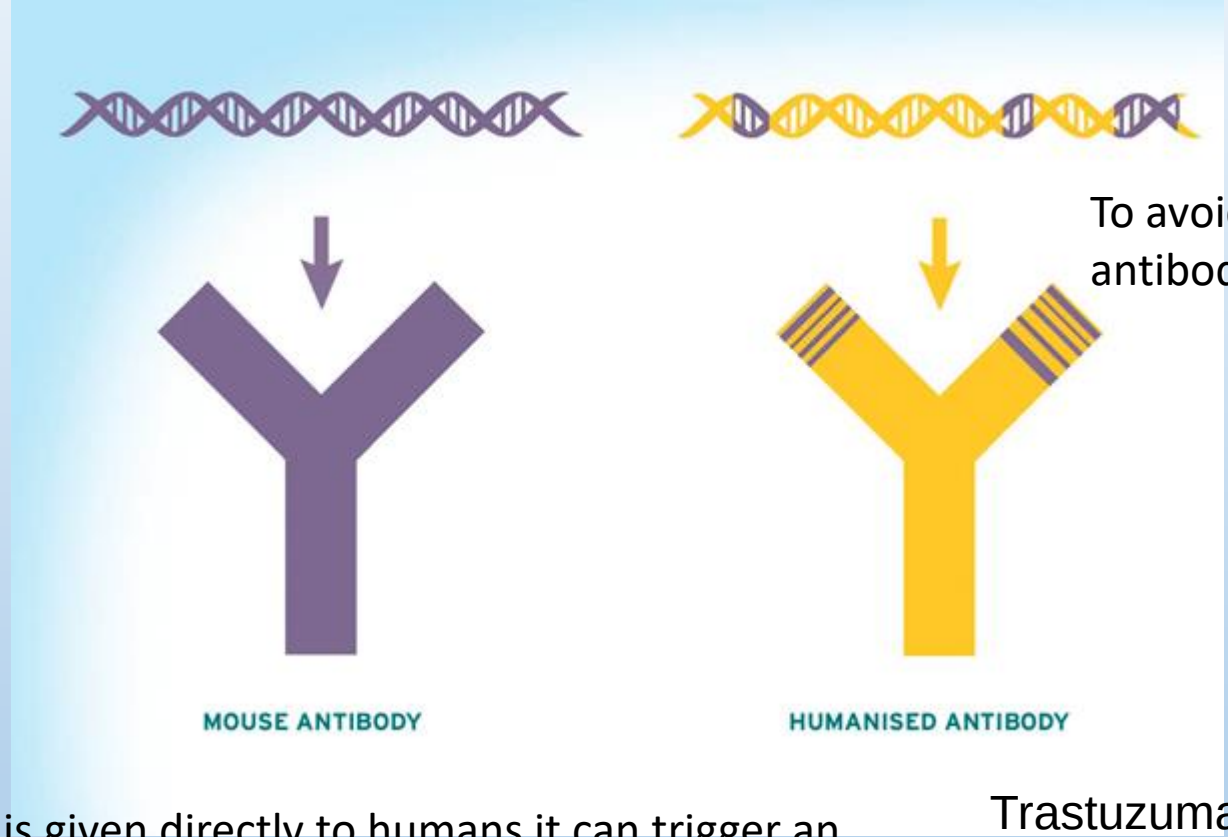


Fuse ***"ETERNAL"*** myeloma cells with mouse B-cells to manufacture hybridomas

"Select" out the hybridoma that '***ONLY*** "produces antibodies specific to HER2

Images derived from https://www.understandinganimalresearch.org.uk/human-diseases/cancer/breast-cancer-treatment [Accessed 21 Jul 2025]

Humanise the anti-HER2 antibody



To avoid this, the genes for producing the Herceptin antibody are altered to make them more human-like

If a mouse antibody is given directly to humans it can trigger an immune reaction.
This is because the human immune system recognises that it is foreign

Trastuzumab DNA is 95% human & 5% mouse.
Hence the immune system is tricked into thinking its human
Meanwhile HER2 targeting section can bind to HER2.

Images derived from https://www.understandinganimalresearch.org.uk/human-diseases/cancer/breast-cancer-treatment [Accessed 21 Jul 2025]

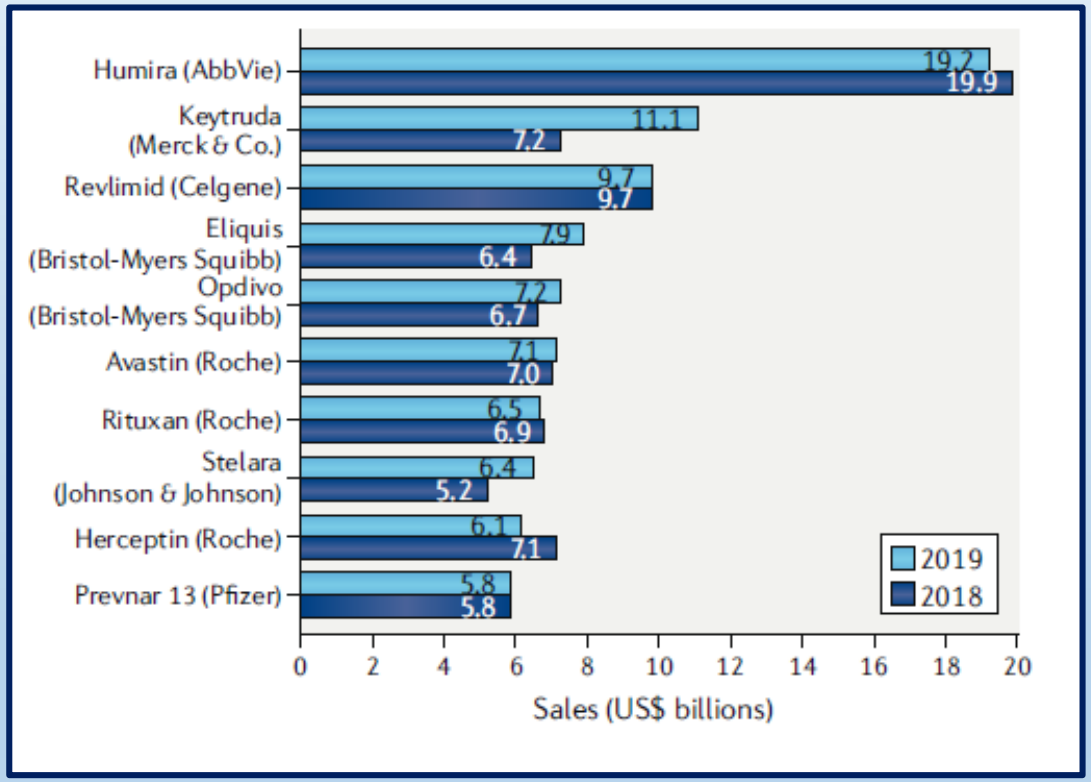
Mass-produce Trastuzumab

- The newly humanised gene for the antibody is then placed inside ovary cells taken from Chinese hamsters
- B-Cells can be grown in unlimited amounts
- Antibodies i.e. Trastuzumab are extracted from them

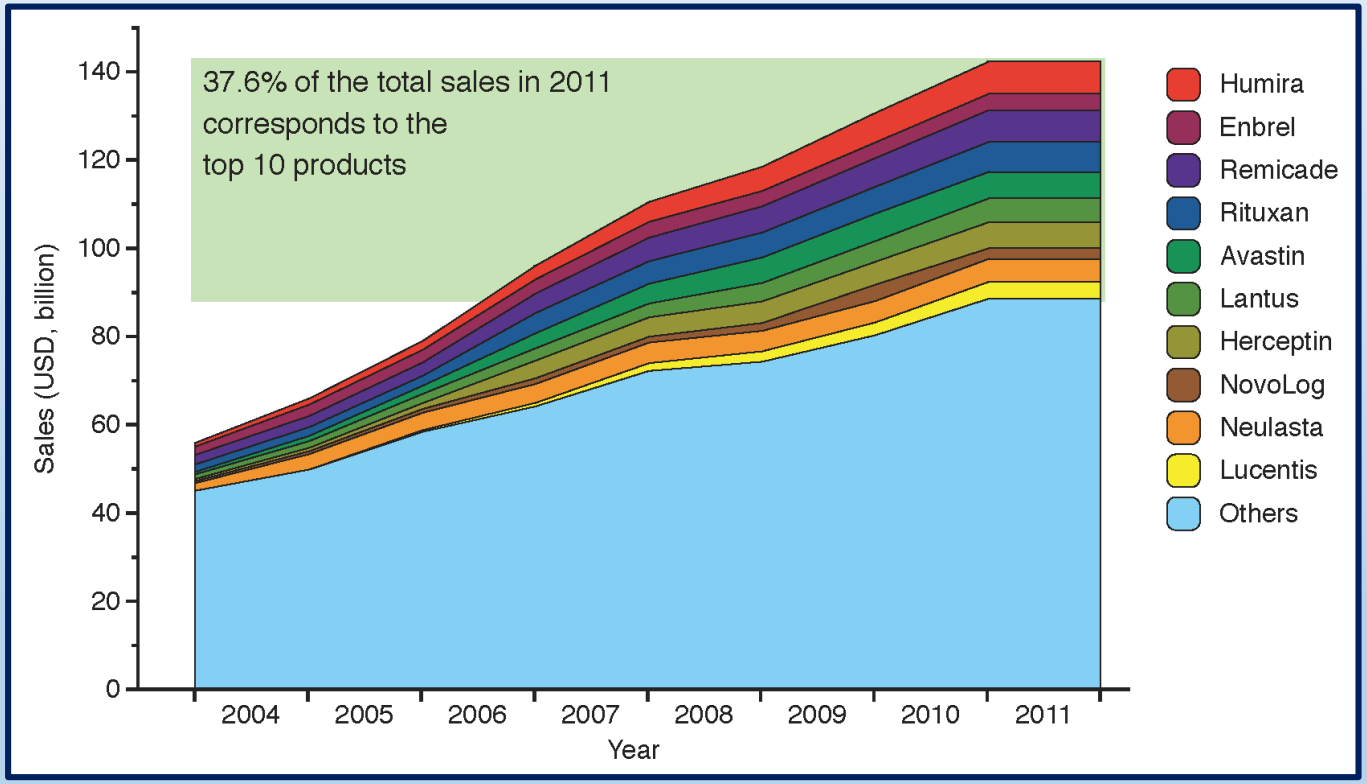
Images derived from https://www.understandinganimalresearch.org.uk/human-diseases/cancer/breast-cancer-treatment [Accessed 21 Jul 2025]

The Trastuzumab Biosimilar Story

Herceptin©: One the Best selling drugs in the 21st Century?

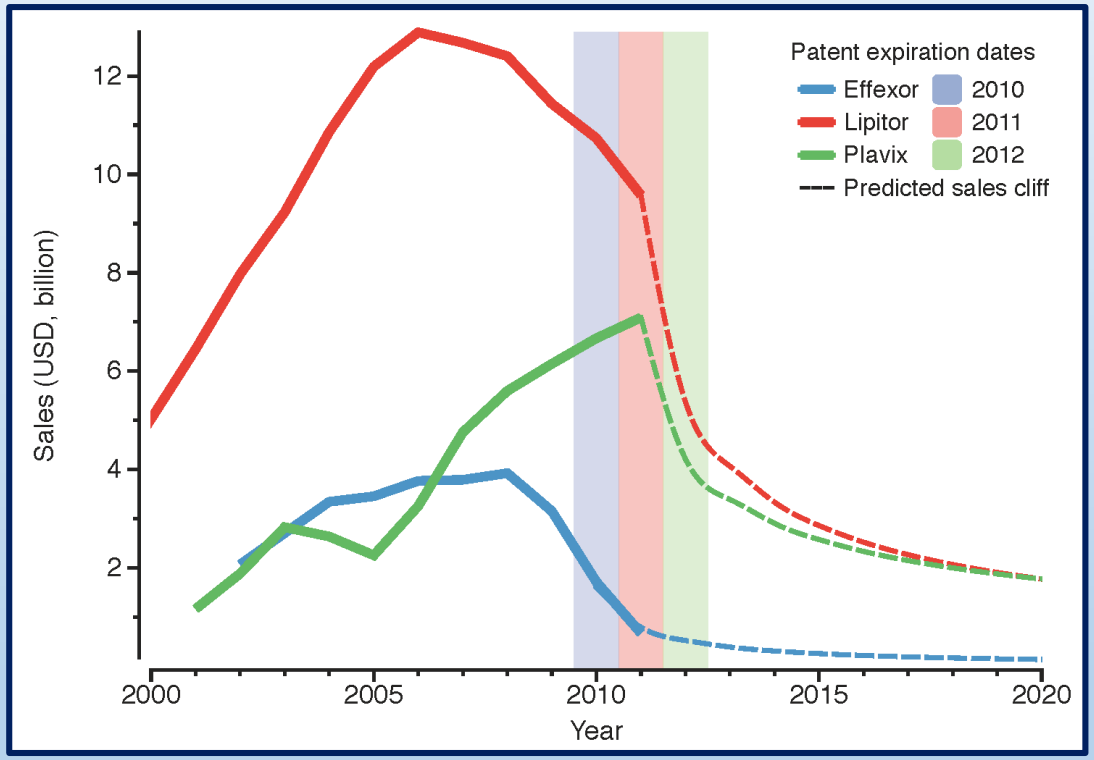


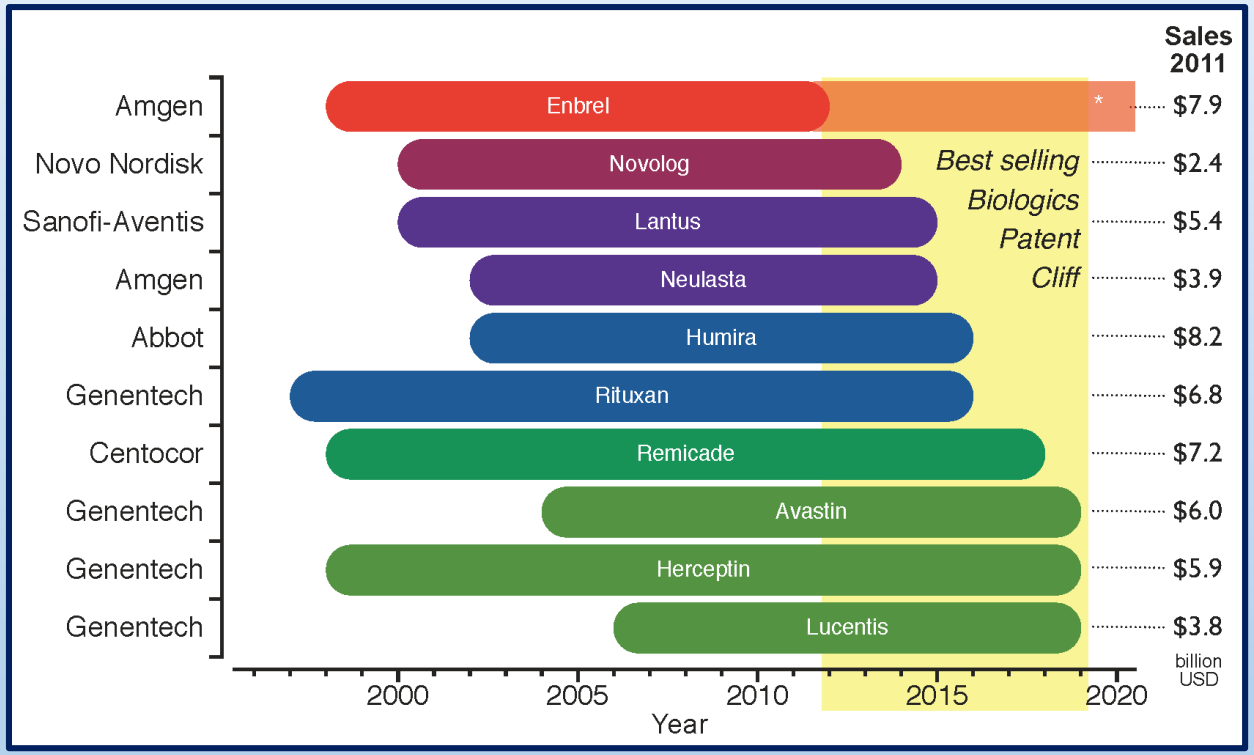
Urquhart L, 2020. Nature Reviews Drug Discovery 19, 228



Calo-Fernández B et al, 2012. Pharmaceuticals (Basel). 12;5(12):1393-408.

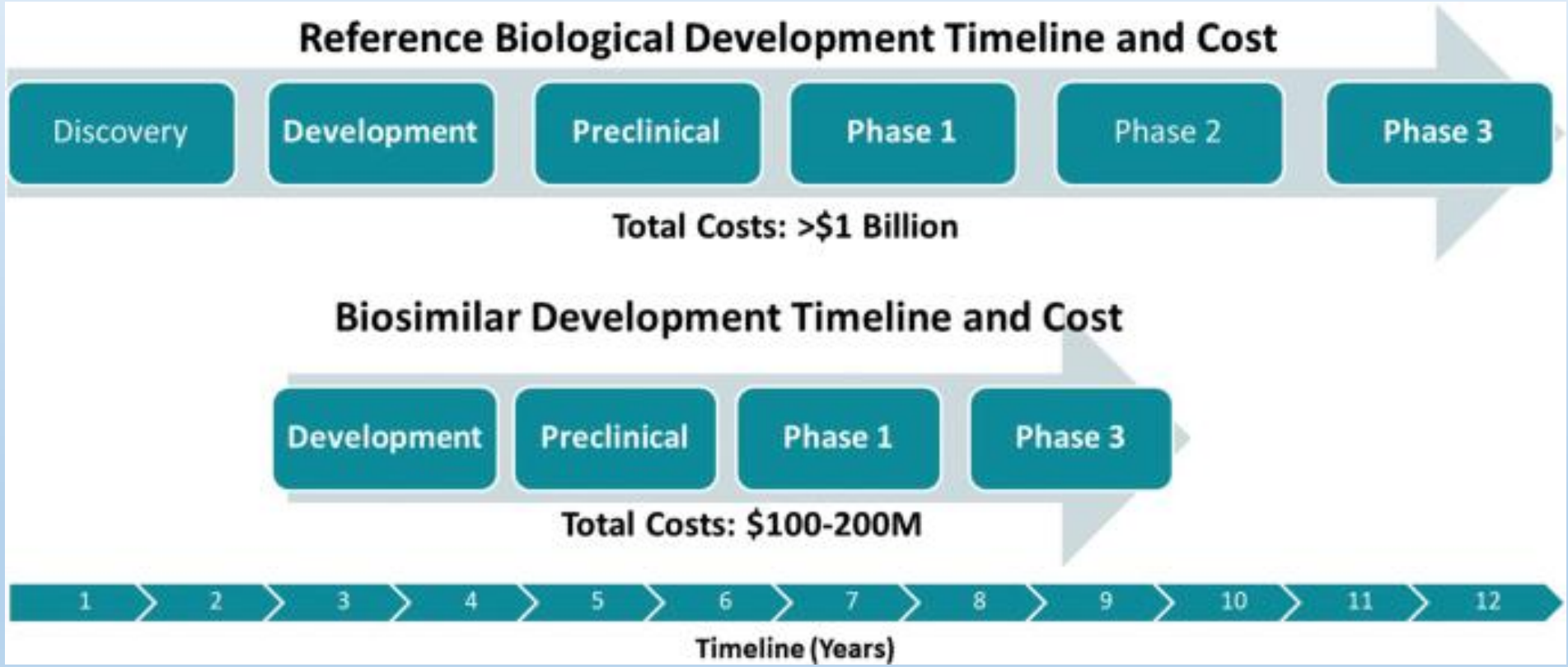
Herceptin©: The Patent Cliff



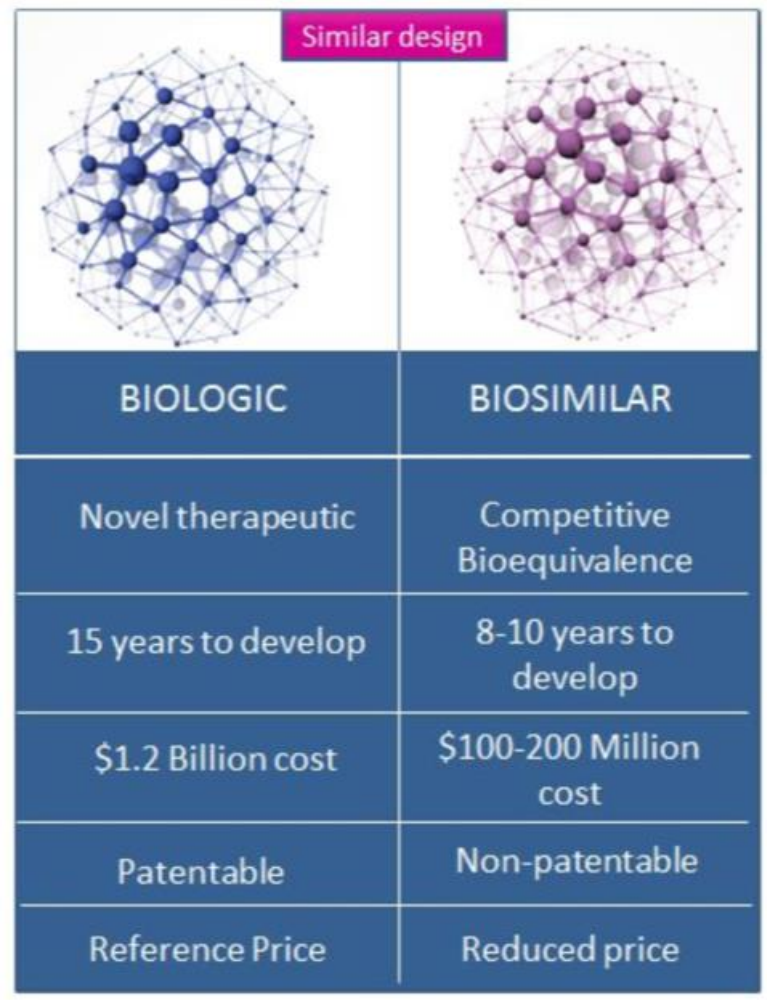


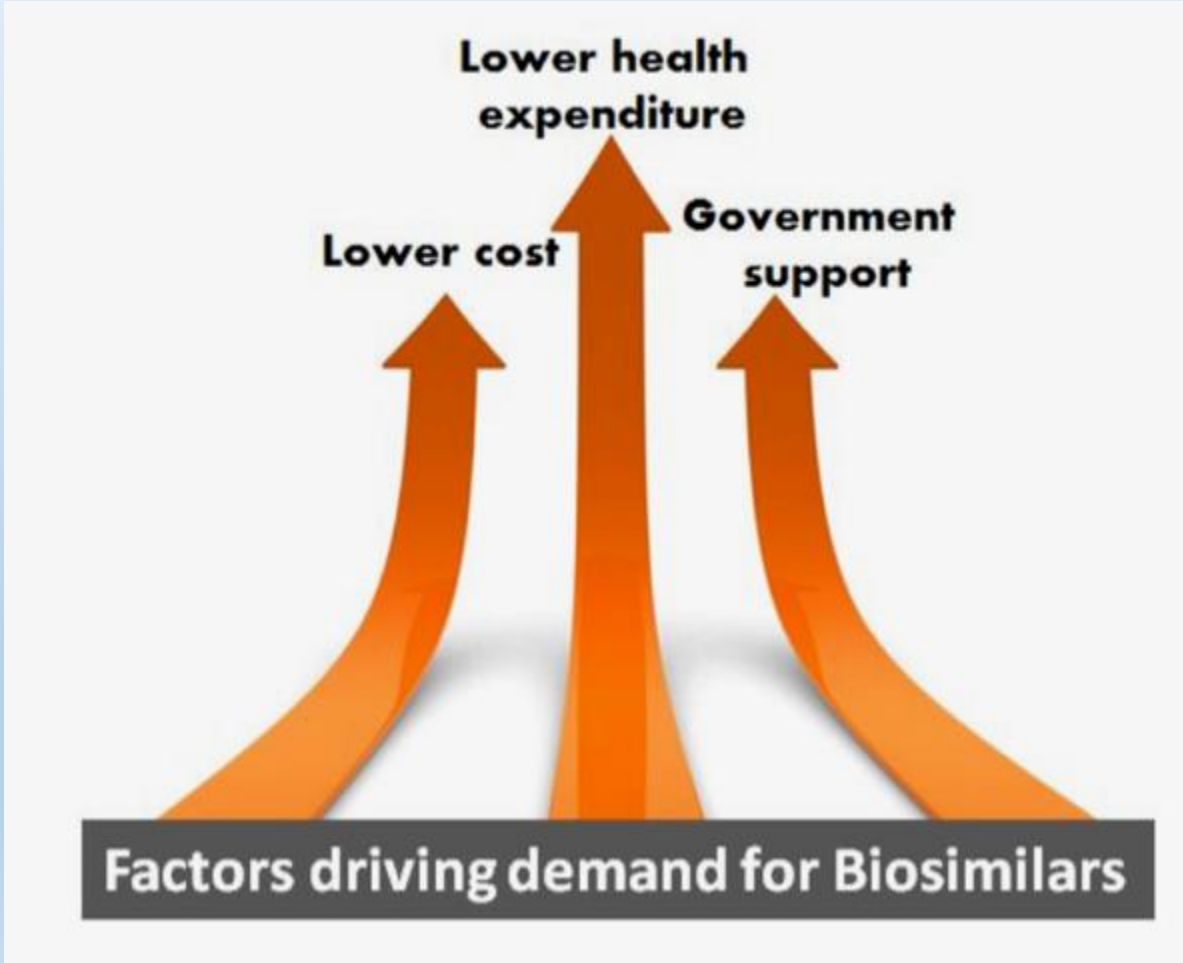
Calo-Fernández B et al, 2012. Pharmaceuticals (Basel). 12;5(12):1393-408.

The Development of “me-too” Trastuzumabs



Herceptin© vs Trastuzumab Biosimilar: What's the difference?





Choosing Between Biosimilars: Can the real Trastuzumab please stand up!

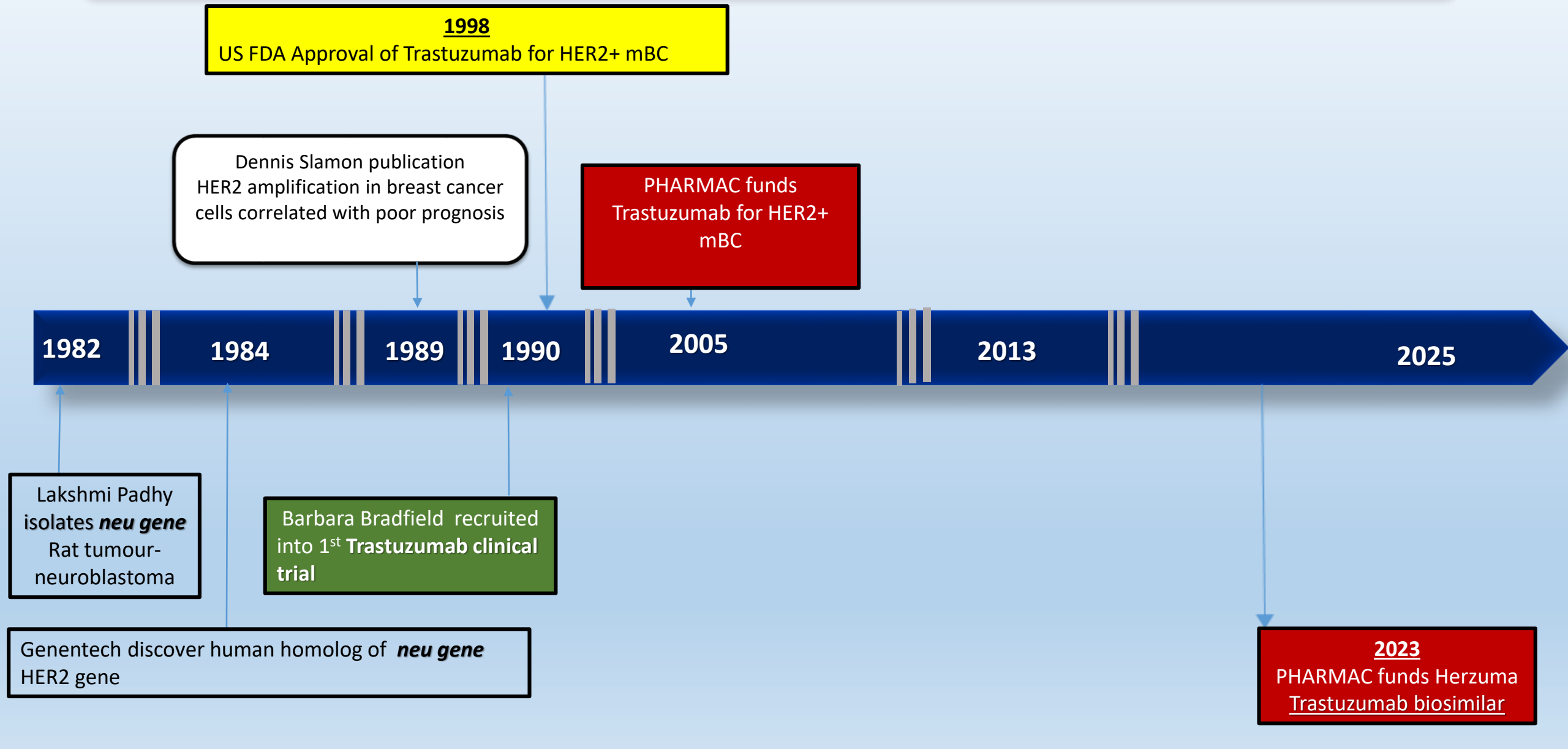
Comparison of the five approved trastuzumab biosimilars.

Agent	Brand name	Approval	Indication	Trial population	Trial results
MYL-1401O	Ogivri	December 2017	Adjuvant early stage and metastatic breast cancer, metastatic gastric or GEJ adenocarcinoma	Metastatic breast cancer (*n* = 500)	MYL-1410 *versus* trastuzumab: Noninferior ORR: 69.6% *versus* 64% (HR 1.09; CI 95% 0.95–1.24)[12,13]
CT-P6	Herzuma	December 2018	Adjuvant early stage and metastatic breast cancer	Early stage breast cancer (*n* = 549)	CT-P6 *versus* trastuzumab: noninferior pCR 46.8% *versus* 50.4% (risk ratio 0.92)[17,18]
SB3	Ontruzant	January 2019	Adjuvant early stage and metastatic breast cancer, metastatic gastric or GEJ adenocarcinoma	Early stage breast cancer (n = 800)	SB3 *versus* trastuzumab: Equivalent in breast pCR 51.7% *versus* 42.0% (adjusted ratio 1.259)[20]
PF-05280014	Trazimera	March 2019	Adjuvant early stage and metastatic breast cancer, metastatic gastric or GEJ adenocarcinoma	Metastatic breast cancer (*n* = 707)	PF-05280014 *versus* trastuzumab: Equivalent in breast ORR 62.5% *versus* 66.5% (RR for ORR 0.94)[24]
ABP980	Kanjinti	June 2019	Adjuvant early stage and metastatic breast cancer, metastatic gastric or GEJ adenocarcinoma	Early stage breast cancer (*n* = 725)	ABP980 *versus* trastuzumab: pCR 48% *versus* 41% (risk ratio 1.188)[28]

GEJ, gastroesophageal junction; HR, hazard ratio; ORR, Overall Response Rate; pCR, pathological complete response; RR, risk ratio.

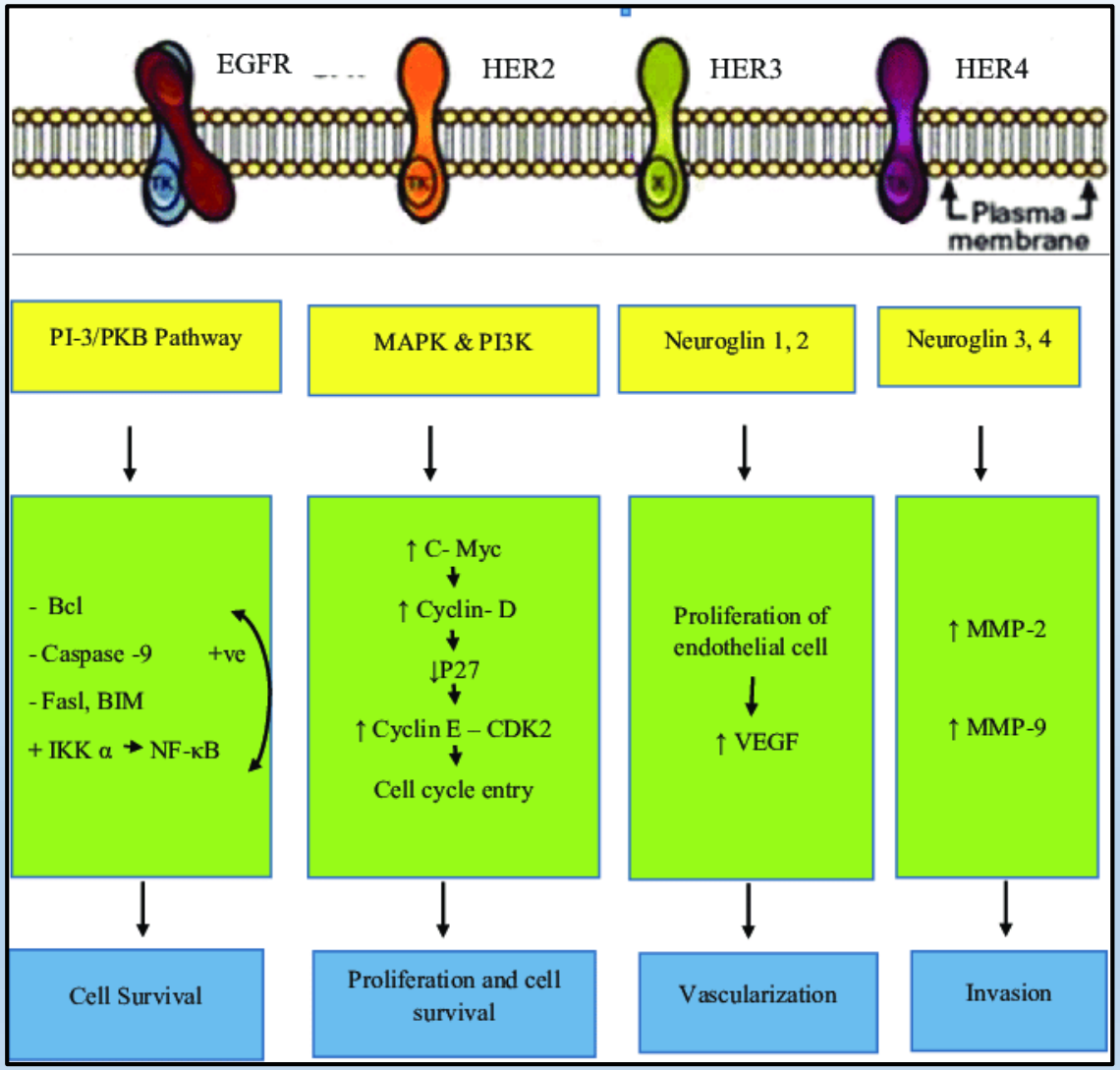
Miller EM & Schwartsberg, 2019. Ther Adv Med Oncol

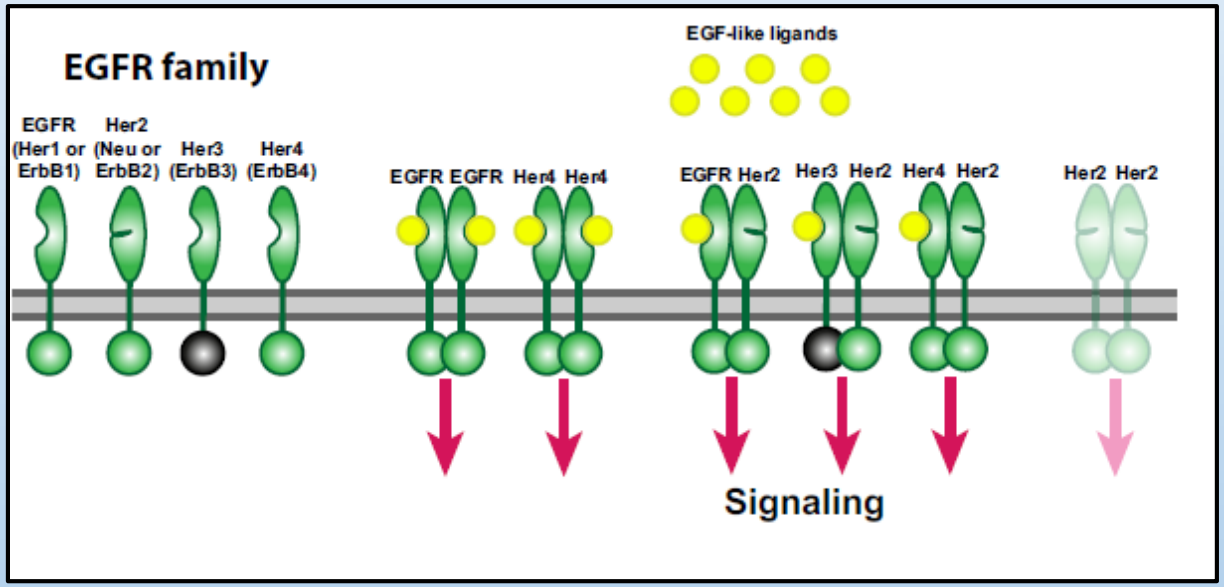
A Brief History anti-HER2 therapy (1982-2025)



The Pertuzumab Story

The EGFR/HER Family

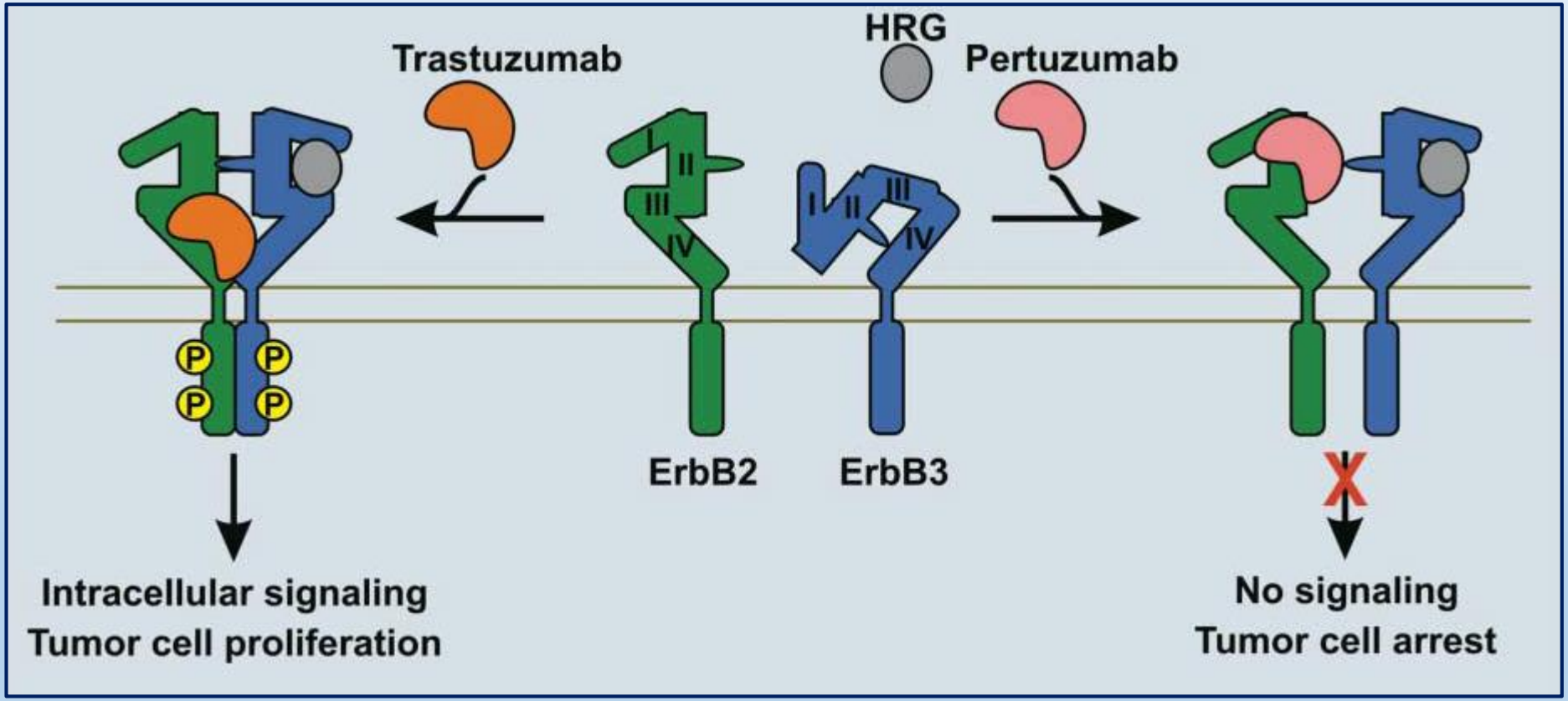




Mirza s , Dr & Irum Hd. (2016). PJMD 43.

Arkhipov et al, 2013. eLife 2:e00708; p1-14

How Pertuzumab overcomes Trastuzumab Resistance by Tumour



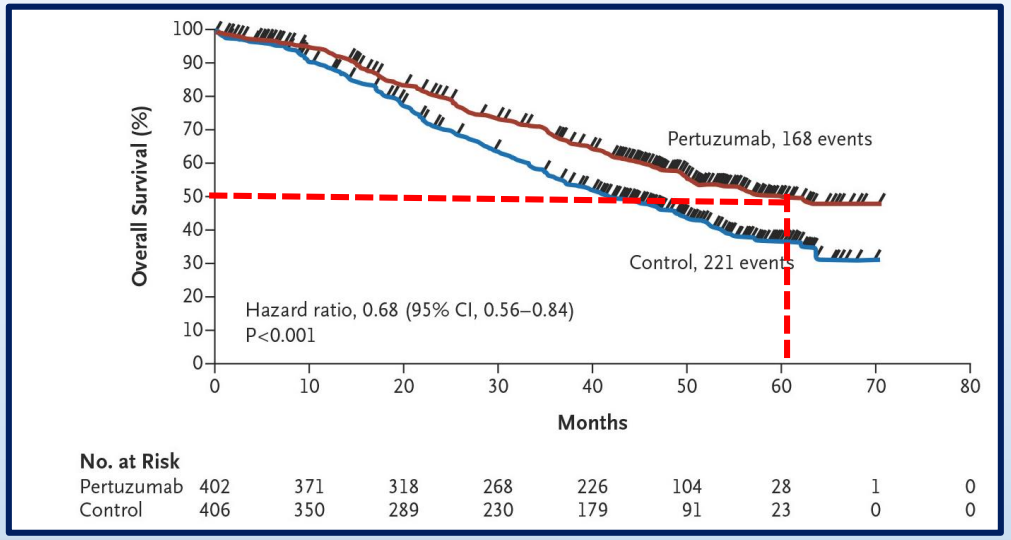
Hynes & Badache, 2004. Cancer Cell, Vol. 5 p299-300

Trastuzumab + Pertuzumab - Practice Changing

ORIGINAL ARTICLE

Pertuzumab, Trastuzumab, and Docetaxel in HER2-Positive Metastatic Breast Cancer

Sandra M. Swain, M.D., José Baselga, M.D., Sung-Bae Kim, M.D., Jungsil Ro, M.D., Vladimir Semiglazov, M.D., Mario Campone, M.D., Eva Ciruelos, M.D., Jean-Marc Ferrero, M.D., Andreas Schneeweiss, M.D., Sarah Heeson, B.Sc., Emma Clark, M.Sc., Graham Ross, F.F.P.M., Mark C. Benyunes, M.D., and Javier Cortés, M.D., for the CLEOPATRA Study Group*

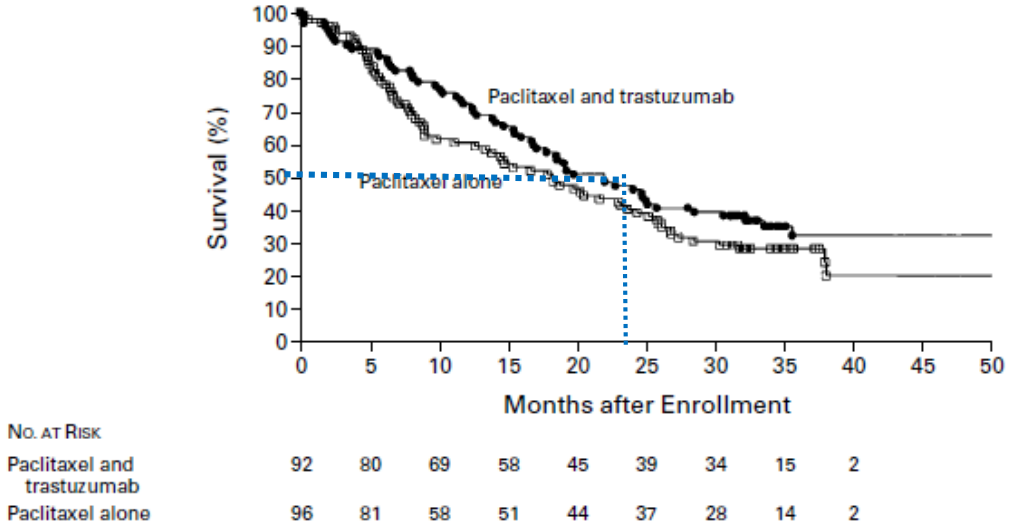


The New England Journal of Medicine

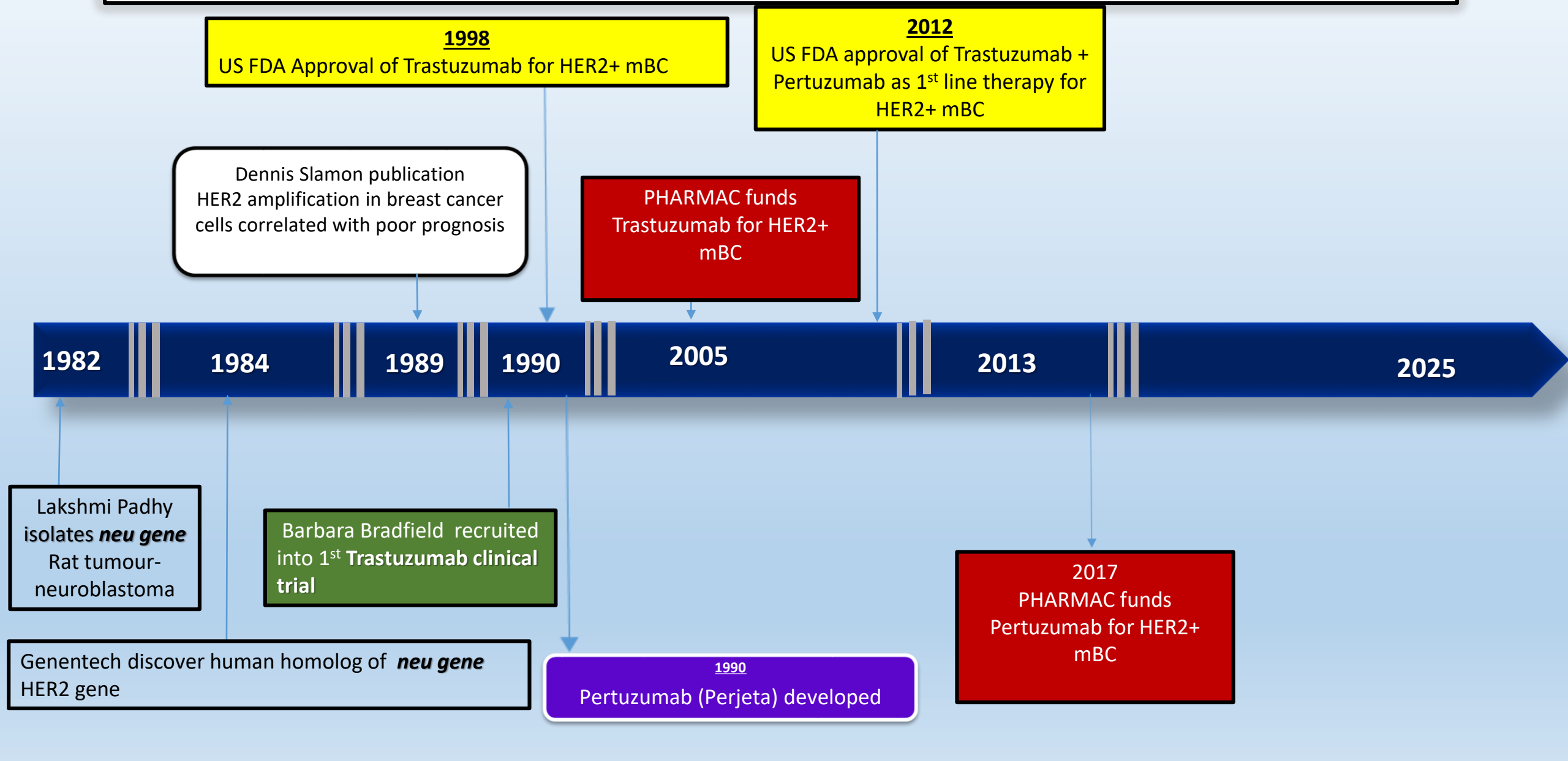
VOLUME 344 MARCH 15, 2001 NUMBER 11

USE OF CHEMOTHERAPY PLUS A MONOCLONAL ANTIBODY AGAINST HER2 FOR METASTATIC BREAST CANCER THAT OVEREXPRESSES HER2

DENNIS J. SLAMON, M.D., PH.D., BRIAN LEYLAND-JONES, M.D., STEVEN SHAK, M.D., HANK FUCHS, M.D., VIRGINIA PATON, PHARM.D., ALEX BAJAMONDE, PH.D., THOMAS FLEMING, PH.D., WOLFGANG EIERMANN, M.D., JANET WOLTER, M.D., MARK PEGRAM, M.D., JOSE BASELGA, M.D., AND LARRY NORTON, M.D.*

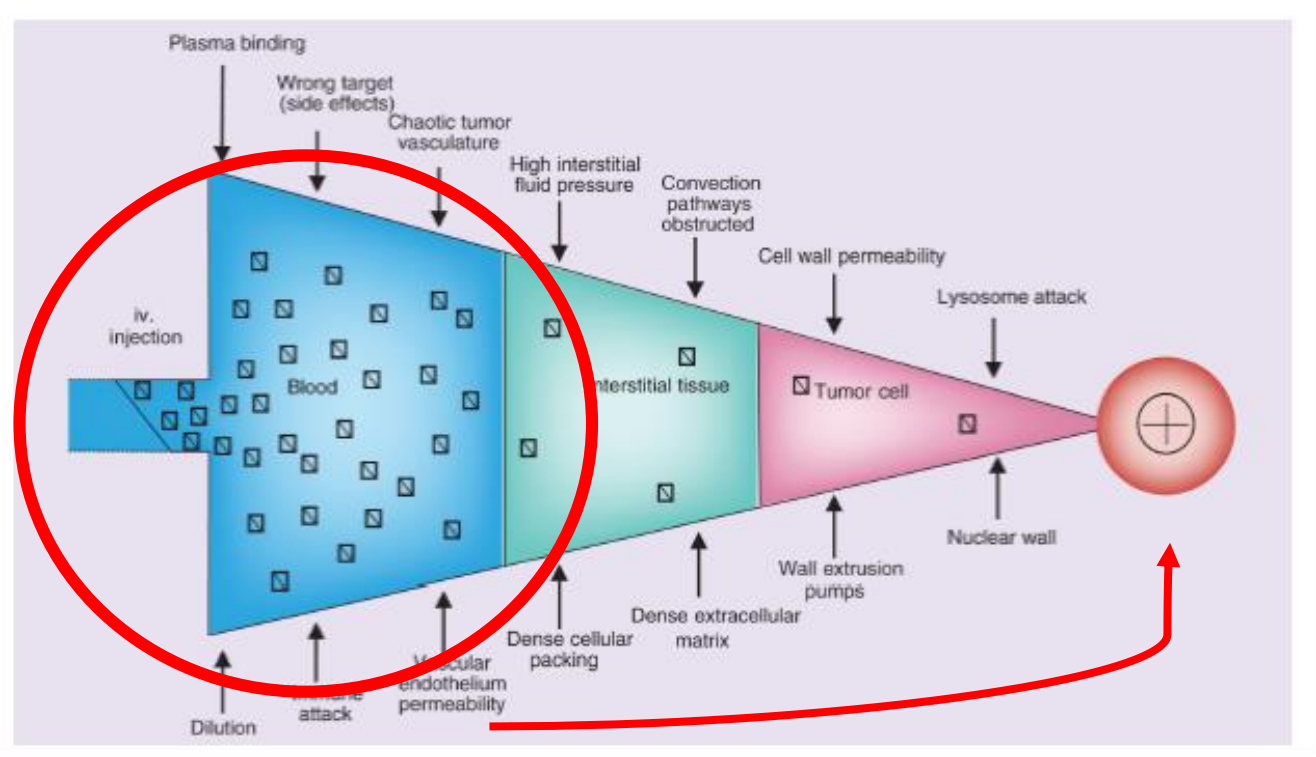


A Brief History anti-HER2 therapy (1982-2025)



The Trastuzumab Emtansine Story (T-DM1/Kadcyla)

The problem with chemotherapy



- Narrow Therapeutic Index
- Wrong target
- Immediate And Intermediate dose limiting toxicities
- Low specificity
- Development of resistance

Selectively deliver potent chemotherapy drugs directly to cancer cells while minimizing damage to healthy tissues

Lane et al, 2018. Future Oncol 14(7). 647-663

The premise for new class of drug: The Magic Bullet

1890's:	Behring hypothesizes conceptualises **"antibodies"** – a chemical produced by your body to fight toxins produces by bacteria
1901:	Receives Nobel prize for characterising diphtheria antibodies produced by body to fight diphtheria toxins
1907:	Nobel Prize laureate Paul Ehrlich hypothesises that antibodies bind antigens through special chemical structures that he called "side chains" (which he later named **"receptors"**). Theorizes that one can attach a 'poison" to this side chain and attempt to deliver the poison to the bacteria- coins the term "Zauberkugel"- **"magic bullet"/ "chemotherapy"** Becomes the laughing stock of the medical fraternity- "Dr Phantasus"

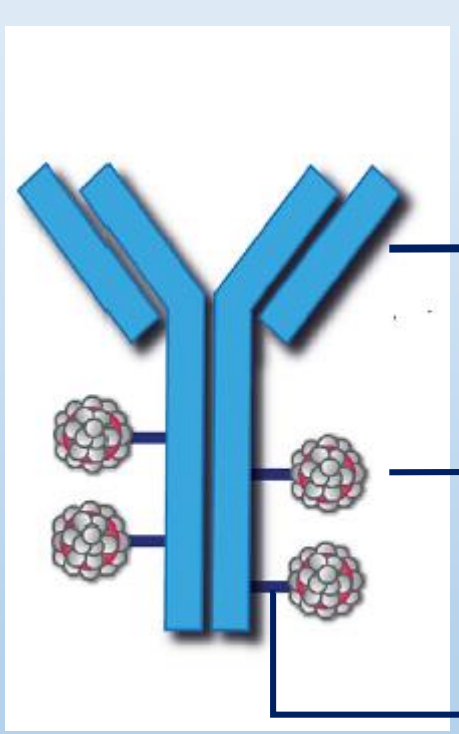
“It always seems impossible, until it is done.”

-Tata Madiba

"You see things; you say, 'Why?' But I dream things that never were; and I say, 'Why not?“”

- George Bernard Shaw

The Anatomy of an Antibody Drug Conjugate



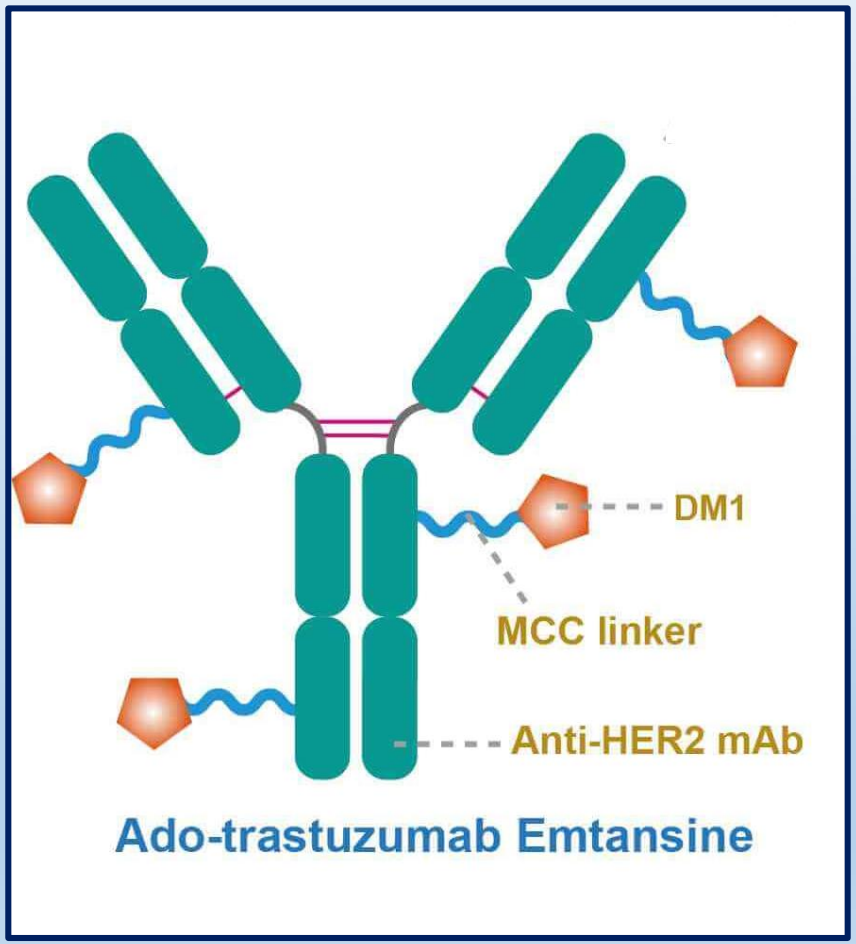
An antibody targeting a specific receptor

The chemotherapy moiety

A linker to attach the chemotherapy payload

Riccardi et al, 2023. Front Pharmacol. 14:1274088.

Trastuzumab emtansine (T-DM1): Structure

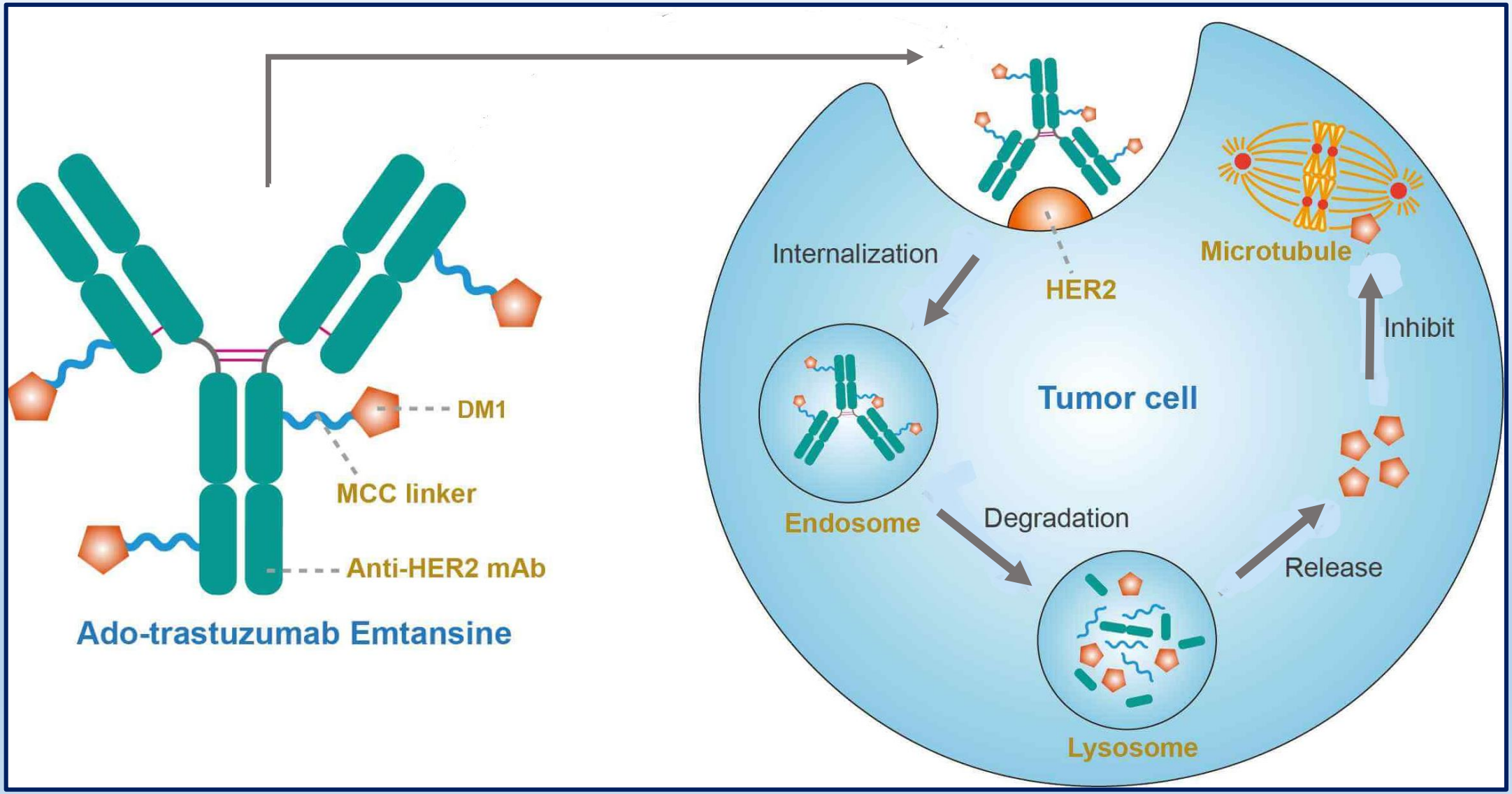


Comprised of:

- An antibody against the HER2 receptor- Trastuzumab
- A potent chemotherapy- tubulin based inhibitor- maytansine
  Derivative of maytansine 1- DM1
- A stable linker that does not contain a cleavage element

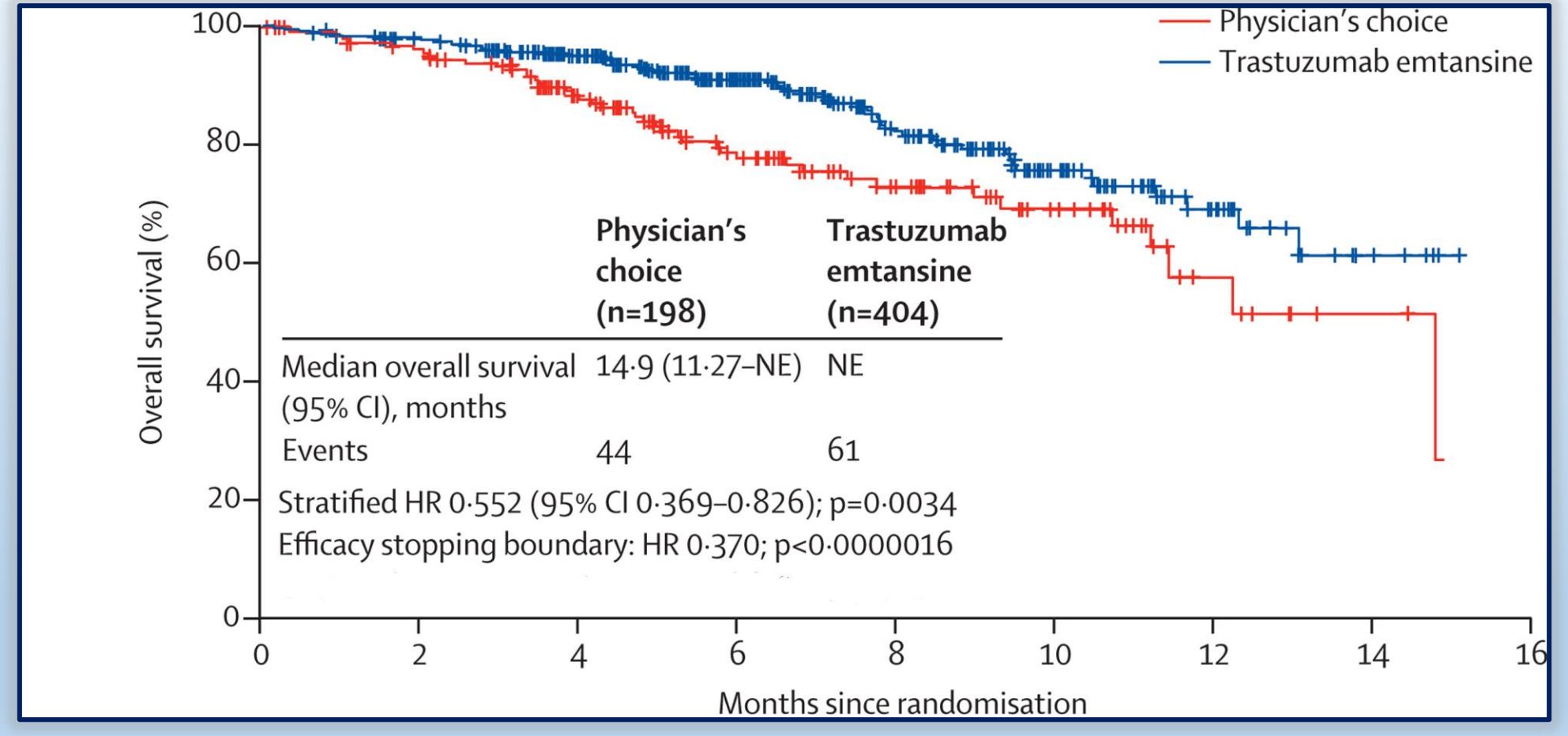
Riccardi et al, 2023. Front Pharmacol. 14:1274088.

Trastuzumab emtansine: How it works



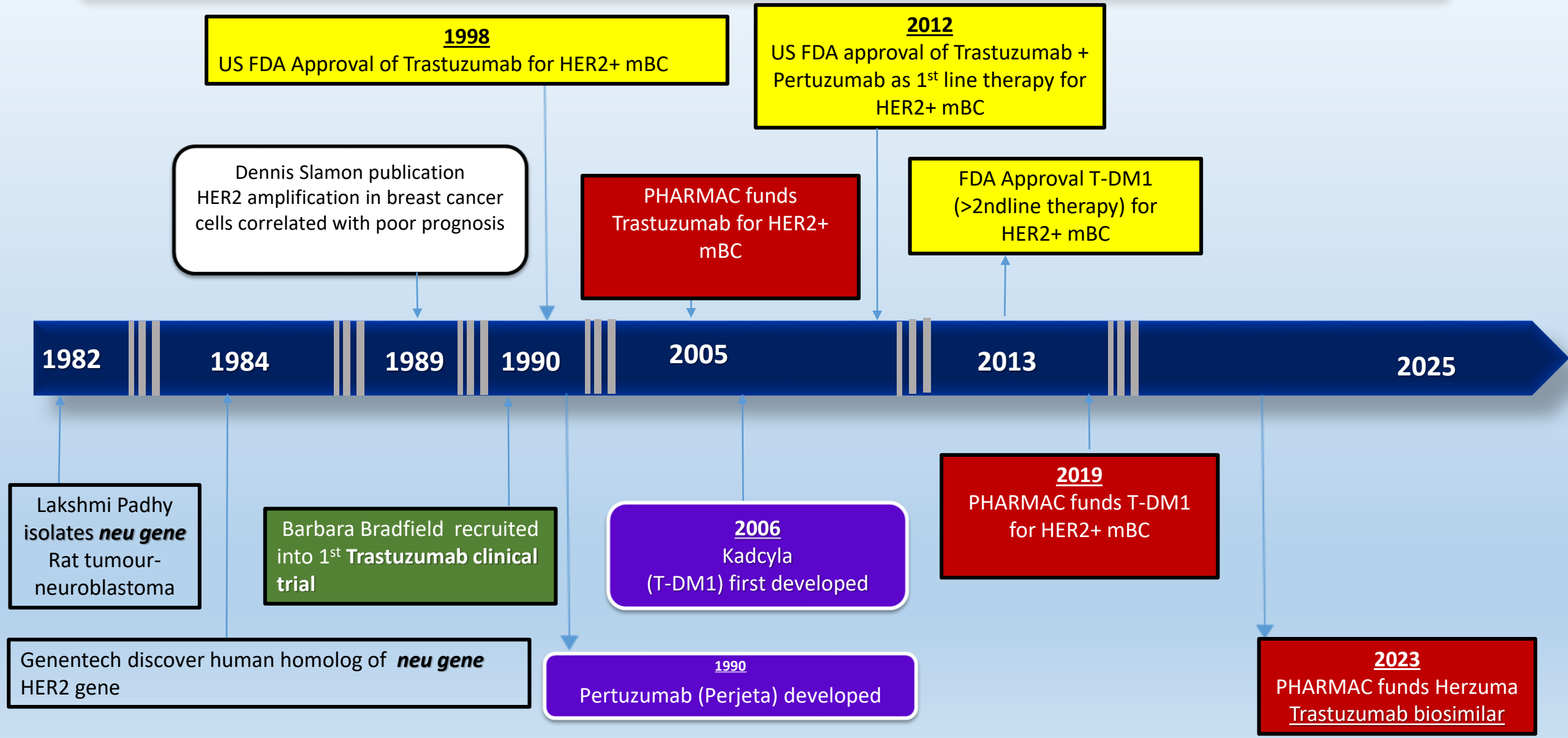
Riccardi et al, 2023. Front Pharmacol. 14:1274088.

Trastuzumab Emtansine- Practice Changing



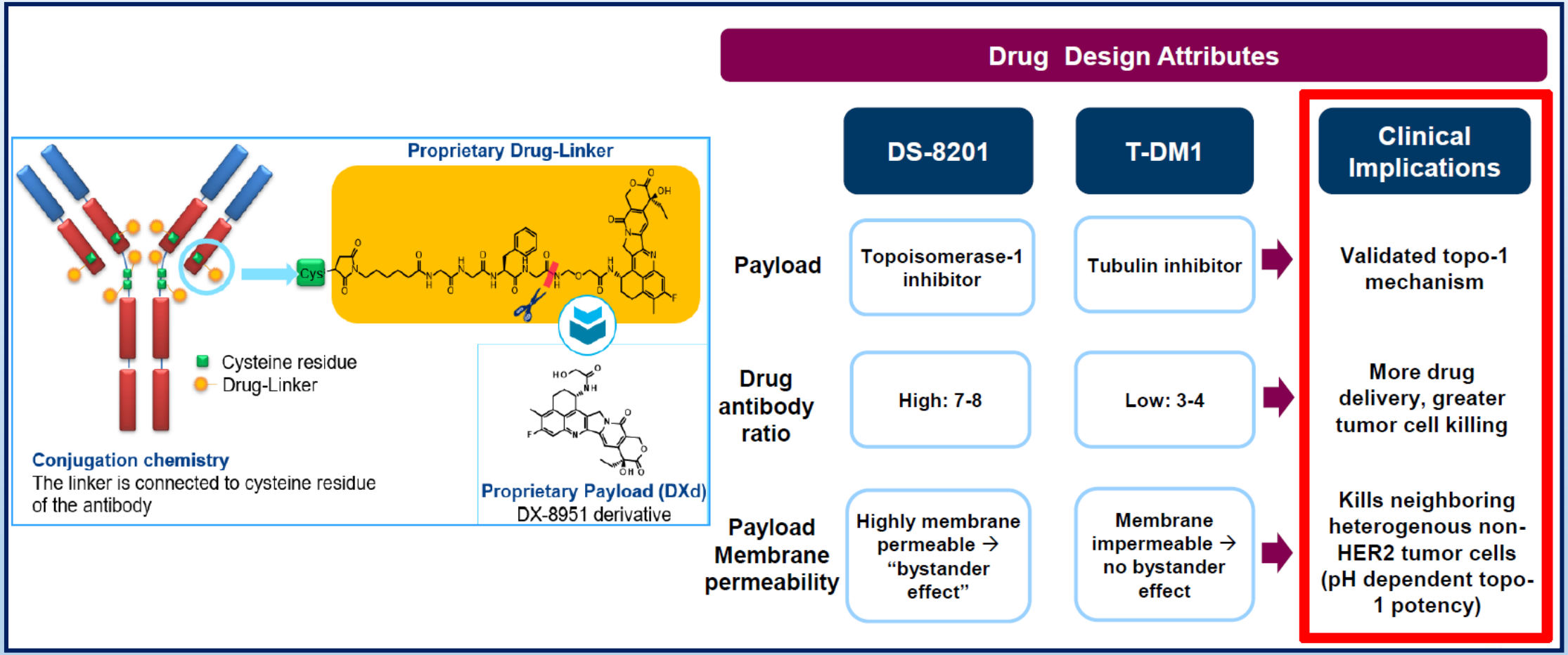
Krop IE et al, 2017. Lancet Oncol. 18(6):743-754.

A Brief History anti-HER2 therapy (1982-2025)



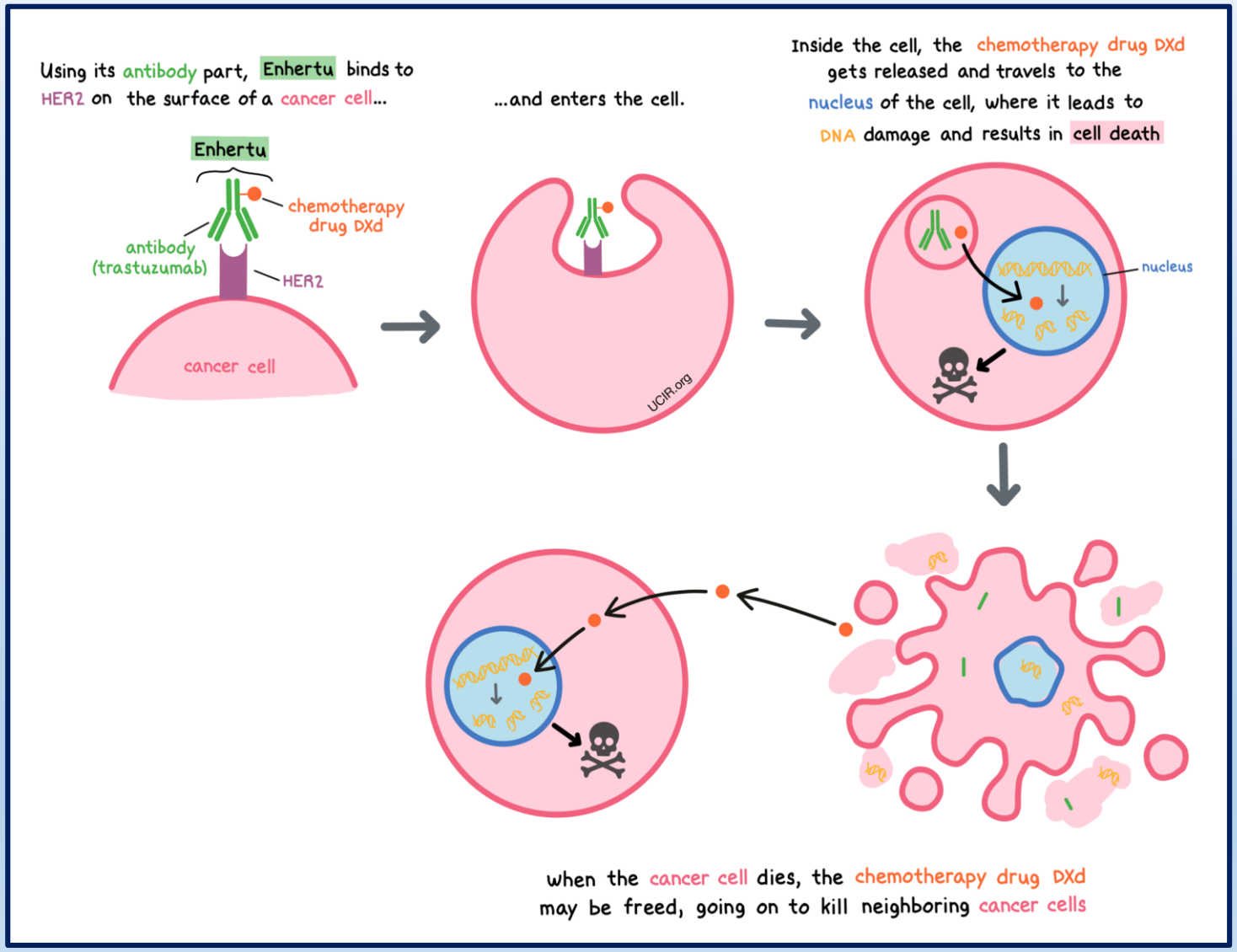
The Trastuzumab Deruxtecan Story (Enhertu)

Why Trastuzumab Deruxtecan is the Business

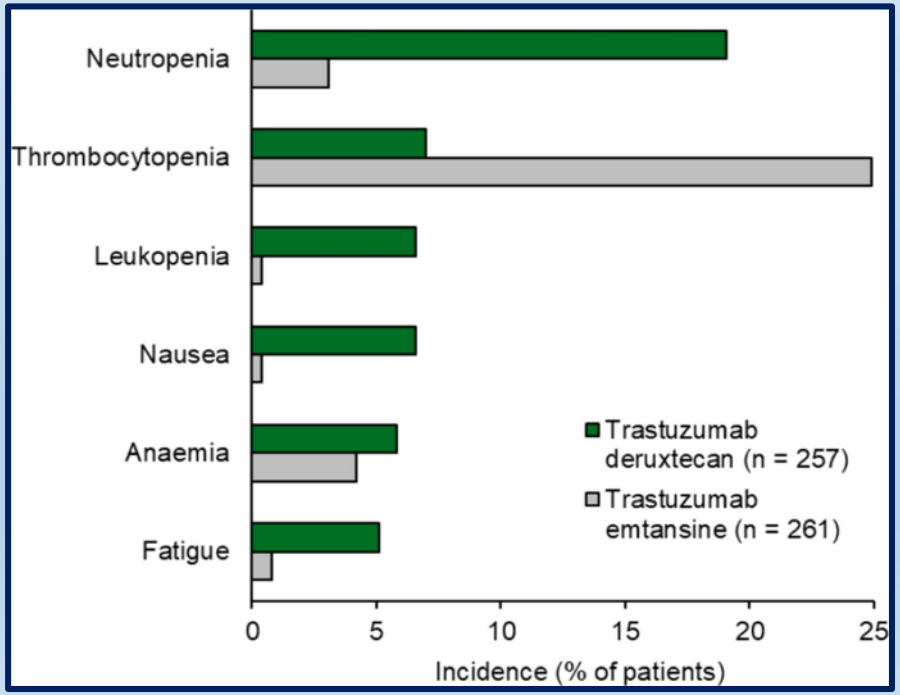


https://www.astrazeneca.com/content/dam/az/PDF/2019/Strategic%20Collaboration%20Trastuzumab%20Deruxtecan%20DS-8201.pdf

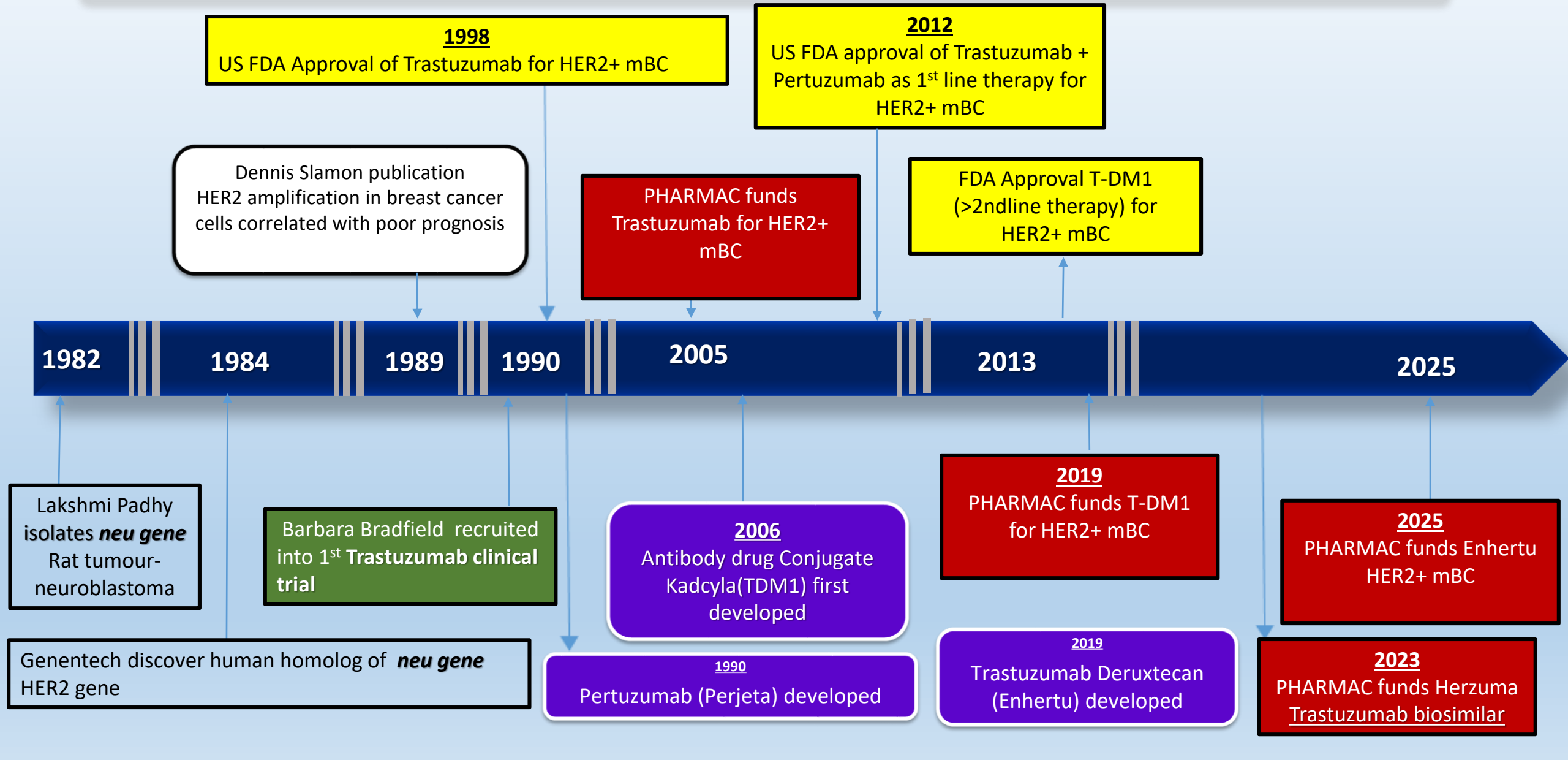
Trastuzumab Deruxtecan (Enhertu)



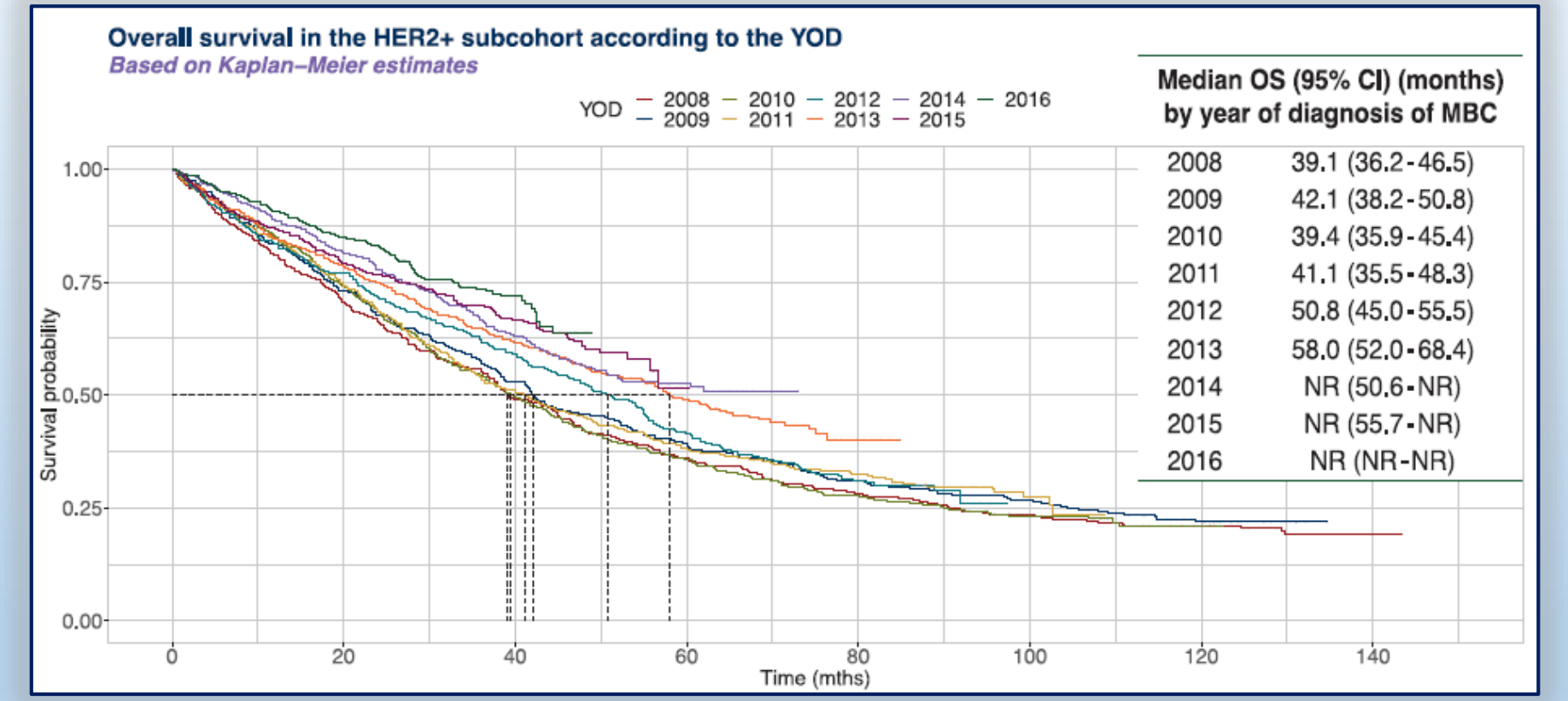
Trastuzumab Deruxtecan	Trastuzumab Emtansine
The disease did not get worse for at least 18 months	The disease did not get worse for a median of 7 months
83% of patients had a response - 16% had their cancer completely disappear - 67% had shrinkage of their cancer	36% of patients had a response - 8% had their cancer completely disappear - 28% had shrinkage of their cancer

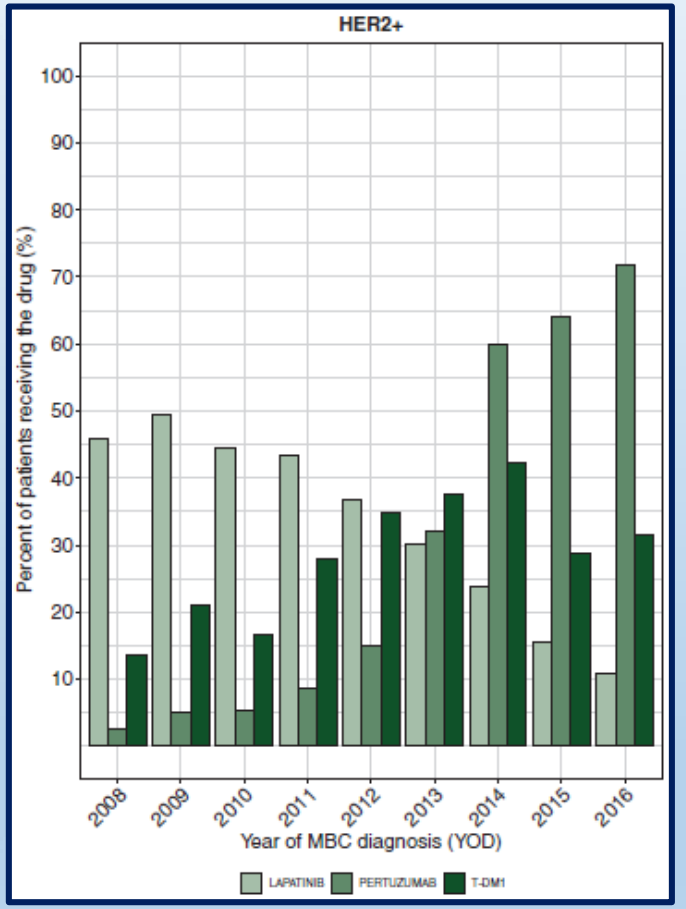


A Brief History anti-HER2 therapy (1982-2025)



Anti-HER2 therapy and Survival: Getting better by the decade?





Grinda et al, 2021. ESMO Open 6(3):100114.

A Brief History anti-HER2 therapy (1982-2025)

1998
US FDA Approval of Trastuzumab for HER2+ mBC

2012
US FDA approval of Trastuzumab + Pertuzumab as 1st line therapy for HER2+ mBC

Dennis Slamon publication HER2 amplification in breast cancer cells correlated with poor prognosis

PHARMAC funds Trastuzumab for HER2+ mBC

FDA Approval T-DM1 (>2ndline therapy) for HER2+ mBC

Barbara Bradfield still alive and cancer free!

1982 | 1984 | 1989 | 1990 | 2005 | 2013 | 2025

Lakshmi Padhy isolates ***neu gene*** Rat tumour-neuroblastoma

Barbara Bradfield recruited into 1st **Trastuzumab clinical trial**

2006
Antibody drug Conjugate Kadcyla(TDM1) first developed

2019
PHARMAC funds T-DM1 for HER2+ mBC

2025
PHARMAC funds Enhertu HER2+ mBC

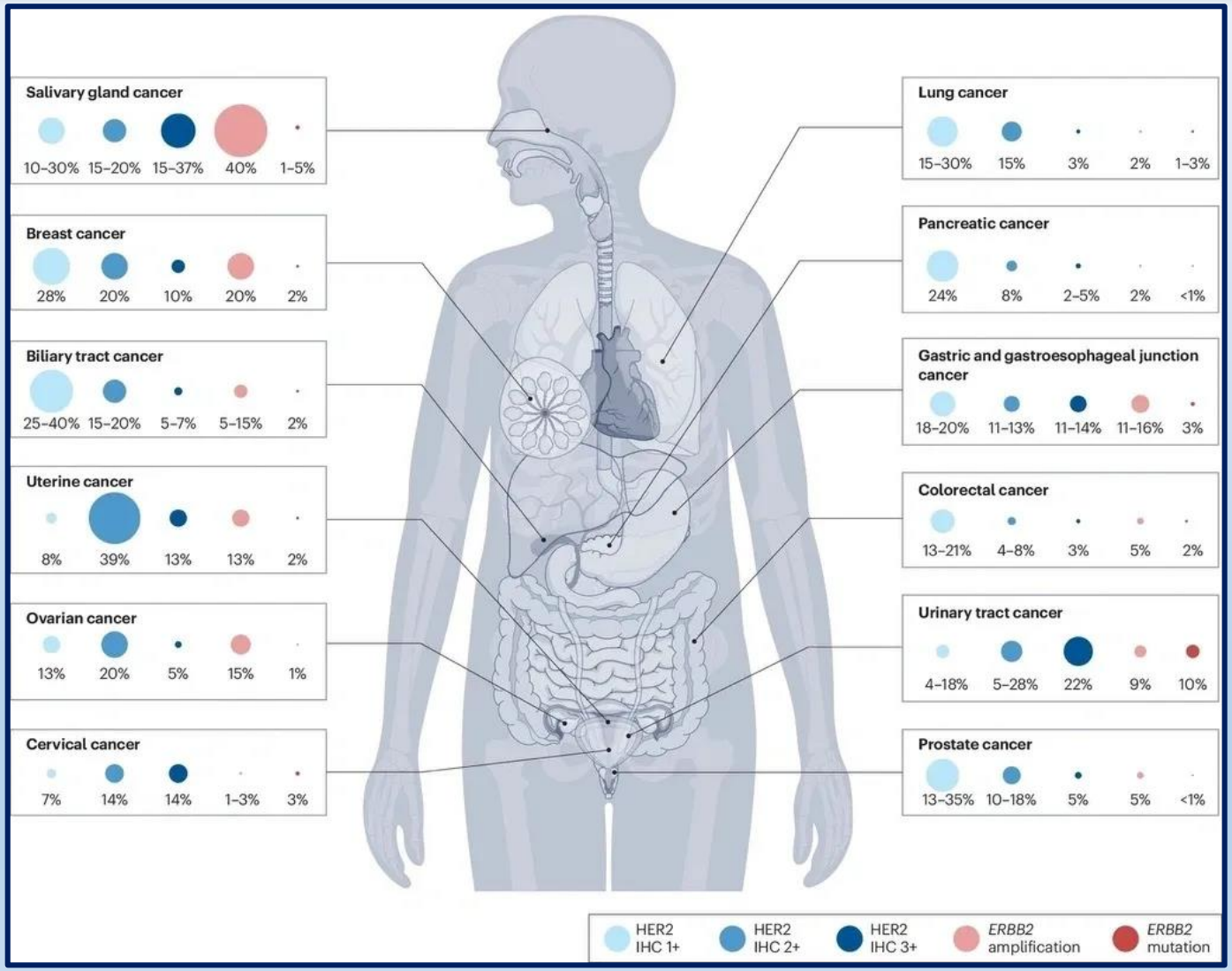
Genentech discover human homolog of ***neu gene*** HER2 gene

1990
Pertuzumab (Perjeta) developed

2019
Trastuzumab Deruxtecan (Enhertu) developed

2023
PHARMAC funds Herzuma Trastuzumab biosimilar

Anti-HER2 therapy in cancer the Future



Swain, et al, 2023. Nat Rev Drug Discov 22, 101–126 (2023).

Questions?