HER2 Targeted Updates in Breast Cancer and Beyond

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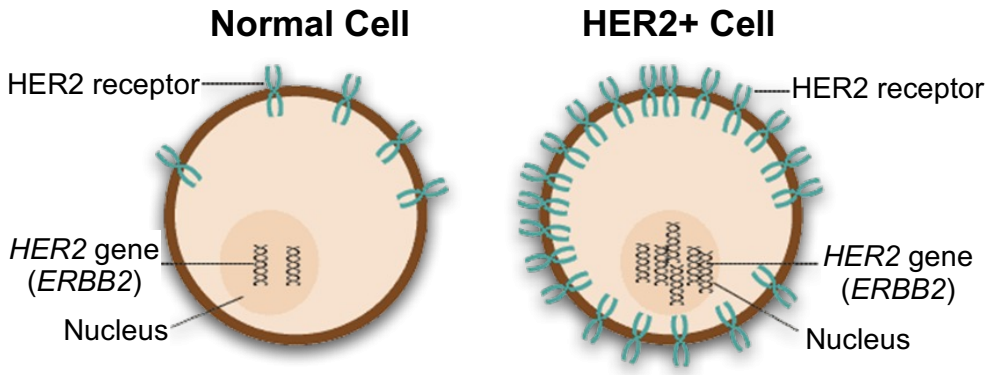
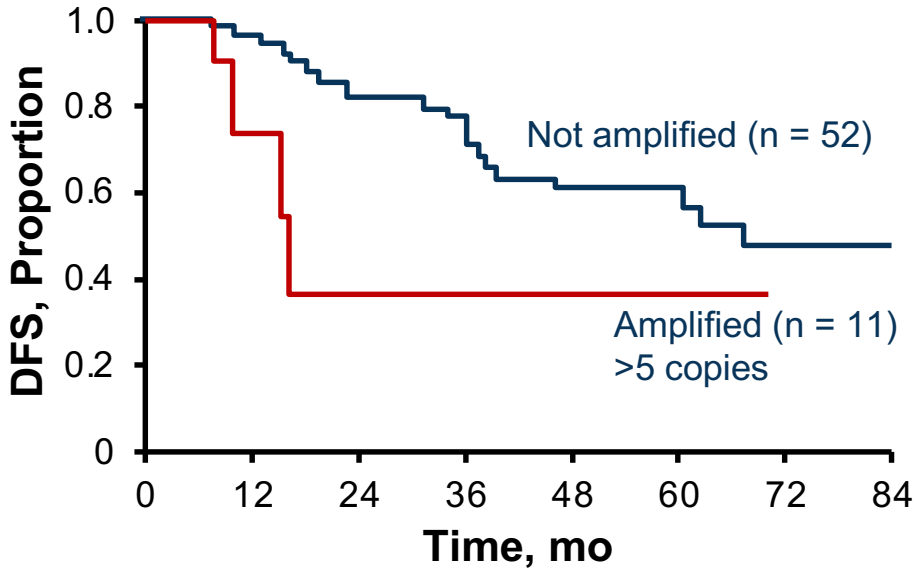
HER2: the dawn

- In the 1980s, Slamon and colleagues reported the **negative prognostic impact of *ERBB2* amplification** in breast cancer and its correlation with the **overexpression of the HER2 receptor**

- **HER2-positive** breast cancer emerged as an **aggressive entity**, with shorter DFS and OS compared with HER2-negative breast cancer



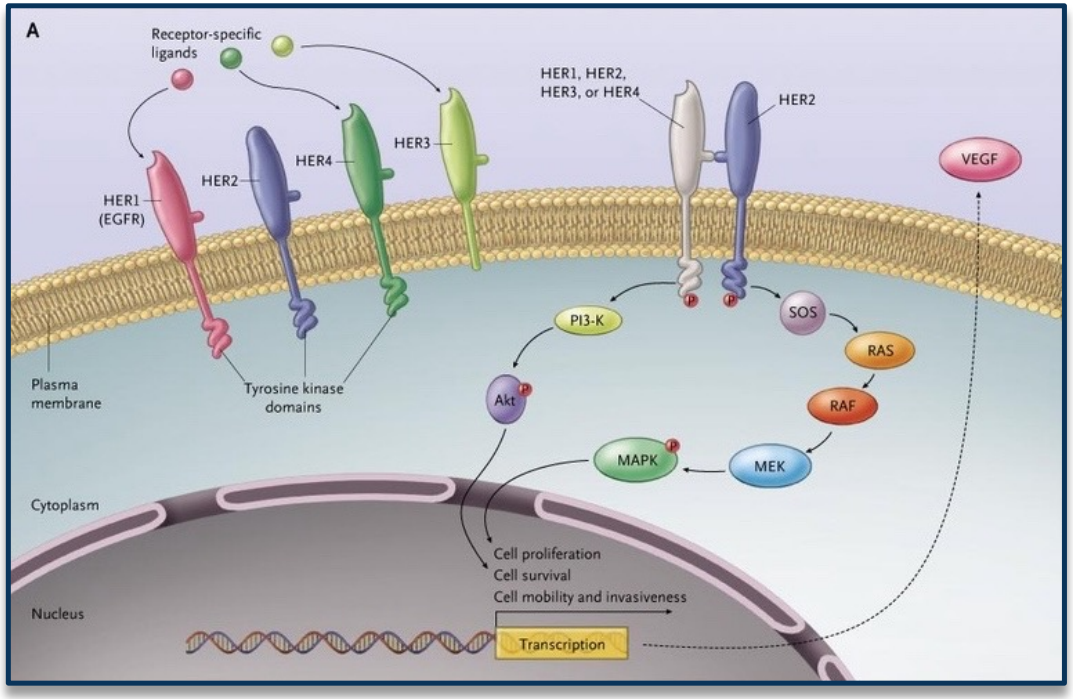
Amplification: multiple *HER2* genes
Overexpression: many HER2 receptors

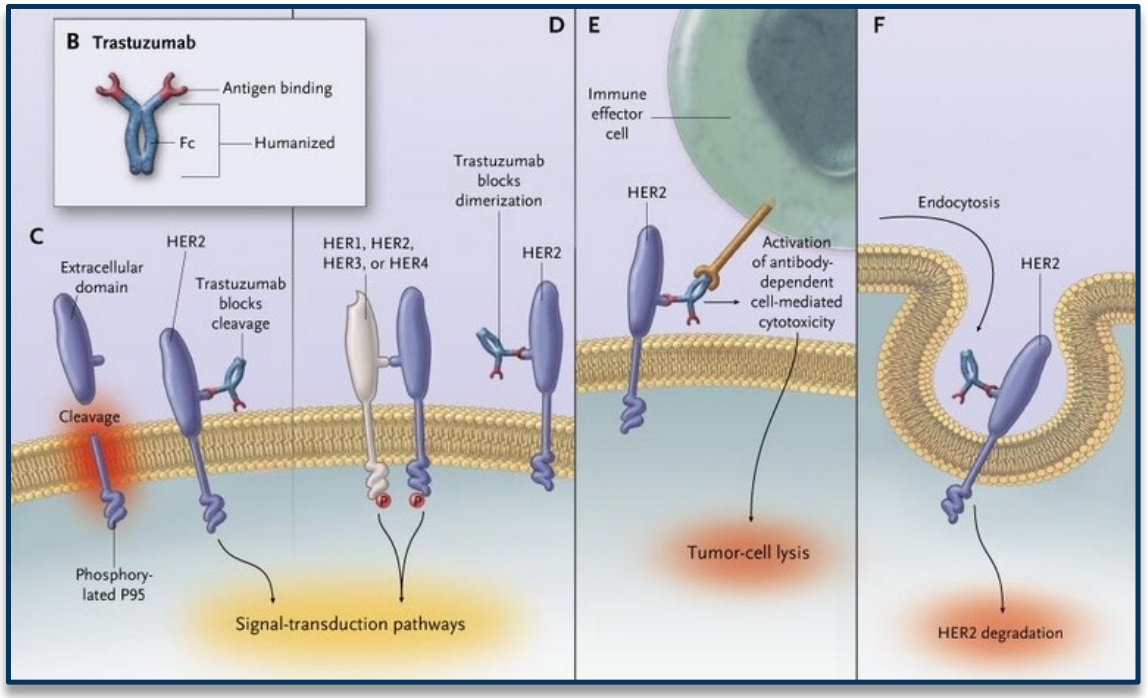


1. Slamon DJ et al. *Science*. 1987;235:177-182. 2. Slamon DJ et al. *Science*. 1989;244:707-712

HER2: the dawn

Blocking the HER2 receptor with the monoclonal antibody **trastuzumab** inhibits its oncogenic pathway, leading to relevant clinical benefits in HER2+ breast cancer

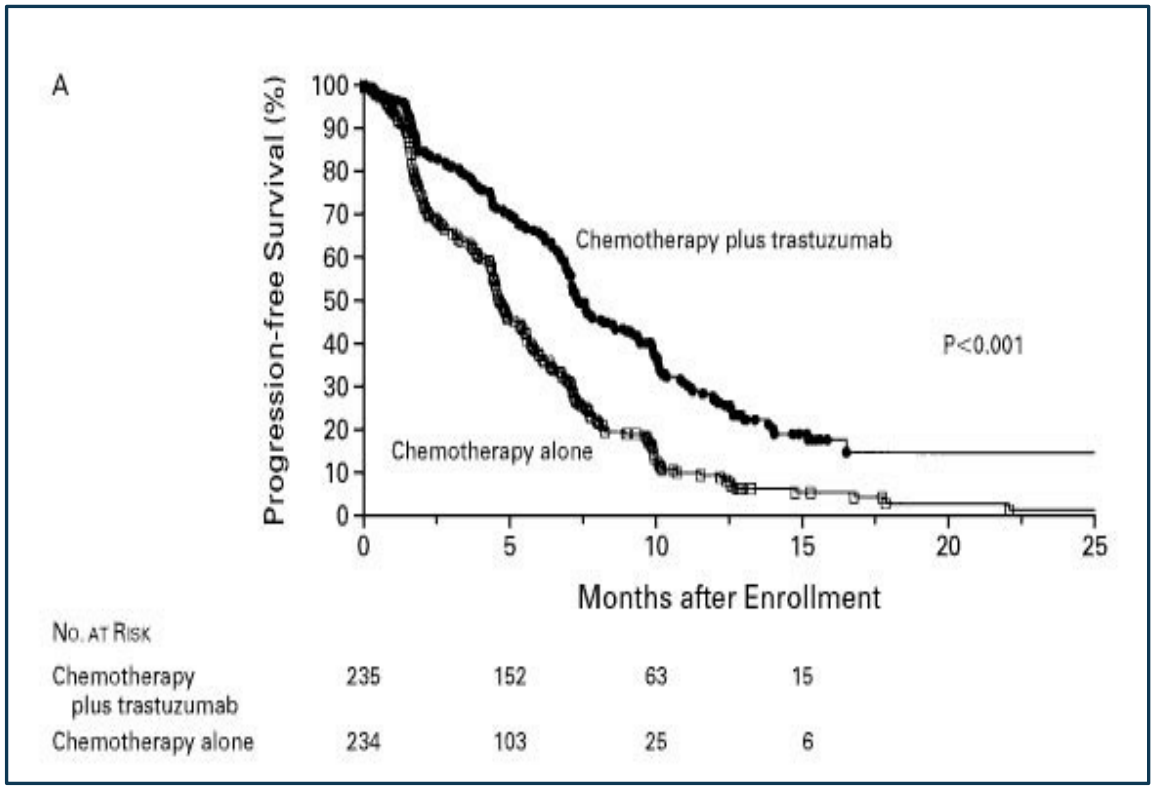


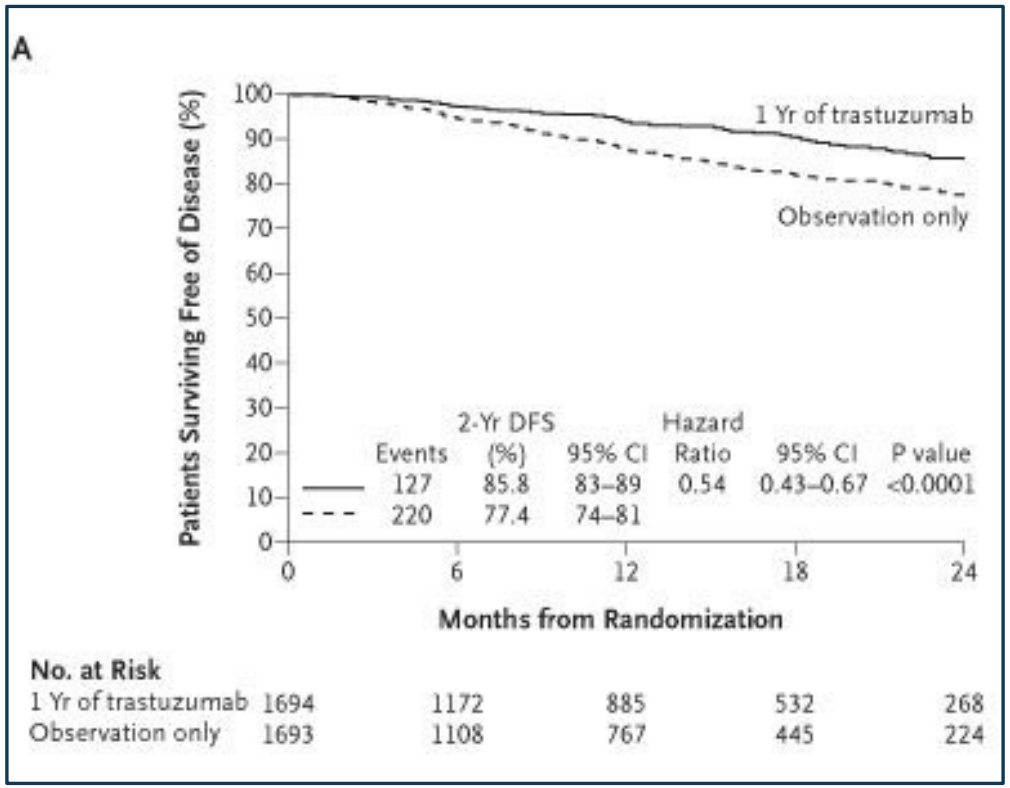


1. Hudis CA. N Engl J Med. 2007;357:39-51.

Trastuzumab for advanced and early-stage HER2+ breast cancer

Within 5 years (2001 – 2005) we learned that **trastuzumab** could significantly improve outcomes for patients with metastatic disease, as well as prevent recurrences when used in the adjuvant setting



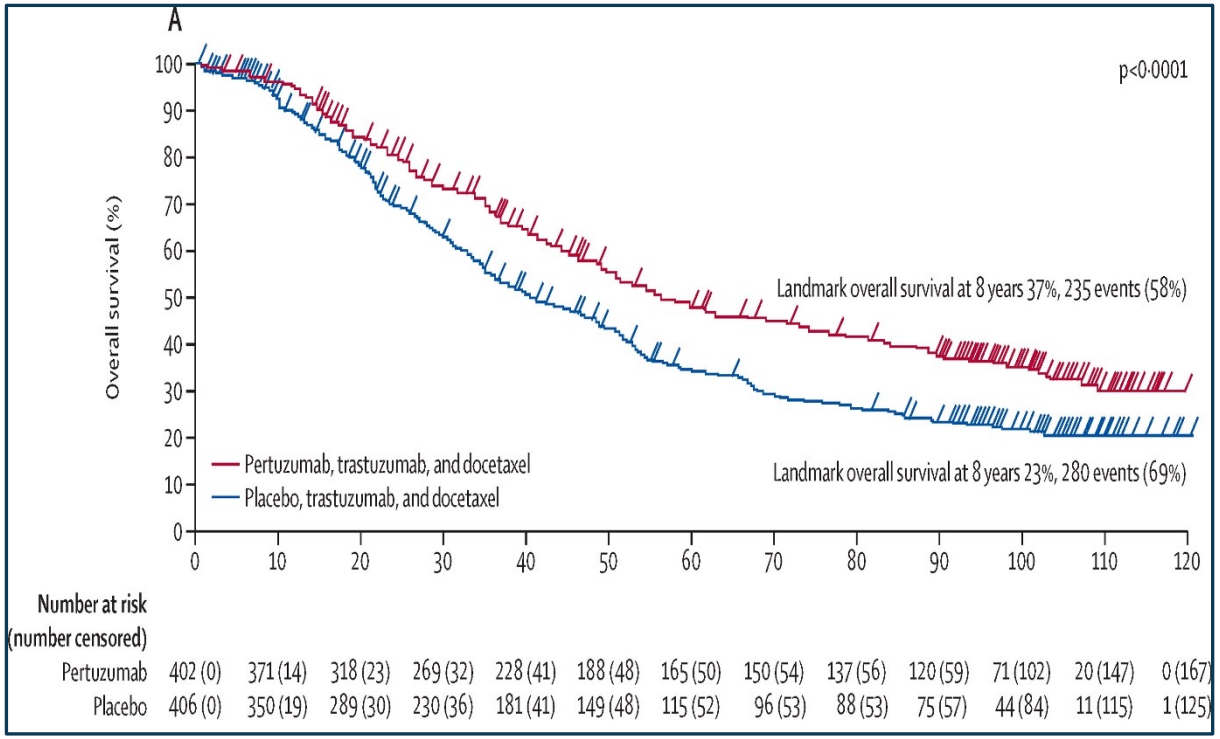


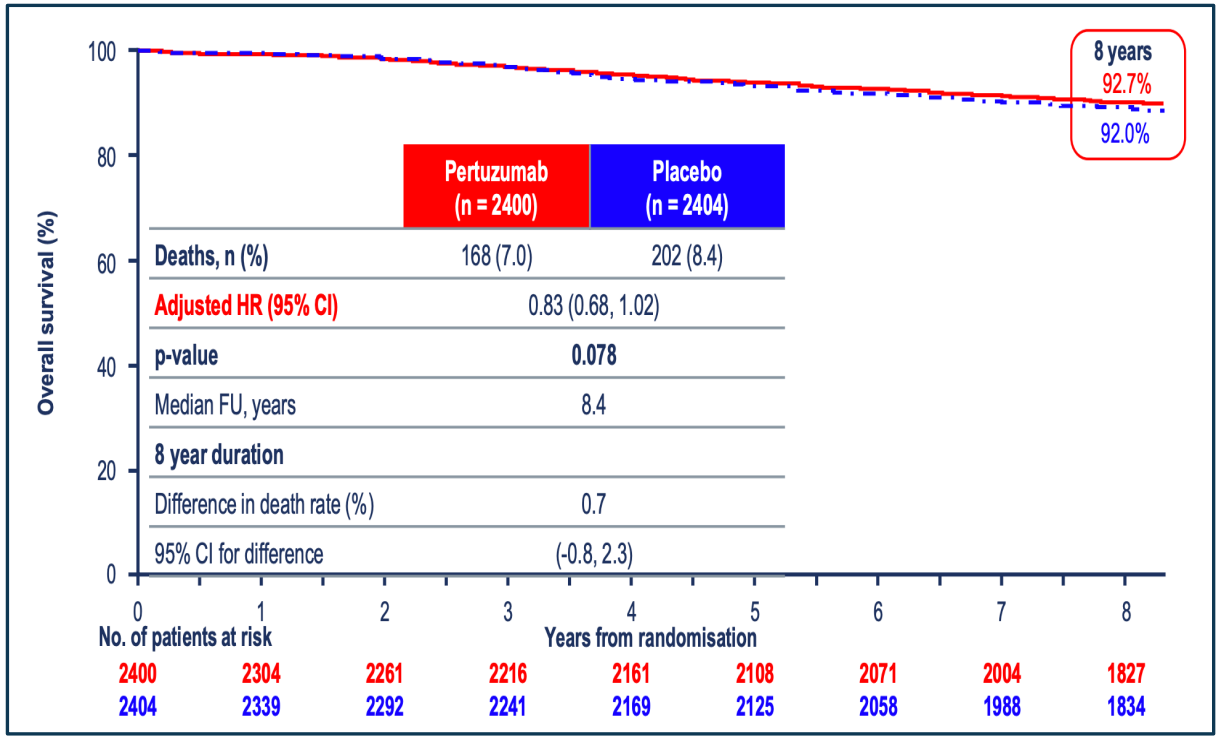
Standing ovation at ASCO 2005!

Slamon D.J. et al NEJM 2001; Piccart M. et al NEJM 2005

Outcomes for HER2+ breast cancer in 2023

After 8 years of follow up, **37%** of the patients with HER2+ MBC and **93%** of the patients with HER2+ eBC are still alive after treatment with dual HER2 blockade





Swain S. et al Lanc Onc 2020; Loibl S. ESMO Virtual Plenary 2022

Approved HER2 targeted therapies in 2023

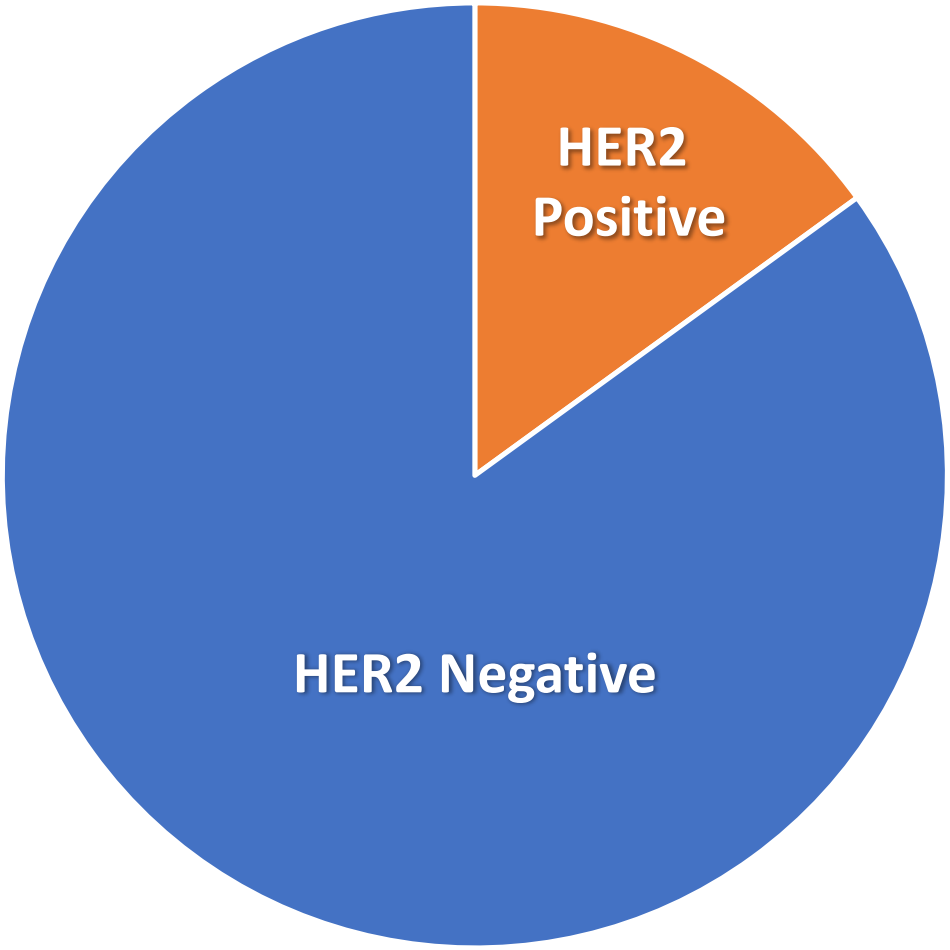
- Nowadays, 8 anti-HER2 agents are approved by the EMA and/or FDA for **HER2-positive** breast cancer, with approvals in both advanced and early settings[1,2]

TRASTUZUMAB	PERTUZUMAB	LAPATINIB	TRASTUZUMAB EMTANSINE
TUCATINIB	NERATINIB	TRASTUZUMAB DERUXTECAN	MARGETUXIMAB

1. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. 2. Gennari A et al. *Ann Oncol*. 2021;32:1475-1495.

Turning a spectrum into a binary definition

Most breast tumors (~80-85%) have been defined **HER2-negative** for decades, despite the presence of detectable HER2 expression



Adapted from Wolff A et al. *J Clin Oncol.* 2018 10;36(20):2105-2122.

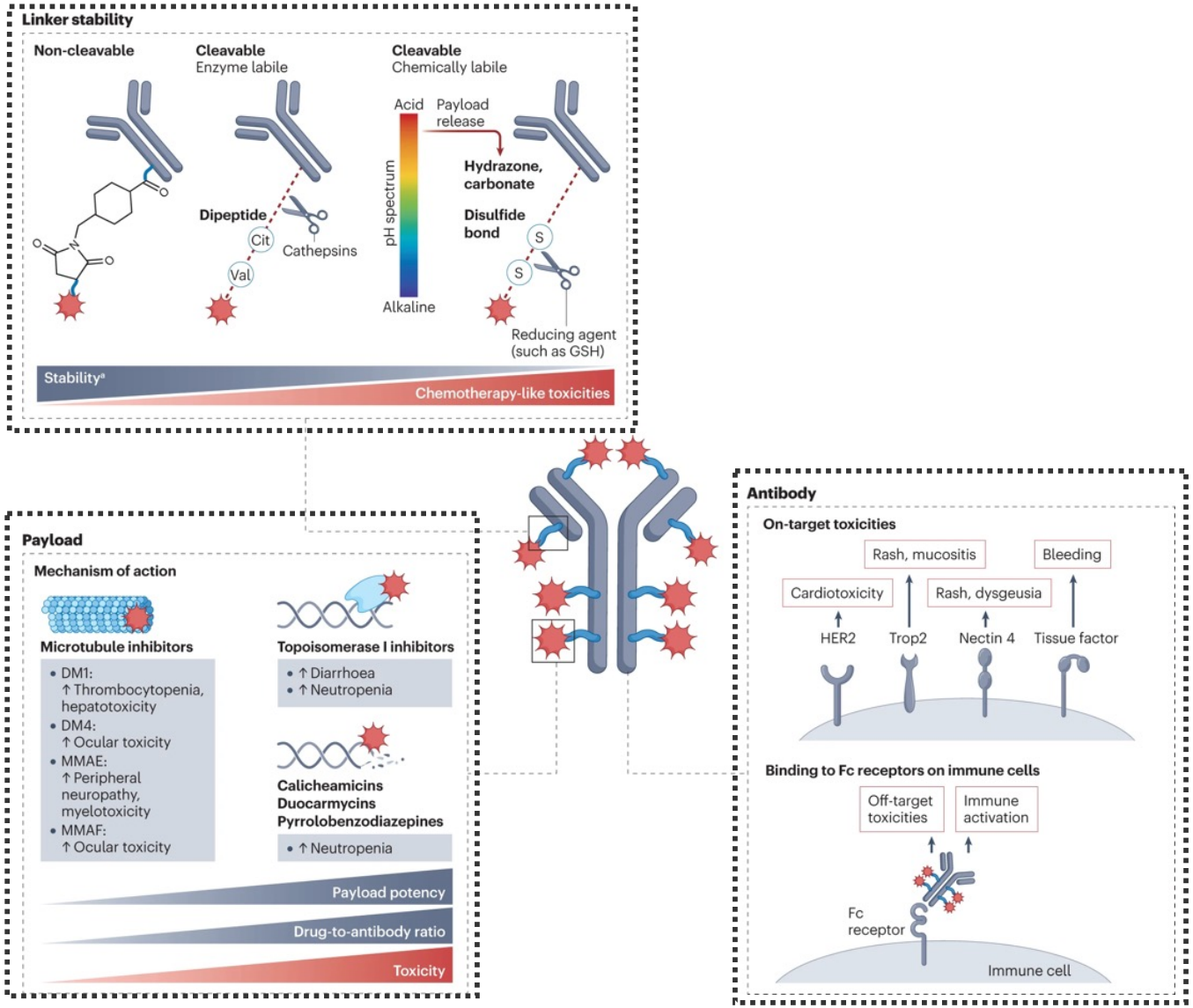
Antibody-drug conjugates

LINKER

Determines the cleavage site and dynamics

PAYLAOD

Key determinant of activity cytotoxicity



TARGET

Determines the specificity

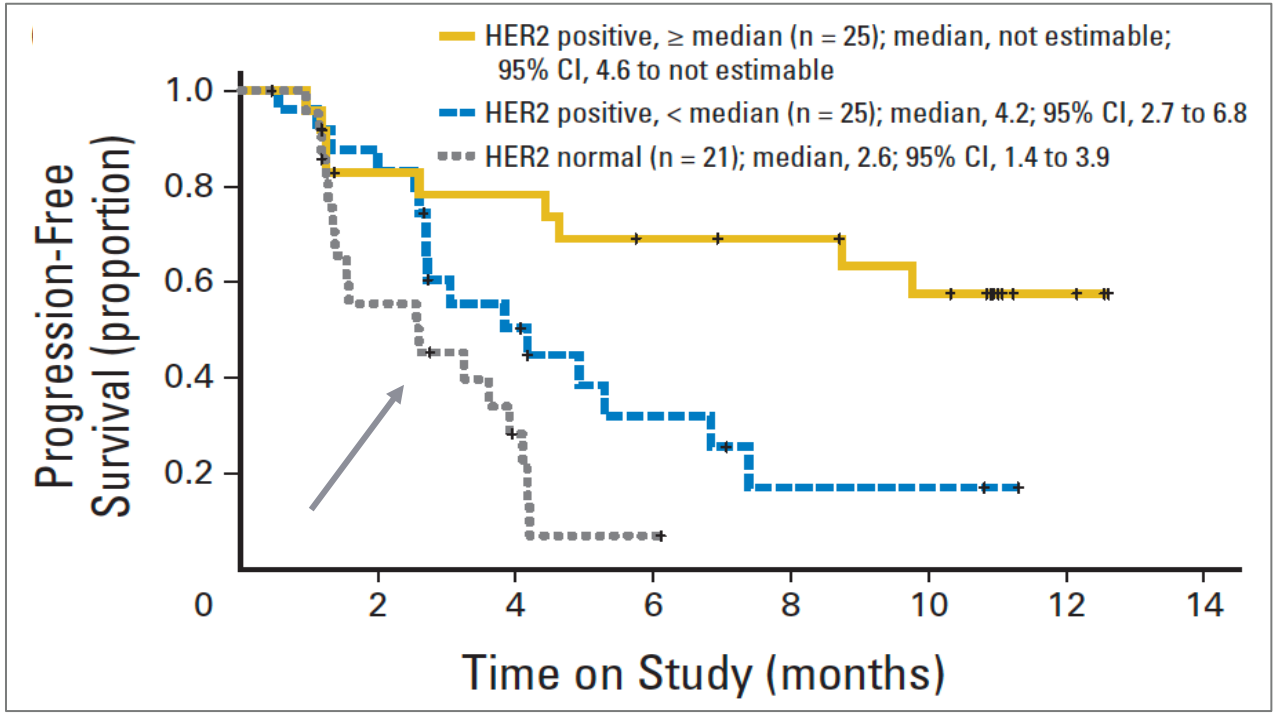
Tarantino P. et al. Nature Rev Clin Onc 2023

T-DM1 for HER2-low MBC

Retrospective evaluation of T-DM1 in 21 cases of HER2-nonamplified MBC

Only 1 response (ORR 4.8%) and mPFS 2.6 months

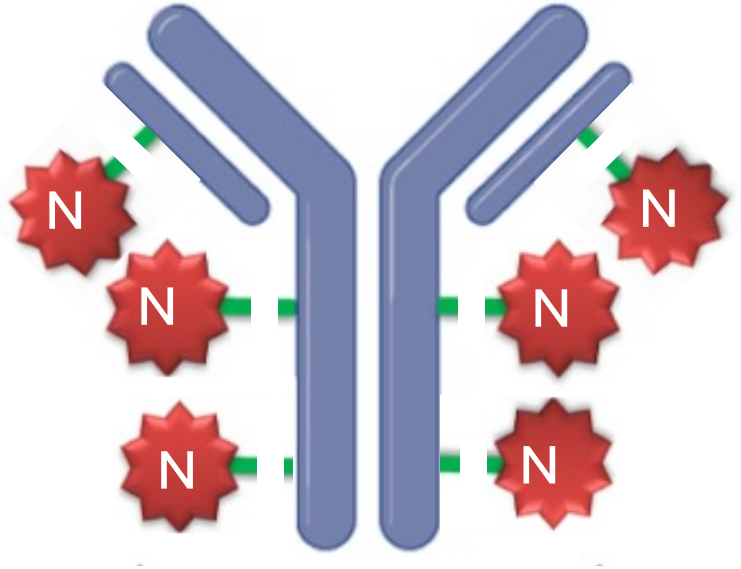
LITTLE ACTIVITY OF T-DM1 IN HER2-NEGATIVE mBC



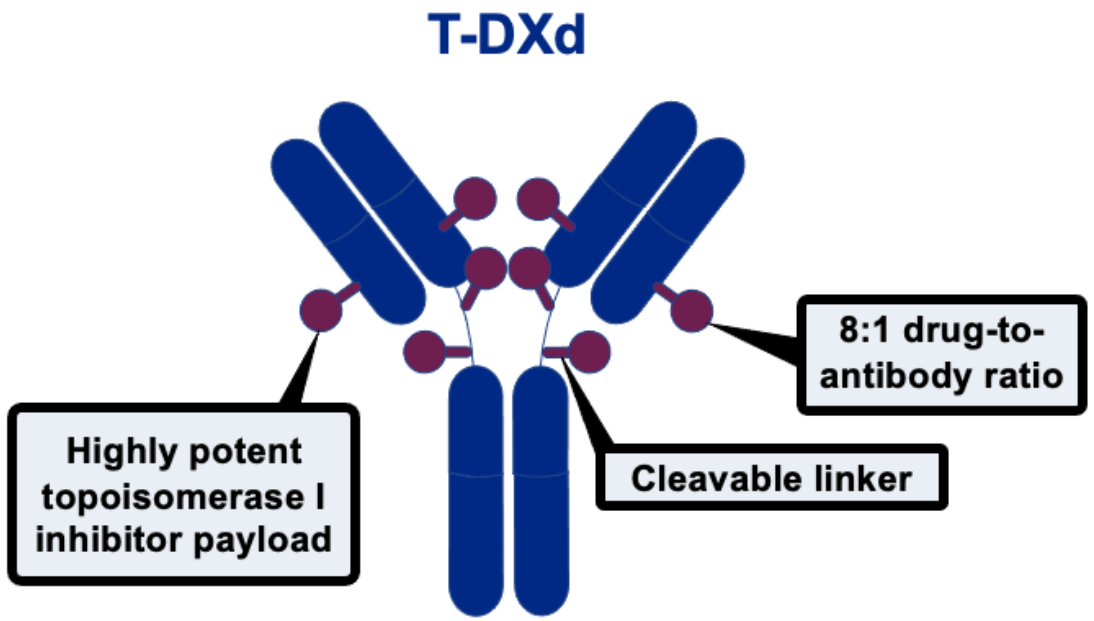
Adapted from Burris HA, et al. *J Clin Oncol.* 2011;29(4):398–405.

Novel conjugates

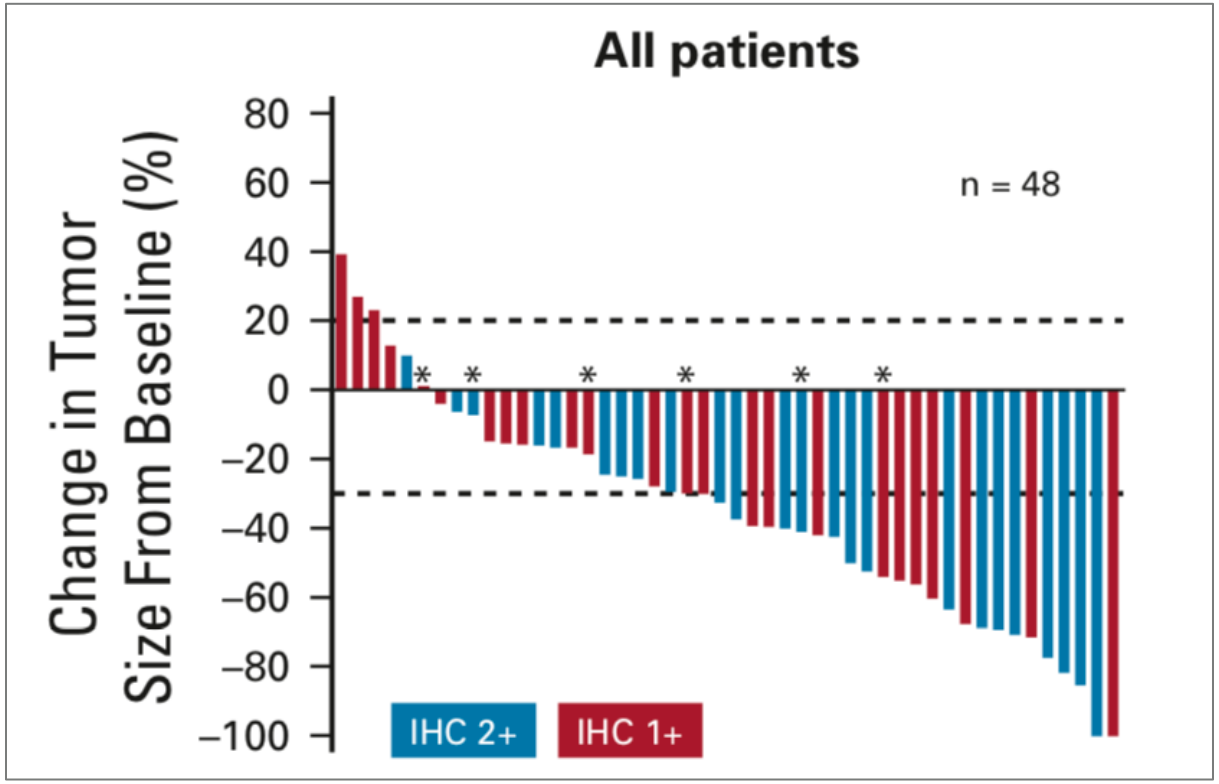
- Higher DAR
- Cleavable Linker
- Novel payloads



Phase 1 trial of DS8201a in HER2-low MBC

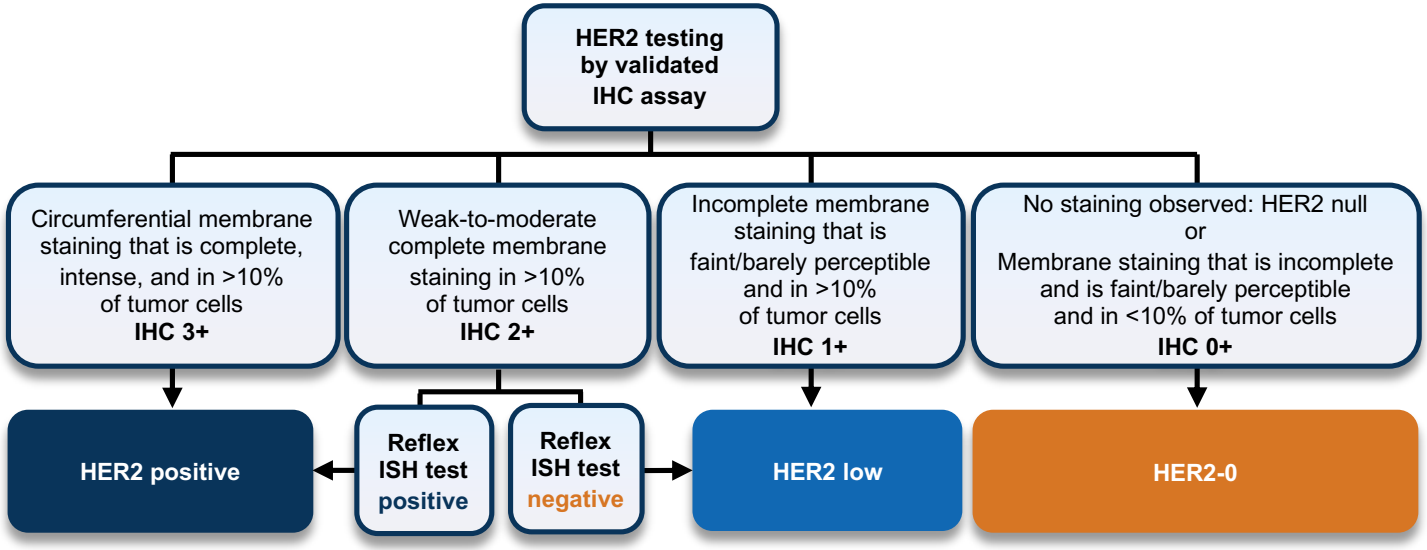


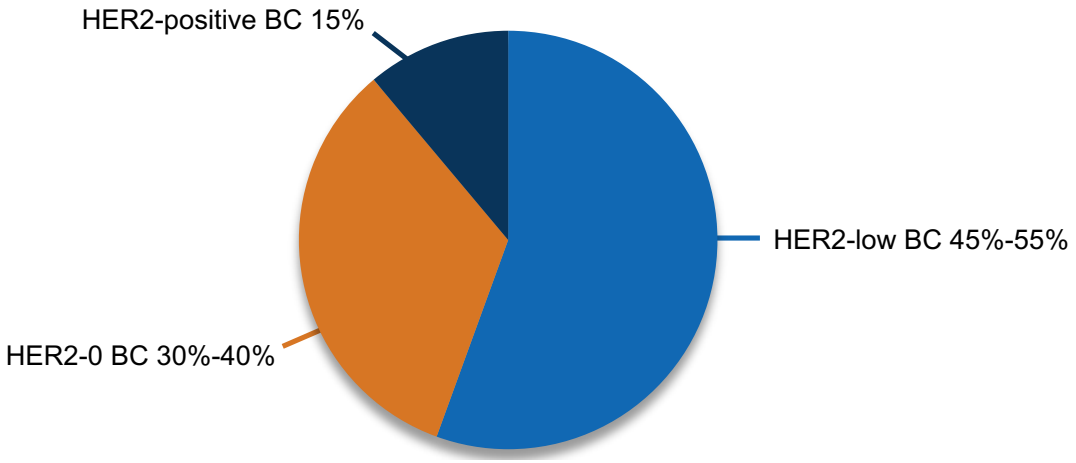
Phase 1b study of trastuzumab deruxtecan (T-DXd) in HER2-low MBC: among 54 highly pre-treated (median 7.5) HER2-low mBC patients T-DXd achieved an **ORR of 37% and mPFS 11 months**



Modi S, et al. *J Clin Oncol.* 2020;38:1887–1896.

2020 – Proposal of a new pie chart for HER2

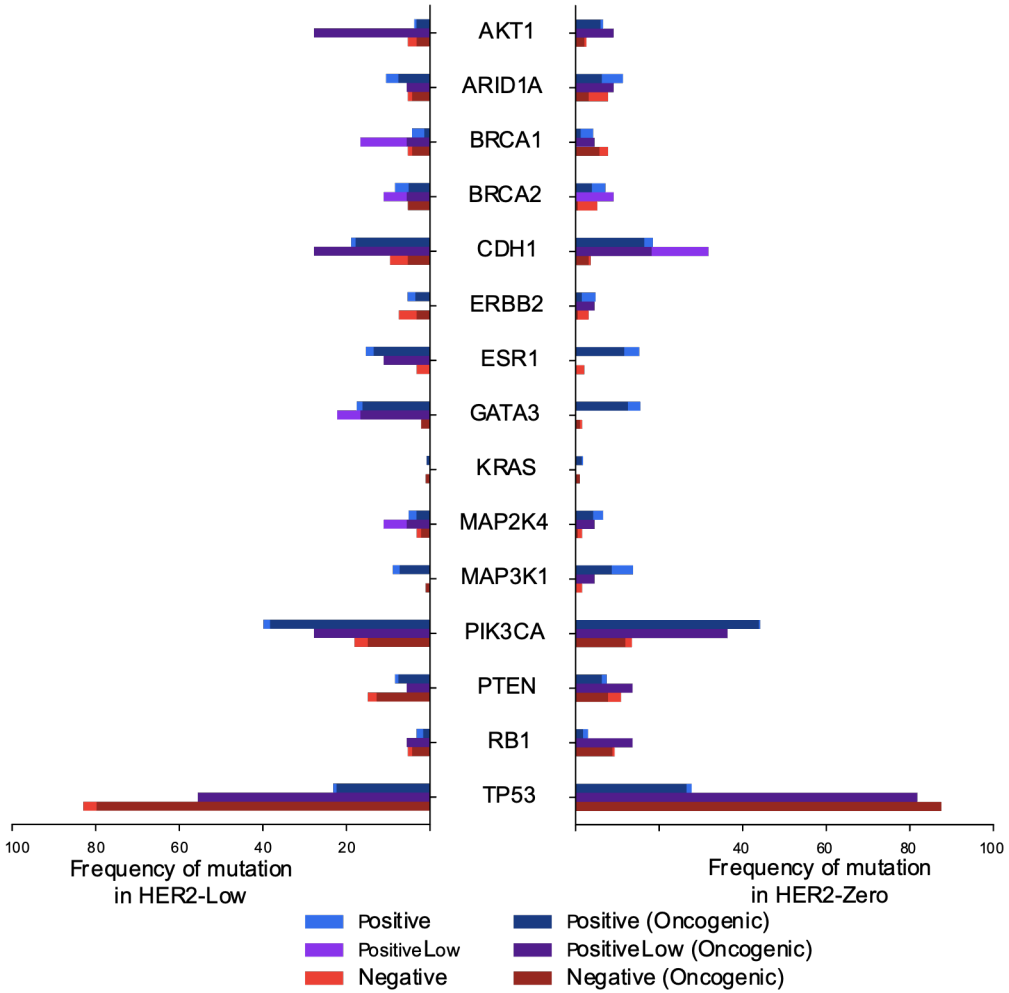




Tarantino P et al. *J Clin Oncol.* 2020

HER2-low: not a distinct molecular entity

In our Dana-Farber cohort of >1000 MBC patients, we found **no significant difference in oncogenic genomic alterations** between HER2-low and HER2-zero tumours, after correcting for hormone receptor expression



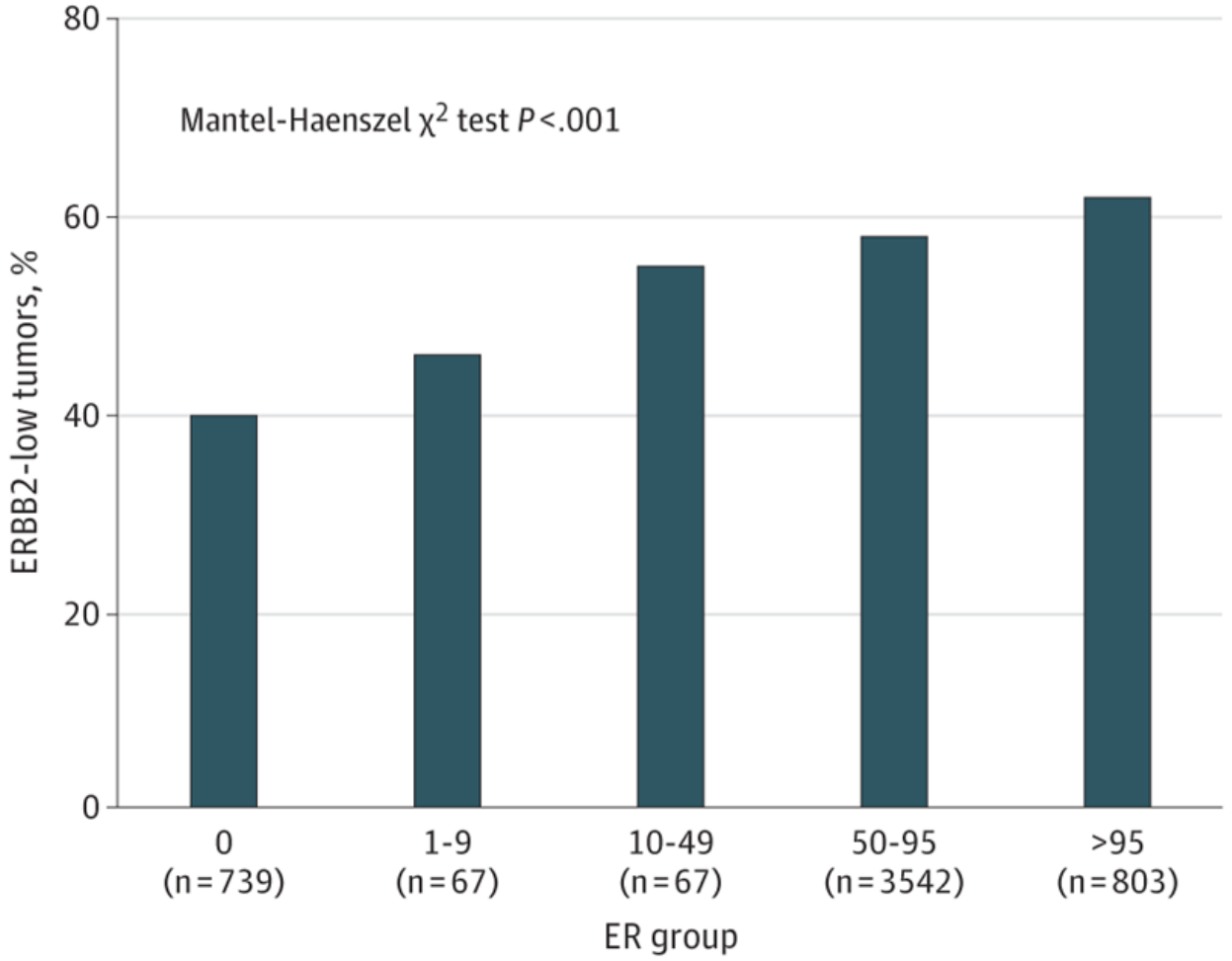
Tarantino P et al. Nature Communications 2023

HER2-low expression: strongly associated with ER expression

The higher the ER expression, the higher the chances of identifying HER2-low expression

- approximately **40% of TNBCs are HER2-low**

- up to **65% of ER+ tumors are HER2-low**

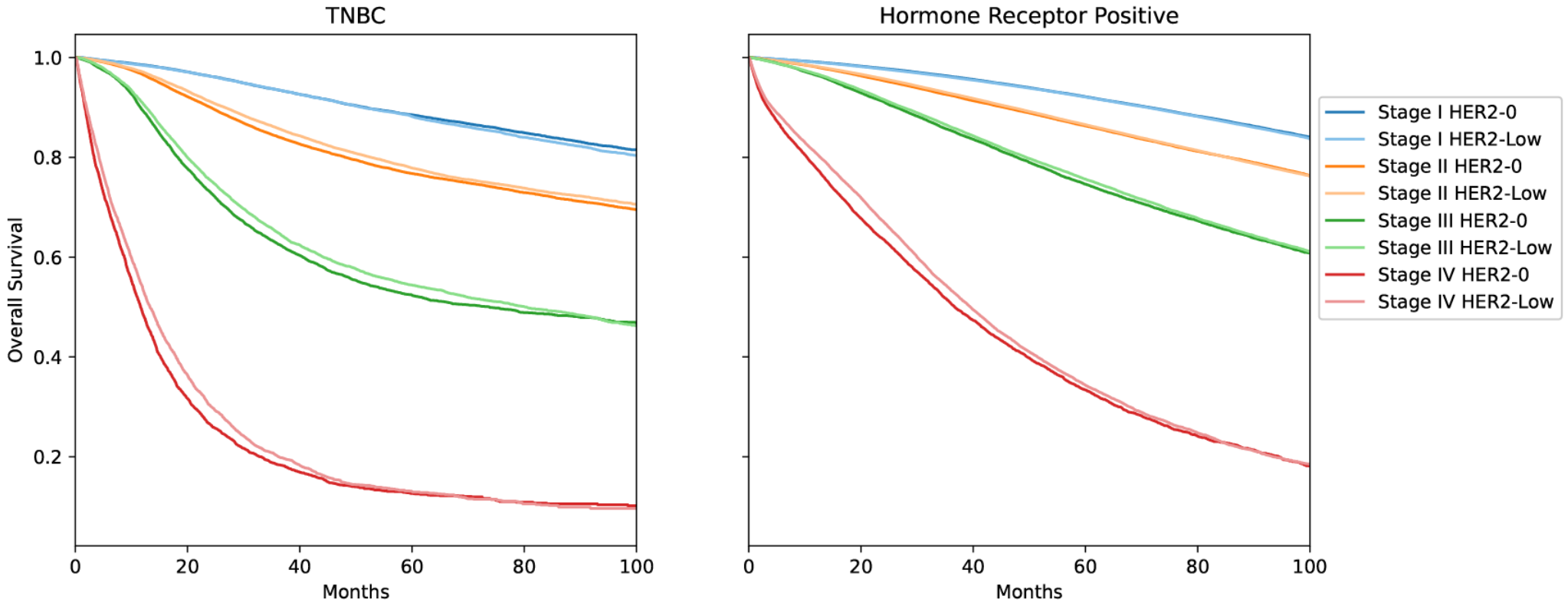


Tarantino P et al. JAMA Oncology 2022

HER2-low: marginal to no prognostic impact

Retrospective Cohort Study: National Cancer Data Base (2010-2019)

N=1,136,016

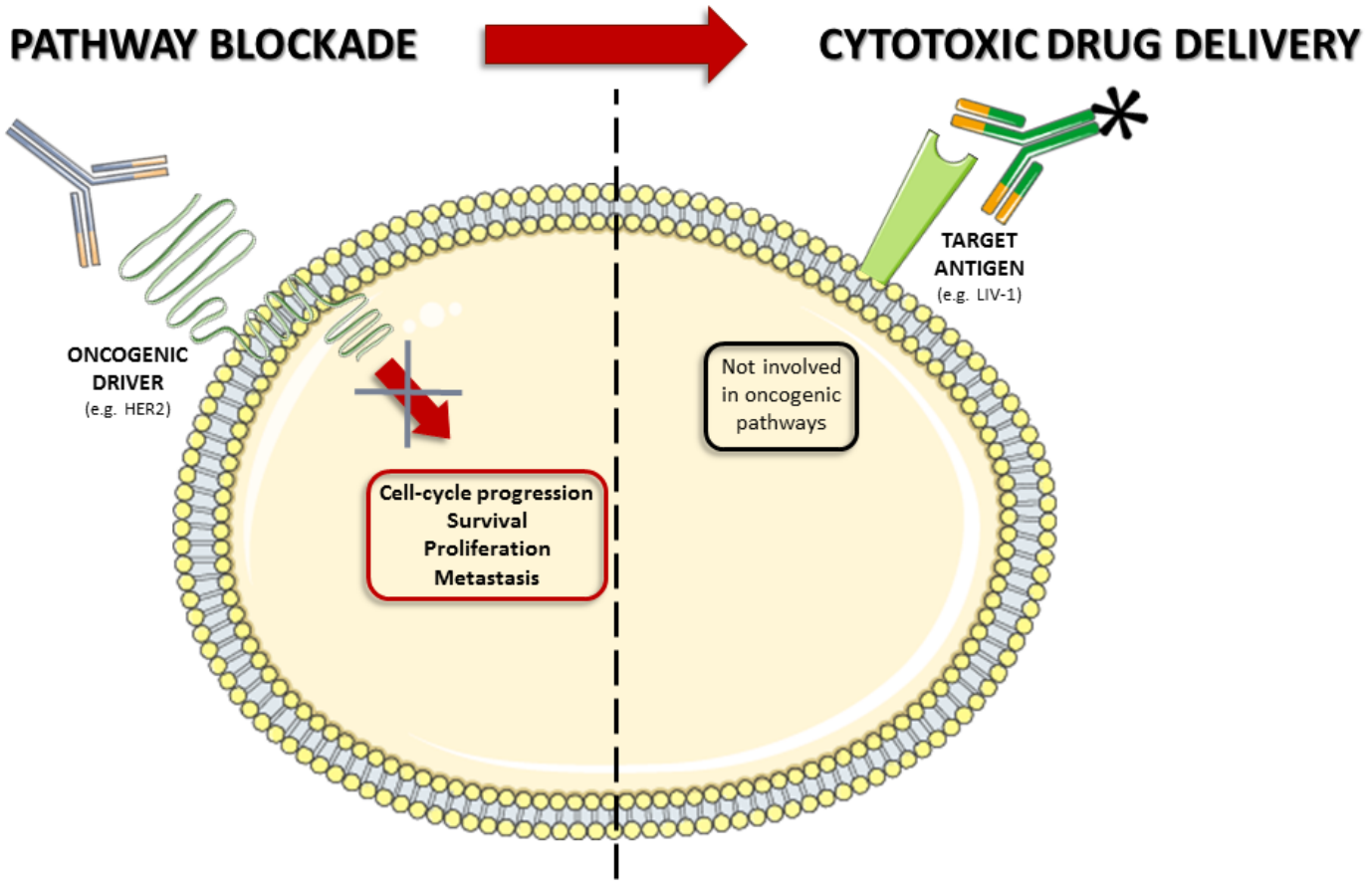


1. Peiffer D et al, SABCS 2022

HER2-low: not an entity, but a target

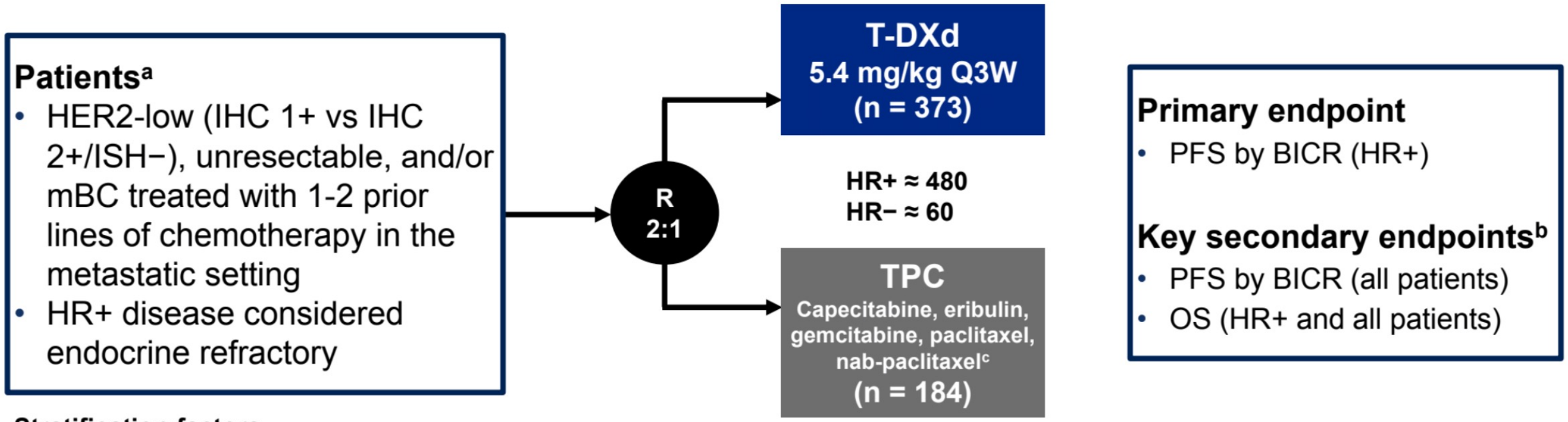
Not a distinct entity

But **encouraging activity with the delivery of cytotoxic payloads through ADCs**.



Tarantino P et al. Exp Opin Biol Ther 2020

DESTINY-Breast04 phase 3 trial



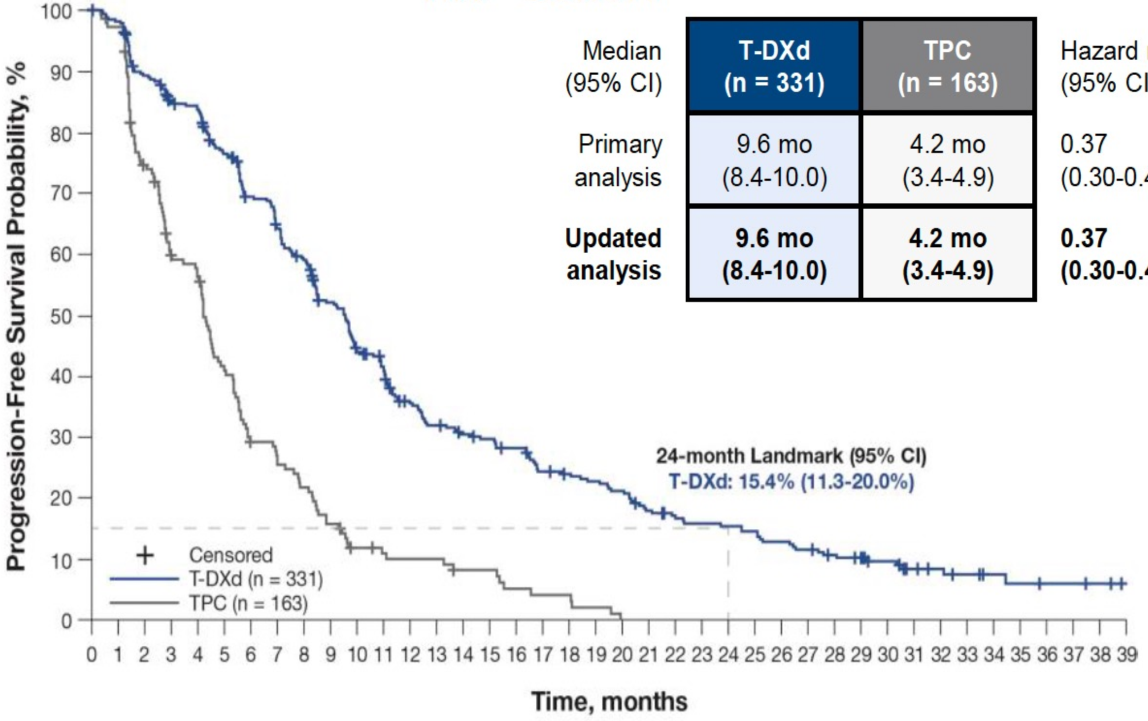
Stratification factors

- Centrally assessed HER2 status[d] (IHC 1+ vs IHC 2+/ISH−)
- 1 versus 2 prior lines of chemotherapy
- HR+ (with vs without prior treatment with CDK4/6 inhibitor) versus HR−

Modi S. et al. NEJM 2022

Significant improvement in OS with T-DXd (vs. chemo)

HR+ Cohort



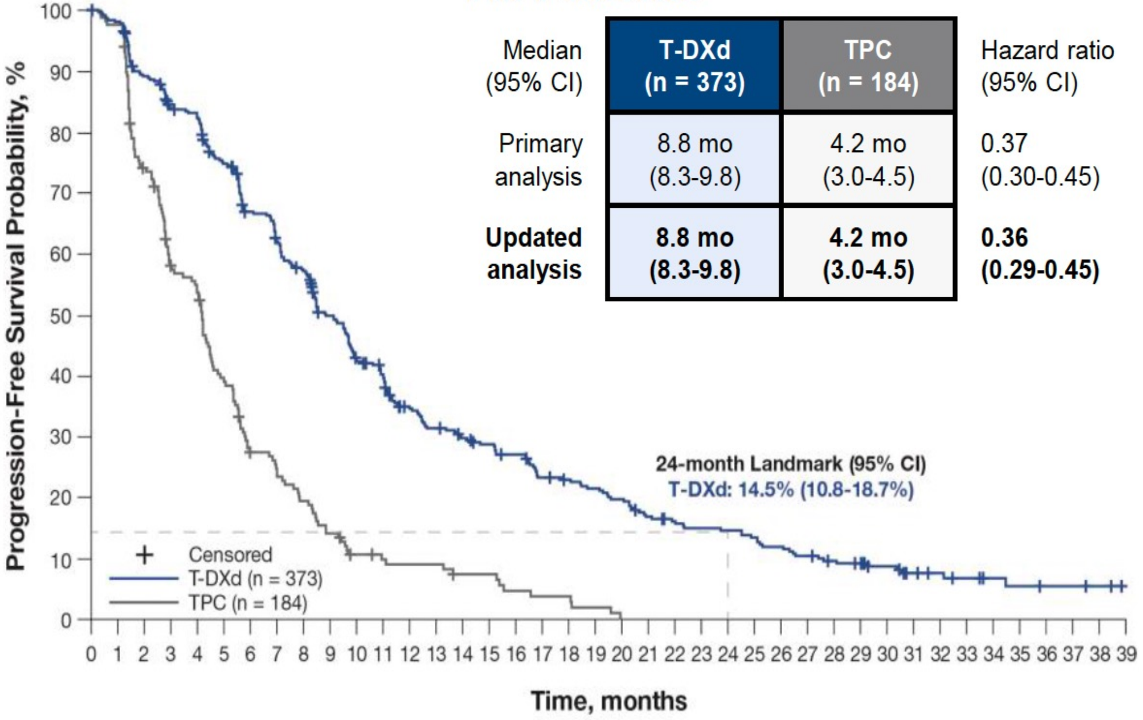
Median (95% CI)	T-DXd (n = 331)	TPC (n = 163)	Hazard ratio (95% CI)
Primary analysis	9.6 mo (8.4-10.0)	4.2 mo (3.4-4.9)	0.37 (0.30-0.47)
Updated analysis	**9.6 mo (8.4-10.0)**	**4.2 mo (3.4-4.9)**	**0.37 (0.30-0.46)**

Patients still at risk:

T-DXd (n = 331) 331 323 290 272 267 241 215 198 181 154 129 119 98 88 82 79 74 63 60 57 53 44 40 37 36 34 30 27 23 21 16 11 9 7 5 4 3 3 2 0

TPC (n = 163) 163 143 107 83 78 56 39 34 29 21 14 12 11 11 8 8 5 4 4 2 0

All Patients



Median (95% CI)	T-DXd (n = 373)	TPC (n = 184)	Hazard ratio (95% CI)
Primary analysis	8.8 mo (8.3-9.8)	4.2 mo (3.0-4.5)	0.37 (0.30-0.45)
Updated analysis	**8.8 mo (8.3-9.8)**	**4.2 mo (3.0-4.5)**	**0.36 (0.29-0.45)**

Patients still at risk:

T-DXd (n = 373) 373 364 327 304 297 267 234 216 198 166 140 130 107 97 90 85 79 67 64 60 55 46 42 39 38 35 31 27 23 21 16 11 9 7 5 4 3 3 2 0

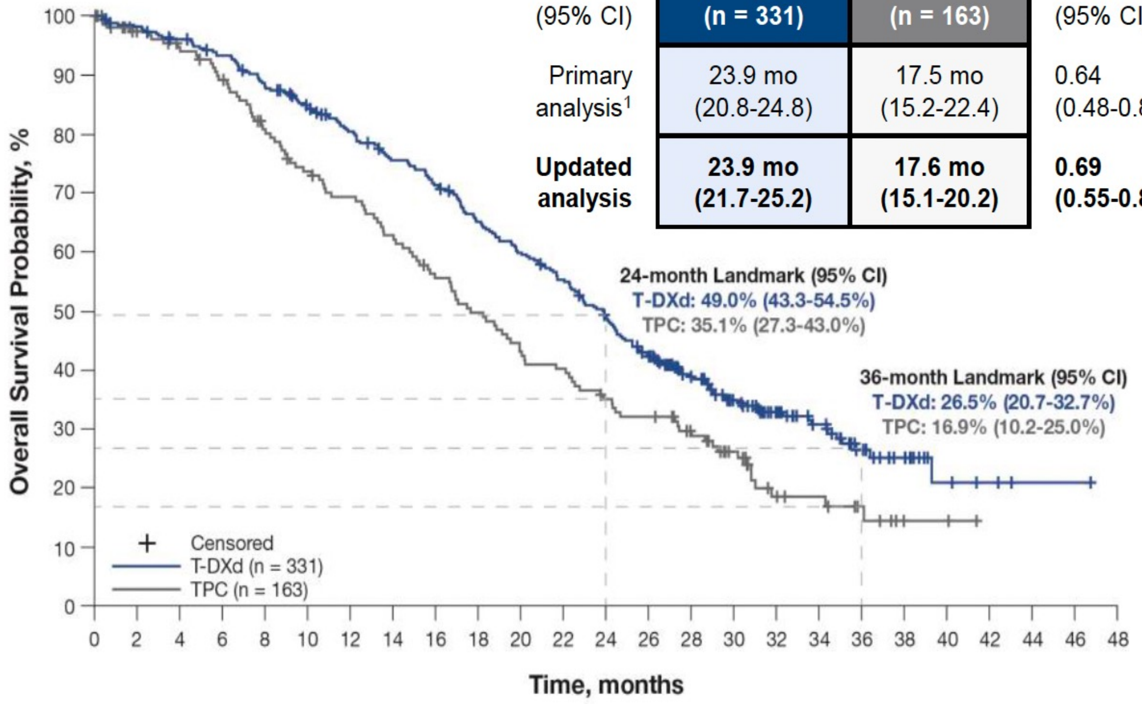
TPC (n = 184) 184 163 121 92 85 61 41 35 29 21 14 12 11 11 8 8 5 4 4 2 0

Modi S et al ESMO 2023. Abstract 376O.

Near doubling of PFS with T-DXd (vs. chemo)

HR+ Cohort

Median (95% CI)	T-DXd (n = 331)	TPC (n = 163)	Hazard ratio (95% CI)
Primary analysis[1]	23.9 mo (20.8-24.8)	17.5 mo (15.2-22.4)	0.64 (0.48-0.86)
Updated analysis	**23.9 mo (21.7-25.2)**	**17.6 mo (15.1-20.2)**	**0.69 (0.55-0.87)**



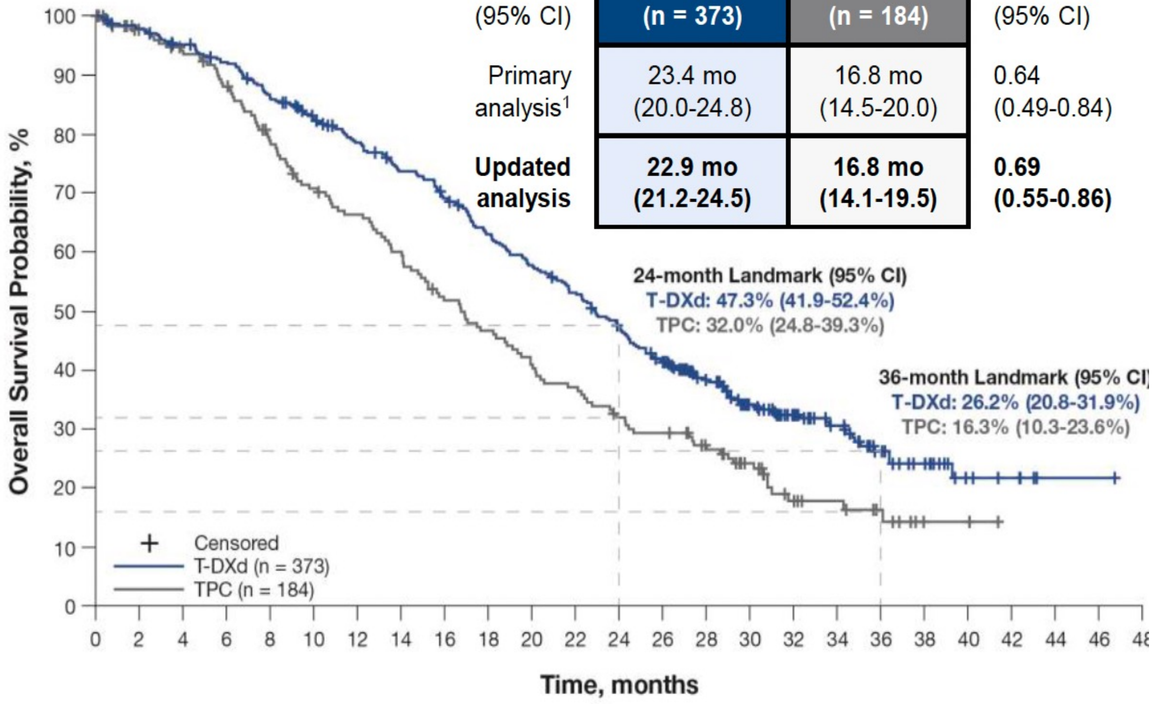
Patients still at risk:

T-DXd (n = 331) 331 325 323 317 313 307 302 292 284 279 267 258 250 243 233 230 220 212 199 189 183 176 168 155 147 135 124 109 94 81 72 66 54 46 42 34 23 17 14 7 5 4 3 2 1 1 1 0

TPC (n = 163) 163 150 144 142 138 134 129 123 114 108 103 97 96 92 87 82 76 71 68 64 59 56 55 50 47 43 43 42 35 31 25 16 13 11 11 9 7 5 2 2 2 1 0

All Patients

Median (95% CI)	T-DXd (n = 373)	TPC (n = 184)	Hazard ratio (95% CI)
Primary analysis[1]	23.4 mo (20.0-24.8)	16.8 mo (14.5-20.0)	0.64 (0.49-0.84)
Updated analysis	**22.9 mo (21.2-24.5)**	**16.8 mo (14.1-19.5)**	**0.69 (0.55-0.86)**

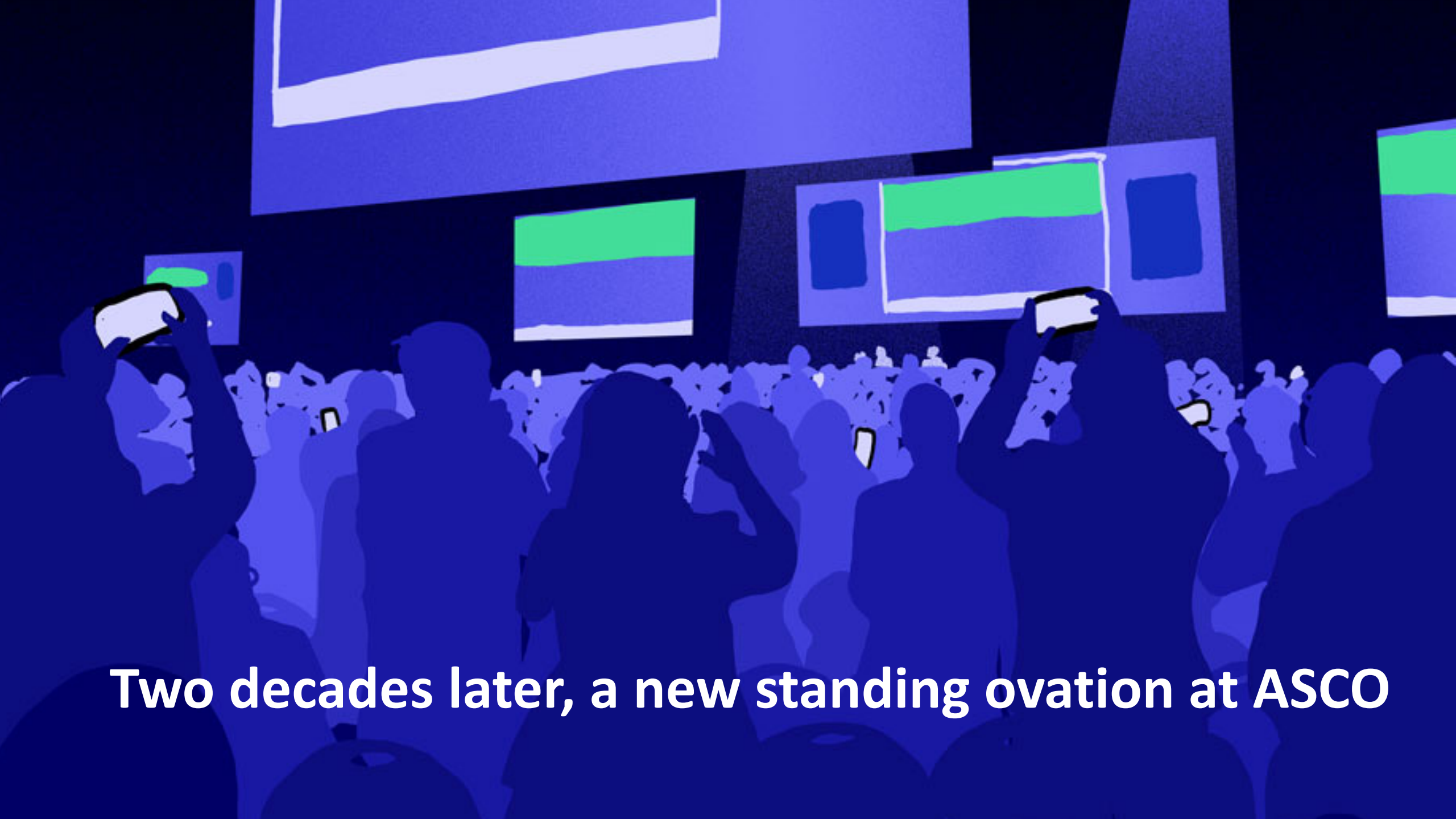


Patients still at risk:

T-DXd (n = 373) 373 366 363 355 350 342 337 325 314 308 295 285 276 269 257 254 240 231 217 205 199 191 182 168 160 148 137 122 107 94 81 75 62 52 48 39 28 21 18 11 7 6 5 3 1 1 1 0

TPC (n = 184) 184 170 165 160 156 152 145 137 127 119 113 107 105 100 95 88 81 76 73 69 64 59 58 53 49 45 45 44 37 33 27 18 15 12 12 10 8 5 2 2 2 1 0

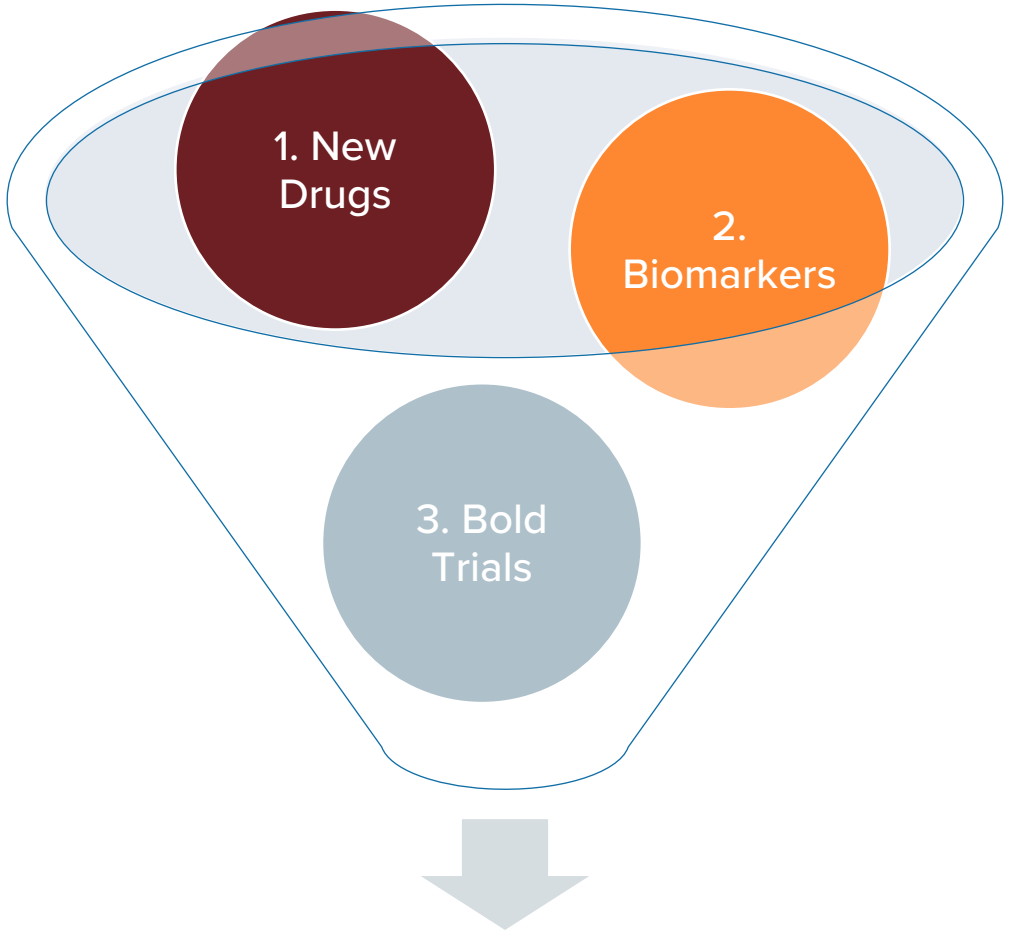
Modi S et al ESMO 2023. Abstract 376O.


Two decades later, a new standing ovation at ASCO

FDA Approval on August 5th, 2022

FDA Approves First Targeted Therapy for HER2-Low Breast Cancer

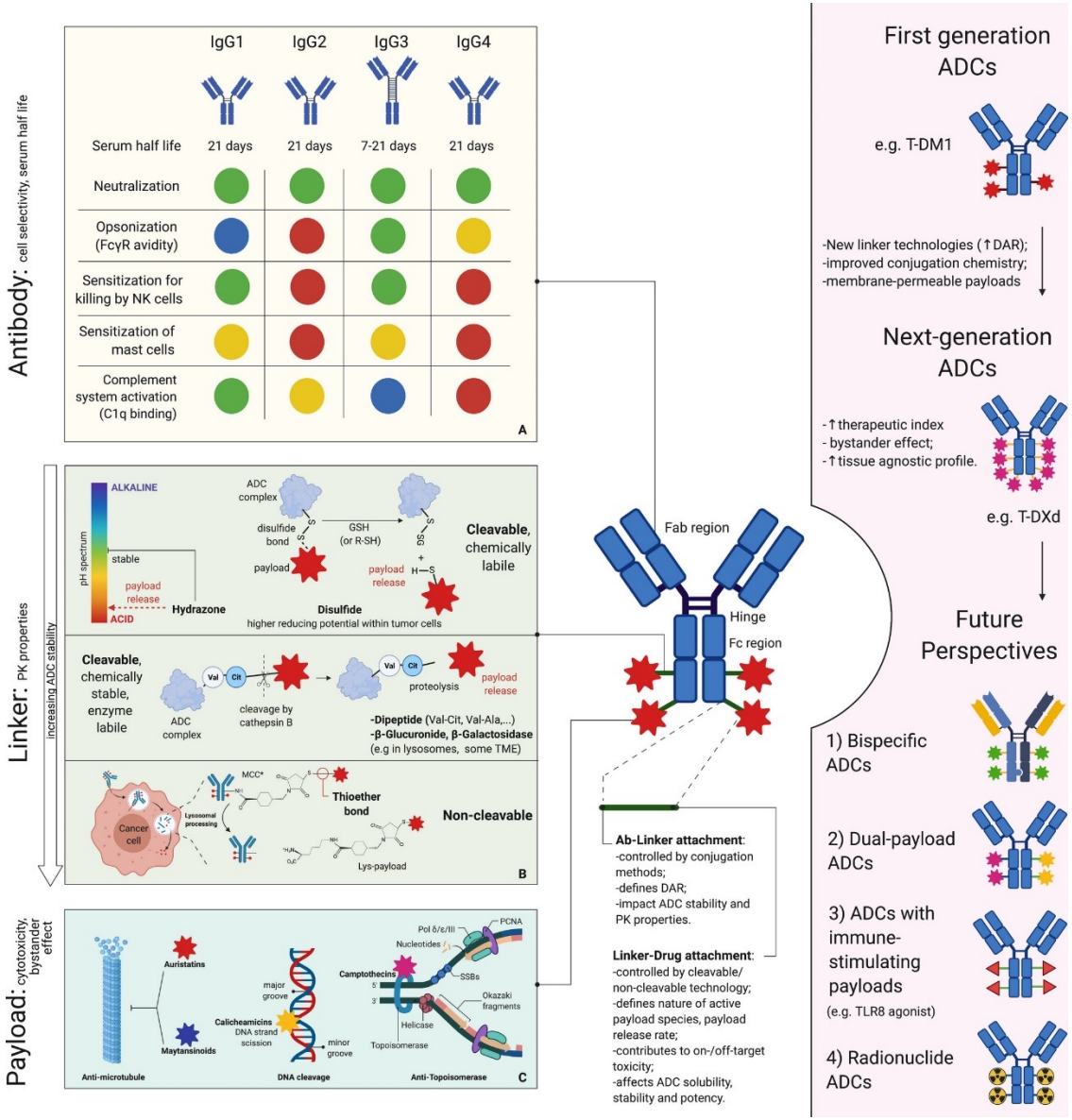
Recipe for further advancement in HER2 Targeting



Future of HER2-targeting

Novel Antibody-Drug Conjugates: Modular Compounds

- ADCs are **modular compounds**. Modifying each component can unlock novel therapeutic opportunities.

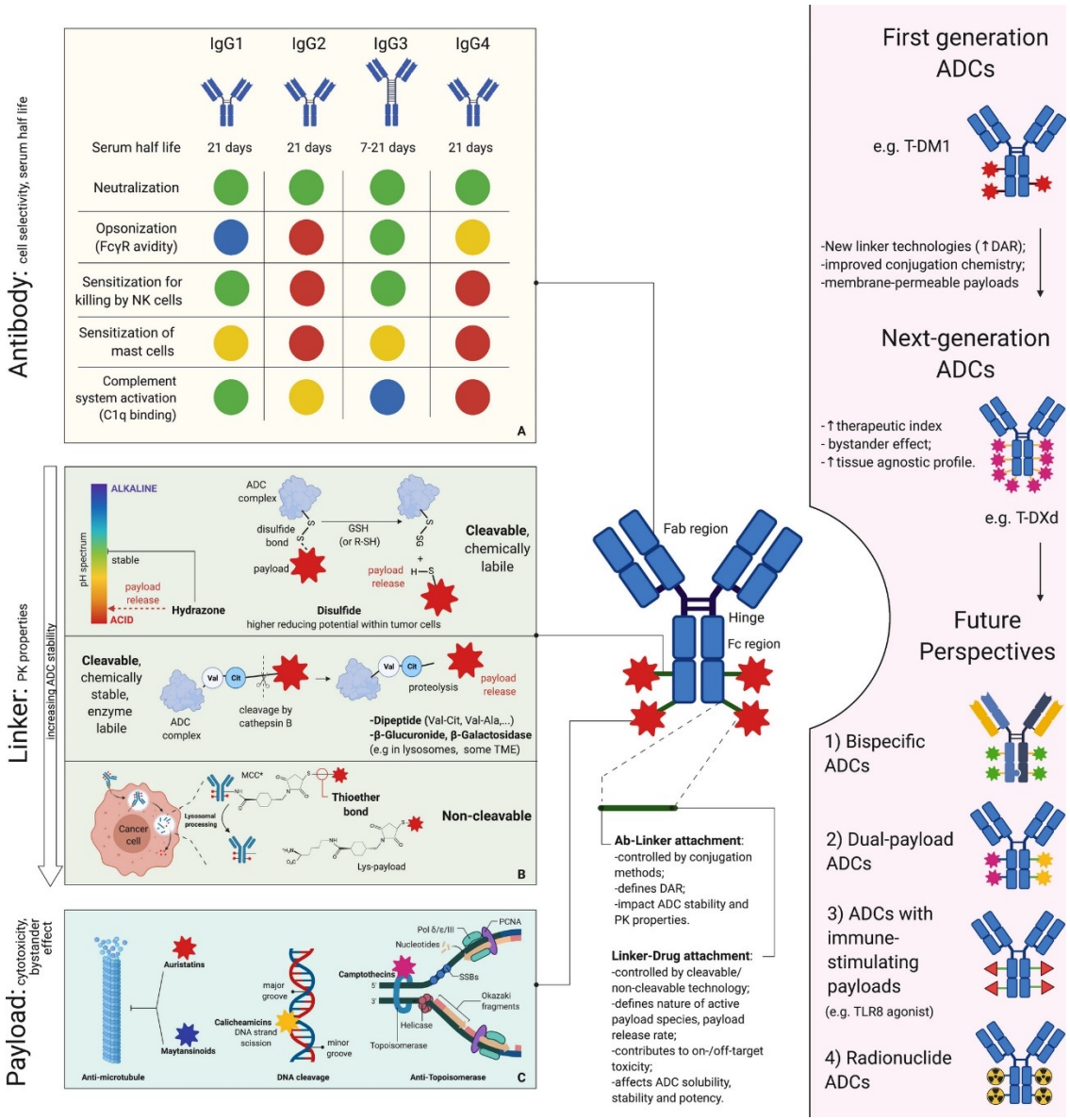


Tarantino P, et al. CA Can J Clin 2022;72:165-182.

Novel Antibody-Drug Conjugates: Modular Compounds

- ADCs are **modular compounds**. Modifying each component can unlock novel therapeutic opportunities.

- **Antibody:** bispecific, trispecific, masked



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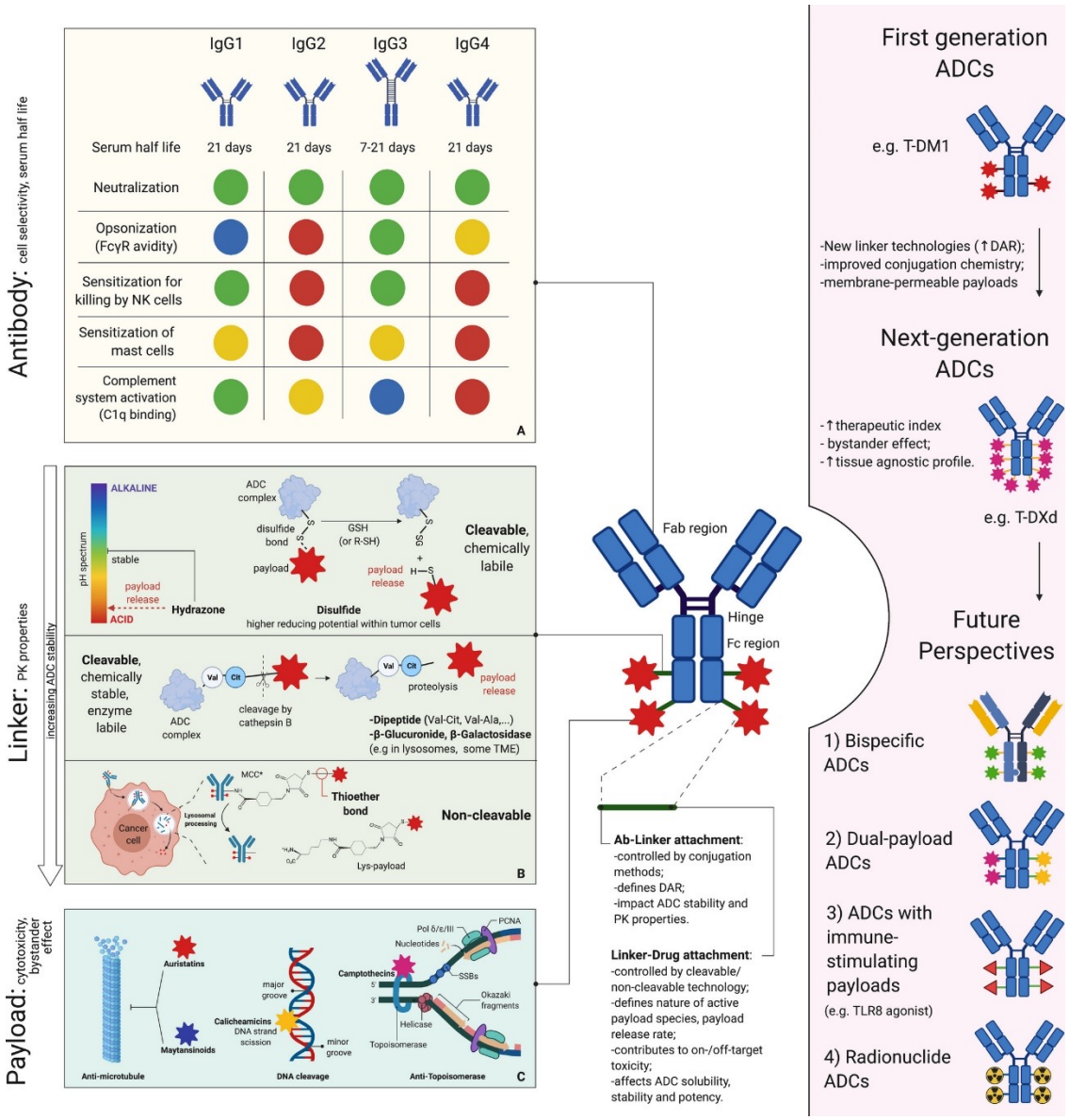
Novel Antibody-Drug Conjugates: Modular Compounds

- ADCs are **modular compounds**. Modifying each component can unlock novel therapeutic opportunities.
- **Antibody:** bispecific, trispecific, masked
- **Linker:** cleavable, site-specific, glycoengineered



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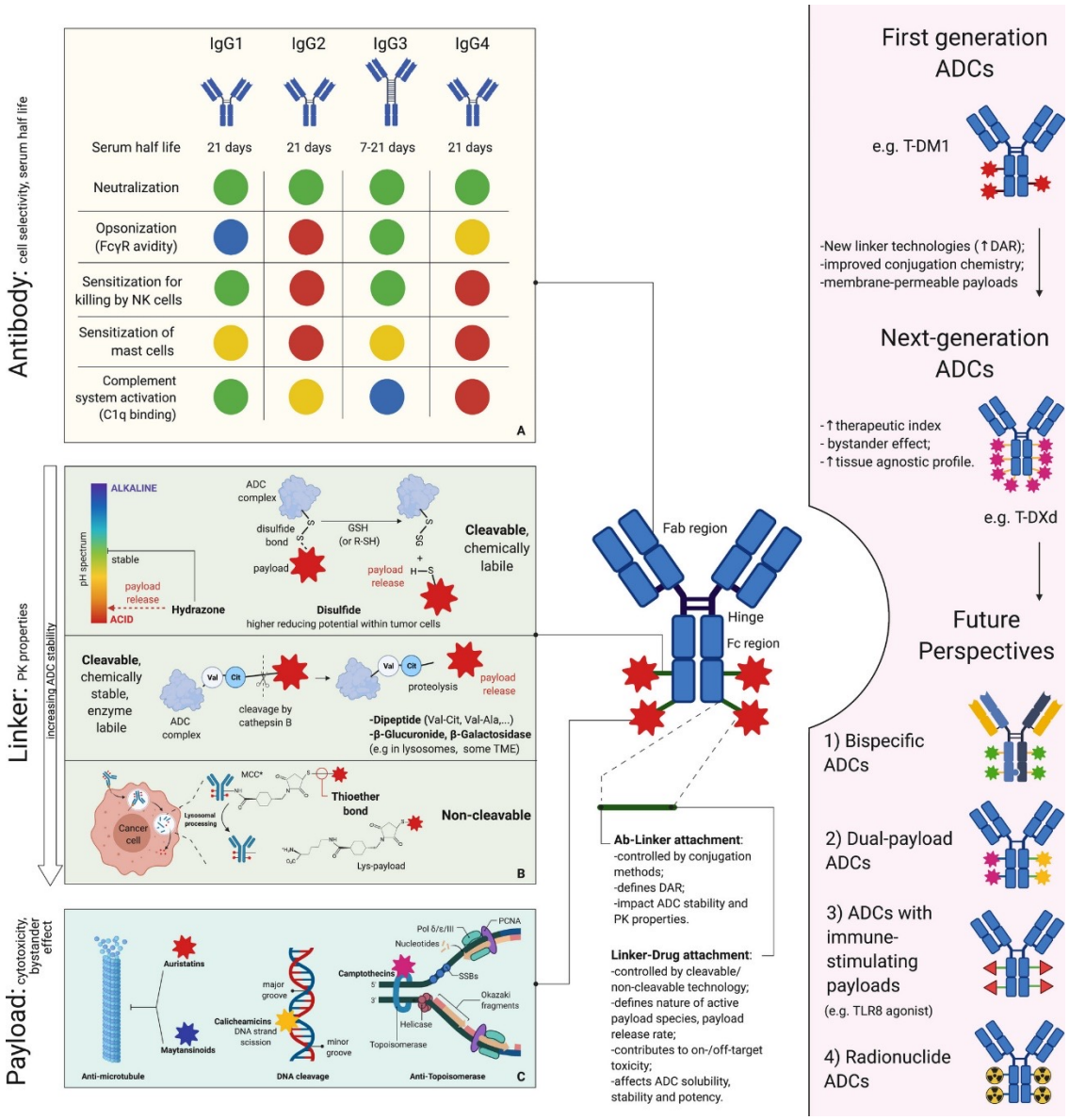
Novel Antibody-Drug Conjugates: Modular Compounds

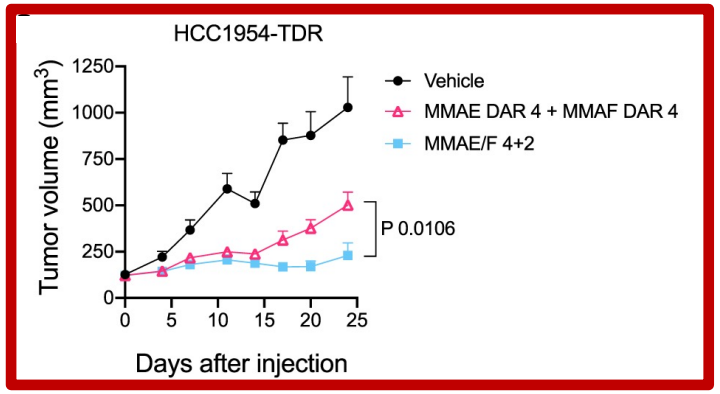
- ADCs are **modular compounds**. Modifying each component can unlock novel therapeutic opportunities.
- **Antibody:** bispecific, trispecific, masked
- **Linker:** cleavable, site-specific, glycoengineered
- **Payload:** dual-payload, immune-stimulating, radionuclide

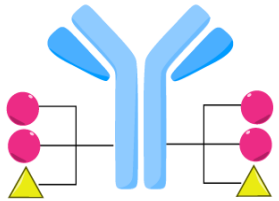


Tarantino P, et al. CA Can J Clin 2022;72:165-182.

Novel Antibody-Drug Conjugates: Future directions

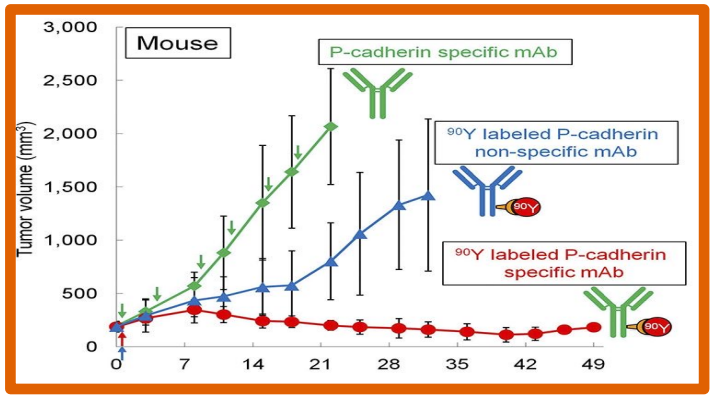
DUAL PAYLOAD ADCs



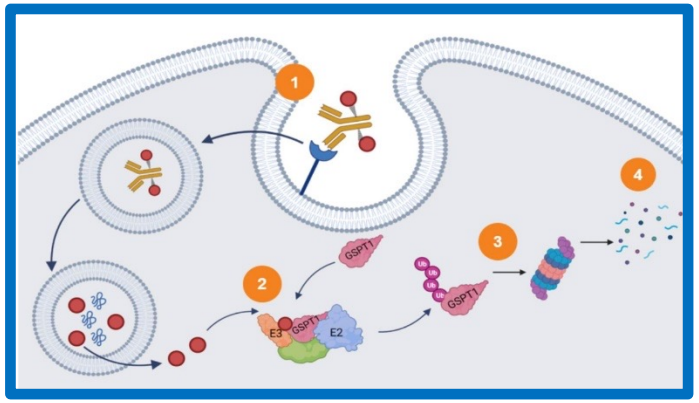


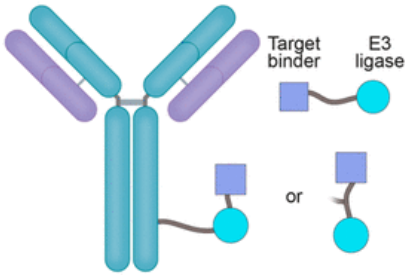
MMAE/F 4+2

RADIO-IMMUNO-CONJUGATES

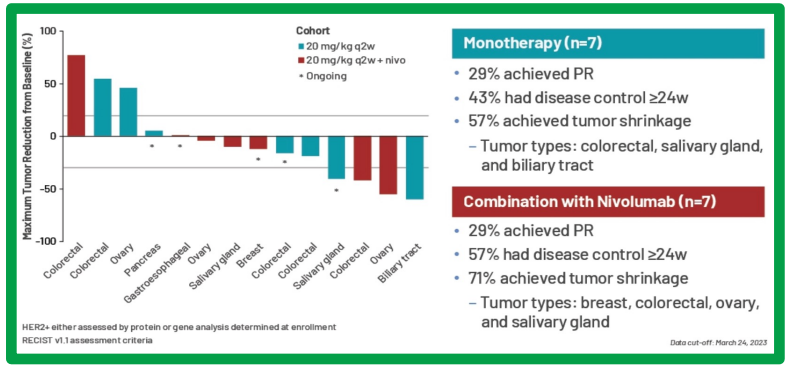


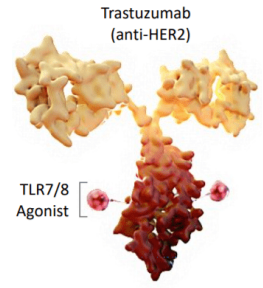
PROTAC-ANTIBODY CONJUGATES





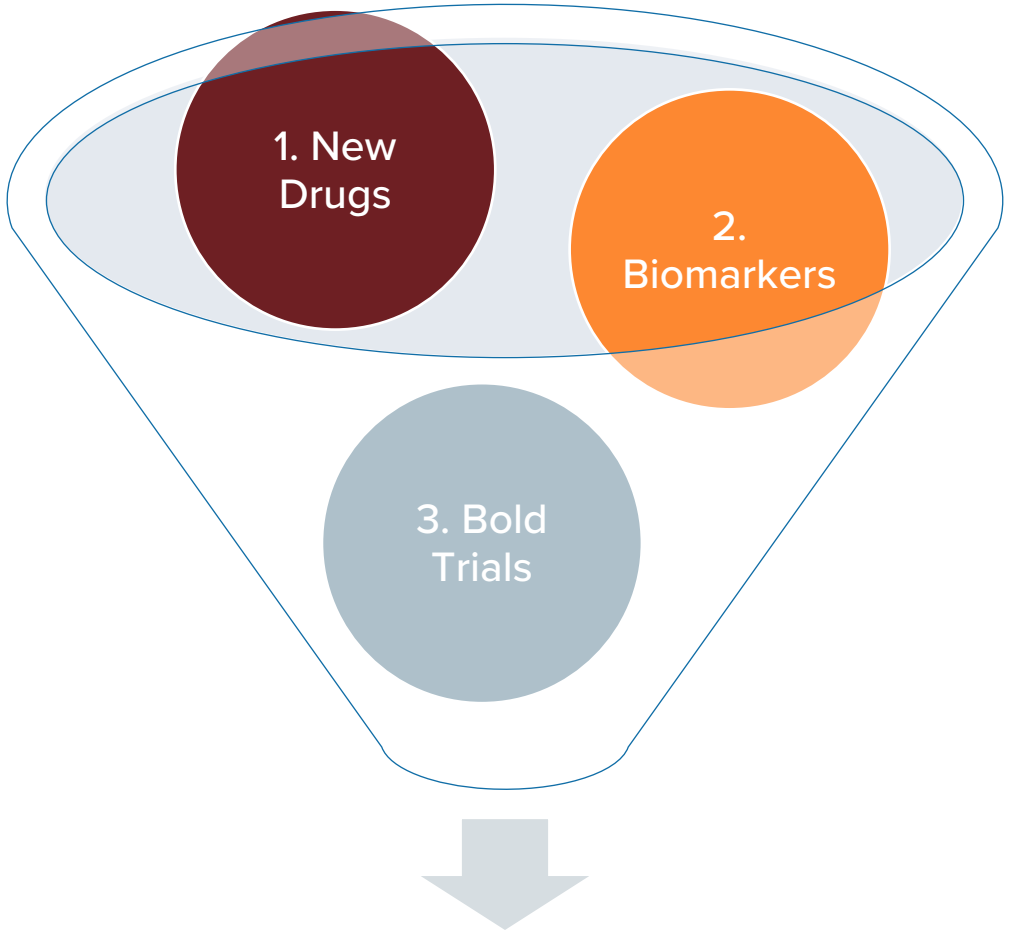
IMMUNO-STIMULATING CONJUGATES (ISACS)





Yamazaki CM. et al *Nat Commun 2021*; Li Bob et al. *ASCO Annual Meeting 2023*; Hurvitz S. et al. *ASCO Annual Meeting 2023;* Funase Y. et al. *J Nuclear Med 2021*

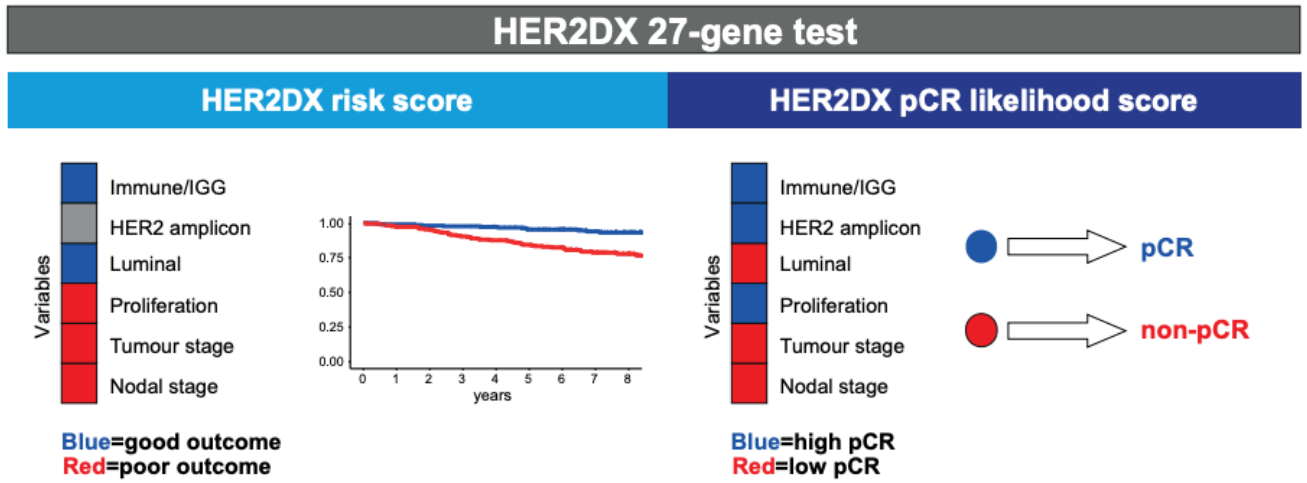
Recipe for Advancement in HER2 Targeting



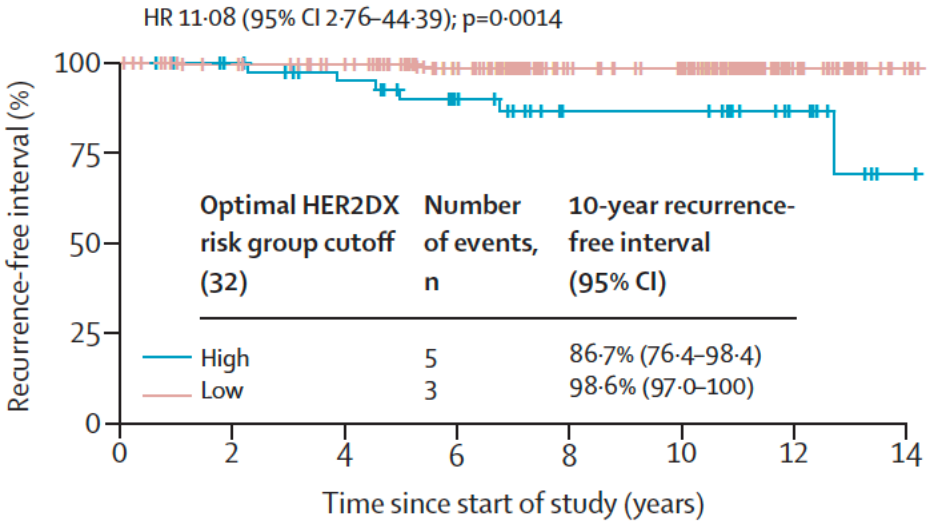
HER2DX

HER2DX is a tool incorporating tumor size, nodal staging, and 4 gene expression signatures tracking immune infiltration, tumor cell proliferation, luminal differentiation, and the expression of the HER2 amplicon, into a single score.

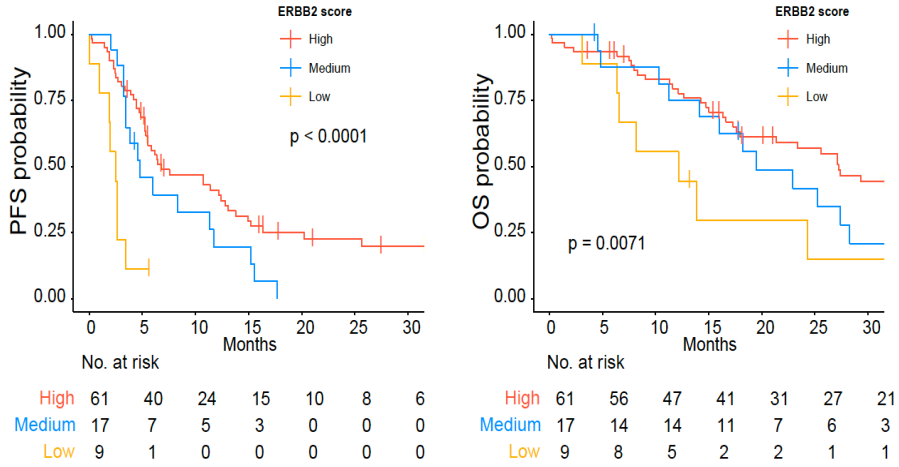
The score was shown in retrospective analyses to be strongly prognosis both in the early and advanced setting (T-DM1)



EARLY SETTING



ADVANCED SETTING

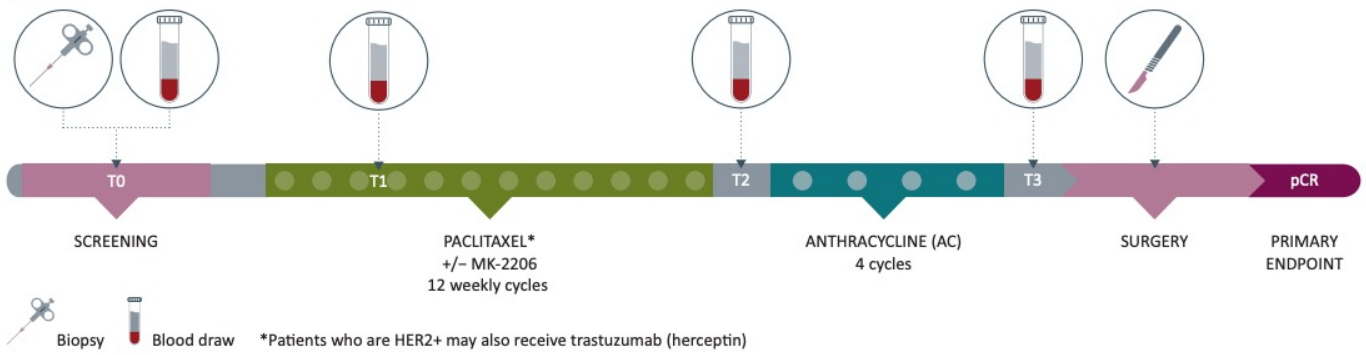


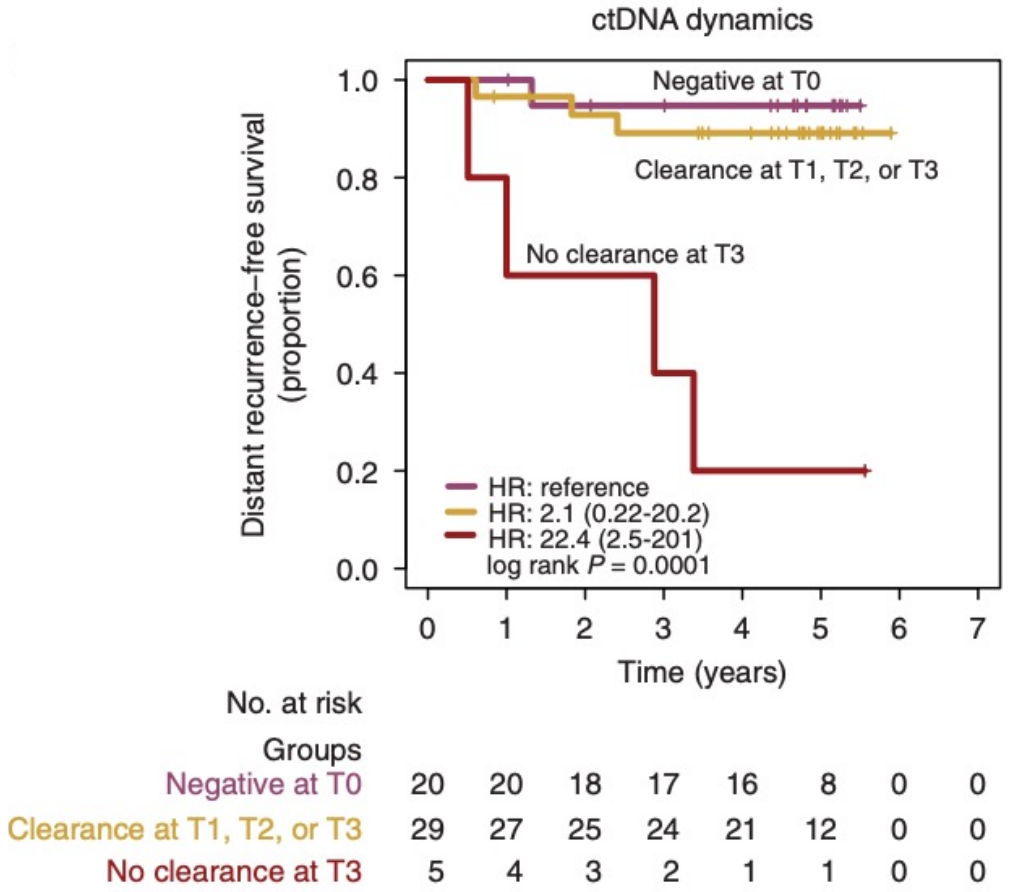
Prat A, et al. EBioMedicine. 2022; Tolaney SM, Tarantino P. et al Lancet Oncology 2023

Circulating Tumor DNA

The dynamics of **circulating tumor DNA** (**ctDNA**) in plasma can provide important prognostic information.

Patients with persistence of detectable ctDNA after (neo)adjuvant treatment have a poor prognosis and may warrant an escalation of treatment.

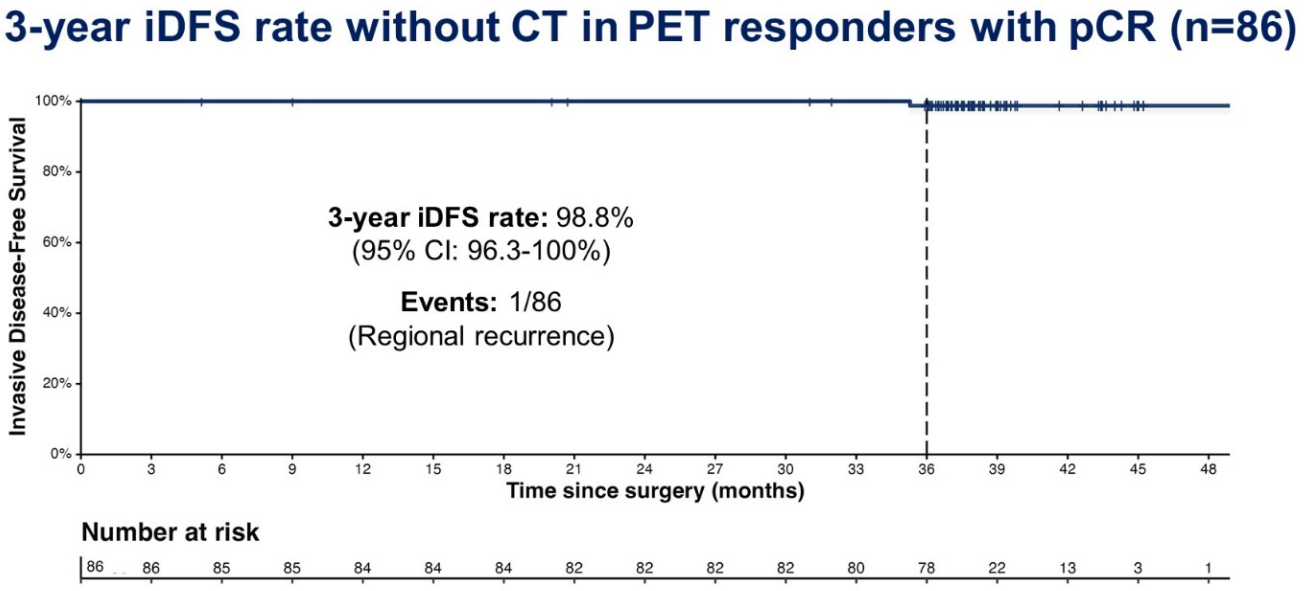


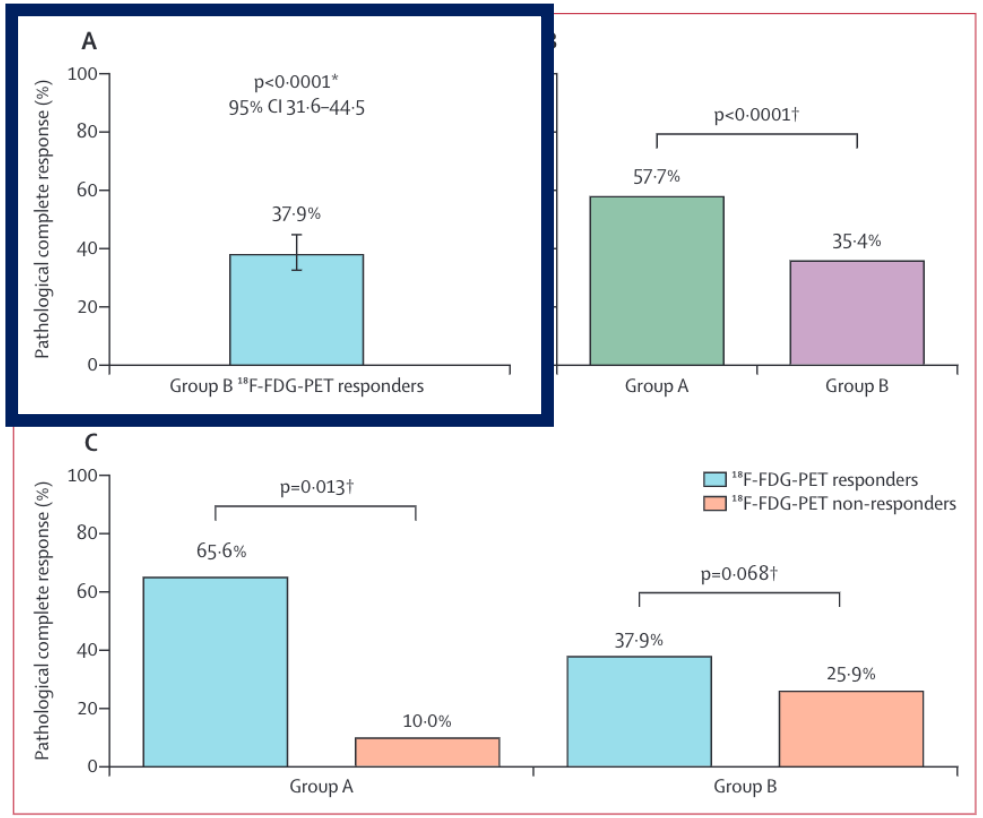


Magbanua MJM, et al. Ann Oncol. 2021;32:229-239.

Positron Emission Tomography (PET)

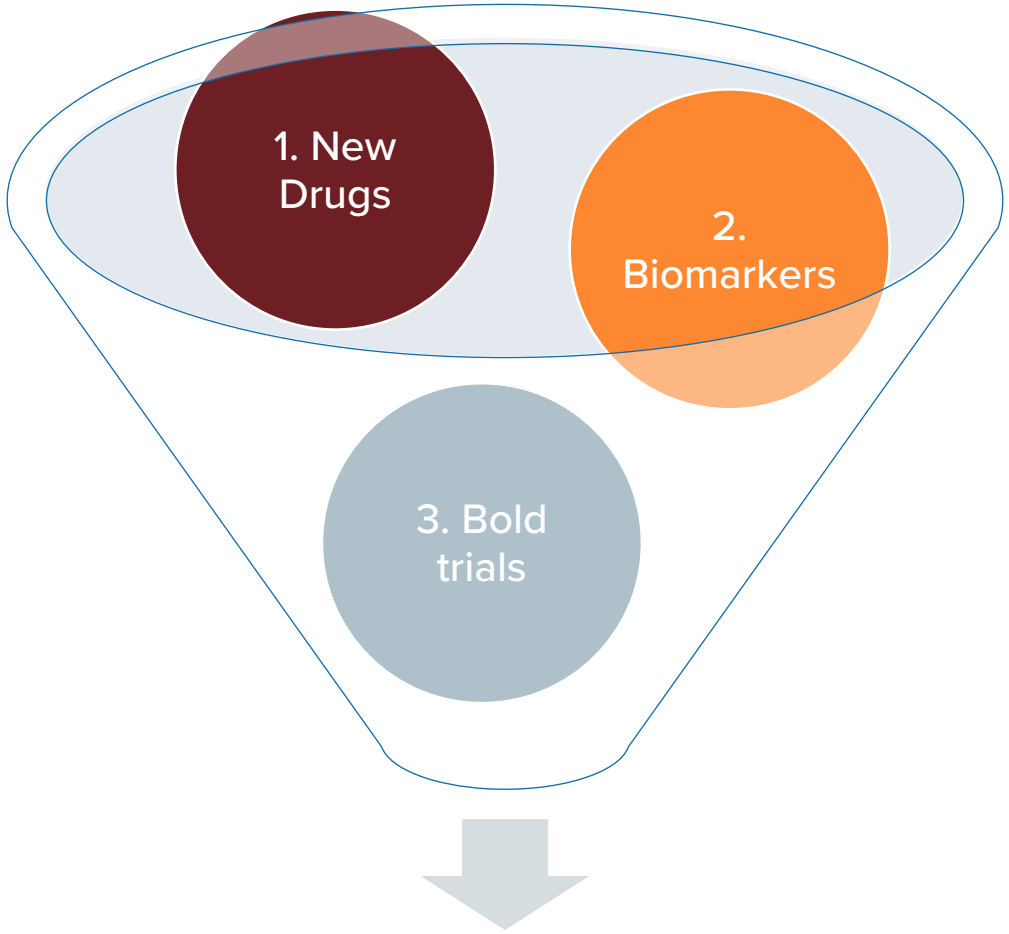
In the **PHERGain trial**, a PET scan after only 2 cycles of **neoadjuvant trastuzumab + pertuzumab** allowed to identify HER2+ EBC patients with a high probability (37.9%) of achieving pCR with **no chemotherapy**





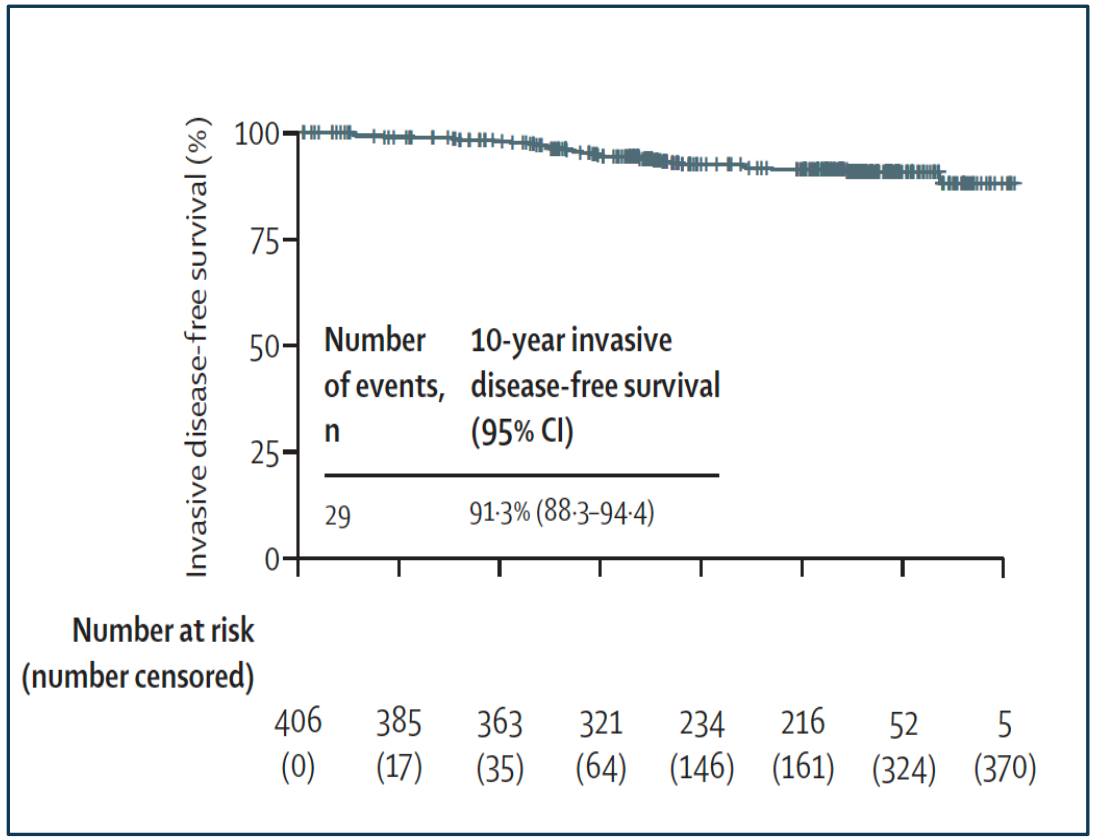
JM Pérez-García et al. Lancet Oncology 2021; JM Pérez-García et al. Lancet 2024

Recipe for Advancement in HER2 Targeting

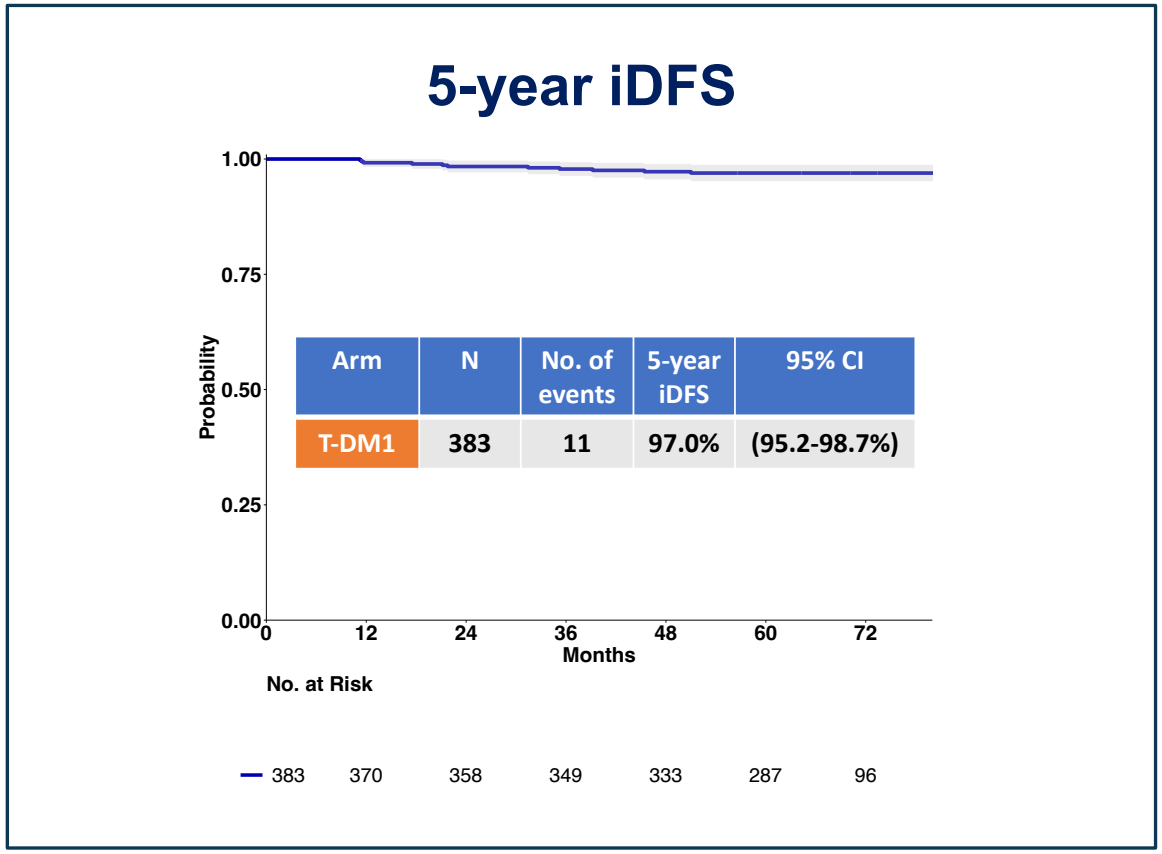


Can We Cure Stage I HER2+ Tumors With Fewer Side Effects?

The **APT** (paclitaxel / trastuzumab) and **ATEMPT** (T-DM1) regimens lead to **outstanding long-term outcomes** and low rate of side effects in patients with stage I HER2+ BC.



Tolaney S.M, Tarantino P. et al. Lancet Oncology 2023



Tarantino P. et al. J Clin Onc, in press

Can We Further Extend the Benefit of Anti-HER2 Treatments?

The DESTINY-Breast06 phase 3 study includes IHC 0 with "ultralow" expression and may expand the population of patients deriving benefit from T-DXd

Archived sample

- HER2 low (IHC 1+ 2+)

  or

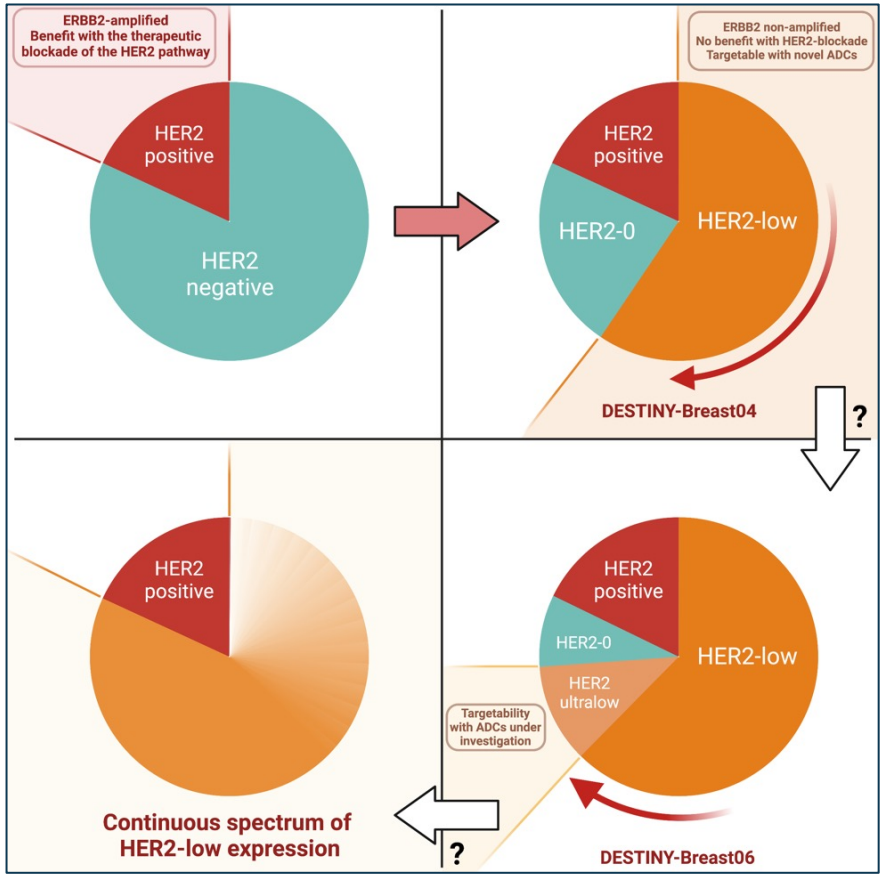
- **HER2 ultralow (IHC >0 <1+)**
- HR+
- ≥2 lines ET or POD on 1st line CDK4/6 inhibitor

R

N = 850

Trastuzumab deruxtecan (T-DXd)

Physician's choice of single-agent
capecitabine, paclitaxel, nab-paclitaxel



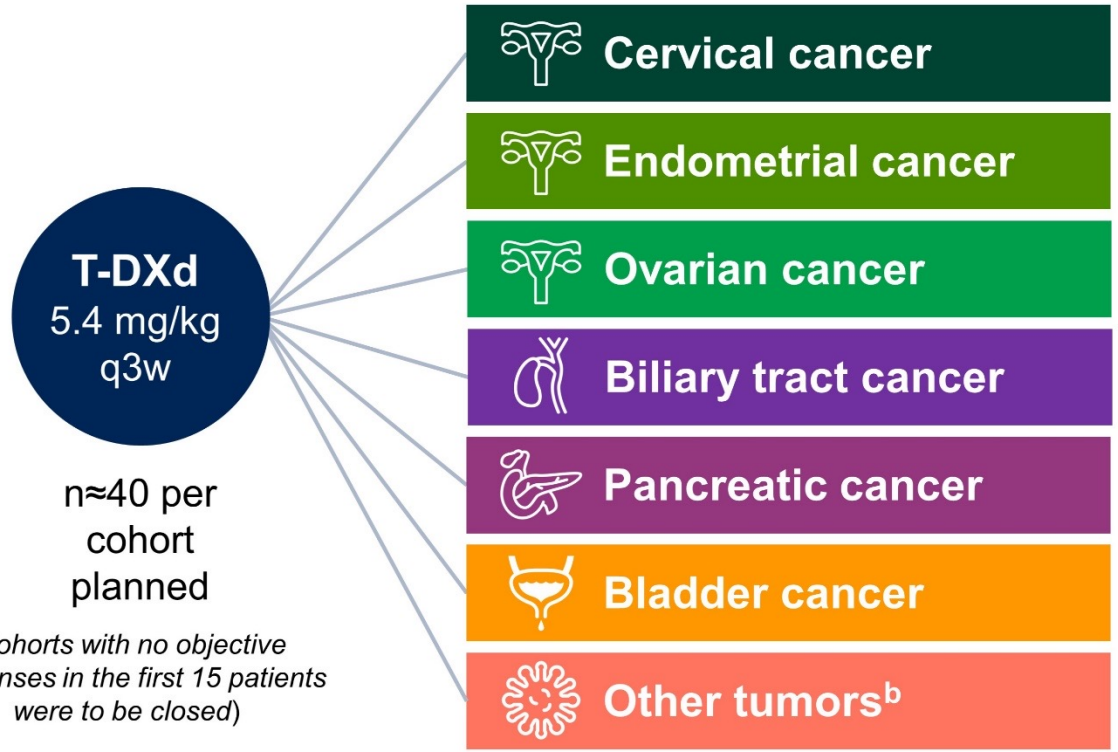
Key differences with DB04: larger (n=850), includes HER2 "ultralow", restricted to HR+ disease, only chemo-naive patients

Tarantino P et al. Cancer Discovery 2022

Can We Expand the Benefit of Anti-HER2 ADCs to all tumor types?

An open-label, multicenter study (NCT04482309)

- Advanced solid tumors not eligible for curative therapy
- 2L+ patient population
- HER2 expression (IHC 3+ or 2+)
  - Local test or central test by HercepTest if local test not feasible (ASCO/CAP gastric cancer guidelines[1])[a]
- Prior HER2-targeting therapy allowed
- ECOG/WHO PS 0–1



n≈40 per cohort planned

(*Cohorts with no objective responses in the first 15 patients were to be closed*)

Primary endpoint

- Confirmed ORR (investigator)[c]

Secondary endpoints

- DOR[c]
- DCR[c]
- PFS[c]
- OS
- Safety

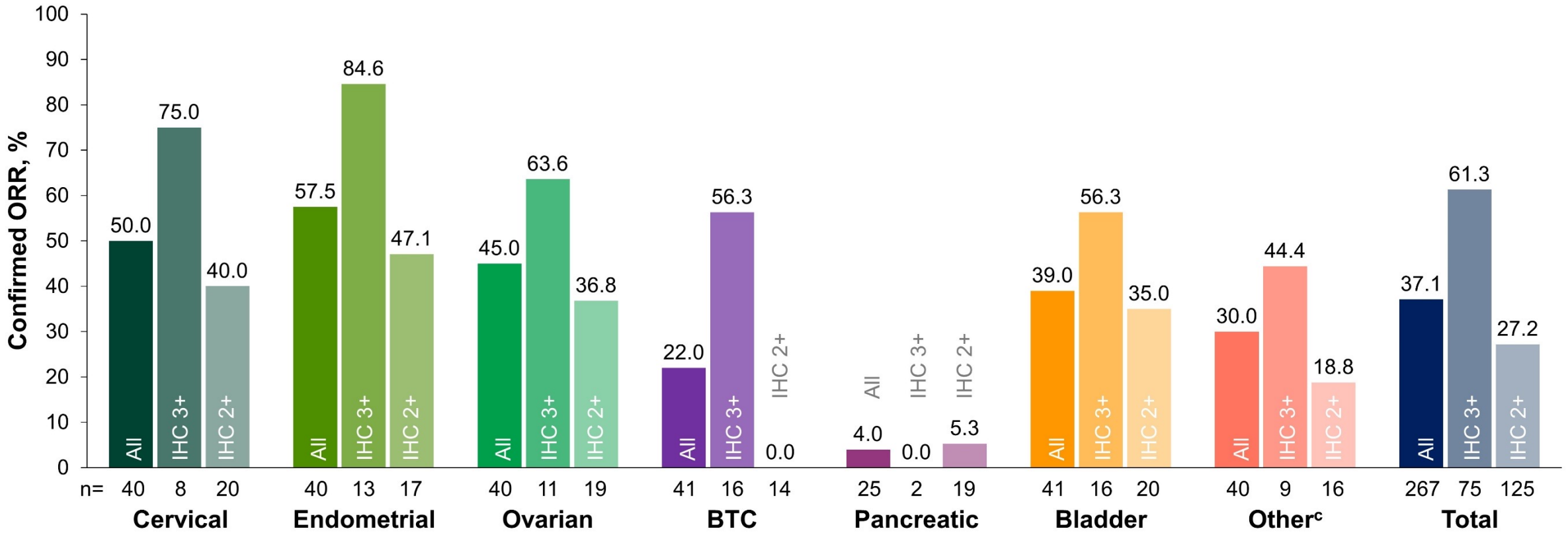
Data cut-off for analysis:

- Nov 16, 2022

Meric-Bernstam F. et al ASCO 2023

DESTINY-Pantumor-02 phase 2 trial

Objective Response Rate by HER2 status



	All patients (N=99)	IHC 3+ (n=46)	IHC 2+ (n=34)
Median DOR, months (95% CI)	11.8 (9.8–NE)	22.1 (9.3–NE)	9.8 (4.2–12.6)

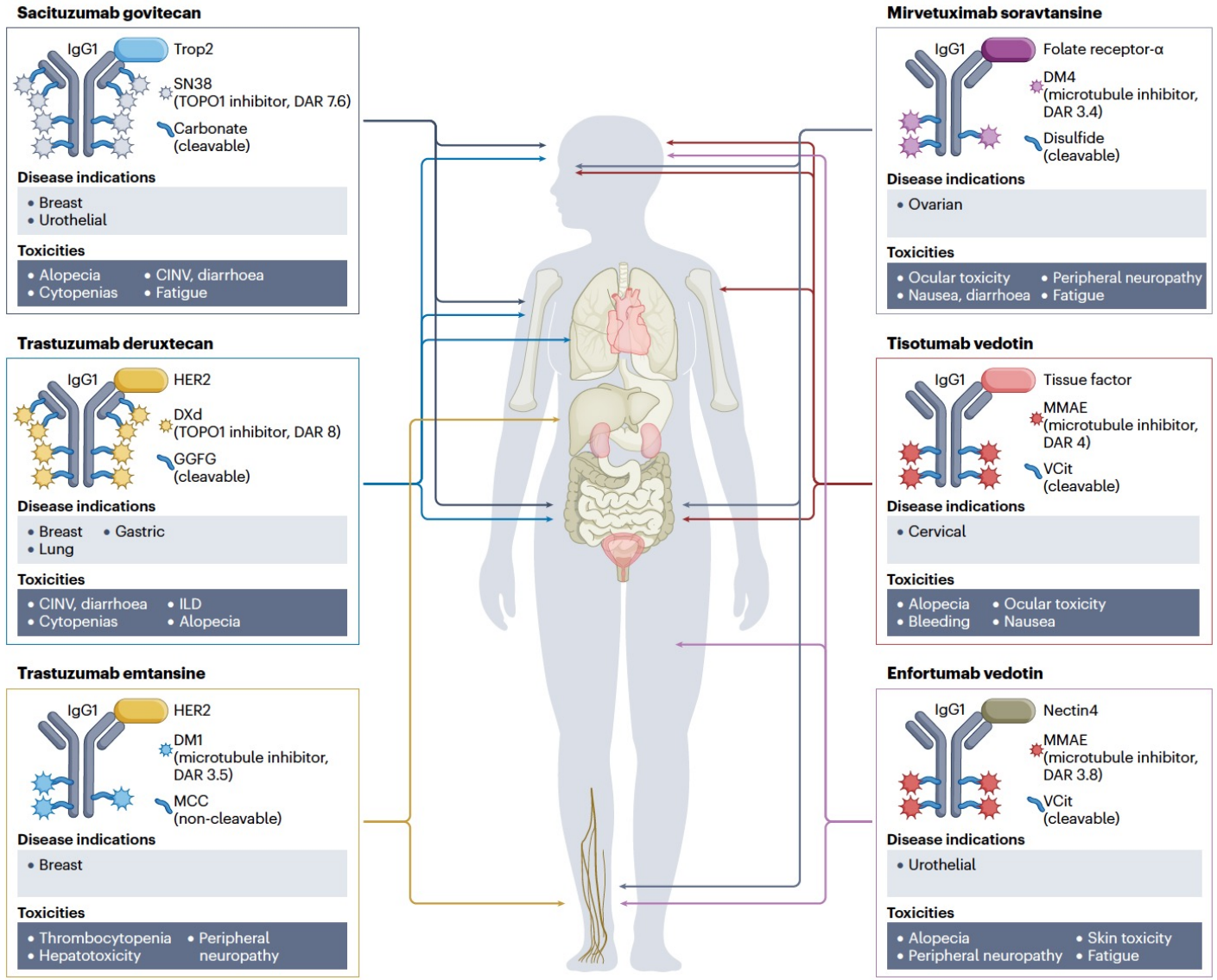
Meric-Bernstam F. et al ASCO 2023

April 5th, 2024

Accelerated approval granted to T-DXd for the treatment of any treatment-refractory HER2+ (IHC 3+) solid tumor

First agnostic approval of an ADC

Toxicities of T-DXd mostly related to the chemo payload



Tarantino P et al. Nat Rev Clin Onc 2023

The 5 S rules to manage ILD

1

Screen

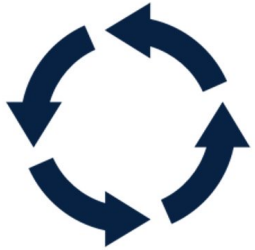
- Careful patient selection is warranted before initiating T-DXd to optimize the monitoring strategies based on the baseline risk
- Screening continues during treatment, with regular clinical assessments to exclude signs/symptoms of ILD

2

Scan

- The fundamental diagnostic tools for ILD remain radiological scans, with preference for high-resolution CT scans of the chest
- A baseline scan is recommended, with repeat scans to be performed every 6-12 weeks

3



Synergy

- Minimizing the risk of ILD involves teamwork, which includes educating patients and all the care team, as well as multidisciplinary management once ILD is suspected

4

Suspend Treatment

- T-DXd should always be interrupted if ILD is suspected; it can only be restarted in the case of asymptomatic ILD that fully resolves

5

Steroids

- The mainstay for treating T-DXd–induced ILD remains corticosteroids, with the dose to be adapted to the toxicity grade

Tarantino P et al. JCO Onc Prac 2022

Take-Away Messages

- Targeting HER2 with mAbs, TKIs and ADCs has led to **remarkable benefits in both early-stage and metastatic HER2+ breast cancer**
- More recently, the development of T-DXd has allowed for an expansion in the role of HER2-targeting to **HER2-low** tumors and **across HER2+ solid tumors**
- The recipe for further advancement in HER2 targeting involves the **refinement of HER2-targeted dfrugs**, **novel biomarkers** and **innovative trials**
- With increasing expansion in the indication for HER2-targeted ADCs, a concomitant **expansion in awareness on their toxicities** will be required

Thank you for your attention!

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