Treating BC in 2022:
Selection strategy for a better outcome

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Disclosures

Advisory role: Amgen, AstraZeneca, Bayer, Daiichi, EISAI, Genomic Health, Hengrui, Innate, Ipsen, Leo Pharma, Lilly, Merck, MSD, Novartis, Pfizer, Seattle Genetics

Speaker fees: Amgen, AstraZeneca, Bayer, Daiichi, EISAI, Genomic Health, Ipsen, Leo Pharma, Lilly, Merck, MSD, Novartis, Pfizer, Seattle Genetics

Research grants to my Institute: BMS, Roche

Therapeutic Approaches to tackle/delay Endocrine Resistance

- Endocrine therapy (single vs combination of ET)
- Maximizing sensitivity to endocrine therapy
  - Strategies targeting CDK4/6
  - Strategies to antagonize the growth factor pathways (mTor (everolimus), PIK3CA (alpelisib),…)
  - Strategies targeting genomic alterations of ESR1 (Elacestrant)
  - Strategies targeting the DNA repair pathway (PARP inhibitors)

Antibody – drug conjugates (targeted chemotherapy) (Sacituzumab govetican; T-DXd)

Advanced luminal breast cancer in clinical practice: Important questions (1)

1. CDK4/6 inhibitors as first-line or later lines ? → First-line
2. Which ET should we prescribe in first-line with CDK4/6 inhibitor (AI or fulvestrant)? → Whenever possible AI
3. Which CDK4/6 inhibitor ?
4. In the presence of non life-threatening visceral disease (lung + liver) : ET + CDK4/6 inh. or chemotherapy ? → ET+ CDK 4/6 inh.

Advanced luminal breast cancer : Important questions (2)

5. Tissue biopsy or liquid biopsy and the role of NGS (PIK3CA mutation ? ERS1 ? BRCA ? …) as predictive biomarkers and when?

→ After first-line therapy (ESMO)

6. Efficacy of PIK3CA inhibitor (Alpelisib) in PIK3CA mutated tumors and in CDK4/6 inhibitors pretreated patients? → Ongoing studies

7. Rechallenge with CDK4/6 inhibitors in patients pretreated with CDK4/6 inhibitors? → Promising early data (MAINTAIN trial)

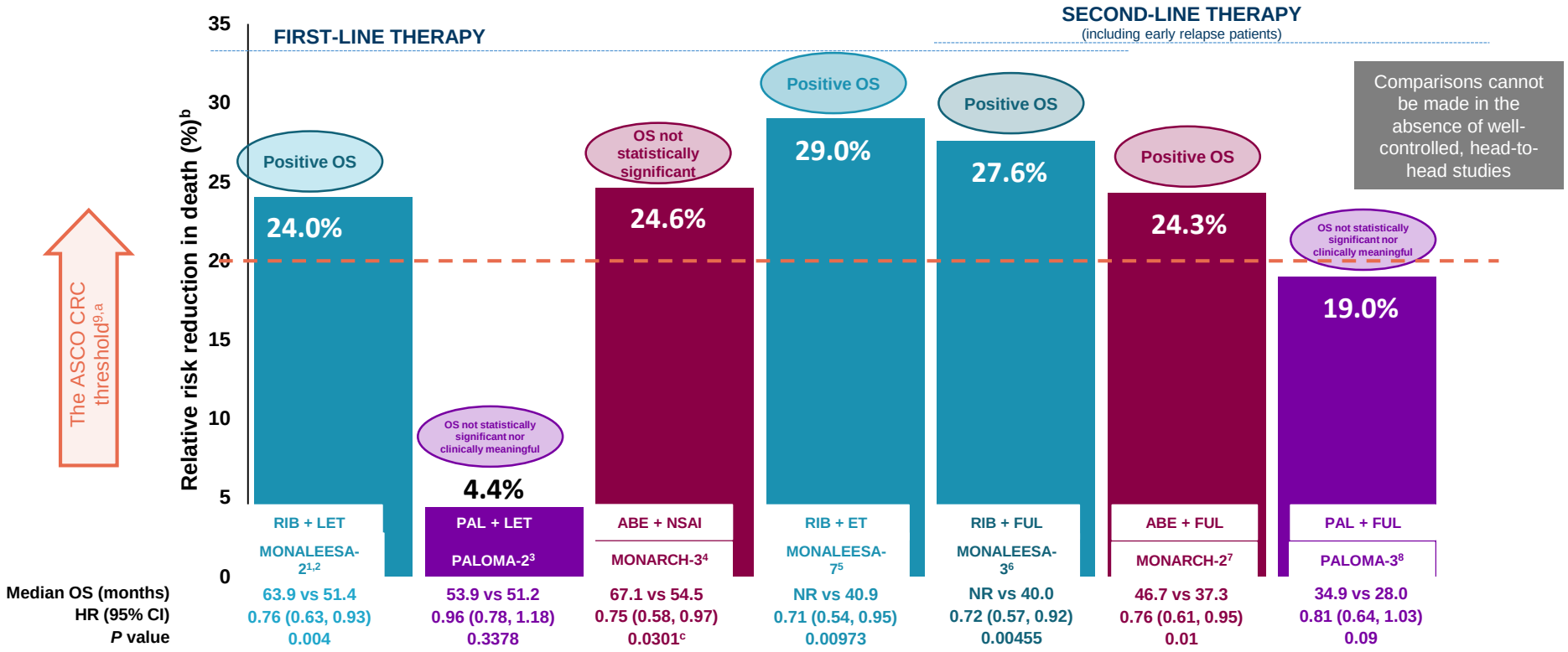
8. Setting of exemestane + everolimus therapy? → Later lines endocrine therapy

CDK 4-6i in Metastatic Breast Cancer: Pivotal Trials
Consistent PFS results for all drugs and settings

	PALOMA 1	PALOMA 2	PALOMA 3	MONALEESA 2	MONALEESA 7	MONALEESA 3	MONARCH 3	MONARCH 2	MONARCH Plus
Phase	II	III	III	III	III	III	III	III	III
No. of pts	165	666	521	668	672	726	493	669	463
Treatment	Palbo + letro vs letro	Palbo + letro vs letro	Palbo + fulvestrant vs fulvestrant	Ribo + letro vs letro	Ribo + tamoxifen or AI and GnRHa vs tamoxifen or AI + GnRHa	Ribo + fulvestrant vs fulvestrant	Abema + NSAI vs NSAI	Abema + fulvestrant vs fulvestrant	Abema + NSAI or fulvestrant vs NSAI or fulvestrant
Setting	1st line MBC	1st line MBC	Prior ET. Up to 1 chemo for MBC	1st line MBC	1st line MBC	≤1st line of ET for MBC	1st line MBC	No more than one ET. No prior chemo for MBC.	≥1st line HR+ HER2– MBC
PFS HR (95% CI)	0.49 (0.32- 0.75)	0.58 (0.46- 0.72)	0.46 (0.36- 0.59)	0.57 (0.46- 0.70)	0.55 (0.44-0.69)	0.59 (0.48- 0.73)	0.54 (0.41-0.72)	0.55 (0.45-0.68)	0.50 (0.35- 0.72) 0.38 (0.24-0.59)
OS HR (95% CI)	0.81 (0.49-1.35)	NM	0.81 (0.64- 1.03)	0.75 (0.52-1.08)	0.71 (0.54-0.95)	0.72 (0.57-0.92)	NM	0.76 (0.61-0.95)	NM

Adapted from Schettini et al, JNCI 2020

Ribociclib and Abemaciclib have demonstrated a consistent significant OS benefit across all phase 3 studies

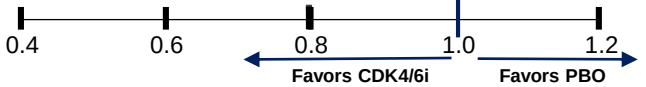


[a] The ASCO Cancer Research Committee defined incremental improvements in HR of OS ≥ 20% over standard therapy as a clinically meaningful outcome; the magnitude of benefit is based on hazard ratios and refers to the proportional improvement achieved with the addition of CDK4/6 inhibitors in comparison to the respective control groups. [b] As measured by 1 minus HR multiplied by 100. [c] P value did not reach threshold for statistical significance at this interim analysis of MONARCH 3

References: 1. Hortobagyi GN, et al. *N Engl J Med*. 2022;386:942-950. 2. Hortobagyi GN, et al. ESMO 2021. Oral LBA17_PR. 3. Finn RS, et al. ASCO 2022. LBA1003 4. Goetz, et al. ESMO 2022. LBA15. 5. Im SA, et al. *N Engl J Med*. 2019;38:307-316. 6. Slamon DJ, et al. *N Engl J Med*. 2020;382:514-524. 7. Sledge GW, et al. *JAMA Oncol*. 2020;6:116-124. 8. Turner NC, et al. *N Engl J Med*. 2018;15;379:1926-1936. 9. Ellis LM, et al. *J Clin Oncol*. 2014;32:1277-80.

Exploratory time to chemotherapy results among CDK4/6is

Trial	Study Tx		PBO, n/N (%)		Hazard Ratio by TTC	Hazard Ratio (95% CI)
	Events/ n	Median TTC, mo	Events/n	Median TTC, mo		
MONALEESA-2[1]	176/334	50.6	200/334	38.9		0.742 (0.606-0.909)
MONALEESA-7[2]	144/335	50.9	173/337	36.8		0.694 (0.556-0.867)
MONALEESA-3[3]	215/484	48.1	131/242	28.8		0.704 (0.566-0.876)
MONARCH 2[4]	200/446	50.2	135/223	22.1		0.625 (0.501-0.779)
PALOMA-2[5]	NR	38.1	NR	29.8		0.730 (0.607-0.879)
PALOMA-3[6]	347[a]	17.6	174[a]	8.8		0.58 (0.47-0.73)



Comparisons cannot be made in the absence of well-controlled, head-to-head studies

[a] The number of events was not reported.

References: 1. Hortobagyi GN, et al. *N Engl J Med*. 2022;386:942-950. 2. Tripathy D. SABCS 2020. Poster PD2-04. 3. Slamon DJ. ASCO 2021. Oral 1001. 4. Sledge GW. *JAMA Oncol*. 2020;6:116-124. 5. Finn RS, et al. ASCO 2022. LBA1003. 6. Turner NC. *N Engl J Med*. 2018;379(20):1926-1936.

NSAI or Fulvestrant ± CDK4/6 Inhibitors : Main Results from Phase III Studies

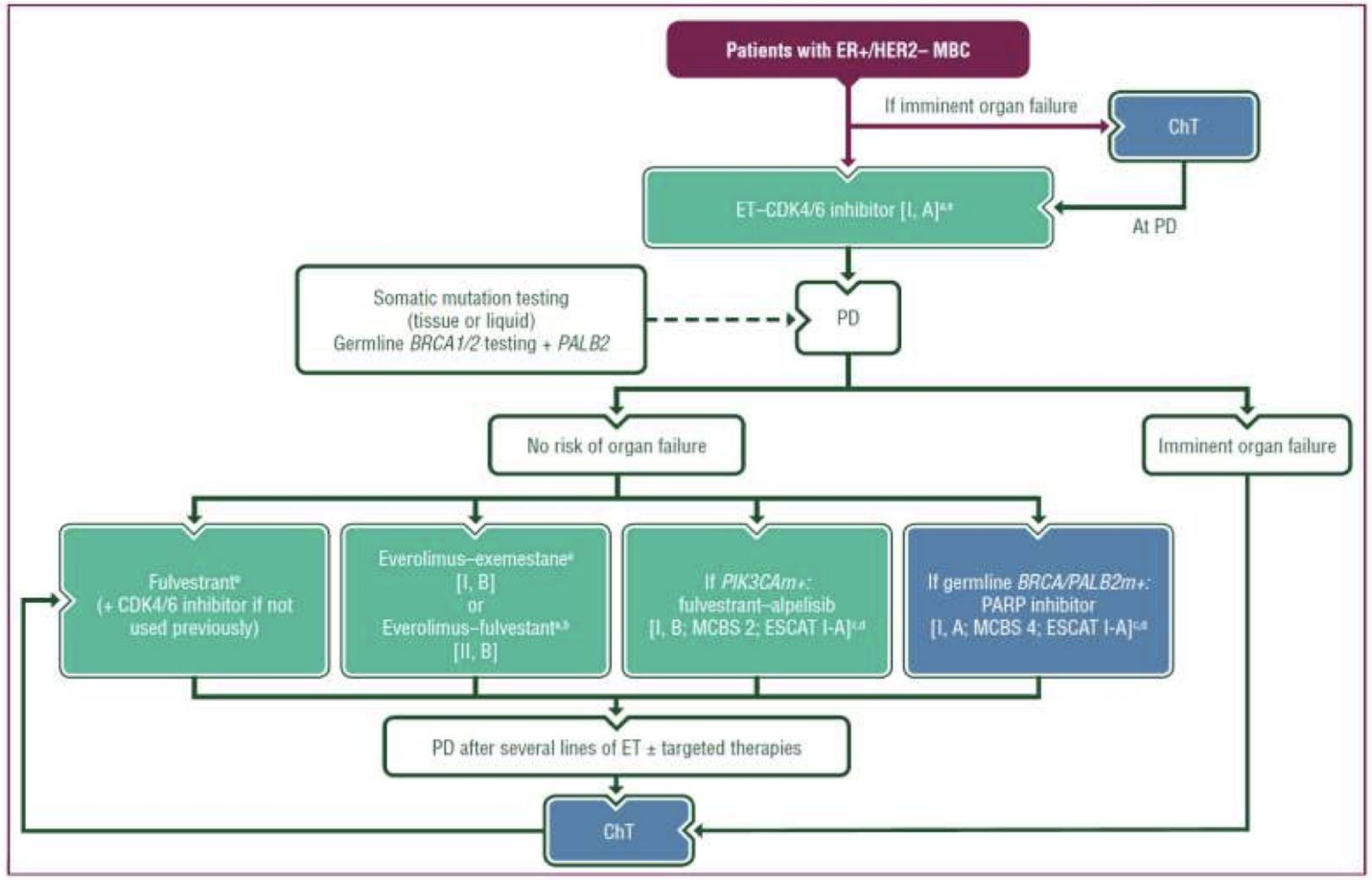
- Differences in doses and schedule, patient characteristics and prior therapies between drugs and studies
- For the 3 agents, basically equivalent PFS results
- Unprecedented increases of OS for Ribociclib + ET in the first-line setting (pre and postmenopausal). Final results from MONARCH-3 are awaited but intermediate OS results are promising
- Clear differences in the main side effects

Palbociclib	Ribociclib	Abemaciclib
• Neutropenia but no significant neutropenia-related events • Fatigue	• Same as palbociclib • ↑ LFTs	• Less neutropenia • GI toxicity (diarrhea) • Reversible increases in creatinine • DVT (4%)

- Early management of AEs is mandatory to preserve QoL

ESMO Algorithm

HR+/HER2-



Gennarini et al.Ann Oncol 2021

Heavily pretreated : Sacituzumab govitecan (TROPICS-02)

HER2 low expressors : T-Deruxtecan (DESTINY – Bo4)

Luminal MBC : Selected reported results in 2022

- Elacestrant (a SERD) is a possible option in ESR mutated tumors (EMERALD trial : Modest PFS benefit/ Giredestrant and amcenestrant : negative results)
- Rechallenge with CDK4/6 inh in CDK4/6 inh pretreated and resistant pts needs confirmation (MAINTAIN Trial)
- Antibody drugs conjugates emerged as a therapeutic option in HR+ (TROPICS – 02)/(DESTINY B-04)
- Given activity in advanced setting, CDK4/6 inhibitors moved to adjuvant setting (PALLAS negative; MONARCHE E positive (longer FU results at SABCS 2022) ; NATALEE with Ribociclib (waiting results).

Ph-2 MAINTAIN Trial: F or E ± Ribociclib after PD on anti-estrogen therapy + CDK4/6 inh.

- N = 120 evaluable pts
- EndocrineTherapy: F: 83% / E: 17%
- Prior Palbo (84%), ribociclib (11%), abemaciclib (2%), other (3%)
- Median PFS: F or E + ribo: 5.33 mo vs 2.76 (placebo) [HR 0.56; P=0.004]
- PD free at : 6mo: 42% vs 24%

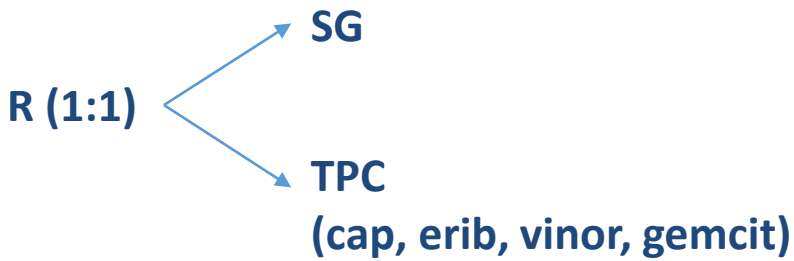
  12mo: 25% vs 7%

F: Fulvestrant; E: Exemestane

Kalinsky K LBA 1004, ASCO 2022

TROPiCS-02: A randomized ph 3 trial of Sacituzumab Govitecan vs TPC in HR+/HER2- MBC Study Design

MBC
PS 0-1
2-4 prior CT for MBC
1 prior CT if PD ≤ 12mo after (Neo)adj
Prior taxane
Prior CDK4/6 inh



Primary endpoint: PFS

Rugo HS LBA 1001, ASCO 2022

TROPiCS-02: A randomized ph 3 trial of Sacituzumab Govitecan (Trop2) vs TPC in HR+/HER2- MBC Results

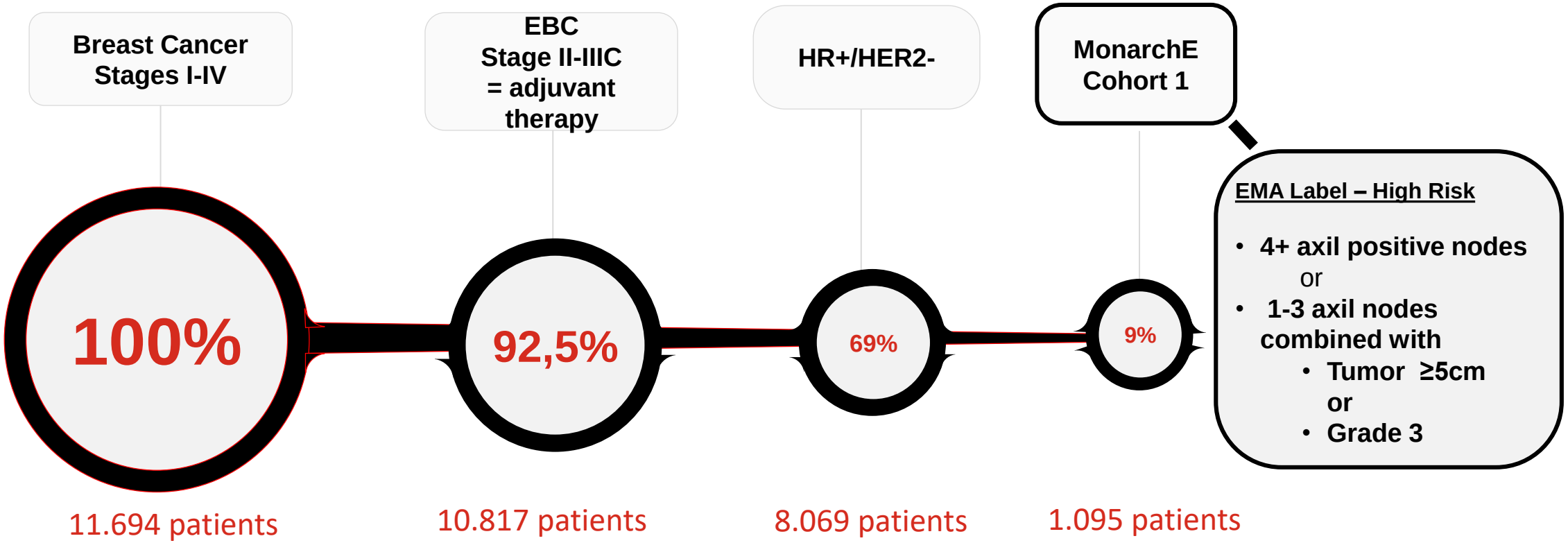
Characteristics	SG	TPC	HR
N° of pts	272	271	
Med prior CT (MBC)	3	3	
Med PFS (mo.)	5.5	4.0	0.66 (P=0.003) (95% CI, 0.53-0.83)
PFS (6mo)	46%	30%	
PFS (12mo)	21%	7%	
OS (mo)	13.9	12.3	0.84 (P=0.143)
ORR	21%	14%	
CBR	34%	22%	

Visceral M^+: 95%

Rugo HS LBA 1001, ASCO 2022

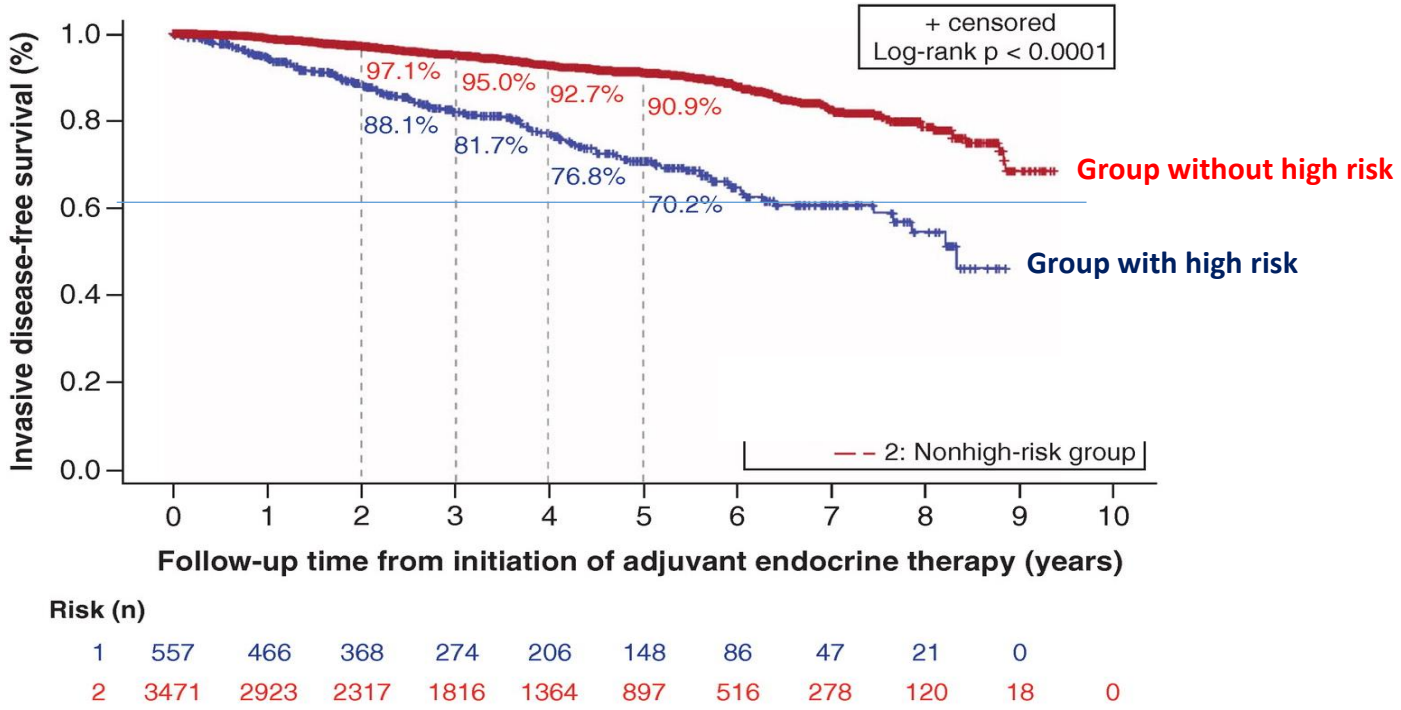
Abemaciclib indicated for High Risk HR+/HER2- eBC patients – added for 2 Years to Hormone Therapy

- **EMA Approved population : Cohort 1 of MonarchE (5.120 (91%) of 5.637 of ITT population)**
- **In Belgium this represents ~ 9% of all new patients with breast cancer**



Belgian Cancer Registry extrapolated for 2023 data; VanWalle et al BJMO 2020; EMA approved label 04/2022

Outcome of standard adjuvant treatments (Chemo / HormoneTx) is insufficient to reduce recurrence in this high risk population



EMA Label – High Risk

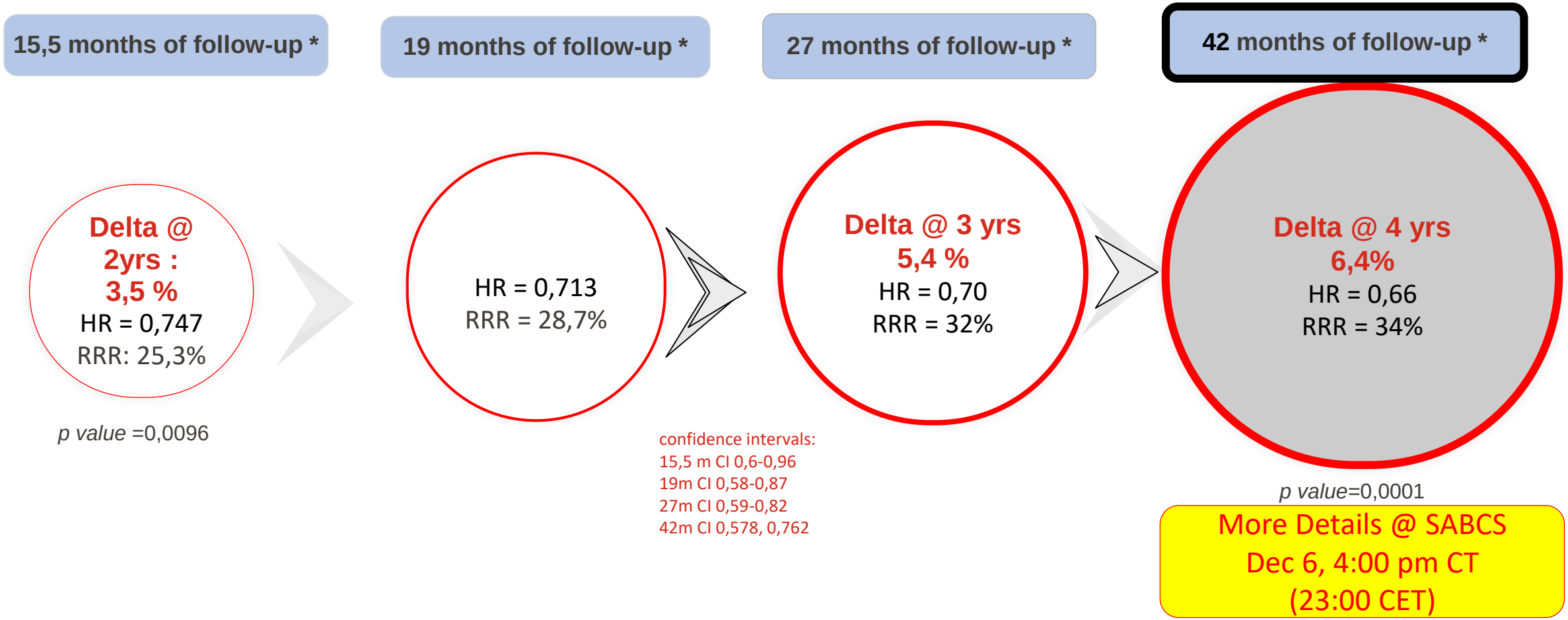
- **4+ axil positive nodes**
  or
- **1-3 axil nodes combined with**
  - **Tumor ≥5cm**
    or
  - **Grade 3**

- **One out of 2** women with high risk factors, **will relapse** over time (**30%** of relapses are metastatic **within 5Y - 50% within 9Y)**
- New therapies are needed to decrease this risk to relapse.

*** RWE data matched with MonarchE trial**

Sheffield KM et al. Future Oncol (2022)18(21),2667-2682.

Abemaciclib 2Y in adj setting
Clinical added value on IDFS (development of new tumor lesions)



➔ Absolute risk reduction on development of new tumor lesion of **6,4% at 4 years**

*: ITT IDFS data

Robust benefit in distant recurrence (DRFS) is expected to increase also the OS benefit

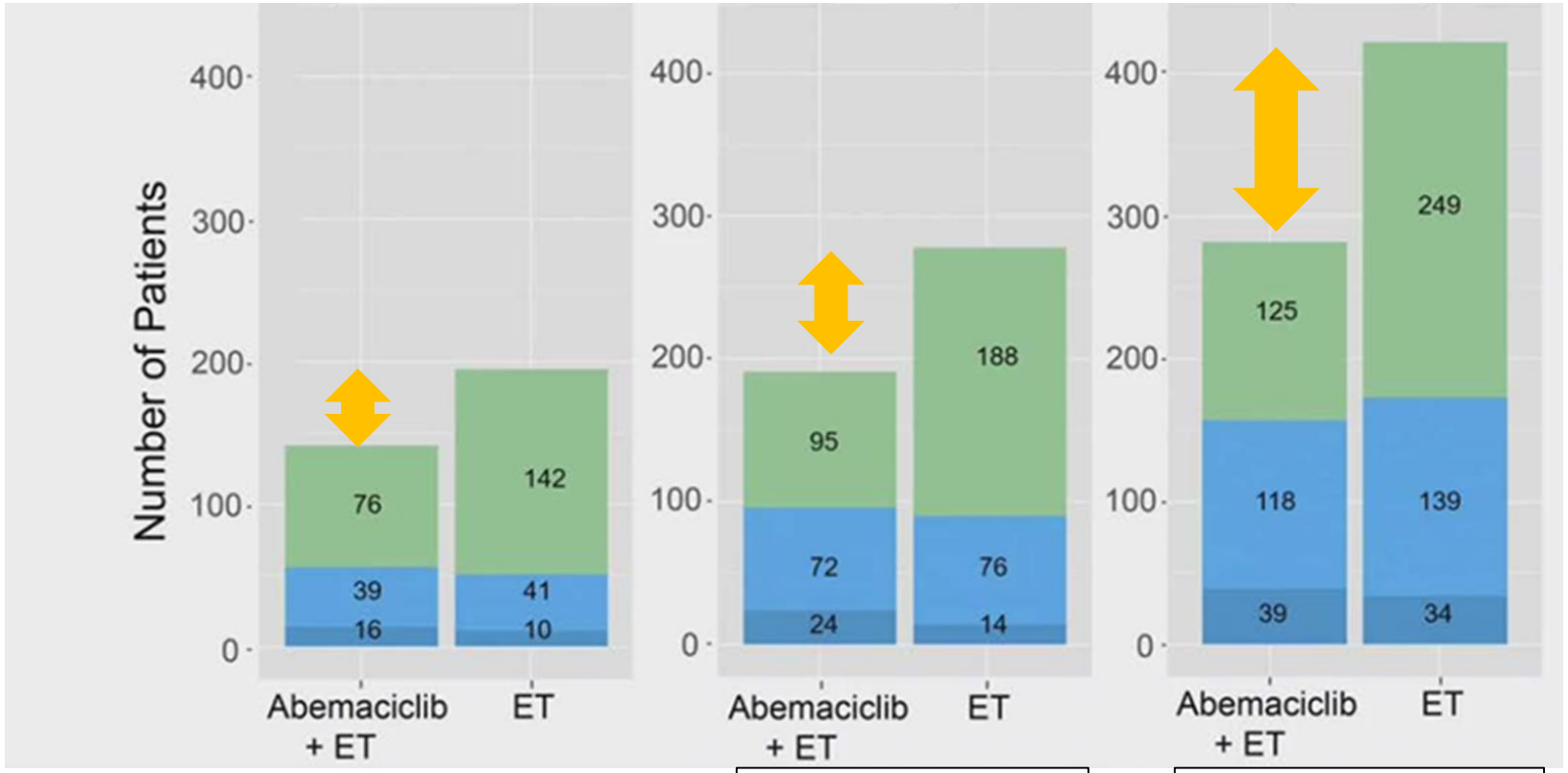
19 months FU

27 months FU

HR OS= 1,044
(CI 0.778, 1.401)

42 months FU ITT

HR OS = 0,929
CI 0.748, 1,153)



90% of patients finished the 2Y adj abemaciclib

100% of patients finished the 2Y adj abemaciclib

More Details @ SABCS
Dec 6, 4:00 pm CT
(23:00 CET)

HR+ / HER2 Non Amplified : Available Biological Agents in Breast Cancer

- Endocrine therapies +
    - CDK 4/6 inhibitors
    - Everolimus
    - Alpelisib (PIK3CA mutated tumors)
- Elacestrant (ESR1 mutated tumors)
- Olaparip, talazoparib (Germline BRCA mut.)
- Low HER2 expressors : Trastuzumab-deruxtecan

MONARCHE : Abemaciclib + ET : Adjuvant in high risk pts

Proposed Therapeutic Algorithm of HER2 amplified MBC in 2022 : An Evolving Field

- 1st L — Taxane + H + P or Vinorelbine + H + P
- 2nd L — T-deruxtecan
  - Active Brain mestastases : Tucatinib + H + Capecitabine
- 3rd L — Tucatinib or Neratinib / Capecitabine-based
  - → T-deruxtecan
- 4th L — Chemo + Margetuximab ⇄ T-DM1
- > 4th L — Chemo + H ⇄ H + Lapatinib

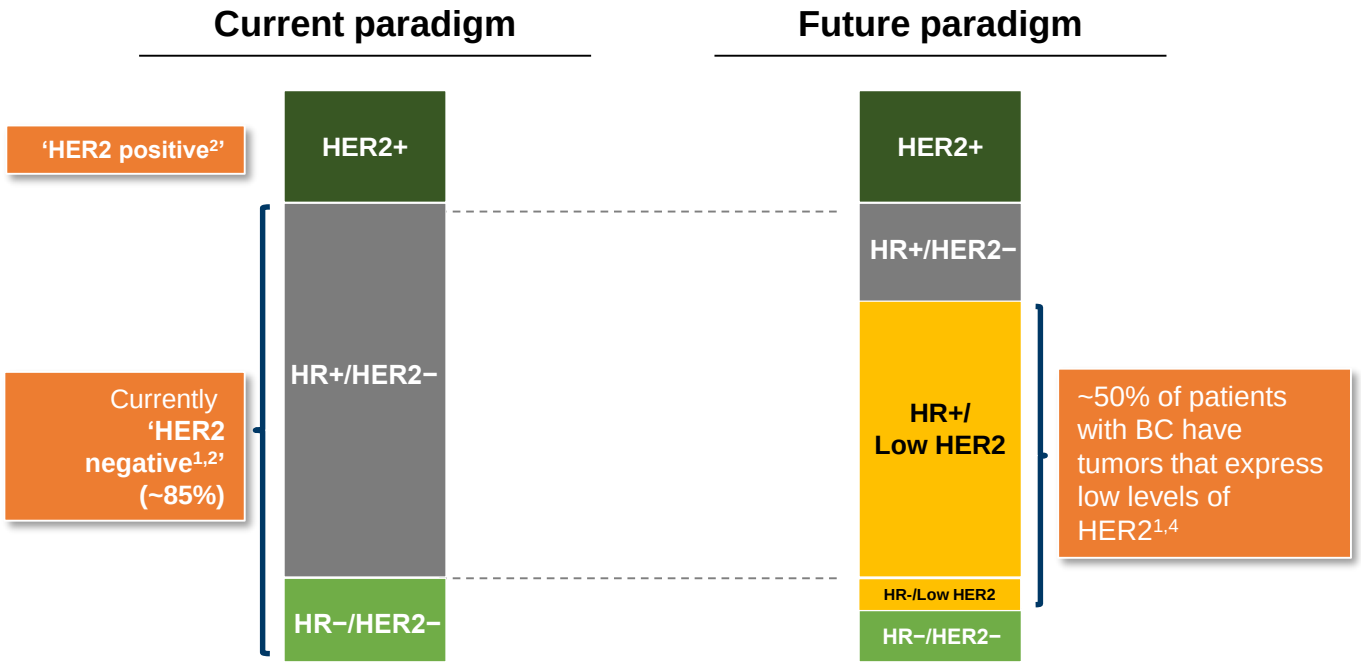
HER2 mutated/HR+ MBC : Neratinib + Fulverstrant + Trastuzumab (SUMMIT trial) → ORR 46% ; mDOR 10.9 mo ; mPFS: 8.3 mo

HER2 Low expressors MBC: T-Dxd (DESTINY-B04)

HER-2 Low Expressors Advanced Breast Cancer

Over half of breast cancers currently categorized as HER2 negative express low levels of HER2, which may be clinically meaningful[1]

Guidelines recommend assessment of HER2 status in all newly diagnosed patients with BC and those patients who develop metastatic disease[3]



1. Tarantino P, et al. *J Clin Oncol.* 2020;38(17):1951-1962; 2. Burstein HJ. *N Engl J Med*. 2005;353(16):1652-1654; 3. Wolff AC, et al. *J Clin Oncol.* 2018;36(20):2105-2122. 4. Marchiò C, et al. *Semin Cancer Biol*. 2021;72:123-135

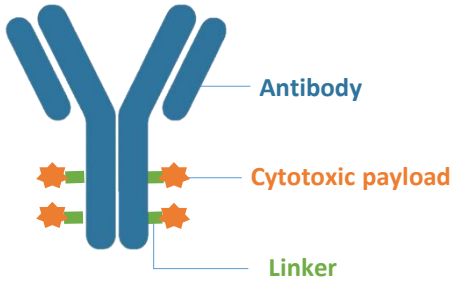
Antibody-drug conjugates = Targeted Chemotherapy!

- ADCs are monoclonal antibodies conjugated with a cytotoxic payload by a linker

- Rationale: To overcome the limitations of chemotherapeutic agents :

→Drug delivery to select therapeutic targets

→Improved therapeutic index (↑ activity and ↓ toxicity). Better QoL



V. Subbiah et al. Current Problems in Cancer 2021

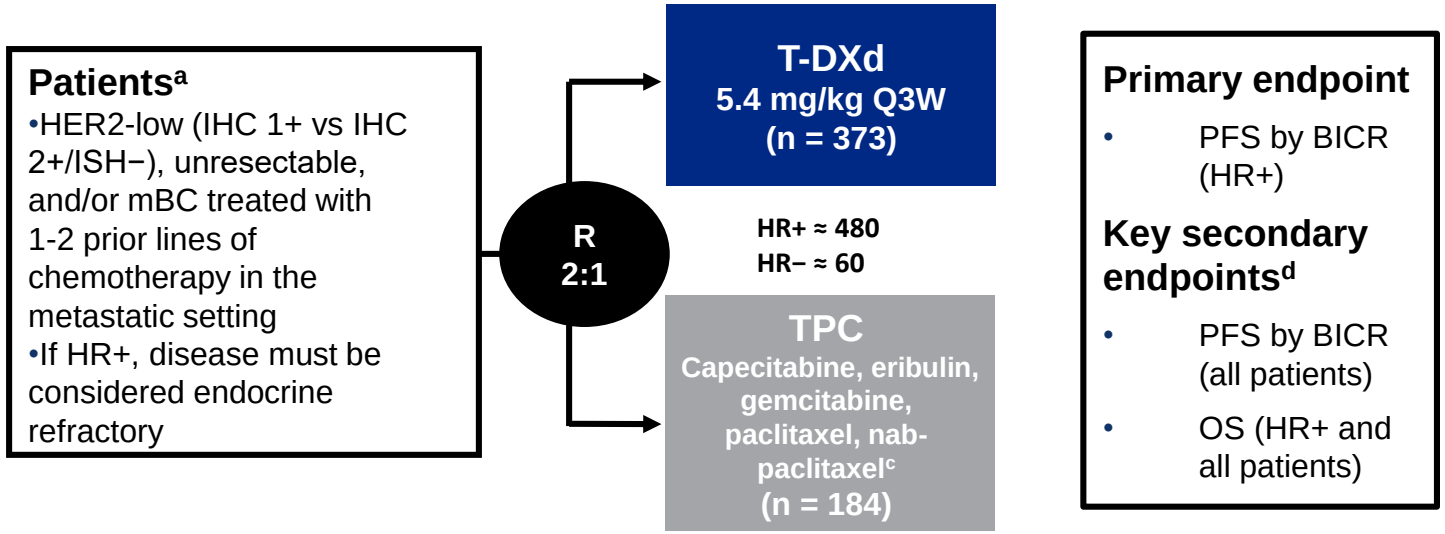
Characteristics of HER2-targeted ADC as an example : Similarities and divergences

Antibody-Drug Conjugate	T-DM1	SYD-986	T-Dxd
HER2 targeting vehicle	Trastuzumab	Trastuzumab	Trastuzumab
Linker	Non-cleavable	Cleavable	Cleavable
Drug–antibody ratio	3.5:1	2.8:1	8:1
Cytotoxic moiety	Maytansine derivative	Seco-DUBA	Exatecan derivative
Cytotoxic moiety MoA	Antimicrotubule (mitotic poison)	Alkylating agent	Topoisomerase I inhibitor
Diffusible cytotoxic moiety?	✗	✗	✓
Bystander killing effect?	✗	✓	✓
Targets HER2-positive or homogenous tumors?	✓	✓	✓
Targets HER2-low or heterogeneous tumors?	✗	✓	✓

Legend: MoA = mechanism of action.

- DESTINY-Breast04: Study Design

An Open-Label, Multicenter, Phase 3 Study (NCT03734029)



Stratification factors

•Centrally assessed HER2 status[b] (IHC 1+ vs IHC 2+/ISH−)

•1 vs 2 prior lines of chemotherapy

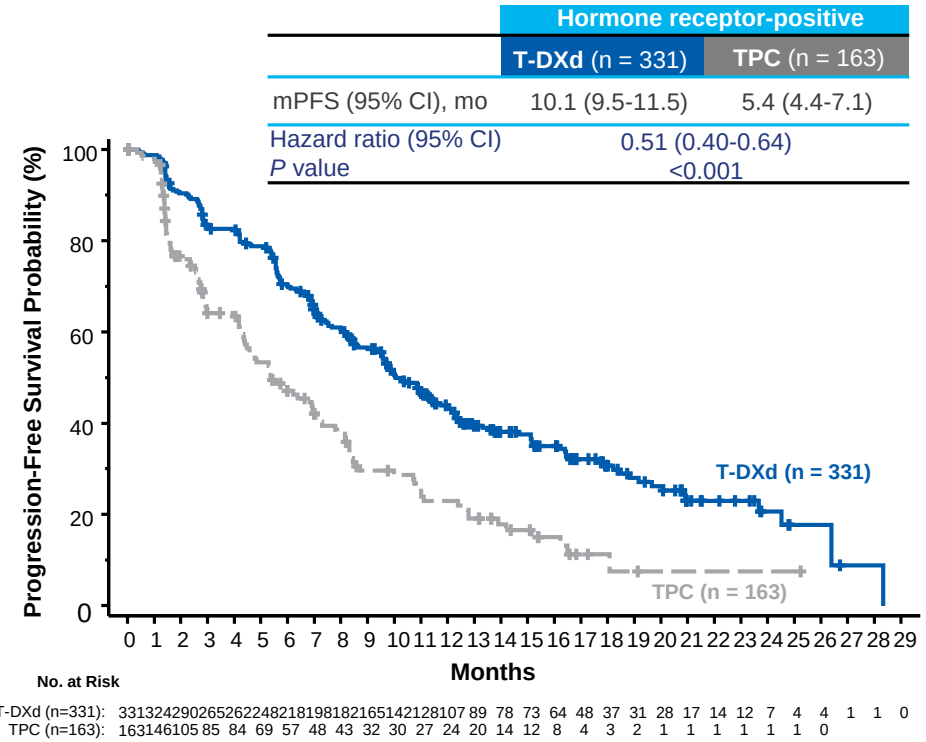
•HR+ (with vs without prior treatment with CDK4/6 inhibitor) vs HR−

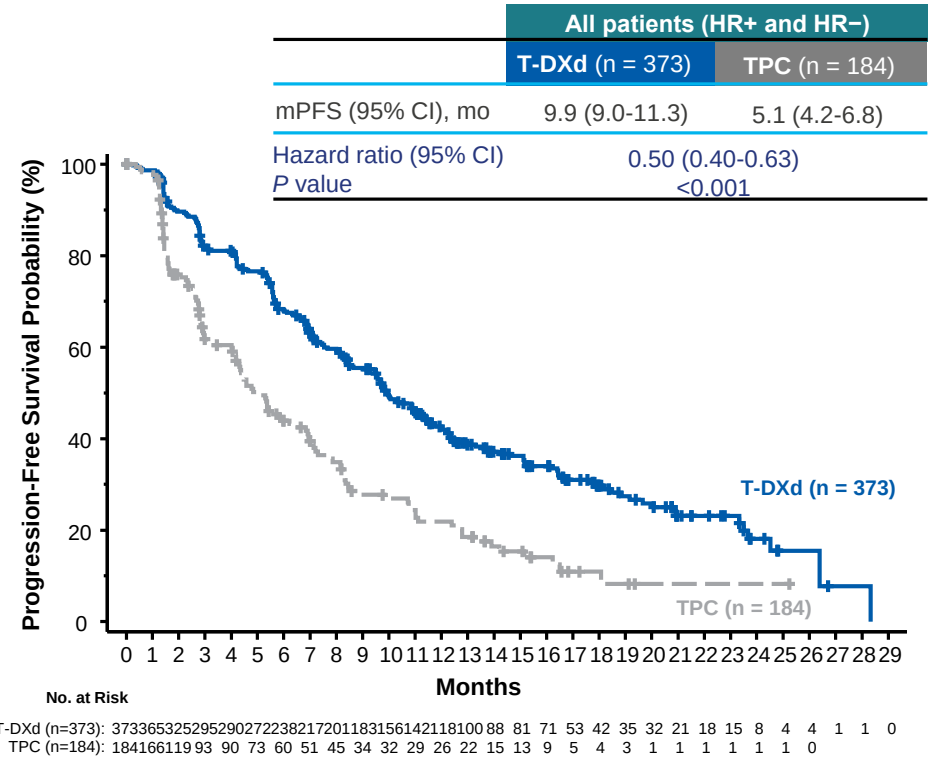
[a]If patients had HR+ mBC, prior endocrine therapy was required. [b]Performed on adequate archived or recent tumor biopsy per ASCO/CAP guidelines using the VENTANA HER2/neu (4B5) investigational use only Assay system. [c]TPC was administered according to the label. [d]Other secondary endpoints included ORR (BICR and investigator), DOR (BICR), and PFS (investigator) in the HR+ cohort and in all patients (HR+ and HR−), and safety in all treated patients; efficacy in the HR− cohort was an exploratory endpoint.

1. Modi S et al. *N Engl J Med*. 2022. doi: 10.1056/NEJMoa2203690. 2. Modi S et al et al. Oral presentation at American Society of Clinical Oncology (ASCO) 2022, June 5 (2022b, LBA3).

- DESTINY-Breast04: January 11, 2022 DCO

PFS in HR+ and All Patients





PFS by blinded independent central review.

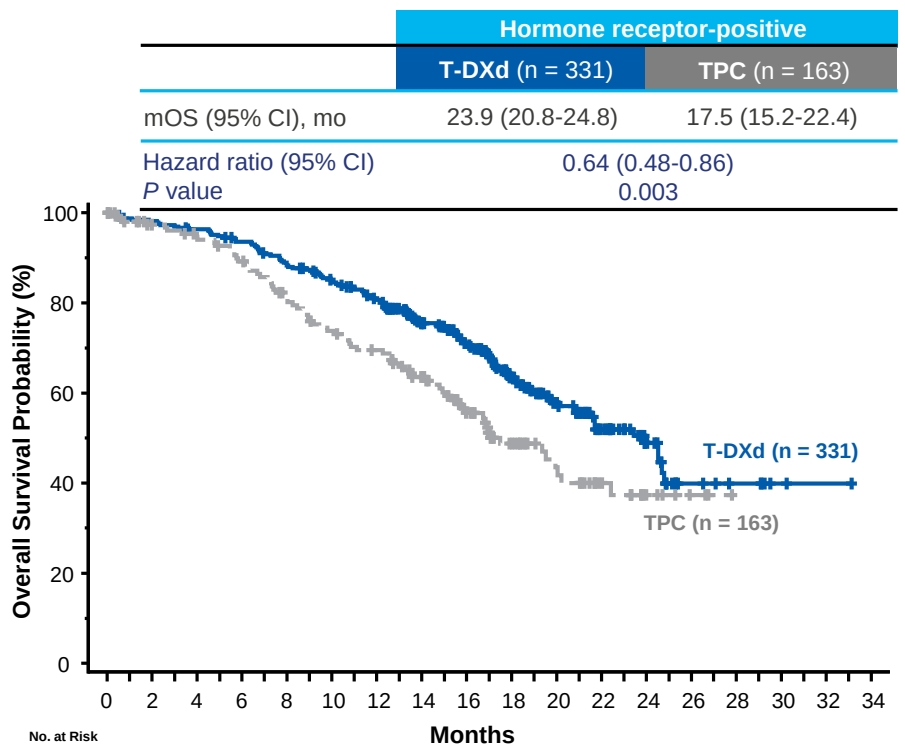
Modi S et al. *N Engl J Med*. 2022. doi: 10.1056/NEJMoa2203690.

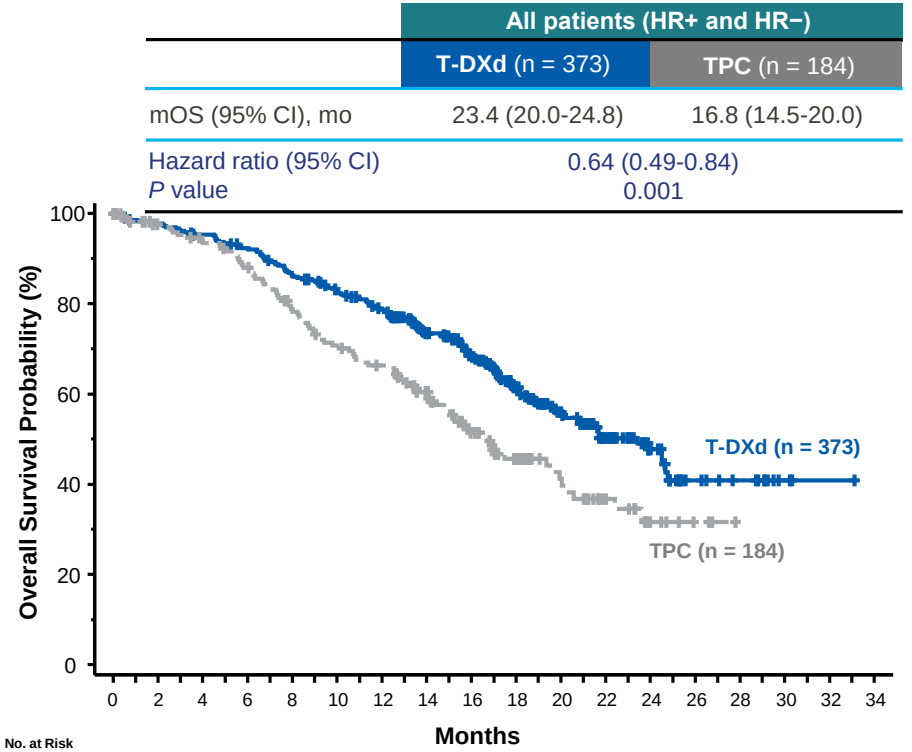
T-DXd is indicated for the treatment of HER2+ mBC after 2 prior anti-HER2 treatments

ADC/22/0185 Date of last revision: June 2022

- DESTINY-Breast04: January 11, 2022 DCO

OS in HR+ and All Patients





Modi S et al. *N Engl J Med*. 2022. doi: 10.1056/NEJMoa2203690.

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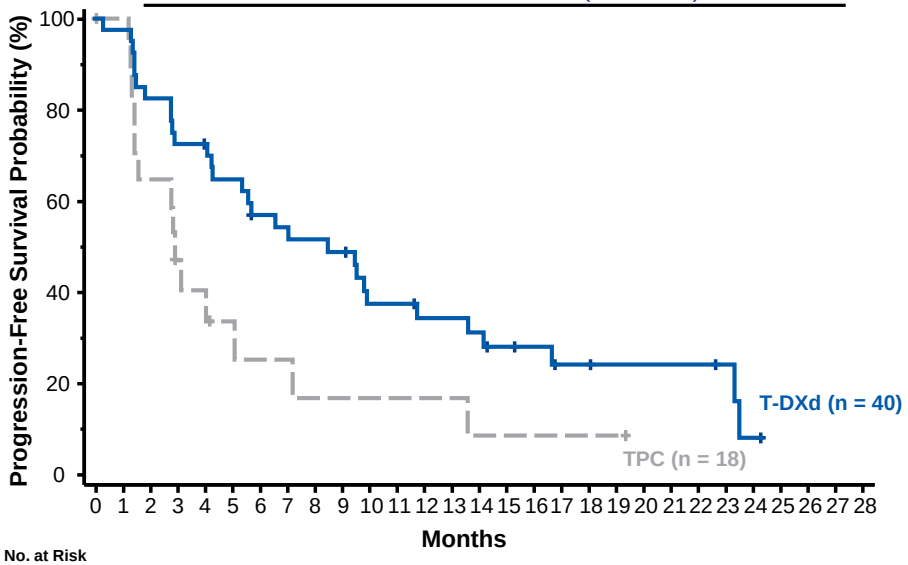
ADC/22/0185 Date of last revision: June 2022

- DESTINY-Breast04: January 11, 2022 DCO

Exploratory Endpoints: PFS and OS in HR–

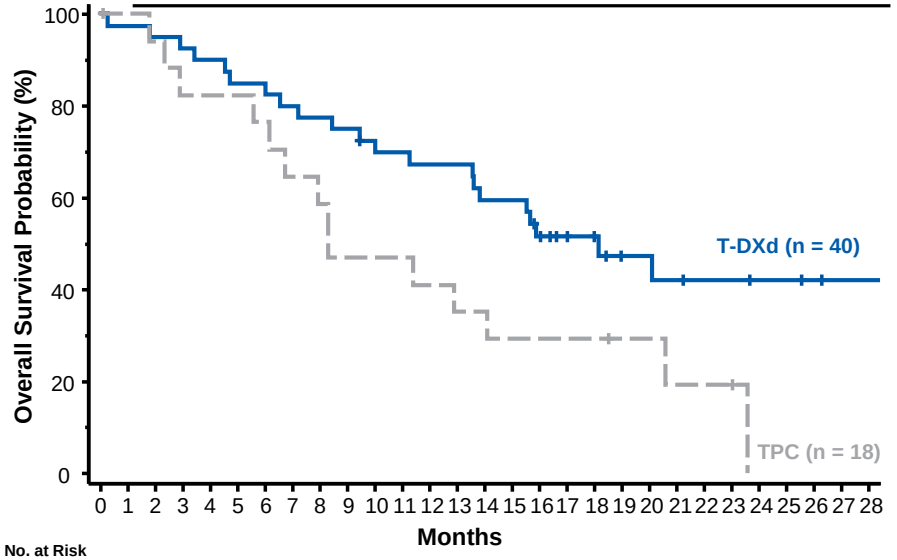
	PFS in hormone receptor-negative	
	T-DXd (n = 40)	**TPC** (n = 18)
mPFS (95% CI), mo	8.5 (4.3-11.7)	2.9 (1.4-5.1)
Hazard ratio (95% CI)	0.46 (0.24-0.89)	



No. at Risk

T-DXd (n=40):	40	39	33	29	28	25	21	20	19	18	13	13	11	11	10	8	7	5	5	4	4	4	4	3	1	0
TPC (n=18):	18	17	11	7	6	4	3	3	2	2	2	2	2	2	1	1	1	1	1	1	0					

	OS in hormone receptor-negative	
	T-DXd (n = 40)	**TPC** (n = 18)
mOS (95% CI), mo	18.2 (13.6-NE)	8.3 (5.6-20.6)
Hazard ratio (95% CI)	0.48 (0.24-0.95)	

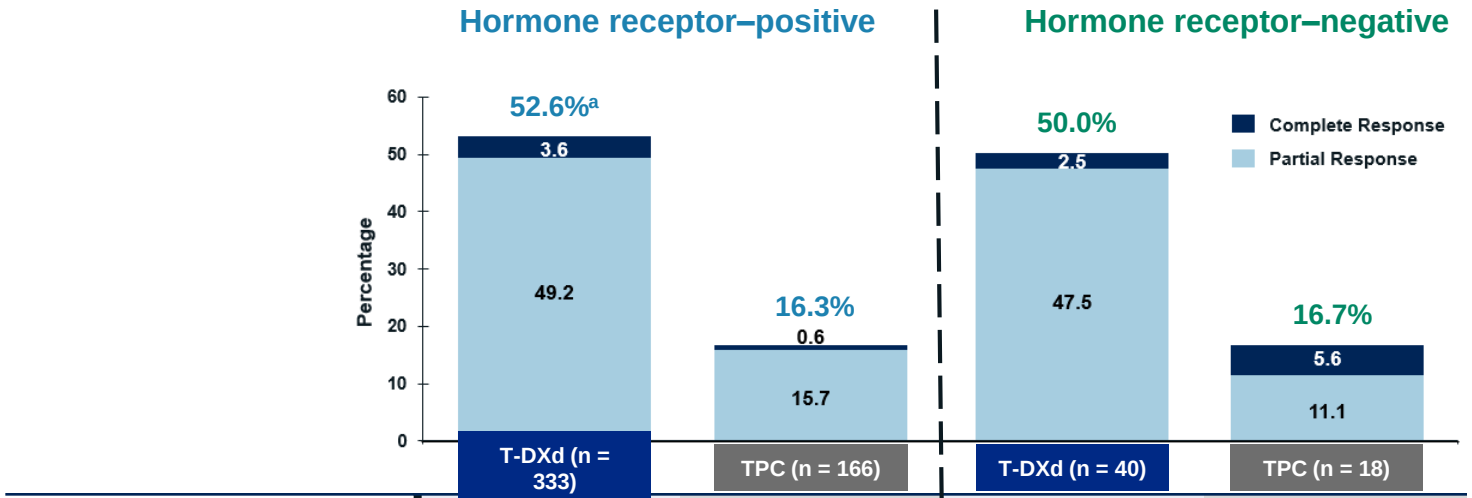


No. at Risk

T-DXd (n=40):	40	39	38	37	36	34	34	32	31	30	28	27	26	26	23	23	19	14	13	9	9	8	7	7	6	6	5	4	4
TPC (n=18):	18	17	16	14	14	14	3	11	10	8	8	8	7	6	6	5	5	5	5	3	3	2	2	2	0				

For efficacy in the hormone receptor negative cohort, hormone receptor status is based on data from the electronic data capture corrected for misstratification.
Modi S et al. *N Engl J Med*. 2022. doi: 10.1056/NEJMoa2203690 and Supplement.

DESTINY-Breast04: Confirmed ORR



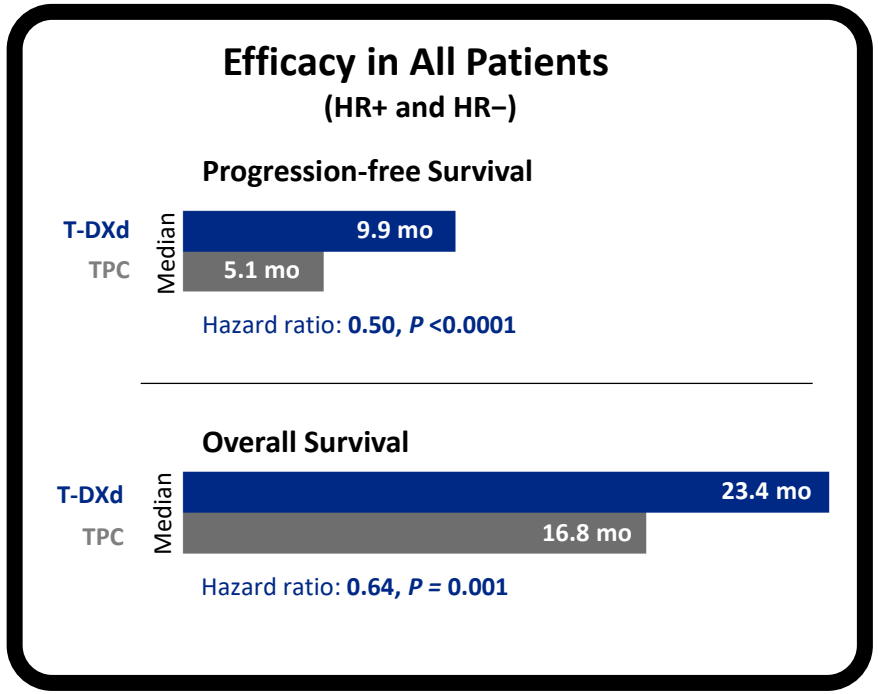
	T-DXd (n = 333)	TPC (n = 166)	T-DXd (n = 40)	TPC (n = 18)
Progressive disease, %	7.8	21.1	12.5	33.3
Not evaluable, %	4.2	12.7	7.5	5.6
Clinical benefit rate,[b] %	71.2	34.3	62.5	27.8
Duration of response, months	10.7	6.8	8.6	4.9

Hormone receptor status is based on data from the electronic data capture corrected for misstratification.
[a]The response of 1 patient was not confirmed. [b]Clinical benefit rate is defined as the sum of complete response rate, partial response rate, and more than 6 months' stable disease rate, based on blinded independent central review.
Modi S, et al. ASCO 2022. Oral presentation at American Society of Clinical Oncology (ASCO) 2022, June 5 (2022b, LBA3).

- DESTINY-Breast04: January 11, 2022 DCO

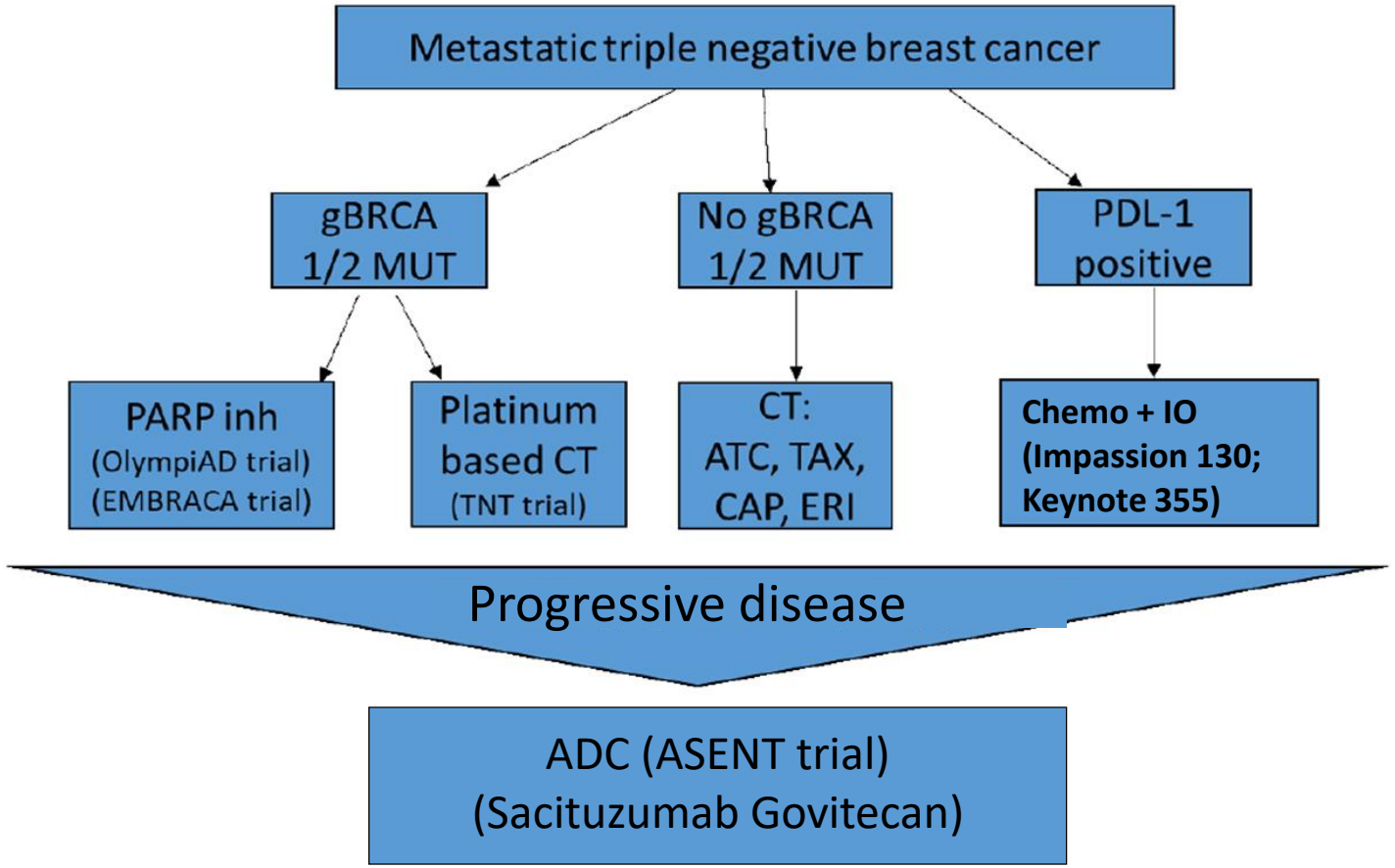
DESTINY-Breast04 establishes T-DXd as a new treatment option in HER2-low, HR+/HR− mBC[1,2]

- T-DXd is the first HER2-targeted therapy to demonstrate unprecedented statistically significant and clinically meaningful improvement in PFS and OS versus TPC
- Similar magnitude of benefit across all subgroups, including HER2 IHC status and prior CDK4/6i use
- Safety is consistent with the known safety profile and showed an overall positive benefit-risk
- DESTINY-Breast04 establishes HER2-low (IHC 1+, IHC 2+/ISH−) mBC as a new targetable patient population



1. Modi S et al. *N Engl J Med*. 2022. doi: 10.1056/NEJMoa2203690. 2. Modi S et al et al. Oral presentation at American Society of Clinical Oncology (ASCO) 2022, June 5 (2022b, LBA3).

Current standard-of-care treatments in metastatic triple-negative breast cancer & future perspectives



Adapted from El Hachem, Awada, 2019

TNBC : Available Biological Agents

- Adjuvant olaparib in BRACA mutated high risks patients
- Chemo + Pembro (neoadjuvant/ adjuvant) : Adjuvant Pembro if PCR ? Role of Cape and/or PARP inh. in residual disease?

- CPIs + chemo (PDL1+)
- PARP inhibitors (BRCA mutated) : Oloparib + talazoparib
- Low HER2 expressors : Trastuzumab-deruxtecan!

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January 2023

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HYBRID MEETING

Breast Cancer Debate of the Year

Best of SABCS

STAY TUNED !

Venue :
MediMix bv
Zone 1 Researchpark 30 - 1731 Zellik

Ahmad Awada, MD, PhD –
Jules Bordet Institute – Brussels

Hans Wildiers, MD, PhD -
UZ Leuven

Thank you !