Recent Advances in Breast Cancer

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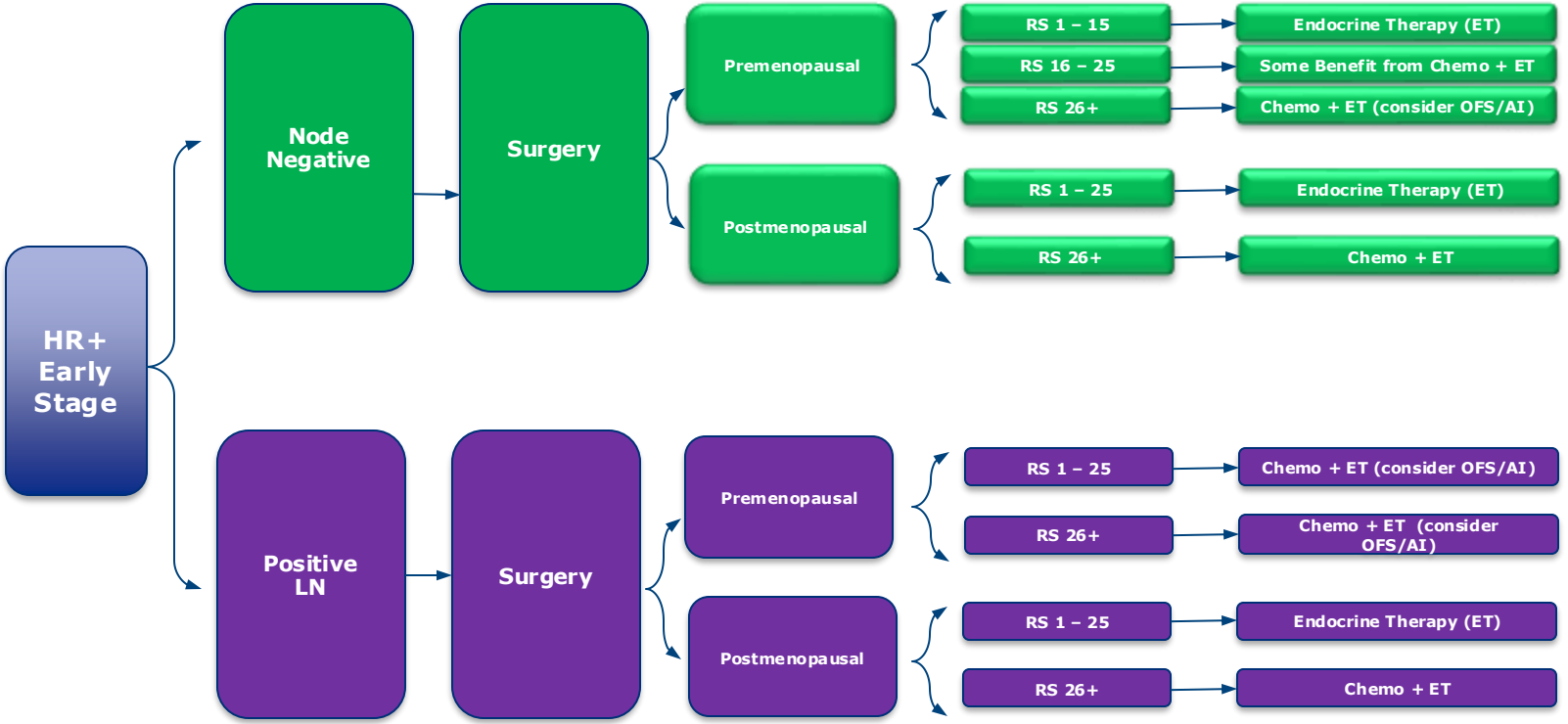
Outline: How I Treat Breast Cancer

I. **HR+/HER2 Neg. Breast Cancer**
   A. Early Stage
   B. Advanced Stage

II. **HER2 Positive Breast Cancer**
   A. Early Stage
   B. Advanced Stage

III. **Triple Negative Breast Cancer**
   A. Early Stage
   B. Advanced Stage

Rx Algorithm: HR+ Early Stage



High-Risk Patients – Consider:

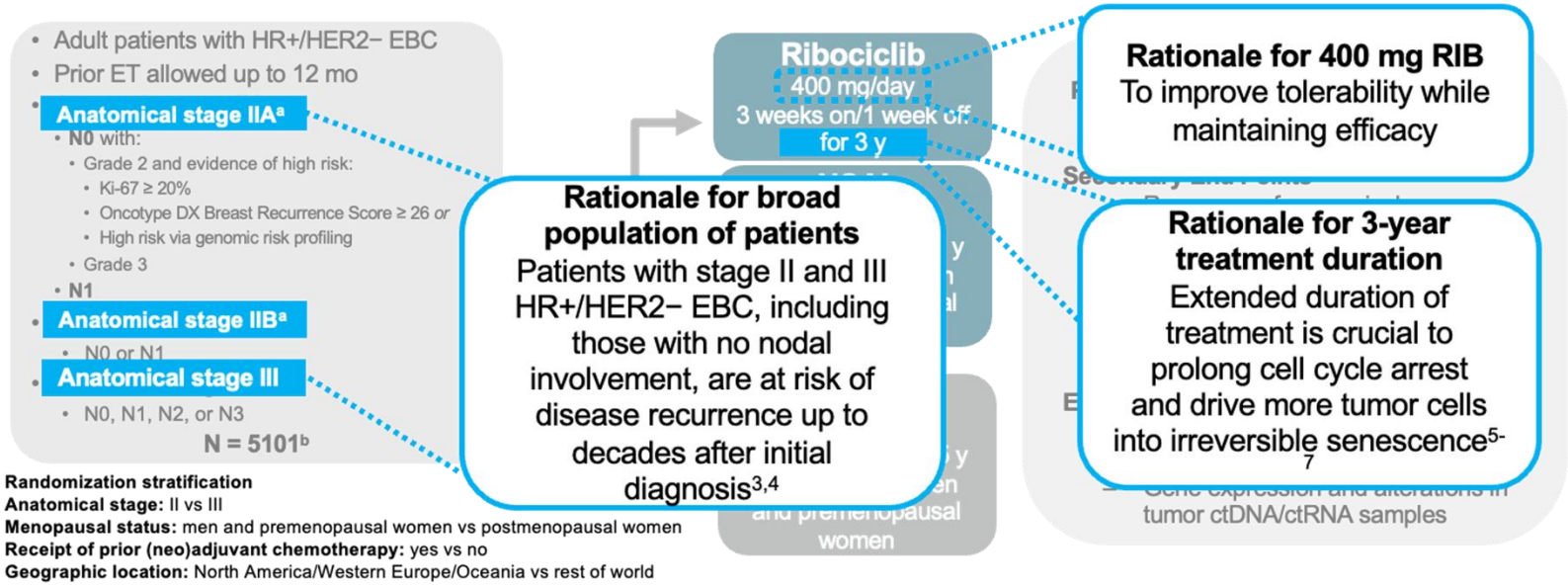
Abemaciblib
- MonarchE
- 4+LN or 1-3 LN + G3 or 5+ cm

NATALEE
- Stage 2A if N1 or N0+ high risk, 2B, 3

gBRCAm

Olaparib
- OlympiA
- 1Y, T2 or 4+ LN

NATALEE: Study Design

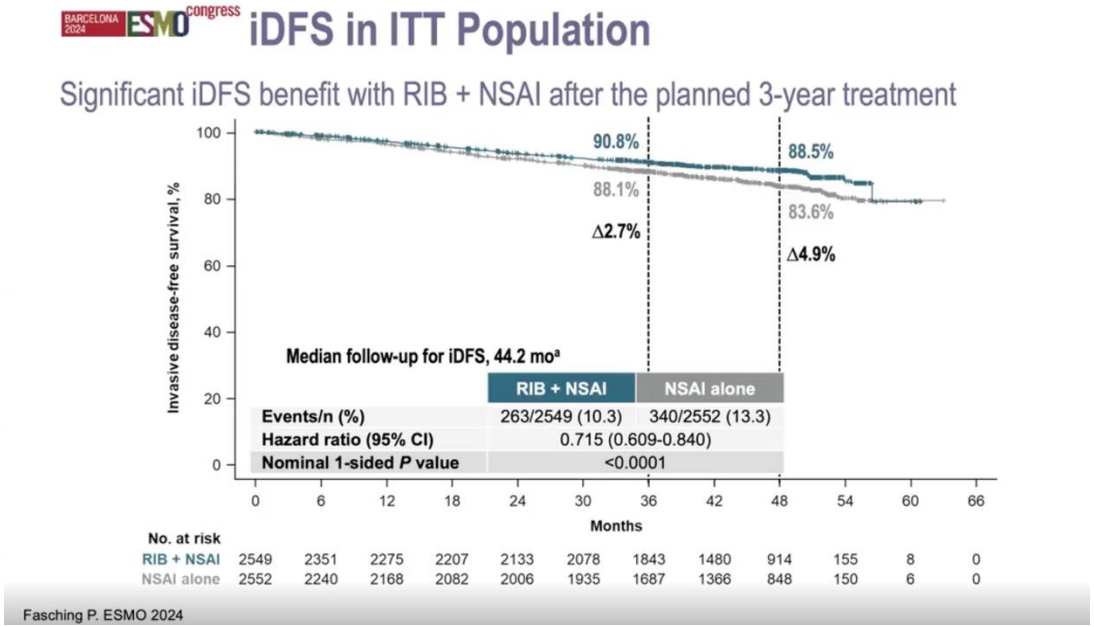


Randomization stratification
Anatomical stage: II vs III
Menopausal status: men and premenopausal women vs postmenopausal women
Receipt of prior (neo)adjuvant chemotherapy: yes vs no
Geographic location: North America/Western Europe/Oceania vs rest of world

[a] Enrollment of patients with stage II disease was capped at 40%. [b] 5101 patients were randomized from 10 Jan 2019 to 20 April 2021. [c] Open-label design. [d] Per investigator choice.
CT, chemotherapy; ctDNA/RNA, circulating tumor DNA/RNA; EBC, early breast cancer; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IDFS, invasive disease-free survival; N, node; NSAI, nonsteroidal aromatase inhibitor; OS, overall survival; PAM50, prediction analysis of microarray 50; PK, pharmacokinetics; PRO, patient reported outcome; R, randomized; STEEP, Standardized Definitions for Efficacy End Points in Adjuvant Breast Cancer Trials.

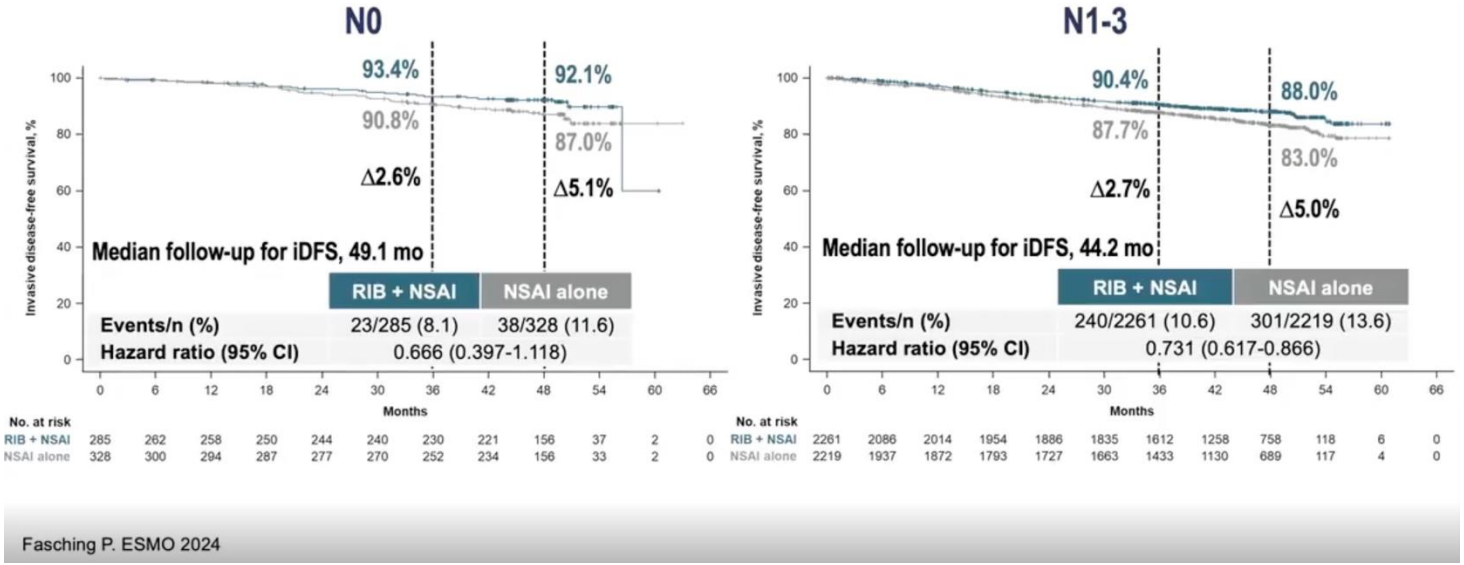
1. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT03701334. Accessed April 6 2023. 2. Slamon DJ, et al. *J Clin Oncol.* 2019;37(15 suppl) [abstract TPS597].

NATALEE: 4 Year iDFS



NATALEE: 4 Year iDFS By Nodal Status

- Increasing magnitude of iDFS benefit over time for N0 and N1-N3 disease



Fasching P. ESMO 2024

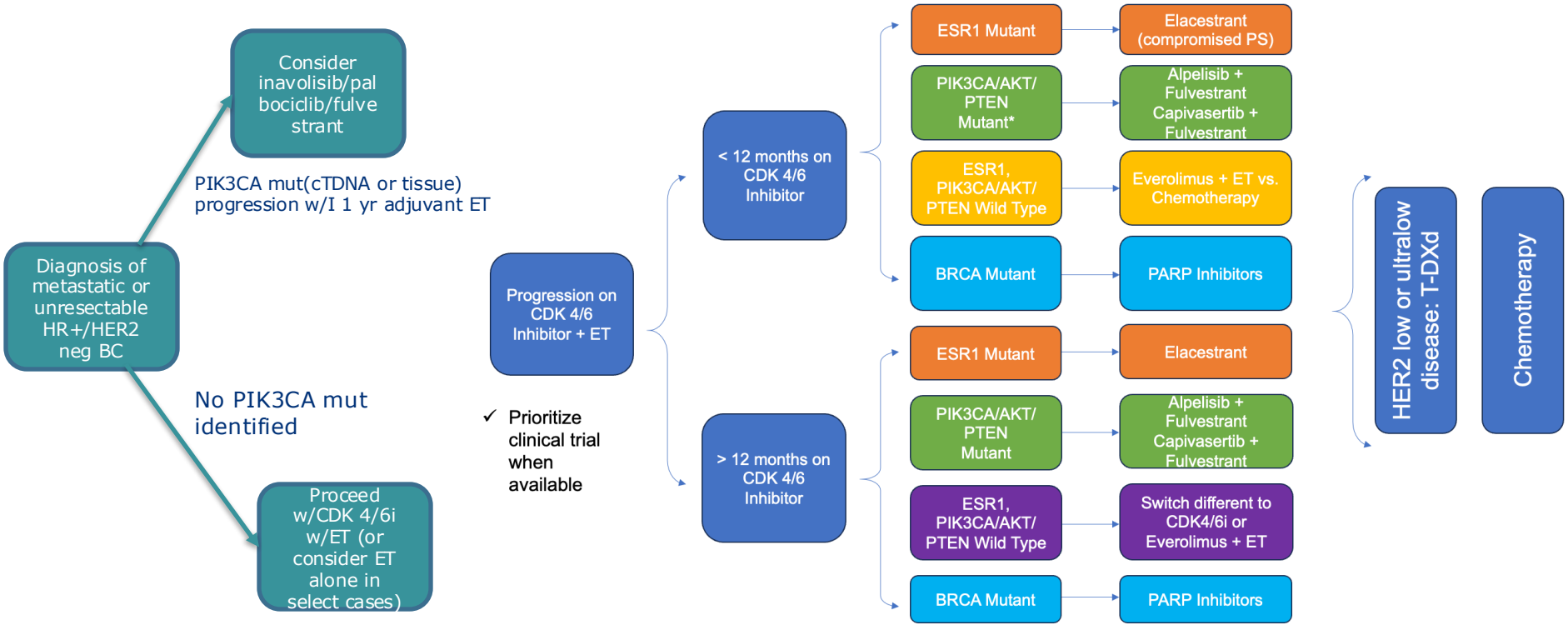
NATALEE: Summary of updated analysis

- Improved DDFS
- Trend towards improvement in OS
- No new toxicities
  - 20% discontinuation rate
- Ribociclib FDA approved adjuvant setting on Sept 17, 2024

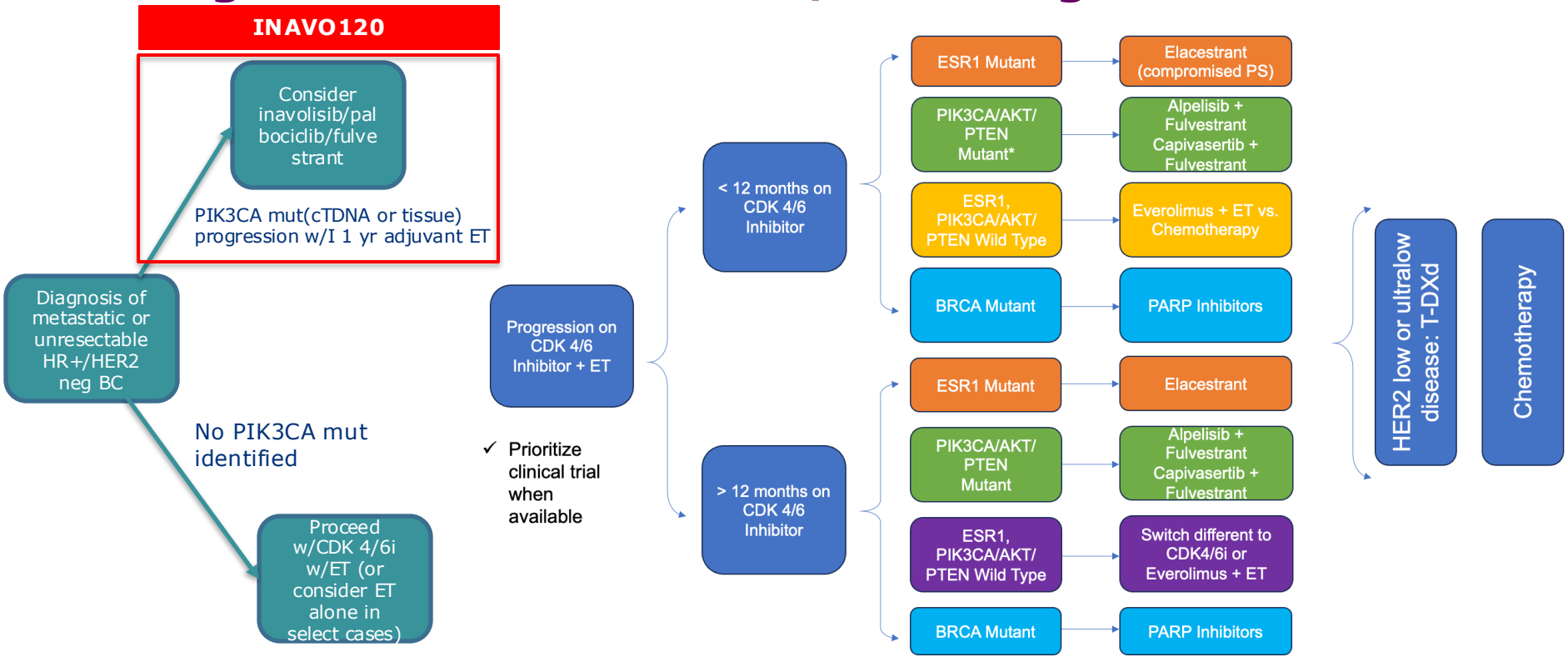
How To Choose The Right Adjuvant CDK 4/6 Inhibitor?

- Patient eligibility
  - NATALEE: includes a broader population of patients – high risk node negative
  - MONARCHe: includes node positive pts
- AE profile
  - NATALEE- Ribociclib: hepatotoxicity, cardiac toxicity
  - MONARCHe- Abemaciclib: GI toxicity
- Duration of therapy
  - NATALEE: Ribociclib 400 mg x 3 yrs
  - MONARCHe: Abemaciclib 150 mg BID x 2 years
- Follow up
  - Longer data available w/abema
- How do we better identify patients who will benefit from an adjuvant CDK 4/6 inhibitor?
  - Biomarkers?

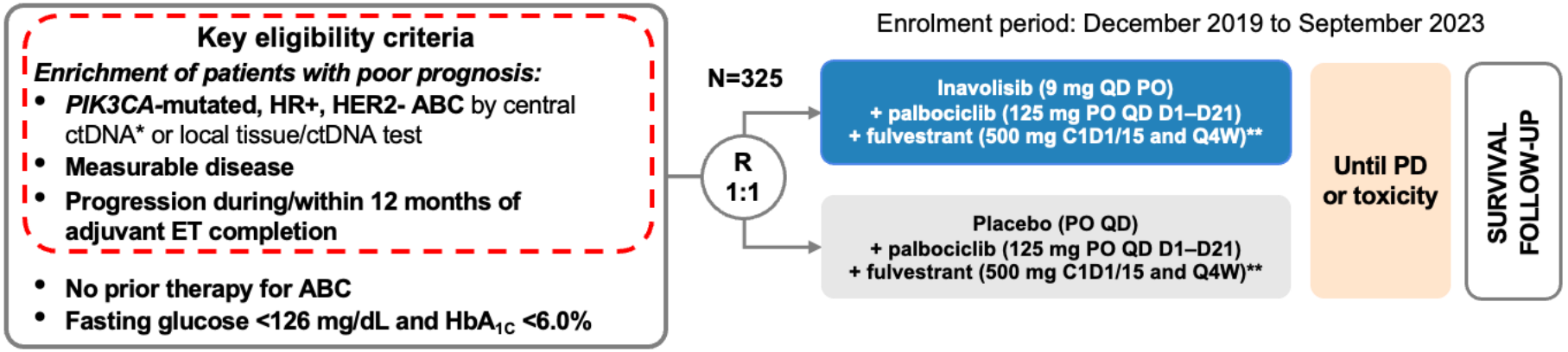
Rx Algorithm: Advanced HR+/HER2 Neg. Breast Cancer



Rx Algorithm: Advanced HR+/HER2 Neg. Breast Cancer



INAVO 120: Study Design



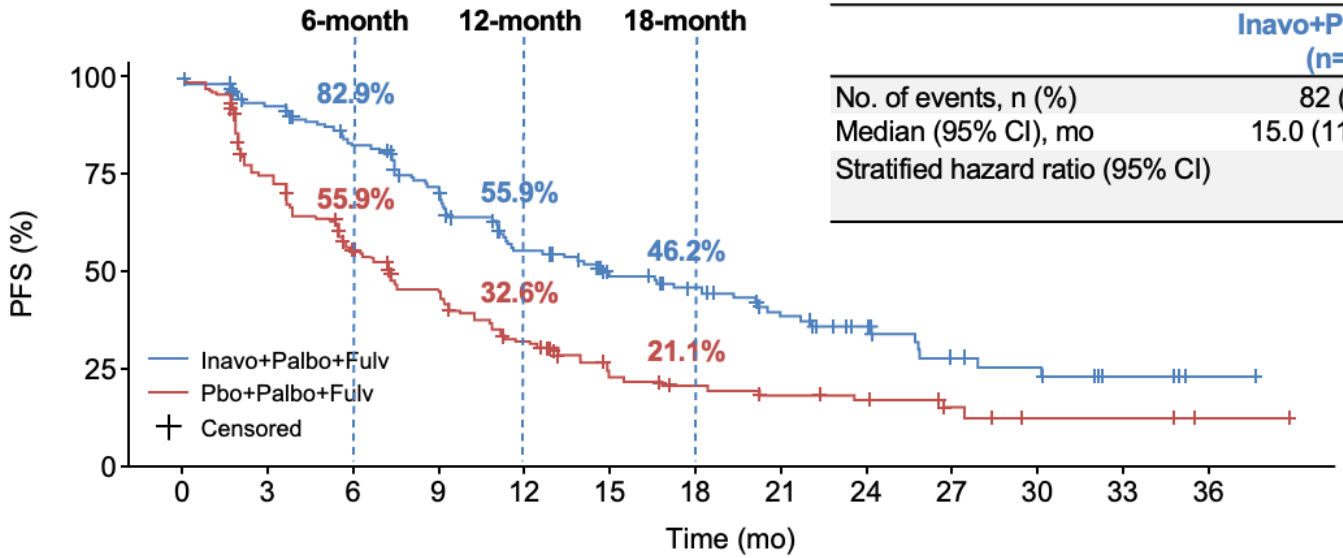
Stratification factors:
- Visceral Disease (Yes vs. No)
- Endocrine Resistance (Primary vs. Secondary)†
- Region (North America/Western Europe; Asia; Other)

Endpoints
- Primary: PFS by Investigator
- Secondary: OS‡, ORR, BOR, CBR, DOR, PROs

Central testing for PIK3CA mutations was done on ctDNA using FoundationOne®Liquid (Foundation Medicine). In China, the central ctDNA test was the PredicineCARE NGS assay (Huidu). † Defined per 4th European School of Oncology (ESO)–European Society for Medical Oncology (ESMO) International Consensus Guidelines for Advanced Breast Cancer.1 Primary: relapse while on the first 2 years of adjuvant ET; Secondary: relapse while on adjuvant ET after at least 2 years or relapse within 12 months of completing adjuvant ET. ‡ OS testing only if PFS is positive; interim OS analysis at primary PFS analysis;
*** Pre-menopausal women received ovarian suppression. ctDNA, circulating tumor DNA; R, randomized. 1. Cardoso F, et al. Ann Oncol 2018;29:1634–1657.*

Source: Jhaveri, SABCS 2023.

INAVO 120: PFS



	Inavo+Palbo+Fulv (n=161)	Pbo+Palbo+Fulv (n=164)
No. of events, n (%)	82 (50.9)	113 (68.9)
Median (95% CI), mo	15.0 (11.3, 20.5)	7.3 (5.6, 9.3)
Stratified hazard ratio (95% CI)	**0.43 (0.32, 0.59) p<0.0001**	

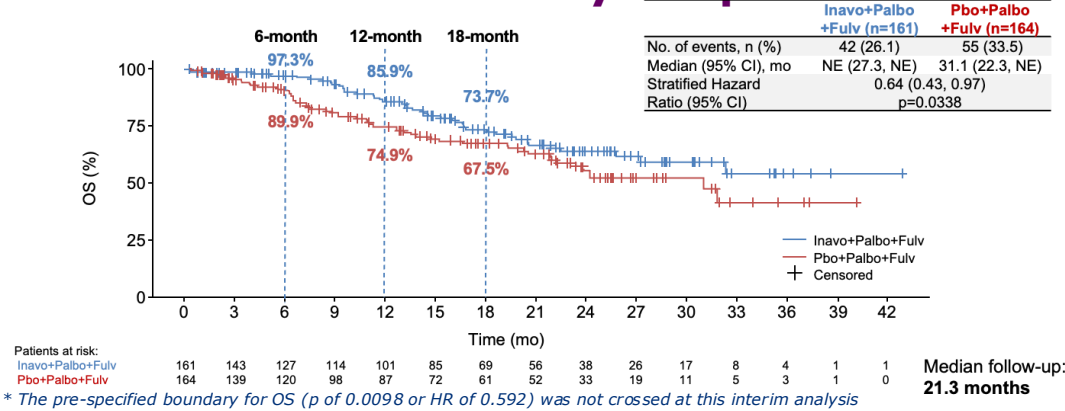
Patients at risk:

Inavo+Palbo+Fulv	161	134	111	92	66	48	41	31	22	13	11	5	1
Pbo+Palbo+Fulv	164	113	77	59	40	23	19	16	12	6	3	3	1

Median follow-up: **21.3 months**

CCOD: 29th September 2023
CI, confidence interval; Fulv, fulvestrant; Inavo, inavolisib; mo, months; Palbo, palbociclib; Pbo, placebo; PFS, progression-free survival.
Source: Jhaveri, SABCS 2023.

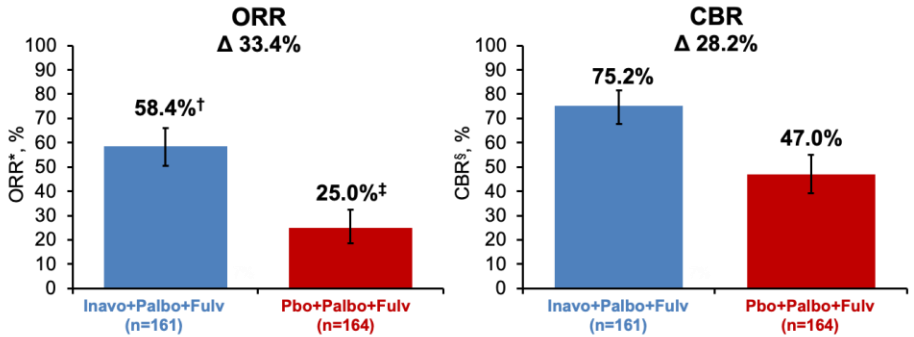
INAVO 120: Secondary Endpoints – Interim Analysis for OS, ORR, CBR



	Inavo+Palbo +Fulv (n=161)	Pbo+Palbo +Fulv (n=164)
No. of events, n (%)	42 (26.1)	55 (33.5)
Median (95% CI), mo	NE (27.3, NE)	31.1 (22.3, NE)
Stratified Hazard Ratio (95% CI)	0.64 (0.43, 0.97) p=0.0338	

Median follow-up: **21.3 months**

** The pre-specified boundary for OS (p of 0.0098 or HR of 0.592) was not crossed at this interim analysis*



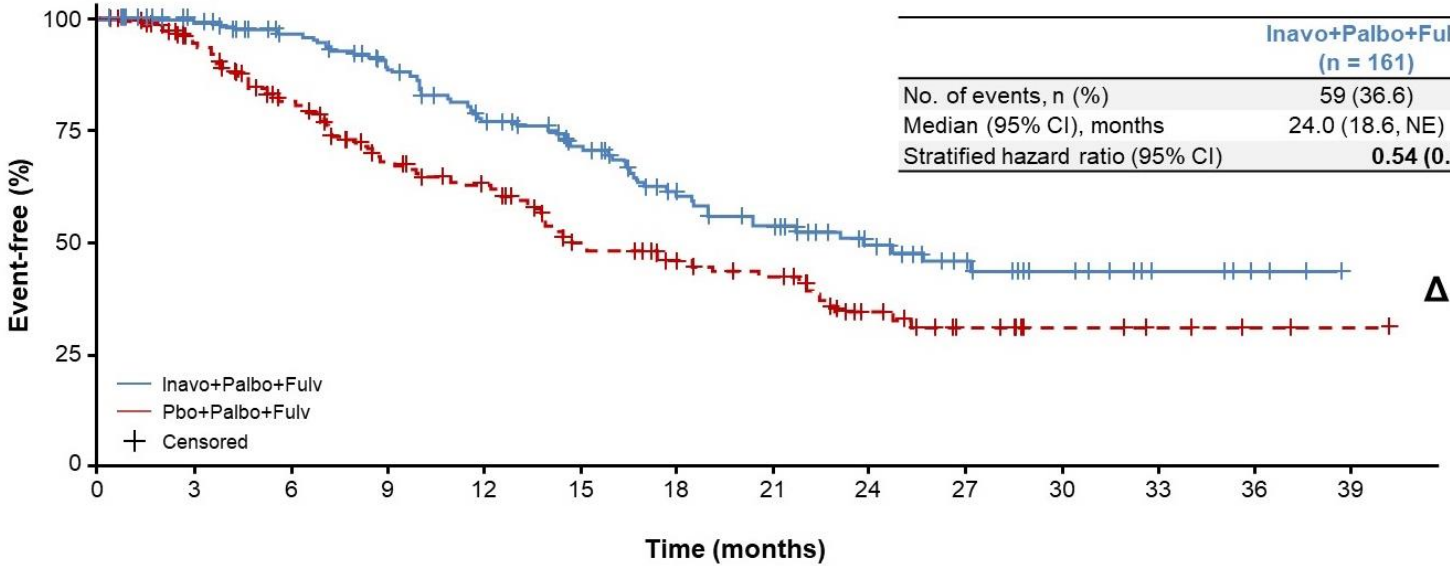
- Median f/up 21.3 mos
- mOS NE in triplet arm vs 31.1 mos in control arm HR 0.64
- Prespecified boundary for OS not crossed at this interim analysis

- Improvement in ORR from 25% in control arm to 58.4% in triplet arm
- Improvement in CBR from 47% in control arm to 75.2% in triplet arm

** CI, confidence interval; Fulv, fulvestrant; Inavo, inavolisib; mo, months; NE, not estimable; OS, overall survival; Palbo, palbociclib; Pbo, placebo.*
** Patients with a CR or PR on two consecutive occasions ≥4 weeks apart per RECIST v1.1. † Seven patients with CR, 87 patients with PR. ‡ One patient with CR, 40 patients with PR, 79 patients with SD, 34 patients with PD, and 10 with missing status. § Patients with a CR, PR, and/or SD for ≥24 weeks per RECIST v1.1. CBR, clinical benefit rate; CR, complete response; Fulv, fulvestrant; Inavo, inavolisib; ORR, objective response rate; Palbo, palbociclib; Pbo, placebo; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.*

Source: Jhaveri, SABCS 2023.

INAVO 120: Time From Randomization To End Or Discontinuation Of Next-line Treatment, Or Death From Any Cause (Proxy For PFS2)



	Inavo+Palbo+Fulv (n = 161)	Pbo+Palbo+Fulv (n = 164)
No. of events, n (%)	59 (36.6)	80 (48.4)
Median (95% CI), months	24.0 (18.6, NE)	15.1 (13.5, 22.3)
Stratified hazard ratio (95% CI)	**0.54 (0.38, 0.77)**	

Patients at risk:														
Pbo+Palbo+Fulv	164	140	110	84	74	52	43	37	22	12	6	4	2	1
Inavo+Palbo+Fulv	161	143	126	111	92	77	58	48	33	22	14	6	3	0

Source: Juric, ASCO 2024.

INAVO 120: Adverse Events

Adverse Events	Inavo+Palbo+Fulv (N=162)		Pbo+Palbo+Fulv (N=162)	
	All Grades	Grade 3–4	All Grades	Grade 3–4
Neutropenia	**144 (88.9%)**	**130 (80.2%)**	**147 (90.7%)**	**127 (78.4%)**
Thrombocytopenia	78 (48.1%)	23 (14.2%)	73 (45.1%)	7 (4.3%)
Stomatitis/Mucosal inflammation	**83 (51.2%)**	**9 (5.6%)**	**43 (26.5%)**	**0**
Anemia	60 (37.0%)	10 (6.2%)	59 (36.4%)	3 (1.9%)
Hyperglycemia	**95 (58.6%)**	**9 (5.6%)**	**14 (8.6%)**	**0**
Diarrhea	**78 (48.1%)**	**6 (3.7%)**	**26 (16.0%)**	**0**
Nausea	**45 (27.8%)**	**1 (0.6%)**	**27 (16.7%)**	**0**
Rash	**41 (25.3%)**	**0**	**28 (17.3%)**	**0**
Decreased Appetite	38 (23.5%)	<2%	14 (8.6%)	<2%
Fatigue	38 (23.5%)	<2%	21 (13.0%)	<2%
COVID-19	37 (22.8%)	<2%	17 (10.5%)	<2%
Headache	34 (21.0%)	<2%	22 (13.6%)	<2%
Leukopenia	28 (17.3%)	11 (6.8%)	40 (24.7%)	17 (10.5%)
Ocular Toxicities	36 (22.2%)	0	21 (13.0%)	0

Key AEs are shown in **bold.** AES were assessed per CTCAE V5. Neutropenia, thrombocytopenia, stomatitis/mucosal inflammation, anemia, hyperglycemia, diarrhea, nausea and rash were assessed as medical concepts using grouped terms

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Fulv, fulvestrant; Inavo, inavolisib; Palbo, palbociclib; Pbo, placebo.

AEs leading to discontinuation:

- *6.2% in triplet arm vs 0.6% in control arm*
- *Dose reductions and interruptions occurred in both arms*

Median Time to Onset of Toxicities:

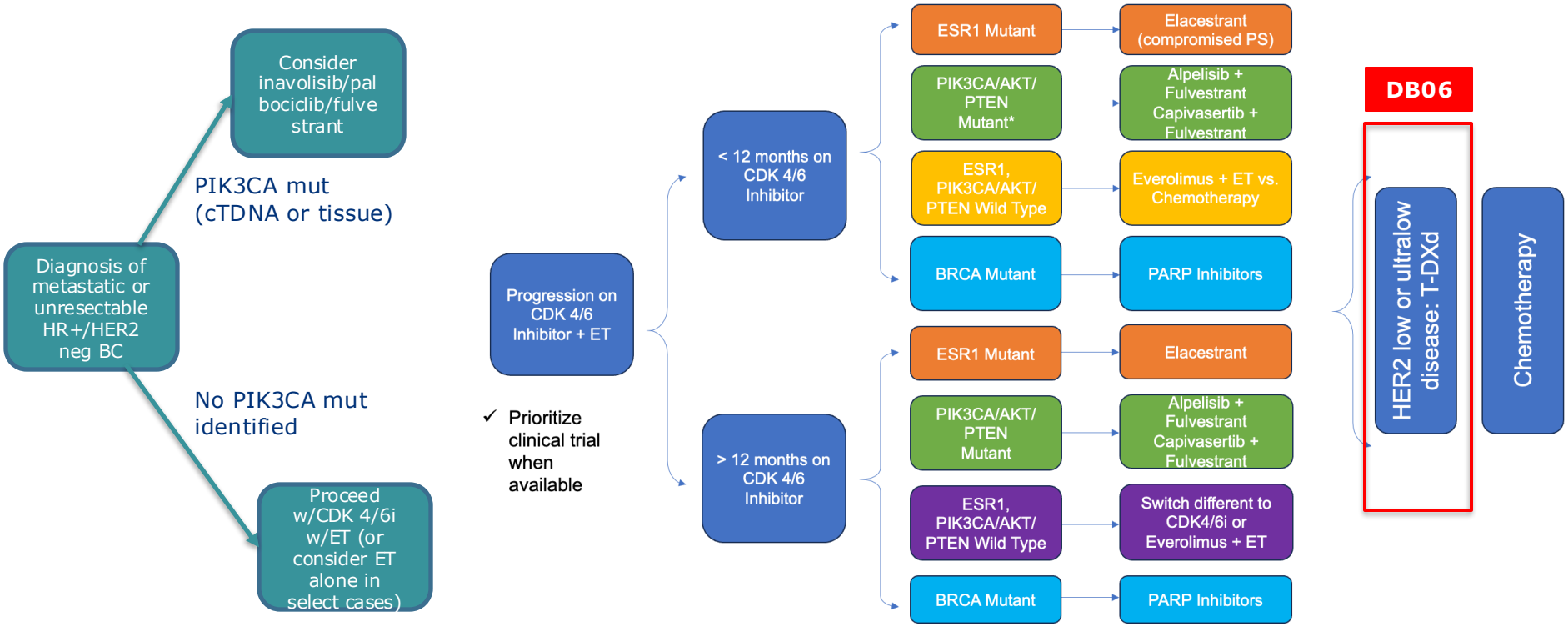
- *Hyperglycemia- 7 days; Rash 29 days; Diarrhea 15 days; Stomatitis 13 days*
- *Dose reductions and interruptions occurred in both arms*

Source: Jhaveri, SABCS 2023.

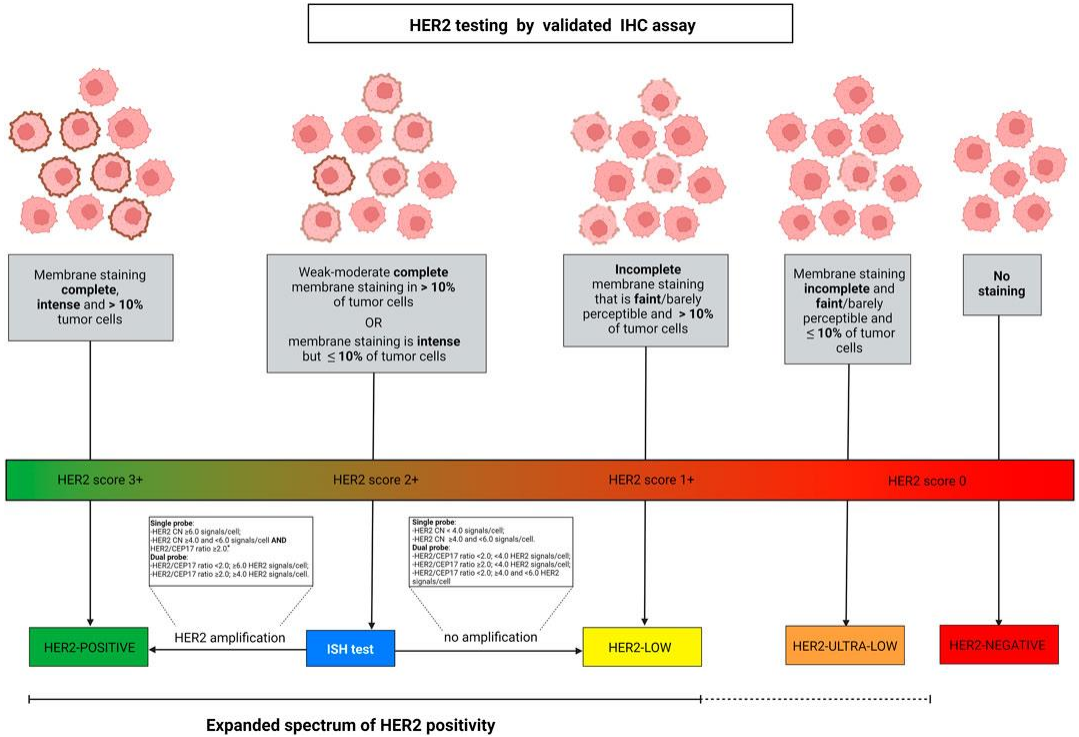
INAVO 120: Summary

- Addition of inavolisib to palbociclib and fulvestrant demonstrated a statistically significant improved PFS for advanced *PIK3CA* mutated advanced HR+, HER2 neg ABC
  - 7.3 mos in control arm vs 15.0 mos in triplet arm (HR 0.43)
  - Sustained benefit beyond progression and delay in initiation of chemotherapy
  - Prolonged time to deterioration in pain severity, maintained HRQoL
- Trend OS improvement at first interim analysis
- Manageable safety consistent with known AEs in this class of drugs
  - Inclusion criteria of hgb a1c < 6% w/5.6% grade 3/4 hyperglycemia
  - No primary ppx for hyperglycemia, rash, diarrhea, stomatitis
  - Low discontinuation rate
- First triplet that appears to overcome resistance seen in this high-risk population with manageable toxicity
- Inavolisib FDA approved Oct 10, 2024 in combination with palbo/fulvestrant for pts who have progressed during or within 1 year on adjuvant ET

Rx Algorithm: Advanced HR+/HER2 Neg. Breast Cancer



Trastuzumab Deruxtecan (T-DXd) and HER2



- DB-04: T-DXd efficacy in HER2 low tumors
  - HER2 low (60-65% HR+ ABC): 2+ or 1+ by IHC
- DB-06: T-DXd **after 1 line of endo rx** and includes **HER2 ultra-low tumors**
  - HER2 ultralow (20-25% HR+ ABC): any staining between 0 and 1+
- 85% of pts can potentially benefit from T-DXd

Source: Venetis, K., et al. (2022). "HER2 Low, Ultra-low, and Novel Complementary Biomarkers: Expanding the Spectrum of HER2 Positivity in Breast Cancer." Frontiers in Molecular Biosciences 9.

DESTINY-Breast06: Trastuzumab Deruxtecan vs CT in Previously Treated HR+/HER2-Low or HER2-Ultralow MBC

- Multicenter, open-label, randomized phase III trial

HER2-low: 713

HER2-ultra low: 153

Stratified by: prior CDK4/6 inhibitor use (yes vs no); HER2 IHC 1+ vs 2+/ISH- vs 0; prior taxane in nonmetastatic setting (yes vs no)

Patients with HR+ metastatic breast cancer with PD on ≥2 previous ET ± targeted therapy (no prior CT) for MBC*; HER2 low (IHC 1+, or 2+/ISH-) or HER2 ultralow (IHC† >0 <1+) based on central IHC assessment using most recent evaluable IHC sample
(N = 866)

1:1

T-DXd
5.4 mg/kg Q3W
(n = 436)

Physician's choice of CT
(capecitabine, paclitaxel, or *nab*-paclitaxel)
(n = 430)

Until PD or toxicity

*Also allowed: 1 prior line for MBC and PD ≤6 mo of starting 1L ET + CDK4/6 inhibitor or 1 prior line for MBC and recurrence ≤24 mo of starting adjuvant ET.
†HER2 IHC >0 defined by any IHC staining up to 10% of tumor cells.

- **Primary endpoint:** PFS (per BICR) in HER2-low population
- **Key secondary endpoints:** OS in HER2-low population, PFS (per BICR) and OS in ITT
- **Other secondary endpoints:** PFS (per INV) in HER2-low population, ORR and DoR (per BICR/INV) in HER2-low population and ITT, safety and tolerability, PROs

Source: Clinicaloption.com, Curigliano, ASCO 2024. Abstr LBA1000. NCT04494425.

DESTINY-Breast06: Baseline Characteristics and Prior Treatment

- ITT population:
  - 54% IHC 1+ disease
  - 26% IHC 2+ disease
  - 29% pts w/primary endo resistant disease
  - 30% de novo disease at diagnosis
  - 3% pts with bone only disease
  - 86% pts with visceral disease

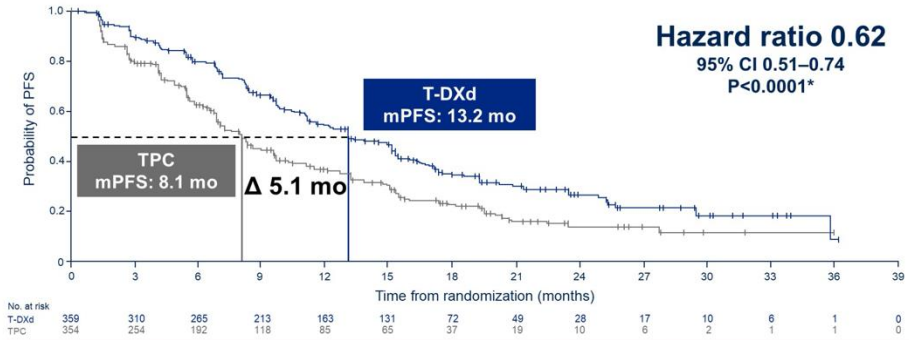
Prior Therapy for MBC	HER2 Low		ITT		HER2 Ultralow	
	T-DXd (n = 359)	CT (n = 354)	T-DXd (n = 436)	CT (n = 430)	T-DXd (n = 76)	CT (n = 76)
Median ET lines, n (range)	2 (1-4)	2 (1-5)	2 (1-4)	2 (1-5)	2 (1-4)	2 (1-5)
No. of ET lines, n (%)						
▪ 1	54 (15.1)	67 (19.0)	65 (14.9)	82 (19.2)	11 (14.5)	15 (19.7)
– ≤6 mo on 1L ET + CDK4/6i	33 (9.2)	33 (9.4)	37 (8.5)	40 (9.3)	4 (5.3)	7 (9.2)
▪ 2	242 (67.6)	236 (67.0)	295 (67.8)	288 (67.3)	52 (68.4)	52 (68.4)
▪ ≥3	62 (17.3)	49 (13.9)	75 (17.2)	58 (13.6)	13 (17.1)	9 (11.8)
Prior ET therapies, n (%)						
▪ Monotherapy	189 (52.6)	183 (51.7)	230 (52.8)	223 (51.9)	41 (53.9)	40 (52.6)
▪ With CDK4/6i	318 (88.6)	316 (89.3)	388 (89.0)	385 (89.5)	69 (90.8)	69 (90.8)
▪ With other targeted therapy	120 (33.4)	105 (29.7)	143 (32.8)	127 (29.5)	22 (28.9)	22 (28.9)
Prior adjuvant/neoadjuvant therapies, n (%)						
▪ ET	227 (63.2)	218 (61.6)	275 (63.1)	256 (59.5)	48 (63.2)	38 (50.0)
▪ Cytotoxic CT	192 (53.5)	196 (55.4)	228 (52.3)	234 (54.4)	36 (47.4)	38 (50.0)
– Taxane	151 (42.1)	151 (42.7)	179 (41.1)	177 (41.2)	28 (36.8)	26 (34.2)
– Anthracycline	167 (46.5)	173 (48.9)	197 (45.2)	206 (47.9)	30 (39.5)	33 (43.4)

- < 10% pts progressed w/i 6 mos of ET+ CDK 4/6i
- 89% pts rec'd ET + CDK 4/6i
- Appx 60% pts rec'd adjuvant ET
- Appx 50% pts rec'd NAC/adjuvant chemo

Source: Clinicaloption.com, Curigliano, ASCO 2024. Abstr LBA1000. NCT04494425.

DESTINY-Breast06

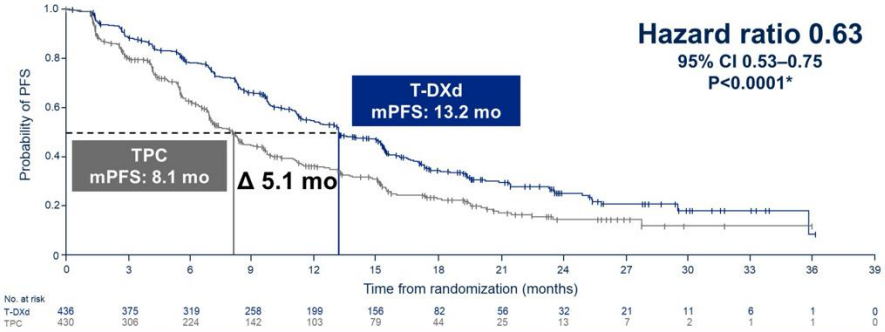
PFS (BICR) in HER2-low: primary endpoint



T-DXd demonstrated a statistically significant and clinically meaningful improvement in PFS compared with standard-of-care chemotherapy in HER2-low

*P-value of <0.05 required for statistical significance
BICR, blinded independent central review; CI, confidence interval; HER2, human epidermal growth factor receptor 2; mo, months; (m)PFS, (median) progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, chemotherapy treatment of physician's choice

PFS (BICR) in ITT: key secondary endpoint



T-DXd demonstrated a statistically significant and clinically meaningful improvement in PFS compared with standard-of-care chemotherapy in ITT

*P-value of <0.015 required for statistical significance
BICR, blinded independent central review; CI, confidence interval; ITT, intent-to-treat; mo, months; (m)PFS, (median) progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, chemotherapy treatment of physician's choice

Source: Curigliano, ASCO 2024. Abstr LBA1000. NCT04494425.

DESTINY-Breast06

OS in HER2-low and ITT: key secondary endpoints (~40% maturity)

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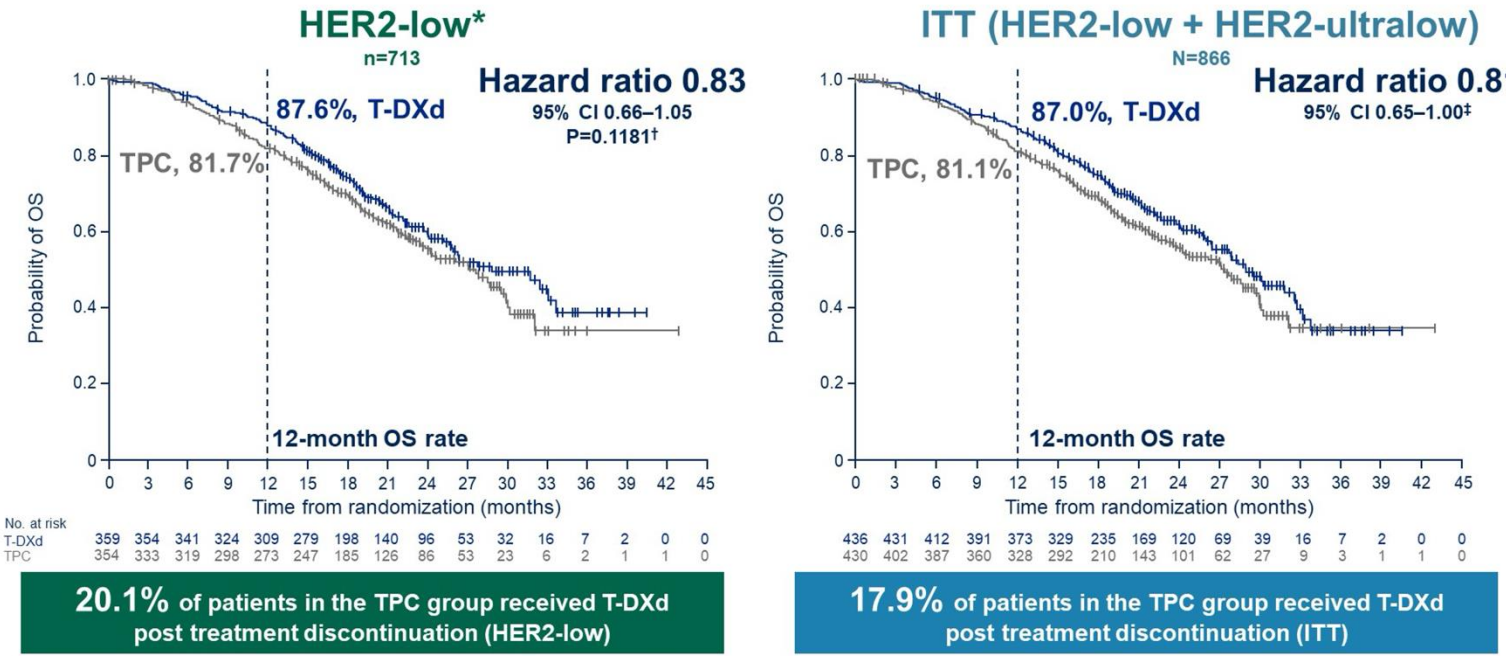

*39.6% maturity (of total N for population) at this first interim analysis; median duration of follow up was 18.6 months (HER2-low); †P-value of <0.0046 required for statistical significance; ‡no test of significance was performed in line with the multiple testing procedure; median duration of follow up was 18.2 months (ITT)
CI, confidence interval; HER2, human epidermal growth factor receptor 2; ITT, intent-to-treat; OS, overall survival; T-DXd, trastuzumab deruxtecan; TPC, chemotherapy treatment of physician's choice

Source: Curigliano, ASCO 2024. Abstr LBA1000. NCT04494425.

DESTINY-Breast06

PFS and OS in HER2-ultralow: prespecified exploratory analyses

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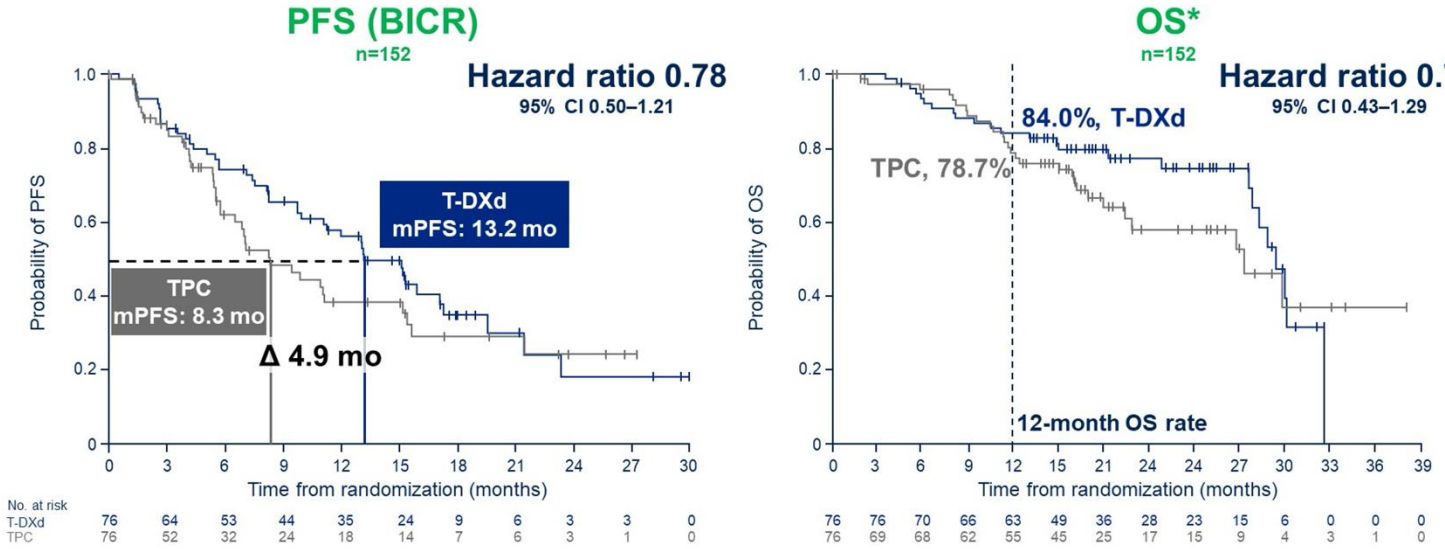


PFS improvement with T-DXd vs TPC in HER2-ultralow was consistent with results in HER2-low

*34.9% maturity (of total N for population) at this first interim analysis; median duration of follow up was 16.8 months
BICR, blinded independent central review; CI, confidence interval; HER2, human epidermal growth factor receptor 2; OS, overall survival; mo, months; (m)PFS, (median) progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, chemotherapy treatment of physician's choice

Source: Curigliano, ASCO 2024. Abstr LBA1000. NCT04494425.

DESTINY-Breast06: TEAEs and AEs of Special Interest

Treatment-Related TEAE in ≥20% of Patients, %	T-DXd (n = 434)		CT (n = 417)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Nausea	65.9	1.6	23.5	0.2
Fatigue	46.8	3.7	34.3	1.4
Alopecia	45.4	0	19.4	0.2
Neutropenia	37.6	20.7	27.6	16.5
Increased transaminases	29.3	2.3	11.0	0
Anemia	28.1	5.8	19.4	2.4
Vomiting	27.2	1.4	9.4	0
Diarrhea	23.7	1.8	22.5	2.4
Decreased appetite	23.5	1.4	9.4	0.5
Leukopenia	23.3	6.9	14.6	5.5
PPE	0.5	0	32.4	6.7

Left ventricular dysfunction, n (%)	T-DXd (n = 434)	CT (n = 417)
Decreased ejection fraction (any)	35 (8.1)	12 (2.9)
▪ Grade 1/2	32 (7.3)	11 (2.6)
▪ Grade 3/4	3 (0.7)	1 (0.2)
▪ Grade 5	0	0
Cardiac failure (any)	0	3 (0.7)
▪ Grade 1/2	0	1 (0.2)
▪ Grade 3/4	0	2 (0.4)
▪ Grade 5	0	0
ILD/Pneumonitis,* n (%)	**(n = 434)**	**(n = 417)**
Any grade	49 (11.3)	1 (0.2)
▪ Grade 1/2	43 (9.9)	1 (0.2)
▪ Grade 3/4	3 (0.7)	0
▪ Grade 5	3 (0.7)	0

*Adjudicated as treatment related.

- Most common AE leading to rx discontinuation: ILD 5.3% w/T-DXd vs peripheral neuropathy w/TPC 1.4% w/TPC
- Most common AE leading to rx reduction: nausea 4.4% w/T-DXd vs PPE 16.5% w/TPC

Source: Clinicaloption.com, Curigliano, ASCO 2024. Abstr LBA1000. NCT04494425.

DESTINY-Breast06 Key Takeaways

- T-DXd clinical and statistical benefit in HR+, HER2 low and ultra low tumors in an earlier line of rx as compared to DB-04
  - HER2-ultra low data is comparable with HER2-low data
- No new safety signals
  - 3 deaths related to ILD
- DESTINY-Breast15: T-DXd efficacy in lower HER2 expressing tumors
- Practice changing?
  - T-DXd may benefit more patients and sooner, however may not be applicable to bone only disease (3%) and SDM will be important given toxicities

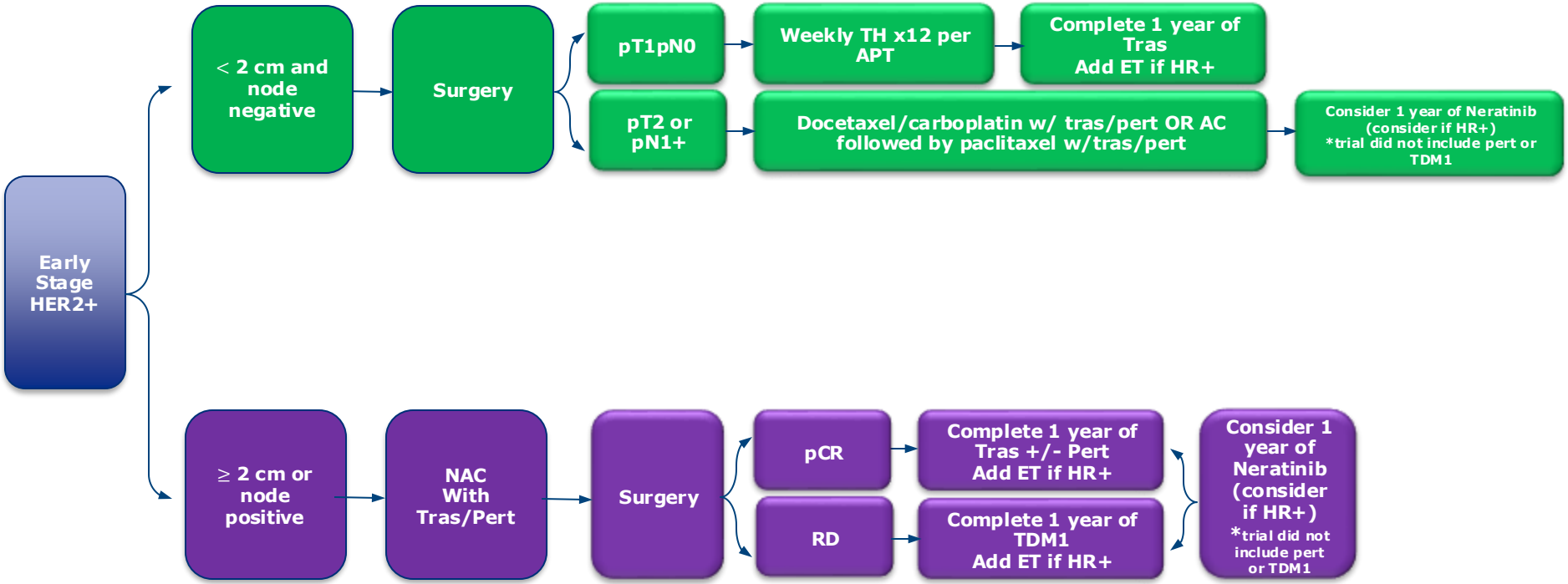
Outline: How I Treat Breast Cancer

I. **HR+/HER2 Neg. Breast Cancer**
   A. Early Stage
   B. Advanced Stage

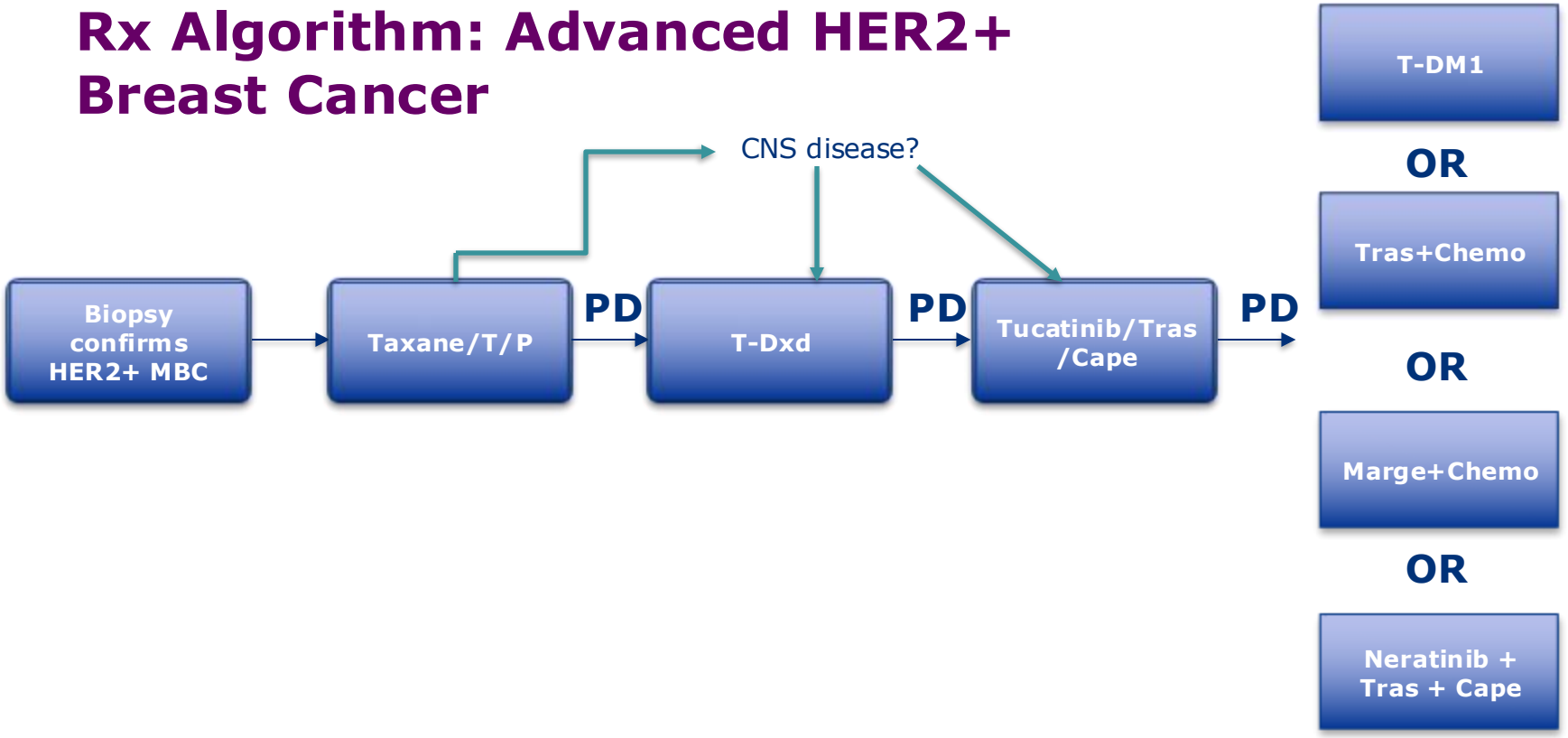
II. **HER2 Positive Breast Cancer**
   A. Early Stage
   B. Advanced Stage

III. **Triple Negative Breast Cancer**
   A. Early Stage
   B. Advanced Stage

Rx Algorithm: Early Stage HER2+

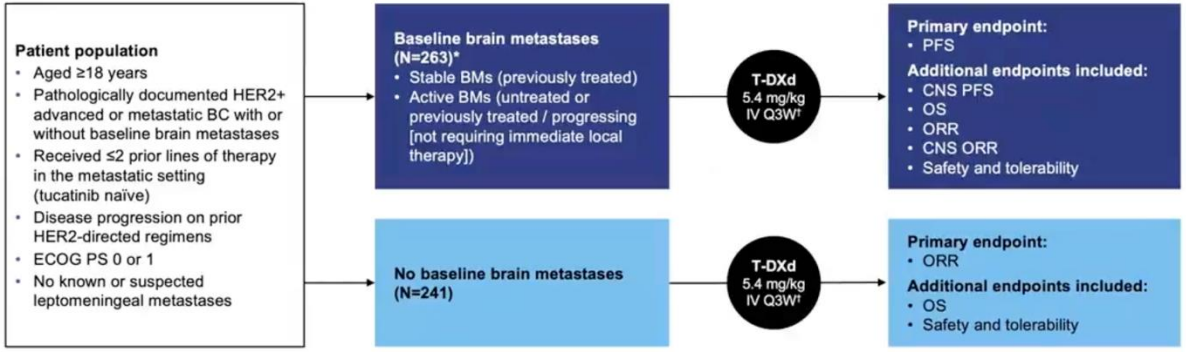


Rx Algorithm: Advanced HER2+ Breast Cancer



DESTINY-Breast12: Study Design

Phase 3b/4, multicenter, single-arm, two-cohort, open-label study of T-DXd in previously treated HER2+ mBC with and without brain metastases (BMs); the largest prospective study of T-DXd in patients with stable or active BMs



Data reported for the full analysis set (all patients enrolled in the study who received at least one treatment dose) and safety analysis set (identical to full analysis set). No hypothesis testing or comparison of cohorts. Response and progression assessed by ICR per RECIST 1.1 in both cohorts. Patients were enrolled from Australia, Canada, Europe, Japan, and United States

***Concomitant use of ≤3 mg of dexamethasone daily or equivalent allowed for symptom control of BMs (baseline BMs cohort only)**; †until RECIST 1.1-defined disease progression outside the CNS

BC, breast cancer; CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; HER2+, HER2-positive; ICR, independent central review; IV, intravenous; mBC, metastatic breast cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Q3W, every 3 weeks; RECIST 1.1, Response Evaluation Criteria in Solid Tumours version 1.1; T-DXd, trastuzumab deruxtecan

NCT04739761. Updated. July 19, 2024. Available from: https://www.clinicaltrials.gov/study/NCT04739761 (Accessed September 9, 2024)

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DESTINY-Breast12: Demographics and Baseline Characteristics

	Baseline BMs (N=263)	No baseline BMs (N=241)
Age, median (range), years	52 (28–86)	54 (24–87)
Female, n (%)	263 (100.0)	241 (100.0)
ECOG PS at baseline, n (%)		
0	163 (62.0)	194 (80.5)
1	100 (38.0)	47 (19.5)
HER2 status, n (%)		
2+	2 (0.8)	5 (2.1)
3+	187 (71.1)	141 (58.5)
Positive*	74 (28.1)	95 (39.4)
HR status, n (%)		
Positive†	165 (62.7)	150 (62.2)
Liver metastases, n (%)	58 (22.1)	66 (27.4)
Lung metastases, n (%)	67 (25.5)	67 (27.8)
Measurable disease, n (%)	198 (75.3)	215 (89.2)

	Baseline BMs (N=263)	No baseline BMs (N=241)
Prior regimens of anticancer therapies for metastatic disease		
Number of regimens, median (range)	1.0 (0–4)	1.0 (0–4)
Number of regimens, n (%)		
0	20 (7.6)	18 (7.5)
1	132 (50.2)	124 (51.5)
2	109 (41.4)	96 (39.8)
≥3	2 (0.8)	3 (1.2)
Prior HER2 inhibitor agents, n (%)	262 (99.6)	240 (99.6)
Trastuzumab	258 (98.1)	233 (96.7)
Pertuzumab	228 (86.7)	207 (85.9)
T-DM1	106 (40.3)	94 (39.0)
Tucatinib‡	2 (0.8)	0
Other TKIs§	15 (5.7)	15 (6.2)
T-DXd	1 (0.4)	0
Specific agent not reported	1 (0.4)	0
Prior therapies for BMs, n (%)		
Intracranial radiotherapy¶	158 (60.1)	–
Whole brain radiation therapy	40 (15.2)	–
Stereotactic radiosurgery	15 (5.7)	–
Time from last intracranial radiotherapy to treatment initiation, median (range), days	164 (9–2115)	–

*Specific HER2 status unknown; †HR status positive if either or both of ER/PR status had a positive result; ‡the two patients with prior tucatinib use were recorded as protocol deviations; §lapatinib and neratinib; ¶the type of intracranial radiotherapy was not always recorded by investigators, and only whole brain radiation therapy and stereotactic radiosurgery were reported
BM, brain metastasis; ECOG PS, Eastern Cooperative Oncology Group performance status; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; PR, progesterone receptor; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TKI, tyrosine kinase inhibitor

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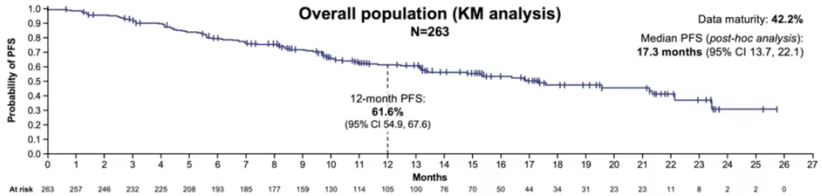
DESTINY-Breast12: Baseline BM- PFS and CNS ORR

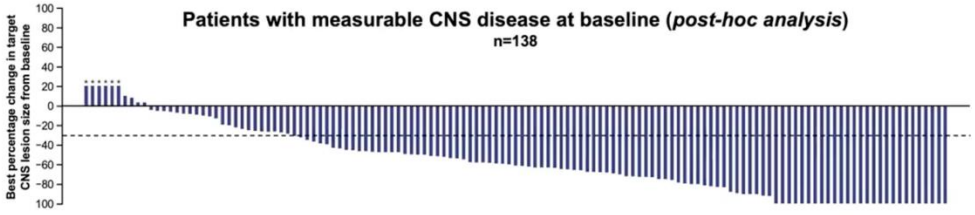


	Overall population (N=263)	Stable BMs (n=157)	Active BMs (n=106)	Active BM subgroups: Untreated (n=39) Post-hoc analysis	Active BM subgroups: Previously treated / progressing (n=67) Post-hoc analysis
Overall no. events	111	64	47	20	27
12-month PFS, % (95% CI)	61.6 (54.9, 67.6)	62.9 (54.0, 70.5)	59.6 (49.0, 68.7)	47.0 (29.6, 62.7)	66.7 (53.4, 76.9)

T-DXd showed consistent 12-month PFS in patients with stable and active BMs

PFS assessed by ICR per RECIST 1.1
BM, brain metastasis; CI, confidence interval; ICR, independent central review; KM, Kaplan-Meier; no., number of; PFS, progression-free survival; RECIST 1.1, Response Evaluation Criteria in Solid Tumours version 1.1; T-DXd, trastuzumab deruxtecan

Lin N. U. ESMO 2024



Measurable CNS disease at baseline	All patients (n=138)	Stable BMs (n=77)	Active BMs (n=61)	Active BM subgroups: Untreated (n=23) Post-hoc analysis	Active BM subgroups: Previously treated / progressing (n=38) Post-hoc analysis
Confirmed CNS ORR, % (95% CI)	71.7 (64.2, 79.3)	79.2 (70.2, 88.3)	62.3 (50.1, 74.5)	82.6 (67.1, 98.1)	50.0 (34.1, 65.9)

T-DXd showed substantial CNS responses in the overall BMs population, including patients with stable and active BMs

Dashed line indicates a 30% decrease in target tumor size (PR)
*Imputed values: a value of +20% was imputed if best percentage change could not be calculated because of missing data if: a patient had a new lesion or progression of non-target lesions or target lesions, or had withdrawn because of PD and had no evaluable target lesion data before or at PD
BM, brain metastasis; CI, confidence interval; CNS, central nervous system; ORR, objective response rate; PD, progressive disease; PR, partial response; T-DXd, trastuzumab deruxtecan

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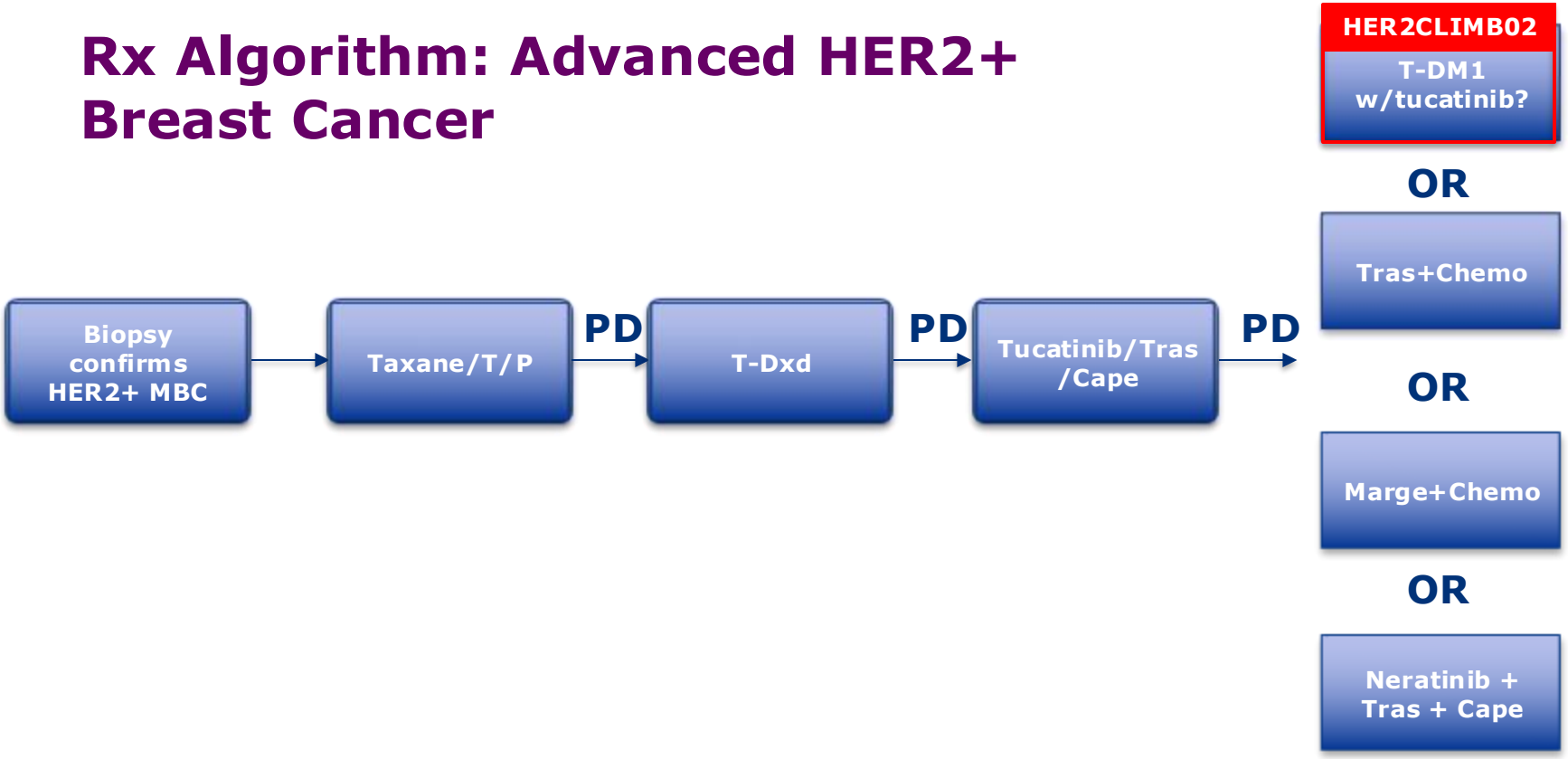
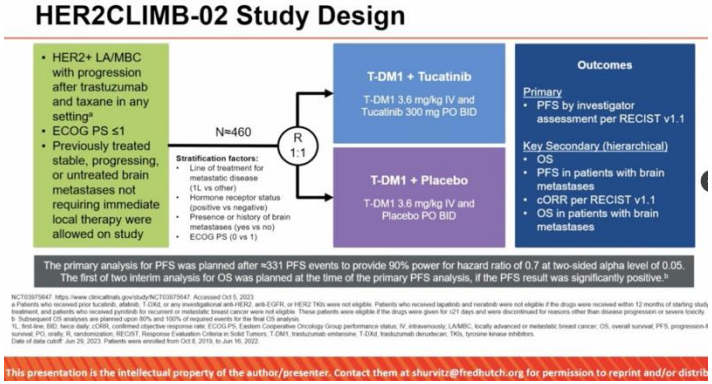
DESTINY-Breast12: Summary

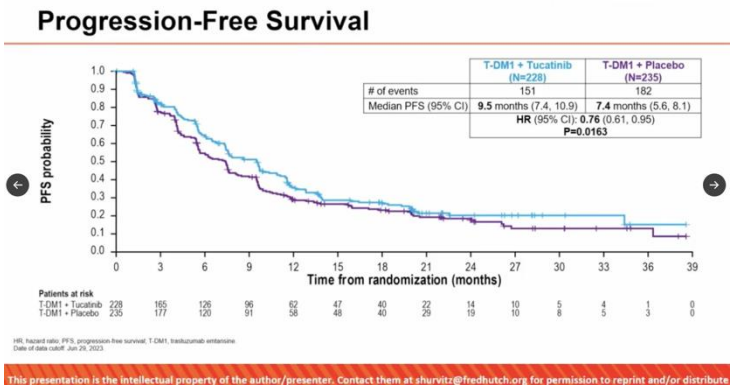
- Substantial and durable intracranial response in pts with HER2 positive breast cancer
- HER2CLIMB intracranial ORR 47.3% in pts w/active BMs
  - Limitations of cross-trial comparison
- Promising CNS activity of T-DXd in pts w/active BMs
  - DEBBRAH: phase II trial n=13; intracranial ORR 46.2%
  - TUXEDO-1: phase II trial n=15; intracranial ORR 73.3%
- Safety consistent with prior trials
  - ILD rate appx 16%
    - 9 pts with grade 5 events, 3 pts w/opportunistic infections

Rx Algorithm: Advanced HER2+ Breast Cancer



HER2CLIMB 02





Toxicity:
-most common TEAE: nausea (65.4% vs 49.4%); diarrhea 56.7% vs 26.6%; fatigue (48.9% vs 37.3%)
-most common G3 TEAE: liver function test abnormalities (elevated AST or ALT) 16.5% vs 2.6%
-discontinuations related to TEAE: 22.1% vs 11.6%

Limitations:
-comparator arm not HER2CLIMB or T-DXd

Not FDA approved regimen

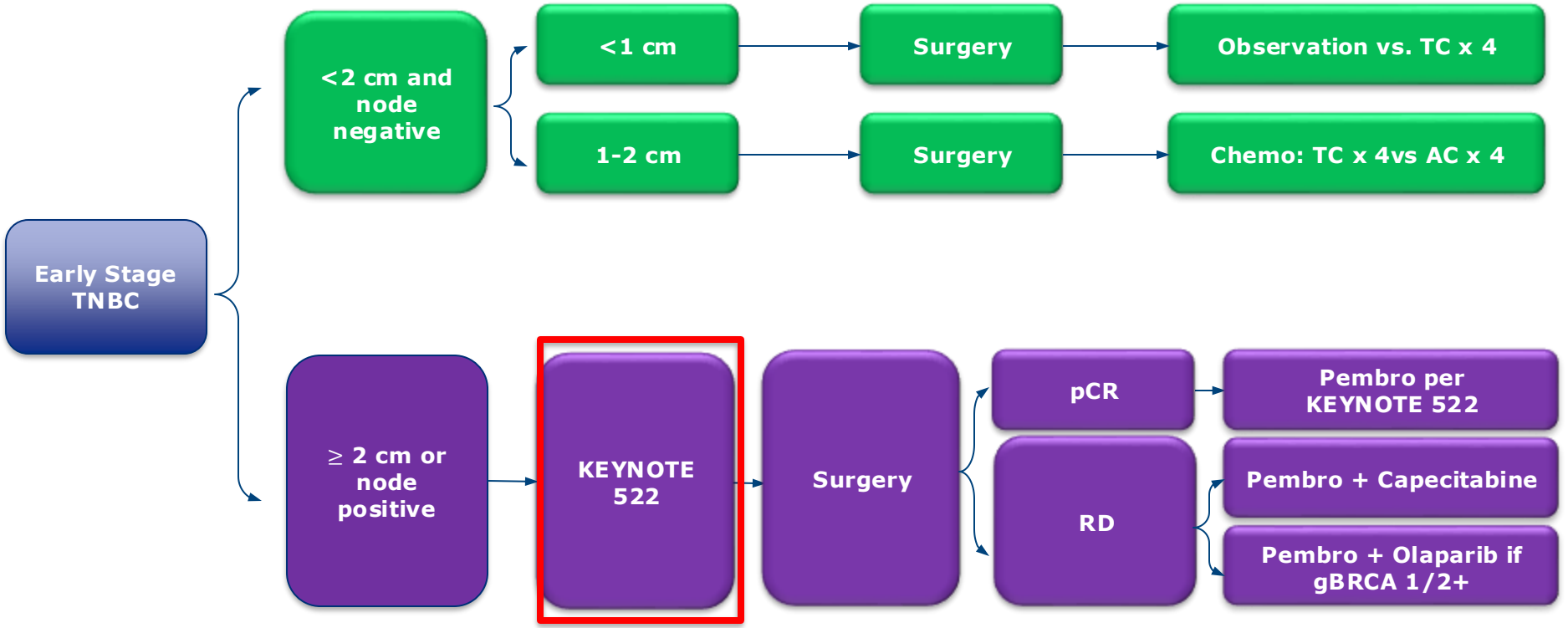
Outline: How I Treat Breast Cancer

I. HR+/HER2 Neg. Breast Cancer
- A. Early Stage
- B. Advanced Stage

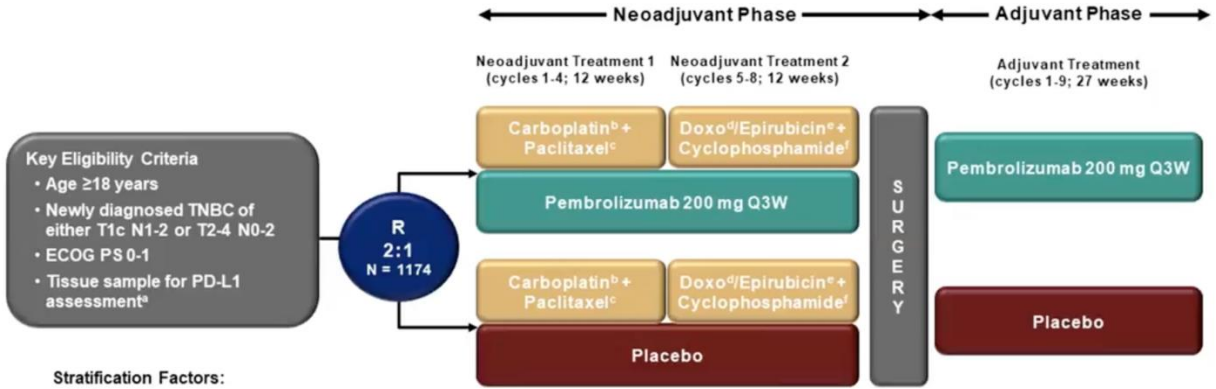
II. HER2 Positive Breast Cancer
- A. Early Stage
- B. Advanced Stage

III. Triple Negative Breast Cancer
- A. Early Stage
- B. Advanced Stage

Rx Algorithm: Early Stage TNBC



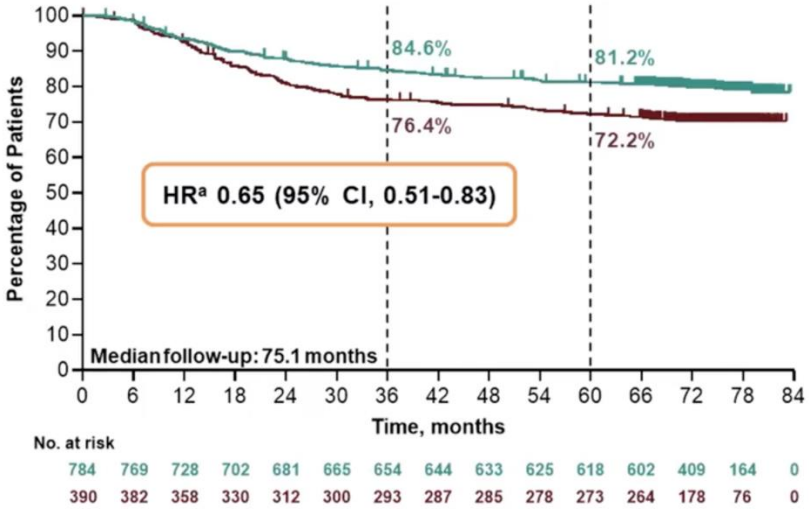
KEYNOTE 522: Study Design



[a]Must consist of at least 2 separate tumor cores from the primary tumor. [b]Carboplatin dose was AUC 5 Q3W or AUC 1.5 QW. [c]Paclitaxel dose was 80 mg/m² QW. [d]Doxorubicin dose was 60 mg/m² Q3W. [e]Epirubicin dose was 90 mg/m² Q3W. [f]Cyclophosphamide dose was 600 mg/m² Q3W.

Schmid P. ESMO 2024

KEYNOTE 522: Updated EFS



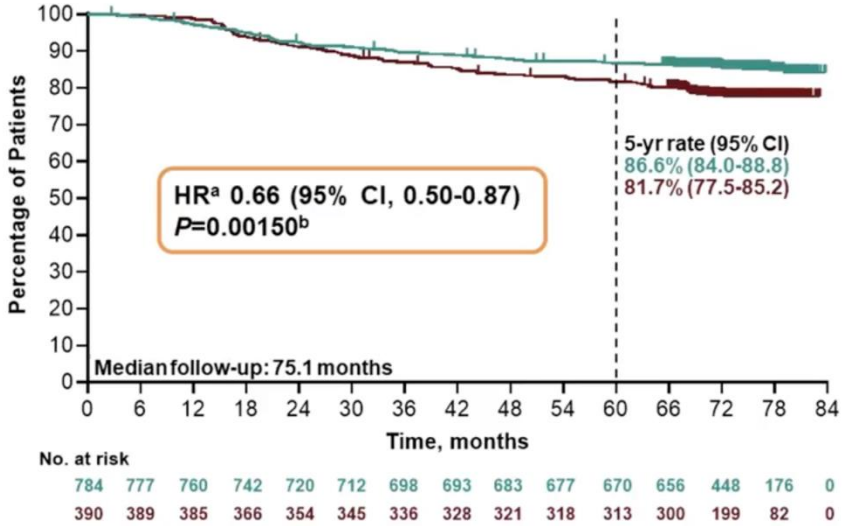
	Pts w/ Event
Pembro + Chemo/Pembro	20.3%
Placebo + Chemo/Placebo	29.2%

[a]Hazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate stratified by the randomization stratification factors. Data cutoff date: March 22, 2024.

Schmid P. ESMO 2024

Median (range) follow-up[c]: 75.1 mo (65.9-84.0)

KEYNOTE 522: Key Secondary Endpoint OS



	Pts w/ Event
Pembro + Chemo/Pembro	14.7%
Placebo + Chemo/Placebo	21.8%

[a]The unstratified piecewise HR was 0.87 (95% CI, 0.57-1.32) before the 2-year follow-up and 0.51 (95% CI, 0.35-0.75) afterwards. The weighted average HR with weights of number of events before and after 2-year follow-up was 0.66. With 200 events (67.3% information fraction), the observed *P*-value crossed the prespecified nominal boundary of 0.00503 (1-sided) at this interim analysis.
Data cutoff date: March 22, 2024.

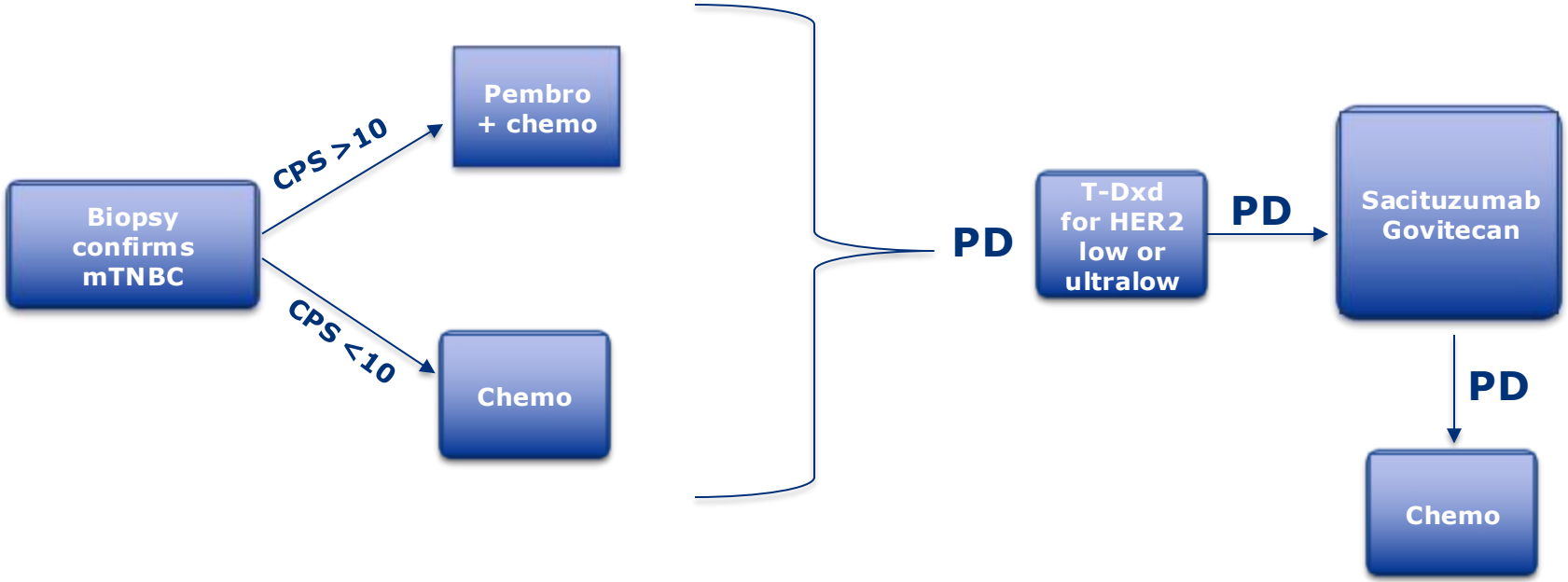
Schmid P. ESMO 2024

Median (range) follow-up[c]: 75.1 mo (65.9-84.0)

KEYNOTE 522: Summary

- Use of neoadjuvant and adjuvant use of pembro improves OS
- OS Benefit is higher in pts with residual disease
  - 71.8% vs 65.7%
- Tailor adjuvant therapy based on response to NAC
  - Ongoing trials

Rx Algorithm: Advanced TNBC



- ✓ Germline testing, pathogenic mutation present HRD pathway, consider PARPi
- ✓ Continuously assess for clinical trial eligibility

Questions?