Future Directions in the Management of HER2-Positive Localized and Metastatic Breast Cancer

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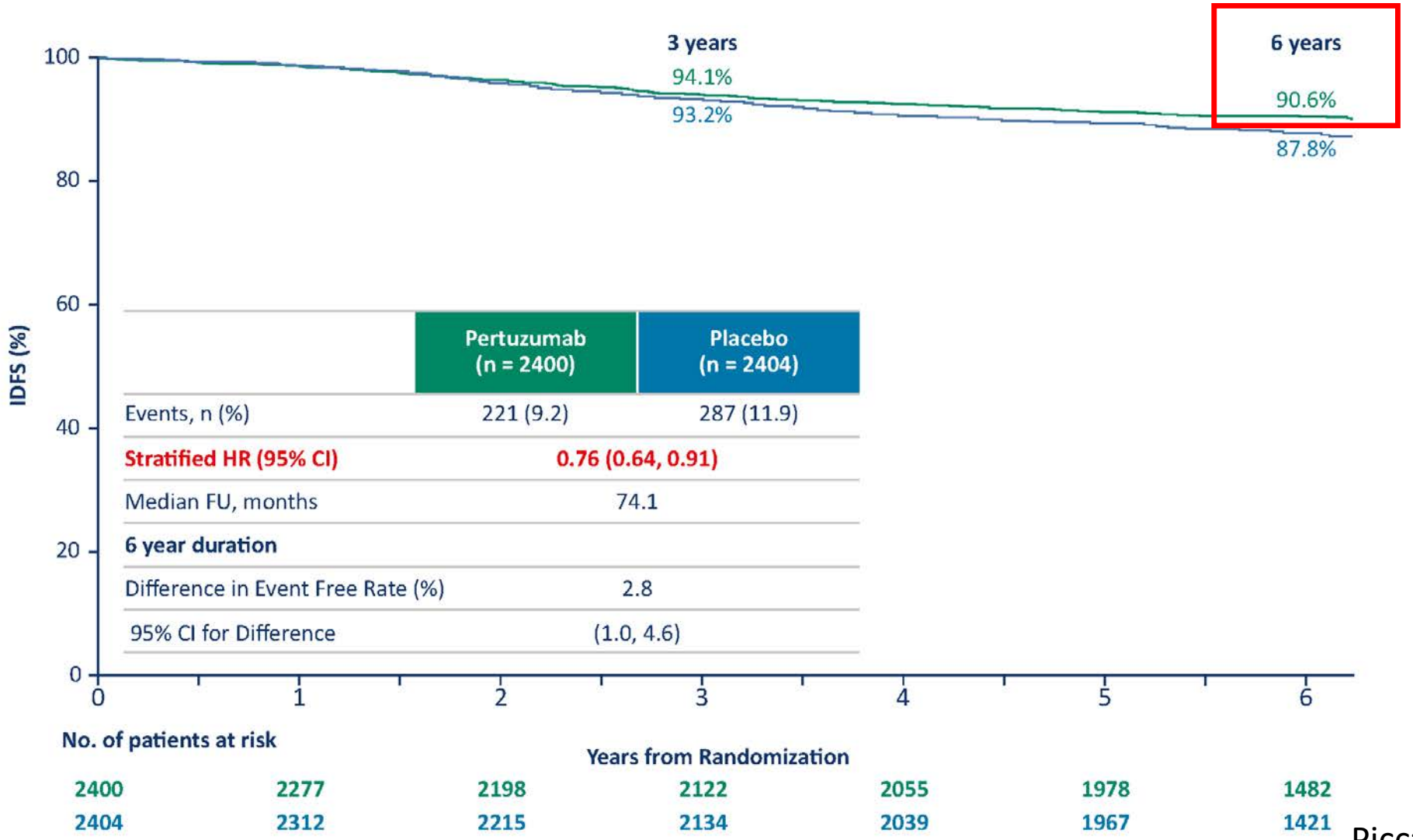
Harvard Medical School

Patients with HER2+ early breast cancer now have generally favorable outcomes

Results from APHINITY study of chemotherapy/trastuzumab±pertuzumab



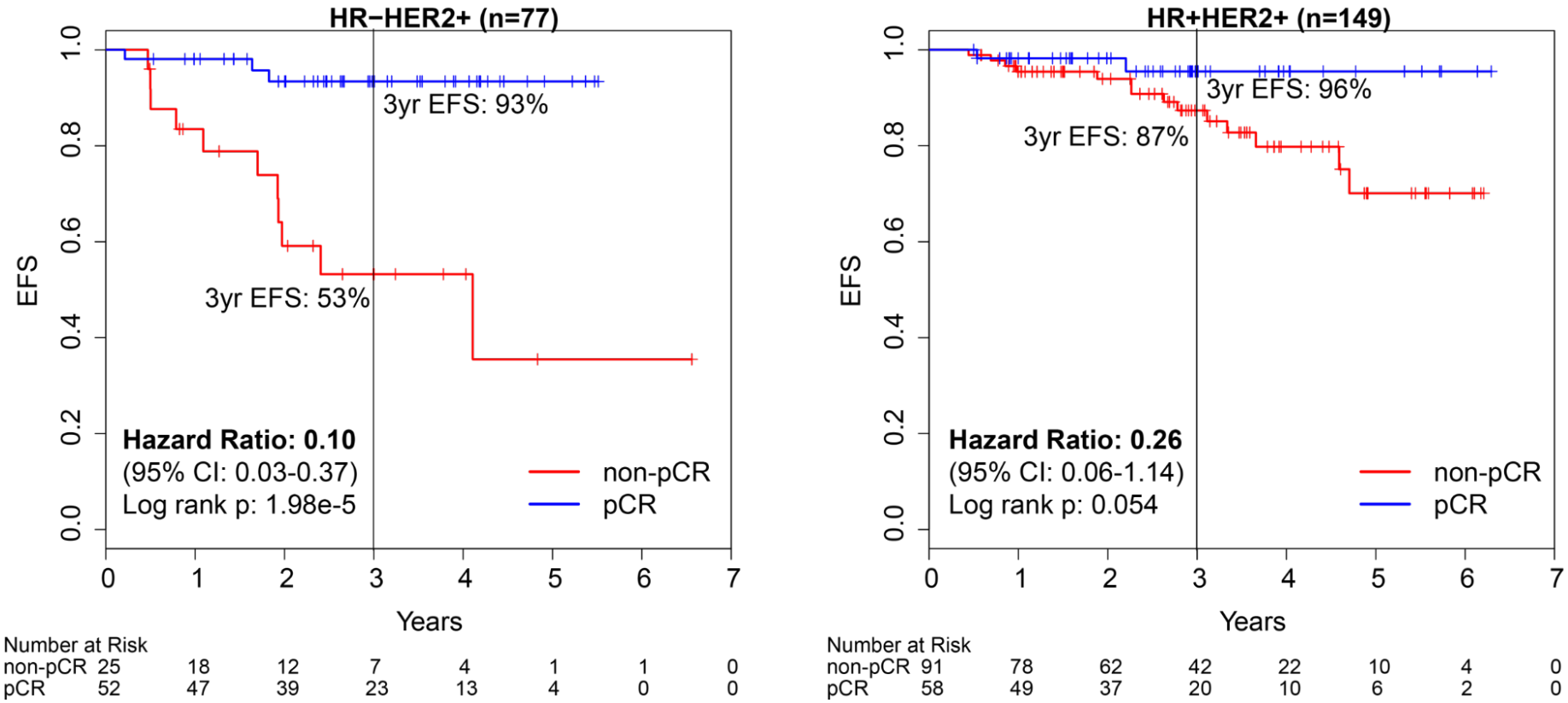
Piccart et al, SABCS 2019

The era of personalized medicine in HER2+ EBC

- The favorable outcomes of HER2+ breast cancers provide opportunity to:
  - De-escalate therapy for lower risk patients to reduce the toxicities of treatment
  - Escalate therapy for minority of patients who are at risk for recurrence despite maximal current management
- To optimally tailor therapy requires effective risk stratification strategies

Achievement of pCR after neoadjuvant HER2-therapy is powerful prognostic marker

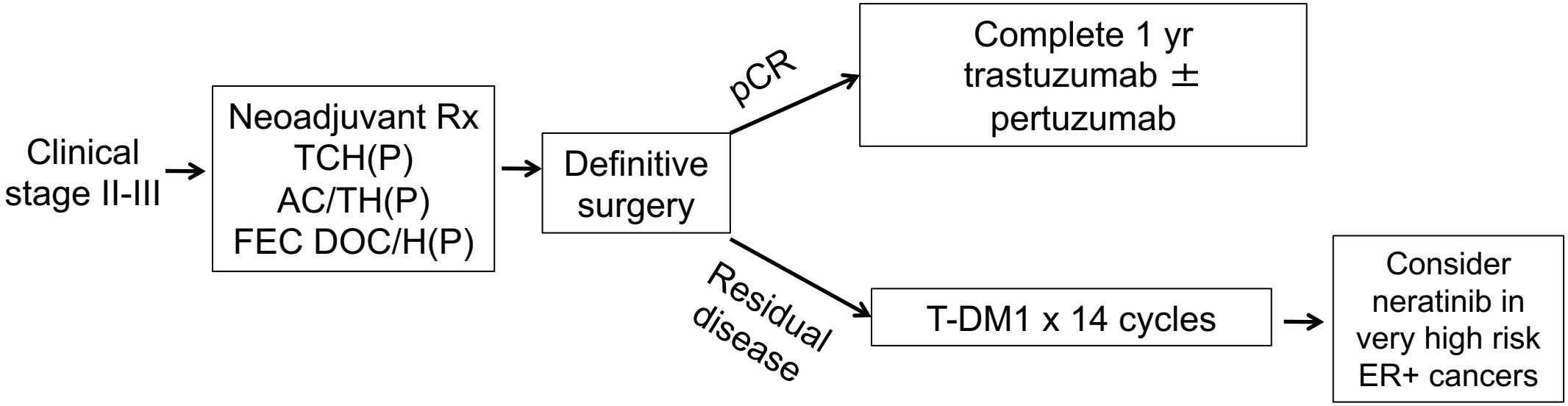
Influence of pCR on EFS in HER2+ Disease: I-SPY



Difference between pCR vs. residual disease greater for ER- and ER+ consistent with meta-analysis from Cortazar et al, Lancet 2014

Yee et al, SABCS 2017

Recommended Treatment Algorithm for Early-Stage HER2+ Breast Cancer



COMPASS Trial Schema

Eligibility
HER2+ breast ca
Stage 2 or 3a
(T2-3, N0-2)
Newly diagnosed,
no prior therapy

Registration

Part 1 preop
THP x 4 (12 weeks)

pac weekly or doc q3w (T)
PLUS
trastuzumab (H) &
pertuzumab (P) q3w

N=1250

Surgery

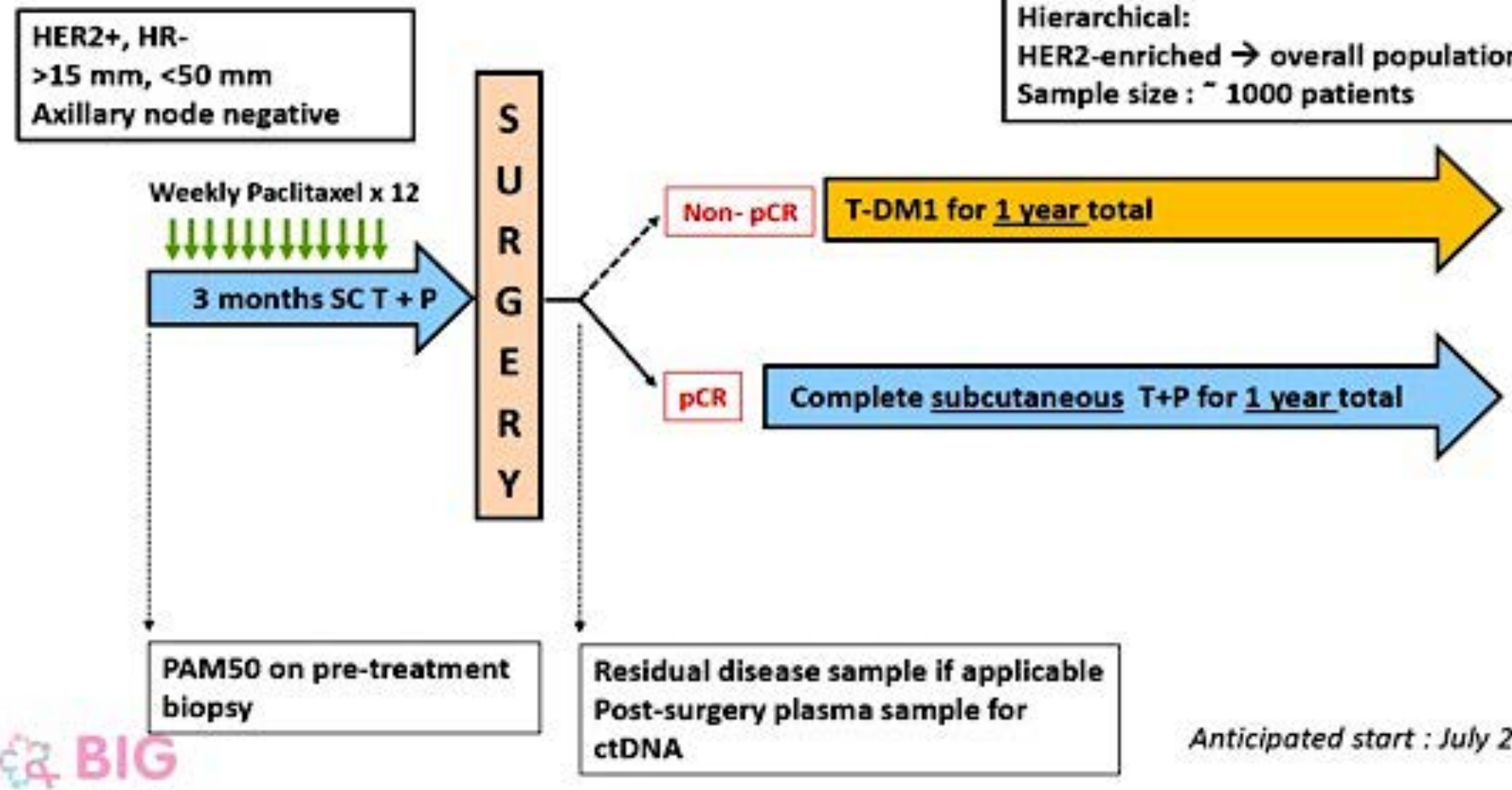
Part 1 pCR (~40-45%)
No further chemo
Complete HP

Part 2 RD (~55%)

SOC adjuvant therapy

Primary Objective: 3y RFS

DECRESCENDO Study design



Anticipated start : July 2020

NCT04675827

Neoadjuvant THP is associated with high pCR rate (DAPHNE Study)

RCB class	All patients (n=97)	ER+ and/or PR+ (n=65)	ER- and PR- (n=32)
0 (pCR)	**55(56.7%)**	**28(43.1%)**	**27(84.4%)**
1	9(9.3%)	8(12.3%)	1(3.1%)
2	26(26.8%)	24(36.9%)	2(6.3%)
3	2(2.1%)	2(3.1%)	0
Non-pCR → more neoadjuvant therapy	5(5.2%)	3(4.6%)	2(6.3%)

Waks et, SABCS 2020 – Abstract PD3-05

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COMPASS RD

Eligibility
HER2+ breast ca
Stage 2 or 3a
(T2-3, N0-2)
Newly diagnosed,
no prior therapy

Registration

Part 1 preop
THP x 4 (12 weeks)

pac weekly or doc q3w (T)
PLUS
trastuzumab (H) &
pertuzumab (P) q3w

Surgery

Part 1 pCR (~40-45%)
No further chemo
Complete HP

Part 2 RD (~55%)

SOC chemo as deemed necessary

Eligibility
HER2+ RD
Any ER-
ER+ if N+
~ 50% Part 1, 50%
outside enrollees

N=981

Registration

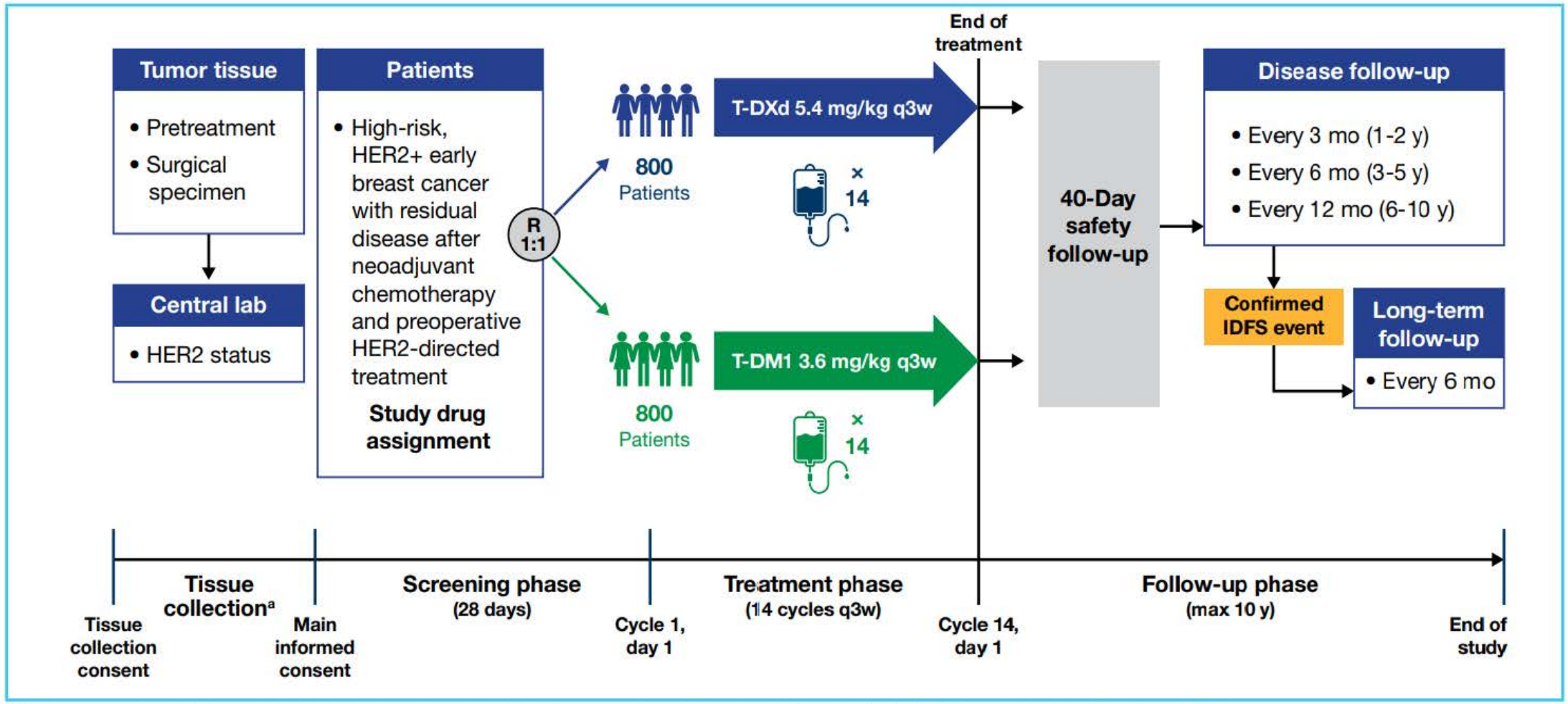
R

T-DM1 x 14 cycles

T-DM1 + tucatinib x14 cycles

Primary Objective: 3y IDFS

DESTINY-Breast05: A Multicenter, Open-Label, Randomized Phase 3 Trial Comparing the Efficacy and Safety of T-DXd vs T-DM1 in High-Risk Patients With HER2-Positive, Residual, Invasive Breast Cancer After Neoadjuvant Therapy (N≈1600)

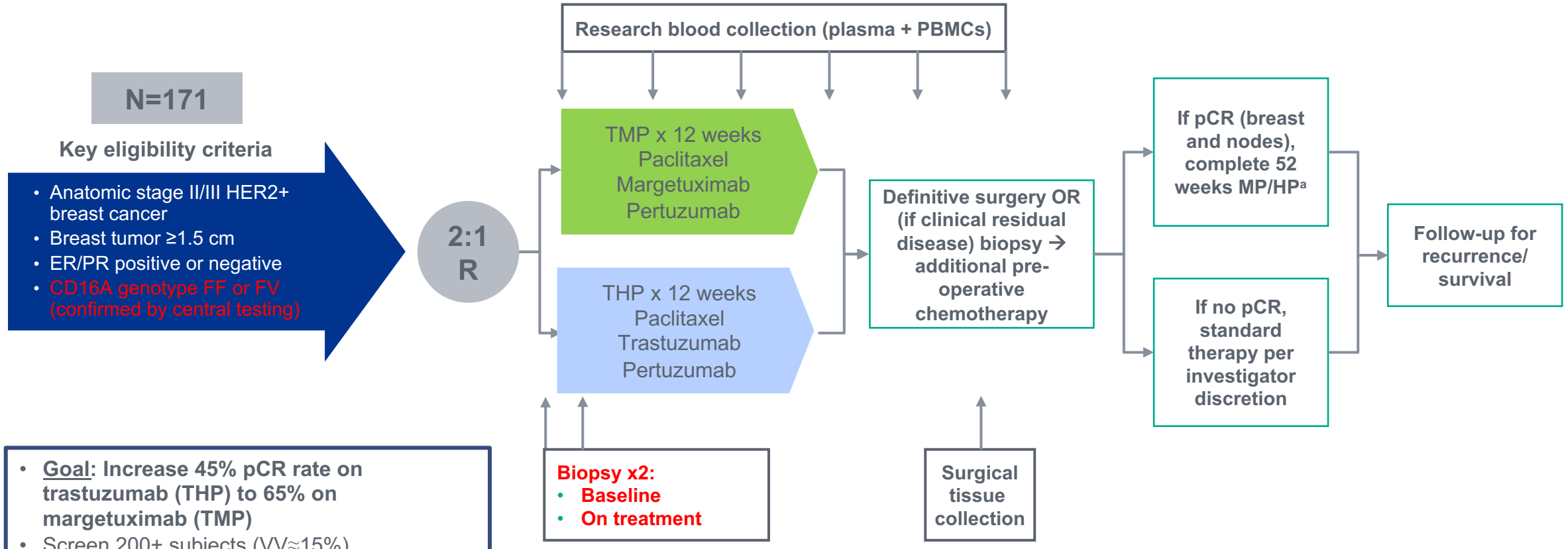


HER2, human epidermal growth factor receptor 2; IDFS, invasive disease–free survival; lab, laboratory; max, maximum; q3w, every 3 weeks; R, randomization; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

[a] Patients may move into the main screening phase before HER2 status results are available from the central laboratory.

Geyer et al. SABCS 2020 OT-03-01

MARGetuximab or Trastuzumab (MARGOT): A Phase 2 Study Comparing Neoadjuvant TMP vs THP in Patients With Stage II/III HER2+ Breast Cancer



- **Goal: Increase 45% pCR rate on trastuzumab (THP) to 65% on margetuximab (TMP)**
- Screen 200+ subjects (VV≈15%)
- Patients will be stratified by ER status (<10% vs >10%) and clinical anatomic stage (II vs III)

[a]Concurrent endocrine treatment allowed if HR+. Adjuvant radiation per standard institutional practice.

CD, cluster of differentiation; ER, estrogen receptor; FPI, first patient in; H, trastuzumab; HER2+, human epidermal growth factor receptor 2 positive; HR, hormone receptor; M, margetuximab; P, pertuzumab; PBMC, peripheral blood mononuclear cells; pCR, pathological complete response (defined as RCB [residual cancer burden]=0); PR, progesterone receptor; T, paclitaxel.

tbcrc Translational Breast Cancer Research Consortium

New approaches in HER2+ MBC

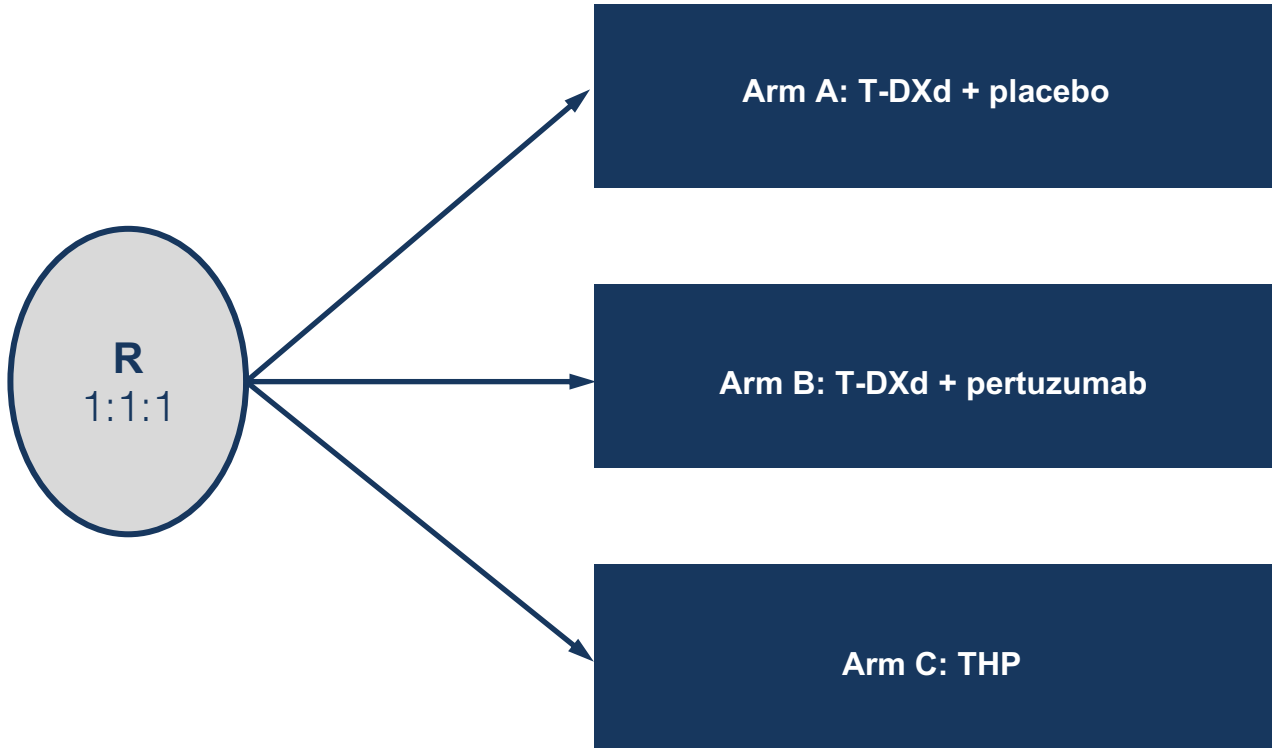
Combination regimens

DESTINY-Breast09: A Phase 3 Trial of T-DXd Alone or in Combination With Pertuzumab in First-Line HER2+ MBC

Will moving T-DXd earlier in disease course further increase its efficacy?

Patient population (N≈1134)

- Advanced and/or metastatic breast cancer
- HER2 positive (IHC 3+ or ISH+) by central confirmation
- No previous chemotherapy or HER2-targeted therapy for advanced or metastatic breast cancer
- Patients will be stratified by prior treatment status (de novo vs recurrent), HR status (positive vs negative), and *PIK3CA* mutation status (detected vs not detected)

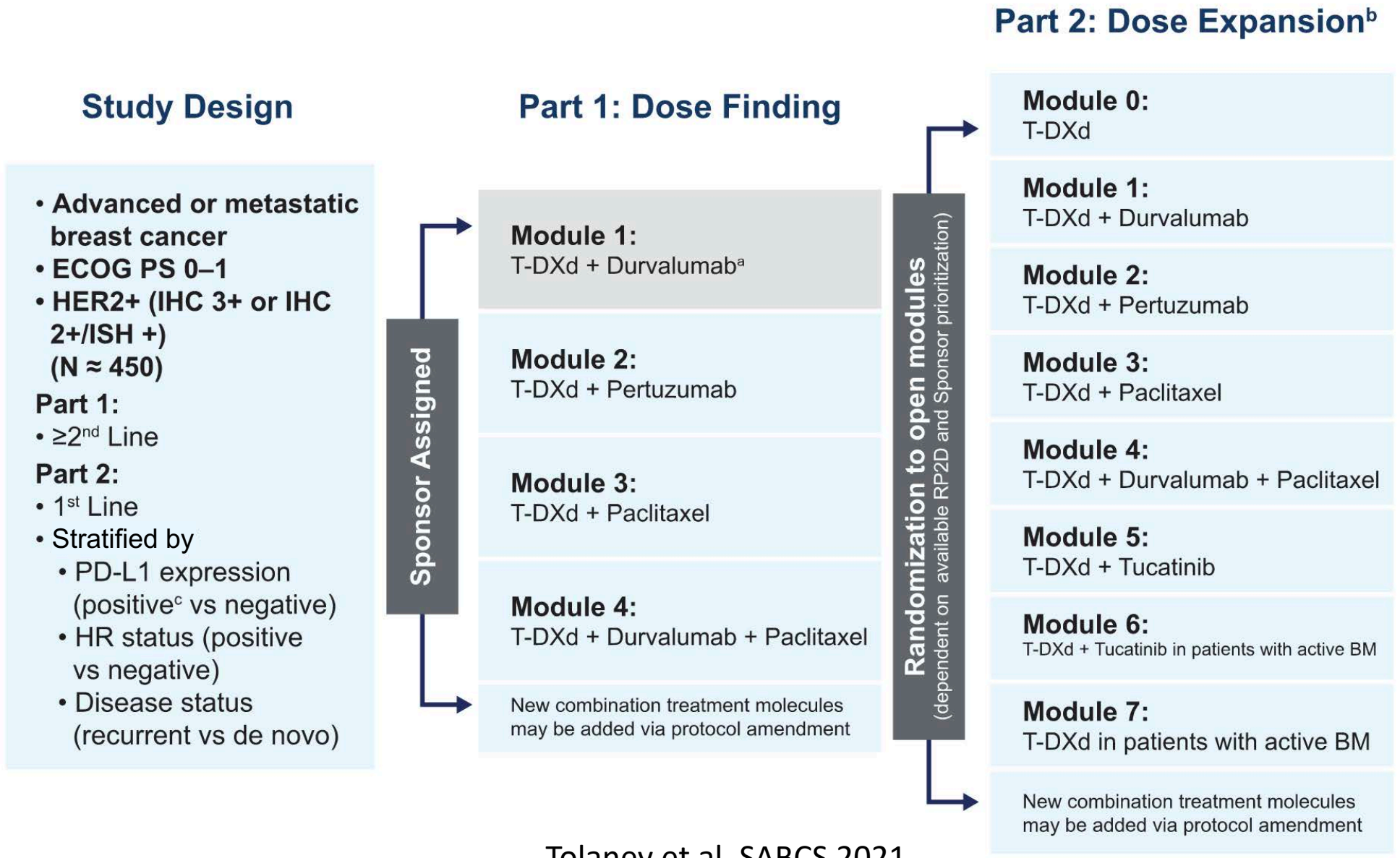


Primary endpoint: PFS by BICR

NCT04784715

Tolaney et al, SABCS 2021

DESTINY-Breast07: A Phase 1b2 Trial of T-DXd in combination with other anti-cancer agents

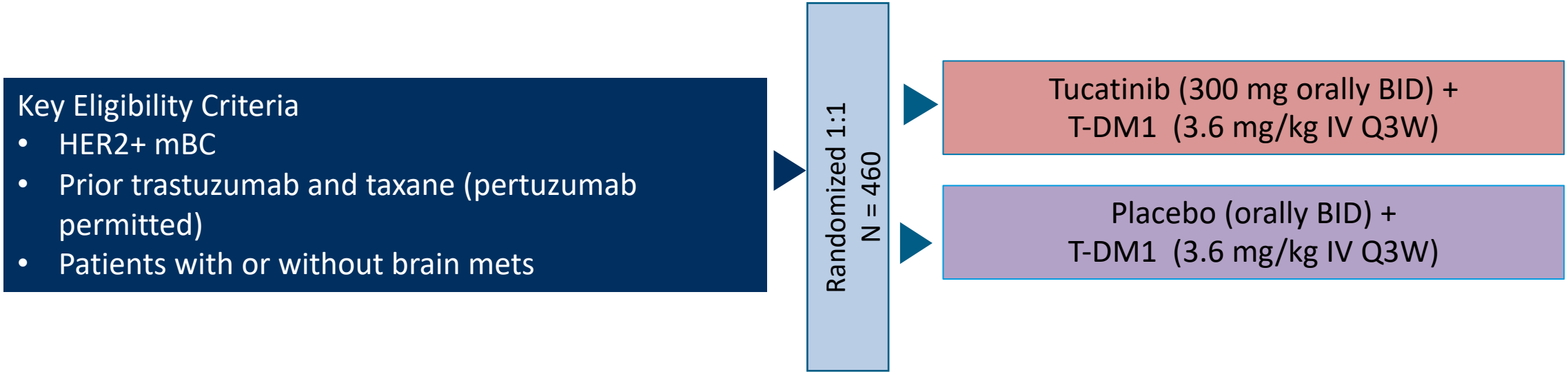


NCT04538742

Tolaney et al, SABCS 2021

HER2CLIMB-02 Trial

Does tucatinib add to T-DM1?



Primary Endpoint: PFS

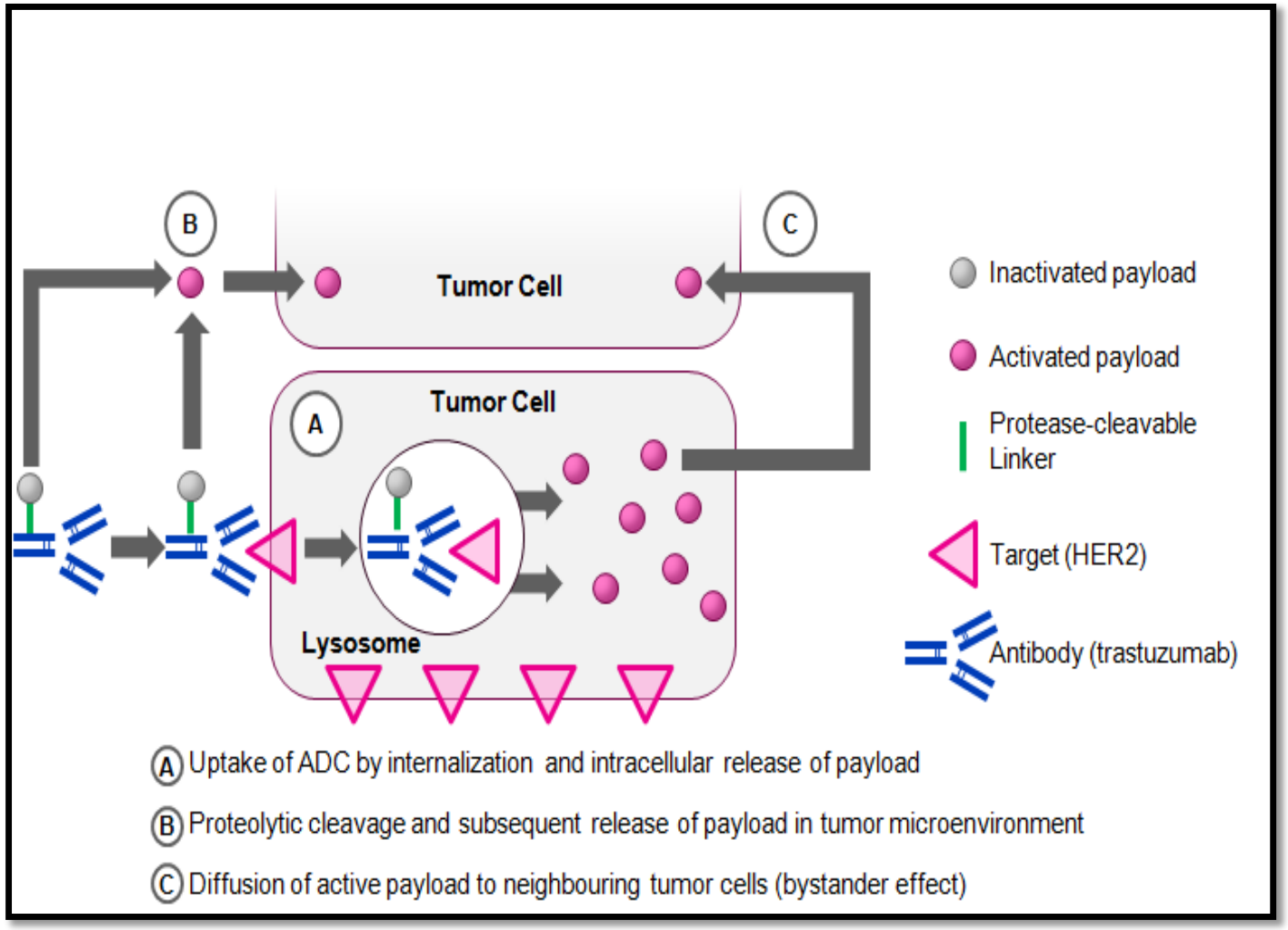
NCT01983501

New approaches in HER2+ MBC

Novel therapies

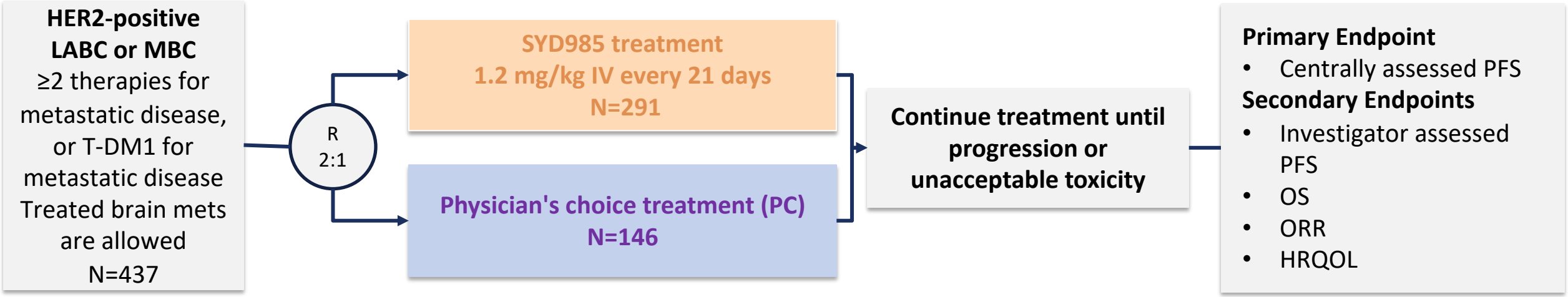
SYD985: [vic-]trastuzumab duocarmazine

- HER2-targeting antibody-drug conjugate (ADC) based on trastuzumab
- Protease cleavable linker with a DNA alkylating toxin duocarmycin
- Toxin incorporated into the linker-drug as an inactive prodrug
- Proteolytic cleavage results in release of the active toxin



Slide adapted from S Tolaney. ASCO 2018.

TULIP - Phase III Trial Design

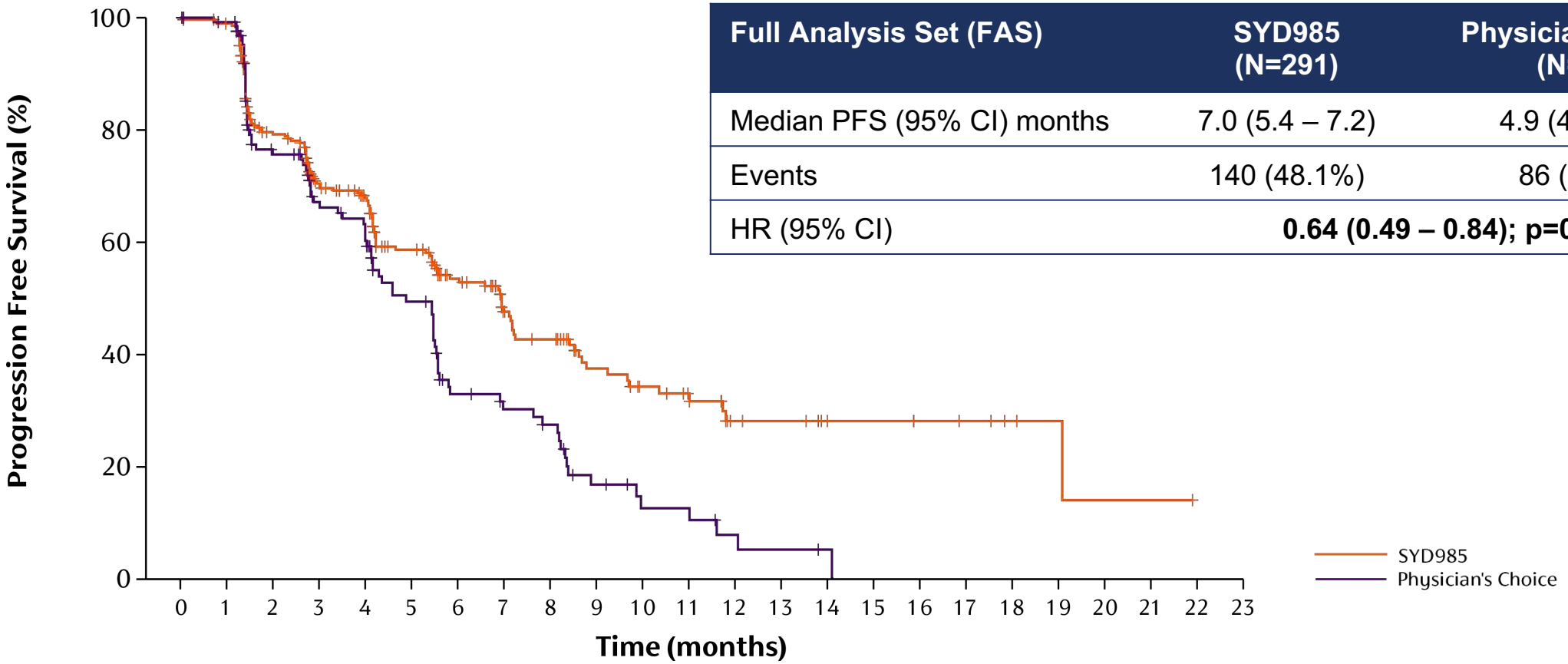


Stratification - Treatment - Participating Countries

- **Stratification factors**
  - Region (EU+Singapore vs North America)
  - Number of prior treatment lines for LMBC/MBC (1-2 vs >2)
  - Prior treatment with pertuzumab (yes vs no)
- **Physician's choice**
  - Lapatinib + Capecitabine
  - Trastuzumab + Capecitabine
  - Trastuzumab + Vinorelbine
  - Trastuzumab + Eribulin
- **NCT03262935**
- **83 sites**
  - USA, Canada, Belgium, Denmark, France, Italy, Netherlands, Spain, Sweden, UK, Singapore

TULIP – Centrally Reviewed PFS

Full Analysis Set (FAS)	SYD985 (N=291)	Physician's choice (N=146)
Median PFS (95% CI) months	7.0 (5.4 – 7.2)	4.9 (4.0 – 5.5)
Events	140 (48.1%)	86 (58.9%)
HR (95% CI)	**0.64 (0.49 – 0.84); p=0.002**	



No. Patients at Risk																							
SYD985	291	278	208	167	150	109	83	59	51	35	28	24	13	12	9	8	6	5	3	2	1	1	0
Physician's Choice	146	125	86	69	64	44	26	22	19	10	6	6	3	2	1	0							

TULIP – Safety – AEs of Special Interest

Eye toxicity: Reported for 78.1% SYD985 patients, physician's choice 29.2%

- Grade ≥ 3 for 21.2% SYD985 patients
- Discontinuation of treatment due to eye toxicity in 20.8% of SYD985 patients
- Dose modifications due to eye toxicity in 22.9% of SYD985 patients

Risk mitigation strategy in trial: Patients with prior keratitis excluded, prophylactic lubricating eye drops, regular eye exams by ophthalmologist, Grade 3 or higher keratitis stop treatment, grade 3 conjunctivitis delay treatment until reduced to grade 2

ILD/pneumonitis: Reported for 7.6% (N=22/288) SYD985 patients, not reported for physician's choice

- Grade ≥ 3 for 2.4% SYD985 patients
- Discontinuation of treatment due to ILD/Pneumonitis in 15 (5.2%) of SYD985 patients
- Dose modifications due to ILD/Pneumonitis in 6 (2.1%) of SYD985 patients

Risk mitigation strategy in trial: Patients with prior pneumonitis excluded, evaluate tumor CT scans for lung changes, do a full diagnostic work-up for new or worsening respiratory symptoms, grade 2 or higher pneumonitis stop treatment, grade 1 pneumonitis delay treatment until resolution

Fatal cases: Reported for 2.1% (N=6) SYD985 patients, not reported for physician's choice

- Related: Respiratory failure (0.3%, N=1), Pneumonia (0.3%, N=1), Pneumonitis (0.7%, N=2)
- Not related: Acute respiratory failure (0.3%, N=1), COVID-19 Pneumonia (0.3%, N=1)

Novel HER2 Antibody-drug Conjugates

	Payload	ORR	Population	Toxicity
R48	MMAE (tubulin inhibitor)	43%	70% pts had prior HER2 rx	Neuropathy, AST/ALT elevation
ARX788	AS269 (tubulin inhibitor)	40%	?	Ocular
A166	Duo-5 (tubulin inhibitor)	60-70%	?	Ocular

Hu X et al. ASCO 2021
Wang et al, ASCO 2021
Hu X et al. SABCS 2019. P1-18-16.

HER2 low cancers

A new breast cancer subtype?

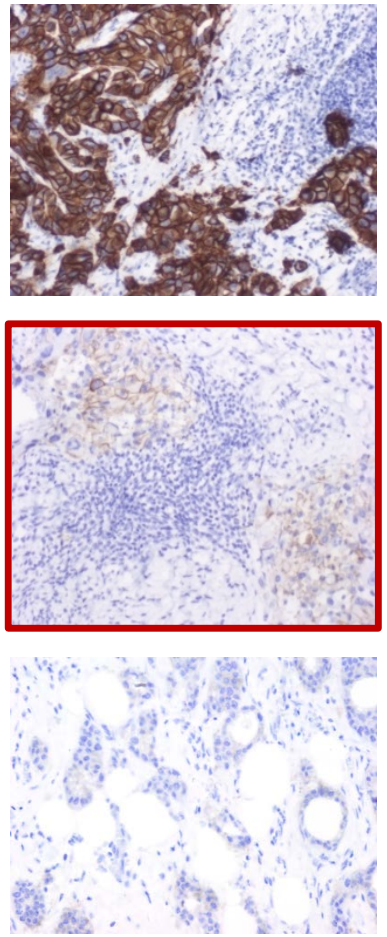
Prevalence of HER2-low Breast Cancer (IHC 1+/2+, FISH negative)

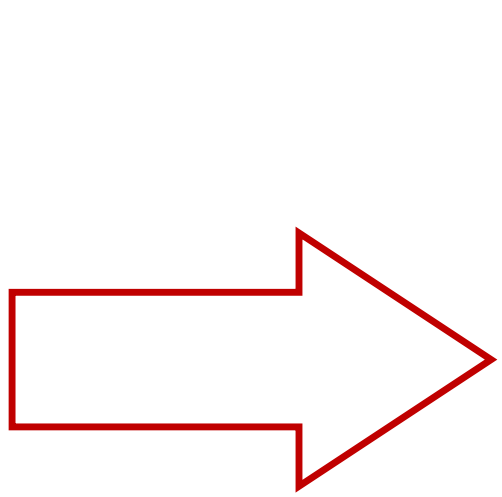
HER2 IHC examples

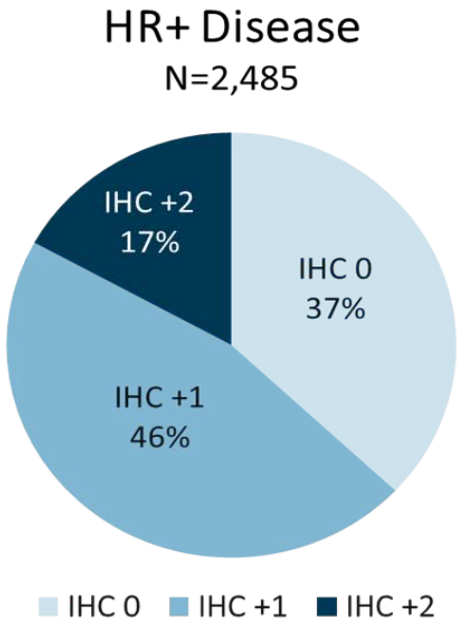
HER2+

HER2-low

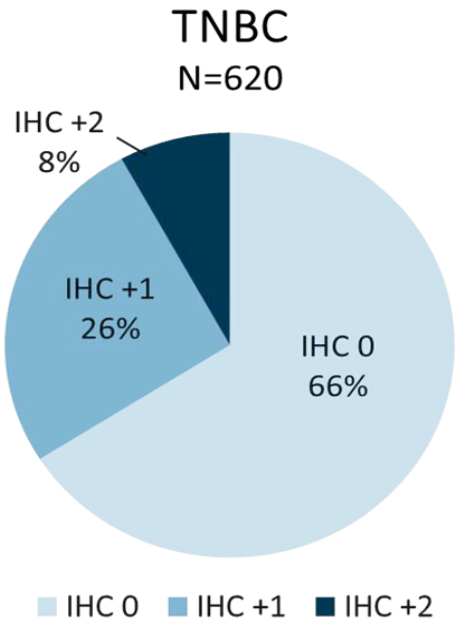
HER2-







63% HER2 Low

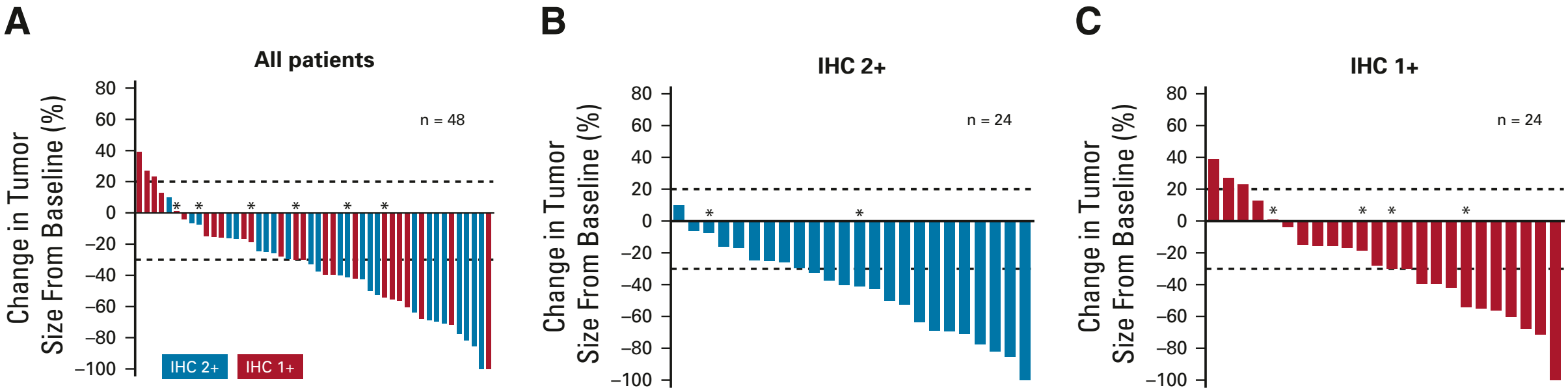


34% HER2 Low

Schettini. ESMO Breast Cancer Virtual Meeting 2020. Abstr 23P. Slide courtesy of Aleix Prat.

Effect of trastuzumab deruxtecan in heavily pretreated* HER2-low metastatic breast cancer

Similar Benefit for HER2 2+ and 1+



ORR=37%

ORR=35.7%

ORR=38.5%

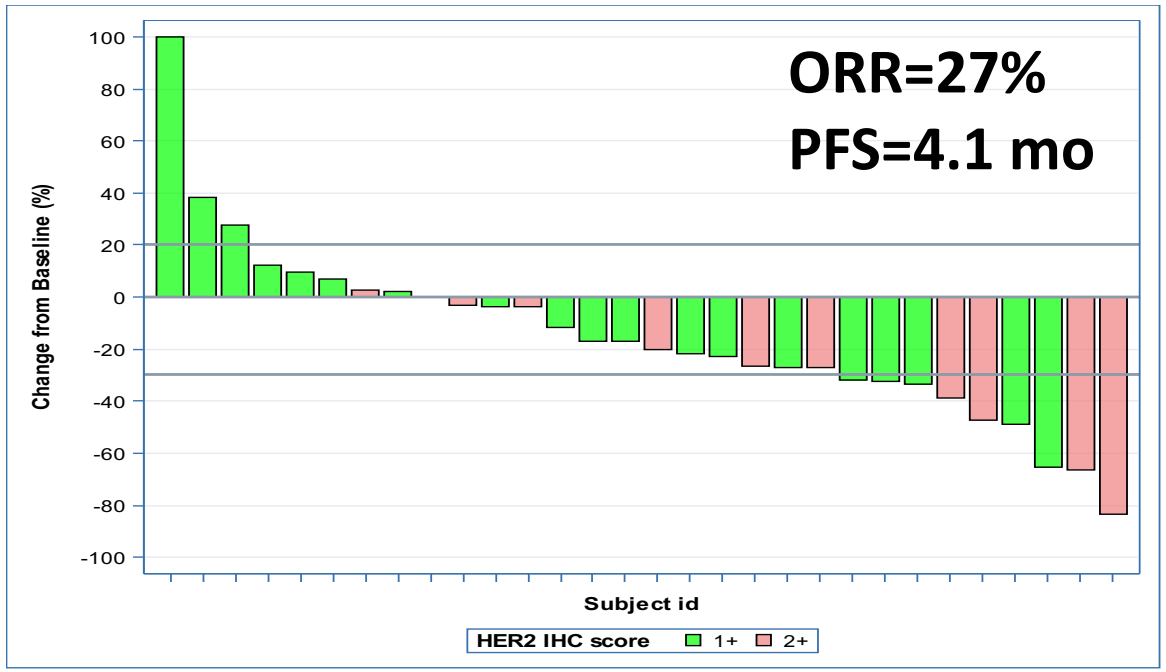
mPFS= 11.1 mo

***median of 7.5 prior regimens**

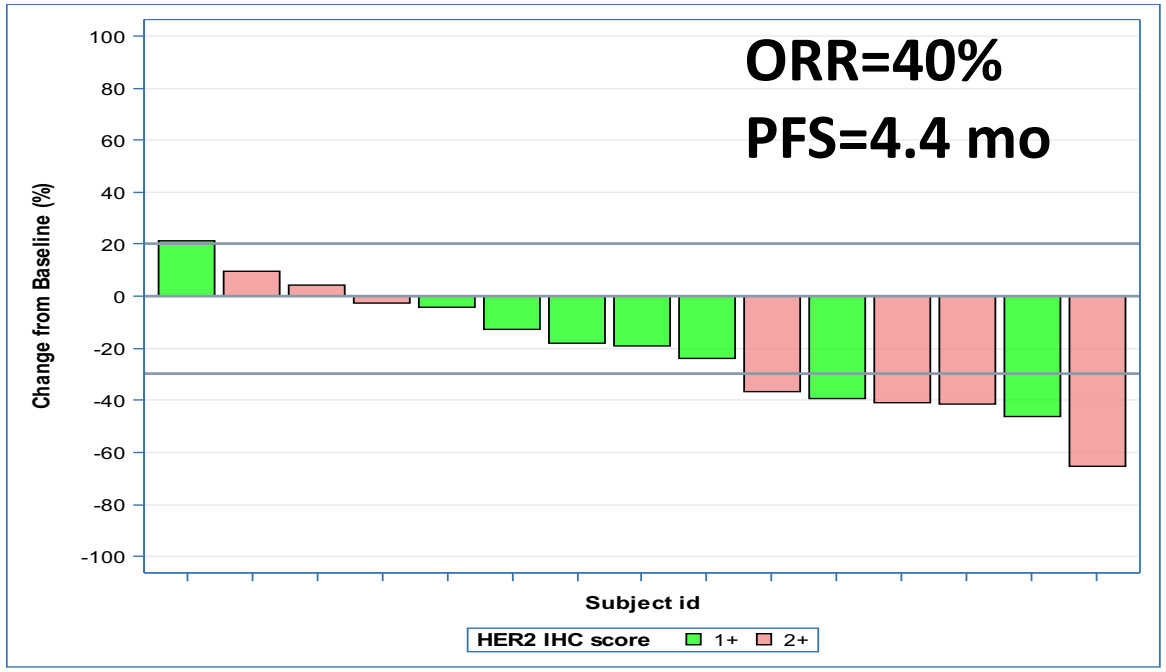
Modi S et al, JCO 2020

SYD985: Efficacy in HER2+ and HER2 low

HR+ HER2 low
N=32



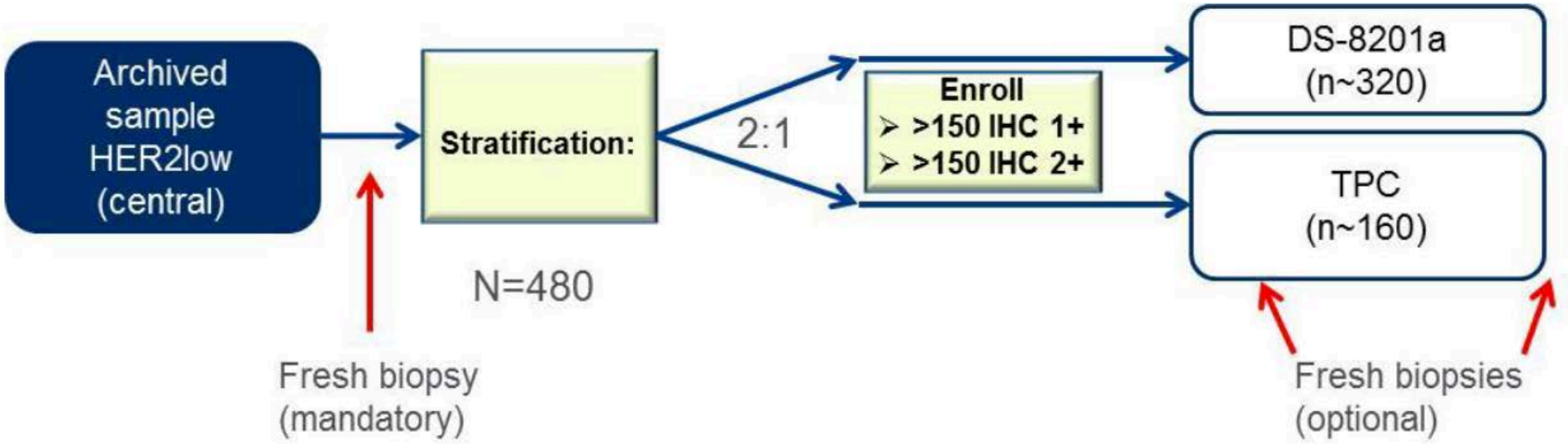
HR- HER2 low
N=17



Median # prior regimens=6

Saura C et al, ASCO Annual Meeting 2018

DESTINY-Breast04: Ph 3 DS8201a vs TPC

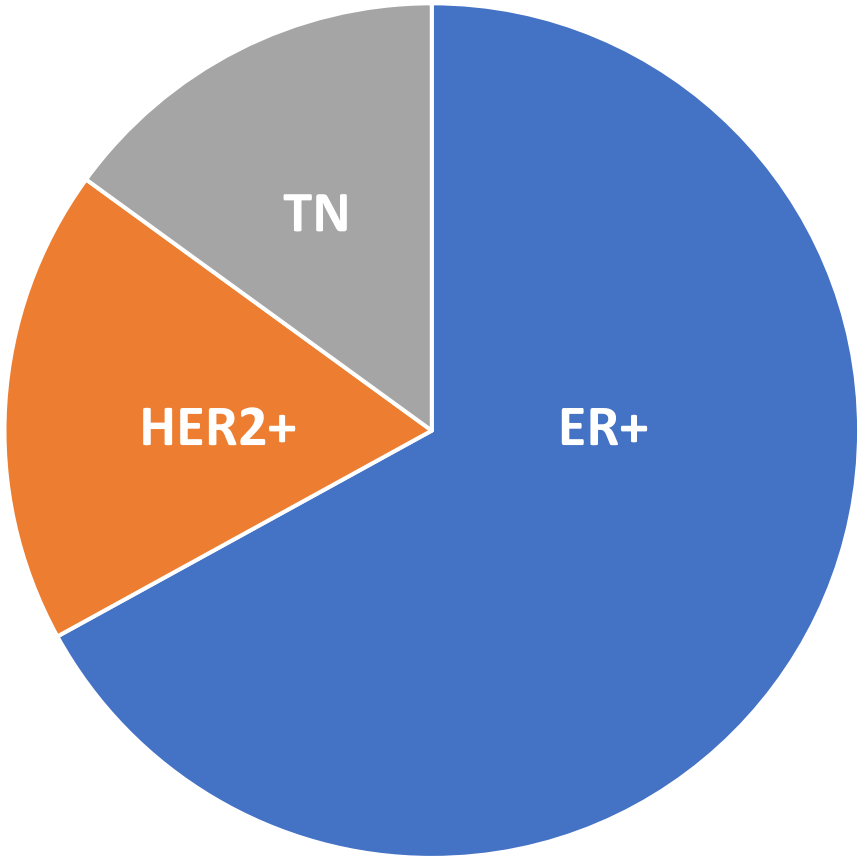


Investigator's choice options will include the following single-agent chemotherapy options:
o Capecitabine
o Eribulin
o Vinorelbine
o Gemcitabine
o A Taxane (e.g. docetaxel, paclitaxel, nab-paclitaxel)

- Primary endpoint: PFS
- Secondary endpoints: OS, ORR, DOR

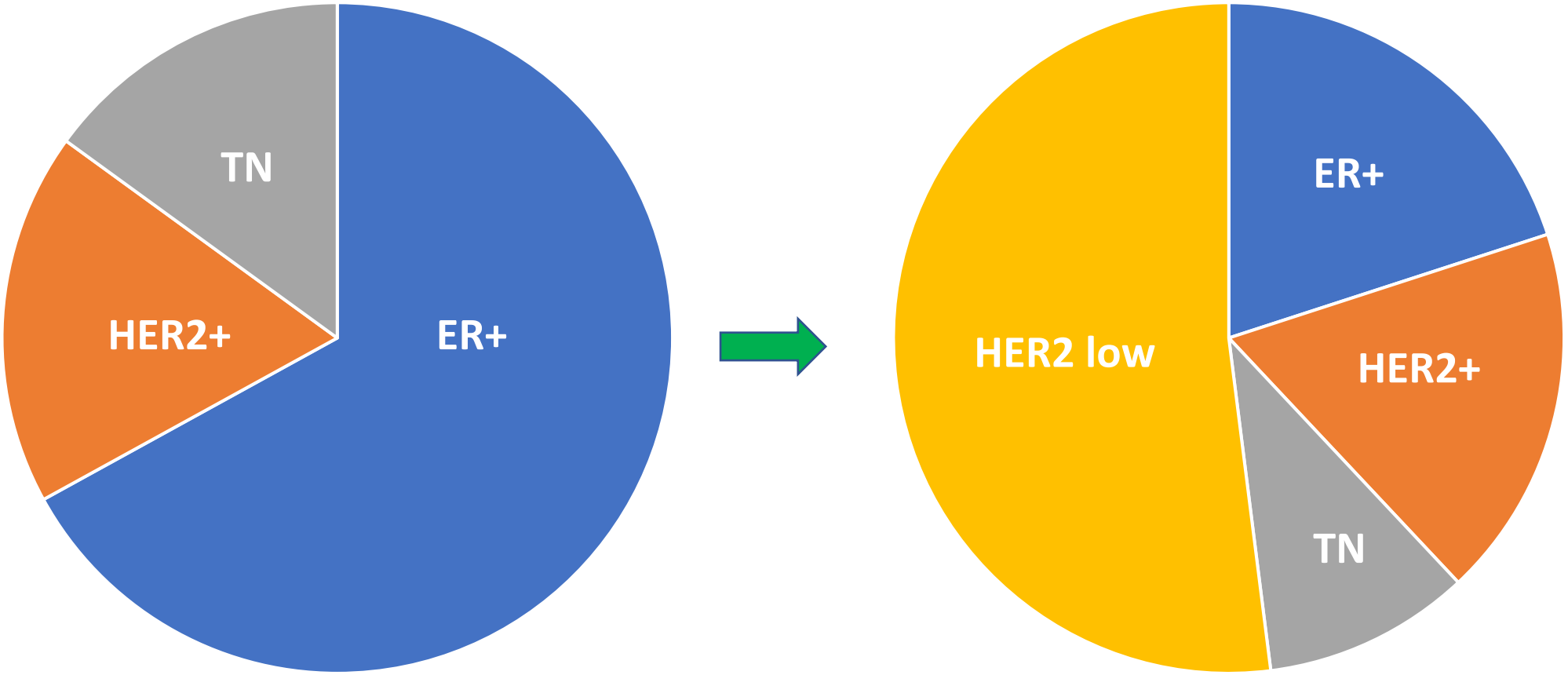
NCT03734029

Breast Cancer Subtypes



Pre-2021

Breast Cancer Subtypes



Pre-2021

Post-2021

Early Disease Summary

- Neoadjuvant therapy for HER2+ cancers provides clinically relevant risk stratification and facilitates tailoring of therapy
  - This approach is the standard of care for stage II-III HER2+ cancers

- There is now the opportunity for more precise tailoring of therapy using the neoadjuvant/adjuvant paradigm
  - Escalation of therapy with additional HER2-targeted therapies in high risk patients who do not achieve pCR
  - De-escalation of therapy in patients with cancers sensitive to HER2-directed therapy

Advanced Disease Summary

- Approaches to further improve outcome for patients with HER2+ MBC are now being evaluated
  - Combinations of HER2-targeted agents
  - Novel HER2 targeted ADCs
    - It may be possible to use HER2 ADCs with different payloads in sequential lines of therapy – potentially replacing conventional chemotherapy
- Next-generation HER2-targeted ADCs appear to have activity in HER2-low expressing cancers
  - If confirmed, this will define a new, common subset of breast cancers, and will provide a targeted therapy approach to these cancers