

...beim metastasierten Mammakarzinom

Thomas Decker

COI

**Advisory board / Beratungstätigkeit / steering board /
Vortragstätigkeit**

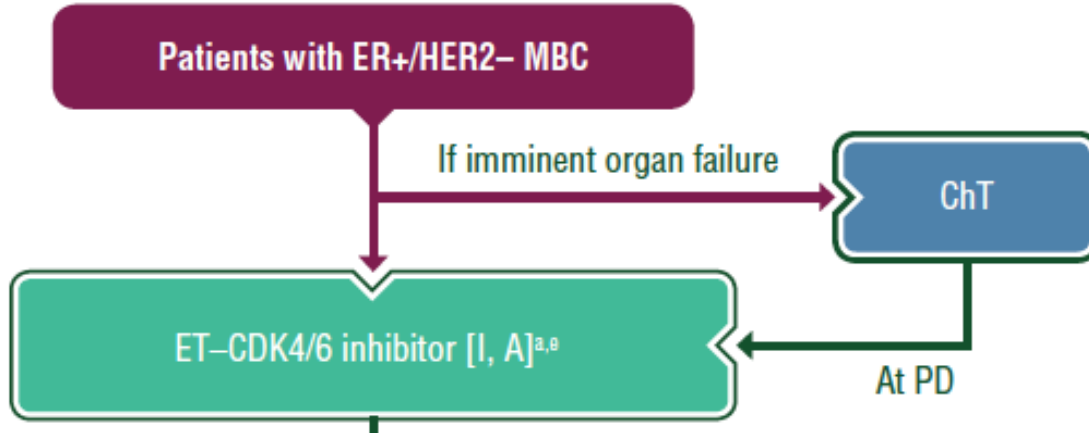
Novartis

Lilly

Daiichi Sankyo

GSK

IOMEDICO

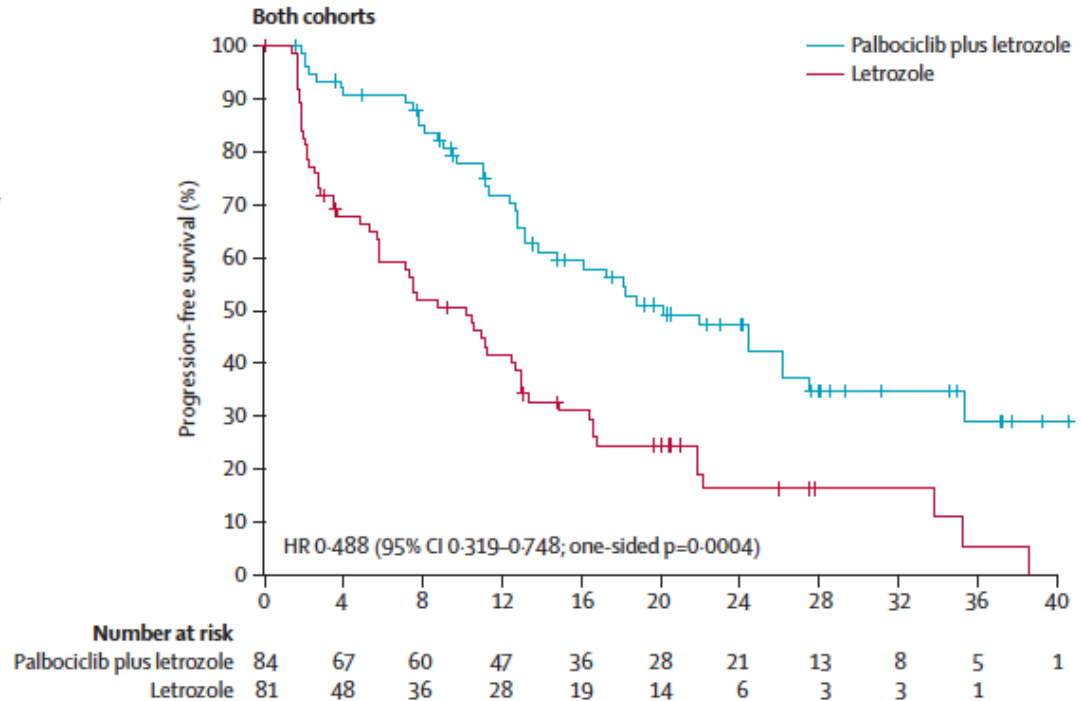


Gennari et al, An Oncol 2021

The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of oestrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): a randomised phase 2 study

Richard S Finn, John P Crown, Istvan Lang, Katalin Boer, Igor M Bondarenko, Sergey O Kulyk, Johannes Ettl, Ravindranath Patel, Tamas Pinter, Marcus Schmidt, Yaroslav Shparyk, Anu R Thummala, Nataliya L Voytko, Camilla Fowst, Xin Huang, Sindy T Kim, Sophia Randolph, Dennis J Slar

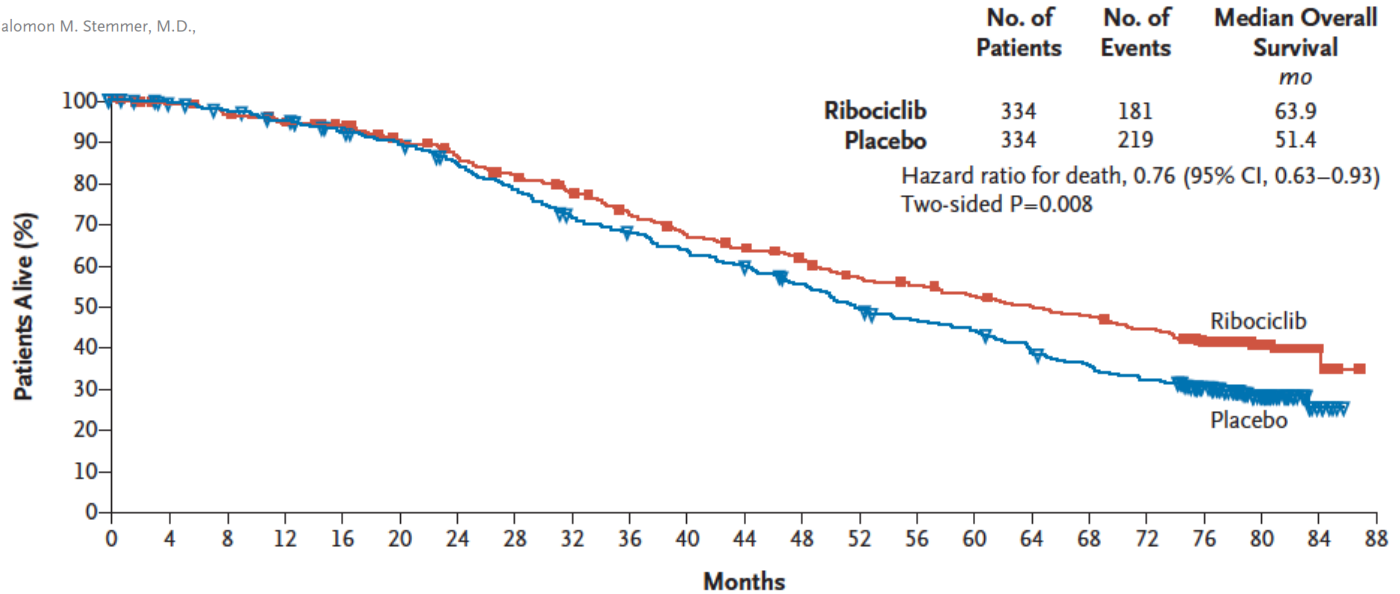
Lancet Oncology 2014



ORIGINAL ARTICLE


Overall Survival with Ribociclib plus Letrozole in Advanced Breast Cancer

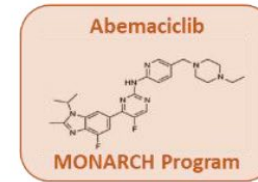
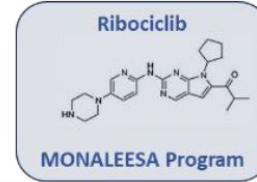
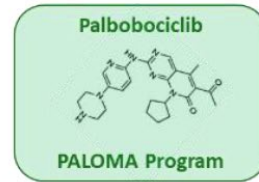
Gabriel N. Hortobagyi, M.D., Salomon M. Stemmer, M.D.,



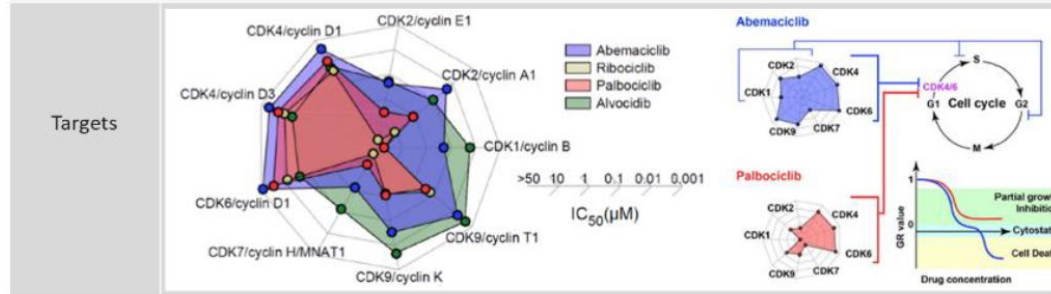
NEJM 22

The CDK4/6 inhibitor revolution — a game-changing era for breast cancer treatment

Laura Morrison¹, Sibylle Loibl¹ & Nicholas C. Turner^{1,2} 

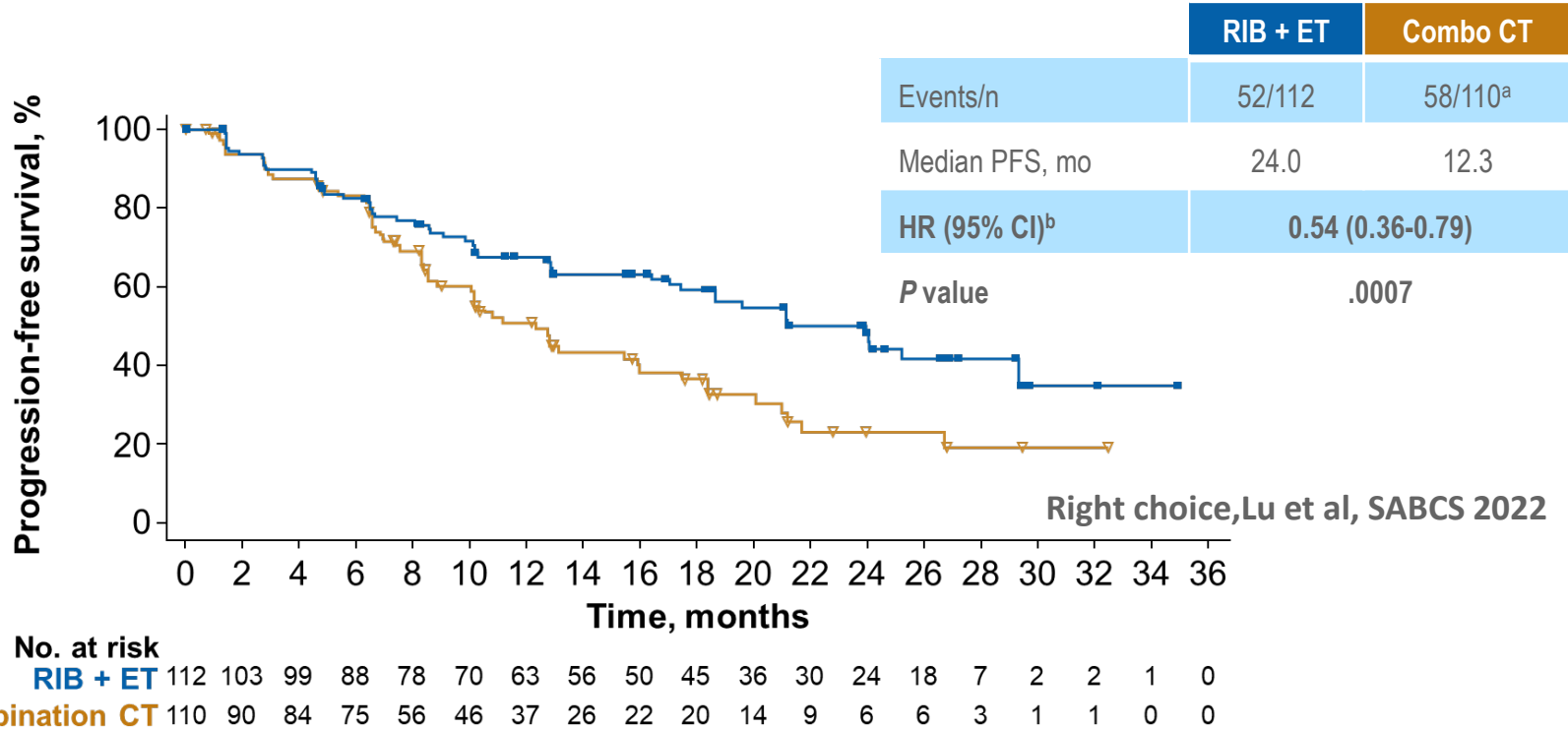
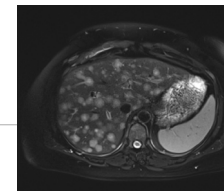


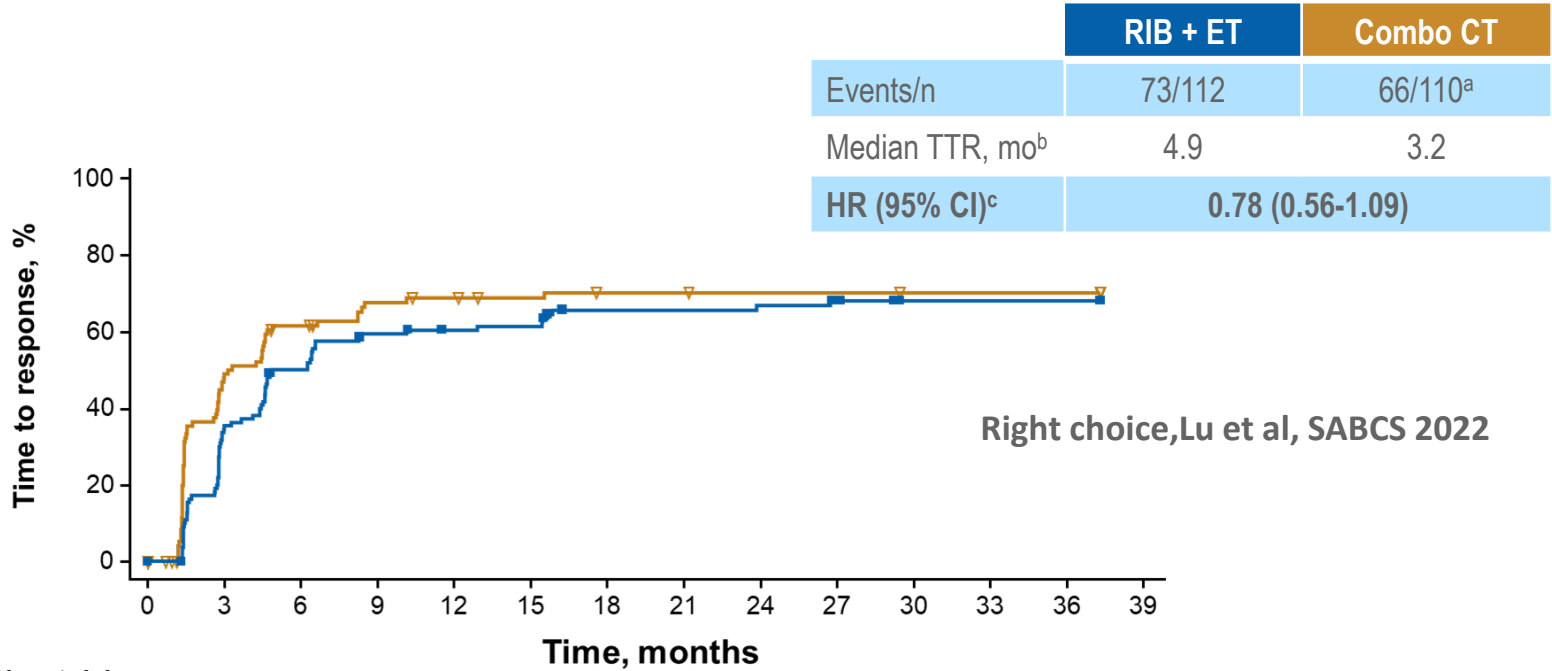
| Characteristic | Palbociclib ^[1-3] | Ribociclib ^[4,5] | Abemaciclib ^[5,6] |
|----------------|------------------------------|-----------------------------|-------------------------------|
| Dose, mg | 125 QD | 600 QD | 150 BID (+ET), 200 BID (mono) |
| Schedule | 3 wks on/1 wk off | 3 wks on/1 wk off | Continuous |
| Half-life, hr | 27 | 32.6 | 17-38 |



Gennari,
Lugano Breast cancer meeting 23

Aktuelle Therapiestandards 24` - viszerale Krise





| No. at risk | 0 | 3 | 6 | 9 | 12 | 15 | 18 | 21 | 24 | 27 | 30 | 33 | 36 | 39 |
|-----------------------|-----|----|----|----|----|----|----|----|----|----|----|----|----|----|
| RIB + ET | 112 | 72 | 53 | 42 | 39 | 38 | 29 | 29 | 28 | 26 | 22 | 22 | 22 | 0 |
| Combination CT | 110 | 50 | 35 | 27 | 25 | 23 | 21 | 21 | 20 | 20 | 19 | 19 | 19 | 0 |



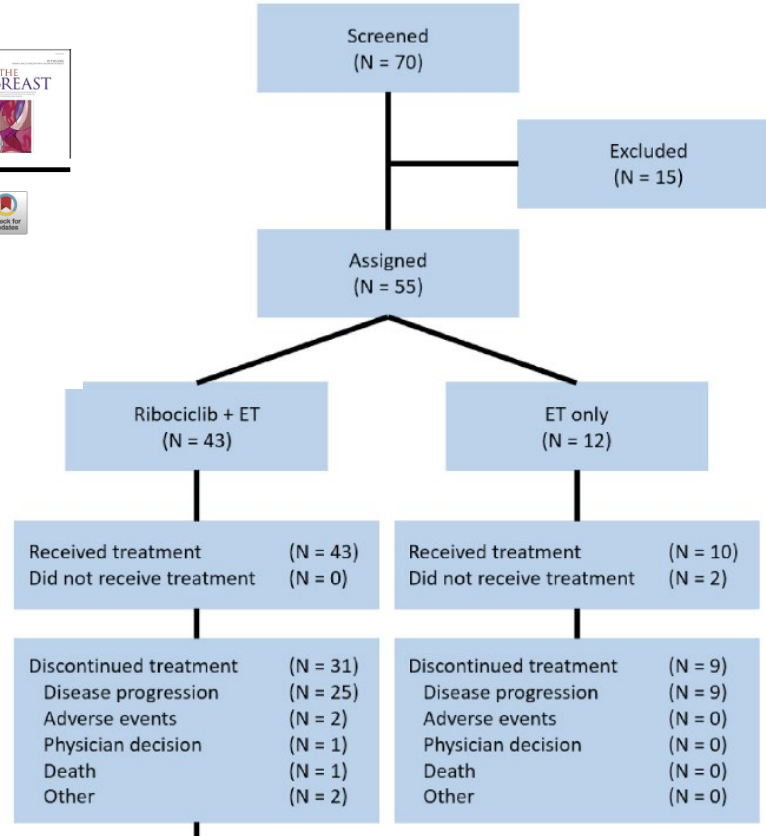
there are **no data** supporting the use of a combination of CDK4/6 inhibitor and ET as maintenance therapy after ChT. Maintenance therapy, in this situation, should be carried out with ET alone (**schlechte Effektivität, geringe Evidenz**)

Cardoso et al, An Oncol 2020



Anti-hormonal maintenance treatment with the CDK4/6 inhibitor ribociclib after 1st line chemotherapy in hormone receptor positive / HER2 negative metastatic breast cancer: A phase II trial (AMICA)

Thomas Decker^a, Kerstin Lüdtk-Heckenkamp^b, Luidmila Melnichuk^c, Nader Hirmas^d, Kristina Lübke^e, Mark-Oliver Zahn^f, Marcus Schmidt^g, Carsten Denkert^h, Ralf Lorenzⁱ, Volkmar Müller^j, Dirk-Michael Zahn^k, Christoph Mundhenke^l, Stefan Bauer^m, Marc Thillⁿ, Peter Seropian^o, Natalie Filmann^d, Sibylle Loibl^{d,p,*}



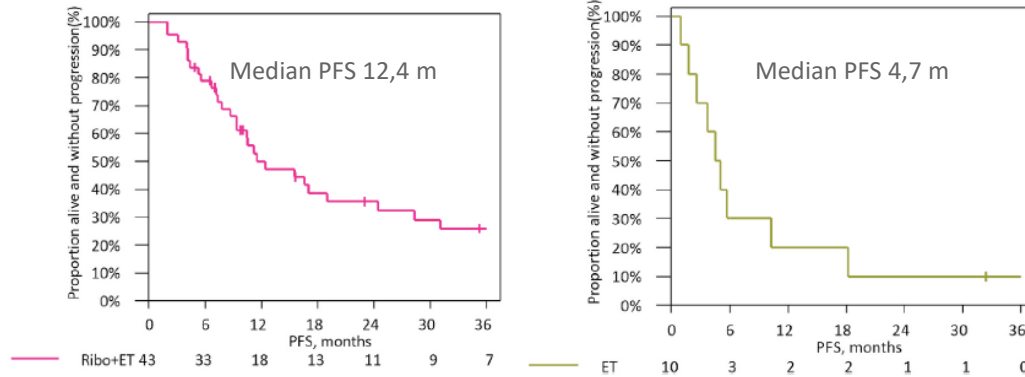
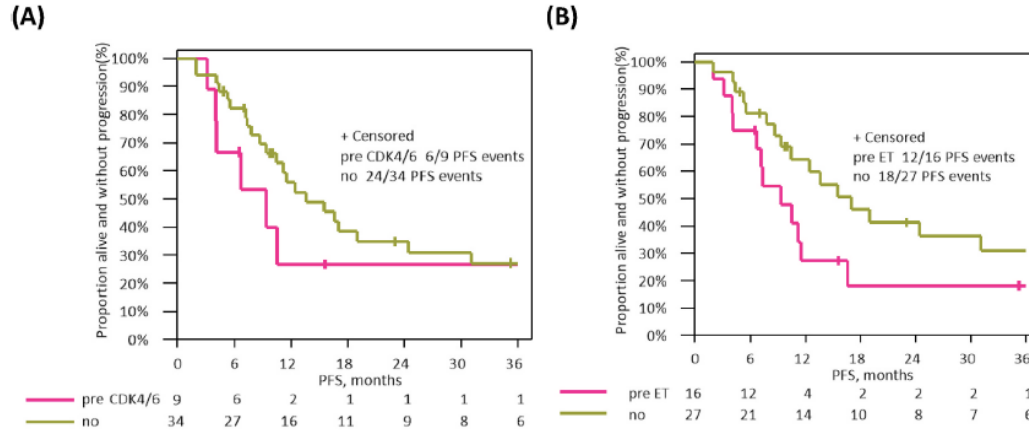


Fig. 2. Locally assessed progression-free survival (PFS).

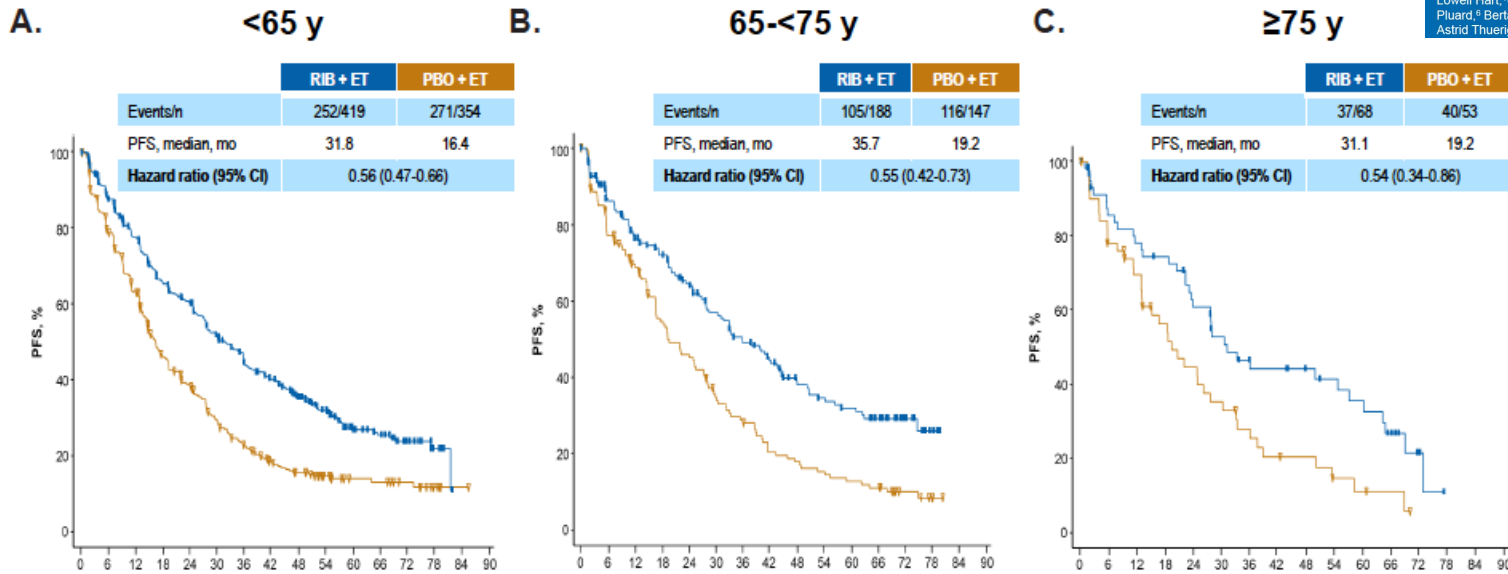


Aktuelle Therapiestandards 24: ältere Patientinnen

Efficacy, safety, and quality of life with ribociclib + endocrine therapy in elderly patients with HR+/HER2- advanced breast cancer across the MONALEESA-2, -3, and -7 trials

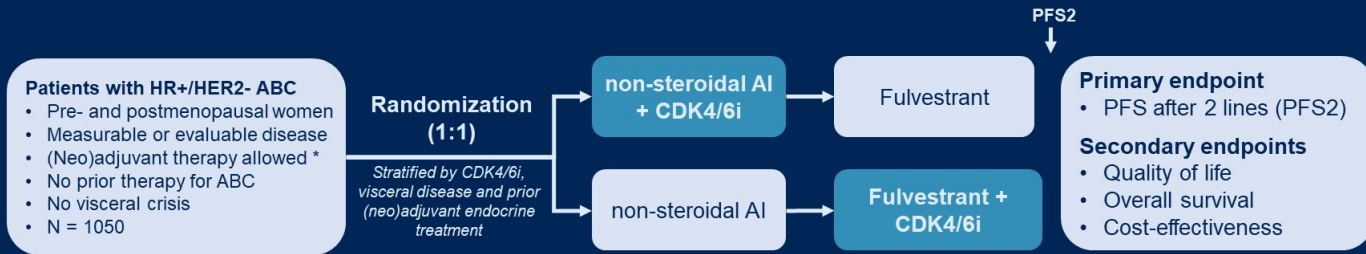
Lowell Hart,^{1,2} Seock-Ah Im,³ Sara M. Tolaney,² Mario Campone,⁵ Timothy Pluard,⁶ Berta Sousa,⁷ Gilles Freyer,⁸ Thomas Decker,⁹ Kevin Kalinsky,¹⁰ Astrid Thuerigen,¹¹ Melissa Gao,¹¹ Hulin Hu,¹² Sherko Kummel¹³

Figure 2. PFS by Age



SONIA trial design

SONIA



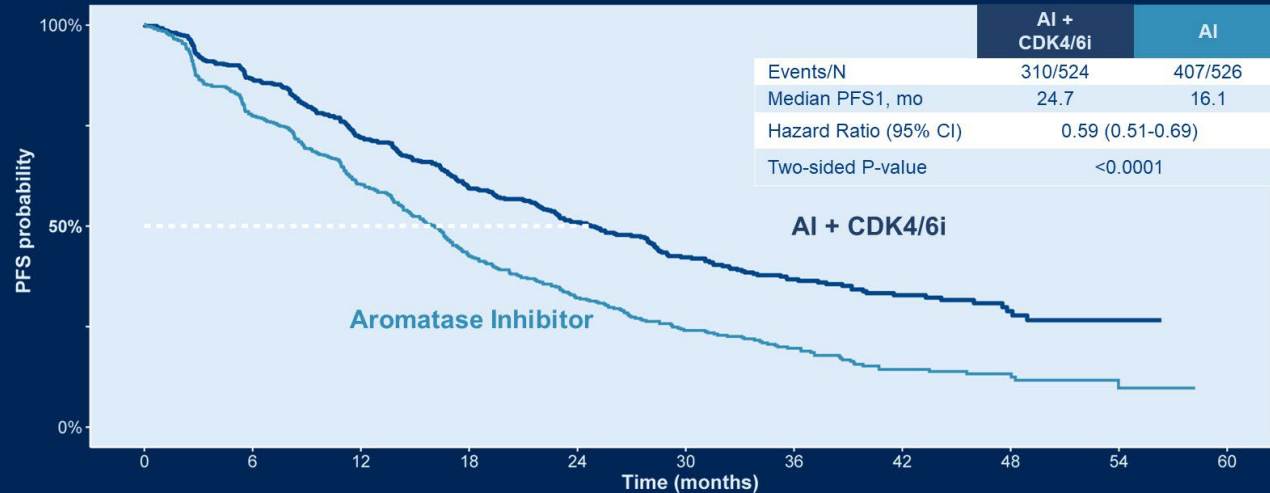
- Tumor assessments every 12 weeks
- PFS locally assessed per RECIST v1.1
- Primary analysis planned after 574 PFS2 events
 - 89% power to detect superiority according to ESMO MCBS (HR lower limit CI ≤ 0.65 and $\Delta \geq 3$ months) with two-sided $\alpha=5\%$ ¹

HR+, hormone receptor positive; HER2-, HER2 negative; ABC, advanced breast cancer; AI, aromatase inhibitor; PFS, progression-free survival
* disease-free interval after non-steroidal aromatase inhibitor >12 months. ClinicalTrials.gov (NCT03425838)
1. Cheryn NJ, et al. Ann Oncol 2017

Therapiestandards: HR+ / Her2- Immer CDK4/6 Inhibitor 1st line?

Progression-free survival in first line

SONIA

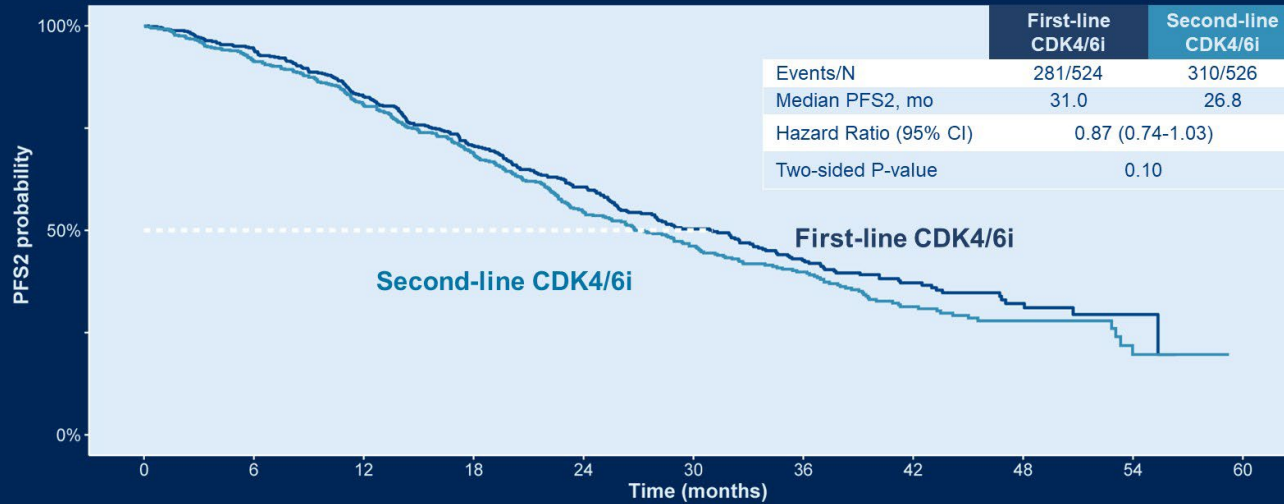


| | 0 | 6 | 12 | 18 | 24 | 30 | 36 | 42 | 48 | 54 | 60 |
|--------------|---------|---------|---------|----------|----------|-----------|-----------|----------|----------|---------|---------|
| AI + CDK4/6i | 524 (0) | 451 (3) | 374 (4) | 285 (30) | 202 (76) | 137 (110) | 101 (129) | 63 (158) | 27 (189) | 4 (210) | 0 (214) |
| AI | 526 (0) | 406 (2) | 315 (4) | 203 (25) | 128 (54) | 84 (68) | 57 (81) | 31 (93) | 17 (105) | 5 (114) | 0 (119) |

Numbers at risk (censored)

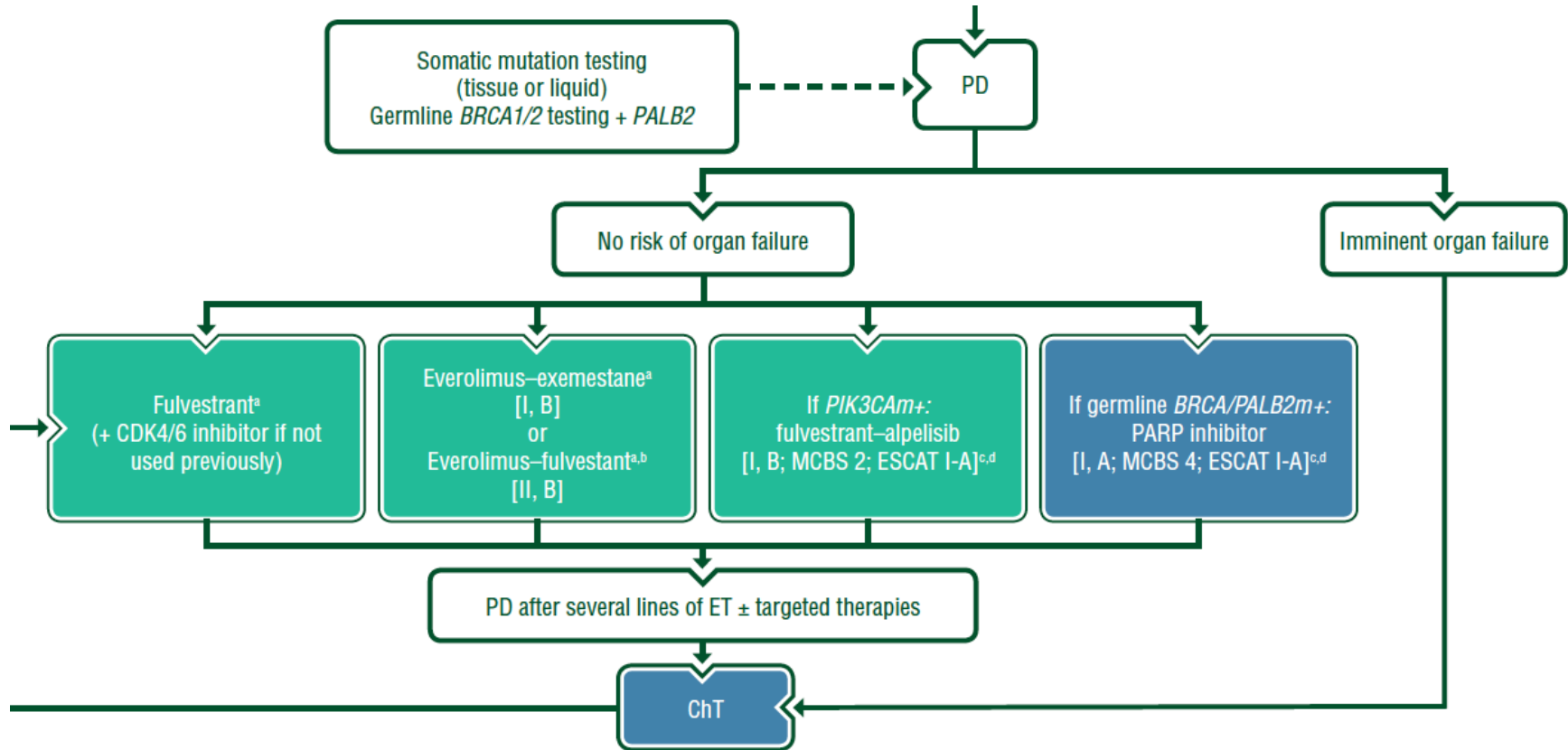
Primary endpoint: PFS2

SONIA



| | | | | | | | | | | | |
|-------------|----------------------------|---------|---------|----------|----------|-----------|-----------|----------|----------|---------|---------|
| First-line | 524 (0) | 491 (3) | 429 (5) | 339 (34) | 244 (84) | 167 (123) | 118 (148) | 69 (184) | 31 (215) | 5 (239) | 0 (243) |
| Second-line | 526 (0) | 478 (2) | 418 (6) | 330 (35) | 225 (76) | 164 (105) | 115 (133) | 65 (161) | 30 (190) | 9 (207) | 0 (216) |
| | Numbers at risk (censored) | | | | | | | | | | |

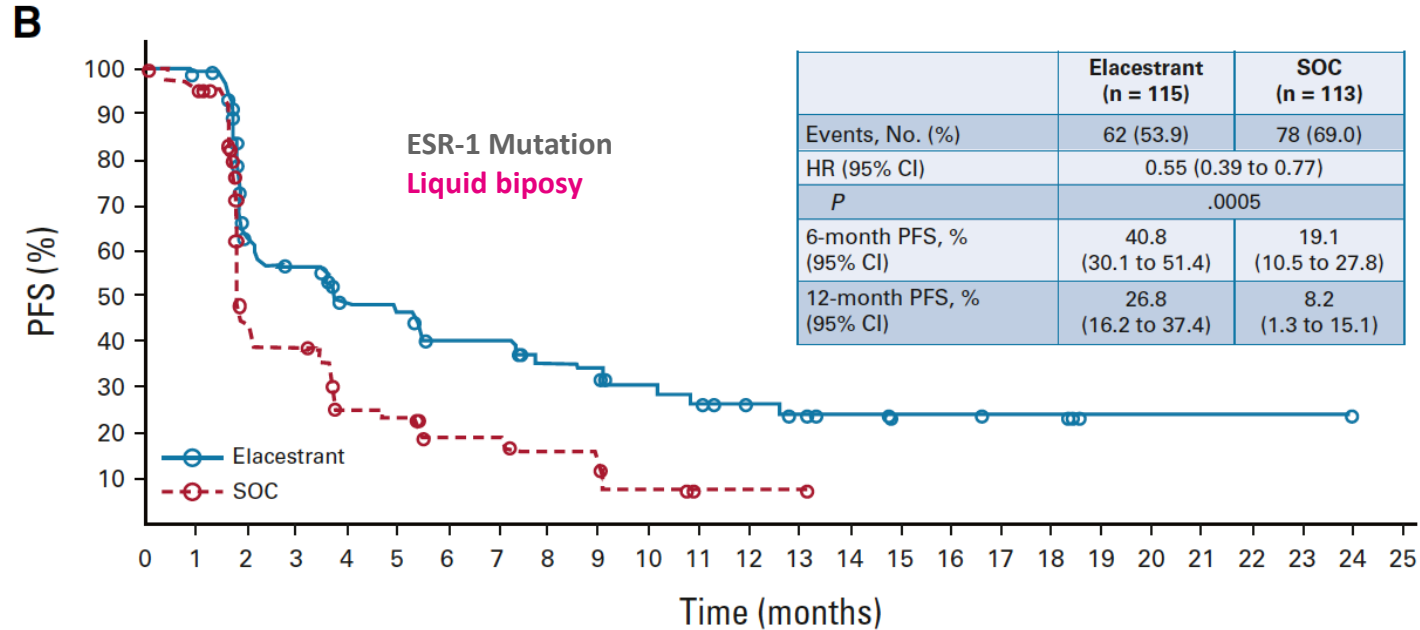
Aktuelle Therapiestandards 24` : HR+/Her-2- 2nd line



| Gene or protein | Alteration | Prevalence | ESCAT score |
|----------------------------|---|---------------------------|------------------------------|
| ER | Protein expression \geq 1% by IHC ESR1 mutation | 75% 40% | NA II-A |
| ERBB2 | Amplifications or 3+ (IHC) HER2-low (IHC (1+, 2+ NA)) | 15%-20% 40%-50% | I-A II-B. - IA/IIA |
| | Hotspot mutations | 4% | II-B |
| BRCA1/2 | Germline mutations | 4% | I-A |
| | Somatic mutations | 3% | II-A |
| PALB2 | Germline mutations | 1% | II-A |
| PD-L1 (TNBC) | Expression by IHC on ICs and tumour cells (CPS) | 40% | I-A |
| PIK3CA (ER+, HER2-) | Hotspot mutations | 30%-40% | I-A |
| MSI | MSI-H | 1%-2% | I-C |
| NTRK | Fusions | <0.1% | I-C |
| ESR1 (ER+, HER2-) | Mutations (mechanism of resistance) | 30% | II-A |
| AR (TNBC) | AR expression (not validated) | ? | II-B |
| AKT1 ^{E17K} | Mutations | 5% | II-B |

A framework to rank genomic alterations as targets for cancer precision medicine: the ESMO Scale for Clinical Actionability of molecular Targets (ESCAT)

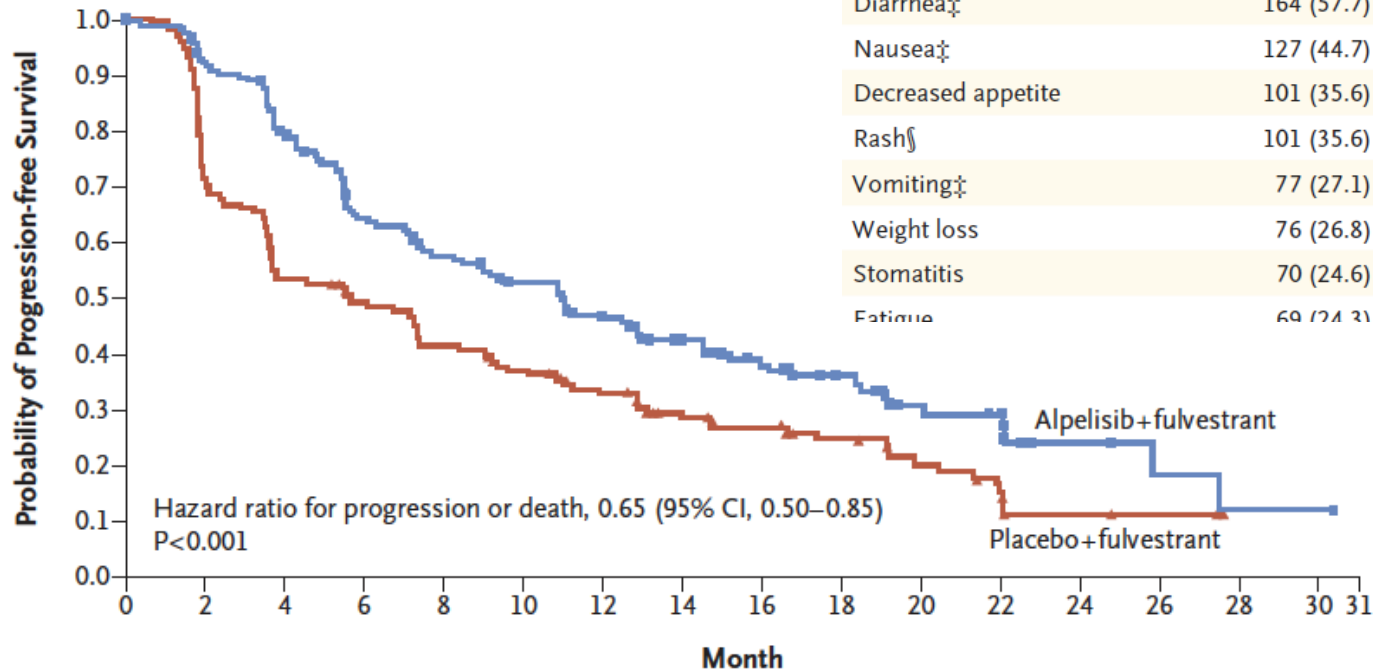
**Erweiterte molekulare
Analyse spätestens vor
2nd line**



Emerald Phase III, Bidard et al, JCO 2022

Aktuelle Therapiestandards 24` PIK3 Mutation

A Cohort with *PIK3CA*-Mutated Cancer

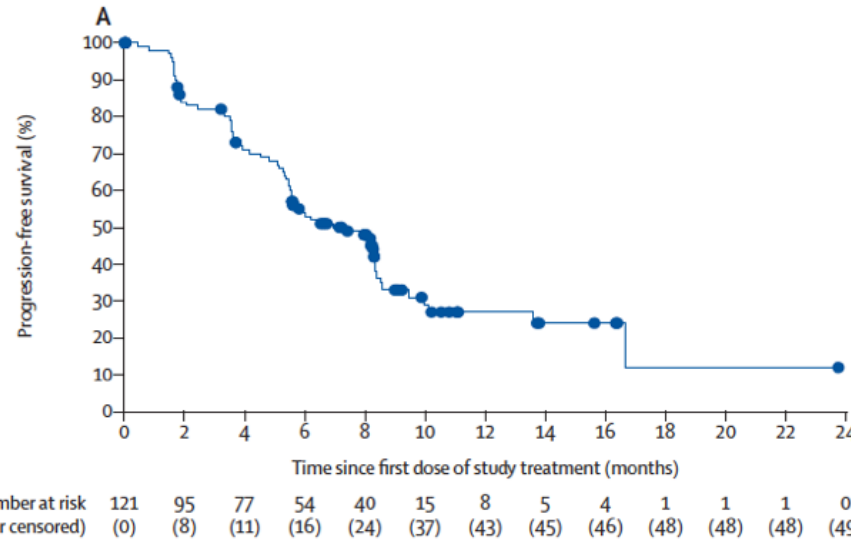
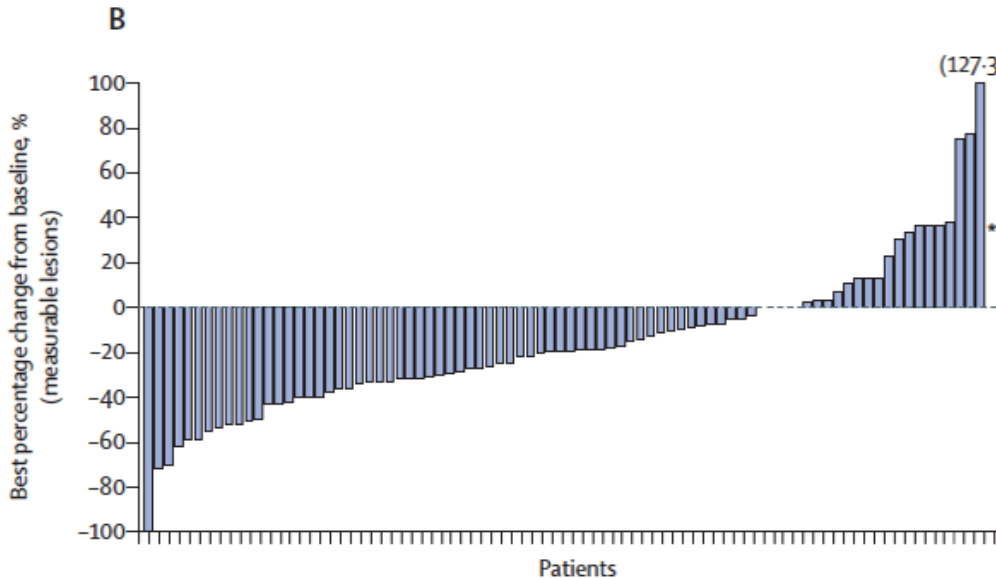


| | | |
|--------------------|------------|------------|
| Any adverse event | 282 (99.3) | 183 (64.4) |
| Hyperglycemia† | 181 (63.7) | 93 (32.7) |
| Diarrhea‡ | 164 (57.7) | 19 (6.7) |
| Nausea‡ | 127 (44.7) | 7 (2.5) |
| Decreased appetite | 101 (35.6) | 2 (0.7) |
| Rash§ | 101 (35.6) | 28 (9.9) |
| Vomiting‡ | 77 (27.1) | 2 (0.7) |
| Weight loss | 76 (26.8) | 11 (3.9) |
| Stomatitis | 70 (24.6) | 7 (2.5) |
| Fatigue | 69 (24.3) | 10 (3.5) |

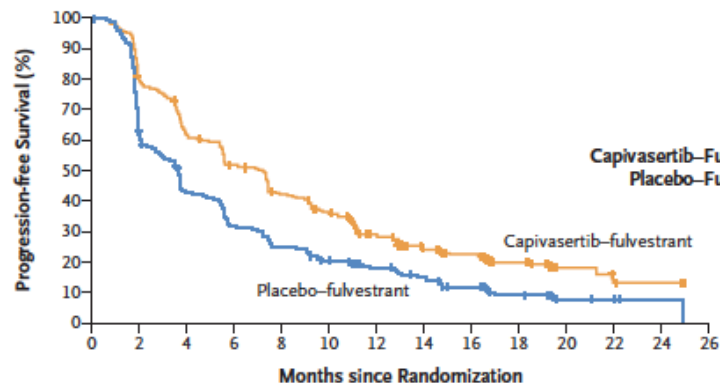
SOLAR-1, Andre, NEJM 2019

Alpelisib plus fulvestrant in PIK3CA-mutated, hormone receptor-positive advanced breast cancer after a CDK4/6 inhibitor (BYLieve): one cohort of a phase 2, multicentre, open-label, non-comparative study

Hope S Rugo, Florence Lerebours, Eva Ciruelos, Pamela Drullinsky, Manuel Ruiz-Borrego, Patrick Neven, Yeon Hee Park, Aleix Prat, Thomas Bachelot, Dejan Juric, Nicholas Turner, Nickolas Sophos, Juan Pablo Zarate, Christina Arce, Yu-Ming Shen, Stuart Turner, Hemanth Kanakamedala, Wei-Chun Hsu, Stephen Chia



A Overall Population



| | No. of Patients | No. of Events | Median Progression-free Survival (95% CI) mo |
|-------------------------|-----------------|---------------|---|
| Capiasertib-Fulvestrant | 355 | 258 | 7.2 (5.5-7.4) |
| Placebo-Fulvestrant | 353 | 293 | 3.6 (2.8-3.7) |

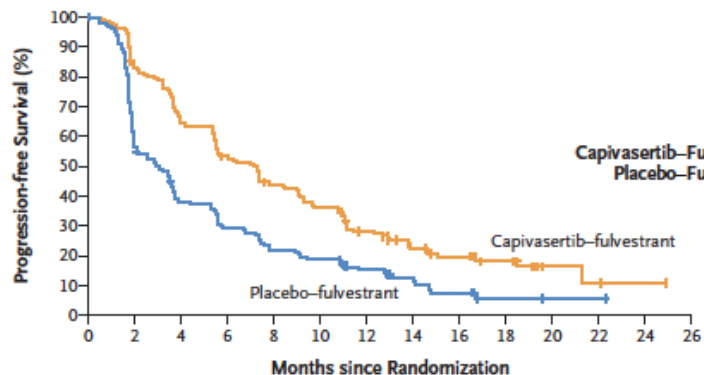
Adjusted hazard ratio for disease progression or death, 0.60 (95% CI, 0.51-0.71)
P<0.001

ORIGINAL ARTICLE

Capiasertib in Hormone Receptor-Positive Advanced Breast Cancer

N.C. Turner, M. Oliveira, S.J. Howell, F. Dalenc, J. Cortes, H.L. Gomez Moreno, X. Hu, K. Jhaveri, P. Krivorotko, S. Loibl, S. Morales Murillo, M. Okera, Y.H. Park, J. Sohn, M. Toi, E. Tokunaga, S. Yousef, L. Zhukova, E.C. de Bruin, L. Grinstead, G. Schiavon, A. Foxley, and H.S. Rugo, for the CAPitello-291 Study Group*

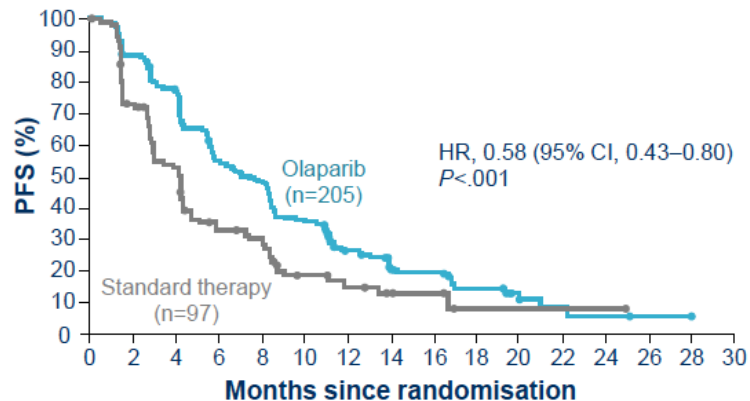
B Patients with AKT Pathway-Altered Tumors



| | No. of Patients | No. of Events | Median Progression-free Survival (95% CI) mo |
|-------------------------|-----------------|---------------|---|
| Capiasertib-Fulvestrant | 155 | 121 | 7.3 (5.5-9.0) |
| Placebo-Fulvestrant | 134 | 115 | 3.1 (2.0-3.7) |

Adjusted hazard ratio for disease progression or death, 0.50 (95% CI, 0.38-0.65)
P<0.001

OlympiAD (olaparib) PFS

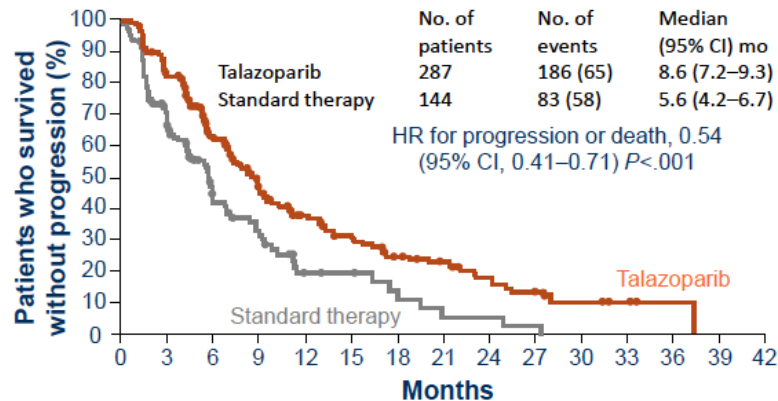


No. at risk

Olaparib 205 201 177 150 155 41 29 107 100 94 73 60 61 40 36 23 21 21 11 11 11 4 3 3 2 2 1 1 1 0

Standard therapy 97 88 63 46 44 29 25 24 21 13 11 11 8 7 4 4 4 1 1 1 1 1 1 1 0 0 0 0

EMBRACA (talazoparib) PFS

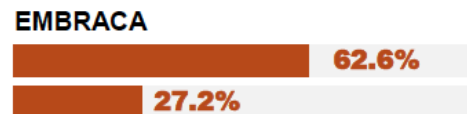
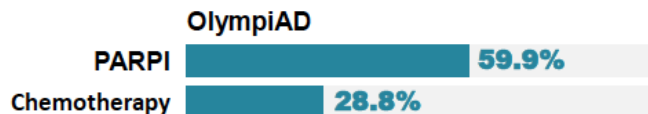


No. at risk

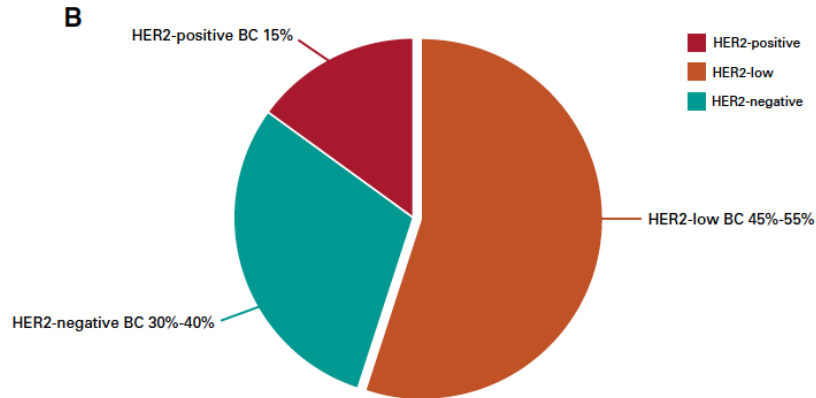
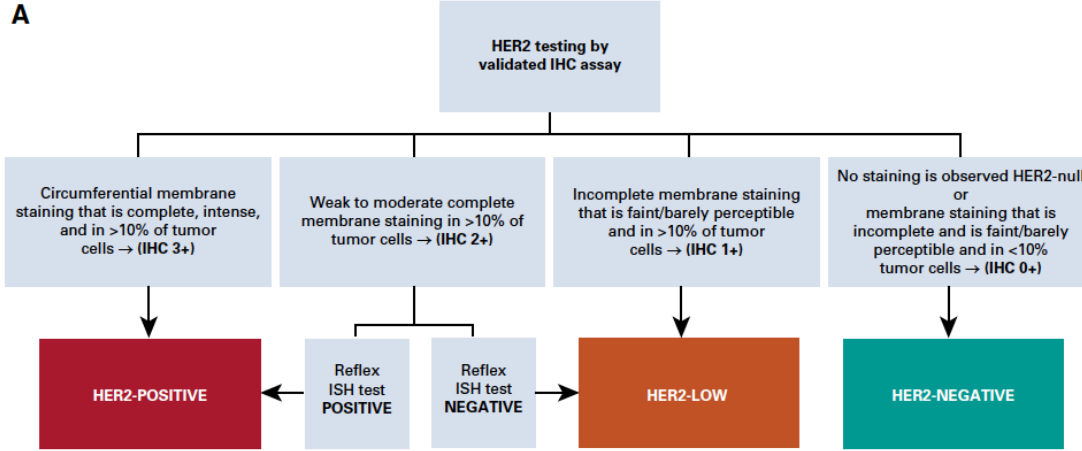
Talazoparib 287 229 148 91 55 42 29 23 16 12 5 3 1 0 0
(0/0) (50/50) (53/103) (34/137) (17/154) (9/183) (9/172) (2/174) (5/179) (4/183) (2/185) (0/185) (0/185) (1/186) (0/186)

Standard therapy 144 88 34 22 9 8 4 2 2 1 0 0 0 0 0
(0/0) (41/41) (20/61) (8/66) (7/76) (0/76) (3/79) (2/81) (0/81) (1/82) (1/83) (0/83) (0/83) (0/83) (0/83)

Objective response rates



Robson NEJM 2017
Liton NEJM 2018

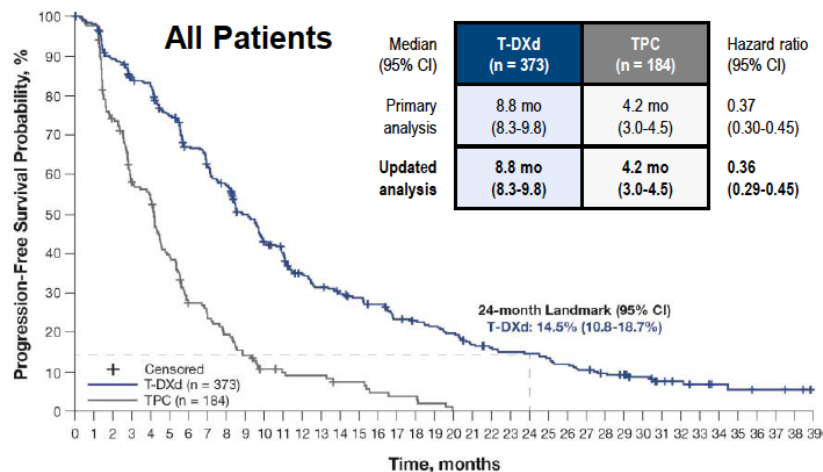


Tarantino JCO 2020

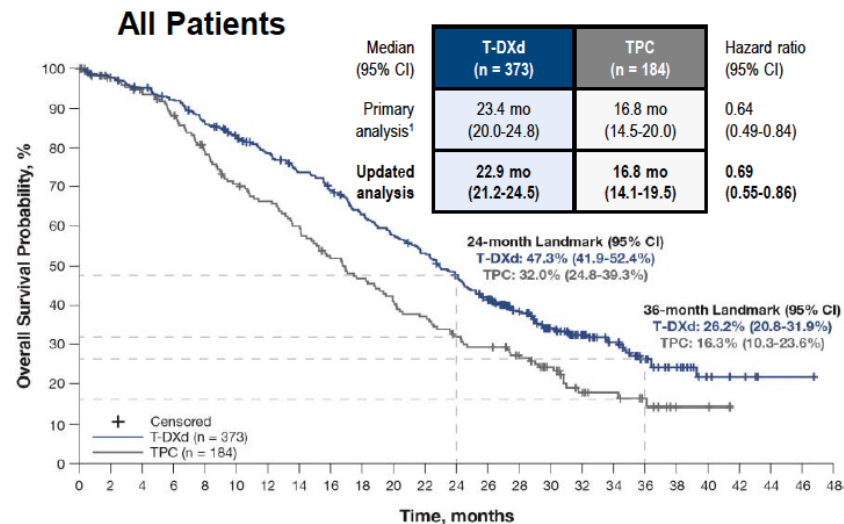
Trastuzumab Deruxtecan (T-DXd) Versus Treatment of Physician's Choice (TPC) in Patients With HER2-Low Unresectable and/or Metastatic Breast Cancer: Updated Survival Results of the Randomized, Phase 3 DESTINY-Breast04 Study



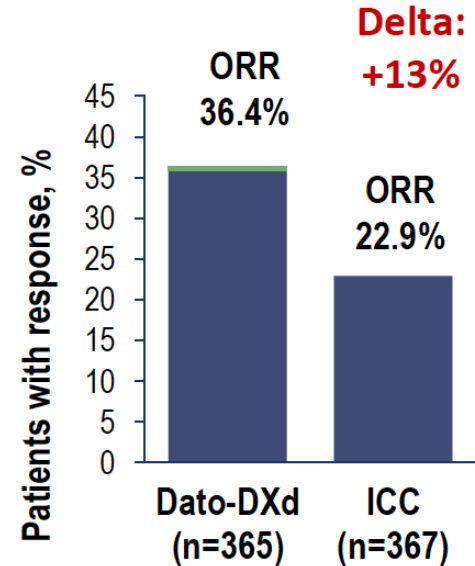
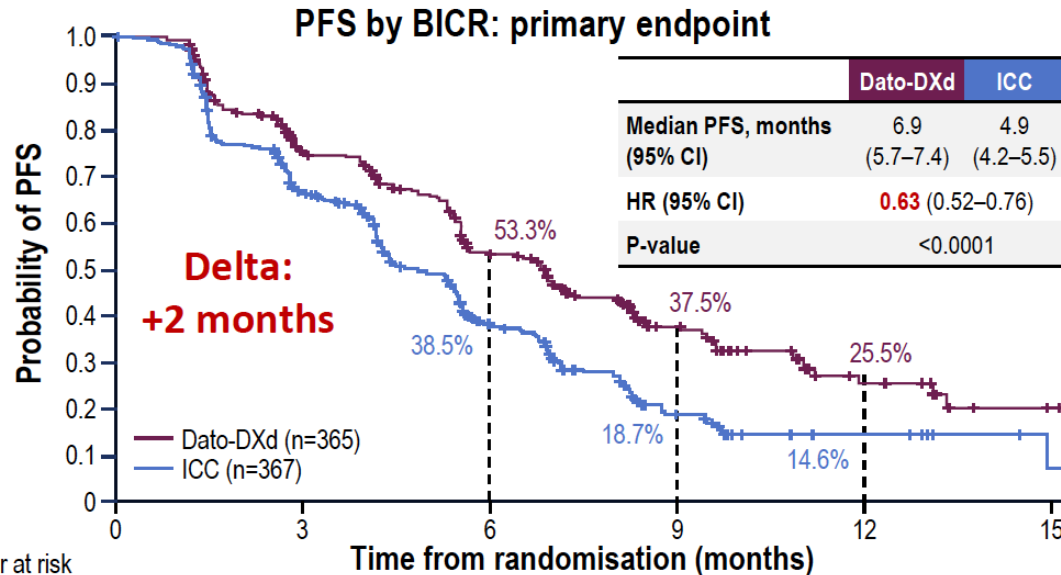
Progression-Free Survival

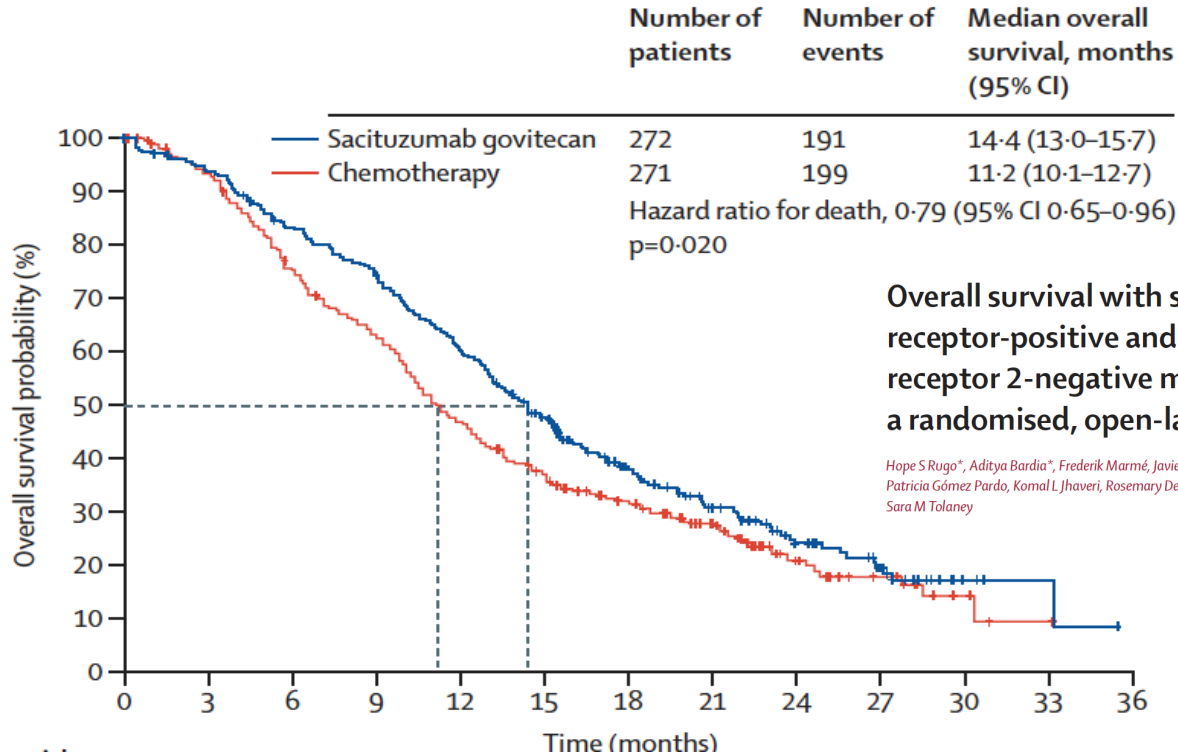


Overall Survival



Datopotamab deruxtecan (Dato-DXd) vs chemotherapy in previously-treated inoperable or metastatic hormone receptor-positive, HER2-negative (HR+/HER2-) breast cancer: Primary results from the randomised



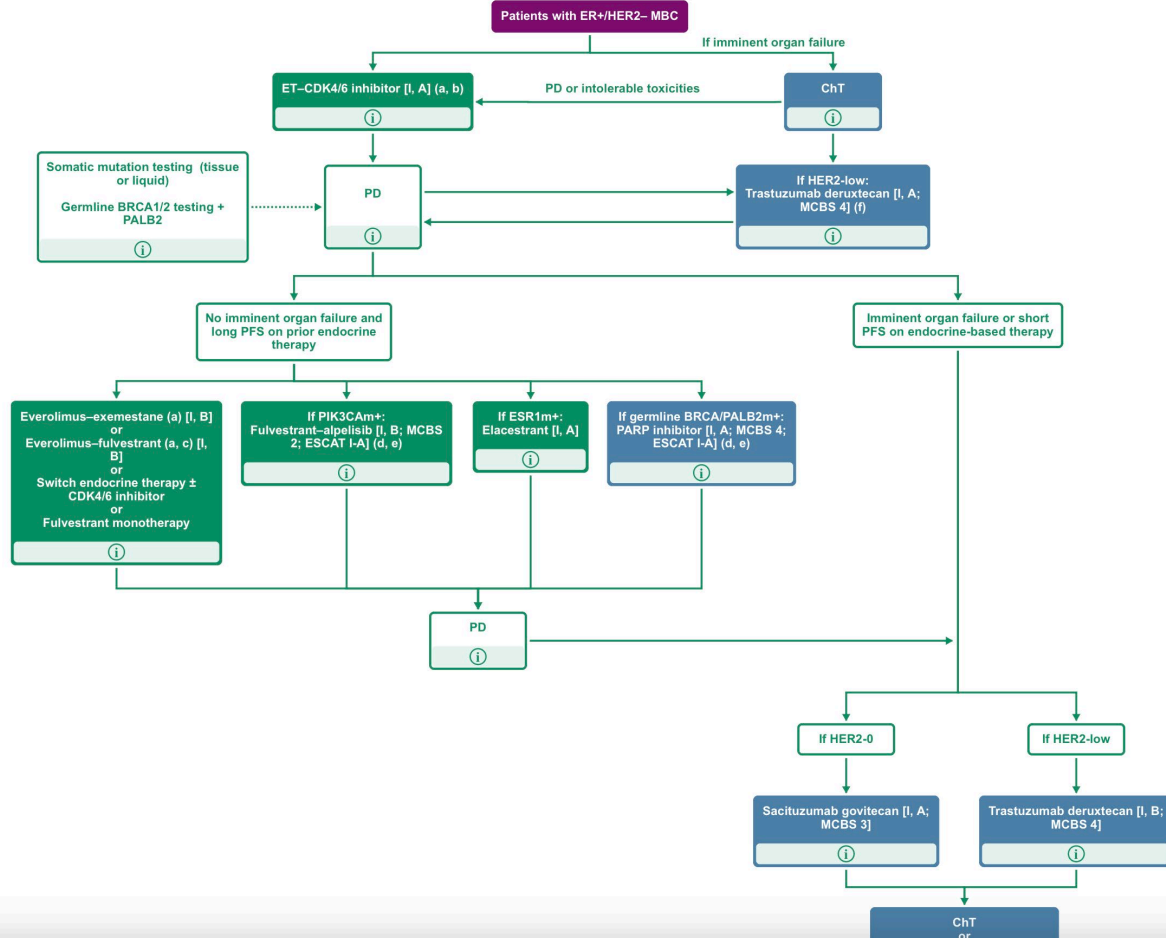


Overall survival with sacituzumab govitecan in hormone receptor-positive and human epidermal growth factor receptor 2-negative metastatic breast cancer (TROPiCS-02): a randomised, open-label, multicentre, phase 3 trial

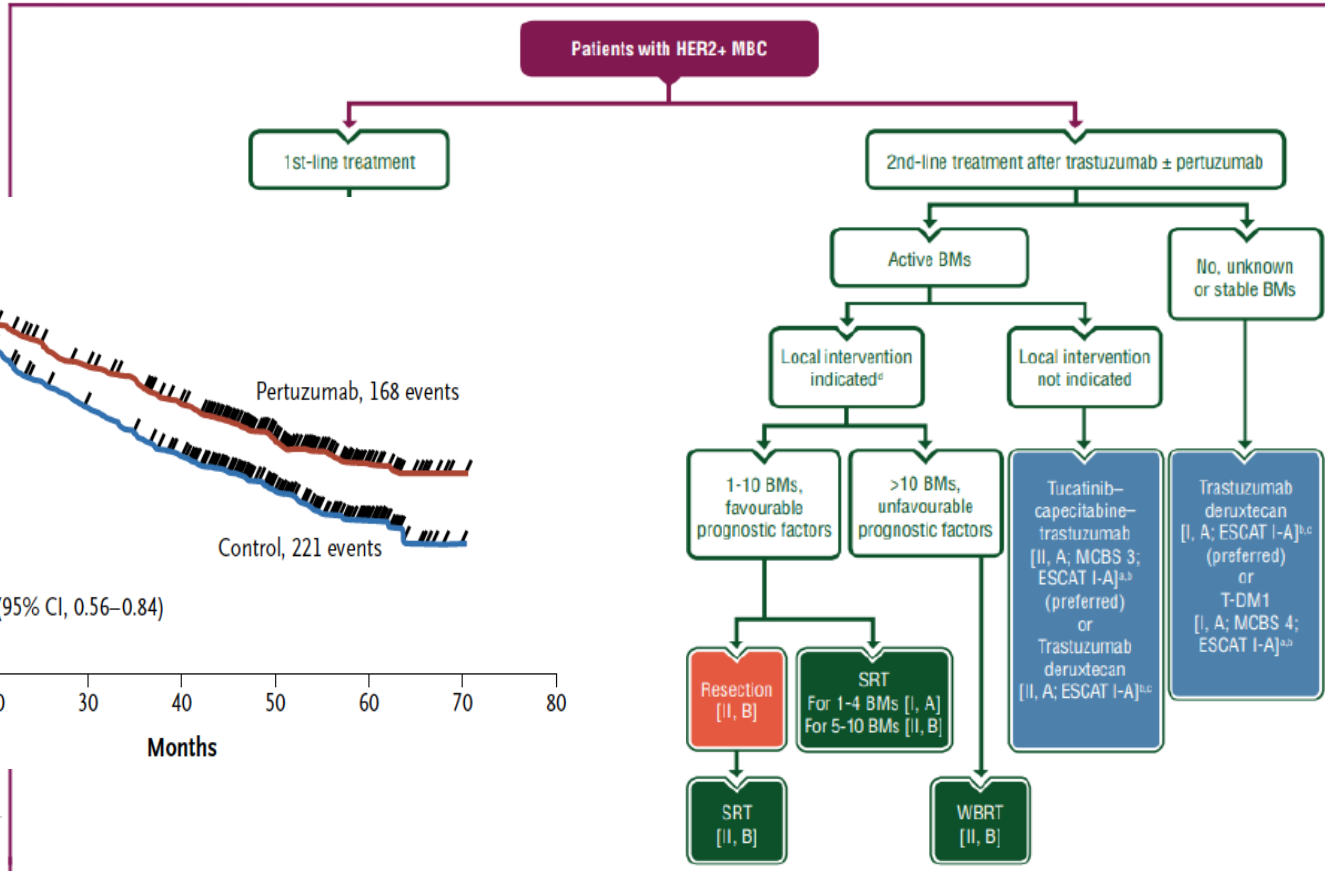
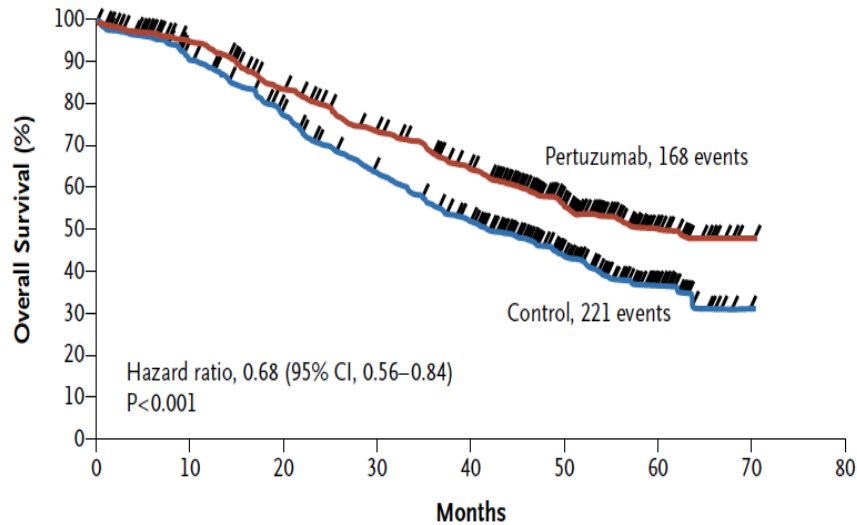
Hope S Rugo, Aditya Bardia*, Frederik Marmé, Javier Cortés, Peter Schmid, Delphine Loirat, Olivier Trédan, Eva Ciruelos, Florence Dalenc, Patricia Gómez Pardo, Komal L Jhaveri, Rosemary Delaney, Theresa Valdez, Hao Wang, Monica Motwani, Oh Kyu Yoon, Wendy Verret, Sara M Tolaney*

Lancet 2023

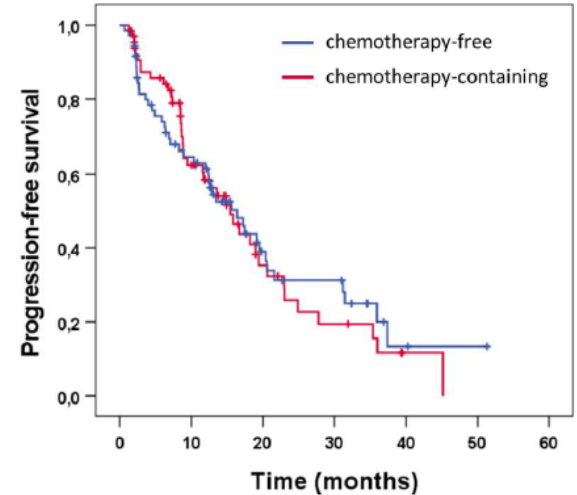
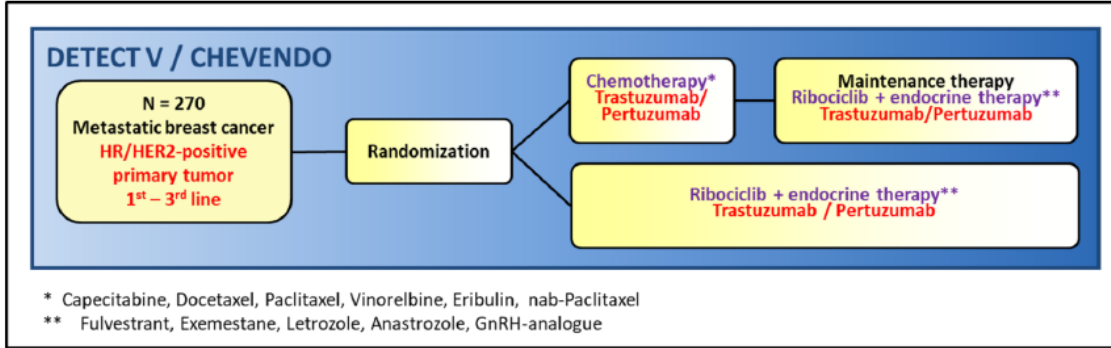
Aktuelle Therapiestandards 24`



Aktuelle Therapiestandards 24` HER2 +



Aktuelle Therapiestandards 24`-HER2+ HR+



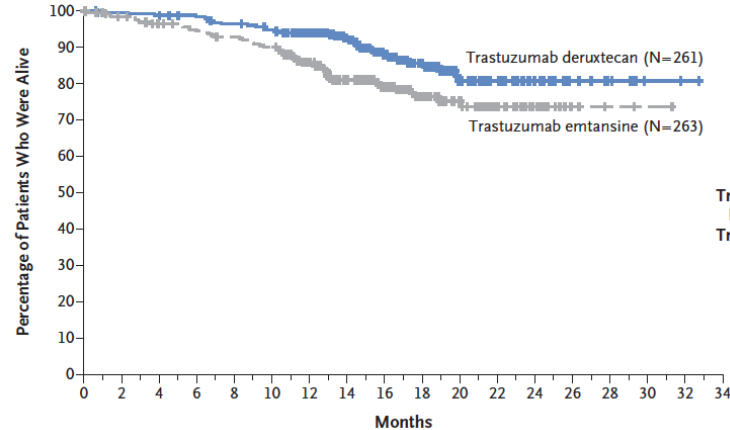
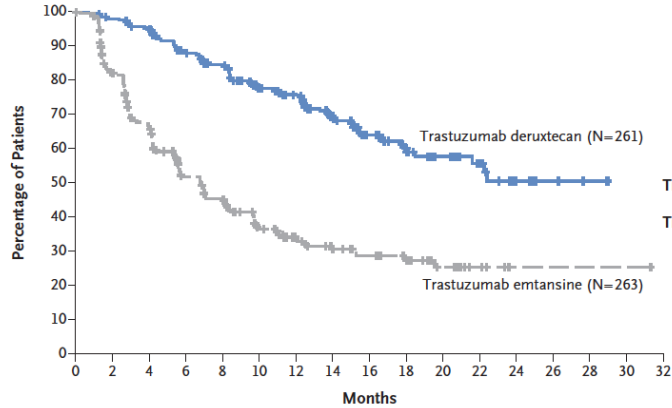
Janni, SABCS 2022

ORIGINAL ARTICLE

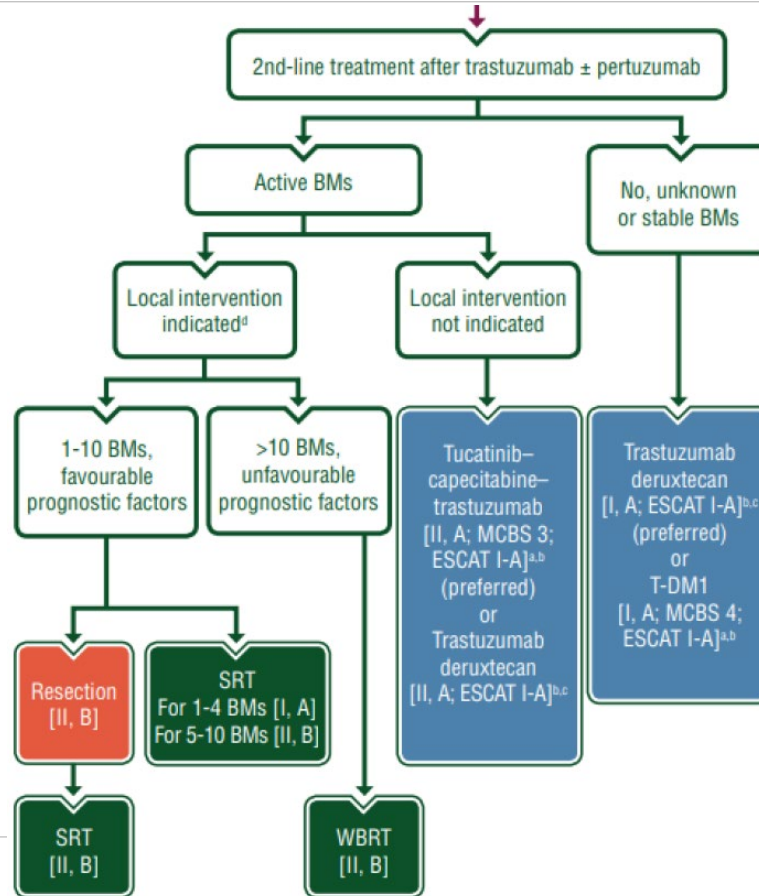
Trastuzumab Deruxtecan versus Trastuzumab Emtansine for Breast Cancer

J. Cortés, S.-B. Kim, W.-P. Chung, S.-A. Im, Y.H. Park, R. Hegg, M.H. Kim, L.-M. Tseng, V. Petry, C.-F. Chung, H. Iwata, E. Hamilton, G. Curigliano, B. Xu, C.-S. Huang, J.H. Kim, J.W.Y. Chiu, J.L. Pedrini, C. Lee, Y. Liu, J. Cathcart, E. Bako, S. Verma, and S.A. Hurvitz, for the DESTINY-Breast03 Trial Investigators*

A Progression-free Survival



Gennari
Ann Oncol 2021





A Pooled Analysis of Trastuzumab Deruxtecan in Patients With HER2-Positive Metastatic Breast Cancer With Brain Metastases (BMs) from DESTINY-Breast01, -02, and -03

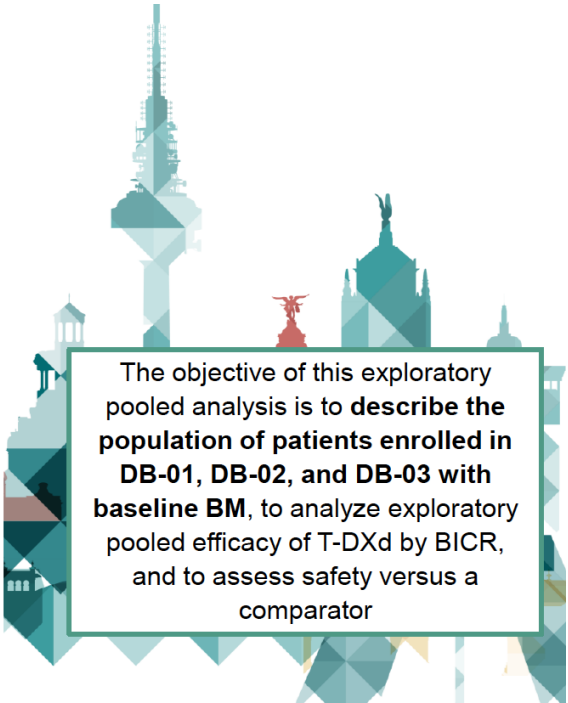
Presentation 3770

Sara A. Hurvitz¹, Shanu Modi, Wei Li, Yeon Hee Park, Wei-Pang Chung, Sung-Bae Kim, Javier Cortes, Toshinari Yamashita, Jose Luiz Pedrini, Seock-Ah Im, Ling-Ming Tseng, Nadia Harbeck, Ian Krop, Giuseppe Curigliano, Elton Mathias, Jillian Cathcart, Antonio Cagnazzo, Shahid Ashfaque, Anton Egorov, Fabrice André

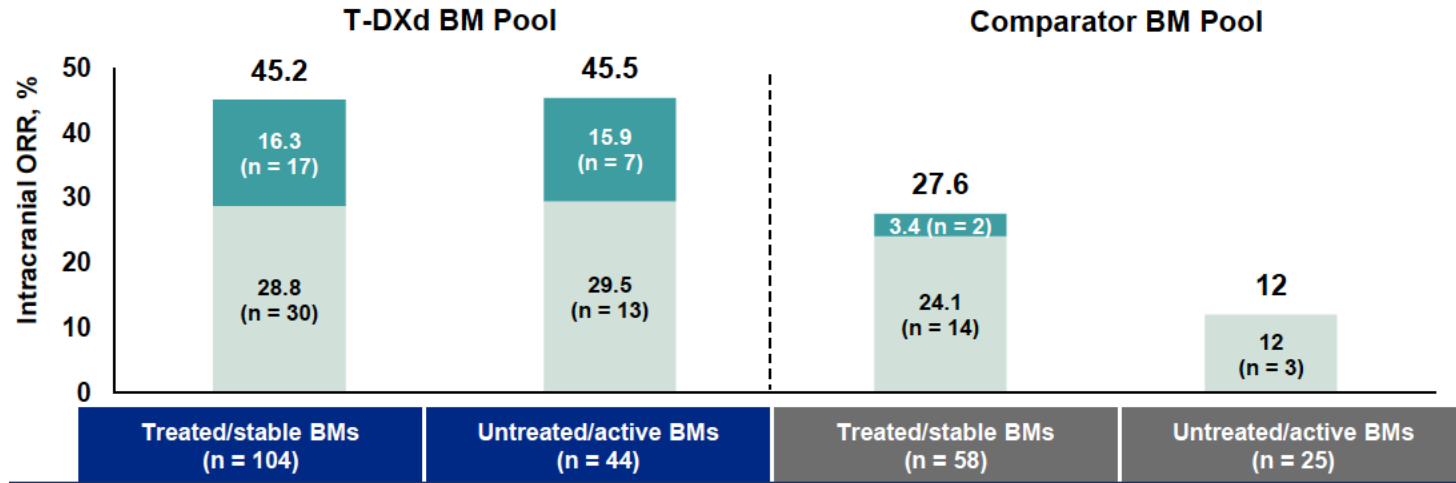
On behalf of the DESTINY-Breast01, -02, and -03 pooled investigators

¹Fred Hutchinson Cancer Center, University of Washington School of Medicine, Seattle, WA, USA

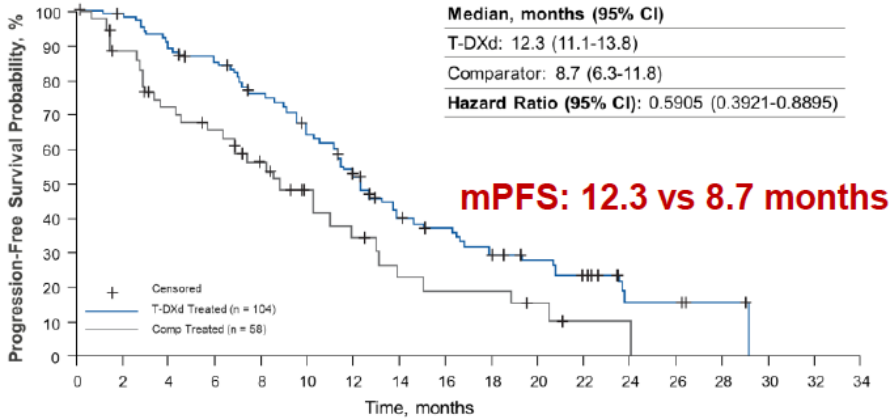
Madrid, Spain, October 20-24, 2023



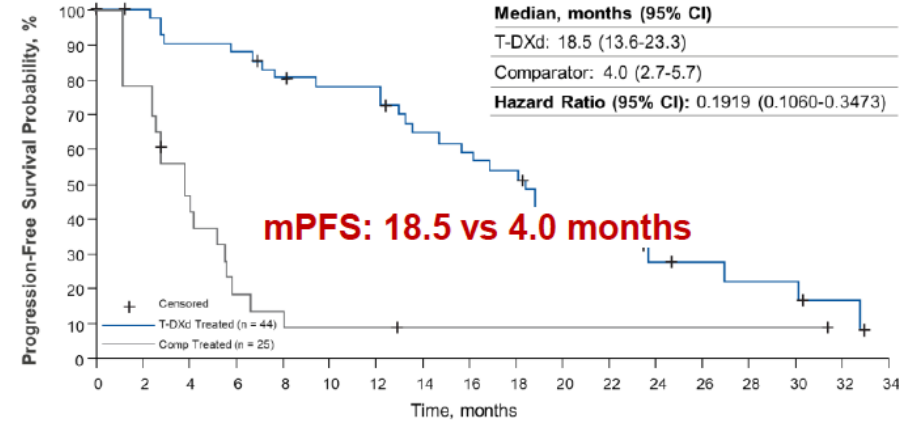
The objective of this exploratory pooled analysis is to **describe the population of patients enrolled in DB-01, DB-02, and DB-03 with baseline BM**, to analyze exploratory pooled efficacy of T-DXd by BICR, and to assess safety versus a comparator



Treated/Stable BMs

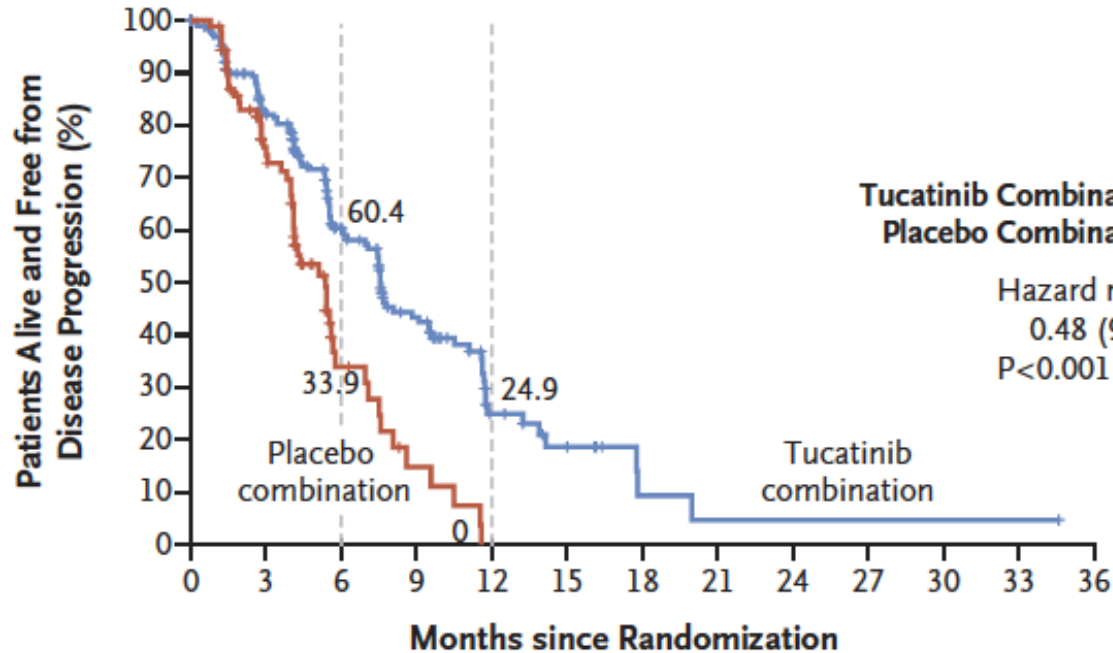


Untreated/Active BMs



NEW ENGLAND

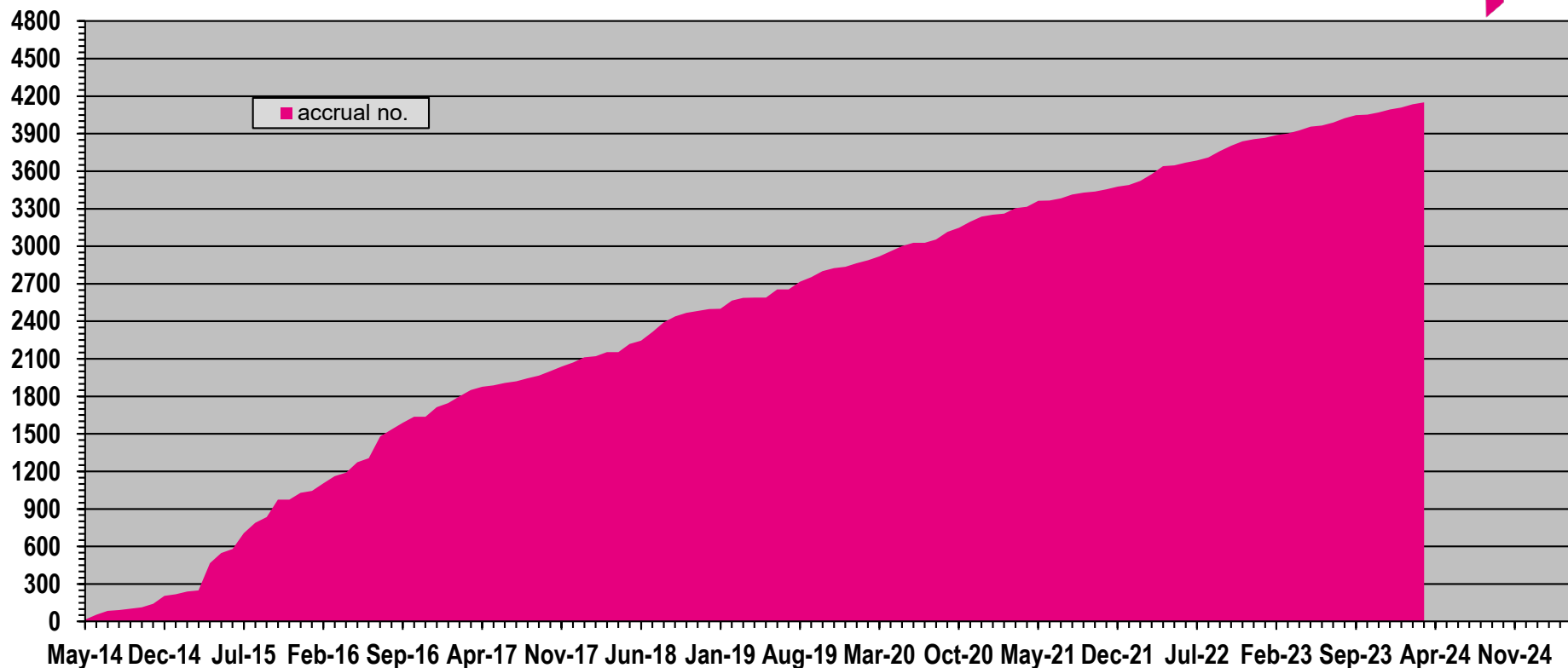
A Kaplan–Meier Estimates of Progression-free Survival among Patients with Brain Metastases

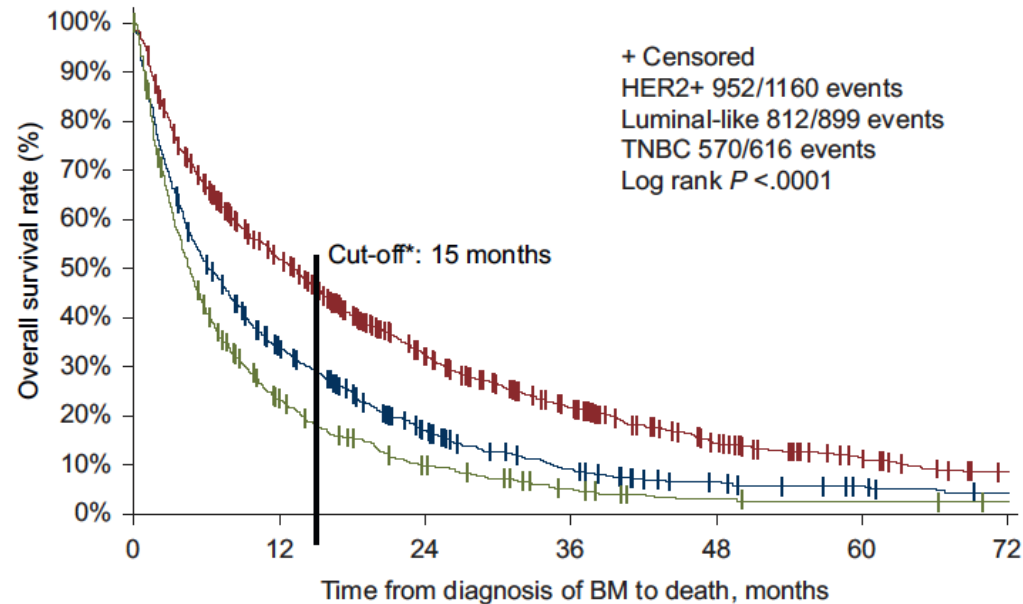


| | No. of Events/ No. of Patients | Median Duration (95% CI) mo |
|-----------------------|-----------------------------------|--------------------------------------|
| Tucatinib Combination | 106/198 | 7.6 (6.2–9.5) |
| Placebo Combination | 51/93 | 5.4 (4.1–5.7) |

Hazard ratio for disease progression or death,
0.48 (95% CI, 0.34–0.69)
P<0.001

Rekrutierung (Stand 15.02.2024) n = 4151



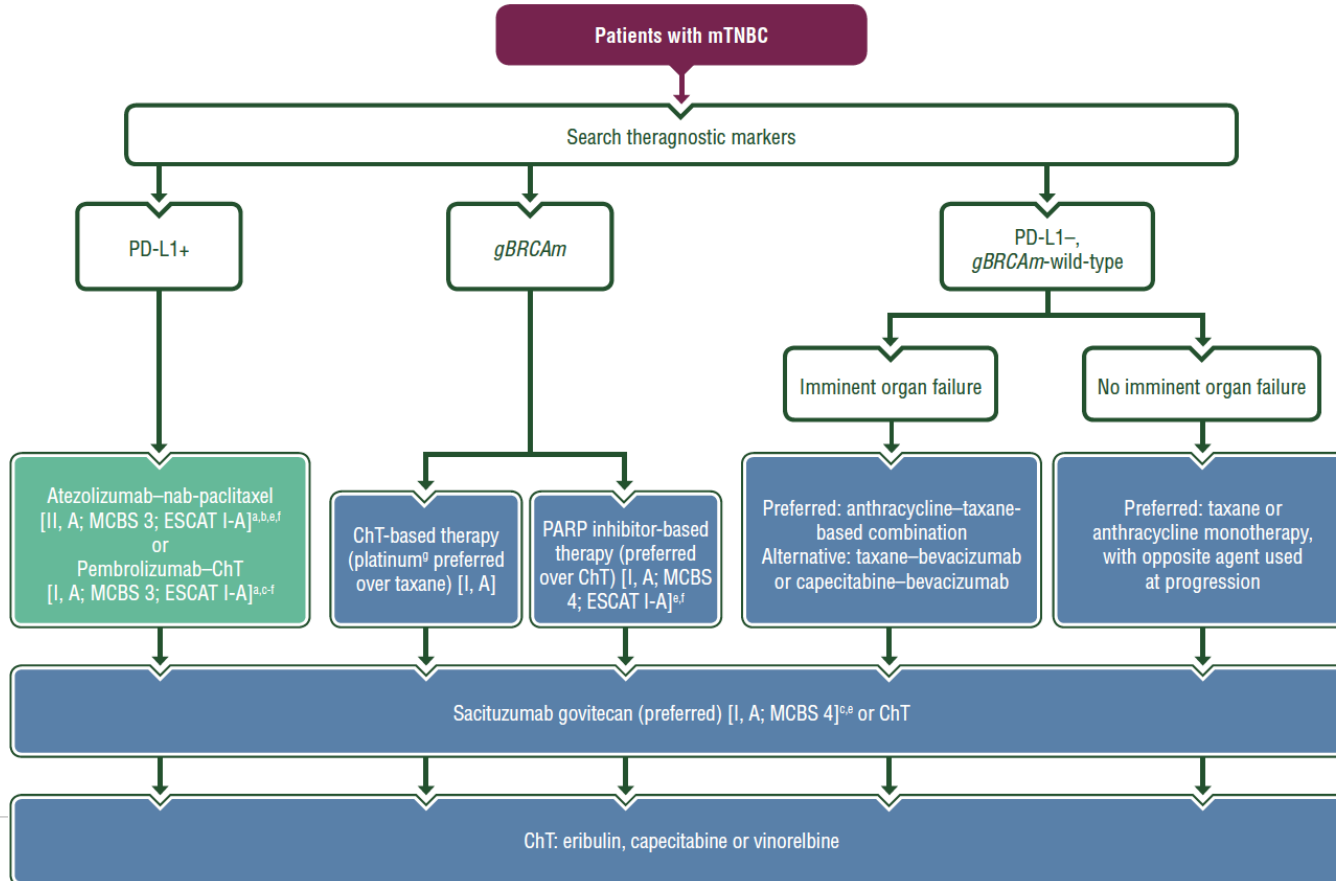


| | | | | | | | |
|----------------|------|-----|-----|-----|-----|----|----|
| — HER2+ | 1160 | 568 | 315 | 187 | 102 | 65 | 40 |
| — Luminal-like | 899 | 291 | 127 | 63 | 35 | 25 | 17 |
| — TNBC | 616 | 131 | 51 | 22 | 10 | 7 | 5 |

Riecke et al, BMBC
ESMO open 2023

Aktuelle Therapiestandards 24` triple negative

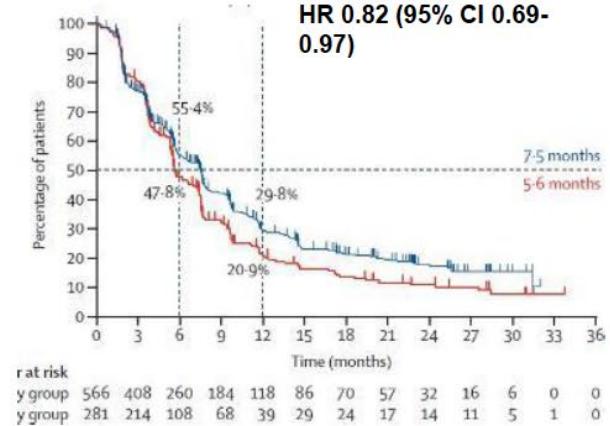
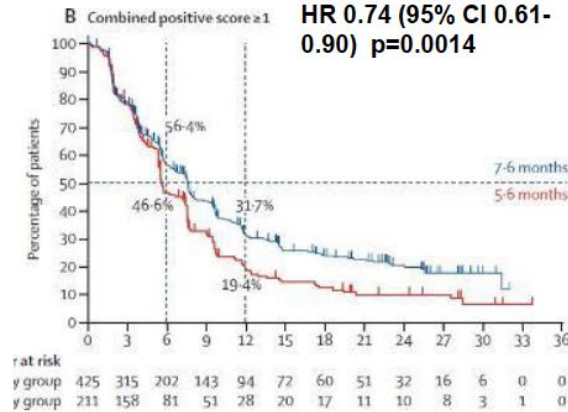
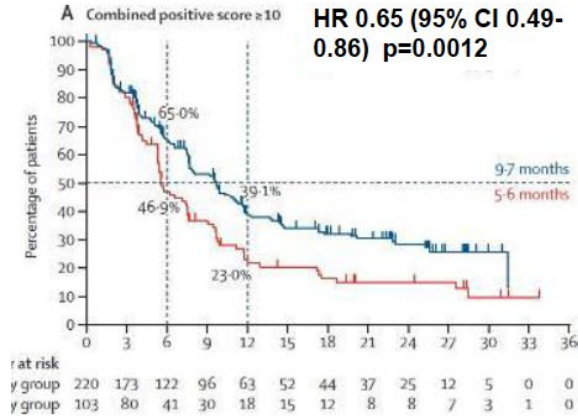
Gennari
Ann Oncol 2021



CPS score ≥ 10 (38% of patients)

CPS score ≥ 1 (75% of patients)

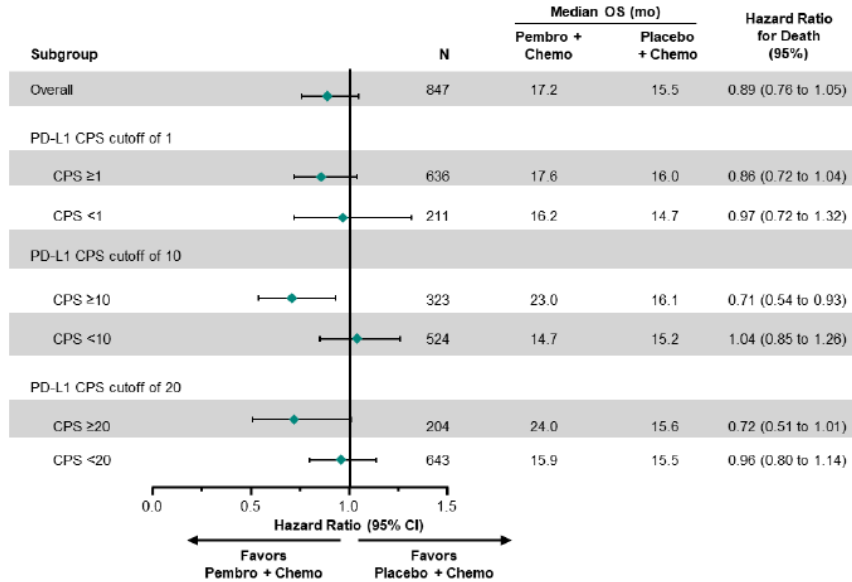
ITT population



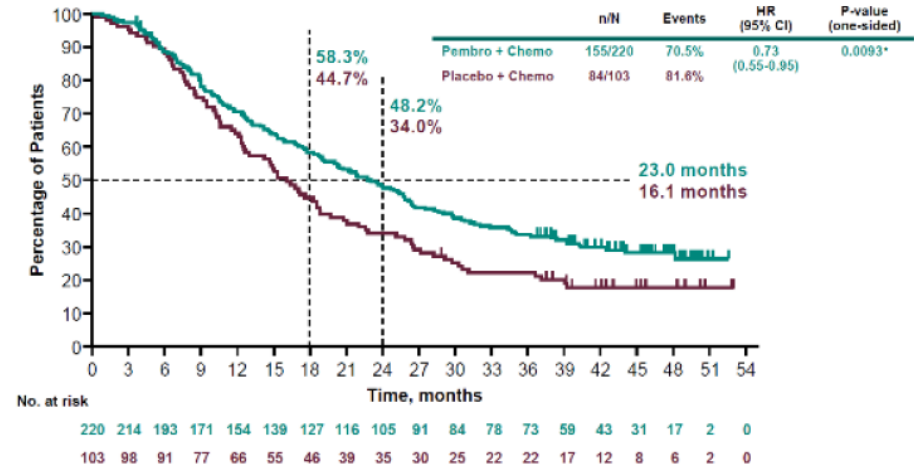
Keynote 355, Cortes et al, The Lancet 2020

KEYNOTE-355: OS

OS subgroups



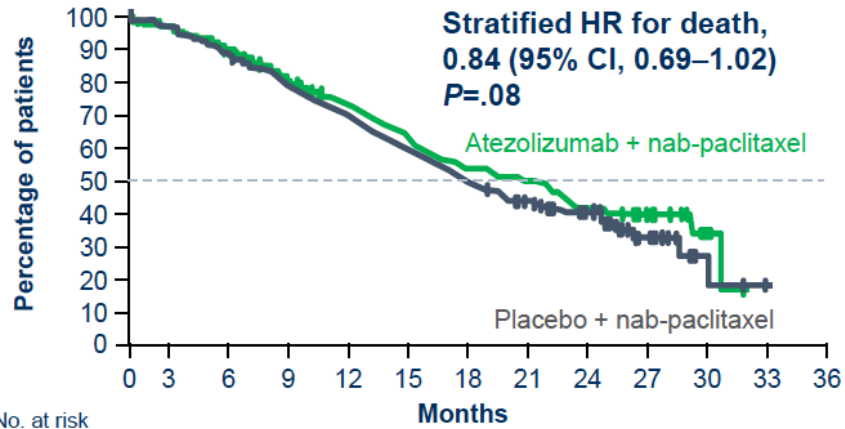
OS PD-L1+ CPS ≥ 10



IMpassion130: OS

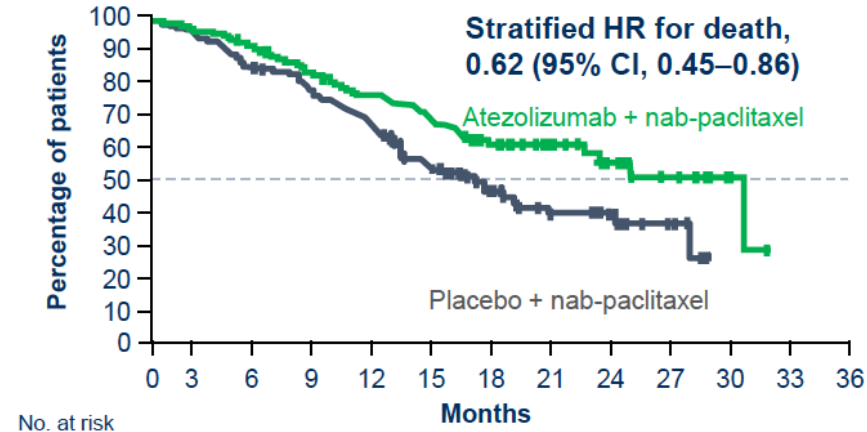
ITT population

| | No. of events/ no. of patients | Median OS (95% CI) mo | 2yr rate of OS (95% CI) % |
|-------------------------------|-----------------------------------|--------------------------|------------------------------|
| Atezolizumab + nab-paclitaxel | 180/452 | 21.3 (17.3–23.4) | 42.1 (34.3–49.9) |
| Placebo + nab-paclitaxel | 208/451 | 17.6 (15.9–20.0) | 39.7 (33.2–46.3) |



PD-L1+ population

| | No. of events/ no. of patients | Median OS (95% CI) mo | 2yr rate of OS (95% CI) % |
|-------------------------------|-----------------------------------|--------------------------|------------------------------|
| Atezolizumab + nab-paclitaxel | 64/185 | 25.0 (22.6–NE) | 53.5 (42.3–64.6) |
| Placebo + nab-paclitaxel | 88/184 | 15.5 (13.1–19.4) | 36.6 (26.4–46.7) |

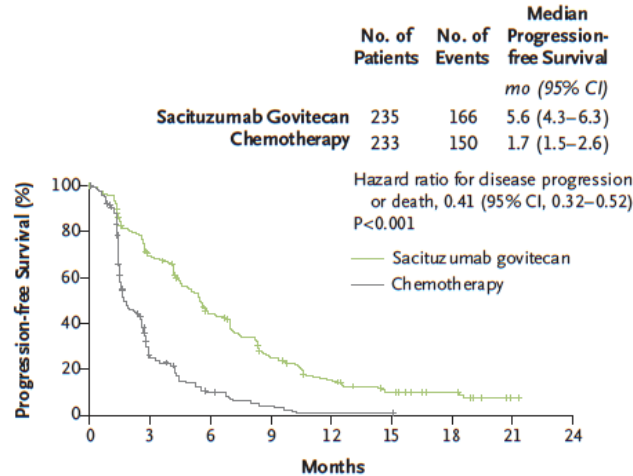


Aktuelle Therapiestandards 24` - triple negative

Sacituzumab Govitecan in Metastatic Triple-Negative Breast Cancer

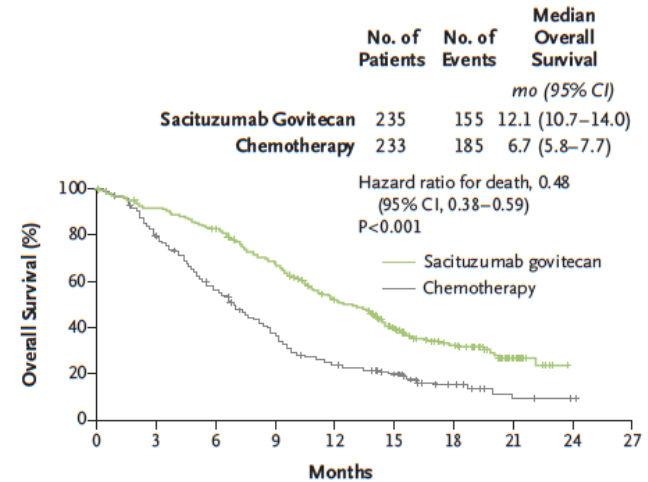
A. Bardia, S.A. Hurvitz, S.M. Tolaney, D. Loirat, K. Punie, M. Oliveira, A. Brufsky, S.D. Sardesai, K. Kalinsky, A.B. Zelnak, R. Weaver, T. Traina, F. Dalenc, P. Aftimos, F. Lynce, S. Diab, J. Cortés, J. O'Shaughnessy, V. Diéras, C. Ferrario, P. Schmid, L.A. Carey, L. Gianni, M.J. Piccart, S. Loibl, D.M. Goldenberg, Q. Hong, M.S. Olivo, L.M. Itri, and H.S. Rugo, for the ASCENT Clinical Trial Investigators*

A Progression-free Survival among Patients without Brain Metastases



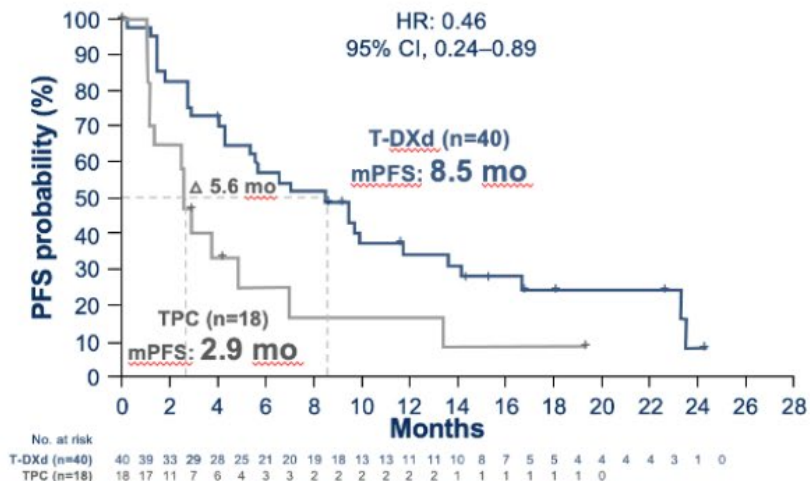
| No. at Risk | 0 | 3 | 6 | 9 | 12 | 15 | 18 | 21 | 24 |
|-----------------------|-----|-----|----|----|----|----|----|----|----|
| Sacituzumab govitecan | 235 | 154 | 91 | 49 | 28 | 15 | 9 | 1 | |
| Chemotherapy | 233 | 39 | 14 | 5 | 1 | 1 | 0 | 0 | |

B Overall Survival among Patients without Brain Metastases

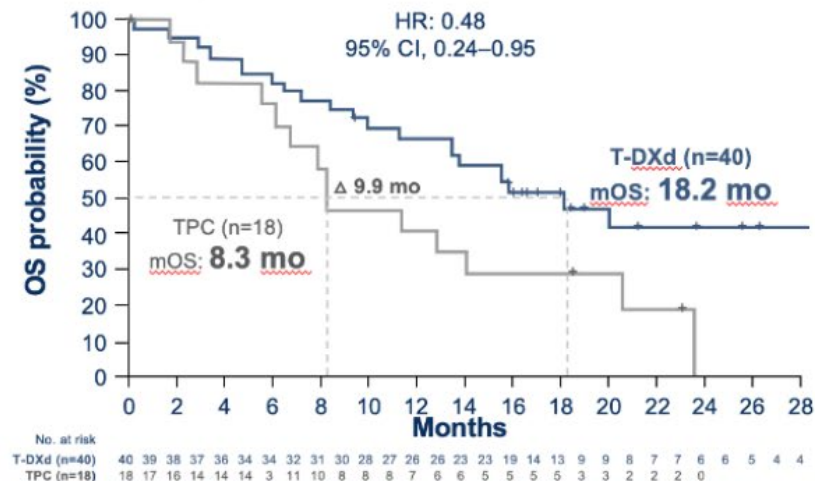


| No. at Risk | 0 | 3 | 6 | 9 | 12 | 15 | 18 | 21 | 24 | 27 |
|-----------------------|-----|-----|-----|-----|-----|----|----|----|----|----|
| Sacituzumab govitecan | 235 | 214 | 190 | 153 | 107 | 70 | 37 | 13 | 0 | |
| Chemotherapy | 233 | 173 | 117 | 74 | 45 | 30 | 11 | 3 | 1 | |

Median PFS with T-DXd was 5.6 months greater vs TPC



Median OS with T-DXd was 9.9 months greater vs TPC



Modi. ASCO 2022. LBA3. Modi. NEJM. 2022;

HR+, HER2- :

1st line cdk4/6, danach noch kein Standard, ESCAT I/II zunehmende Rolle
Liquid biopsy, ADC auf dem Vormarsch

HER2+:

Derzeit klare Sequenzen, nach Trastuzumab Deruxtecan kein Standard
Situation bei Hirnmetastasen bessert sich

Triple negativ

Immuntherapie / CTX Kombination, PARP Inhibitoren, ADC