IKIM 2024
Mammakarzinom
20.02.2024

Rupert Bartsch

Univ.-Klinik für Innere Medizin 1

Klinische Abteilung für Onkologie

Medizinische Universität Wien

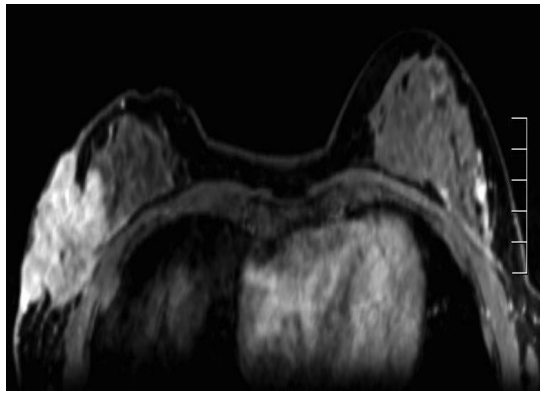
Disclosures

- Advisory Role: Astra-Zeneca, Daiichi, Eisai, Eli-Lilly, Gilead, Gruenenthal, MSD, Novartis, Pfizer, Pierre-Fabre, Puma, Roche, Seagen. Stemline

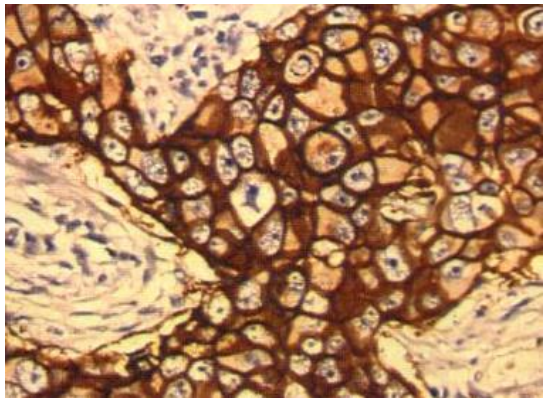
- Lecture Honoraria: Astra-Zeneca, Daichi, Eisai. Eli-Lilly, Gilead, Gruenenthal, MSD, Novartis, Pfizer, Pierre-Fabre, Roche, Seagen, Stemline

- Research Support: Daiichi, MSD, Novartis, Roche

Interdisziplinarität

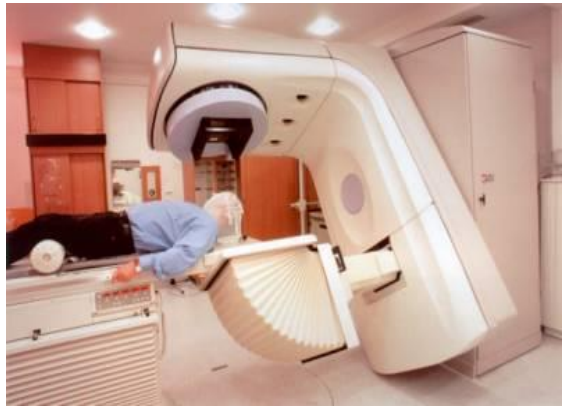


Radiologie



Pathologie

Operation



Strahlentherapie

Chemotherapie

Zielgerichtete Therapie

Überblick

- Häufigstes Malignom bei Frauen weltweit[1]
- Risiko altersabhängig[2,3]
- Bis in die frühen 2000er Jahre steigende Inzidenz[3]

- Reduzierte Mortalität durch Screening und Fortschritte in der adjuvanten Therapie[3]

- 95% aller Fälle werden im Frühstadium diagnostiziert

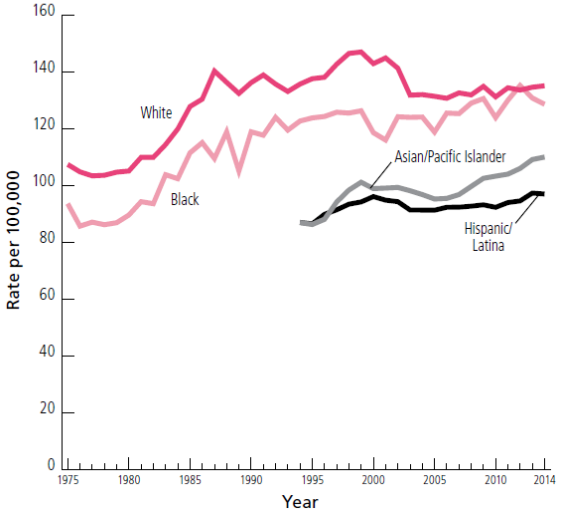
1 Available at http://www.wcrf.org/int/cancer-facts-figures/data-specific-cancers/breast-cancer-statistics; last accessed January 23rd 2020.; 2 Available at https://www.breastcancer.org/symptoms/understand_bc/risk/understanding; last accessed January 23rd 2020.; 3 Available at https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/breast-cancer-facts-and-figures/breast-cancer-facts-and-figures-2017-2018.pdf; last accessed January 23rd 2020.

Age-specific Probability of Developing Invasive Breast Cancer for US Women

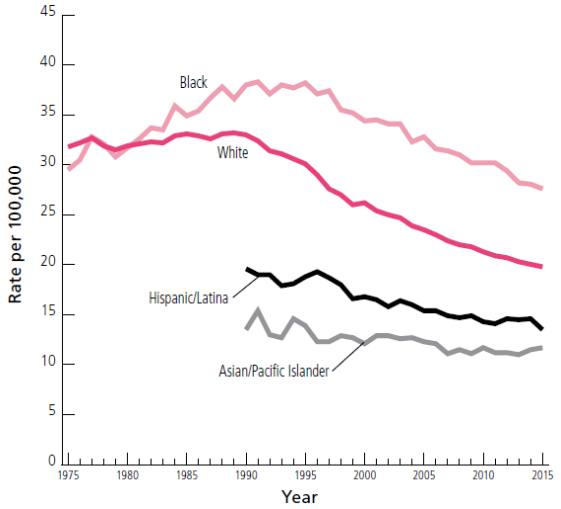
Current age	10-year probability:	or 1 in:
20	0.1%	1,567
30	0.5%	220
40	1.5%	68
50	2.3%	43
60	3.4%	29
70	3.9%	25
Lifetime risk	**12.4%**	**8**

Note: Probability is among those free of cancer at beginning of age interval. Based on cases diagnosed 2012-2014. Percentages and "1 in" numbers may not be numerically equivalent due to rounding.

Trends in Female Breast Cancer Incidence Rates by Race/Ethnicity, 1975-2014, US



Trends in Female Breast Cancer Death Rates by Race/Ethnicity, 1975-2015, US



Risikofaktoren[1-3]

Factors That Increase the Relative Risk for Breast Cancer in Women

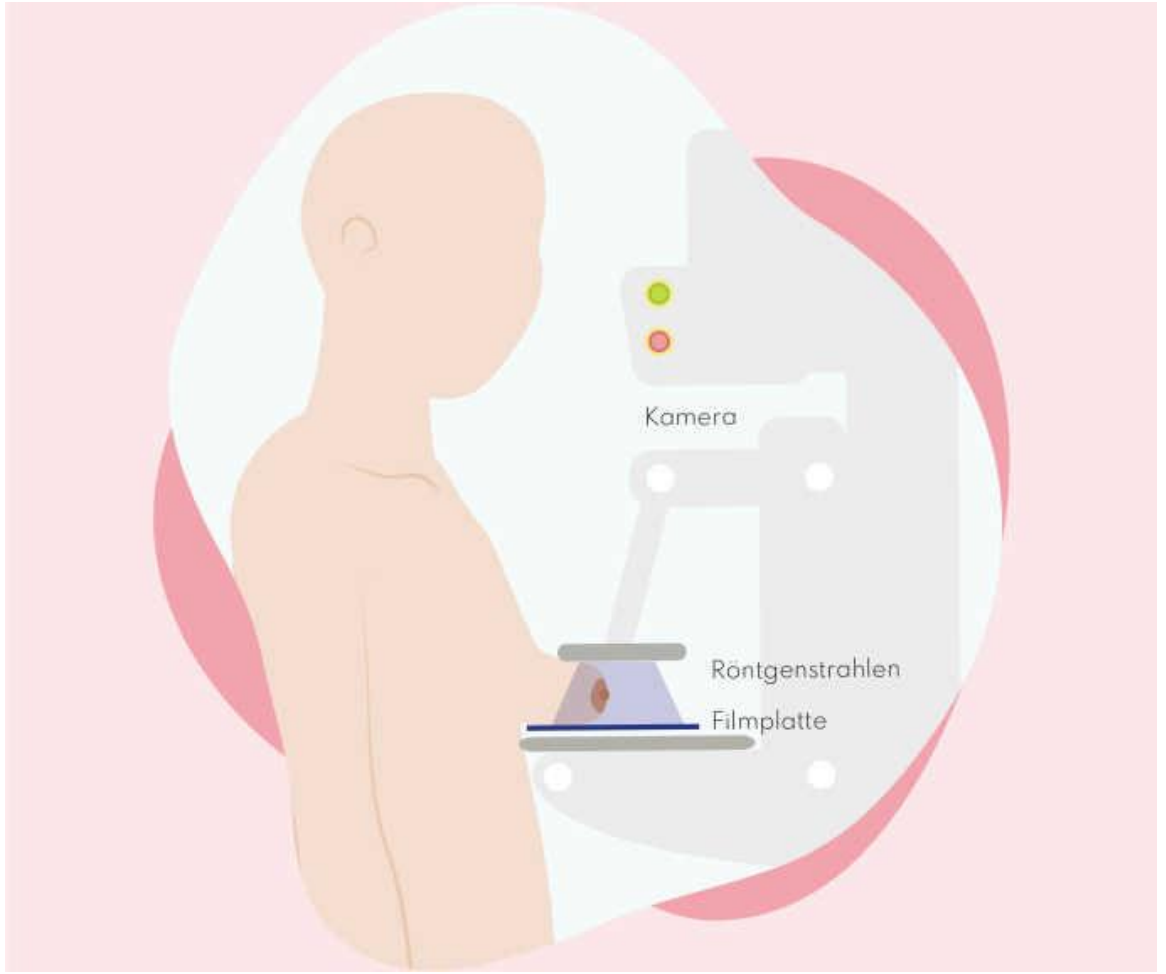
Relative Risk	Factor
>4.0	• Female • Age (65+ versus <65 years, although risk increases across all ages until age 80) • Certain inherited genetic mutations for breast cancer (BRCA1 and/or BRCA2) • Two or more first-degree relatives with breast cancer diagnosed at an early age • Personal history of breast cancer • High breast tissue density • Biopsy-confirmed atypical hyperplasia
2.1-4.0	• One first-degree relative with breast cancer • High-dose radiation to chest • High bone density (postmenopausal)
1.1-2.0	
Factors that affect circulating hormones	• Late age at first full-term pregnancy (>30 years) • Early menarche (<12 years) • Late menopause (>55 years) • No full-term pregnancies • Never breastfed a child • Recent oral contraceptive use • Recent and long-term use of hormone replacement therapy • Obesity (postmenopausal)
Other factors	• Personal history of endometrium, ovary, or colon cancer • Alcohol consumption • Height (tall) • High socioeconomic status • Jewish heritage

Adapted with permission from Hulka et al, 2001.

1 Lichtenstein P et al. N Engl JMed 2000;343:78-85.; 2 ASCO policy statement update: genetic testing for cancer susceptibility. J Clin Oncol 2003;21:2397-2406.; 3 Hulka BS and Moorman PG. Maturitas 2001;38:103-113.

Screening[1-4]

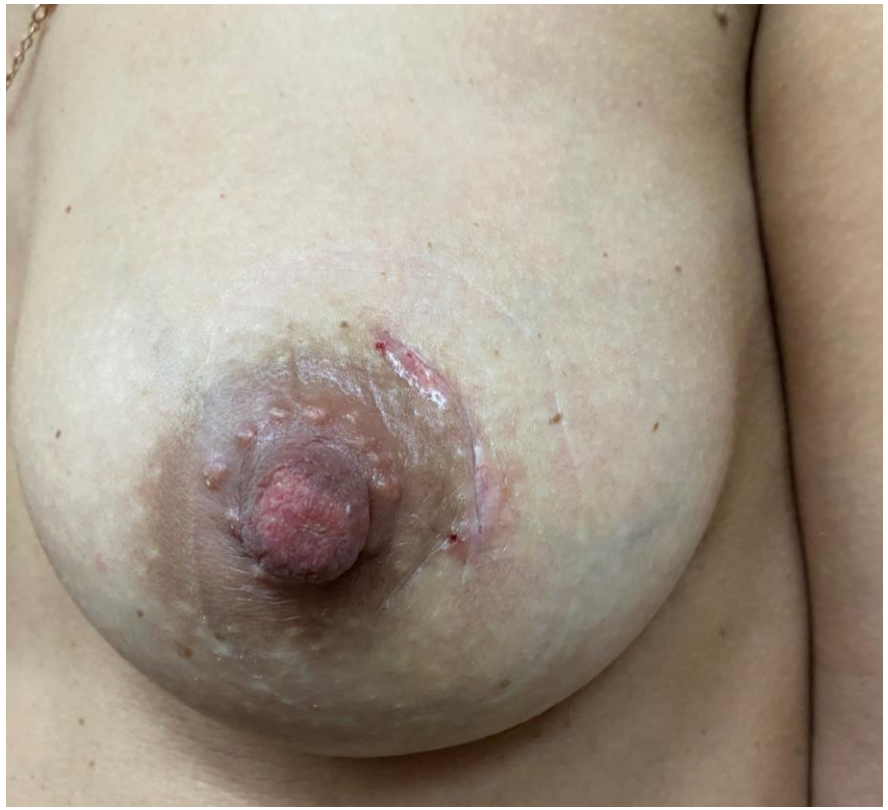
- Ziel:
  - Vorverlegung des Diagnosezeitpunktes auf ein prognostisch günstiges Stadium
  - Verbesserung der Heilungschancen durch schonendere Therapiemethoden
  - Reduktion der erkrankungs- und therapiebedingten Leiden
  - Senkung der Mortalität
- Österreichisches Screeningprogramm:
  - Mammographie und Ultraschall alle 2 Jahre
  - 45-74 Jahre
  - Opt-in 40-44
- Früherkennung senkt Sterblichkeit um 10%-25%



1 S3-Leitlinie Mammakarzinom https://www.awmf.org/leitlinien; 2 https://www.frueh-erkennen.at/; 3 https://www.leben-mit-brustkrebs.de/wissen/frueherkennung-und-diagnose/mammografie-sonografie; 4 Kalager M et al. Ann Oncol 2014;25:1137-1143

Operation[1]

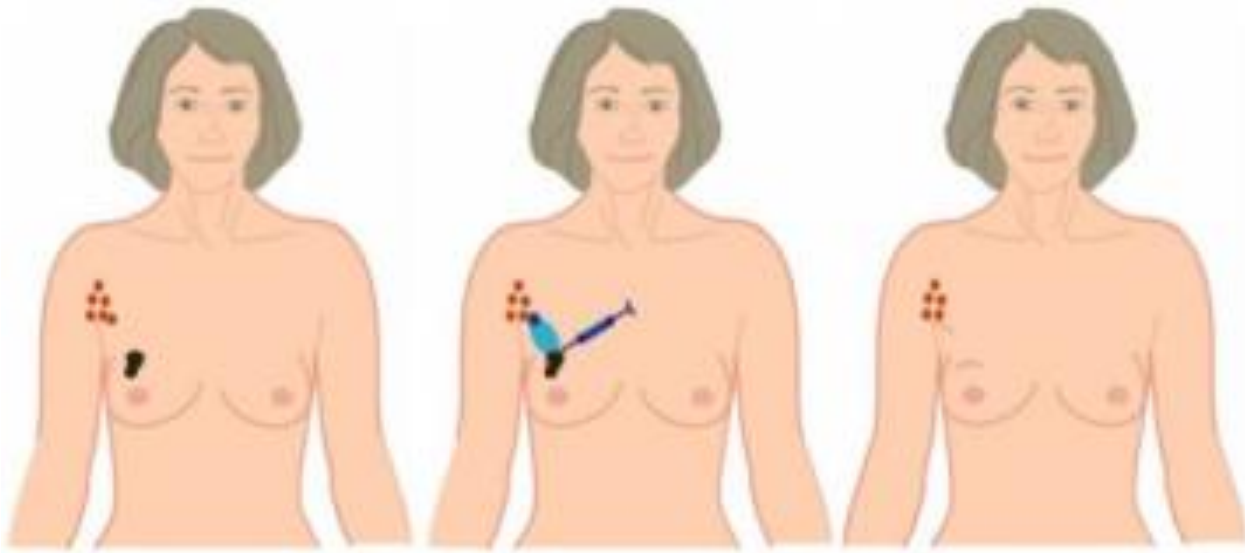
- Biopsie, Clipmarkierung aller suspekten Herde
- Besprechung im Tumorboard - eventuell systemische Therapie präoperativ (Tumorbiologie, Brusterhalt)?
- Genetische Beratung bei familiärer Risikosituation
- Präoperative Markierung nicht tastbarer Herde
- IMMER: Brusterhalt wenn möglich!
- Kontraindikationen u.a. *BRCA* Keimbahnmutation, inflammatorisches Ca
- Gleichzeitig: Operation der Lymphknoten
- Bei brusterhaltender Operation üblicherweise auch Strahlentherapie

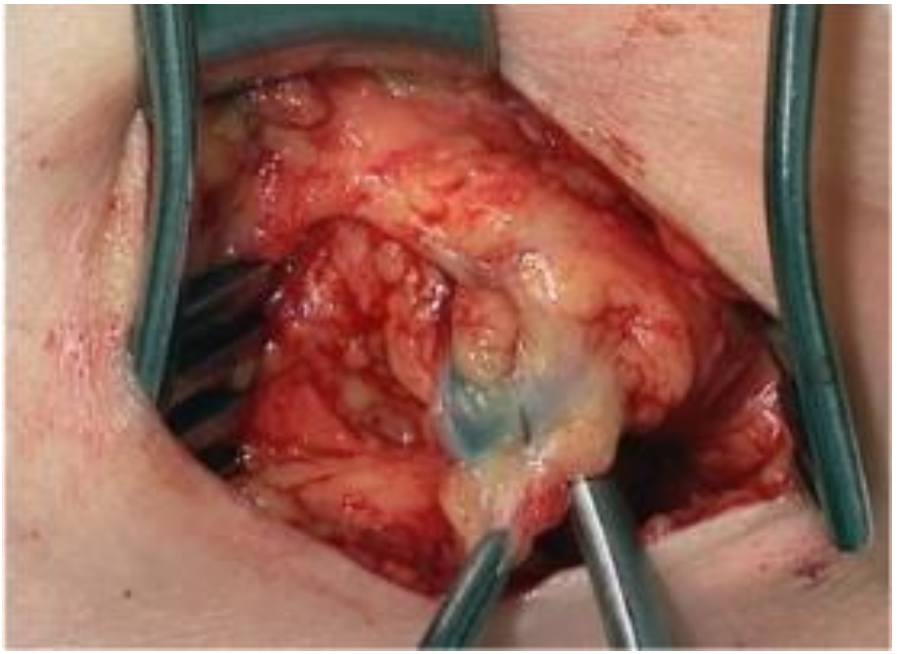


1 Exner R. Brustkrebs Forum 2021/2022.

Operation[1]

- Sentinellymphknoten = erster Lymphknoten im Lymphabflussgebiet der Axilla
- Diagnostische Operation
- Markierung mit Patentblau und/oder radioaktiv (Tc99m)
- Axilläre Dissektion nur bei befallenem Wächterlymphknoten – nicht in jedem Fall verpflichtend

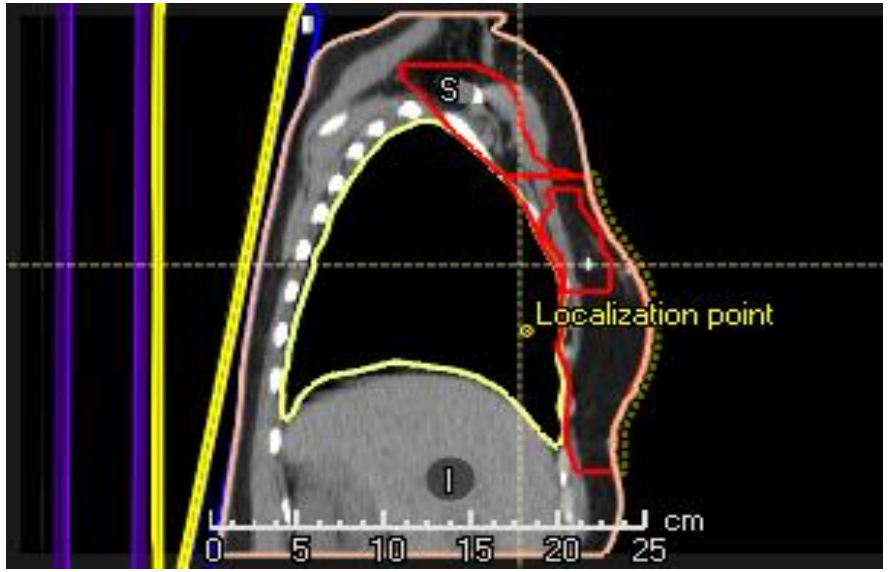


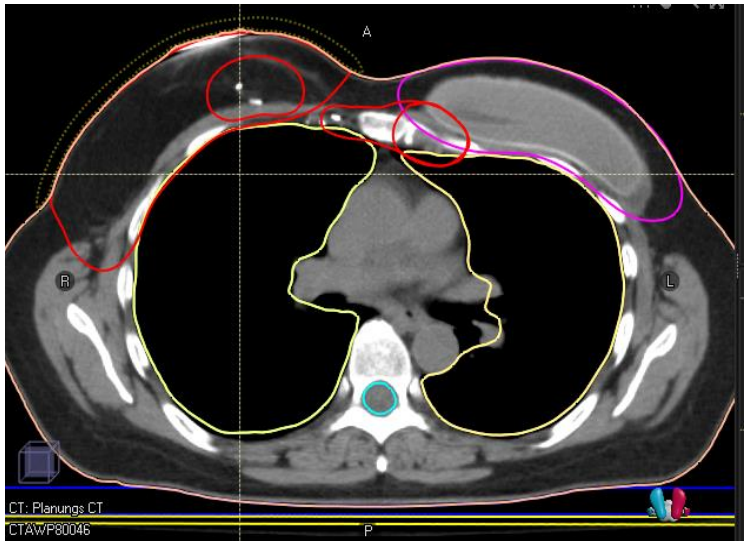


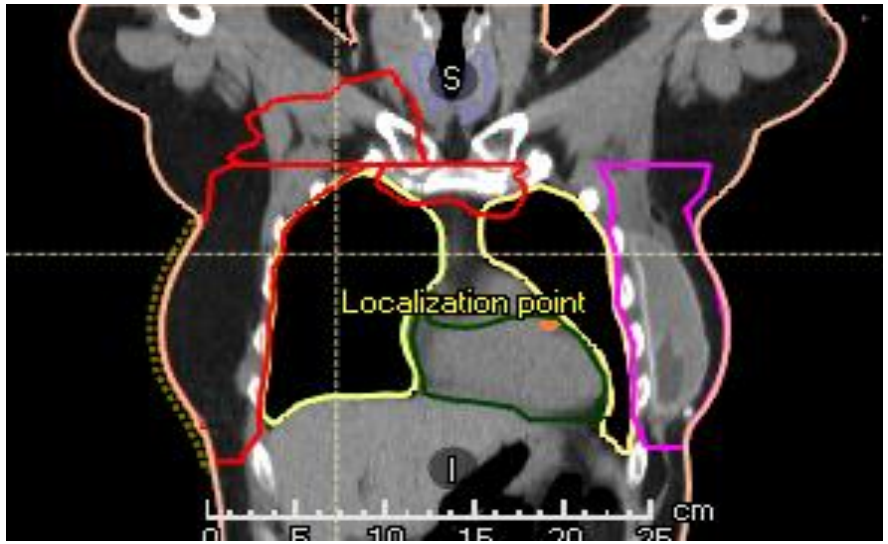
1 Exner R. Brustkrebs Forum 2021/2022.

Strahlentherapie[1]

- BET + RT reduziert Rezidivrate um bis zu 75%
- BET + RT führt zu einer Überlebensverbesserung
- Dreidimensionale Planung zum Schutz von Herz und Lunge

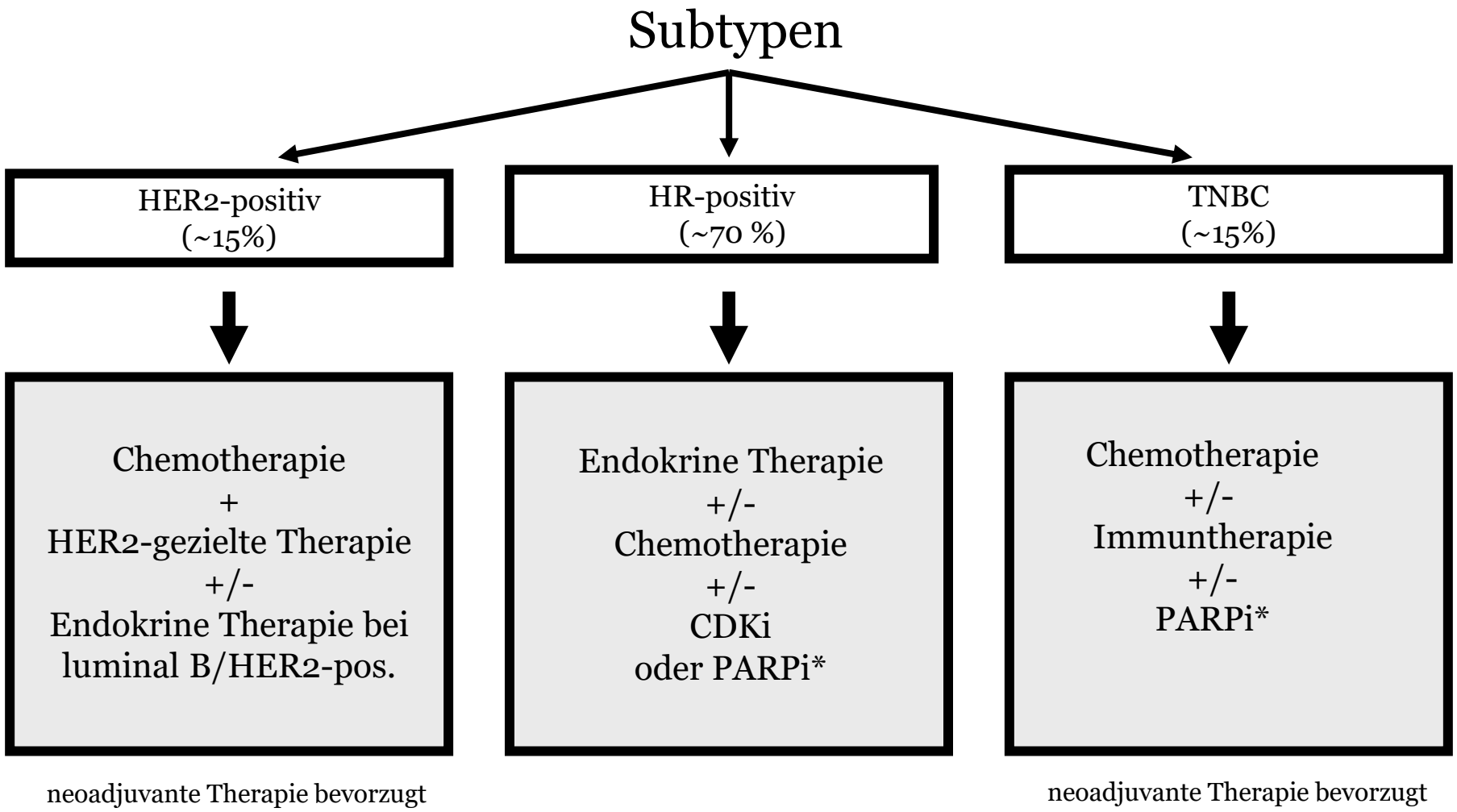






1 Fastner G. Brustkrebs Forum 2021/2022.

Medikamentöse Behandlungsprinzipien



* Bei *BRCA*mut

Wonach richtet sich die Therapieempfehlung?

- Tumorgröße
- Lymphknotenbefall
- Lymphgefässinvasion

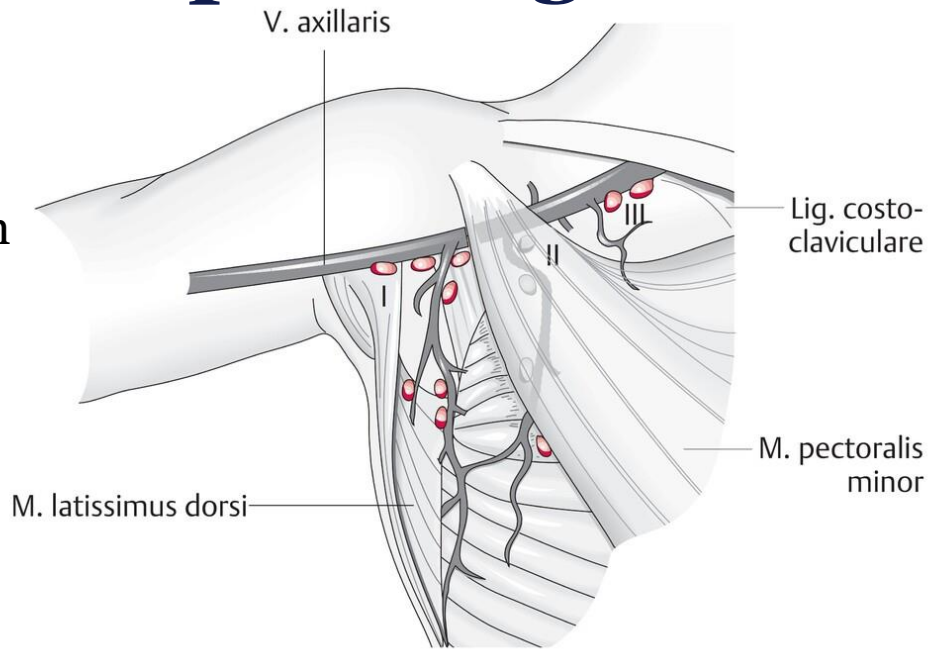
- Grading
- Hormonrezeptorexpession
- HER2-Status
- Proliferation (ki67)
- Genexpressionsprofile

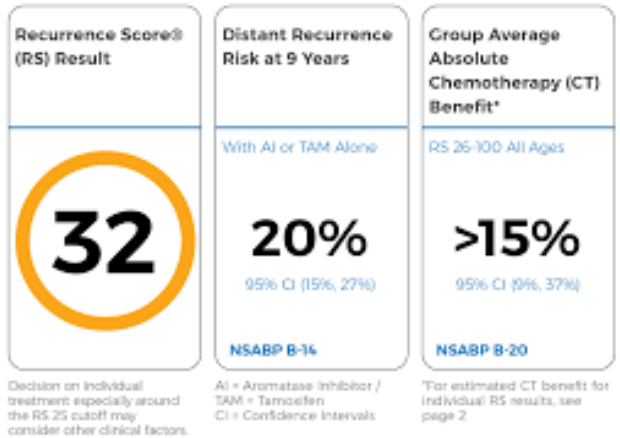
- Alter
- Begleiterkrankungen
- Patientinnenwunsch

Klinisches Stadium

Tumorbiologie

Patientinnen-spezifische Faktoren

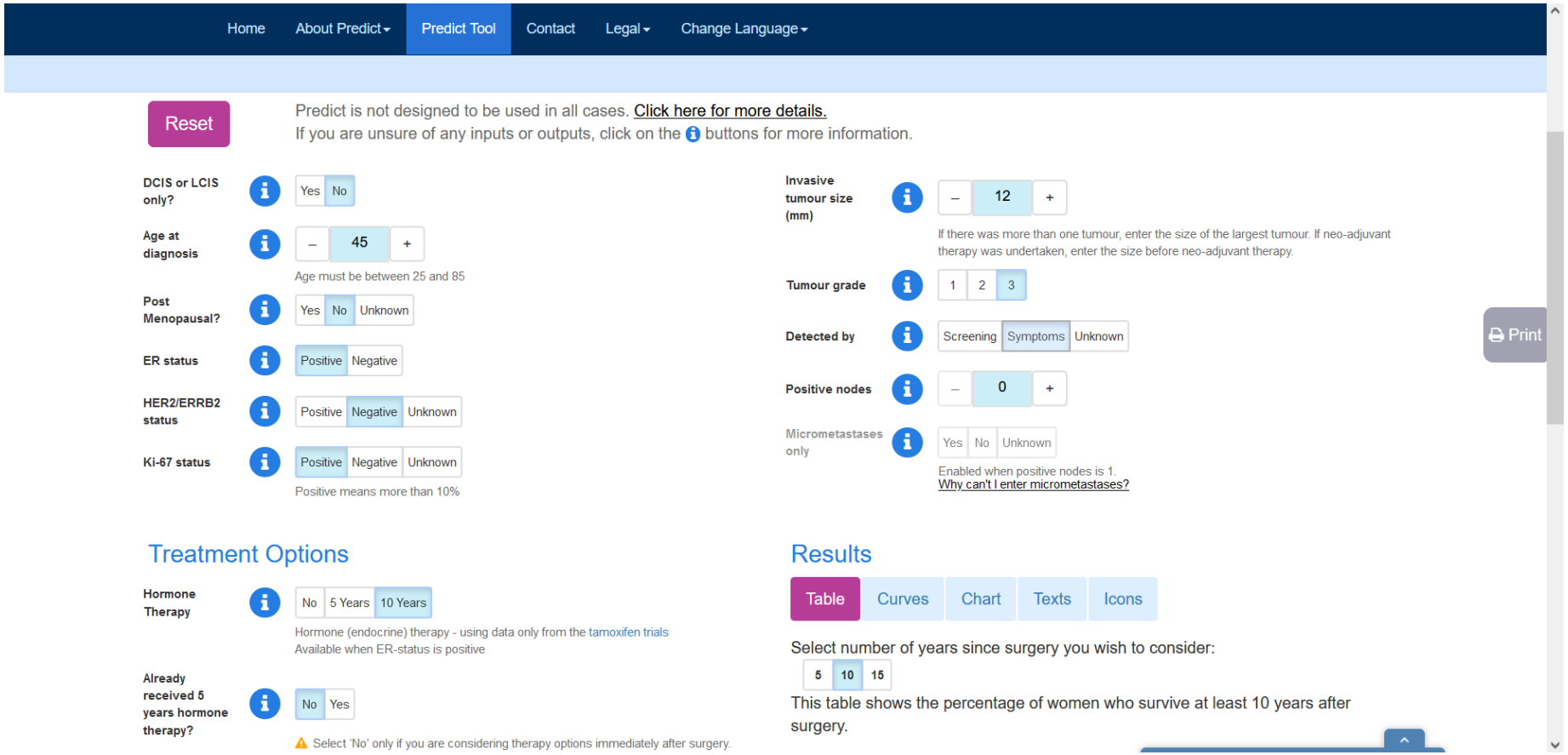




Predict Breast Cancer[1]

- OS Benefit durch Chemotherapie nach 10 Jahren?

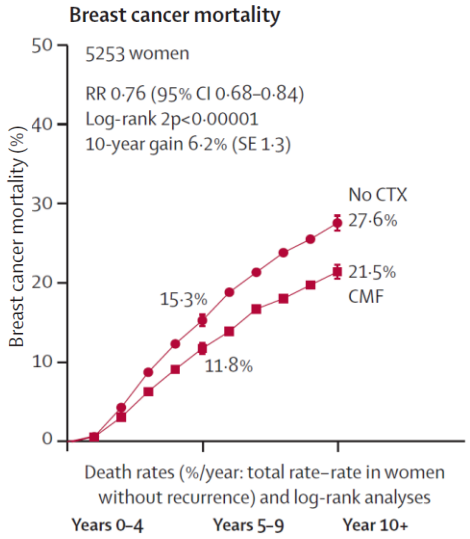
- Online Prognosetool

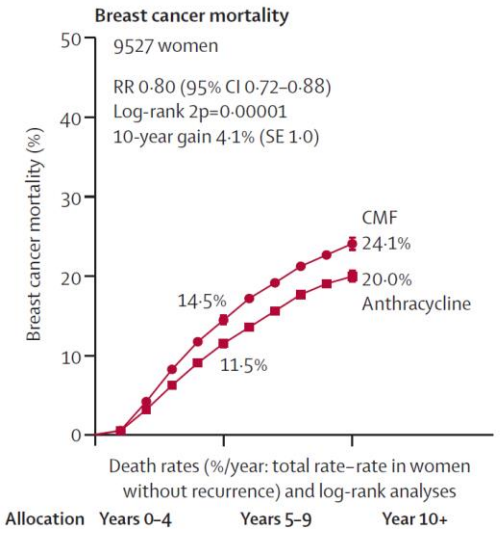


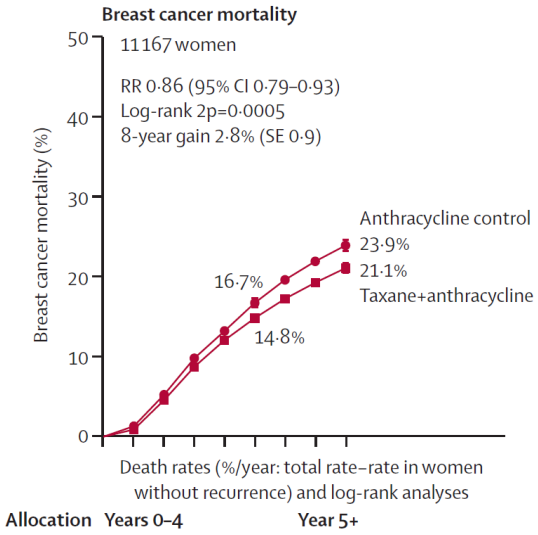
1 available at: https://breast.predict.nhs.uk/tool; last accessed December 21st , 2022.

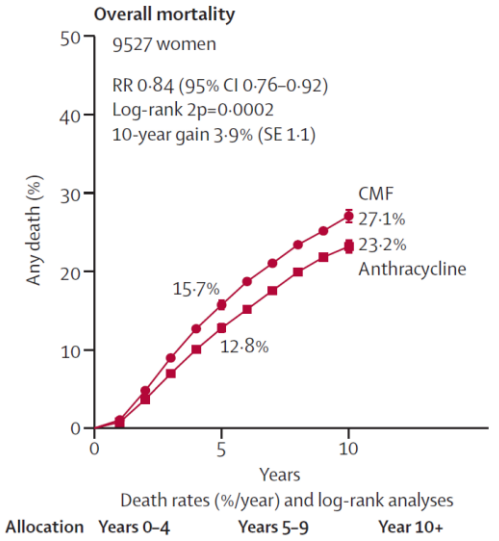
Chemotherapie: Mortalitätsreduktion[1]

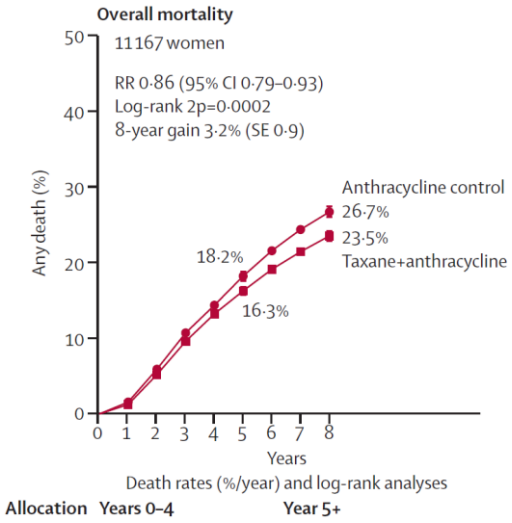
- Brustkrebs-spezifische Mortalität und Gesamtmortalität bei adjuvanter Chemotherapie der 1-3. Generation







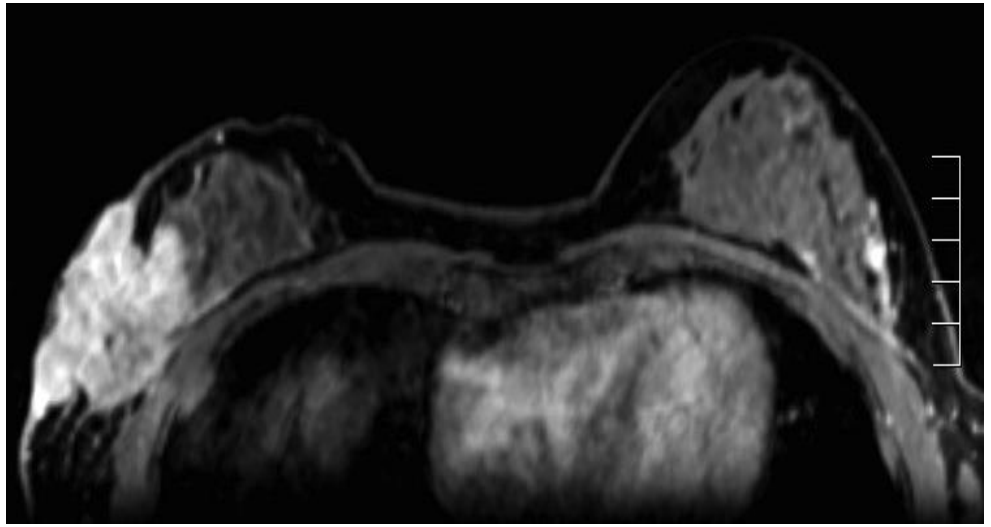


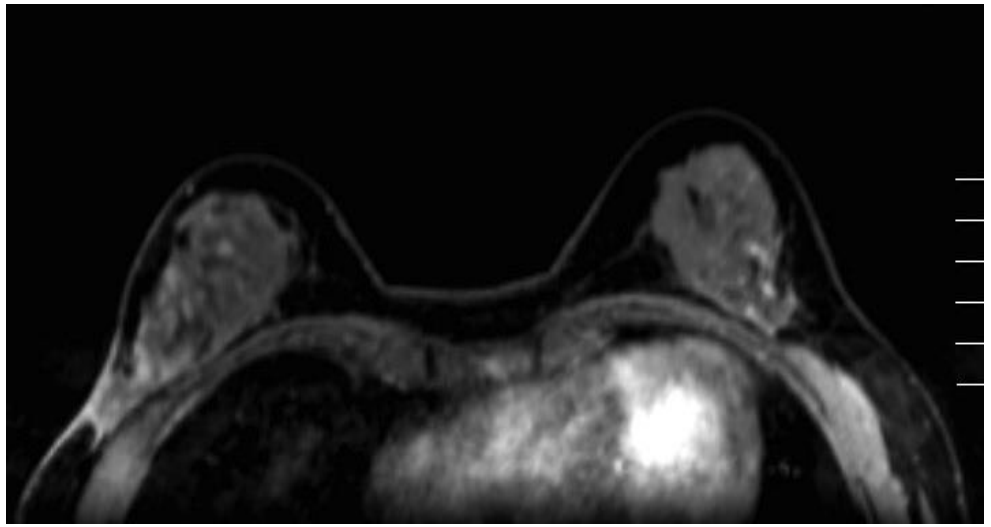


1 EBCTCG. Lancet 2012;379:432-444.

Präoperative Systemische Therapie

- **Chemotherapie vor Operation**
- V.a. bei aggressiven Brustkrebsformen[1]
- Ziele:
  - Operabilität bei primär inoperablen Tumoren
  - Sekundärer Brusterhalt, Verbesserung der Kosmesis
  - *In vivo* Sensitivitätstestung
  - Pathologische Komplettremission
  - Responseadaptierte postneoadjuvante Therapie
  - Qualität des Ansprechens korreliert mit Prognose[3,4]



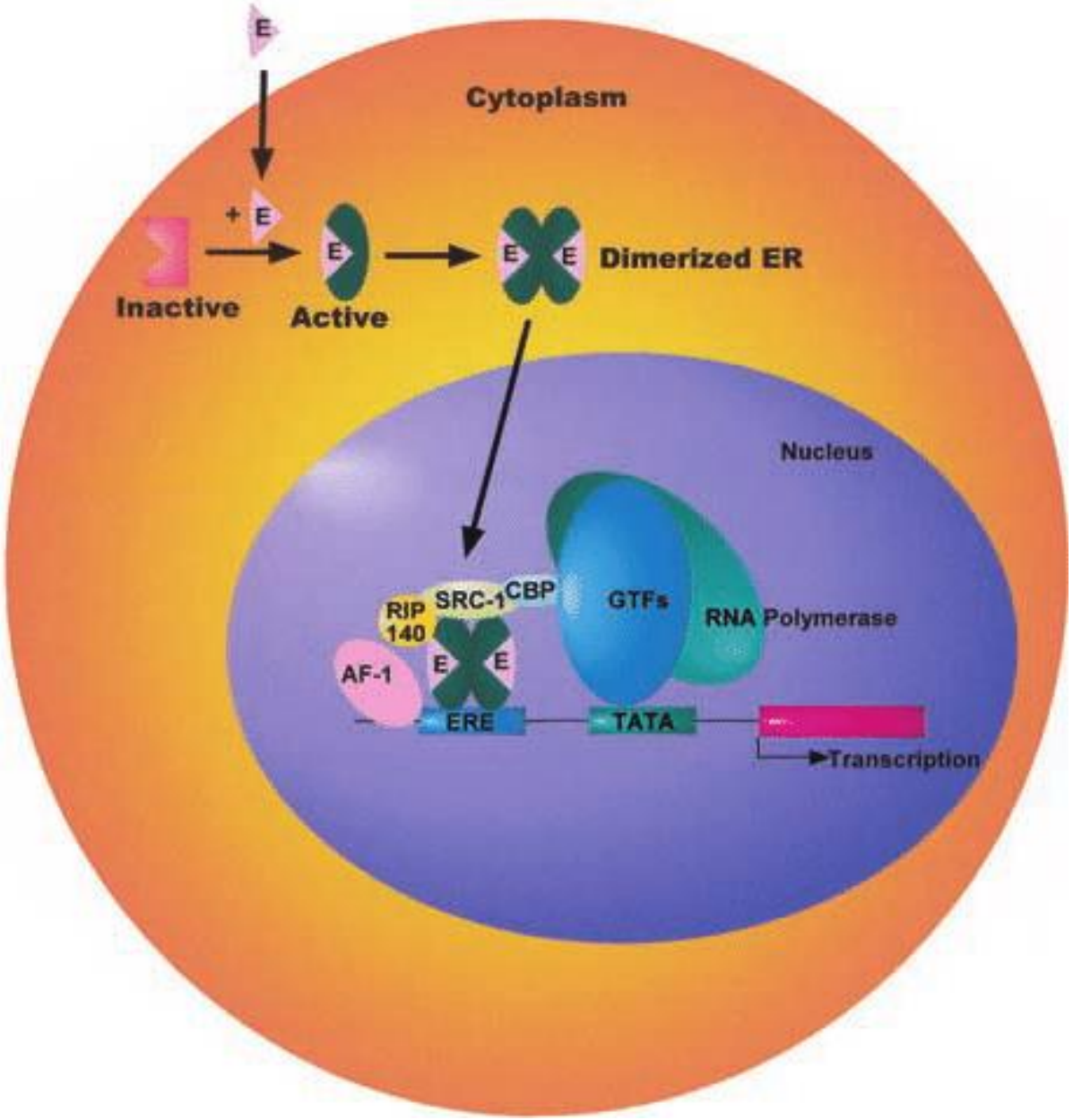


1 Curigliano G et al. Ann Oncol 2017;28:1700-1712.; 2 Von Minckwitz G et al. J Clin Oncol 2012;30:1796-1804.;

3 Cortazar P et al. Lancet 2014;384:164-172.

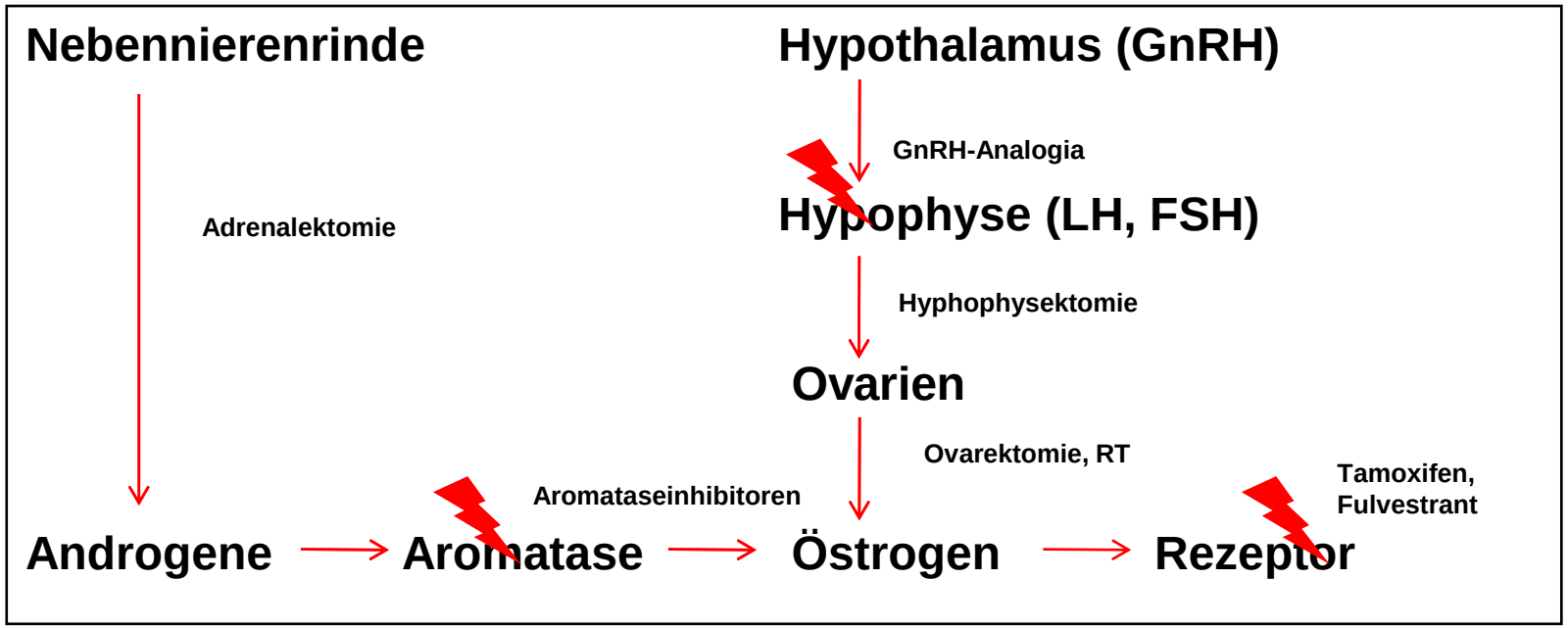
Antihormontherapie

- Östrogen - Wirkmechanismus[1]
  - Östrogen bindet an den native Rezeptor
  - Rezeptortransformation, Dimerisierung
  - Translokation in den Nukleus
  - Bindung an ein estrogen-responsive element (ERE)
  - Transkription Östrogen-abhängiger Gene



1 Jensen EV and DeSombre ER. Science 1973;182:126–134.

Antihormontherapie



Moderne Interventionen mit Blitz markiert

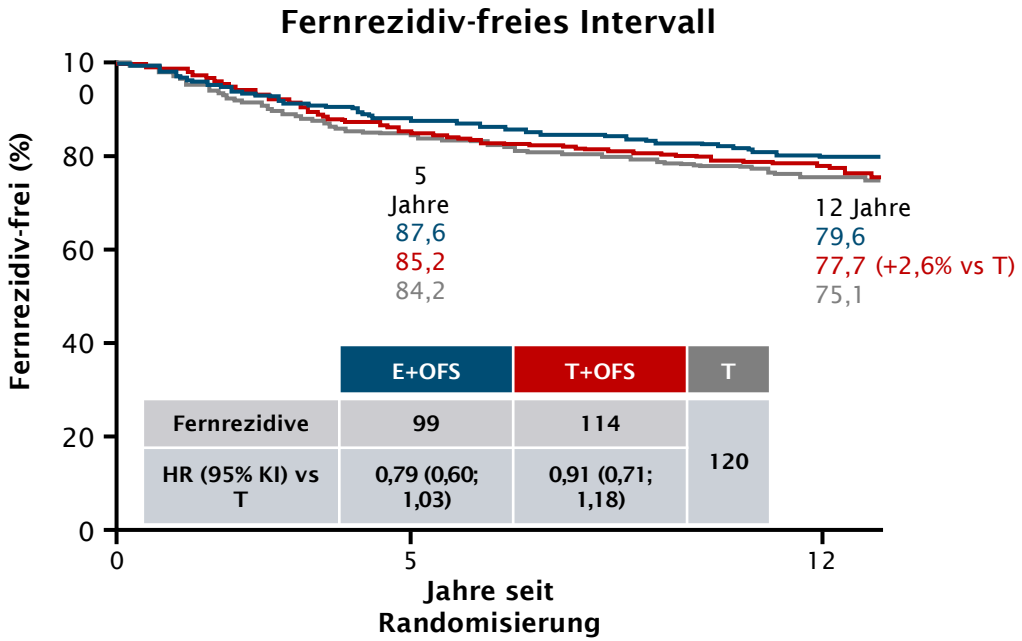
Antihormontherapie - Nebenwirkungen

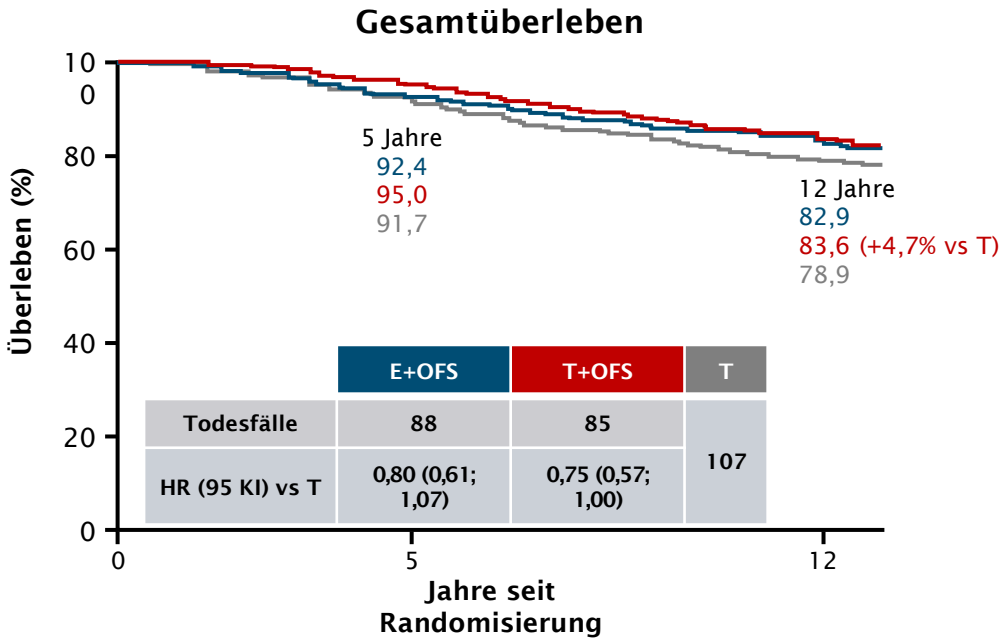
- **Rezeptorblockade**
  - Tamoxifen: Thrombose, Endometriumhyperplasie, EndometriumCa, vaginaler Ausfluss
  - Fulvestrant: Schmerzen an der Injektionsstelle

- **Blockade der Hormonproduktion**
  - Hitzewallungen
  - Gelenksbeschwerden
  - Schleimhauttrockenheit
  - Schmerzen beim Geschlechtsverkehr, Libidoveränderungen
  - Gewichtsveränderungen
  - Osteoporose
  - Schlafstörungen

Endokrine Therapie in der Prämenopause[1]

- SOFT: 12 Jahre mFU
- Chemotherapie Kohorte



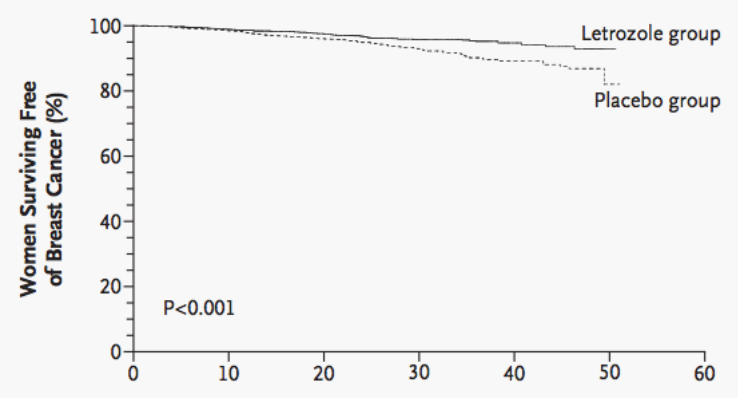


- Non-Chemotherapie Kohorte:
- DDFS 95,8% (T), 95,9% (T+OFS), 97,7% (AI-OFS)
- OS 95,8% (T), 95,2% (T+OFS), 97,1% (AI+OFS)

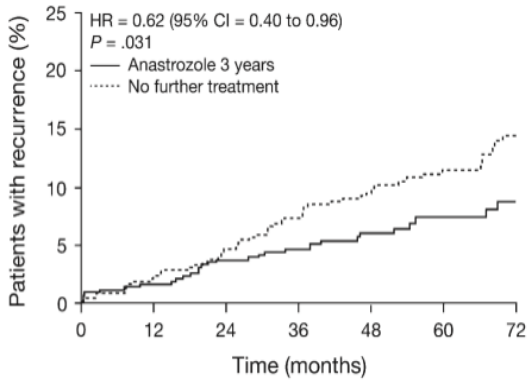
1 Reagen MM et al. GS2-05; SABCS 2021.

Dauer der endokrinen Therapie

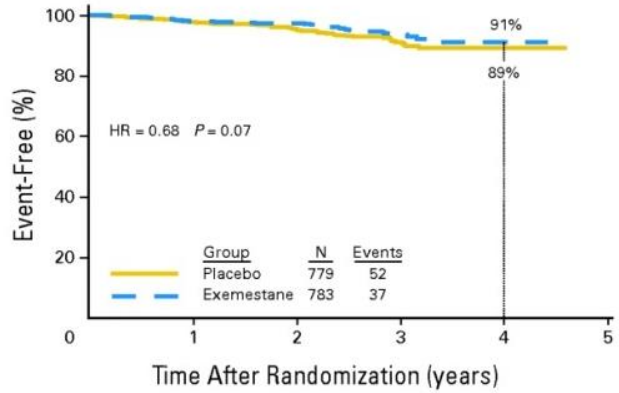
- Rückfallrate 1-2% pro Jahr – Risiko persistiert für zumindest 20 Jahre[1]
- Verlängerung der endokrinen Therapie kann Rückfallrisiko senken[2-4]



MA.17 HR 0.57 [2]



ABCSG 6a HR 0.62 [3]

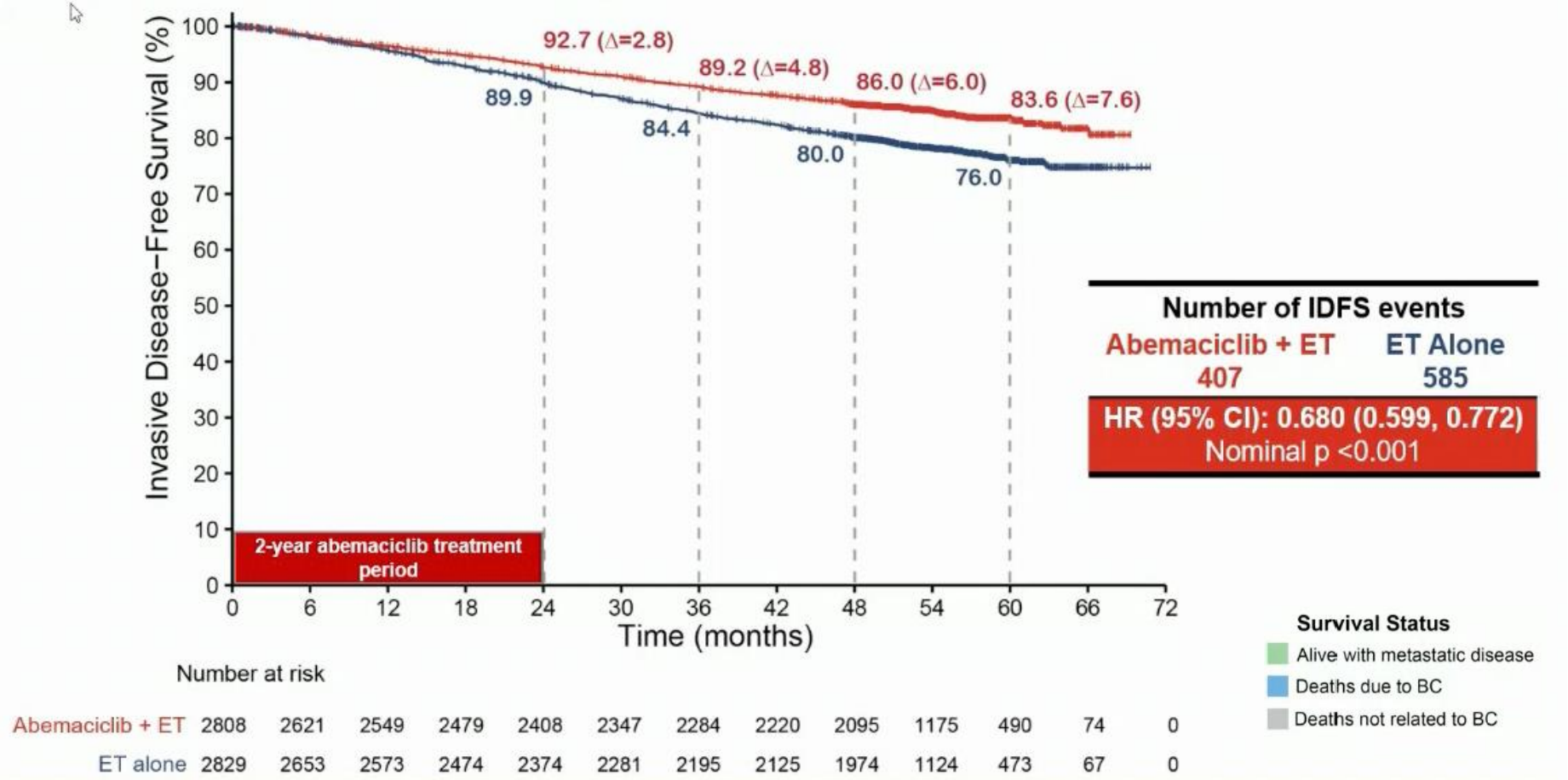


NSABP-B33 HR 0.68 [4]

1 Pan H et al. N Engl J Med 2017;377:1836-1846.; 2 Goss PE et al. N Engl J Med 2003;349:1793-1802.; 3 Jakesz R et al. J Natl Cancer Inst 2007;99:1845-1853.; 4 Mamounas EP et al. J Clin Oncol 2008;26:1965-1971.

MonarchE[1]

- iDFS; medianes Follow-Up 54 Monate



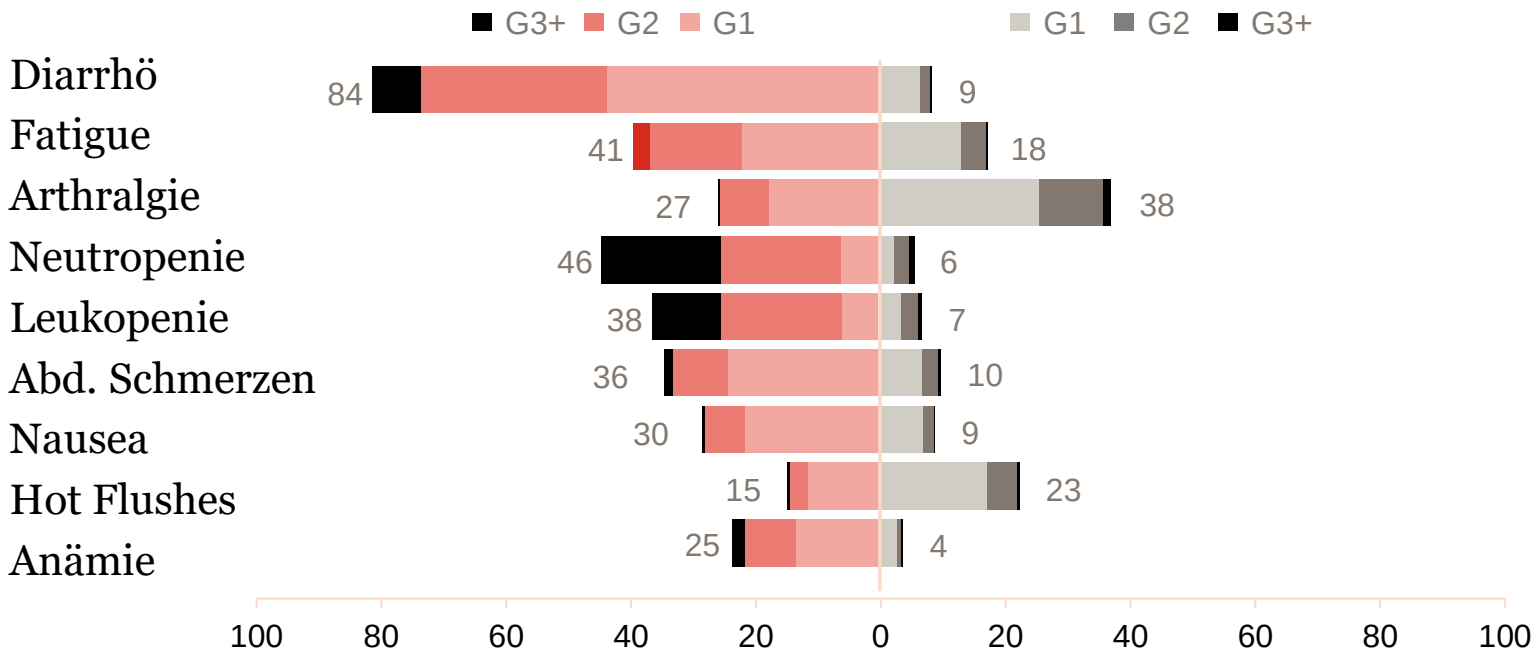
1 Harbeck B et al. LBA17; ESMO 2023.

- Benefit nimmt im zeitlichen Verlauf zu – carry-over effect

- Effekt Kohorte 1 und Kohorte 2:
- HR Kohorte 1: 0.643
- HR Kohorte 2 0.662

MonarchE[1,2]

- Toxizität
- Nebenwirkungen ≥20% in jedem Behandlungsarm



- Inzidenz von Thrombosen und Embolien

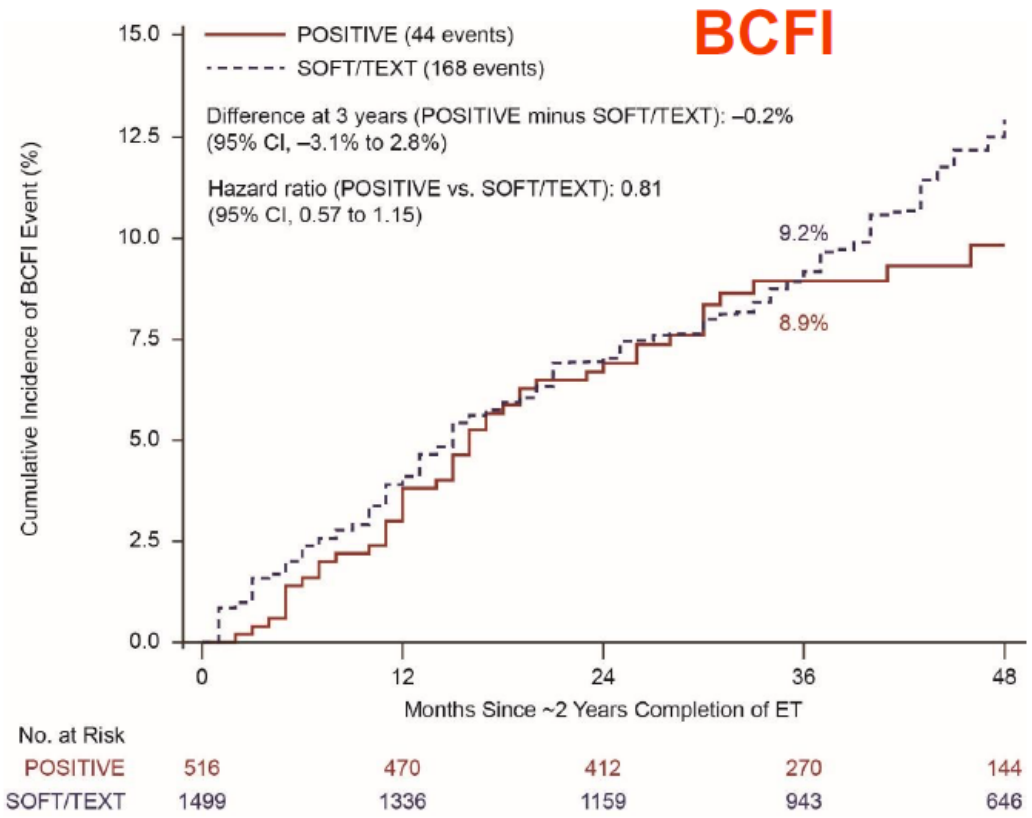
Other events of interest, any grade	Abemaciclib + ET N=2791 (%)	ET alone N=2800 (%)
VTE	2.5	0.7
PE	1.0	0.1
ILD	3.3	1.3

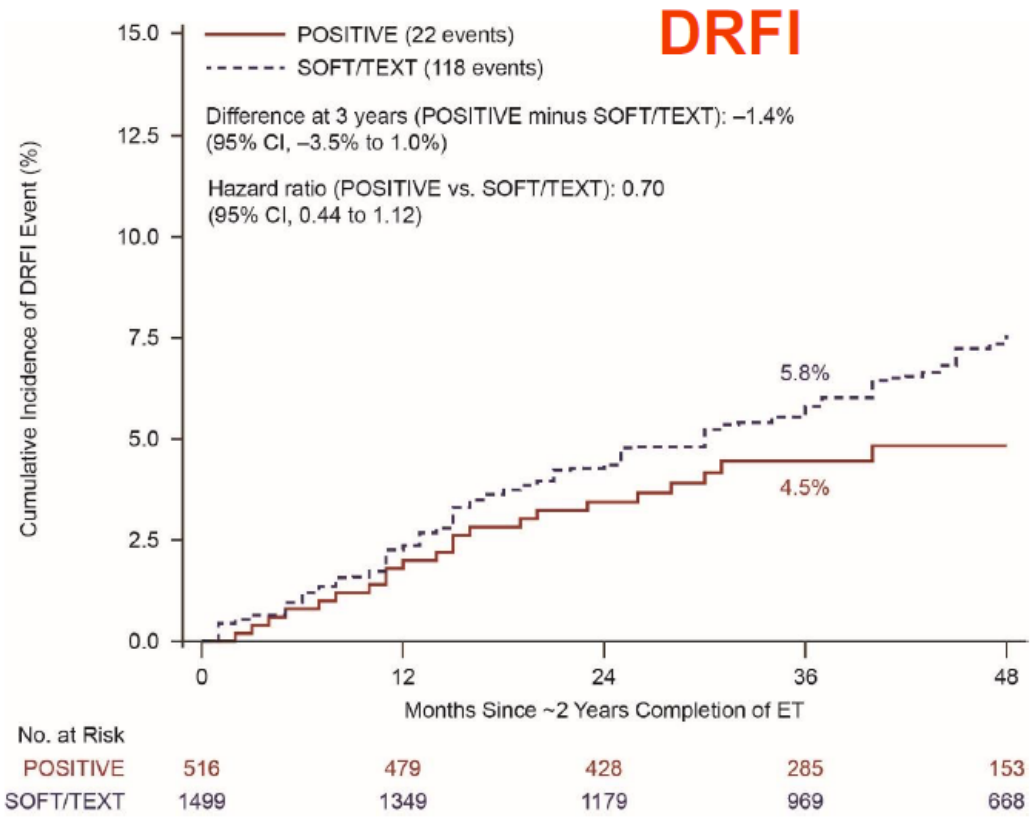
1 Rugo HS et al. Ann Oncol. 2022;33:616-627.; 2 Johnston SRD et al. Lancet Oncol. 2023;24:77-90.

POSITIVE[1]

Medianes FU: 41 Monate

- Ergebnisse POSITIVE / Korrelation SOFT/TEXT

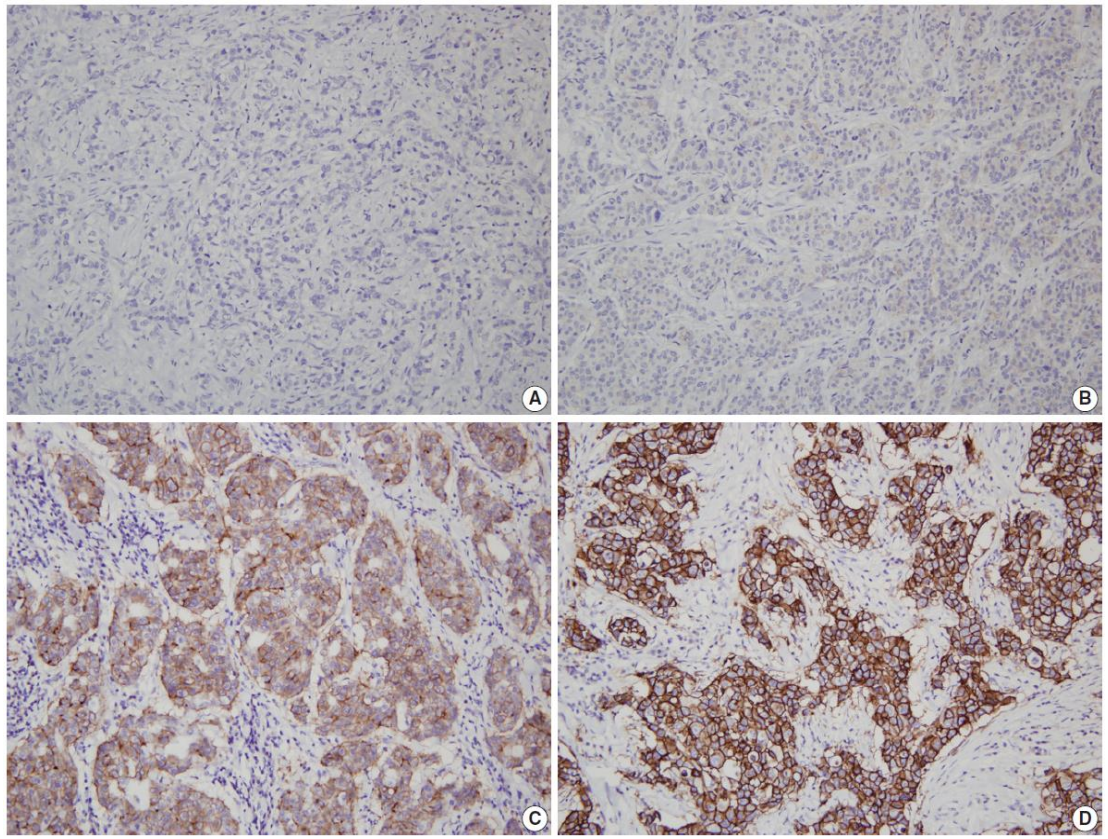




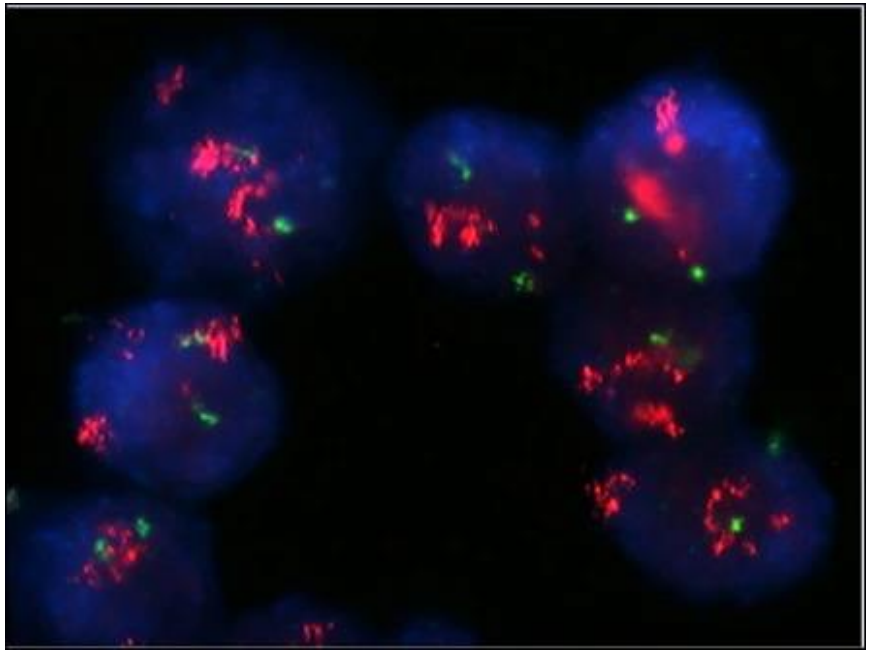
1 Partridge AH et al. GS4-09; SABCS 2022.

HER2

- HER2 IHC[1] und ISH[2]



HER2 IHC (links)
A, HER2 negativ
B, HER2 1+
C, HER2 2+
D, HER2 3+



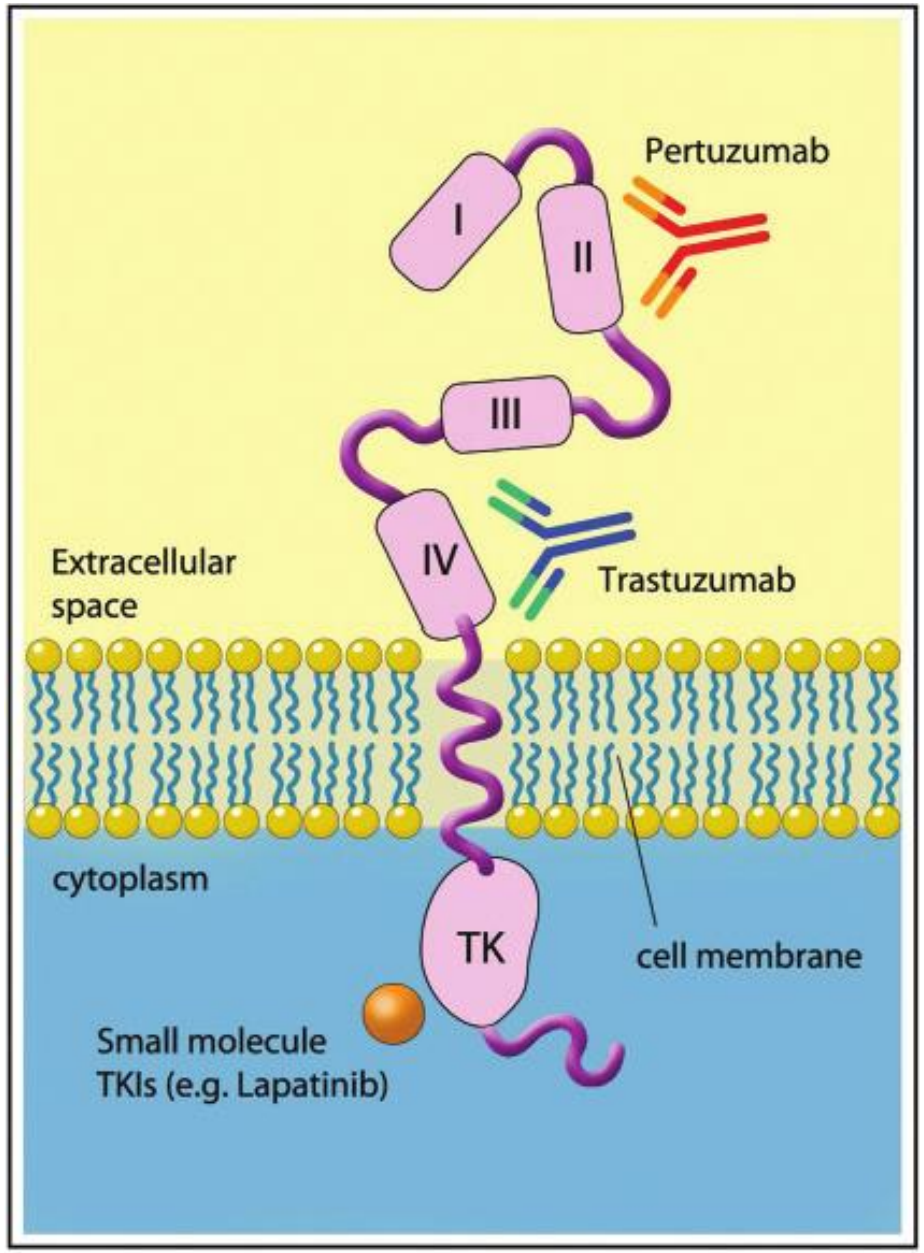
HER2 ISH (rechts)
Rot; *ErbB2* Signal
Grün; CEP17 Signal

IHC; immunohistochemistry; ISH; in-situ hybridization

1 Ahn S et al. J Pathol Transl Med 2020;54:34-44.; 2 Shigematsu H et al. World J Surg Oncol 2011;9:146.

HER2

- Wachstumsfaktor-Rezeptor[1]
  - 15-20% aller Brustkrebserkankungen HER2-positiv
  - HER2 als Antrieb des Tumorwachstums
- Diagnose mittels IHC und/oder ISH
- Therapie
  - Antikörper
  - Kleine Moleküle
  - Konjugate aus Antikörper und Chemotherapie



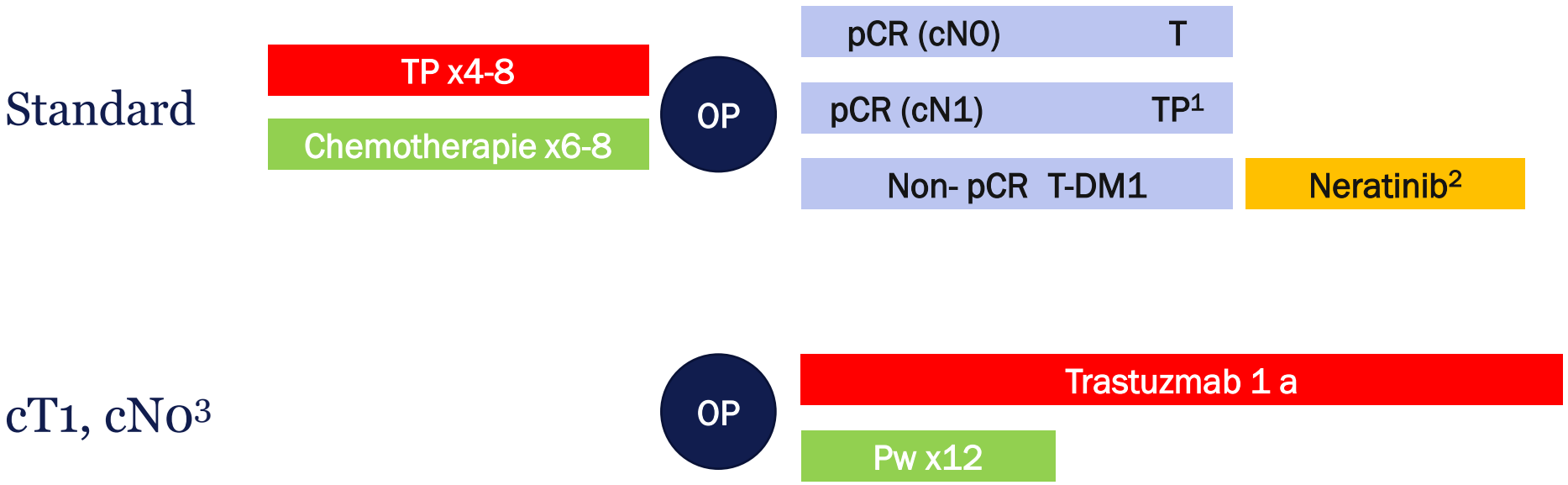
1 Slamon D et al. Science 1987;235:177-182.; 2 Image adapted from Okines AFC and Cunningham D. Ther Adv Gastroenterol 2012;5:301-318.

HER2-Therapie - Nebenwirkungen

- **Alle HER2-Medikamente**
  - Verminderte Herzleistung – v.a. bei Kombination mit Anthrazyklinen
  - Anstieg Leberfunktionswerte
  - Pneumonitis (sehr selten –bei T-DXd ~15%)

- **Spezielle Substanzen oder Kombinationen**
  - Trastuzumab + Pertuzumab: Durchfälle, Hautausschlag, Paronychie
  - Neratinib, Lapatinib, Tucatinib: Durchfälle
  - T-DM1: Verminderung der Blutplättchen, Neuropathie
  - T-DXd: Pneumonitis

Standards bei HER2-positivem eBC



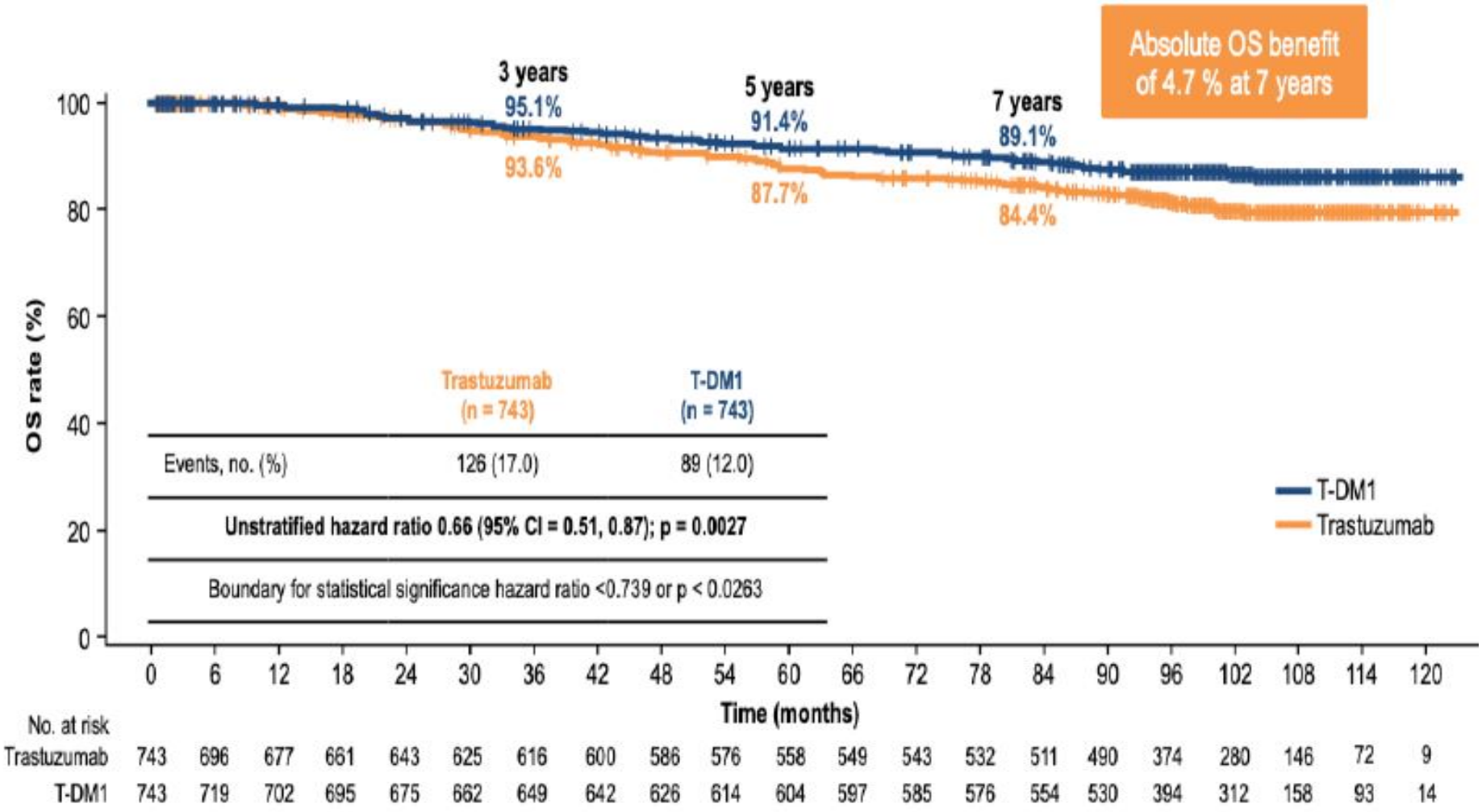
1 Postneoadjuvant TP in cN0 on an individual basis in the presence of further risk factors (e.g., cT3/4)

2 Extended adjuvant neratinib in luminal B/HER2-negative BC at increased recurrence risk

3 Potential standard in tumours <T2/N0; preferred cT1a,b

KATHERINE[1]

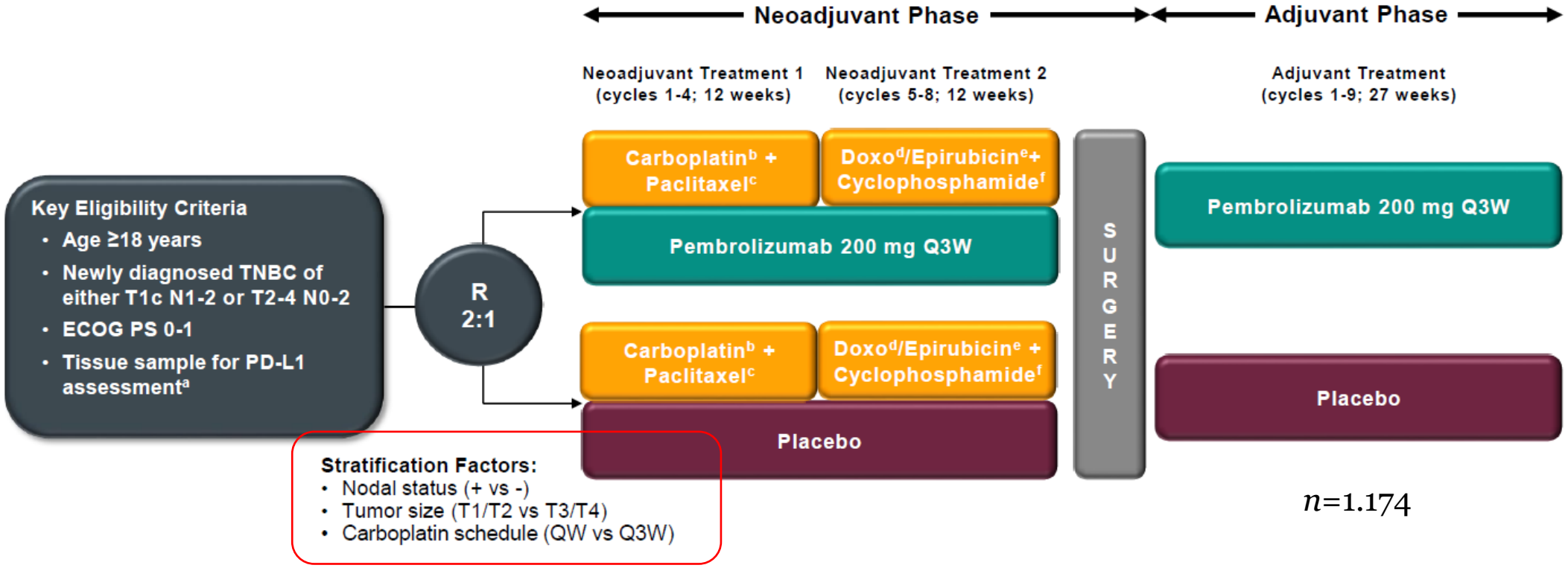
- Update SABCS 2023
  - mFU 8,4 Jahre
  - OS



1 Loibl S et al. GS03-12; SABCS 2023.

Keynote-522[1]

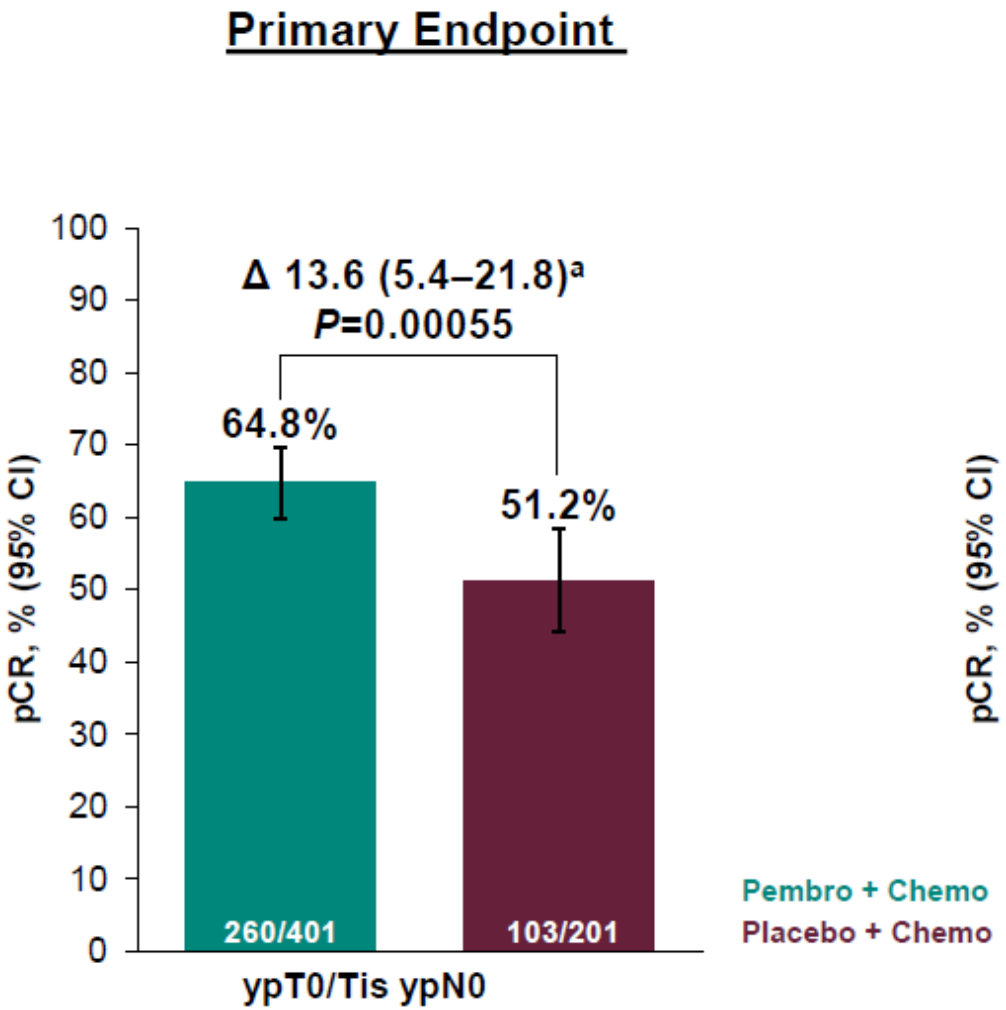
- Keynote-173: Hohe pCR Raten und akzeptables Verträglichkeitsprofil bei Kombination von IT mit Standardchemotherapie plus Carboplatin[2]



1 Schmid P et al. N Engl J Med 2020;382:810-821.; 2 Schmid P et al. Abstr.#556; ASCO 2017.

Regulation der Immunantwort

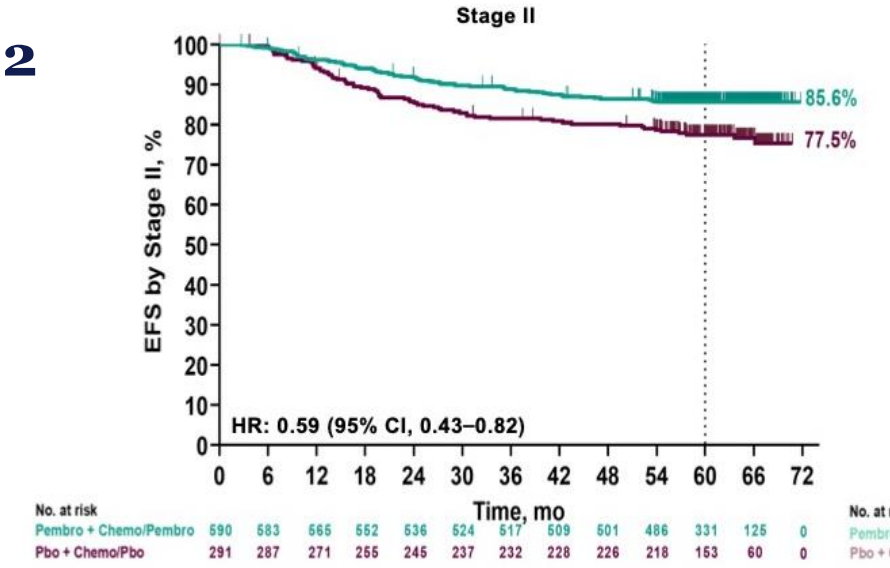
- Addition von Pembrolizumab zu präoperativer Chemotherapie verbessert die Wirksamkeit und senkt das Rückfallrisiko

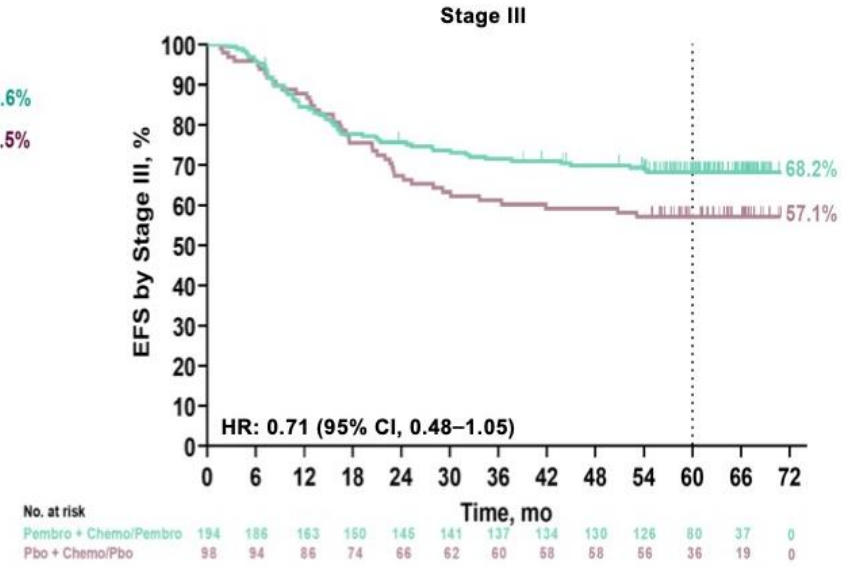


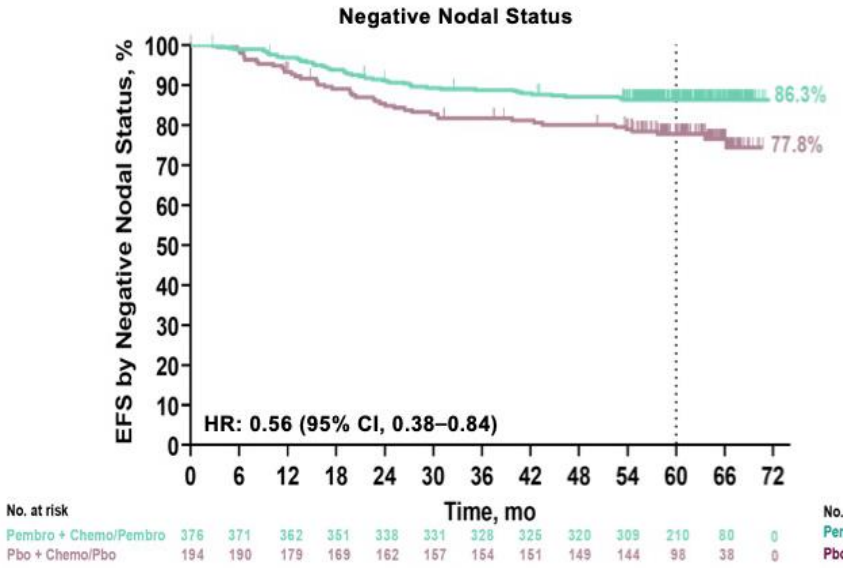
1 Schmid P et al. N Engl J Med 2020;382:810-821.; 2 Schmid P et al. Abstr.#556; ASCO 2017.

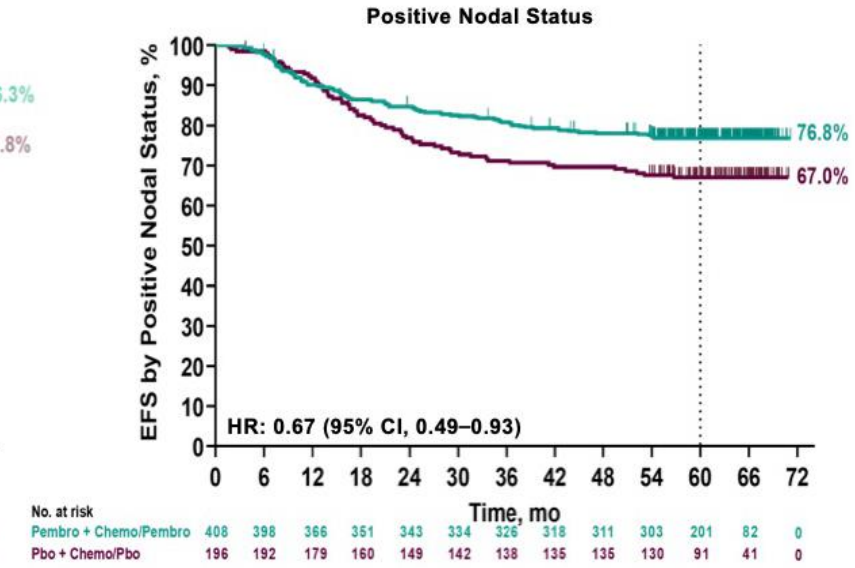
KEYNOTE-522[1,2]

- Update SABCS 2023[1]
  - mFU 63,1 Monate
  - Subgruppen IA6[2]





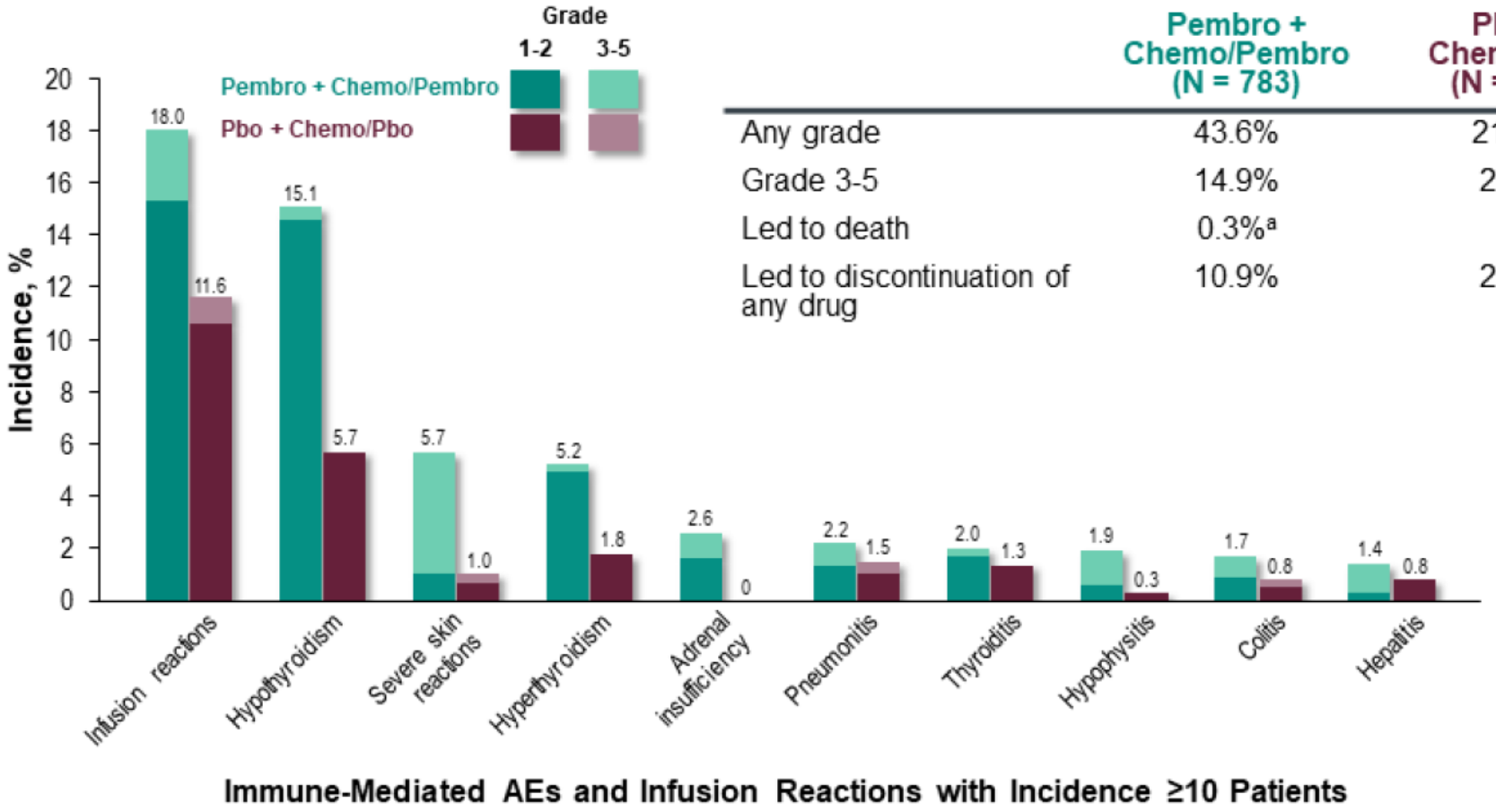




1 Schmid P et al. LA01-01; SABCS 2023.; 2 Schmid P et al. LBA18; ASCO 2023.

Immuntherapie – Nebenwirkungen[1]

Immune-Mediated AEs and Infusion Reactions in Combined Phases



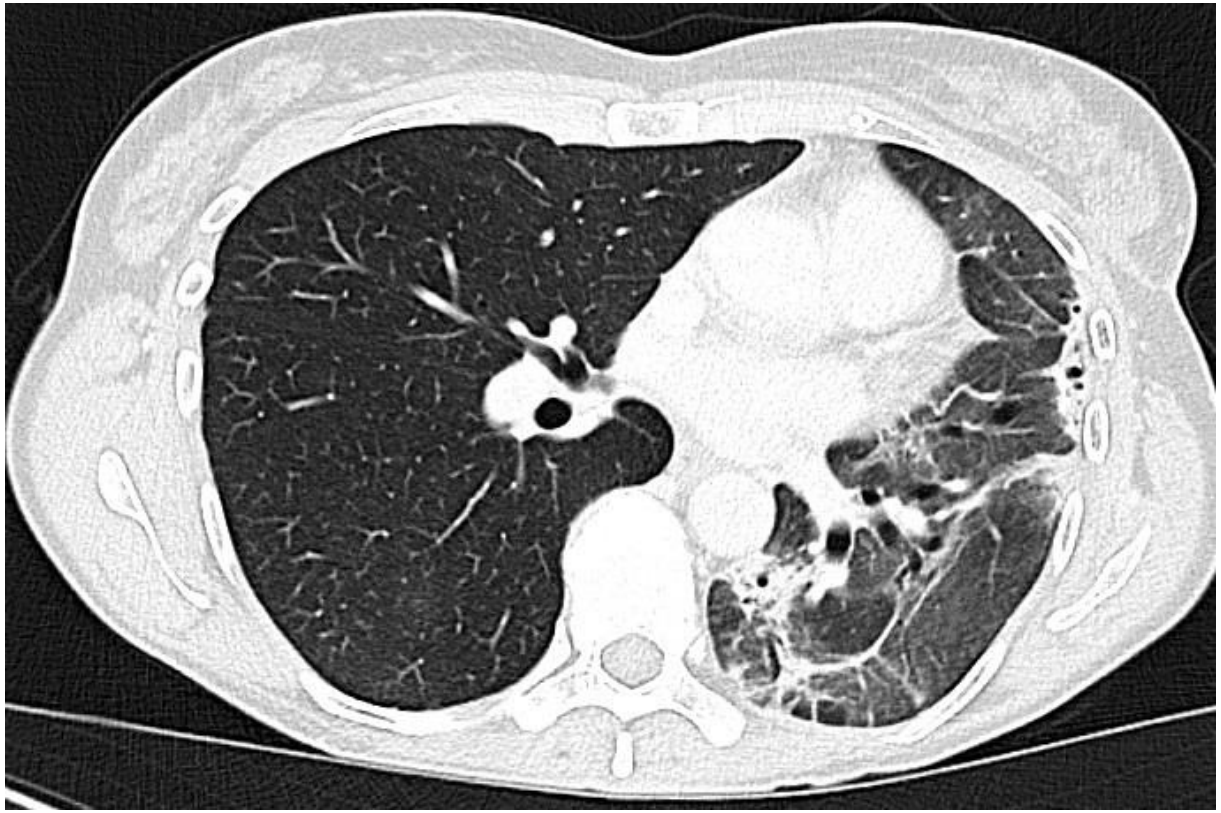
	Pembro + Chemo/Pembro (N = 783)	Pbo + Chemo/Pbo (N = 389)
Any grade	43.6%	21.9%
Grade 3-5	14.9%	2.1%
Led to death	0.3%[a]	0
Led to discontinuation of any drug	10.9%	2.6%

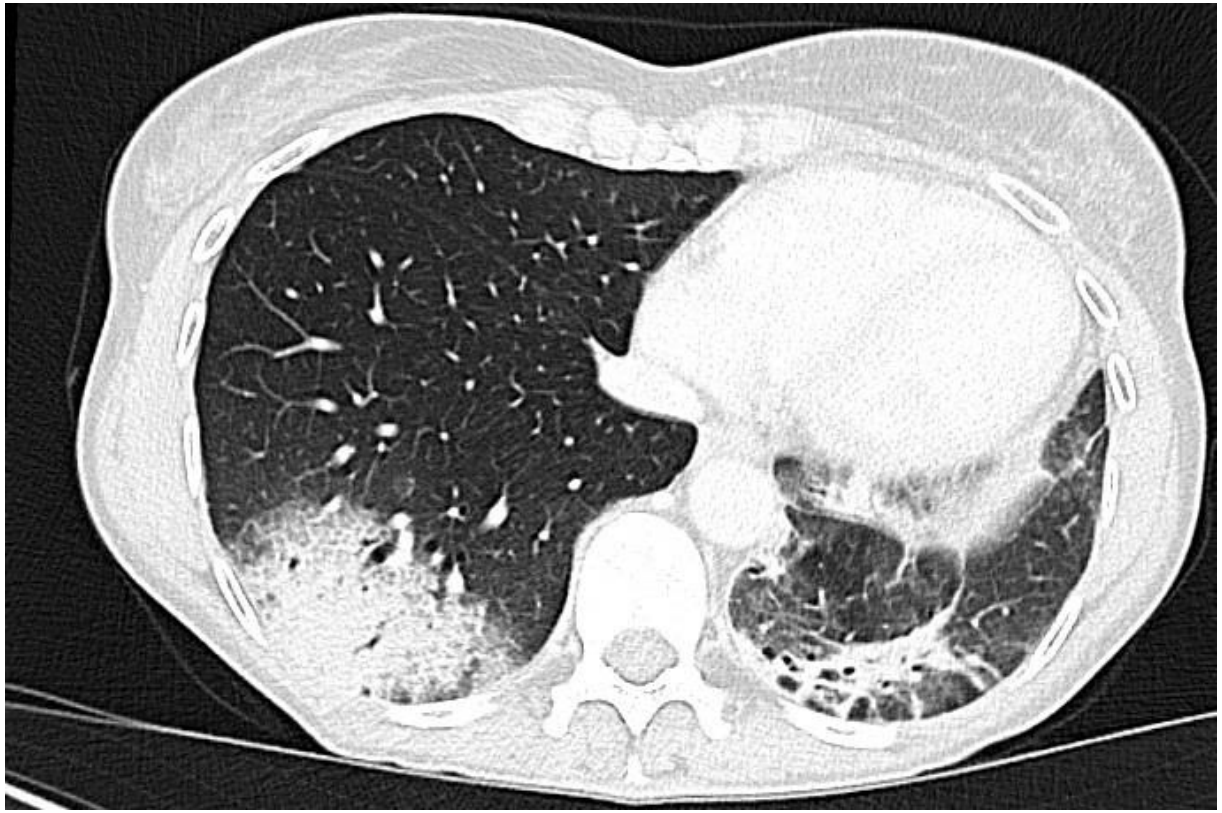
Immune-Mediated AEs and Infusion Reactions with Incidence ≥10 Patients

1 Schmid P et al. Abstr. VP7; ESMO 2021.

irAEs

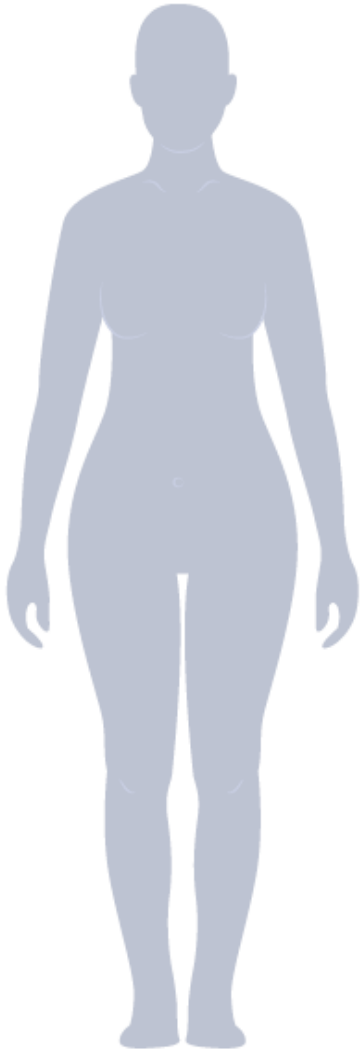
Pneumonitis





Images courtesy of Prof. Kapetas, Department of Radiology, Medical University of Vienna

irAEs[1]



- Myasthenia gravis
- Guillain–Barré
- Ocular toxicity
- Dermatitis
- Pruritus
- Vitiligo
- Oesophagitis
- Pneumonitis
- Persistent wheezing/coughing
- Hepatitis
- Colitis/diarrhoea
- Coeliac disease
- Neuropathy
- Hypophysitis
- Mucositis
- Xerostomia
- Thyroiditis/ hypothyroidism
- Myocarditis
- Adrenal insufficiency
- Pancreatic insufficiency
- Diabetes*
- Arthritis

Possible incidence of development into subacute/chronic toxicity

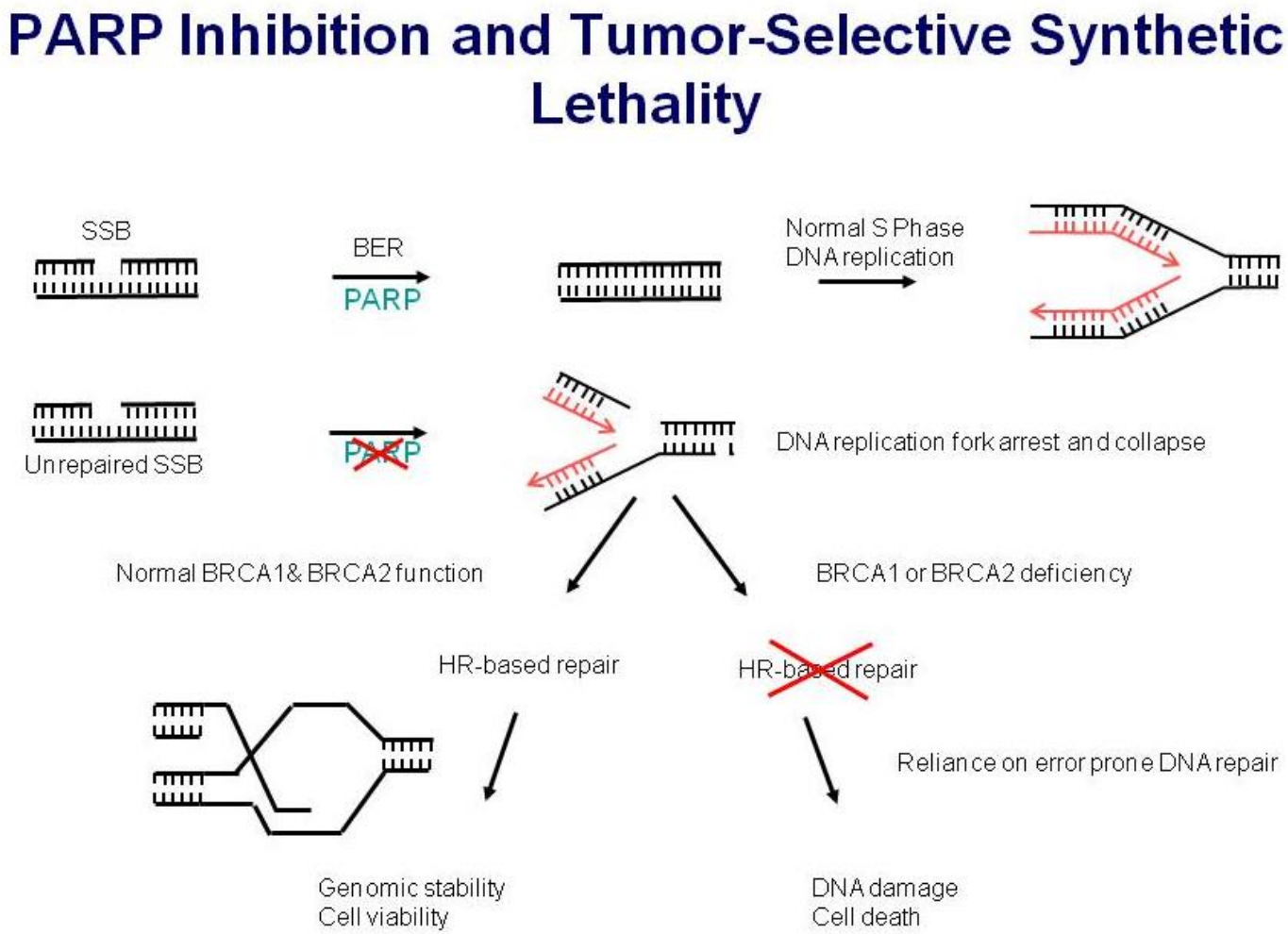
- 80–100%
- 60–80%
- 40–60%
- 20–40%
- 0–20%
- Unknown/<5 cases

*<5 cases in our series but reportedly high rates of chronicity in other series

1 Johnson DB et al. Nat Rev Clin Oncol 2022;19:254-267.

DNA Schäden und Reparatur

- PARP: Gerüst an Hand dessen Schäden an einem DNA Strang repariert werden
- BRCA für Reparatur von Doppelstrangbrüchen notwendig
- PARP-Blockade und *BRCA* Mutation - Zelltod

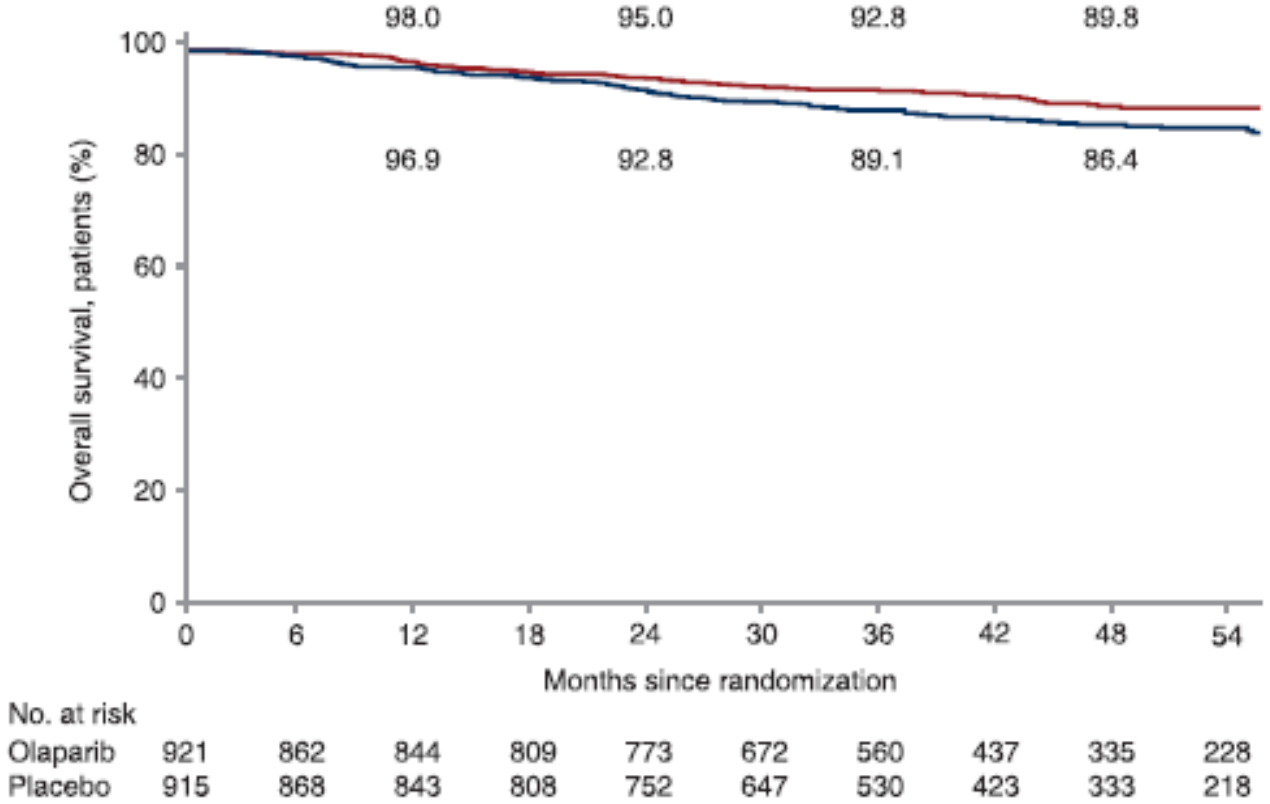


1 Tan RA et al. J Clin Oncol 2010;25(Suppl.18):233S.; 2 Farmer H et al. Nature 2005;434:917-921.

OlympiA: OS[1]

- Overall Survival

mFU 3.5



Olaparib, 75 deaths
Placebo, 109 deaths

Difference: 4-year OS rate
3.4% (95% CI –0.1% to 6.8%)

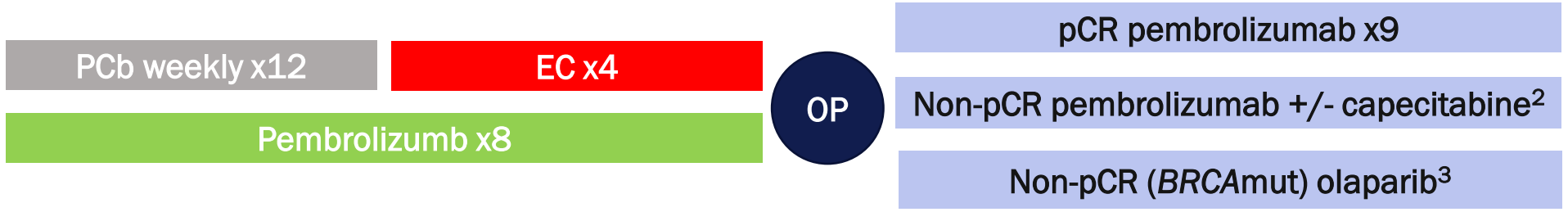
Difference: 3-year OS rate
3.8%[a] (95% CI 0.9% to 6.6%)

Stratified hazard ratio, 0.68
(98.5% CI 0.47-0.97)
P = 0.009

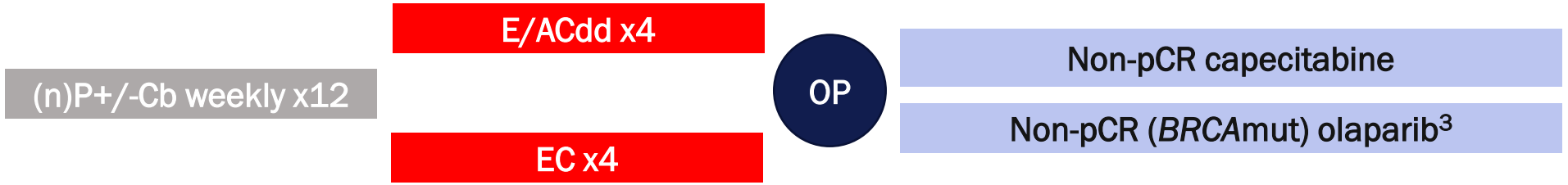
1 Geyer CE et al. Ann Oncol 2022;33:1250-1268.

Potential Standards in eTNBC

Stage II/III[1]



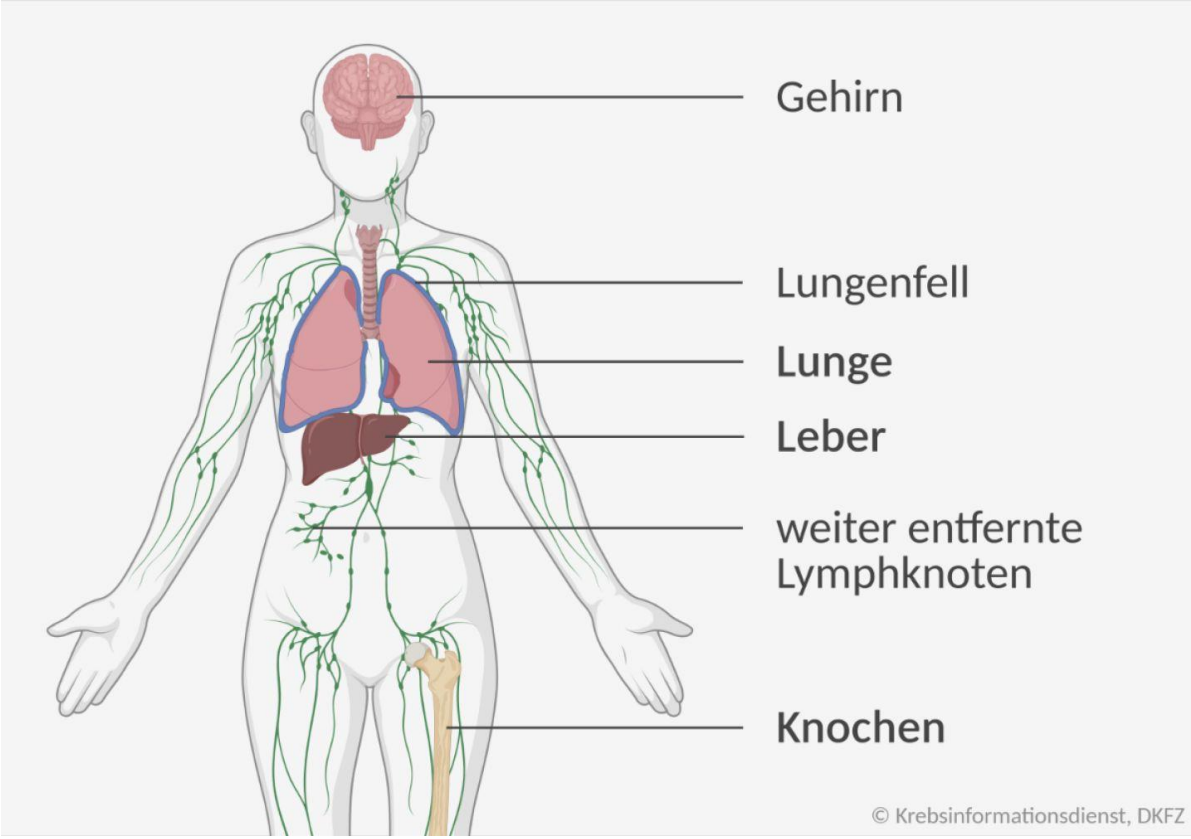
Alternative options (e.g., stage I)[4]



1 Inclusion Criteria KN522: ≥T2; T1 and N1
2 Postneoadjuvant capecitabine plus pembrolizumab not based upon clinical evidence
3 Postneoadjuvant olaparib plus pembrolizuman on an individual basis in the absence of clinical evidence
4 Optimal approach for stage I TNBC not defined (only GeparSepto included stage I disease)

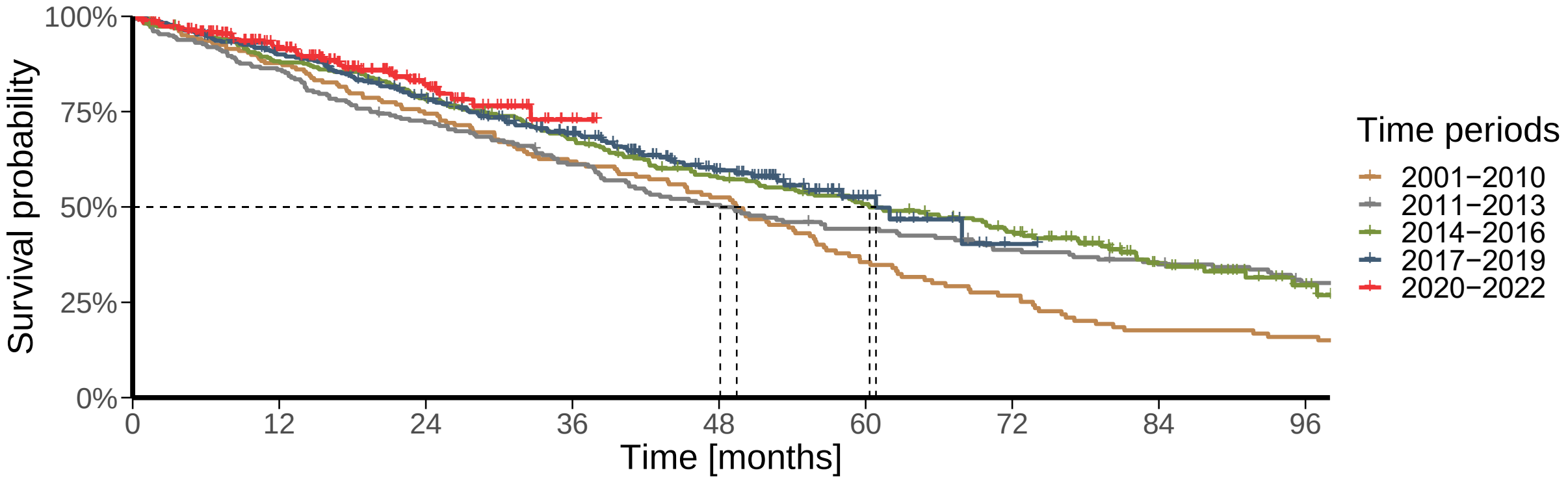
Fortgeschrittener Brustkrebs

- Brustkrebs mit Fernmetastasen gilt als unheilbare Erkrankung
- Ziele:
  - Erhalt der Lebensqualität
  - Vermeidung/Behandlung von Beschwerden die Zusammenhang mit der Erkrankung stehen
  - Chronifizierung - Verlängerung des Überlebens
  - Antihormonelle Therapie
  - Anti-HER2 Therapie
  - Chemotherapie nur wenn notwendig



Graduelle OS Verbesserung[1,2]

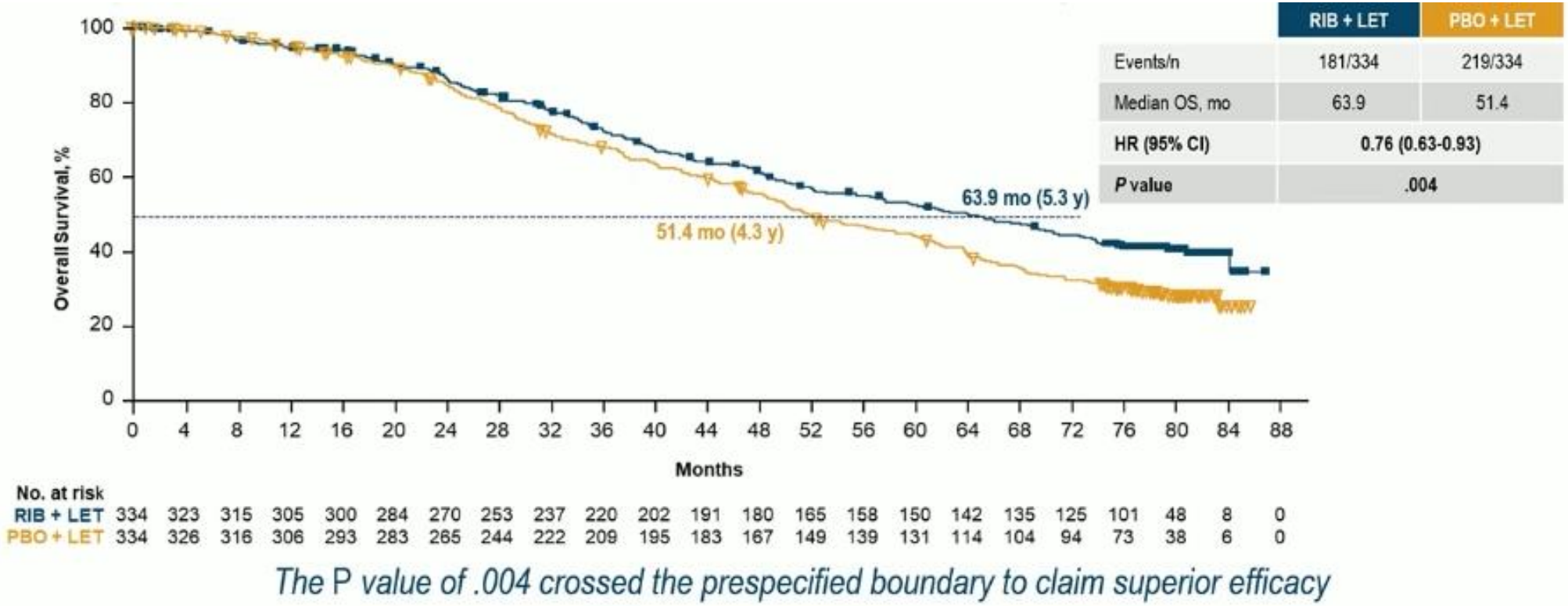
- Verbesserung des Gesamtüberlebens bei HR pos./HER2 neg. mBC 2001-2022 – AGMT Register



1 Rinnerthaler G et al. P04-04-14; SABC 2023.

MonaLEEsa-2[1,2]

- OS



Letrozol+/-Ribociclib
First-line
mFUP 80 Monate

1 Hortobagyi GN et al. Abst. LBA17_PR; ESMO 2021.; 2 Hortobagyi GN et al. Engl J Med 2022;386:942-950.

Potentielle Standards bei luminalen mBC

ET + CDKi

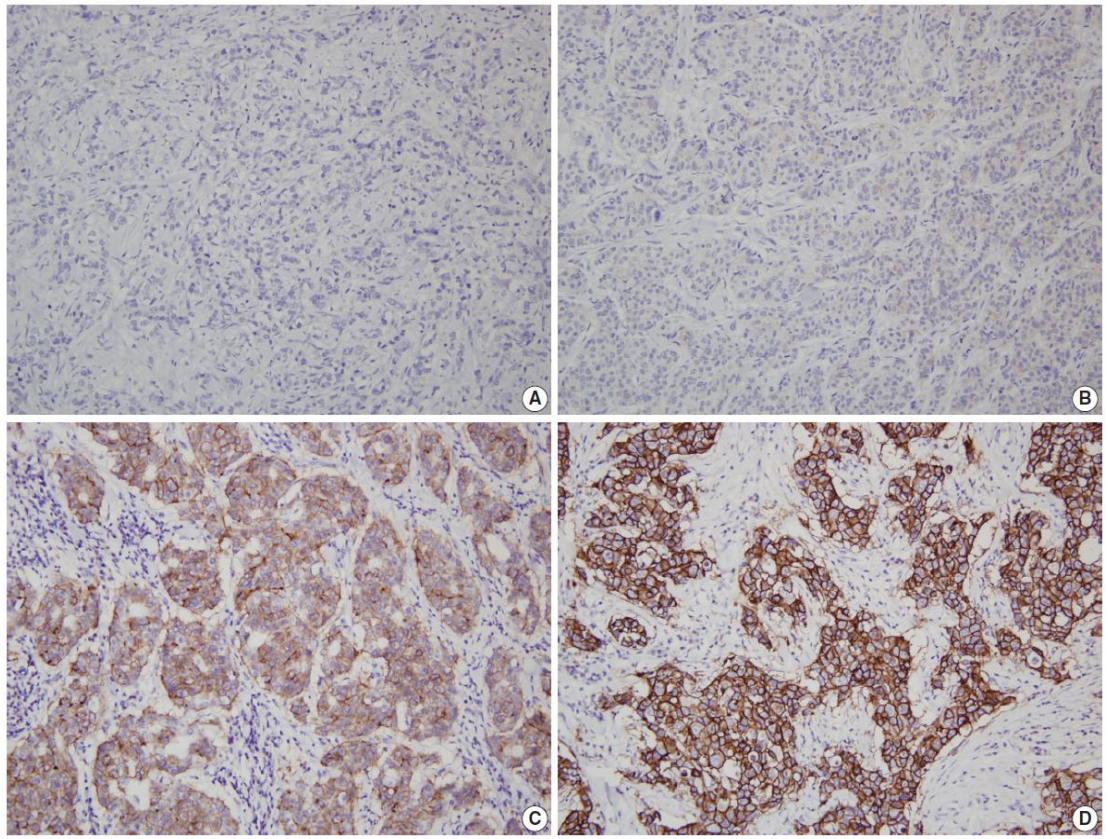
Scenario	Potential 2nd-line
*ESR1*mut, PFS 1st-line ≥12 months, non-high risk	elacestrant
*PIK3CA*mut	alpelisib + ET*
*BRCA*mut	PARPi
*ESR1*wt, *PIK3CA*wt, *BRCA*wt	everolimus + ET* or ribociclib + ET* (in case of prolonged CDKi benefit 1st-line)
HER2 low, high-risk, endocrine resistance	chemotherapy§ or T-DXd
HER2 0 neg., high-risk, endocrine resistance	Chemotherapy§ or SG

Alternative ET* +/- targeted therapy or chemotherapy or ADC depending upon prior treatment, risk profile and disease biology

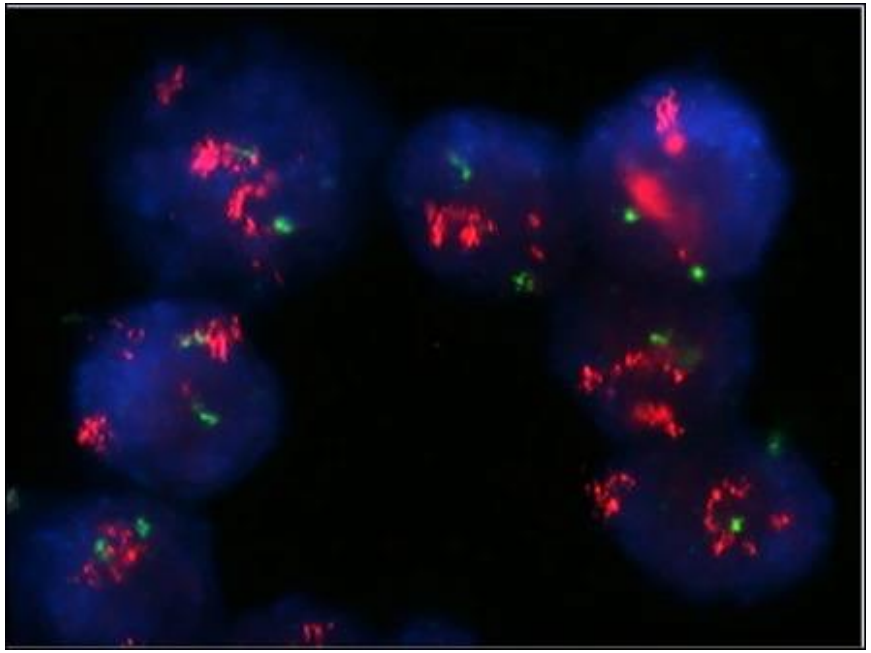
*depending upon prior therapy; §DPYD testing for capecitabine

HER2

- HER2 IHC[1] und ISH[2]



HER2 IHC (links)
A, HER2 negativ
B, HER2 1+
C, HER2 2+
D, HER2 3+



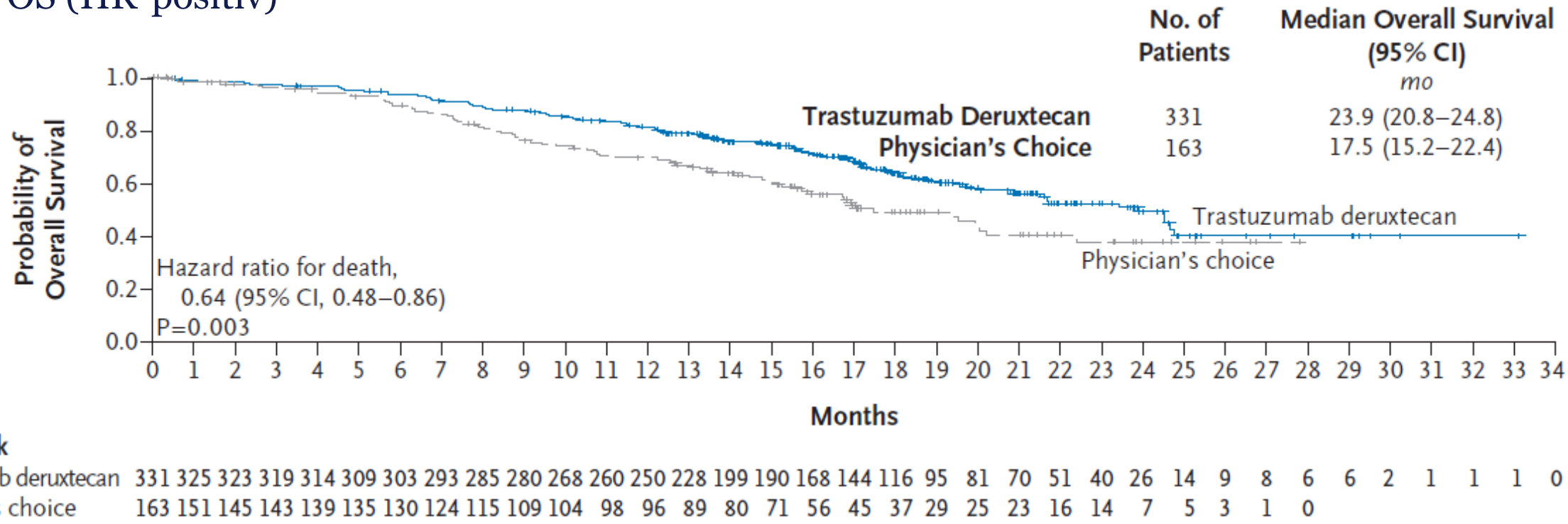
HER2 ISH (rechts)
Rot; *ErbB2* Signal
Grün; CEP17 Signal

IHC; immunohistochemistry; ISH; in-situ hybridization

1 Ahn S et al. J Pathol Transl Med 2020;54:34-44.; 2 Shigematsu H et al. World J Surg Oncol 2011;9:146.

DESTINY-Breast04[1,2]

- OS (HR-positiv)



1 Modi S et al. Abst. LBA3; ASCO 2022.; 2 Modi S et al. N Engl J Med 2022;387:9-20.

TROP2

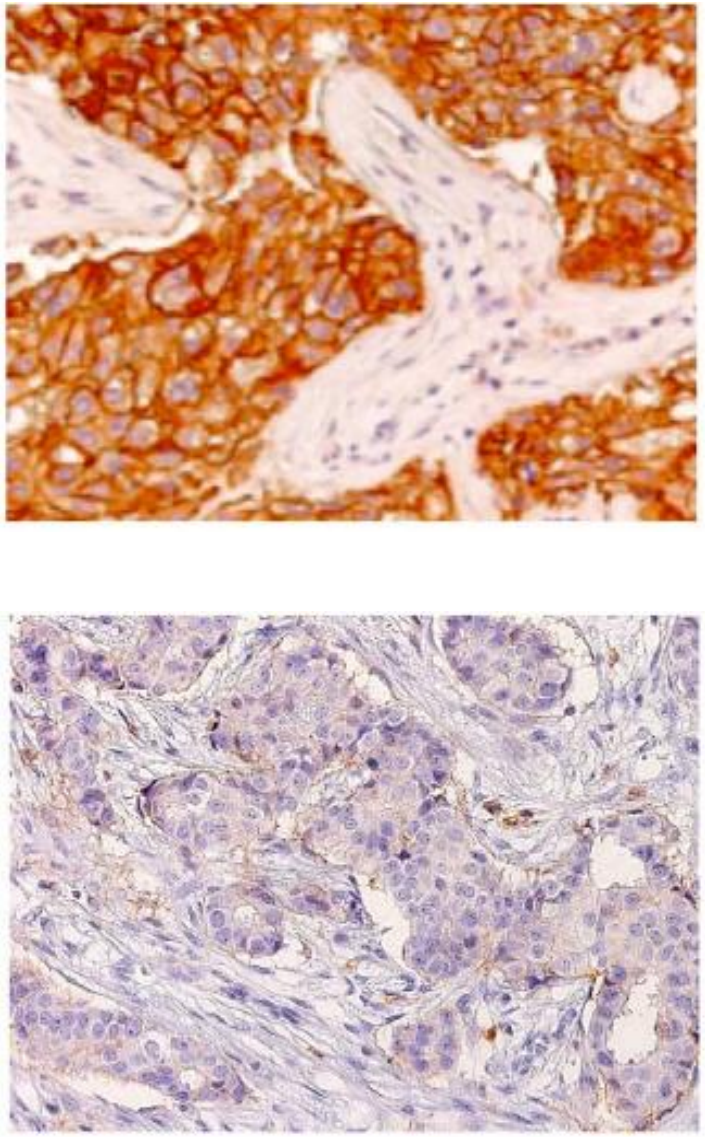
- Tumor-associated calcium signal transducer 2; Trophoblast cell-surface antigen 2
- Transmembranöses Glykoprotein kodiert durch das *TACSTD2* Gen

- TROP2 spielt einer kritische Rolle in der embryonalen Entwicklung (Placentaformation, embryonale Implantation, Stammzellproliferation, Organentwicklung)[1]

- *TACSTD2* Gen Knockout reduziert die Proliferation von Tumorzellen[2,3] - Trop2 Upregulation steigert Tumorwachstum[2]

- Trop2 interagiert mit anderen Faktoren die zum Tumorwachstum beitragen (IGF-1, claudin-1 und 7, cyclin D1, PKC) und aktiviert die ERK/MAPK Signaltransduktion[4]

- TROP2 Expression wird von zahlreichen onkogenen Transkriptionsfaktoren reguliert: CREB1, nuclear factor-κB, HOXA10, HNF4A, TP63, TP53, ERG, HNF1A/TCF-1, FOXP3[5,6]



High (above) and low (below) Trop2 expression in NST breast cancer[7]

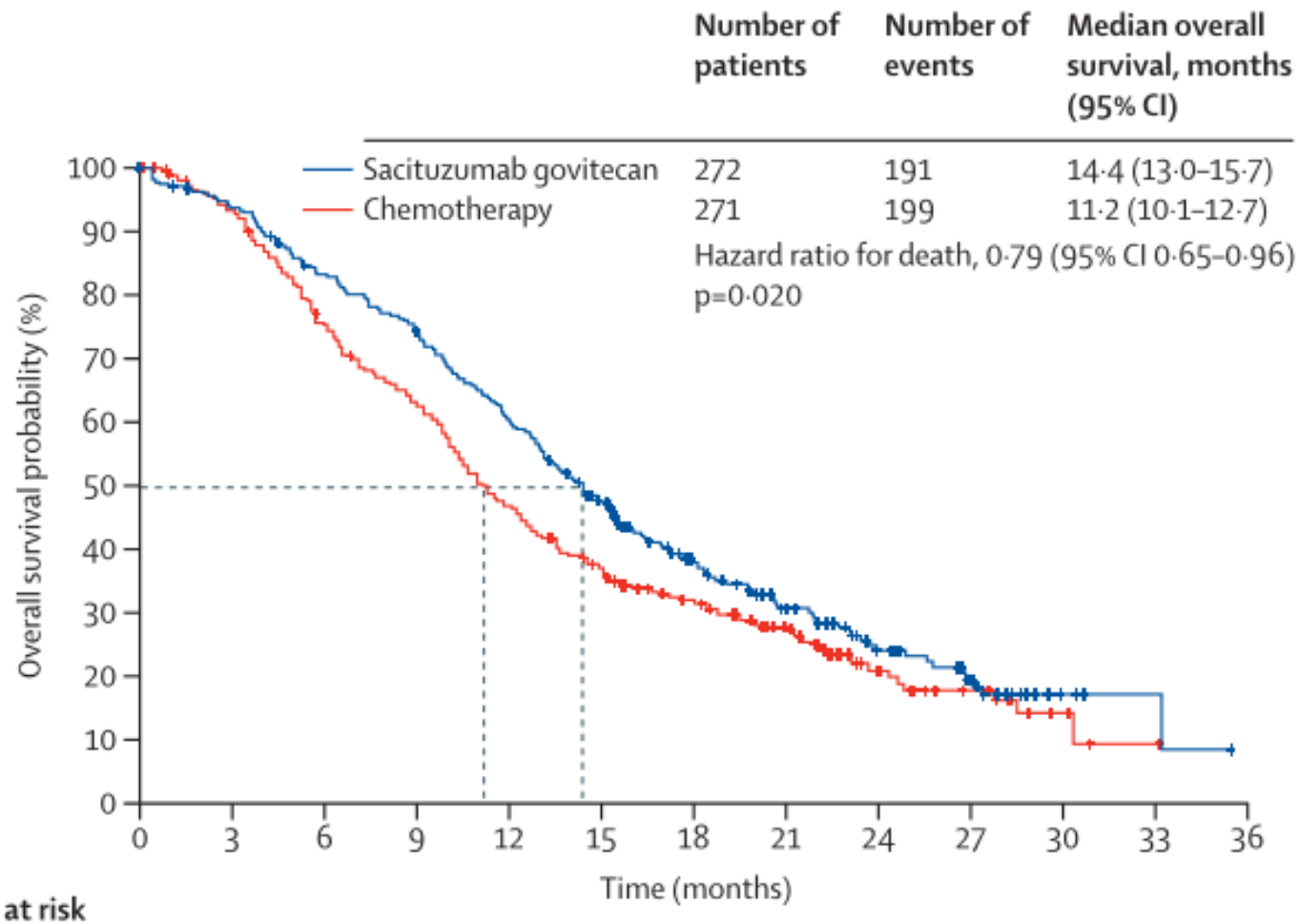
1 Cubas R et al. Biochim Biophys Acta. 2009;1796:309-314.; 2 Trerotola M et al. Oncogene 2013;32:222-233., 3 Liu T et al. PLoS One 2013;8:e75864.; 4 reviewed in: Shvartsur A and Bonavida B. Genes Cancer 2015; 6: 84–105.; 5 Guerra E et al. Oncogene. 2013;32:1594-1600.; 6 Zaman S et al. Onco Targets Ther 2019;12:1781-1790.; 7 Ambrogi F et al. PLoS One 2014;9: e110606.

TROPIcS-02[1,2]

- OS Update[2]
- Medianes FU 12,5 Monate

- RR 21% *vs.* 14%; OR 1,63; 95% CI 1,03-2,56; *p*=0,035

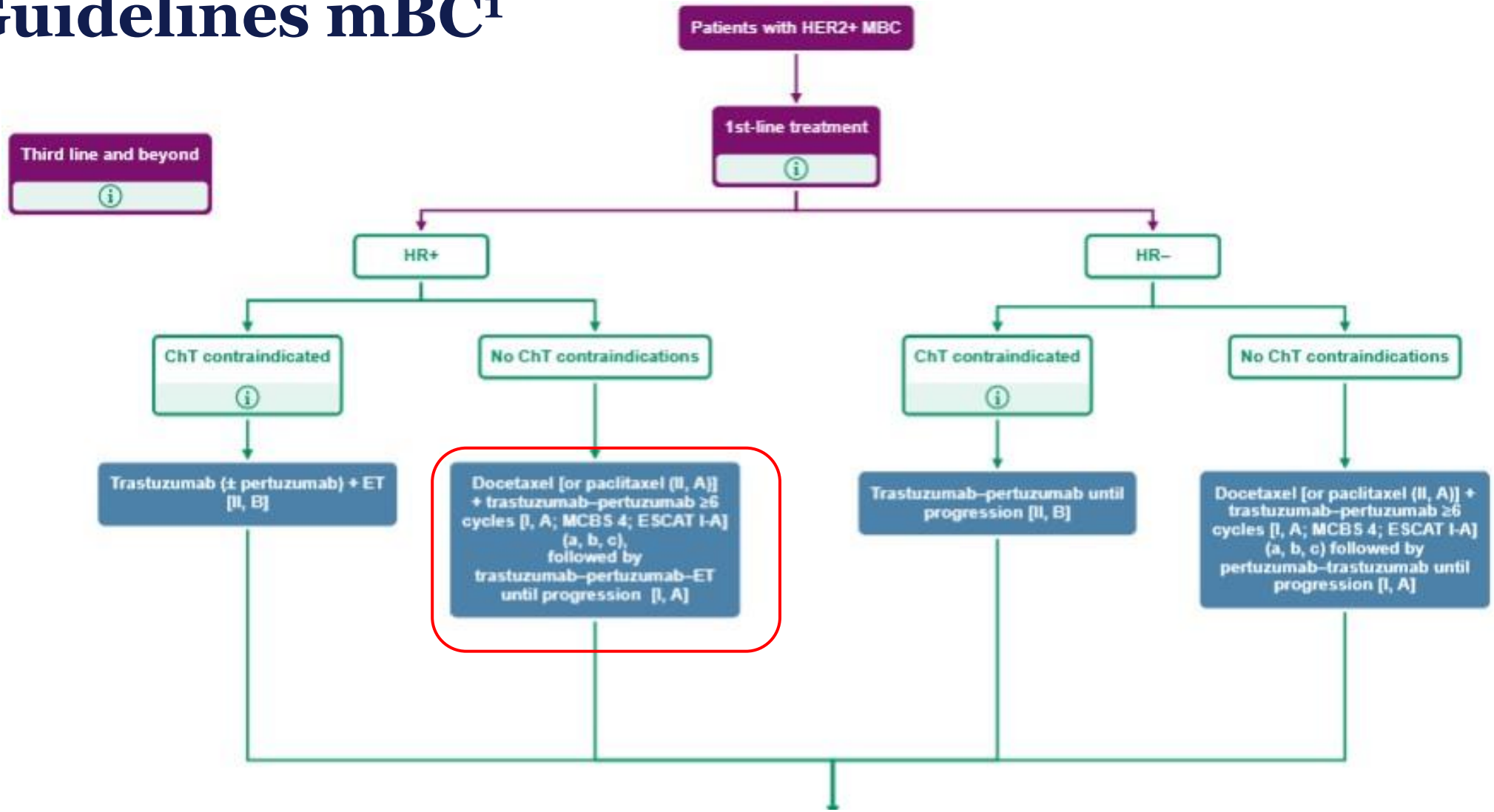
- Time to deterioration von GHS und QoL 4,3 Monate *vs.* 3,0 Monate (HR 0,75; 95% CI 0,61-0,92; *p*=0,0059)



1 Rugo H et al. LBA76; ESMO 2022.; 2 Rugo HS et al. Lancet 2023;online ahead of print.

ESMO Guidelines mBC[1]

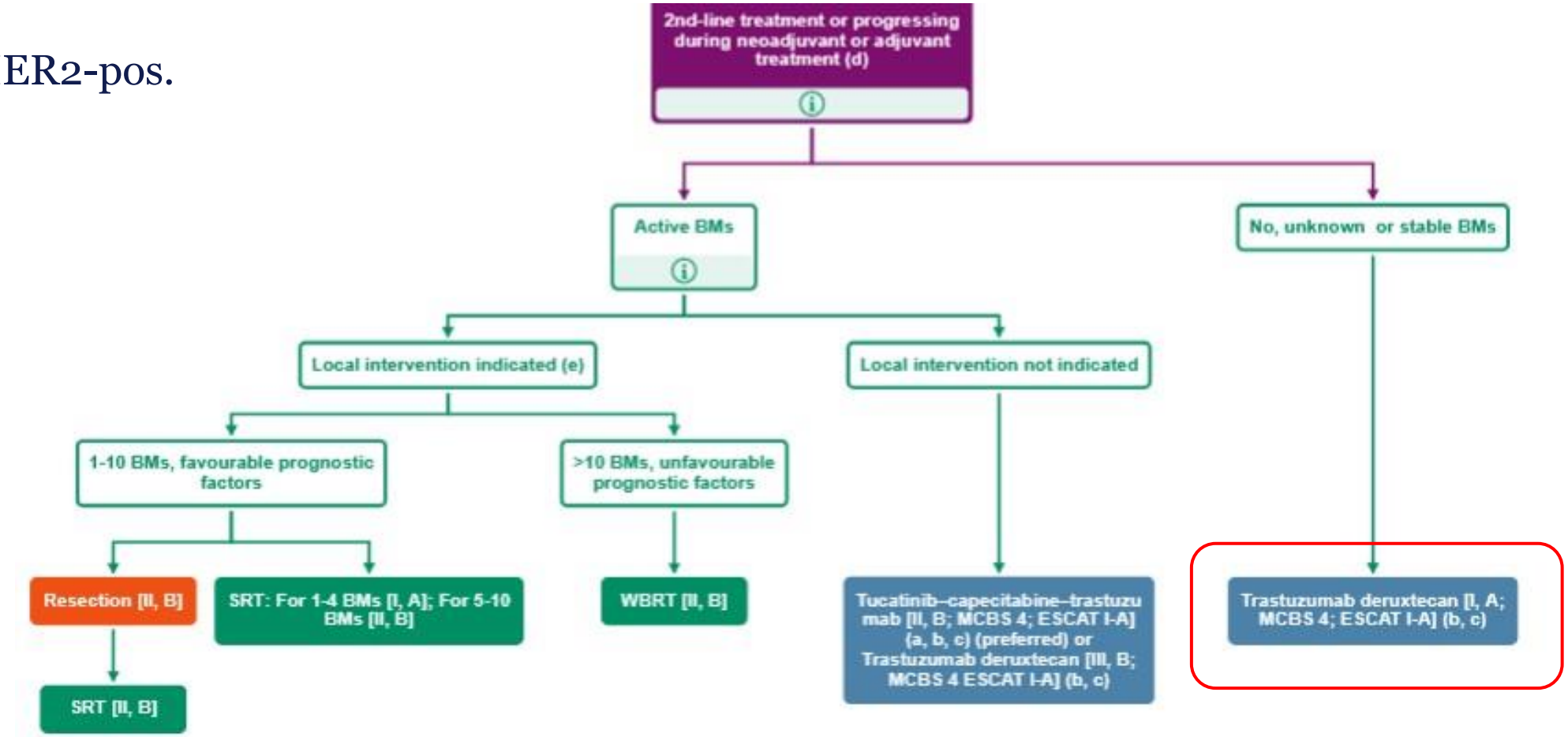
- HER2-pos.



1 Available at: https://www.esmo.org/living-guidelines/esmo-metastatic-breast-cancer-living-guideline/her2-positive-breast-cancer; last accessed December 14°, 2023.

ESMO Guidelines mBC[1]

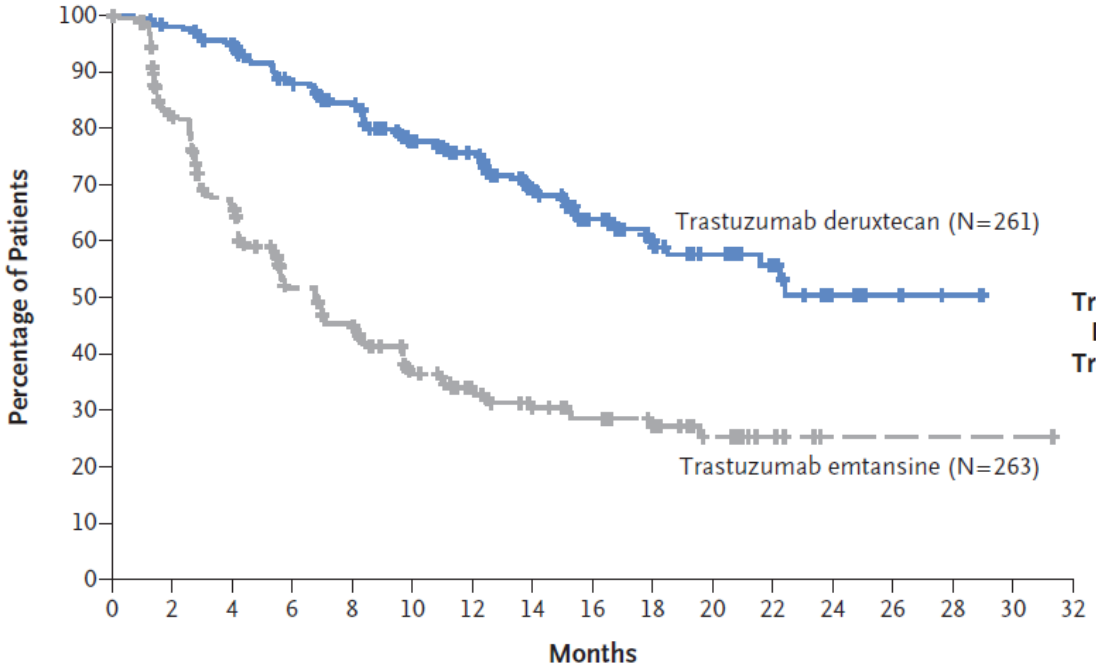
- HER2-pos.



1 Available at: https://www.esmo.org/living-guidelines/esmo-metastatic-breast-cancer-living-guideline/her2-positive-breast-cancer; last accessed December 14°, 2023.

DESTINY-Breast03[1,2]

- Primäre Endpunktanalyse: PFS nach unabhängigem Review



No. at Risk																
Trastuzumab deruxtecan	261	250	240	214	200	168	150	112	79	53	36	25	10	5	2	
Trastuzumab emtansine	263	200	155	108	93	65	51	37	29	21	12	6	1	1	1	0

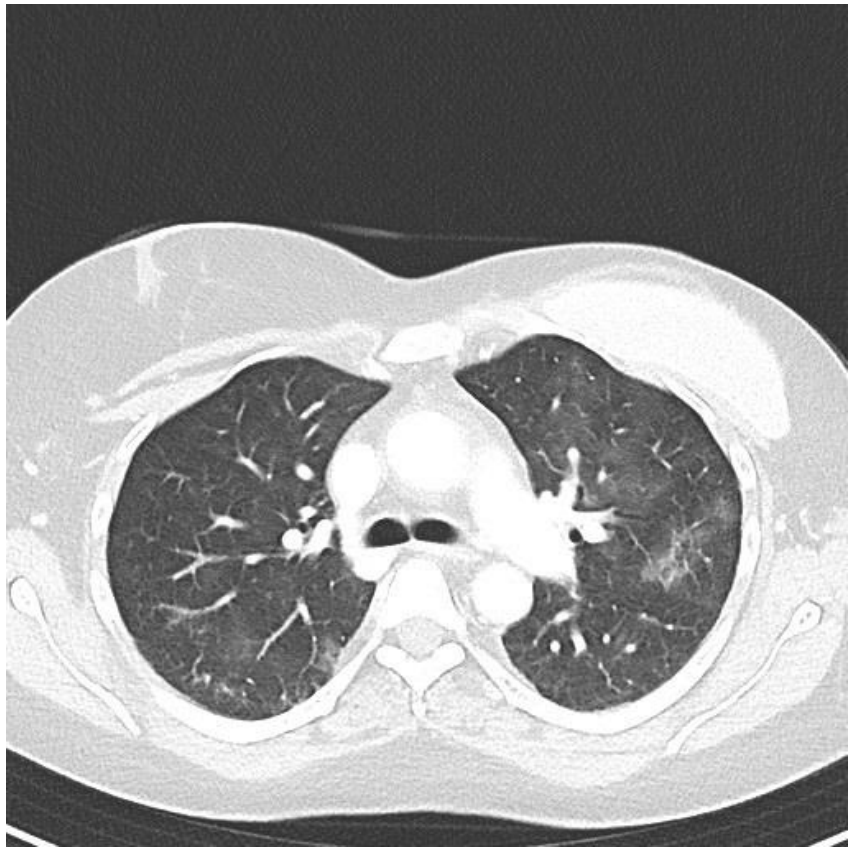
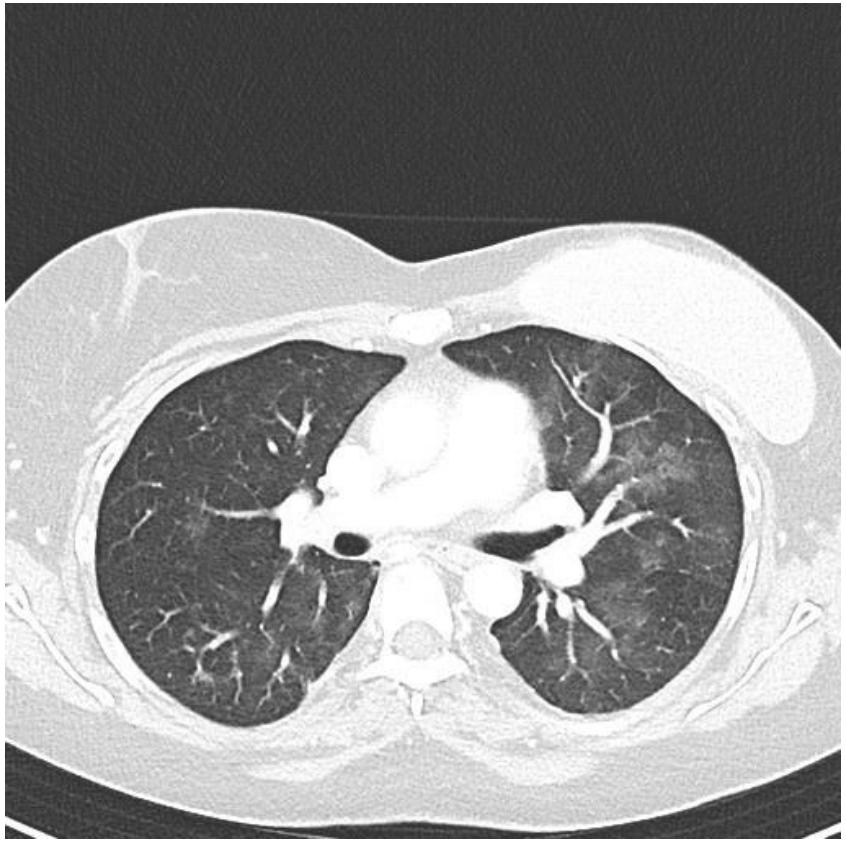
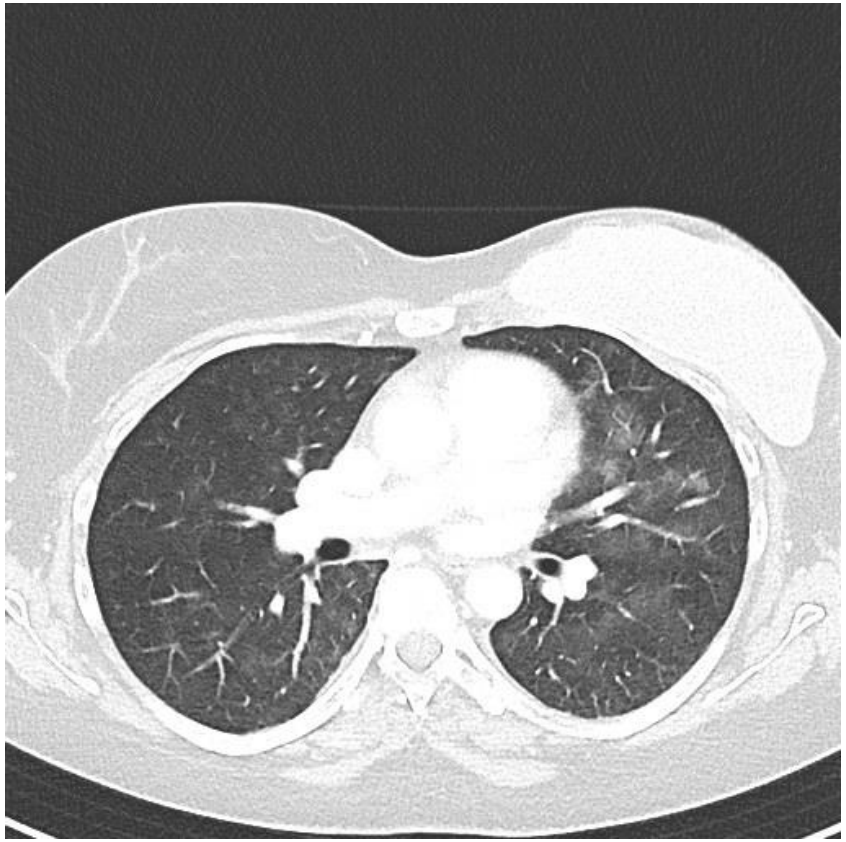
	Median Progression-free Survival (95% CI)	12-Mo Progression-free Survival (95% CI)
	mo	%
Trastuzumab Deruxtecan	NR (18.5–NE)	75.8 (69.8–80.7)
Trastuzumab Emtansine	6.8 (5.6–8.2)	34.1 (27.7–40.5)

Hazard ratio for disease progression or death, 0.28 (95% CI, 0.22–0.37)
P<0.001

1 Cortes J et al. Abstr. LBA1; ESMO 2021.; 2 Cortes J et al. N Engl J Med. 2022;386:1143-1154.

ILD

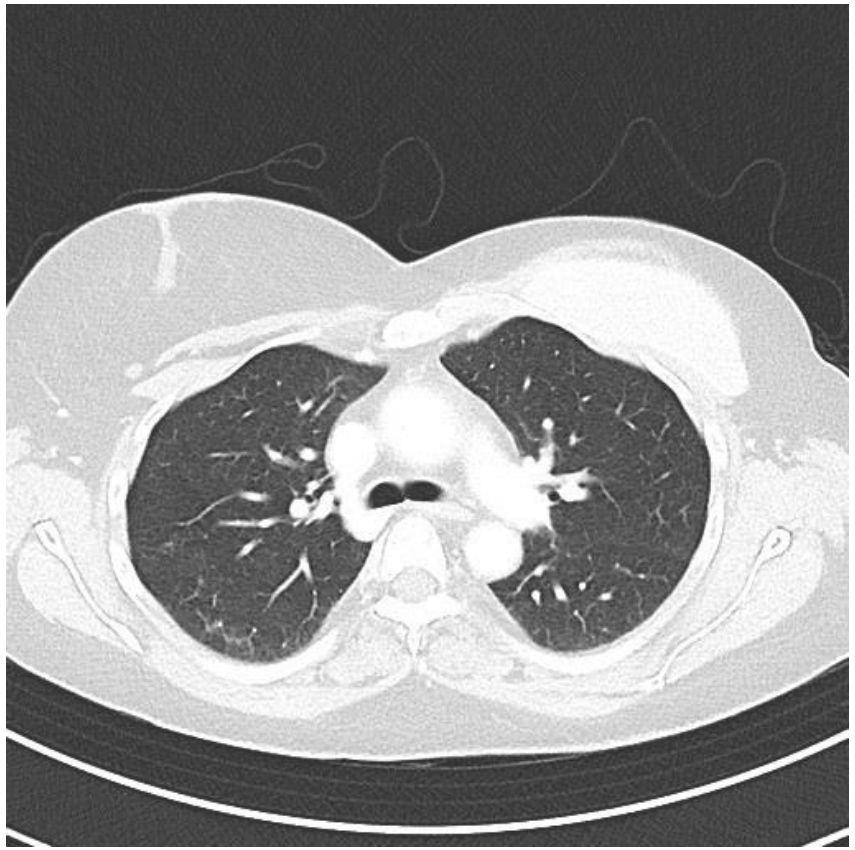
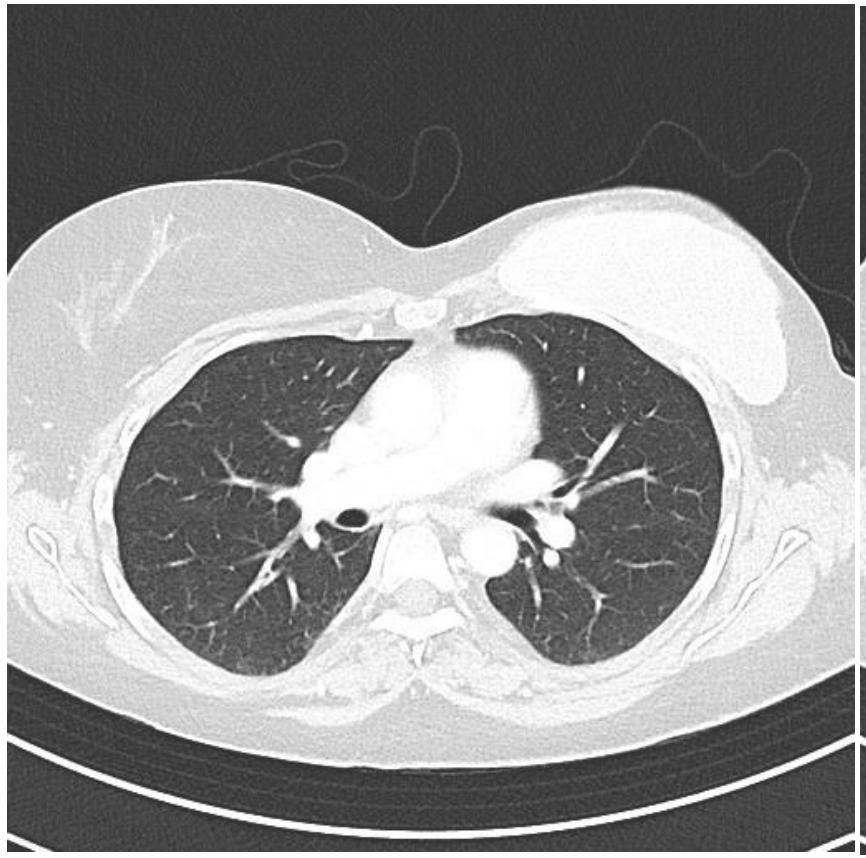
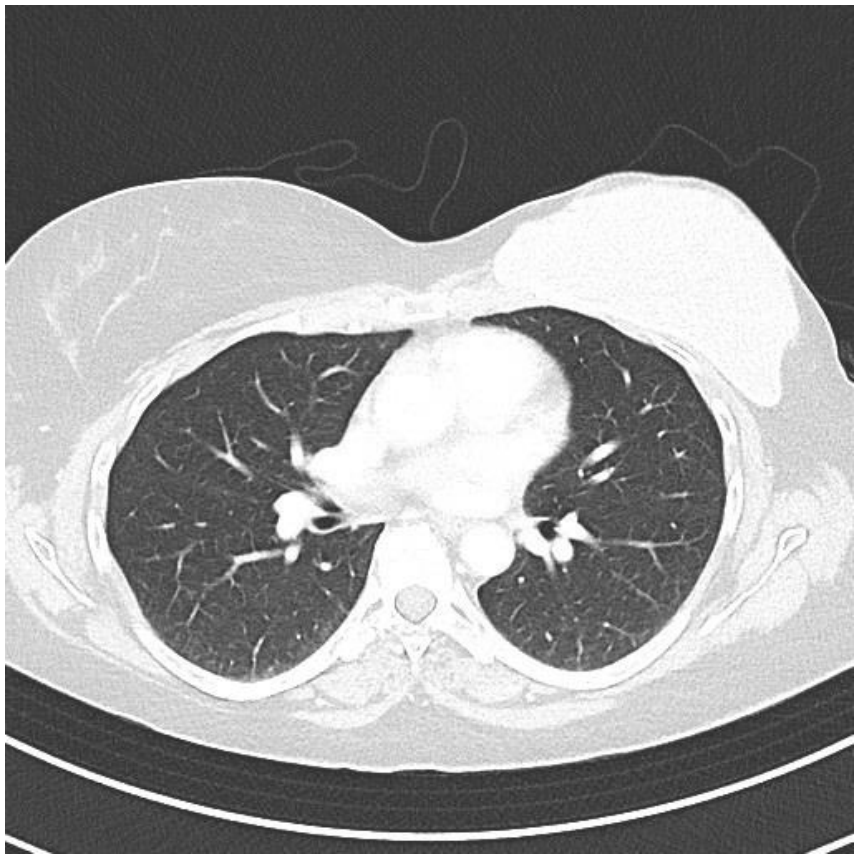
- ILD Grad 2

08/2021

ILD

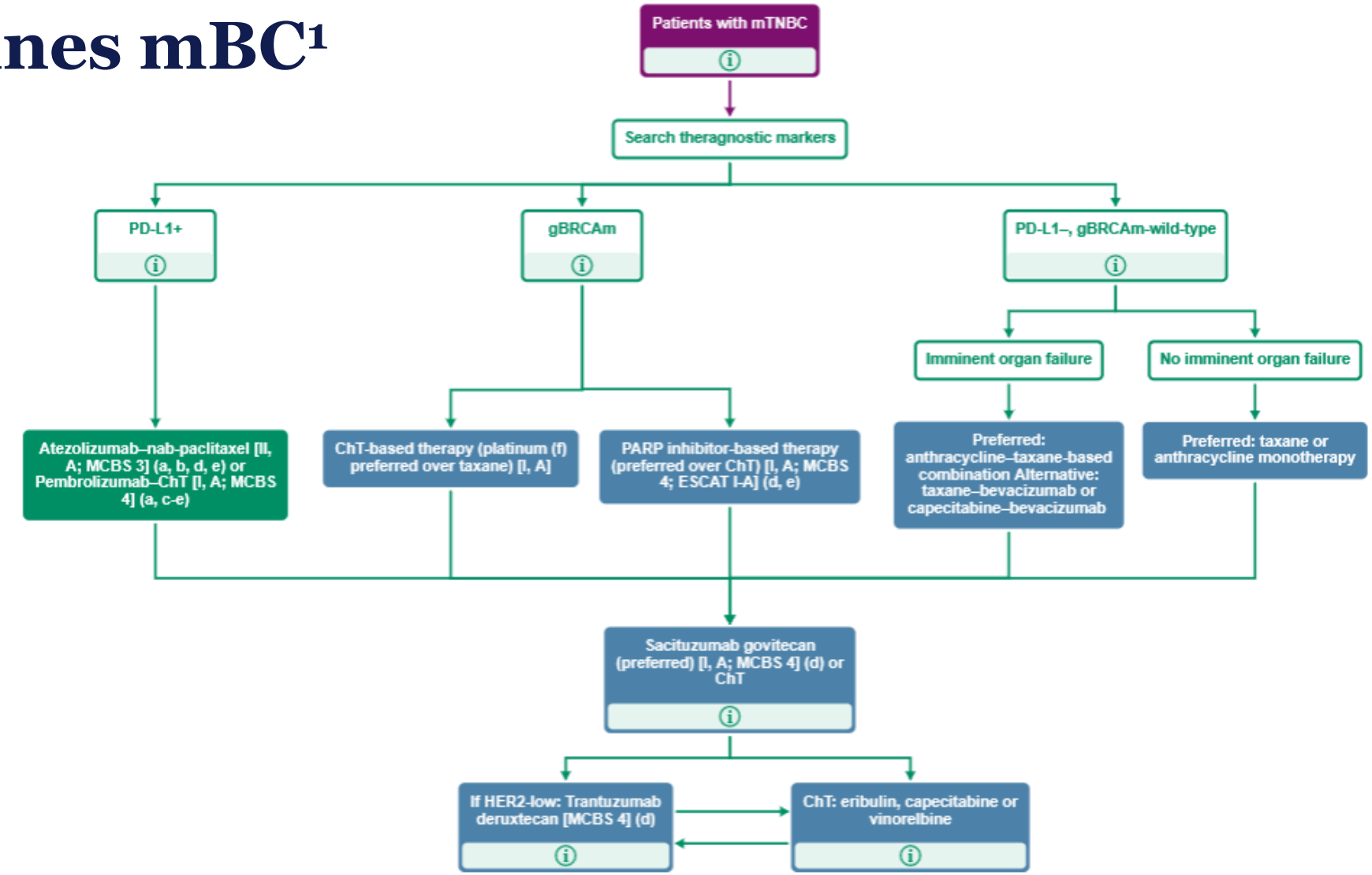
- ILD Grad 2 nach 6 Wochen Therapie

10/2021

ESMO Guidelines mBC[1]

- TNBC



1 Available at: https://www.esmo.org/living-guidelines/esmo-metastatic-breast-cancer-living-guideline/triple-negative-breast-cancer; Last accessed January 1st, 2024.

Acknowledgments

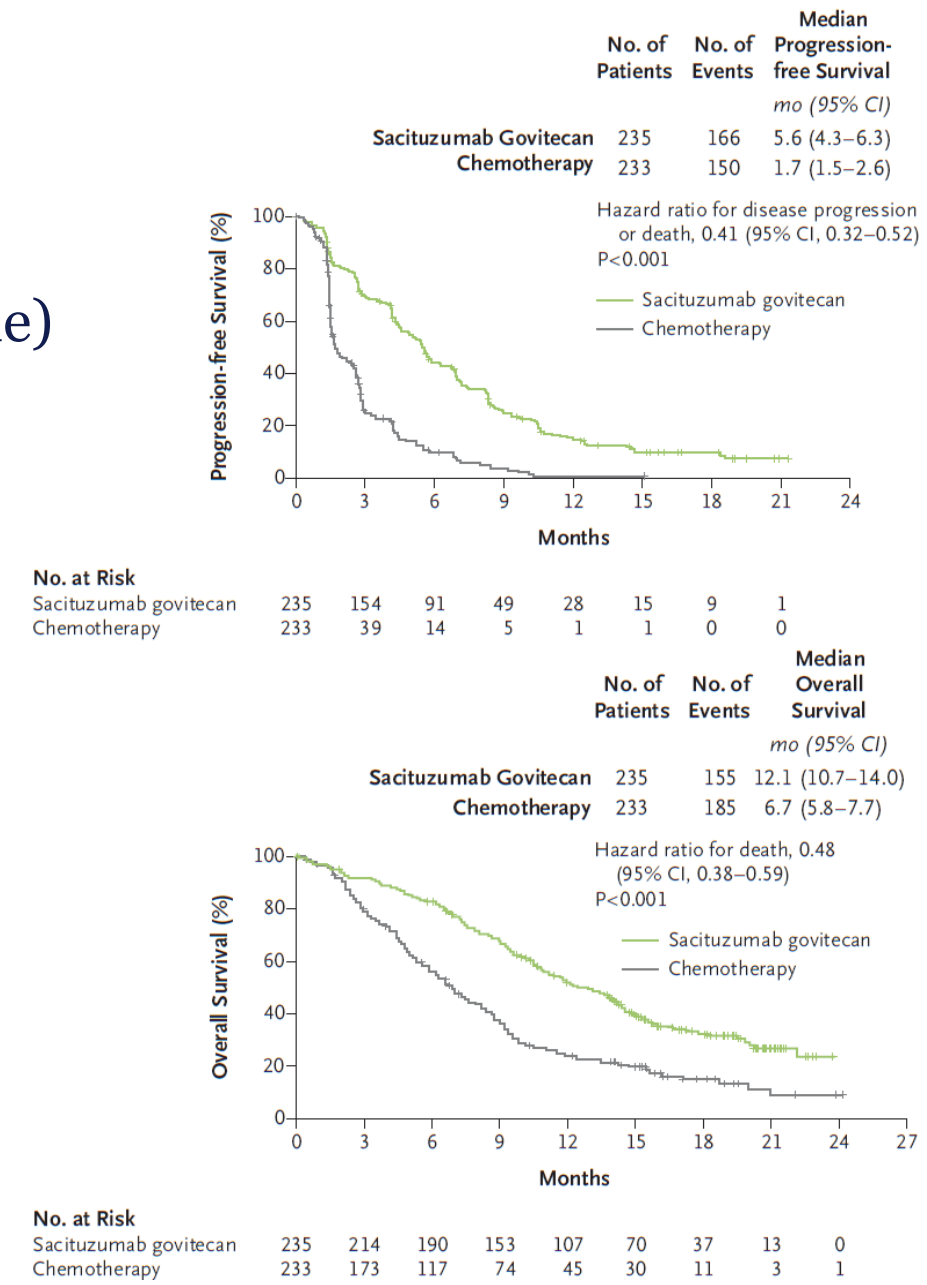
Anna Berghoff
Elisabeth Bergen
Thorsten Füreder
Christoph Minichsdorfer
Maximilian Marhold
Zsuzsanna Bago-Horvath
Margaretha Rudas
Kristina Tendl
Karin Dieckmann
Daniela Kauer-Dorner
Ruth Exner
Jelena Devyatko
Florian Fitzal
Bernadette Aretin
Robert Mader
Werner Haslik
Thomas Hofmann-Bachleitner
Raimund Jakesz
Günther G. Steger
Michael Gnant
Christoph C. Zielinski
Christian Singer
Matthias Preusser

Claudia Bartsch
Ursula Pluschnig
Marija Balic
Daniel Egle
Arik Galid
Peter Dubsky
Michael Knauer
Catharina de Vries
Ursula Vogl
Leopold Öhler
Alexander de Vries

Backup

Sacituzumab-Govitecan[1,2]

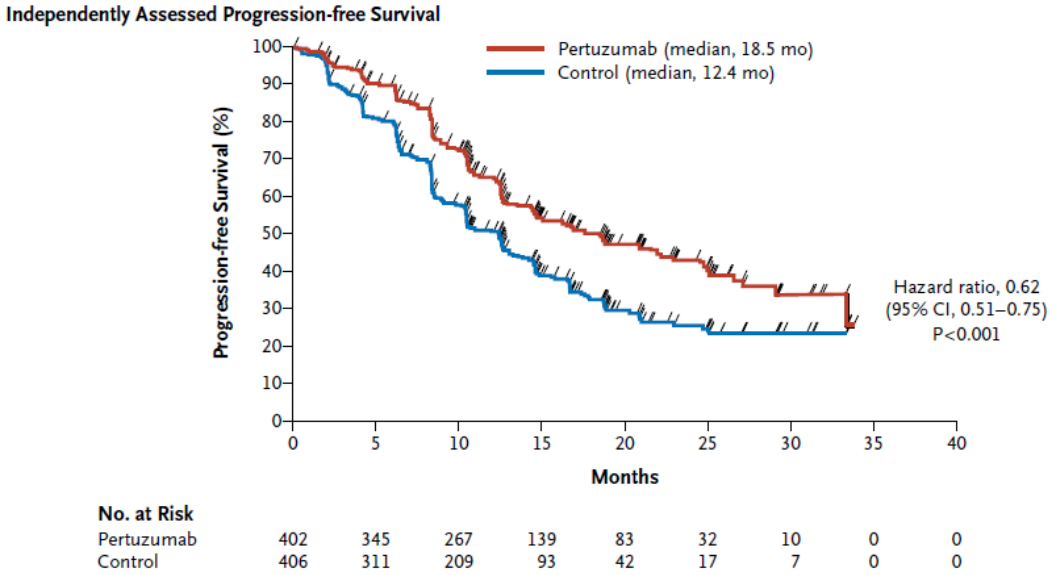
- Ergebnisse (Population ohne BM bei Baseline)
  - PFS
  - 5,6 *vs.* 1,7 Monate
  - HR 0,41; 95% CI 0,32-0,52
  - OS
  - 12,1 *vs.* 6,7 Monate
  - HR 0,48; 95% CI 0,38-0,59

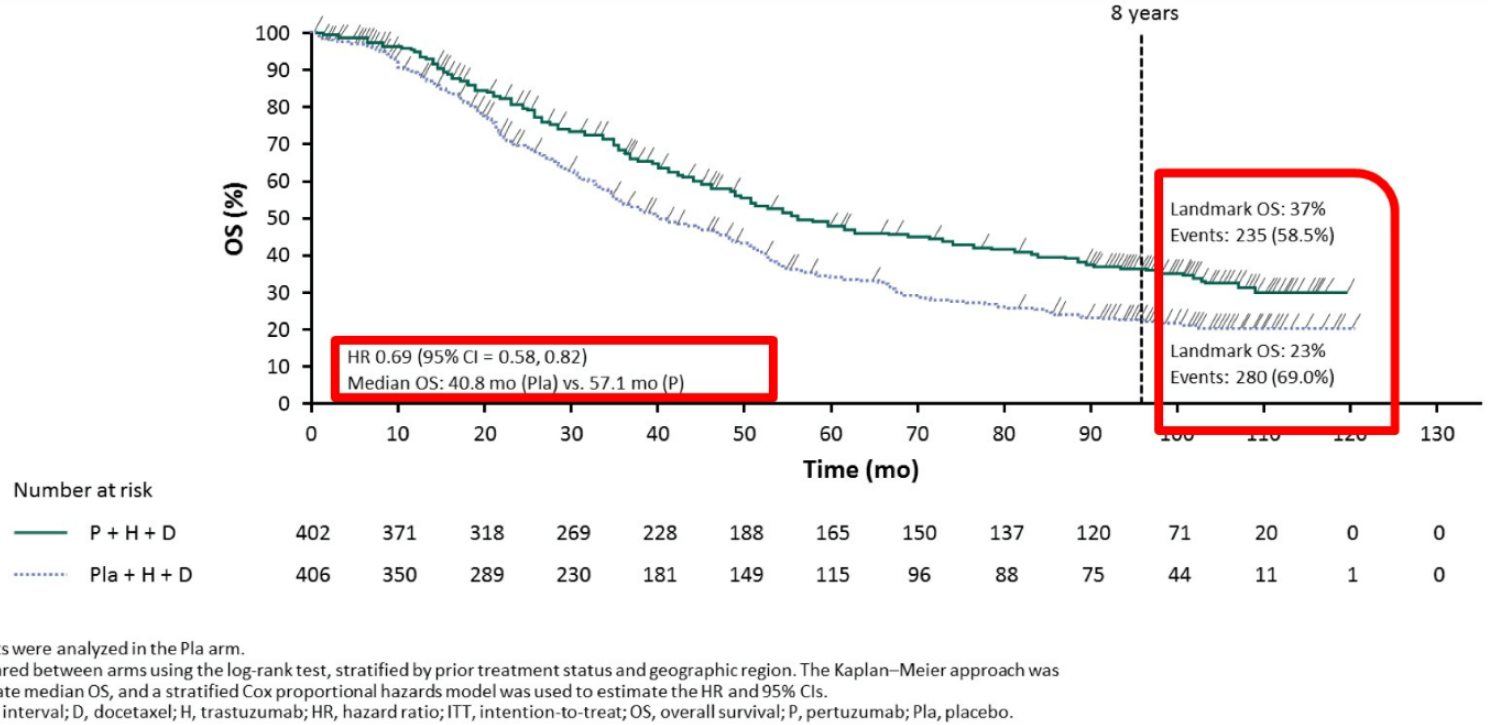


1 Bardia A et al. LBA17; ESMO 2020.; 2 Bardia A et al. N Engl J Med 2021;384:1529-1541.

Trastuzumab und Pertuzumab

- CLEOPATRA: Phase III Studie, 808 Pat., MBC, HER2-pos., first-line, DT +/- Pertuzumab
  - PFS: 18,5 *vs.* 12,4 Monate (HR 0.62; 95% CI 0,51-0,75; p<0.001)[1]
  - End-of-Study Analyse: OS 57,1 vs. 40,8 Monate (HR 0,69; 95% CI 0,58-0,82; Δ 16,3 Monate)[2]
  - 8-Jahres OS-Rate: 37% vs. 23%



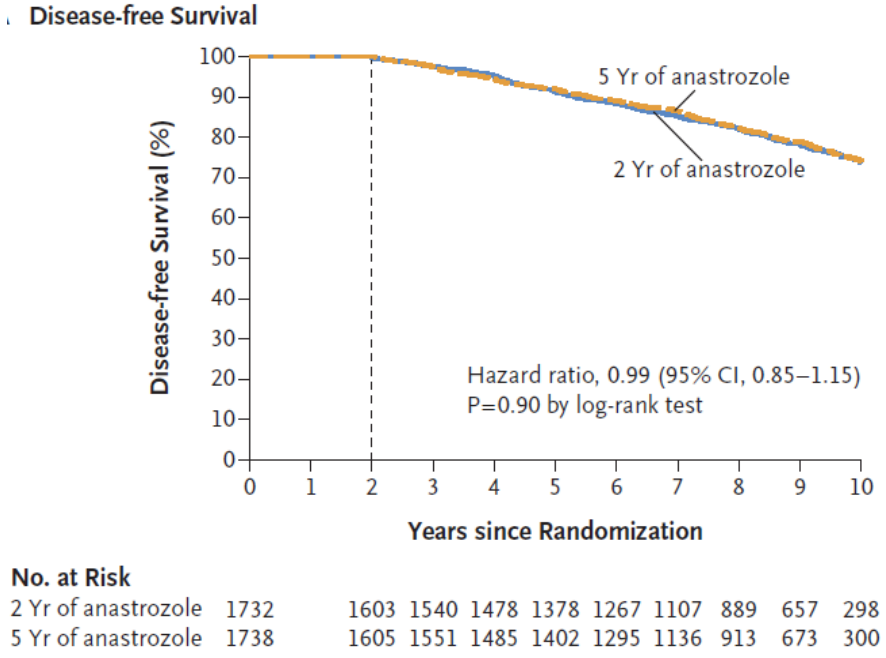


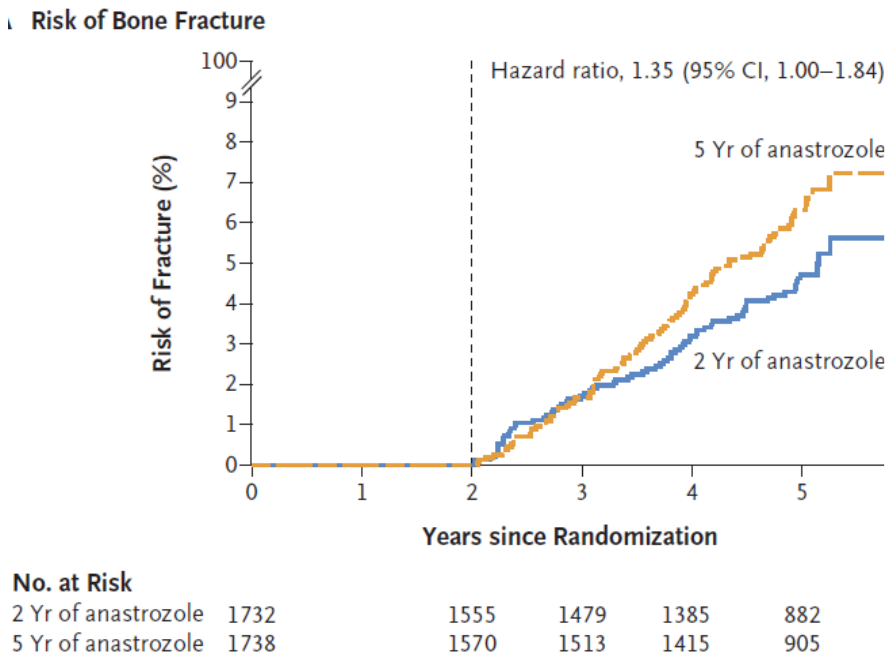
* Crossover pts were analyzed in the Pla arm.
OS was compared between arms using the log-rank test, stratified by prior treatment status and geographic region. The Kaplan–Meier approach was used to estimate median OS, and a stratified Cox proportional hazards model was used to estimate the HR and 95% CIs.
CI, confidence interval; D, docetaxel; H, trastuzumab; HR, hazard ratio; ITT, intention-to-treat; OS, overall survival; P, pertuzumab; Pla, placebo.

1 Baselga J et al. N Engl J Med 2012;366:109-119.; 2 Swain SM et al. ASCO 2019; Abstr. #1020.

Dauer der endokrinen Therapie

- Optimale Dauer der adjuvanten endokrinen Therapie?
- ABCSG-16: randomisierte Phase III; 2 *vs.* 5 Jahre nach initalen 5 Jahren endokriner Therapie[1]



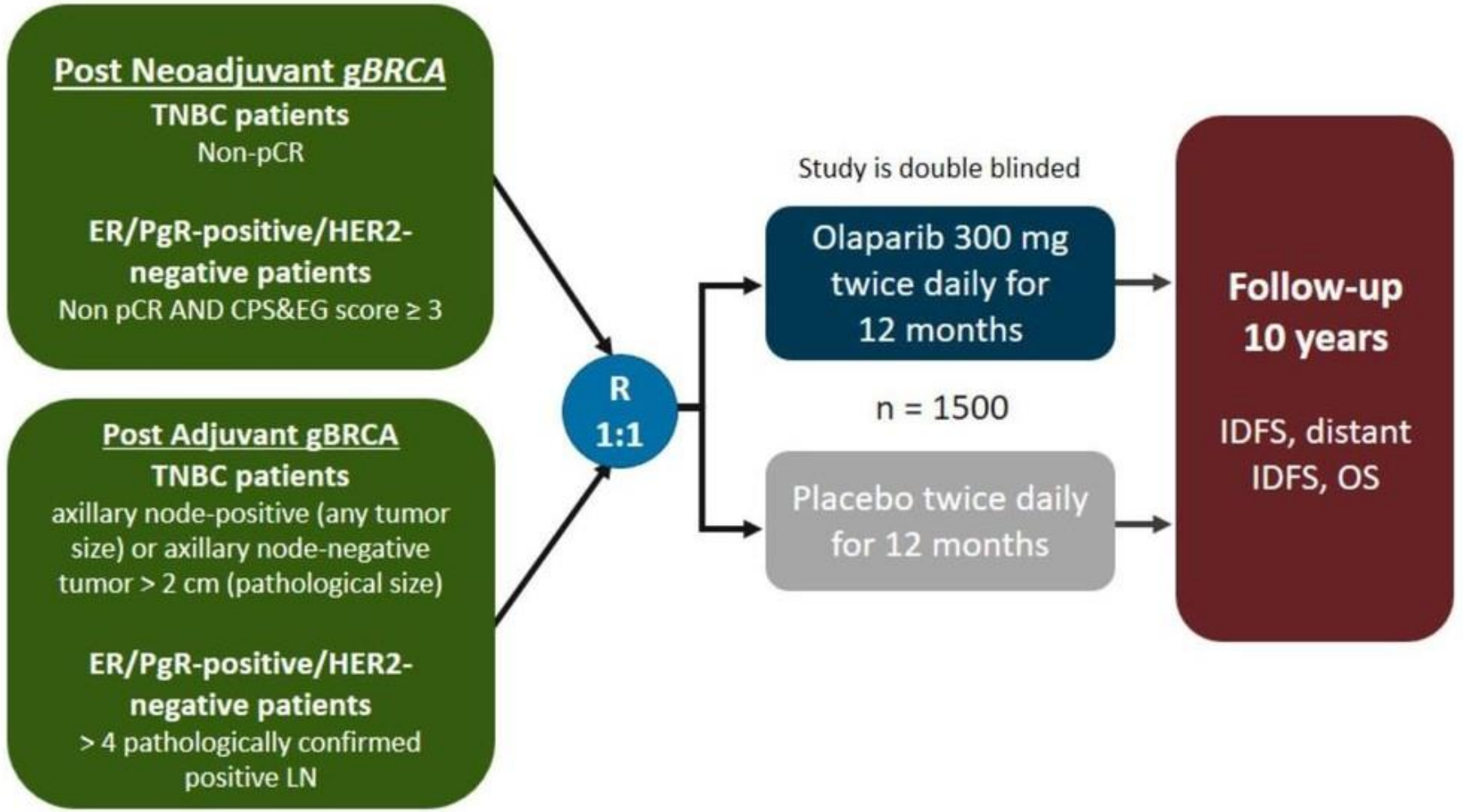


1 Gnant M et al. N Engl J Med 2021;385:395-405.

OlympiA[1,2]

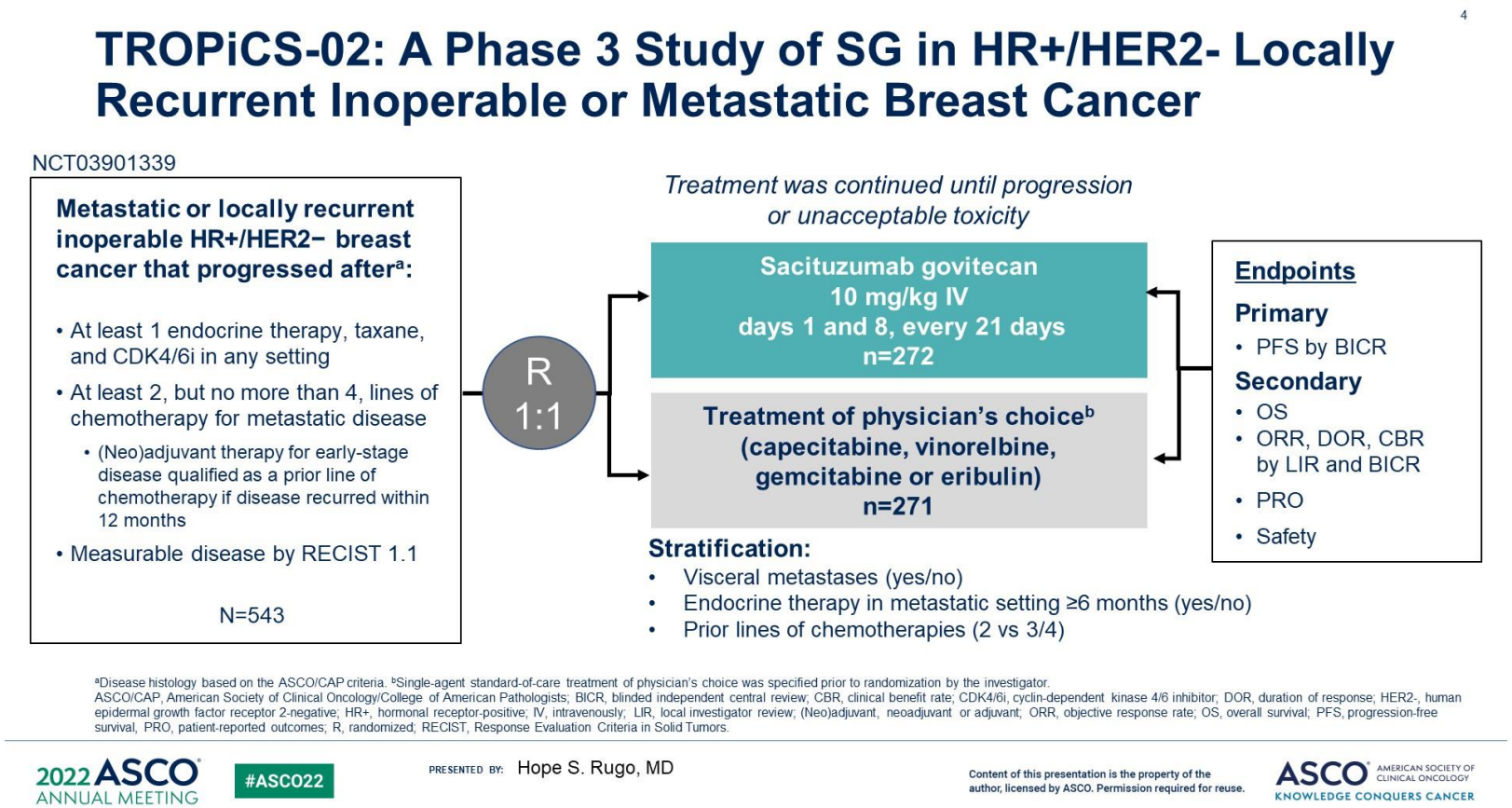
- Studiendesign

- Prospektiv randomisierte Phase III
- (postneo)adjuvante Therapie Olaparib 300 mg oder Placebo
- HER2-negativ, gBRCA Mutation
- Stratifizierungsfaktoren: HR Status, adjuvante/neoadj. Therapie, Vortherapie mit Platinen



1 Tutt A et al. LBA1; ASCO 2021., 2 Tutt ANJ et al. N Engl J Med 2021;384:2394-2405.

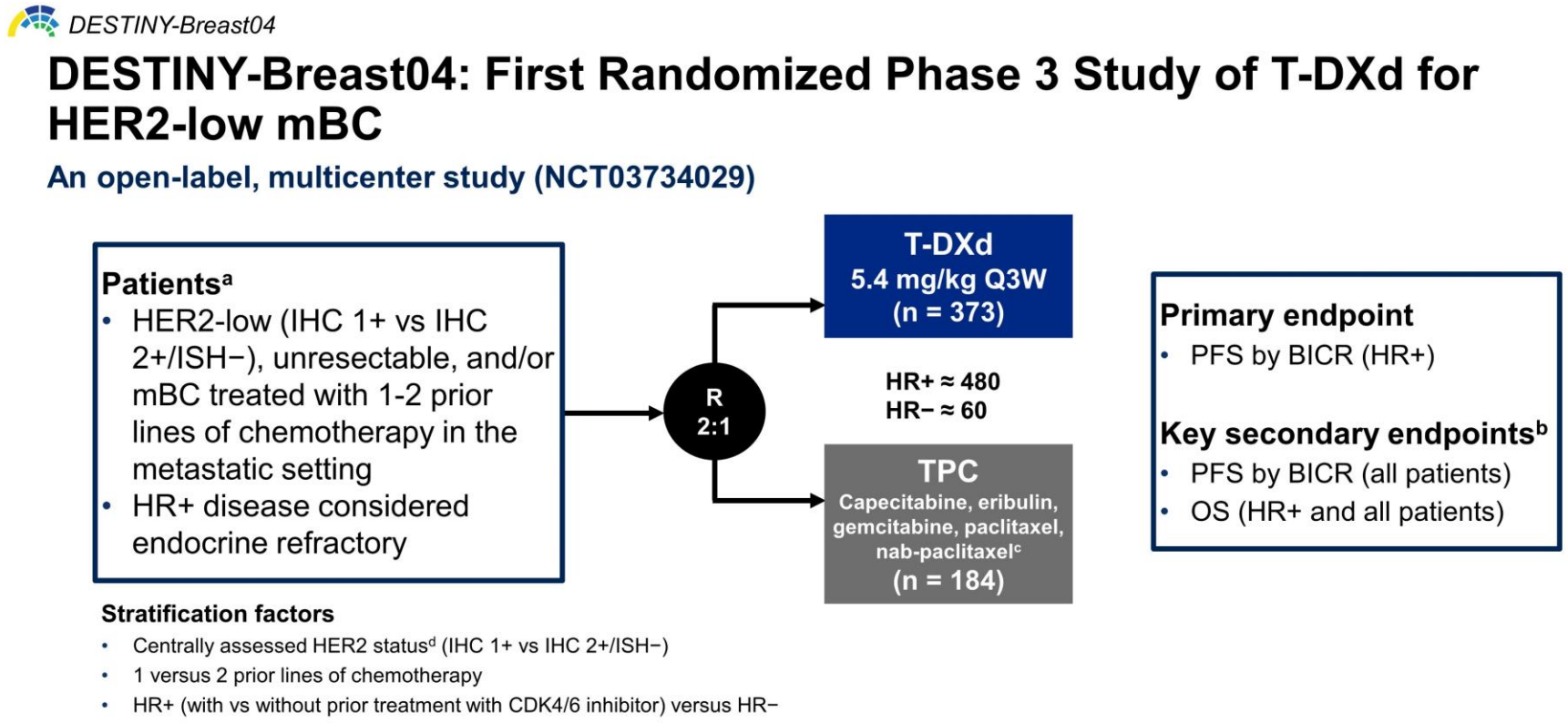
TROPIcS-02[1]



- SG *vs*. TPC bei HR-positivem mBC
- Mediane Zahl an vorherige Chemotherapielinien *n*=3

1 Rugo HS et al. Abst. 1001; ASCO 2022.

DESTINY-Breast04[1]

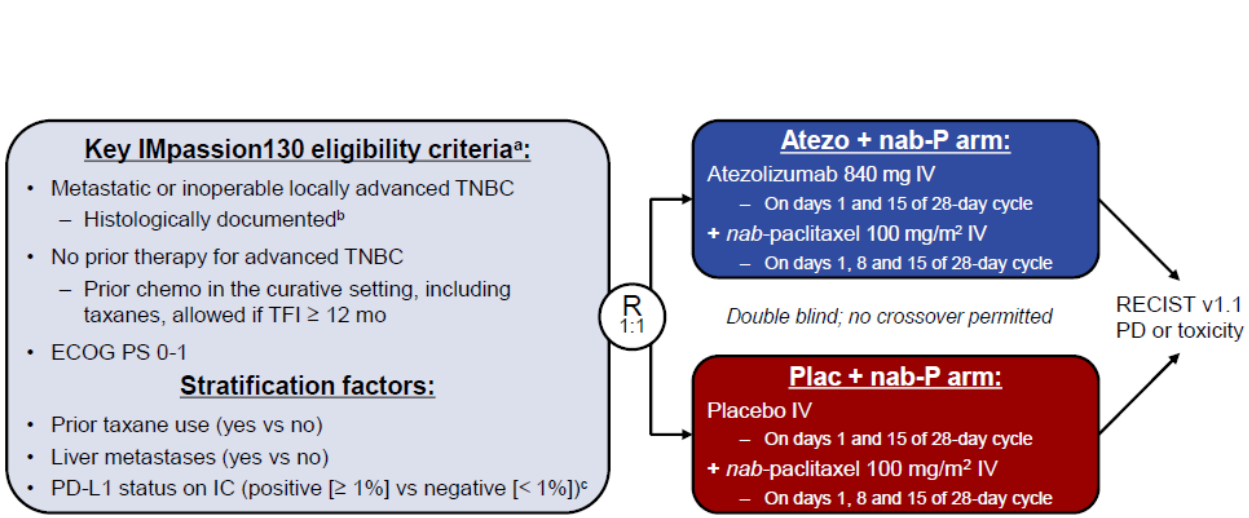


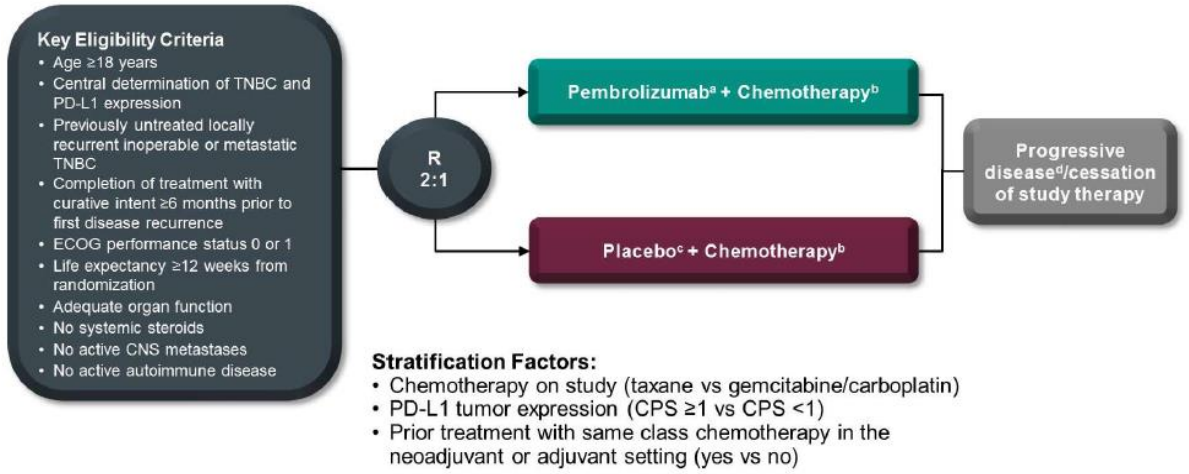
1 Modi S et al. Abst. LBA3; ASCO 2022.

[5]
- 10% TNBC
- Mediane Zahl an vorherige Chemotherapielinien *n*=1
- CDKi (HR-positive) ~70%
- Lebermetastasen ~70%

Immuntherapie bei TNBC

- Pivotale Phase III Studien mit Chemotherapoe + IO/Placebo, mTNBC, first-line[1,2]
  - IMpassion130 nab-Paclitaxel +/- Atezolizumab/Placebo
  - Keynote-355 nP, P, CbG +/- Pembrolizumab/Placebo





[a]Pembrolizumab 200 mg intravenous (IV) every 3 weeks (Q3W)
[b]Chemotherapy dosing regimens are as follows:
Nab-paclitaxel 100 mg/m² IV on days 1, 8, and 15 every 28 days
Paclitaxel 90 mg/m² IV on days 1, 8, and 15 every 28 days
Gemcitabine 1000 mg/m²/carboplatin AUC 2 on days 1 and 8 every 21 days

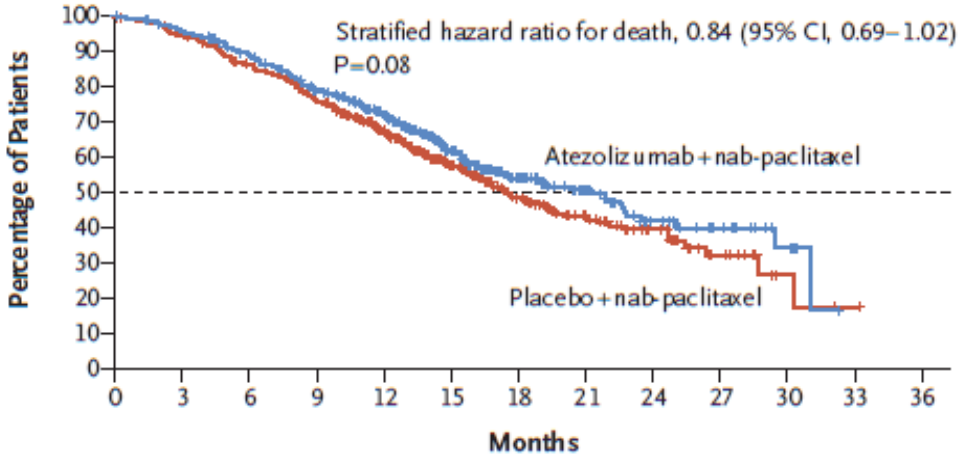
[c]Normal saline
[d]Treatment may be continued until confirmation of progressive disease
CNS=central nervous system; ECOG=Eastern Cooperative Oncology Group; PD-L1=programmed death ligand 1; R=randomized; TNBC=triple-negative breast cancer

1 Schmid P et al. N Engl J Med 2018;379:2108-2121.; 2 Cortes J et al. Lancet 2020;396:1817-1828.

IMpassion130[1-3]

C Overall Survival in the Intention-to-Treat Population

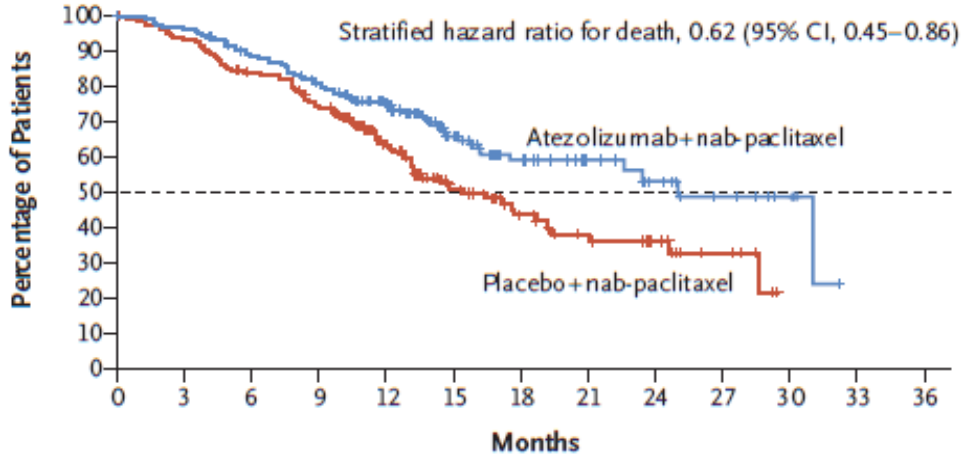
	No. of Events/ No. of Patients	Median Overall Survival (95% CI)	2-Yr Rate of Progression-free Survival (95% CI)
		mo	%
Atezolizumab+Nab-Paclitaxel	181/451	21.3 (17.3–23.4)	42.1 (34.3–49.9)
Placebo+Nab-Paclitaxel	208/451	17.6 (15.9–20.0)	39.7 (33.2–46.3)



No. at Risk													
Atezolizumab+ nab-paclitaxel	451	426	389	337	271	146	82	48	26	15	6	NE	NE
Placebo+ nab-paclitaxel	451	419	375	328	246	145	89	52	27	12	3	1	NE

D Overall Survival in the PD-L1–Positive Subgroup

	No. of Events/ No. of Patients	Median Overall Survival (95% CI)	2-Yr Rate of Progression-free Survival (95% CI)
		mo	%
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)



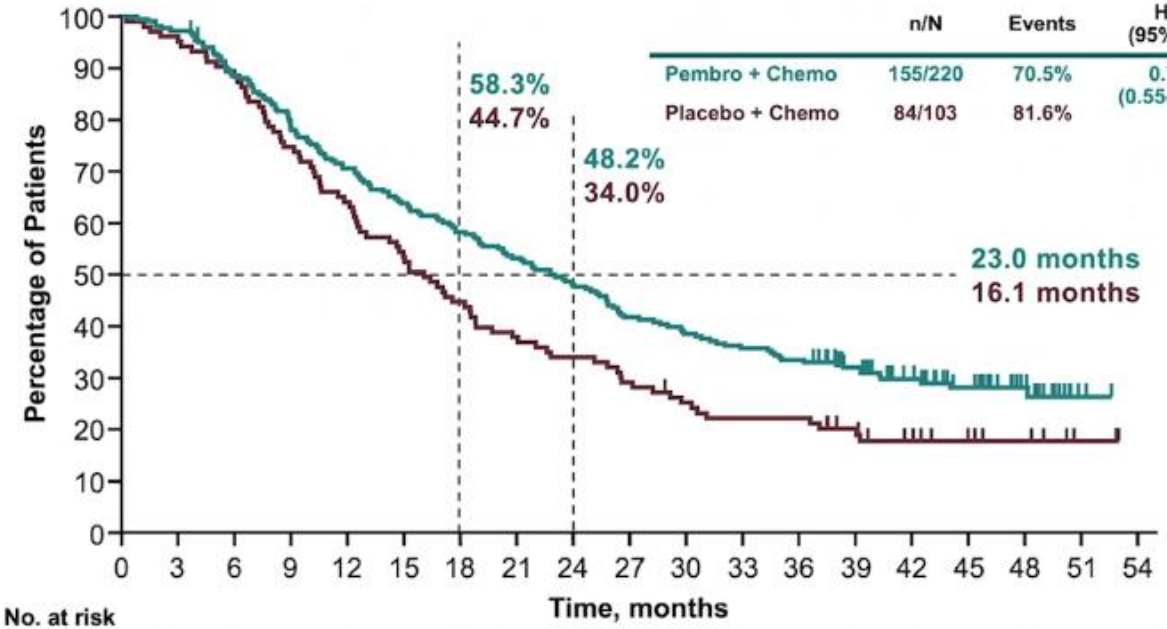
No. at Risk													
Atezolizumab+ nab-paclitaxel	185	177	160	142	113	61	36	22	15	9	5	NE	NE
Placebo+ nab-paclitaxel	184	170	147	129	89	44	27	19	13	6	NE	NE	NE

- OS in the ITT (C) and the PD-L1 pos. population (D)
- OS Update ASCO 2019: 25.0 vs. 18.0 months (HR 0.71; 95% CI 0.54-0.93)[3]

1 Schmid P et al. LBA1. ESMO 2018.; 2 Schmid P et al. N Engl J Med 2018;379:2108-2121.; Schmid P et al. Abstr. #1003; ASCO 2019..

KEYNOTE-355[1,2]

Overall Survival: PD-L1 CPS ≥10

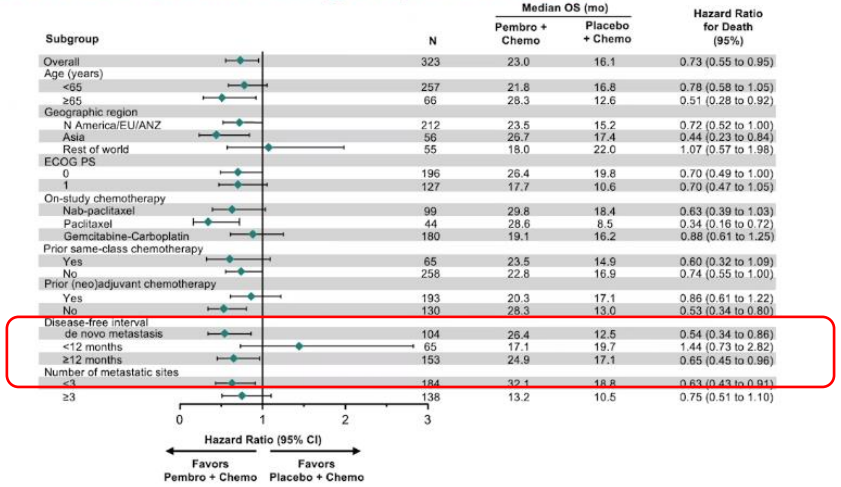


[a]Prespecified *P* value boundary of 0.0113 met.
Hazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate stratified by the randomization stratification factors. Data cutoff: June 15, 2021.

Update ESMO 2021

- Medianes Follow Up 44,1 Monste
- Finale Ergebnisse mit OS

Overall Survival in Subgroups: CPS ≥10



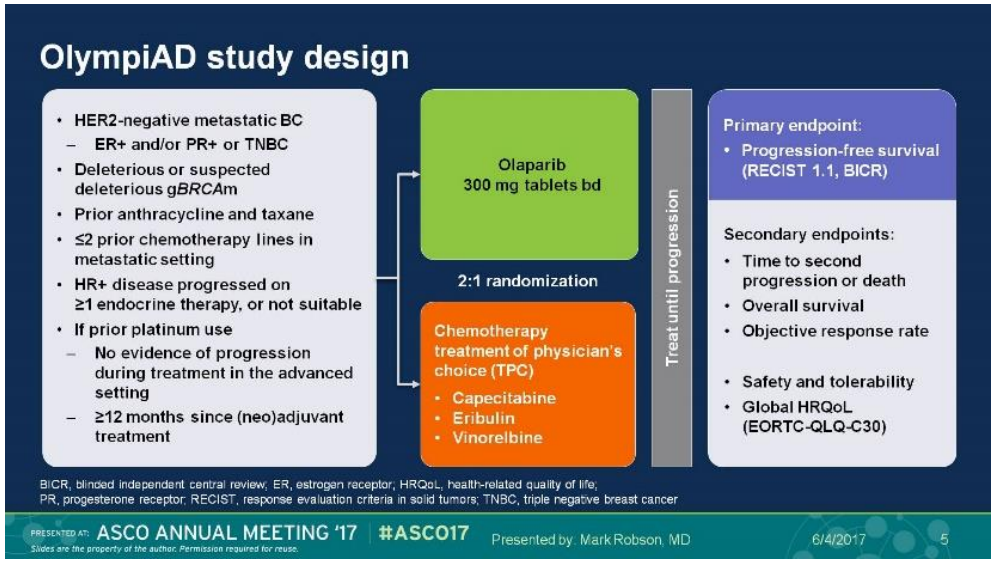
Analysis (HR and 95% CI) in the overall population is based on the stratified Cox regression model; analysis in the subgroups is based on the unstratified Cox model.
Data cutoff: June 15, 2021.

1 Rugo H et al. Abstr. LBA16; ESMO 2021.; 2 Cortes J et al. New Engl J Med 2022;387:217-226

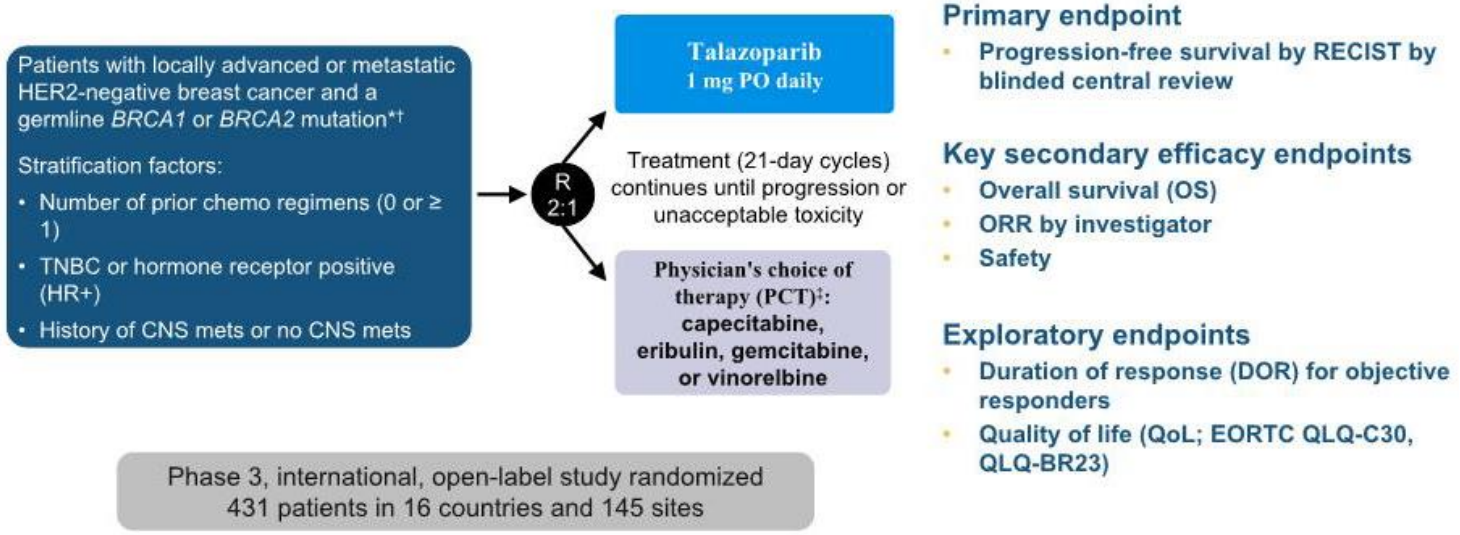
PARPi bei *BRCA*mut mBC[1-3]

- OlympiAD und EMBRACA: Vergleich PARPi *vs*. Chemotherapie bei *BRCA* Mutationsträgerinnen
  - Phase III, mBC, HER2-negativ, PARPi *vs*. TPC
  - Bis zu zwei vorheriger Chemotherapielinien

Design OlympiAD



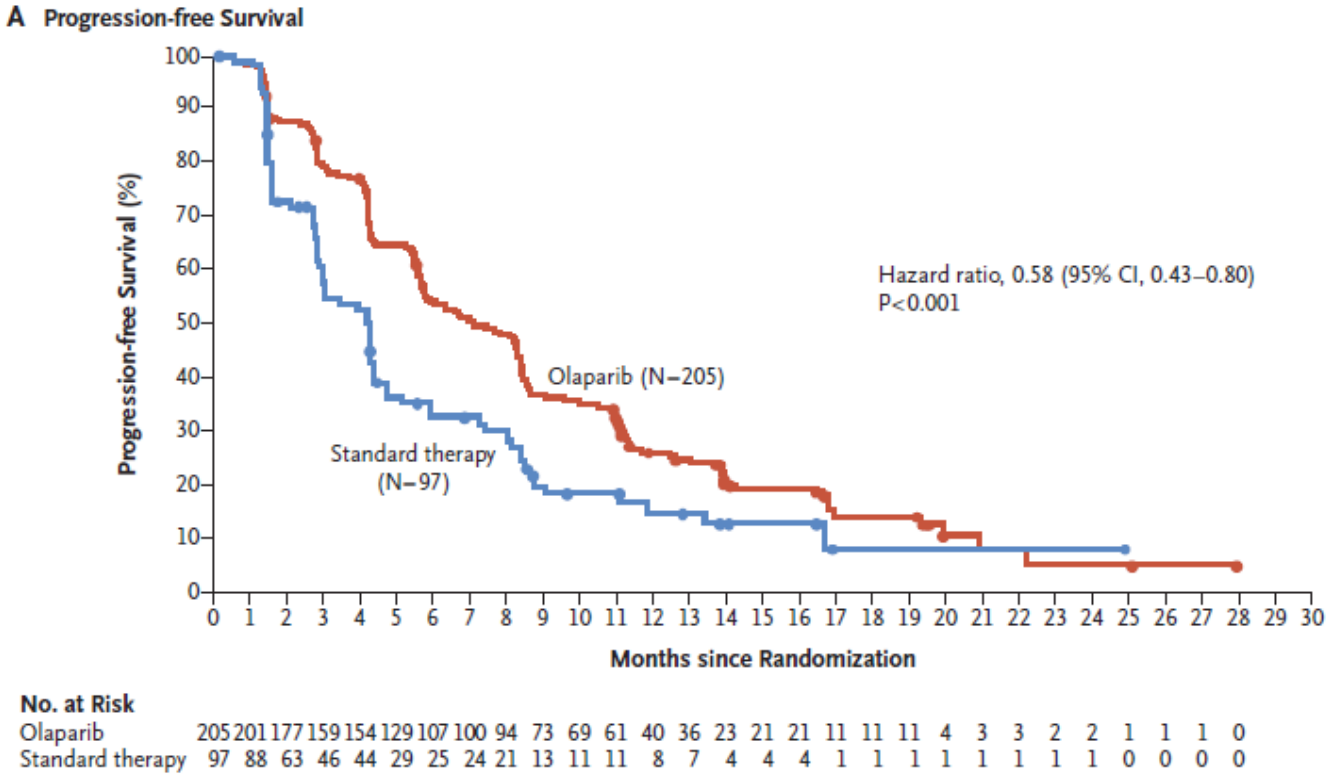
Design EMRCACA

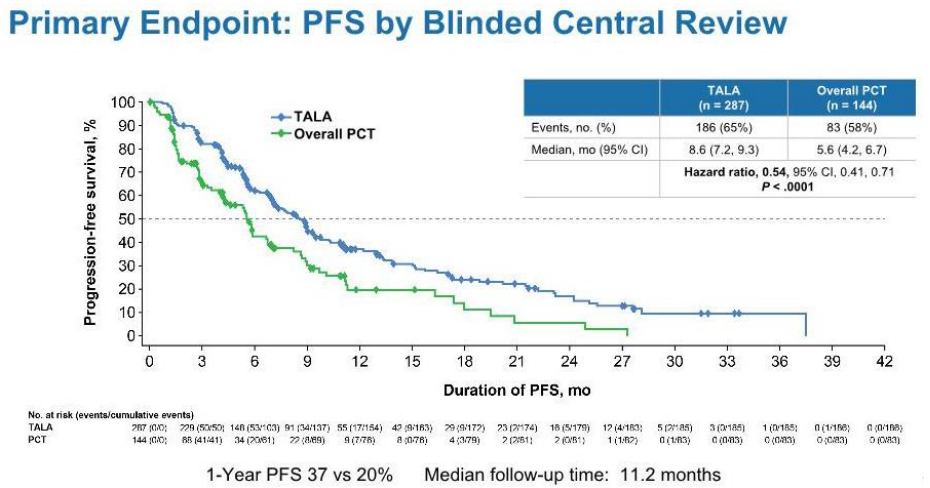


1 Robson ME et al. Abst. #LBA4; ASCO 2017.; 2 Robson M et al. N Engl J Med 2017;377:523-533.; 3 Litton JK et al. N Engl J Med 2018;379:753-763.

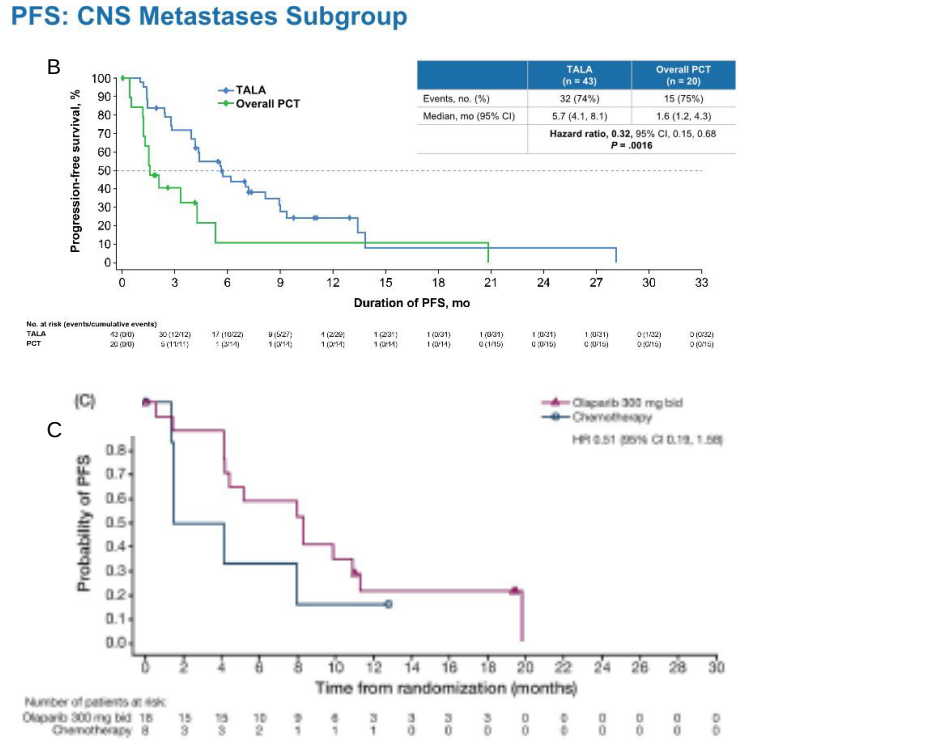
PARPi bei *BRCA*mut mBC[1-3]

- PFS in den PARPi Gruppen überlegen (right, A)
  - Effekt bei TNBC prädominant
  - Effekt auch bei Pat. mit stabilen BM bei Baseline (B,C)





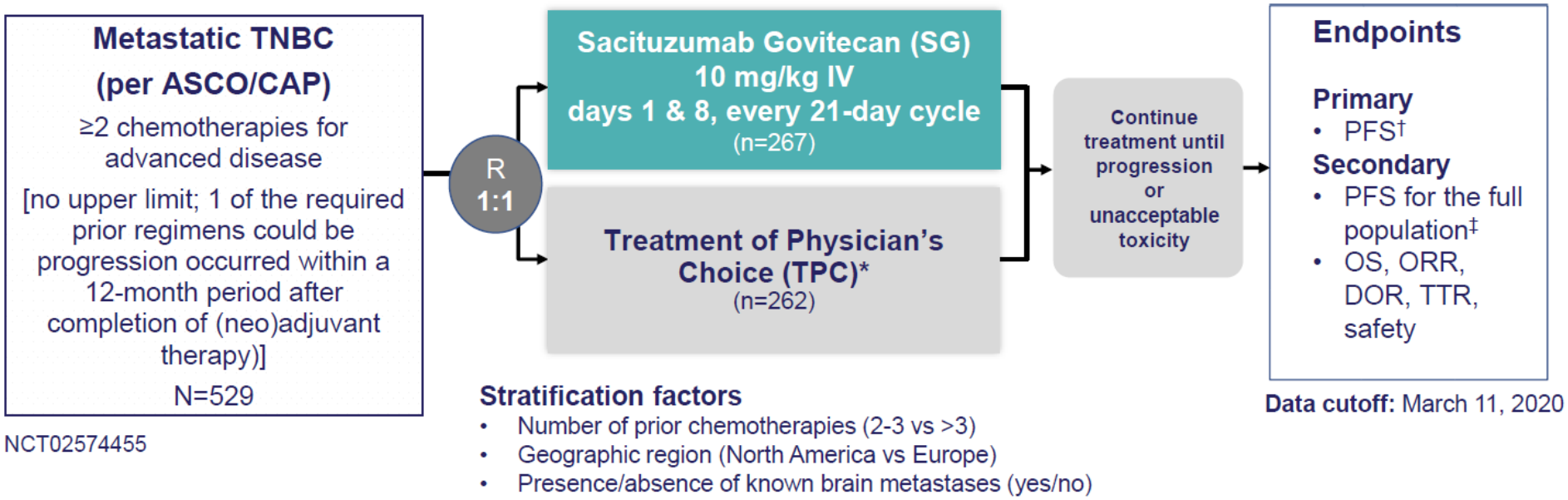
1-Year PFS 37 vs 20% Median follow-up time: 11.2 months



1 Robson ME et al. Abst. #LBA4; ASCO 2017.; 2 Robson M et al. N Engl J Med 2017;377:523-533.; 3 Litton JK et al. N Engl J Med 2018;379:753-763.

Sacituzumab-Govitecan[1,2]

- ASCENT: Randomisierte Phase III Studie
- Sacituzumab Govitecan *vs*. TPC
  - Capecitabine, Gemcitabine, Eribulin, Vinorelbine
  - *n*=468



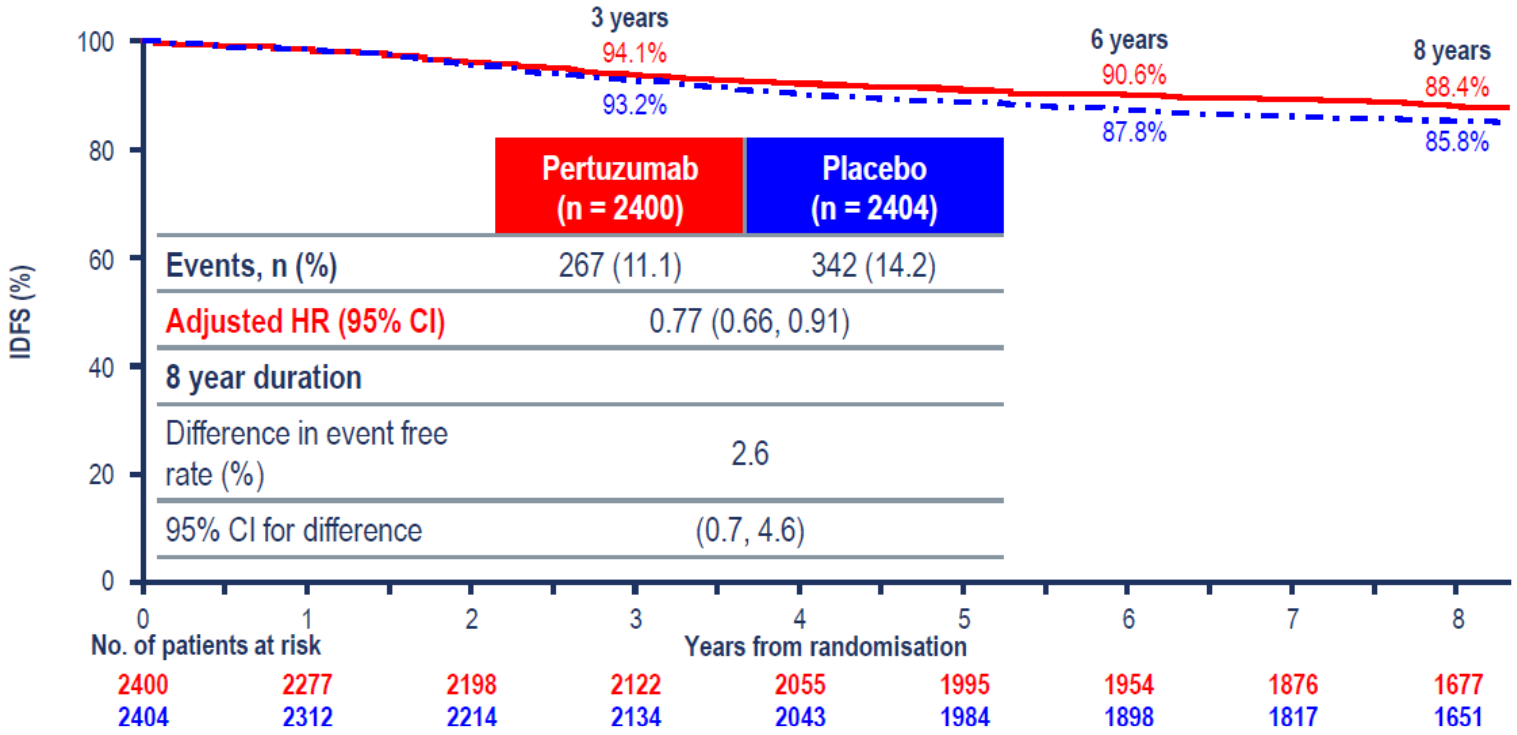
1 Bardia A et al. LBA17; ESMO 2020.
2 Bardia A et al. N Engl J Med 2021;384:1529-1541.

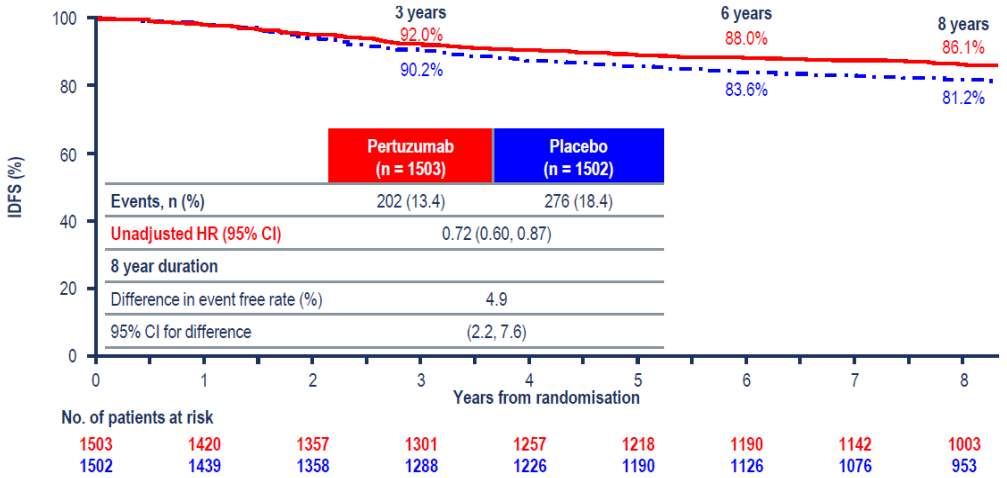
Trial	Endocrine Therapy	Menopause Status	Population	PFS (months)	PFS (HR)	OS (HR; 95% CI)
PALOMA-2	Letrozole	postmenopausal	1st-line ~35% *de novo* met. ~22% TFI <=12	24.8 *vs.* 14.5	HR 0.58	HR 0.96[1] 95% CI 0.78-1.18
MonaLEEsa-2	Letrozole	postmenopausal	1st-line ~34% *de novo* met. <5% DFS <=12	25.3 *vs.* 16.0	HR 0.57	HR 0.76[2] 95% CI 0.63-0.93
MonaLEEsa-7	Gosereline + anastrozole/ letrozole or tamoxifen	premenopausal	1st-line (one line of orior chemotheraoy für advanced BC allowed; ~14%)	23.8 *vs.* 13.0	HR 0.55	HR 0.71[3] 95% CI 0.54-0.95
MONARCH-3	Anastrozole/ letrozole	postmenopausal	1st-line ~40% *de novo* met.	28.2 *vs.* 14.7	HR 0.54	HR 0.80[4] 95% CI 0.637-1.015
PALOMA-3	Fulvestrant +/- OFS	pre-/perimenopausal allowed	Pretreated; 1st-line ~25% (progression on adj. ET or ≤12 months)	9.2 *vs.* 3.8	HR 0.42	HR 0.81[5] 95% CI 0.64-1.03
MonaLEEsa-3	Fulvestrant	postmenopausal	1st- and 2nd-line; 1st-line, PFS >12 months ~50%	20.5 *vs.* 12.8	HR 0.59	HR 0.72[6] 95% CI 0.57-0.92
MONARCH-2	Fulvestrant +/- OFS	pre-/perimenopausal allowed	1st- and 2nd-lin; 1st-line 40% (progression on adj. ET or ≤12 month) ~25% primary endocrine resistence	16.4 *vs.* 9.3	HR 0.55	HR 0.76[7] 95% CI 0.61-0.95

1 Finn RS et al. Abst. LBA1003; ASCO 2022; 2 Hortobagyi GN et al. Engl J Med 2022;386:942-950.; 3 Im AH et al. N Engl J Med 2019;381:307-316.; 4 Goetz MP et al. GS01-12; SABCS 2023.; 5 Turner NC et al. N Engl J Med 2018;379:1926-1936.; 6 Slamon DJ et al: N Engl J Med 2020;382:514-524.; 7 Sledge JW et al. JAMA Oncol 2020;6:116-124.

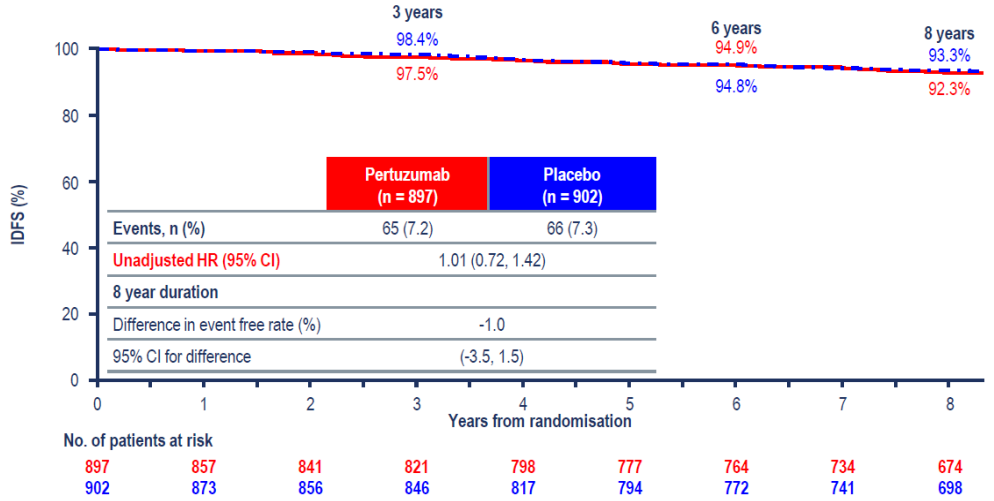
Eskalation

- APHINITY: Deskriptive iDFS Analyse[1]





Nodal positiv



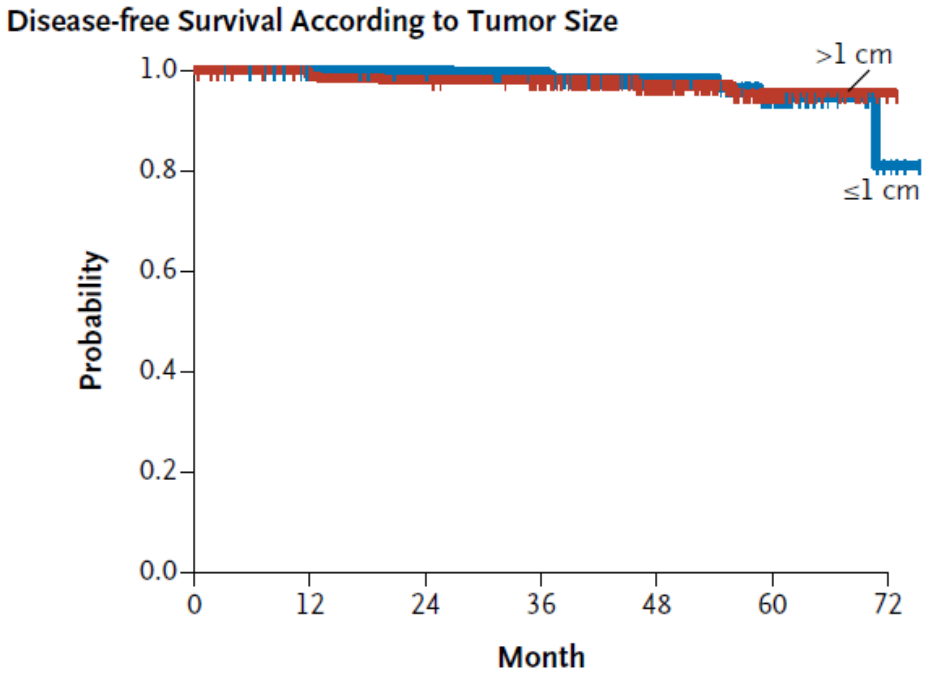
Nodal negativ

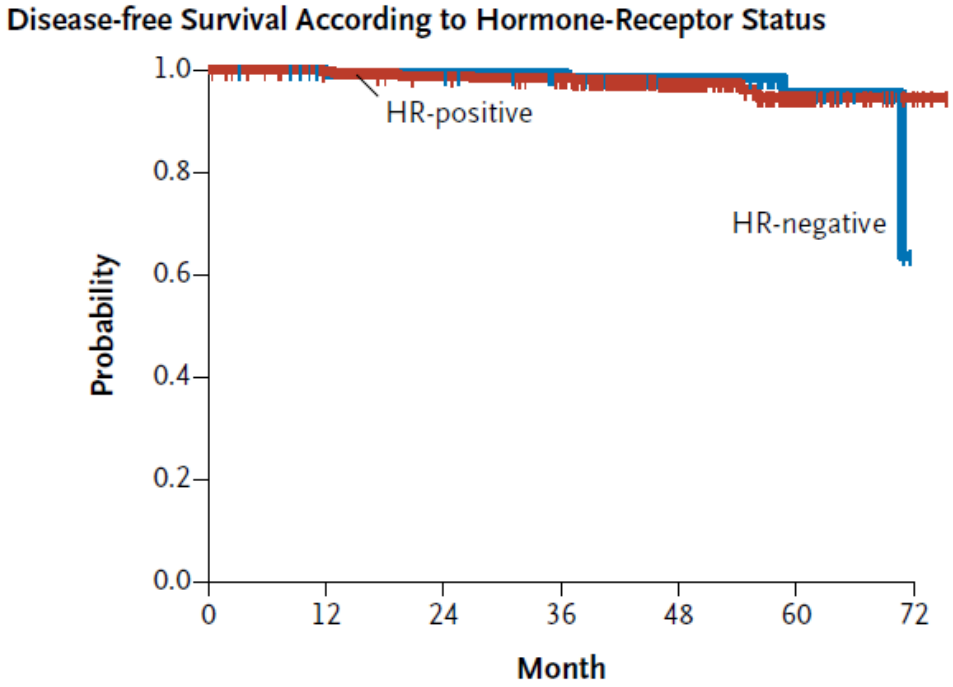
1 Loibl S et al. ESMO Virtual Plenary; VP6 2022.

Deeskalation

- APT[1,2]
- Single arm phase II study, Pw x12 plus Trastuzumab 1 a
- 410 Pat., pN0, pT <3 cm

7-Jahres DFS: 93% (95% CI 90,4-96,2)
n=4 (1.0%) distant recurrence events





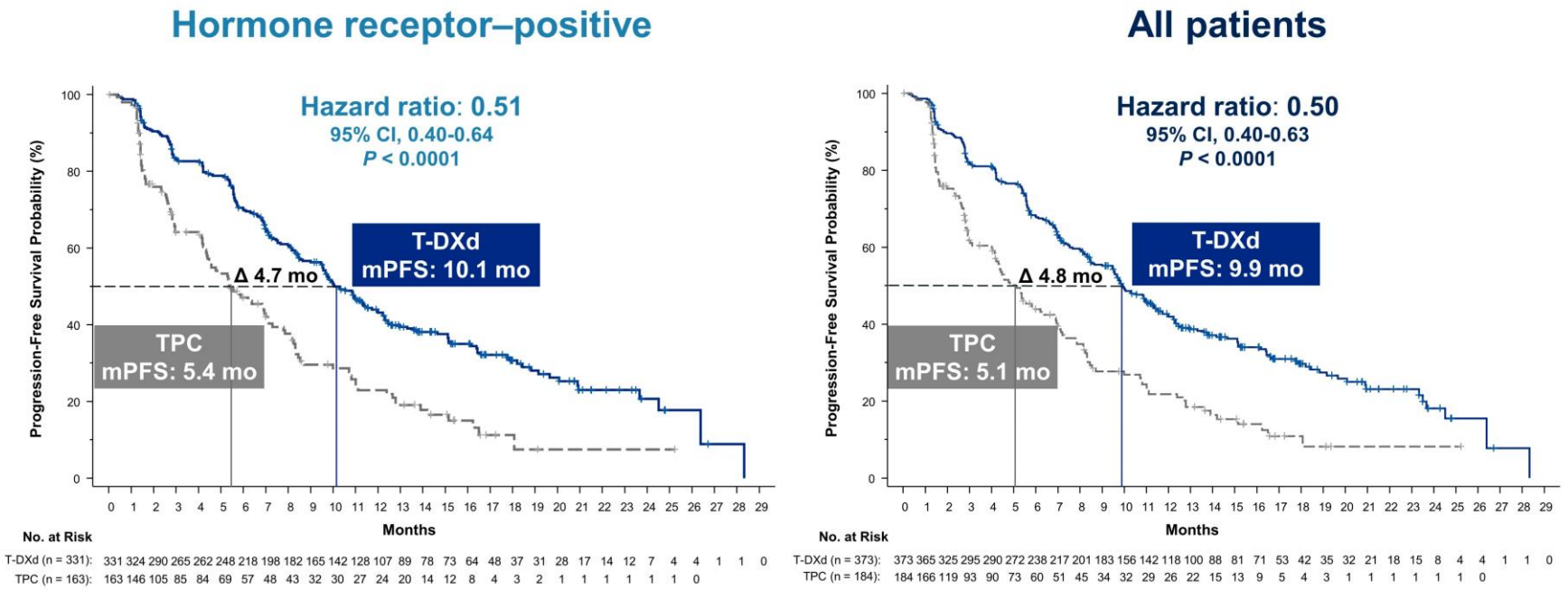
1 Tolaney SM et al. N Engl J Med 2015;372:134-141.2 Tolaney SM et al. J Clin Oncol 2019;37:1868-1875.

DESTINY-Breast04[1]

DESTINY-Breast04

10

PFS in HR+ and All Patients



PFS by blinded independent central review.
HR, hormone receptor; mPFS, median progression-free survival; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

2022 ASCO ANNUAL MEETING #ASCO22

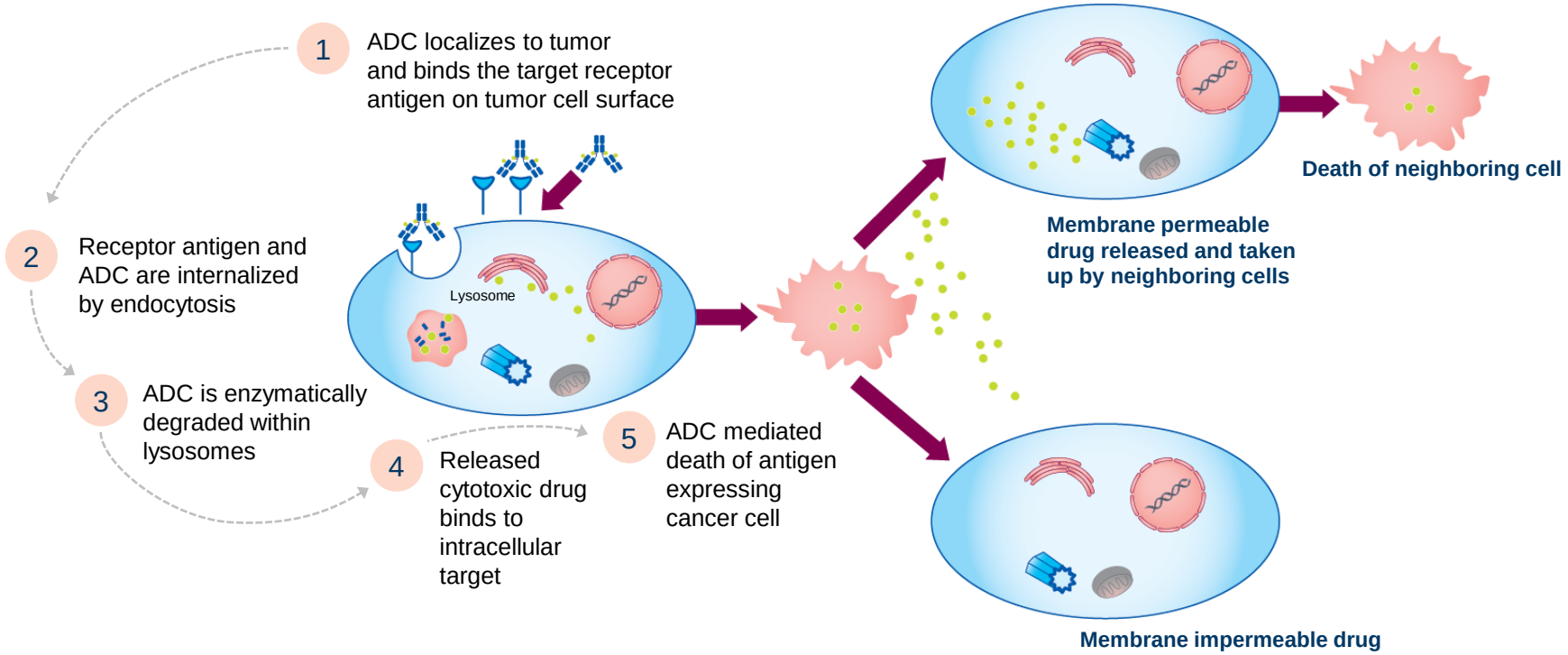
PRESENTED BY:
Shanu Modi, MD

ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY
KNOWLEDGE CONQUERS CANCER

1 Modi S et al. Abst. LBA3; ASCO 2022.

Antikörper-Medikamenten Konjugate (ADCs)[1,2]

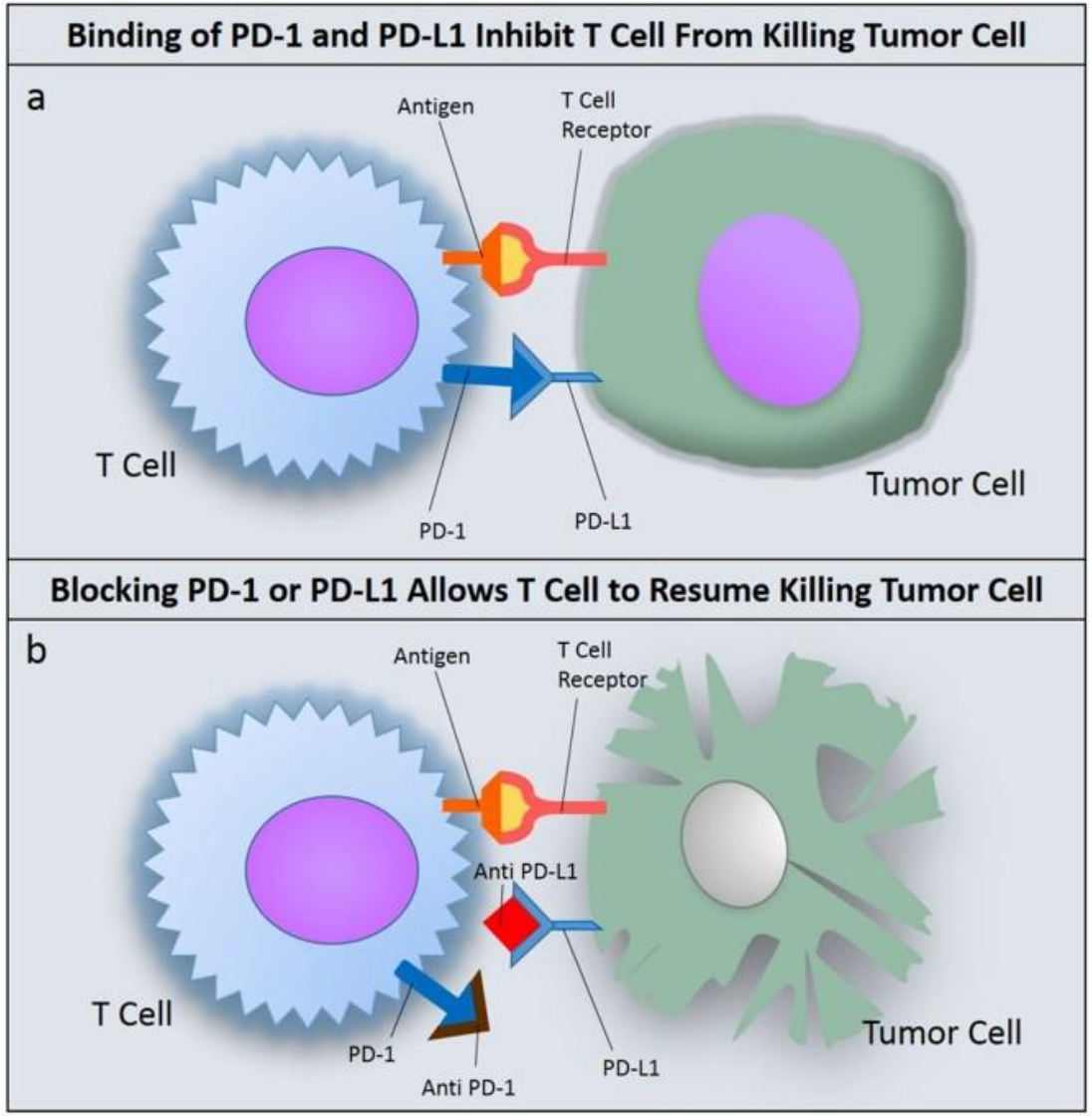
- Zielgerichtete Chemotherapie durch ADCs
- Potentieller Effekt auf umliegende Zellen



1 Trail PA, et al. Pharmacol Ther 2018;181:126-142.

Regulation der Immunantwort[1]

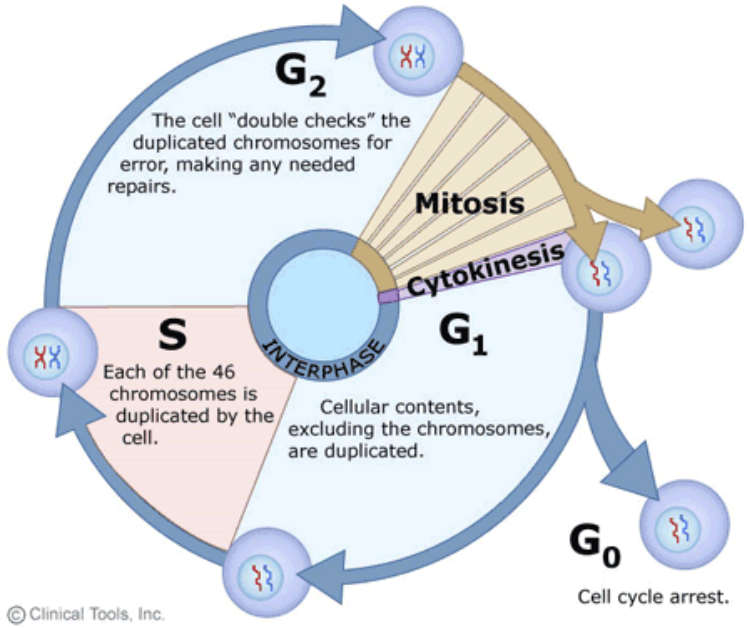
- Tumorzellen blockieren die Aktivierung von T-Lymphozyten über die PD-1/PD-L1 Achse (a)
- Immuntherapie blockiert die Verbindung von PD-1/PD-L1 (b)
- T-Lymphozyten werden aktiviert und können einen Immunresponse gegen die Erkrankung auslösen

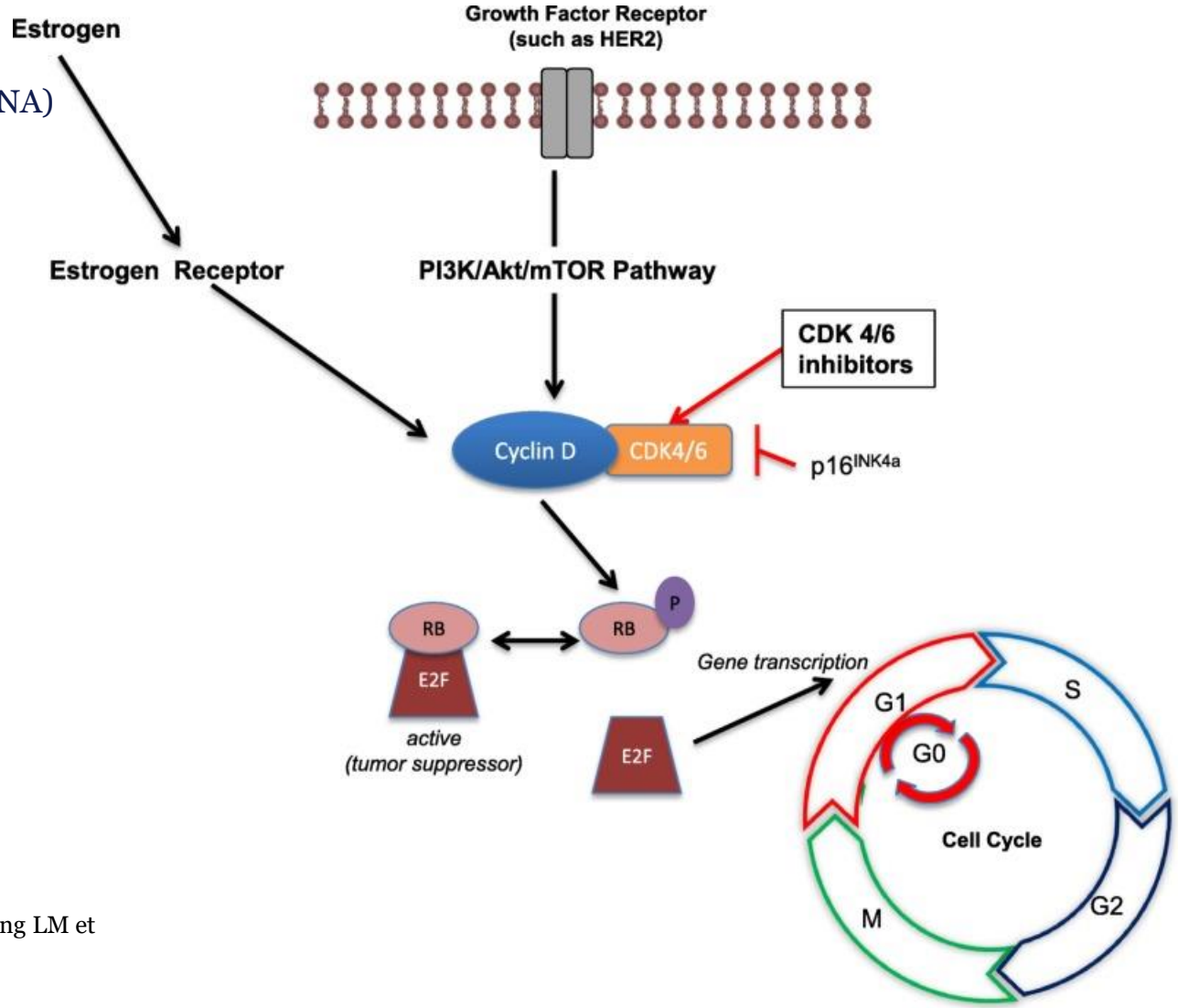


1 Caldwall C et al. Scientific Reports 2017; 7:13682.

Blockade des Zellzyklus – CDK4/6-Inhibitoren[1,2]

- Blockade der Verdoppelung der Erbinformation (DNA) vor Zellteilung

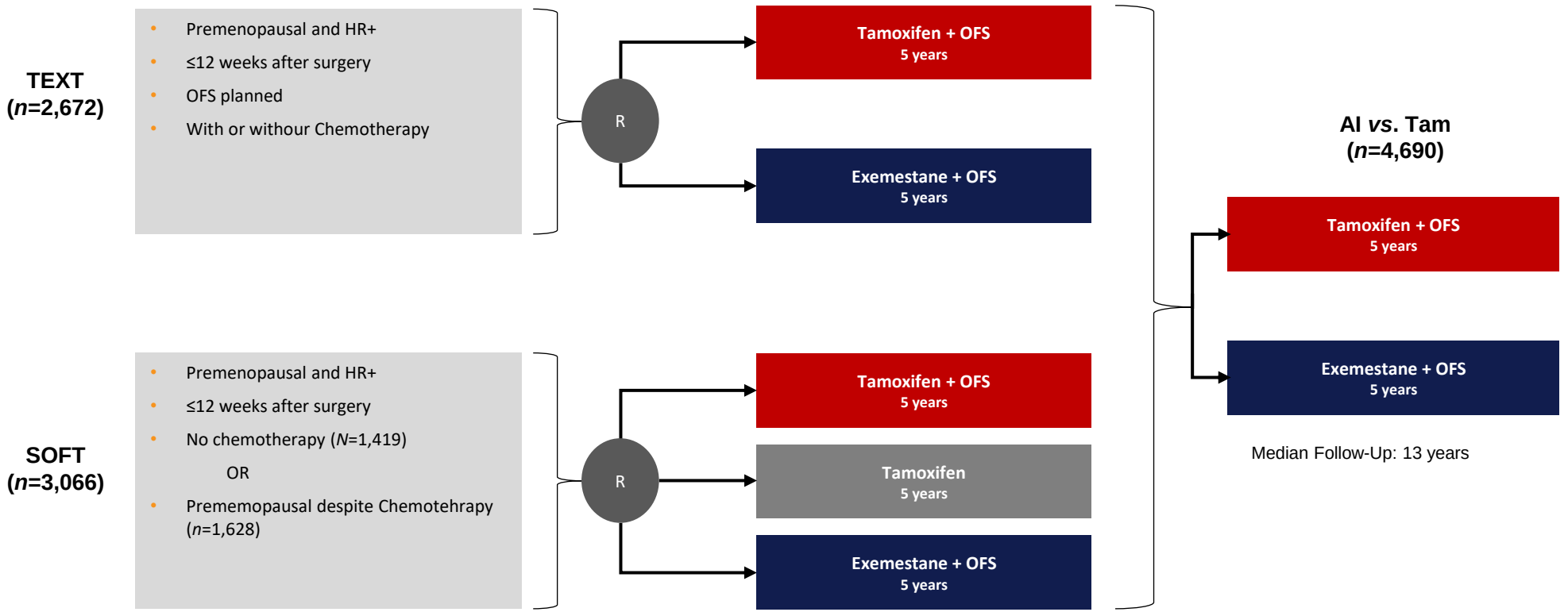




1 Caldon CE et al. J Cell Biochem 2006;97:261-274.; 2 Adapted from: Spring LM et al. Oncologist 2017,22:1039-1104.

Endokrine Therapie in der Prämenopause[1]

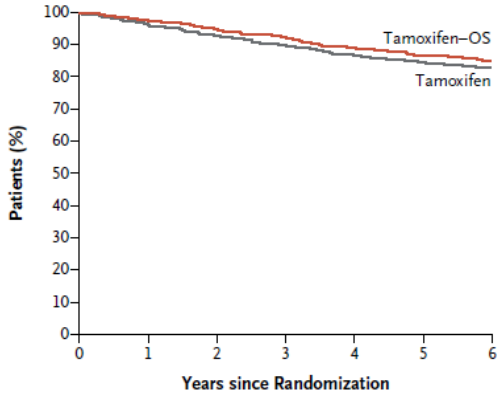
- SOFT und TEXT



1 Reagen MM et al. GS2-05; SABCS 2021.

Endokrine Therapie in der Prämenopause[1]

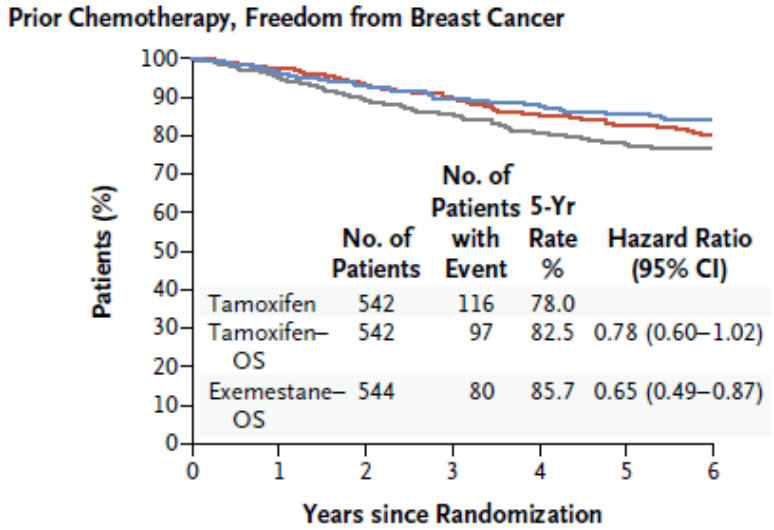
- SOFT: Tamoxifen *vs.* Tamoxifen + OFS (*vs.* Exemestan + OFS)[1]



	No. of Patients	No. of Patients with Event	5-Yr Rate %
Tamoxifen	1018	160	84.7
Tamoxifen–OS	1015	139	86.6

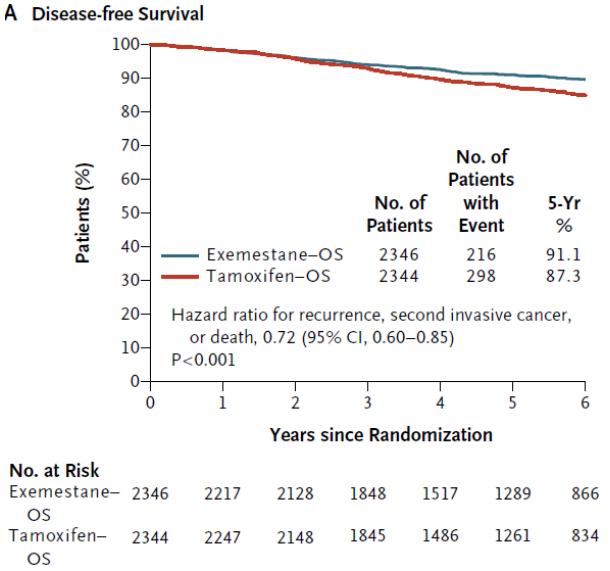
Hazard ratio for recurrence, second invasive cancer, or death, 0.83 (95% CI, 0.66–1.04)
P=0.10

- 3.066 Pat., eBC
- 350 Pat. <35 a: DFS 67,7% *vs.* 78,9% *vs.* 83,4%
- (94% vorherige Chemotherapie)



	No. of Patients	No. of Patients with Event	5-Yr Rate %	Hazard Ratio (95% CI)
Tamoxifen	542	116	78.0	
Tamoxifen–OS	542	97	82.5	0.78 (0.60–1.02)
Exemestane–OS	544	80	85.7	0.65 (0.49–0.87)

- Gemeinsame Analyse SOFT/TEXT[2]
- Tam + OFS *vs.* Exemestan + OFS
- 4.690 Pat.

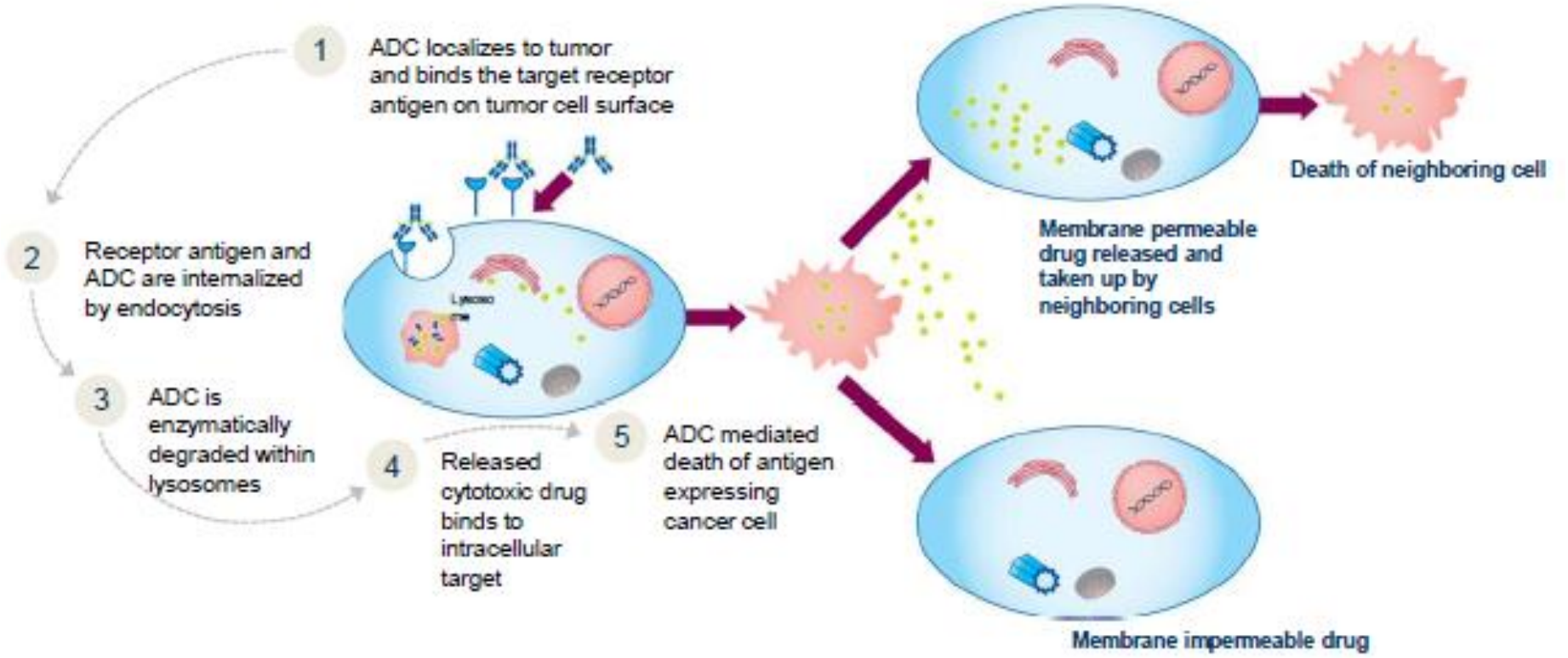


	No. of Patients	No. of Patients with Event	5-Yr %
Exemestane–OS	2346	216	91.1
Tamoxifen–OS	2344	298	87.3

1 Francis PA et al. N Engl J Med 2015;372:436-446.; 2 Pagani O et al. N Engl J Med 2014;371:107-118.

Antikörper-Medikamenten Konjugate (ADCs)

- Bystander Effekt[1]



1 Trail PA et al. Pharmacol Ther 2018;181:126-142.