

Offene Fragen, aktuelle Trends und neue Studien in der Adjuvanz

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Disclosures

Vorträge

Roche, Pfizer, Novartis, Novartis, ExactSciences, MSD, AstraZeneca, Lilly, Seagen,

Advisory Boards

Roche, Astra Zeneca, Pfizer, Novartis, MSD, Amgen, ExactSciences, Stemline, Lilly, Novartis

Offene Fragen

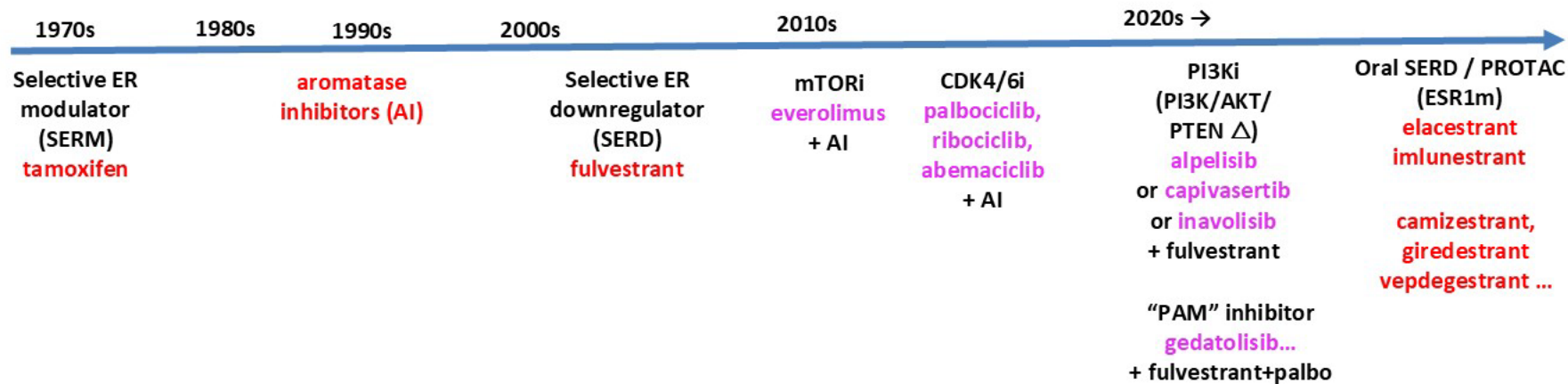
- Wohin steuert die adjuvante endokrine Therapie? SERD's – AI – Tamoxifen – PROTAC
- Adjuvant verlängerte Therapie bei intensivierter Therapie noch notwendig?
- Immer Chemo und CDK4/6i? Oder kann ein CDK4/6i die Chemo ersetzen?
- ADC's statt Chemo? ...neoadjuvant oder (postneo-)adjuvant?....mit oder ohne IO?
....oder nur AK und zielgerichtete Therapie ohne Chemo?
- Wert der IO bei pCR

Aktuelle Trends in der Adjuvanz

- Deeskalation (non inferiority)
- Therapie Tailoring und Monitoring - Biomarker (ctDNA, TIL's)
- Rescue Strategien bei non pCR nach NACT (TNBC und HER2+)
- Intensiviertes Follow-up – Survive Studie (Patientenperspektive)

Entwicklung der Antihormontherapie HR+ MaCa

Metastatic breast cancer



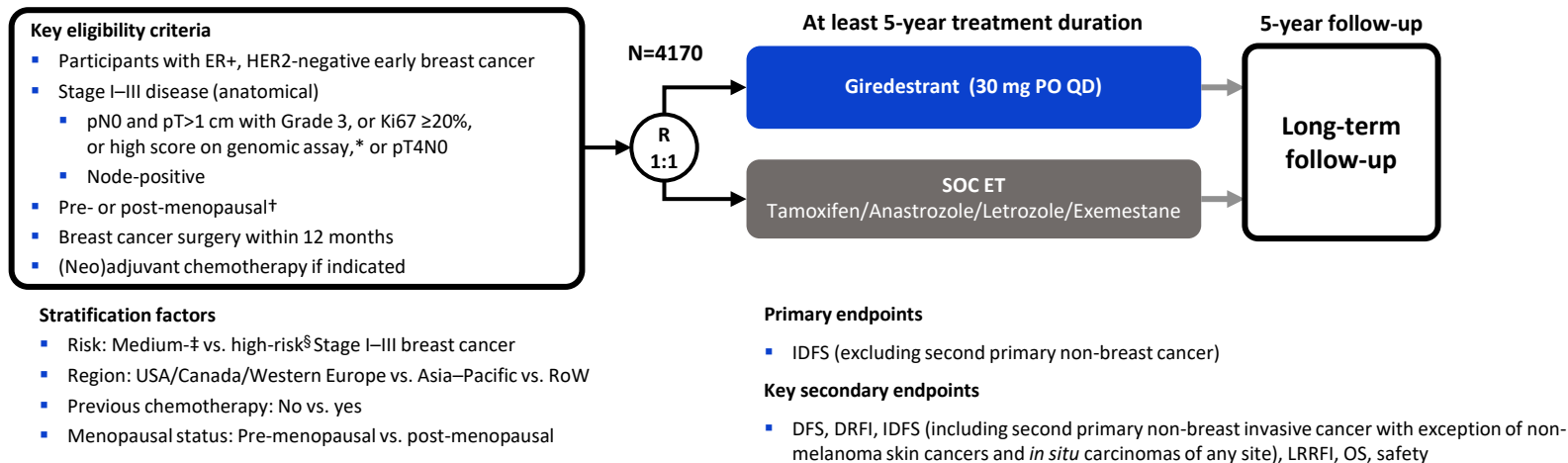
Nonmetastatic breast cancer



lidERA – Study Design

Phase 3, HR+/HER2- high risk eBC, Giredestrant vs. SOC, N=4.170

A global, randomized, open-label, multicenter Phase III trial



Giredestrant is currently also being investigated in combination with Abemaciclib in the adjuvant setting (lidERA Breast Cancer substudy 1).

Enrollment: August 2021 to September 2023. Up to 12 weeks of ET ± CDK4/6i were allowed. ER+ was defined as ≥1% positive cells by immunohistochemistry. *OncotypeDx ≥26 or high-risk MammaPrint. †Pre-menopausal patients on aromatase inhibitors or Giredestrant had to receive ovarian function suppression with an approved luteinizing hormone-releasing hormone agonist. ‡Medium risk: pN0 and primary tumor >1 cm with high-risk biologic features (Grade 3, or Ki67 ≥20%, or high score on genomic assay [if available]) and pN1 with low-risk biologic features (Grade 1/2 and Ki67 <20% and tumor ≤5 cm and low score on genomic assay [if available]). §High risk: pT4, or pN2, or pN3 and pN1 with high-risk biologic features (Grade 3, or Ki67 ≥20%, or tumor >5 cm, or high score on genomic assay [if available]). CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; DFS, disease-free survival; DRFI, distant recurrence-free interval; ER+, Estrogen receptor-positive; ET, Endocrine therapy; IDFS, invasive disease-free survival; LRRFI, locoregional recurrence-free interval; OS, overall survival; PO, orally; QD, once daily; R, randomization; RoW, rest of the world; SOC, standard-of-care. ClinicalTrials.gov number, NCT04961996. Adapted from Geyer CE, et al. ASCO 2023 (TP5616), with permission.

IdERA – Risk Score

Phase 3, HR+/HER2- high risk eBC, Giredestrant vs. SOC, N=4.170

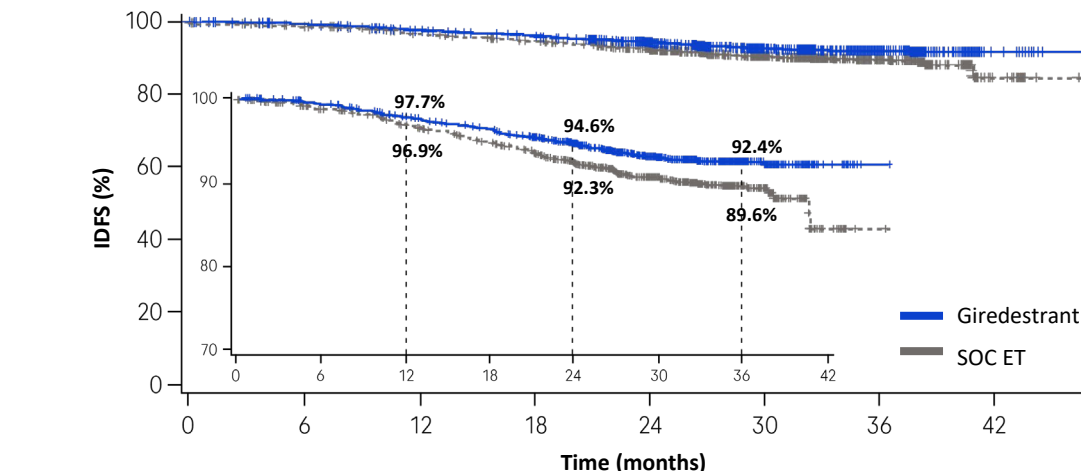
One of the stratification factors (with region, prior chemo, menopause)

- Medium risk:
 - pN0 (>1 cm) with high-risk biology - Grade 3, Ki67 $\geq$ 20%, or high genomic score
 - pN1 with low-risk biology - Grade 1/2 + Ki67 <20% + tumor $\leq$ 5 cm (+ low genomic score if done)
- High risk:
 - pT4, pN2, or pN3
 - pN1 with high-risk biology - Grade 3, Ki67 $\geq$ 20%, tumor >5 cm, or high genomic score

70% in this category

IdERA – Primary endpoint: IDFS

Phase 3, HR+/HER2- high risk eBC, Giredestrant vs. SOC ET, N=4.170



	Giredestrant n=2084	SOC ET n=2086
Events, n (%)	140 (6.7)	196 (9.4)
Stratified HR (95% CI)	0.70 (0.57, 0.87); <i>p</i> =0.0014*	

HR 0.70
3-J-IDFS +2,8%

Median follow-up: 32.3 months

Statistically significant and clinically meaningful improvement in IDFS:
Giredestrant reduced the risk of invasive disease recurrence or death by 30% compared with SOC ET

Data cutoff: August 8, 2025. Median follow-up, 32.4 months in the Giredestrant arm and 32.3 months in the SOC ET arm; maximum follow-up, 46.6 months and 46.3 months, respectively. *Log-rank (2-sided). *p*-value boundary for IDFS interim analysis was 0.0217 (2-sided). AI, aromatase inhibitor; CI, confidence interval; ET, Endocrine therapy; HR, hazard ratio; IDFS, invasive disease-free survival; SOC, standard-of-care.

GBG 23. ANNUAL SCIENTIFIC MEETING

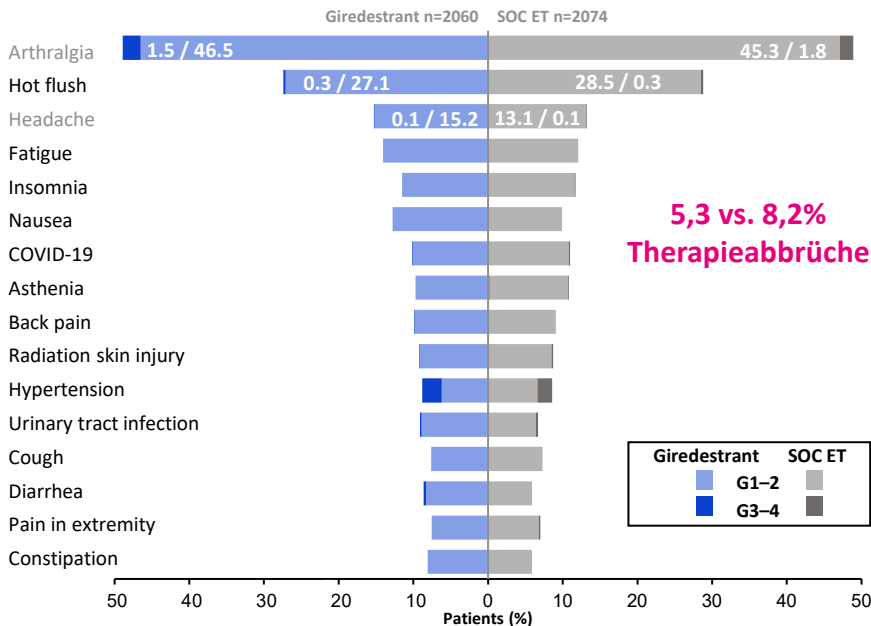
GERMAN
BREAST
GROUP

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IdERA – AE overview (safety-evaluable population)

Phase 3, HR+/HER2- high risk eBC, Giredestrant vs. SOC, N=4.170

Common TEAEs (≥7.5% of patients in either arm at any grade)



Selected AEs

	Giredestrant n=2060	SOC ET n=2074
Patients, n (%) with treatment discontinuations due to AEs		
Musculoskeletal disorders	38 (1.8)	92 (4.4)
Arthralgias (PT)	32 (1.6)	76 (3.7)
Vasomotor disorders	2 (<0.1)	18 (0.9)
Hot flush (PT)	1 (<0.1)	16 (0.8)

	Giredestrant n=2060			SOC ET n=2074		
Patients, n (%) with selected AEs by medical concept*						
	G1	G2	G3–4	G1	G2	G3–4
Bradycardia [†]	217 (10.5)	15 (0.7)	0	64 (3.1)	2 (<0.1)	0
Venous thromboembolic events	4 (0.2)	12 (0.6)	2 (<0.1) [‡]	3 (0.1)	7 (0.3)	7 (0.3)

Data cutoff: August 8, 2025. *Assessed as medical concepts using grouped terms; all other AEs by medical concept were comparable between arms, including four patients per arm (0.2%) who experienced photopsia. [†]G2 events occurred in 17 patients; 13 resolved, four patients discontinued treatment and the events resolved. [‡]G3 only. AE, adverse event; ET, Endocrine therapy; G, grade; PT, preferred term; SOC, standard-of-care; TEAE, treatment-emergent adverse event.

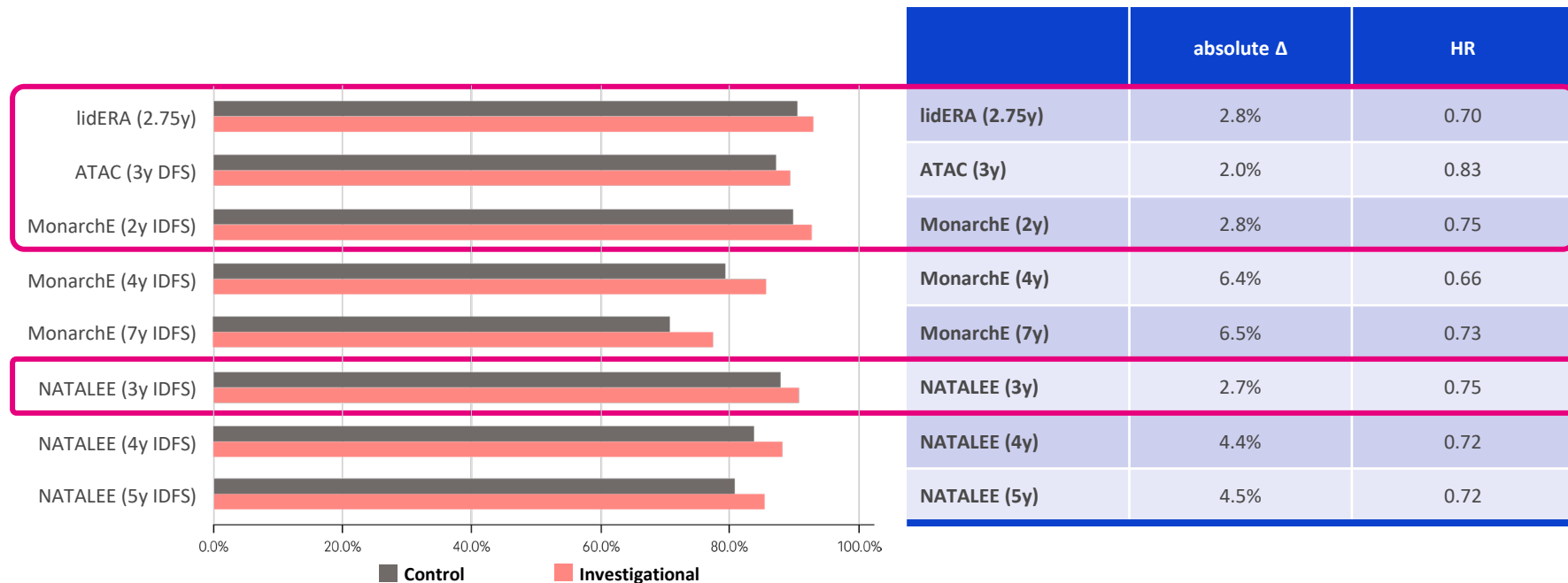
GBG 23. ANNUAL SCIENTIFIC MEETING

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lidERA – in Context of Other Adjuvant Advances

Phase 3, HR+/HER2- high risk eBC, Giredestrant vs. SOC, N=4.170



Bardia A, SABCS2025; ATAC Trialists, Lancet 2005; Johnston S, JCO2020; Lancet Oncol 2023; ESMO2025; Hortobagyi G, Ann Oncol2025; Fasching PA, JAMA Oncol 2025; Crown J,

Aktuelle Trends in der Adjuvanz – Einfluss der lidERA?

- Derzeit ist der absolute Benefit noch klein – kann aber mit zunehmender Nachbeobachtung steigen
- Evidenz für den Einsatz von Giredestrant in der Hochrisikogruppe wenn eine Mono-ET gegeben werden soll
- In der Gruppe mit mittlerem Risiko kann man nur wenige Events beobachten. Hier ist längeres follow up wichtig
- Die Kombination mit CDK4/6i ist bislang noch nicht untersucht.

Orale SERDs adjuvante Studien

Trial Name	N	Arms	Patient Population	Adjuvant CDK4/6i allowed	Trial Identifier
CAMBRIA-2	5500	Camizestrant vs ET	High-risk ER+/HER2-, first adjuvant therapy	Yes	NCT05952557
lidERA	4200	Giredestrant vs ET	Medium to high-risk ER+/HER2-, first adjuvant therapy	No	NCT04961996
ELEGANT	4220	Elacestrant vs SoC	ER+/HER2-, Early Breast Cancer With High Risk of Recurrence; 2-5y of prior ET	Prior to trial entry	NCT06492616
EMBER-4	6000	Imlunestrant vs ET	High-risk ER+/HER2-, 2-5 yr of adjuvant ET	Prior to trial entry	NCT05514054
CAMBRIA-1	4300	Camizestrant vs ET	Intermediate to high-risk ER+/HER2-, 2-5 yr of adjuvant ET	Prior to trial entry	NCT05774951
TREAT ctDNA	220	Elacestrant vs ET	↑ risk ER+/HER2-, ctDNA relapse, 2-7 yr adjuvant ET	≥12 mo prior to trial entry	NCT05512364

Adapted from Clinical Care Options (clinicaloptions.com)

Spielt die ESR1m eine Rolle für die lidERA Ergebnisse?

Vergleich der oralen SERDs mit IM Fulvestrant

Trial	N	PO SERD	Control % fulvestrant	ESR1m %	HR (ITT) (ESR1m)
EMERALD	477	Flacestrant	69%	48%	0.70 (0.55-0.88) 0.77
SERENA-					82)* .58)
aceIERA	303	Giredestrant	75%	39%	0.61 (0.33-1.10) 0.60 (0.35-1.03)
EMBER-3	874	Imlunestrant**	88%	39%	0.87 (0.72-1.04) 0.62 (0.46-0.82)

Orales SERD alleine ist besser als IM SERD mit ESR1 Mutation

Orales SERD ist vergleichbar mit IM SERD bei wild-type ESR1

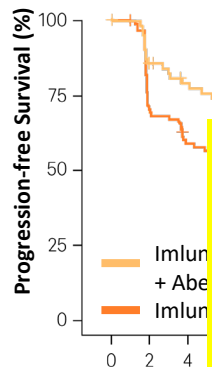
*75mg arm, ** monotherapy arm

Ember-3-Subgroup Analysis

Phase 3, HR+/HER2- mBC, Imlunestrant vs. SOC vs. Im.+Abemaciclib nach ET, 2. OS Interim

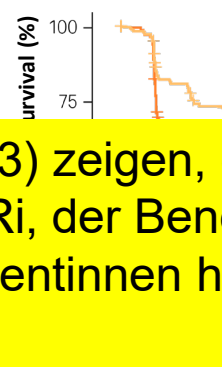
Investigator-assessed PFS by *ESR1*m status: Imlunestrant + Abemaciclib vs. Imlunestrant

Patients with *ESR1*m



	Imlunestrant + Abemaciclib n=67	Imlunestrant n=92
No. of events	36	71
Median (95% CI)	11.1	5.5

Patients without *ESR1*m



	Imlunestrant + Abemaciclib n=146	Imlunestrant n=121
No. of events	78	78
Median (95% CI)	9.1 (4.4–14.4)	5.5 (3.6–5.8)
HR (95% CI)	0.59 (0.43–0.81)	

Einige Studien (evERA, EMBER-3) zeigen, dass durch die Hinzunahme von CDK4/6i, mTORi, der Benefit der SERDs über die Gruppe der *ESR1*m Patientinnen hinaus erweiterbar ist

No. at Risk

Time (months)	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30
Imlunestrant + Abemaciclib	67	54	47	39	33	22	14	7	6	3	1	1	0	0	0	0
Imlunestrant	92	62	50	35	28	20	12	9	7	3	0	0	0	0	0	0

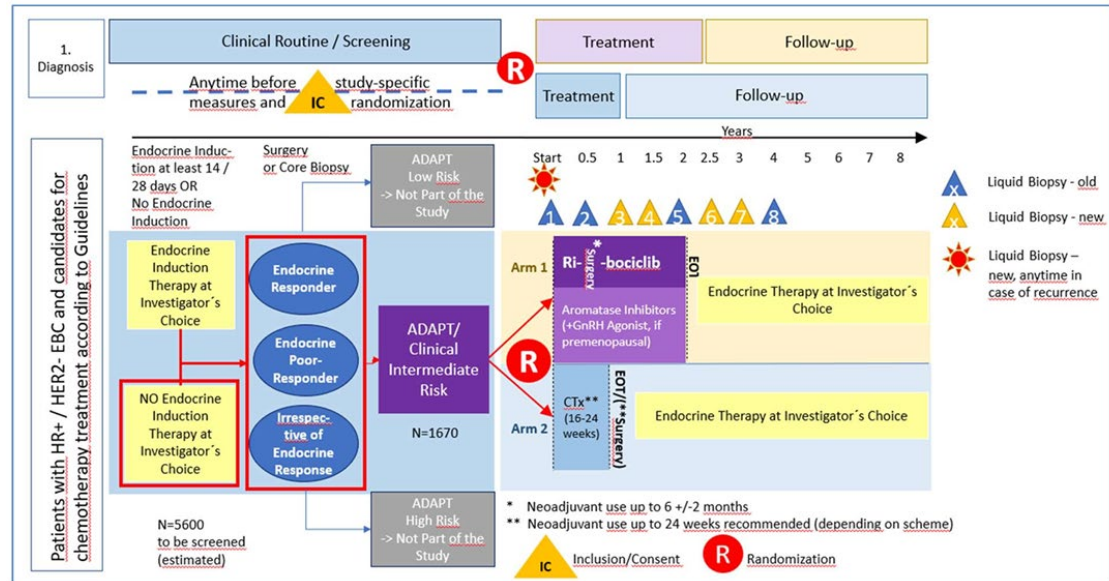
No. at Risk

Time (months)	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30
Imlunestrant + Abemaciclib	146	111	94	83	63	50	34	22	19	10	5	4	3	0	0	0
Imlunestrant	121	78	56	42	39	28	17	11	11	7	3	2	0	0	0	0

First instance where oral SERDs appear to 'break out' from the *ESR1* mutation 'box,' perhaps reflecting a more active endocrine agent in combination with effective targeting of cross-talk pathway in tumors that fundamentally remain ER-dependent

Aktuelle Trends in der Adjuvanz

- Wer braucht den dann noch Chemo?
- Kann der CDK4/6 Inhibitor die Chemo ersetzen?



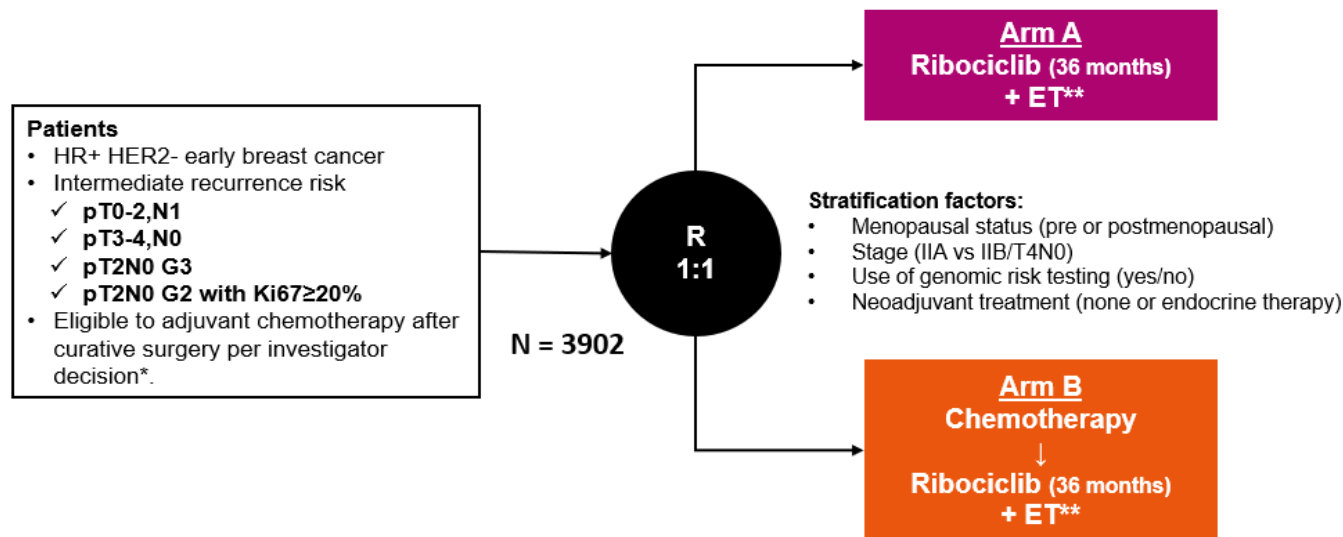
Neue Studien in der Adjuvanz

NoLEEta

Unicancer UCBG227/GBG121

No chemotherapy in intermediate-risk HR+ HER2- early breast cancer treated with Ribociclib (LEE-011) in the adjuvant setting, a non-inferiority Phase III trial

Studiendesign – Non Inferiority Trial



Primäres Studienziel
iBCFS

Sekundäre Ziele
iDFS, DDFS
OS n. 3, 5, 8, 10 Jahren
Sicherheit
QoL

* based on clinicopathological findings or the results of any genomic signature

** AI +/-OFS during ribociclib treatment, per investigator choice thereafter

Einschluss-/ Ausschlusskriterien

Einschlusskriterien

- pT2 pN0 Grad 3 oder pT2 pN0 Grad 2 mit Ki67≥20 % oder pT0-2 pN1 oder pT3-4 pN0

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Kr

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▪ Ke
Be

- Kurative Operation der invasiven Erkrankung muss mit negativen Operationsrändern innerhalb von 12 Wochen vor der Randomisierung erfolgt sein

Ausschlusskriterien

- Neoadjuvante Chemotherapie oder vorherige Therapie mit CDK4/6-Inhibitor

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	MonarchE			NATALEE			NoLEEta		
	N0	N1	N2/N3	N0	N1	N2/N3	N0	N1	N2/N3
T1		G3 or Ki67≥ 20%							
T2				G3 or (G2 & [Ki67 ≥ 20% or genomic high risk])			G3 or G2 + Ki67≥ 20%		
T3									
T4									

Zeitplan

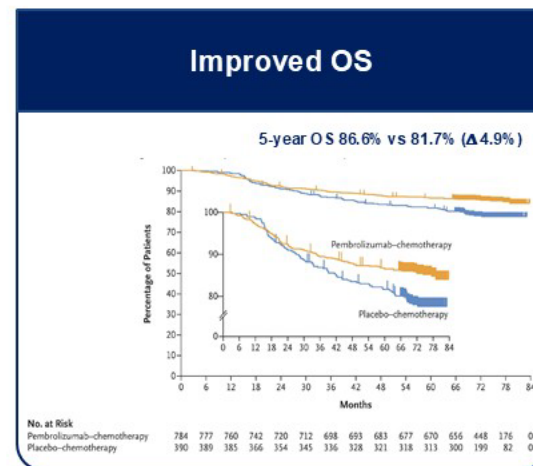
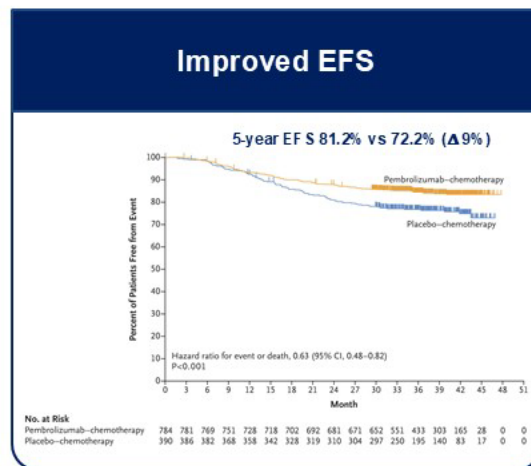
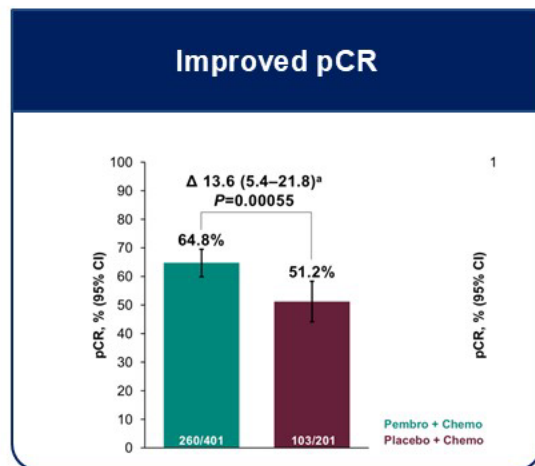
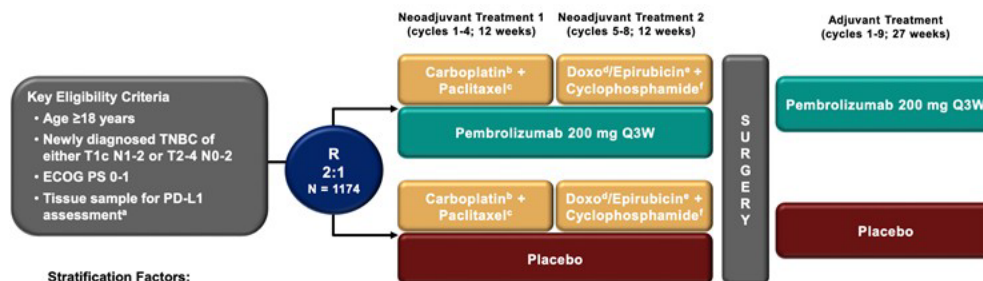
- Rekrutierungszeitraum: 42 Monate
- Behandlungszeitraum:
 - Control Arm: ~ 42 Monate
 - Investigational Arm (Ribociclib): 36 Monate
- Follow-up: 102 Monate
- Gesamtdauer der Studie: 144 Monate (12 Jahre)
- Anzahl Zentren DEU: 30
- Geplante Anzahl Patientinnen DEU: 500

Kontakt

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Neuer Therapiestandard TNBC Stadium II-III – Keynote 522

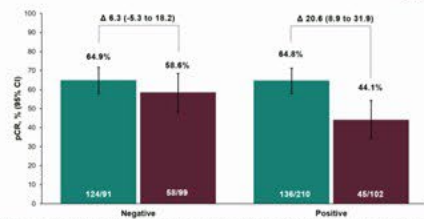


Keynote 522 Ergebnisse nach Stadium und RCB score

Higher stage - Higher benefit

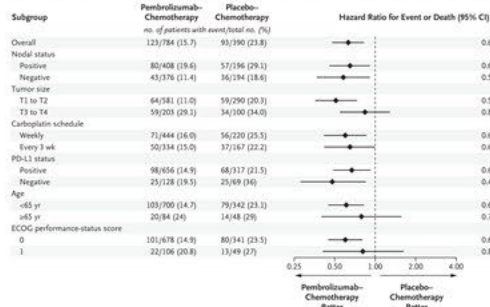
Tumor burden vs IO benefit?

pCR by Lymph Node Involvement



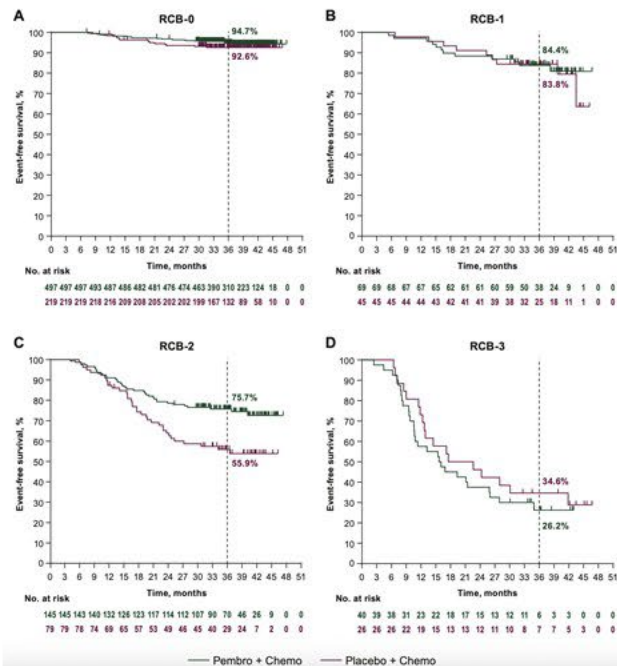
EFS benefit consistent across subgroups

Benefit in node negative; PD-L1 not biomarker

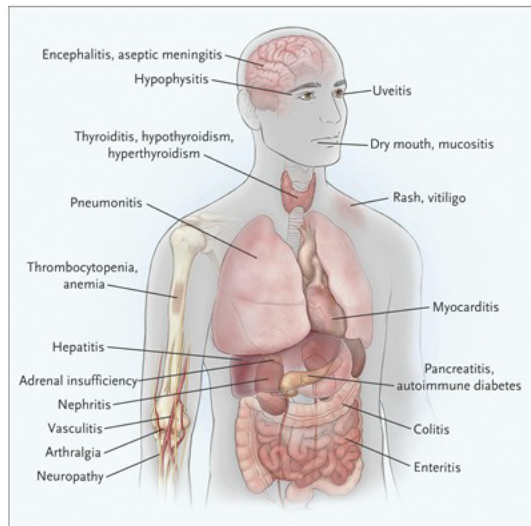


Residual disease – high risk of relapse

Role of adjuvant Pembrolizumab?



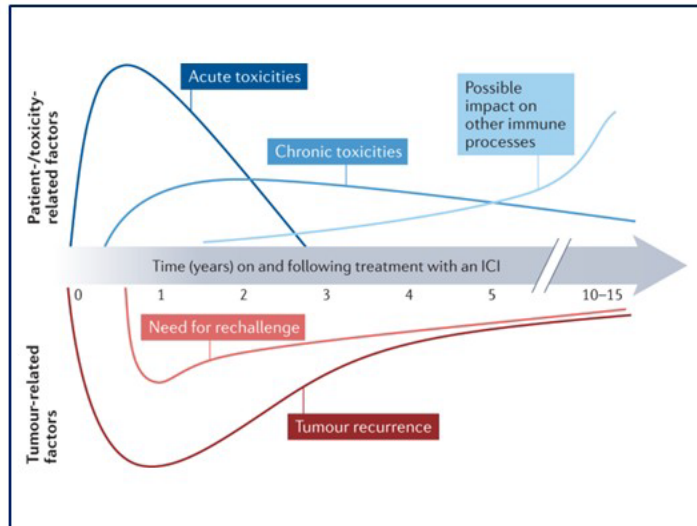
Immunvermittelte NW und chronische Veränderungen



Doxorubicin-induced heart toxicity 2-4%

Pembrolizumab: Hypothyroidism 15%; Hyperthyroidism 5.2%; Adrenal insufficiency 2.6%; Hypophysitis 1.9%

Impact on fertility to be defined.



PREDICTING irAEs

- Demographics
- Autoimmune disease
- Biomarkers (on-treatment, autoantibodies, genetic predisposition, etc.)

No validated biomarker

Early Intervention – Chronic disease – Impact long-term quality of life

Real-World Daten Effektivität und Sicherheit Keynote 522

	Keynote 522 (Pembro arm)	Brazil	US	UK	France	US	Japan
N	783	311 (181 ddAC)	86	608	100	577	69
pCR	64.8%	58.7% (65.4% ddAC)	59.3%	57%	58%	54.5%	56.5%
pCR BRCAm	NA	73%	NR	70%	80%	NR	NR
AE grade ≥3	77.1%	30.7% (40.5% ddAC)	NR	59%	NA	NR	80.4%
irAE (any grade)	43.6%	31%	52%	65%	61%	54%	42.3%
irAE grade ≥ 3	14.9%	13.6%	34.9% (grade ≥2)	19%	30%	31%	15.2%
Discontinuation	27.7%	20.1% (25.1% ddAC)	NR	42% (52% P adjuvant)	35% (75% P adjuvant)	39.5%	35%

NR: not reported

Slight lower pCR rates. Higher toxicity especially irAEs grade ≥ 3 and discontinuation rate.

Schmid P. NEJM 2022; Andrade The Breast 2025; Bonadio RC NPJ Breast Cancer 2024; Tavares M. J Clin Oncol 43, e12618(2025); Connors C Ann Surg Oncol 2025; Daniels E. ESMO Open, Volume 10, 104758 204P; Rached L. ESMO Real World Data and Digital Oncology 2024; Hofherr M. SABCS 2023 PS14-06; Aoyama Y Breast Cancer 2024

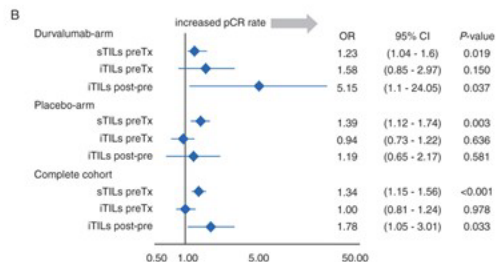
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Aktuelle Trends in der Adjuvanz TNBC

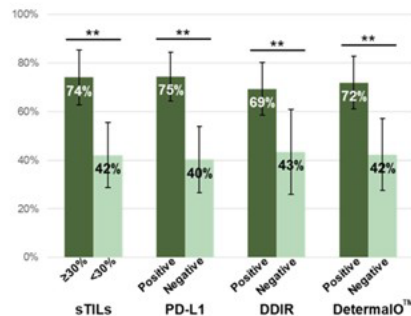
- Wie kann ein Tailoring der **neoadjuvanten Therapiephase** aussehen?
 - Prädiktive und/oder prognostische Biomarker für IO Ansprechen
 - Low Dose Pembrolizumab
 - Ersatz der Chemotherapie durch ADCs
 - Dynamische Marker und Bildgebung zur Deeskalation

Hohe TILs, PD-L1+, DetermalO assoziiert mit höherer pCR Rate

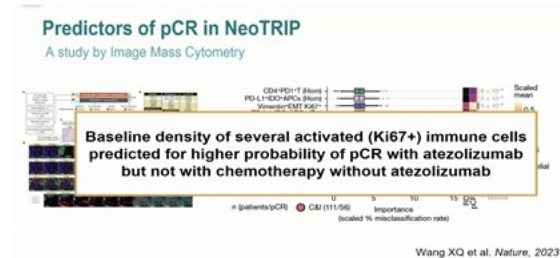
GEARNUEVO Durvalumab



NEOPACT Pembrolizumab



NEOTRIP Atezolizumab



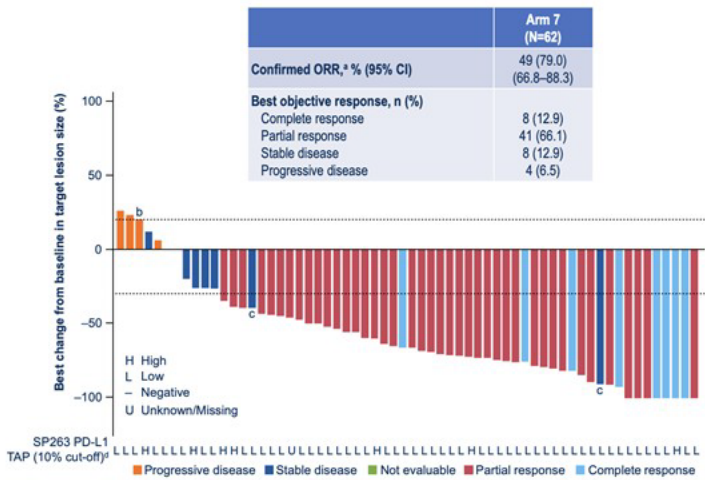
Prädiktive und prognostische Marker auch für den IO-Benefit
Immunologisch „kalte“ Tumore, Biomarker-negative Subgruppen mit
Resistenzen für CT+IO

Standard NACT-IO backbone vs ADC-IO Kombination

BEGONIA

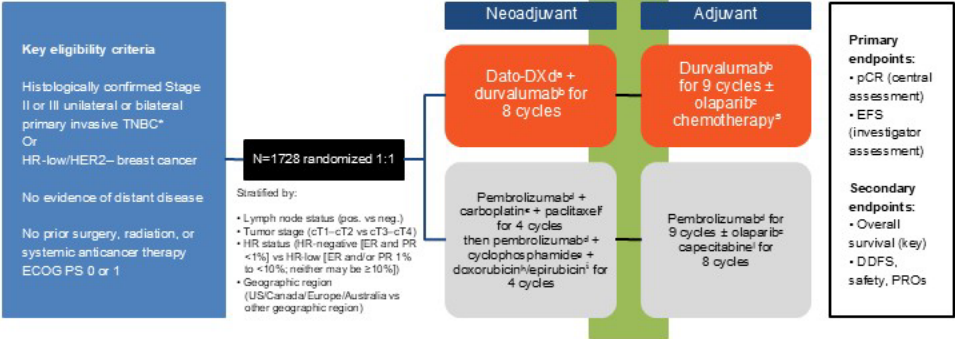
1L Dato-DXd + Durvalumab in mTNBC

11.3% patients had PD-L1 high tumours and 87.1% had PD-L1 low tumours



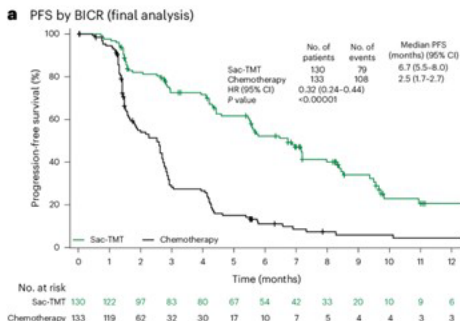
Responses were observed in patients with PD-L1 high and PD-L1 low tumours

TROPION-Breast04

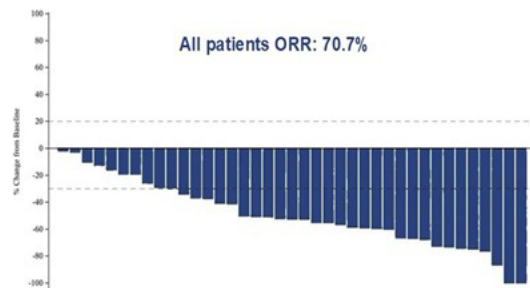


Anthracyclinfreie NACT mit ADC-IO Kombination

OptiTROP-Breast01 2L Sacituzumab tirumotecan in mTNBC



OptiTROP-Breast05 1L Sacituzumab tirumotecan in mTNBC



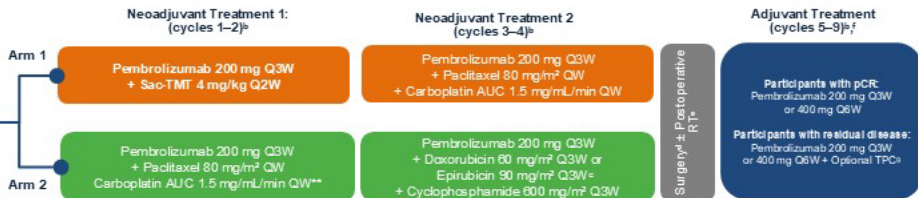
Grade 3≥ 63.4%
(mono therapy)
mPFS 11.4 months

TroFuse-032

Key eligibility criteria

- Centrally confirmed TNBC or HR-low+/HER2- breast cancer*
- cT1c, N 1-2 or cT2-4, N0-2
- No metastases
- No prior systemic therapy
- No previous excision of primary tumor
- ECOG PS 0 or 1

R (1:1)
N ~ 2400



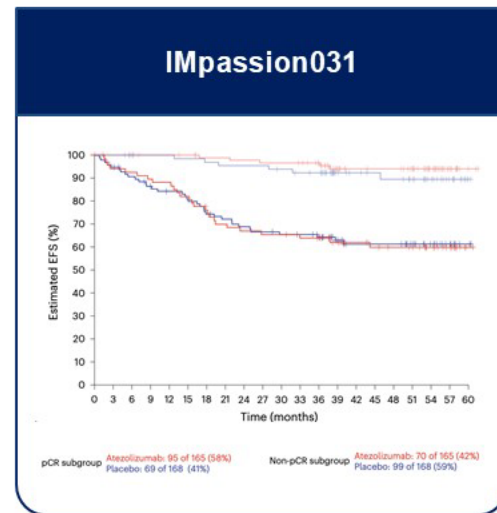
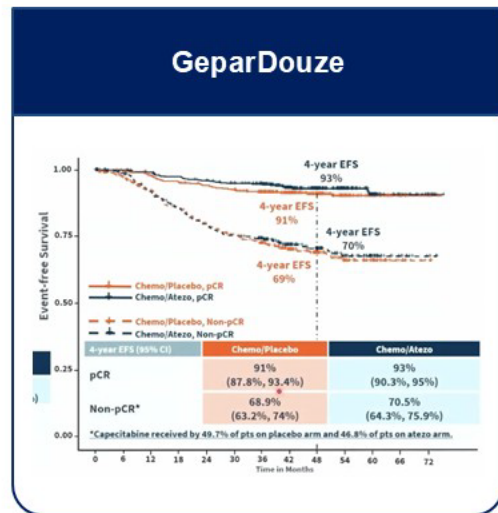
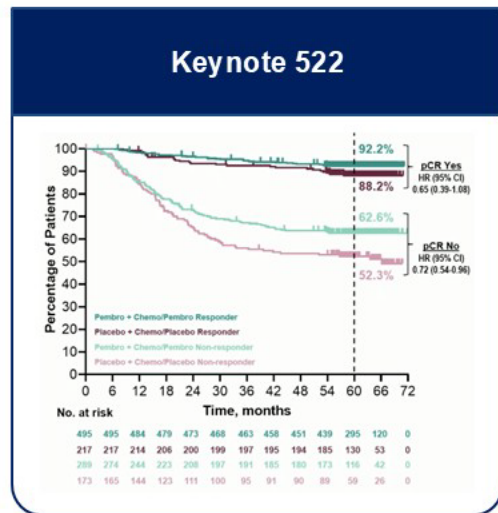
Primary endpoints

- pCR (ypT0/Ts ypN0)
- EFS

Aktuelle Trends in der Adjuvanz TNBC

- Wie kann ein Tailoring der **adjuvanten Therapiephase** aussehen?
 - De-eskalation der Immuntherapie
 - Prognostische Biomarker im residuellen Tumor
 - ctDNA guided adjuvante Therapie
 - ADC Einsatz+/- IO bei residuellem Tumor

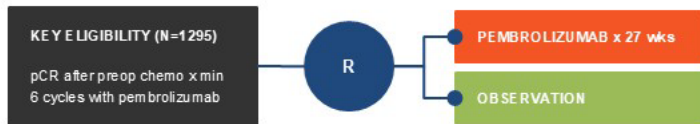
Prognose der Patientinnen mit pCR nach NACT + IO



Patients with stage II-III TNBC that achieve pCR have an excellent prognosis, regardless of previous treatment received.

De-escalation der adjuvanten Immuntherapie post pCR

OptimICE-pCR

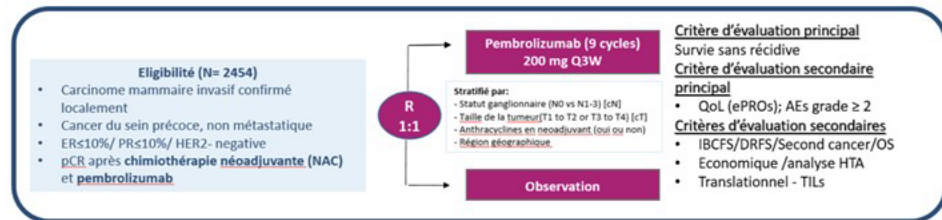


Primary endpoint: RFS (non-inferiority)

Stratification Factors

Baseline Nodal Status Receipt of Anthracycline: Yes vs. No

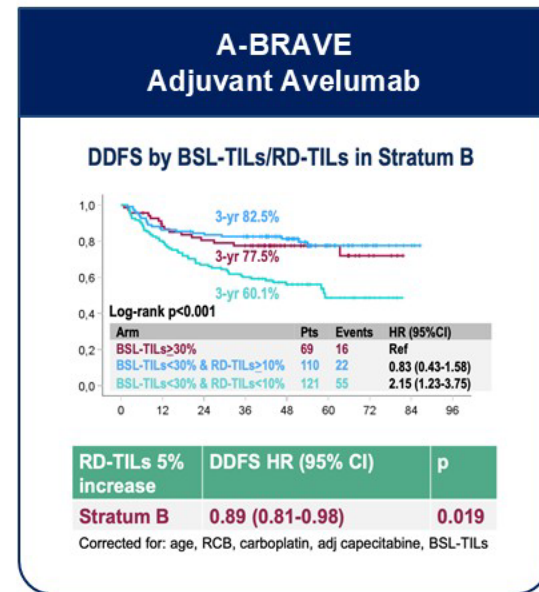
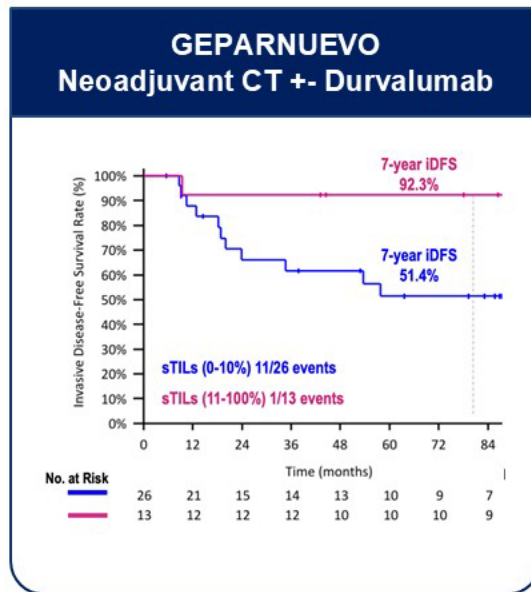
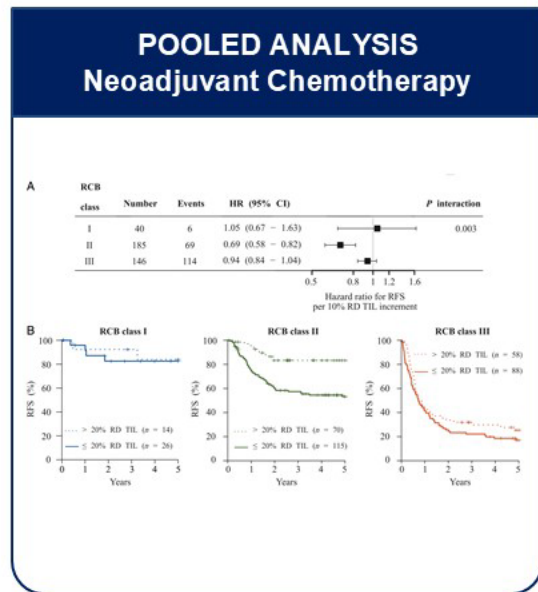
Opt-PEMBRO



Meta-analysis is planned

Both studies highlight the essential role of academic research groups to advance breast cancer treatment and outcome

Sind TILs im residuellen Tumor prognostisch?



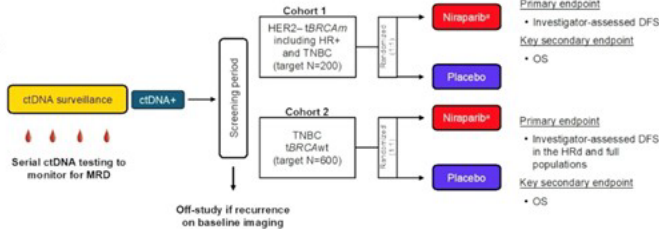
TILs in residual disease are highly prognostic and merit validation for tailoring adjuvant therapy in TNBC.

ctDNA in der Nachsorge bei hoch Risiko/non-pCR TNBC

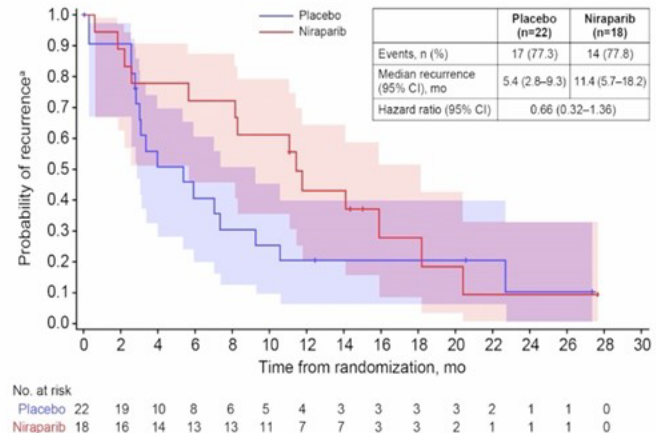
ZEST Niraparib for ctDNA+

Key eligibility criteria

- Stage I–III breast cancer
- TNBC (regardless of BRCA status) or tBRCAm HR+HER2–
- Completed prior standard therapy for curative intent
- HR+ allowed adjuvant endocrine therapy
- TNBC allowed adjuvant pembrolizumab
- No clinical sign of recurrence
- Patients who had neoadjuvant chemotherapy and tumor showed no response were excluded



- Low rate of ctDNA detection (8%)
- In TNBC 60% ctDNA+ ≤ 6 months of treatment
- High rate (50%) of metastatic disease at time of ctDNA+



Investigators were unblinded at the time the study was terminated (April 25, 2023)

Challenges for future MRD trials are test sensitivity vs. specificity and lead time to metastatic disease.

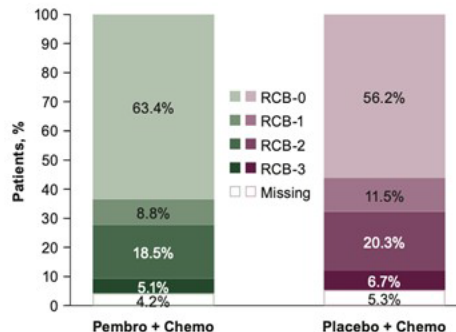
Laufende klinische Studien mit ADCs bei TNBC und non-pCR

Neoadjuvant Phase

Chemotherapy
+ Carboplatin
+ Pembrolizumab

Surgery

Residual Disease in 35-45%



**30% didn't initiate
Adjuvant Phase
(Keynote 522)**

Adjuvant Phase

SASCIA

Sac-Gov vs. SOC

ASCENT 05/ OptimICE-RD

Sac-Gov + Pembro vs. SOC

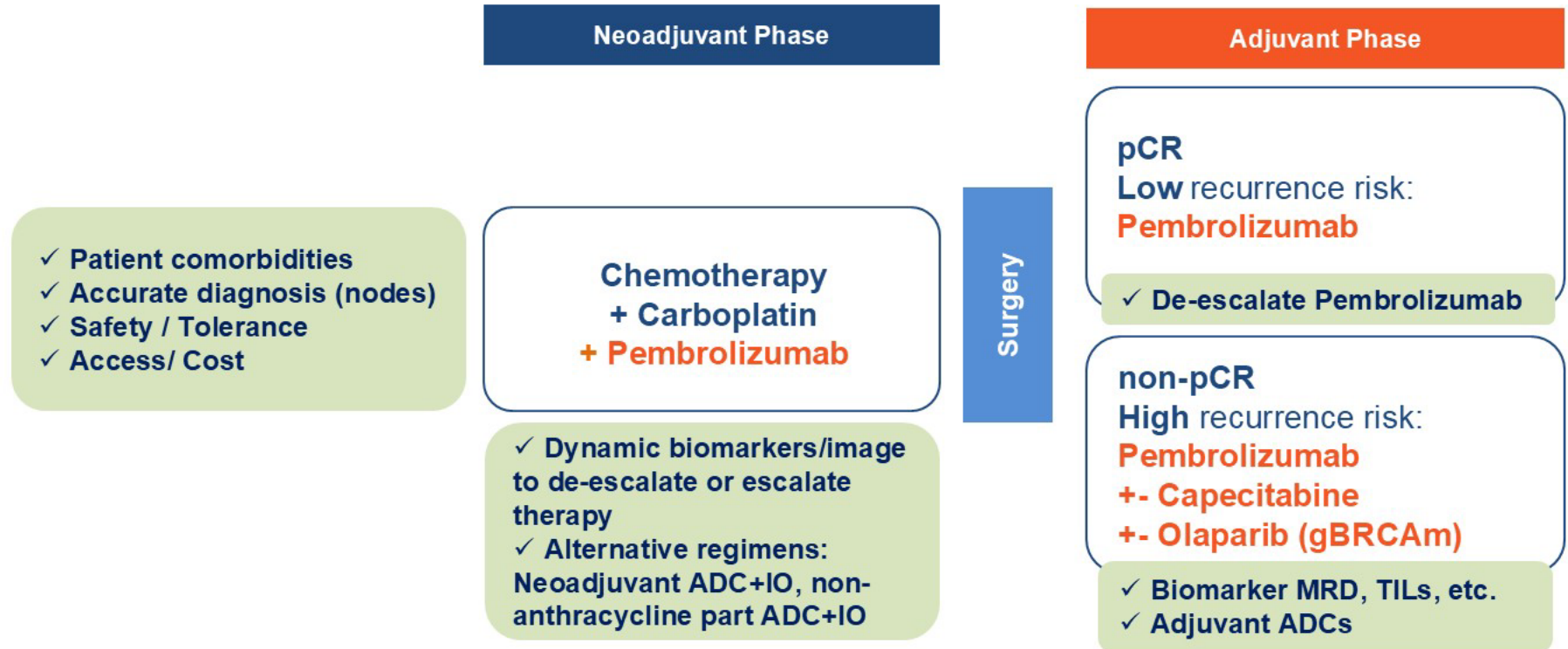
TROPION-Breast03

Dato-DXd +/- Durva vs. SOC

TroFuse-012

Sac-TMT +/- Pembro vs. SOC

Möglichkeiten zur Therapieadaptation bei TNBC Stadium II-III





Heilung durch Innovation, Kompetenz
und Partnerschaft – führend in der
Brustkrebs-Forschung

23. ANNUAL SCIENTIFIC MEETING

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