SURVIVE - aktive Nachsorge

Wolfgang Janni

Universitätsfrauenklinik Ulm

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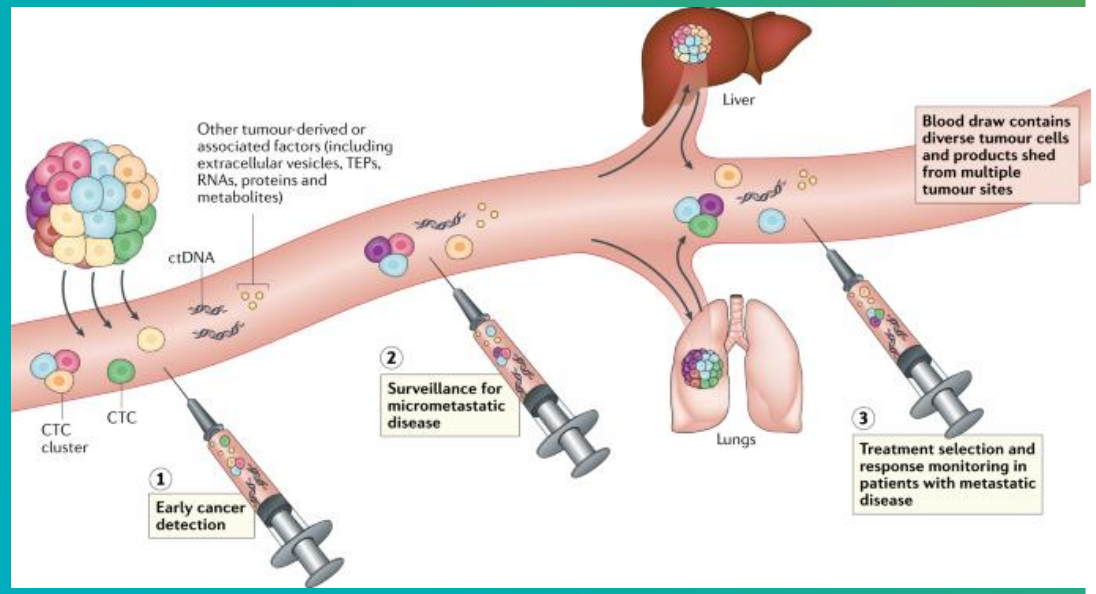
GBG-Jahrestreffen



Disclosures

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Sanofi-Aventis, Novartis, Roche, Pfizer, AstraZeneca, Chugai, GSK, Eisai, Cellgene, Lilly, Janssen, Menarini

Brustkrebs Nachsorge
Ziele

Guidelines Breast
Version 2021.1D

	Oxford		
	LoE	GR	AGO
Früherkennung von heilbaren Rezidiven			
▪ Intramammäre Rezidive	1a	B	++
▪ Lokoregionäre Rezidive*	1a	B	++
Früherkennung kontralateraler Karzinome	1a	B	++
Früherkennung von Metastasen			
▪ Früherkennung symptomatischer Metastasen	3b	C	+
▪ Früherkennung asymptomatischer Metastasen	1a	A	-

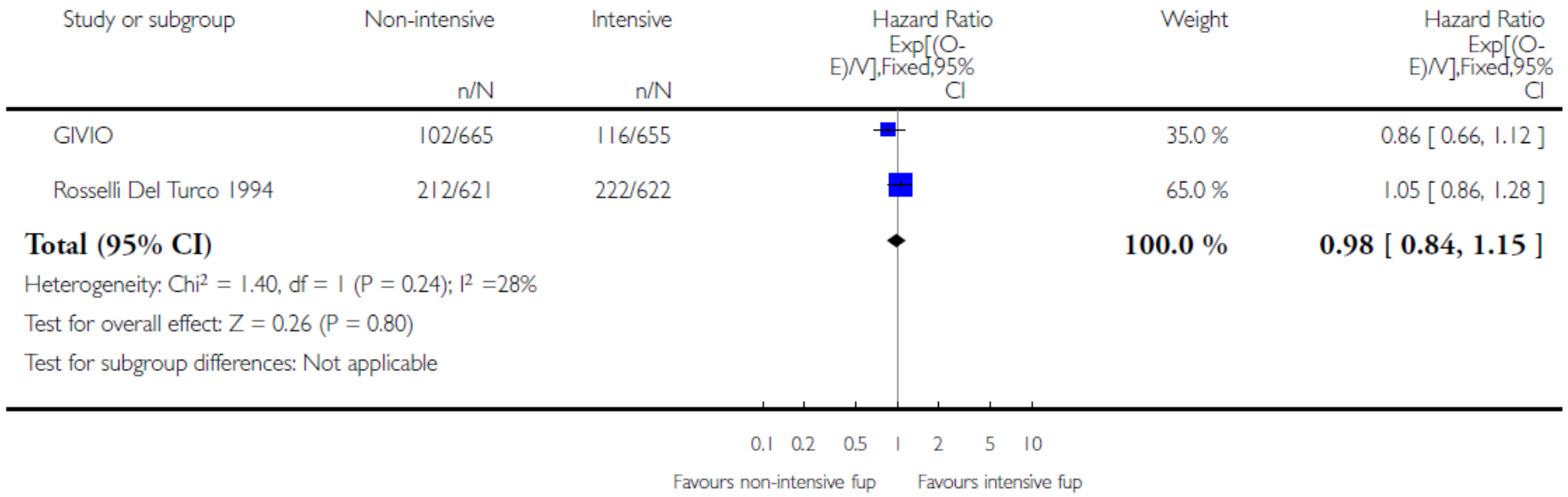
* Das lokoregionäre Rezidiv ist mit einem erhöhten Mortalitätsrisiko bei nodalpositiven, PR-negativen, jüngeren Patientinnen und einem kurzen Zeitintervall von Erstdiagnose bis Rezidiv verbunden.

Routine-Nachsorgeuntersuchungen bei asymptomatischen Patientinnen

Guidelines Breast
Version 2021.1D

	Oxford		
	LoE	GR	AGO
▪ Routinelabor (inkl. Tumormarker)	1a	A	-
▪ Labor zum Monitoring der Akut- und Spättoxizitäten der Therapien	5	D	+
▪ Lebersonographie	1a	A	-
▪ Skelettszintigraphie	1a	A	-
▪ Thorax-Röntgen	1a	A	-
▪ CT-Untersuchungen (Thorax, Abdomen und Becken)	2a	D	-
▪ Detektion isolierter / zirkulierender Tumorzellen	2a	D	-
▪ PET-CT	2b	B	-
▪ Ganzkörper-MRT	2b	B	-

Die Evidenzbasis – Cochrane Analyse



Moschetti et al. Cochrane Database 2016
GIVIO investigators, JAMA 1994
Palli et al., JAMA 1999; Rosselli del Turco et al., JAMA 1994

Hintergrund: Datenlage

May 25, 1994

Intensive Diagnostic Follow-up After Treatment of Primary Breast Cancer

A Randomized Trial

Marco Rosselli Del Turco, MD; Domenico Palli, MD; Angelo Cariddi, MD; et al

» Author Affiliations

JAMA. 1994;271(20):1593-1597. doi:10.1001/jama.1994.03510440053032

May 25, 1994

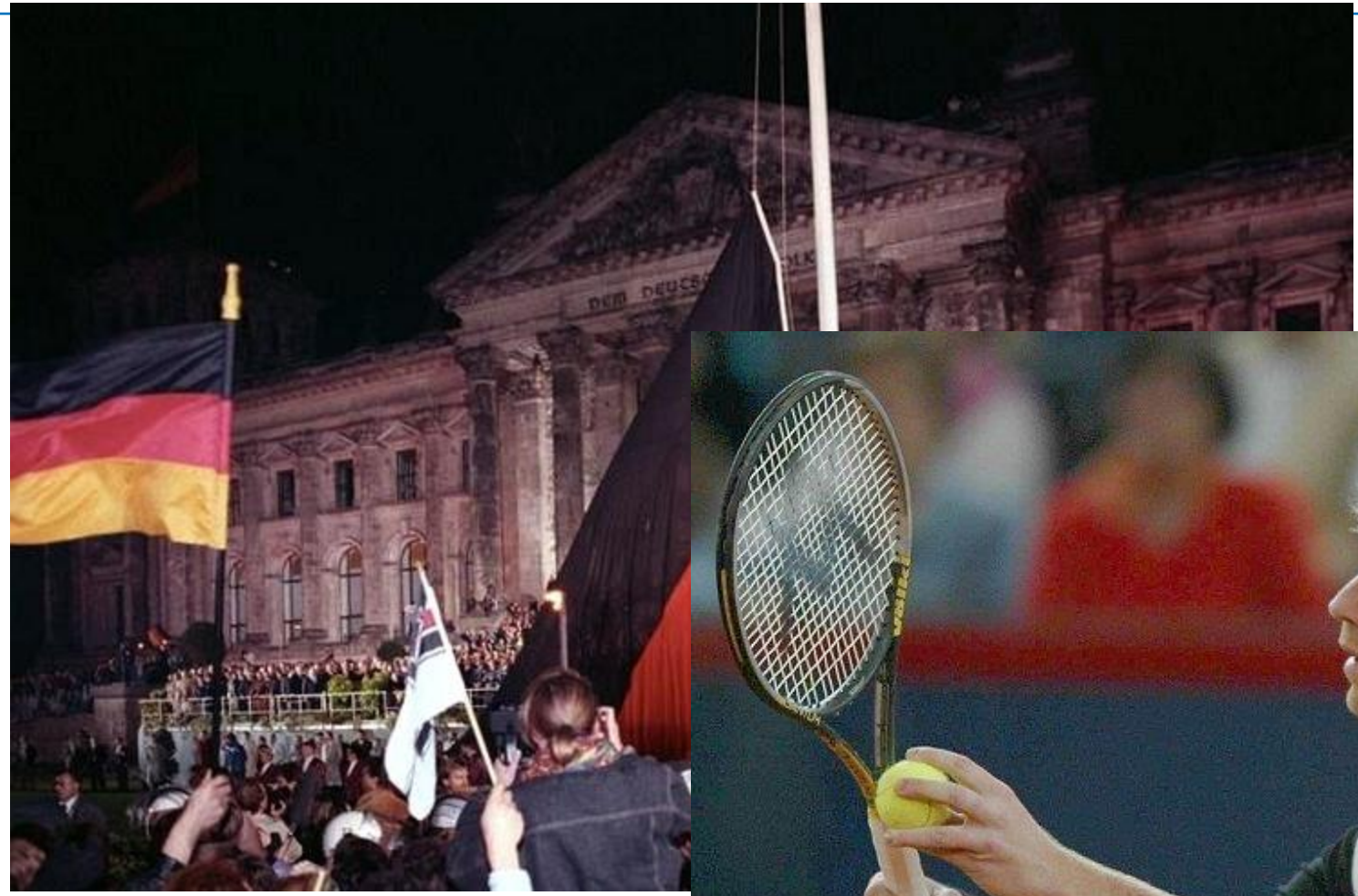
Impact of Follow-up Testing on Survival and Health-Related Quality of Life in Breast Cancer Patients

A Multicenter Randomized Controlled Trial

P. Ghezzi, MD; S. Magnanini, MD; M. Rinaldini, MD; et al

» Author Affiliations

JAMA. 1994;271(20):1587-1592. doi:10.1001/jama.1994.03510440047031

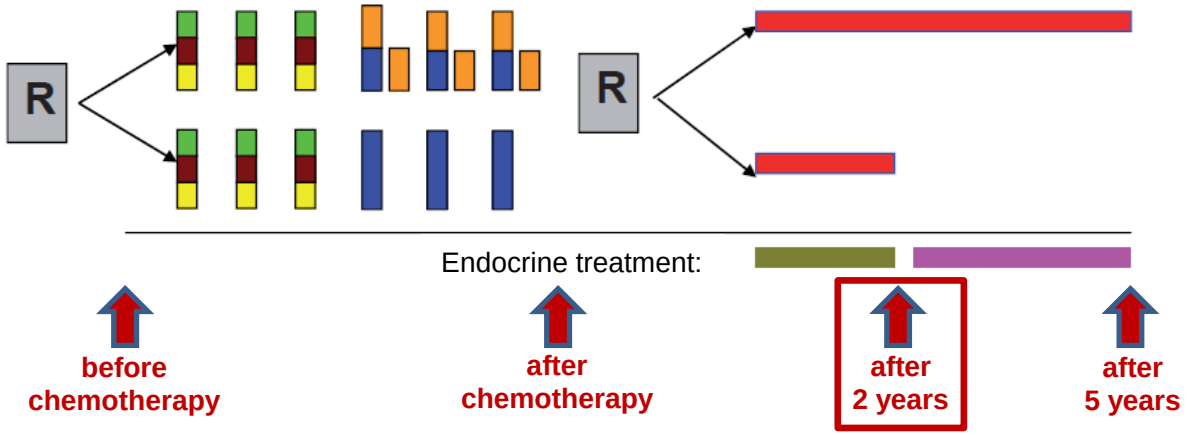


1990 **2021**

1980er/1990er vs. Heute

- Weiterentwicklung der Chemotherapie (Taxane, peg. Anthrazykline, ADCs, etc.)
- Endokrine Therapie: Aromataseinhibitoren, SERDs
- HER2-zielgerichtete Therapie
- Weitere zielgerichtete Substanzen (CDK4/6-Inhibitoren, PARP-Inhibitoren, Immun-Onkologie)
- Effektive lokale Therapieverfahren
- Liquid Biopsy

SUCCESS A – study design



Blood sampling for CTC assessment

First randomization:
3 cycles FEC100 followed by 3 cycles docetaxel vs. 3 cycles FEC100 followed by 3 cycles docetaxel plus gemcitabine

Second randomization:
2 years vs. 5 years of zoledronate

5- FU 500 mg/m^2, Epirubicin 100 mg/m^2, Cyclophosphamide 500 mg/m^2 q3w

Docetaxel 100 mg/m^2 q3w

Docetaxel 75 mg/m^2, Gemcitabine 1.000 mg/m^2 d1,8 q3w

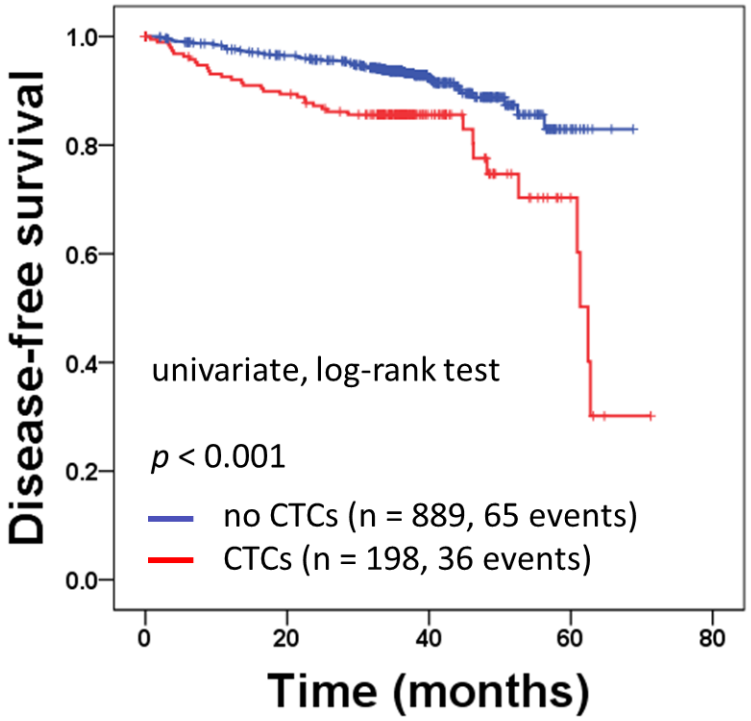
Zoledronate 4mg x 2a vs 5a (q3mx24m, vs q3mx24m followed by q6mx36m)

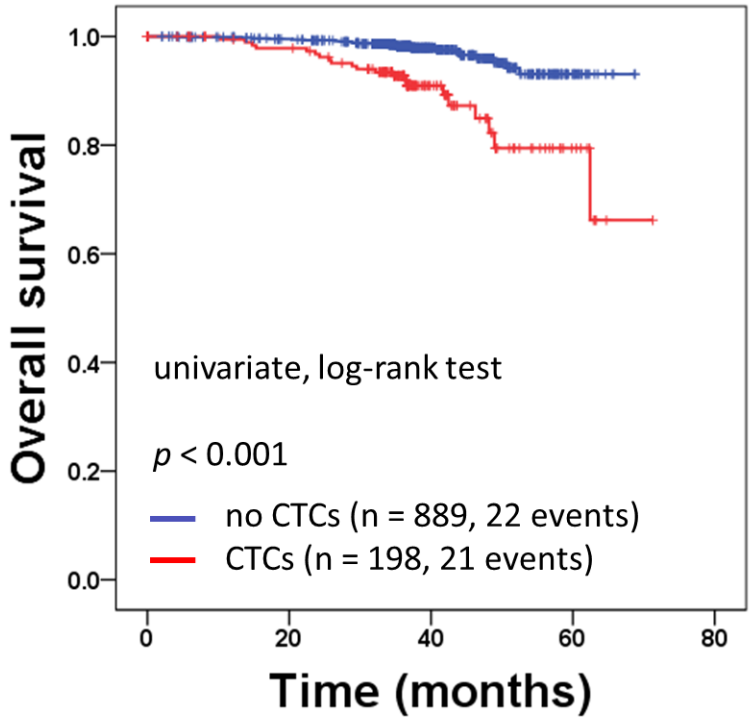
Tamoxifen 20 mg qid p.o. x 2a
(plus Goserelin 3.6 mg depot x 2a in premenopausal pts

Anastrozole 1 mg qid p.o. x 3a in postmenopausal pts
(Tam in premenopausal pts)

Trapp, Janni et al, JNCI 2018

Results III: Prognostic value of CTCs assessed two years after adjuvant chemotherapy





Trapp, Janni et al, JNCI 2018

Results IV: Prognostic value of CTCs assessed two years after adjuvant chemotherapy

Multivariate Cox regression adjusted for age, menopausal status, tumor size, nodal stage, tumor grade, histological type, hormone receptor status, HER2 status, and presence of CTCs before chemotherapy

- **DFS: Hazard ratio 2.28; 95% CI 1.48 – 3.50; p < 0.001**
- **OS: Hazard ratio 3.82; 95% CI 1.99 – 7.31; p < 0.001**

➔ **The presence of CTCs assessed during follow-up two years after adjuvant chemotherapy is a significant independent prognostic factor for poor OS and DFS**

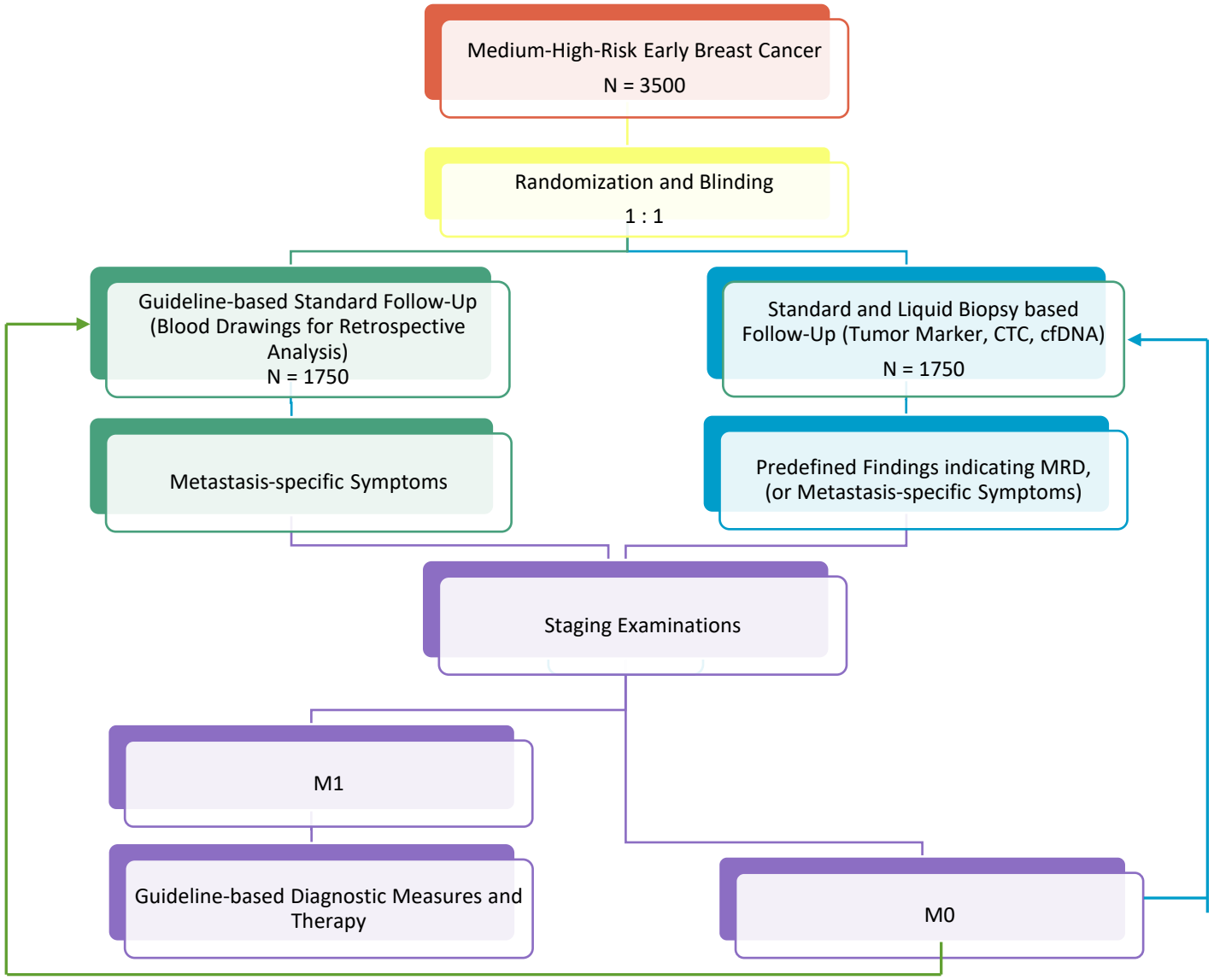
Trapp, Janni et al, JNCI 2018

Nationale Dekade gegen Krebs

Ziele:

- Lebensqualität der Betroffenen verbessern
- Weniger Krebserkrankungen, Prävention stärken
- Zugang zu onkologischer Versorgung für alle Menschen in Deutschland
- Aktive Teilnahme der Bürgerinnen und Bürger
- Deutschland als führender Standort der patientenorientierten Krebsforschung

Studiendesign Survive-Studie BMBF-Antrag 2021



Studiendesign

- Prospektiv-randomisierte Phase III Studie
- Einschluss 4 Wochen – 24 Monate nach der letzten primären Therapie (OP, Radiatio, Chemotherapie, welches auch immer als letztes erfolgte)
- Geplante Rekrutierungszeit: 24 Monate
- Studiendauer/Interventionsdauer: 5 Jahre
- Follow-Up: 5 Jahre

Intervention

- Analog zur leitliniengetreuen Standardnachsorge: q3m in den Jahren 1-3, q6m in den Jahren 4-5
- Bestimmung von
  - Konventionellen Tumormarkern
  - CTCs
  - ctDNA
- Analyse der Blutentnahmen mit Handlungskonsequenz erfolgt nur im Interventionsarm
- Anlage einer Biobank für retrospektive Analysen/zusätzliche, nicht therapierelevante Analysen mit zusätzlichem Biomaterial des Interventionsarmes und dem des Standard-Armes
- Lebensqualitätserfassung in beiden Armen (EORTC QLQ-C30, HADS-D und PA-F12) q6m

Liquid Biopsy

Tumormarker: CA15.3, CEA, CA125

- Baseline-Bestimmung zu Studieneinschluss (2 Bestimmungen im Abstand von 4 Wochen, Referenz über ganze Studiendauer)
- Dynamischer TM-Anstieg eines TM (CA15.3 Δ+75%, CEA Δ+100%, CA125 Δ+150%) triggert nach einer Bestätigungsanalyse (14 ± 3 Tage später) eine Bildgebung (CT Thorax/Abdomen + Knochenszintigraphie)

CTCs

- Bestimmung bei auffälligem Tumormaker
- Bestimmung für Alle im Interventionsarm 1 Jahr nach Studieneinschluss
- Bei Detektion ≥ 1 CTC erfolgt eine Bildgebung (CT Thorax/Abdomen + Knochenszintigraphie)

ctDNA

- Inivata tumor-derived individualized ctDNA-Assay (RaDaR), ESMO 2021

A personalised sequencing approach for liquid biopsy-based detection of recurrent disease in early-stage breast cancer

Wolfgang Janni[1], Jens Huober[1], Sophia Huesmann[1], Christodoulos Pipinikas[2], Tatjana Braun[1], Volkmar Müller[3], Giovanni Marsico[2], Angelina Fink[1], Paula Freire-Pritchett[2], Karin Koretz[4], Charlene Knape[2], Amelie de Gregorio[1], Brigitte Rack[1], Thomas WP Friedl[1], Lisa Wiesmueller[1], Peter Möller[4], Karen Howarth[2], Klaus Pantel[5], Nitzan Rosenfeld[2]

[1] Department of Obstetrics and Gynecology, University Hospital Ulm, Ulm, Germany; [2] Inivata Ltd, Babraham Research Park, Cambridge, United Kingdom; [3] Department of Obstetrics and Gynecology, University Hospital Hamburg, Hamburg, Germany; [4] Department of Pathology, University Hospital Ulm, Ulm, Germany; [5] Department of Tumour Biology, University Hospital Hamburg, Hamburg, Germany

Poster 144P
Abstract 3446

BACKGROUND

- Routine surveillance after primary therapy for early breast cancer (BrCa) is currently limited to imaging.
- Follow-up surveillance using circulating tumour DNA (ctDNA) to detect molecular residual disease (MRD) may be a useful tool for identifying patients who may eventually develop distant metastases and holds promise for earlier intervention and improved overall survival.
- However, such follow-up surveillance requires ultrasensitive ctDNA assays due to the heterogeneous nature of the genomic alterations seen in BrCa.
- Here, we evaluate the clinical utility of RaDaR™ (**Figure 1**), a personalised sequencing assay for MRD detection and monitoring disease recurrence, in early-stage BrCa patients after standard treatment.

METHODS

- This is a retrospective pilot study on 37 early-stage BrCa patients recruited through the BRandO BiO registry study (**Table 1**).
- Somatic variants, identified through whole exome sequencing (WES) of patients' formalin-fixed, paraffin-embedded (FFPE) tumour tissue obtained from curative-intent surgery, were selected and used in the design of personalised RaDaR assays (38-54 variants/assay; median: 49).
- Plasma samples from 21 patients with confirmed clinical progression (median interval of 18.9 months from primary diagnosis) and 16 case-control patients with no recurrence at the time of 3-years follow-up, were analysed using the corresponding patient-specific RaDaR assay.
- RaDaR data analysis was blinded to disease outcome.

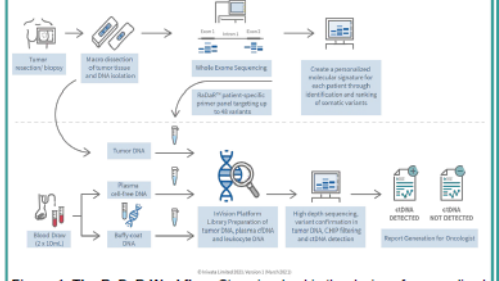


Figure 1. The RaDaR Workflow. Steps involved in the design of personalised RaDaR assays, from WES profiling of a patient's tumour, to variant identification and selection for panel design and plasma analysis for the detection of molecular residual disease and monitoring for disease recurrence.

RESULTS

Study Cohort

Table 1. Baseline characteristics of all 37 patients included in the study.

Variable		Patients with confirmed clinical recurrence (N = 21)	Patients with no evidence of clinical recurrence (N = 16)
Age at primary diagnosis (years)	*Median*	62	60.5
	Range	35 - 82	31 - 83
Histological grading	*G1*	0 (0.0%)	0 (0.0%)
	G2	14 (66.7%)	14 (87.5%)
	G3	7 (33.3%)	2 (12.5%)
Histological type	*Ductal*	15 (71.4%)	12 (75.0%)
	Lobular	4 (19.0%)	4 (25.0%)
	Other	2 (9.5%)	0 (0.0%)
Hormone receptor status	*Negative*	6 (28.6%)	1 (6.3%)
	Positive	15 (71.4%)	15 (93.8%)
HER2 status	*Negative*	20 (95.2%)	14 (87.5%)
	Positive	1 (4.8%)	2 (12.5%)
Neoadjuvant chemotherapy	*No*	14 (66.7%)	11 (68.8%)
	Yes	6 (28.6%)	4 (25.0%)
	Unknown	1 (4.8%)	1 (6.3%)

ctDNA detection is strongly associated with distant recurrence in early-stage BrCa patients

- ctDNA was detected in 15 of 21 patients with confirmed clinical recurrence (71%) at an estimated median variant allele frequency (VAF) of 0.827% (range: 0.0029% to 37.8%).
- When ctDNA detection was evaluated by type of recurrence, 12/13 patients with distant disease were ctDNA positive (92%) compared to 3/8 patients with local recurrence (38%) (**Figure 2**).
- Patients with distant recurrence had the highest plasma ctDNA levels (estimated median VAF: 6.947%, Range: 0.0276% to 37.8%) (**Figure 3A**)
- The lowest ctDNA levels were seen in the 3 patients with local recurrence (0.0029%, 0.0146% and 0.0248%; **Figure 2 and 3B**).
- Of the remaining 6 patients with clinically confirmed recurrence but no detectable ctDNA levels, 5 had local and one distant recurrence.
- Pathological review of the ctDNA negative distant recurrence specimen (ovary) revealed an unusual histology, when compared to the primary breast tumour, indicative of either an alternative origin or a second primary tumour.

- Of the 16 patients without a documented clinical recurrence, only one patient with a luminal A, stage I tumour was positive for ctDNA.
- ctDNA detection levels in this patient were, however, low (0.0085% VAF), potentially indicating the presence of early molecular recurrence that precedes clinical progression (**Figure 2 and 3C**).

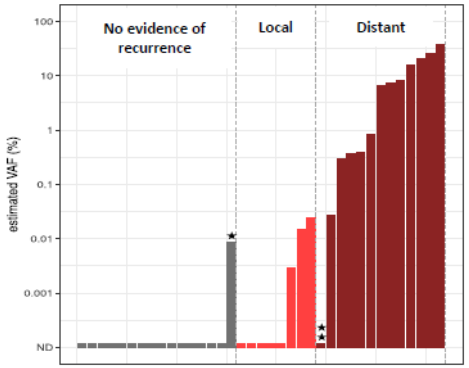


Figure 2. Use of personalised RaDaR assays for the detection of recurrent disease in early-stage BrCa patients. ctDNA detection in patients with no evidence of disease recurrence (control cases) and in those with clinical confirmation of either local (light red bars) or distant (dark red bars) recurrence. (★) Patient with no documented recurrence and plasma ctDNA detected at low levels, (★★) Patient with distant recurrence and ctDNA not detected. **ND**, No detection.

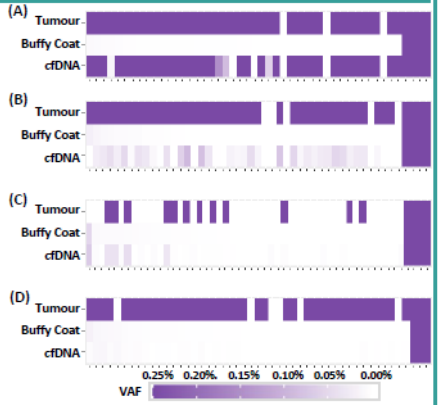


Figure 3. ctDNA detection heatmaps. Each column represents a different WES-derived variant, each row a different sample type (tumour DNA, buffy coat and plasma) analysed by RaDaR. Variants present in the buffy coat are identified as germline or CHIP variants and are excluded from the analysis, as well as variants that are not confirmed in the tumour specimens. (**A**) Patient with distant recurrence showing high ctDNA plasma levels (estimated VAF: 25.4%) (**B**) Detection of ctDNA at an estimated VAF of 0.0248% in a patient with local recurrence (**C**) Patient with no documented recurrence and ctDNA detected at low levels (estimated VAF: 0.0085%) indicating potential presence of early molecular recurrence (**D**) A patient with no documented recurrence and ctDNA not detected.

CONCLUSIONS

- In this pilot study, the RaDaR assay was able to detect the presence of ctDNA in plasma to levels as low as 0.0029% VAF.
- Results indicate that the sensitive detection of ctDNA is strongly associated with distant recurrence in early-stage BrCa, with 12 of 13 cases being successfully detected (sensitivity of 92%).
- These findings warrant further validation in a larger study population.

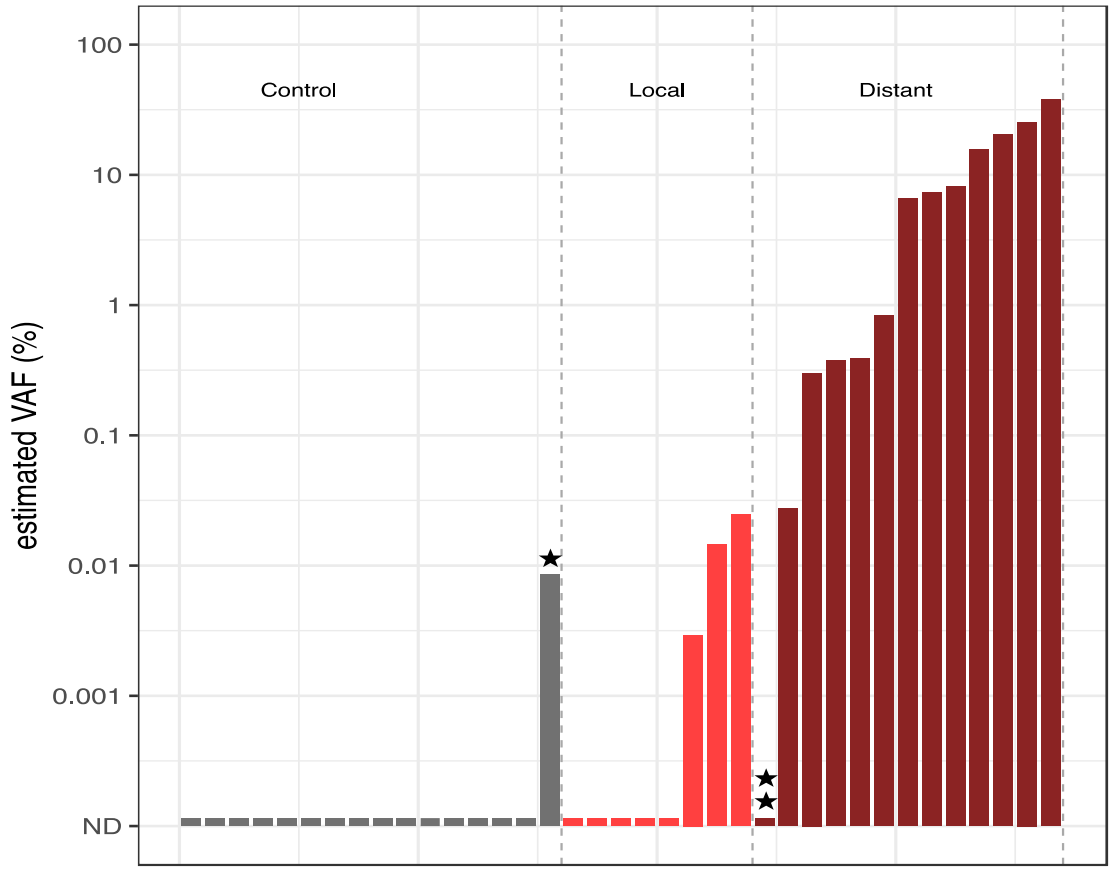
ACKNOWLEDGEMENTS

The authors would like to acknowledge the following:
- All patients and their families for agreeing to participate in the study.
- Inivata's Product Development, Computational Biology and US Laboratory Clinical Operations teams.

DISCLOSURES

- The presenting author (Wolfgang Janni; wolfgang.janni@uniklinik-ulm.de) has no conflicts of interest to declare.
- The authors were fully responsible for all content and editorial decisions, were involved in all stages of poster development and have approved the final version.

ctDNA-Nachweis bei Patientinnen in Abhängigkeit des Rezidivstatus



Einschlusskriterien

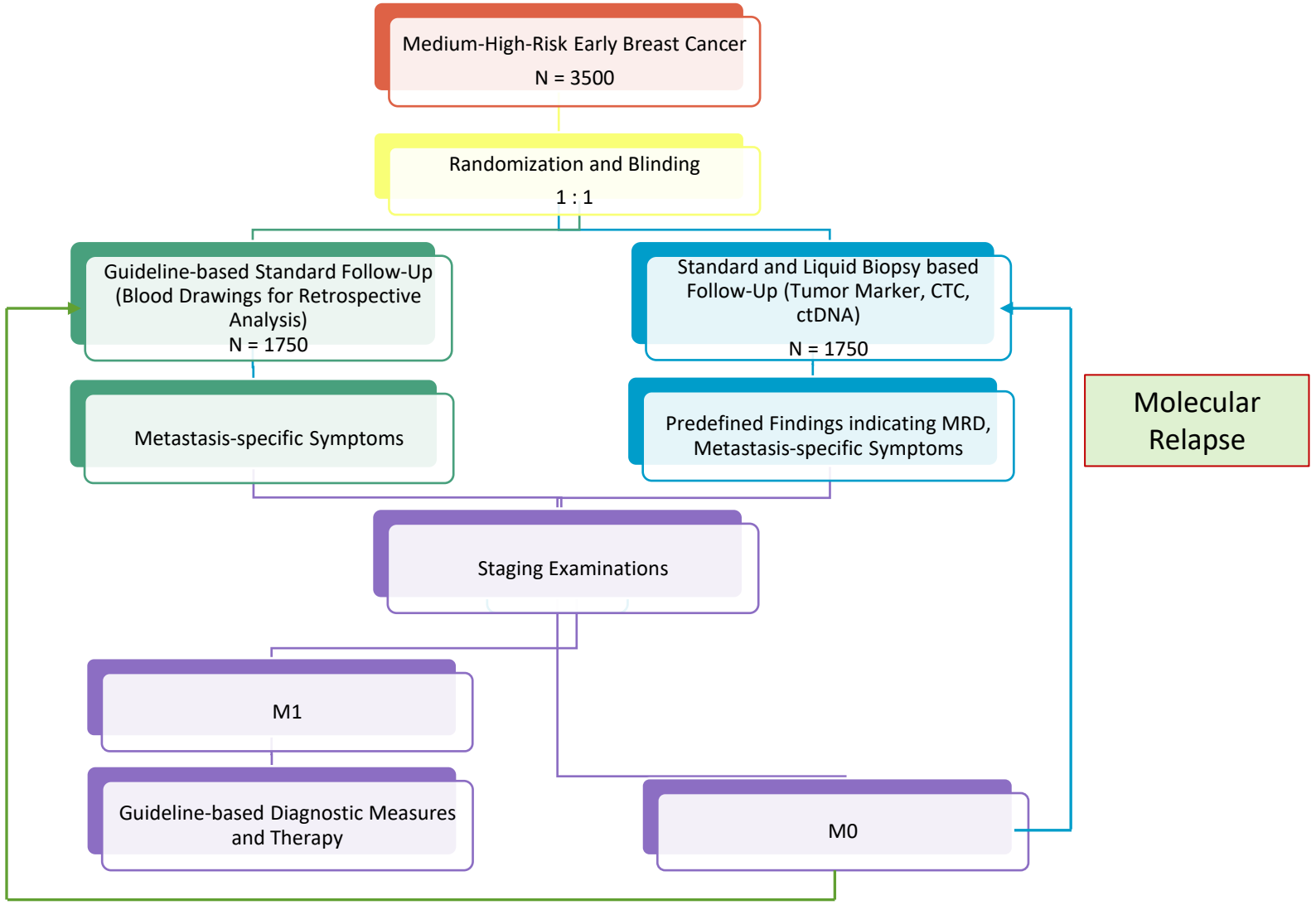
- Primäres Mammakarzinom
- Abgeschlossene primäre Therapie innerhalb der letzten 4 Wochen – 24 Monate (OP, Radiatio, Chemotherapie, welches auch immer als letztes erfolgte)
- **High Risk** Konstellation mit Indikation zur Chemotherapie (unabhängig davon, ob diese durchgeführt wird oder nicht)
- **Intermediate Risk** Konstellation im Sinne von T3 oder N+ oder G3
- Alter ≤ 75 Jahre
- ECOG ≤ 1

Primäre Co-Endpunkte

- **OS** (including death from any cause as event)

- **Overall Lead Time** (Molecular to via Imaging verified Recurrence Lead Time + DFS-Difference between the Arms; for each Marker separately and, where applicable, in combination)

Studiendesign



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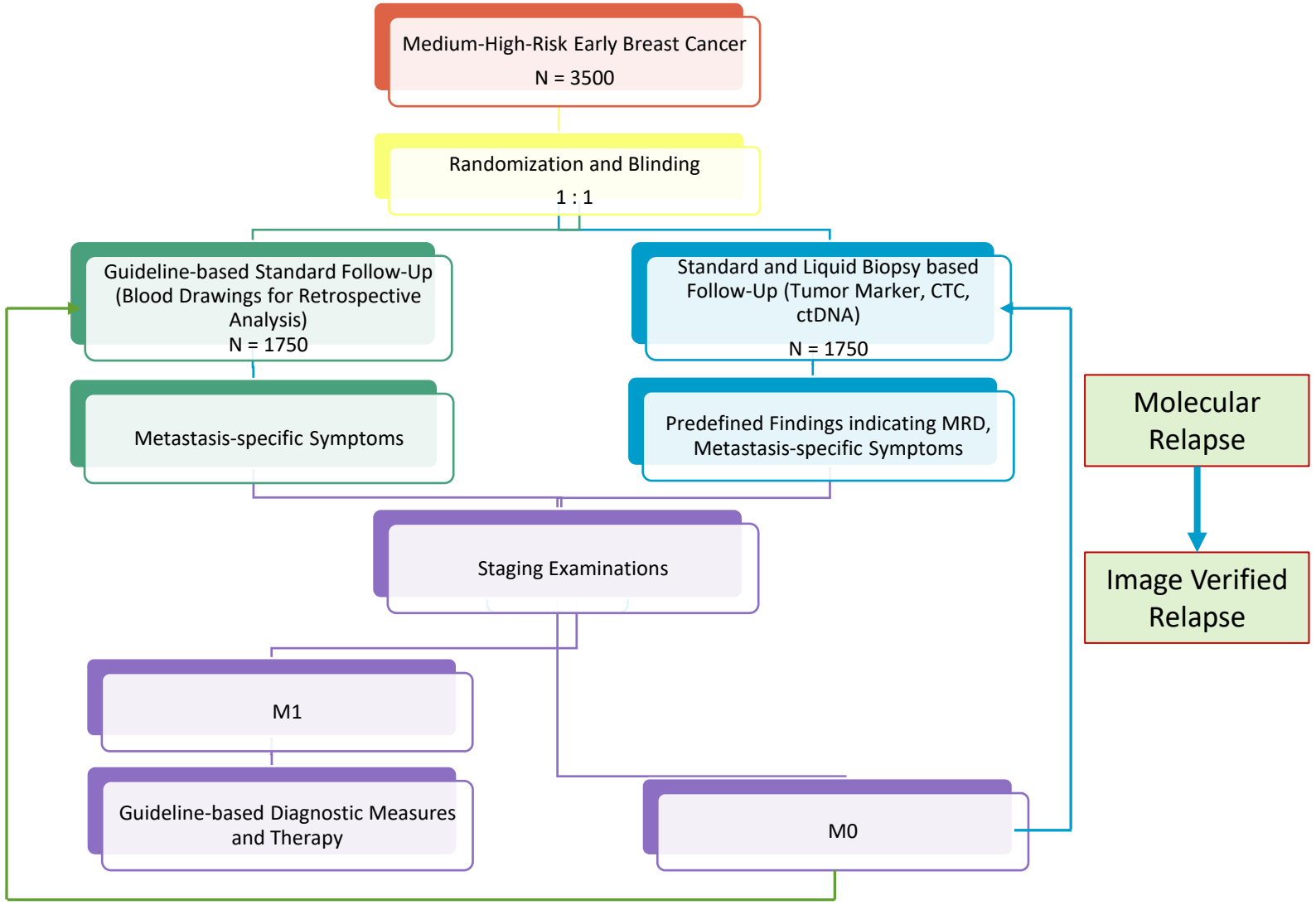

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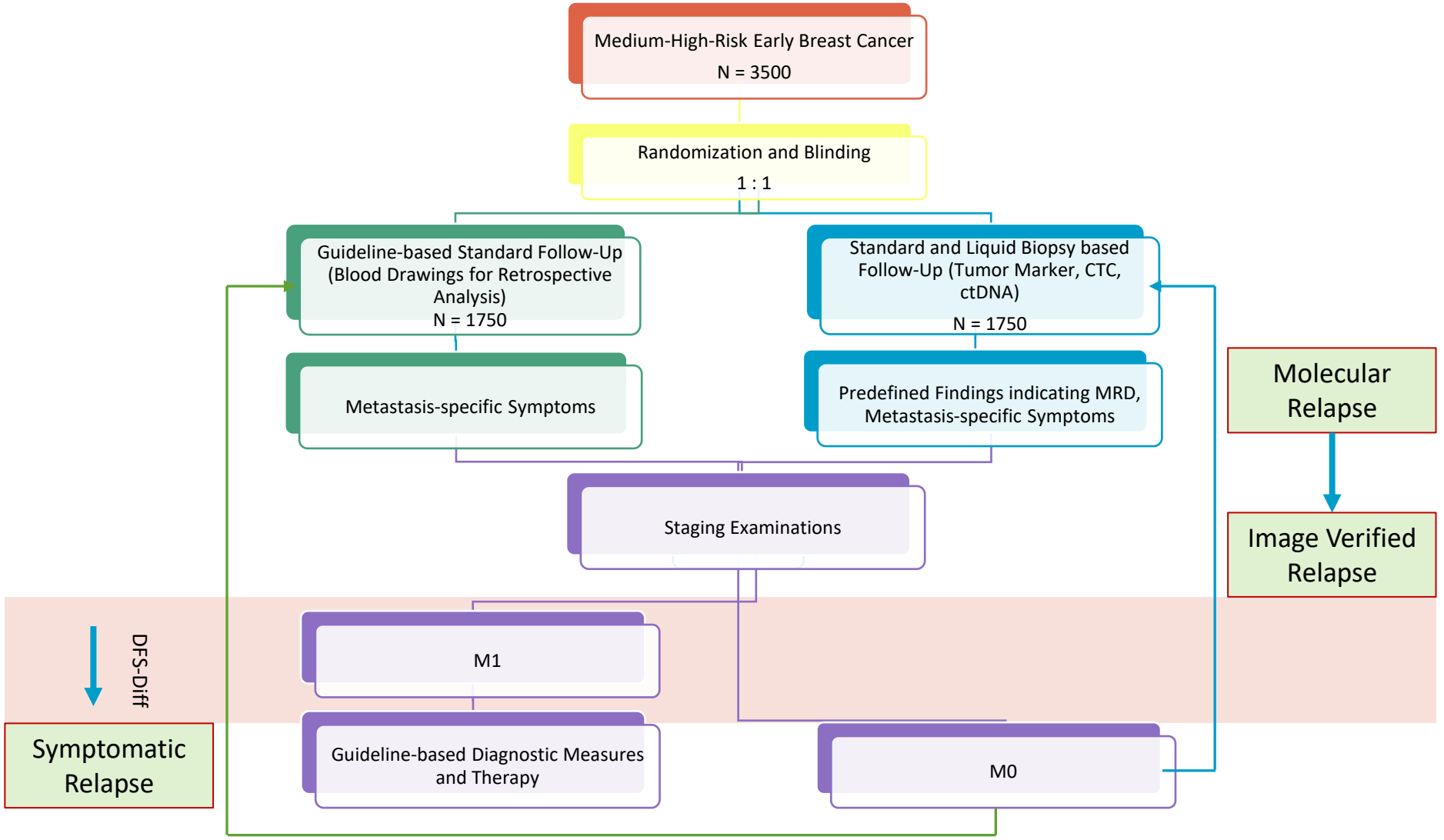

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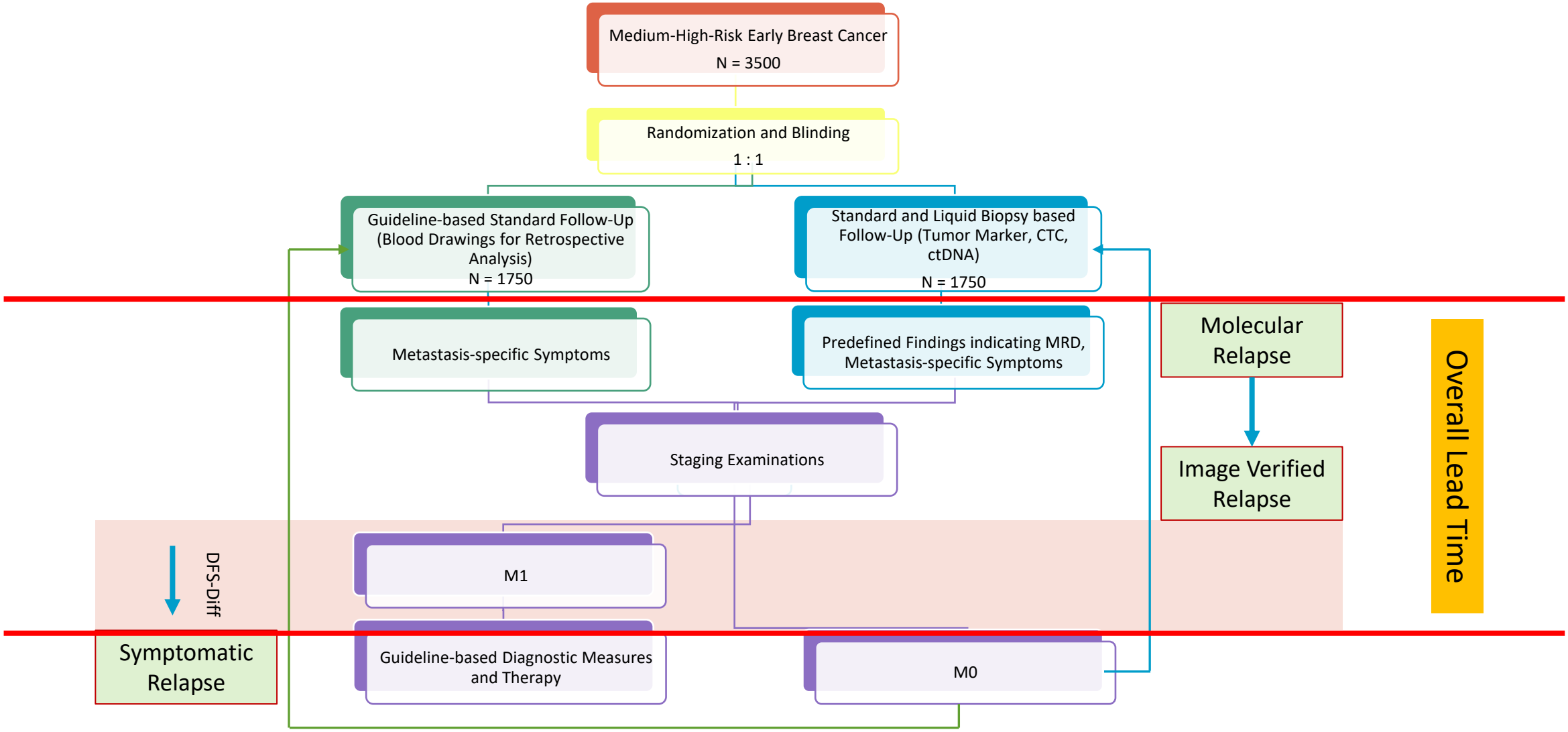

Sekundäre Endpunkte

- **Molecular to via Imaging verified Recurrence Lead Time in the intensive surveillance arm**
- **Molecular Lead Time**
- iDFS (including any invasive ipsilateral, regional, contralateral, and distant disease recurrence, second primary tumors, or death from any cause as event; non-invasive, in-situ cancer events were excluded)
- DDFS (including metastasis, second primary tumors and death from any cause as event)
- DRFS (including metastasis and second primary tumors as event; death from any cause is not included as event)
- Occurrence of Metastasis in asymptomatic patients
- **Quality of life (QoL)** with questionnaires: EORTC QLQ-C30, HADS-D and PA-F12
- **Liquid biopsy sensitivity** (CA15.3, CEA, CA125, CTC and ctDNA), individually and in combination, where applicable
- **Liquid biopsy specificity (**CA15.3, CEA, CA125, CTC and ctDNA) individually and in combination, where applicable
- False-Positive Liquid Biopsy Rate in the intensive surveillance arm (no clinical relapse 36 months after first and persistent molecular relapse)
- Breast cancer specific survival (BCSS)

Zusammenfassung

- Nach 35 Jahren wissenschaftlichem Stillstand bei der Nachsorge des Mammakarzinoms wird die Fragestellung neu untersucht
- Laufende **italienische** Studie: PET-CT zur intensivierten Bildgebung
- Deutsche **SURVIVE-Studie**: Liquid Biopsy als Grundlage für intensivierte Nachsorge
- Optimaler Zeitpunkt für die Studie:
    - Neue, verlässliche Technologien in der Liquid Biopsy
    - Sensitive Bildgebung
    - Großes Spektrum der frühen Therapieintervention bei Nachweis einer Oligometastasierung
    - Potential für Langzeitremission/Kuration?