

Hemmung des Zellzyklus: Wege und Möglichkeiten

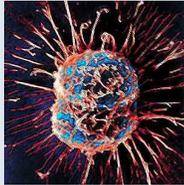
Priv.-Doz. Dr. med. C. Liedtke / Priv.-Doz. Dr. med. D. Fischer

Klinik für Gynäkologie und Geburtshilfe

- Direktor: Prof. Dr. med. Achim Rody -

Universitätsklinikum Schleswig-Holstein / Campus Lübeck

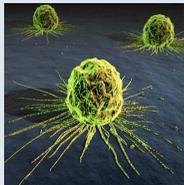
Überblick



Tumorbiologie und Hintergrund



Präklinische Daten der CDK4/6 Inhibition

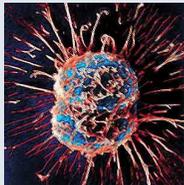


Klinische Daten neuer CDK Inhibitoren

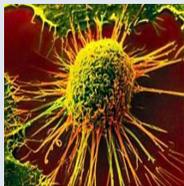


Laufende Studien

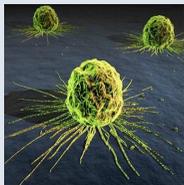
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Tumorbiologie und Hintergrund



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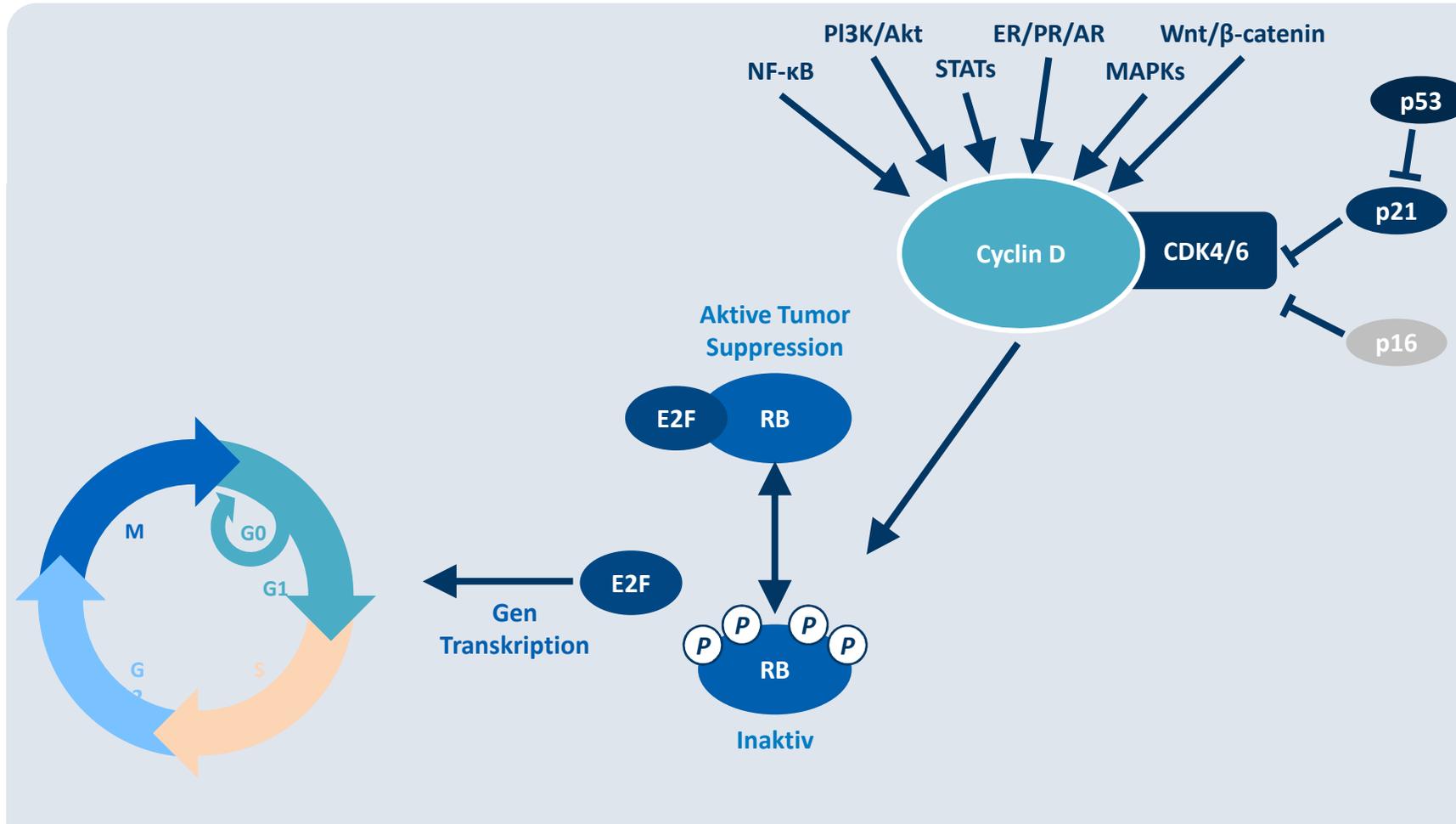


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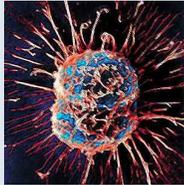


Laufende Studien

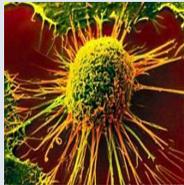
Hemmung des Zellzyklus (G1/S Checkpoint) bei BC



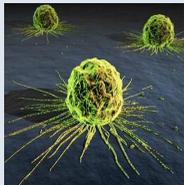
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Tumorbiologie und Hintergrund



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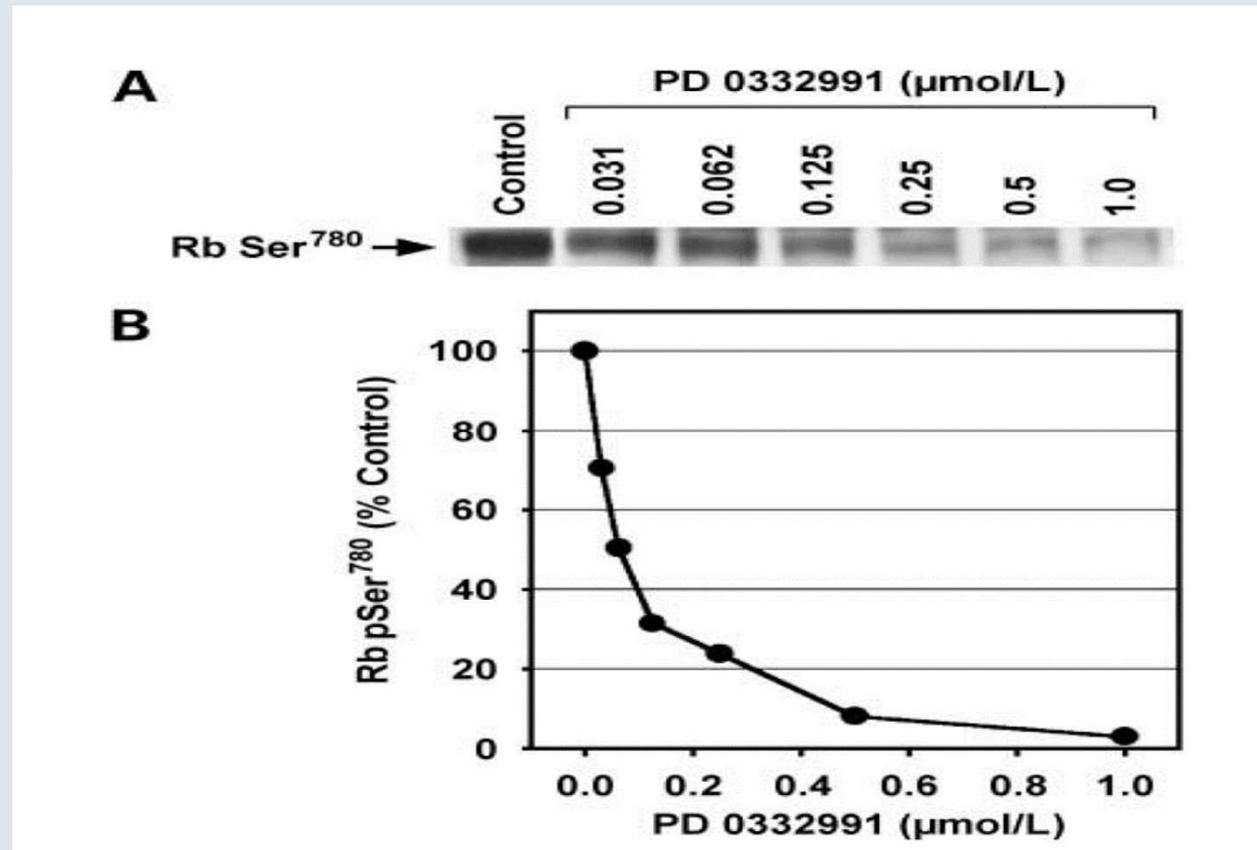


Klinische Daten neuer CDK Inhibitoren



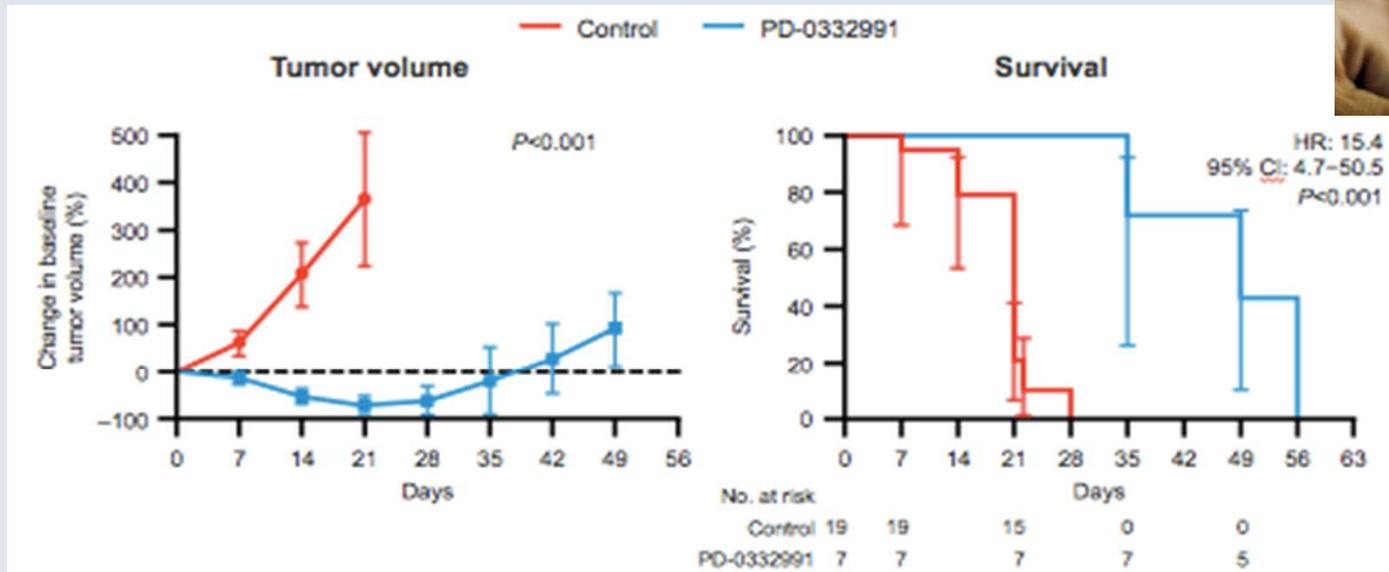
Laufende Studien

Reduktion der Rb-Phosphorylierung durch CDK4/6 Inhibition



Fry et al., Mol Cancer Ther. 2004

Antitumor-Aktivität im CDK4/6-Mausmodell

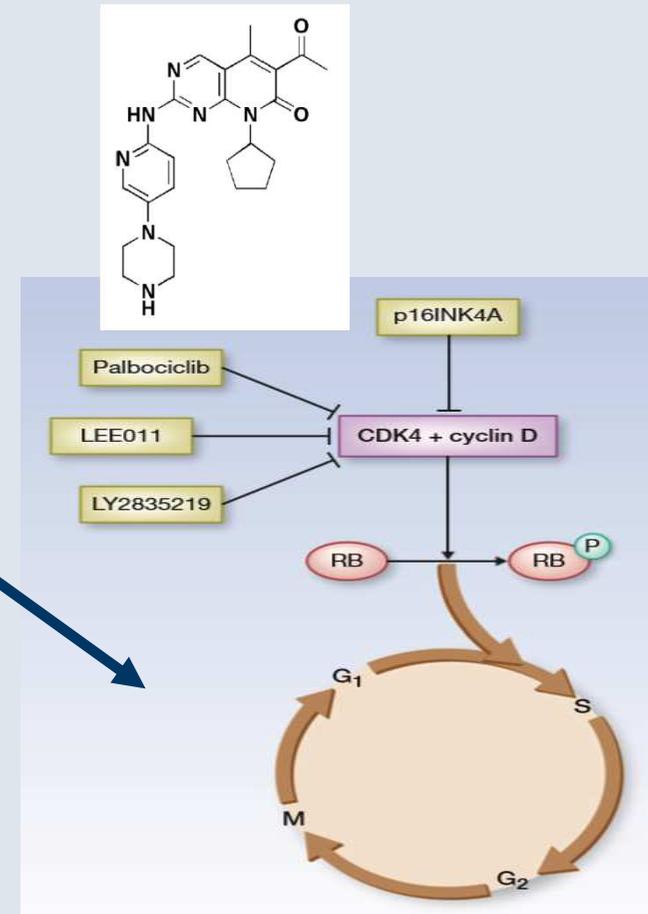


RB-competent MMTV-c-neu mice treated with PD-0332991 (100 mg/kg/day) for 21 days showed marked reduction in tumor volume and improved median survival vs. controls

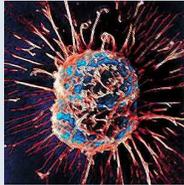
Roberts et al., J Natl Cancer Inst. 2012

Selektive CDK4/6 Inhibitoren

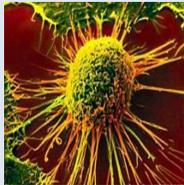
| Substanz | Firma | Studien- ergebnisse |
|----------------------------|----------|------------------------|
| Palbociclib (PD0332991) | Pfizer | Phase III |
| Ribociclib (LEE011) | Novartis | Phase II |
| Bemeciclib (LY28335219) | Lilly | Phase II |



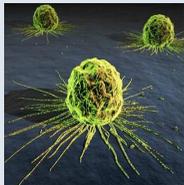
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Klinische Daten neuer CDK Inhibitoren



Laufende Studien

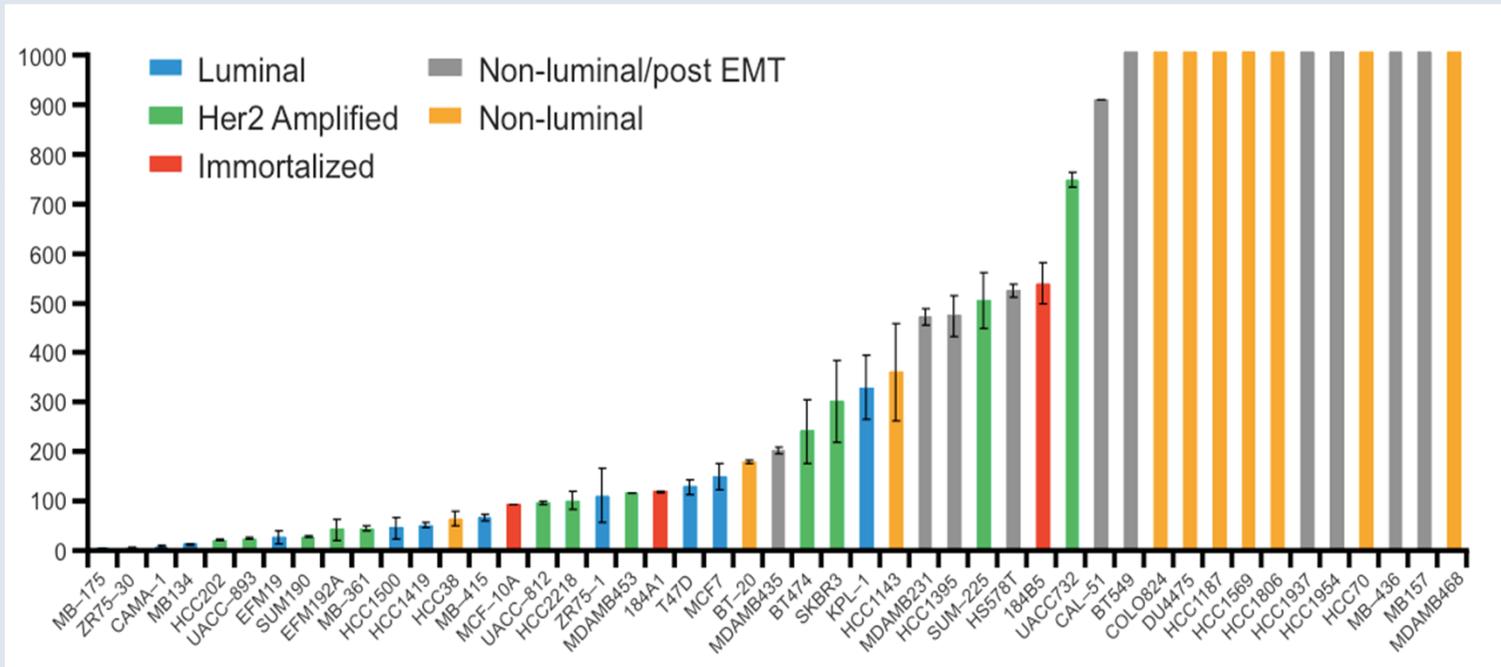
Palbociclib mono beim Rb-positive Mammakarzinom

- **Gute Verträglichkeit**
 - Neutropenie und Thrombocytopenie als einzige G 3/4 Toxizität
- **Mäßige Aktivität bei stark vorbehandelten Patientinnen**
 - CBR 19% gesamt, 21% bei ER+, 29% bei ER-; PFS gleich
- **Biomarker: Rb, Ki-67, p16 Verlust, CCND1 Amplifikation**
 - Positiver Trend bei Nukleärem Rb \uparrow , p16 \downarrow .
 - Keine Assoziation mit CCND1 amp oder Ki-67

DeMichele, et al. ASCO 2014

Clark, et al. SABCS 2013

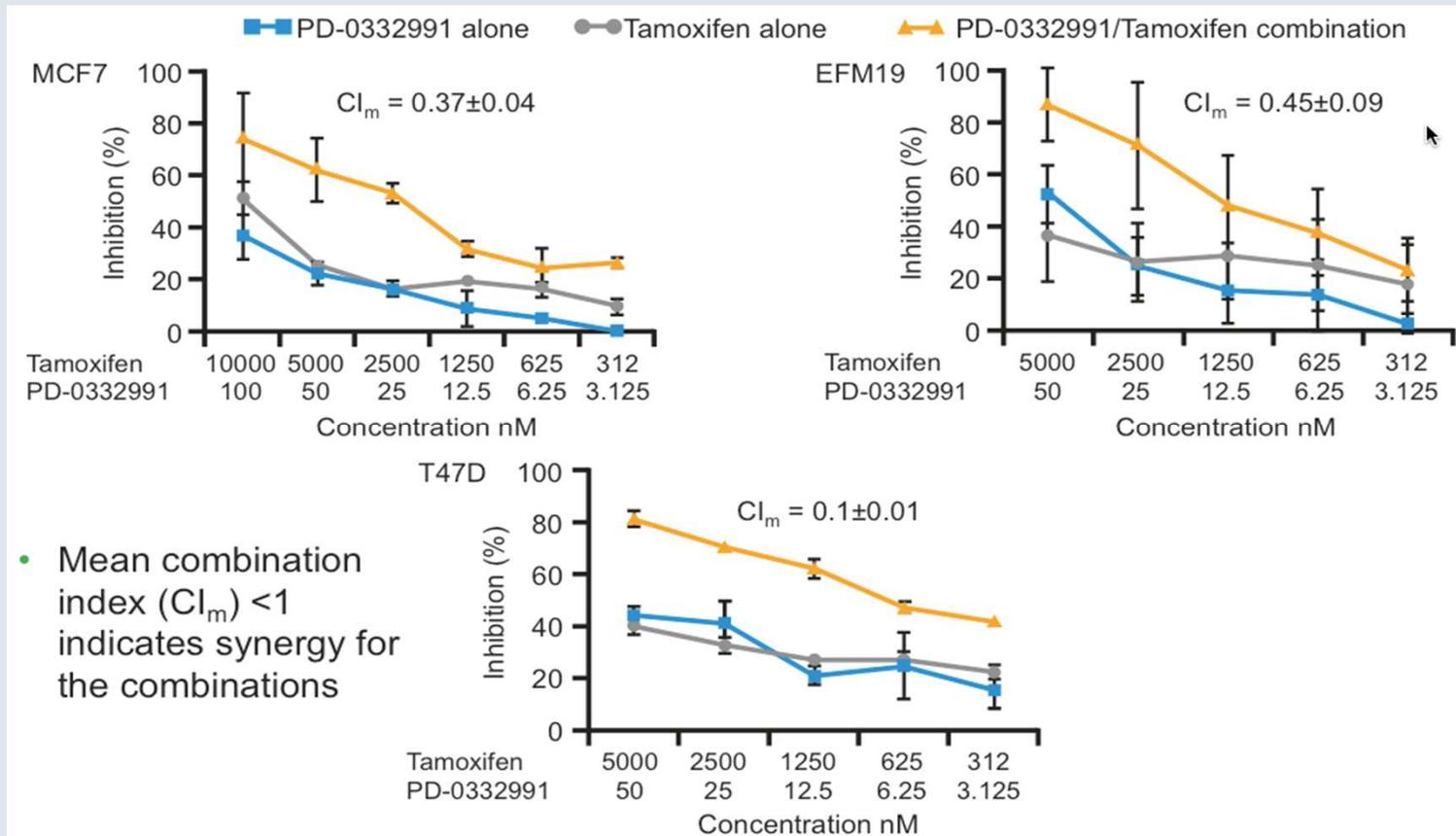
Proliferationshemmung bei unterschiedlichen BC Zelltypen in vitro



Luminale ER+/ Her2+ BC Zelllinien sind am empfindlichsten gegenüber einer CDK4/6 Inhibition

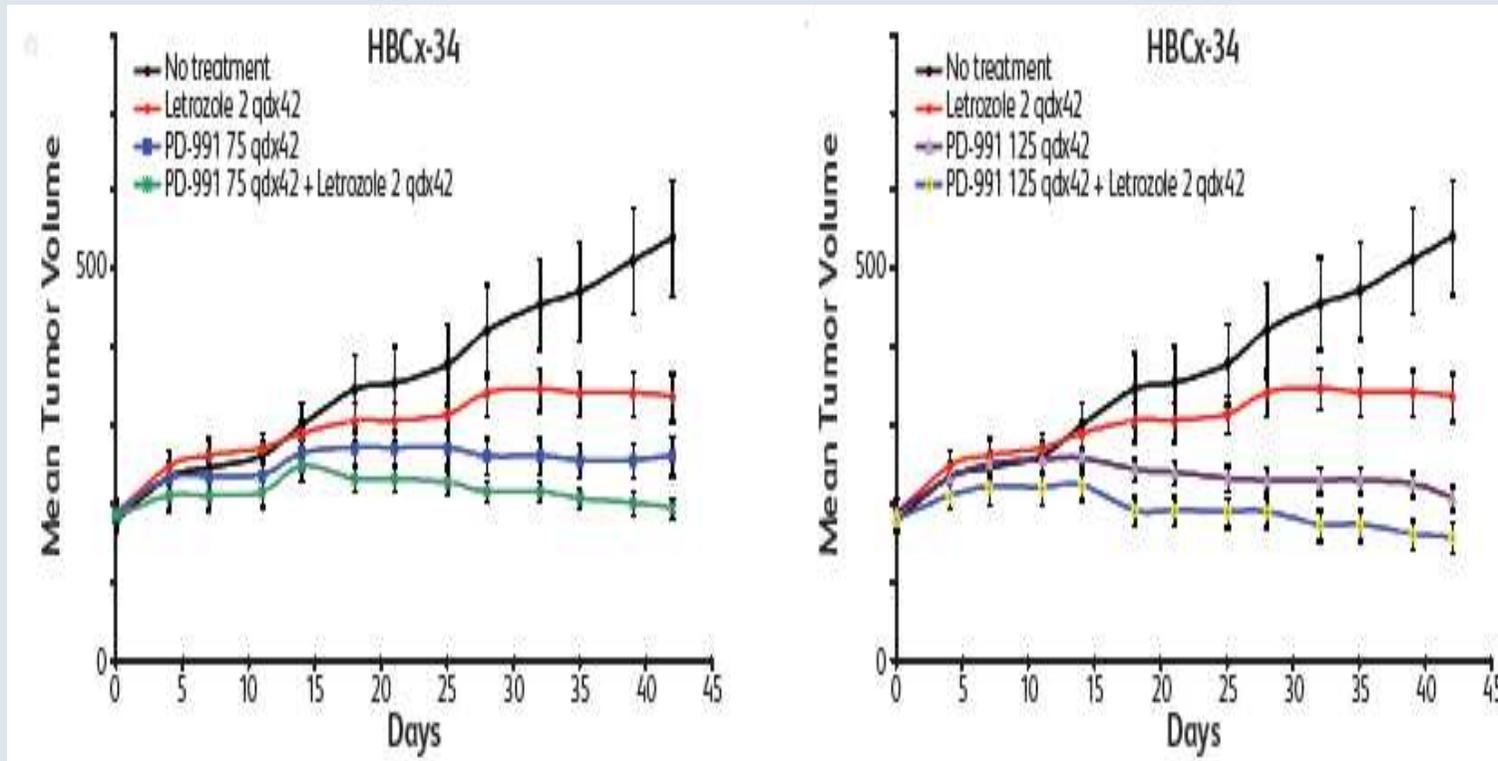
Finn, et al., Breast Cancer Res 2009

Synergistische Zellzyklushemmung mit Tamoxifen bei ER+ BC Zelllinien



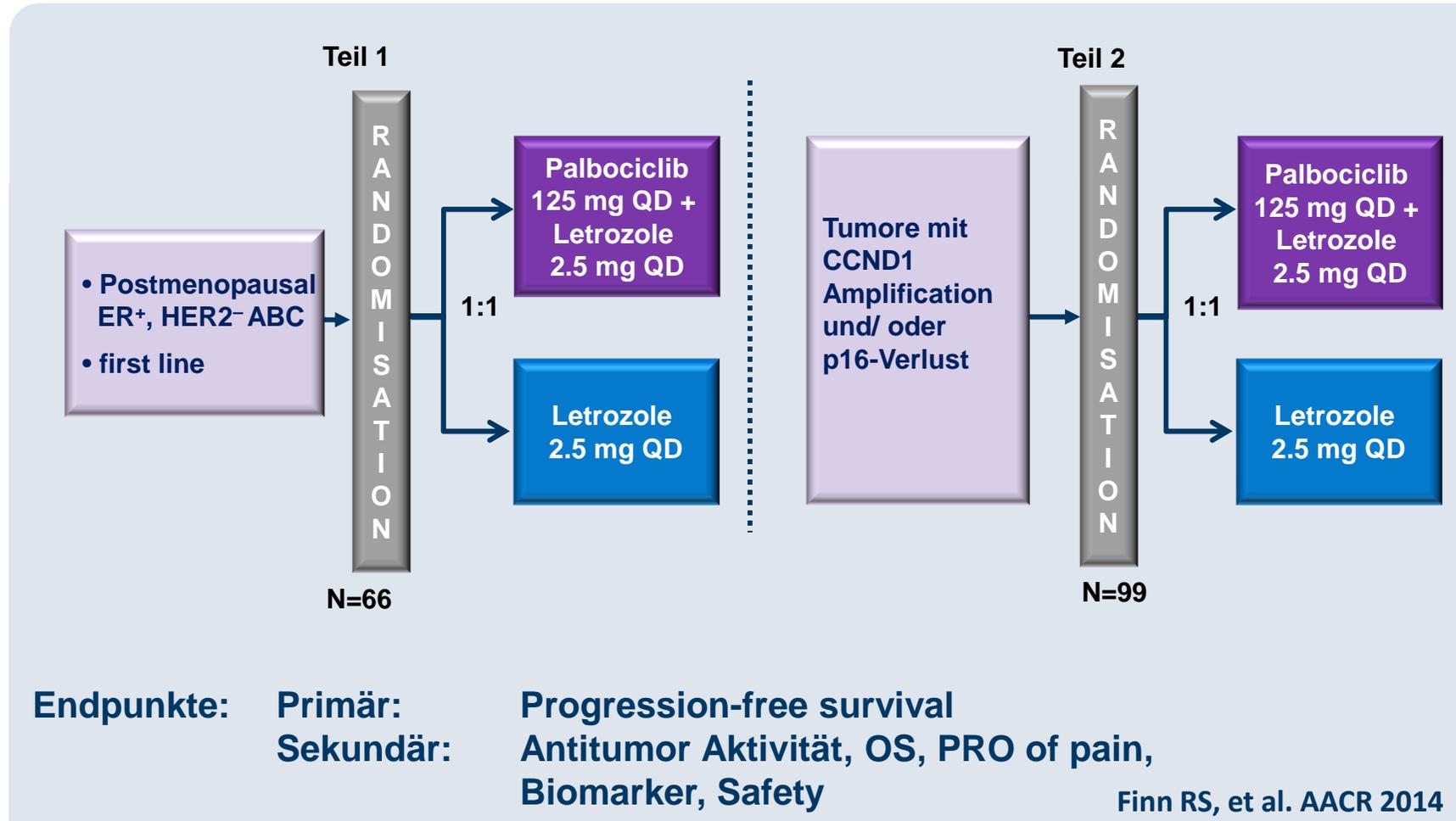
Finn, et al. Breast Cancer Res 2009

Synergistische Proliferationshemmung mit Letrozol im Mausmodell

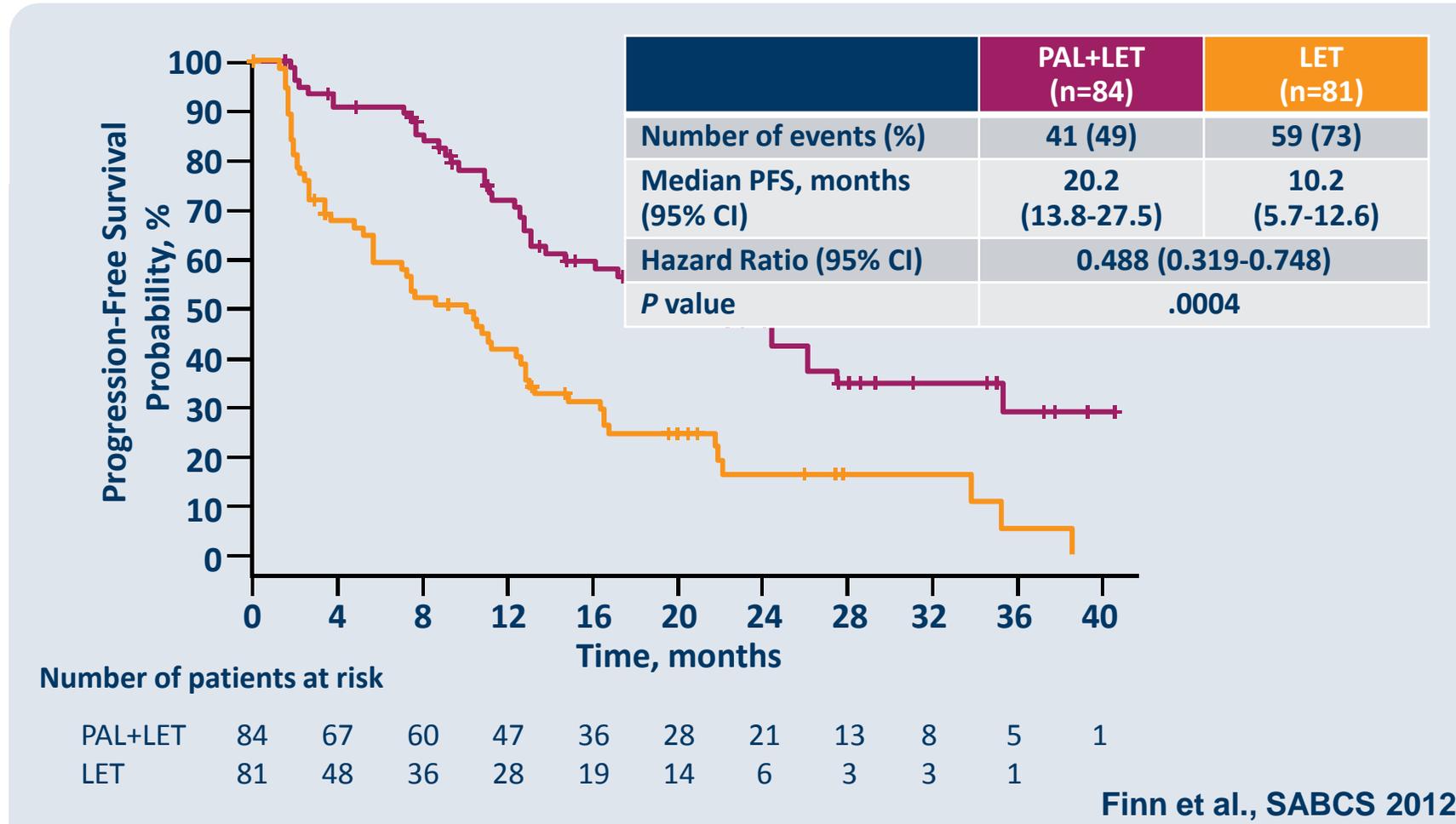


Koehler et al., IMPAKT 2014

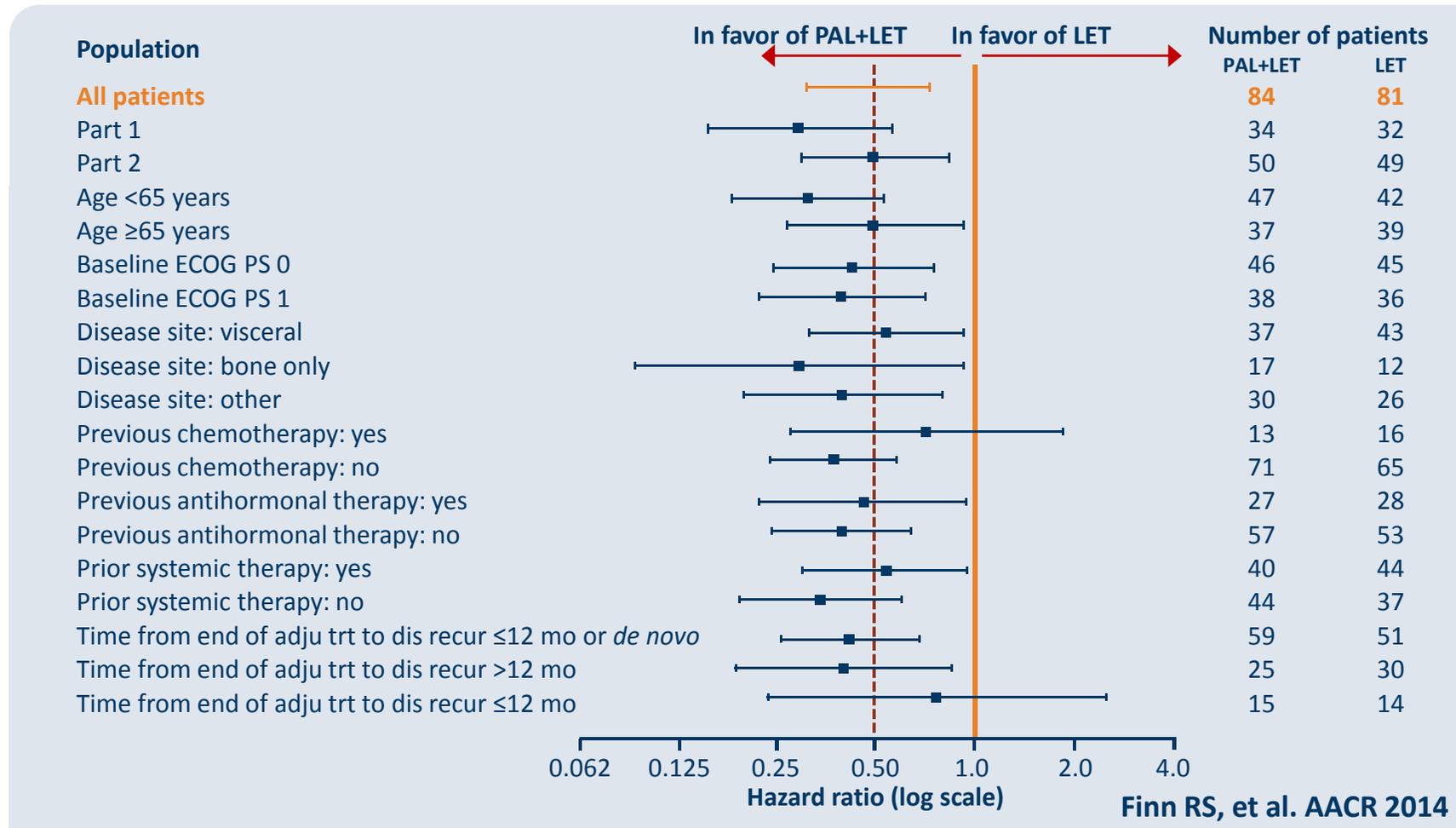
PALOMA-1 / TRIO-18 (Phase 1/2)



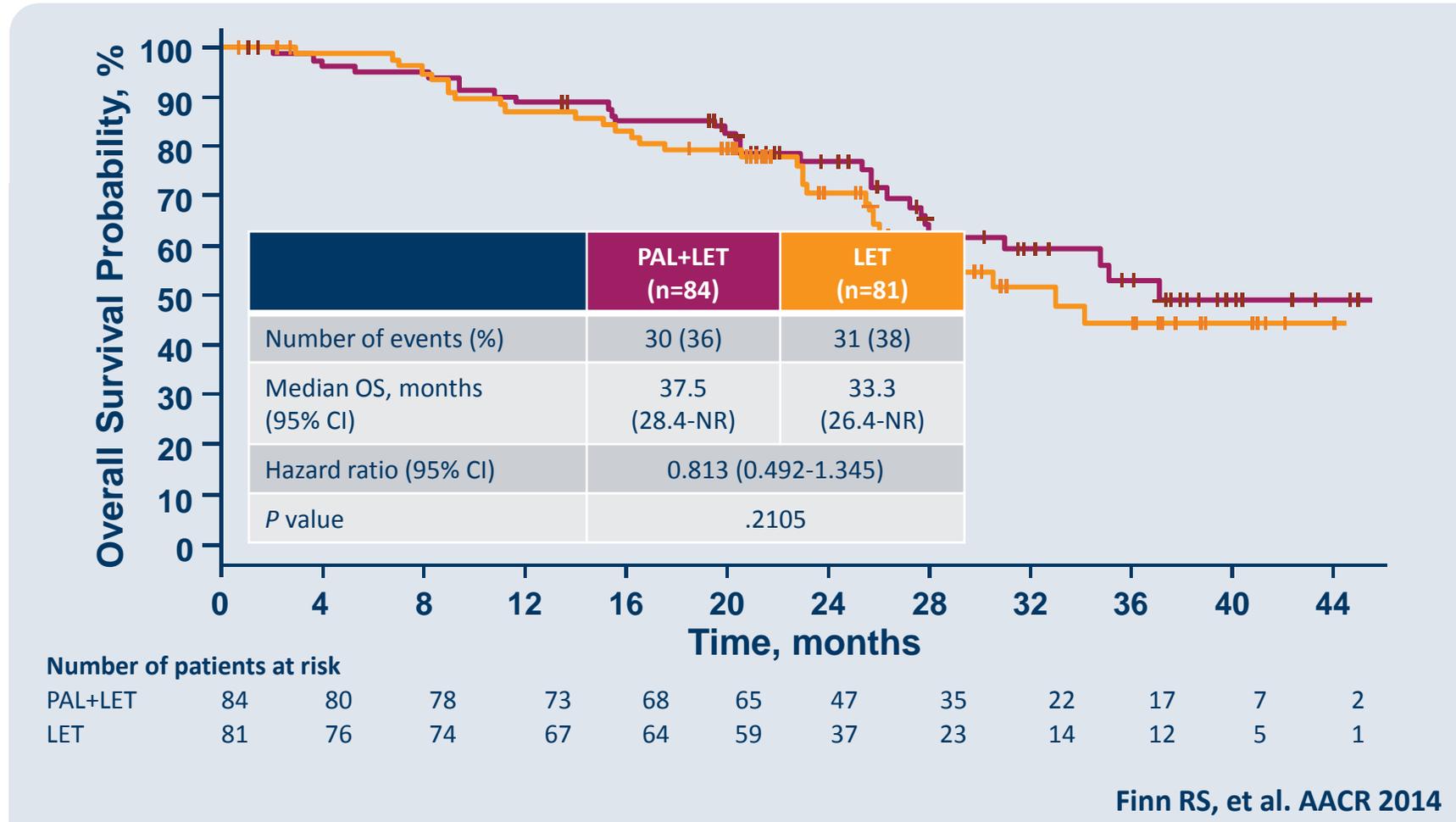
Primärer Studienendpunkt der PALOMA-1/TRIO-18 (PFS)



Subgruppenanalyse für PFS (PALOMA-1)



OS-Ergebnisse (PALOMA-1)



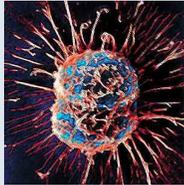
Toxizitätsdaten (PALOMA-1)

| | Palbociclib + Letrozole (n=83) | | | Letrozole (n=77) | | |
|--|-----------------------------------|-----------|-----------|---------------------|-----------|-----------|
| Most Common All-Causality Adverse Events | | | | | | |
| | G1/2 (%) | G3 (%) | G4 (%) | G1/2 (%) | G3 (%) | G4 (%) |
| Neutropenia | 20 | 48 | 6 | 4 | 1 | 0 |
| Leukopenia | 24 | 19 | 0 | 3 | 0 | 0 |
| Anemia | 29 | 5 | 1 | 5 | 1 | 0 |

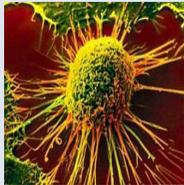
Keine Komplikationen durch Infektionen

Abbruchrate 13%

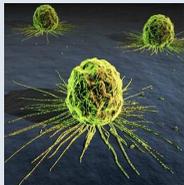
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Klinische Daten neuer CDK Inhibitoren



Laufende Studien

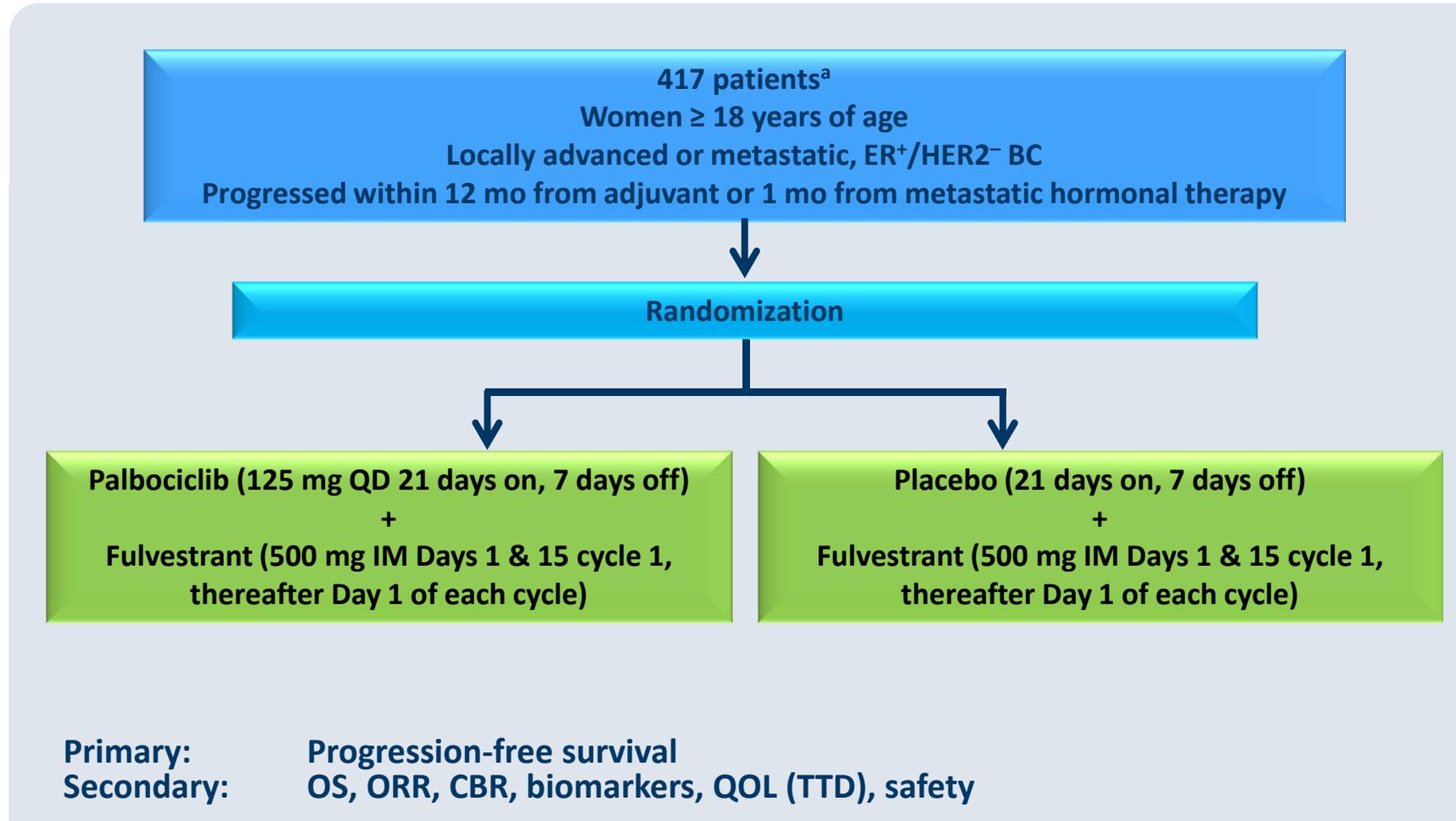
Phase-III-Studien zu Palbociclib

| | Metastatic Breast Cancer | | | Early |
|--------------------------|---|---|--|--------------------------------------|
| Study | 1008 (PALOMA-2) | 1023 (PALOMA-3) | PEARL | PENELOPE |
| Setting | Endocrine sensitive | Endocrine resistant | Endocrine resistant | High risk |
| Menopausal status | Postmenopausal | Premenopausal + postmeno-pausal | Postmeno-pausal | Premeno-pausal + postmeno-pausal |
| No. of patients | 650 | 521 | 348 | 800 |
| Treatment | Palbociclib + letrozole vs placebo + letrozole | Palbociclib + fulvestrant vs placebo + fulvestrant | Palbociclib + exemestane vs capecitabine | Palbociclib vs placebo |
| 1° endpoint | PFS | PFS | PFS | iDFS |

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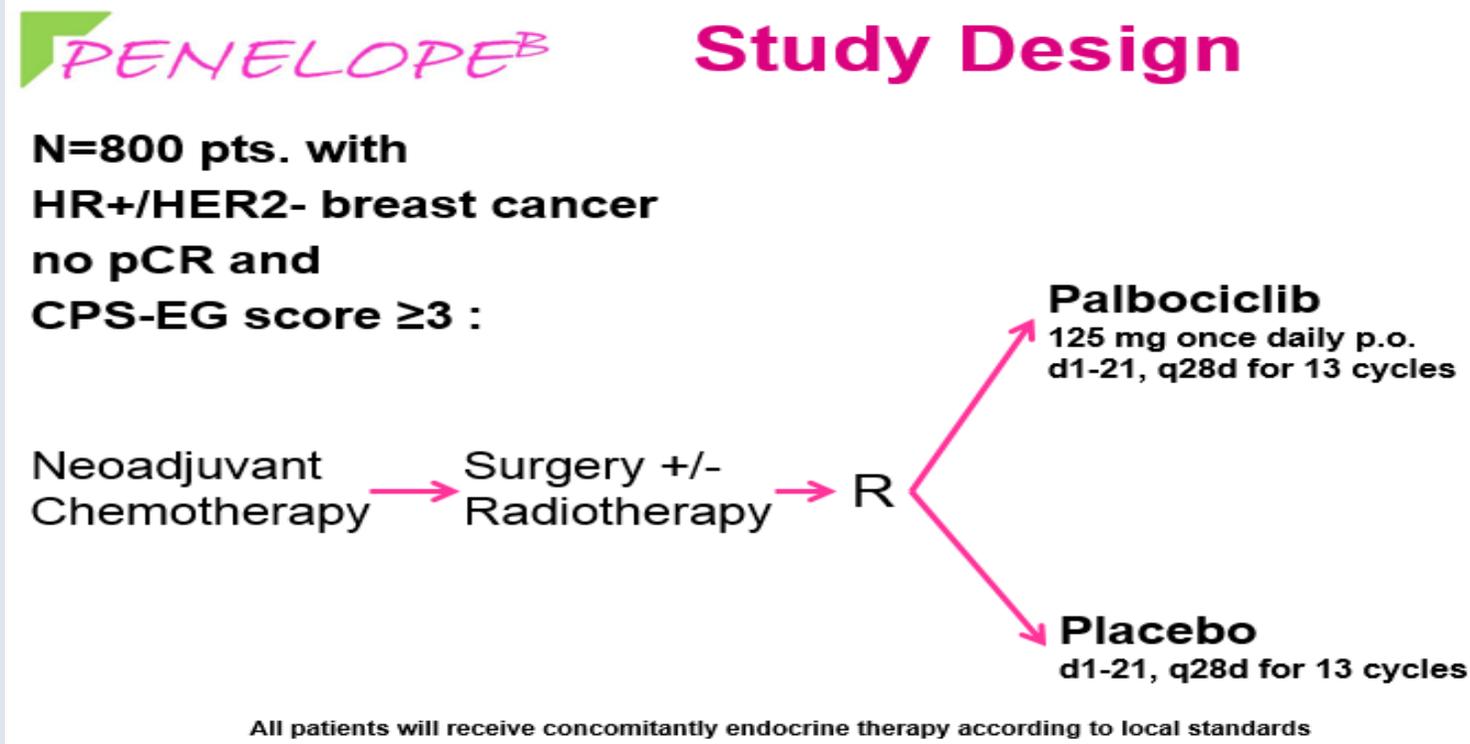
Fulvestrant +/- Palbociclib (PALOMA-3)



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Design der PENELOPE-Studie



Von Minckwitz et al., SABCS 2013

| Substanz | Phase | Regime | Patienten (Einschlusskriterien, N) |
|----------------------------|---|-----------------------------|---|
| Ribociclib (LEE011) | Phase 3 (MONALEESA-2) (NCT01958021) | LEE011+LET vs LET+PBO | ER ⁺ , HER2 ⁻ ABC, no prior systemic therapy for ABC (500) |
| | Phase 1/2 (NCT01857193) | LEE011+EVE +EXE | ER ⁺ , HER2 ⁻ MBC or LABC resistant to LET or ANA (185) |
| | Phase 1/2 (NCT01872260) | LEE011+BYL719 +LET | ER ⁺ MBC or LABC (130) |
| Abemaciclib (LY2835219) | Phase 3 (MONARCH-2) NCT02107703 | Abemaciclib + FUL vs FUL | ER ⁺ , HER2 ⁻ MBC (no prior endocrine therapy OR progression on prior AI/antiestrogen) (550) |

| Substanz | Phase | Regime | Patienten (Einschlusskriterien, N) |
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MONALEESA-2 (Phase 3): First-line Letrozol ± LEE011

Phase 3 Trial Initiating

N ≈ 500

(Data expected in December
2016)

- Postmenopausal HR⁺, HER2⁻ ABC
- No prior therapy for ABC
- *De novo* or >12 months after adjuvant therapy

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LEE011 (600 mg/day) + LET

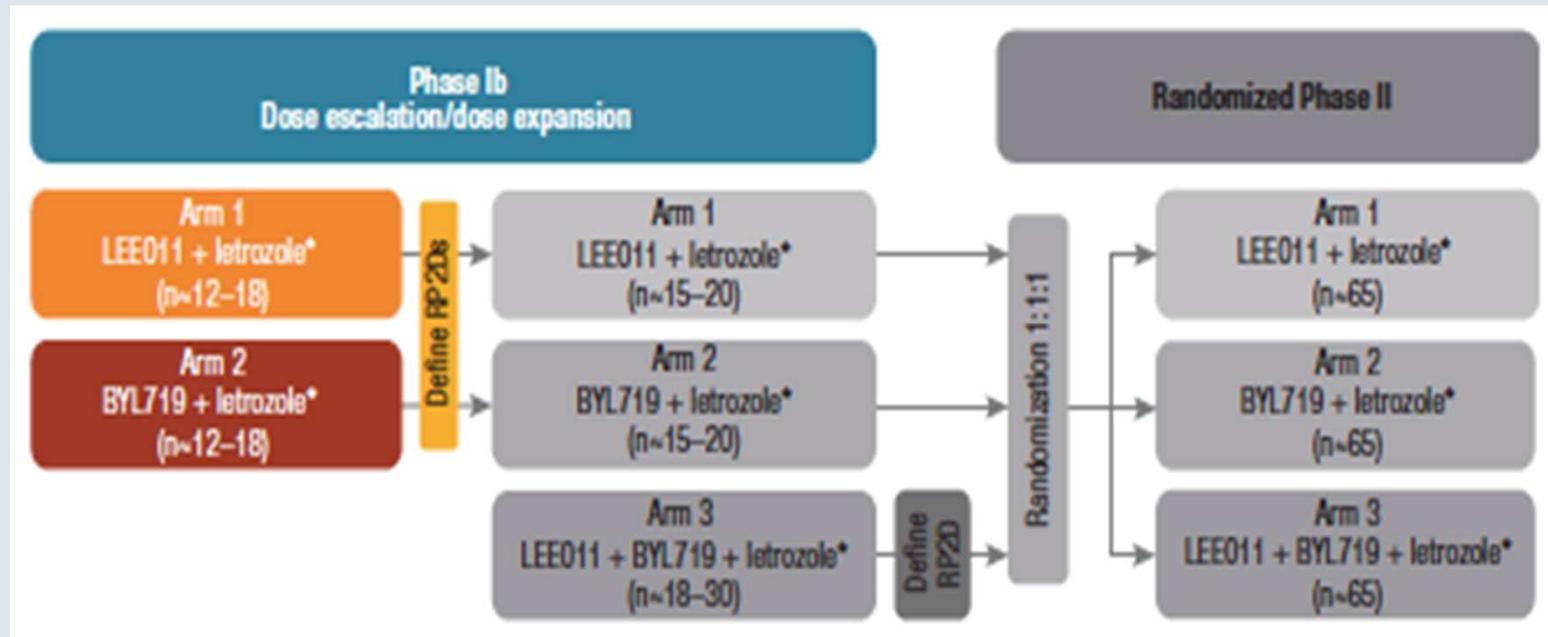
Placebo + LET

Key endpoints

Primary: PFS

Secondary: OS, ORR, QOL, Safety, PK

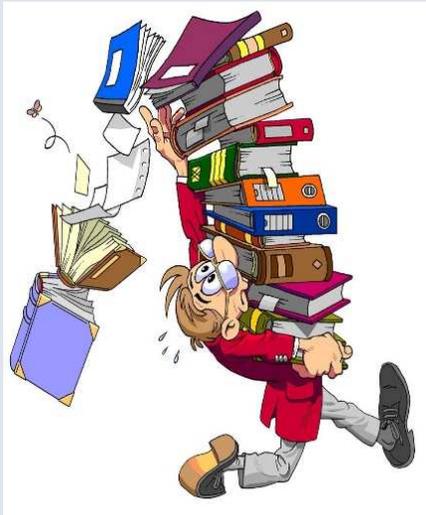
Phase Ib LEE011 + Letrozole + BYL719 (PI3K inhibitor)



- Ongoing study: Still defining MTD in first 2 arms
- Tolerable, with cytopenias as DLT
- Some clinical activity

Munster et al., ASCO 2014

Take-Home-Message



- Die Hemmung des Zellzyklus spielt eine elementare Rolle beim Mammakarzinom
- Cross talks bestehen insbesondere zwischen der Wachstumshormon-Transduktion und den Hormonrezeptoren
- Selektive CDK-Inhibitoren scheinen potente antitumorale Substanzen zu sein
- Klinische Studien an postmenopausalen Patientinnen mit ER+ Mammakarzinom zeigen einen großen Benefit



17. OSTSEE-SEMINAR
5. und 6. Dezember 2014 in Lübeck

UK SH Klinik für Gynäkologie und Geburtshilfe Campus Lübeck

Wissenschaftlicher Leiter:
Prof. Dr. med. Achim Rody

Die Universitäten
Greifswald Hamburg Kiel Lübeck Rostock

sowie
Berufsverband der Frauenärzte e.V.
Landesverbände Mecklenburg-Vorpommern,
Schleswig-Holstein, Hamburg
DAOG Deutsche Akademie für Gynäkologie und Geburtshilfe

Wissen schafft Gesundheit

Klinik für Gynäkologie und Geburtshilfe