A.O. PAPARDO
MESSINA
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## Sessione 6:
## La malattia metastatica HER2 positiva

### Nuove Associazioni: T-DM1 e Ribociclib


# G. Ricciardi

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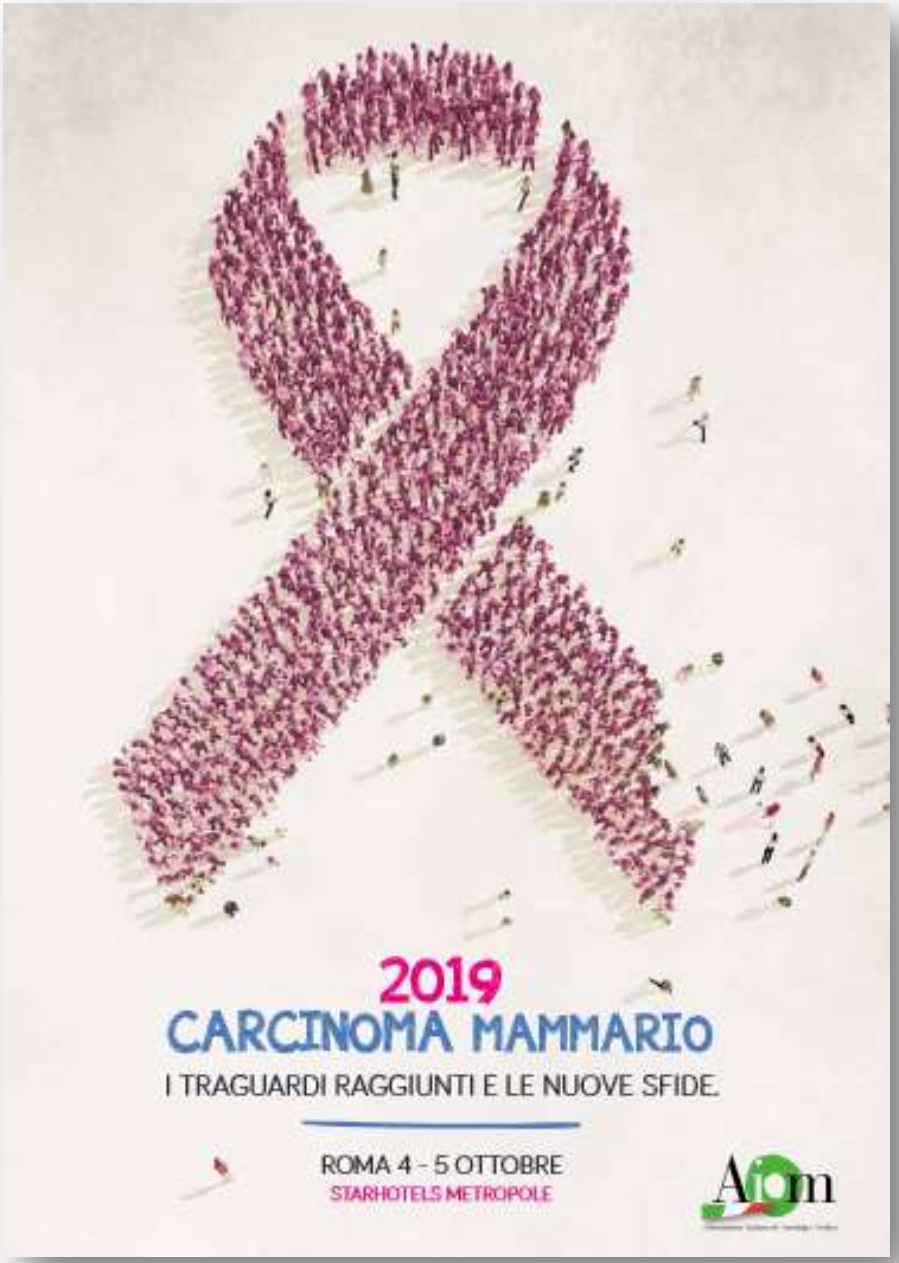
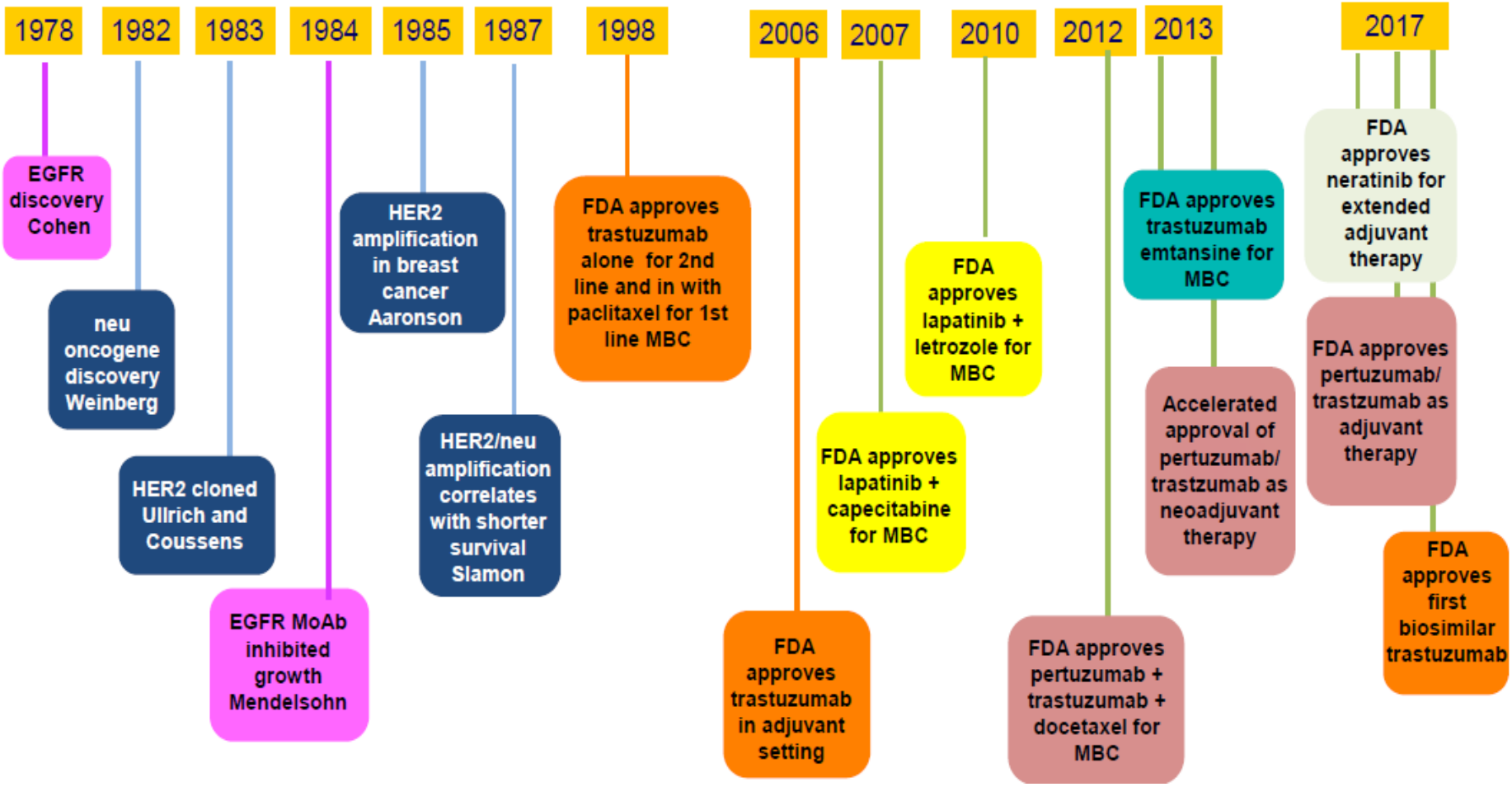
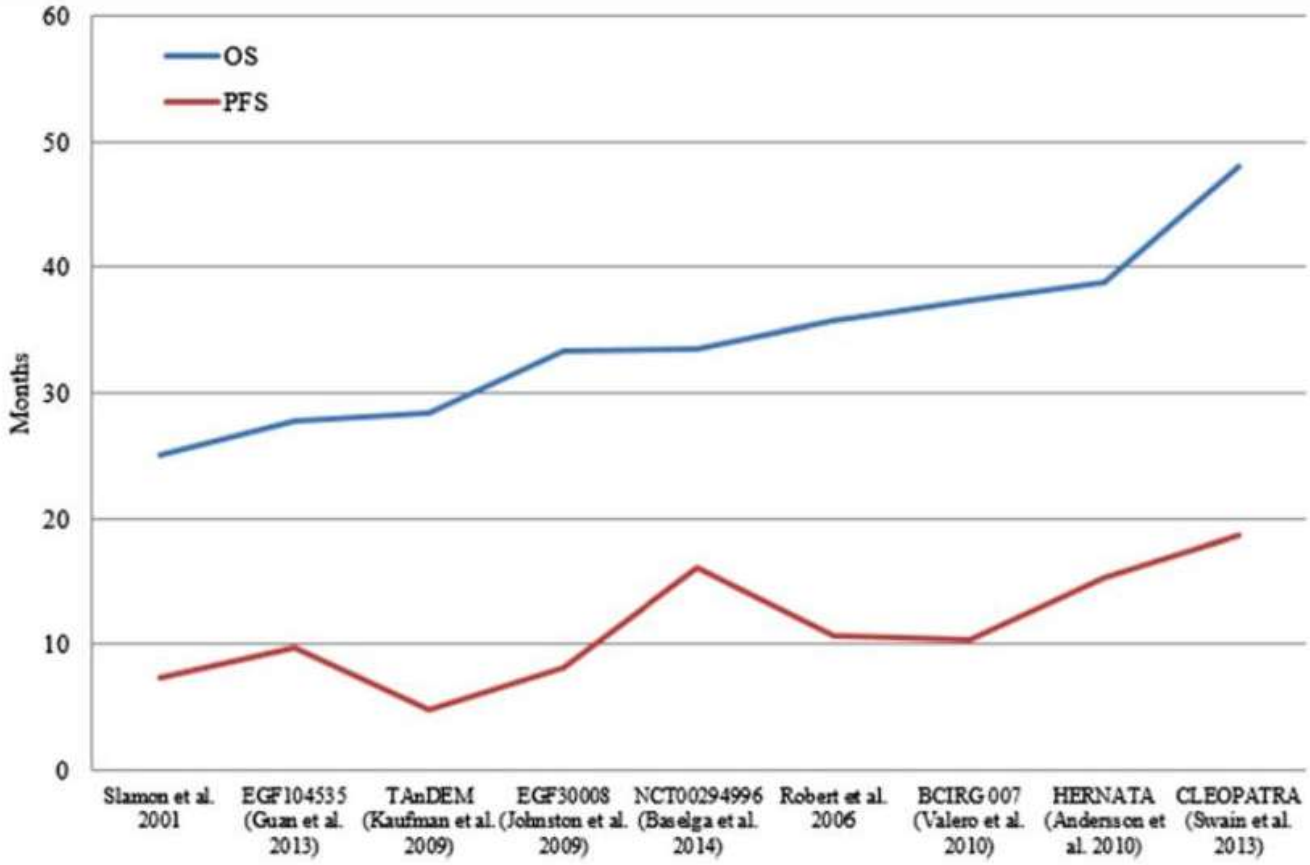


# Milestone of HER2/anti-HER2 Therapies in BC



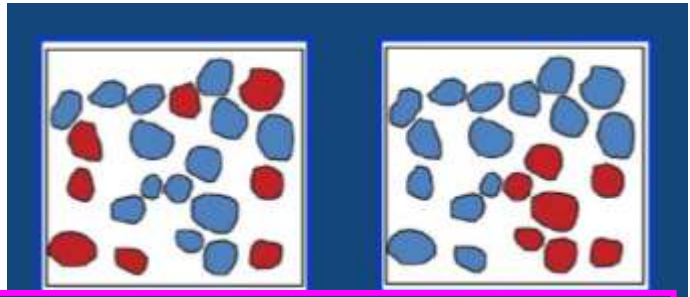
# Survival with HER2+ Metastatic Disease




*Tolaney S, ASCO 2018*

# HER2 Heterogeneity

- HER2 heterogeneity is defined by the presence of at least 2 distinct clones of cells with different levels of HER2 amplification within a tumor



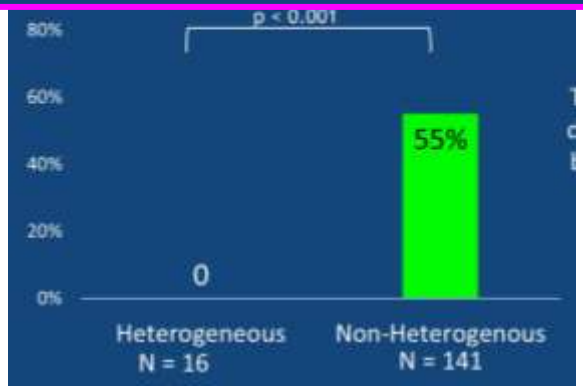
**HER2 heterogeneous cancers may represent a distinct subset of HER2+ breast cancer**

- Lower rates of pCR
- Lower levels of HER2 protein expression
- Possibly require different treatment approaches

HR+, 3/16 HR-) using the following definition:

- HER2+ by FISH in >5% and <50% of tumor cells
- an area of tumor that tested HER2 negative

- HER2 heterogeneity was associated with lower pCR rates after neoadjuvant T-DM1 + pertuzumab



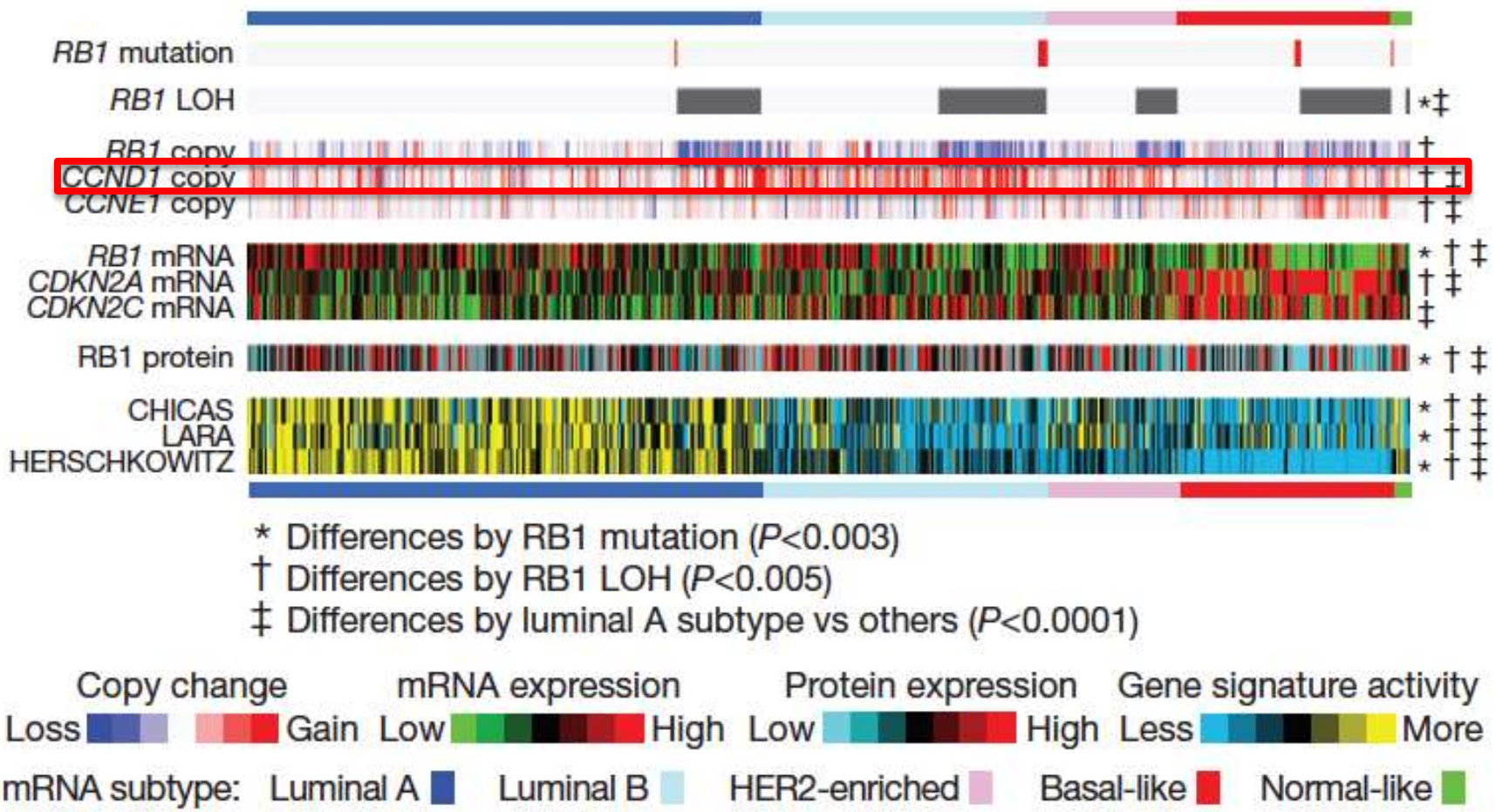

*Metzger Filho O, et al. ASCO 2019*

# Mechanisms of resistance to anti-HER2 agents

| Anti HER2 agent(s) | Mechanism of resistance | Factors involved |
|---|---|---|
| Trastuzumab (T) | Impaired HER2 binding | Low HER2 levels |
| | Parallel/downstream pathways | Splicing variants (p95HER2; Δ16 HER2) |
| | Enhanced lipid metabolism | PI3KCA mutations, PTEN loss |
| | ER signaling | FASN |
| | Cell cycle regulation | ER-PgR expression |
| | Escape from ADCC | Cyclin D1-CDK 4/6 expression |
| | | Poor binding to CD16A |
| Lapatinib (L) | HER2 signaling | *HER2* mutations |
| | Cell cycle regulation | Cyclin D1-CDK 4/6 expression |
| | Parallel/Downstream pathways | PI3K/AKT/mTOR pathway alterations |
| | ER signaling | ER-PgR expression |
| T-DM1 | Impaired HER2 binding | p95HER2; MUC4 expression |
| | Parallel/downstream signaling | NRG, HER2-HER3, *PIK3CA* mutations |
| | T-DM1 internalization/release | SLC46A3, MDR1 |
| Trastuzumab plus Lapatinib (T + L) | Impaired HER2 binding | Low HER2 levels |
| | FGFR1 signaling | *HER2* mutations |
| | Downstream pathways | *FGFR1* amplification |
| | ER signaling | *PI3KCA* mutations, |
| | Cell cycle regulation | ER-PgR expression |
| | | Cyclin D1-CDK 4/6 expression |
| Trastuzumab plus Pertuzumab (T + P) | Altered intracellular pathways | *PIK3CA* mutations |
| | HER2 signaling | *HER2* mutations |

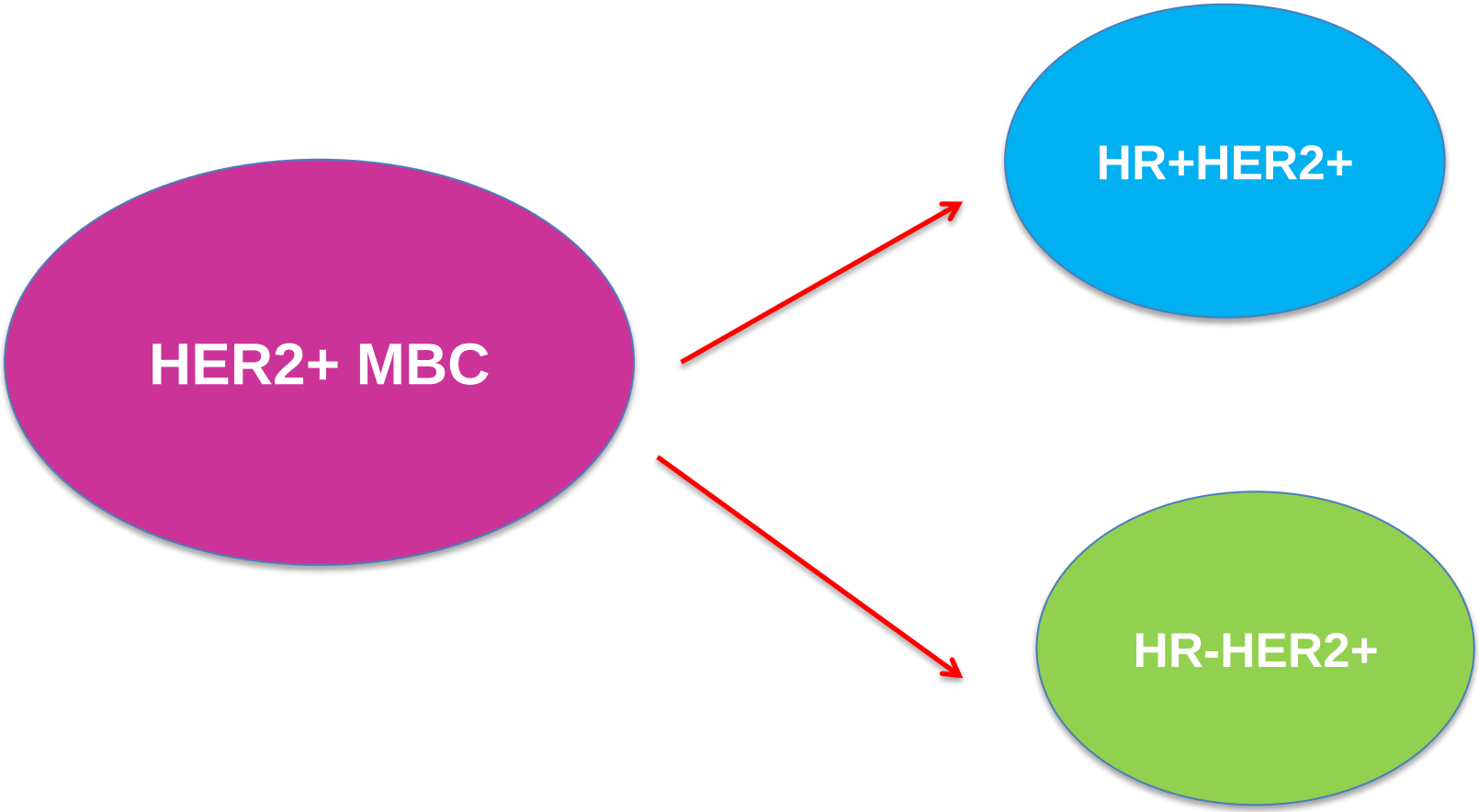
*Vernieri C, et al. Crit Rev Oncol Hematol 2019*

# Amplification of cyclin D1 gene (CCND1) in Breast Cancer

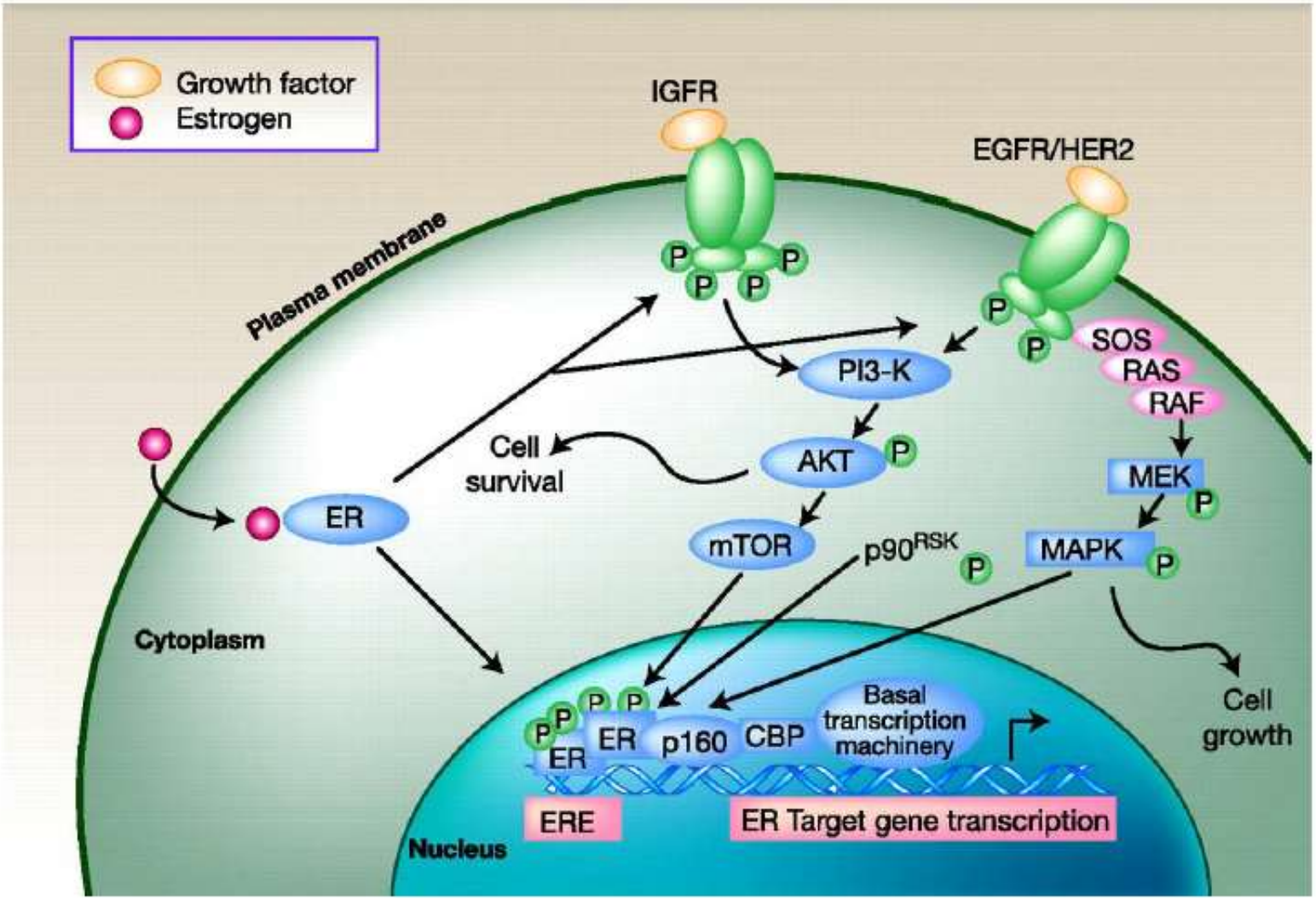



"...a common oncogenic event was **cyclin D1 amplification and high expression, which preferentially occurred within luminal tumors, and more specifically within luminal B and HER2 positive BCs**..."

*TCGA, Nature 2012*

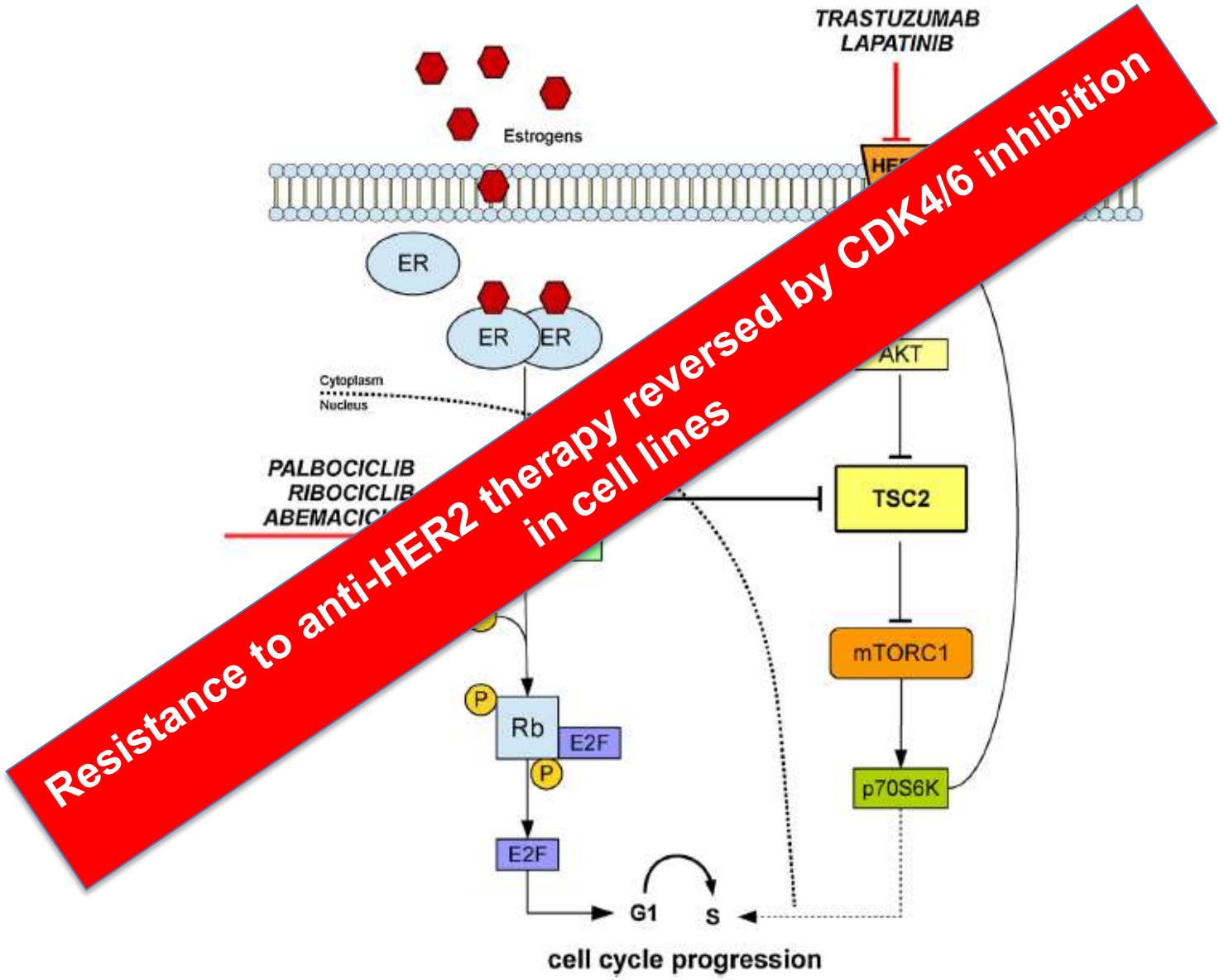

HER2+ MBC
HR+HER2+
HR-HER2+

# Cross-talk Between ER and HER2 Pathways



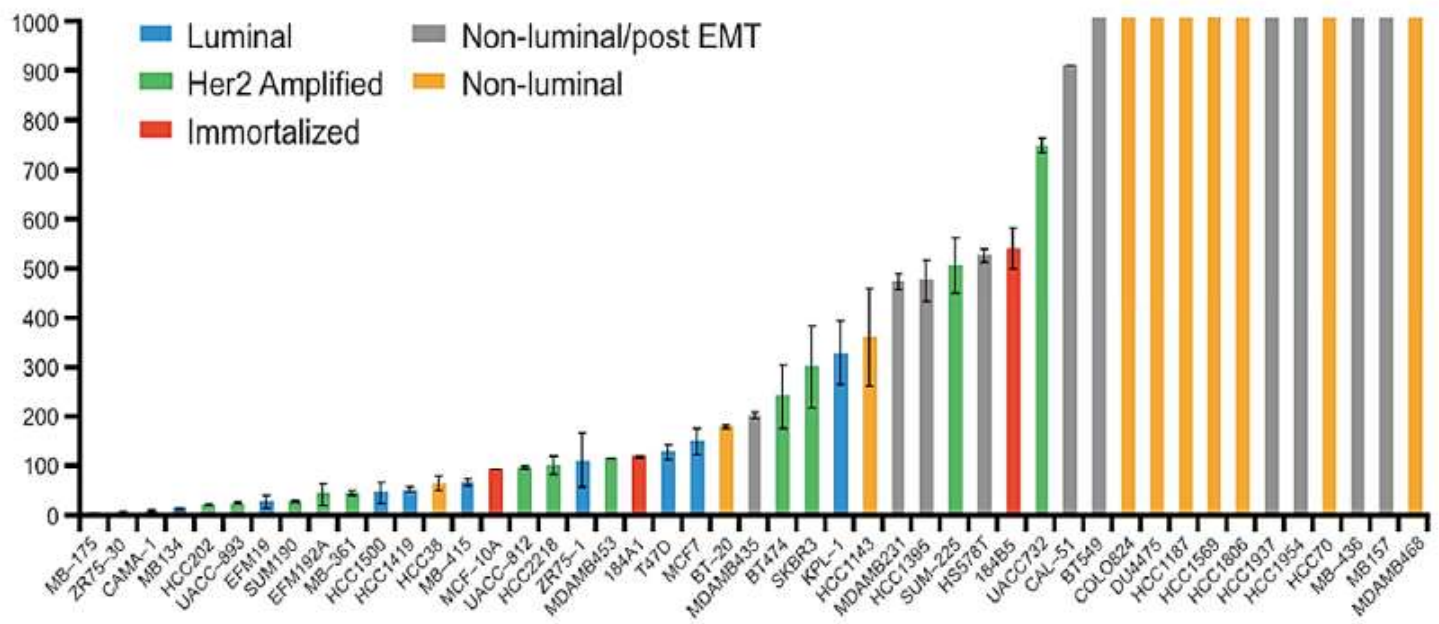

*Johnston SRD. ClinCancer Res 2010*

# CDK4/6 and anti-HER2 resistance




*Corona SP, Crit Rev Oncol Hemat 2017*

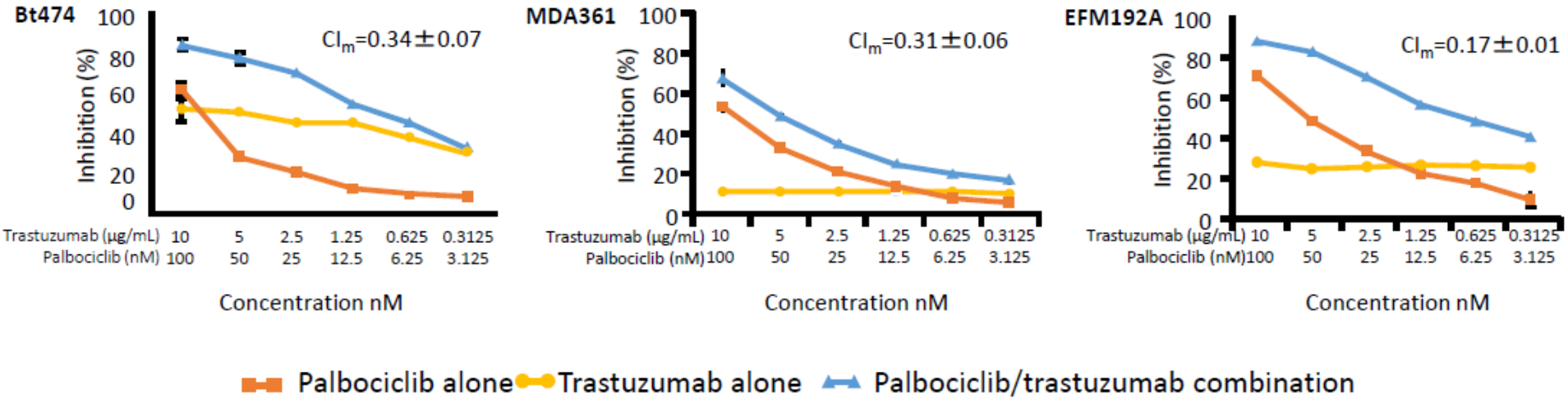
# CDK4/6 inhibitors in HER2+ BC




**Luminal *ER*-positive and *HER2*-amplified BC cell lines are most sensitive to CDK4/6 inhibition of proliferation**

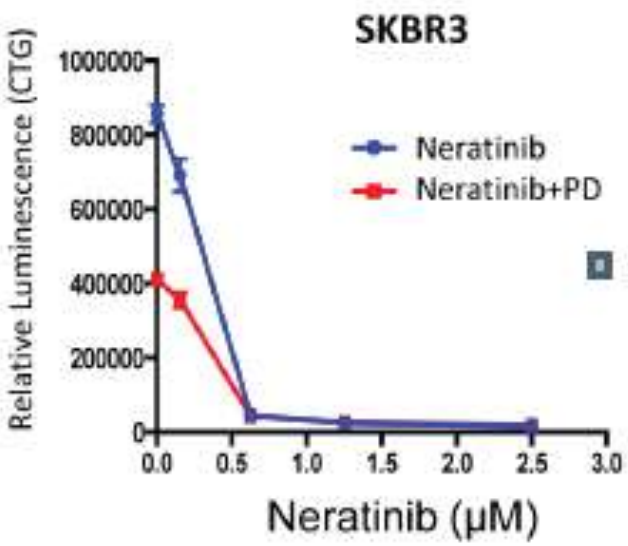
Finn RS, et al. *Breast Cancer Res.* 2009;11(5):R77.

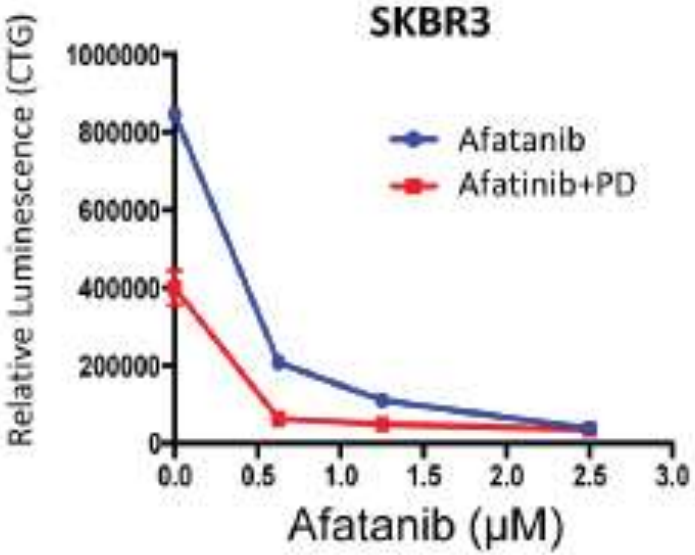
# The synergistic effect on cell proliferation with the Palbociclib and Trastuzumab combination in HER2-amplified BC cell lines




*Finn RS, Breast Cancer Res 2009*

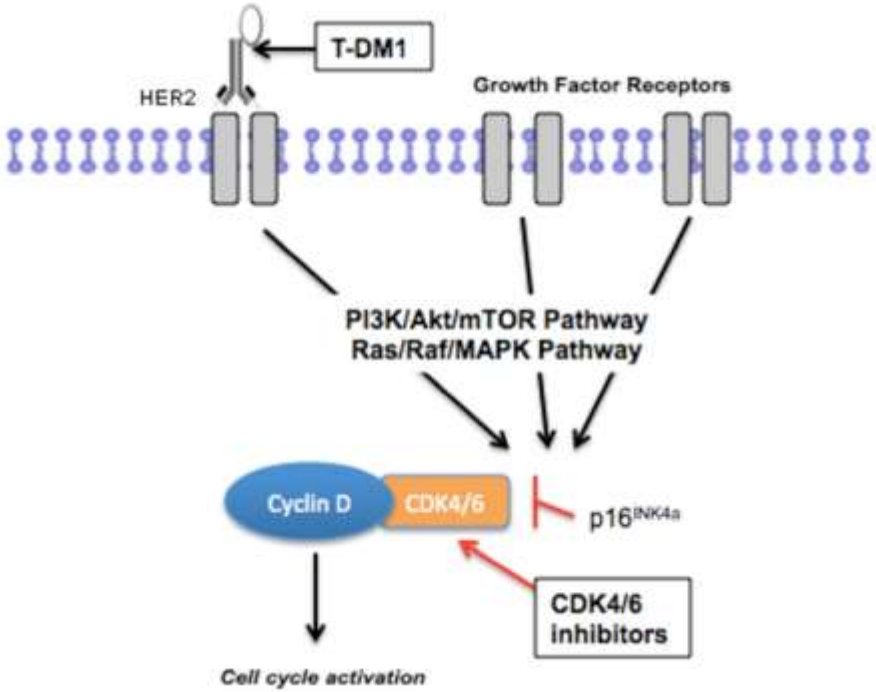
# CDK4/6 Inhibitor had additive activity with TKIs




*Witkiewicz AK, et al. Genes Cancer. 2014*

# T-DM1 & CDK4/6 inhibitor




- In models of acquired resistance to HER2-targeted therapies, cyclin D1 and CDK4/6 activation play an important role, and inhibition of CDK4/6 can block proliferation, resulting in tumor inhibition.[1-2]
- Pre-clinical work has demonstrated CDK4/6 inhibition provided a complementary mechanism of action to T-DM1, and efficiently suppressed the proliferation of residual HER2-positive tumor cell populations that survived T-DM1.[1]

*Spring L, et al. ASCO 2017*

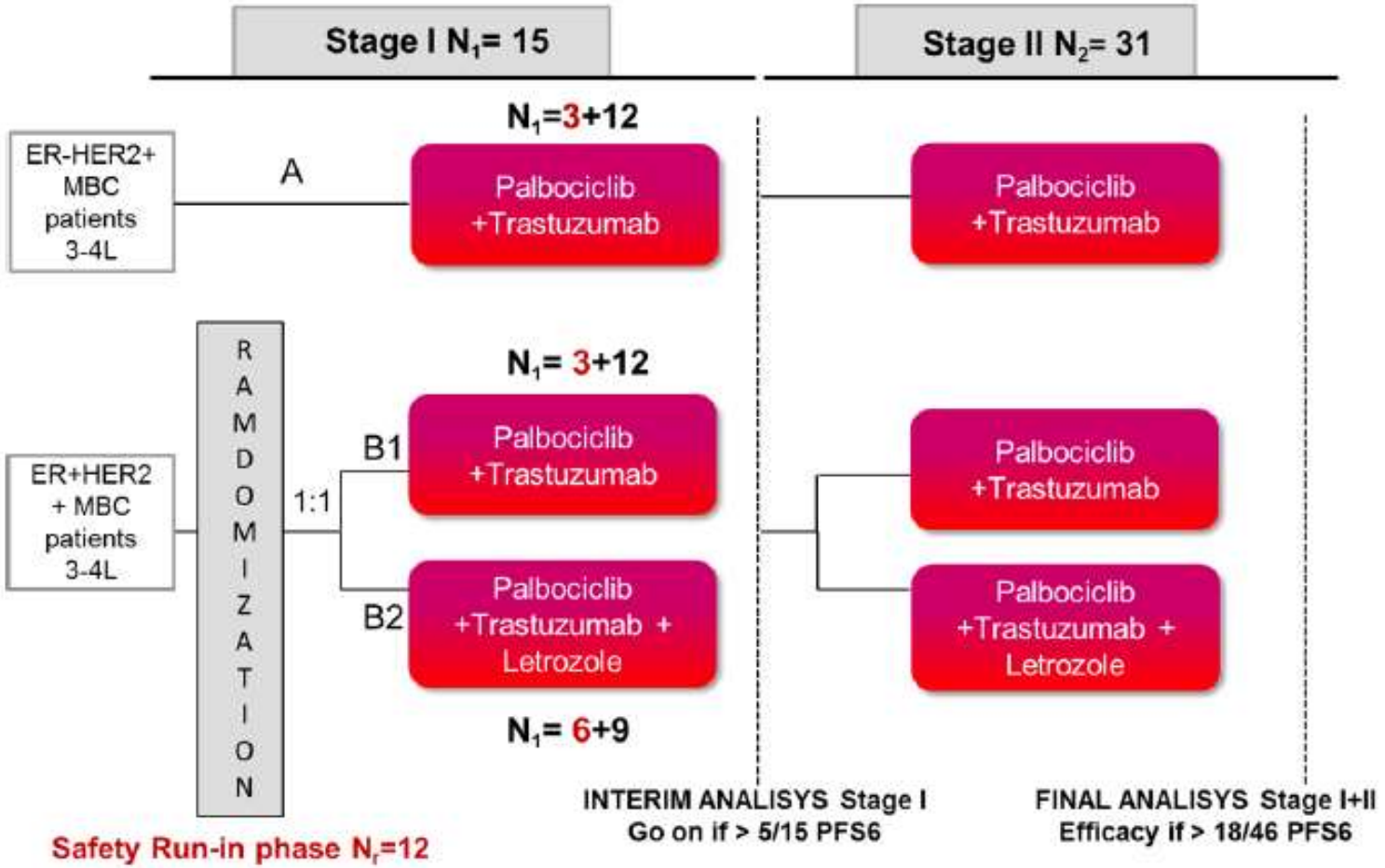
*[1]Witkiewicz AK, et al. Genes Cancer. 2014; [2]Finn RS, et al. Breast Cancer Res 2009*

# Trials with Palbociclib in HER2-positive breast cancer

| Trial ID | Status | Phase | Arms | Population | Results | Primary outcome |
|---|---|---|---|---|---|---|
| **Metastatic breast cancer** | | | | | | |
| **(1) Studies with reported results** | | | | | | |
| DeMichele and colleagues[27] | Recruiting (arm 1: metastatic breast cancer) has stopped recruitment; arm 5: any tumor type if tissue tests positive for CCND1 amplification, CDK4/6 mutation, CCND2 amplification or any other functional alteration at the G1/S checkpoint is still recruiting | II | Single arm: palbociclib | Metastatic | Two patients (5%) HR-positive HER2-positive, no prior HER2-directed therapy. Of these, one had a partial response and the other had a stable disease lasting 5 months on palbociclib; Rb nuclear expression, Ki-67 proliferation index, p16 loss, and cyclin D amplification were not associated with response. | ORR; safety and tolerability |
| **(2) Studies underway with approved HER2 therapies** | | | | | | |
| NCT02448420 (PATRICIA) | Recruiting | II | 1. HR negative: palbociclib + trastuzumab<br>2. HR-positive: palbociclib + trastuzumab<br>3. HR-positive: palbociclib + trastuzumab + letrozole | Metastatic | Pending | PFS at 6 months |
| NCT02774681 | Recruiting | II | Single arm: palbociclib | Metastatic with brain metastases, HR-negative | Pending | Radiographic response rate in CNS |
| NCT03304080 | Recruiting | I/II | Single arm: anastrozole + palbociclib + trastuzumab + pertuzumab | Metastatic, HR-positive | Pending | Dose-limiting toxicity, MTD, CBR |
| NCT02947685 (PATINA) | Recruiting | III | Induction treatment with anti-HER2 therapy (standard chemotherapy + anti-HER2 therapy with trastuzumab and pertuzumab), followed by randomization:<br>1. Endocrine therapy + anti-HER2 therapy + palbociclib<br>2. Endocrine therapy + anti-HER2 therapy | Metastatic, HR-positive | Pending | PFS |
| **(3) Studies underway with other investigational drugs** | | | | | | |
| NCT03054363 | Recruiting | Ib/roll-over phase II | Single arm: tucatinib + palbociclib + letrozole | Metastatic, HR-positive | Pending | AEs, PFS |
| NCT03065387 | Recruiting | I | 1. Neratinib + everolimus<br>2. Neratinib + palbociclib<br>3. Neratinib + trametinib | Metastatic, EGFR mutation/ amplification, HER2 mutation/ amplification or HER3/4 mutation | Pending | Dose-limiting toxicity, MTD |

*Matutino A, et al. Ther Adv Med Oncol 2018*

# PATRICIA: A Phase II study of Palbociclib and trastuzumab with or without letrozole in pretreated postmenopausal HER2-positive MBC



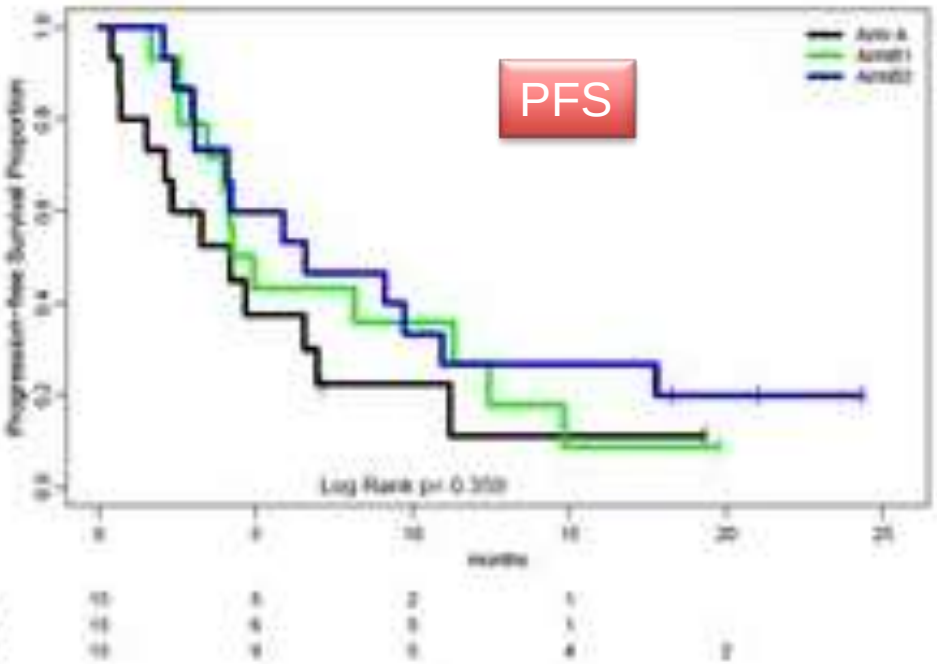

Palbociclib: oral, 200 mg daily during 2 weeks, followed by one week off; Trastuzumab: 8mg/kg loading dose, then 6 mg/kg every 3 weeks; subcutaneous trastuzumab (600 mg/3 weeks) is allowed; Letrozole: Daily oral 2.5 mg; Cycles of 3 weeks.

*Villagrasa P, et al. ASCO 2018*

# PATRICIA - Stage I: preliminary results


| Safety data | Cohort A (n=15) | Cohort B1 (n=15) | Cohort B2 (n=15) |
|---|---|---|---|
| **Number of patients with adverse event [n (%)]** | 14 (93.3%) | 15 (100.0%) | 15 (100.0%) |
| Neutropenia | 10 (66.7%) | 12 (80.0%) | 14 (93.3%) |
| Anemia | 5 (33.3%) | 5 (33.3%) | 5 (33.3%) |
| Thrombocytopenia | 3 (20.0%) | 2 (13.3%) | 8 (53.3%) |
| Febrile Neutropenia | 2 (13.3%) | - | - |
| Asthenia | 8 (53.3%) | 9 (60.0%) | 10 (66.7%) |
| Diarrhea | 1 (6.7%) | 4 (26.7%) | 2 (13.3%) |
| Nausea | 2 (13.3%) | 2 (13.3%) | 3 (20.0%) |
| **Patients with adverse events grade III or IV [n (%)]**** | 12 (80.0%) | 12 (80.0%) | 14 (93.3%) |
| Neutropenia* | 9 (60.0%) | 10 (66.7%) | 12 (80.0%) |
| Anemia | - | - | 1 (6.7%) |
| Thrombocytopenia | 2 (13.3%) | - | 4 (26.7%) |
| Febrile Neutropenia | 2 (13.3%) | - | - |
| Asthenia | 2 (13.3%) | 1 (6.7%) | - |
| Nausea | - | 1 (6.7%) | - |

*Most G3 Neutropenia occurred in the first 2 cycles
**Dose reductions were required in 60% of patients




6-month PFS rates

| | % | Number of patients |
|---|---|---|
| Cohort A | 33.3 % | 5 /15 |
| Cohort B1 | 40.0 % | 6 / 15 |
| Cohort B2 | 53.3 % | 8 / 15 |

*Ciruelos E, et al. SABCS 2018*

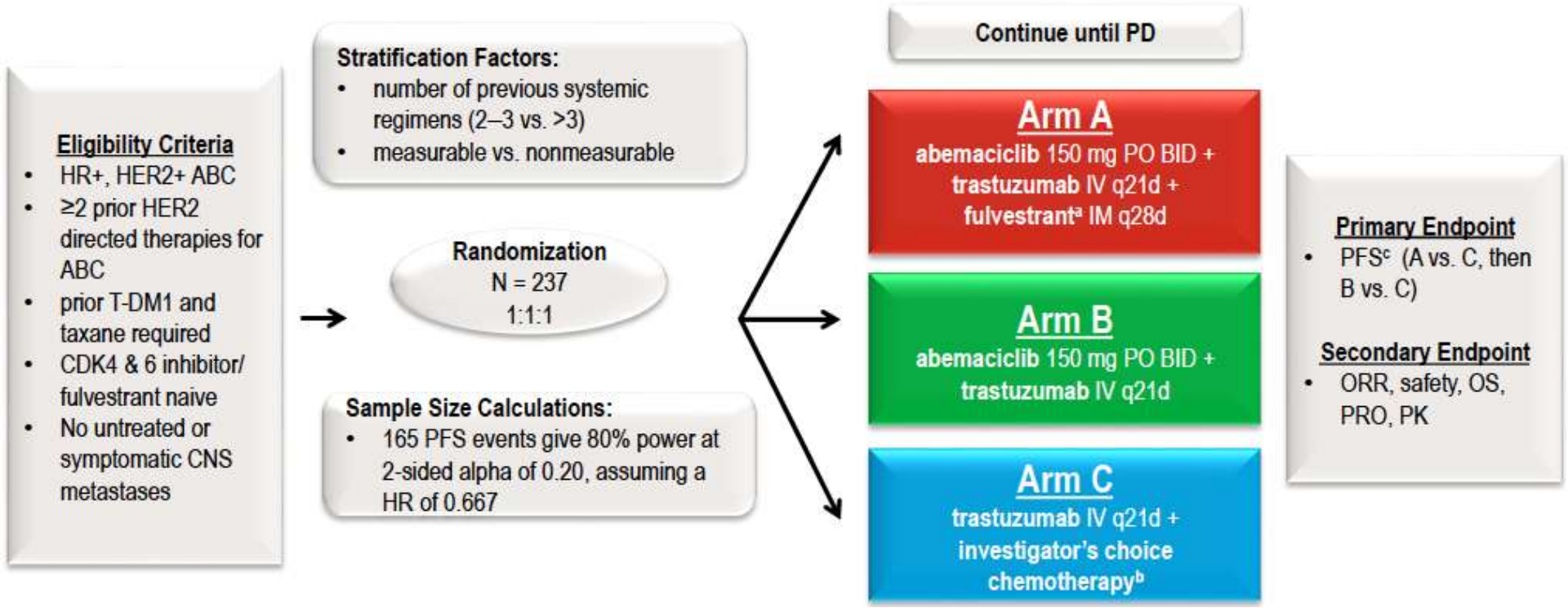
# Trials with Abemaciclib in HER2-positive MBC

| Trial ID | Status | Phase | Arms | Population | Results | Primary outcome |
|---|---|---|---|---|---|---|
| **Abemaciclib** | | | | | | |
| **(1) Studies with reported results** | | | | | | |
| Patnaik and colleagues[28] | Completed | I | Single arm: abemaciclib | Metastatic | PR 36%; SD 64% | Safety; tolerability |
| Fujiwara and colleagues[29] | Completed | I | Single arm: abemaciclib | Metastatic | One patient with HR-negative HER2-positive had a 30% decrease in tumor size | MTD; dose-limiting toxicity |
| **(2) Studies underway with approved HER2 therapies** | | | | | | |
| NCT02675231 (monarcHER) | Active, not recruiting | II | 1. Abemaciclib + trastuzumab + fulvestrant<br>2. Abemaciclib + trastuzumab<br>3. Trastuzumab + standard of care chemotherapy | Metastatic | Pending | PFS |

CBR, clinical benefit rate; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; MTD, maximum tolerated dose; NCT, ClinicalTrials.gov identifier; PFS, progression-free survival; PR, partial response; SD, stable disease; T-DM1, trastuzumab emtansine.

*Matutino A, et al. Ther Adv Med Oncol 2018*

# monarcHER STUDY DESIGN

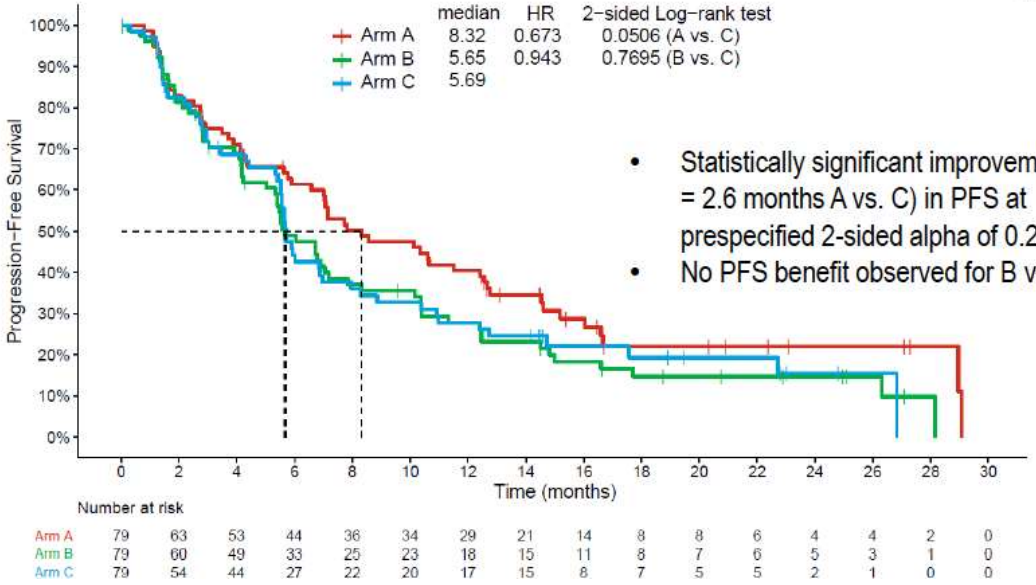



| | >3 Lines of therapy | Visceral metastasis |
|---|---|---|
| Arm A | 55.7% | 73.4% |
| Arm B | 44.3% | 70.9% |
| Arm C | 49.4% | 60.8% |

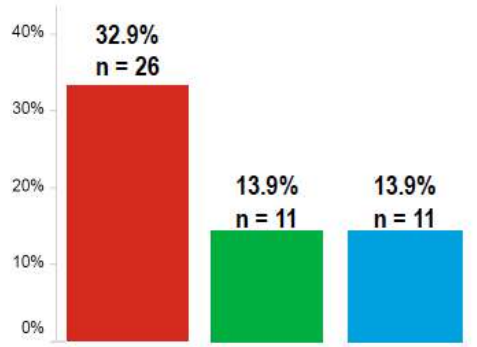
*Tolaney SM, et al. ESMO 2019*

# PRIMARY ENDPOINT: PFS

Arm A= abemaciclib + trastuzumab + fulvestrant
Arm B= abemaciclib + trastuzumab
Arm C= trastuzumab + chemotherapy




- Statistically significant improvement (Δ = 2.6 months A vs. C) in PFS at prespecified 2-sided alpha of 0.2
- No PFS benefit observed for B vs. C




ITT Population
Total N = 237

| | Arm A N=79 | Arm B N=79 | Arm C N=79 |
|---|---|---|---|
| 95% CI (%) | (22.5-43.3) | (6.3-21.6) | (6.3-21.6) |
| Stratified 2-sided p-value (vs Arm C) | 0.0042 | 1.0000 | - |
| Duration of Response, months | 12.5 | 9.5 | not reached |

| | Arm A N=78 | Arm B N=77 | Arm C N=72 |
|---|---|---|---|
| Duration of Treatment, median (cycles) | 10.0 | 8.0 | 7.5[a] |
| Patients with ≥ 1 CTCAE Grade ≥ 3 TEAE, n (%)[b] | 44 (56.4) | 29 (37.7) | 24 (33.3) |
| Patients with ≥ 1 SAE, n (%)[b] | 8 (10.3) | 4 (5.2) | 5 (6.9) |
| Deaths due to AE on study treatment, n (%)[c] | 2 (2.6) | 1 (1.3) | 1 (1.4) |
| Patients with treatment discontinuation due to AE | 6 (7.7) | 11 (14.3) | 6 (8.3) |
| Due to Diarrhea | 0 | 1 (1.3) | 0 |
| Due to Neutropenia | 1 (1.3) | 1 (1.3) | 0 |

[a]most common chemotherapy: Vinorelbine (37.5%) , Capecitabine (26.4%) , Eribulin (16.7%), Gemcitabine (11.1%)
[b]related to study treatment
[c]deaths on study treatment due to AE: Arm A (cardio-pulmonary arrest, adult respiratory distress syndrome), Arm B (pulmonary fibrosis), Arm C (febrile neutropenia)
AE = Adverse Event, TEAE =Treatment- Emergent Adverse Event, CTCAE = Common Terminology Criteria for Adverse Events, SAE = Serious Adverse Event

*"...This is the first phase 2 study of a CDK4 & 6 inhibitor and ET vs. standard-of-care chemotherapy, together with HER2 directed treatment in HR+, HER2+ ABC to report positive results..."*

*Tolaney SM, et al. ESMO 2019*

# Efficacy of trials with anti-HER2 agents in ≥2 line

| Trial | Arms | HR+ | >3 lines for MBC | Prior T-DM1 | Prior Pertuzumab | PFS (months) | ORR |
|---|---|---|---|---|---|---|---|
| monarcHER | Arm A | 100% | 55.7% | 97.5% | 54.4% | 8.32 | 35.7% |
| | Arm B | 100% | 44.3% | 98.7% | 46.8% | 5.65 | 16.2% |
| | Arm C | 100% | 49.4% | 97.5% | 49.4% | 5.69 | 15.9% |
| NALA[1] | Nera + Cape | 59% | 30%† | 19% | 8% | 8.8* | 33.0% |
| | Lapa + Cape | 59% | 32%† | 20% | 7% | 6.6* | 27.0% |
| Sophia[2] | Margetux + CT | 62% | 34%† | 91% | 100% | 5.8 | 22.1% |
| | Trastuz + CT | 63% | 33%† | 92% | 100% | 4.9 | 16.0% |
| Th3resa[3] | T-DM1 | 52% | 67% | NA | 0% | 6.2 | 31.0% |
| | Trastuz + CT | 51% | 61% | | 0% | 3.3 | 9.0% |

† ≥3 lines | *Mean PFS reported

BARCELONA 2019 ESMO congress

[1] Saura C et al, ASCO 2019 | [2]Rugo H et al, ASCO 2019 | [3]Krop I et al. Lancet Oncol 2014; 15: 689–99

*Oliveira M. ESMO 2019*

# Active trials with Ribociclib in HER2 positive Breast Cancer

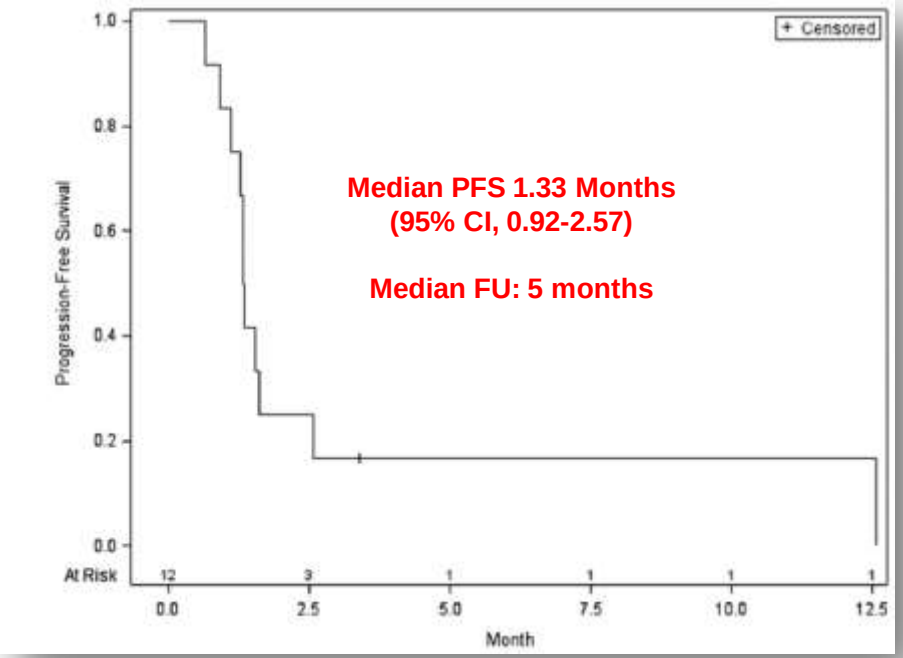
| Trial ID | Status | Phase | Arms | Population | Results | Primary outcome |
|---|---|---|---|---|---|---|
| **Ribociclib** | | | | | | |
| **(1) Studies underway with approved HER2 therapies** | | | | | | |
| NCT02657343 | Recruiting | I/II | 1. Ribociclib + T-DM1<br>2. Ribociclib + trastuzumab<br>3. If HR-positive: ribociclib + trastuzumab + fulvestrant | Metastatic | Pending | Phase I: MTD phase II: dose; CBR |

*Matutino A, et al. Ther Adv Med Oncol 2018*

# Phase 1b/2 clinical trial with Ribociclib + trastuzumab

| Characteristics of 12 Patients | |
|---|---|
| **Characteristic** | **Value** |
| **Age (y)** | 51 (42-72) |
| **White race/ethnicity** | 12 (100%) |
| **ECOG Performance Status** | |
| 0 | 10 (83%) |
| 1 | 2 (17%) |
| **ER and/or PR positive** | 8 (67%) |
| **No. of metastatic sites** | 4 (1-4) |
| **Previous Therapy in Any Setting** | |
| Trastuzumab | 12 (100%) |
| Pertuzumab | 12 (100%) |
| T-DM1 | 12 (100%) |
| **No. of prior lines of systemic therapy for metastatic disease** | 5 (0[a]-14) |
| **No. of prior chemotherapies for metastatic disease** | 4 (0[a]-11) |

| Best Response of 12 Subjects by RECIST 1.1 | |
|---|---|
| **Characteristic** | **N (%)** |
| **Complete response** | 0 |
| **Partial response** | 0 |
| **Stable Disease** | |
| < 12 wk | 1 (8.3%) |
| 12-24 wk | 1 (8.3%) |
| > 24 wk | 1 (8.3%) |
| **Progressive disease+** | 9 (75%) |

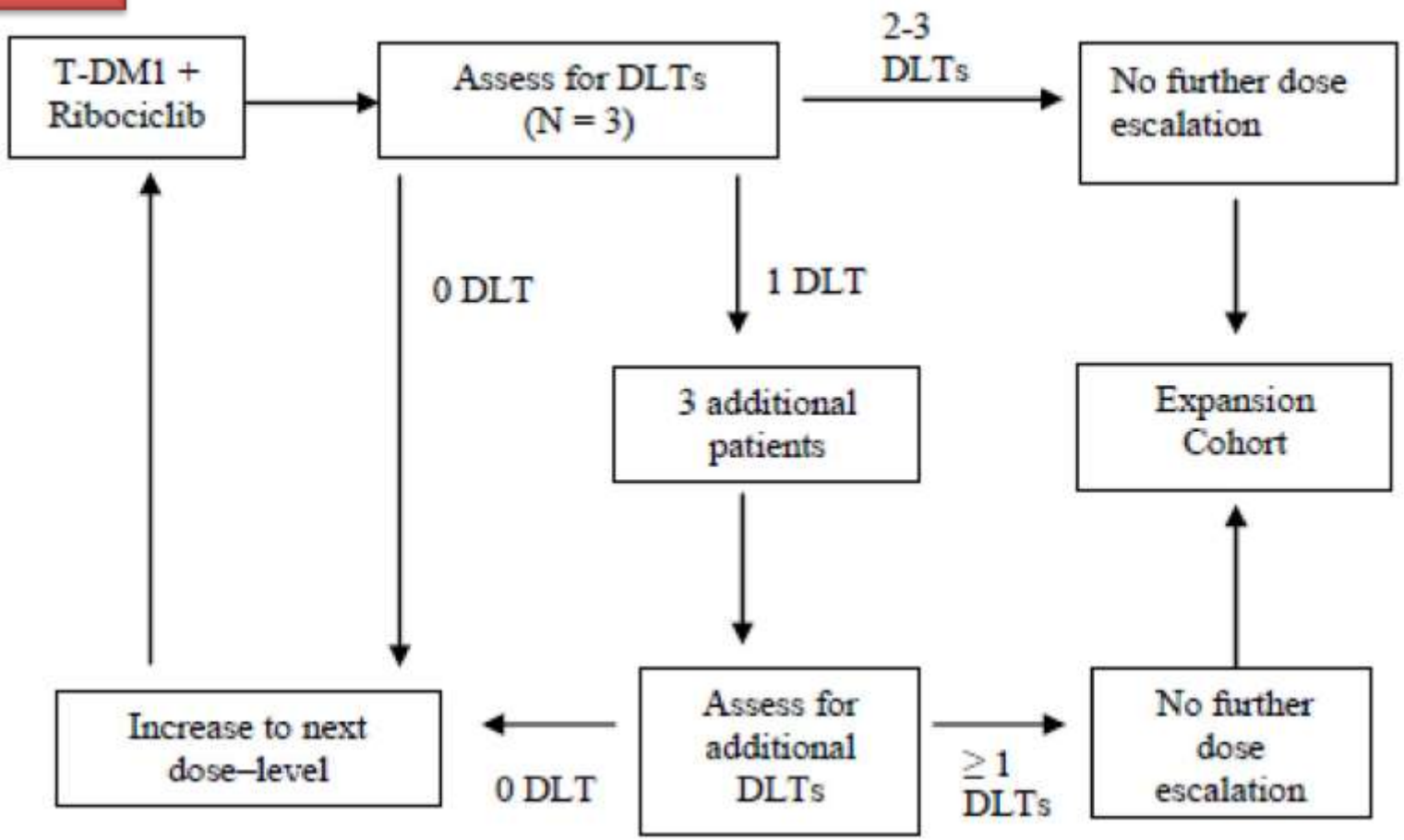



*"...**Continuous low-dose ribociclib (400 mg) plus trastuzumab is safe**, with no new safety concerns. The li**mited activity observed in this study** suggests that **further study of CDK4/6 inhibitor/anti-HER2 combinations should focus on a less pretreated population**..."*

*Goel S, et al. Clin Breast Cancer 2019*

# Phase 1b clinical trial with Ribociclib + T-DM1

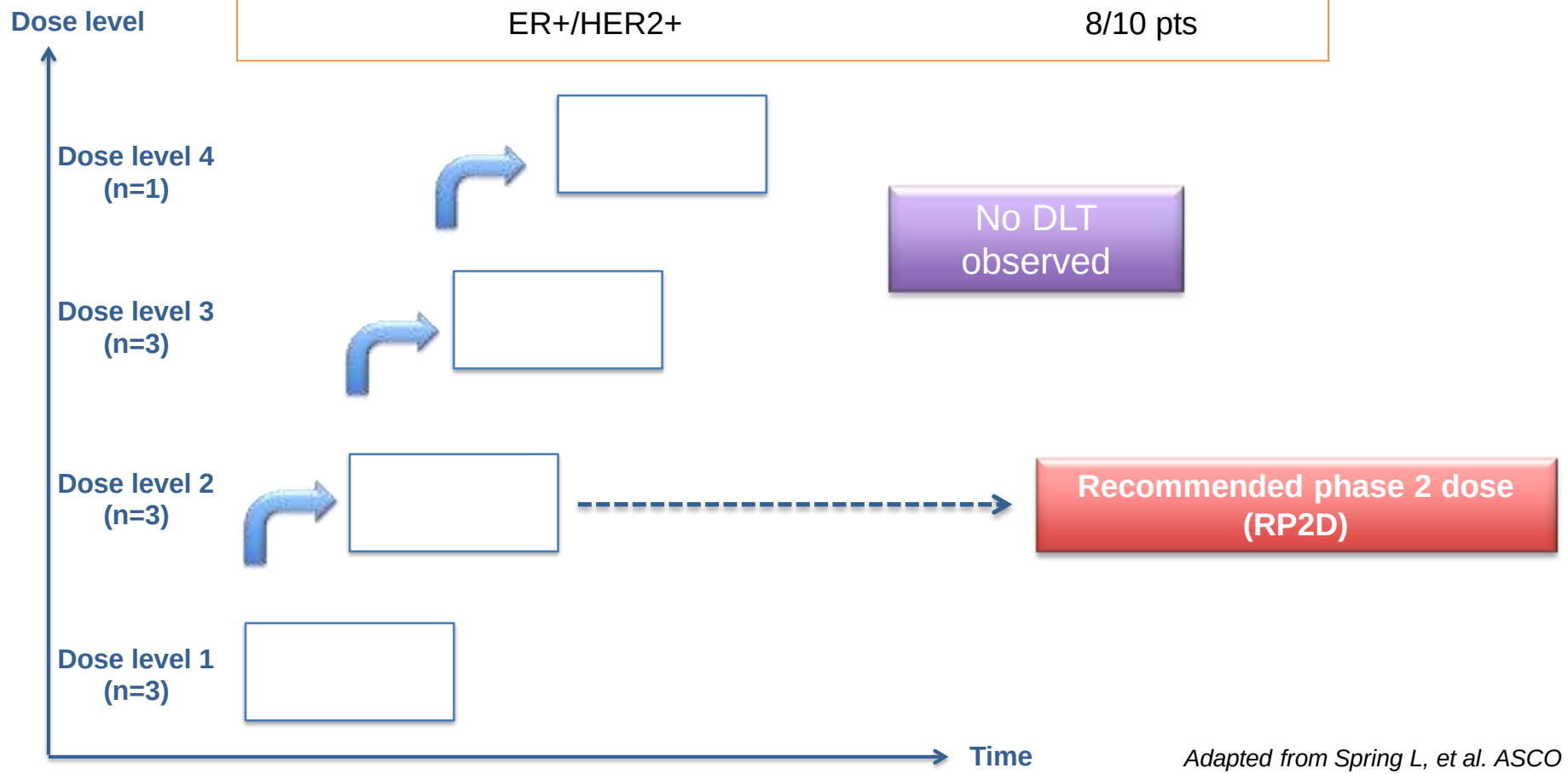
3 + 3 design




*Spring L, et al. ASCO 2019*

# Ribociclib + T-DM1 phase 1b

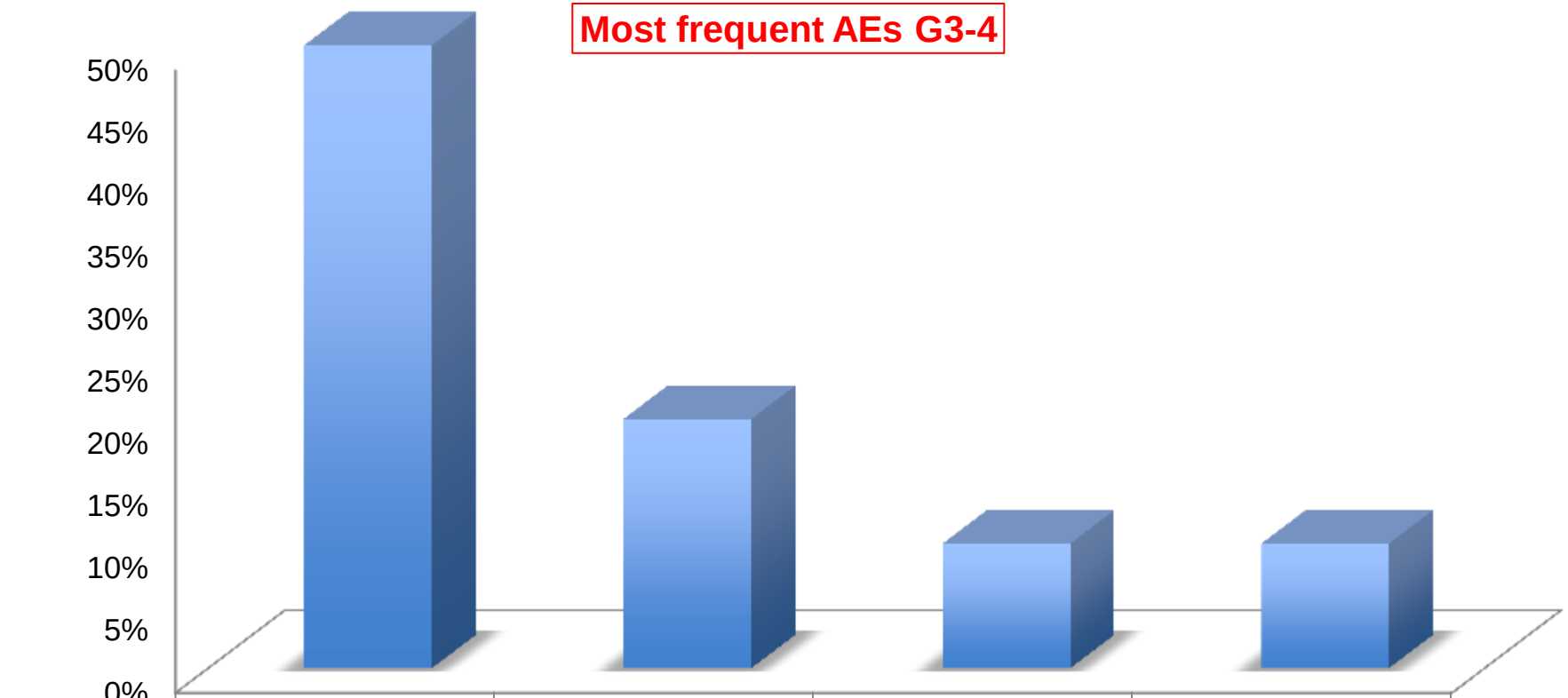
| Patients characteristics (n=10) | |
|---|---|
| Median age (range) | 53 (38-72) |
| Median prior therapy lines (range) for MBC | 1 (0-2) |
| Median follow-up | 10.9 mos |
| ER+/HER2+ | 8/10 pts |




*Adapted from Spring L, et al. ASCO 2019*

# Preliminary safety results

**Most frequent AEs G3-4**

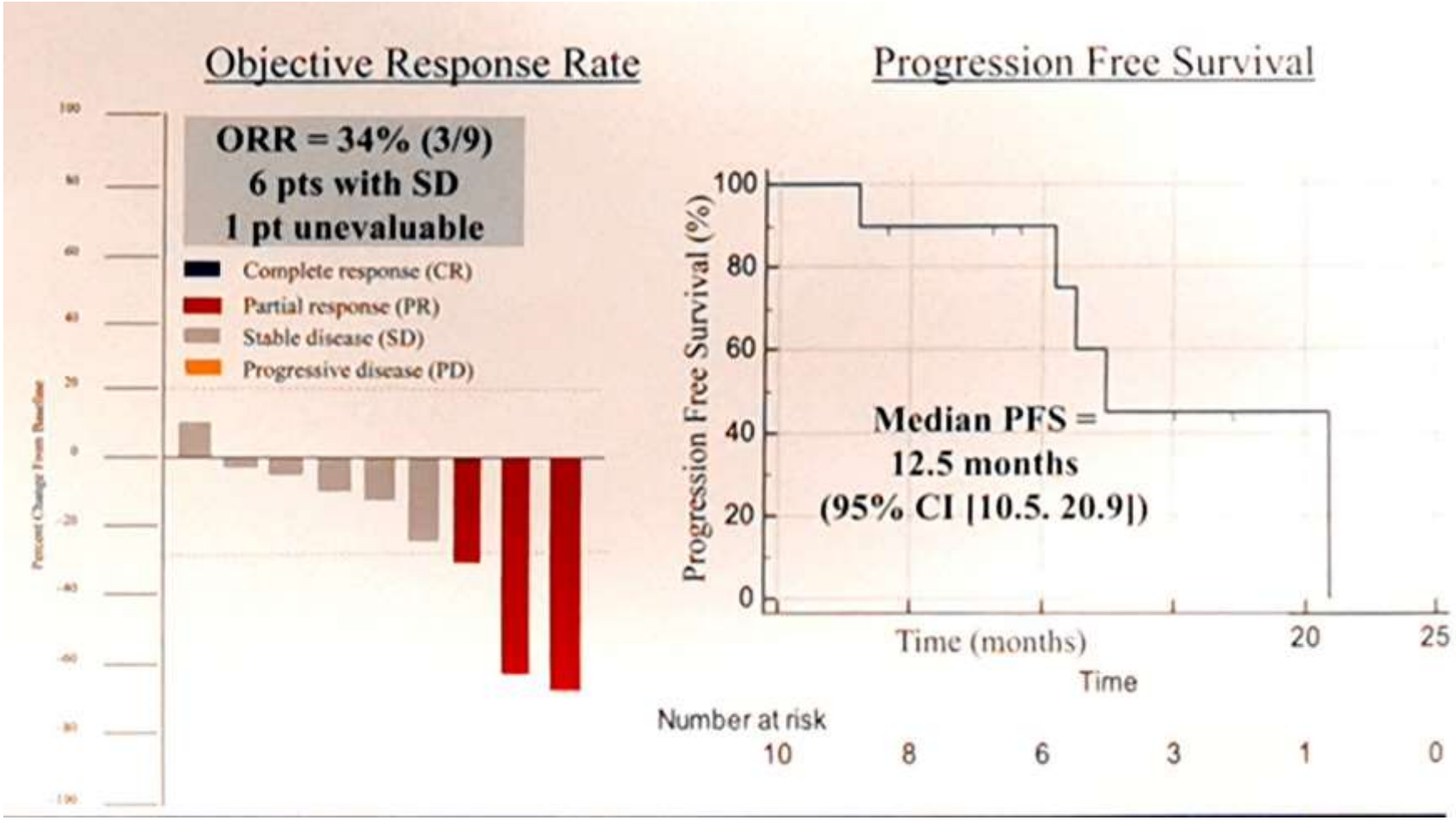



| | Neutropenia | Infection | Anemia | Thrombocytopenia |
|---|---|---|---|---|
| AEs G3-4 | 50% | 20% | 10% | 10% |

4/10 pts required dose reductions due to toxicity

*Adapted from Spring L, et al. ASCO 2019*

# Ribociclib + T-DM1: preliminary efficacy data




*Spring L, et al. ASCO 2019*

# Final Remarks

- The introduction of anti-HER2 agents has led to improvements in survival in advanced settings.
- Despite this breakthrough, nearly all pts with HER2+ MBC eventually progress on anti-HER2 Therapy.
- A better understanding not only of the resistance mechanisms but of tumor heterogeneity is essential for the development of new strategies to furhter improve patients outcome
- Preclinical studies demonstrate a clear synergy between anti-HER2 therapy and CDK4/6 inhibitors.
- Early preclinical data support the use of CDK4/6 inhibitors in HER2-driven breast cancer and preliminary efficacy data with Ribociclib + T-DM1 are relatively safe, with promising results and warrant further investigation

*GRAZIE!*