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ONCODISTINCT NETWORK

# Update on breast cancer systemic therapy for clinical practice


**Ahmad Awada MD, PhD**
**Head of Oncology Medicine Department**
**Institut Jules Bordet - Université Libre de Bruxelles**
**Brussels - Belgium**

# Disclosure

**Advisory role, research grants to my Institute, Speaker fees:**

**Roche, Lilly, Amgen, EISAI, BMS, Pfizer, Novartis, MSD, Genomic Health, Ipsen, AstraZeneca, Bayer, Leo Pharma**

# Molecular oncology in breast cancer

- HR+ (expression)
- HER2+ (amplification, mutations)
- PIK3CA/AKT mutations
- ESR1 mutations/epigenetic alterations
- BRCA1 and 2 mutations

# At least seven molecular subtypes of breast cancer with therapeutic implications

- ER+ and/or PgR+ (70% of patients)
- ER+ and/or PgR+ and PI3K-mutated (40% of patients)
- ER+ and/or PgR+ and BRCA-mutated
- ER+ and/or PgR+ and HER2+ (triple positive)
- HER2+ and HR- ± BRCA-mutated
- TNBC ± BRCA mutation
- TNBC + PD-L1-positive on IC (≥1%)

IC, immune cells; PD-L1, programmed death ligand 1; PgR, progesterone receptor; PI3K, phosphoinositide 3-kinase; TNBC, triple-negative breast cancer.

# Progress on the management of Breast Cancer in 2019: Luminal disease

- OS data from CDK4/6 inhibitors in ABC
- Perspectives
  - SERD
  - Antibody drugs conjugates

# Use of CDK4/6 inhibitors in early setting (Δ~10 months) or later lines (Δ~6 months) significantly and consistently improved PFS and ORR

| | PALOMA-2[1] | MONALEESA-2[2] | MONARCH 3[3] | MONALEESA-7[4] | PALOMA-3[5] | MONARCH 2[6] | MONALEESA-3[7] |
|---|---|---|---|---|---|---|---|
| **Study design** | Phase 3, placebo-controlled **1st-line** (n=666) | Phase 3, placebo-controlled **1st-line** (n=668) | Phase 3, placebo-controlled **1st-line** (n=493) | Phase 3, placebo-controlled **1st-line** (n=672) | Phase 3, placebo-controlled **≥2nd-line** (n=521) | Phase 3, placebo-controlled **2nd-line** (n=672) | Phase 3, placebo-controlled **1st- or 2nd-line** (n=726) |
| **Prior therapy** | No prior systemic therapy **for ABC** | No prior systemic therapy **for ABC** | No prior systemic therapy **for ABC** | No prior ET up to 1 chemo **for ABC** | Prior ET up to 1 chemo **for ABC** | **No more than one ET No prior chemo for ABC** | **≤1 line of ET for ABC** |
| **Endocrine therapy** | Letrozole | Letrozole | NSAI | Tamoxifen NSAI/LHRHa | Fulvestrant | Fulvestrant | Fulvestrant |
| **CDK4/6 inhibitor** | Palbociclib | Ribociclib | Abemaciclib | Ribociclib | Palbociclib | Abemaciclib | Ribociclib |
| **HR PFS** | **0.56** | **0.57** | **0.55** | **0.55** | **0.50** | **0.55** | **0.59** |
| **Median PFS (mo)** | **27.6 vs 14.5** | **25.3 vs 16.0** | **NR vs 14.7** | **23.8 vs 13.0** | **11.2 vs 4.6** | **16.4 vs 9.3** | **20.5 vs 12.8** |

Cross-trial comparisons must be made with caution due to differences in trial design. ABC, advanced breast cancer; LHRHa, luteinising hormone-releasing hormone agonist; mo, months; NR, not reached; NSAI, non-steroidal aromatase inhibitor.

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1. Rugo HS, et al. Cancer Res. 2018;78(Suppl.):abstract P5-21-03; 2. Hortobagyi G, et al. J Clin Oncol. 2017;35(Suppl.):abstract 1038;
3. Goetz MP, et al. J Clin Oncol. 2017;35:3638–3646; 4. Tripathy D, et al. Cancer Res. 2018;78(Suppl.):abstract GS2-05;
5. Turner NC, et al. Cancer Res. 2017;abstract P4-22-06; 6. Sledge GW, et al. J Clin Oncol. 2017;35:2875–2884;
7. Slamon DJ, et al. J Clin Oncol. 2018;36(Suppl.):Abstract 1000.


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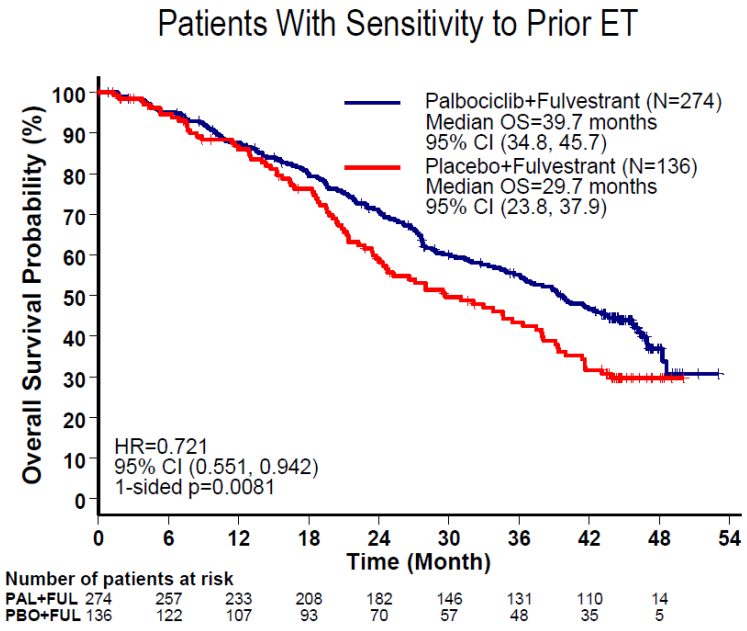
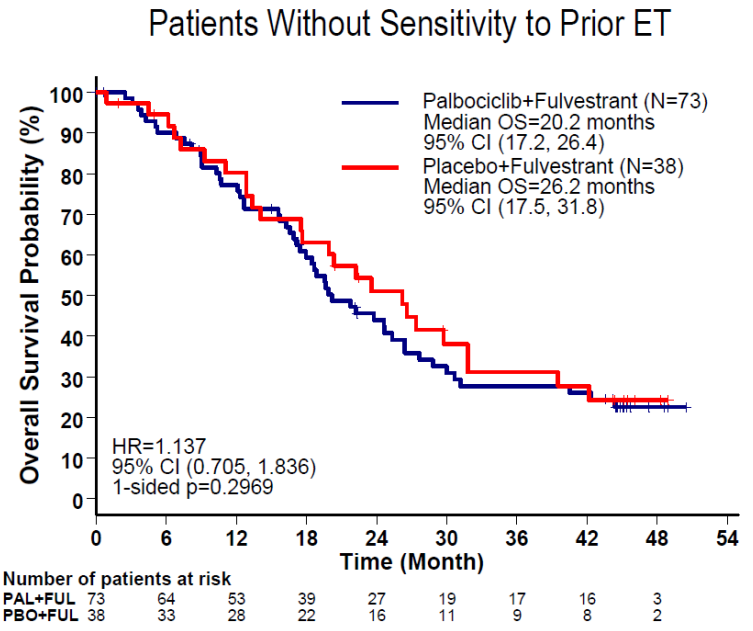
# PALOMA-3: Overall survival by sensitivity to prior ET




FUL, fulvestrant; PAL, palbociclib; PBO, placebo.

- **In patients with sensitivity to prior ET, absolute improvement in median OS in the palbociclib arm vs the placebo arm was 10.0 months**

Cristofanilli M, et al. Ann Oncol. 2018;29(Suppl):abstract LBA2_PR.

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# Phase III MONALEESA-7 Trial of Premenopausal Patients With HR+/HER2– Advanced Breast Cancer Treated With Endocrine Therapy ± Ribociclib: Overall Survival Results

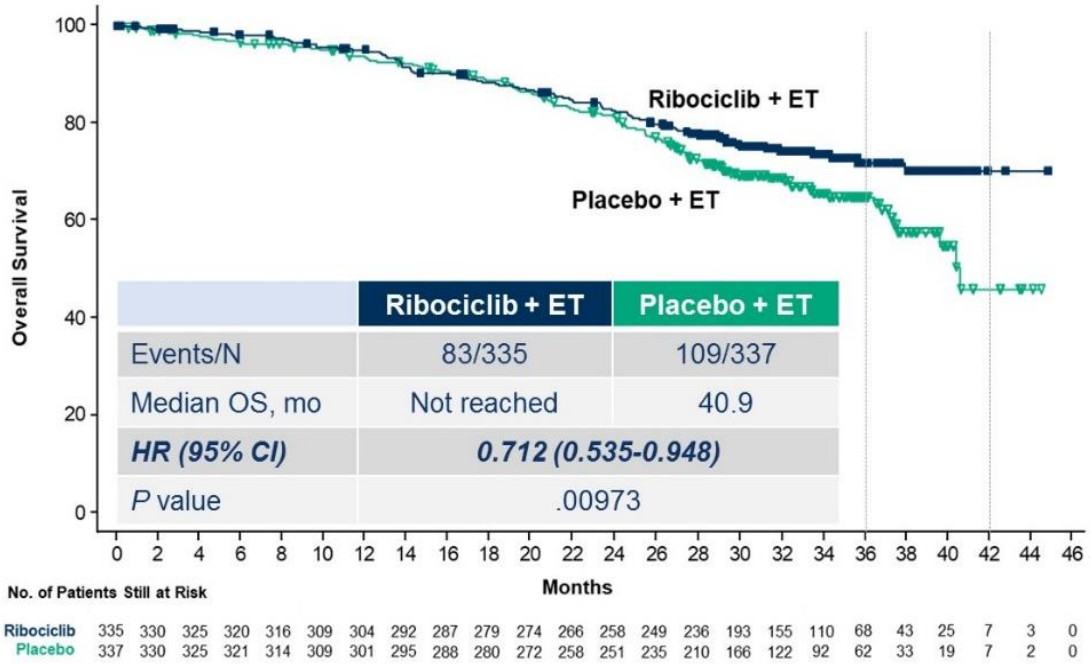
Sara Hurvitz,[1] Seock-Ah Im,[2] Yen-Shen Lu,[3] Marco Colleoni,[4] Fabio Franke,[5] Aditya Bardia,[6] Nadia Harbeck,[7] Louis Chow,[8] Joohyuk Sohn,[9] Keun Seok Lee,[10] Saul Campos-Gomez,[11] Rafael Villanueva Vazquez,[12] Kyung Hae Jung,[13] Arunava Chakravartty,[14] Gareth Hughes,[15] Ioannis Gounaris,[15] Karen Rodriguez Lorenc,[14] Tetiana Taran,[14] Debu Tripathy[16]

[1]UCLA Jonsson Comprehensive Cancer Center, Los Angeles, CA, USA; [2]Seoul National University Hospital, Cancer Research Institute, Seoul National University College of Medicine, Seoul, Korea; [3]National Taiwan University Hospital, Taipei, Taiwan; [4]Division of Medical Senology, Istituto Europeo di Oncologia, Milan, Italy; [5]Hospital de Caridade de Ijuí, CACON, Ijuí, Brazil; [6]Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA, USA, [7]Department of Obstetrics and Gynecology, Breast Center, Ludwig-Maximilians-University Munich, Munich, Germany; [8]Organisation for Oncology and Translational Research, Hong Kong; [9]Severance Hospital, Yonsei University Health System, Seoul, Korea; [10]Center for Breast Cancer, National Cancer Center, Gyeunggi-do, Korea; [11]Centro Oncológico Estatal, Instituto de Seguridad Social del Estado de México y Municipios, Toluca, Mexico; [12]Institut Català d'Oncologia, Hospital de Sant Joan Despí Moisès Broggi, Barcelona, Spain; [13]Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea; [14]Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA; [15]Novartis Pharmaceuticals Corporation, Basel, Switzerland; [16]The University of Texas MD Anderson Cancer Center, Houston, TX, USA

HR, hormone receptor.

Hurvitz S, et al. J Clin Oncol. 2019;37(Suppl.):abstract LBA1008.

# MONALEESA-7: Overall survival




| | Ribociclib + ET | Placebo + ET |
|---|---|---|
| Events/N | 83/335 | 109/337 |
| Median OS, mo | Not reached | 40.9 |
| ***HR (95% CI)*** | ***0.712 (0.535-0.948)*** | |
| *P* value | .00973 | |

- ≈ 29% relative reduction in risk of death
- The *P* value of .00973 crossed the prespecified boundary to claim superior efficacy

**Landmark Analysis**

| Kaplan-Meier Estimate | Ribociclib + ET | Placebo + ET |
|---|---|---|
| 36 months | 71.9% | 64.9% |
| ***42 months*** | ***70.2%*** | ***46.0%*** |

Hurvitz S, et al. J Clin Oncol. 2019;37(Suppl.):abstract LBA1008.

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# Overall Survival Results From the Phase III MONALEESA-3 Study of Fulvestrant ± Ribociclib in Postmenopausal Patients With HR+/HER2− Advanced Breast Cancer

Dennis J. Slamon,[1] Patrick Neven,[2] Stephen Chia,[3] Peter A. Fasching,[4] Michelino De Laurentiis,[5] Seock-Ah Im,[6] Katarina Petrakova,[7] Giulia Val Bianchi,[8] Francisco J. Esteva,[9] Miguel Martín,[10] Arnd Nusch,[11] Gabe S. Sonke,[12] Luis De la Cruz-Merino,[13] J. Thaddeus Beck,[14] Xavier Pivot,[15] Manu Sondhi,[16] Yingbo Wang,[17] Arunava Chakravartty,[16] Karen Rodriguez-Lorenc,[16] Guy Jerusalem[18]

[1]David Geffen School of Medicine at UCLA, Los Angeles, CA, USA; [2]Multidisciplinary Breast Centre, Universitair Ziekenhuis Leuven, Leuven, Belgium; [3]British Columbia Cancer Agency, Vancouver, British Columbia, Canada; [4]University Hospital Erlangen, Friedrich-Alexander University Erlangen-Nuremberg, Erlangen, Germany; [5]Istituto Nazionale Tumori "Fondazione G. Pascale," Naples, Italy; [6]Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Republic of Korea; [7]Masaryk Memorial Cancer Institute, Brno, Czech Republic; [8]Fondazione Istituto di Ricovero e Cura a Carattere Scientifico, Istituto Nazionale dei Tumori, Milan, Italy; [9]New York University Langone Health, New York, NY, USA; [10]Instituto de Investigación Sanitaria Gregorio Marañon, Centro de Investigación Biomédica en Red de Cáncer, Grupo Español de Investigación en Cáncer de Mama, Universidad Complutense, Madrid, Spain; [11]Practice for Hematology and Internal Oncology, Velbert, Germany; [12]Netherlands Cancer Institute/Borstkanker Onderzoek Groep Study Center, Amsterdam, the Netherlands; [13]Hospital Universitario Virgen Macarena, Seville, Spain; [14]Highlands Oncology Group, Fayetteville, AR, USA; [15]Institut Régional du Cancer, Strasbourg, France; [16]Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA; [17]Novartis Pharma AG, Basel, Switzerland; [18]Centre Hospitalier Universitaire de Liège and Liège University, Liège, Belgium

Slamon DJ, et al. Ann Oncol. 2019;30(Suppl.):abstract LBA7-PR.

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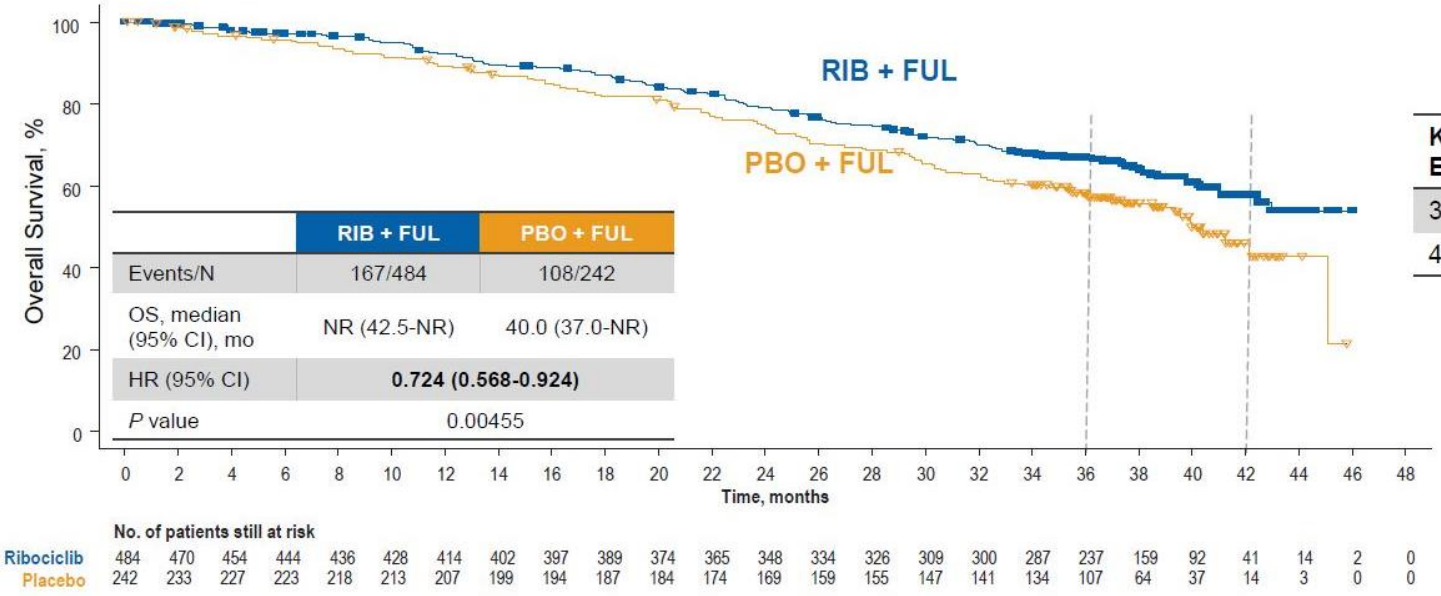
# Overall survival: The reduction in relative risk of death with ribociclib was 28%




| | RIB + FUL | PBO + FUL |
|---|---|---|
| Events/N | 167/484 | 108/242 |
| OS, median (95% CI), mo | NR (42.5-NR) | 40.0 (37.0-NR) |
| HR (95% CI) | **0.724 (0.568-0.924)** | |
| *P* value | 0.00455 | |

**Landmark Analysis**

| KM Estimate | RIB + FUL | PBO + FUL |
|---|---|---|
| 36 months | 67.0% | 58.2% |
| 42 months | 57.8% | 45.9% |

- The *P* value of 0.00455 crossed the prespecified boundary to claim superior efficacy (*P* <0.01129)

FUL, fulvestrant; RIB, ribociclib.

Slamon DJ, et al. Ann Oncol. 2019;30(Suppl.):abstract LBA7-PR.

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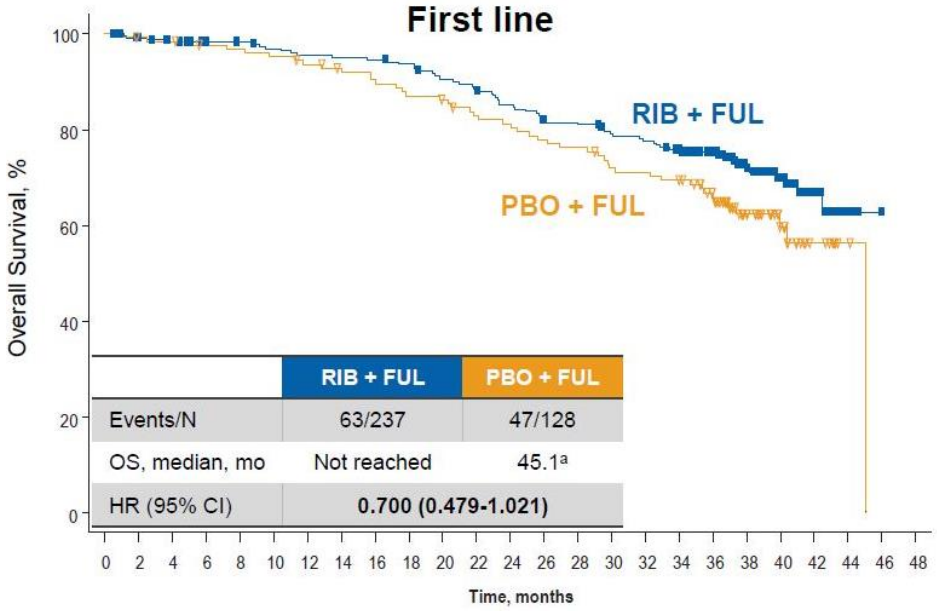
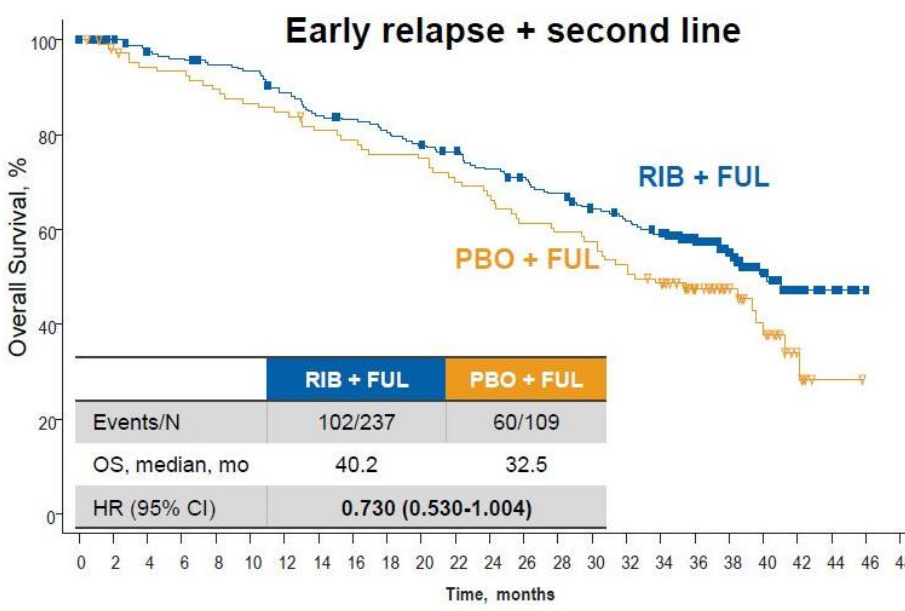
# Overall survival by line of therapy was consistent with the overall population




Slamon DJ, et al. Ann Oncol. 2019;30(Suppl.):abstract LBA7-PR.

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# MONARCH 2: OVERALL SURVIVAL OF ABEMACICLIB PLUS FULVESTRANT IN PATIENTS WITH HR+, HER2- ADVANCED BREAST CANCER

**George W. Sledge Jr.**[1], Masakazu Toi[2], Patrick Neven[3], Joohyuk Sohn[4], Kenichi Inoue[5], Xavier Pivot[6], Olga Burdaeva[7], Meena Okera[8], Norikazu Masuda[9], Peter A. Kaufman[10], Han Koh[11], Eva-Maria Grischke[12], PierFranco Conte[13], Yi Lu[14], Susana Barriga[15], Karla Hurt[14], Martin Frenzel[14], Stephen Johnston[16], Antonio Llombart-Cussac[17]

[1]Stanford University School of Medicine, Stanford, CA; [2]Graduate School of Medicine, Kyoto University, Kyoto, Japan; [3]Universitaire Ziekenhuizen Leuven, Leuven, Belgium; [4]Yonsei Cancer Center, Seoul, Korea; [5]Saitama Cancer Center, Saitama, Japan; [6] Centre Paul Strauss, INSERM 110, Strasbourg, France; [7]Arkhangelsk Regional Clinical Oncology Dispensary, Arkhangelsk, Russia; [8]Adelaide Cancer Centre, Adelaide, Australia; [9]National Hospital Organization, Osaka National Hospital, Osaka, Japan; [10]University of Vermont Cancer Center, Burlington, VT; [11]Kaiser Permanente, Bellflower, CA; [12]Universitäts-Frauenklinik Tubingen, Eberhard Karls University, Tubingen, Germany; [13] DiSCOG, University of Padova and Medical Oncology 2, Istituto Oncologico Veneto, I.R.C.C.S., Padova, Italy; [14]Eli Lilly and Company, Indianapolis, IN; [15]Eli Lilly and Company, Madrid, Spain; [16] The Royal Marsden NHS Foundation Trust, London, UK; [17]Hospital Arnau Vilanova, Valencia, Spain

esmo.org

Sledge GW, et al. Ann Oncol. 2019;30(Suppl.):abstract LBA6-PR.

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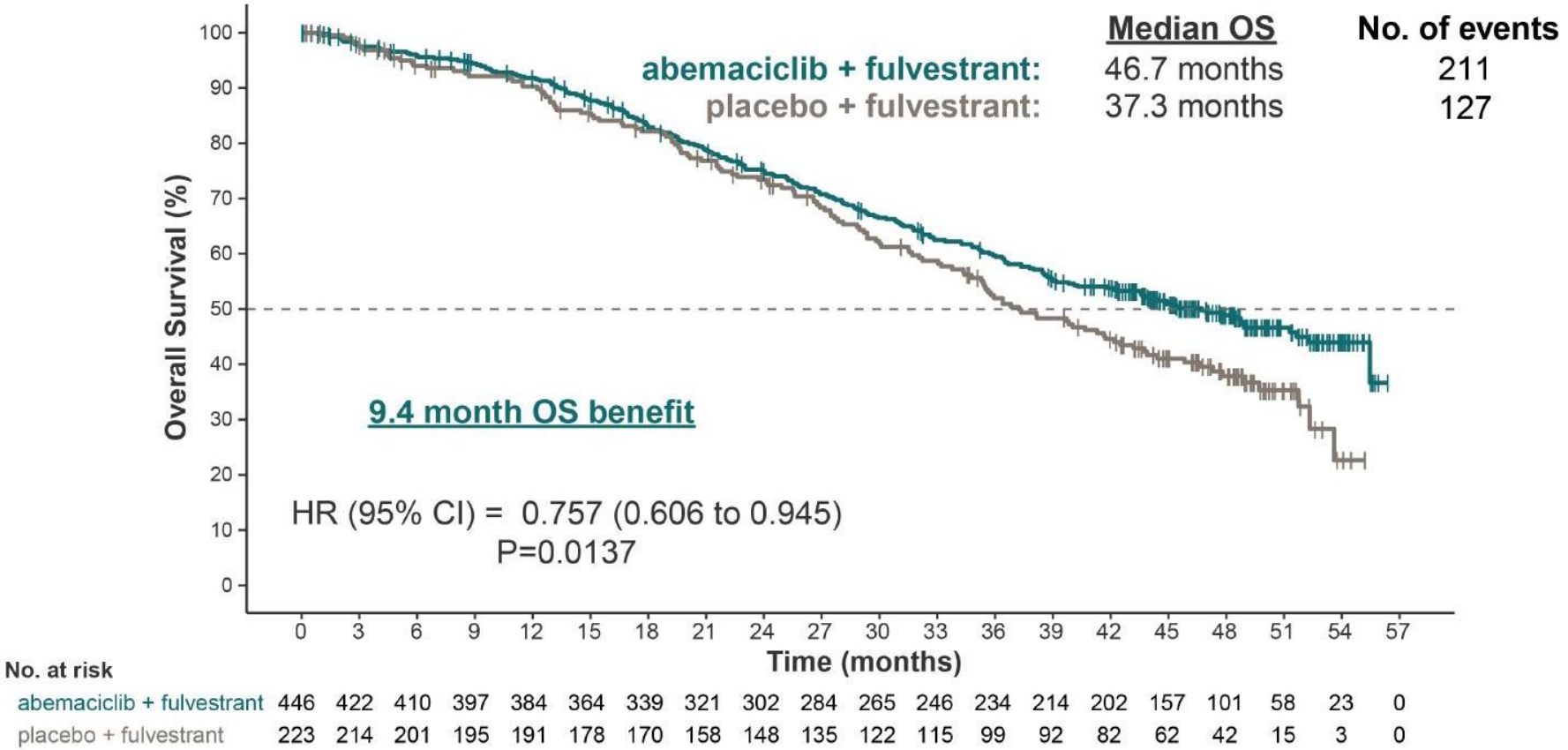
# Overall survival




Sledge GW, et al. Ann Oncol. 2019;30(Suppl.):abstract LBA6-PR.

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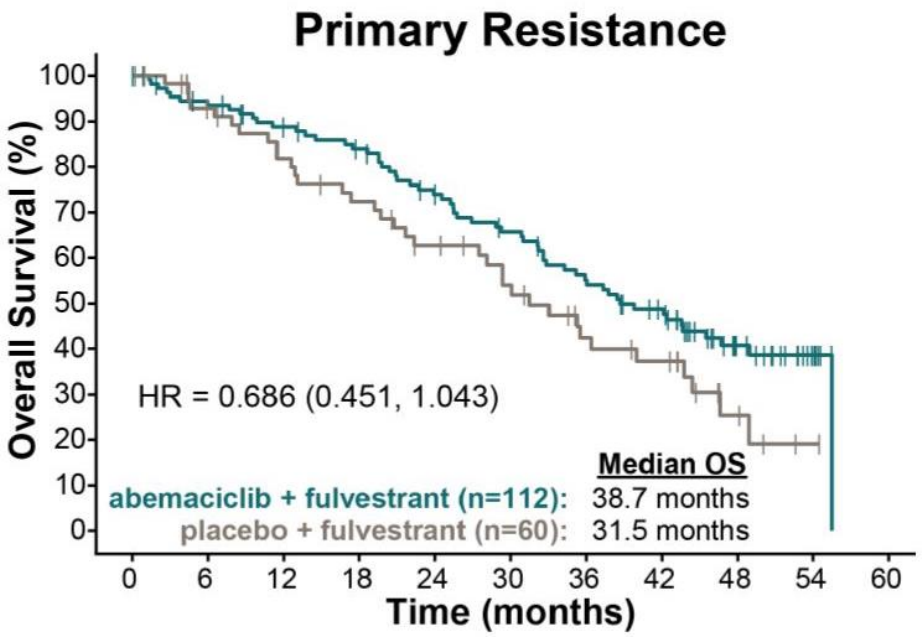
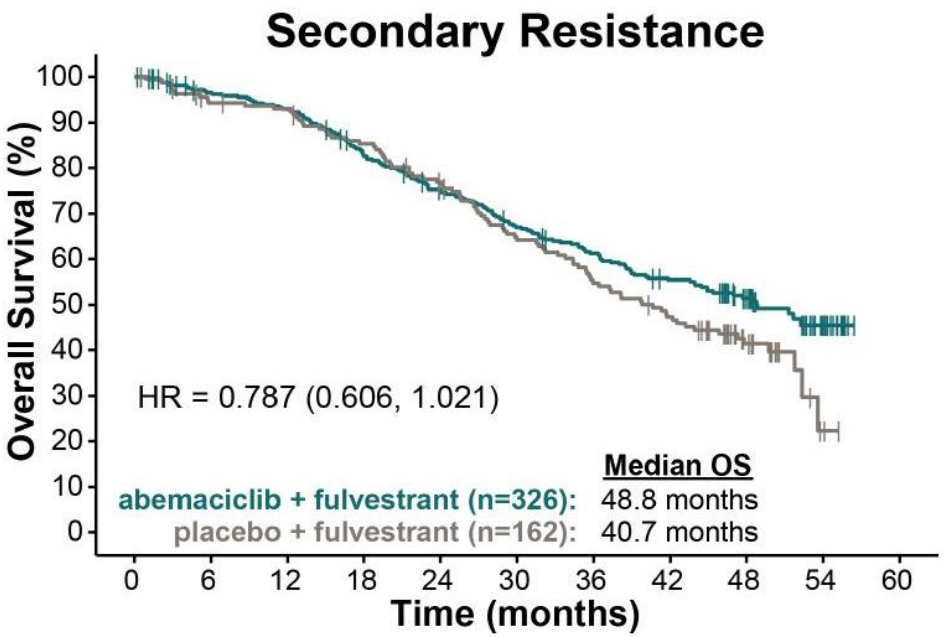
# Overall survival by resistance to endocrine therapy




Sledge GW, et al. Ann Oncol. 2019;30(Suppl.):abstract LBA6-PR.

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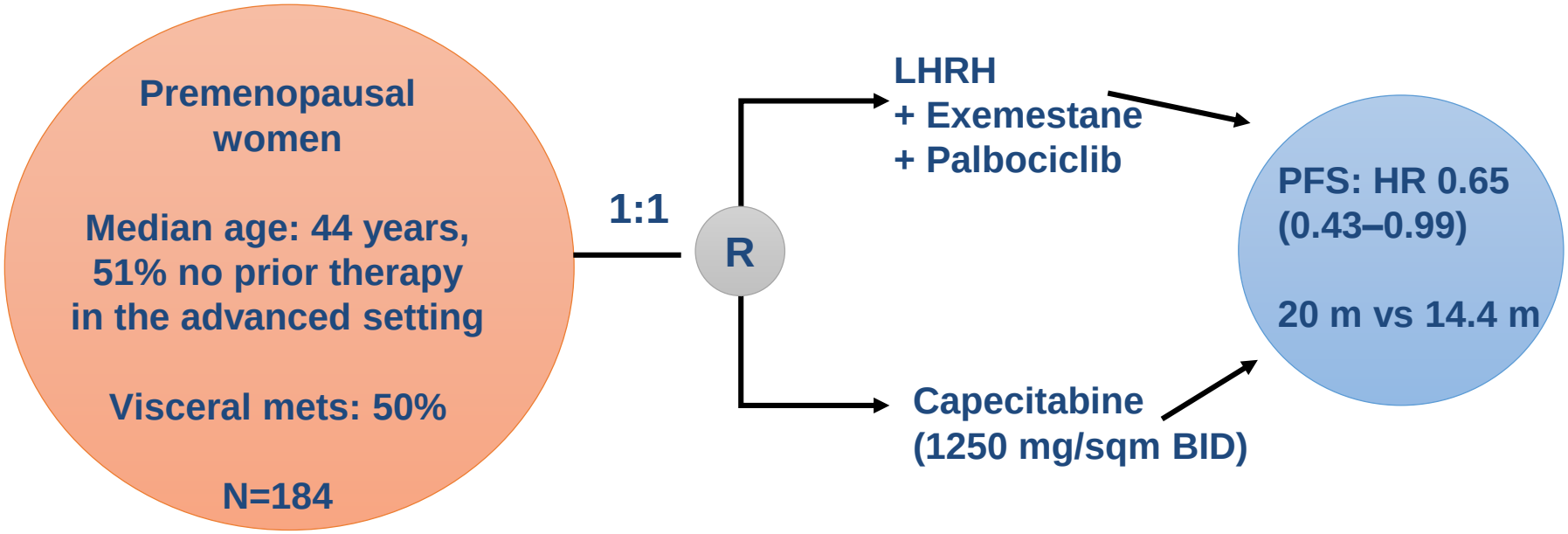
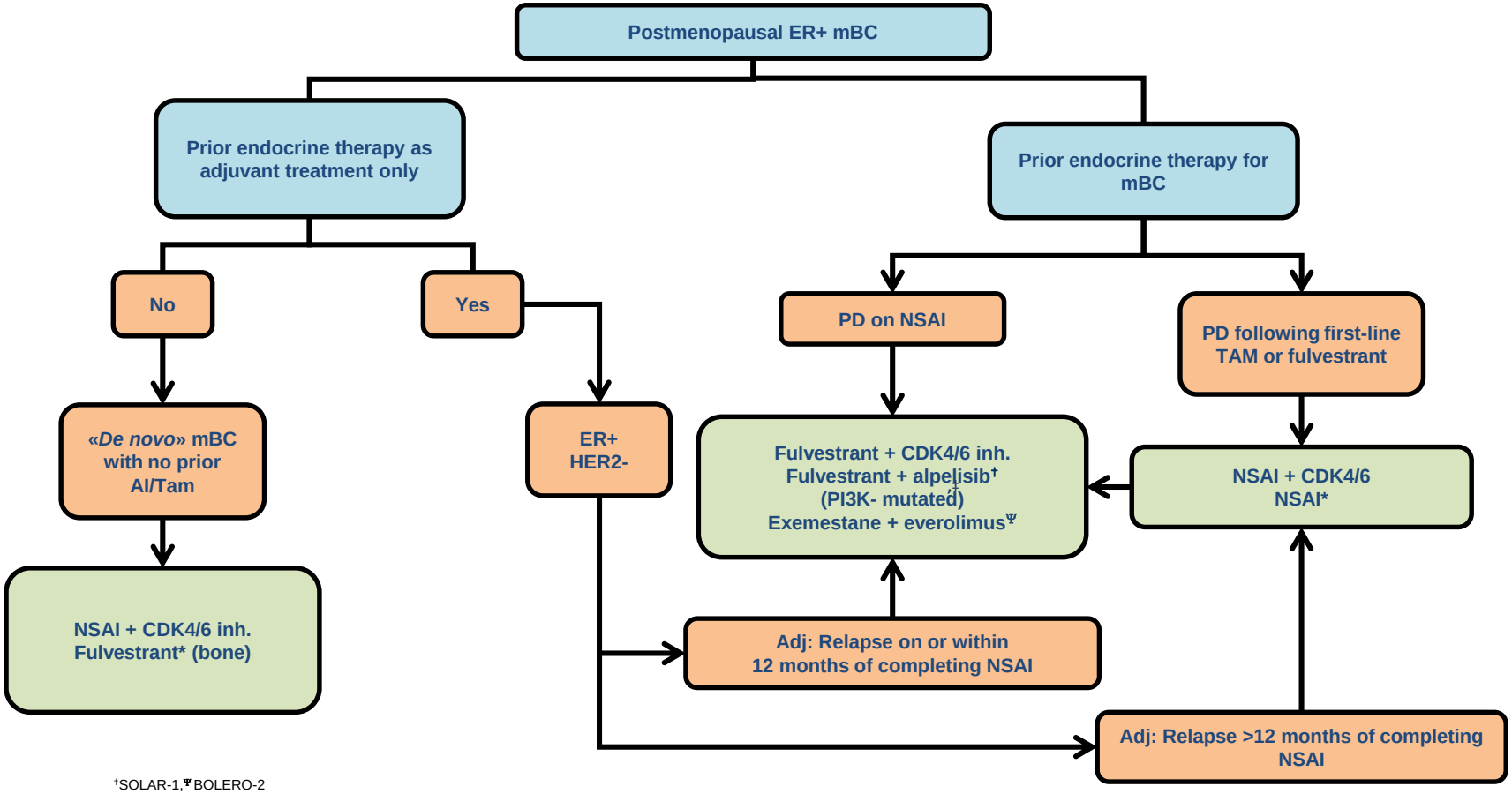
# ASCO 2019, advanced luminal breast cancer: The “Young PEARL” study (Korea)




BID, twice daily; mets, metastases.
Park YH, et al. ASCO 2019; Abstract 1007.

# Proposed therapeutic algorithm for luminal subtype in 2019




†SOLAR-1, ΨBOLERO-2

*Patients with very limited bone disease.

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Awada A, et al. ESMO Open. 2019; In Press.

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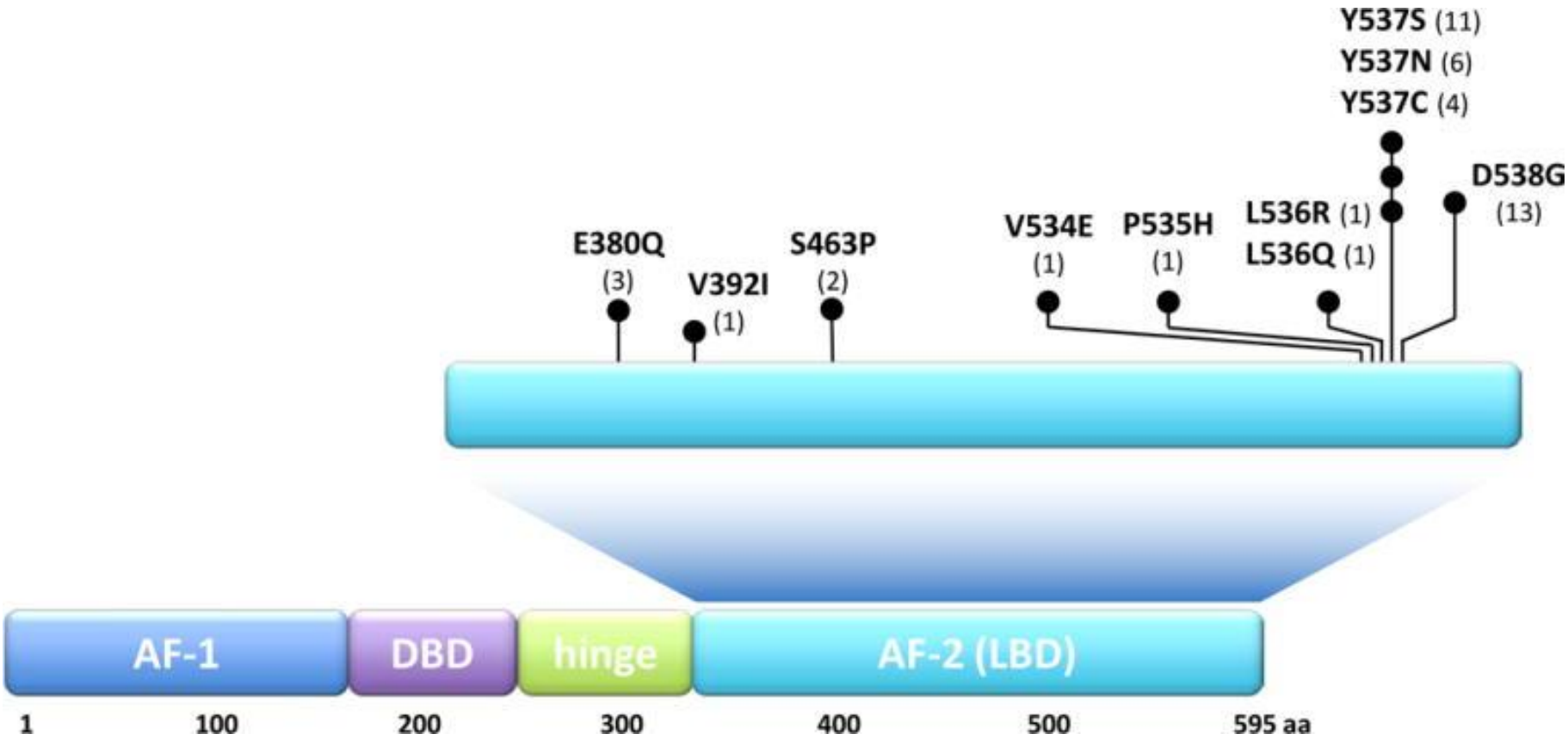
# The point mutations reported in metastatic ER+ breast cancers




AF-1, activation function-1; AF-2, activation function-2; DBD, DNA-binding domain; ER, oestrogen receptor; LBD, ligand-binding domain

Jeselsohn R, et al. *Nat Rev Clin Oncol* 2015;12:573-83

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# Strategies targeting genomic alterations in *ESR1*:

## Novel therapeutic strategies for *ESR1* alterations include the following:

- Oral SERD (several in trial Phase I/II)
- Tamoxifen metabolites
- 3rd generation SERM

**Investigational agents in this indication**

ABC, advanced breast cancer; ESR1, oestrogen receptor 1 gene; ET, endocrine therapy; PET, positron emission tomography; SERDs, selective oestrogen receptor degraders

. Dickler M, et al. AACR 2015 (Abstract CT231); 2. Clinicaltrials.gov: NCT01823835; 3. Clinicaltrials.gov: NCT02569801; 4. Clinicaltrials.gov: NCT02650817; 5. Weir HM, et al. *Cancer Res* 2016;76:3307-18; 6. Clinicaltrials.gov: NCT02248090; 7. Clinicaltrials.gov: NCT03236974 ; 8. Goetz MP et al JCO 2017; 9. Lewis-Wambi J. et al. *Mol Pharmacology* 2011;80:610-20; 10. Clinicaltrials.gov: NCT02448771

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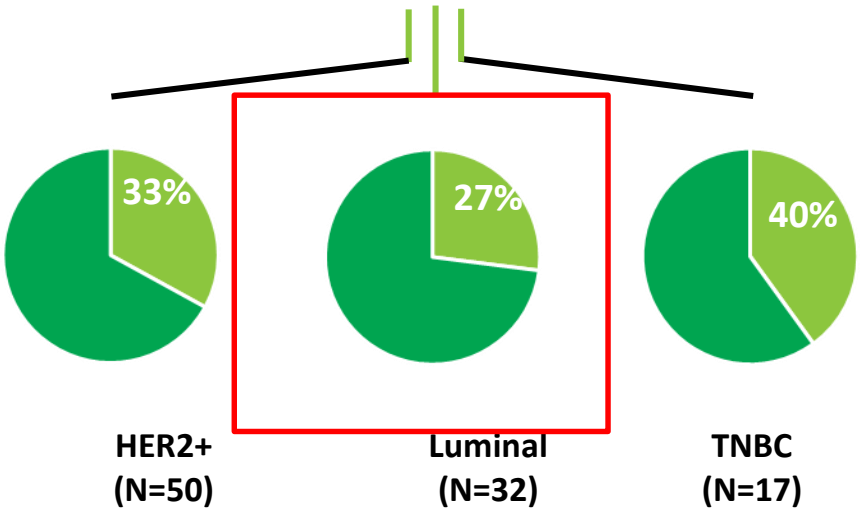
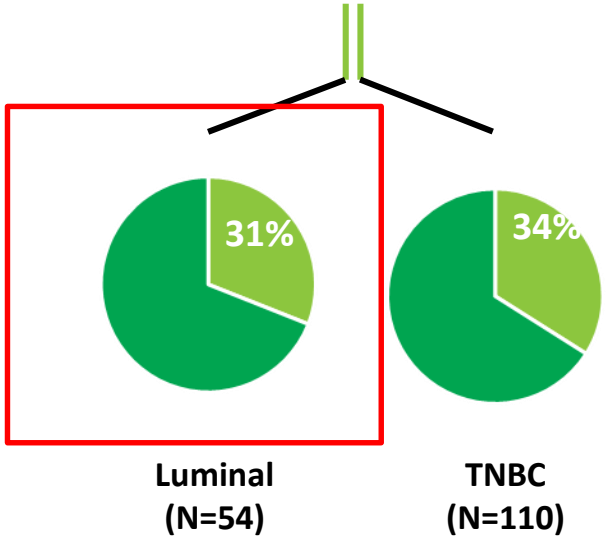
# Antibody drug conjugates for MBC: Initial Phase I Results

**SYD 985**
**= trastuzumab-duocarmazine**
**with a protease cleavable linker**




**Ocular toxicity**

**Sacituzumab Govitecan**
**= an anti-Trop 2 SN38 ADC**

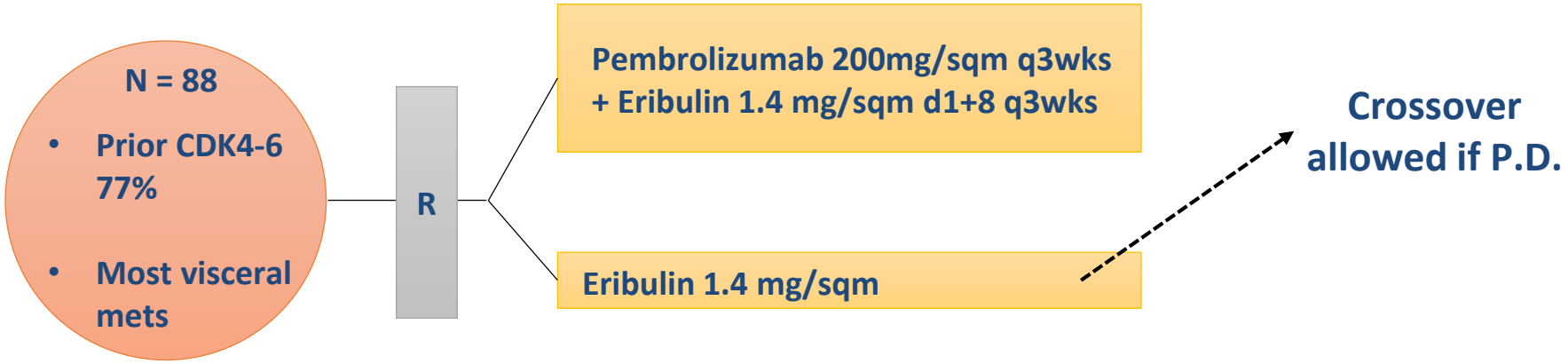



**"off target" side effects**

**Neutropenia**
**Alopecia**

*Abst 1014 and 1004*

# ASCO 2019 Advanced Luminal Disease
# Attemps to enhance chemotherapy efficacy




- Identical PFS (4.1m) and OS (13m)
- 2 toxic † in pembro arm !

(1) abst 1004 (Dana Farber)

# MBC: Therapeutic armamentrium
# HER2 + disease

- Taxane + trastuzumab + Pertuzumab
- T-DM1
- Capecitabine + lapatinib
- Dual HER-2 inhibition
- Other chemo + HER-2 therapy

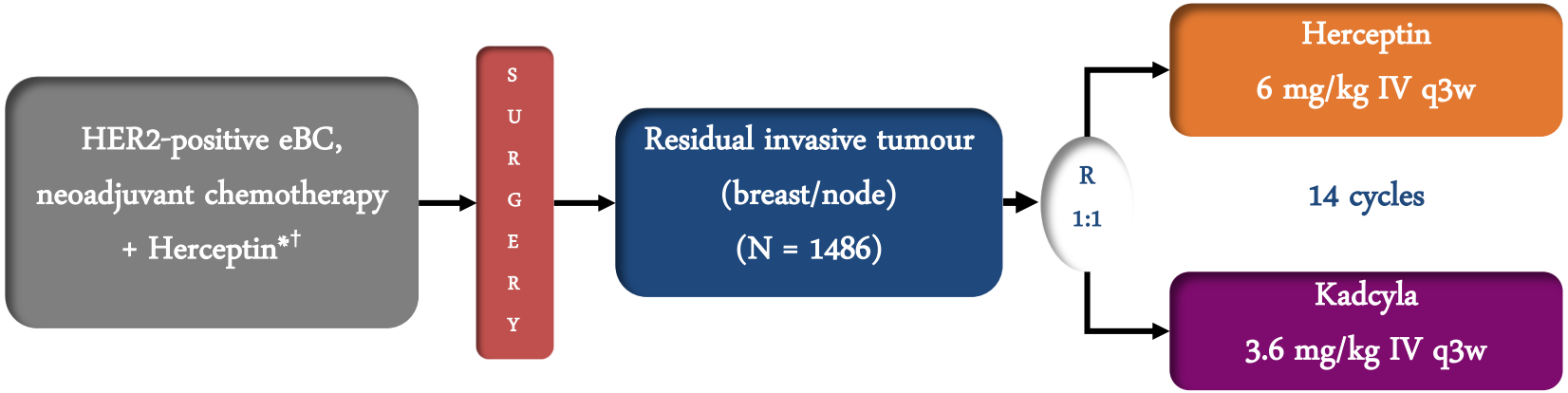
- Chemotherapy is the backbone of therapy!

# Progress on the management of Breast Cancer in 2019: HER2 disease

- Role of T-DM1 in residual disease following neoadjuvant therapy
- New HER2 agents in ABC
  - More data on neratinib (NALA)
  - Margetuximab (SOPHIA)
  - Tucatinib
  - Bifunctional antibodies
- Perspectives
  - Antibody drugs conjugates (high and low HER2 expressors!)

# KATHERINE STUDY

# KATHERINE : Study Design[1,2]




**Primary endpoint:** IDFS
**Key secondary endpoints:** IDFS (second primary non-breast cancers incl.), DFS, OS, DRFI, safety

**Stratification factors:**

- Clinical stage at presentation: inoperable vs. operable
- Hormone receptor status: ER- or PR-positive vs. ER- and PR-negative
- Neoadjuvant HER2-directed therapy: Herceptin vs. dual HER2 targeting
- Pathological nodal status evaluated after neoadjuvant therapy: positive vs. negative

DFS, disease-free survival; DRFI, distant recurrence-free interval; ER, oestrogen receptor; IDFS, invasive disease-free survival; OS, overall survival; PR, progesterone receptor

* Neoadjuvant systemic treatment was given for at least 6 cycles, with a total duration of at least 16 weeks, including at least 9 weeks of anti-HER2 therapy and at least 9 weeks of taxane-based chemotherapy (or, if receiving dose-dense chemotherapy regimens, at least 8 weeks of taxane-based therapy and at least 8 weeks of anti-HER2 therapy). † Dual anti-HER2 therapy was also permitted in the neoadjuvant setting.

1. Roche. Data on File. Protocol BO27938 (KATHERINE) – version 6; 2. von Minckwitz G, *et al. N Engl J Med*; 2018

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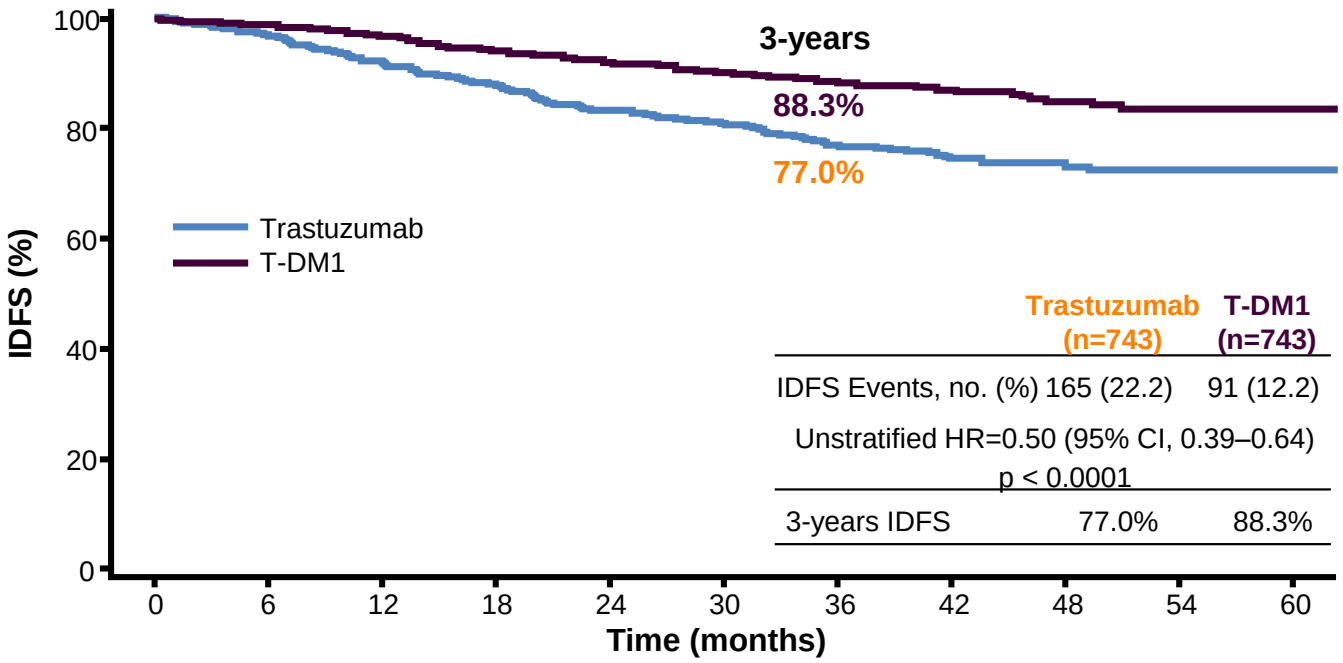
# KATHERINE: Prior therapy

| | Trastuzumab n = 743 | T-DM1 n = 743 |
|---|---|---|
| **Prior anthracycline** | | |
| Received prior anthracycline | 564 (75.9%) | 579 (77.9%) |
| Did not receive prior anthracycline | 179 (24.1%) | 164 (22.1%) |
| **Neoadjuvant HER2-targeted therapy** | | |
| Trastuzumab alone | 596 (80.2%) | 600 (80.8%) |
| Trastuzumab plus additional HER2-targeted agent(s)* | 147 (19.8%) | 143 (19.2%) |
| **Neoadjuvant pertuzumab** | | |
| Received pertuzumab | 139 (18.7%) | 133 (17.9%) |
| Did not receive pertuzumab | 604 (81.3%) | 610 (82.1%) |

*Other non-pertuzumab HER2-targeted agents (neratinib, dacomitinib, afatinib, lapatinib)

# KATHERINE: Kaplan-Meier Plot of IDFS (ITT)




No. at Risk

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Trastuzumab | 743 | 676 | 635 | 594 | 555 | 501 | 342 | 220 | 119 | 38 | 4 |
| T-DM1 | 743 | 707 | 681 | 658 | 633 | 561 | 409 | 255 | 142 | 44 | 4 |

1. Roche. Data on File. Protocol BO27938 (KATHERINE) – version 6; 2. von Minckwitz G, *et al. N Engl J Med*; 2018

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# Neratinib plus capecitabine versus lapatinib plus capecitabine in patients with HER2-positive metastatic breast cancer previously treated with ≥2 HER2-directed regimens: Findings from the multinational, randomized, phase 3 NALA trial

**Cristina Saura, Mafalda Oliveira, Yin-Hsun Feng, Ming-Shen Dai, Sara A Hurvitz, Sung-Bae Kim, Beverly Moy, Suzette Delaloge,**
**William Gradishar, Norikazu Masuda, Marketa Palacova, Maureen E Trudeau, Johanna Mattson, Yoon Sim Yap, Richard Bryce, Bin Yao, Judith Bebchuk, Kiana Keyvanjah, Adam Brufsky, NALA Investigators**

***Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; Chi Mei Medical Centre, Tainan, Taiwan; Tri-Service General Hospital, Taipei, Taiwan; UCLA Hematology/Oncology Clinical Research Unit, Santa Monica, CA; University of Ulsan College of Medicine, Seoul, Republic of Korea; Massachusetts General Hospital Cancer Center, Boston, MA; Institut Gustave Roussy, Villejuif, France; Robert H Lurie Comprehensive Cancer Center of Northwestern University, Chicago, IL; NHO Osaka National Hospital, Osaka, Japan; Masaryk Memorial Cancer Institute, Brno, Czech Republic; Sunnybrook Health Sciences Centre, Toronto, ON; Helsinki University Hospital Comprehensive Cancer Center, Helsinki, Finland; National Cancer Centre Singapore, Singapore, Singapore; Puma Biotechnology Inc, Los Angeles, CA; Magee-Womens Hospital of UPMC, Pittsburgh, PA***



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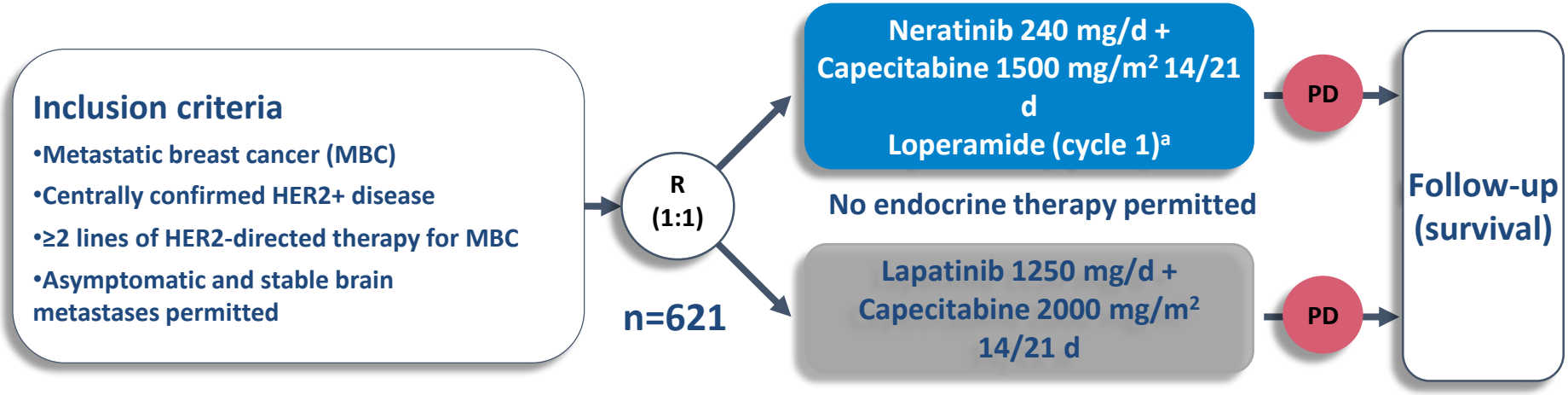
# NALA study design




## Stratification variables

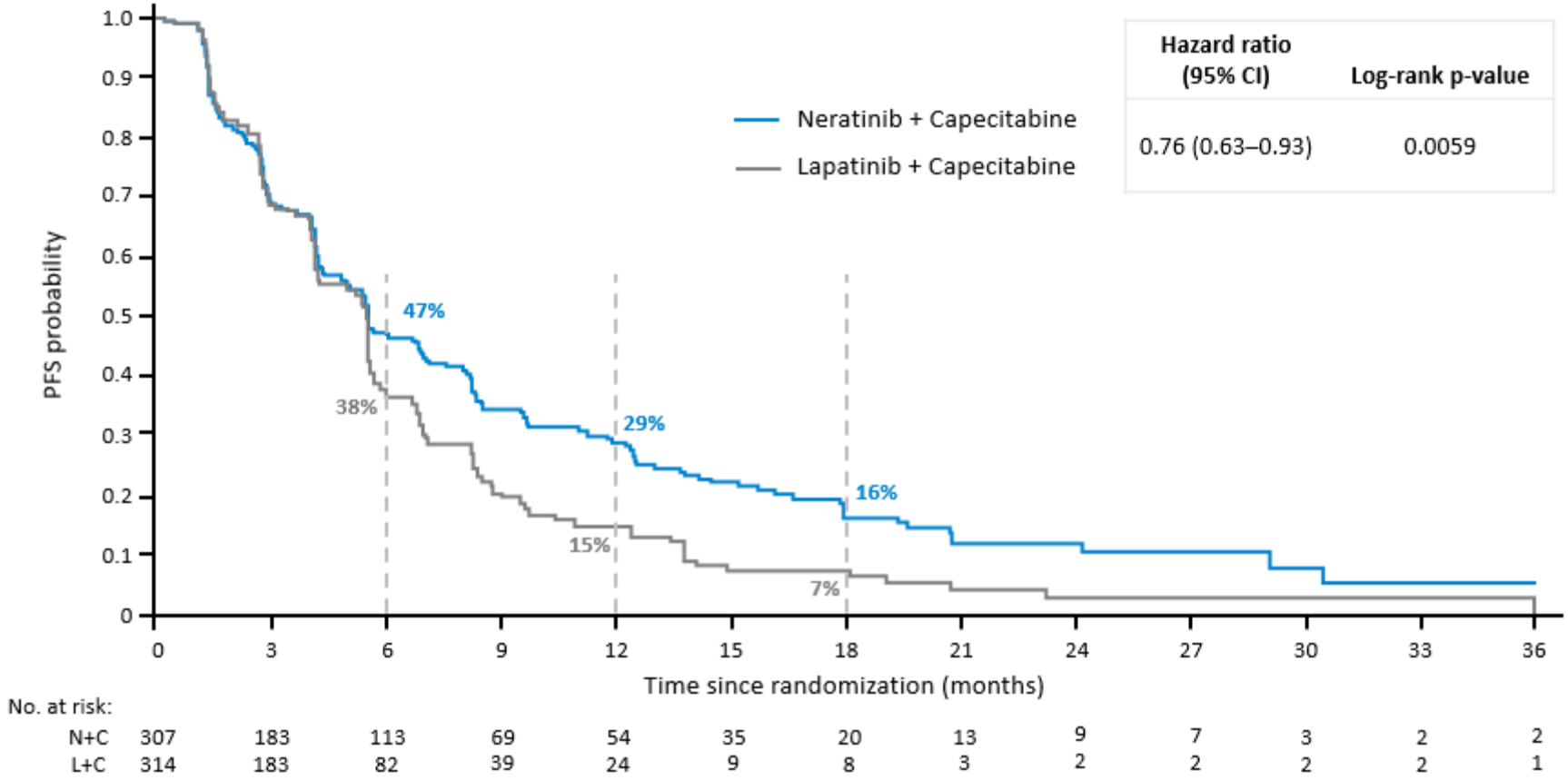
- Number of prior HER2 therapies for MBC
- Disease location
- HR status
- Geographic location

## Endpoints

- Co-primary: PFS (centrally confirmed) and OS
- Secondary: PFS (local), ORR, DoR, CBR, intervention for CNS metastases, safety, health outcomes

Loperamide 4 mg with first dose of neratinib, followed by 2 mg every 4 h for first 3 d, then loperamide 2 mg every 6–8 h until end of Cycle 1. Thereafter as needed

# Centrally confirmed PFS (co-primary endpoint)

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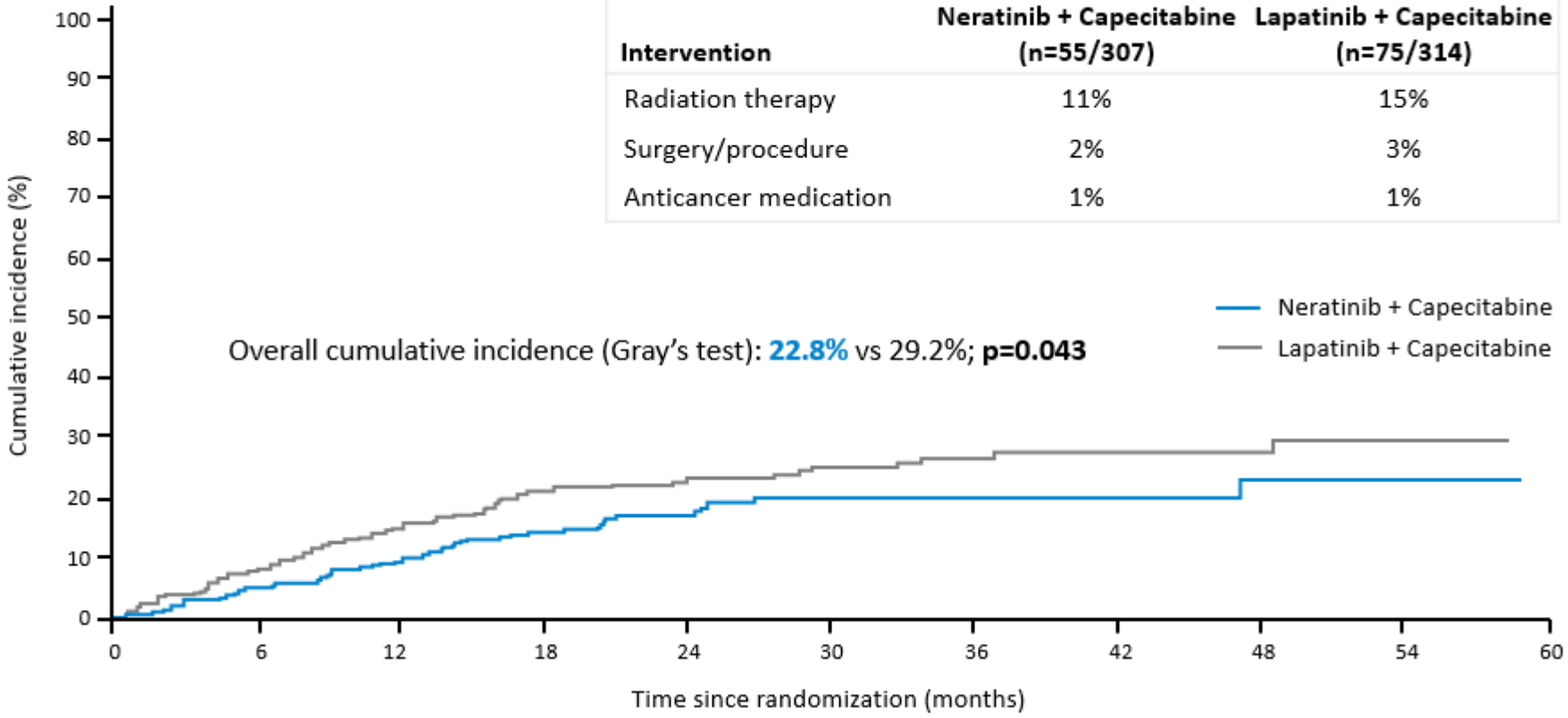
# Time to intervention for CNS metastases

| Intervention | Neratinib + Capecitabine (n=55/307) | Lapatinib + Capecitabine (n=75/314) |
|---|---|---|
| Radiation therapy | 11% | 15% |
| Surgery/procedure | 2% | 3% |
| Anticancer medication | 1% | 1% |

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# SOPHIA Primary PFS Analysis: A Phase 3 Study of Margetuximab + Chemotherapy vs Trastuzumab + Chemotherapy in Patients With HER2+ Metastatic Breast Cancer After Prior Anti-HER2 Therapies

Hope S. Rugo, MD,[1] Seock-Ah Im, MD, PhD,[2] Gail S. Wright, MD, FACP, FCCP,[3] Santiago Escrivá-de-Romaní, MD,[4] Michelino De Laurentiis, MD, PhD,[5] Javier Cortes, MD, PhD,[6] Shakeela W. Bahadur, MD,[7] Barbara B. Haley, MD,[8] Raul H. Oyola, MD,[9] David A. Riseberg, MD,[10] Antonino Musolino, MD, PhD, MSc,[11] Fatima Cardoso, MD,[12] Giuseppe Curigliano, MD, PhD,[13] Peter A. Kaufman, MD,[14] Mark D. Pegram, MD,[15] Sutton Edlich,[16] Shengyan Hong, PhD,[16] Edwin Rock, MD, PhD,[16] William J. Gradishar, MD,[17] on behalf of the SOPHIA Study Group

[1]University of California San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, CA, USA; [2]Seoul National University Hospital
Cancer Research Institute, Seoul, Korea; [3]Florida Cancer Specialists & Research Institute, New Port Richey, FL, USA; [4]Vall d'Hebron Institute of Oncology, Barcelona, Spain;
[5]National Cancer Institute Fondazione Pascale, Naples, Italy; [6]IOB Institute of Oncology, Madrid & Barcelona; Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain;
[7]Bannerer MD Anderson Cancer Center, Gilbert, AZ, USA; [8]University of Texas Southwestern Medical Center, Dallas, TX, USA; [9]Northwest Georgia Oncology Centers, Marietta Cancer Center, Marietta, GA, USA; [10]Mercy Medical Center, Baltimore, MD, USA; [11]University Hospital of Parma, Parma, Italy; [12]Champalimaud Clinical Center/Champalimaud Foundation, Lisbon, Portugal; [13]University of Milano, European Institute of Oncology, Milan, Italy; [14]University of Vermont Cancer Center, Division of Hematology/Oncology, Burlington, VT, USA; [15]Stanford Women's Cancer Center, Palo Alto, CA, USA; [16]MacroGenics, Inc., Rockville, MD, USA; [17]Northwestern University, Chicago, IL, USA

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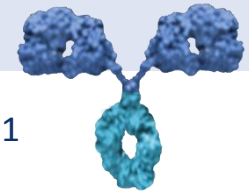
# Margetuximab: Fc-engineered to Activate Immune Responses

## Trastuzumab

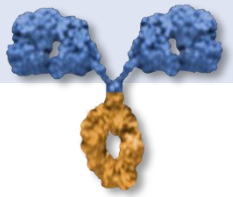
**Fab:**
- Binds HER2 with high specificity
- Disrupts signaling that drives cell proliferation and survival



**Fc:**
- Wild-type immunoglobulin G1 (IgG1) immune effector domains
- Binds and activates immune cells

## Margetuximab[1,2]

**Fab:**
- Same specificity and affinity
- Similarly disrupts signaling



**Fc engineering:**
- ↑ Affinity for activating FcγRIIIA (**CD16A**)
- ↓ Affinity for inhibitory FcγRIIB (**CD32B**)

**Margetuximab Binding to FcγR Variants:**

| Receptor Type | Receptor | Allelic Variant | Relative Fc Binding | Affinity Fold-Change |
|---|---|---|---|---|
| Activating | **CD16A** | 158F | Lower | 6.6x ↑ |
| | | 158V | Higher | 4.7x ↑ |
| | **CD32A** | 131R | Lower | 6.1x ↓ |
| | | 131H | Higher | ↔ |
| Inhibitory | **CD32B** | 232I/T | Equivalent | 8.4x ↓ |

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1. Nordstrom JL, et al. *Breast Cancer Res*. 2011;13(6):R123. 2. Stavenhagen JB, et al. *Cancer Res*. 2007;67(18):8882-8890.

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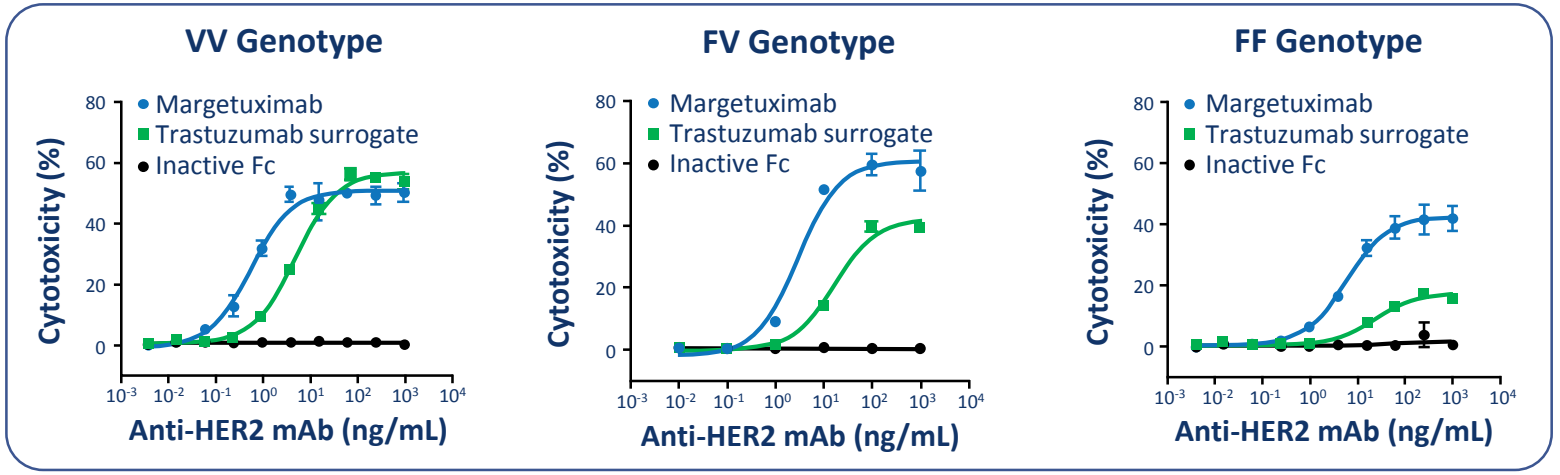
# Margetuximab Enhances Innate Immunity *In Vitro*

*Greater relative cytotoxicity of margetuximab with NK cells from CD16A-158F allele carriers*



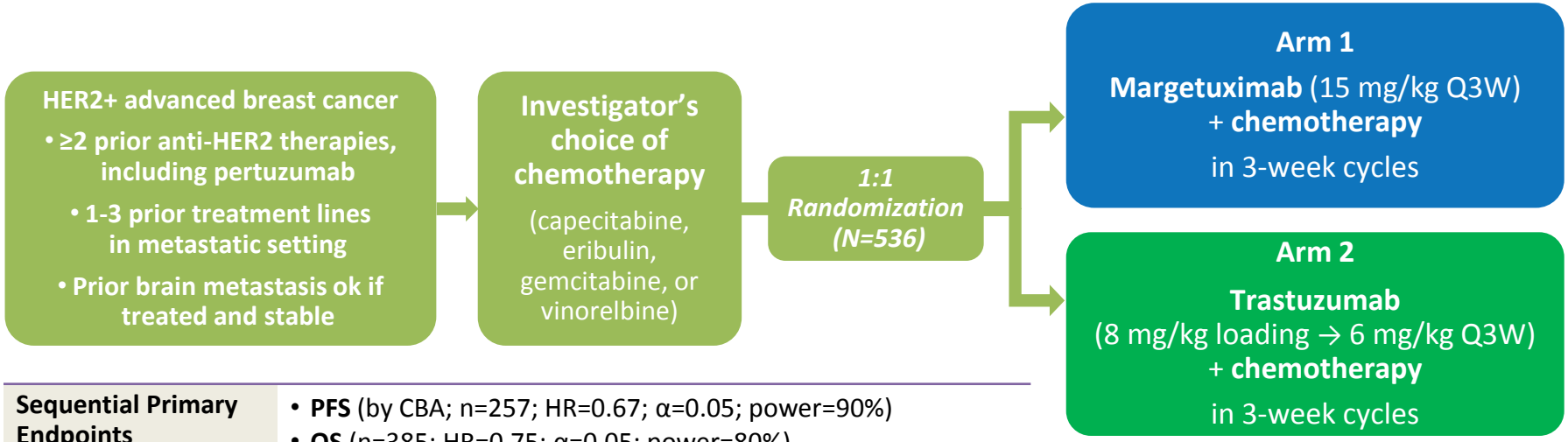

## Preclinical Assay of Antibody-Dependent Cellular Cytotoxicity (ADCC)[1]

**Effector Cells:** Human NK cells from donors with CD16A genotypes 158VV, 158FV, and 158FF
**Target Cells**: JIMT-1 HER2+ breast cancer cell line resistant to trastuzumab antiproliferative activity
**Cellular Assay**: 3:1 Effector:Target ratio; 24-hour incubation time; endpoint: % lactate dehydrogenase release

mAb=monoclonal antibody; NK=natural killer.

Nordstrom JL, et al. *Breast Cancer Res*. 2011;13(6):R123.

# Study CP-MGAH22-04 (SOPHIA) Design[1,2]




| | |
|---|---|
| **Sequential Primary Endpoints** | • **PFS** (by CBA; n=257; HR=0.67; α=0.05; power=90%)<br>• **OS** (n=385; HR=0.75; α=0.05; power=80%) |
| **Secondary Endpoints** | • PFS (Investigator assessed)<br>• Objective response rate (by CBA) |
| **Tertiary/Exploratory Endpoints** | • Clinical benefit rate (CBR), duration of response (DoR)<br>• Safety profile, antidrug antibody<br>• Effect of CD16A, CD32A, and CD32B on margetuximab efficacy |

**Stratification:**
- Chemotherapy choice
- Prior therapies (≤2 *vs* >2)
- Metastatic sites (≤2 *vs* >2)

HR=hazard ratio; CBA=central blinded analysis.

1. Rugo HS, et al. *J Clin Oncol*. 2016;34(suppl 15):TPS630. 2. Clinicaltrials.gov. NCT02492711. www.clinicaltrials.gov/ct2/show/NCT02492711. Accessed April 8, 2019.

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# ITT Population: Prior Cancer Therapy

| | Margetuximab + Chemotherapy (n=266) | Trastuzumab + Chemotherapy (n=270) |
|---|---|---|
| **Settings of prior therapy** | | |
| Adjuvant and/or neoadjuvant | **158 (59%)** | **145 (54%)** |
| Metastatic only | 108 (41%) | 125 (46%) |
| **Prior metastatic lines of therapy** | | |
| ≤2 | 175 (66%) | 180 (67%) |
| >2 | 91 (34%) | 90 (33%) |
| **Prior anti-HER2 therapy** | | |
| **Trastuzumab** | **266 (100%)** | **270 (100%)** |
| **Pertuzumab** | **266 (100%)** | **269 (100%)** |
| **T-DM1** | **242 (91%)** | **247 (92%)** |
| Lapatinib | 41 (15%) | 39 (14%) |
| Other HER2 | 6 (2%) | 6 (2%) |
| **Prior chemotherapy** | | |
| Taxane | 252 (95%) | 249 (92%) |
| Anthracycline | 118 (44%) | 110 (41%) |
| Platinum | 34 (13%) | 40 (15%) |
| **Prior endocrine therapy** | 126 (47%) | 133 (49%) |

***Treatment arms overall balanced***

ITT population: N=536.

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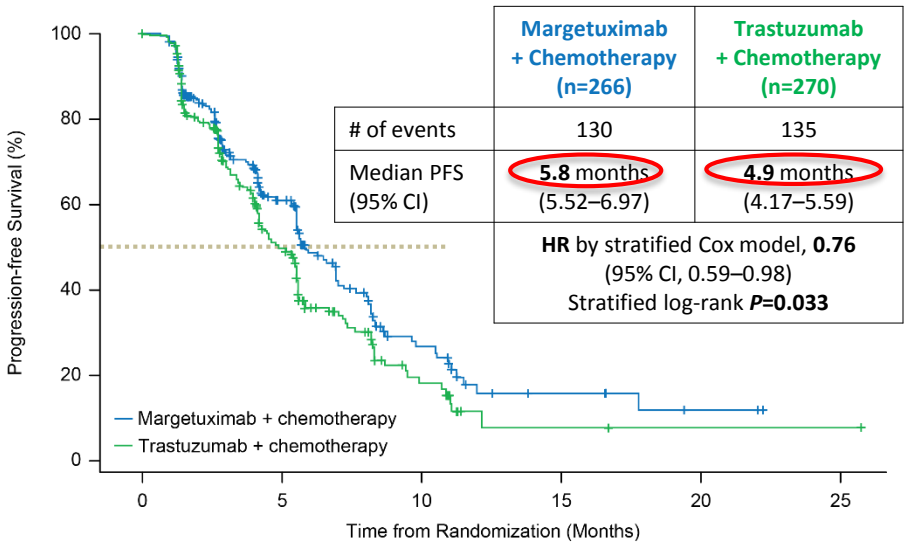
# PFS Analysis in ITT Population

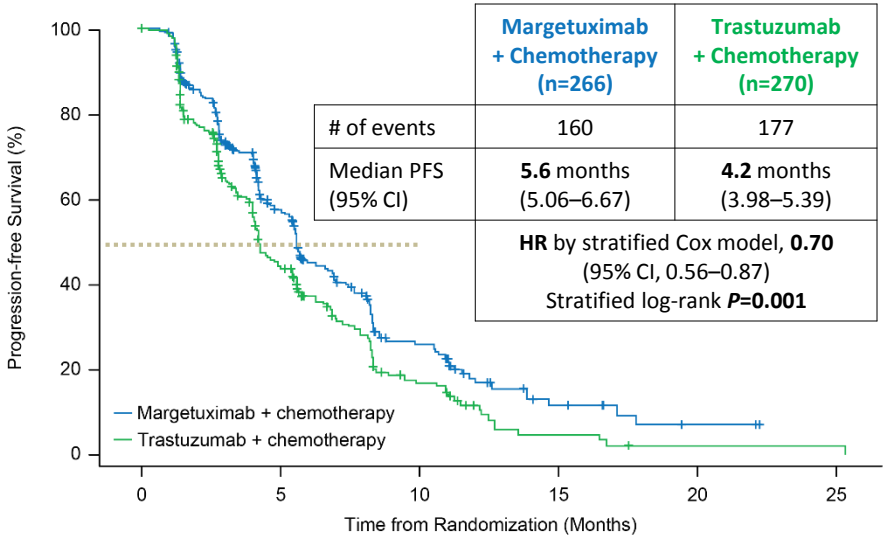
## 24% Risk Reduction of Disease Progression
### Central Blinded Analysis (Primary Endpoint)




| | Margetuximab + Chemotherapy (n=266) | Trastuzumab + Chemotherapy (n=270) |
|---|---|---|
| # of events | 130 | 135 |
| Median PFS (95% CI) | **5.8** months (5.52–6.97) | **4.9** months (4.17–5.59) |
| | **HR** by stratified Cox model, **0.76** (95% CI, 0.59–0.98) Stratified log-rank ***P*=0.033** | |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Margetuximab | 266 | 174 | 94 | 45 | 21 | 8 | 6 | 4 | 2 | 0 | |
| Trastuzumab | 270 | 158 | 74 | 33 | 13 | 2 | 2 | 1 | 1 | 1 | 1 |

## 30% Risk Reduction of Disease Progression
### Investigator Assessed (Secondary Endpoint)




| | Margetuximab + Chemotherapy (n=266) | Trastuzumab + Chemotherapy (n=270) |
|---|---|---|
| # of events | 160 | 177 |
| Median PFS (95% CI) | **5.6** months (5.06–6.67) | **4.2** months (3.98–5.39) |
| | **HR** by stratified Cox model, **0.70** (95% CI, 0.56–0.87) Stratified log-rank ***P*=0.001** | |

| | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Margetuximab | 266 | 206 | 155 | 112 | 72 | 61 | 33 | 32 | 16 | 13 | 8 | 7 | 3 | 2 | 2 | 0 |
| Trastuzumab | 270 | 184 | 130 | 87 | 59 | 45 | 25 | 21 | 10 | 5 | 4 | 3 | 1 | 1 | 1 | 1 | 0 |

- PFS analysis was triggered by last randomization on October 10, 2018, after 265 PFS events occurred

ITT population: N=536. CI=confidence interval.

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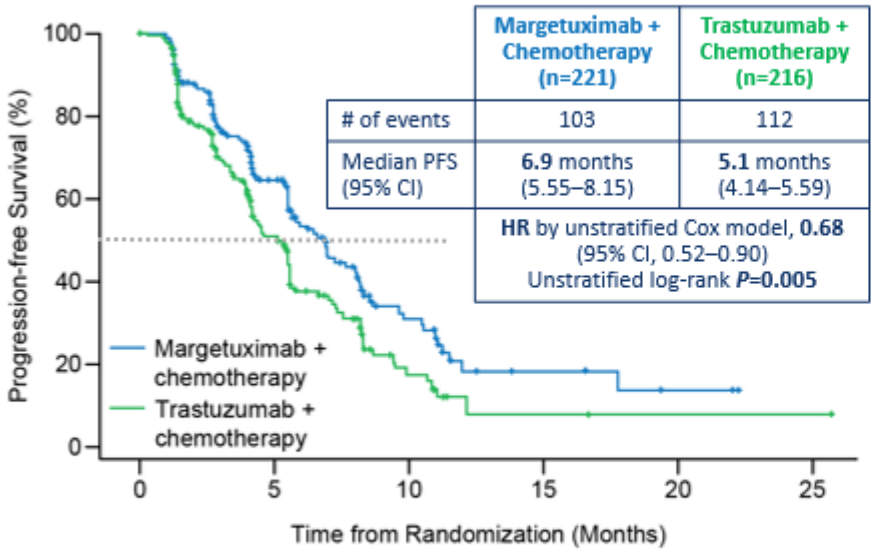
# Planned Exploratory PFS Analysis by CD16A Genotype, by CBA

## 506 patients genotyped (94%)

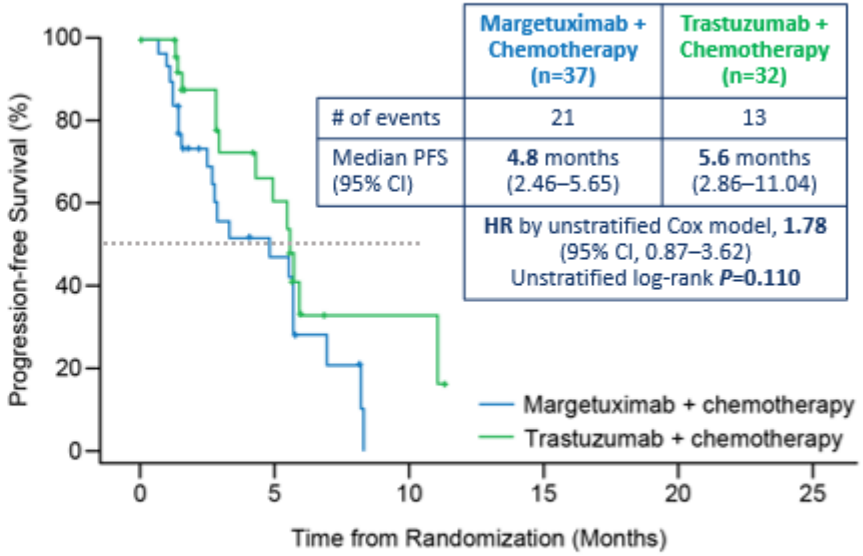
### FF or FV, n=437 of 506 (86%)




| | Margetuximab + Chemotherapy (n=221) | Trastuzumab + Chemotherapy (n=216) |
|---|---|---|
| # of events | 103 | 112 |
| Median PFS (95% CI) | **6.9** months (5.55–8.15) | **5.1** months (4.14–5.59) |
| **HR** by unstratified Cox model, **0.68** (95% CI, 0.52–0.90) Unstratified log-rank ***P*=0.005** | | |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Margetuximab | 221 | 157 | 84 | 42 | 21 | 8 | 6 | 4 | 2 | 0 | |
| Trastuzumab | 216 | 129 | 62 | 30 | 11 | 2 | 2 | 1 | 1 | 1 | 1 |

### VV, n=69 of 506 (14%)




| | Margetuximab + Chemotherapy (n=37) | Trastuzumab + Chemotherapy (n=32) |
|---|---|---|
| # of events | 21 | 13 |
| Median PFS (95% CI) | **4.8** months (2.46–5.65) | **5.6** months (2.86–11.04) |
| **HR** by unstratified Cox model, **1.78** (95% CI, 0.87–3.62) Unstratified log-rank ***P*=0.110** | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Margetuximab | 37 | 16 | 10 | 3 | 0 | |
| Trastuzumab | 32 | 18 | 10 | 2 | 2 | 0 |

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# New Antibody drug conjugates (ADCs) targeting HER2

| Agent | Target | Phase of development | Initial Phase I Results | Main Side Effects |
|---|---|---|---|---|
| DS8201a[1] | Humanized HER2 antibody + topoisomerase-I inhibitor exatecan | Ongoing phase II (DESTINY-Breast01) and III (NCT03529110) | RR: 64.2%<br>PFS:10.4 mo.<br>(heavily pre-treated patients) | Gastrointestinal and haematological |
| SYD985[2] | Trastuzumab + duocarmazine | Ongoing phase III (TULIP) | RR: 33%[2]<br>PFS: 9.4 mo. | Ophthalmologic effects (conjunctivitis and keratitis) |
| RC48- ADC[3] | HER2 antibody + MMAE | Ongoing phase II (NCT03500380) | RR: 36.7% | Transaminases elevations<br>Neutropenia |

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[1] Iwata H et al. J Clin Oncol. 2018, [2] Saura C et al. J Clin Oncol. 2018, [3] Xu B et al. J Clin Oncol. 2018

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# Progress on the management of Breast Cancer in 2019: Triple negative breast cancer

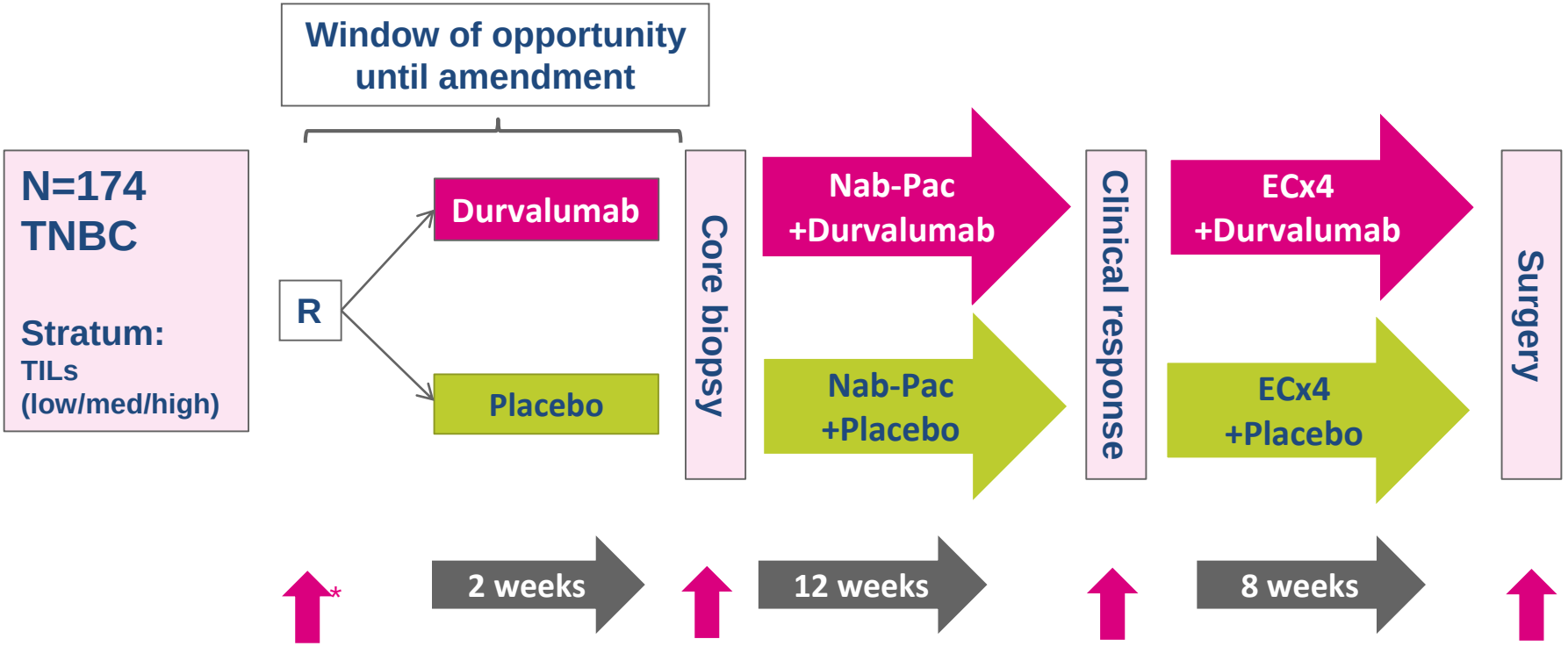
- Checkpoints inhibitors-based combination on the neoadjuvant setting
- Update on the role of CPIs in the metastatic setting
- Perspectives
    - Antibody drugs conjugates

# Randomized Phase II Neoadjuvant Study (GeparNuevo) to Investigate the Addition of Durvalumab to a Taxane-Anthracycline Containing Chemotherapy in Triple Negative Breast Cancer (TNBC)

Sibylle Loibl, Michael Untch, Nicole Burchardi, Jens Huober, Jens-Uwe Blohmer, Eva-Maria Grischke, Jenny Furlanetto, Hans Tesch, Claus Hanusch, Mahdi Rezai, Christian Jackisch, Wolfgang D Schmitt, Gunter von Minckwitz, Jörg Thomalla, Sherko Kümmel, Beate Rautenberg, Peter A Fasching, Kerstin Rhiem, Carsten Denkert, Andreas Schneeweiss

-This is a joint study by GBG and AGO-B-

# GeparNUEVO Study Design




*Tissue: FFPE, fresh frozen; Liquid biopsies: full blood; plasma, serum;

Durvalumab (0.75g) 1.5g d1q28

nab-Paclitaxel 125mg/m² weekly

Epirubicin 90mg/m²; Cyclophosphamide 600mg/m² d1q14

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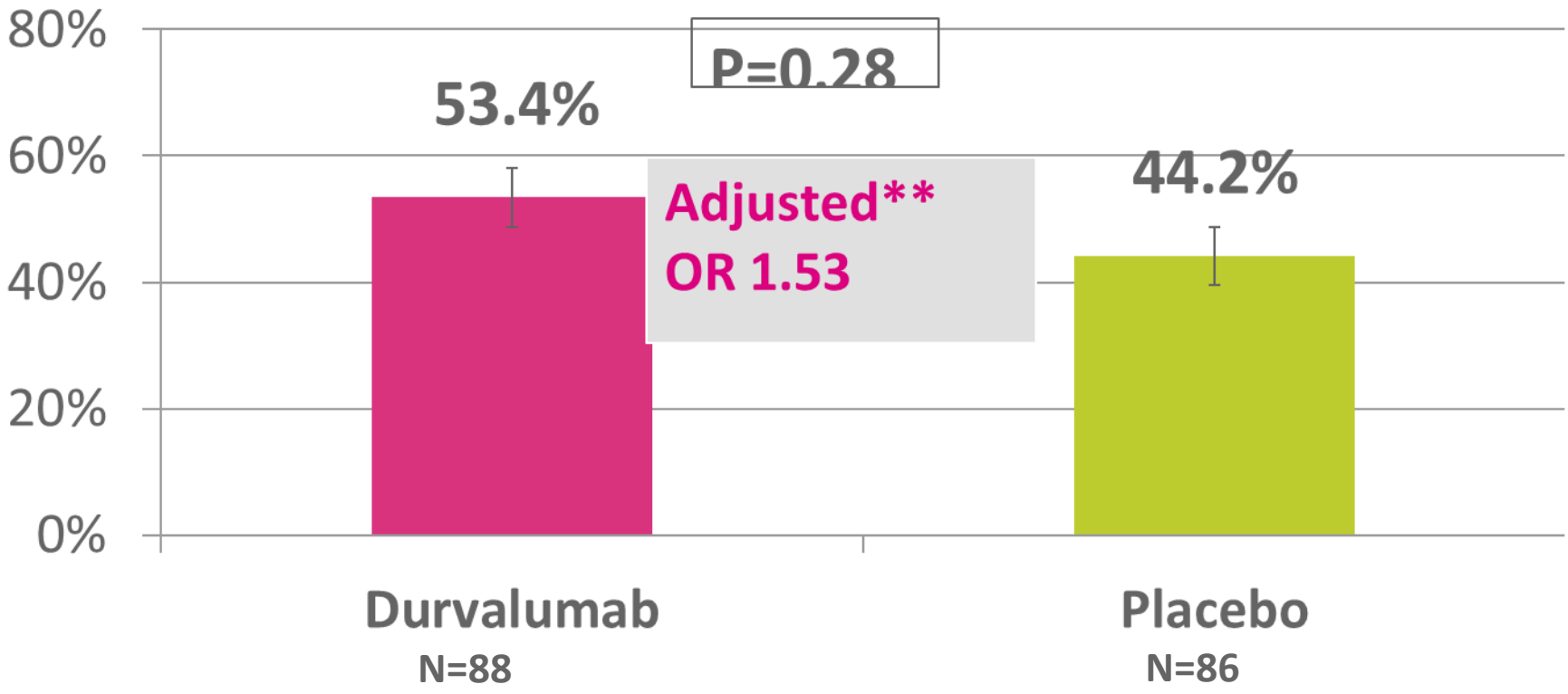
# Primary Endpoint - pathological complete response pCR – ypT0, ypN0




* Continuous corrected $\chi^2$ test
** For stratification factor (TIL groups)

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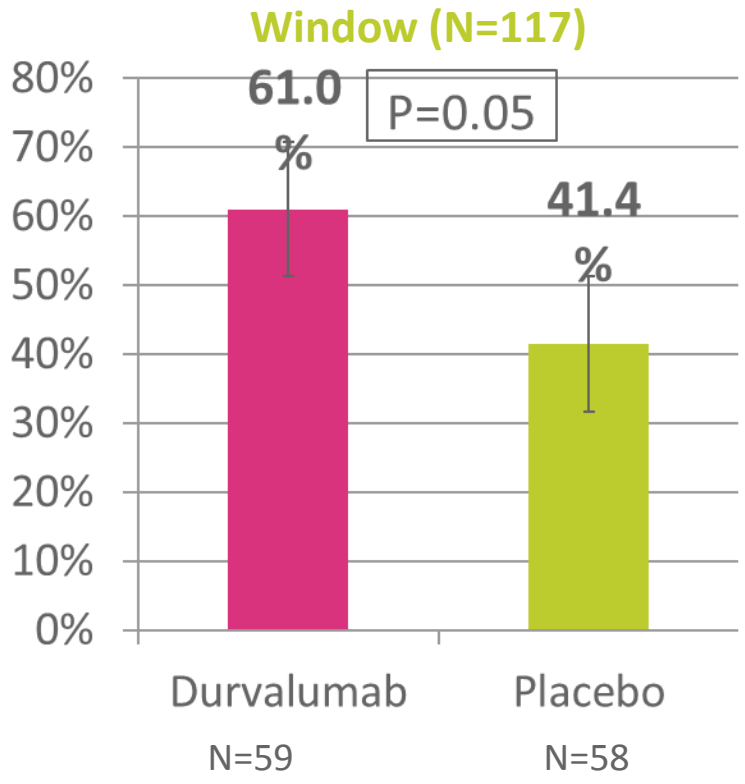
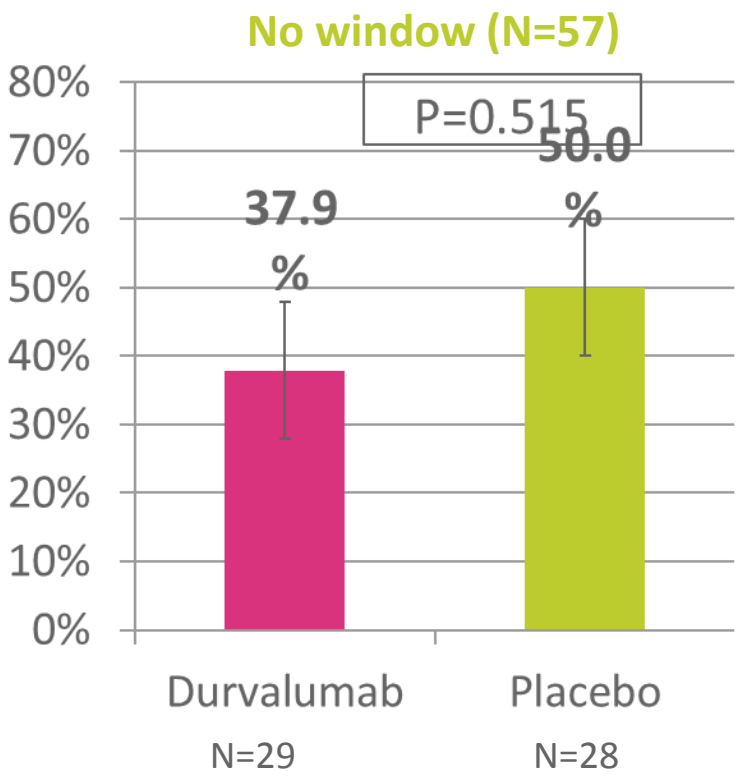
# Subgroup Analysis of the Window Cohort

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BARCELONA 2019 ESMO congress

# KEYNOTE-522: Phase 3 Study of Pembrolizumab + Chemotherapy versus Placebo + Chemotherapy as Neoadjuvant Treatment, Followed by Pembrolizumab versus Placebo as Adjuvant Treatment for Early Triple-Negative Breast Cancer (TNBC)

Peter Schmid[1], Javier Cortes[2], Rebecca Dent[3], Lajos Pusztai[4], Heather McArthur[5], Sherko Kümmel[6], Jonas Bergh[7], Carsten Denkert[8], Yeon Hee Park[9], Rina Hui[10], Nadia Harbeck[11], Masato Takahashi[12], Theodoros Foukakis[7], Peter A. Fasching[13], Fatima Cardoso[14], Liyi Jia[15], Vassiliki Karantza[15], Jing Zhao[15], Gursel Aktan[15], Joyce O'Shaughnessy[16]

1. Barts Cancer Institute, Queen Mary University London, London, UK; 2. IOB Institute of Oncology, Quiron Group; Vall d'Hebron Institute of Oncology (VHIO), Madrid & Barcelona, Spain; 3. University of Toronto, Toronto, Ontario, Canada; 4. Yale School of Medicine, Yale Cancer Center, New Haven, CT, USA; 5. Cedars-Sinai Medical Center, Los Angeles, CA, USA; 6. Breast Unit, Kliniken Essen-Mitte, Essen, Germany; 7. Department of Oncology-Pathology, Karolinska Institutet and Breast Cancer Centre, Cancer theme, Karolinska University Hospital, Solna, Sweden; 8. Institute of Pathology, Philipps-University Marburg and University Hospital Marburg (UKGM), Marburg, Germany; 9. Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; 10. Westmead Breast Cancer Institute, Westmead Hospital and the University of Sydney, Sydney, NSW, Australia; 11. Breast Center, University of Munich (LMU), Munich, Germany; 12. Hokkaido Cancer Center, Sapporo, Japan; 13. University Hospital Erlangen, Comprehensive Cancer Center Erlangen-EMN, Erlangen, Germany; 14. Breast Unit, Champalimaud Clinical Center/Champalimaud Foundation, Lisbon, Portugal; 15. Merck & Co., Inc., Kenilworth, NJ, USA; 16. Baylor University Medical Center, Texas Oncology, US Oncology, Dallas, TX, USA

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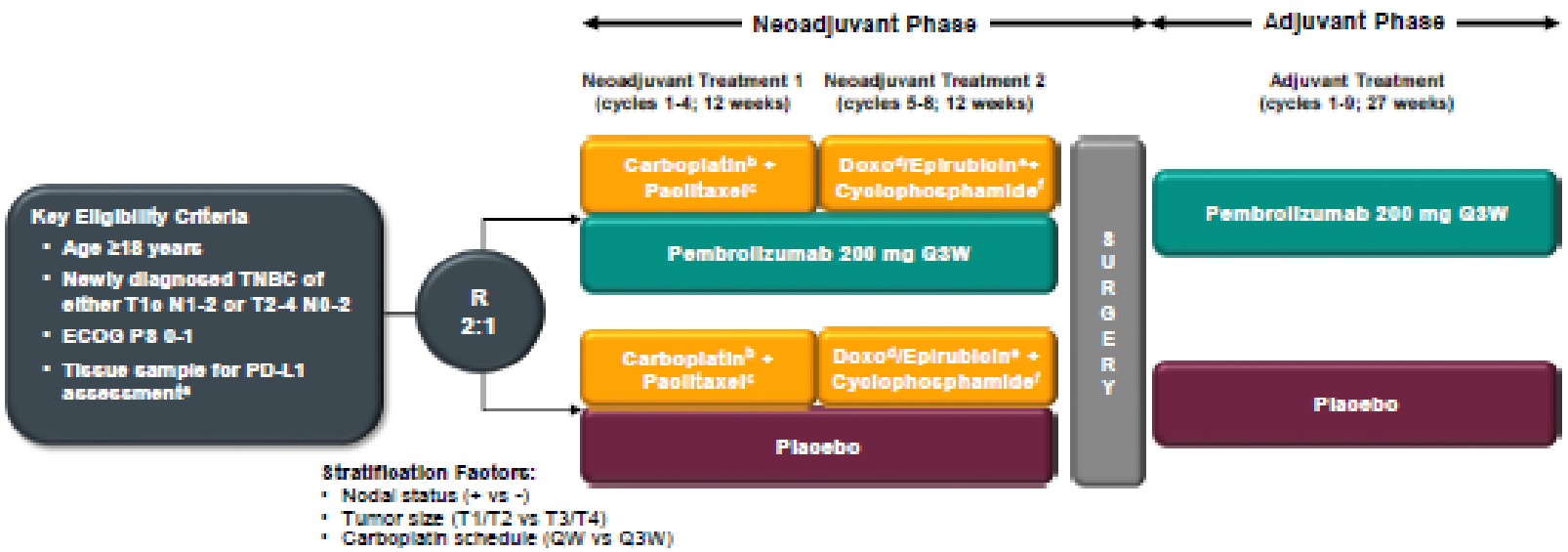
# KEYNOTE-522 Study Design (NCT03036488)




**Neoadjuvant phase:** starts from the first neoadjuvant treatment and ends after definitive surgery (post treatment included)

**Adjuvant phase:** starts from the first adjuvant treatment and includes radiation therapy as indicated (post treatment included)

[a]Must consist of at least 2 separate tumor cores from the primary tumor.
[b]Carboplatin dose was AUC 5 Q3W or AUC 1.5 QW.
[c]Paclitaxel dose was 80 mg/m$^2$ QW.
[d]Doxorubicin dose was 60 mg/m$^2$ Q3W.
[e]Epirubicin dose was 90 mg/m$^2$ Q3W.
[f]Cyclophosphamide dose was 600 mg/m$^2$ Q3W.

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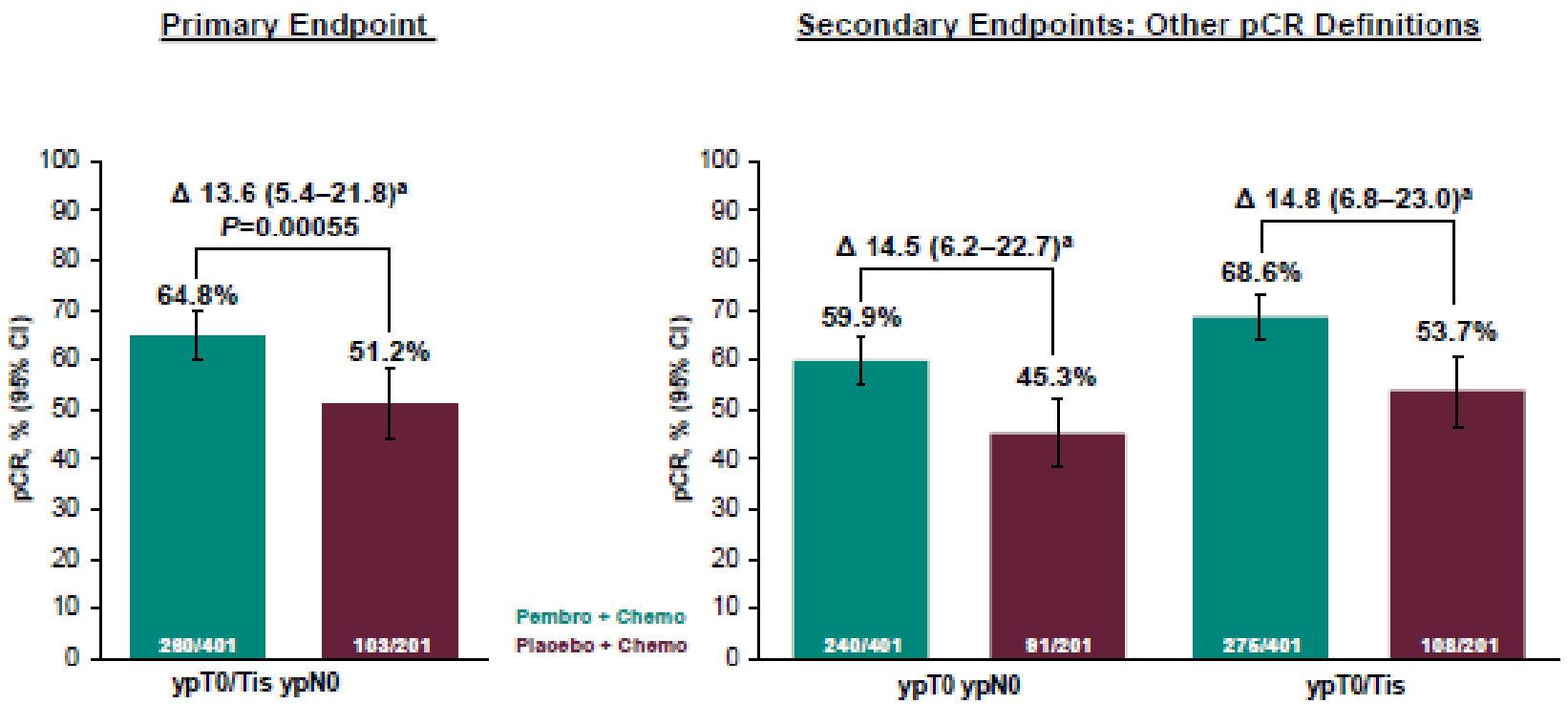
# Pathological Complete Response at IA1




[a]Estimated treatment difference based on Miettinen & Nurminen method stratified by randomization stratification factors.
Data cutoff date: September 24, 2018.

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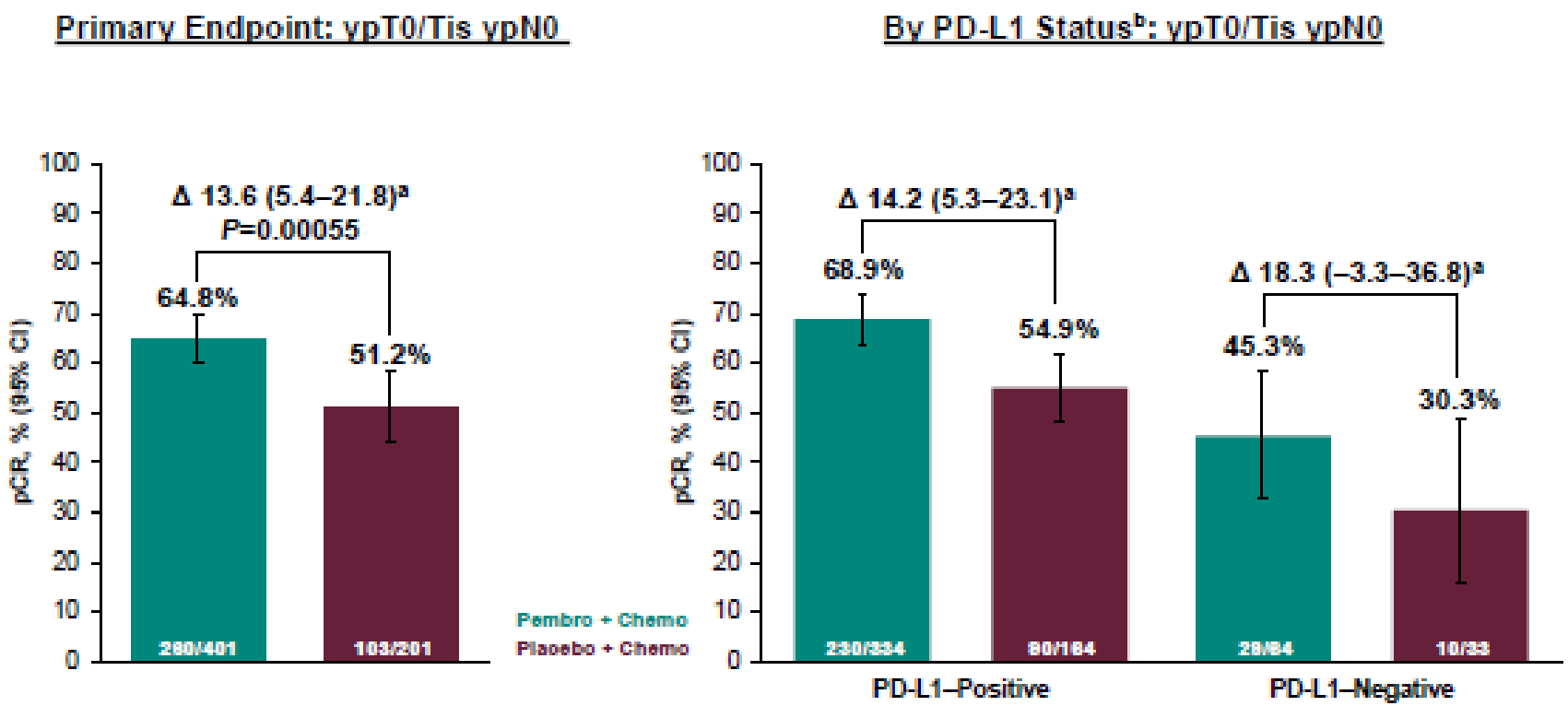
# Pathological Complete Response at IA1




[a]Estimated treatment difference based on Miettinen & Nurminen method stratified by randomization stratification factors. [b]PD-L1 assessed at a central laboratory using the PD-L1 IHC 22C3 pharmDx assay and measured using the combined positive score (CPS; number of PD-L1–positive tumor cells, lymphocytes, and macrophages divided by total number of tumor cells x 100); PD-L1–positive = CPS ≥1. Data cutoff date: September 24, 2018.

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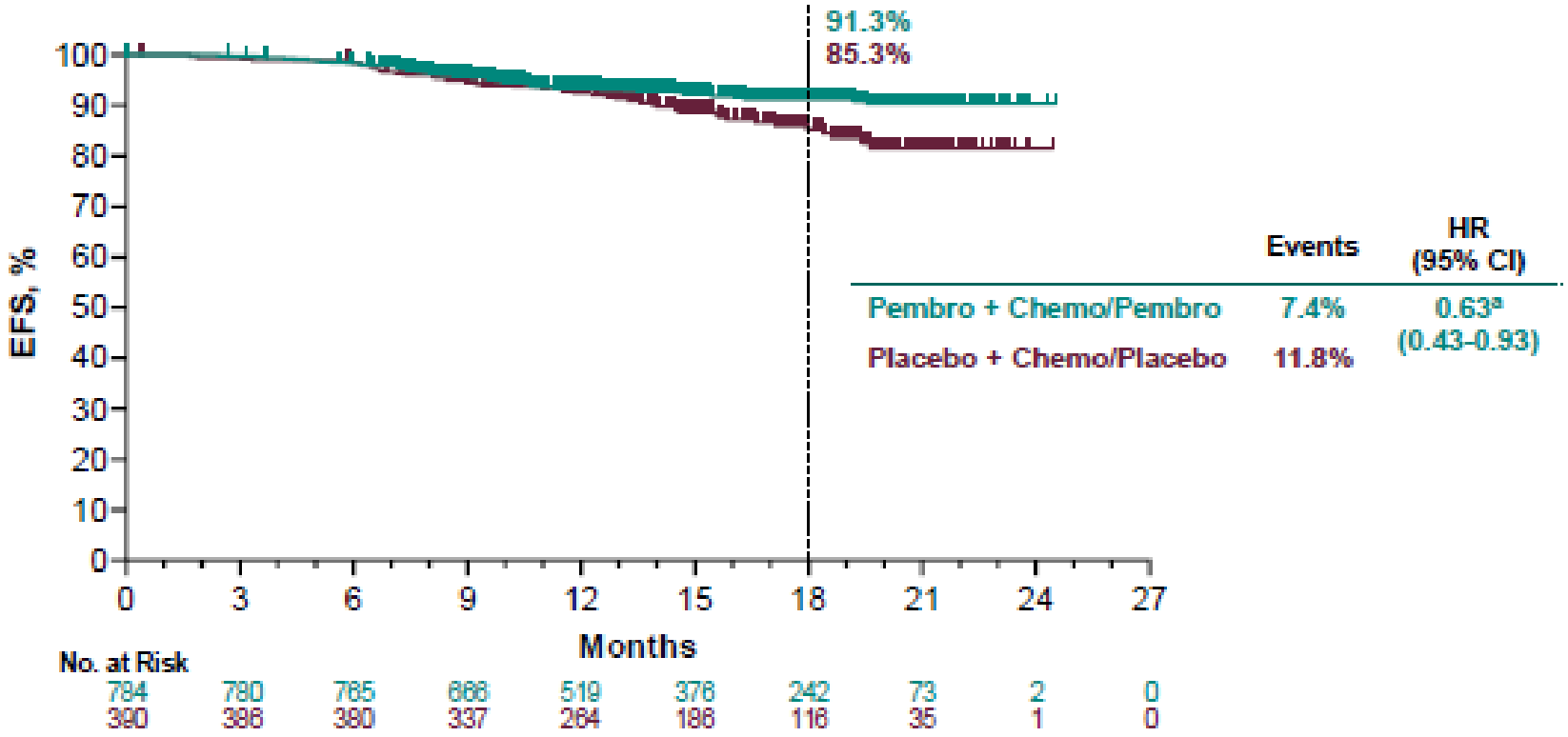
# Event-Free Survival at IA2




[a]Prespecified *P* value boundary of 0.000051 not reached at this analysis (the first interim analysis of EFS).
Hazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate stratified by the randomization stratification factors. Data cutoff April 24, 2019.

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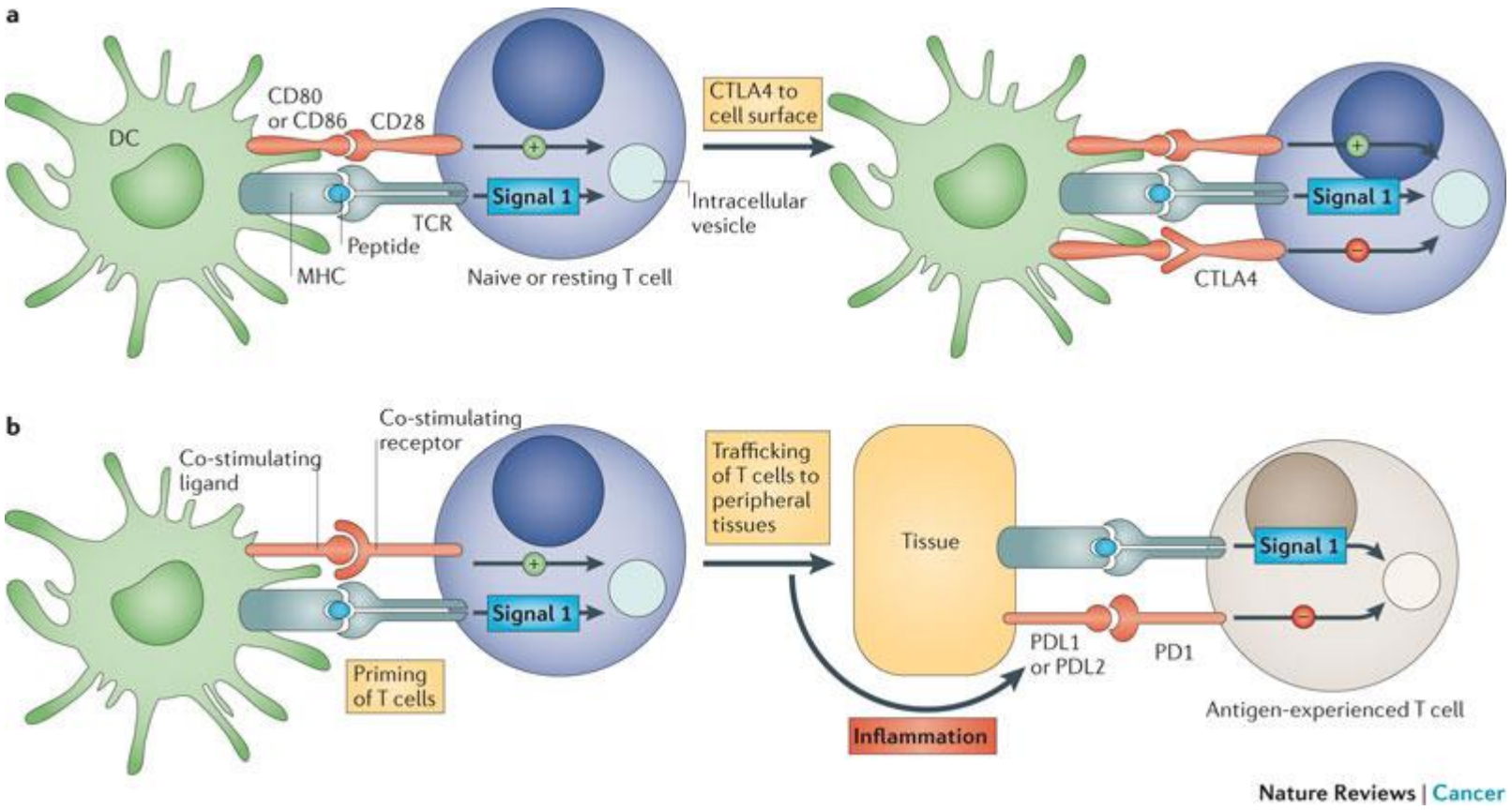
# Immune Checkpoints in Cancer




**CTL4 immune checkpoint regulates initial T-cell response to antigen, whereas PD1 pathway regulates inflammatory responses in peripheral tissues by effector T cells**

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Pardoll et al. Nature Reviews Cancer 2012

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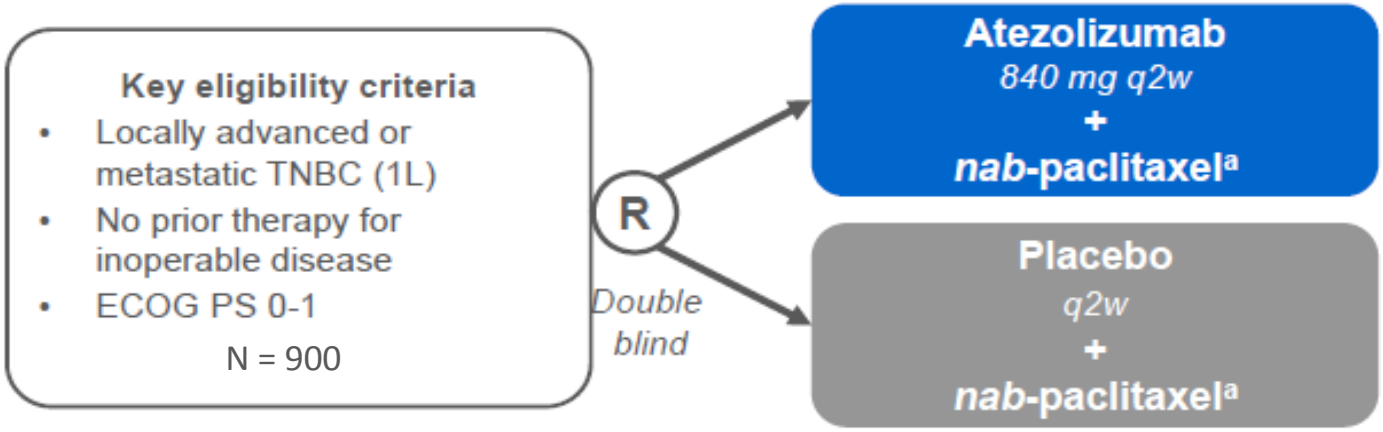
# Atezolizumab + Nab-paclitaxel: Phase III IMpassion 130 study

## TNBC (1L metastatic)




**Primary endpoints**

- PFS (RECIST v1.1): ITT and PD-L1 selected
- OS: ITT and PD-L1 selected

Additional endpoints

- ORR: ITT and PD-L1 selected
- DOR
- TTD
- Safety: AEs

[a] 100 mg/m² on D1, D8 and D15 (28-d cycle).

Study: WO29522.
ClinicalTrials.gov: NCT02425891 currently recruiting

Atezolizumab is an investigational agent in this setting

# IMpassion 130 study: Updated Data

| | | |
|---|---|---|
| **Median PFS (mo):** | **7.2 vs 5.5** | **[HR 0.80]** |
| **Med. PFS, PD-L1 ≥ 1% on TC:** | **7.5 vs 5** | **[HR 0.62]** |
| **Med. OS (mo):** | **21 vs 18.7** | **[HR 0.86]** |
| **Med OS, PD-L1$^{+}$:** | **25 vs 18** | **[HR 0.71]** |
| **ORR (%):** | **58.9% vs 42.6%** | |

**Schmid et al., ASCO 22019 Abs1003**

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# Sacituzumab Govitecan (IMMU-132), an Anti-Trop-2-SN-38 Antibody-Drug Conjugate, as ≥3rd-line Therapeutic Option for Patients With Relapsed/Refractory Metastatic Triple-Negative Breast Cancer (mTNBC): Efficacy Results

Aditya Bardia,[1] Linda T. Vahdat,[2,†] Jennifer R. Diamond,[3] Kevin Kalinsky,[4] Joyce O'Shaughnessy,[5] Rebecca L. Moroose,[6] Steven J. Isakoff,[1] Sara M. Tolaney,[7] Alessandro D. Santin,[8] Vandana Abramson,[9] Nikita C. Shah,[6] Serengulam V. Govindan,[10] Pius Maliakal,[10] Robert M. Sharkey,[10] William A. Wegener,[10] David M. Goldenberg,[10] Ingrid A. Mayer[9]

[1]Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA; [2]Weill Cornell Medicine, New York, NY; [3]University of Colorado Cancer Center, Aurora, CO; [4]Columbia University-Herbert Irving Comprehensive Cancer Center, New York, NY; [5]Texas Oncology, Baylor University Medical Center, US Oncology, Dallas, TX; [6]UF Health Cancer Center, Orlando, FL; [7]The Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA; [8]Yale University School of Medicine, New Haven, CT; [9]Vanderbilt-Ingram Cancer Center, Nashville, TN; [10]Immunomedics, Inc., Morris Plains, NJ; [†]Current affiliation: Memorial Sloan Kettering Cancer Center, New York, NY.

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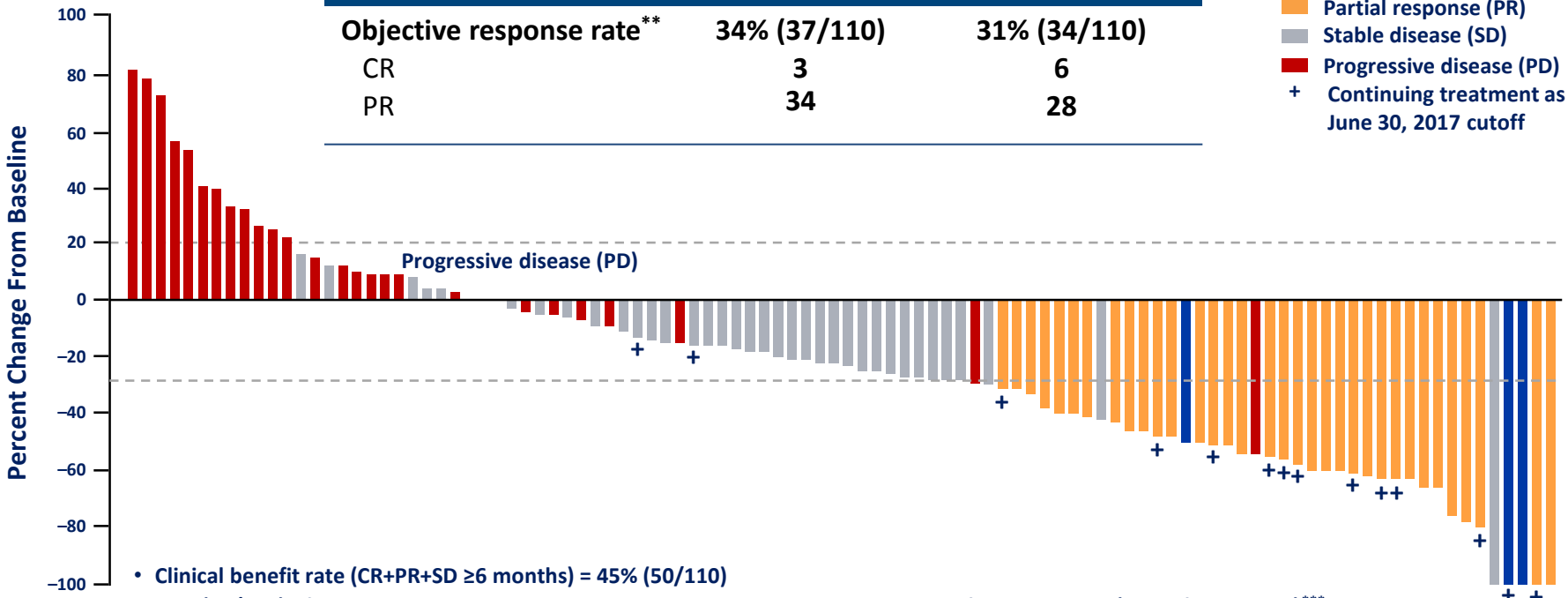
# Tumor Response to Treatment

| | Local | BICR* |
|---|---|---|
| **Objective response rate**** | **34% (37/110)** | **31% (34/110)** |
| CR | **3** | **6** |
| PR | **34** | **28** |




- Clinical benefit rate (CR+PR+SD ≥6 months) = 45% (50/110)
- 74% (75/102) of patients with at least one CT response assessment had reduction of target lesions (sum of diameters)***
- 102 patients had ≥1 scheduled CT response assessment. 8 patients withdrew prior to assessment (4 PD, 4 MRI brain metastases)

*Patients with at least 20% tumor reduction (n = 56) were reviewed; **Confirmed objective response rate per RECIST; ***Waterfall is based on local assessment; BICR = Blinded Independent Adjudicated Central Review.

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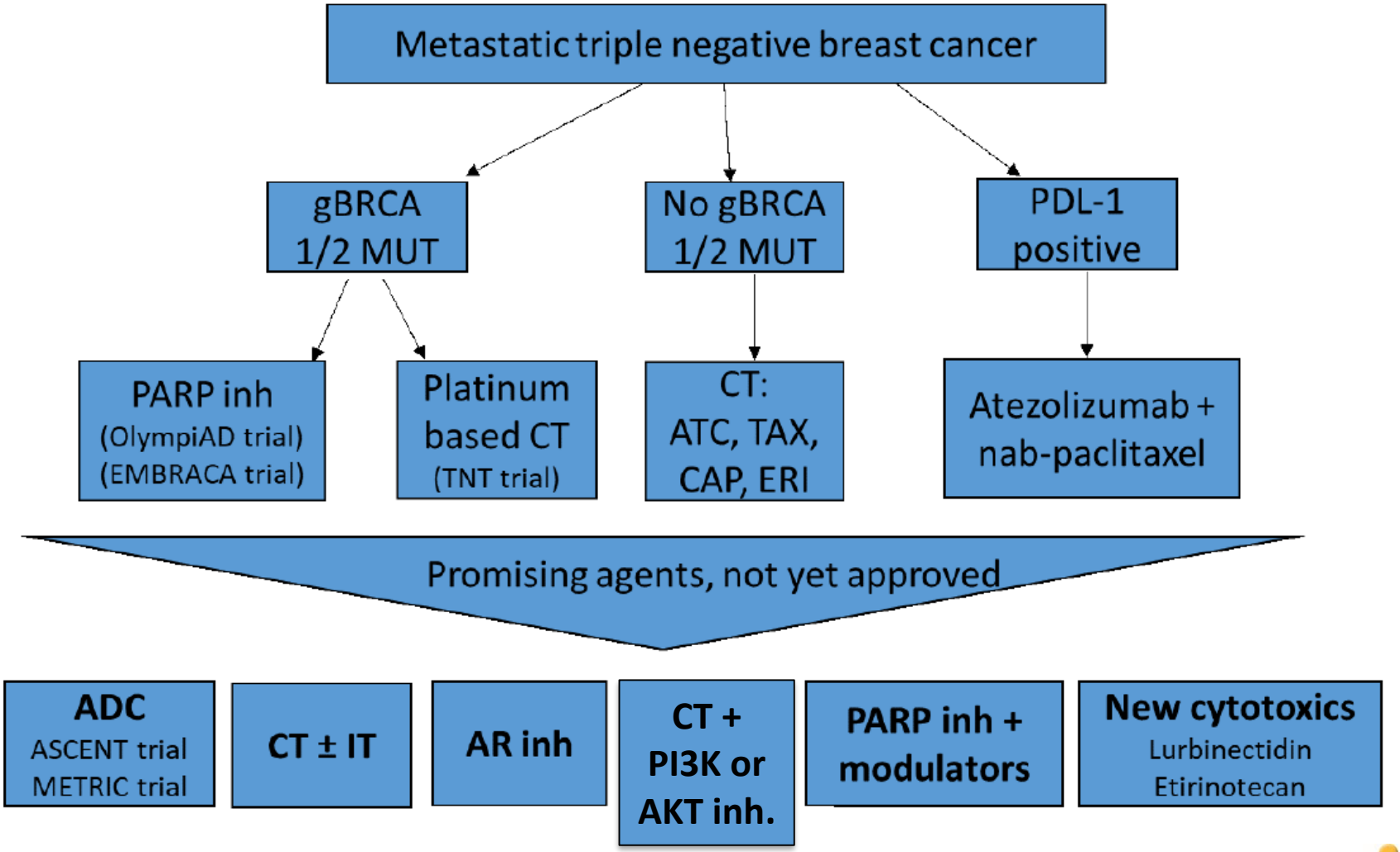
# Current standard-of-care treatments in metastatic triple-negative breast cancer and perspectives

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El Hachem, A Awada, F1000Research 2019, Apr 30, 8 pii

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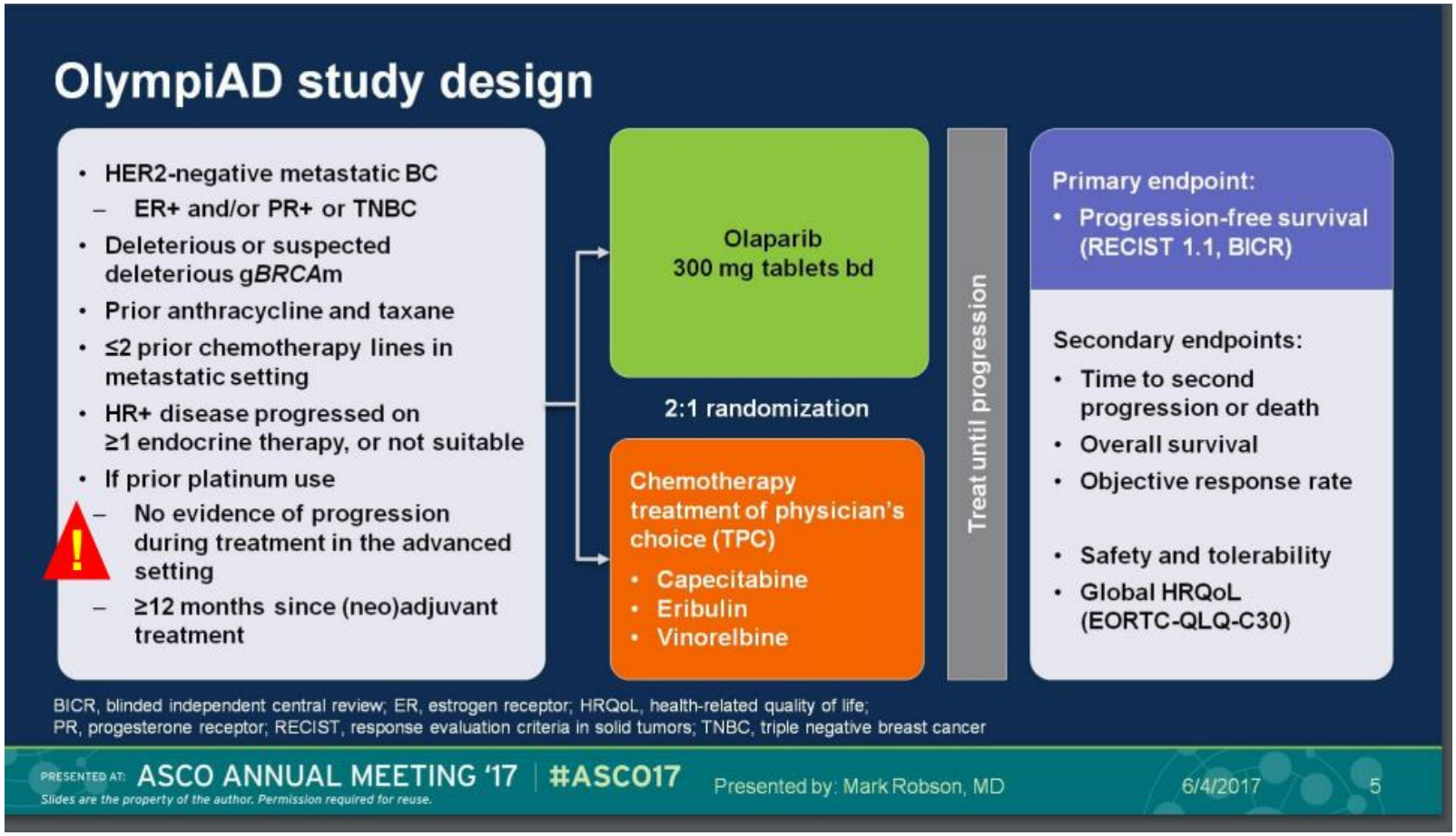
# Progress on the management of Breast Cancer in 2019: gBRCA mutated BC

- Role of PARP inhibitors
  - as single agents (olaparib, talazoparib)
  - in combination (veliparib)
- Therapeutic strategy in gBRCA-mutated breast tumors?

# BRCA positive tumors : Role of PARP inhibitors in MBC

- Olaparib
- Talazoparib
- Veliparib

# OlympiAD Study (Olaparib) in HR+ or TNBC (g*BRCA*m+)




**Olaparib is an investigational agent in this setting**

**Robson ME, et al. ASCO 2017 (Abstract LBA4)**

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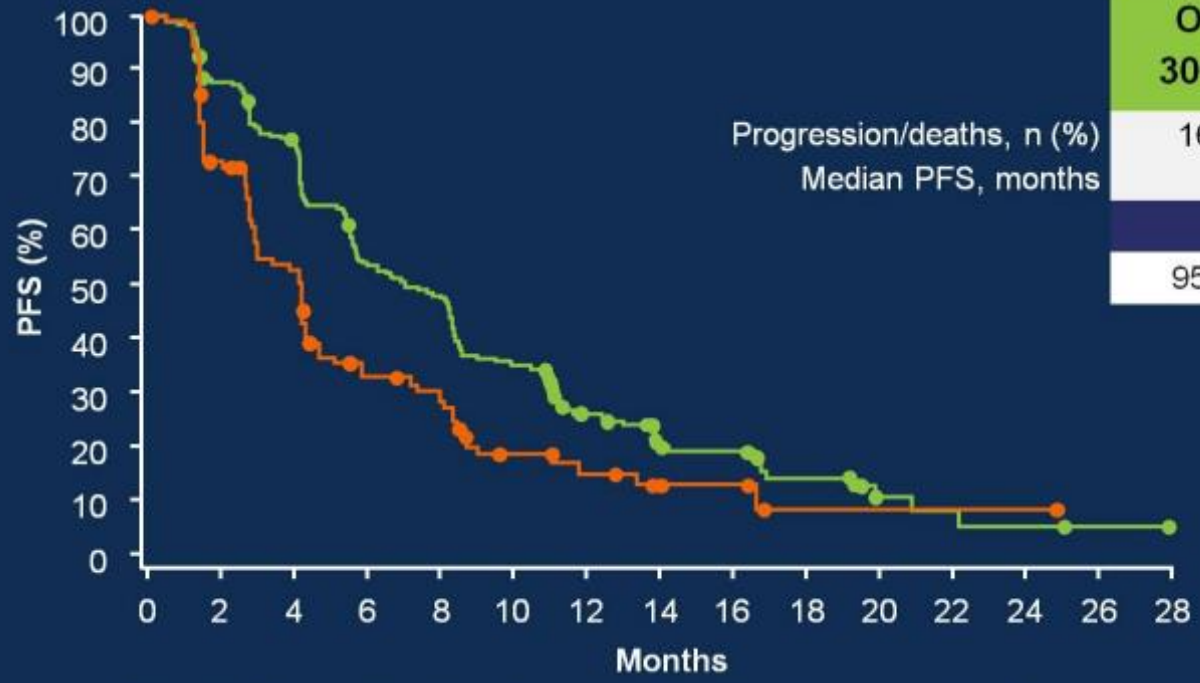
# Primary endpoint: progression-free survival by BICR




| | Olaparib 300 mg bd | Chemotherapy TPC |
|---|---|---|
| Progression/deaths, n (%) | 163 (79.5) | 71 (73.2) |
| Median PFS, months | 7.0 | 4.2 |
| HR 0.58 | | |
| 95% CI 0.43 to 0.80; *P*=0.0009 | | |

| At risk, n | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Olaparib 300 mg bd | 205 | 177 | 154 | 107 | 94 | 69 | 40 | 23 | 21 | 11 | 4 | 3 | 2 | 1 | 0 | |
| Chemotherapy TPC | 97 | 63 | 44 | 25 | 21 | 11 | 8 | 4 | 4 | 1 | 1 | 1 | 1 | 0 | 0 | |




**Olaparib is an investigational agent in this setting**

***Robson ME, et al. ASCO 2017 (Abstract LBA4)***

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# Study Design: EMBRACA

Patients with locally advanced or metastatic HER2-negative breast cancer and a germline *BRCA1* or *BRCA2* mutation*†

Stratification factors:

- Number of prior chemo regimens (0 or ≥ 1)
- TNBC or hormone receptor positive (HR+)
- History of CNS mets or no CNS mets

R 2:1

**Talazoparib**
**1 mg PO daily**

Treatment (21-day cycles) continues until progression or unacceptable toxicity

**Physician's choice of therapy (PCT)‡: capecitabine, eribulin, gemcitabine, or vinorelbine**

Phase 3, international, open-label study randomized 431 patients in 16 countries and 145 sites

## Primary endpoint

- Progression-free survival by RECIST by blinded central review

## Key secondary efficacy endpoints

- Overall survival (OS)
- ORR by investigator
- Safety

## Exploratory endpoints

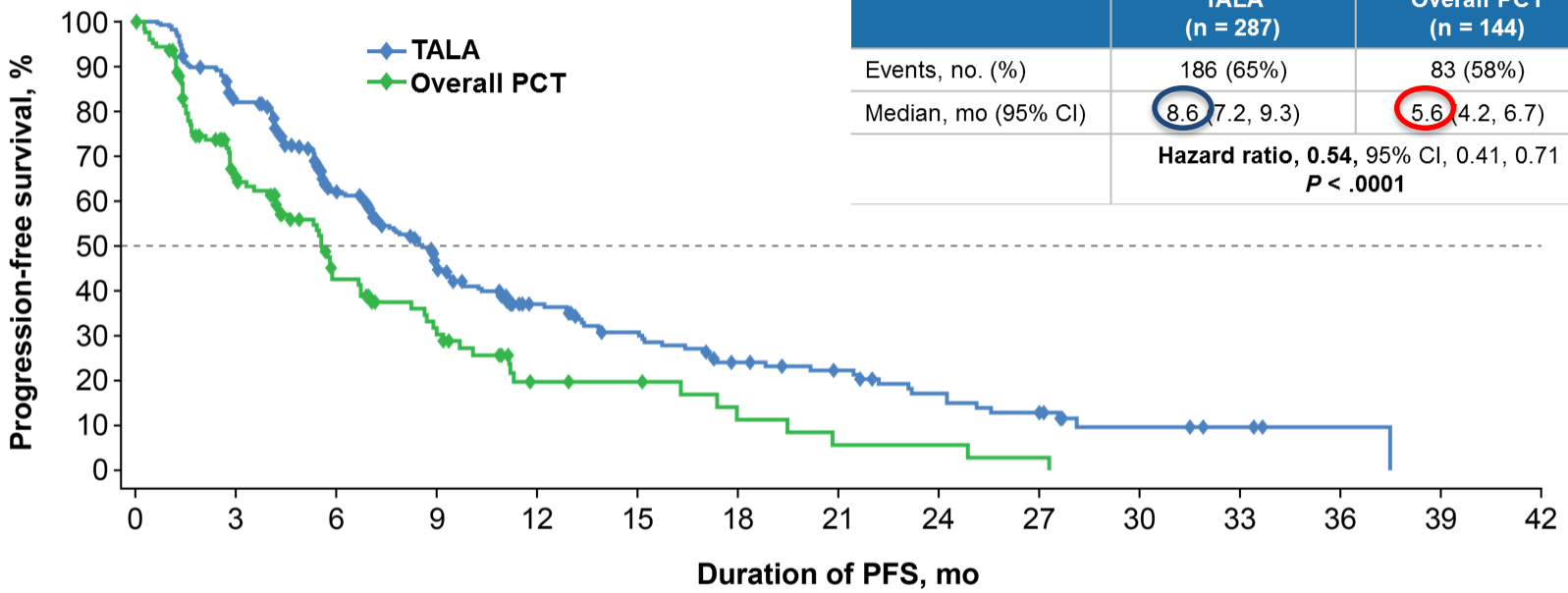
- Duration of response (DOR) for objective responders
- Quality of life (QoL; EORTC QLQ-C30, QLQ-BR23)

Abbreviations: CNS, central nervous system; EORTC, European Organisation for Research and Treatment of Cancer; HER2, human epidermal growth factor receptor 2; mets, metastases; PO, orally (per os); QLQ-BR23, Quality of Life Questionnaire breast cancer module; QLQ-C30, Quality of Life Questionnaire Core 30; R, randomized; RECIST, Response Evaluation Criteria In Solid Tumors version 1.1; TNBC, triple-negative breast cancer.

*Additional inclusion criteria included: no more than 3 prior cytotoxic chemotherapy regimens for locally advanced or metastatic disease; prior treatment with a taxane and/or anthracycline unless medically contraindicated. †HER2-positive disease is excluded. ‡Physician's choice of therapy must be determined prior to randomization.

www.clinicaltrials.gov (NCT01945775)

# Primary Endpoint: PFS by Blinded Central Review




| | TALA (n = 287) | Overall PCT (n = 144) |
|---|---|---|
| Events, no. (%) | 186 (65%) | 83 (58%) |
| Median, mo (95% CI) | 8.6 (7.2, 9.3) | 5.6 (4.2, 6.7) |
| | **Hazard ratio, 0.54,** 95% CI, 0.41, 0.71 ***P* < .0001** | |

| No. at risk (events/cumulative events) | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| TALA | 287 (0/0) | 229 (50/50) | 148 (53/103) | 91 (34/137) | 55 (17/154) | 42 (9/163) | 29 (9/172) | 23 (2/174) | 16 (5/179) | 12 (4/183) | 5 (2/185) | 3 (0/185) | 1 (0/185) | 0 (1/186) | 0 (0/186) |
| PCT | 144 (0/0) | 68 (41/41) | 34 (20/61) | 22 (8/69) | 9 (7/76) | 8 (0/76) | 4 (3/79) | 2 (2/81) | 2 (0/81) | 1 (1/82) | 0 (1/83) | 0 (0/83) | 0 (0/83) | 0 (0/83) | 0 (0/83) |

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



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# Phase 3 study of veliparib with carboplatin and paclitaxel in HER2-negative advanced/metastatic g*BRCA*-associated breast cancer: BROCADE3

Véronique Diéras[1], Hyo S. Han[2], Bella Kaufman[3], Hans Wildiers[4], Michael Friedlander[5], Jean-Pierre Ayoub[6], Shannon L. Puhalla[7], Igor Bondarenko[8], Mario Campone[9], Erik H. Jakobsen[10], Mathilde Jalving[11], Cristina Oprean[12], Marketa Palácová[13], Yeon Hee Park[14], Yaroslav Shparyk[15], Eduardo Yañez[16], Matthew Dudley[17], Christine K. Ratajczak[17], David Maag[17], Banu K. Arun[18]

[1]Institut Curie, Paris, and Centre Eugène Marquis, Rennes, France; [2]Moffitt Cancer Center, Tampa, FL, USA; [3]Sheba Medical Center, Tel Hashomer, Israel; [4]Department of General Medical Oncology, University Hospitals Leuven, Leuven, Belgium; [5]Prince of Wales Clinical School UNSW and Prince of Wales Hospital, Sydney, Australia; [6]Centre hospitalier de l'Université de Montréal, Montreal, QC, Canada; [7]UPMC Cancer Centers, Pittsburgh, PA, USA; [8]Dnipropetrovsk Medical Academy, City Hospital No.4, Dnipro, Ukraine; [9]Institut de Cancérologie de l'Ouest - Pays de la Loire, France; [10]Vejle Hospital/Lillebaelt Hospital, Vejle, Denmark; [11]University Medical Center Groningen, University of Groningen, Groningen, The Netherlands; [12]University of Medicine and Pharmacy Timisoara; Oncomed SRL, Timisoara, Romania; [13]Masaryk Memorial Cancer Institute, Brno, Czech Republic; [14]Samsung Medical Center, Seoul, Korea; [15]Lviv State Regional Treatment and Diagnostic Oncology Center, Lviv, Ukraine; [16]Universidad de la Frontera, Temuco, Chile; [17]AbbVie Inc., North Chicago, IL, USA; [18]The University of Texas M.D. Anderson Cancer Center, Houston, TX, USA

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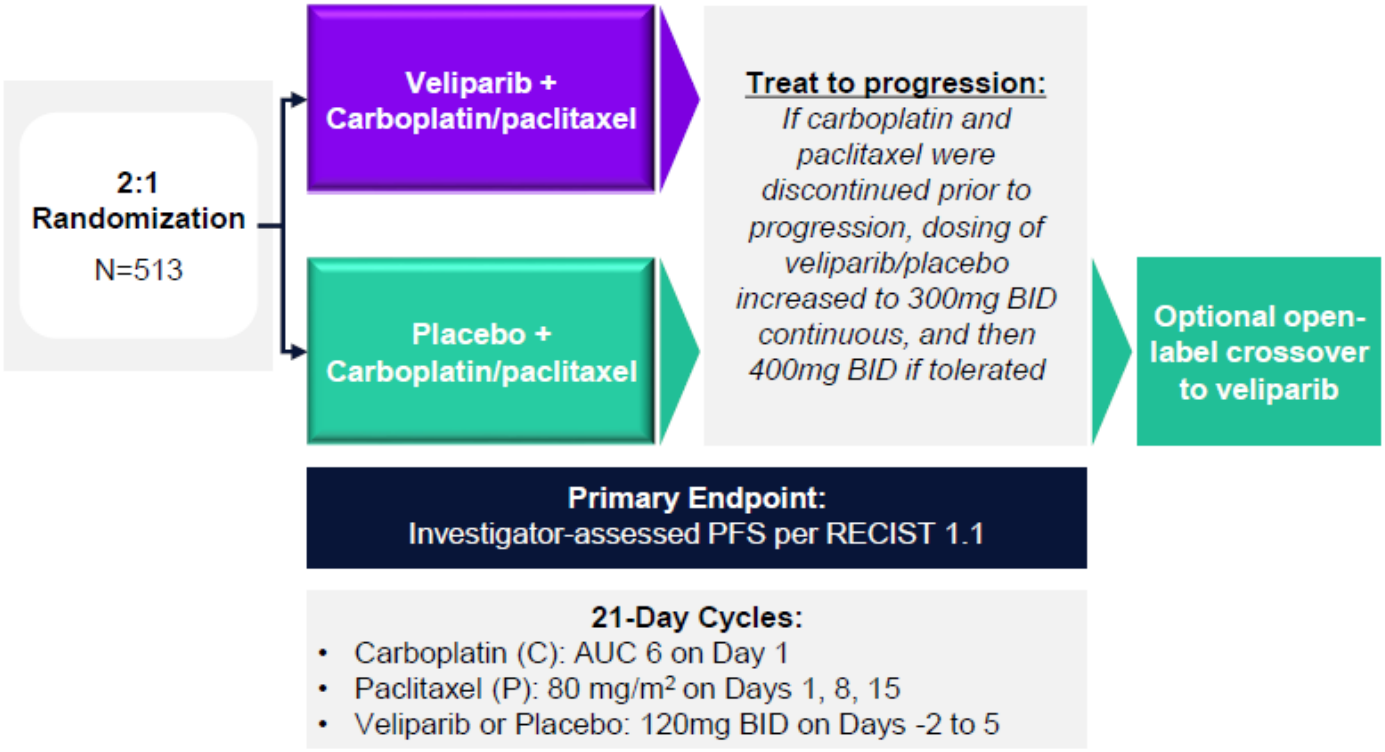
# **Study Design:** BROCADE3 (NCT02163694)

**Patient Population**

- Advanced HER2-negative breast cancer
- Germline *BRCA1* or *BRCA2* mutation
- ≤2 prior lines cytotoxic therapy for metastatic disease
- ≤1 prior lines of platinum; no progression ≤12 months of completing

**Stratification Factors**

- Hormone Receptor Expression
- Prior Platinum
- CNS Metastasis

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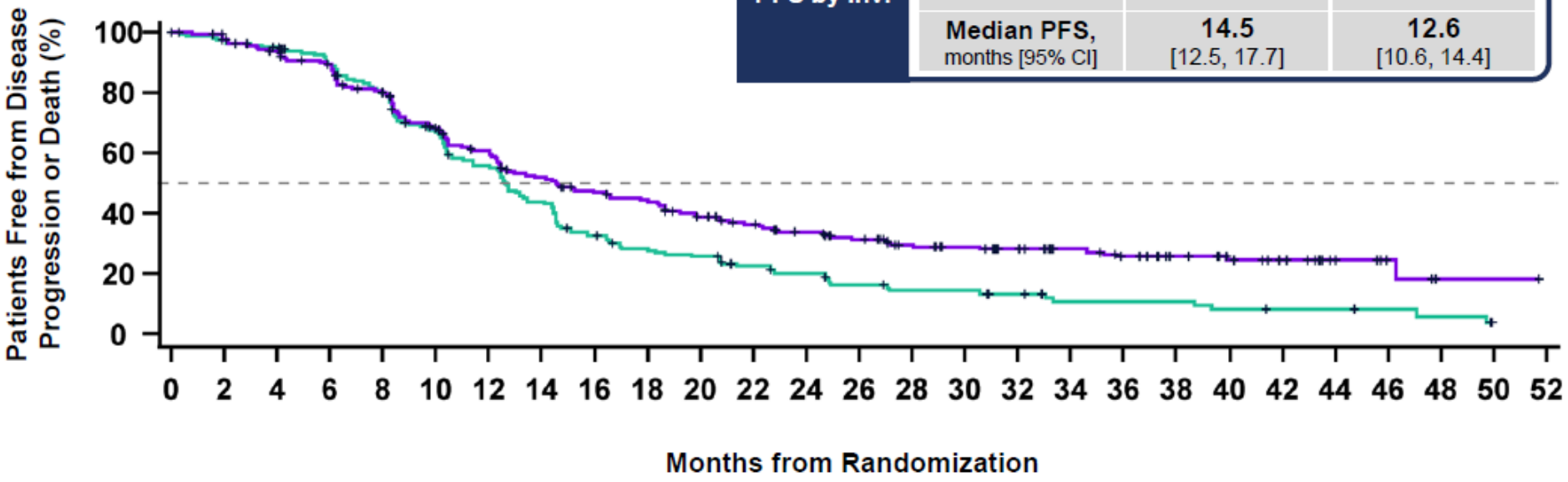
# Primary Endpoint: PFS by Investigator Assessment

**HR 0.705**
[95% CI 0.566-0.877], p = 0.002

**PFS by Inv.**

| | Veliparib + C/P | Placebo + C/P |
|---|---|---|
| PFS Events, n/N | 217/337 | 132/172 |
| **Median PFS,** months [95% CI] | **14.5** [12.5, 17.7] | **12.6** [10.6, 14.4] |




No. at Risk

| | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Control | 172 | 160 | 153 | 140 | 123 | 99 | 82 | 64 | 47 | 39 | 35 | 27 | 23 | 18 | 15 | 15 | 12 | 8 | 8 | 8 | 6 | 5 | 5 | 4 | 3 | 0 | |
| Veliparib | 337 | 316 | 301 | 282 | 250 | 207 | 181 | 154 | 137 | 126 | 107 | 92 | 81 | 72 | 60 | 51 | 45 | 38 | 32 | 25 | 20 | 16 | 8 | 4 | 1 | 1 | 0 |

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C/P: Carboplatin and Paclitaxel

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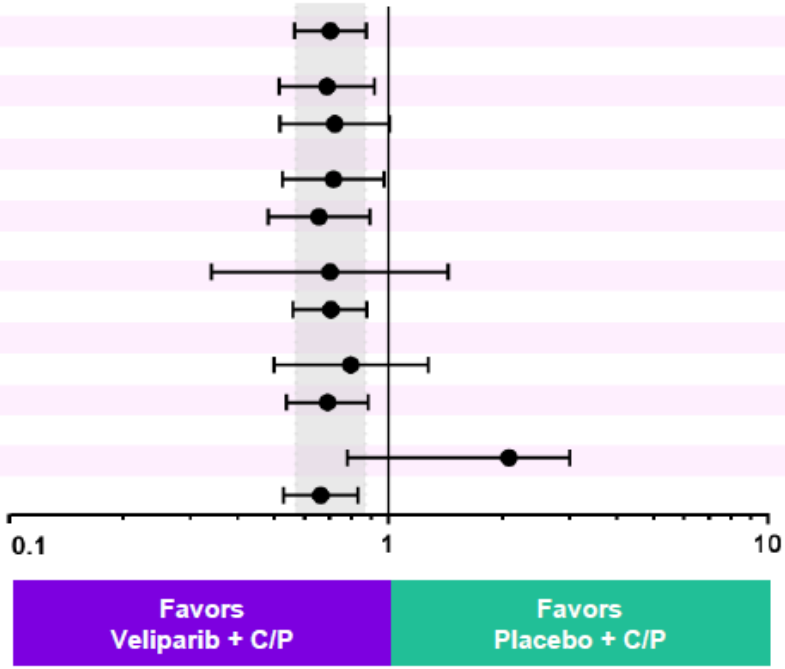
# PFS Subgroup Analysis (Investigator-Assessed)

| Subgroup | Veliparib+C/P | Placebo+C/P | Hazard Ratio for Disease Progression or Death (95% CI) |
|---|---|---|---|
| | *No. of patients with events/total* | | |
| **All patients** | 217/337 | 132/172 | 0.70 (0.57, 0.87) |
| **Hormone receptor status** | | | |
| ER positive and/or PgR positive | 124/174 | 74/92 | 0.69 (0.52, 0.92) |
| ER negative and PgR negative (TNBC) | 93/163 | 58/80 | 0.72 (0.52, 1.01) |
| ***BRCA* status** | | | |
| *BRCA1* mutation | 113/177 | 68/89 | 0.72 (0.53, 0.97) |
| *BRCA2* mutation | 106/167 | 67/86 | 0.66 (0.48, 0.89) |
| **Prior platinum therapy** | | | |
| Prior platinum therapy | 19/27 | 14/16 | 0.70 (0.34, 1.44) |
| No prior platinum therapy | 198/310 | 118/156 | 0.71 (0.56, 0.89) |
| **Prior cytotoxic therapy for metastatic disease** | | | |
| Prior chemotherapy in metastatic setting | 46/63 | 29/33 | 0.80 (0.50, 1.27) |
| No prior chemotherapy in metastatic setting | 171/274 | 103/139 | 0.69 (0.54, 0.88) |
| **History of CNS metastases** | | | |
| Yes | 14/16 | 8/10 | 2.08 (0.78, 5.52) |
| No | 203/320 | 124/161 | 0.66 (0.53, 0.83) |

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C/P: Carboplatin and Paclitaxel

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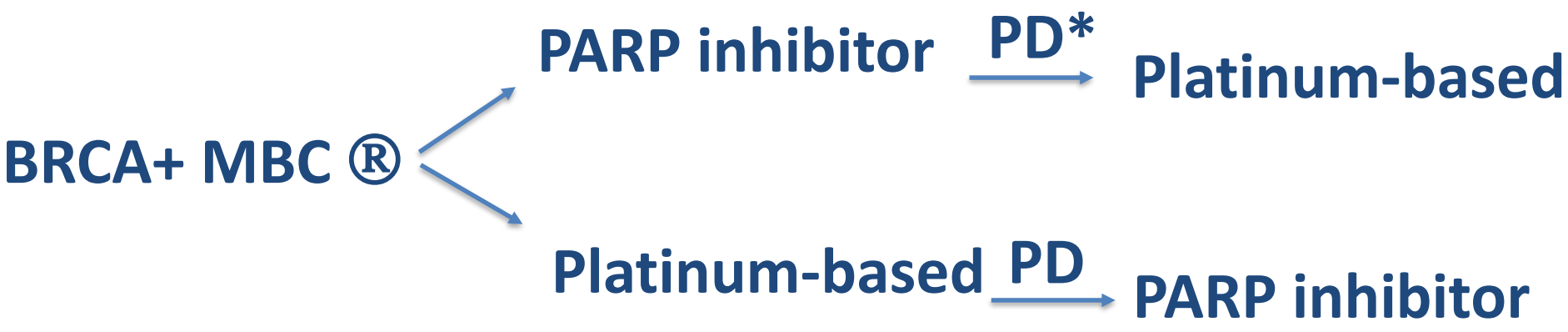
# Proposition for a clinical trial design including platinum compounds and PARP inhibitors in BRCA+ metastatic breast cancer




* Progressive disease

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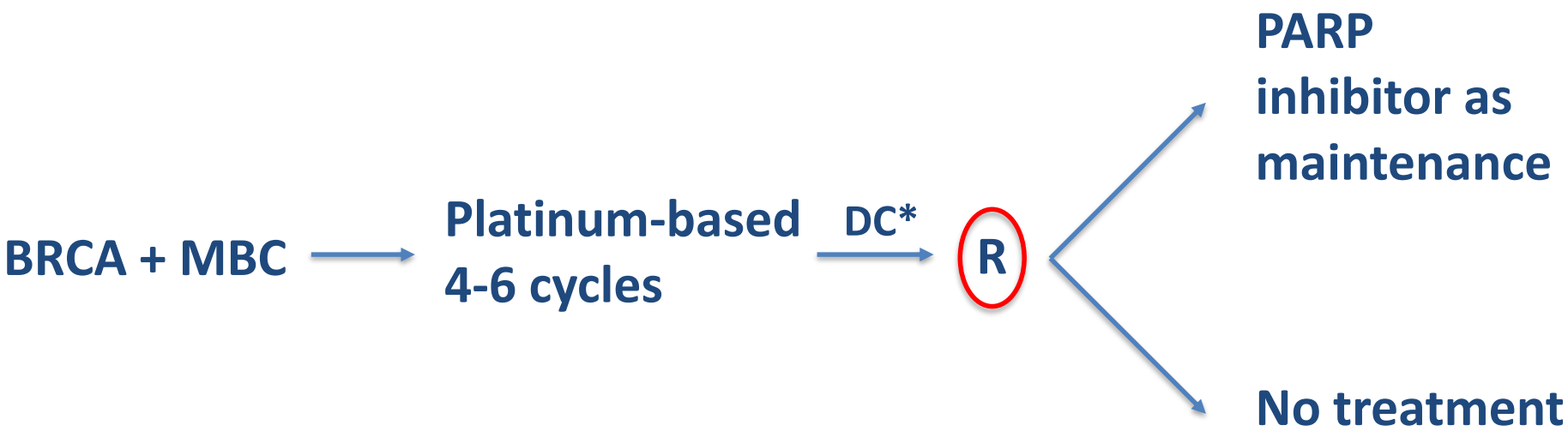
# Proposition for a clinical trial design including platinum compounds and PARP inhibitors in BRCA+ metastatic breast cancer (2)




*Disease Control

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# THANK YOU

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