THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

# Evolving Treatments for the Oncology Practice
# New Orleans Louisiana

# Target Therapy in Metastatic Breast Cancer Beyond ER/PR


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**Houston, Texas**

# Genomically-Informed Targeted Therapy

- Identifying genomic alterations that are
  - Drivers of tumor growth and progression
  - Targetable directly or indirectly with approved or investigational agents

- Mutations
  - Somatic and germline
  - SNVs and indels

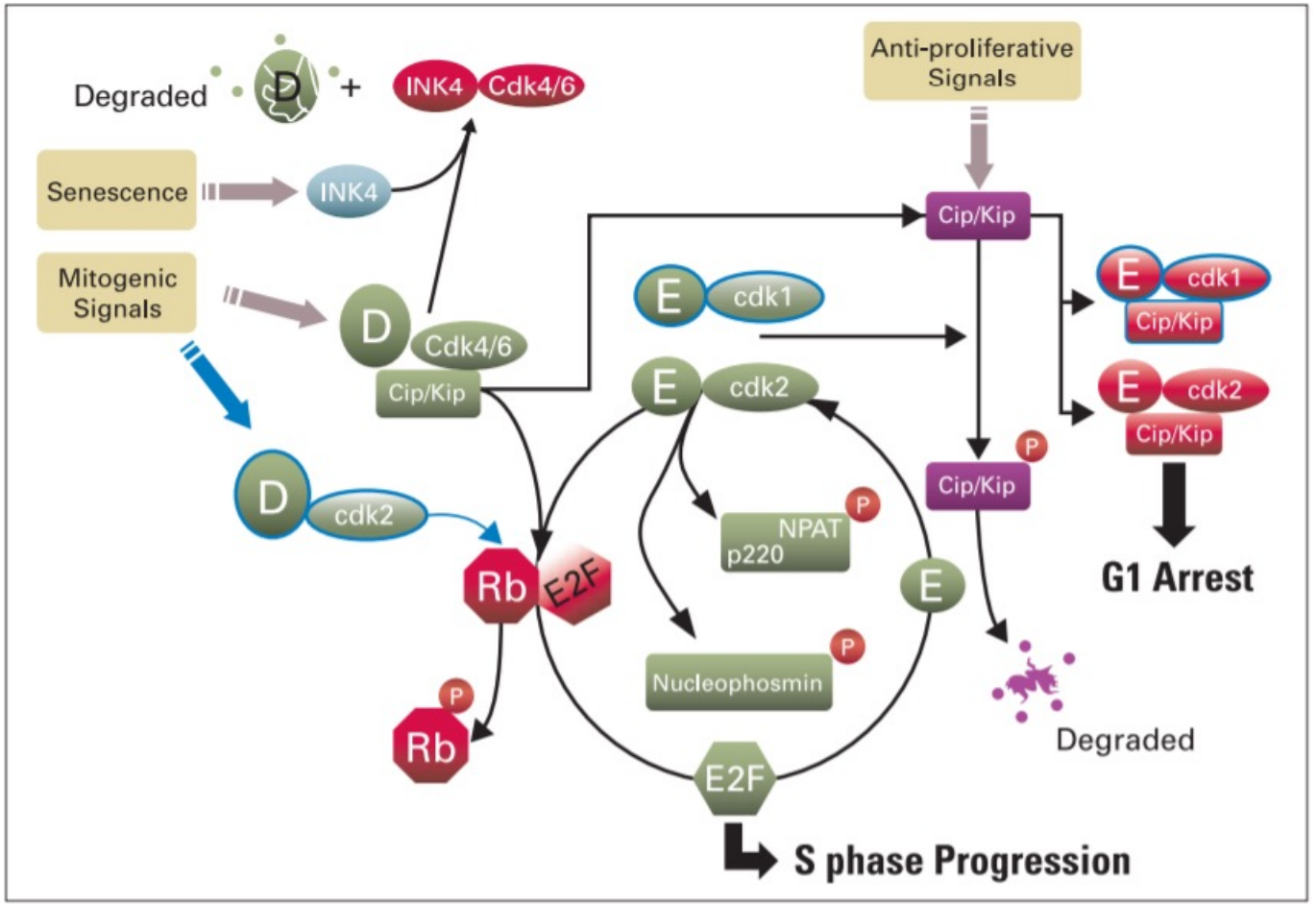
- Copy number changes
  - Amplifications/deletions

- Fusions

# Targeted Therapy in Metastatic breast cancer

- CDK4/6
- MTHOR
- PIK3CA
- BRCA
- HER-2 positive
- HER-2 low

# Cell Cycle Control in Breast Cancer and CDK Inhibition




One mechanism of resistance is the up-regulation of the CDK-cyclin D1-Rb pathway. The use of CDK4/6 inhibitors can stave off endocrine resistance by blocking phosphorylation of Rb and hence preventing cell cycle progression and inducting G1 phase arrest.



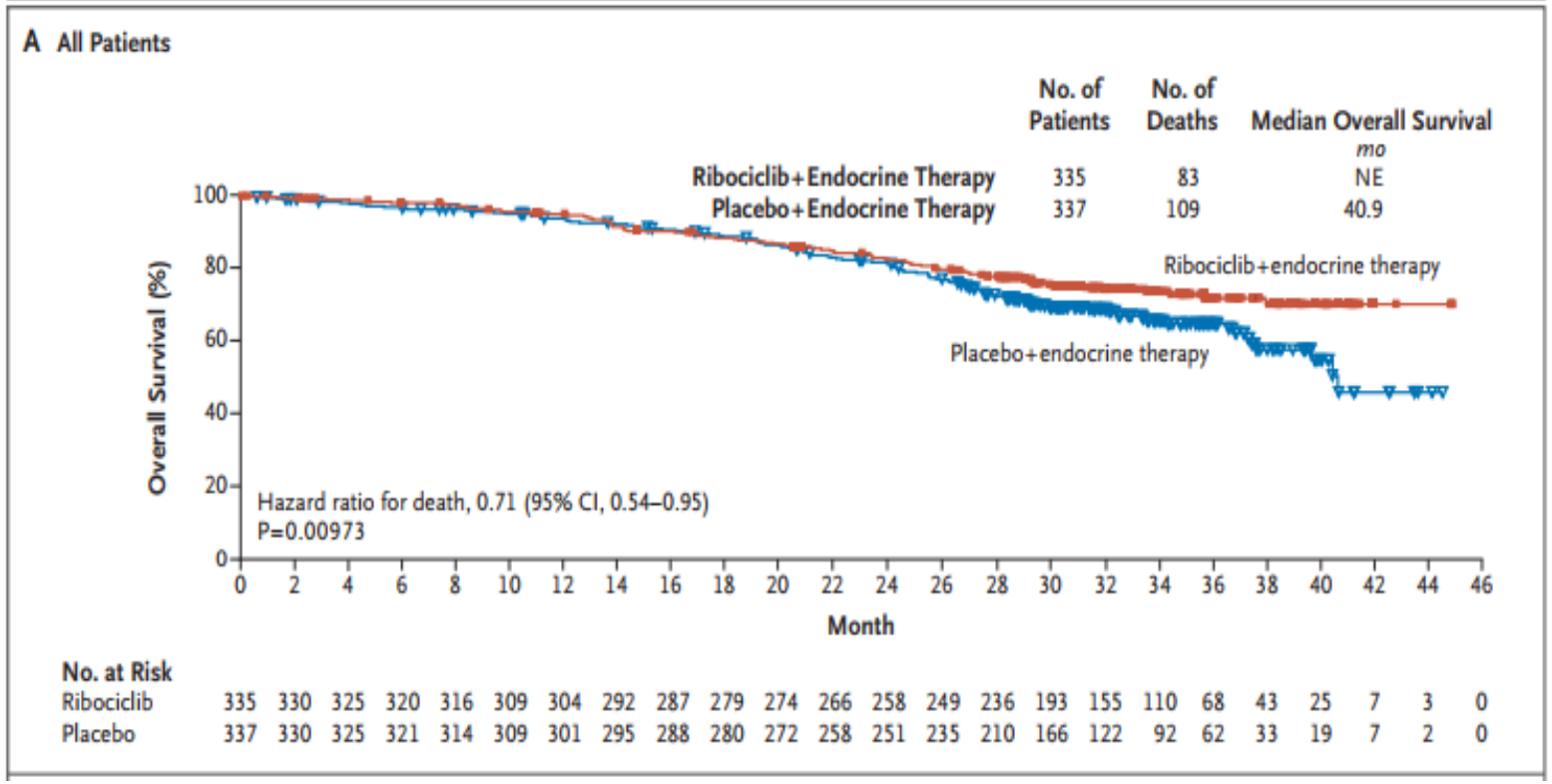
Shapiro GI. *J Clin Oncol*. 2006.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 25, 2019 VOL. 381 NO. 4

# Overall Survival with Ribociclib plus Endocrine Therapy in Breast Cancer

S.-A. Im, Y.-S. Lu, A. Bardia, N. Harbeck, M. Colleoni, F. Franke, L. Chow, J. Sohn, K.-S. Lee, S. Campos-Gomez, R. Villanueva-Vazquez, K.-H. Jung, A. Chakravartty, G. Hughes, I. Gounaris, K. Rodriguez-Lorenc, T. Taran, S. Hurvitz, and D. Tripathy



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# Overall Survival with Ribociclib plus Letrozole in Advanced Breast Cancer

Gabriel N. Hortobagyi, M.D., Salomon M. Stemmer, M.D., Howard A. Burris, M.D., Yoon-Sim Yap, M.D., Gabe S. Sonke, M.D., Ph.D., Lowell Hart, M.D., Mario Campone, M.D., Ph.D., Katarina Petrakova, M.D., Ph.D., Eric P. Winer, M.D., Wolfgang Janni, M.D., Ph.D., Pierfranco Conte, M.D., Ph.D., David A. Cameron, M.D., Fabrice André, M.D., Ph.D., Carlos L. Arteaga, M.D., Juan P. Zarate, M.D., Arunava Chakravartty, Ph.D., Tetiana Taran, M.D., Fabienne Le Gac, Ph.D., Pharm.D., Paolo Serra, M.Sc., and Joyce O'Shaughnessy, M.D.

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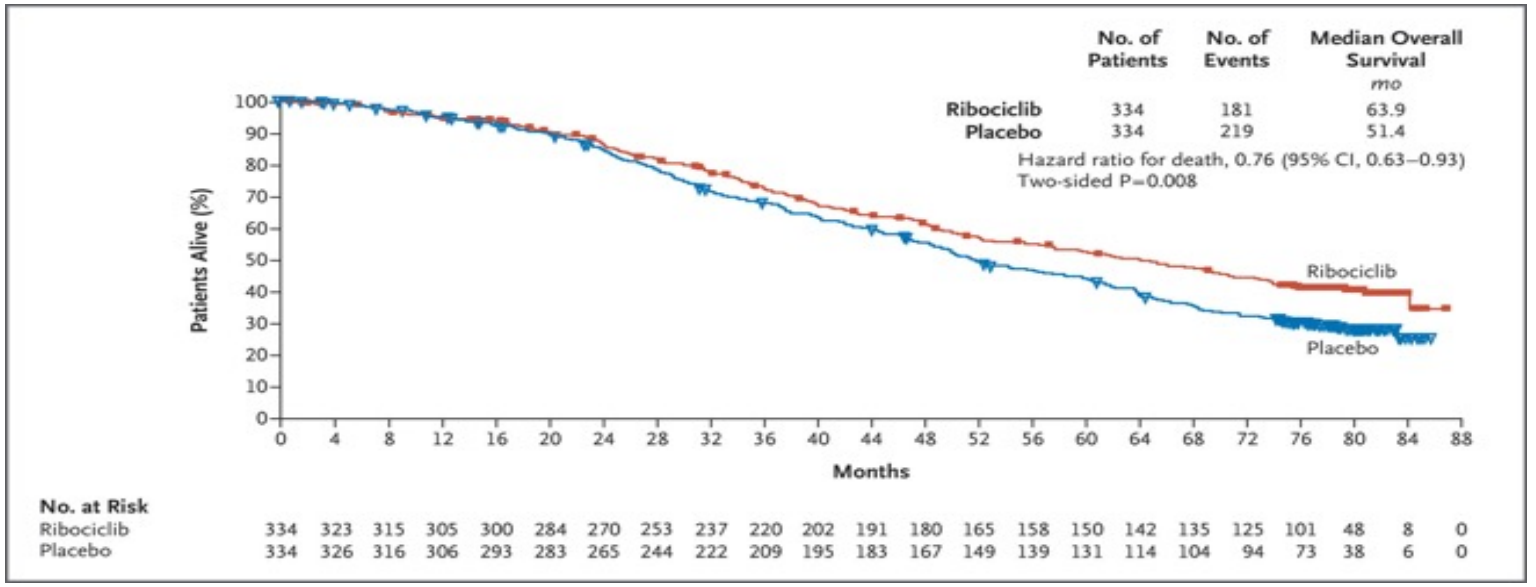
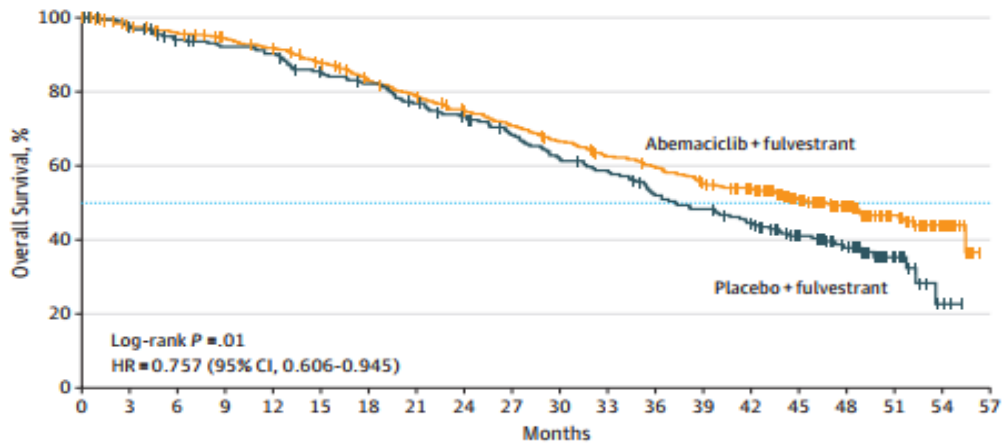


JAMA Oncology | Original Investigation

# The Effect of Abemaciclib Plus Fulvestrant on Overall Survival in Hormone Receptor–Positive, ERBB2-Negative Breast Cancer That Progressed on Endocrine Therapy—MONARCH 2
## A Randomized Clinical Trial

George W. Sledge Jr, MD; Masakazu Toi, MD, PhD; Patrick Neven, MD, PhD; Joohyuk Sohn, MD; Kenichi Inoue, MD, PhD; Xavier Pivot, MD, PhD; Olga Burdaeva, MD; Meena Okera, MD; Norikazu Masuda, MD, PhD; Peter A. Kaufman, MD; Han Koh, MD; Eva-Maria Grischke, MD; PierFranco Conte, MD; Yi Lu, PhD; Susana Barriga, PhD; Karla Hurt, BSN; Martin Frenzel, PhD; Stephen Johnston, MD, PhD; Antonio Llombart-Cussac, MD, PhD

Figure 2. Kaplan-Meier Curve of Overall Survival in the Intent-to-Treat Population




No. at risk

| | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Abemaciclib + fulvestrant | 446 | 422 | 410 | 397 | 384 | 364 | 339 | 321 | 302 | 284 | 265 | 246 | 234 | 214 | 202 | 157 | 101 | 58 | 23 | 0 |
| Placebo + fulvestrant | 223 | 214 | 201 | 195 | 191 | 178 | 170 | 158 | 148 | 135 | 122 | 115 | 99 | 92 | 82 | 62 | 42 | 15 | 3 | 0 |

The number of events in the abemaciclib plus fulvestrant arm was 211 vs 127 in the placebo plus fulvestrant arm. Median overall survival in the abemaciclib plus fulvestrant arm was 46.7 months vs 37.3 months in the placebo plus fulvestrant arm. HR indicates hazard ratio.

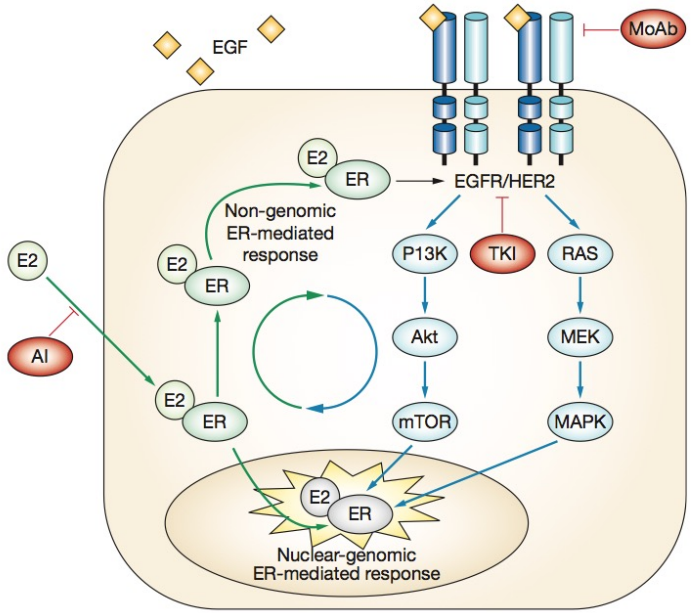
# Conclusions:
# CDK4/6 Inhibitors in ER+ MBC

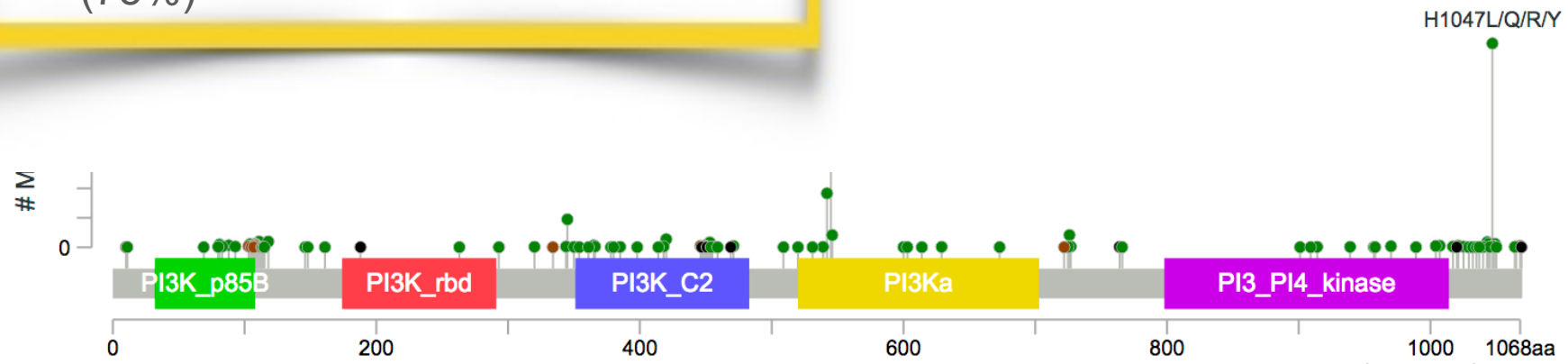
- CDK4/6 inhibitors, palbociclib, ribociclib and abemaciclib,  seem to be consistent and comparable in prolonging PFS in combination with endocrine therapy in the metastatic setting with acceptable toxicity.

- Ribociclib and abemaciclib showed significant improvement in overall survival in first and second line therapy, and second line, respectively.

# Targeting of downstream signaling pathways such as mTOR and PI3K

- PI3K/mTOR/Akt pathway involved in tumor growth and survival
- PIK3CA most common oncogenic mutation in BC
- Mutations in 30-35% of HR positive BC
- Implicated in resistance to endocrine and chemotherapy
- Commonly seen in metaplastic BC (75%)



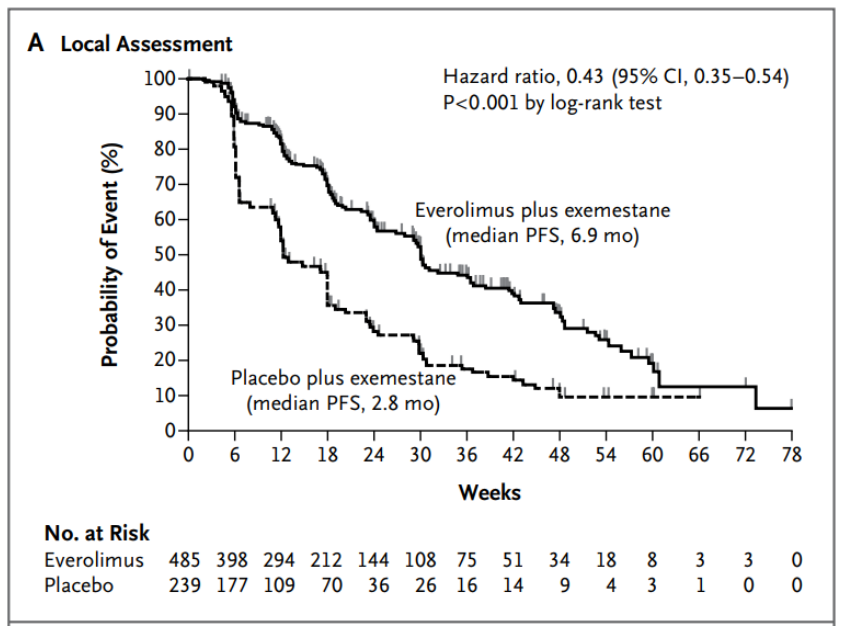

Source: cbioportal

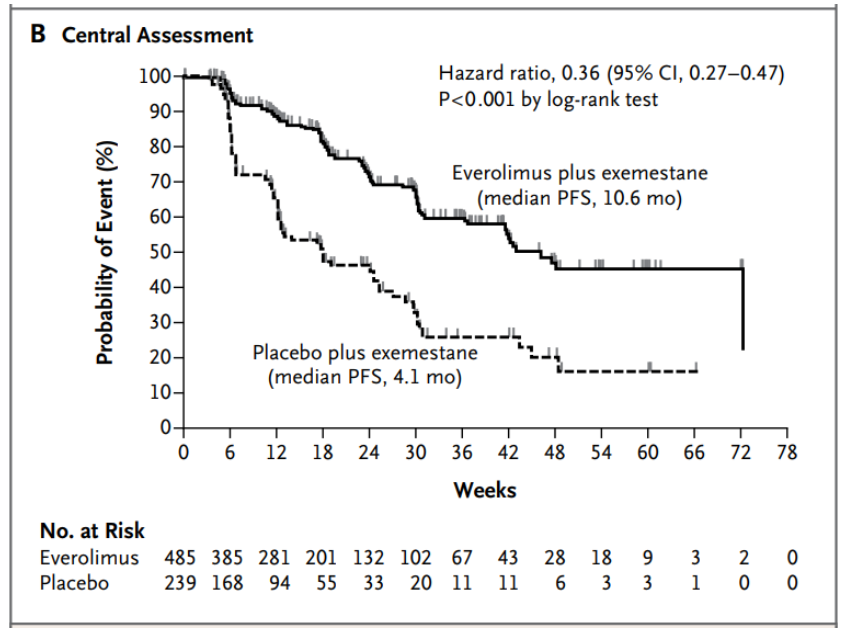
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# Everolimus in Postmenopausal Hormone-Receptor–Positive Advanced Breast Cancer

José Baselga, M.D., Ph.D., Mario Campone, M.D., Ph.D., Martine Piccart, M.D., Ph.D., Howard A. Burris III, M.D., Hope S. Rugo, M.D., Tarek Sahmoud, M.D., Ph.D., Shinzaburo Noguchi, M.D., Michael Gnant, M.D., Kathleen I. Pritchard, M.D., Fabienne Lebrun, M.D., J. Thaddeus Beck, M.D., Yoshinori Ito, M.D., Denise Yardley, M.D., Ines Deleu, M.D., Alejandra Perez, M.D., Thomas Bachelot, M.D., Ph.D., Luc Vittori, M.Sc., Zhiying Xu, Ph.D., Pabak Mukhopadhyay, Ph.D., David Lebwohl, M.D., and Gabriel N. Hortobagyi, M.D.



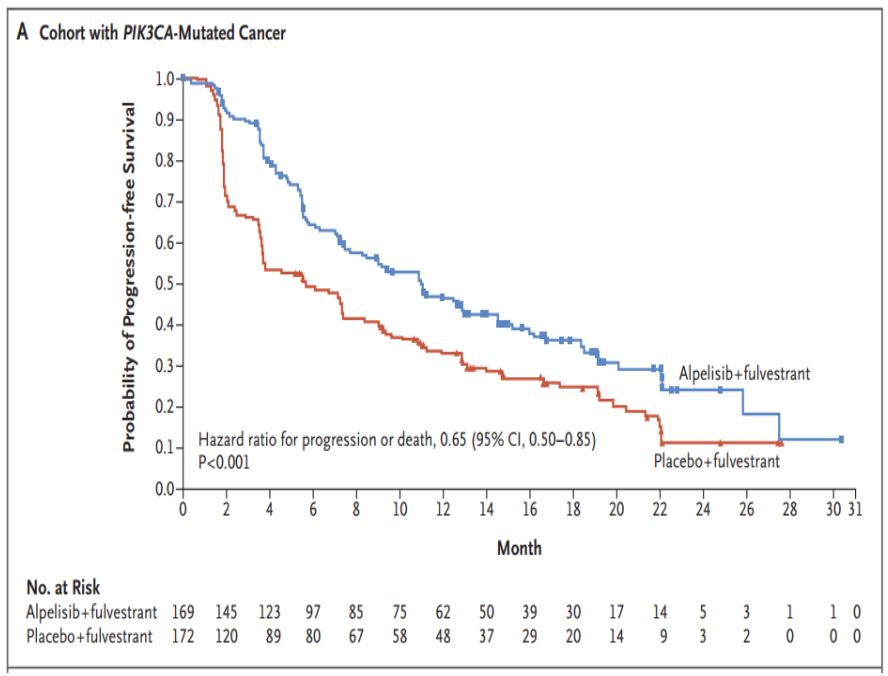



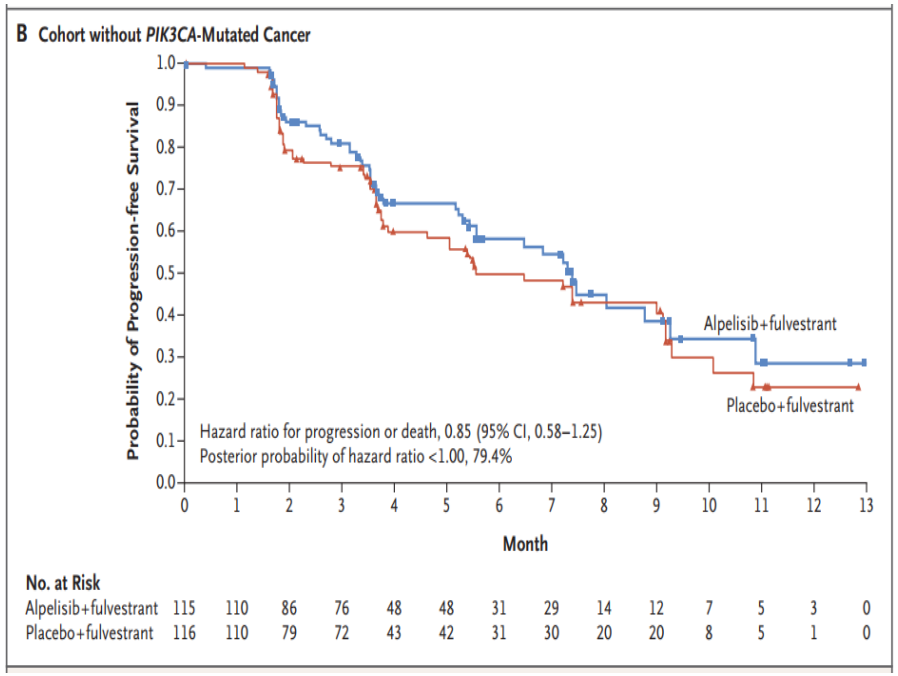
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

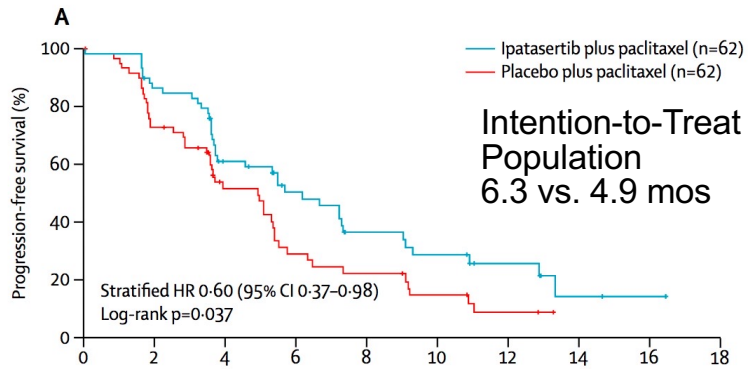
# Alpelisib for *PIK3CA*-Mutated, Hormone Receptor–Positive Advanced Breast Cancer

F. André, E. Ciruelos, G. Rubovszky, M. Campone, S. Loibl, H.S. Rugo, H. Iwata, P. Conte, I.A. Mayer, B. Kaufman, T. Yamashita, Y.-S. Lu, K. Inoue, M. Takahashi, Z. Pápai, A.-S. Longin, D. Mills, C. Wilke, S. Hirawat, and D. Juric, for the SOLAR-1 Study Group*

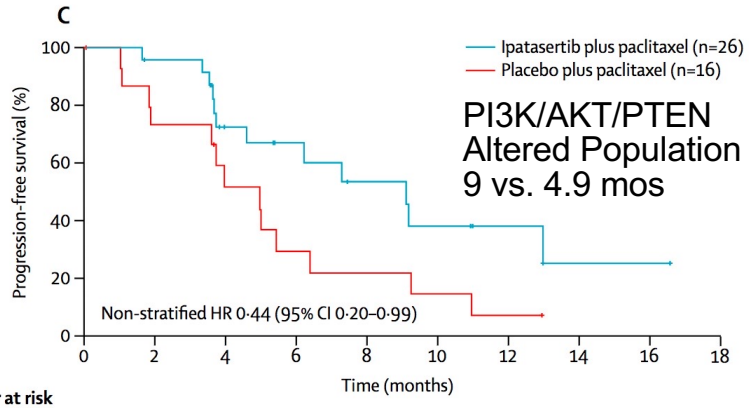


# Ipatasertib plus paclitaxel versus placebo plus paclitaxel as first-line therapy for metastatic triple-negative breast cancer (LOTUS): a multicentre, randomised, double-blind, placebo-controlled, phase 2 trial




| Number at risk (number censored) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Ipatasertib plus paclitaxel | 62 | 50 (4) | 31 (9) | 22 (13) | 14 (15) | 11 (15) | 6 (19) | 2 (21) | 1 (22) | 0 (23) |
| Placebo plus paclitaxel | 62 | 43 (3) | 23 (12) | 13 (12) | 10 (12) | 6 (13) | 3 (14) | 0 (17) | | |




| Number at risk (number censored) | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Ipatasertib plus paclitaxel | 26 | 22 (3) | 13 (7) | 10 (9) | 7 (10) | 5 (10) | 3 (12) | 1 (13) | 1 (13) | 0 (14) |
| Placebo plus paclitaxel | 16 | 11 (1) | 7 (2) | 4 (2) | 3 (2) | 2 (2) | 1 (2) | 0 (3) | | |

| | Intention-to-treat population | | PTEN-low subgroup by Immunohistochemistry | | *PIK3CA/AKT1/PTEN*-altered subgroup by next-generation sequencing | |
|---|---|---|---|---|---|---|
| | Ipatasertib plus paclitaxel (n=62) | Placebo plus paclitaxel (n=62) | Ipatasertib plus paclitaxel (n=25) | Placebo plus paclitaxel (n=23) | Ipatasertib plus paclitaxel (n=26) | Placebo plus paclitaxel (n=16) |
| Objective response | 25 (40%) | 20 (32%) | 12 (48%) | 6 (26%) | 13 (50%) | 7 (44%) |
| Duration of response (months) | 7·9 (5·6–NA) | 7·4 (3·9–9·2) | 6·5 (4·4–NA) | 7·5 (7·3–NA) | 11·2 (5·6–NA) | 6·1 (3·8–7·6) |
| Clinical benefit | 30 (48%) | 23 (37%) | 14 (56%) | 7 (30%) | 14 (54%) | 7 (44%) |

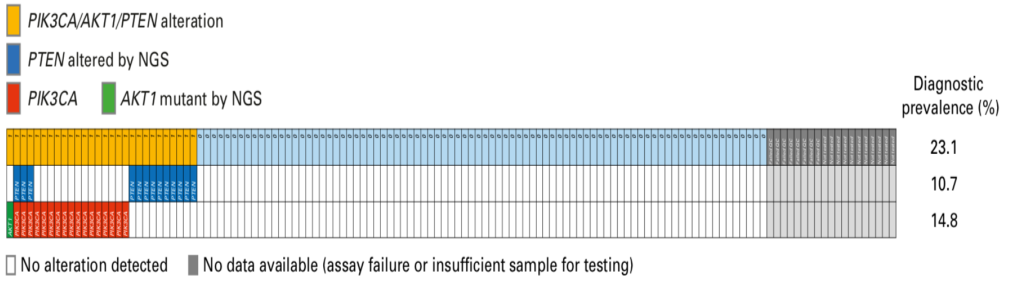
**Phase III 1st line IPATunity130 in PI3K/AKT1/PTEN Altered HER2- MBC Recruiting**

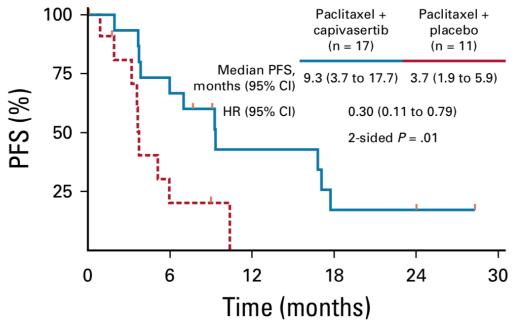
*Kim S-B et al. Lancet Oncology 2017*

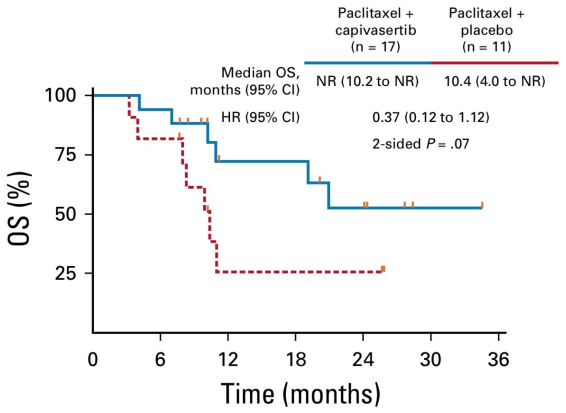
# Capivasertib in TNBC

## Capivasertib plus paclitaxel vs. paclitaxel

- Metastatic TNBC (ER/PR <1%)
- First line MBC, 140 patients, 1:1
- No taxane < 12 months
- PFS 5.9 vs.4.2. OS 19 vs. 12.6 months
- PFS 9.3 vs. 3.7months in PIK3CA/AKT1/PTEN mutations
- G3 -Diarrhea 13%, Rash 4%




Schmid et al. 2019

# PI3K/mTHOR/AKT inhibition: Summary

- The addition of everolimus to fulvestrant or exemestane ortamoxifen results in a significant improvement in PFS, and is standard option in patients who progress on CDK 4/6 inhibition.
- Everolimus is also an active agent in ER+ hormonal therapy resistant MBC
- Alpelisib, showed significant improvements in RR and PFS, and is now FDA approved for PIK3CAm ER+ breast cancer
- Activity of akt inhibitors with endocrine therapy and with chemotherapy appears promising results including PFS and OS from phase II data in patients with ER+ and TNBC respectively, and will need to await registrational studies

# AKT Inhibitors in TNBC

- LOTUS (ipatasertib): modest, but significant improvement in PFS in ITT population with trend for improvement in OS
- PAKT (Capivasertib): significant ~6 month improvement in OS in ITT population with trend for improvement in PFS
- Both studies demonstrated statistically significant (as well as clinically relevant) improvements in PFS in PI3K pathway altered tumors identified using NGS
- Toxicity considerations: substantially higher rates of diarrhea; also rash and fatigue
- Randomized phase III trials, IPATunity (NCT # 03337724) is underway
- Encouraging activity seen in AKT-immunotherapy based therapy in TNBC
- FAIRLANE trial, ipatasertib-based neoadjuvant shows high pCR rate

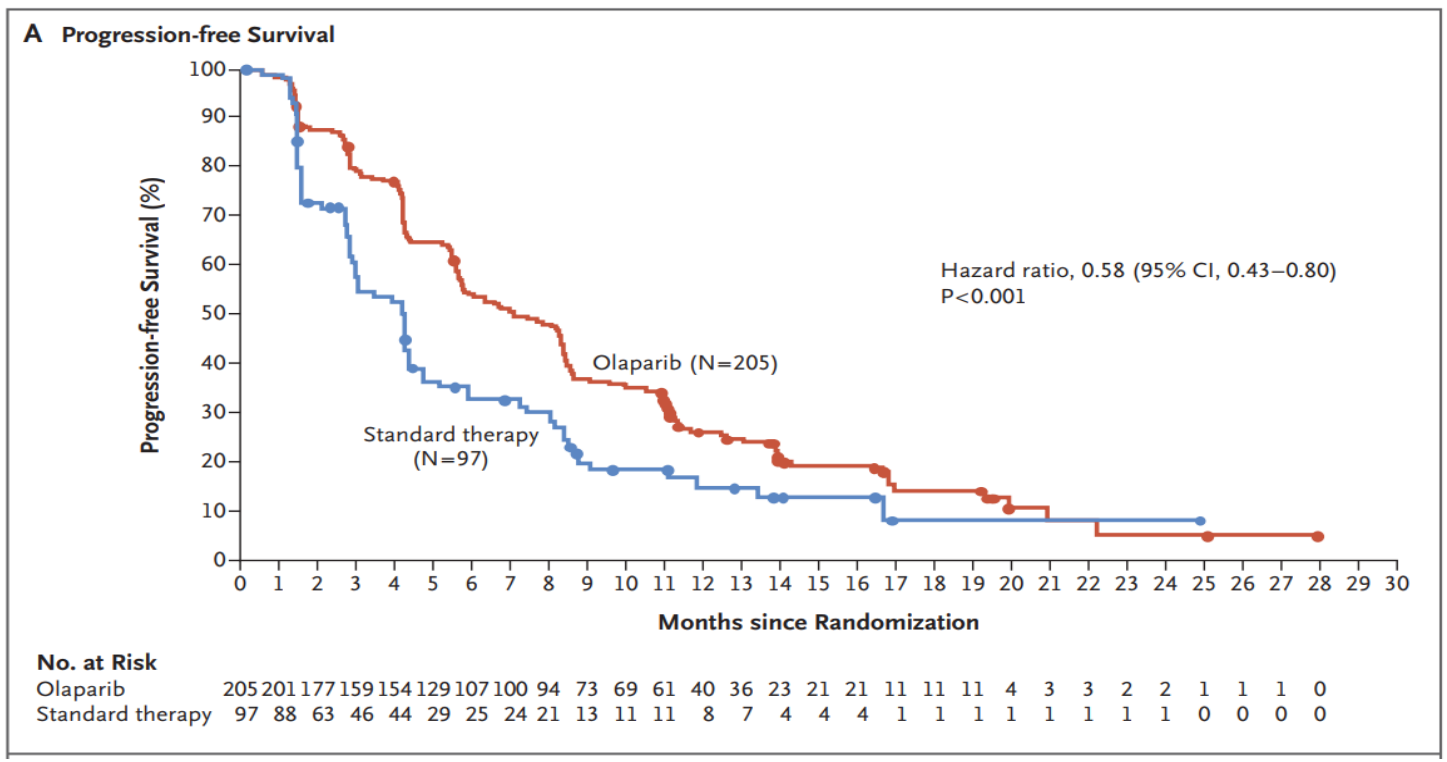
# PARP Inhibitors

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# Olaparib for Metastatic Breast Cancer in Patients with a Germline *BRCA* Mutation

Mark Robson, M.D., Seock-Ah Im, M.D., Ph.D., Elżbieta Senkus, M.D., Ph.D., Binghe Xu, M.D., Ph.D., Susan M. Domchek, M.D., Norikazu Masuda, M.D., Ph.D., Suzette Delaloge, M.D., Wei Li, M.D., Nadine Tung, M.D., Anne Armstrong, M.D., Ph.D., Wenting Wu, Ph.D., Carsten Goessl, M.D., Sarah Runswick, Ph.D., and Pierfranco Conte, M.D.

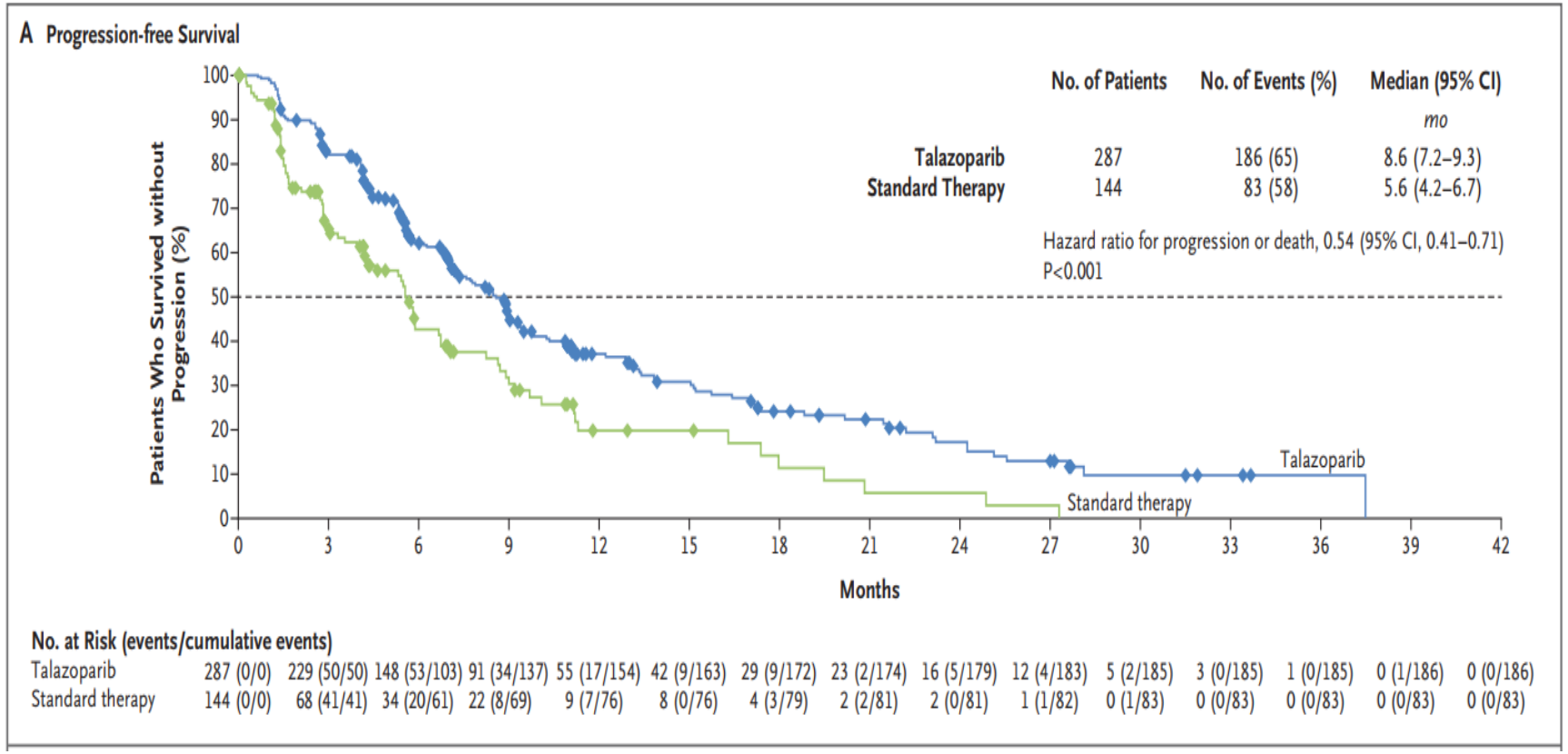


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# Talazoparib in Patients with Advanced Breast Cancer and a Germline *BRCA* Mutation

Jennifer K. Litton, M.D., Hope S. Rugo, M.D., Johannes Ettl, M.D., Sara A. Hurvitz, M.D., Anthony Gonçalves, M.D., Ph.D., Kyung-Hun Lee, M.D., Ph.D., Louis Fehrenbacher, M.D., Rinat Yerushalmi, M.D., Lida A. Mina, M.D., Miguel Martin, M.D., Ph.D., Henri Roché, M.D., Ph.D., Young-Hyuck Im, M.D., Ph.D., Ruben G.W. Quek, Ph.D., Denka Markova, Ph.D., Iulia C. Tudor, Ph.D., Alison L. Hannah, M.D., Wolfgang Eiermann, M.D., and Joanne L. Blum, M.D., Ph.D.



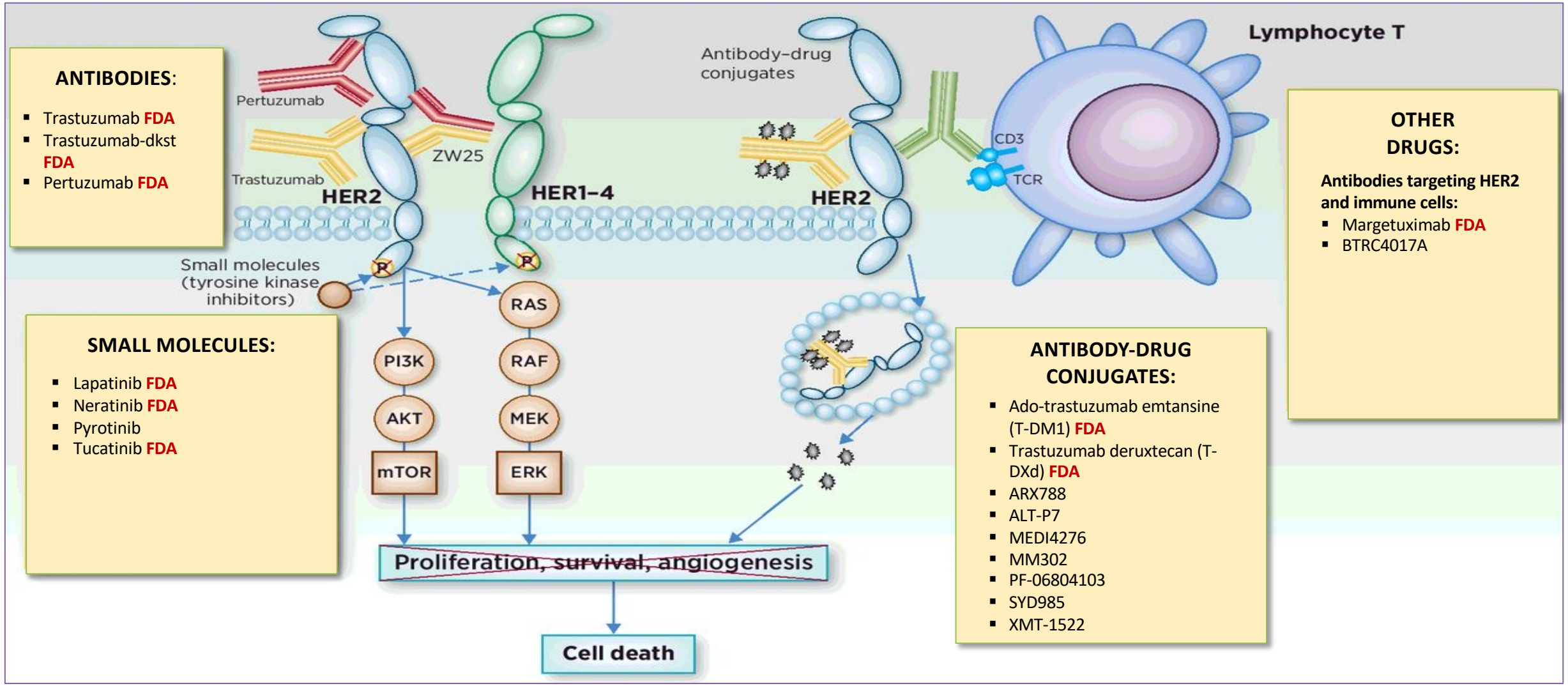
# ASCO Guidelines

***Recommendation 9.1***

For *BRCA1/2* mutation carriers with metastatic human epidermal growth factor receptor 2 (HER2) –negative breast cancer, olaparib or talazoparib should be offered as an alternative to chemotherapy in the first- to third-line settings. For *BRCA1/2* mutation carriers with metastatic HER2-negative breast cancer, there are no data directly comparing efficacy of poly (ADP-ribose) polymerase (PARP) inhibitors with platinum chemotherapy (Type: evidence based; Evidence quality: high; Strength of recommendation: strong).

Tung et al. Journal of Clinical Oncology, 2020 vol 38 (18):2080-2106.

# Agents in HER2+ MBC




**ANTIBODIES**:

- Trastuzumab **FDA**
- Trastuzumab-dkst **FDA**
- Pertuzumab **FDA**

**SMALL MOLECULES:**

- Lapatinib **FDA**
- Neratinib **FDA**
- Pyrotinib
- Tucatinib **FDA**

**ANTIBODY-DRUG CONJUGATES:**

- Ado-trastuzumab emtansine (T-DM1) **FDA**
- Trastuzumab deruxtecan (T-DXd) **FDA**
- ARX788
- ALT-P7
- MEDI4276
- MM302
- PF-06804103
- SYD985
- XMT-1522

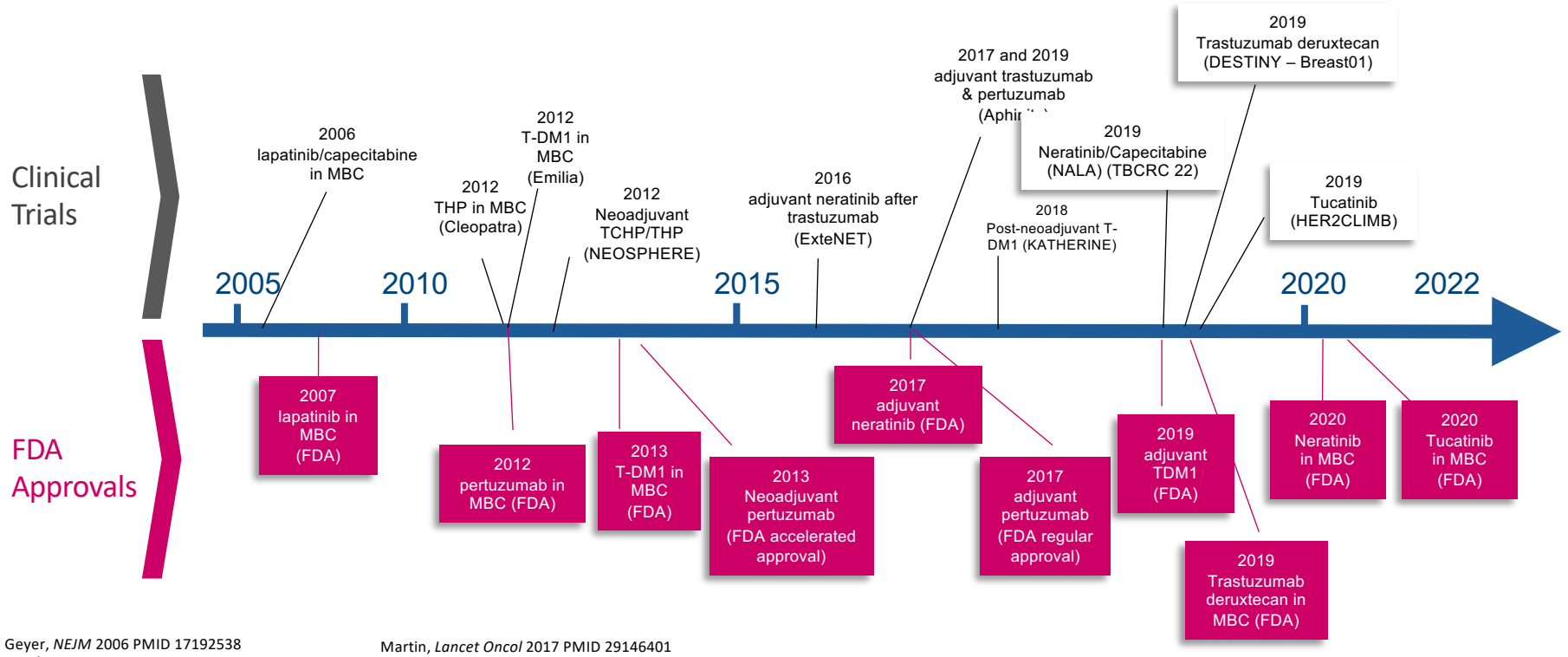
**OTHER DRUGS:**

**Antibodies targeting HER2 and immune cells:**

- Margetuximab **FDA**
- BTRC4017A

Modified from CCR Reviews 2018

# HER2+ BC: A rapidly changing landscape...





Geyer, *NEJM* 2006 PMID 17192538
Baselga, *NEJM* 2012 PMID 22149875
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Chan, *Lancet Oncol* 2016 PMID 26874901

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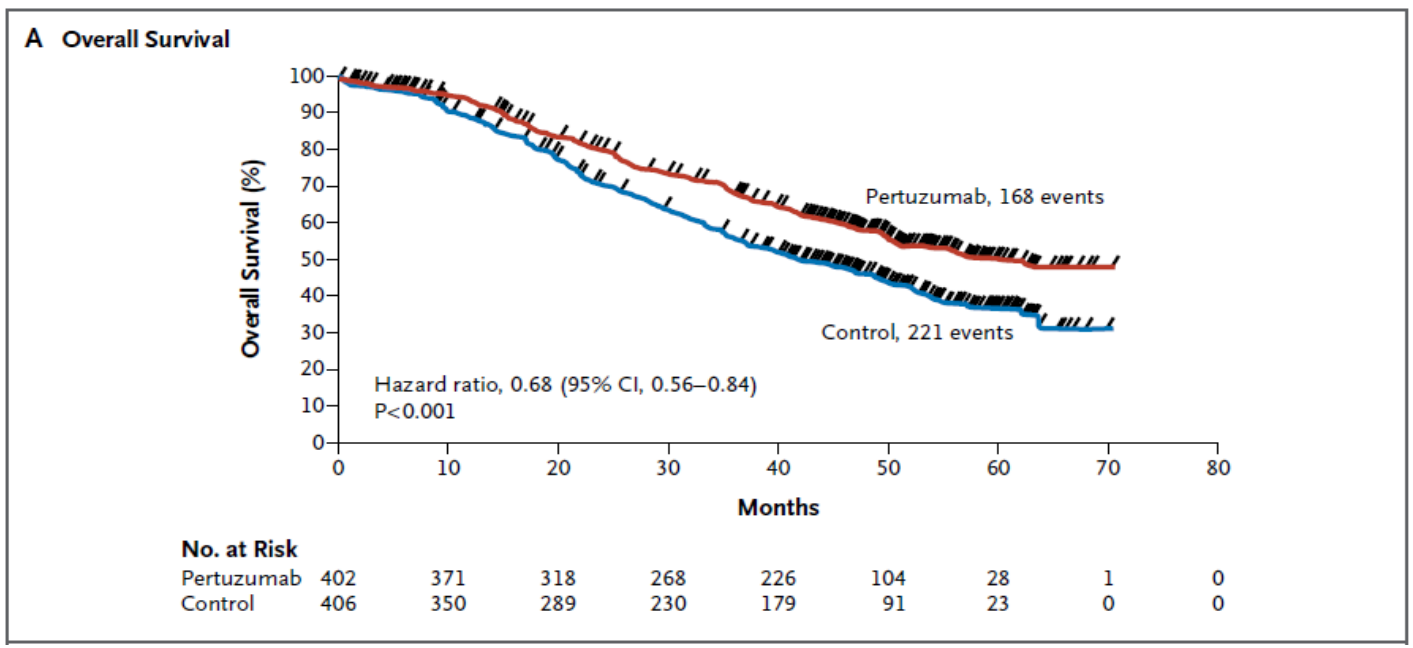
Modi, *NEJM* 2019 PMID: 31825192
Murthy, *NEJM* 2019 PMID: 31825569
Lin, *JCO* 2020 PMID: 32468955

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# Pertuzumab, Trastuzumab, and Docetaxel in HER2-Positive Metastatic Breast Cancer

Sandra M. Swain, M.D., José Baselga, M.D., Sung-Bae Kim, M.D., Jungsil Ro, M.D., Vladimir Semiglazov, M.D., Mario Campone, M.D., Eva Ciruelos, M.D., Jean-Marc Ferrero, M.D., Andreas Schneeweiss, M.D., Sarah Heeson, B.Sc., Emma Clark, M.Sc., Graham Ross, F.F.P.M., Mark C. Benyunes, M.D., and Javier Cortés, M.D., for the CLEOPATRA Study Group*

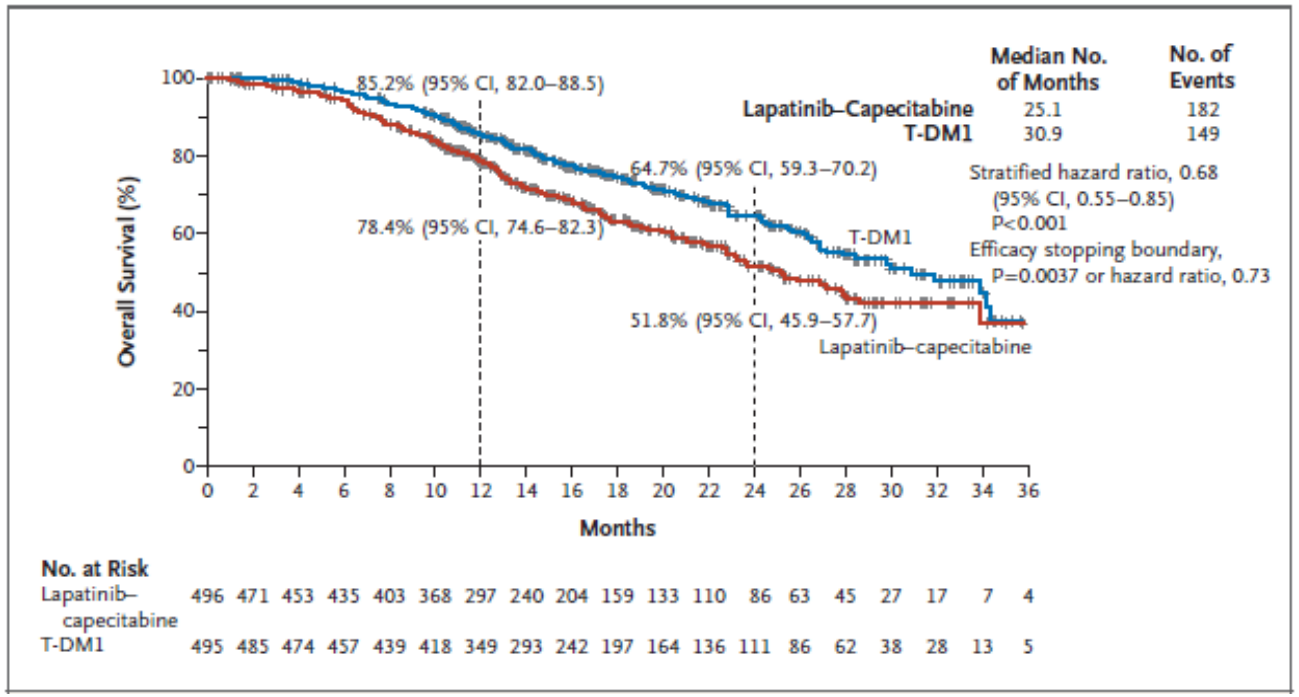


The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 8, 2012 VOL. 367 NO. 19

# Trastuzumab Emtansine for HER2-Positive Advanced Breast Cancer

Sunil Verma, M.D., David Miles, M.D., Luca Gianni, M.D., Ian E. Krop, M.D., Ph.D., Manfred Welslau, M.D., José Baselga, M.D., Ph.D., Mark Pegram, M.D., Do-Youn Oh, M.D., Ph.D., Véronique Diéras, M.D., Ellie Guardino, M.D., Ph.D., Liang Fang, Ph.D., Michael W. Lu, Pharm.D., Steven Olsen, M.D., Ph.D., and Kim Blackwell, M.D., for the EMILIA Study Group

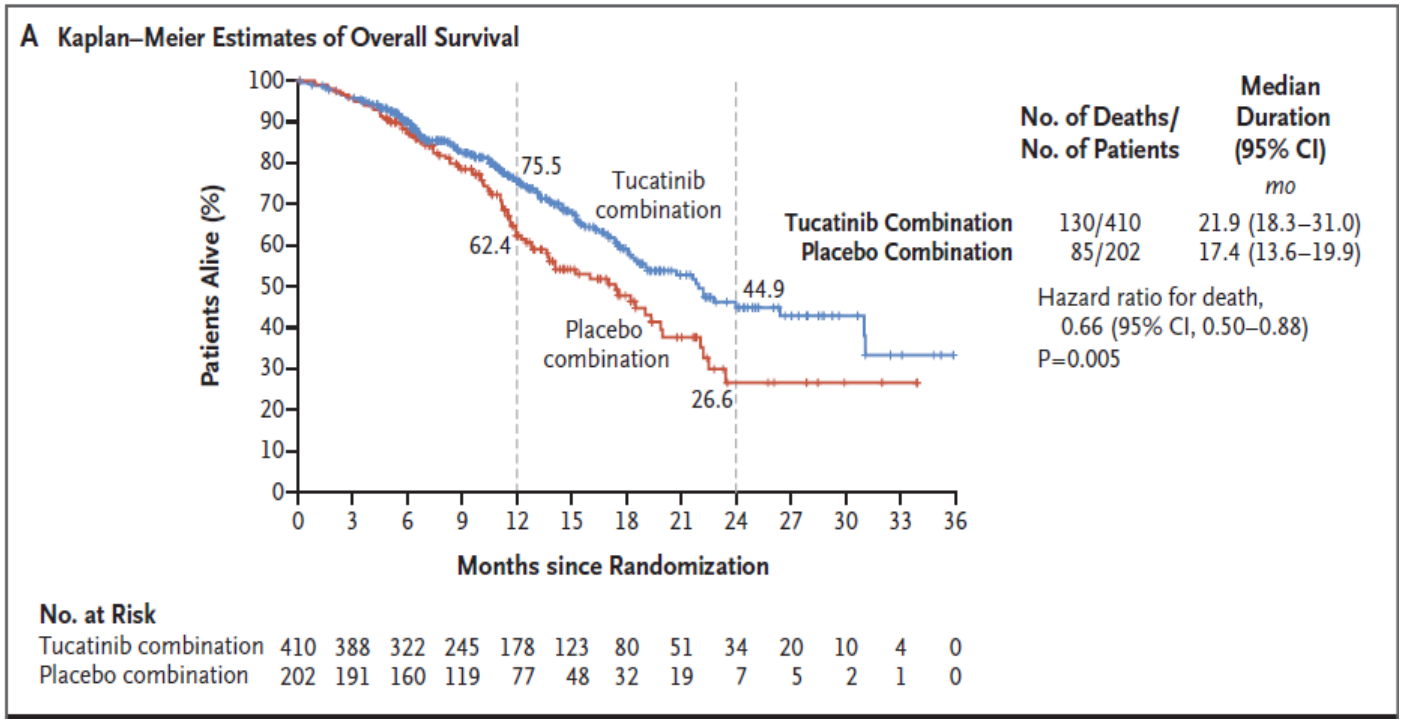


The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 13, 2020 VOL. 382 NO. 7

# Tucatinib, Trastuzumab, and Capecitabine for HER2-Positive Metastatic Breast Cancer

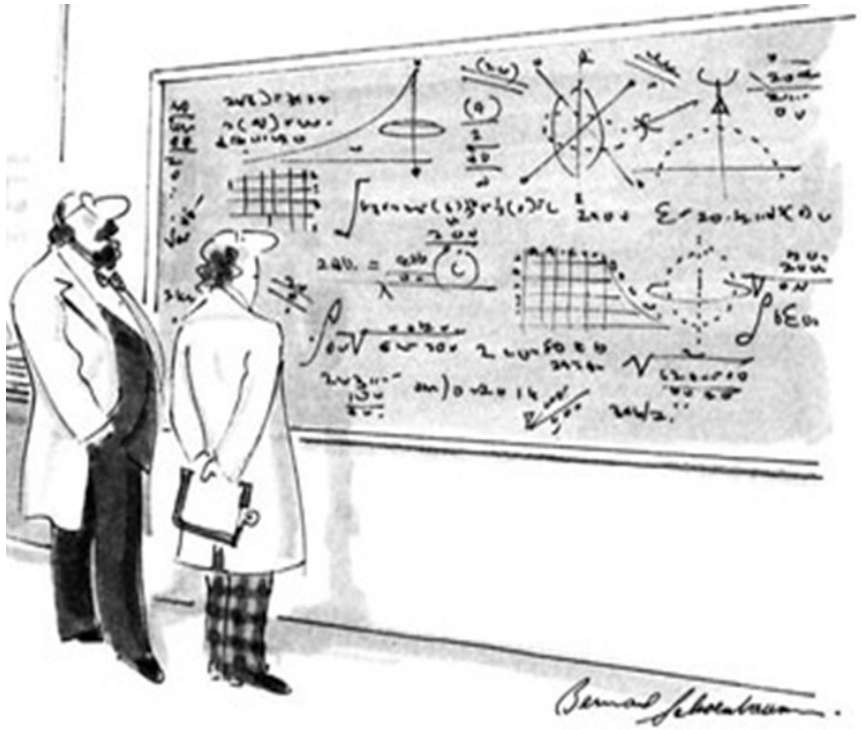
R.K. Murthy, S. Loi, A. Okines, E. Paplomata, E. Hamilton, S.A. Hurvitz, N.U. Lin, V. Borges, V. Abramson, C. Anders, P.L. Bedard, M. Oliveira, E. Jakobsen, T. Bachelot, S.S. Shachar, V. Müller, S. Braga, F.P. Duhoux, R. Greil, D. Cameron, L.A. Carey, G. Curigliano, K. Gelmon, G. Hortobagyi, I. Krop, S. Loibl, M. Pegram, D. Slamon, M.C. Palanca-Wessels, L. Walker, W. Feng, and E.P. Winer



## SYSTEMIC THERAPY REGIMENS FOR RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE[h]

| HER2-Positive | | | |
|---|---|---|---|
| **Setting** | **Regimen** | **NCCN Category of Preference** | **NCCN Category of Evidence** |
| **First line**[i] | Pertuzumab + trastuzumab + docetaxel[k] | Preferred Regimen | 1 |
| | Pertuzumab + trastuzumab + paclitaxel[k] | Preferred Regimen | 2A |
| **Second line**[j] | Fam-trastuzumab deruxtecan-nxki[j,l,m] | Preferred Regimen | 1 |
| | Ado-trastuzumab emtansine (T-DM1)[j] | Other Recommended Regimen | 2A |
| **Third line and beyond (optimal sequence is not known)** | Tucatinib + trastuzumab + capecitabine[k,n] | Other Recommended Regimen[n] | 1 |
| | Trastuzumab + docetaxel or vinorelbine[k,o] | Other Recommended Regimen | 2A |
| | Trastuzumab + paclitaxel ± carboplatin[k,o] | Other Recommended Regimen | 2A |
| | Capecitabine + trastuzumab or lapatinib[k,o] | Other Recommended Regimen | 2A |
| | Trastuzumab + lapatinib[k,o] (without cytotoxic therapy) | Other Recommended Regimen | 2A |
| | Trastuzumab + other agents[k,o,p,q] | Other Recommended Regimen | 2A |
| | Neratinib + capecitabine[o] | Other Recommended Regimen | 2A |
| | Margetuximab-cmkb + chemotherapy[o] (capecitabine, eribulin, gemcitabine, or vinorelbine) | Other Recommended Regimen | 2A |
| **Additional targeted therapy options** (See BINV-R) | | | |

# New Strategies to Conquer MBC



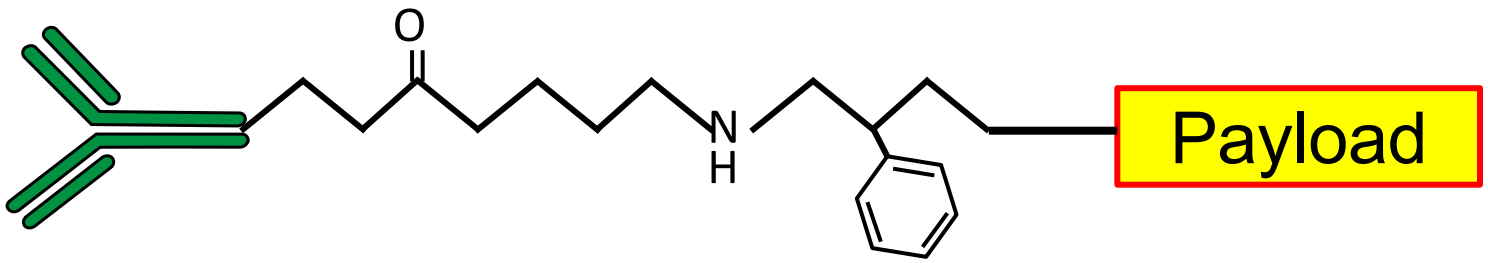
Courtesy of Lisa Carey, M.D.

# New Frontier in Precision Oncology

- Most precision oncology efforts have focused on genomically-matched therapy
- Many patients do not have actionable genomic alterations
- Single agent therapy in patients with genomic alterations often due not lead to objective responses
- Responses with targeted therapy are often not durable

- There is a great need for novel strategies
  - Novel combinations
  - Novel therapies such as ADC
  - Novel approaches to treatment selection

# The Promise of Antibody-Drug Conjugates (ADCs)

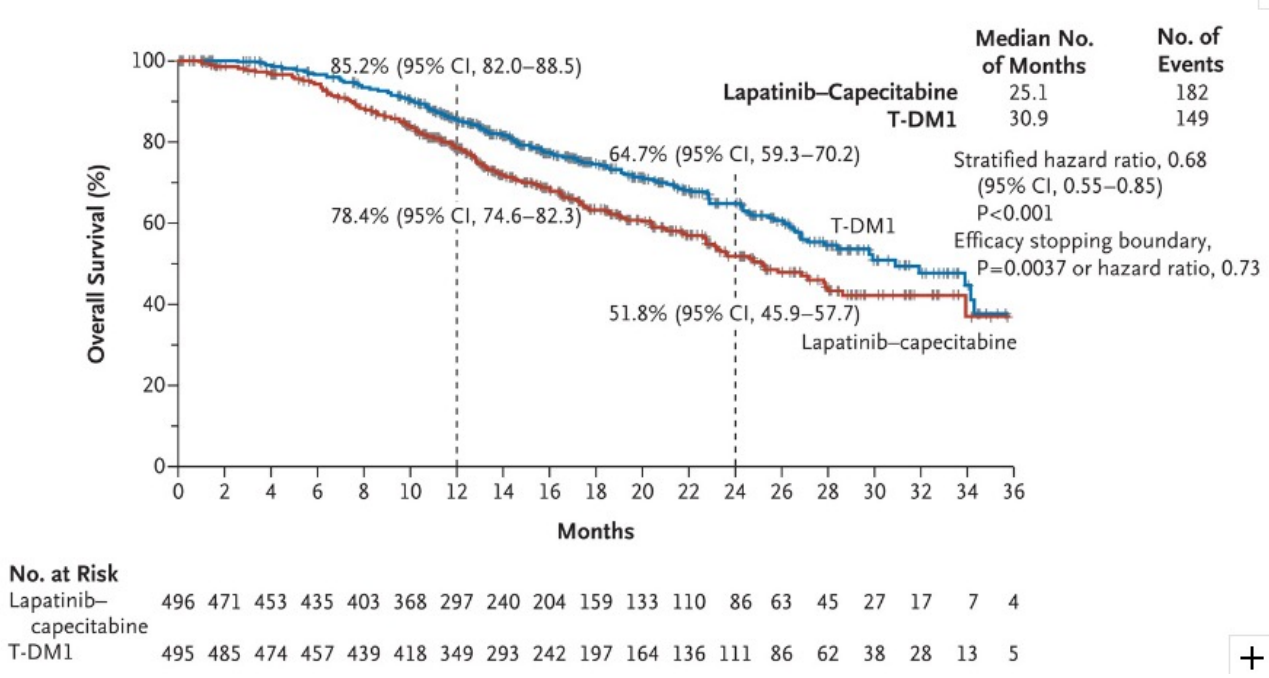



- **Antibody (Ab) component bind to cell surface molecules that internalize, best Ab has high affinity and low immunogenicity**
- **Degree of tumor specificity need unclear**
- **Linker releases payload upon internalization (pH-dependent), and degree of cleavability of linker balances less off-target vs. more**
- **Payload highly toxic and released selectively in tumor cells and tumor microenvironment. Tend to be anti-microtubular or DNA-damaging.**
- **Optimization of drug-antibody ratio (DAR) and location in antibody chain is important**
- **Diffusibility of payload into tumor microenvironment may overcome tumor heterogeneity of target expression**

Krug K, et al. Cell 2020

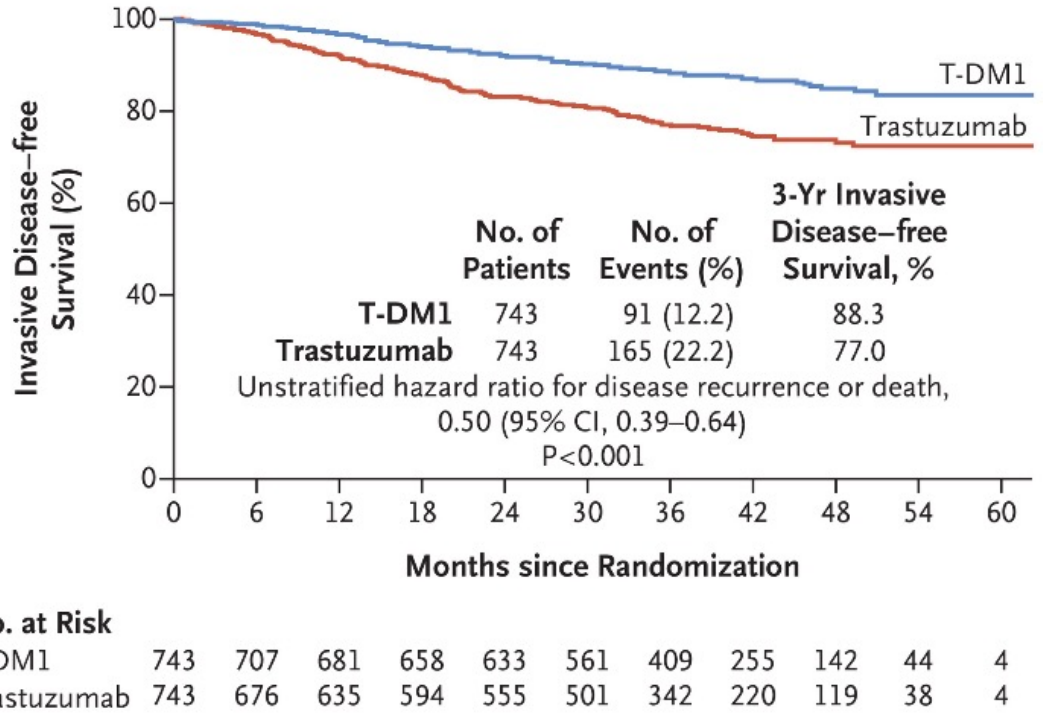
# First Antibody Drug Conjugates for Early and Metastatic Disease Trastuzumab Emtansine (T-DM1) for HER2+ Breast Cancer

EMELIA trial: OS with T-DM1 vs lapatinib-capecitabine in HER2+ advanced breast cancer




Verma et al, NEJM 2012

KATHERINE trial: Invasive DFS with adjuvant the T-DM1 vs trastuzumab for residual invasive HER2+ Breast Ca

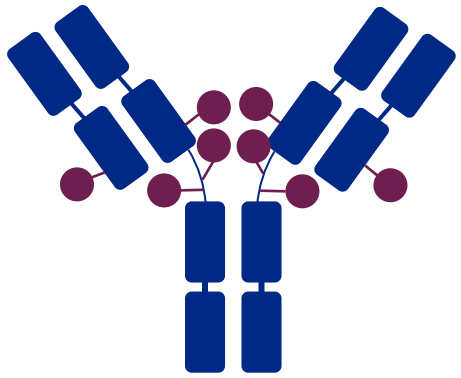



Von Minckwitz et al, NEJM, 2019

# Characteristic Differences Between T-DXd and T-DM1

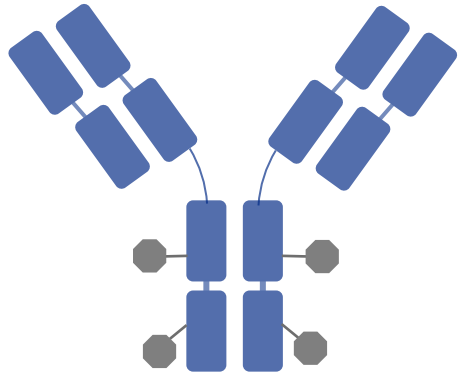
HER2-Targeting ADCs With Similar mAB Backbone

**Trastuzumab deruxtecan (T-DXd)[1]**



| T-DXd[1-4,a] | ADC Attributes | T-DM1[3-5] |
|---|---|---|
| Topoisomerase I inhibitor | **Payload MoA** | Anti-microtubule |
| ~8:1 | **Drug-to-antibody ratio** | ~3.5:1 |
| Yes | **Tumor-selective cleavable linker?** | No |
| Yes | **Evidence of bystander anti-tumor effect?** | No |

**Trastuzumab emtansine (T-DM1)[5]**



ADC, antibody-drug conjugate; MoA, mechanism of action
[a]The clinical relevance of these features is under investigation.

Cortes J et al. ESMO 2021. Abstract LBA1.
1. Nakada T et al. *Chem Pharm Bull (Tokyo).* 2019;67(3):173-185. 2. Ogitani Y et al. *Clin Cancer Res.* 2016;22(20):5097-5108. 3. Trail PA et al. *Pharmacol Ther.* 2018;181:126-142. 4. Ogitani Y et al. *Cancer Sci.* 2016;107(7):1039-1046. 5. LoRusso PM et al. *Clin Cancer Res*. 2011;17(20):6437-6447.

# Original Article
# Trastuzumab Deruxtecan versus Trastuzumab Emtansine for Breast Cancer

Javier Cortés, M.D., Ph.D., Sung-Bae Kim, M.D., Ph.D., Wei-Pang Chung, M.D., Seock-Ah Im, M.D., Ph.D., Yeon Hee Park, M.D., Ph.D., Roberto Hegg, M.D., Ph.D., Min Hwan Kim, M.D., Ph.D., Ling-Ming Tseng, M.D., Vanessa Petry, M.D., Chi-Feng Chung, M.D., Hiroji Iwata, M.D., Ph.D., Erika Hamilton, M.D., Giuseppe Curigliano, M.D., Ph.D., Binghe Xu, M.D., Ph.D., Chiun-Sheng Huang, M.D., Ph.D., M.P.H., Jee Hyun Kim, M.D., Ph.D., Joanne W.Y. Chiu, M.B., B.S., Jose Luiz Pedrini, M.D., Ph.D., Caleb Lee, M.D., Ph.D., Yali Liu, Ph.D., Jillian Cathcart, Ph.D., Emarjola Bako, M.D., Sunil Verma, M.D., Sara A. Hurvitz, M.D., for the DESTINY-Breast03 Trial Investigators

The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

# Trastuzumab Deruxtecan versus Trastuzumab Emtansine for Breast Cancer

Cortés J et al. DOI: 10.1056/NEJMoa2115022

## CLINICAL PROBLEM

The antibody–drug conjugate trastuzumab deruxtecan is approved in the United States to treat patients with human epidermal growth factor receptor 2 (HER2)–positive metastatic breast cancer who have received at least two previous anti-HER2 regimens in the context of metastatic disease. The benefits of trastuzumab deruxtecan as second-line therapy are unknown.

## CLINICAL TRIAL

**Design:** A phase 3, multicenter, open-label, randomized, controlled trial compared trastuzumab deruxtecan with standard second-line treatment, trastuzumab emtansine, in patients with HER2-positive metastatic breast cancer.

**Intervention:** 524 patients with metastatic cancer that had progressed during or after treatment with trastuzumab and a taxane or that had progressed within 6 months after neoadjuvant or adjuvant treatment with trastuzumab or a taxane were assigned to receive either trastuzumab deruxtecan or trastuzumab emtansine intravenously every 3 weeks. The primary end point was progression-free survival.

## RESULTS

**Efficacy:** During a median follow-up of approximately 15 or 16 months, progression-free survival was significantly longer with trastuzumab deruxtecan than with trastuzumab emtansine.

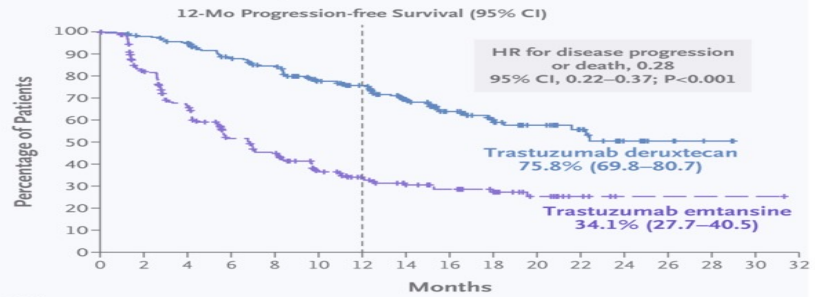
**Safety:** The incidence of drug-related adverse events was higher with trastuzumab deruxtecan than with trastuzumab emtansine. In particular, drug-related interstitial lung disease or pneumonitis was more common with trastuzumab deruxtecan; all such events in both groups were of grade 3 or lower.

## LIMITATIONS AND REMAINING QUESTIONS

- Longer follow-up is needed to assess the effect of trastuzumab deruxtecan on overall survival.
- Whether trastuzumab deruxtecan is associated with late toxic effects is unknown.

**Links: Full Article | NEJM Quick Take**

### Progression-free Survival




No. at Risk

| | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Trastuzumab deruxtecan | 261 | 250 | 240 | 214 | 200 | 168 | 150 | 112 | 79 | 53 | 36 | 25 | 10 | 5 | 2 | |
| Trastuzumab emtansine | 263 | 200 | 155 | 108 | 93 | 65 | 51 | 37 | 29 | 21 | 12 | 6 | 1 | 1 | 1 | 1 | 0 |

### Drug-Related Adverse Events

| Adverse Event | Trastuzumab deruxtecan (N=257) | Trastuzumab emtansine (N=261) |
|---|---|---|
| Drug-related events, any grade — % | 98.1 | 86.6 |
| Drug-related events, grade ≥3 — % | 45.1 | 39.8 |
| Interstitial lung disease or pneumonitis, any grade — no. (%) | 27 (10.5) | 5 (1.9) |
| Grade 1 | 7 (2.7) | 4 (1.5) |
| Grade 2 | 18 (7.0) | 1 (0.4) |
| Grade 3 | 2 (0.8) | 0 |

## CONCLUSIONS

In patients with HER2-positive metastatic breast cancer and disease progression after treatment with trastuzumab and a taxane, trastuzumab deruxtecan showed a progression-free survival benefit over standard second-line treatment with trastuzumab emtansine, although close monitoring for interstitial lung disease and pneumonitis is warranted.

Original Article

# Trastuzumab Deruxtecan in Previously Treated HER2-Low Advanced Breast Cancer

Shanu Modi, M.D., William Jacot, M.D., Ph.D., Toshinari Yamashita, M.D., Ph.D., Joohyuk Sohn, M.D., Maria Vidal, M.D., Ph.D., Eriko Tokunaga, M.D., Ph.D., Junji Tsurutani, M.D., Ph.D., Naoto T. Ueno, M.D., Ph.D., Aleix Prat, M.D., Ph.D., Yee Soo Chae, M.D., Ph.D., Keun Seok Lee, M.D., Ph.D., Naoki Niikura, M.D., Ph.D., Yeon Hee Park, M.D., Ph.D., Binghe Xu, M.D., Ph.D., Xiaojia Wang, M.D., Ph.D., Miguel Gil-Gil, M.D., Ph.D., Wei Li, M.D., Ph.D., Jean-Yves Pierga, M.D., Ph.D., Seock-Ah Im, M.D., Ph.D., Halle C.F. Moore, M.D., Hope S. Rugo, M.D., Rinat Yerushalmi, M.D., Flora Zagouri, M.D., Ph.D., Andrea Gombos, M.D., Sung-Bae Kim, M.D., Ph.D., Qiang Liu, M.D., Ph.D., Ting Luo, M.D., Cristina Saura, M.D., Ph.D., Peter Schmid, M.D., Ph.D., Tao Sun, M.D., Dhiraj Gambhire, M.D., M.P.H., Lotus Yung, Pharm.D., Yibin Wang, Ph.D., Jasmeet Singh, M.D., M.P.H.A., Patrik Vitazka, M.D., Ph.D., Gerold Meinhardt, M.D., Nadia Harbeck, M.D., Ph.D., David A. Cameron, M.D., for the DESTINY-Breast04 Trial Investigators

The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

# Trastuzumab Deruxtecan in Previously Treated HER2-Low Advanced Breast Cancer

Modi S et al. DOI: 10.1056/NEJMoa2203690

## CLINICAL PROBLEM

Patients with HER2-low metastatic breast cancer, which lacks overexpression or amplification of HER2, have limited targeted treatment options. The antibody–drug conjugate trastuzumab deruxtecan has shown efficacy in these patients in phase 1 and 2 trials.

## CLINICAL TRIAL

**Design:** A phase 3, open-label, randomized trial examined the efficacy and safety of trastuzumab deruxtecan in patients with previously treated unresectable or metastatic HER2-low breast cancer. Low HER2 was defined by a score of 1+ on immunohistochemical (IHC) analysis or by an IHC score of 2+ and negative results on in situ hybridization.

**Intervention:** 557 patients with HER2-low metastatic breast cancer were randomly assigned in a 2:1 ratio to receive either trastuzumab deruxtecan intravenously every 3 weeks at a dose of 5.4 mg per kilogram of body weight or the physician's choice of untargeted chemotherapy. The primary end point was progression-free survival among patients with hormone receptor–positive cancer (approximately 89% of all patients).

## RESULTS

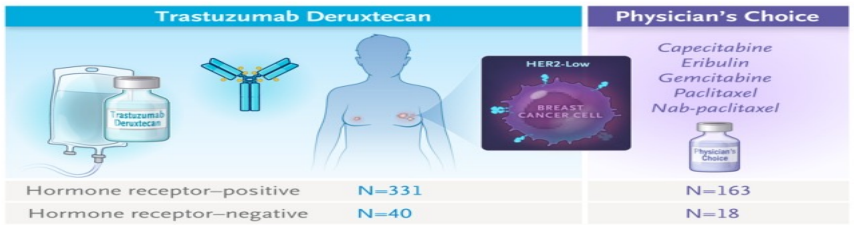
**Efficacy:** The median progression-free survival among patients with hormone receptor–positive cancer was significantly longer with trastuzumab deruxtecan than with the physician's choice of chemotherapy. Results for key secondary end points of overall survival among patients with hormone receptor–positive cancer and of progression-free and overall survival among all patients were significantly better with trastuzumab deruxtecan.

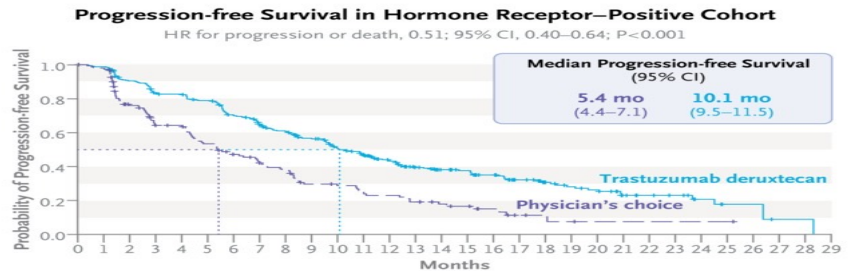
**Safety:** Grade ≥3 adverse events, most commonly neutropenia, occurred frequently in both groups. Adjudicated drug-related interstitial lung disease or pneumonitis occurred in 45 patients (12.1%) receiving trastuzumab deruxtecan; most cases were mild or moderate.

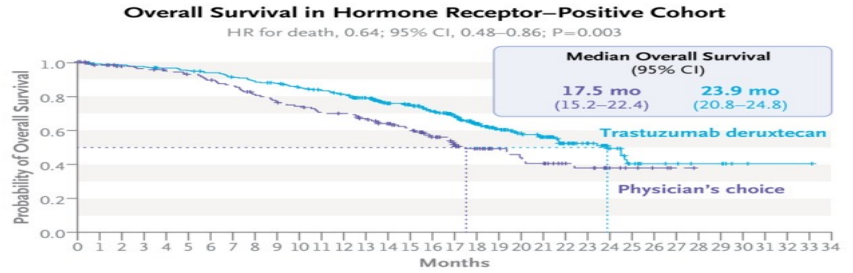
## REMAINING QUESTIONS

- Is current HER2-low scoring accurately identifying patients who might benefit from trastuzumab deruxtecan? Are there more accurate methods?

**Links: Full Article | NEJM Quick Take | Editorial**



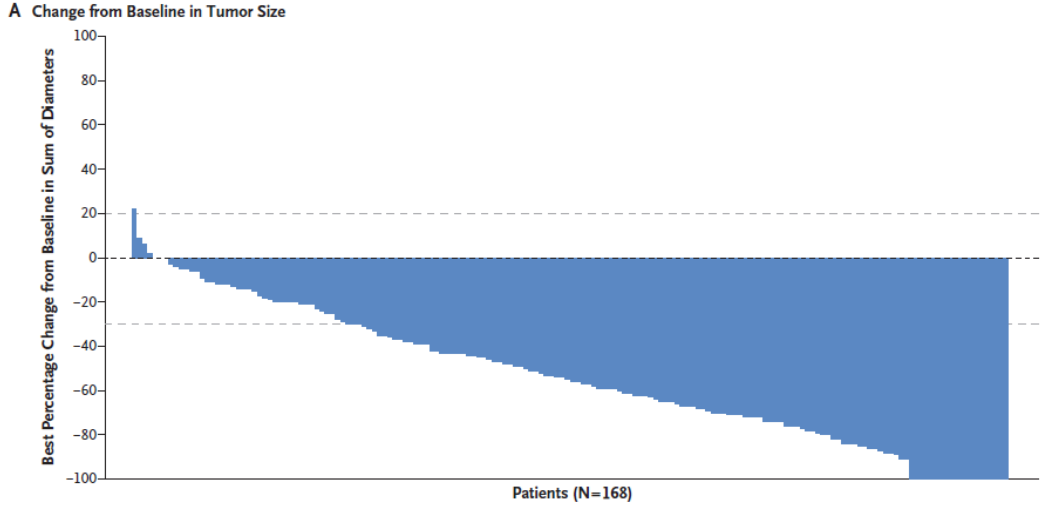




## CONCLUSIONS

**Trastuzumab deruxtecan significantly prolonged progression-free and overall survival among previously treated patients with HER2-low metastatic breast cancer, regardless of hormone-receptor status.**

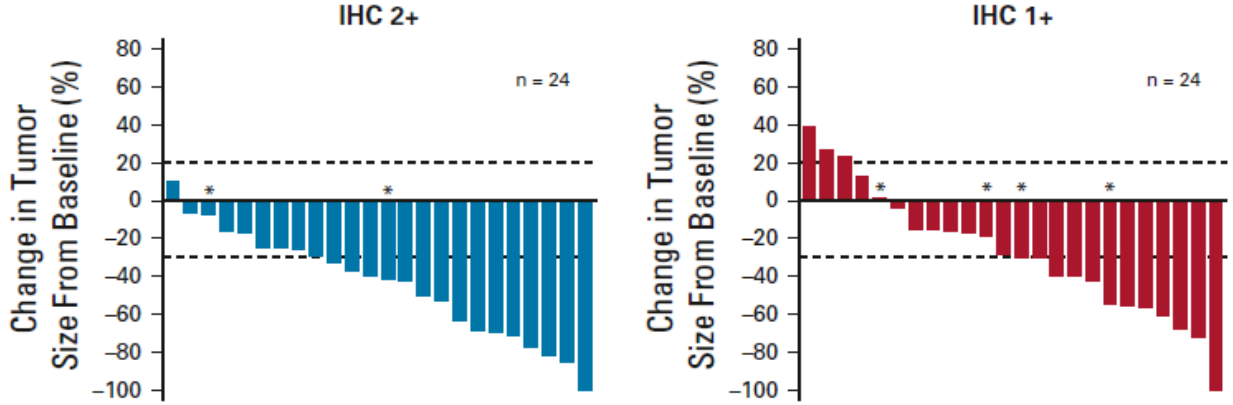
# How Much Target Expression is Necessary?

Trastuzumab Deruxtecan (DS-8201a) for HER2 positive breast cancer




Modi et al NEJM 2020

Trastuzumab Deruxtecan for HER2 Low Expressing breast cancer

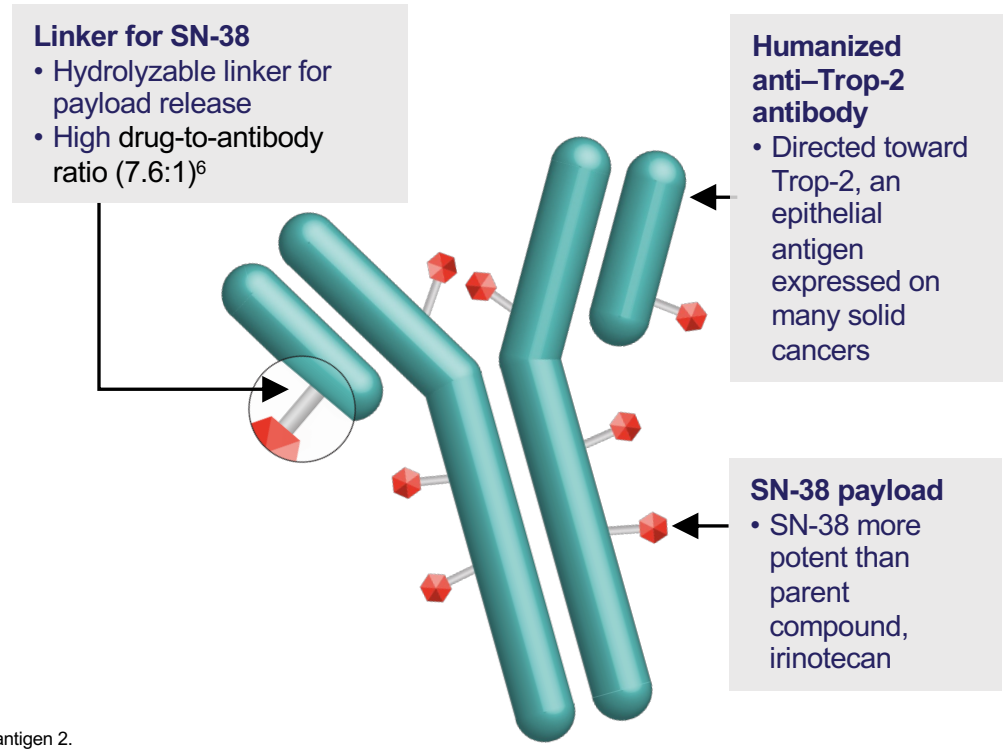



Modi et al JCO, 2020

Trastuzumab Deruxtecan: humanized monoclonal antibody targeting HER2, a cleavable tetrapeptide-based linker, and a potent topoisomerase I inhibitor

# Sacituzumab Govitecan (SG) Is a First-in-Class Trop-2–Directed ADC

- First-in-class trophoblast cell-surface antigen 2 (Trop-2)-directed antibody-drug-conjugate (ADC)
- Trop-2 is expressed in all subtypes of breast cancer and linked to poor prognosis[1,2]
- SG is distinct from other ADCs[3-6]
  - Antibody highly specific for Trop-2
  - High drug-to-antibody ratio (7.6:1)
  - Internalization and enzymatic cleavage by tumor cell not required for the liberation of SN-38 from the antibody
  - Hydrolysis of the linker also releases the SN-38 cytotoxic extracellularly in the tumor microenvironment, providing a bystander effect
- Granted accelerated approval by the FDA for metastatic TNBC and fast-track designation in metastatic urothelial cancer[7]




ADC, antibody−drug conjugate; TNBC, triple-negative breast cancer; Trop-2, trophoblast cell surface antigen 2.

1. Vidula N et al. *J Clin Oncol.* 2017;35:15(suppl):Abstract 1075. 2. Ambrogi et al. *PLoS One.* 2014;9(5):e96993. 3. Goldenberg DM et al. *Expert Opin Biol Ther*. 2020 Aug;20(8):871-885. 4. Nagayama A et al. *Ther Adv Med Oncol*. 2020;12:1758835920915980. 5. Cardillo TM et al. *Bioconjugate Chem.* 2015;26:919-931. 6. Goldenberg DM et al. *Oncotarget*. 2015;6:22496-224512. 7. Press Release. https://www.fda.gov/drugs/drug-approvals-and-databases/fda-grants-accelerated-approval-sacituzumab-govitecan-hziy-metastatic-triple-negative-breast-cancer. Accessed August 26, 2020.

# Original Article
# Sacituzumab Govitecan in Metastatic Triple-Negative Breast Cancer

Aditya Bardia, M.D., Sara A. Hurvitz, M.D., Sara M. Tolaney, M.D., M.P.H., Delphine Loirat, M.D., Ph.D., Kevin Punie, M.D., Mafalda Oliveira, M.D., Ph.D., Adam Brufsky, M.D., Ph.D., Sagar D. Sardesai, M.D., Kevin Kalinsky, M.D., Amelia B. Zelnak, M.D., Robert Weaver, M.D., Tiffany Traina, M.D., Florence Dalenc, M.D., Philippe Aftimos, M.D., Filipa Lynce, M.D., Sami Diab, M.D., Javier Cortés, M.D., Ph.D., Joyce O'Shaughnessy, M.D., Véronique Diéras, M.D., Cristiano Ferrario, M.D., Peter Schmid, M.D., Ph.D., Lisa A. Carey, M.D., Luca Gianni, M.D., Martine J. Piccart, M.D., Ph.D., Sibylle Loibl, M.D., Ph.D., David M. Goldenberg, Sc.D., M.D., Quan Hong, Ph.D., Martin S. Olivo, M.D., Loretta M. Itri, M.D., Hope S. Rugo, M.D., for the ASCENT Clinical Trial Investigators

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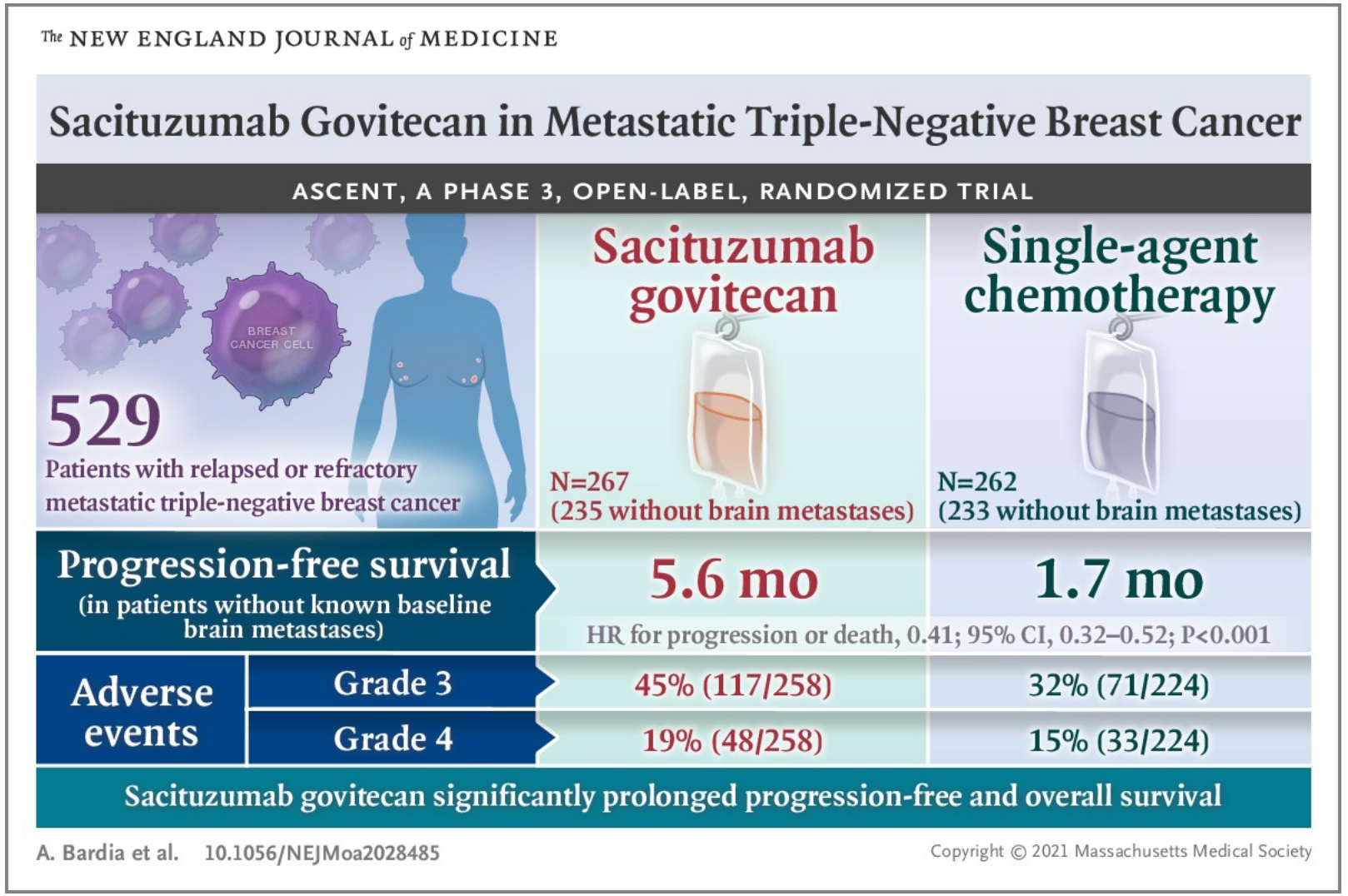
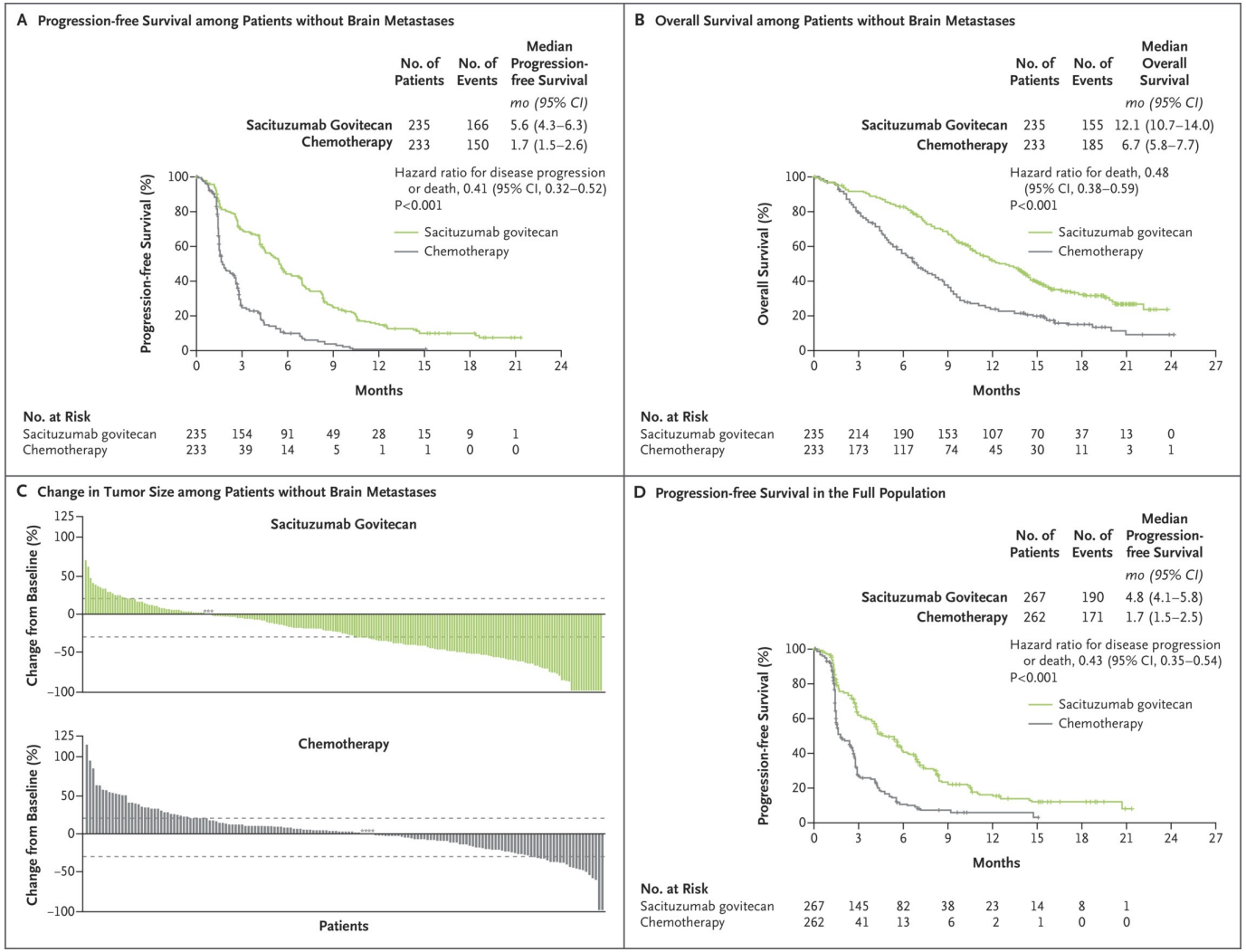
# Sacituzumab Govitecan in TNBC



# Efficacy Results in Patients without Brain Metastases at Baseline and in the Full Population.

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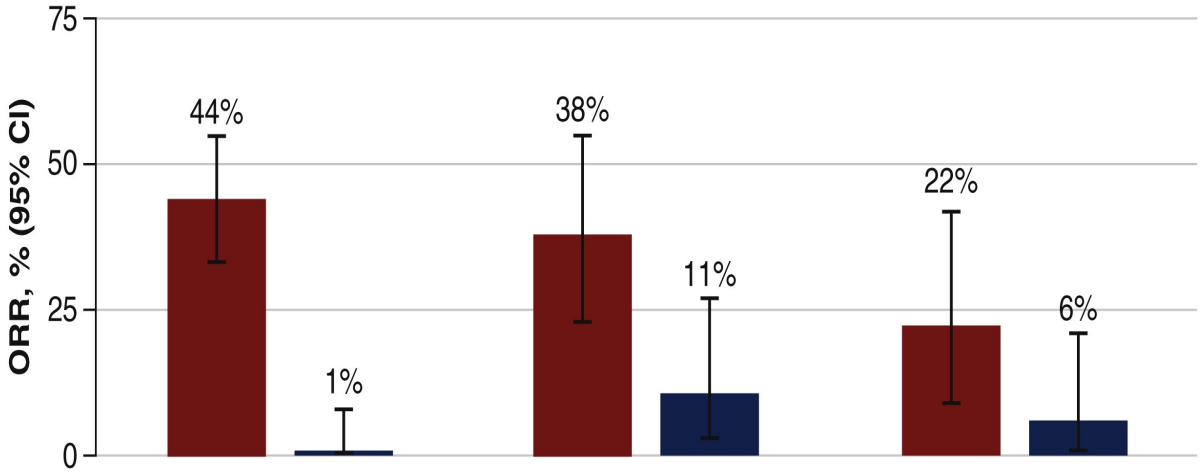
# Response vs TROP2 Expression
# Phase III ASCENT study of sacituzumab govitecan versus chemotherapy in patients with metastatic TNBC




| | Trop-2 high H-score: >200-300 (*n* = 157) | | Trop-2 medium H-score: 100-200 (*n* = 74) | | Trop-2 low H-score: 0 to <100 (*n* = 59) | |
|---|---|---|---|---|---|---|
| | SG (*n* = 85) | TPC (*n* = 72) | SG (*n* = 39) | TPC (*n* = 35) | SG (*n* = 27) | TPC (*n* = 32) |
| ORR, % (*n*) | 44 (37) | 1 (1) | 38 (15) | 11 (4) | 22 (6) | 6 (2) |
| 95% CI | 33-55 | 0-8 | 23-55 | 3-27 | 9-42 | 1-21 |

88% of 48 primary or mTNBC tumors had moderate to strong Trop-2 staining, with the majority expressing Trop-2 in >50% of tumor cells. All responders had moderate to strong Trop-2 staining,

SG benefits patients with previously treated mTNBC expressing high/medium Trop-2 compared with standard-of-care chemotherapy.

The small number of patients with low Trop-2 expression precludes definitive conclusions on the benefit of SG in this subgroup but still ORR higher than with chemotherapy

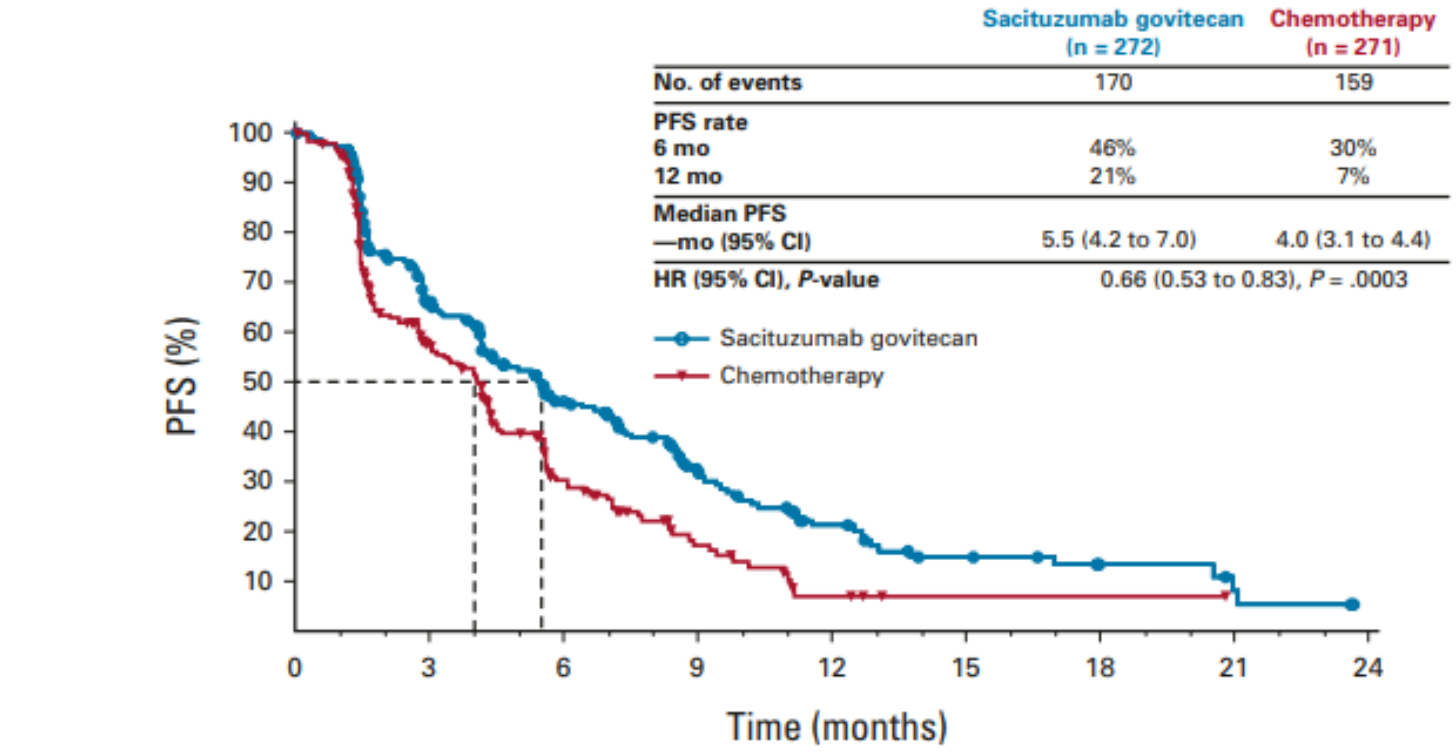
Bardia et al Ann Oncol 2021

# Sacituzumab Govitecan in Hormone Receptor–Positive/Human Epidermal Growth Factor Receptor 2–Negative Metastatic Breast Cancer

Hope S. Rugo, MD[1]; Aditya Bardia, MD, MPH[2]; Frederik Marmé, MD, PhD[3]; Javier Cortes, MD, PhD[4,5]; Peter Schmid, MD, PhD[6]; Delphine Loirat, MD, PhD[7]; Olivier Trédan, MD, PhD[8]; Eva Ciruelos, MD, PhD[9]; Florence Dalenc, MD, PhD[10]; Patricia Gómez Pardo, MD[11]; Komal L. Jhaveri, MD[12]; Rosemary Delaney, MPH[13]; Olivia Fu, MD[14]; Lanjia Lin, PhD[15]; Wendy Verret, PhD[13]; and Sara M. Tolaney, MD, MPH[16]; on behalf of the TROPiCS-02 Study Investigators

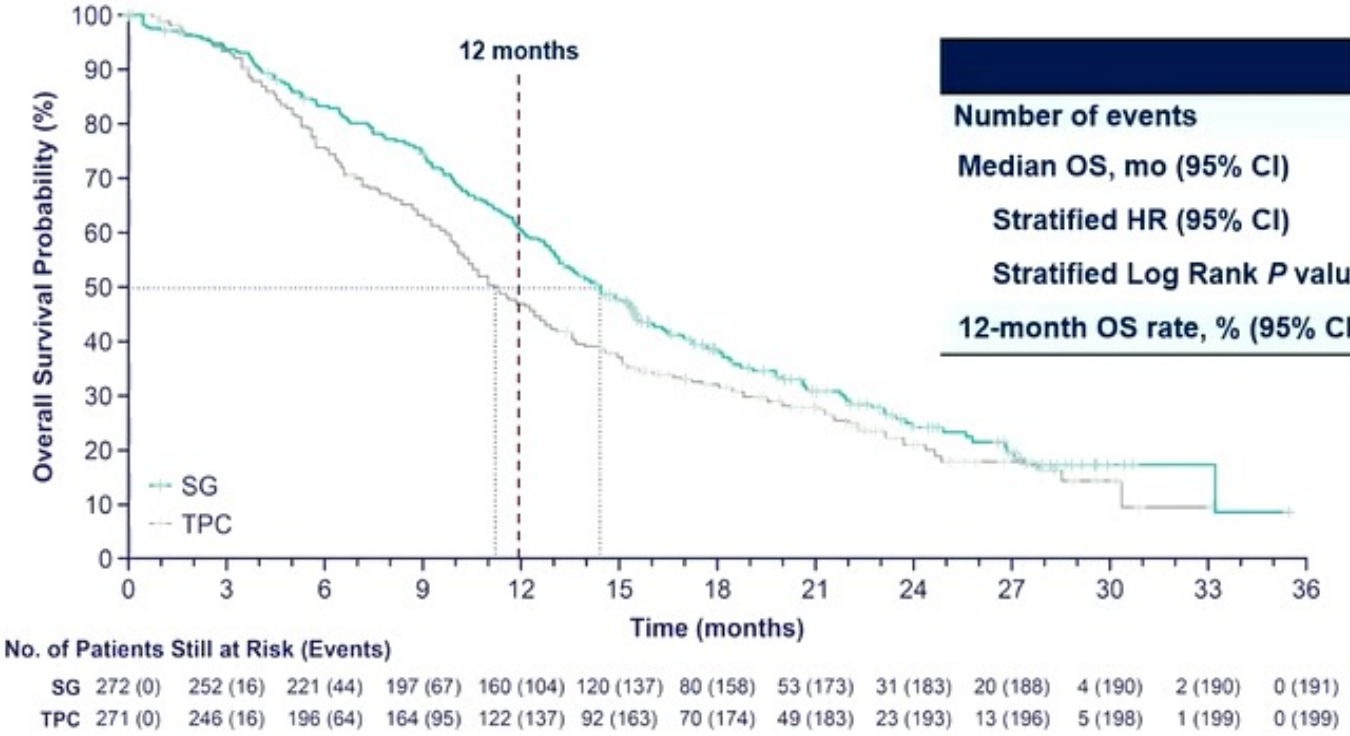
THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

# Progression-Free Survival



# Second interim analysis of TROPiCS-02, ESMO 2022

## Key Secondary Endpoint: Overall Survival (2nd Interim Analysis)




| | SG (n=272) | TPC (n=271) |
|---|---|---|
| Number of events | 191 | 199 |
| Median OS, mo (95% CI) | 14.4 (13.0–15.7) | 11.2 (10.1–12.7) |
| Stratified HR (95% CI) | **0.79** (0.65–0.96) | |
| Stratified Log Rank *P* value | *P*=0.020 | |
| 12-month OS rate, % (95% CI) | 61 (55–66) | 47 (41–53) |

- SG demonstrated a statistically significant improvement in OS vs TPC with 21% reduction in the risk of death; having met statistical significance, no further formal statistical testing of OS will occur
- Patients who received SG survived a median of ***3.2 months longer*** than those who received TPC

# Updated NCCN Guidelines

National Comprehensive Cancer Network®

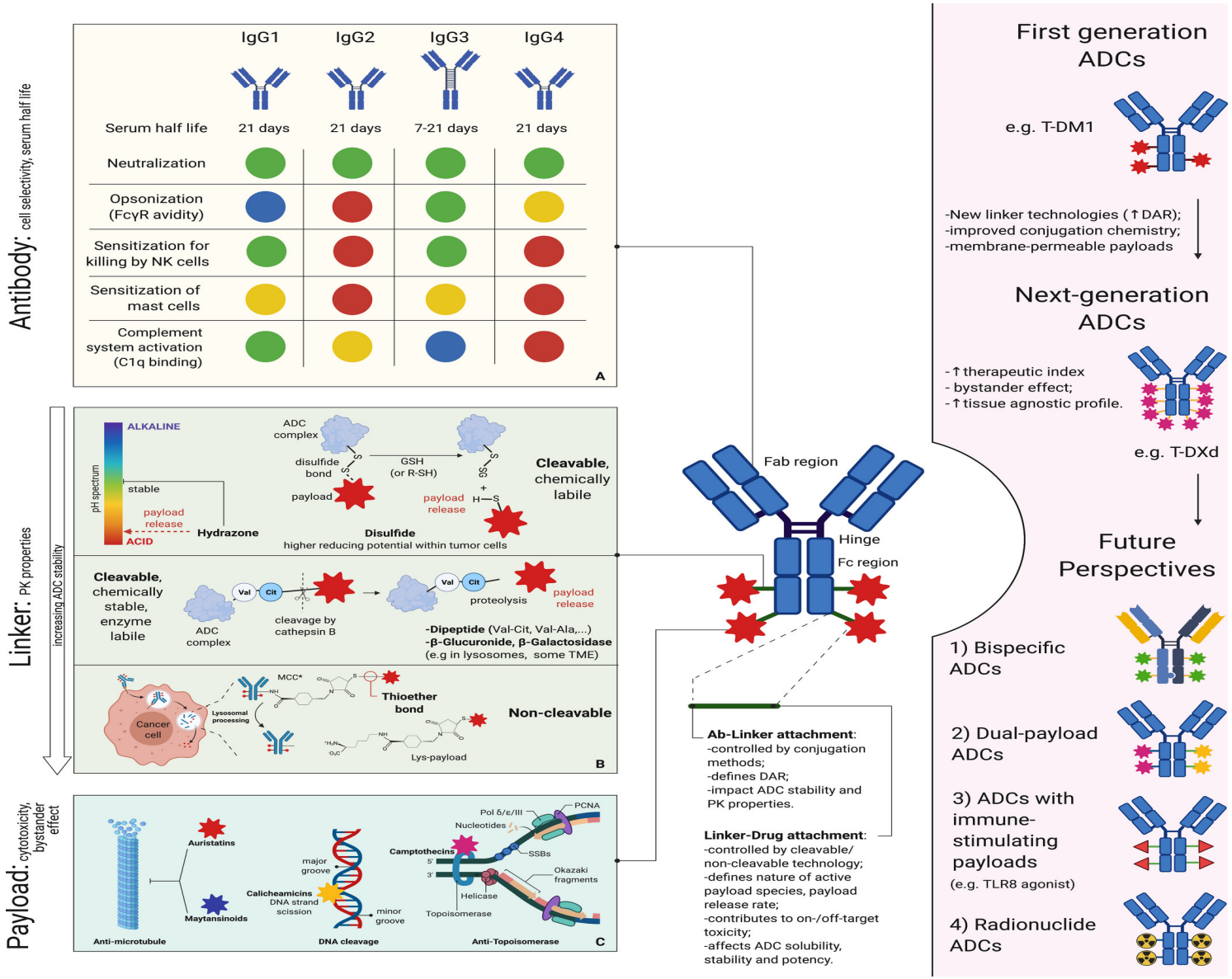
## NCCN Guidelines Version 4.2022
## Invasive Breast Cancer

NCCN Guidelines Index
Table of Contents
Discussion

**SYSTEMIC THERAPY REGIMENS FOR RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE[a,b,c]**

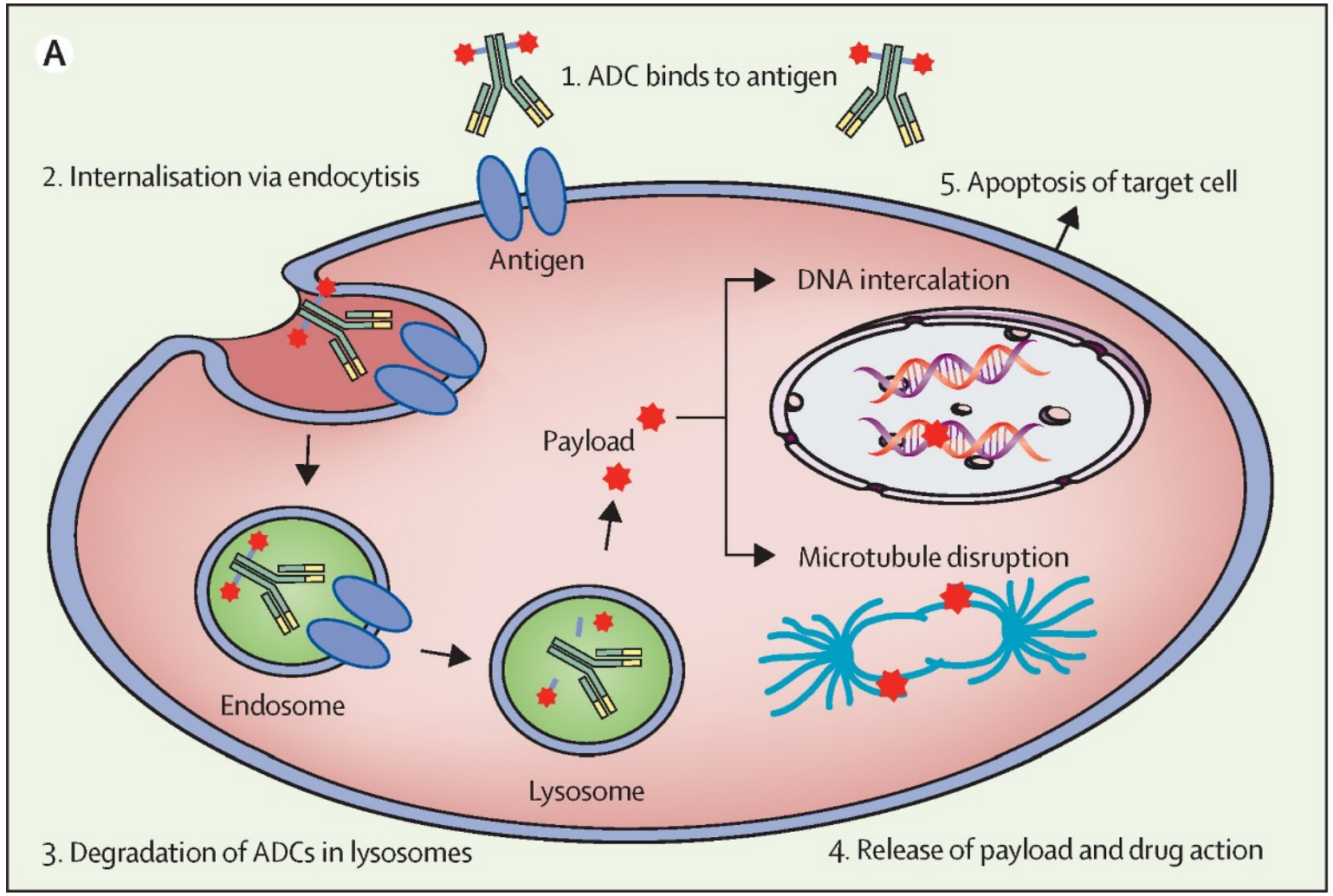
| HER2-Negative | | | |
|---|---|---|---|
| **Preferred Regimens** | | **Other Recommended Regimens[i]** | **Useful in Certain Circumstances[i]** |
| • Anthracyclines<br>▸ Doxorubicin<br>▸ Liposomal doxorubicin<br>• Taxanes<br>▸ Paclitaxel<br>• Anti-metabolites<br>▸ Capecitabine<br>▸ Gemcitabine<br>• Microtubule inhibitors<br>▸ Vinorelbine<br>▸ Eribulin<br>• Sacituzumab govitecan-hziy (for TNBC [category 1] or HR+/HER2-)[d] | • For HER2 IHC 1+ or 2+/ISH negative:<br>▸ Fam-trastuzumab deruxtecan-nxki[e,f] (category 1)<br>• For germline *BRCA1/2* mutations[g] see additional targeted therapy options (BINV-R)[h]<br>• Platinum (for TNBC and germline *BRCA1/2* mutation)[g]<br>▸ Carboplatin<br>▸ Cisplatin<br>• For PD-L1–positive TNBC see additional targeted therapy options (BINV-R)[h] | • Cyclophosphamide<br>• Docetaxel<br>• Albumin-bound paclitaxel<br>• Epirubicin<br>• Ixabepilone | • AC (doxorubicin/cyclophosphamide)<br>• EC (epirubicin/cyclophosphamide)<br>• CMF (cyclophosphamide/ methotrexate/fluorouracil)<br>• Docetaxel/capecitabine<br>• GT (gemcitabine/paclitaxel)<br>• Gemcitabine/carboplatin<br>• Carboplatin + paclitaxel or albumin-bound paclitaxel |

# Evolution in ADCs




Tarantino et al CA A Cancer J Clinicians, 2021

# Other Considerations for Sensitivity/Resistance




B

Mechanisms of resistance in:

1. ADC binding to target antigen
   - Target downregulation
   - Loss of antigen expression
   - Mutated antigen affects target recognition
2. Receptor-mediated ADC internalisation:
   - Reduced cell-surface trafficking causing insufficient ADC internalisation
   - Defects in internalisation and trafficking pathways
3. The degradation of ADCs in lysosomes
   - Impaired lysosomal function (eg, acidification)
   - Reduced lysosomal proteolytic activity
4. Payload release to the cytosol
   - Loss of lysosomal transporter expression (eg, SLC46A3)
   - Overexpression of drug efflux transporters
5. Apoptosis of the target cell
   - Loss of the bystander effect

Chau et al *The Lancet* 2019

# Conclusions:
# Targeted Therapy in Metastatic Breast Cancer

- The landscape of targeted therapy have substantially change in the last 8 years and continues to change as I speak today
- CDK inhibitor have increase dramatically PFS and OS in patients with ER+ MBC, first and second line
- PIK3CA/mTHOR/AKT inhibitor are improving PFS in second and third therapy in ER+ MBC and showed promising results in metastatic TNBC
- PARP inhibitors have significantly improved PFS in BRCA-1 and 2 MBC
- Antibodies, TKI and recently conjugates have substantially improved PFS and OS of patients with HER-2+ MBC including those with brain metastasis
- Novel agents such conjugates have improved PFS and OS in all subtypes of metastatic breast cancer
- There are many new ADCs in development
- New clinical trial designs are needed to rapidly evaluate new of targeted therapeutics, optimize patient selection and develop potential biomarkers of drug sensitivity and resistant.

# Incorporating ADCs into Precision Oncology