
# Advanced Breast Cancer: State of the Art

CALIFORNIA CANCER™ CONSORTIUM CONFERENCE

Mili Arora, MD
UC Davis Comprehensive Cancer Center
November 1, 2020

# Disclosures

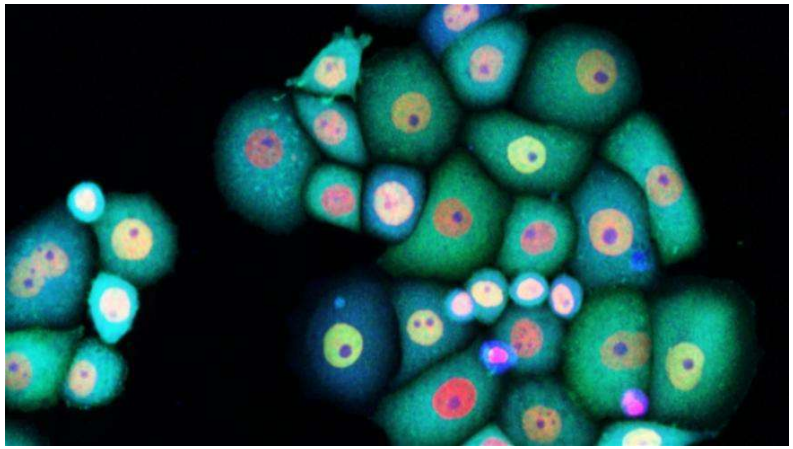
- No relevant financial disclosures to report

# Outline

I. HER2 positive breast cancer
   - HER2 CLIMB

II. TNBC
   - KEYNOTE-355
   - IMpassion131
   - S1416

III. Hormone positive breast cancer



# HER2 positive breast cancer

*Source: Pharmaceutical Intelligence, 2016.*

# HER2 CLIMB Background

- Up to 50% of pts with HER2+ MBC will develop brain metastases
  - Isolated CNS disease with HER2 positive disease
- Tucatinib potent oral TKI to HER2 with less EGFR inhibition
  - Less diarrhea, rash PPE

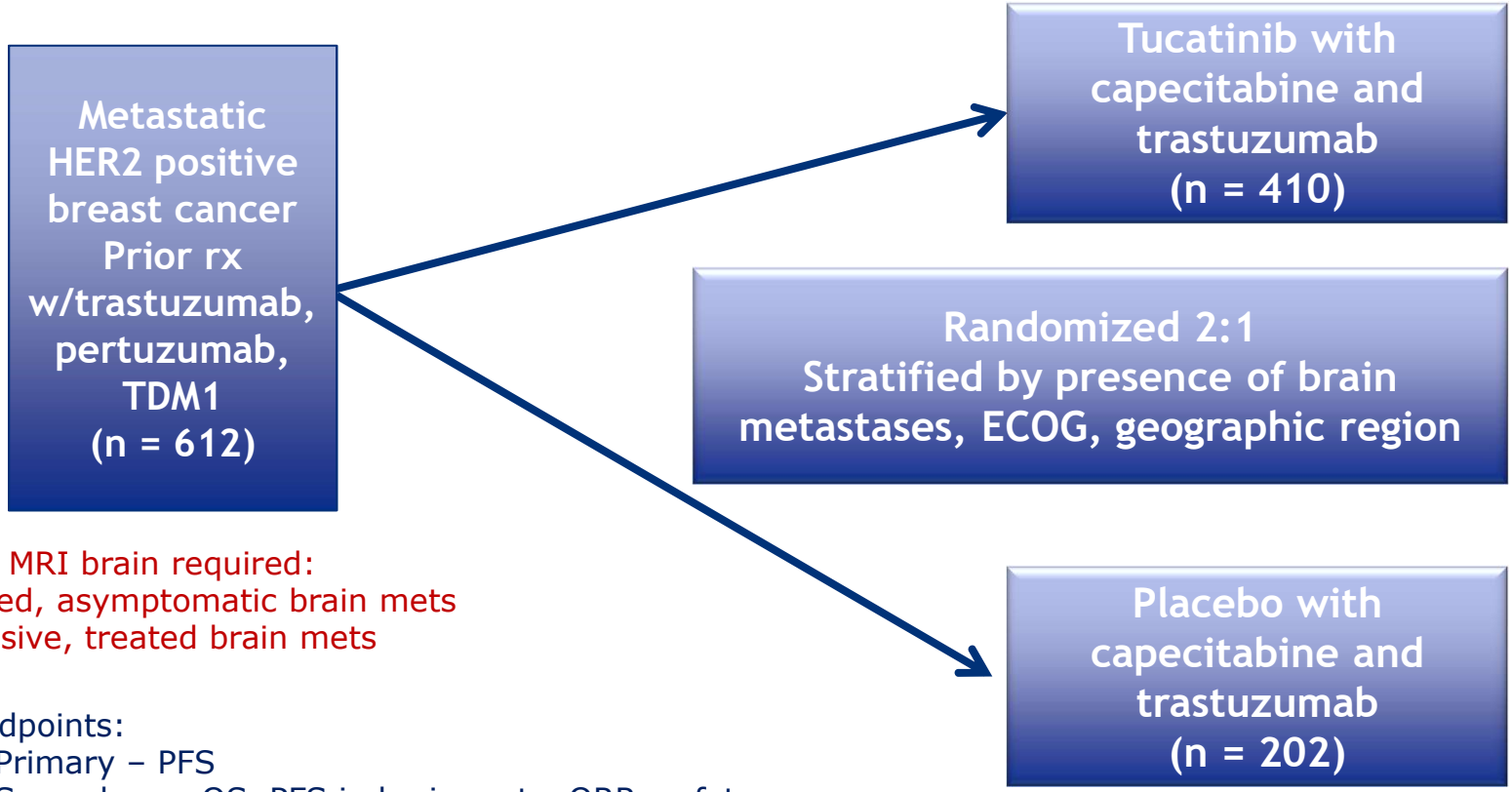
The NEW ENGLAND JOURNAL of MEDICINE

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

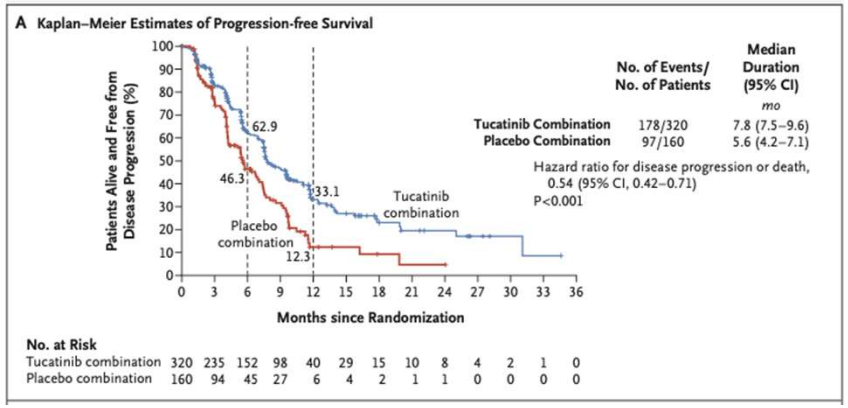
# HER2 CLIMB – Trial Design



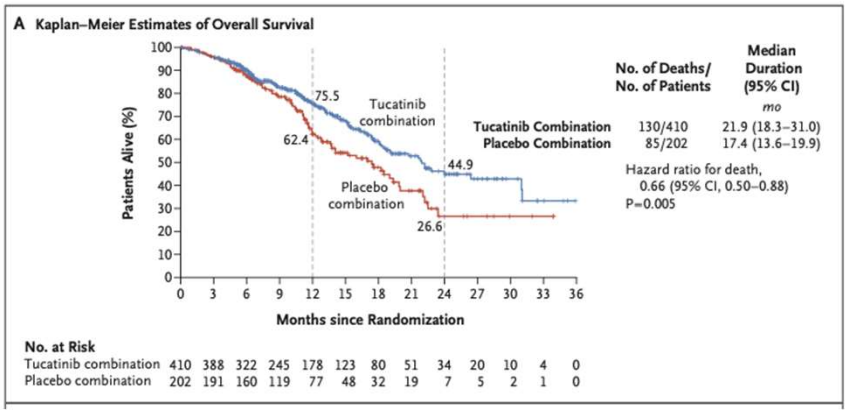

Baseline MRI brain required:
-untreated, asymptomatic brain mets
-progressive, treated brain mets

Endpoints:
- Primary – PFS
- Secondary – OS, PFS in brain mets, ORR, safety

# HER2 CLIMB PFS and OS




PFS by BICR- decreased risk of progression or death by 46%




Risk of death reduced by 34%

*Source: Murthy, R.K. et al (2018). Tucatinib, Trastuzumab, and Capecitabine for HER2-Positive Metastatic Breast Cancer. New England Journal of Medicine, 382 (7), 597-609.*

# Adverse Events

| Event | Tucatinib-Combination Group (N=404) | | Placebo-Combination Group (N=197) | |
|---|---|---|---|---|
| | Any Grade | Grade ≥3 | Any Grade | Grade ≥3 |
| | *number of patients (percent)* | | | |
| Any adverse event | 401 (99.3) | 223 (55.2) | 191 (97.0) | 96 (48.7) |
| Diarrhea | 327 (80.9) | 52 (12.9) | 105 (53.3) | 17 (8.6) |
| PPE syndrome | 256 (63.4) | 53 (13.1) | 104 (52.8) | 18 (9.1) |
| Nausea | 236 (58.4) | 15 (3.7) | 86 (43.7) | 6 (3.0) |
| Fatigue | 182 (45.0) | 19 (4.7) | 85 (43.1) | 8 (4.1) |
| Vomiting | 145 (35.9) | 12 (3.0) | 50 (25.4) | 7 (3.6) |
| Stomatitis | 103 (25.5) | 10 (2.5) | 28 (14.2) | 1 (0.5) |
| Decreased appetite | 100 (24.8) | 2 (0.5) | 39 (19.8) | 0 |
| Headache | 87 (21.5) | 2 (0.5) | 40 (20.3) | 3 (1.5) |
| Aspartate aminotransferase increased | 86 (21.3) | 18 (4.5) | 22 (11.2) | 1 (0.5) |
| Alanine aminotransferase increased | 81 (20.0) | 22 (5.4) | 13 (6.6) | 1 (0.5) |

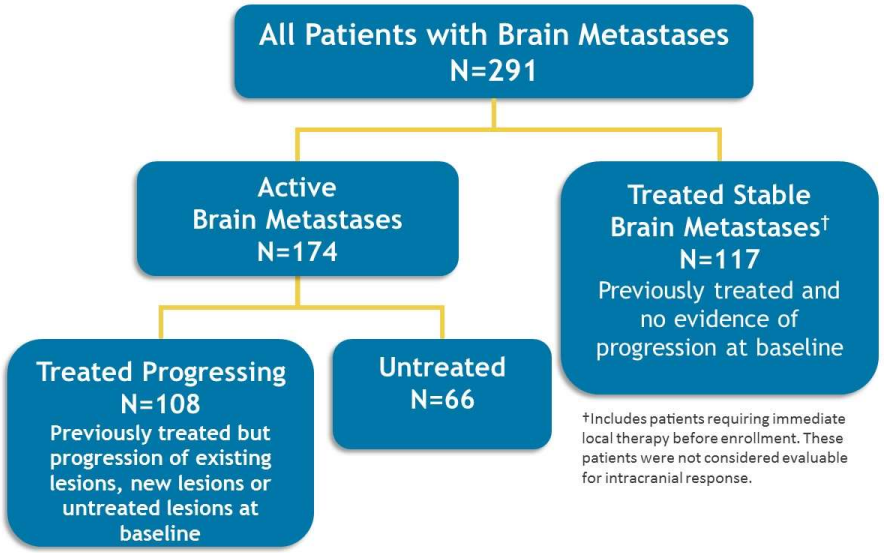
*Source: Murthy, R.K. et al (2018). Tucatinib, Trastuzumab, and Capecitabine for HER2-Positive Metastatic Breast Cancer. New England Journal of Medicine, 382 (7), 597-609.*

# Intracranial Efficacy and Survival With Tucatinib Plus Trastuzumab and Capecitabine for Previously Treated HER2-Positive Breast Cancer With Brain Metastases in the HER2CLIMB Trial

Nancy U. Lin, MD[1]; Virginia Borges, MMSc, MD[2]; Carey Anders, MD[3]; Rashmi K. Murthy, MD, MBE[4]; Elisavet Paplomata, MD[5]; Erika Hamilton, MD[6]; Sara Hurvitz, MD[7]; Sherene Loi, MD, PhD[8]; Alicia Okines, MBChB, MD[9]; Vandana Abramson, MD[10]; Philippe L. Bedard, MD[11]; Mafalda Oliveira, MD, PhD[12]; Volkmar Mueller, MD[13]; Amelia Zelnak, MD[14]; Michael P. DiGiovanna, MD, PhD[15]; Thomas Bachelot, MD[16]; A. Jo Chien, MD[17]; Ruth O'Regan, MD[5]; Andrew Wardley, MBChB, MSc, MD[18]; Alison Conlin, MD, MPH[19]; David Cameron, MD, MA[20]; Lisa Carey, MD[21]; Giuseppe Curigliano, MD, PhD[22]; Karen Gelmon, MD[23]; Sibylle Loibl, MD, PhD[24]; JoAl Mayor, PharmD[25]; Suzanne McGoldrick, MD, MPH[25]; Xuebei An, PhD[25]; and Eric P. Winer, MD[1]

# HER2CLIMB Analysis of Patients with Brain Metastases

- Brain MRI at baseline for all patients
- Brain MRI for brain metastases patients every 6 weeks in first 24 weeks, every 9 weeks thereafter
- Eligible brain metastases patients:
  - Not requiring immediate local therapy
  - Requiring local therapy during screening could be eligible after washout*




*These patients were included in the Treated Stable group for analysis.



PRESENTED BY: Nancy Lin, nlin@partners.org


*Source: Nancy Lin, ASCO 2020.*

# Baseline Characteristics of HER2CLIMB Patients with Brain Metastases

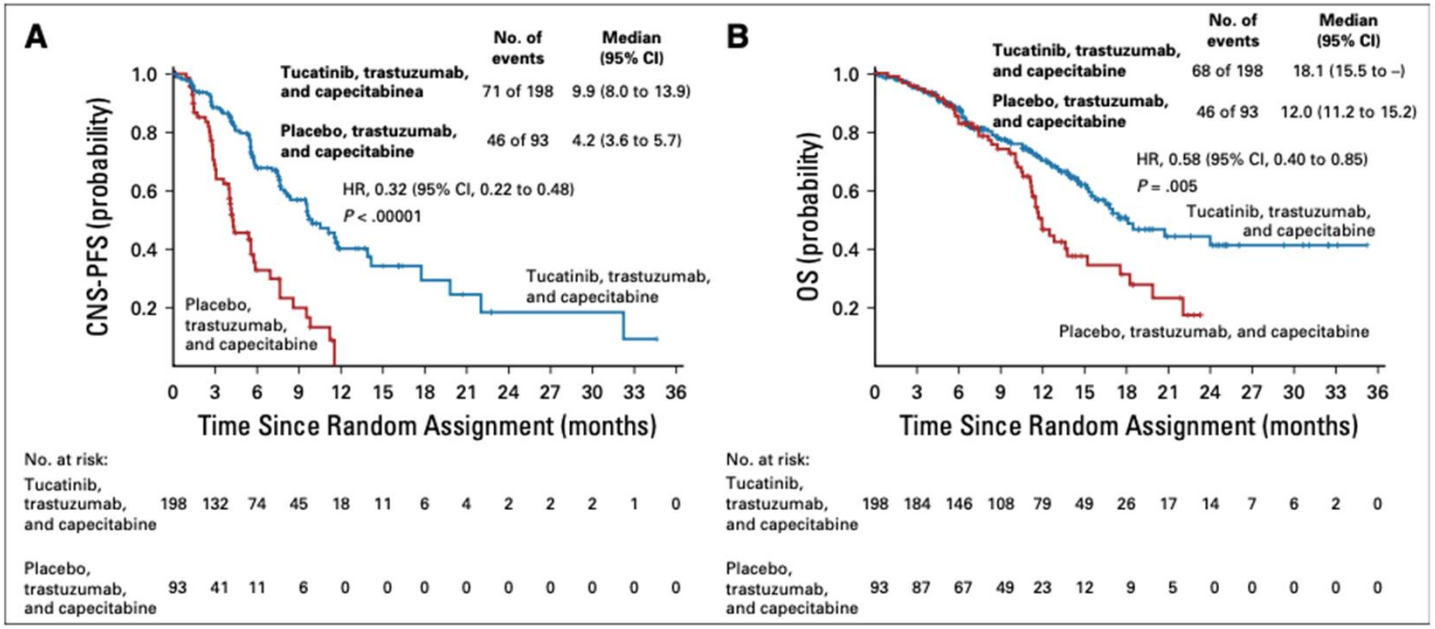
| | | TUC+Tras+Cape (N=198) | Pbo+Tras+Cape (N=93) |
|---|---|---|---|
| Age (years), median (range) | | 53 (22, 75) | 52 (25, 75) |
| Female, n (%) | | 197 (99.5) | 92 (98.9) |
| ECOG PS, n (%) | 0 | 92 (46.5) | 38 (40.9) |
| | 1 | 106 (53.5) | 55 (59.1) |
| Histology, n (%) | ER and/or PR positive | 107 (54.0) | 59 (63.4) |
| | ER and PR negative | 88 (44.4) | 34 (36.6) |
| Metastatic (any location) at initial diagnosis, n (%) | | 77 (38.9) | 39 (41.9) |
| Non-CNS metastatic disease | | 192 (97.0) | 90 (96.8) |
| Prior local therapy for brain metastases | Prior radiotherapy | 140 (70.7) | 64 (68.8) |
| | Whole brain radiation | 77 (38.9) | 45 (48.4) |
| | Targeted radiation | 92 (46.5) | 32 (34.4) |
| | Prior surgery | 33 (16.7) | 13 (14.0) |



PRESENTED BY: Nancy Lin, nlin@partners.org

*Source: Nancy Lin, ASCO 2020.*

# PFS and OS in Brain Mets

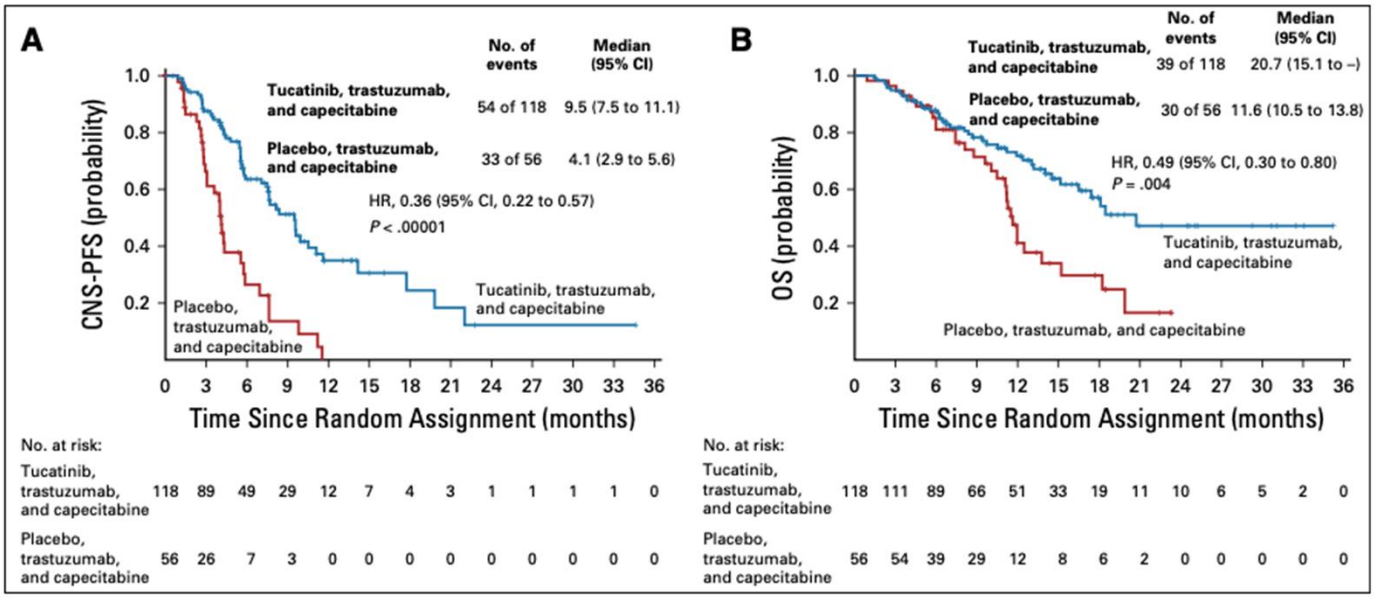



At 1 year PFS 40% in tucatinib vs 0% in placebo arm were alive and free of CNS progression

At 1 year OS 70% in tucatinib vs 46% in placebo arm

*Source: Lin, N.U. et al (2020). Intracranial Efficacy and Survival With Tucatinib Plus Trastuzumab and Capecitabine for Previously Treated HER2-Positive Breast Cancer With Brain Metastases in the HER2CLIMB Trial. Journal of Clinical Oncology, 38:23, 2610-2619.*

# PFS and OS in Active Brain Mets

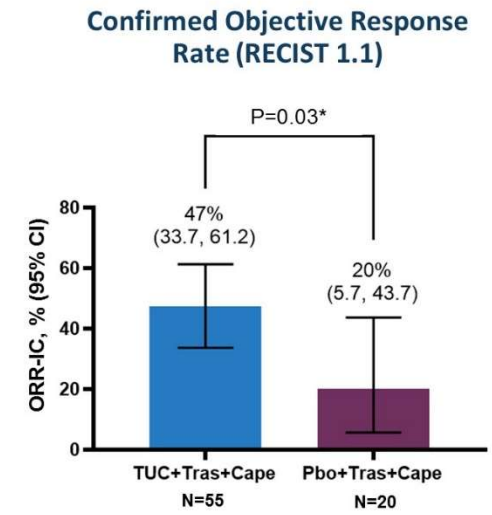



At 1 year PFS 35% in tucatinib vs 0% in placebo arm were alive and free of CNS progression

At 1 year OS 72% in tucatinib vs 41% in placebo arm

*Source: Lin, N.U. et al (2020). Intracranial Efficacy and Survival With Tucatinib Plus Trastuzumab and Capecitabine for Previously Treated HER2-Positive Breast Cancer With Brain Metastases in the HER2CLIMB Trial. Journal of Clinical Oncology, 38:23, 2610-2619.*

# Intracranial Response Rate (ORR-IC) in Patients with Active Brain Metastases and Measurable Intracranial Lesions at Baseline




*Stratified Cochran-Mantel-Haenszel P value

| | TUC+Tras+Cape (N=55) | Pbo+Tras+Cape (N=20) |
|---|---|---|
| Best Overall Intracranial Response[a], n (%) | | |
| Complete Response (CR) | 3 (5.5) | 1 (5.0) |
| Partial Response (PR) | 23 (41.8) | 3 (15.0) |
| Stable Disease (SD) | 24 (43.6) | 16 (80.0) |
| Progressive Disease (PD) | 2 (3.6) | 0 |
| Not Available[b] | 3 (5.5) | 0 |
| Subjects with Objective Response of Confirmed CR or PR, n | 26 | 4 |
| Duration of Intracranial Response (DOR-IC)[e] (95% CI)[f], months | 6.8 (5.5, 16.4) | 3.0 (3.0, 10.3) |

(a) Confirmed Best overall response assessed per RECIST 1.1. (b) Subjects with no post-baseline response assessments. (c) Two-sided 95% exact confidence interval, computed using the Clopper-Pearson method (1934). (d Cochran-Mantel-Haenszel test controlling for stratification factors (ECOG performance status: 0/1, and Region of world: North America/Rest of World) at randomization. (e) As estimated using Kaplan-Meier methods. (f) Calculated using the complementary log-log transformation method (Collett, 1994).



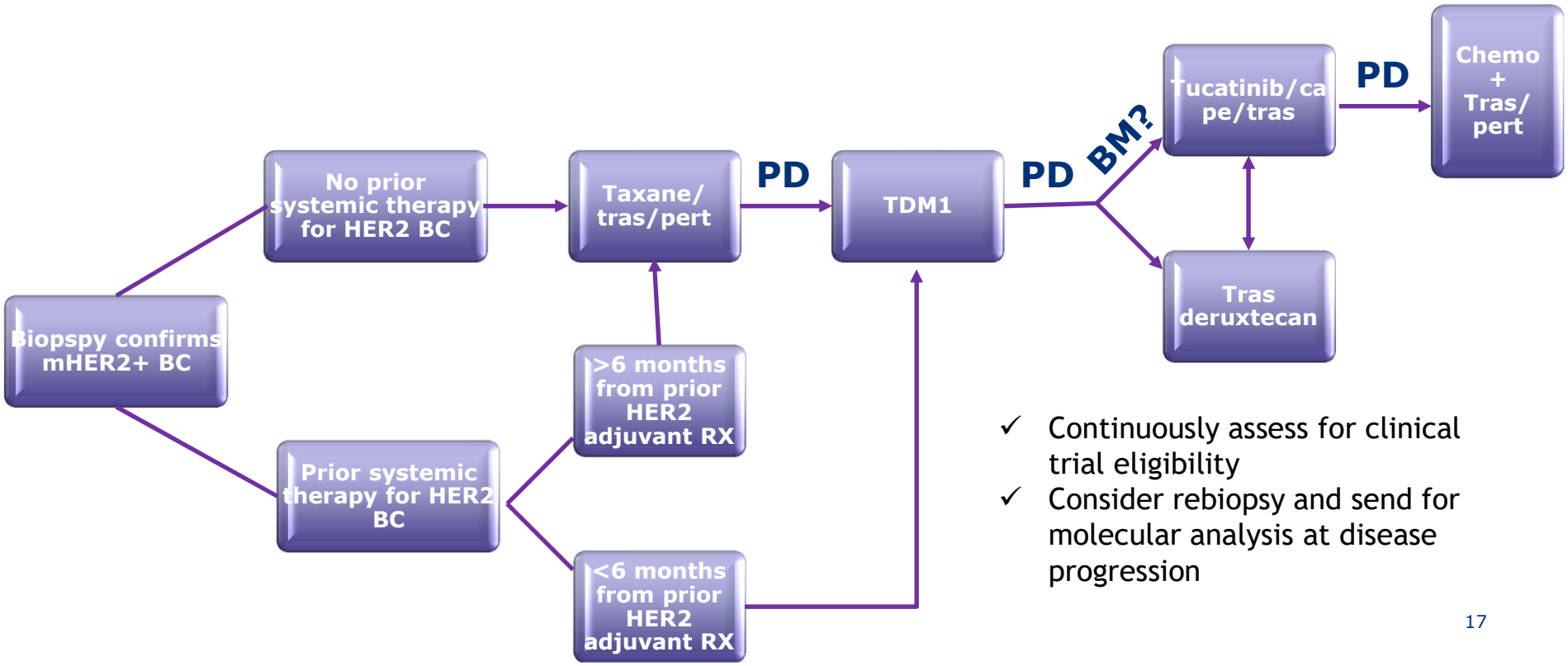
PRESENTED BY: Nancy Lin, nlin@partners.org

*Source: Nancy Lin, ASCO 2020.*

# HER2 CLIMB Summary

- HER2 CLIMB primary analysis showed clinically meaningful improvement of PFS and OS including patients with brain mets
- Tolerable safety profile
- Tucatinib, capecitabine, and trastuzumab doubled intracranial response, reduced risk of CNS progression or death by two thirds, and reduced the risk of death by nearly half
- Tucatinib is the first TKI to improve OS in patients with MBC with brain mets in a RCT

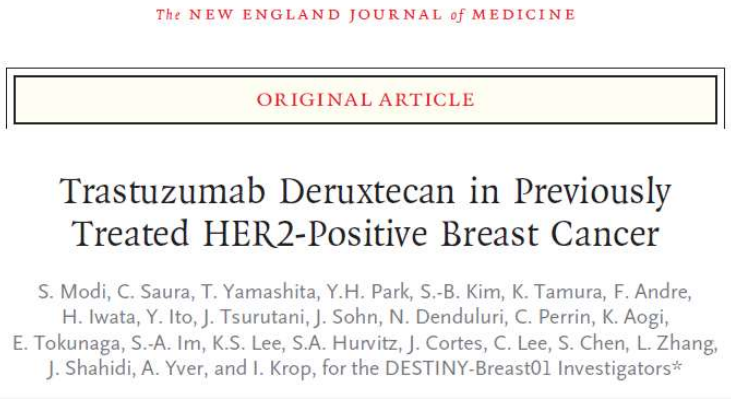
# State of the Art Management HER2+ MBC




- ✓ Continuously assess for clinical trial eligibility
- ✓ Consider rebiopsy and send for molecular analysis at disease progression

# Trastuzumab Deruxtecan

- Antibody drug conjugate- topoisomerase 1 inhibitor bound to trastuzumab
  - Higher payload to antibody ratio-8:1
  - Membrane permeable – preclinical studies kills neighboring cells
- DESTINY-Breast-01
  - Phase II, single arm, multi-institution
  - 184 patients
  - Median 6 prior lines therapy
  - All progressed on trastuzumab and TDM-1
  - 5.4 mg/kg IV q 21 days
  - ORR- 60.3%
    - CR 4.3%
    - PR 56%
  - Median response duration 14.8 months
  - Interstitial lung disease – fatal in 2.6% patients


The NEW ENGLAND JOURNAL of MEDICINE

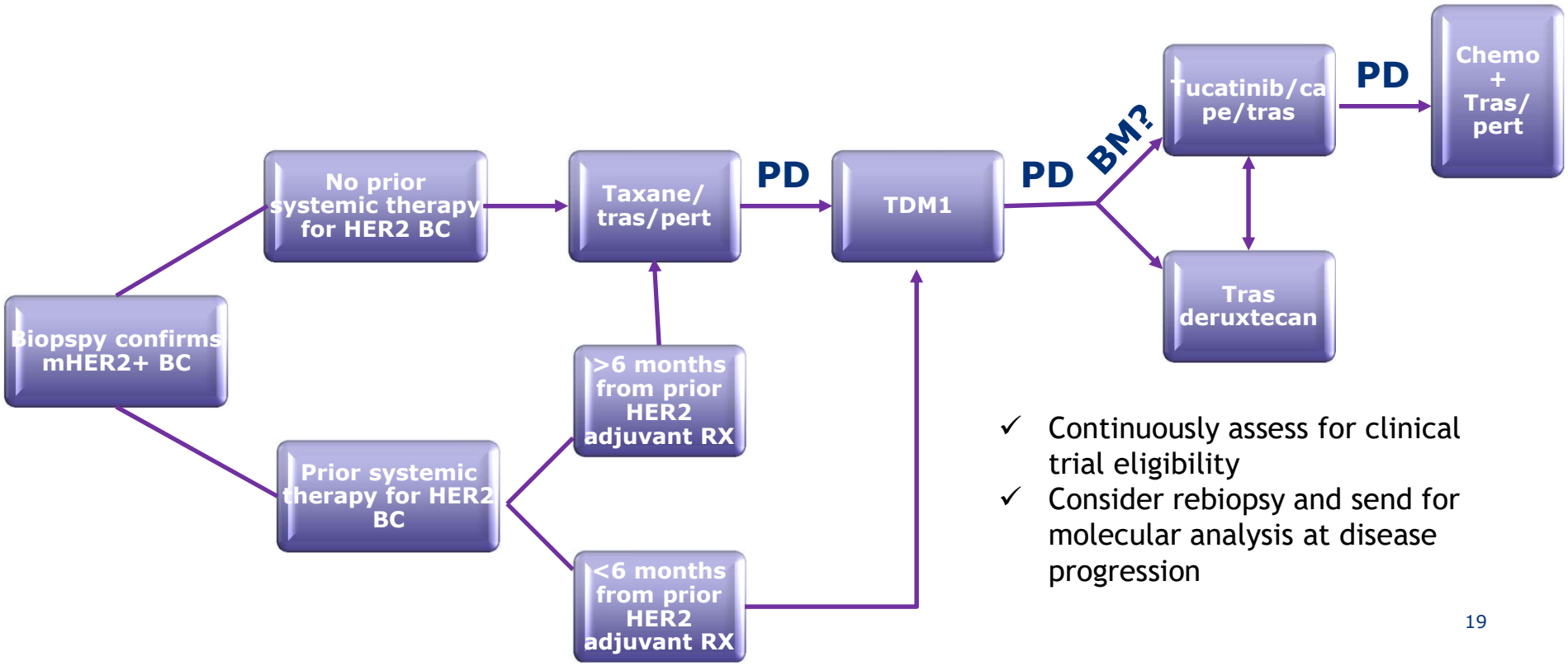
ORIGINAL ARTICLE

Trastuzumab Deruxtecan in Previously Treated HER2-Positive Breast Cancer

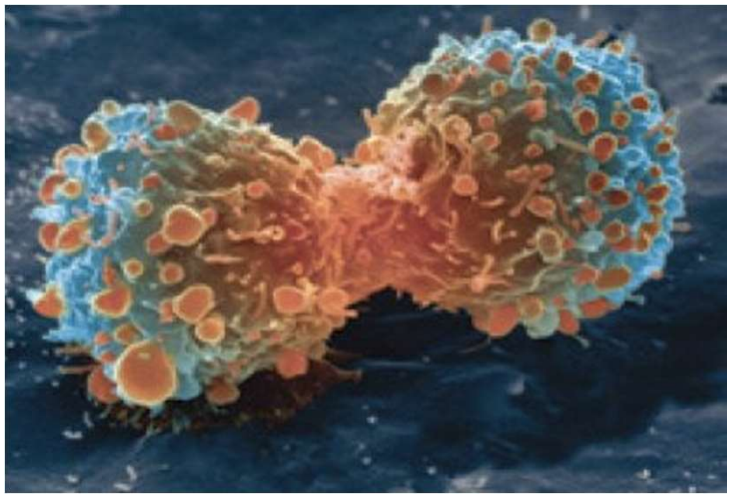
S. Modi, C. Saura, T. Yamashita, Y.H. Park, S.-B. Kim, K. Tamura, F. Andre, H. Iwata, Y. Ito, J. Tsurutani, J. Sohn, N. Denduluri, C. Perrin, K. Aogi, E. Tokunaga, S.-A. Im, K.S. Lee, S.A. Hurvitz, J. Cortes, C. Lee, S. Chen, L. Zhang, J. Shahidi, A. Yver, and I. Krop, for the DESTINY-Breast01 Investigators*

- FDA approved in Dec 2019

# State of the Art Management HER2+ MBC




- ✓ Continuously assess for clinical trial eligibility
- ✓ Consider rebiopsy and send for molecular analysis at disease progression

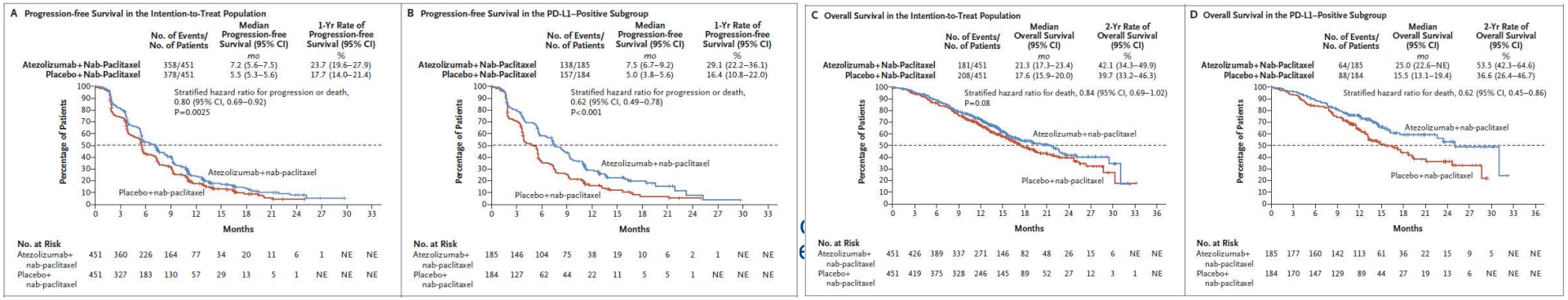


# Triple negative breast cancer

*Source: Harvard Stem Cell Institute*

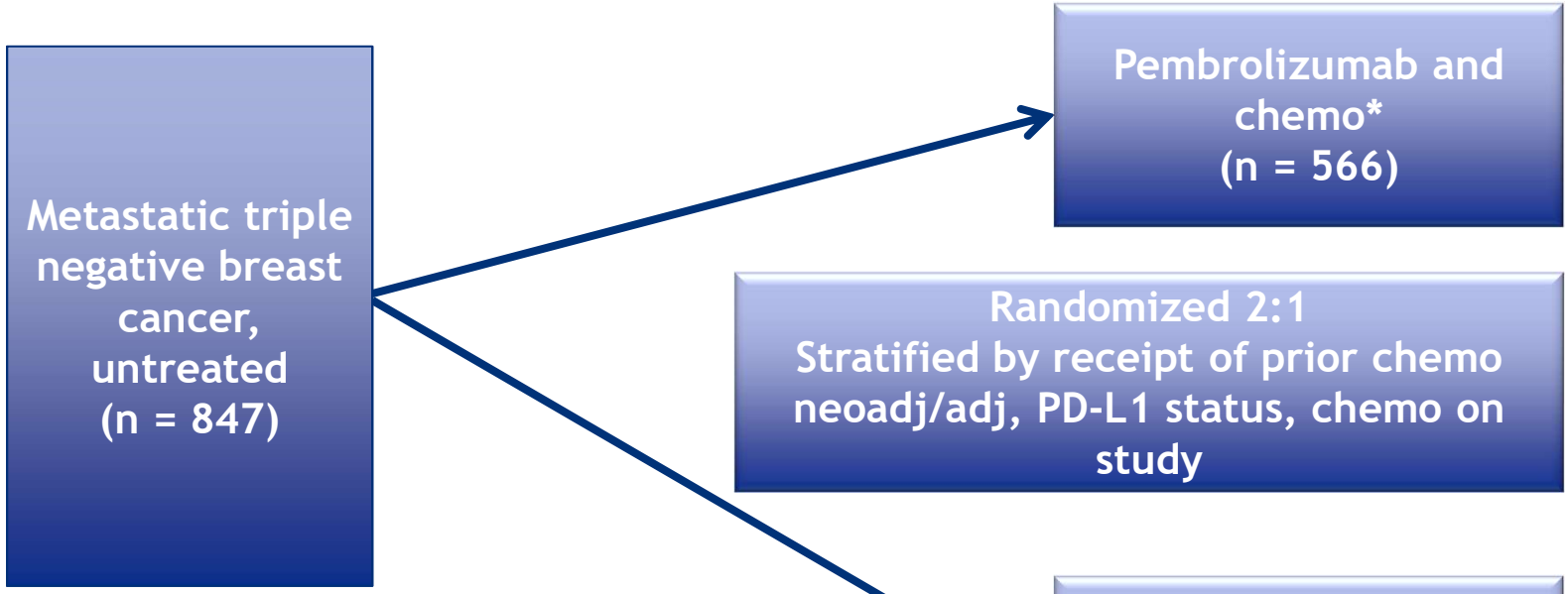
# Immunotherapy in TNBC

- IMpassion130:
  - 847 pts w/untreated mTNBC randomized to atezolizumab w/nab-paclitaxel vs placebo w/nab-paclitaxel




*Source: Schmid, P., Adams, S., Rugo, H. S., Schneeweiss, A., Barrios, C. H., Iwata, H., … Emens, L. A. (2018). Atezolizumab and Nab-Paclitaxel in Advanced Triple-Negative Breast Cancer. New England Journal of Medicine, 379(22), 2108–2121.*

# Keynote 355 – Trial Design



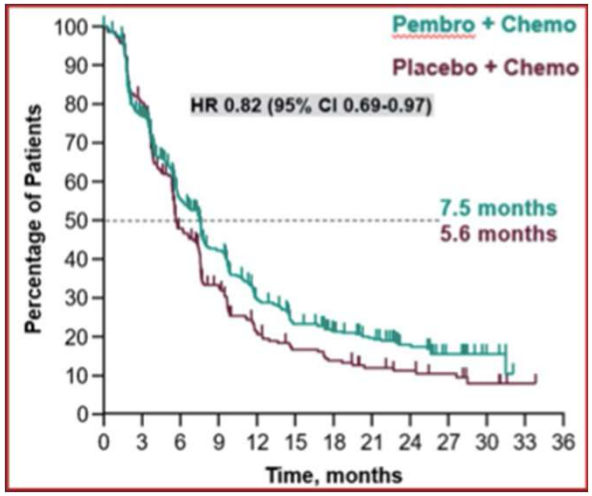

*Chemo options:
- -Nab-paclitaxel
- -Paclitaxel
- -Gemcitabine/carboplatin

Primary Endpoints:
- PFS, OS in ITT & PDL1+

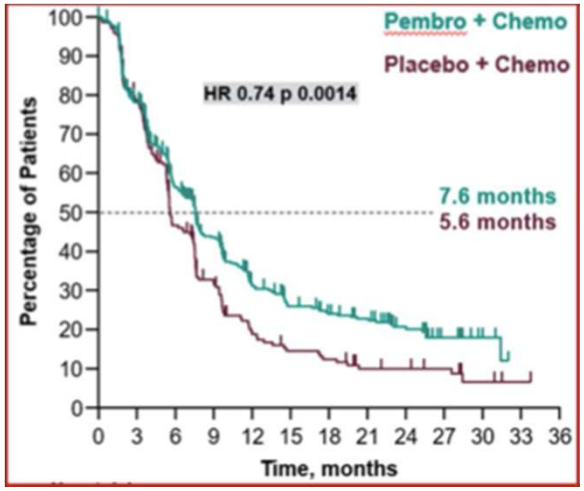
Secondary Endpoints:
- ORR, DOR, DCR, Safety

# Keynote 355 – PFS

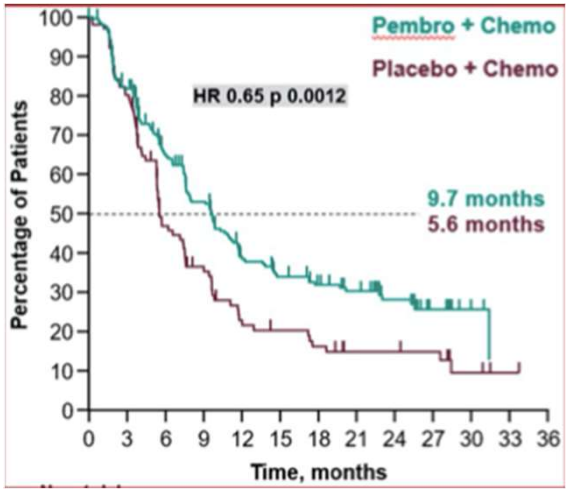
## ITT




## PD-L1 CPS ≥ 1



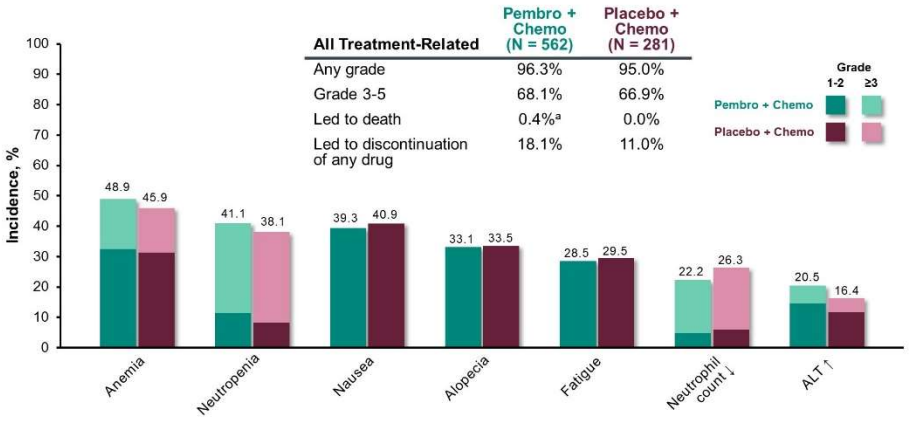

## PD-L1 CPS ≥ 10




*Source: ASCO, 2020.*

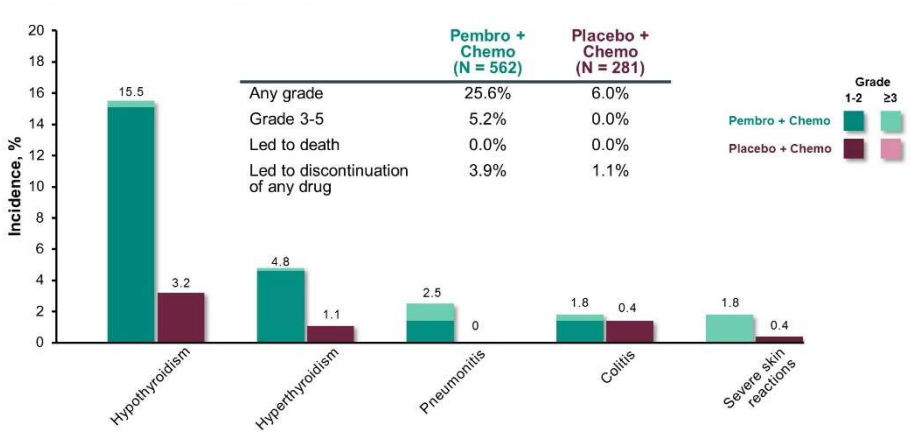
# Keynote 355 – Adverse Events

## Treatment-Related AEs




| All Treatment-Related | Pembro + Chemo (N = 562) | Placebo + Chemo (N = 281) |
|---|---|---|
| Any grade | 96.3% | 95.0% |
| Grade 3-5 | 68.1% | 66.9% |
| Led to death | 0.4%[a] | 0.0% |
| Led to discontinuation of any drug | 18.1% | 11.0% |

## Immune-Mediated AEs



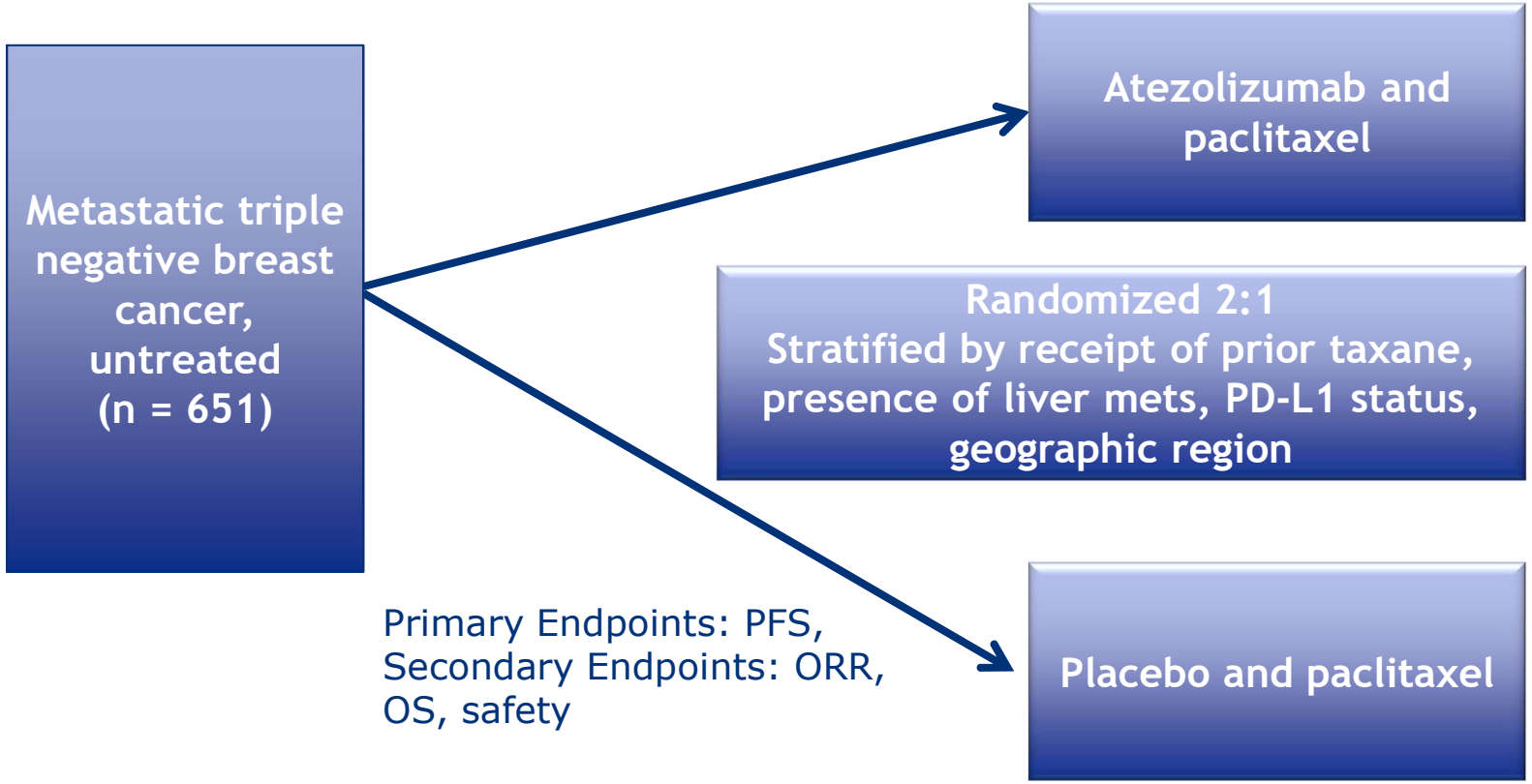

| | Pembro + Chemo (N = 562) | Placebo + Chemo (N = 281) |
|---|---|---|
| Any grade | 25.6% | 6.0% |
| Grade 3-5 | 5.2% | 0.0% |
| Led to death | 0.0% | 0.0% |
| Led to discontinuation of any drug | 3.9% | 1.1% |

*Source: ASCO, 2020.*

# KEYNOTE-355 Summary

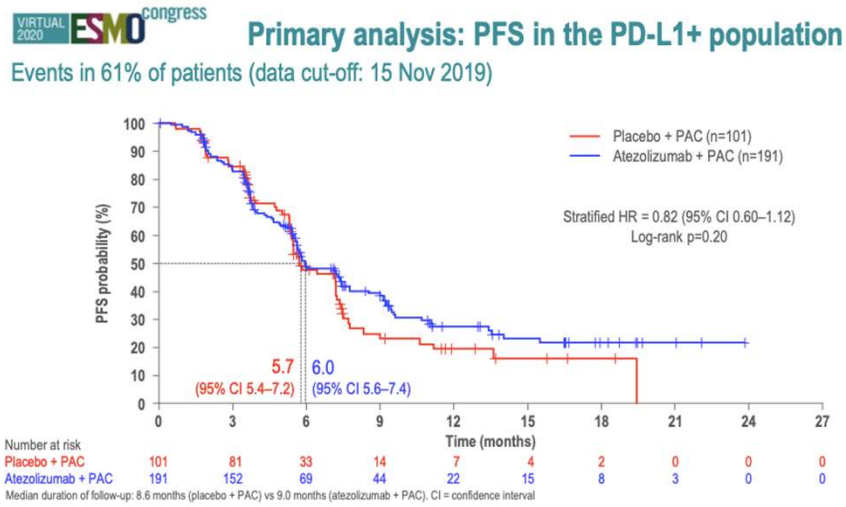
- Met primary endpoint of PFS of adding pembrolizumab to chemo in patients w/CPS > 10
- No benefit of PFS in CPS < 1
- Safety consistent with known treatments
- OS data not yet available

# IMpassion131 – Trial Design

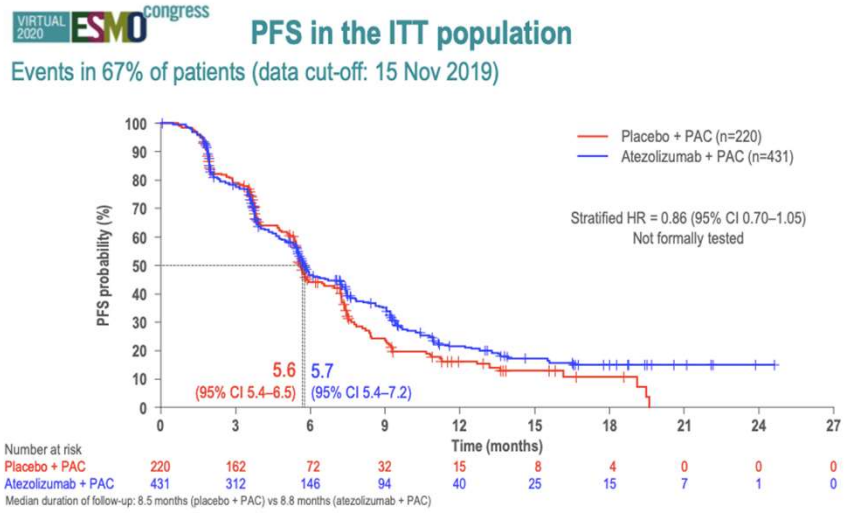


# IMpassion131 PFS

## PFS PDL1+

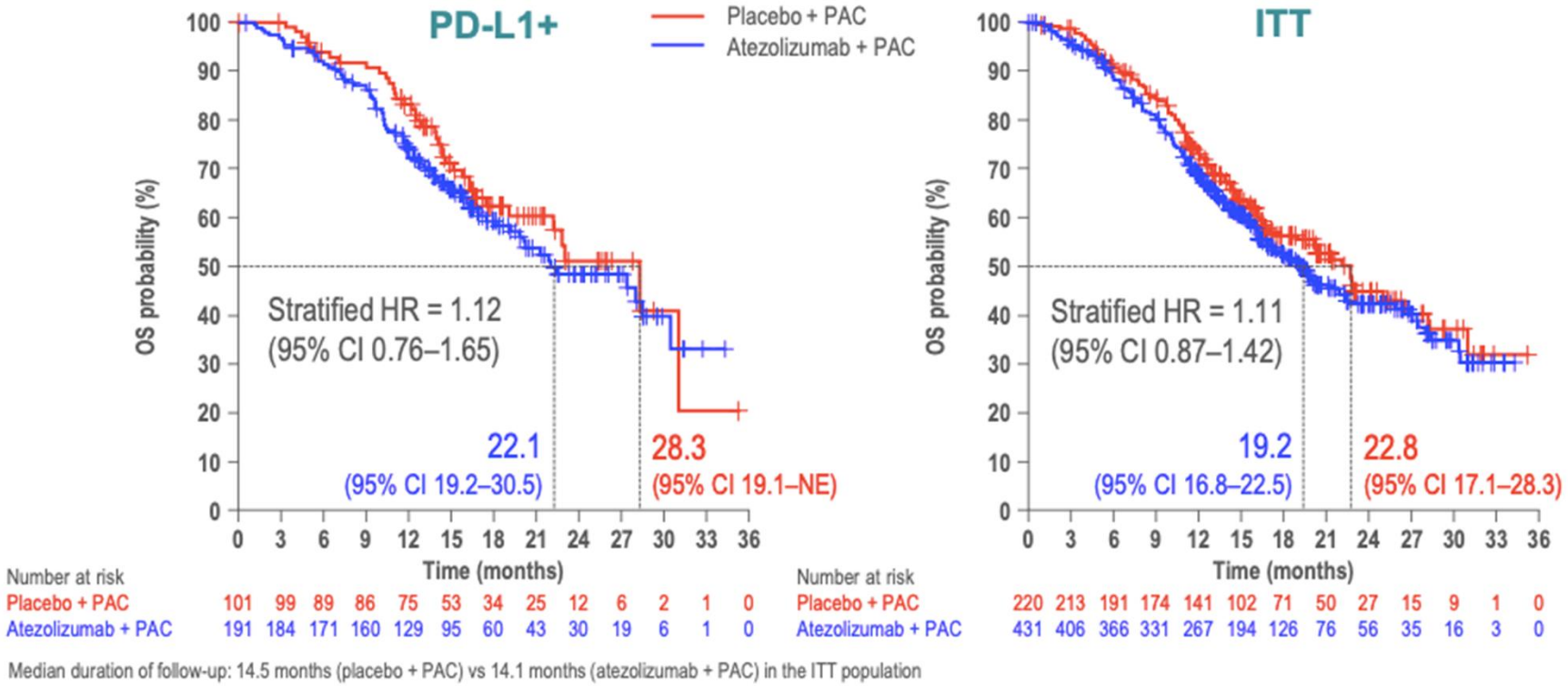



## PFS ITT




*Source: ESMO, 2020.*

# IMpassion131 OS




Median duration of follow-up: 14.5 months (placebo + PAC) vs 14.1 months (atezolizumab + PAC) in the ITT population

*Source: ESMO, 2020.*

# IMpassion131 Summary

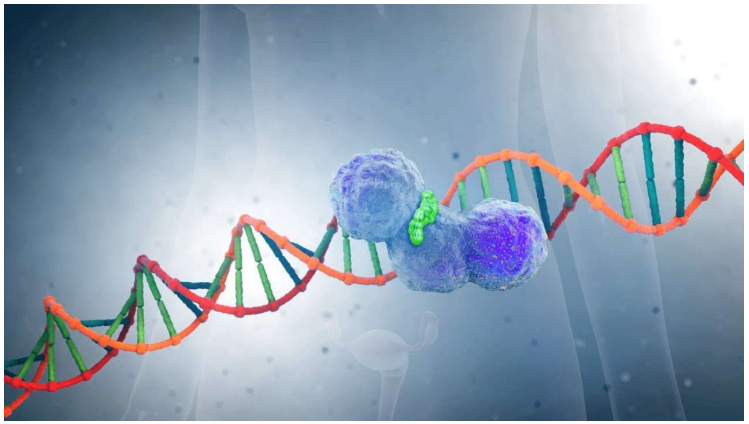
- Did not meet primary or secondary endpoints:

No benefit of the addition of atezolizumab to paclitaxel in PFS in PDL1+ patients. No benefit in OS.

- Safety profile consistent with known effects from individual drugs
- Further exploration indicated to explain the discordance between IMpassion130 and IMpassion131

# Why The Difference? What do we do now?

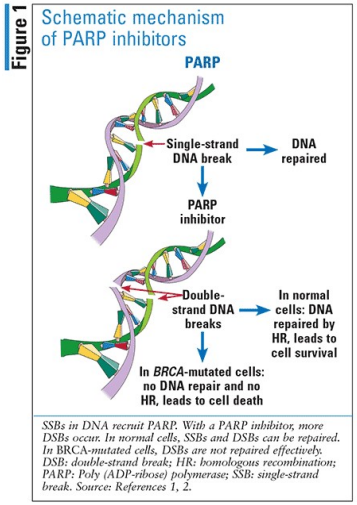
- Chemotherapy backbone may matter
  - Steroids with paclitaxel
- Why a benefit with KEYNOTE-355 and KEYNOTE-522?
  - Microenvironment matters
    - Primary vs metastatic
- Could this be chance?
- What we do know:
  - For PDL1 + (Ventana SP142) > 1% would use atezolizumab
  - Would not combine paclitaxel



# PARP Inhibitors

# PARP Inhibitors (PARPi)

- Cancer cells synthetic lethality in homologous recombinant deficient (HRD) cells → cell death
- 2 FDA approved PARPi for gBRCA 1/2 mutated breast cancer in 2018: olaparib and talozaparib
- Up to 60% TNBC show homologous recombination deficiencies- BRCA like phenotype or BRCA-ness
  - Treat with PARPi
- Combination with platinums

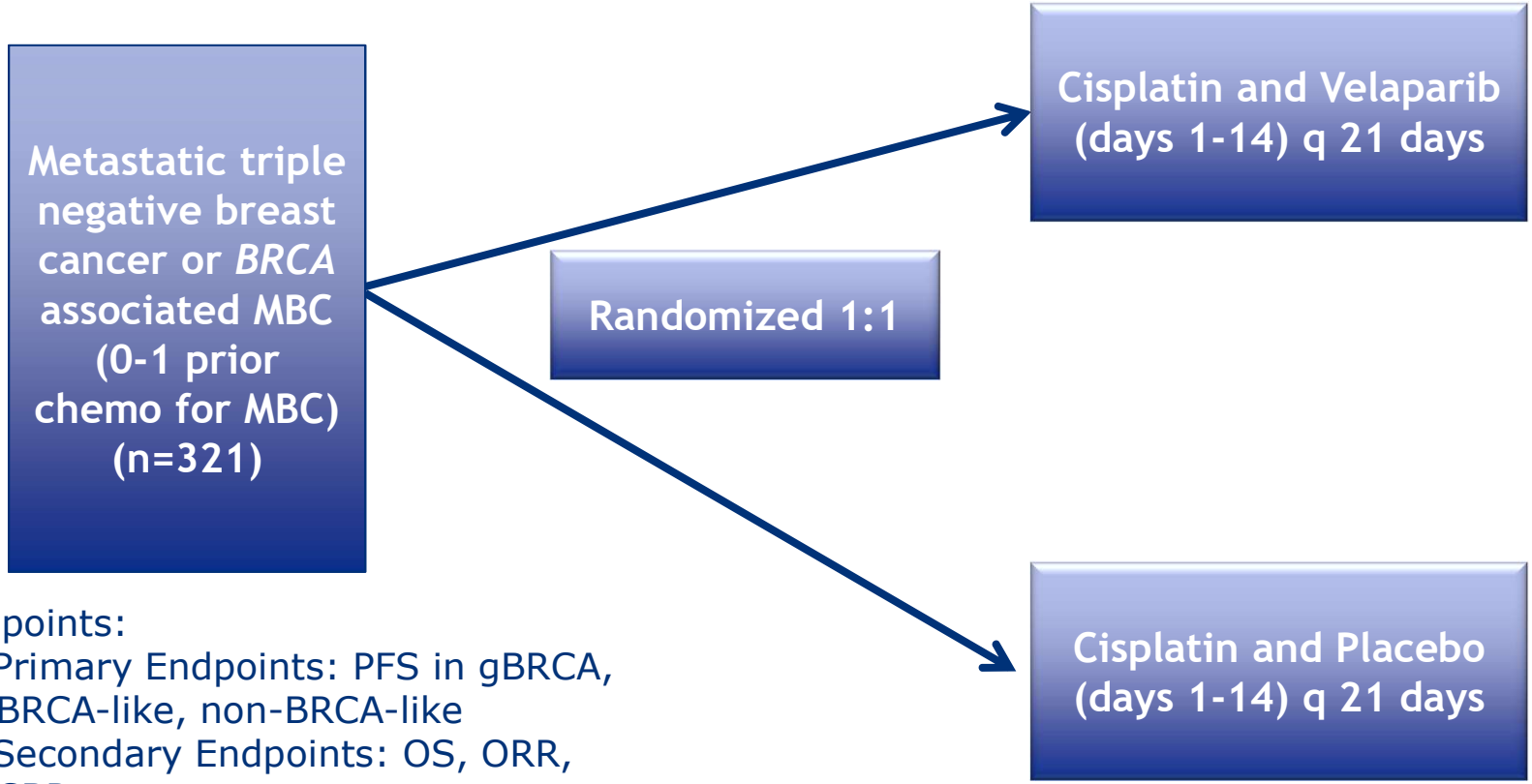



*Source: Iqbal, S & Rattu, Mohammad & Shah, N. (2018). Role of PARP inhibitors in BRCA-related malignancies. U.S. Pharmacist. 43. HS-10.*

# SWOG S1416

- Phase II Randomized Placebo Controlled Trial of Cisplatin with or without Veliparib in Metastatic TNBC and or *BRCA* mutation associated breast cancer

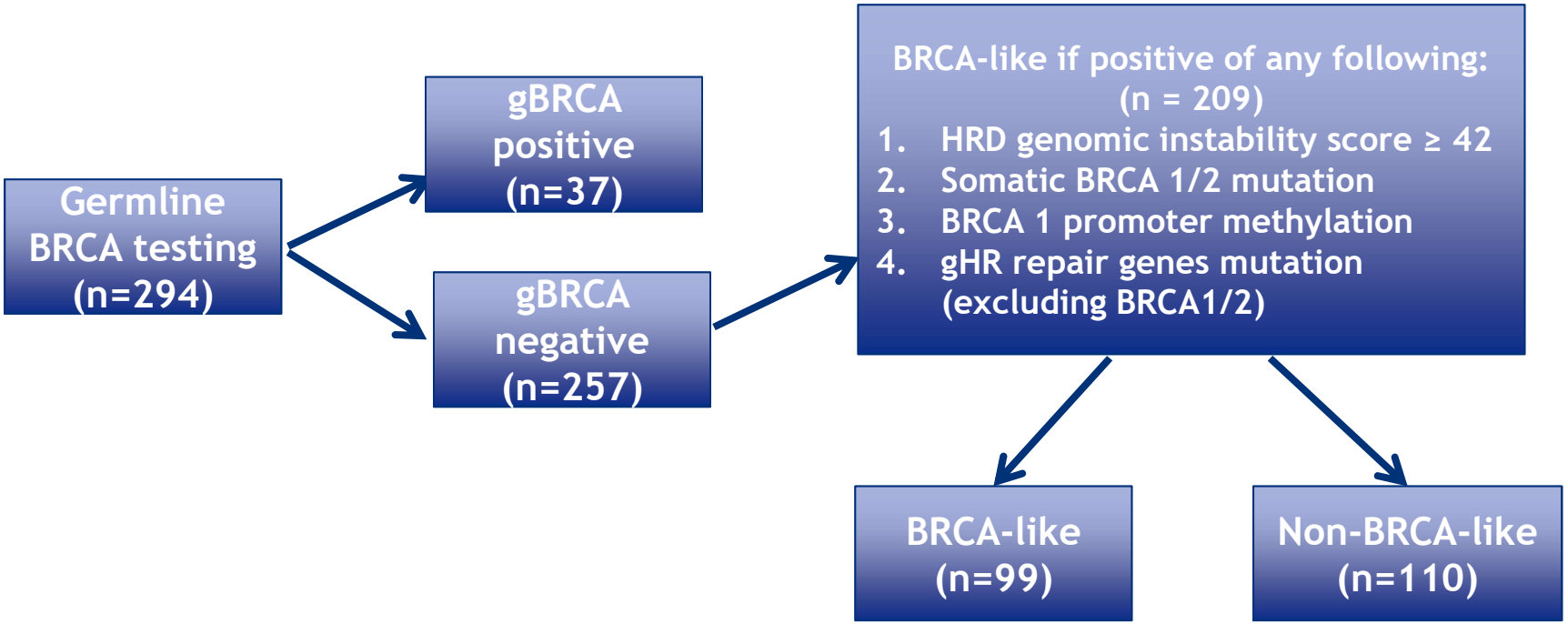
# S1416 – Trial Design




Endpoints:

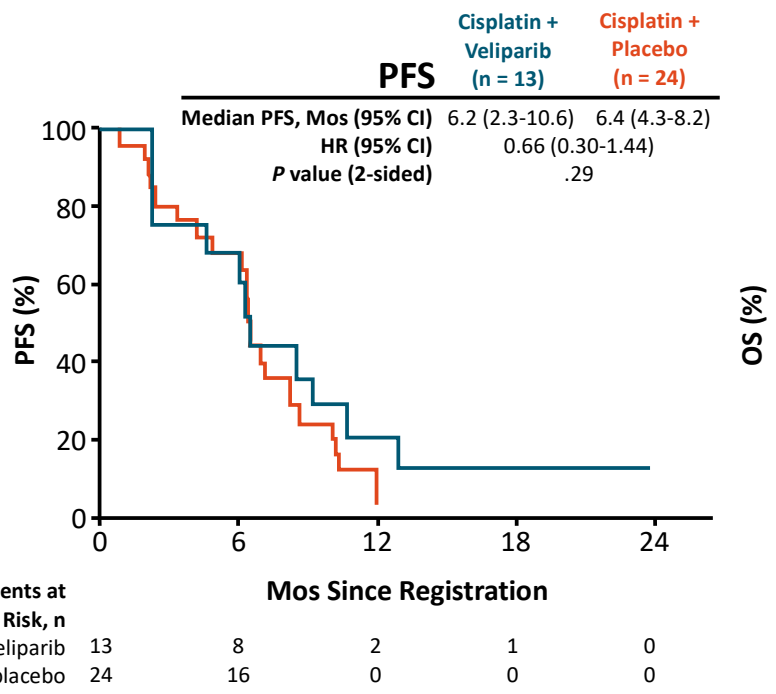
- Primary Endpoints: PFS in gBRCA, BRCA-like, non-BRCA-like
- Secondary Endpoints: OS, ORR, CBR

# S1416 Germline Testing

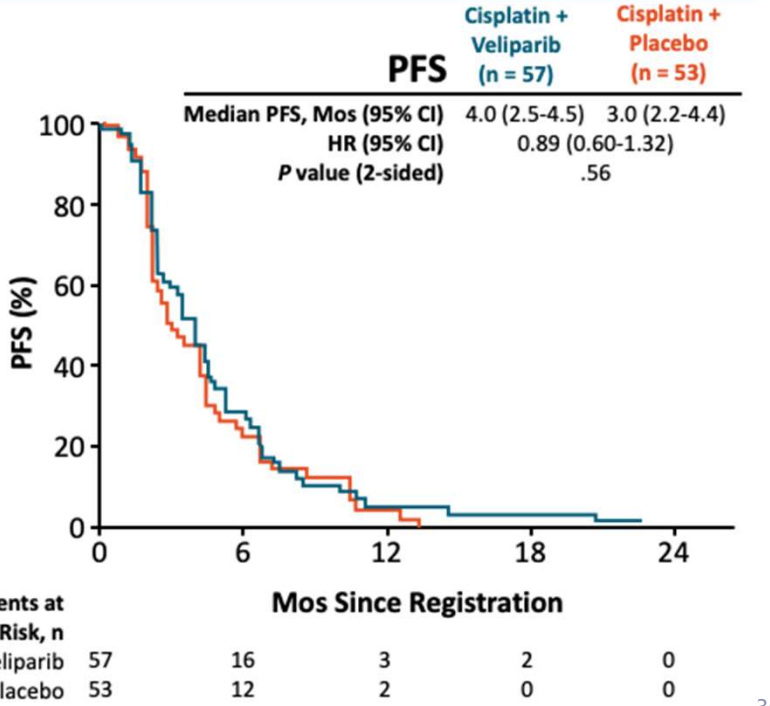


# Germline BRCA Group and Non-BRCA-Like Group

## g*BRCA*



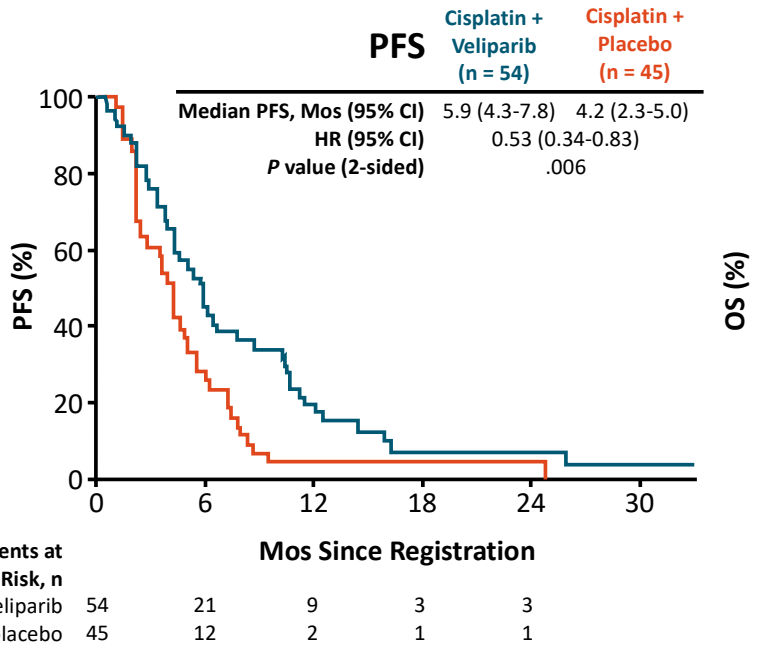

## Non-BRCA-Like



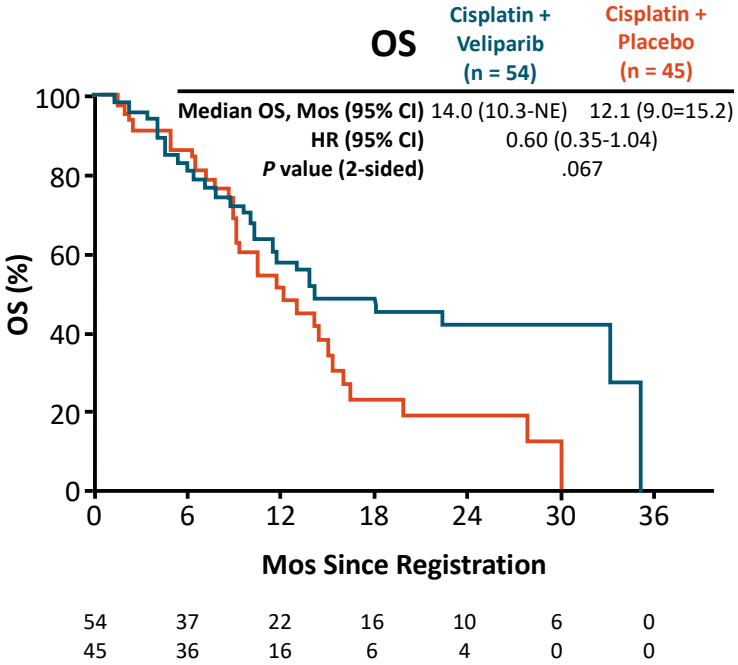

*Source: University of Pennsylvania, 2020; Clinical Care Options, 2020.*

# BRCA-like Group

## Progression Free Survival (PFS)




## Overall Survival




*Source: University of Pennsylvania, 2020; Clinical Care Options, 2020.*

# SWOG 1416: Safety

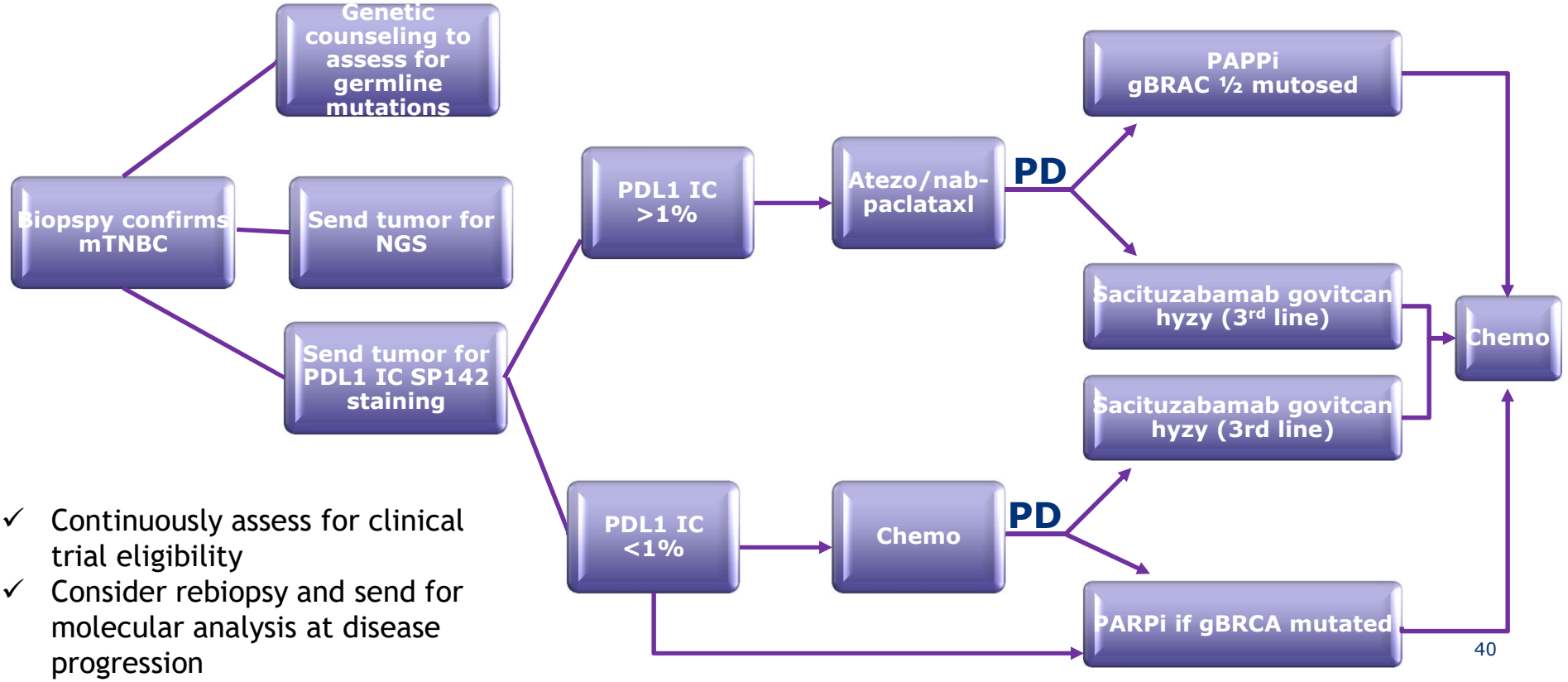
| Adverse Event, % | Cisplatin + Veliparib (n = 154) | | Cisplatin + Placebo (n = 149) | |
|---|---|---|---|---|
| | All Grades | Grade 3/4 | All Grades | Grade 3/4 |
| Nausea | 75 | 12 | 62 | 7 |
| Fatigue | 62 | 5 | 56 | 6 |
| Anemia | 61 | 23 | 56 | 7 |
| Neutropenia | 59 | 46 | 42 | 19 |
| Leukopenia | 53 | 27 | 46 | 7 |
| Vomiting | 45 | 6 | 35 | 3 |
| Thrombocytopenia | 52 | 19 | 24 | 3 |
| Anorexia | 29 | -- | 23 | -- |
| Peripheral sensory neuropathy | 26 | -- | 26 | -- |
| Lymphocyte count decreased | 24 | 7 | 27 | 6 |

*Source: Clinical Care Options, 2020.*

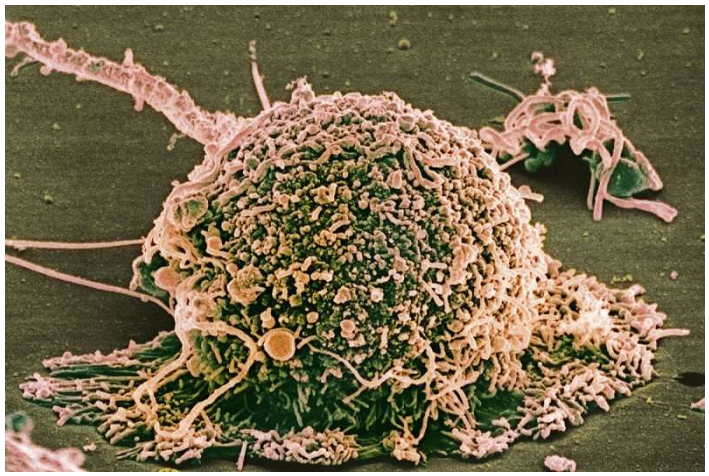
# S1416 Summary

- Combination of veliparib to cisplatin improved PFS in BRCA-like phenotype
- No benefit in gBRCA, but underpowered for analysis
  - BROCADE- phase III veliparib w/platinum improved PFS for gBRCA mutated MBC
- More grade 3/4 hematologic toxicities associated with the addition of PARPi, but otherwise tolerable
- Further analysis needed for HRD biomarker

# State of the Art Management of TNBC



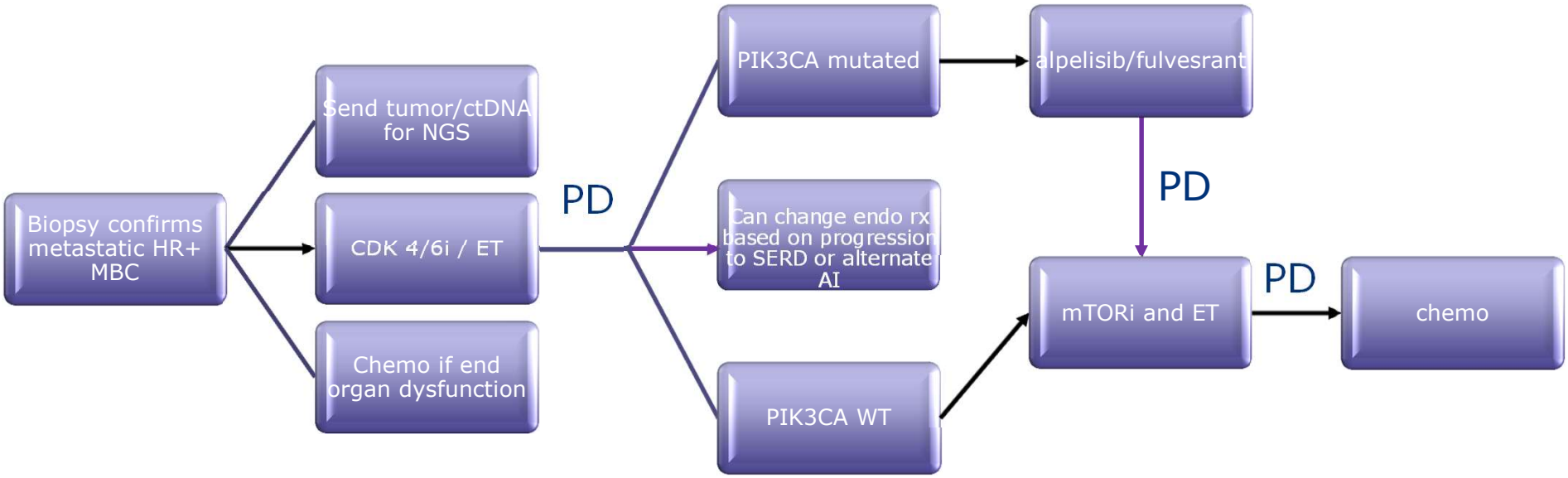

- ✓ Continuously assess for clinical trial eligibility
- ✓ Consider rebiopsy and send for molecular analysis at disease progression



# Hormone positive breast cancer

*Source: Memorial Sloan Kettering Cancer Center, 2020.*

# State of the Art Management HR+ MBC




- ✓ Continuously assess for clinical trial eligibility
- ✓ Consider rebiopsy and send for molecular analysis at disease progression

# Summary

- Advanced breast cancer becoming increasingly personalized
- New therapies in HER2+ breast cancer
  - How to sequence?
- Immunotherapy for TNBC if PDL1+
- Clinical trial whenever possible

# Questions?