# MANAGEMENT OF METASTATIC BREAST CANCER

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## MANAGEMENT OF METASTATIC BREAST CANCER

RELEVANT FINANCIAL RELATIONSHIPS IN THE PAST TWELVE MONTHS BY PRESENTER OR SPOUSE/PARTNER.

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SPEAKERS BUREAU: BMS AND MERCK

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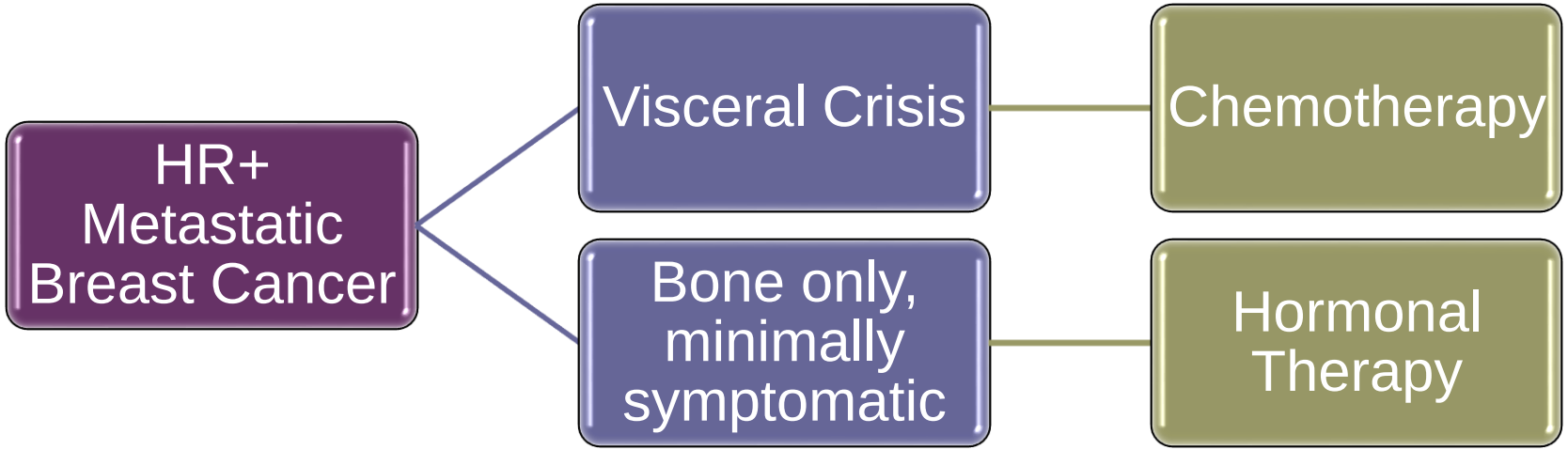
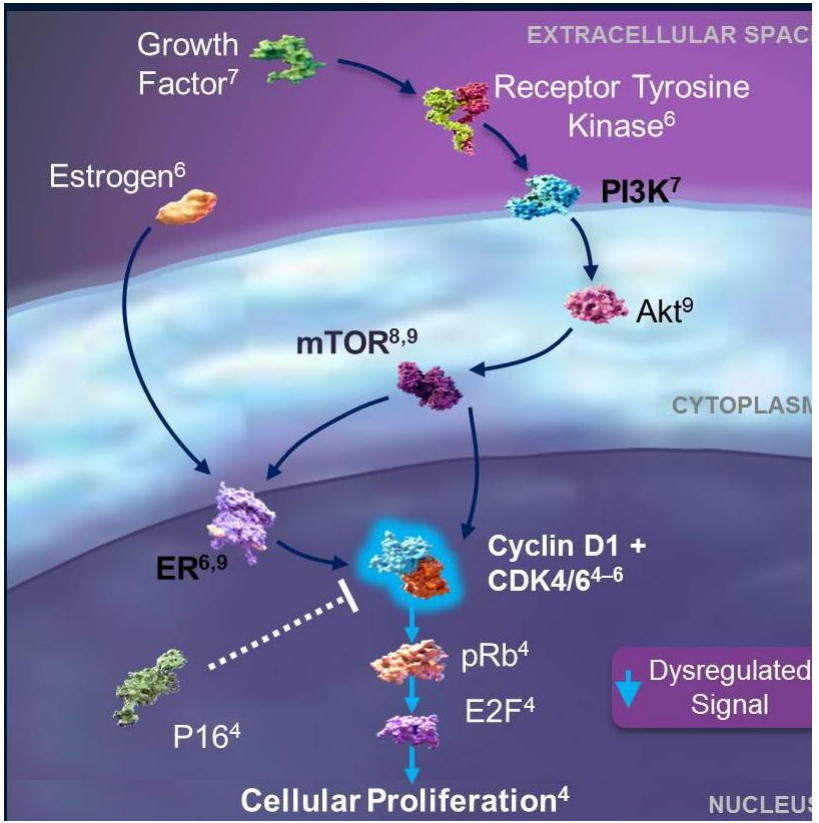
# HORMONE RECEPTOR + BREAST CANCER


HR+ Metastatic Breast Cancer
Visceral Crisis
Chemotherapy
Bone only, minimally symptomatic
Hormonal Therapy

# CDK 4/6 Inhibition

- Cyclin dependent kinases (CDK's) partner with cyclins to regulate cell cycle progression.
- Cyclin D1: CDK4/6:Rb pathway pathway mediates the progression of G1 to S phase in the cell cycle. This pathway is essential to allow the cancer cell division and growth
- Overexpression and  overactivation of the ER pathway leads to an increase in Cyclin D1 and activation of CyclinD:CDk4/6 pathway and dyslegulation of the cell cycle.



# Available CDK4/6 Inhibitors in 2018

| | Palbociclib | Ribociclib | Abemaciclib |
|---|---|---|---|
| Route | PO | PO | PO |
| Dose, mg | 125 QD | 600 QD | 200 BID |
| Schedule | 3 wks on/1 wk off | 3 wks on/1 wk off | Continuous |
| Half-life, hr | 27 | 32.6 | 17-38 |
| ORR (single agent) % | 6 | 2.3 | 19.7 |
| CNS penetration | Uncertain | No | Yes |
| Approval | • With an AI, First Line Metastatic HR+<br>• With with fulvestrant after failing another endocrine therapy | In combination with AI first line metastatic HR+ | • With an AI, First Line Metastatic HR+<br>• With with fulvestrant or as monotherapy after failing another endocrine therapy |

# Comparative Toxicities of CDK4/6 Inhibitors: Early Phase Trials

| Adverse Event (All Grades), % | Palbociclib[1] (N = 37) | Ribociclib[2] (N = 67) | Abemaciclib[3] (N = 173) |
|---|---|---|---|
| Neutropenia | 94 | 46 | 23 |
| Anemia | 70 | 28 | 20 |
| Thrombocytopenia | 76 | 34 | 23 |
| Nausea | 24 | 45 | 45 |
| Vomiting | 5 | 25 | 25 |
| Diarrhea | 16 | 27 | 63 |
| Fatigue | 68 | 33 | 41 |
| QTc prolongation | No | 9 | No |

1. DeMichele A, et al. Clin Cancer Res. 2015;21:995-1001.
2. Infante JR, et al. Clin Cancer Res. 2016;22:5696-5705.
3. Patnaik A, et al. Cancer Discov. 2016;6:740-753.

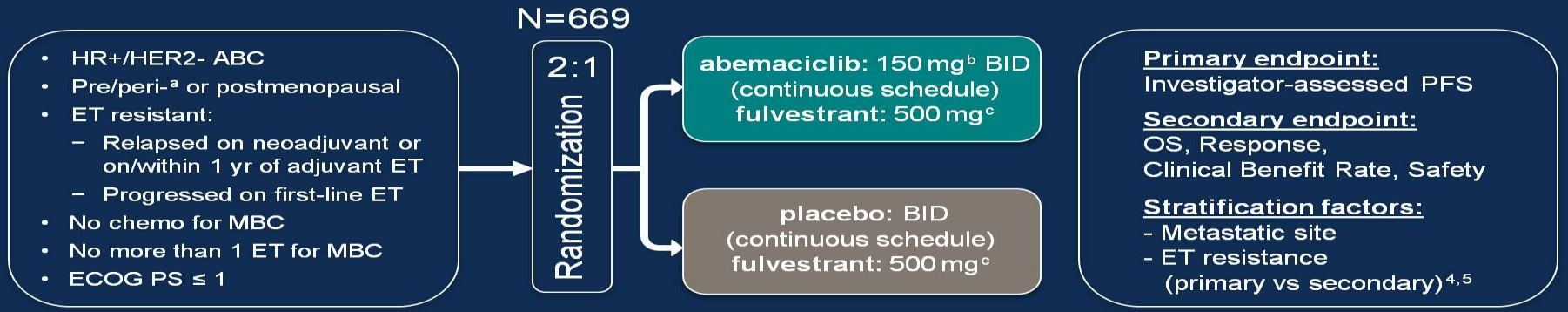
# PFS with CDK4/6 Inhibitors Comparison

| | PALOMA-1 | PALOMA-2 | MONALEESA-2 | MONARCH-3 | PALOMA-3 | MONARCH-2 |
|---|---|---|---|---|---|---|
| Design | Phase II open label, 1st line | Phase III placebo control, 1st line | Phase III placebo control, 1st line | Phase III placebo control, 1st line | **Phase III placebo control, 2nd line** | **Phase III placebo control, 2nd line** |
| Endocrine partner | Letrozole | Letrozole | Letrozole | Letrozole | **Fulvestrant** | **Fulvestrant** |
| CDK4/6 Inhibitor | Palbociclib | Palbociclib | Ribociclib | **Abemaciclib** | **Palbociclib** | **Abemaciclib** |
| Patients on study, n | 165 | 666 | 668 | 493 | **521** | **669** |
| **Efficacy (CDK4/6 inhibitor vs. control arm)** | | | | | | |
| **Primary end point: PFS** | | | | | | |
| HR | 0.49 | 0.58 | 0.56 | 0.54 | **0.46** | **0.55** |
| Median PFS, months | 20.2 vs 10.2 (10 mo) | 24.8 vs 14.5 (10.3 mo) | 25.3 vs 16 (9.3 mo) | NR vs 14.7 | **9.5 vs 4.6 (4.9 mo)** | **16.4 vs 9.3 (7.1 mo)** |

Presented By Ingrid Mayer at 2017 ASCO Annual Meeting

# MONARCH-2 Study: Abemaciclib + Fulvestrant

## Study Design




- **Statistics: 378 events for 90% power at one-sided α of .025 assuming a true HR of .703**
- Patients enrolled in 142 centers in 19 countries

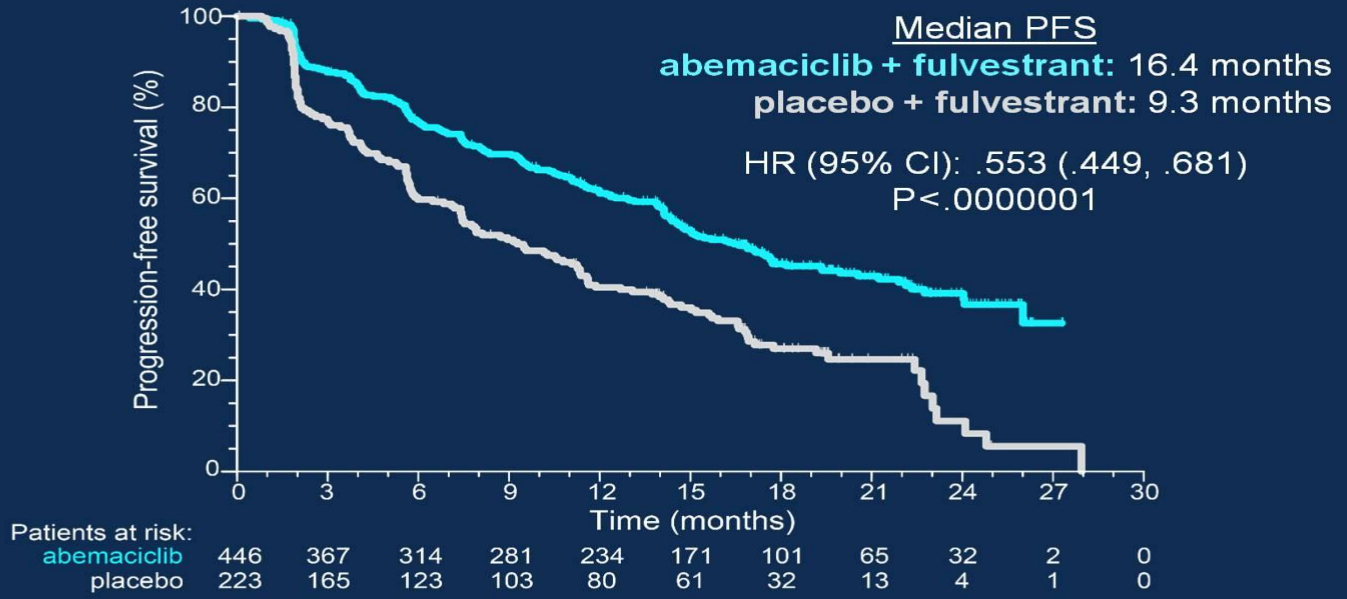
[a]Required to receive GnRH agonist
[b]Dose reduced by protocol amendment in all new and ongoing patients from 200 mg to 150 mg BID after 178 patients enrolled
[c]Fulvestrant administered per label

4. Cardoso F et al. *The Breast* 6:489-502, 2014; 5. Cardoso F et al. *Ann Oncol* 25:1871-88, 2014.

| | | | |
|---|---|---|---|
| **Metastatic site[a]** | **Visceral** | **245 (54.9)** | **128 (57.4)** |
| | **Bone only** | **123 (27.6)** | **57 (25.6)** |
| | **Other (non-visceral soft tissue)** | **75 (16.8)** | **38 (17.0)** |

# MONARCH-2 Results

## Primary Endpoint: PFS (ITT)




PFS benefit confirmed by blinded independent central review (HR: .460; 95% CI: .363, .584; P<.000001)

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# PALOMA-3 and MONARCH-2 Different Population

| | PALOMA-3 | MONARCH-2 |
|---|---|---|
| Population | HR+/HER2- | HR+/HER2- |
| Prior ET | PD on previous ET on/within 1 yr of adjuvant or on therapy for MBC | PD on previous ET on/within 1 yr of adjuvant or on therapy for MBC |
| Dosing | Palbociclib: 125 mg daily, 3 wks on, 1 wk off; Fulvestrant: 500 mg (per label) | Abemaciclib: 150mg BD, continuous; Fulvestrant: 500 mg (per label) |
| Prior chemotherapy for MBC | ≤1 | Not permitted |
| # lines of ET in MBC | Any | 1 |

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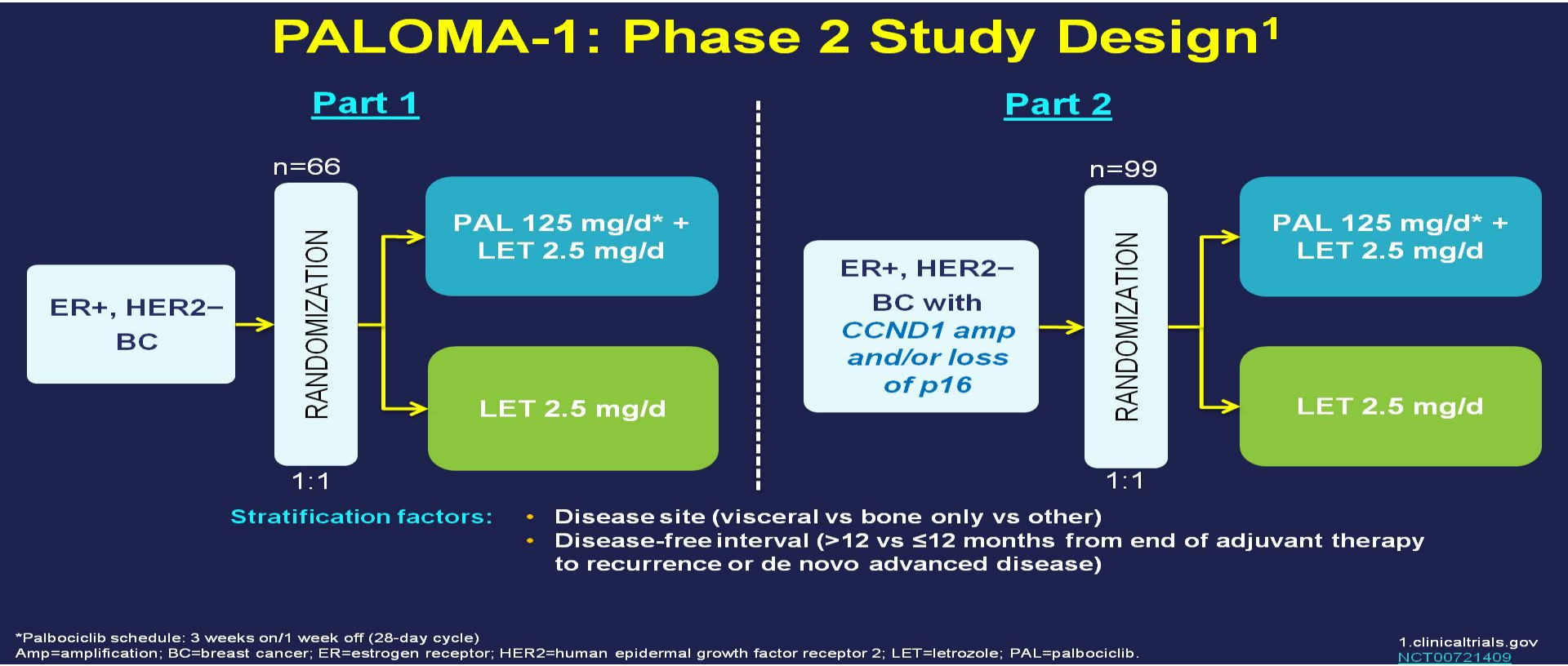
# ASCO 2017 Palbociclib OS Update




*Palbociclib schedule: 3 weeks on/1 week off (28-day cycle)
Amp=amplification; BC=breast cancer; ER=estrogen receptor; HER2=human epidermal growth factor receptor 2; LET=letrozole; PAL=palbociclib.

1.clinicaltrials.gov NCT00721409

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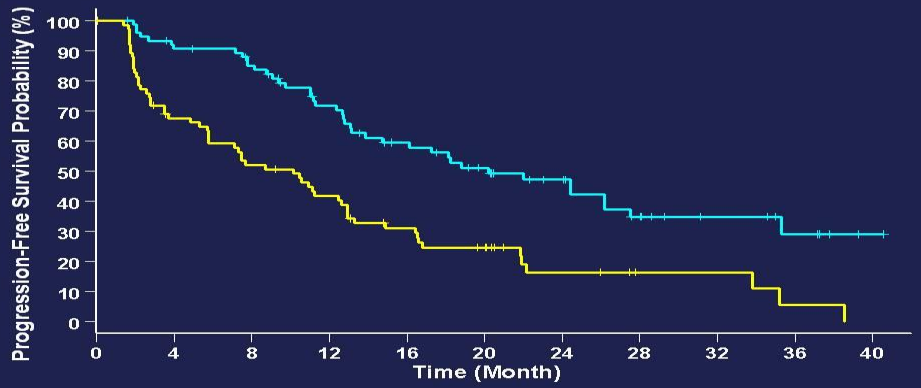
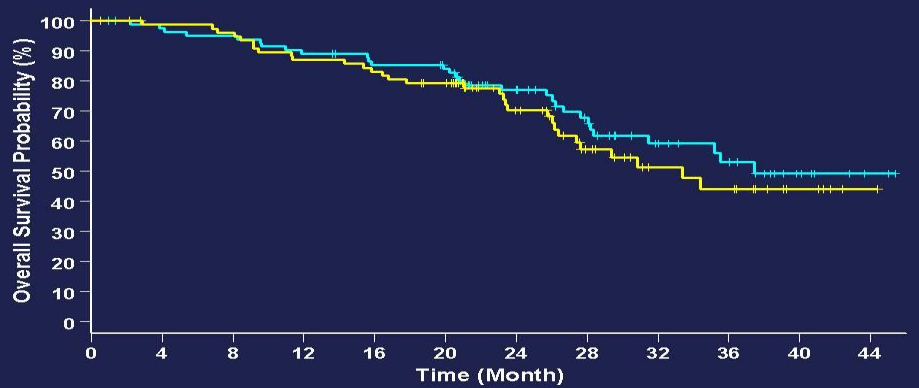
# ASCO 2017 Palbociclib OS Update

## PFS and OS (ITT)
### (Data Cut-Off: Nov 29, 2013)

| PFS | PAL+LET (N=84) | LET (N=81) |
|---|---|---|
| Patients with events, n (%) | 41 (49) | 59 (73) |
| Median PFS, months (95% CI) | 20.2 (13.8, 27.5) | 10.2 (5.7, 12.6) |
| Hazard Ratio (95% CI) | 0.488 (0.319, 0.748) | |
| *P* value | 0.0004 | |

| OS | PAL+LET (N=84) | LET (N=81) |
|---|---|---|
| Patients with events, n (%) | 30 (36) | 31 (38) |
| Median OS, months (95% CI) | 37.5 (28.4, NR) | 33.3 (26.4, NR) |
| Hazard Ratio (95% CI) | 0.813 (0.492, 1.345) | |
| *P* value | 0.42 | |




- Median duration of follow-up: PAL+LET, 29.6 months (95% CI: 27.9, 36.0); LET, 27.9 months (95% CI: 25.5, 31.1)

Finn RS, et al. *Lancet Oncol*. 2015;16:25-35. NR=not reached.

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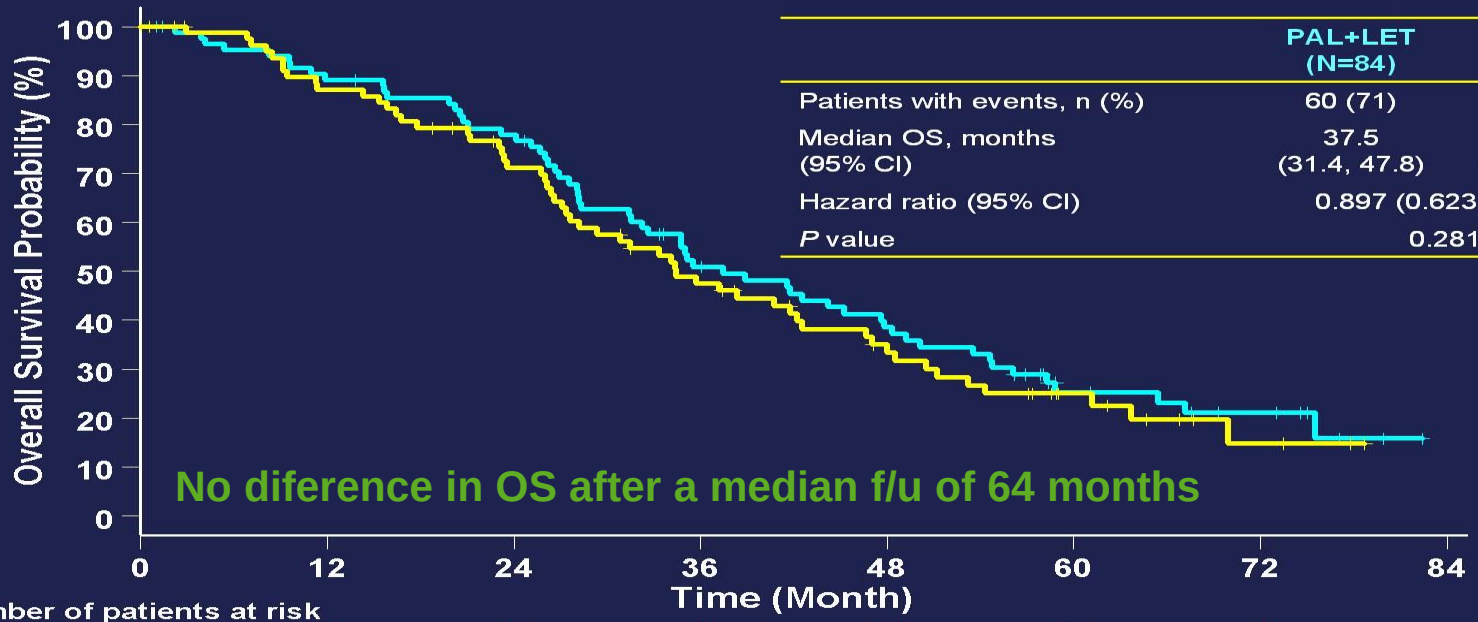
# ASCO 2017 Palbociclib OS Update

## OS: Phase 2 (ITT)




| | PAL+LET (N=84) | LET (N=81) |
|---|---|---|
| Patients with events, n (%) | 60 (71) | 56 (69) |
| Median OS, months (95% CI) | 37.5 (31.4, 47.8) | 34.5 (27.4, 42.6) |
| Hazard ratio (95% CI) | 0.897 (0.623, 1.294) | |
| *P* value | 0.281 | |

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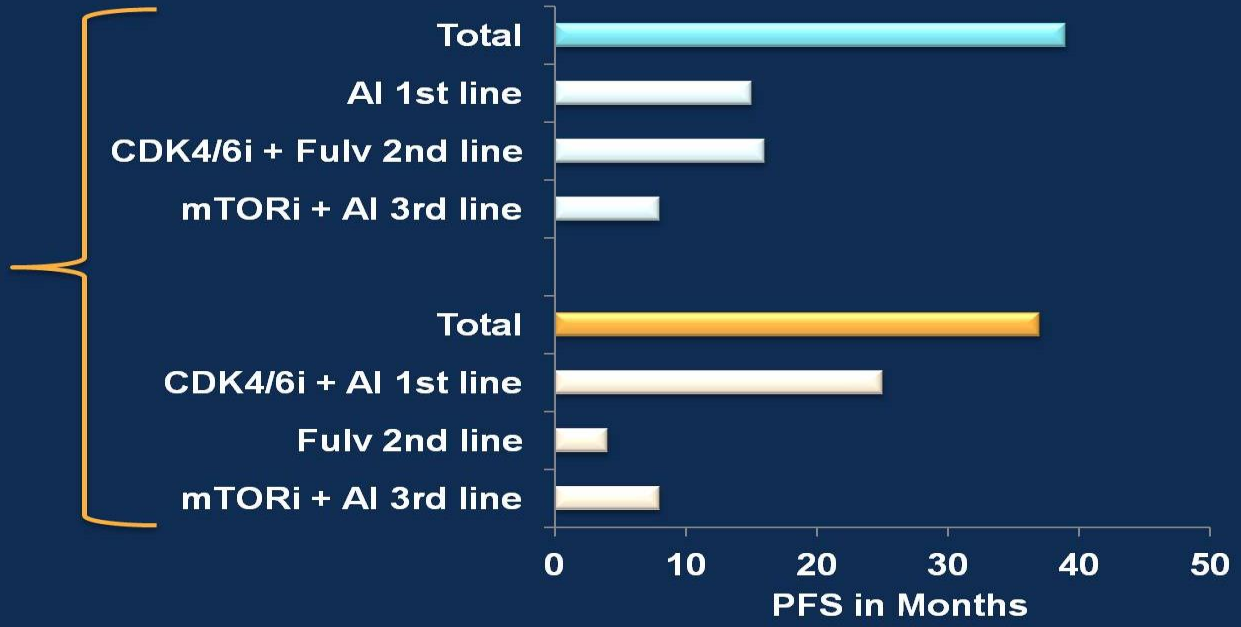
# What to do in our practice?

**2 different treatment strategies; choice should probably rely on BIOLOGY (i.e. primary vs acquired ET resistance…)**

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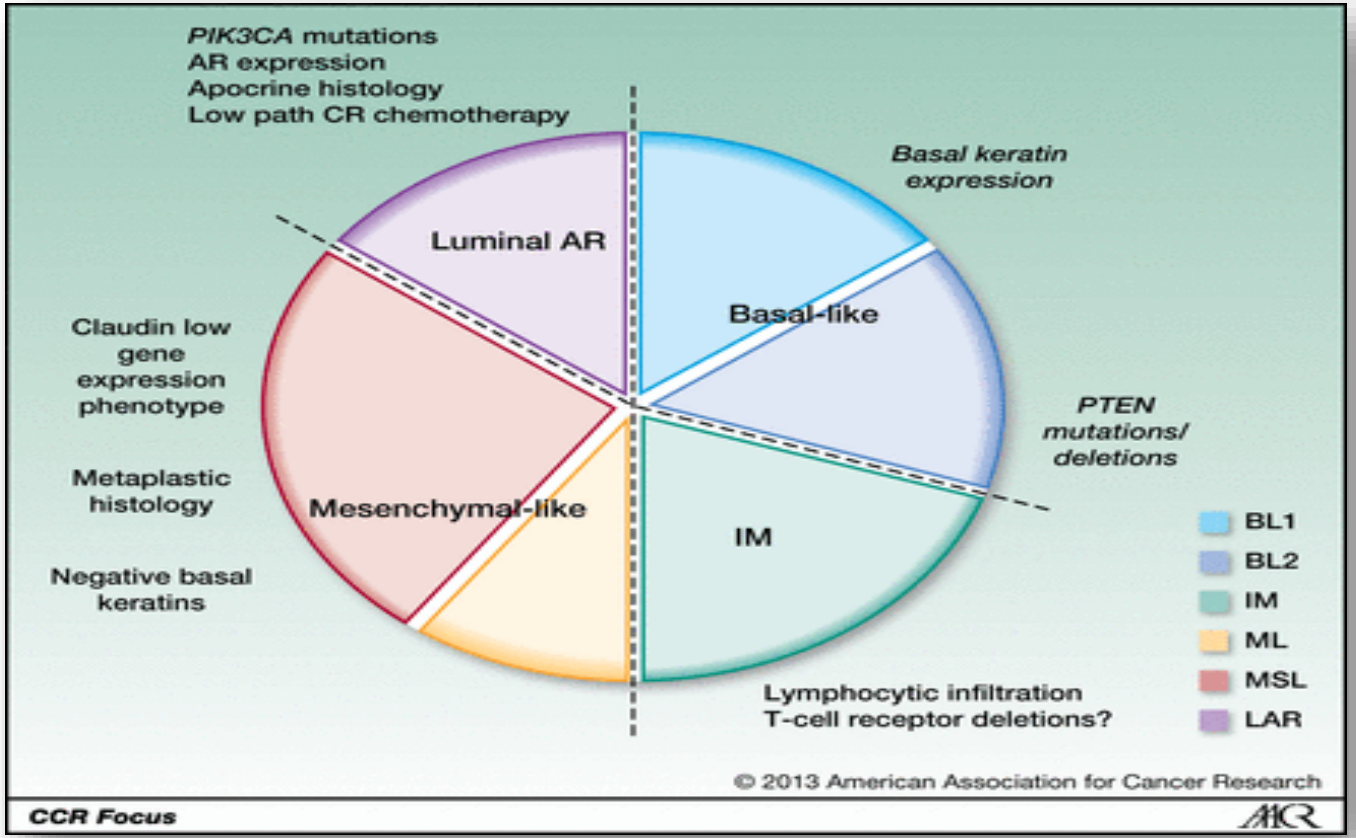
# TRIPLE NEGATIVE BREAST CANCER

# TNBC Heterogeneity



# When to Test for *BRCA1/2* Mutations in MBC

Pts diagnosed at young age, with specific subtypes, or with family history of breast or ovarian cancer should be referred for genetic testing and counseling

## Pt Factors

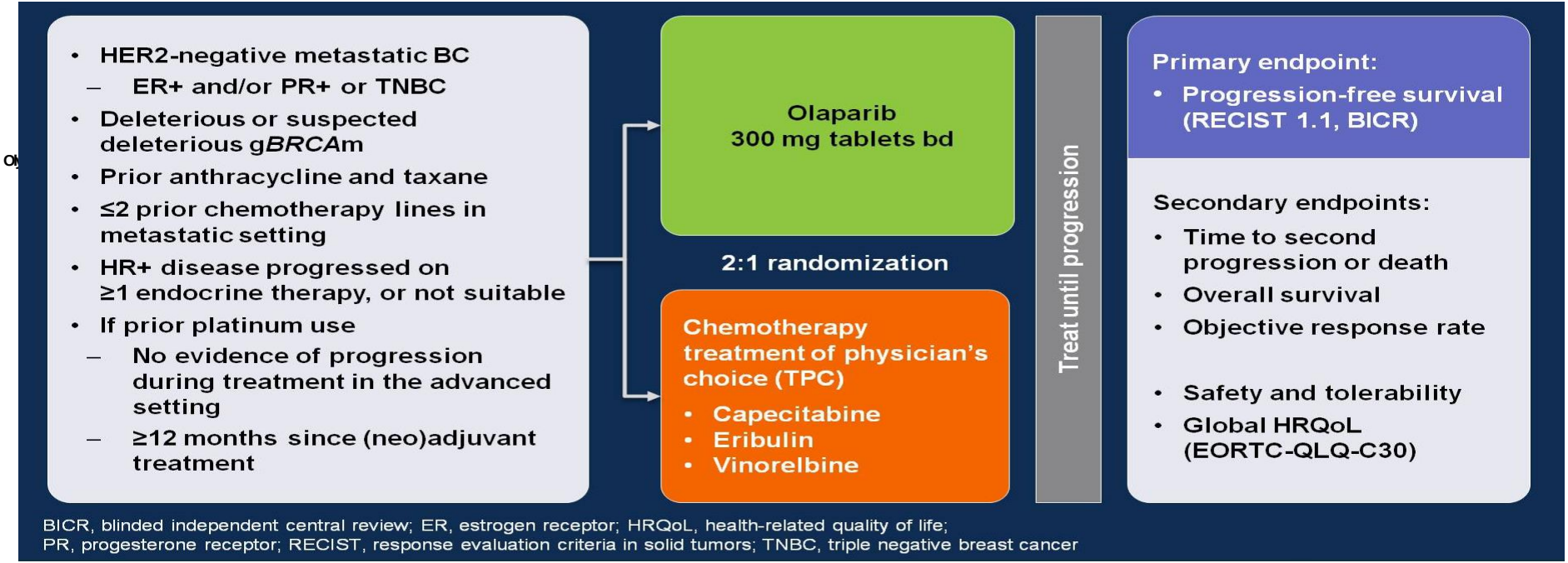
- < 50 yrs of age at diagnosis of BC
- ≤ 60 yrs of age at diagnosis of TNBC
- Diagnosis of bilateral BC
- History of ovarian cancer at any age or in any first- or second-degree relative

## Family History

- First-degree relative diagnosed with BC at < 50 yrs of age
- ≥ 2 first- or second-degree relatives diagnosed with BC at any age
- Any male relative diagnosed with BC
- ≥ 1 grandparent of Ashkenazi Jewish heritage

Runowicz CD, et al. J Clin Oncol. 2016;34:611-635.

# OlympiAD: BRCA TNBC or HR+




BICR, blinded independent central review; ER, estrogen receptor; HRQoL, health-related quality of life; PR, progesterone receptor; RECIST, response evaluation criteria in solid tumors; TNBC, triple negative breast cancer

## 49% of Patients were TNBC

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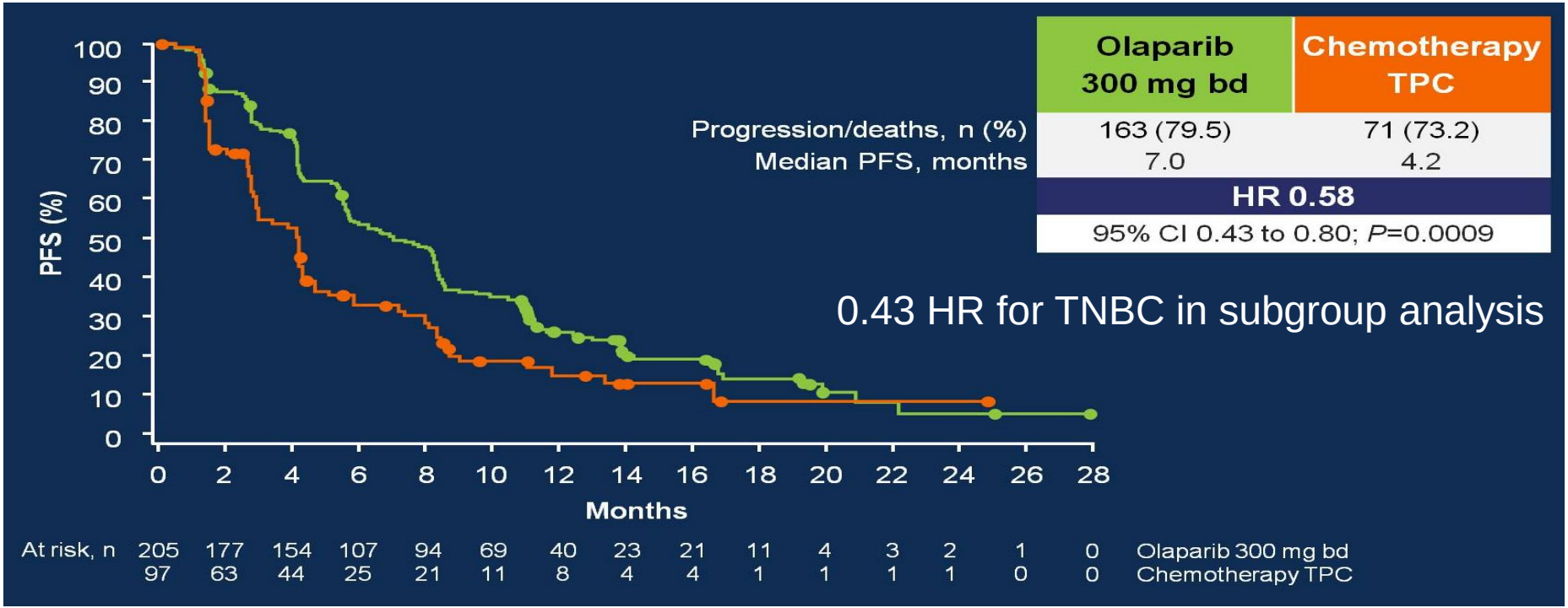
# OlympiAD: Primary Endpoint PFS




| | 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 | | |

0.43 HR for TNBC in subgroup analysis

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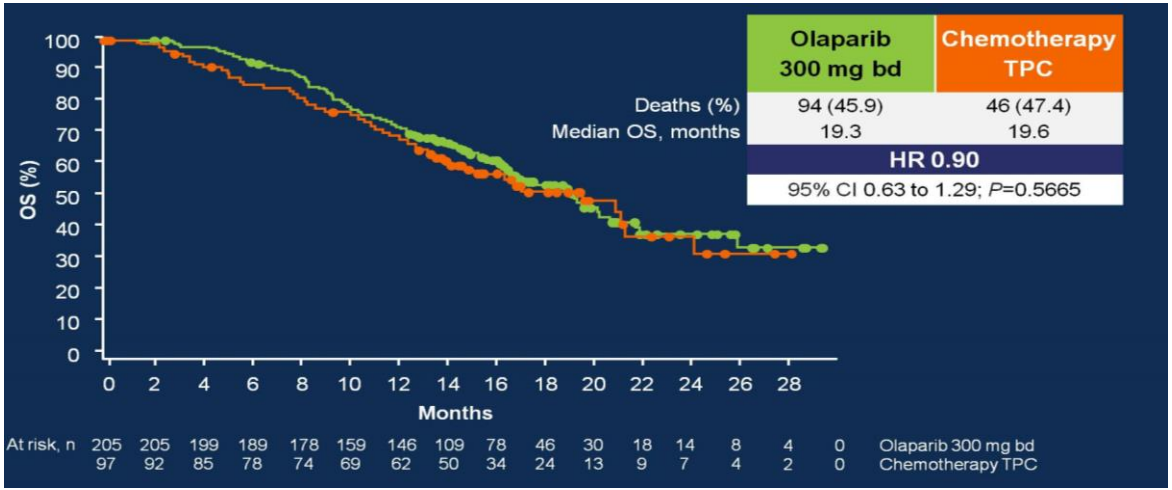
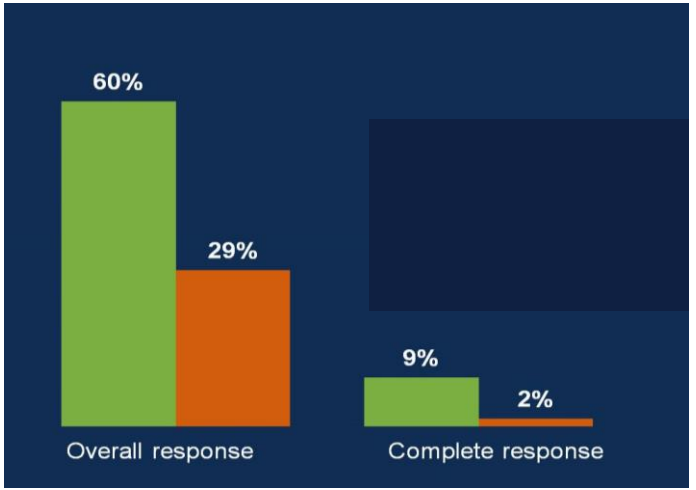
# OlympiAD: OS and ORR




On January 12, 2018, FDA granted regular approval to olaparib for the treatment of patients with deleterious or suspected deleterious germline BRCA-mutated (gBRCAm), HER2-neg MBC who have been treated with chemotherapy either in the neoadjuvant, adjuvant, or metastatic setting

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# Why is TNBC a good target for immunotherapy?

- High mutation rate, which can produce neoantigens that induce an immune response

- Increased number of tumor-infiltrating lymphocytes, which can facilitate an immune response

- Higher PD-L1 expression levels, which can inhibit T-cell antitumor responses, as compared with other breast cancer subtypes

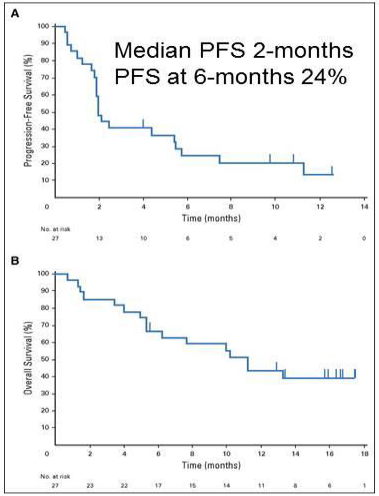
# Efficacy of single agent PDL-1 antibodies in heavily pre-treated TNBC

## KEYNOTE-012

TNBC
PD-L1+
Median prior Rx 2

→ Pembrolizumab 10mg/kg q2w

| Best response | n=27 |
|---|---|
| Overall response | 19% |
| Complete response | 4% |
| Partial response | 15% |
| Stable disease | 26% |
| Progressive disease | 48% |



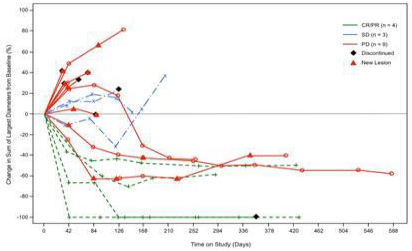

Nanda et al J Clin Oncol 2016

TNBC
69% PD-L1+ (IHC 2/3)
89% prior Rx ≥ 4#

→ Atezolizumab q3w*

* 15mg/kg, 20mg/kg or 1200 flat dose
\# not all in metastatic setting

| Best response | n=21 |
|---|---|
| Overall response | 19% |
| Complete response | 9% |
| Partial response | 9% |
| PFS at 24-weeks | 33% |




Median DOR: NR
(range: 18 to 56+ weeks)

Emens et al Proc AACR 2015

# Ongoing Trials of PD-1/PD-L1 Inhibitors in mTNBC

| Phase III Trial | Population | Investigational | Comparator | Primary Endpoint |
|---|---|---|---|---|
| KEYNOTE-119 | TNBC after 1-2 prior systemic tx for MBC | Pembrolizumab | Physician's choice Single-agent chemo | OS |
| KEYNOTE-355 | TNBC with no previous chemo for MBC | Pembrolizumab + chemo | Placebo + chemo | Part 1: safety<br>Part 2: PFS, OS |
| IMpassion130 | TNBC not previously treated for MBC | Atezolizumab + nab-paclitaxel | Placebo + nab-paclitaxel | PFS and OS |
| IMpassion131 | TNBC not previously treated for MBC | Atezolizumab + paclitaxel | Placebo + paclitaxel | PFS |
| Select Phase II Studies | | | | |
| DORA | mTNBC following clinical benefit with platinum-based tx | Durvalumab + olaparib and durvalumab | | PFS |
| Study 2151-169 | PD-L1+ mTNBC | Durvalumab + paclitaxel | | AEs |
| NCI Trial | HDR-deficient mTNBC (with known BRCA status) | Veliparib, atezolizumab, or veliparib + atezolizumab | | PFS |
| SNDX-275-0602 | mTNBC with 1-2 previous lines of Tx | Entinostat + atezolizumab, or placebo + atezolizumab | | MTD, PFS |
| MORPHEUS | An open-label, multicenter, randomized umbrella study evaluating multiple immunotherapy-based combinations | | | |

ClinicalTrials.gov.

Slide credit: clinicaloptions.com

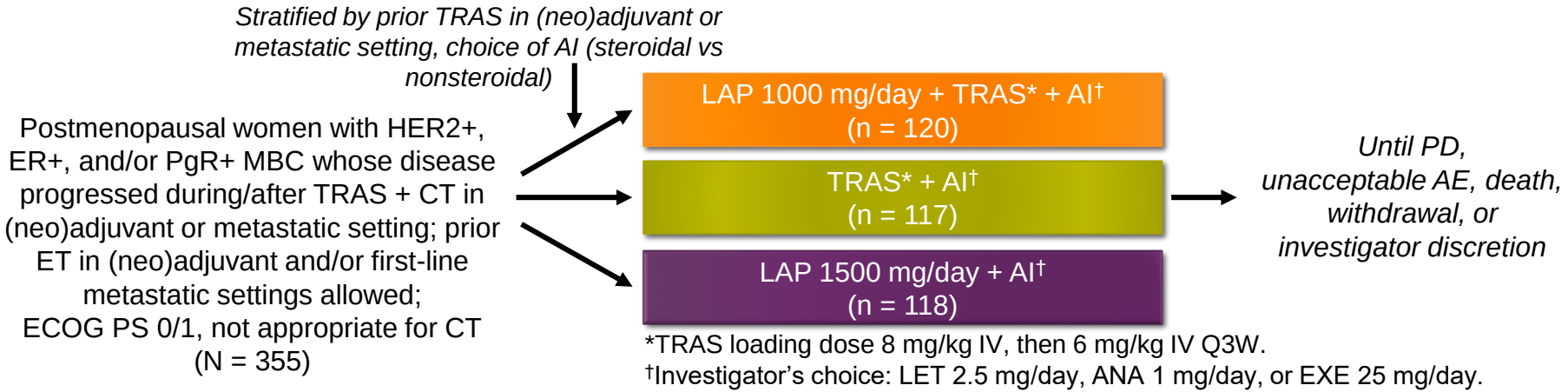
# Other Approaches Under Evaluation For TNBC

| Pathway/Drug type | Drugs in development |
|---|---|
| DNA repair | PARP inhibitors (olaparib, rucaparib, veliparib), platinum agents (cisplatin, carboplatin) |
| PI3K/Akt/mTOR | PI3K inhibitors (buparlisib, taselisib, GDC0941, AZD8186, many others); Akt inhibitors (GDC0068, others), mTOR inhibitors (everolimus, others) |
| Androgen (testosterone) signaling | Anti-androgens (bicalutamide, enzalutamide) |
| Immune | CTLA4 blockade (ipilumumab), PD1/PD-L1 blockade (nivolumab, pembrolizumab, atezolizumab), |
| Antibody-drug conjugates | IMMU-132, SGN-LIV1A, PF06647263, CDX-011 |
| Cell cycle | Dinaciclib, seleciclib |
| Chk1 | GDC0575 |
| Bromodomain | TEN-101, GSK525762 |
| Heat shock (stress) | Ganetespib, others |
| Angiogenesis | Ramucirumab, cedirinib |

# METASTATIC HER-2+ BREAST CANCER

# ALTERNATIVE: Study Design

- International, randomized phase III trial (data cutoff: March 11, 2016)




Primary endpoint: PFS with LAP + TRAS + AI vs TRAS + AI (investigator assessed by radiographic imaging)

Secondary endpoints: other PFS comparisons, ORR, CBR, OS, safety, QoL

Gradishar WJ, et al. ASCO 2017. Abstract 1004.

Slide credit: clinicaloptions.com

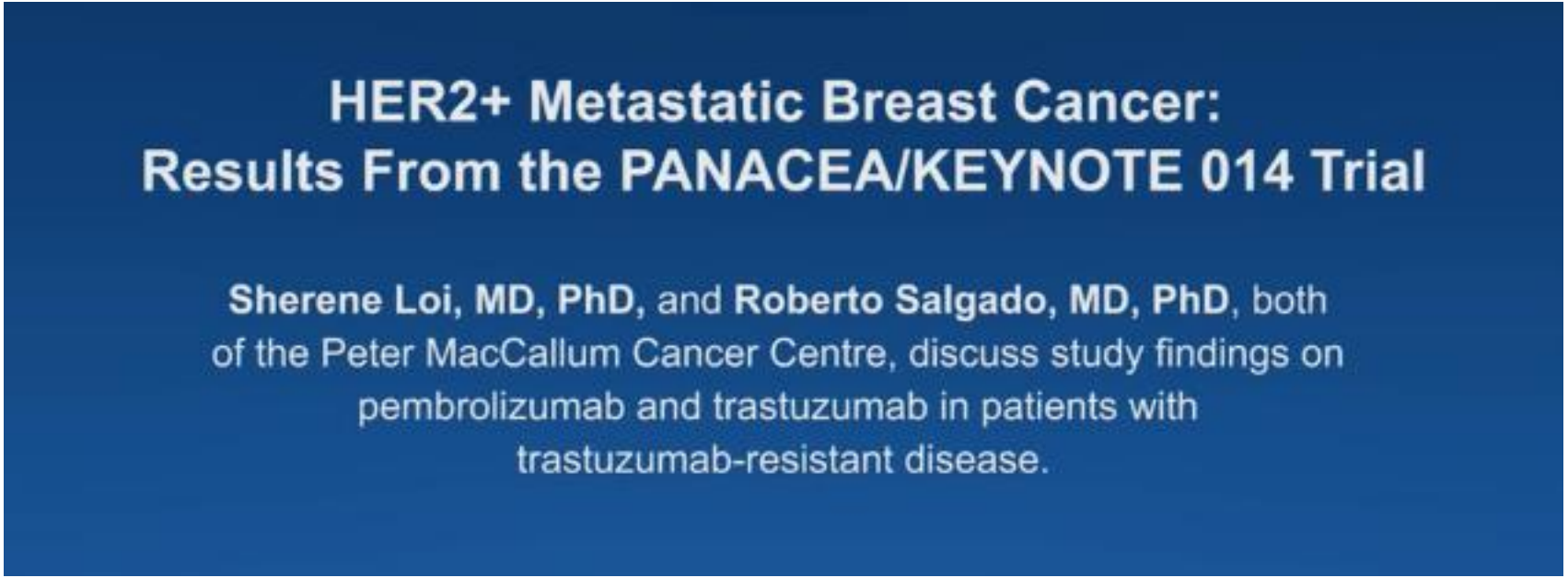
# ALTERNATIVE: PFS and OS

- Primary endpoint: 38% reduction in risk of progression with LAP + TRAS + AI vs TRAS + AI in ITT population

| | Endpoint | LAP + TRAS + AI (n = 120) | TRAS + AI (n = 117) | LAP + AI (n = 118) |
|---|---|---|---|---|
| PFS | PFS events, n (%) | 62 (52) | 75 (64) | 74 (63) |
| | mPFS, mos (95% CI) | 11.0 (8.3-13.8) | 5.7 (5.5-8.4) | 8.3 (5.8-11.2) |
| | HR (95% CI) vs TRAS + AI | 0.62 (0.45-0.88) P = .0064 | - | 0.71 (0.51-0.98) P = .0361 |
| OS | OS events, n (%) | 21 (18) | 30 (26) | 31 (26) |
| | mOS, mos (95% CI) | 46.0 (46.0-NR) | 40.0 (23.0-NR) | 45.1 (22.3-NR) |
| | HR (95% CI) vs TRAS + AI | 0.60 (0.35-1.04) P = .070 | - | 0.82 (0.49-1.36) P = .440 |
| Response | ORR: CR + PR,* % (95% CI) | 31.7 (23.5-40.8) | 13.7 (8.0-21.3) | 18.6 (12.1-26.9) |

Gradishar WJ, et al. ASCO 2017. Abstract 1004.

# Immunotherapy in HER2 Positive




- Presented at SABCS 2017

# Panacea/KEYNOTE 014 Results

- Phase Ib/II included 58 patients with advanced breast cancer HER2 + that had progressed on prior trastuzumab-based therapies.  Tumors were assessed for quantity of tumor-infiltrating lymphocytes (TILs) and PD-L1 status.

- Patients received 200mg of pembrolizumab every 3 weeks in combination with the standard dose of trastuzumab for 24 months or until disease progression.

- In the PD-L1–positive,ORR of 15% and disease control rate of 25%.
  - In a subgroup of PD-L1–positive patients with 5% or more TILs present, the ORR was 39% and the DCR was 47%, suggesting that quantification of TILs may help identify patients who will most benefit from this treatment.

  - No responses were observed in the PD-L1–negative cohort.

# Summary

- Breast cancer is a very heterogeous disease
- More options with single agent CDK4/6 or in combination with hormonal therapy for HR+BC provides longer time off chemotherapy
- Molecular signatures in TNBC provides multiple opportunities for a more personalized treatment
- Chemo free options for HER-2+ MBC can be considered
- Immunotherapy might benefit some subgroups fo patients, but not all of them